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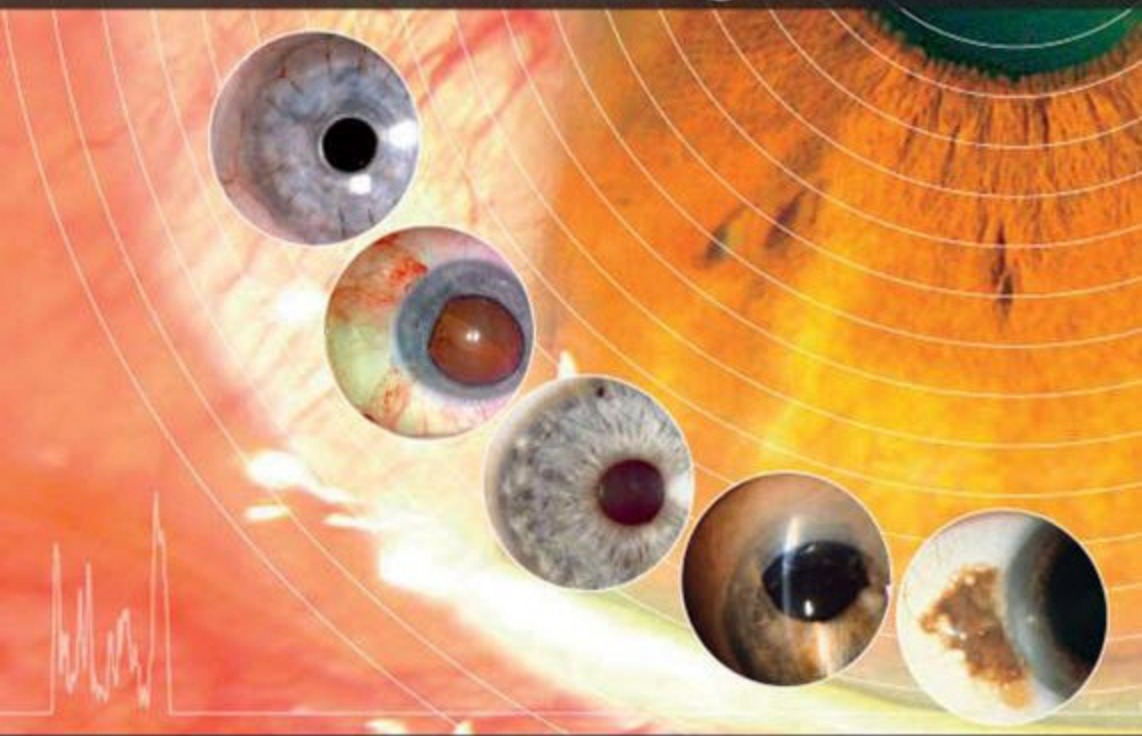
FOURTH EDITION

CORNEAL SURGERY

THEORY, TECHNIQUE AND TISSUE



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PREFACE

The 'face' and 'faces' of this Fourth Edition text for 2008 have changed as the reader will note immediately on viewing our front cover. In the hope of appealing to a broader international readership, we are joined by Olivia Serdarevic (Paris and New York) and Charles McGhee (Auckland, New Zealand). Peter McDonnell (Baltimore) and Ayad Farjo (Ann Arbor) complement our editorship, which seemed an increasingly daunting task involving three continents and our book publisher across the Atlantic. Add in the mix of an older editor (FSB) trying to keep up with the world of multiple contributors, frequently changing e-mail addresses, along with on-line manuscript corrections, and the task seemed overwhelming.

This book arose 22 years ago from an Eye Bank Association of America meeting in San Diego when keratoplasty began to flourish and eye banks created more stringent standards and were led by fellowship-trained corneal surgeons. We trained and were mentored by outstanding corneal surgeons and influenced directly by the likes of Dohlman, Kaufman, Laibson, Fine, Peyton, Polack, Troutman, Maumenee, Castroviejo and indirectly by Paufique and Rycroft among others.

The publication of Krachmer, Mannis and Holland's first and second editions of Cornea stands as a monument to absolutely the best of our current generation of corneal specialists with much to tell us about both the medical and surgical aspects of the diagnosis and treatment of corneal disease. Our mutual publishing company Elsevier suggested that this text should accentuate the surgical aspects of the cornea, and we have achieved this. In doing so we have strived to retain appropriate research chapters which aide our understanding of corneal anatomy and physiology.

This Fourth Edition again utilizes marvelous additional illustrations of Laurel Cook Lhowe to emphasize surgical technique and there is a return to color figures throughout the text. The refractive surgery portion of Cornea Surgery has been extensively revised and lengthened with Section Four reviewing 'Endothelial keratoplasty' and Part Six providing in-depth coverage of 'Surgical Correction of Refractive Errors'. The reader will note the retention of previous edition upgraded chapters such as 'Penetrating Keratoplasty' but the loss of all but one eye-banking chapter. Eye banks under the direction of the Eye Bank Association of America in fact have not disappeared—to the contrary we use them more than ever as they take on additional roles such as processing tissue for lamellar keratoplasty.

So as to not forget the lessons of the past; Peter Laibson, both in his lecture in Chicago two years ago, and in Chapter One of this text, has provided historical perspective on modern day corneal surgery.

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July, 2008

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CNJM: On a large, wide-ranging endeavor such as this fourth edition one always gratefully recalls the knowledge and skills passed on by mentors, peers and junior staff. I am particularly indebted to my early mentors in ocular pathology, Professor William Lee in Glasgow and Professor Dan Albert in Boston who taught me much about research and academic writing. My clinical career in ophthalmology owes a huge debt to far too many to name individually, but my clinical and surgical skills were molded at key stages by Dr John Williamson and Dr Jeffrey Jay in Scotland and Dr Geoffrey Crawford in Western Australia. Of course many corneal fellows have kept me up to date and have been enthusiastically involved in my various projects over the years and I often feel I have learned as much as I have given on this two way street. Finally, my career and my contribution to this book and other academic activities would have been absolutely impossible without the understanding and loving support of my dear wife Jane.

OS: I want to thank Fred Brightbill for his excellent previous editions; his stamina to complete this edition; and his invitation to include me in this most worthy project.

I also thank my mother and late father whose courage, fortitude, determination, integrity, wisdom and kindness inspired me to both pursue and foster knowledge and innovations for improving life.

DEDICATION

To the researchers, clinicians, teachers and patients—past and present—who have clarified our understanding of cornea and anterior segment function, leading us to remarkable new surgeries for treating disease and improving vision.

1 History of corneal transplantation

Peter R. Laibson

The first visually successful human corneal transplant was performed 101 years ago, on December 7, 1905, in Olmutz, a small Moravian city near Prague in Slovakia, formerly Czechoslovakia. It was performed by Dr Eduard Zirm on Alois Golgar, who was blind bilaterally from a lime injury.[1] Both corneas were severely scarred centrally, leaving some peripheral clarity. His vision was hand motions in both eyes.

Karl Braur, an 11-year-old boy, was the donor. He had lost vision following an intraocular metallic foreign body injury in July 1905. Zirm enucleated the blind eye and used the donor's clear cornea to form two 5.0-mm donor corneas. He removed the corneas with a 5.0-mm von Hippel trephine, which was first used by von Hippel in 1888 (Fig. 1.1). The same principle of using round trephines to remove the donor button and cut the host cornea is used today. Zirm kept the transplants in place with a bridge of conjunctiva sutured over the corneas. The patient's left corneal transplant was trephined from a more central part of Braur's donated cornea. The right corneal transplant failed and had to be removed but the left transplant cleared and Golgar was sent home 15 weeks after the operation. A year afterward an ophthalmologist checking Golgar's visual acuity found it to be 6/36 with a stenopeic disc. He could read J-4 with glasses[2] (Fig. 1.2). Zirm died in March 1944 without recording any other corneal transplants in his 45 publications. Golgar lived for 3 years after the operation.

The successful corneal transplant performed by Eduard Zirm, even though a single case, followed a century of keratoplasty investigation and failure. Keratoplasty in the 19th century was doomed to failure because of a total lack of knowledge concerning many basic concepts that would prevent failure, such as the germ theory and sepsis, immunology and tissue biology, anatomy and physiology of the cornea, and anesthesia. Even today immunologic rejection is not clearly understood, although it is successfully treated in most instances, usually with topical corticosteroids.

The concept of removing a clouded cornea was discussed by Charles Darwin's grandfather, Erasmus Darwin, in 1796. He felt that after an ulcer of the cornea perhaps the scar could be cut out and have it heal with a transparent scar. He recommended this 'strongly to some ingenious surgeon or oculist.' In 1824, Franz Reisinger coined the term 'keratoplasty' and it is he who is credited with this term, although controversy surrounds this attribution.[3] In those years it was felt that the human cornea could be replaced with an animal cornea from another species. The history of corneal transplantation in the 19th century has been reviewed by Castroviejo,[4] Paton,[5] and particularly Sir Benjamin Rycroft[6] in his Doyne Memorial Lecture of 1966. An outstanding book on the history of corneal transplantation was written by Manus and Manus in 1999.[7]

Sir Benjamin Rycroft in his Doyne lecture divided keratoplasty evolution into four periods:

I. Inspiration (1789–1824)
II. Trials and Frustration (1825–1872)
III. Conviction (1873–1905)
IV. Achievement (1906–1965)

I suggest a fifth category, V. Refinement and Innovation (1966–present).

At the start of the Inspiration period, from 1789 to 1824, a French surgeon, Pellier de Quengsy, in 1789 actually suggested that a glass cornea could be used to replace the human cornea. He illustrated what was perhaps the first keratoprosthesis but this was never done (Fig. 1.3). Erasmus Darwin in 1797 suggested that by surgically removing corneal pathology the scar might grow back clear. This, of course, was wishful thinking.

In the first part of the 19th century little was done in transplantation until Reisinger suggested that living tissue grafts might be used to perform a corneal transplant. This, of course, was doomed to failure as, among other things, different species were used for the transplantation. Wilhelmus Thome, in 1834, was the first to use the term 'corneal transplantation', although he did not do one. Perhaps the first successful transplant was done by James Bigger, who when captured by Sahara Bedouins was able to achieve his freedom, it is thought, by transplanting the opaque cornea of the pet gazelle of the head sheik using another gazelle's cornea.[8] Most attempts at transplantation in the 19th century used corneas of different species or heterografts and they failed. Kissam, in 1844, discussed guidelines for keratoplasty which although written 165 years ago are actually accurate for current keratoplasty techniques.[9] He suggested the donor and recipient should be of the same size. There should

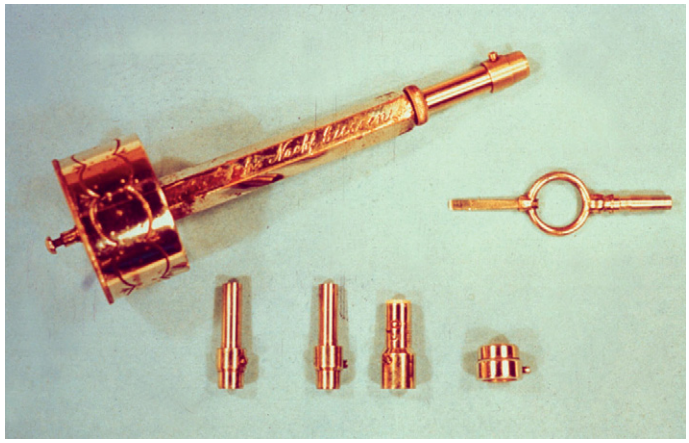

Figure 1.1. Round corneal trephine first used by Arthur von Hippel in 1888. This was a mechanical trephine with a key wind-up utilizing a spring mechanism, which rotated the trephine to remove corneal tissue. This gold-plated trephine photograph provided courtesy of Berthold Seitz, MD.

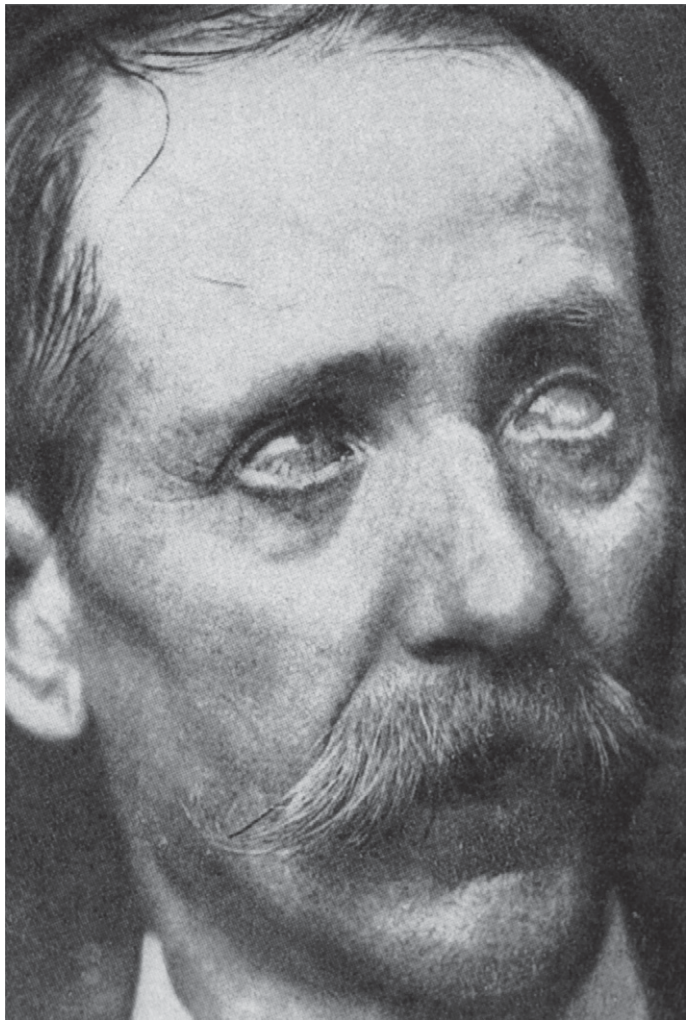

Figure 1.2. Alois Golgar, the first patient with a successful penetrating corneal transplant in 1905. His left eye shows a small clear corneal transplant, 4 mm in diameter. The corneal scarring in the right eye is from an alkali burn with corneal transplant failure in that eye.

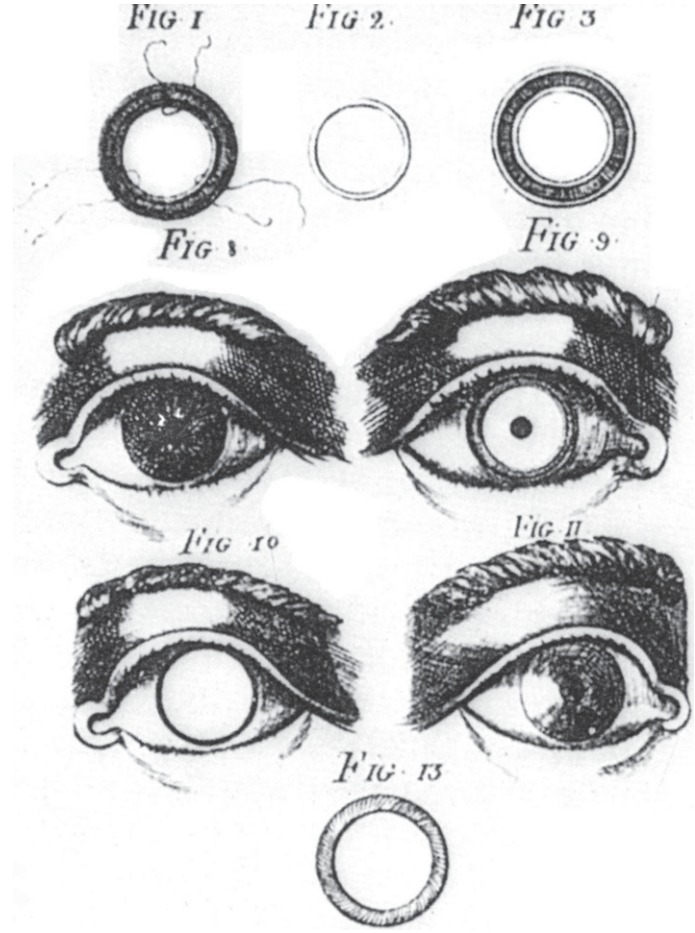

Figure 1.3. Illustration from Pellier de Quengsy's article in 1789 suggesting that a glass cornea might be used to replace a clouded human cornea.

be a rapid and atraumatic transfer of donor tissue with minimal tissue damage and there should be careful corneal fixation and protection of the intraocular contents, such as the lens, iris, and vitreous. It is significant that these concepts are all important today.

The third period, that of Conviction, from 1873 to 1905, saw Henry Power recommend transplantation within the same species.[10] In 1877, von Hippel started publishing his studies using circular mechanical trephines to remove the donor and recipient corneas. This principle is the same for keratoplasty today (Fig. 1.4). He did, however, set back keratoplasty for a time, as he recommended heteroplastic over homoplastic tissue. Other factors leading to success of corneal transplantation included the development of general anesthesia. Ether was first used in 1846, in the etherdome at Massachusetts General Hospital, chloroform in 1847, and in 1867 Lister first brought our attention to an aseptic setting for successful surgery. Topical cocaine was discovered by Kohler in 1884. Without anesthesia and asepsis, keratoplasty was unsuccessful even if done within the same species.

The period of Achievement, from 1906 to 1965, was actually started with Edward Zirm's successful transplantation of Alois Golgar's cornea. Despite Zirm's success with a single penetrating keratoplasty, this operation was not accepted in the first two decades of the 20th century. The lamellar graft was more often used, if any graft was done at all. Direct suturing was years away and penetrating grafts almost always failed. Most research into keratoplasty was

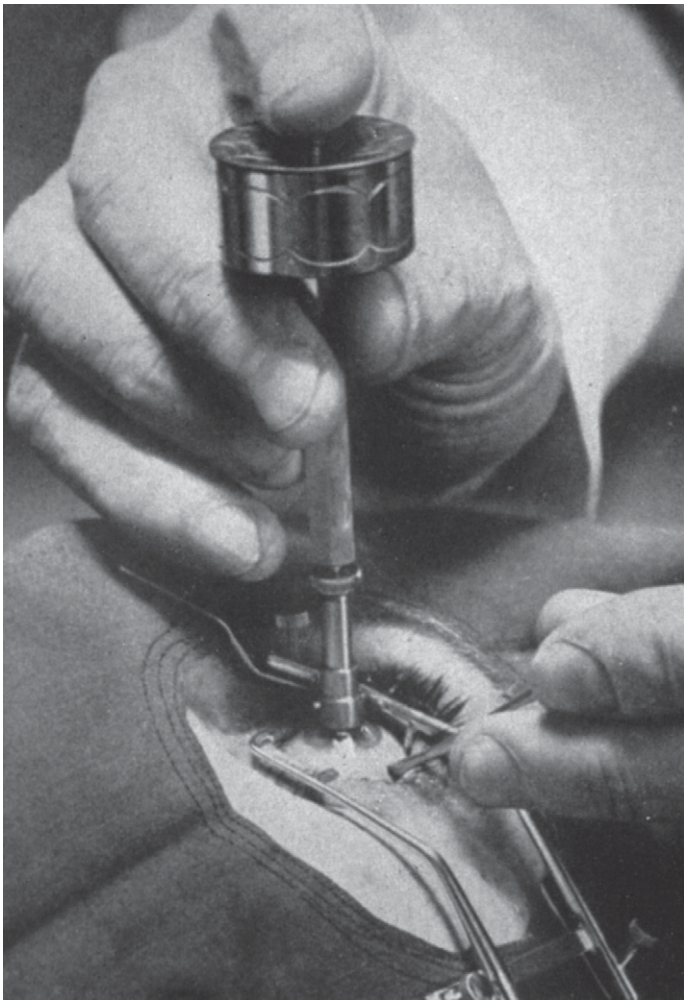

Figure 1.4. von Hippel trephine vertically in place over an eye being used to trephine the donor cornea.

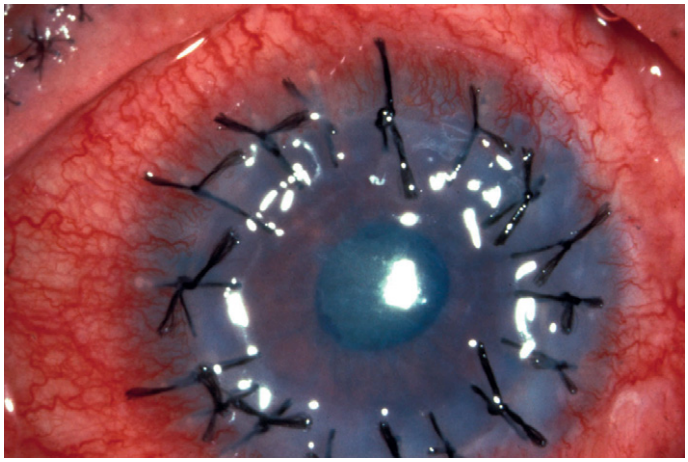

Figure 1.5. Edge to edge appositional sutures using 8–0 silk. Notice the extreme inflammation in this eye. The knots were tied on the surface and long ends left in place for 3 weeks.

carried out in Europe by the giants of that time, including Magitot,[11] in 1912, who first used preserved human corneas, and by Elschnig[12] in Prague. By 1930 his clinic had done 170 corneal transplants, with an amazing 22% success rate without the use of topical antibiotics or steroids! In these years most of the corneal transplants were small, about 4.0 mm, and were kept in place either by conjunctival flaps, with lid closure, or by fixation sutures placed across the cornea as had been done by Zirm.

Harry Gradle published one of the first articles in the US literature on the present status of keratoplasty in the *American Journal of Ophthalmology* in 1921.[13] He found that keratoplasty results were uniformly dismal up to that time. Only single case reports were published and in only one instance were two cases published. No patient had good vision and he concluded that a transplantation from another species is a biologic impossibility (whether or not transplants could be done successfully within the same species was not completely agreed upon). He did not refer to Elschnig's work in Prague, where corneal transplants in humans had been done for at least 10 years with some modicum of success. In those years, of course, US ophthalmology looked toward Europe, and many US ophthalmologists who were interested in furthering their careers studied there.

Sir Tudor Thomas, a leading figure working in England in the 1930s, experimented with corneal transplantation. He felt that it was premature to operate on humans when the results were so dismal.[14] In the early years of the 20th century, Elschnig was the leading advocate for corneal transplantation. In 1930, Elschnig and Vorisek[12] reported their 20 years of corneal transplantation experience in humans. They believed that the only successful method was that of a partial penetrating corneal transplant, where full-thickness human corneal tissue was used. This tissue was usually 4.0–5.0 mm in diameter and was removed from the donor with the von Hippel round trephine. A bridle suture from limbus to limbus in a double-arm fashion was used to maintain the cornea in position until healing occurred. Elschnig's clinic and laboratory results were remarkable considering he was still using techniques from the 19th century. His scrupulous concern in cleaning the cul-de-sac to prevent infection was important, as was his care with proper corneal alignment using overlying sutures, even if this suture was cut 2 days after the operation. The final bandage was removed at 3 weeks and one can imagine the suffering these helpless patients underwent with double patching and bed rest for that period of time. It is interesting to note that even in the early 1950s and 1960s, when edge to edge 8–0 silk sutures were used, 8–12 of these sutures were placed (Fig. 1.5), with a 5.0–7.0-mm-sized transplant. Patients were maintained on bed rest for 3 weeks with their head sandbagged so they would not move. At the end of 3 weeks, all sutures were removed (Fig. 1.6). Even in the 1960s, only about 50–60% of these transplants remained clear.

Although Magitot[11] had successfully transplanted preserved human corneas as early as 1911, freshly enucleated nonpreserved human corneas from eyes with pathology were the source for the corneal transplant donor in most cases. By the middle of the 1930s, when transplantation became more successful, there were not enough diseased eyes with clear corneas that required enucleation to satisfy the needs of the corneal transplant surgeons, who had many cases of bilaterally blind patients on their lists. Elschnig did support the use of cadaver corneas but it was Vladimir Filatov who was primarily responsible for popularizing the use of cadaver corneas for corneal transplant purposes. Filatov, in a review of corneal transplantation, mentions the use of cadaver corneas stored in an ice chest at 4°C.[15] The eyes were enucleated 'within 2–3 h before the body was taken to the morgue, or while in the morgue, certainly within just a few hours of death.' The corneas were used within 20–56 h after death. These early principles of cadaver

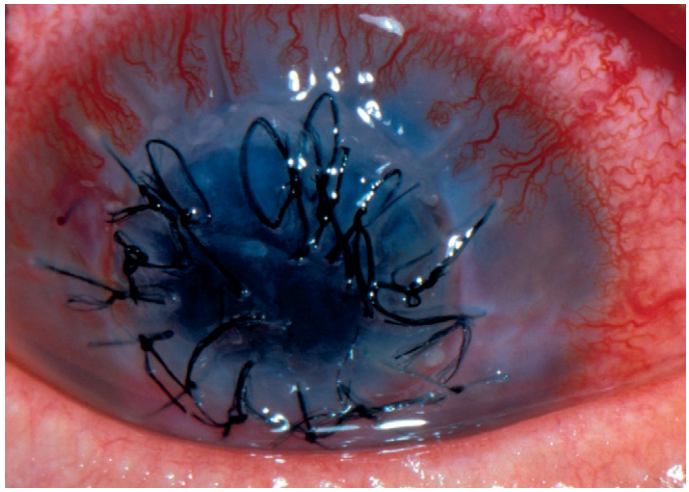

Figure 1.6. Three weeks after the silk appositional sutures were placed in a penetrating graft. There is marked vascularization and suture loosening, requiring all sutures to be removed at the same sitting 3 weeks after the initial surgery.

enucleations are techniques still used today in many countries. Other corneal surgeons preceded Filatov with individual case reports of cadaver cornea use but it is Filatov who was credited with popularizing cadaver corneas for corneal transplantation.

Equally important in the outcome of corneal transplantation is the fixation technique. Many methods have been used to ensure the proper alignment of the donor cornea, beginning with just conjunctival flaps and crossed sutures over the cornea. In the beginning only small grafts, less than 4.0 mm, were used. With these small grafts, overlay sutures were satisfactory for stabilization when the best suture material was probably equivalent to 4–0 or 5–0 silk. Numerous techniques were described in literature[15a] a for fixating corneas (Fig. 1.7). Most of these fixation techniques preceded edge to edge appositional sutures. The sutures were anchored in the sclera beyond the cornea and were removed soon after corneal transplantation because of loosening and vascularization. Ramon Castroviejo's unusual technique of square corneal transplants created with a parallel razorblade was utilized until the 1960s, mostly for keratoconus. He felt that a square graft, with one point directed toward 6 o'clock provided better stability in keratoconus (Figs 1.8 and 1.9). Castroviejo's investigations of keratoplasty, his design of unique instruments and his exquisite skill almost single-handedly improved our techniques and popularized corneal transplants in the 1940s and 1950s[16,17] (Fig. 1.10). Aside from Ramon Castroviejo, few ophthalmologists in the USA were performing corneal transplantation, either experimentally or on humans, before World War II.

A corneal transplant symposium, sponsored by the American Academy of Ophthalmology, occurred for the first time at Palmer House in Chicago in October 1947. A panel of physicians, including R Townley Paton, John M McLean, Ramon Castroviejo, and Edward Maumenee, presented at this symposium. Paton[18] wrote about patient selection while McLean[19] discussed keratoplasty technique, quoting liberally from Castroviejo's work, which dated back to 1932. Castroviejo[20] reviewed complications and illustrated the overlay suture for fixation in his article. Complications of keratoplasty included significant anterior synechiae, iris prolapse, infections (penicillin was the only antibiotic in use), glaucoma, vascularization, inflammation, edema, and deformity due to the protruding edges of the transplant during the postoperative period.

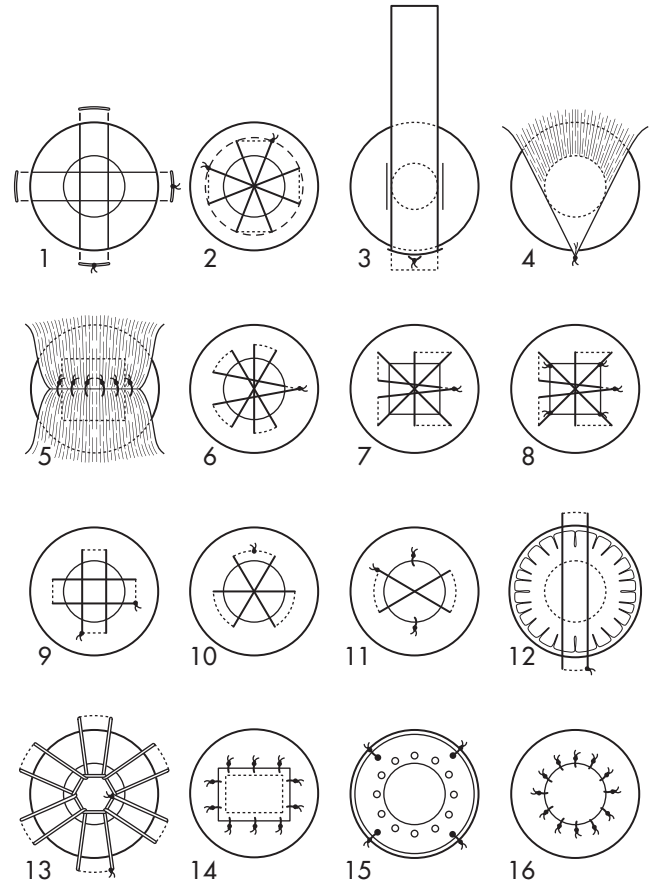

Figure 1.7. Various ways of fixing a corneal transplant with overlay sutures, conjunctival flaps, and in the bottom row eventually edge to edge appositional sutures.

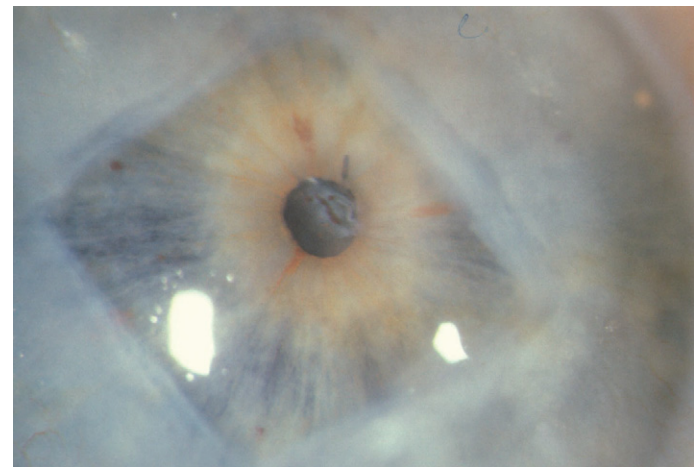

Figure 1.8. A Castroviejo square corneal transplant 30 years after this procedure was done in a patient with keratoconus. The cornea was moderately clear centrally and the patient still had 20/70 vision.

Maumenee and Kornblueth[21] discussed the physiopathology of corneal transplants. In 1948, it was not clear whether the new graft was merely a framework for ingrowth of recipient cells or if the donor stromal cells and endothelium persisted. The importance of the corneal endothelium in maintaining corneal hydration was still not appreciated. It was Stocker's[22] work in 1952 that called our attention to the donor endothelium in keratoplasty. Davson in

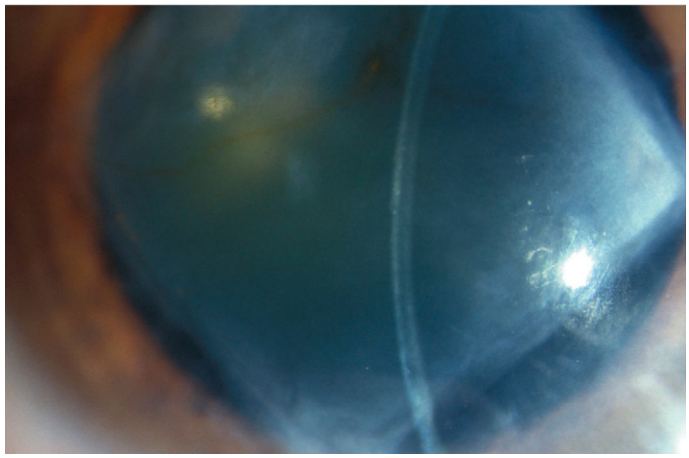

Figure 1.9. Slit view to show the clarity of another square corneal graft done for keratoconus, 28 years after keratoplasty by Ramon Castroviejo.

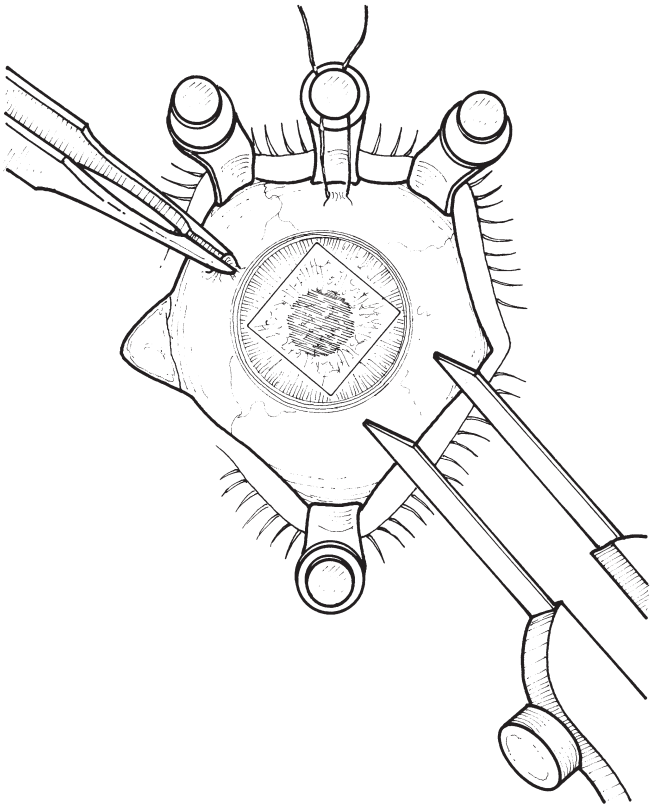

Figure 1.10. Castroviejo's parallel razor blade cutting knife to produce a square cornea. This is just one of many instruments designed by Castroviejo to make keratoplasty a better procedure in the years before microsurgery.

England, Harris and Nordquist, Mishima and Hedbys and Dohlman, as well as Morris, all in the USA, were to make major contributions concerning our understanding of the importance of the corneal endothelium. Specular microscopy was not done until the mid-1960s, and the longevity of the endothelium in keratoplasty is still being looked at, particularly by Bourne.[23]

In Europe, Paufique, Sourdille, and Offret in Paris, Billingham and Boswell in England, and Pollack in New York, as well as Khodadoust and Silverstein in Baltimore were working on graft

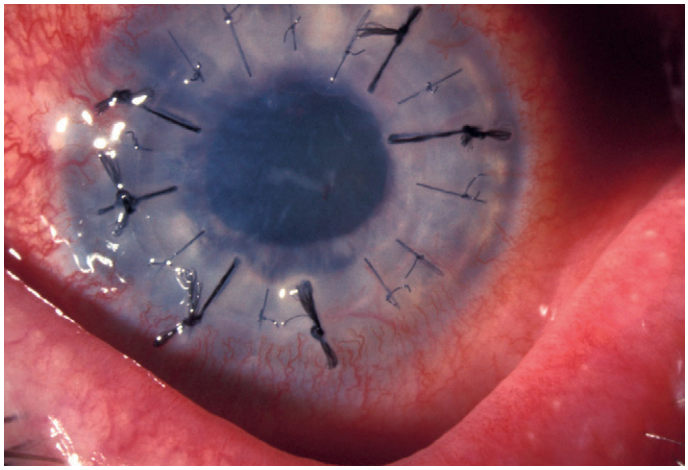

Figure 1.11. Beginning of nylon suture use. These sutures were not entirely trusted initially so there are some silk sutures tied on the surface and some nylon sutures, also with the knots tied on the surface.

rejection. The endothelial rejection line was named after Ali Khodadoust, an ophthalmologist still working in Connecticut today.[24] In the results section of this first American Academy of Ophthalmology Symposium on corneal transplantation, Owens[25] discussed a study of 417 grafts where 36.5% remained clear. The best results were with keratoconus, where 66% were clear, and hereditary dystrophies, 59%. There were no clear grafts obtained in patients who had Fuchs' corneal dystrophy. Max Fine,[26] in San Francisco, was the first corneal surgeon to do a transplant west of the Mississippi and to advocate keratoplasty for Fuchs' dystrophy and aphakic bullous keratopathy.

The surgical techniques for keratoplasty were slowly changing due to better instrumentation and suture material. By 1950, José Barraquer, a pioneer in keratoplasty in Barcelona, Spain, was using donor tissue up to 6.5 mm in diameter and utilized direct suturing with fine silk sutures, using very sharp Grieshaber needles (Grieshaber, Schaffhausen, Switzerland).[27] Mackensen and Harms at the University of Tubingen, in West Germany, in the late 1950s and early 1960s, initiated the use of nylon sutures. They were among the first to change from silk to nylon for direct appositional suturing. Richard Troutman, in 1963, introduced these sutures to the USA, along with the microscope, for keratoplasty.[28] In 1968, 10–0 nylon for keratoplasty was introduced commercially by Ethicon (Johnson & Johnson) (Figs 1.11 and 1.12).

As corneal transplantation grew to be more successful, the need for corneas from cadavers became greater. Eye banking began in the 1940s, when Paton established the first eye bank in the USA. This was the Eye Bank for Sight Restoration founded in New York in 1944. In 1961, the Eye Bank Association of America was established. Statistics for corneal transplants compiled by the Eye Bank Association of America, in their first year, showed that approximately 2000 transplants were done in 1961. In 2005, approximately 36 000 transplants were done in the USA from tissue obtained from the Eye Bank Association of America collaborating eye banks, while another 9000 corneas were sent overseas for transplantation.

In the era of cadaver cornea usage from whole eyes it was necessary to operate within 48 h of death to preserve the donor endothelium. This was inconvenient for the patient, the surgeon, and the operating room staff, as well as marginally healthy for the corneal endothelium bathed in aging aqueous fluid, which usually began

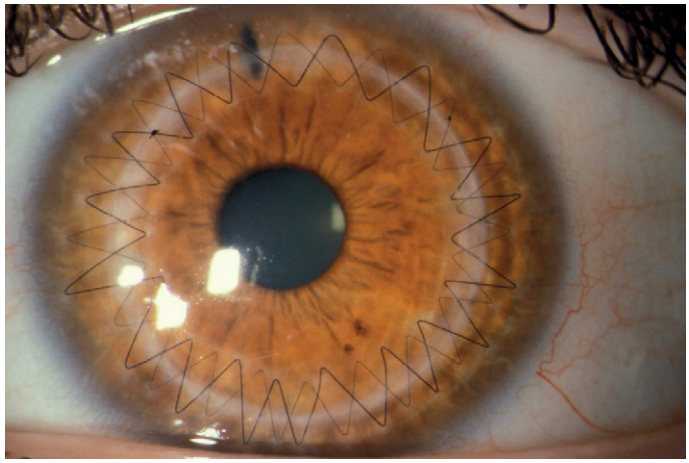

Figure 1.12. Modern corneal transplant with a double running 10-0 nylon buried suture, and an 11-0 running nylon buried suture.

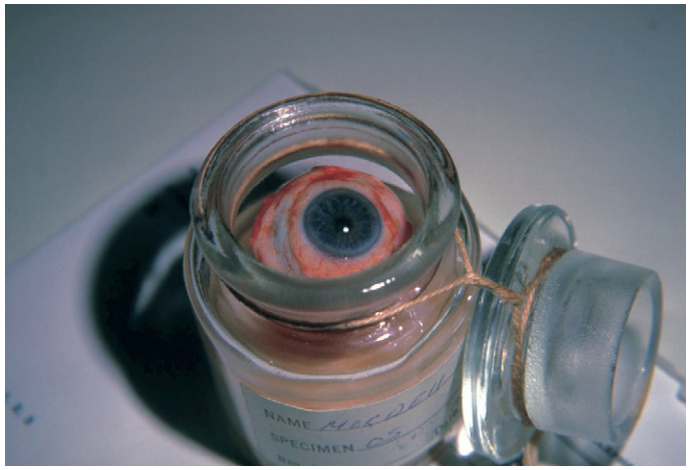

Figure 1.13. Glass jar storage of whole enucleated eye placed on a moist cotton sponge in the bottom of the jar. These eyes were kept refrigerated and had to be used within 48 h, as the endothelium of the donor was bathed by stagnant aqueous.

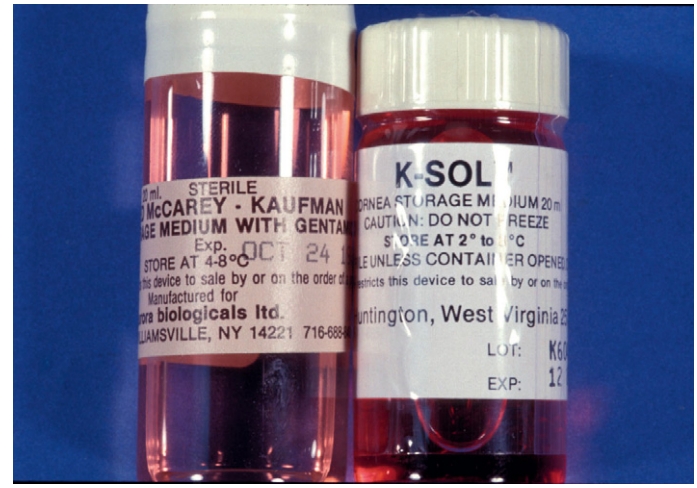

Figure 1.14. The tissue culture media on the left was first developed by McCarey and Kaufman.[29] This was sterile tissue culture media which allowed the cornea, with a small scleral rim, to be preserved for 3–4 days. On the right is later media known as K-Sol, which stretched the preservation period to 5–6 days. The currently available media, Optisol, allows use of the cornea for 7 days and beyond with excellent preservation of the endothelium.

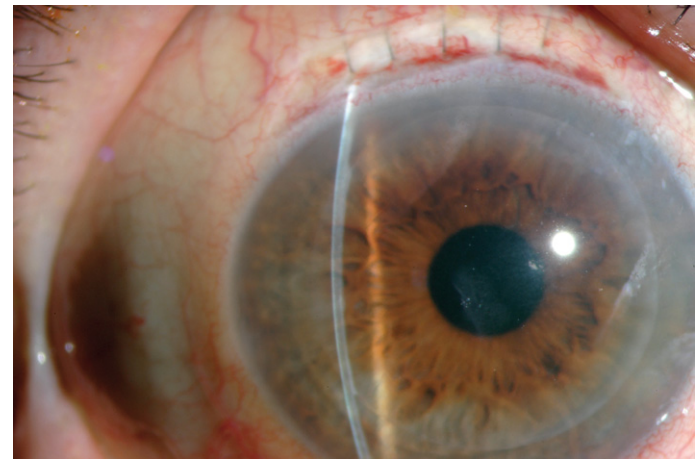

Figure 1.15. Cornea several days after a DSAEK procedure for Fuchs' dystrophy where Descemet's membrane and endothelium is peeled away from the host cornea and replaced by donor Descemet's and endothelium. Note the slit view to show corneal clarity with the host's own stroma remaining. Photograph courtesy of Christopher J Rapuano, MD.

to fail if the corneas were not used within 48–60 h of death (Fig. 1.13). The concept of corneal storage in artificial media was introduced by McCarey and Kaufman[29] in the early 1970s (Fig. 1.14). They employed tissue culture media and various enhancements to maintain the endothelium, and later antibiotics were added to prevent infection. Almost all corneal transplants in the USA are performed today using corneas that have been stored at 4°C in corneal storage media. In the UK and Europe organ culture is the storage method of choice.

Cornea storage media have improved continually so that corneas now may be stored for at least a week, maintaining excellent corneal endothelial physiology. The endothelium continues to be an important subject of research, as even 15 years after keratoplasty, endothelial failure is a major cause of graft failure.[30] New surgical techniques are now looking toward just transplanting endothelium and Descemet's membrane (Fig. 1.15).

In the *100-Year Review of the Cornea*, by Laibson and Rapuano, published in 1996[31] for the 100th anniversary of the American Academy of Ophthalmology Surgery, corneal transplantation was well accepted with a success rate in the 90% range for keratoconus, Fuchs' dystrophy, and pseudophakic bullous keratopathy, the three most important diseases requiring keratoplasty. Just 10 years later, in 2006, there is a very exciting new field in corneal transplantation. There are of course several problems with penetrating corneal transplants. The length of time for best corrected vision after penetrating keratoplasty can be 18 months or longer because of selective suture removal. Although fine nylon sutures ushered in the fifth period of keratoplasty, that of Refinement and Innovation (1966 to present), these nylon sutures did alter the rate of wound healing. With silk sutures knotted on the surface healing was usually complete by 21 days, after which the sutures were removed. With nylon sutures, which quickly bury beneath the surface, the healing period of a corneal transplant is much longer. It is now routine for surgeons to leave interrupted and running sutures in place for at least a year, and if vision is good with or without cor-

rection and with little astigmatism the sutures are left in even longer. One of the problems with the nylon suture is that it can break and breakage is relatively unpredictable. Also, astigmatism after corneal transplantation has been one of the main problems leading to unsatisfactory vision even though the graft may be clear.

Endothelial transplantation with posterior lamellar keratoplasty was first discussed many years ago by Polack[32] and brought to our attention more recently by Ko et al[33] and Melles et al.[34] The field of endothelial keratoplasty has recently been reviewed by Mark Terry[35] and is the most exciting new surgical technique since the introduction of nylon sutures and microsurgery. Surgical techniques for endothelial keratoplasty are still in evolution, including the use of lasers for the lamellar dissection. It has been very exciting to witness the changes in penetrating keratoplasty from the 1960s and even more exciting to see the current explosion of ideas in the field dealing with endothelial transplantation and anterior lamellar transplantation.

Our skill with corneal transplantation has greatly improved the visual prognosis for patients with corneal disease. Hopefully, in the years to come with further refinement of these new surgical techniques along with a better understanding of corneal transplantation rejection and wound healing, corneal endothelial replacement will prove even better for our patients than current penetrating keratoplasty techniques.

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2 Eyelid malpositions: entropion, ectropion, and trichiasis

Jeremy Van Buren, Cat Nguyen Burkat

INTRODUCTION

Maintenance of corneal surface integrity requires proper eyelid position and functioning. Precise apposition of the eyelid margin to the cornea is essential to distribute the tear film evenly, to maintain an appropriate tear lake, and to remove debris. With entropion, inward rotation of the eyelid margin may result in ocular irritation and severe abrasion by offending lashes. Conversely, in ectropion, outward rotation of the margin leads to breakdown of tear film protection with subsequent exposure keratopathy. Lastly, trichiasis and distichiasis are conditions where misdirected or abnormal lashes lead to abrasion and compromised corneal integrity.

The pathophysiology of these common eyelid disorders is best understood by considering the eyelid anatomy. The posterior lamella refers to the tarsus and tarsal conjunctiva, and the anterior lamella refers to the skin with the underlying orbicularis oculi muscle. The eyelash follicles and associated glandular appendages are located in the anterior lamella. The posterior border of the anterior lamella is the gray line, which corresponds to the orbicularis muscle of Riolan. The mucocutaneous junction is located on the margin, posterior to the meibomian gland orifices.

The vast majority of ectropion and entropion cases involve the lower eyelid. The inferior retractor complex of the lower eyelid is composed of aponeurotic expansions from the inferior rectus muscle.[1] These expansions form the capsulopalpebral head, which divides to envelop the inferior oblique muscle, before fusing anteriorly with Lockwood's ligament to form the capsulopalpebral fascia. The fascia connects Lockwood's ligament to the inferior fornix, to the inferior border of the tarsus, and to the preseptal orbicularis muscle and skin at the level of the eyelid crease. The inferior orbital septum joins with the capsulopalpebral fascia 4–5 mm below the inferior tarsal border, and then inserts onto the inferior tarsus (Fig. 2.1). Abnormalities of the precise anatomic interrelationships of these structures can result in the aforementioned eyelid malpositions.

ENTROPION

Entropion refers to an inward rotation of the eyelid in such a way that the eyelid margin, skin, and eyelashes directly rub against the globe. If untreated, entropion can lead to surface irritation, tearing, keratoconjunctivitis, corneal ulceration, and vision loss.[2]

EVALUATION

The clinical examination of entropion is aimed at classification, assessment of eyelid laxity, cicatricial changes, and secondary effects on surrounding structures.[3] Proper assessment begins with a detailed history, which will help distinguish between the major entropion etiologies (involutional, congenital, acute spastic, and cicatricial).

Initial physical evaluation begins with assessing eyelid laxity. Laxity comprises three components: medial canthal tendon laxity, lateral canthal tendon laxity, and tarsal degeneration. The medial canthal tendon normally does not allow the inferior punctum to be pulled laterally more than approximately 2 mm. Lateral displacement of greater than 5–6 mm, or punctal distraction to medial limbus or pupil, are indications for surgical correction (Fig. 2.2, *A* and *B*). Likewise, lateral canthal tendon tone should not allow the lateral canthal angle to be pulled medially over the lateral limbus. The snapback test is performed by pulling the eyelid anteriorly and measuring the distance of displacement. One should not be able to pull the eyelid more than 6 mm away from the cornea. When released, the eyelid should return sharply to its former apposition against the globe. Failure to do so indicates tarsal attenuation or lateral canthal tendon laxity (Fig. 2.2, *C* and *D*). Lastly, the inferior fornix should also be examined for inferior retractor dehiscence.

Cicatricial entropion may be due to scar tissue contracture within the posterior lamella. The tarsal conjunctival surface and fornices should be evaluated for subepithelial fibrosis and tarsal deformation. Eyelid retraction refers to the amount of scleral show seen when the eyelid margin is not located at its normal height (1 mm inferior to the superior limbus for the upper eyelid, or at the level of the inferior limbus for the lower eyelid). In retraction, the eyelid margin itself is correctly apposed to the globe without anterior or posterior rotation. The anterior lamella should be evaluated for hypertrophy or orbicularis muscle spasms.

The entropic eyelid and lashes can result in corneal abrasions, ulcers, scarring, and chronic inflammation. Therefore, a thorough

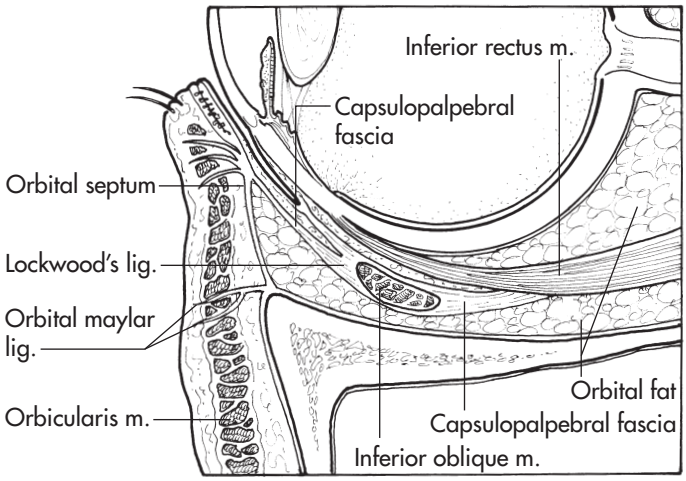


Figure 2.1. Normal anatomy of the lower eyelid in cross section.

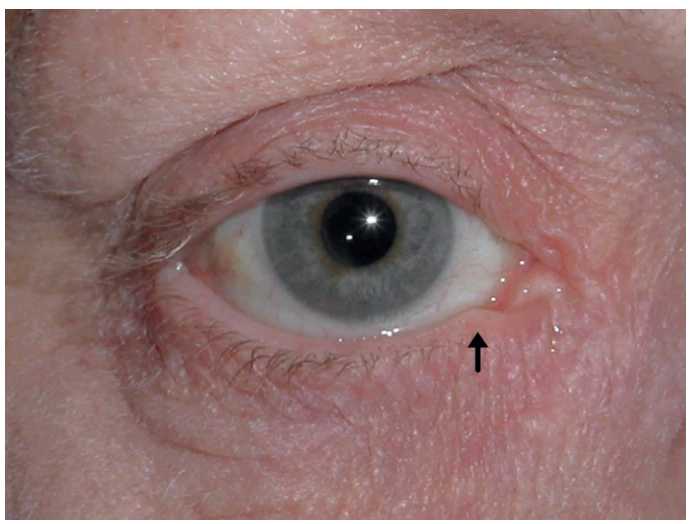
evaluation of the cornea, including fluorescein staining, is required in all patients.

CLASSIFICATION

Involutional entropion

The most common type of entropion, involutional entropion, usually affects elderly persons and involves mainly the lower eyelids (Fig. 2.3, *A*). In the upper eyelid, eyelash ptosis may cause chronic irritation and keratopathy, and be confused with entropion. Three main factors contribute to development of involutional entropion: horizontal laxity, retractor complex disinsertion, and orbicularis muscle override. Others have suggested age-related enophthalmos and the 'hammer effect' of orbicularis contraction as less significant factors.[4,5]

Disinsertion or attenuation of the retractor complex allows the lower tarsus to move anterior and superior, causing the lid margin to turn inward. Dehiscence of the inferior retractors from the inferior tarsal edge may be seen as a white horizontal line deep in the fornix, corresponding to the leading edge of the disinserted retractor



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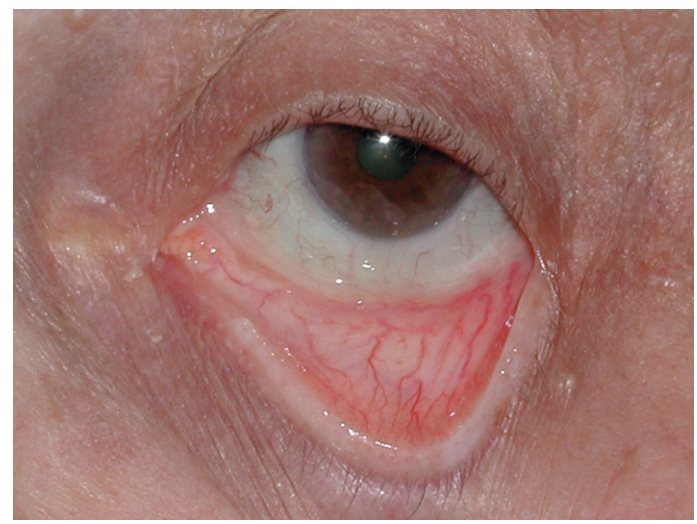

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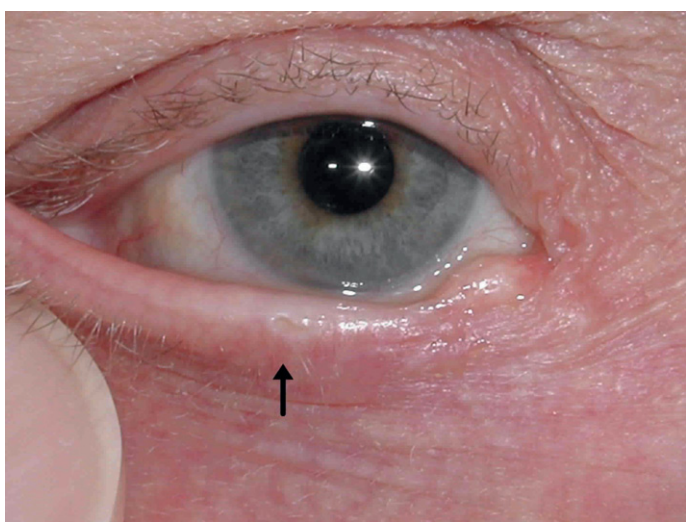

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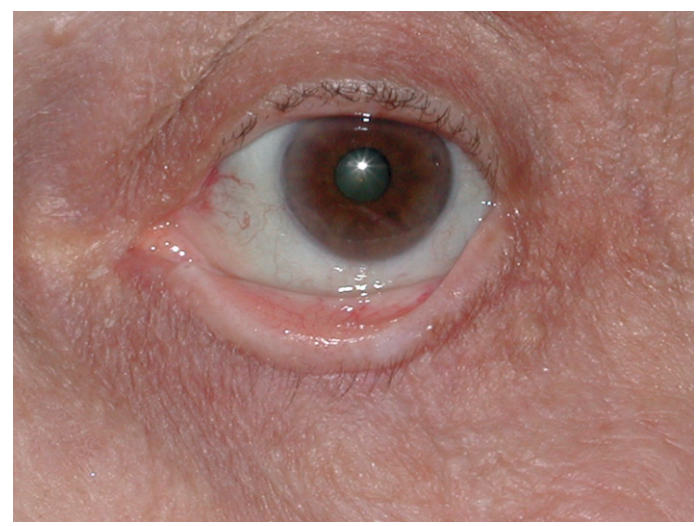
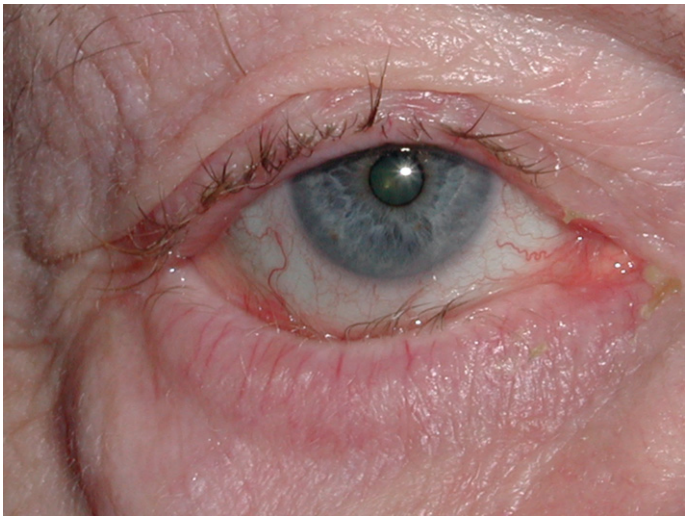


D

Figure 2.2. Evaluation of lower eyelid laxity. *A* and *B,* Lateral horizontal traction distracts the inferior punctum past the pupil, demonstrating severe medial canthal tendon laxity. *C* and *D,* The snapback test. After release, the lower eyelid does not return to its proper apposition on the globe.



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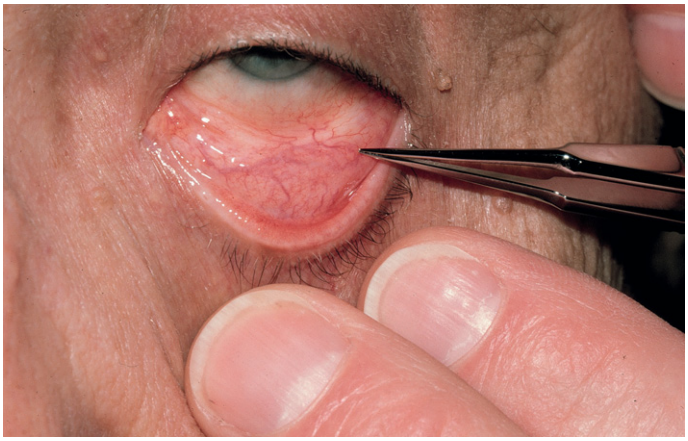

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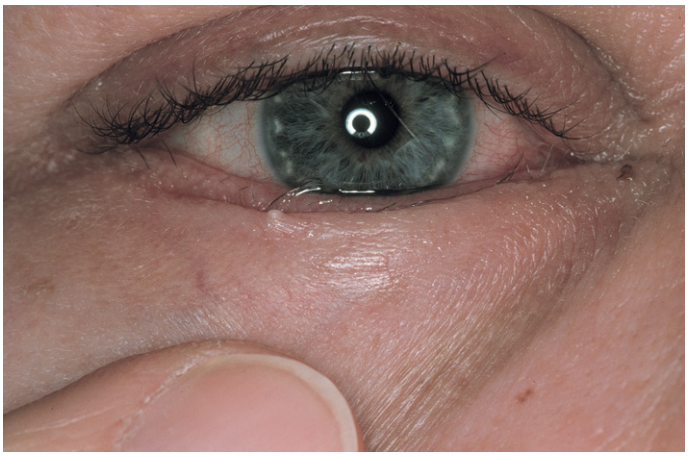

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Figure 2.3. Involutional entropion. *A,* Involutional entropion of the lower eyelid. *B,* Inferior retractor dehiscence with instrument pointing to white line that represents the disinserted inferior retractors. *C,* Orbicularis muscle override.

layer. The pinkish-red tissue seen between the tarsus and white line is the preseptal orbicularis muscle now visible through the conjunctiva (Fig. 2.3, *B*). Because the attachment of the capsulopalpebral fascia to the inferior fornix remains intact, the inferior fornix may appear deepened when compared to the normal eye. The affected eyelid may also fail to retract fully during downgaze.

Figure 2.4. Epiblepharon of the lower eyelid with fine eyelashes oriented toward the cornea, but a normally apposed eyelid margin.

These anatomic findings can also cause ectropion. A factor that contributes to whether the unstable lower lid is going to turn inward is the preseptal fibers of the orbicularis muscle overriding the pretarsal fibers (Fig. 2.3, *C*). When this occurs, inward pressure is applied to the margin. The exact cause of this phenomenon is still speculative. Interestingly, Asians may be more predisposed to involutional entropion due to a more anterior and superior protruding position of orbital fat within the eyelid.[6]

Congenital entropion

This rare condition can affect both lower and upper eyelids.[7] Mechanisms are complex and involve tarsal dysgenesis (kinked tarsus) or disinsertion of the lower lid retractors. As opposed to epiblepharon in which a fold of skin pushes the lashes inward toward the globe, this condition does not improve spontaneously. Anomalies of the eye can also be present.

Epiblepharon is a congenital condition that occurs most commonly in Asians.[8] A horizontal fold of lower eyelid skin and underlying orbicularis muscle override the margin in such a way that the eyelashes are flipped backward toward the cornea and assume a vertical or posterior orientation (Fig. 2.4). In contrast to congenital entropion, the tarsus and posterior margin remain in their normal positions. The contact of the eyelashes with the cornea can be present all the time or only in downgaze, resulting in recurrent, bilateral ocular irritation or chronic epiphora of unclear etiology. Fortunately, eyelashes in children are fine and soft, so the problem is usually well tolerated. With growth of the facial bones, spontaneous resolution is common, more so in Caucasians than in Asians. Treatment is reserved for cases with significant threat to corneal integrity.

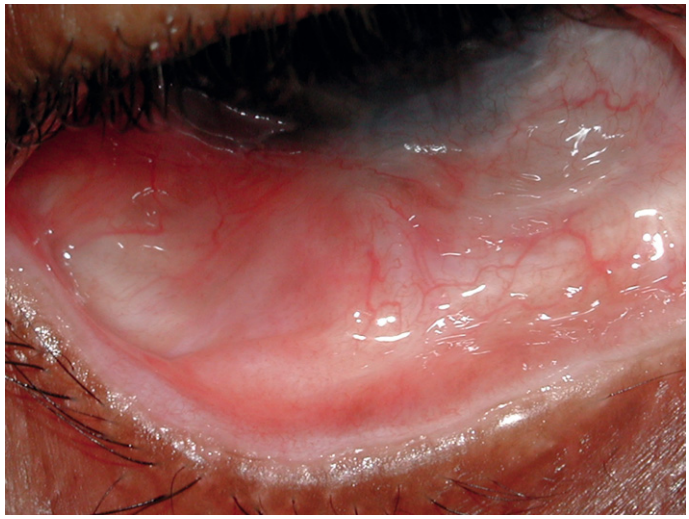
Acute spastic entropion

Any ocular irritation (e.g. after cataract surgery, corneal transplantation, or infection) can induce significant blepharospasm and subsequent entropion.[2,3] The eyelids are squeezed so tightly that the orbicularis muscle causes an inward rotation of the margin. This condition can affect any age group and lasts up to 6 weeks. In older patients it may be a manifestation of latent involutional entropion that may require subsequent surgical intervention.

Cicatricial entropion

Many conditions cause contracture of the posterior lamella and subsequent entropion[9] (Fig. 2.5, *A* and *B*). It is important to carefully

A



B

Figure 2.5. Cicatricial entropion due to ocular cicatricial pemphigoid (*A*), with shortening of the posterior lamella and subsequent cicatricial entropion, trichiasis, distichiasis, and symblepharon (*B*).

review the patient history and past examinations for conditions such as surgical or trauma-related scarring, chemical burns, and inflammatory entities such as trachoma, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, acne rosacea, atopic conjunctivitis, and chronic meibomitis. Any long-standing irritation can induce an added cicatricial component to prior eyelid malposition. In contrast to other forms of entropion, cicatricial entropion commonly affects the upper and lower eyelids.

MANAGEMENT

Involutional entropion

The nonincisional suture technique described by Quickert et al[7] and modified by Feldstein[10] is a valuable temporizing measure that can be performed in the office setting. Three or four absorbable sutures (i.e. 4–0 mild chromic) are passed through the eyelid and left in place until spontaneously resorbed. One needle of a double-armed suture is passed deep into the fornix, picking up the disinserted retractors, continues adjacent to the lower border of tarsus, and exits through the skin at the level of mid-tarsal height. The second needle is then similarly passed 3–5 mm lateral to the first. The knot is tied with such tension that a slight ectropion appears (Fig. 2.6, *A*). Typically, three sutures are placed along the lower eyelid in this fashion. This procedure should be considered temporary due to a high recurrence rate.

Definitive treatment addresses each factor causing eyelid laxity.[11] Anterior and posterior approaches have been advocated. The advantage of the anterior approach is a good success rate but involves more dissection.[5] The posterior approach through the conjunctiva avoids a visible scar.[12] Meticulous correction of the three main factors (horizontal laxity, inferior retractor disinsertion, and orbicularis override) results in a very low recurrence rate.

Medial canthal tendon laxity, if present, must also be addressed. Many techniques have been advocated with variable success. An important consideration is to properly tighten the posterior limb of the medial canthal tendon to the posterior lacrimal crest, in order to avoid iatrogenic anterior distraction of the medial eyelid and punctum away from the globe. Next, residual horizontal laxity can be corrected with a lateral tarsal strip procedure.[13,14] A strip of tarsus is exposed and denuded of eyelid margin, skin, and eyelashes (Fig. 2.6, *B*). The tarsal strip is anchored to the periorbita at the level of Whitnall's orbital tubercle inside the lateral orbital rim. Disinserted lower eyelid retractors are reattached to the inferior tarsal border, and a horizontal strip of preseptal orbicularis muscle can be carefully excised (Fig. 2.6, *C*).

Congenital entropion

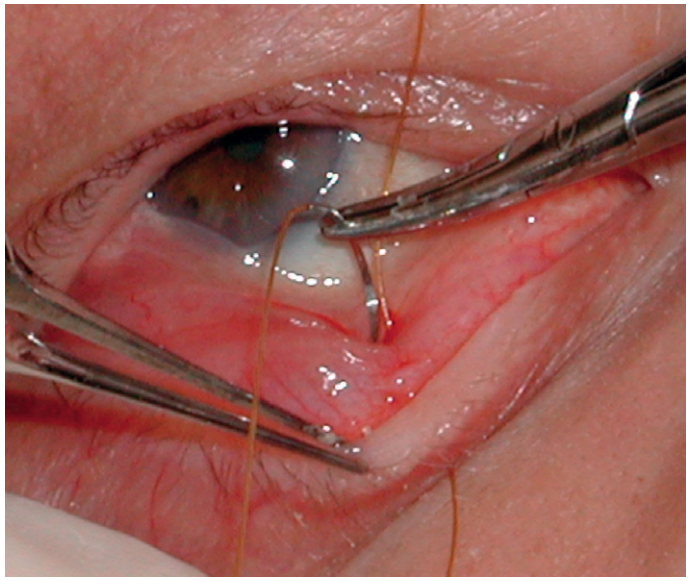
Techniques have included cauterization, everting sutures, skin and muscle excision, blepharotomy, tarsal incision or splitting, excision of the kinked area with margin rotation, and tarsal fracture with reanastomosis of the retractor complex to achieve better margin apposition. Anatomically, there may be lack of cutaneous-capsulopalpebral fascia attachment as in congenital epiblepharon, but intraoperative findings also suggest dehiscence of normal tarsal-capsulopalpebral fascia attachment. Repair has been advocated to include attaching the retractors to tarsus, as well as attaching skin to tarsus and the retractors to correct the lid malposition and create a normal eyelid crease.[15]

Spastic entropion

Medical management may be helpful by breaking a cycle in spastic entropion with lubricating ointments, bandage contact lenses, or taping of the eyelid. Tape is applied to pull the eyelid down and away from the eye, or horizontally and superiorly to mimic a lateral tarsal strip procedure. Injection of botulinum toxin into orbicularis muscle treats the spastic entropion component in essential blepharospasm or hemifacial spasm. However, injection of botulinum could turn an involutional entropion into a flaccid ectropion if initially mistaken for spastic entropion, or if significant lower eyelid laxity is also present.

Cicatricial entropion

Every attempt must first be made to control any inflammatory conditions before surgery is performed. The severity and extent of posterior lamellar involvement guide the surgical planning.[9] Surgical repair may be considered in three broad categories: margin rotation procedures with a partial or full-thickness tarsal plate incision, eyelid margin splitting procedures with anterior lamellar recession with or without mucous membrane grafting to the margin, and spacer grafts to elongate the posterior lamella. Mild cases may require only marginal rotation procedures. A transverse blepharot-



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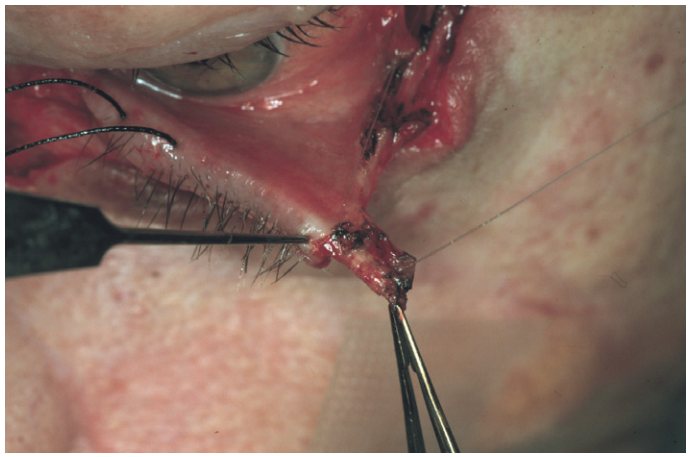

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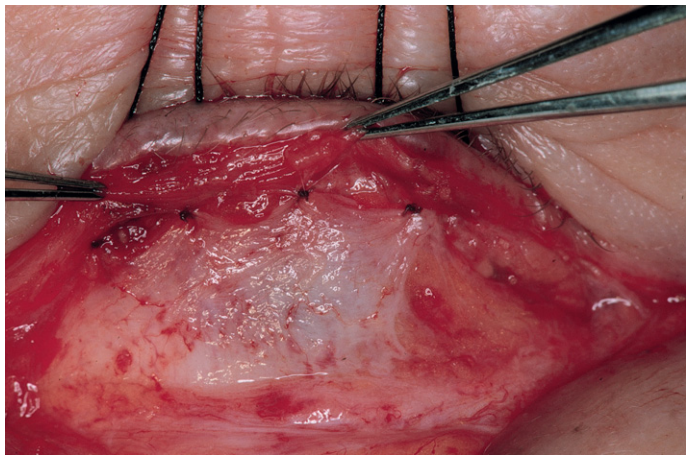


C

Figure 2.6. Surgical repair of involutional entropion. *A,* Quickert suture technique for repair of involutional entropion. *B,* Lateral tarsal strip procedure with exposed tarsus being reattached to lateral periosteum. *C,* Disinserted inferior retractors are reattached to the inferior tarsal border.

omy and margin rotation described by Weis can be effective in repairing a cicatricial entropion.[16] In effect, this procedure creates a full-thickness blepharotomy scar between the retractors, the tarsus, and the anterior lamella.

Full-thickness tarsal margin rotation with super-advancement of the posterior lamella 2–3 mm past the new rotated margin may allow for contraction to occur without recurrence of the entropion.[17] A horizontal V-wedge resection of anterior tarsus has been described to correct the abnormal tarsal shape while avoiding surgery on the conjunctiva and subsequent reactivation of inflammatory disease.[18] An additional effect can be achieved with shortening or repositioning of the anterior lamella with a lid splitting procedure or tarsoconjunctival advancement.[19] Graft materials, such as tarsus, hard palate, ear cartilage, acellular dermis, and buccal mucous membrane, can be used for severe scarring or retraction of the posterior lamella.[20]

ECTROPION

In ectropion, the lid margin is everted from its normal apposition to the globe.[21] If left untreated, ectropion can lead to chronic epiphora, chronic conjunctivitis, exposure keratitis, corneal scarring, ulceration, and perforation. The epiphora, conjunctivitis, and keratitis may accompany eyelid laxity before frank ectropion becomes manifest.

EVALUATION

Evaluation should include assessment of eyelid laxity by snapback test, medial or lateral canthal tendon laxity, disinsertion of the lower lid retractors, punctal ectropion, inferior scleral show, retraction, lagophthalmos, and corneal surface integrity. Cicatricial vertical shortening of the anterior lamella from past trauma, burns, dermal inflammatory conditions, or chronic eyelid rubbing from eye irritation or epiphora should be noted.[22] In eyelid retraction, the orientation of the tarsal plate and eyelid margin are normal, but the resting height of the margin is retracted beyond the limbus, usually with evidence of scleral show. Eyelid retraction is a common finding in Graves' ophthalmopathy. Lagophthalmos is present when normal contraction of the orbicularis muscle fails to close the eyelids.

CLASSIFICATION

Congenital ectropion

This rare condition can present alone or in combination with other malformations, including blepharophimosis, euryblepharon, ocular anomalies, and systemic pathology such as trisomy.[21] The eyelid ectropion may appear minimal at rest. However, the condition is accentuated on upgaze, lid closure, or when opening the mouth due to a shortage of midfacial skin. Treatment involves graft techniques to compensate for a short anterior lamella. Congenital ectropion must be differentiated from total bilateral eversion of the upper eyelids in the newborn (Fig. 2.7). If total bilateral eversion is present, conservative treatment with lubrication and patching is usually sufficient.

Involutional ectropion

This condition is encountered frequently in elderly persons.[22–24] Similar to entropion, eyelid instability is a key factor and can be caused by horizontal laxity, vertical laxity with dehiscence of the

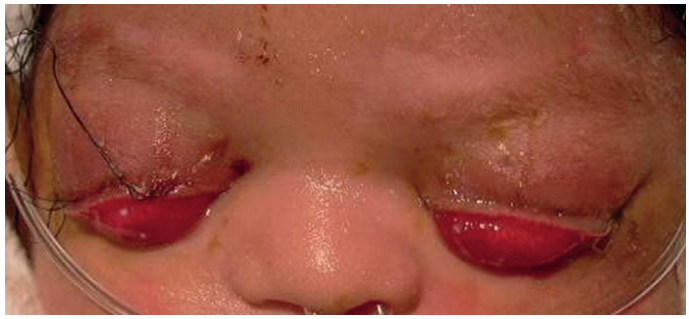
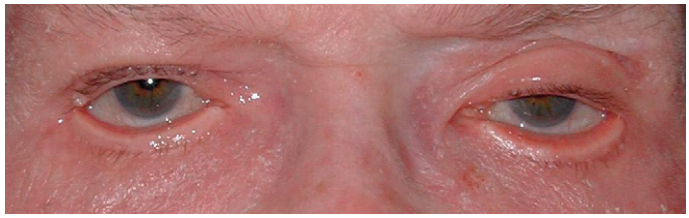
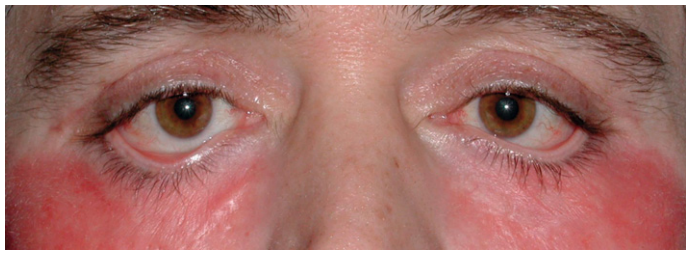


Figure 2.7. Total eversion of the upper eyelids, bilateral, in a newborn.



A



B

Figure 2.8. Cicatricial ectropion with vertical shortage of the anterior lamella due to chronic allergic dermatitis (*A*) and aggressive chemical peeling of the midface (*B*).

retractors, tarsal thinning, and age-related enophthalmos. Without adequate support, the lower lid is stretched further by gravity and the natural descent of the midface with age. Moreover, constant eye wiping from surface irritation or epiphora stretches the tissues further and leads to worsened malposition. In ectropion, orbicularis overriding is absent, thus allowing the unstable eyelid to turn outward. Histopathologically, focal degeneration of the orbicularis muscle with arteriosclerotic changes of the marginal artery can be found, suggesting chronic muscle ischemia.[23]

Cicatricial ectropion

Cicatricial ectropion occurs when there is a shortening of the anterior lamella due to cutaneous or subcutaneous scarring.[21] Trauma, burns, sun damage, inflammatory skin disease, herpes zoster, skin contraction as a result of chronic ectropion, maceration from epiphora and rubbing, excessive skin resection from blepharoplasty, and aggressive chemical peeling and cosmetic laser procedures are common causes (Fig. 2.8, *A* and *B*). The presence of vertical skin striae may suggest existing cicatricial changes. The ectropion may also worsen in upgaze and when the mouth is opened widely.

Paralytic, mechanical, and inflammatory ectropion

Paralytic ectropion results from orbicularis oculi paresis or paralysis secondary to facial nerve palsy (Fig. 2.9). More than 80 etiologies

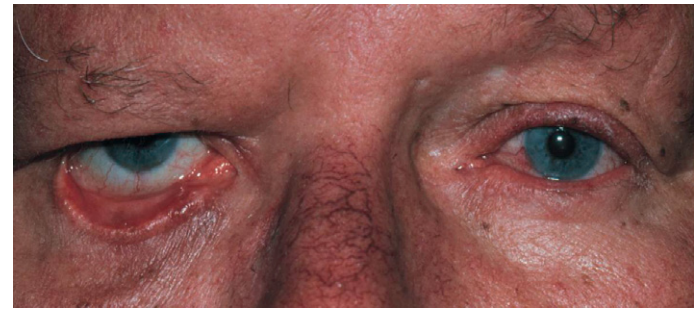


Figure 2.9. Paralytic ectropion following Bell's palsy, illustrating an ectropic atonic lower eyelid, lagophthalmos, midfacial ptosis, and paralytic brow ptosis.

of seventh nerve palsy have been described, the most common being trauma, infection, idiopathic Bell's palsy, and tumor.[25] An atonic lower eyelid is particularly susceptible to gravitational forces and will exacerbate any previous eyelid malposition, and result in eventual ectropion and eyelid retraction with time. Loss of orbicularis tone can lead to retraction of the skin, adding a cicatricial component to the ectropion. Mechanical ectropion is caused by the effect of gravity from a large lesion or tumor of the eyelid or cheek, pendulous edema, or by heavy glasses resting on the cheek. Inflammatory ectropion can result from many causes of inflammation or allergy of the eyelids, as well as from a long-standing ectropion.[21] Inflammatory ectropion will typically have an anterior cicatricial component as well.

MANAGEMENT

Medical management

Cicatricial, inflammatory, and paralytic ectropion have medical components to their management. In cicatricial and allergic ectropion, cosmetics and ointments or eye drops may be potential causes of chronic inflammation or allergy. In the presence of a chronic hypertrophic conjunctivitis, antibiotic-steroid ointment can be used to reduce inflammation. Surgery should be delayed until the inflammation improves. In ectropion, the lacrimal pump is incapacitated, thus disrupting the normal maintenance of a healthy tear film. Aggressive lubricating drops and ointments are essential. In paralytic ectropion, taping the eyelids at night or wearing moisture chambers may provide additional relief if there is a poor Bell's phenomenon. In idiopathic facial nerve palsy, the orbicularis paresis frequently resolves over a few months, therefore conservative treatment is indicated as long as corneal exposure is minimal. However, when significant eyelid laxity precedes the paresis, the ectropion is usually permanent and surgical management is generally necessary.

Surgical management

Involutional ectropion

When present, medial canthal tendon laxity is corrected first by a tucking or suspension procedure to the posterior lacrimal crest as described for entropion repair. Punctal position is next evaluated. If reposition is indicated, an elliptical incision is made in the conjunctiva and eyelid retractors.[26] Buried sutures are placed to close the defect, which rotates the punctum inward. Lower eyelid medial ectropion is repaired by medial canthal tendon tightening and/or reinsertion of inferior retractors.[27] Whether the approach is transcutaneous or transcaruncular,[27,28] the medial edge of the tarsus or

the medial canthal tendon itself is secured to the posterior lacrimal crest, taking care to avoid injury to the nasolacrimal sac. This provides vertical support of the lid while maintaining the medial canthal angle posteriorly on the globe. Residual horizontal laxity is then reduced by performing a tarsal strip procedure or canthus-sparing canthopexy,[13,14] in which the lateral canthoplasty has been modified to avoid a lateral canthotomy and cantholysis.[29]

Any long-standing malposition of the eyelid can induce additional scarring, resulting in shortening of the anterior lamella and thus secondary cicatricial ectropion. Vertical tightness of the lid skin can be subtle and not immediately detected. An early sign can be disappearance of the horizontal wrinkles. Asking the patient to open the mouth widely can also help reveal any eyelid skin deficit. A shortened anterior lamella requires correction with a skin graft or flap.

Congenital ectropion

Shortening of the anterior lamella is corrected with skin grafts, and any concomitant horizontal laxity is reduced by aforementioned horizontal lid-shortening techniques.

Paralytic ectropion

Conservative treatment with a temporary tarsorrhaphy using non-absorbable suture over bolsters can protect the cornea for days to weeks. The suture may be tied in a fashion that allows opening for repeated eye drops or examinations. A lateral tarsorrhaphy may be appropriate and simple to perform. The adjacent eyelid margins of the lateral upper and lower eyelids are excised and the lids sutured together through the gray line. A medial tarsorrhaphy can be performed if lagophthalmos is prominent medially, with care to avoid injury to the canaliculi. Permanent adhesion can be achieved through transposition of a tarsal segment from one lid to the other. The adjacent upper and lower lateral lid margins are split along the gray line for the desired length of closure to a depth of approximately 3 mm. A flap of upper lid tarsus and conjunctiva is created laterally and a smaller matching area is resected from the lower lid tarsus. A double-armed suture is then passed through the upper lid tarsal flap to exit the edge, then through the lower lid defect and tied over the skin, resulting in a tongue-in-groove apposition. Thus, the cut edges of the upper tarsal flap appose the lower tarsal defect for a stronger effect.

Implantation of a gold weight under the pretarsal orbicularis muscle of the upper eyelid can help upper eyelid closure.[30] Different weights are tested preoperatively in the office to ensure adequate closure while minimizing ptosis. When permanent surgical solutions are needed, horizontal laxity often must be treated with eyelid tightening or shortening laterally.[25] A fascia lata or temporalis fascia sling, or a midface lift may also lessen the gravitational pull on the atonic lower eyelid.[25,31]

Cicatricial ectropion

Depending on the extent of cicatricial involvement, treatment incorporates scar revision with excision of scar, complete release of superficial or deeper layer cicatrix, geometric Z-, W-, M-plasties, and horizontal eyelid tightening. Once the cicatrix is released and the anterior lamella allowed to recess to its relaxed position, the amount of anterior lamellar shortage can be determined. Anterior lamellar deficits can be addressed with a combination of pedicle flaps, advancement or rotational flaps, or free skin grafts from the upper eyelid, preauricular, retroauricular, or supraclavicular areas.[32] Any flaps should avoid vertical tension, while maximizing horizontal tension. Z-plasties lessen the effect of scars and redirect tension along more natural skin tension lines. The lower eyelid may be bolstered superiorly with a temporary tarsorrhaphy or Frost suture through the eyebrow for several weeks to minimize postoperative eyelid retraction or graft contraction.

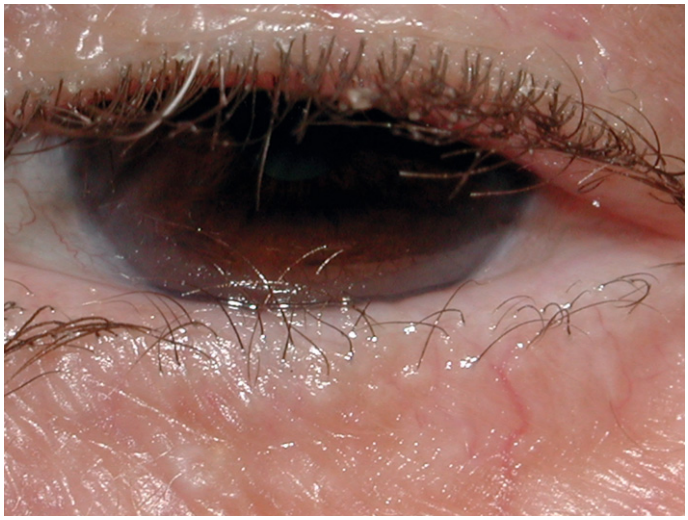


Figure 2.10. Trichiasis, central right lower eyelid.

TRICHIASIS AND DISTICHIASIS

Trichiasis refers to a condition in which eyelashes emerging from their normal anterior origin are misdirected backward toward the cornea, while the tarsal plate maintains a normal apposition to the globe (Fig. 2.10).[2] It is distinguished from an entropion by assessing the eyelash orientation when the eyelid is in proper position. Trichiasis can be idiopathic or secondary to chronic inflammatory conditions such as trachoma, ocular cicatricial pemphigoid, Stevens–Johnson syndrome, blepharitis, chronic conjunctivitis, or chemical burns.

Distichiasis is a congenital or acquired condition in which an extra row of eyelashes emerges from the ducts of the Meibomian glands.[2] In this typically autosomal dominant condition, embryonic common pilosebaceous units differentiate into hair follicles rather than Meibomian glands. These eyelashes can be fine and well-tolerated, or coarser and a threat to corneal integrity. Trauma and chronic inflammatory conditions of the eyelids or conjunctiva as mentioned previously are frequent causes of acquired distichiasis.

MANAGEMENT OF TRICHIASIS

A few misdirected eyelashes can be treated first by epilation and observed. They will usually grow back within 4–6 weeks. Electrolysis is another option that treats several eyelashes at a time.[2] The eyelid is first anesthetized with local infiltration. The tip of the electrolysis fine-wire needle is inserted adjacent and parallel to the hairshaft down to the eyelash follicle, and the current is applied until a small bubble can be observed at the surface beside the hairshaft. The eyelash is then easily wiped or pulled away without resistance. If the eyelashes recur, treatment can be repeated, although frequent retreatment may eventually result in eyelid notching.

Cryotherapy is effective for groups of abnormal eyelashes.[33,34] Following infiltration of local anesthesia, a nitrous oxide-cooled probe covered with water-soluble petroleum jelly is applied to the

involved eyelid margin until a temperature of −20°C is reached. After allowing for thawing, a second cycle is applied, and the eyelashes are epilated. Cryotherapy induces more loss of normal adjacent eyelashes than electrolysis, and is associated with possible complications such as eyelid notching, necrosis, skin depigmentation, and recurrence. Postoperative edema and erythema can be expected for up to 1 week following treatment.

Argon laser ablation has been used more widely to treat trichiasis, although with variable results.[35,36] Complications are few but may include mild hypopigmentation, eyelid notching, and recurrence. In a study of trachomatous trichiasis, argon laser ablation was successful in 55.5% of lids after one session, with an increase in success rate to 89% after several sessions.[37] Several treatments will often be necessary to completely ablate the abnormal follicles. Segmental areas of trichiatic eyelashes can be treated definitively with a full-thickness wedge resection, which offers good cosmesis and minimal complications.

MANAGEMENT OF DISTICHIASIS

Focal areas may be treated by simple epilation or electrolysis. Cryotherapy applied to the posterior lamella or electrolysis also can be used for a few eyelashes. In the case of more extensive distichiasis, the affected eyelid margin can be split along the gray line, and the posterior lamella treated with cryotherapy or focal hyfrecation, or the posterior margin and tarsal plate containing the distichiatic hair follicles can be excised.[2] Splitting the eyelid margin minimizes injury to the normal eyelashes in the anterior lamella, while effectively treating the distichiatic eyelashes emerging from the Meibomian gland orifices posteriorly. Revision of the anterior lamella or mucous membrane grafting may also be indicated in some instances; therefore, treatment should be individualized for each patient.

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3 Conjunctiva and tear film

Ilya M. Leyngold, Roy S. Chuck

The crucial role of the preocular tear film in the maintenance of healthy corneal and conjunctival surfaces has been well established. Conversely, a healthy ocular surface is necessary to ensure the integrity of the tear film. Proper functioning of the tear film is dependent upon its adequate production, distribution, and preservation. Thus, a disruption in any of these processes may result in ocular surface damage with associated clinical symptoms. Tear film abnormalities are intimately related to the conjunctival topography and function in addition to the proper function of many other periocular structures. This chapter focuses on the conjunctival structural and functional components, and their role in the renewal of the preocular tear film. Also, other factors that are salient to the maintenance and formation of the tear film are discussed. Finally, abnormalities of the tear film and secondary ocular surface damage with their respective causes are explained.

CONJUNCTIVAL ANATOMY, STRUCTURE, AND FUNCTION

ANATOMY

The conjunctiva is a thin, translucent mucous membrane overlying the anterior portion of the sclera and the inner surface of the eyelids.[1] It is divided into the palpebral conjunctiva, the bulbar conjunctiva, and the superior and inferior fornices.

The palpebral conjunctiva consists of orbital and marginal tarsal components.[1] The orbital portion forms a convoluted structure with many folds in contrast to the tarsal component, which is smoother and closely adherent to the tarsal plate. Bulbar and palpebral conjunctiva come together at the superior and inferior fornices, forming a loose attachment to the underlying tissues. The bulbar conjunctiva lines the anterior sclera, or the 'white' of the eye. This structure has loose attachments to the orbital septum in the fornices, Tenon's capsule (except at the limbus), and the underlying sclera.[2] It also contains multiple folds, which increase the surface area for secretion.

Each eye contains specialized conjunctival structures called semilunar folds (plica semilunaris) and the lacrimal caruncle located in the medial canthi. The plica semilunaris is a delicate and movable fold divided from the bulbar conjunctiva by a 2-mm-deep concavity.[1] Upon lateral rotation of the eye, the lacrimal caruncle is conspicuous directly medial to the semilunar fold. Superficially, it is lined by a nonkeratinized stratified epithelium and contains meibomian-like sebaceous glands similar to the glands of Zeis.[1]

STRUCTURE AND FUNCTION

Conjunctiva is covered by both stratified columnar and nonkeratinized stratified squamous epithelium. Two to five layers of stratified epithelial cells, superficial and basal, cover the largest conjunctival surface area. Structures lined by the stratified squamous epithelium include the limbus, caruncle, and the areas of the mucocutaneous junctions at lid margins.[2] Mucus-secreting goblet cells are dispersed throughout the superficial and middle epithelial cells, especially in the semilunar fold and fornices,[3] playing an important role in the maintenance of the preocular tear film. Langerhan's cells are also found in the conjunctival epithelium.

Numerous other glands are found within the conjunctival epithelium in addition to the mucin-secreting goblet cells. These are also important in maintaining moisture of the ocular surface and the proper physiological composition of the tear film. The glands histologically similar to the main lacrimal gland proper, accessory lacrimal glands of Krause, secrete the minor component of the tear film aqueous layer. They are mostly located in the temporal conjunctiva. Glands found less frequently, Manz and Wolfring, secrete mucinous substance resembling that of the goblet cells.[1] Superiorly and inferiorly to the tarsal plate, the crypts of Henle create a papillary pattern at the conjunctival surface.

The area underlying the epithelial layers is substantia propria. It is composed of the fibrovascular connective tissue connecting the epithelium and the tarsus together in the palpebral region.[3] The structure is infiltrated by fibroblasts and inflammatory cells. Lymphatic follicles with germinal centers may arise during childhood and/or in response to ocular inflammation; however, true lymphatic follicles are generally not found in a healthy adult conjunctiva.[1]

Conjunctiva is a very vascular structure. The extensive vascular network is formed primarily from the anastomoses of the anterior

ciliary and palpebral arteries, and abundance of conjunctival veins. Lymphatics arise from both the deep and superficial layers of the conjunctiva, eventually draining into the lymphatics of the eyelid, creating a rich lymphatic plexus.[2] Conjunctiva is innervated by both sensory and sympathetic nerve fibers. Sensory innervation of the conjunctiva is by branches of the ophthalmic and maxillary divisions of the cranial nerve V (CN V) and the long ciliary nerve.[1]

STRUCTURE AND FUNCTION OF THE TEAR FILM

The milieu of the preocular tear film ensures normal function and structure of the ocular surface epithelium.[4] The tear film is also important as a refracting surface of the eye, contributing to a sharper visual image. This phenomenon is due to its ability to fill and flatten the microscopic depressions of the corneal surface created by the reticulations (0.5 µm high and 0.3 µm wide) on the epithelial surface.[5] The preocular tear film is formed by three individual layers measuring a total of about 7 µm in thickness. The outermost layer is composed of lipid compounds produced by the meibomian glands. The intermediate layer is mostly formed by the aqueous secretions of the main and accessory lacrimal glands. The innermost layer of the tear film is thought to consist of two components: the inner, glycocalyx, and the outer, mucin. The former is secreted by the surface epithelium and the latter, more loosely associated layer, produced by the conjunctival goblet cells.[6]

THE LIPID LAYER

The hydrophobic moieties secreted by the meibomian glands of the lids comprise the lipid layer of the tear film. Around 20 meibomian glands are found in each upper and lower lid.[7] Although mechanisms responsible for meibomian gland secretion rates are still poorly understood, Cermak et al demonstrated that patients with primary and secondary Sjogren's syndromes, conditions with poor meibomian gland function, have low levels of androgens.[8] This finding led the investigators to hypothesize that this hormonal imbalance contributes to meibomian gland dysfunction, leading to tear film instability and evaporative dry eye, common features of this autoimmune disorder. They showed that androgens control production of commonly secreted lipids by meibomian gland such as nonpolar sterols, wax esters, and phospholipids, in turn promoting production of the lipid layer. Secreted lipids spread uniformly on the aqueous portion of the tear film forming a two-layered structure. The resultant duplex film is quite stable and allows the lipid layer to undergo significant compression and decompression during blinking without the loss of its integrity. In addition to reducing evaporative losses from the tear film, the lipid phase prevents contamination of the tear film by the sebaceous gland excreta of the eyelids,[7] and facilitates thickening of the aqueous layer by lowering the surface tension of tears.[9]

THE AQUEOUS LAYER

The aqueous phase forms an intermediate layer of the tear film, providing close to 90% of the total tear film thickness.[10] The isotonic or slightly hypotonic aqueous component is secreted at a rate of approximately 1.2 µL/min.[11] Both main and accessory lacrimal gland secretions are mostly reflex dependent and appear to be identical.[12] Following the tear vesicle fusion with the inner portion of the lacrimal acinar cell plasma membrane, the tears are released and flow through the ductular openings of the main and accessory lacrimal glands. The flow continues through the forniceal spaces into lacrimal rivers and over the exposed ocular surface.[7] Contraction of the orbicularis oculi muscle drives the fluid in the temporal-to-medial direction. Upon relaxation of the muscle, immediately following the blink, most of the tears are drawn into the two punctal openings located near the medial canthus. The fluid then flows into the lacrimal canaliculi, the lacrimal sac, the nasolacrimal duct, and finally into the inferior meatus of the nasal cavity.[13,14] As the tears flow through the nasolacrimal duct, a significant portion of the fluid is reabsorbed across the mucosal surface.[7] Aqueous fluid that fails to exit through the nasolacrimal system is either evaporated or reabsorbed through the conjunctiva.

THE MUCIN LAYER

The mucin layer is a thin structure measuring approximately 0.5 µm in thickness.[15] The glycocalyx-based innermost component of the mucin layer is secreted by the subsurface epithelial vesicles,[6,16] forming a strong bond with the epithelial surface. Overlying the glycocalyx is a loosely adherent mucous layer derived from the conjunctival goblet cells. The stimulus for mucous secretion is not fully understood; however, there is evidence that 15(*S*)-hydroxyeicosatetraenoic acid (15(*S*)-HETE) serves as a potent mucin secretagogue in the goblet cells of the ocular surface epithelium.[17] The outer component is thought to impart a fragile covering over epithelial cells, in turn enabling the aqueous layer to provide continuous covering.[7] Therefore, the presence of the outer component is essential for the stability of the aqueous phase. On the other hand, the importance of the interaction between the outer and inner portions of the mucin layer is still under investigation.

MAINTENANCE OF THE TEAR FILM

Action of the lids plays a vital role in the formation and maintenance of the preocular tear film. Lid closure or blinking allows a uniform distribution of the tear film over the ocular surface. The upper lid is mostly responsible for this function as it sweeps three-quarters of the corneal surface and has considerably more force compared with the lower lid.[7] Blinking re-establishes a smooth and evenly distributed tear film after evaporative losses create disruptions and thinning of the tear film. Evaporation of the aqueous phase occurs if blinking is absent or incomplete, causing the lipid layer to invade and contaminate the mucin layer. The interaction between the outermost and innermost layers of the tear film causes further breakup of the tear film and increased drying of the epithelium.[18] Tear film maintenance is dependent on adequate tear production and distribution. Dysfunction of the variables responsible for these actions may result in the ocular surface disease.

TEAR FILM ABNORMALITIES

Dry eye is a prevalent disease affecting up to 15% of individuals 65 years or older.[19] It is commonly seen in patients with low androgen levels, including those with autoimmune diseases, peri- or post-menopausal women, and the elderly.[20,21] Dry eye has been classified by the National Eye Institute into two major categories based on the mechanism of preocular tear film disturbance: tear insufficiency and evaporative tear loss.[22] Although this classifica-

tion is very useful in the initial evaluation of the dry eye patient, there is often a significant overlap between the two categories such as seen, for example, in Sjogren's syndrome.[22] For organizational purpose, the discussion of dry eye conditions will be based on the aforementioned classifications. Major ocular conditions classically associated with tear-deficient dry eye addressed in this chapter include those of Sjogren's and non-Sjogren's type. Dry eye pathologies associated with evaporative tear loss such as meibomian gland dysfunction, abnormalities of the conjunctival mucin secretion, lid closure defects, and abnormal ocular surfaces are also discussed in detail.

AQUEOUS TEAR-DEFICIENT DRY EYE

Aqueous tear deficiency represents one of the most common causes of dry eye.[7] If severe enough, it may lead to ocular irritation and ocular surface disease, also called keratoconjunctivitis sicca (KCS). Most individuals experience decrease in tear secretion with age, but only a fraction of those are affected significantly enough to develop KCS. Thus, even though lacrimal gland function diminishes with age, ocular surface disease is not a normal part of the aging process as previously believed. Generally, patients with clinically significant aqueous tear deficiency complain of foreign body sensation, burning, and ocular surface pain. This condition is more frequent among women. Both history and clinical findings are used to diagnose KCS. Physical examination features suggestive of the disorder include tear film mucous threads and debris, decreased tear meniscus height, wetting length of Shirmer test strips, and tear breakup time (i.e. under 5 s). Interpalpebral surface supravital staining with fluorescein, rose bengal, and/or lissamine green are also used to diagnose KCS.[7,22]

It is important to diagnose and initiate treatment early to prevent complications of KCS such as filamentary keratitis and corneal ulcerations. Deficiency in aqueous tear production leads to decrease in nonspecific immune mechanisms of the ocular surface. For example, lysozyme and lactoferrin, protective enzymes of the tear film, were found to be significantly lower in the tears of patients with dry eye.[23,24] In addition to decreased immune defenses, ocular surface flushing is impaired, leading to even greater pathogen susceptibility.[7] Thus, frequent ocular infections develop, leading to blepharitis with secondary development of conjunctivitis and keratitis.

Sjogren's syndrome tear deficiency

Connective tissue disorders are frequent systemic causes of KCS. These represent a subset of autoimmune disorders that are generally linked by diffuse vasculopathy and characterized by inflammatory damage to multiple vital organs including the eye. For example, up to 15% of patients with rheumatoid arthritis develop KCS.[7] Within the variety of rheumatologic disorders KCS has been divided into two categories—primary and secondary Sjogren's syndromes—that can both cause severe ocular surface disease. Primary Sjogren's syndrome is characterized by exocrine gland dysfunction with prominent involvement of salivary and lacrimal glands. In addition, patients with this disease may manifest inflammatory damage to musculoskeletal, gastrointestinal, urogenital, integumentary, and respiratory systems.[25] When there is an association with a specific autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, polymyositis, or polyarteritis nodosa a diagnosis of secondary Sjogren's syndrome is given. Tear deficiency can be quite severe among these patients. This is thought to result from an immunologically mediated inflammatory damage to the lacrimal gland and the ocular surface. Those with Sjogren's syndrome and poorly controlled KCS may develop severe complications, including peripheral ulcerative keratitis (sometimes leading to perforation), scleritis, and rheumatoid scleral nodules.[7] It has been shown that patients with Sjogren's disease have decreased serum levels of circulating androgens[8] linking androgenic activity to the presence of ocular surface damage.

Non-Sjogren's syndrome tear deficiency

Multiple studies have demonstrated that maintenance of the healthy ocular surface with adequate quantity and quality of aqueous tear secretion is dependent upon sufficient hormonal balance.[26–29] Just like in Sjogren's syndrome, decreased serum concentrations of androgens have been associated with the development of aqueous tear deficiency in some non-Sjogren's patients.[30] This phenomenon explains the increased prevalence of dry eye disease in women, particularly those in postmenopausal age groups, elderly, and any of the individuals with low endogenous androgen levels. Animal studies have shown the dependence of normal lacrimal gland secretion on hormonal levels. For example, androgen deficiency following orchiectomy has been demonstrated to increase the volume of secreted tear fluid, while reducing the concentration of secretory component and of IgA in the tear fluid.[31,32] Testosterone administration reverses these changes. However, pituitary gland removal prevents this reversal. Mechanistically, androgens appear to downregulate lacrimal gland lymphocytes, thereby suppressing the inflammatory ocular surface damage.[33]

Aqueous tear deficiency may occur with other systemic conditions such as HIV and sarcoidosis. These can also be viewed as a relative imbalance between immunologic and hormonal activities. Other causes of non-Sjogren's tear-deficient dry eye include those secondary to lacrimal gland obstruction (secondary aqueous deficiency) such as occurs in trachoma, ocular cicatricial pemphigoid, Stevens–Johnson syndrome, and burns.[34,35] Also, patients with reflex abnormalities tend to develop tear-deficiency dry eye such as seen in cranial nerve VII palsy. Although both Sjogren's and non-Sjogren's dry eye syndromes are described here under classification of aqueous tear deficiency, they can be further complicated by evaporative loss arising from overlapping pathogenic mechanisms.

EVAPORATIVE DRY EYE

Tear film stability is in large part determined by the composition and interactions of the lipids covering the surface of the aqueous layer and the mucin-rich inner layer of the tear film. Increased evaporation of tears with resultant tear film instability arises from a variety of abnormalities affecting the structures that serve to protect the tear film. Structural and functional defects in the meibomian gland, conjunctiva, cornea, or lids may result in evaporative dry eye. Increased tear evaporation secondary to these abnormalities commonly exacerbates aqueous deficient dry eye because the diseases are often concurrent.[36,37] In addition, similar to tear deficiency dry eye, disturbances in androgenic and estrogenic regulation appear to play a pivotal role in pathogenesis of the most common etiology of evaporative dry eye, meibomian gland dysfunction.

Meibomian gland dysfunction

Meibomian gland dysfunction more often results from the acquired disease of glandular tissue rather than intrinsic paucity of

meibomian acinar cells. There are conditions such as congenital anhidrotic ectodermal dysplasia that are associated with hypoplasia of meibomian glandular epithelium, but those are quite rare. More commonly, it is the abnormality of the composition and volume of meibomian gland excreta that results in KCS. Studies have demonstrated that in similarity to the lacrimal gland, the meibomian gland also contains estrogen and androgen receptors responsible for its proper function.[38–40] For example, in androgen-deficient states, such as congenital androgen insensitivity disease, menopause, or Sjogren's syndrome, there is an alteration in synthesis and type of lipid molecules in the meibomian gland, resulting in abnormalities in chemical composition of the lipid layer.[8] In severe cases, where an obstructive meibomian gland dysfunction occurs, there is a dramatic increase in tear film osmolality, resulting in accelerated evaporative tear loss.

Secondary infection of the meibomian gland, such as occurs in blepharitis, may also change the lipid content of the tear film causing symptomatic dry eye. Upregulation of tissue and bacterial lipases during infection results in increased concentrations of liberated diacylglycerides and free fatty acids. This alteration in chemical composition of the lipid layer contributes to the instability of the tear film.[41,42]

Abnormalities of conjunctival mucin secretion

Changes in conjunctival morphology leading to a paucity of goblet cells and their secretions may also result in instability of the tear film similar to that seen in meibomian gland disease. Conjunctival surface and consequently goblet cell populations are affected by a number of conditions including trachoma, vitamin A deficiency, ocular cicatricial pemphigoid, erythema multiforme, and chemical burns.[7]

A classic condition associated with mucin deficiency is hypovitaminosis A. Characteristic goblet cell destruction, and keratinization of the conjunctiva and cornea are seen. Keratinomalacia and foamy gray triangular areas on the conjunctival surface of poor wettability (Bitot's spots) eventually develop. Despite initially normal lacrimal and meibomian gland functions, the tear break-up time and clearance decrease, resulting in symptomatic evaporative dry eye. Ultimately, however, increased scarring develops leading to obstruction of main and accessory lacrimal gland ductules with subsequent secondary aqueous tear deficiency.[34,35]

Lid closure defects

Tear film stability is in large part dependent upon normal blink function. If there is blinking impairment or lid incongruity with ocular surface the tear film cannot be properly reformed. This results in nonuniform layering of the tear film with discrete areas of poor wettability, leading to localized drying secondary to evaporative losses. Keratinization occurs in these areas, resulting in even greater desiccation. This creates a vicious cycle that leads to severe dry eye signs and symptoms.

Lesions to the seventh cranial nerve such as those seen in patients with strokes or Bell's palsy impair proper lid closure with resultant exposure keratitis. Adhesions between the tarsal and bulbar conjunctiva (symblepharons) commonly seen in patients with severe chemical burns, erythema multiforme, and cicatrizing ocular pemphigoid may restrict lid movement compromising the stability of the tear film.

Lid-globe incongruity such as occurs with ectropion or lid inflammation may cause a nonuniform distribution and improper surfacing of the pre-ocular tear film. Moreover, poor congruity of lids with ocular surface may lead to punctual mal-apposition with consequent decreased removal of contaminated tear film.

Abnormal ocular surfaces

Primary abnormality of the ocular surface arising from the alteration of the morphologic characteristics of the corneal epithelium can compromise the stability of the tear film. These surface irregularities prevent the normal adsorption of tear mucin to the multiple microvillous projections of the corneal epithelium.[7] This leads to abnormal tear surfacing, resulting in evaporative tear loss, epithelial abrasions, and ulcerations. As in the other causes of dry eye, corneal surface damage from primary ocular surface abnormality may lead to impairment of sensory corneal innervation. The resultant corneal anesthesia often leads to further epithelial abnormalities ranging anywhere from punctate keratopathy to corneal perforation.[7]

PATHOGENESIS OF DRY EYE

Over the past decade much progress has been made in understanding the pathophysiologic mechanisms leading to KCS. It has been recognized that the normal tear homeostasis is dependent upon an intact communication within the specialized unit consisting of the ocular surface, the main and accessory lacrimal glands, lids with their associated structures, and the interconnecting enervation.[43]

A disruption of this unit from the damage to either of its constituents leads to the signs and symptoms of KCS. Extensive research through animal models and immunomodulatory therapies with topical corticosteroids and steroid sparing agents has shown that the key mechanism leading to the disruption of the tear film and resultant KCS is inflammation.[44–50] In both evaporative and aqueous tear-deficient dry eye the presence of proinflammatory markers in tears and conjunctiva underscores the role of inflammation in pathogenesis of dry eye. Abundance of inflammatory mediators in tears and epithelium of aqueous tear deficiency and rosacea-associated meibomian gland dysfunction implicates the role of matrix metalloproteinase-9 as an activator of various cytokines, including interleukin-1, contributing to the cellular damage of the ocular surface.[51,52] Other findings suggesting the pivotal role of inflammation include increased concentrations of other proteases such as plasmin, in the tear fluid,[53,54] and increased conjunctival expression of immune activation markers such as HLA-DR, CD-40, and intercellular adhesion molecule (ICAM)-1.[55–57] A positive correlation has also been demonstrated between the levels of conjunctival inflammatory markers and the degree of conjunctival squamous metaplasia, severity of dry eye symptoms, and corneal fluorescein staining.[58,59]

The exact mechanisms triggering the inflammatory response at the ocular surface and lacrimal glands are unknown, but several possible explanations have been proposed. As detailed previously, patients with low levels of androgens such as postmenopausal women, the elderly, those undergoing anti-androgen therapies, and those with Sjogren's disease are especially prone to dry eye. Animal studies have suggested that androgen suppresses ocular surface inflammation in both aqueous deficient and meibomian gland dysfunction associated dry eye, and its reduction leads to inflammation that precipitates dry eye.[30,60] T-lymphocytes continuously migrating through the lacrimal glands and associated structures normally

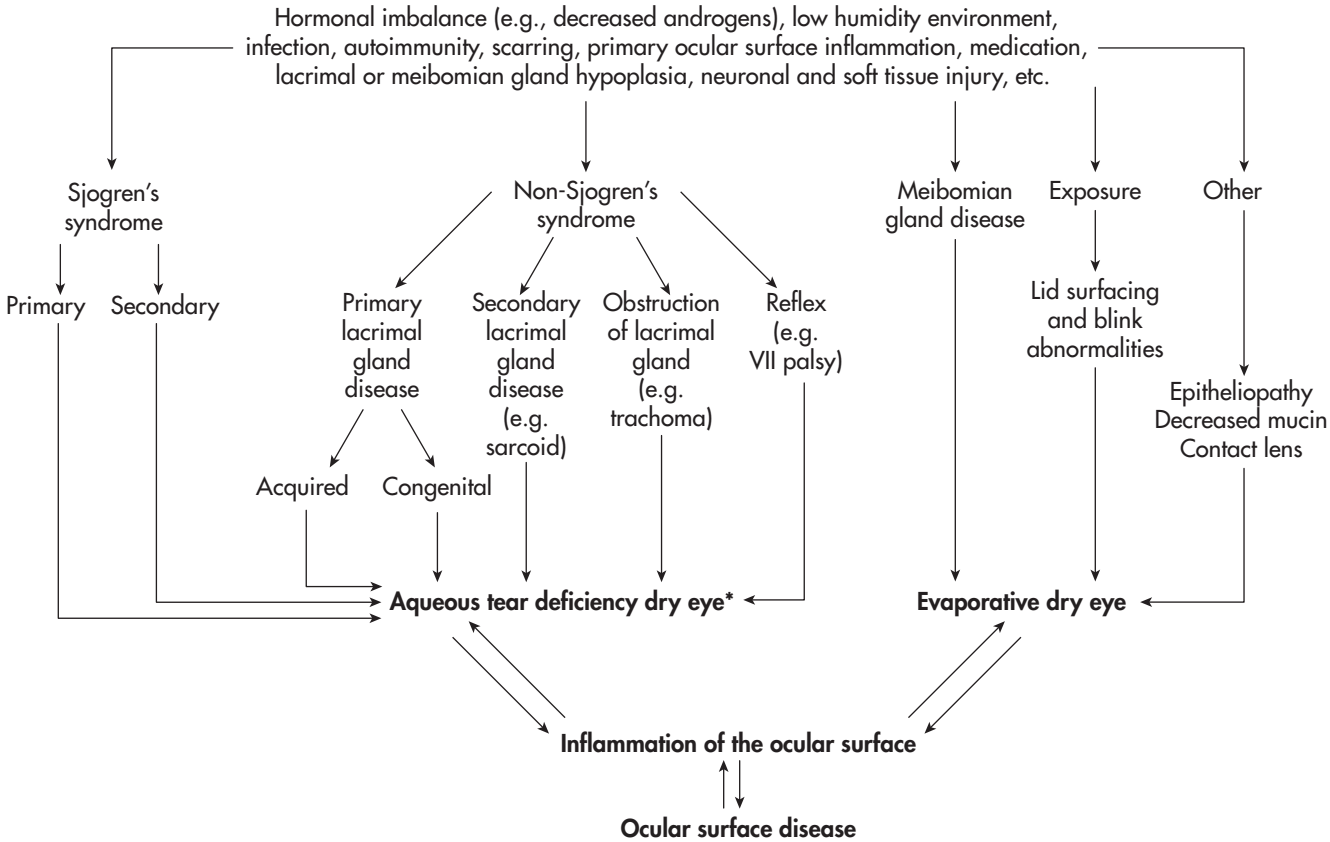

Figure 3.1. Pathogenesis of keratoconjunctivitis sicca. *For simplicity, Sjogren's and non-Sjogren's syndromes are shown in association with aqueous tear deficiency only. In reality, many patients with aqueous tear deficiency also exhibit evaporative dry eye. Double errors indicate the interchangeable relationship between cause and effect. (Modified from Lemp MA. Report of the NEI/industry workshop on clinical trials in dry eye. CLAO J 1995; 21: 221–232; permission pending.)

undergo apoptosis as they leave the ocular surface. In androgen-deficient states, there is increased trafficking of lymphocytes through the neural-epithelial junction in the lacrimal glands and ocular surface with concurrent expression of lymphocyte-activating antigens on the cellular membranes of lacrimal and ocular surface epithelia.[61] As lymphocytes undergo activation, their apoptotic pathway becomes inhibited, and they continue to secrete more proinflammatory cytokines, further upregulating cell surface lymphocyte-activating antigens. This creates a self-perpetuating cycle of ocular surface inflammation with resultant ocular surface damage.

Inflammation of the ocular surface is also sustained by decreased ocular surface sensitivity. It has been shown that as tear clearance and production decreases ocular sensitivity becomes depressed.[22] Consequently, there is a decrease in sensory-stimulated reflex tearing, leading to poor tear response to ocular surface damage. Injury to the ocular surface exacerbates the inflammatory response, resulting in increased ocular surface and lacrimal gland lymphocytic infiltration, further depressing sensory-stimulated reflex tearing. Through this vicious cycle inflammation is perpetuated leading to KCS.

Although numerous experiments have demonstrated the inflammatory nature of dry eye with similar histopathological and immunological findings,[58] the origins of KCS are diverse. In fact, many cases of KCS are probably multifactorial. Commonly, the presence of both aqueous deficiency and evaporative dry eye exists reflecting similar etiological factors. Figure 3.1 is a schematic representing the complex pathogenesis of KCS.

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4 Corneal epithelium and stem cells

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CORNEAL EPITHELIUM

The cornea is a transparent avascular tissue that is highly specialized to refract and transmit light and is essential for ideal visual function.[1]

MACROSCOPIC FEATURES OF THE CORNEA AND ITS PHYSIOLOGIC PROPERTIES

Optical properties

The adult human cornea measures 11–12 mm horizontally and 9–11 mm vertically. It is approximately 0.5 mm thick at the center, and its thickness is about 0.7 mm at the periphery.[2] The anterior corneal surface is convex and aspheric, with the radius of curvature measuring between 7.5 and 8.0 mm at the central 3 mm optical zone of the cornea, giving the cornea a refractive power of 40–44 D.[1]

Corneal transparency mainly depends on the special anatomic arrangement of collagen fibers in the stroma, which is responsible for the cancellation of interference of scattering of an incident light ray by a collagen fiber from other scattered light, allowing light to pass through the cornea.[3] The corneal epithelium and tear film help to maintain the smooth epithelial surface, which has been reported to be very important for the attainment of good functional visual acuity, a new technology thought to reflect the visual function related to daily activities.[4,5] The total refractive index of the cornea reflects the sum of refraction at the anterior and posterior corneal interfaces as well as the transmission properties of the tissue. The refractive indices of air, tear fluid, corneal tissue, and aqueous humor are 1.000, 1.336, 1.376, and 1.336, respectively.[1]

Innervation

Sensory nerves in the cornea are mainly derived from the ciliary nerves of the ophthalmic branch of the trigeminal nerve, which can be detected as thin fibers with a slit lamp microscope or with confocal microscopy (Fig. 4.1).[1,6]

Vascular system

The anterior ciliary artery, which is derived from the ophthalmic artery, forms a vascular arcade in the limbal region anastomosing with vessels derived from the facial branch of the external carotid artery, providing nutrients and factors that play important roles in corneal metabolism and wound healing.[1]

MICROSCOPIC ANATOMY AND PHYSIOLOGY OF THE CORNEAL EPITHELIUM

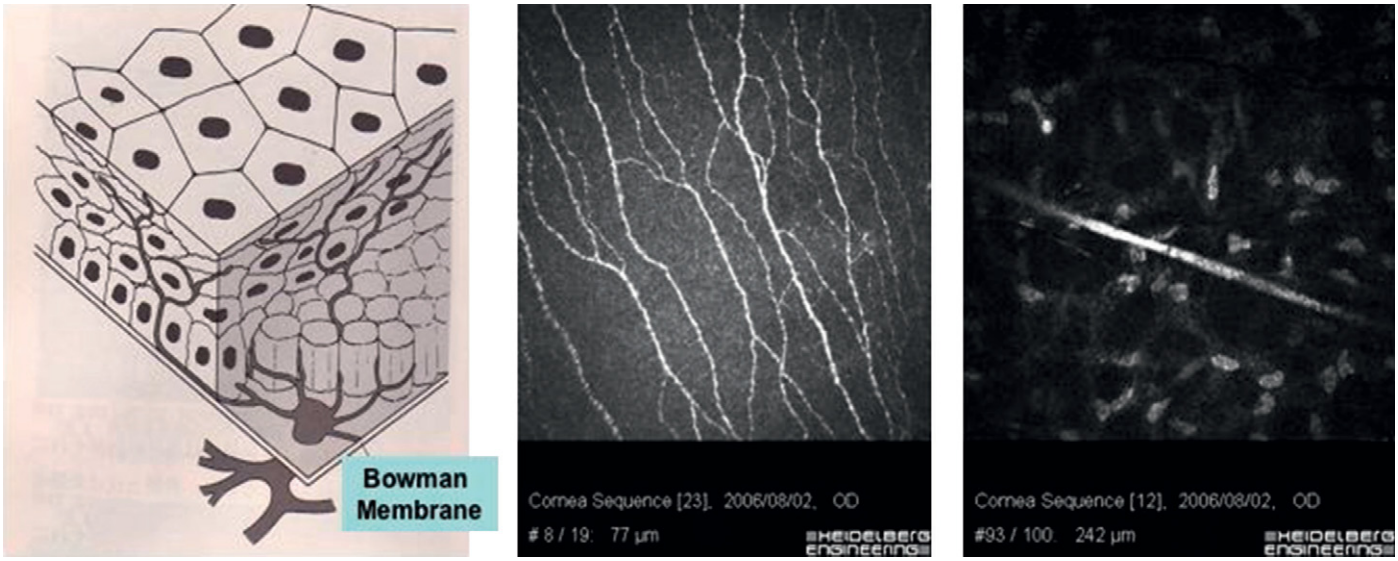
The cornea consists of five layers: the epithelium (Fig. 4.1), Bowman's layer, the stroma, Descemet's membrane, and the endothelium. It has three major functions: (1) it acts as a mechanical barrier to debris and microorganisms and, via Langerhans cells; (2) it creates a transparent optical surface by adsorption of the tear film; and (3) it maintains a barrier to the diffusion of water, solutes, and drugs.[1,7–9]

Microscopic anatomy

The human corneal epithelium is a stratified, squamous nonkeratinized epithelium consisting of five to seven layers of cells, including two to three layers of terminally differentiated superficial cells, two to three layers of wing cells, and a single layer of columnar basal cells (Fig. 4.3).[7–9]

Superficial cells: The superficial cells are flat and polygonal (diameter: approximately 40–60 μm), the surfaces of which are covered with numerous microvilli and glycocalyx coat interacting with, and stabilizing, the precorneal tear film.[7–10] Superficial cells are joined laterally to the adjacent cells with tight junctional complexes, which with the very low permeability of the membranes of the superficial cells form the barrier property of the corneal epithelium.[10]

Wing cells: Wing cells have lateral, thin, wing-like extensions from a more rounded cell body,[1,6] and they are interconnected by desmosomal junctions and gap junctions that serve as electrochemical conduits.[9]



A B C

Figure 4.1. *A,* Schematic drawing for corneal nerves perforating through the Bowman's membrane with fine distribution throughout the epithelium. *B,* Confocal scan of superficial corneal nerves within the epithelium; depth: 77 µm. *C,* Confocal scan of corneal nerves within the stroma; depth: 242 µm.

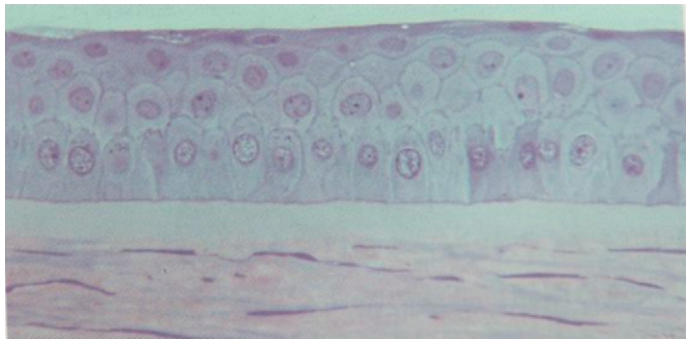


Figure 4.2. Section of human corneal tissue. Superficial, middle and basal epithelial cells, Bowman's membrane and anterior corneal stroma clearly visible. HE staining, 200x magnification.

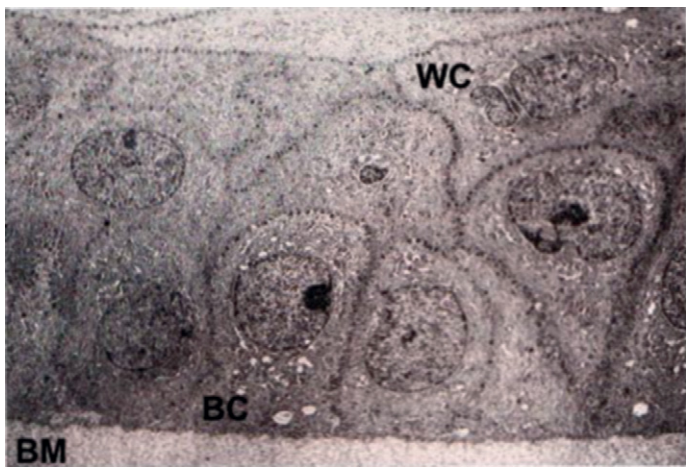


Figure 4.3. Scanning electron micrograph of the wing cells (WC) and basal cells (BC) sitting on the Bowman's membrane (BM).

Basal cells: The basal cells are the mitotically active cells of the epithelium containing ribosomes, rough endoplasmic reticulum, mitochondria, centrioles, microfilaments, microtubules, and glycogen granules.[1,8]

Basal cells of the corneal epithelium adhere to the basement membrane via hemidesmosomes that are linked to anchoring fibrils of type VII collagen.[11] The basal cells secrete type VII collagen, which aggregate to form[12] the anchoring fibrils penetrating the basement membrane, where they form anchoring plaques with type I collagen. E-cadherins, a component of zonula adherens, are present at the lateral surfaces of the basal cells of the corneal epithelium and mediate cell–cell interaction.[1,13]

EPITHELIAL CELL TURNOVER

The corneal epithelium renews itself within approximately 5–7 days, with the superficial cells being constantly shed into the tear pool. Terminal differentiation of cells, coupled with cell death by apoptosis, prompts the cell loss via desquamation, which is aided by blinking.[7,8,14,15] The maintenance of the corneal epithelium is thought to be achieved by the unipotent stem cells (SC) located in the basal epithelium of the corneoscleral limbus.[16–19]

LIMBAL STEM CELLS

LIMBUS

The corneal limbus is a highly vascularized, innervated, and pigmented zone between the cornea, conjunctiva, and the sclera. The zone has pigmented spikes called the Palisades of Vogt which are thought to bear the limbal stem cells (Fig. 4.4).[20]

LIMBAL STEM CELLS

At present, the general criteria for defining stem cells are: (A) slow cycling during homeostasis in vivo; (B) poor differentiation with

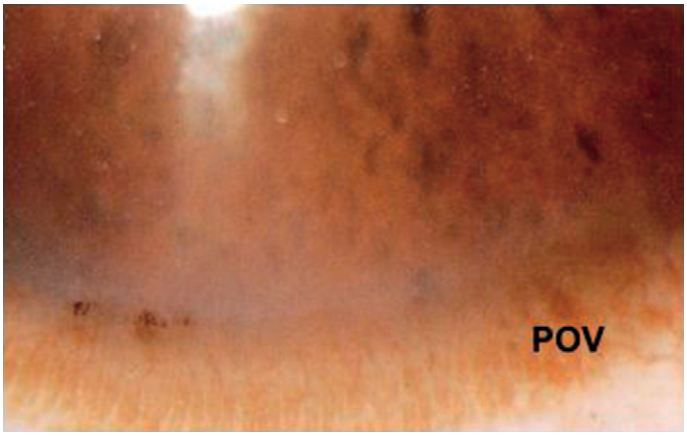


Figure 4.4. Palisades of Vogt (POV) at the corneal limbus thought to harbor the limbal stem cells.

primitive cytoplasm; (C) high capacity for error-free self renewal; and (D) activation to proliferate by wounding or replacement in culture.[21–24] Stem cells can mitose to generate transient amplifying cells (TAC) that are short-lived and function primarily to amplify cell numbers. The transient amplifying cells finally differentiate into postmitotic cells that are committed to cellular differentiation.

The current evidence of the limbal location of corneal stem cells may be summarized as follows:

1. The limbal basal epithelium lacks the corneal epithelial differentiation-associated keratin pair keratin 3 (K3) and keratin 12 (K12),[17,23,25] which led to the hypothesis that the limbal basal epithelium harbors the stem cells.
2. Limbal basal epithelium cells have a higher proliferative potential in culture than central and peripheral cornea epithelium cells.[26,27] Cotsarelis et al[28] found that tritiated thymidine was incorporated for long time intervals only into limbal basal cells, suggesting that the limbal basal epithelium contains slow-cycling cells identified as the 'label-retaining cells'.[28,29] These cells are also resistant to the induction of differentiation.[28,30–32]
3. Abnormal corneal wound healing with conjunctivalization, vascularization, and chronic inflammation occurs when the limbal epithelium is partially or completely removed.[33–36] The effectiveness of limbal transplantation for the treatment of experimentally induced stem cell deficiency, confirmed in rabbits by Tsai and coworkers, further supported the limbal location of corneal epithelial stem cells.[37]
4. The limbal location of corneal epithelial stem cells can account for the relative preponderance of limbal neoplasms and the scarcity of corneal epithelial tumors, assuming that neoplasms arise mainly from relatively 'undifferentiated cells'.[38]
5. A mathematical analysis of the kinetics of maintenance of the corneal epithelial mass confirms that the corneal epithelium can be maintained by cellular proliferation originating from limbal stem cells without contribution of the adjacent conjunctiva.[39]

Collectively, these data leave little doubt that corneal epithelial stem cells reside in the limbus.

IDENTIFICATION OF LIMBAL STEM CELLS

The major molecular markers proposed for limbal stem cells in ocular or nonocular tissues in the past decade can be categorized into the following groups.[40]

Cytokeratins

Cytokeratins are a group of cytoskeletal proteins that forms intermediate filaments in epithelial cells and are expressed in distinct patterns during epithelial development and differentiation. The subfamily comprises at least 20 different polypeptides, which are expressed in paired combination of acidic and basic molecules according to the type of epithelium and its state of differentiation.[40,41]

K3/K12: The keratin pair K3/K12 is specially expressed in corneal epithelial cells and is regarded as markers of corneal epithelial differentiation.[40,42–44] When specific antibodies are used, epithelial cells in the basal layer of the limbus are devoid of these two cornea-specific keratins, underlining their undifferentiated nature.[17,23,25,40,45,46]

K5/K14: Basal cells of both corneal and limbal epithelia express the keratin pair K5/K14.[47]

K15: It has recently been discovered that K15 is expressed in superior and basal limbal epithelial cells with lack of expression in central corneal epithelium.

K19: No significant difference in K19 staining could be found between limbal and corneal epithelia in two studies.[23,48]

The expression patterns of K12, K14, K15 and K19 are shown in Figs 4.5 and 4.6.

Cytosolic proteins

Several proteins, including enzymes such as cytochrome oxidase, Na/K-ATPase, and carbonic anhydrase, have been identified and found in higher concentration in basal cells of the limbal epithelium than that of central corneal epithelium.[49,50]

a-enolase: Recent reports of Chen et al[23] and Schrehardt et al[40] showed that a-enolase was not only expressed by basal but also by suprabasal epithelial cells at the limbus and occasionally by basal corneal epithelial cells, indicating mitotically or metabolically active cells, rather than a limbal SC localization.

PKC: PKC-gamma has been identified as specific to the limbus, whereas all other subtypes can be found both in the central and limbal epithelium.[51]

Cyclins: Cell-cycle associated proteins, such as cyclins D, E, and A, have been also identified as proteins preferentially localized to basal epithelial cells at the human limbus.[52] Calcium-linked protein, associated with early epithelial differentiation, and protein S100A12, which is involved in Ca^{2+}-dependent signal transduction processes in differentiated cells, is expressed in corneal epithelial basal cells but not in limbal calls.[40,53]

Nuclear proteins

P63: Transcription factor p63, involved in tumor suppression and morphogenesis, is expressed by basal epithelial cells that have the ability to proliferate, and is a nuclear marker for corneal epithelial SC.[40]

Cell surface proteins

Cx43: In the corneal epithelium, only two gap junction proteins have been identified so far: connexin 43 (Cx43) and connexin 50 (Cx50). Connexin 43 has been reported to be absent from the basal layer of the human limbal epithelium, whereas suprabasal limbal cells showed slightly positive staining.[23,54,55]

E-cadherin: In human cornea, negative staining was observed in basal layers and positive staining was observed in suprabasal layers at the limbus.[25] Recent reports[40] reveal a weak reaction

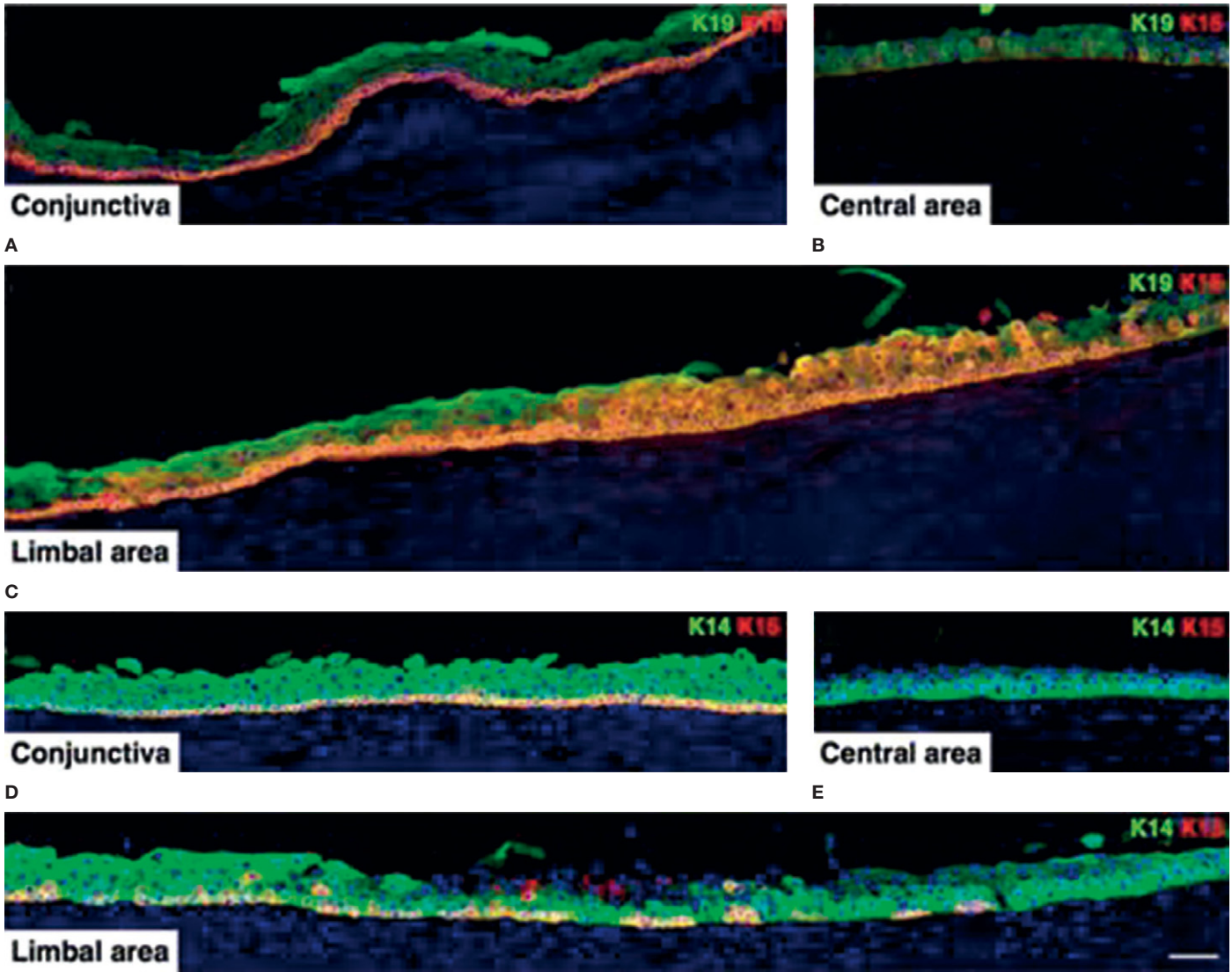


Figure 4.5. Expression pattern of K15, 19 and K14 in human corneal and conjunctival epithelium. Images of serial sections stained with anti-K19 (green, FITC) and anti-K15 (red, Cy3) antibodies (*A–C*) and with anti-K14 (green) and anti-K15 (red) antibodies (*D–F*) Conjunctiva (*A* and *D*) and central (*B* and *E*) or limbal area (*C* and *F*) of the cornea. Together with the expression of K15, a strong expression of K19 was observed in the basal and suprabasal layers of the conjunctival and limbal epitheliae. (*A, C, D* and *F*) Cells weakly positive for K19 were also found in the central area (*B*). K14 was observed in the conjunctiva and in the basal and suprabasal layers of the limbus and central corneal epithelium. Published with permission of the copyright holder The Association for Research in Vision and Ophthalmology, Fig. 4.1 in Yoshida S, Shimmura S, Kawakita T, et al. Cytokeratin 15 can be used to identify the limbal phenotype in normal and diseased ocular surfaces. Invest Ophthalmol Vis Sci 2006; 47: 4780–4786.

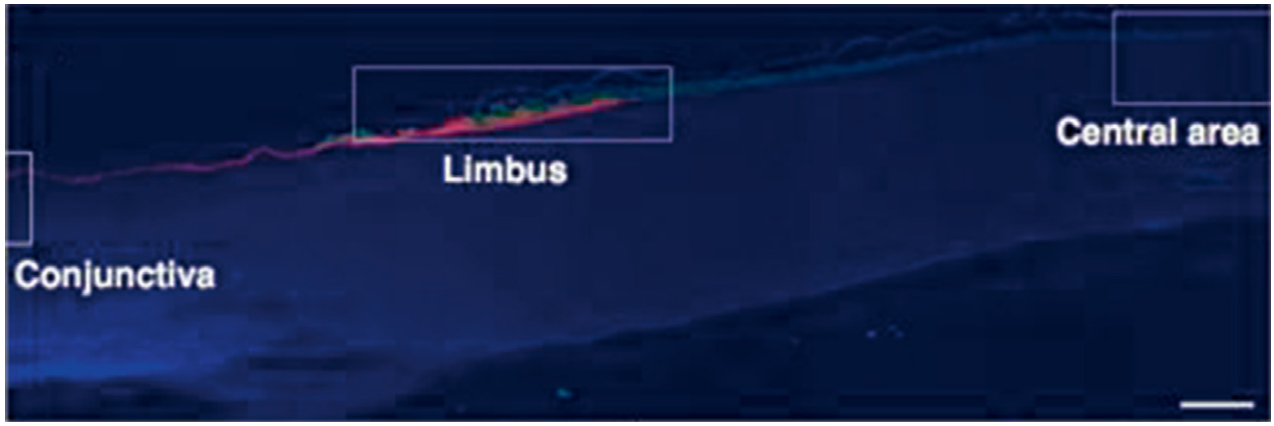
in all limbal basal cells and throughout the conjunctival epithelium.

Beta-catenin: Uniform labeling of all cell membranes throughout ocular surface epithelia without any differences in staining pattern of the basal limbal cornea has been reported.[40]

Integrins: In human cornea, integrin β1 is uniformly expressed by basal cells of both limbus and cornea and lacks any real specificity in distinguishing human limbal from corneal basal cells.[19,23]

EGF-R: Growth factor receptors are proteins that preferentially localize to the cell membranes of limbal basal cells. The presence of high levels of growth factor receptors may allow limbal basal cells to be differentially stimulated by fibroblast- or blood-derived growth factors to maintain their undifferentiated nature or to undergo proliferation upon wounding.[40] Although a strong expression of EGF-R in limbal basal cells was also confirmed in human cornea, there was no clear difference in staining intensity between the basal cells of the limbus, corneal, and conjunctiva.[23,40,56]

ABCG2: ATP-binding cassette subfamily G, member 2 (ABCG2), has been identified as a molecular determinant for hematopoietic stem cells, and has been proposed as a universal marker of stem cells. Chen et al demonstrated that this protein is immunolocalized to the cell membrane and cytoplasm of some human limbal basal epithelial cells, but not in most limbal suprabasal cells and corneal epithelial cells.[23]



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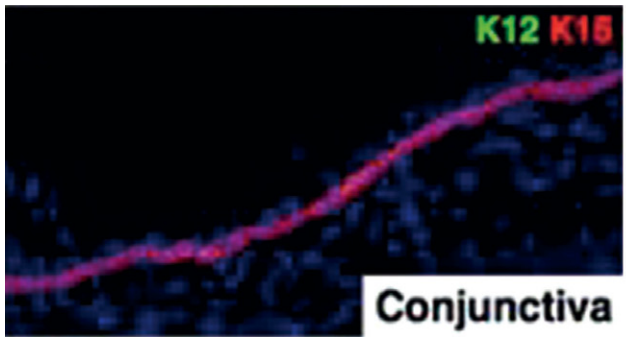

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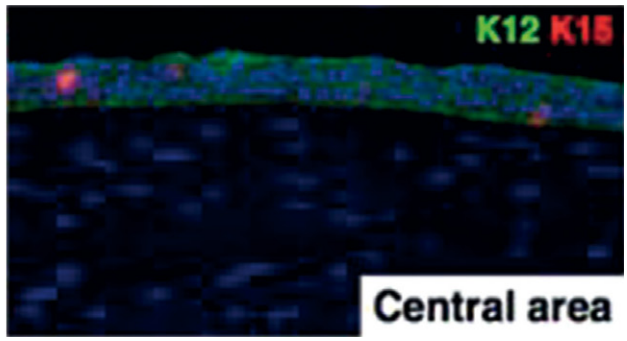

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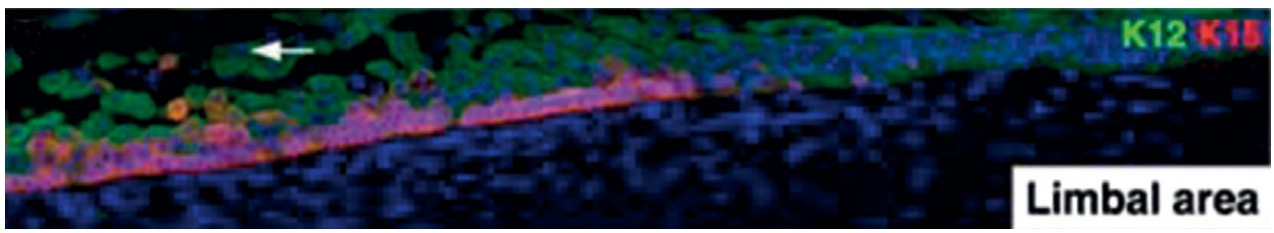

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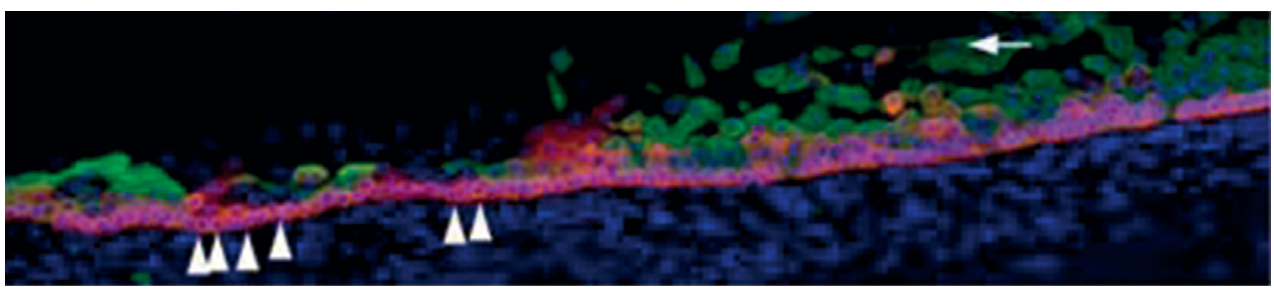

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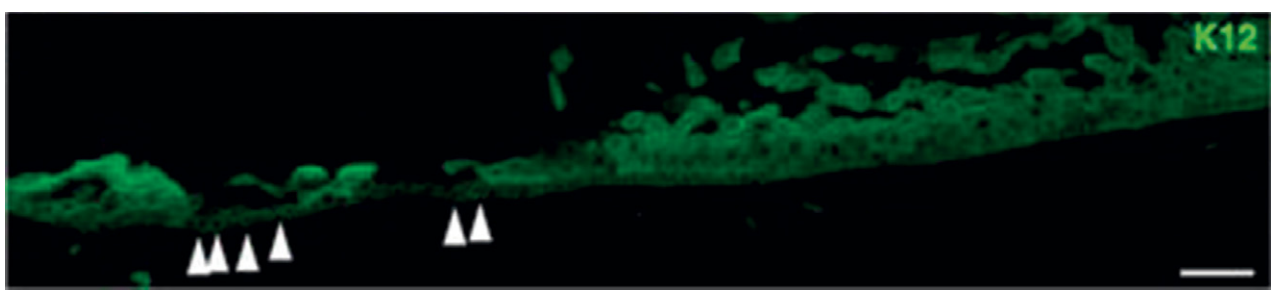

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Figure 4.6. Expression of K15 and K12 in human corneal and conjunctival epithelium. *A,* Overview of human ocular surface immunostained with anti-K12 (green, FITC), and anti-K15 (red, Cy3). Boxes: magnified regions shown in conjunctiva (*B*) central cornea (*C*) and limbal area (*D, D'* and *E*). (*D* and *D'*) Images across the limbus; white arrow: same cell in each image. In the conjunctiva, K15 is expressed only in basal cells (*B,* K15 bas/K12 -). In contrast, K15+ cells were found in the suprabasal layers of the limbus (*A, D* and *D',* K15 bas-sup/K12 sup). Isolated K15 positive cells were observed in the central area that was also K12 positive. C, The expression of K15 was highest in basal cells of the limbal area (*D',* arrowheads). These cells also expressed low levels of K12 (*E,* arrowheads). Scalebars: *A–D',* 200 μm; *E,* 50 μm. Published with permission of the copyright holder The Association for Research in Vision and Ophthalmology, Fig. 4.1 in Yoshida S, Shimmura S, Kawakita T, et al. Cytokeratin 15 can be used to identify the limbal phenotype in normal and diseased ocular surfaces. Invest Ophthalmol Vis Sci 2006; 47: 4780–4786.

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5 Shape, structure, and biomechanical properties

Pierre Fournié, Gabriel M. Gordon, Dolena R. Ledee, Cynthia J. Roberts, M. Elizabeth Fini

Biomechanics is the study of the mechanics of living systems. The cornea is not mechanically inert. Biomechanical changes can manifest clinically as an immediate reduction in corneal transparency, changes in corneal shape, shape instability over time, and increased sensitivity to shape changes caused by altered hydration, hypoxia, and subsequent injury or surgery. The cornea is similar in tissue organization to skin, but it is simpler, being avascular and lacking appendages. However, it is also more complex, as corneal tissues have many unique structural features. Understanding the biomechanical properties of the cornea is confounded by this, its layered structure, and its molecular heterogeneity. The corneal stroma comprises approximately 90% of the corneal thickness. It provides the cornea with its mechanical properties via its unique structure of interlacing layers of collagen fibrils embedded in a hydrated matrix or 'ground substance' rich in proteoglycans, glycoproteins, other soluble proteins and inorganic salts. Cells called keratocytes scattered sparsely through the stroma form an interconnected network that contributes to the maintenance of corneal structure. The microscopic properties of the corneal stroma are responsible for corneal transparency, whereas the macroscopic arrangement of the collagen lamellae is the basis of shape and physical strength.

MICROSCOPIC ORGANIZATION

THEORY OF CORNEAL TRANSPARENCY

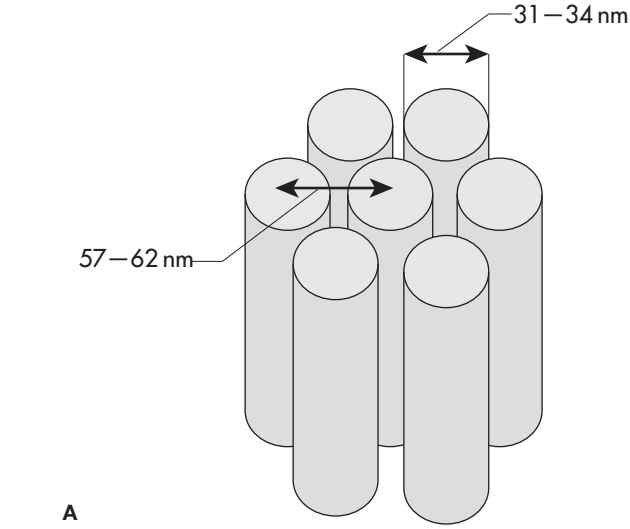
Investigation into the mechanics underlying corneal transparency has occupied scientists for many decades.[1–10] Despite considerable advances in our understanding, there is still no universally accepted explanation. As summarized by Farrell and McCally,[11] all currently viable transparency theories have three common factors:

1. Individual collagen fibrils inefficiently scatter light.
2. The large number of fibrils, however, requires destructive interference of scattered light.
3. Light scattering is directly proportional to thickness, and the cornea is thin.

EXTRACELLULAR MATRICES

Collagens are a family of extracellular matrix proteins found throughout the body. They function in the extracellular space in a variety of ways, from architectural support to filtering of debris, to cell signaling. The majority (~68%) of the collagen comprising the dry weight of the stroma is type I,[12] which is intertwined with collagen V into heterotypic fibrils.[13] X-ray diffraction techniques have shown that these heterotypic fibrils are a constant 31–34 nm wide throughout the central stroma (fibrils thicken toward the limbus) (Fig. 5.1, *A* and *B*) and are organized into orthogonally layered, parallel arrays called lamellae. These layers span the entire cornea like thin laths. At the limbus—the transitional zone between cornea and sclera—they merge with the limbal lamellae.[14] The interfibrillar distance within each lamella varies depending on where the fibril is located. The interfibrillar space in the center of the cornea is about 57 nm, which increases to about 62 nm toward the limbus[15] (Fig. 5.1, *A* and *B*). The fibrils are also packed together more densely in the posterior stroma.[16] While the diameter of individual fibrils does not vary with stromal depth, each lamella is composed of various number of collagen fibrils that does vary depending on the stromal depth. The lamellae in the anterior third of the stroma are about 0.5–30 μm wide and 0.2–1.2 μm thick and are much more disorganized compared to the posterior lamellae, which can grow to about 100–200 μm wide and 1–2.5 μm thick.[17]

Maurice proposed that the collagen fibrils within the stromal lamellae are arranged in a perfect crystalline lattice and that corneal transparency results from the phenomenon that light scattered by individual fibers is canceled by destructive interference from scattered light of neighboring fibers; therefore, light is transmitted only in the forward direction.[1] Although subsequent studies revealed a high degree of order, the lattice structure is not perfect.[6,18,19] Nevertheless, a lattice-like structure may be sufficient (Fig. 5.1, *A* and *B*). Refractive elements in tissues whose dimensions are small (<200 nm) compared with the wavelength of light (~500 nm) should not scatter very much light on the basis of the interference effects



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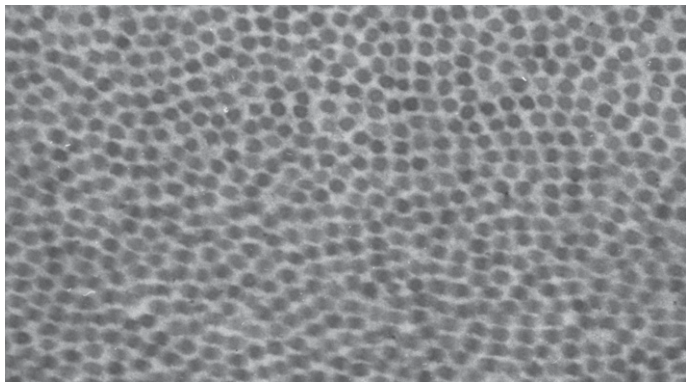

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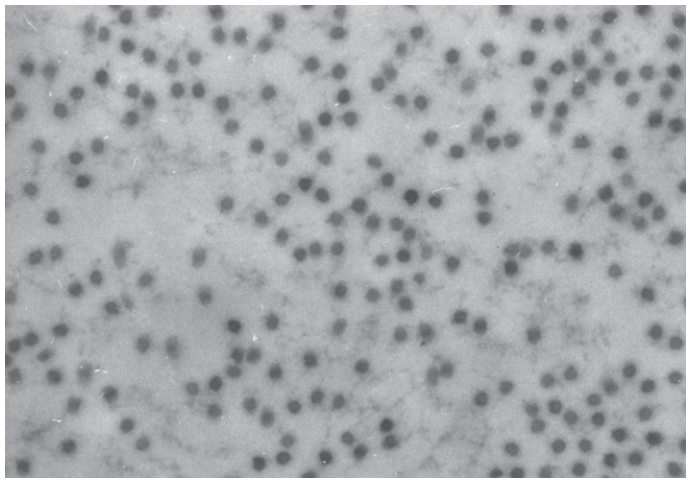


C

Figure 5.1. Arrangement of collagen fibrils within the stromal lamellae. *A,* Scheme of the average size and spacing of some collagen fibrils in a lamella. *B,* Electron microscope (EM) (×95 400) images of normal cornea showing the regularly spaced collagen fibrils cut transversally. *C,* EM image (×95 400) of corneal edema. Note the irregular spacing between collagen fibrils, forming stromal 'lakes.' (Fig. 5.1, *B* and *C* were generously donated by Dr Henry Edelhauser.)

proposed by Maurice.[5,20] Consequently, the normal stroma only minimally scatters incident light because of the regular distribution and size of the collagen fibrils. The heterotypic pairing of type I with type V collagen in the corneal fibrils results in a uniquely narrow fibril diameter, which is thought to aid transparency.[21]

The mechanisms that govern assembly of the stromal architecture are not well understood. Besides the unique heterotypic collagen fibrils, many of the other constituents of the stroma may also act to establish and maintain this design. Collagen III seems to have a similar distribution as collagen I, although its exact role is undefined.[22] Collagen VI has been shown to be present in the interfibrillar space where it binds the collagen I/V fibrils laterally to help maintain fibril spacing.[23] Collagen XII has been localized to Bowman's layer as well as the entire stroma, where it seems to contribute to proper fibril spacing as well as playing a role in structural stability, connecting Bowman's layer to both the underlying stroma and the epithelial basement membrane.[24] Collagen XIII was unassociated with the extracellular matrix alone but has been localized to the plasma membranes of stromal cells in the posterior two-thirds of the stroma,[25] perhaps indicating a role in lamellar organization. Collagens XV and XVIII have anti-angiogenic properties attributed to their carboxy terminal domains which can be cleaved to form angiogenesis inhibitors (endostatins and neostatins); thus they may help to maintain the avascular status of the cornea. Collagen XV has shown a diffuse immunolocalization throughout the adult stroma,[26] while collagen XVIII seems to be localized to the posterior stroma adjacent to Descemet's membrane.[27]

After collagens, proteoglycans are the next major component of the corneal stroma. Proteoglycans function in diverse processes throughout the body. They are composed of a core protein covalently bound to anywhere from 1 to over 100 carbohydrate chains. There are seven types of these carbohydrate chains, called glycosaminoglycans (GAGs), which can be attached during intracellular processing and help determine their function. The two main types of proteoglycans found in the corneal stroma are the keratan sulfate-containing proteoglycans keratocan, lumican, and mimecan, and a chondroitin/dermatan sulfate-containing proteoglycan called decorin. The specific proteoglycan profile of the corneal stroma is linked to transparency. These molecules bind collagen fibrils and may act as mediators of fibril and lamellar assembly.[28] They also are likely to contribute to the control of corneal hydration (and thus swelling) through their specific abilities to bind water. Lumican has been localized to the entire corneal stroma although it is much more heavily expressed in the posterior two-thirds. Lumican-deficient mice develop cloudy corneas at 3 months of age, which persists into adulthood. Transmission electron microscopy imaging has shown that the posterior stroma in mice lacking lumican contains fibrils with significantly larger diameters as well as large fibril aggregates, improper interfibrillar spacing, and much more disorganized lamellae.[29] Interestingly, no such abnormalities are detected in the anterior stroma of these mice, implying a different mechanism for maintaining the fibrillar arrangement. Similarly, X-ray diffraction has shown that keratocan-deficient mice possess a thinner corneal stroma with collagen fibrils of increased diameter and larger interfibrillar spacing.[30] Unlike lumican-deficient mice, however, keratocan-deficient mice do not show any stromal cloudiness. Mutation of the keratocan gene in humans has recently been shown to cause cornea plana, which is characterized by a flattened corneal surface.[31,32] Mimecan-deficient mice seem to have no corneal defects. Corneas are clear with fibril diameters and interfibrillar spacing showing no difference from wild-type littermates.[33] Decorin

has been localized throughout the corneal stroma, including strong expression in Bowman's layer, bound to collagen I/V heterodimers as well as the laterally connecting collagen VI.[34] While the cornea has not been examined in detail in decorin-deficient mice, the skin of these mice is very fragile with irregular collagen fibril diameters as well as abnormal interfibrillar spacing.[35]

Bowman's layer is an 8–12 μm region located between the stroma and the epithelial basement membrane. Bowman's layer lacks lamellae and is instead a densely interwoven but unorganized array of collagen types I, III, V, VI, and XII composed of three or four stratified layers in the center which blend together toward the limbal region.[36] Unlike stromal fibrils, however, which have a 31–34 nm diameter, fibrils in Bowman's layer can be as small as 20 nm in diameter. Bowman's layer is even more acellular than the stroma, the only cells being nerve bundles which pass perpendicularly from the stroma into the epithelial basement membrane where they enervate the cornea epithelium. Bowman's layer is, however, relatively transparent, presumably because spatial fluctuations in the refractive index are small, collagen fibers are small, and this layer is thin.

STROMAL CELLS

Keratocytes are the major cellular components of the human corneal stroma. The origin of these cells is controversial, with either neural crest or mesenchymal origin being possible. Hayashi et al identified the presence of both neuronal and mesenchymal cell markers in immunostained keratocytes and concluded that keratocytes originate from neural crest cells and differentiate into mesenchymal cells.[37] In the adult cornea, keratocytes exhibit a slow turnover: approximately every 2–3 years. They appear as a sparse population of flattened cells located between the collagen lamellae of the corneal stroma. The major function of keratocytes in the normal cornea is to maintain the collagen scaffold and extracellular matrix of the stroma. The keratocytes synthesize new collagens and proteoglycans, while also secreting collagenases and other enzymes to degrade the old stromal matrix. Although each stromal cell scatters light, the total light scattered is small because of the low cellular density. The keratocytes occupy 2–3% of the volume of the stroma.

While appearing scattered and disconnected in corneal cross-sections, keratocytes can be seen in en face views to form an interconnected cellular network by extension of dendritic processes (Fig. 5.2). Gap junctions at the tips of the cellular processes allow for communication between the cells.[38] There is clear evidence that this extensive and highly coupled stromal keratocyte network is much more dynamic than previously thought. In this avascular tissue, the keratocyte network provides a means by which nutrients and metabolites are passed into the central regions of the stroma and waste products are excreted. Advances in corneal and refractive surgery have highlighted the importance of understanding keratocyte function.

Recent studies report the presence of additional cell types in the adult corneal stroma that express stem cell markers and have the ability to divide extensively and generate differentiated keratocytes.[39] These progenitor cells express the ocular development gene PAX6, which is not expressed by the resident stromal keratocytes.[40] The origin of these cells in the corneal stroma is not yet determined. An understanding of their properties might have important implications for cell-based corneal therapy or for the development of bioengineered corneas.

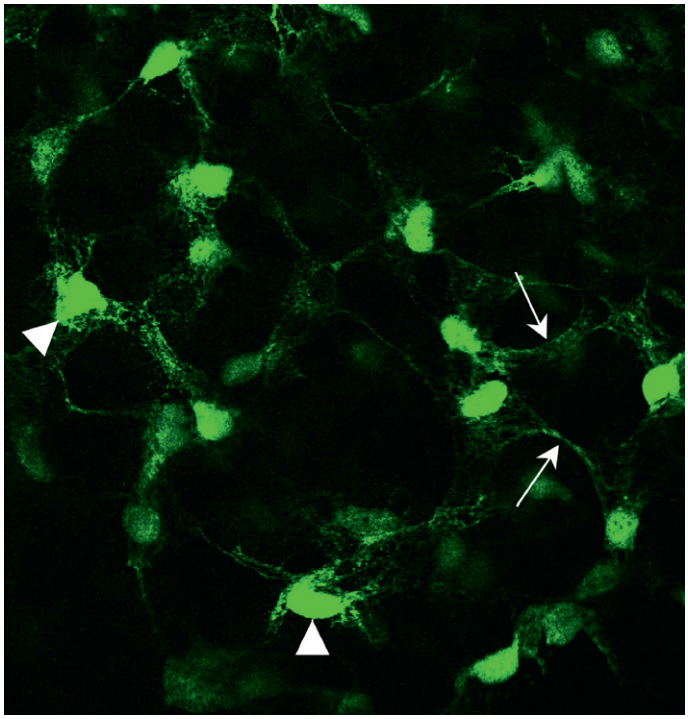


Figure 5.2. Confocal microscopy (×400) of the corneal stroma of a transgenic mouse carrying the Green Fluorescent Protein. Green cells indicate keratocytes with their cell body (arrowheads) and dendritic processes (arrows) forming a three-dimensional interconnected cellular network.

Finally, it was recently demonstrated that bone marrow-derived stem cells are normal components of the corneal stroma in most or all corneas, even in the absence of inflammation (Fig. 5.3).[41–43] As a result, the consensus that the cornea is devoid of resident antigen-presenting cells was profoundly revised. The usual explanation for the extraordinary success of orthotopic corneal allografts, either in humans or in experimental animals, is related to the phenomenon termed 'immune privilege.' This immune privilege concerns both the site of engraftment and the corneal tissue. This notion has lost favor since the demonstration of a large number of resident bone marrow-derived antigen-presenting cells from different lineages—such as dendritic cells and monocytes or macrophages—in both the epithelium and stroma of the normal cornea.[41–43] The immune-privilege of corneal allografts, however, does not rely on a single mechanism for evading immune destruction and the function of these 'wandering cells' in the corneal graft rejection process remains to be investigated. Most of these cells have an immature phenotype lacking major histocompatibility complex class II expression and are extremely inefficient at activating T lymphocytes.[42] They are capable of expressing class II antigens after trauma and surgery.[44]

There are also important functional differences between dendritic cells and macrophages that should be emphasized. Dendritic cells are found in small numbers in the peripheral parts of the cornea and they are not detected in the central parts under normal conditions. Macrophages are found in both parts, but mostly in the periphery.[45] Dendritic cells are much more potent at initiating and expanding secondary immune responses involved in corneal rejection than macrophages, which have a high phagocytic and a low T-cell stimulatory capacity. Macrophages thus seem to have a pivotal role as effector cells and are less likely to trigger an immune rejection reaction. The exact roles of resident tissue macrophages

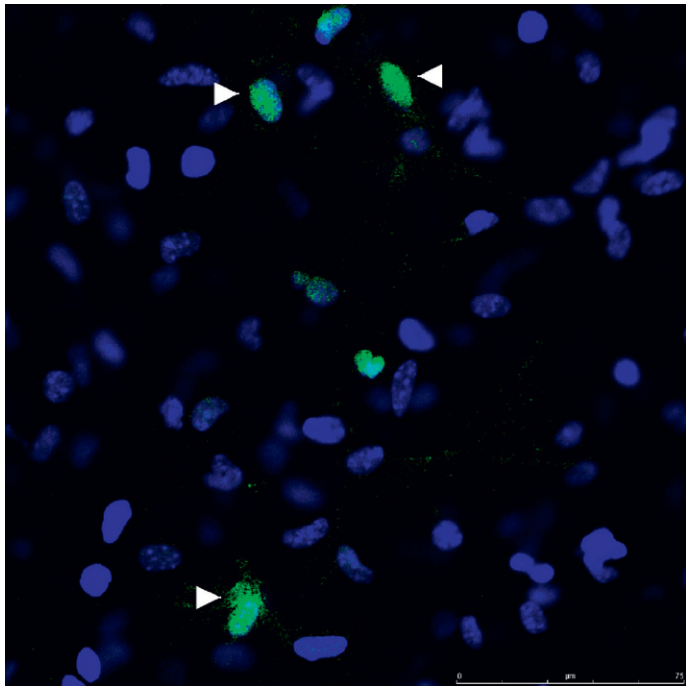


Figure 5.3. Confocal microscopy (×400) of the corneal stroma of a chimeric mouse. A lethally irradiated wild-type mouse has been transplanted with bone marrow-derived cells from a Green Fluorescent Protein transgenic mouse. Green cells (arrowheads) indicate bone marrow-derived cells and blue cells indicate the nuclei of keratocytes.

are not well defined. They are highly phagocytic, facilitating their role in clearing tissue of damaged, infected, or senescent cells. Macrophages also perform essential tasks in wound healing via tissue remodeling through the secretion of appropriate enzymes and growth factors. Their immunologic function remains to be determined. Whereas the macrophages might provide a critical first line of defense against pathogens that breach the epithelial barrier by producing antimicrobial substances and other inflammatory cytokines and chemokines, their role as antigen-presenting cells is unclear. Instead of activating T cells, macrophages in the stroma that are exposed to transforming growth factor-β might, on the contrary, contribute to the immune-privileged status of the cornea by downregulating the T-cell response and inducing tolerance to antigens acquired within the tissue.[46]

NERVES

Electron microscopy images of the corneal stroma show up to 30 sensory nerve fiber bundles of up to 20 μm in diameter with individual fiber diameters ranging from 0.5 to 2.5 μm which enter the stroma from the periphery in a radial pattern. These bundles, found mostly in the anterior stroma, run parallel to the collagen lamellae.[47] While Schwann cell cytoplasm has been localized along the nerve bundles, the individual nerve fibers are not myelinated, implying that the Schwann cells play a role in stromal nervous system survival rather than conduction of the electrical impulse. In addition to being surrounded by Schwann cells, nerve bundles are also embedded in amorphous extracellular matrix structure. Nerve bundles toward the central anterior of the stroma are usually arrayed in the superior to inferior direction while those in the periphery seem to prefer a nasal-temporal pattern.[48] Some nerve fibers in the stroma have been shown to come in direct contact with keratocytes before the bundles make a 90° turn and pass through pores in Bowman's layer to enervate the corneal epithelium.

STROMAL RESPONSE TO STRESS OR INJURY

Any disturbance in the uniformity of collagenous fiber spacing, fibril composition, or proteoglycan content can result in a loss of corneal transparency. This can result from corneal edema, physical damage to the stroma, or deposition of fibrotic tissue in the stroma subsequent to acute damage or as part of a chronic wound healing situation.

The limiting layers of the cornea are sites of active ion transport that regulate the hydration of the hydrophilic stroma.[49,50] The ideal physiologic corneal hydration is approximately 78% in humans. Reduced corneal metabolism (i.e. due to hypoxia or lowered temperature) adversely affects the barrier properties and transport functions of both the epithelium and endothelium, resulting in an increase in corneal thickness and a loss of transparency.[49,51] Corneal edema also results from damage to the corneal endothelium, disrupting the pumping action of its Na/K ATPase ion channels.[52]

In edematous corneas, the diameter of the collagen fibrils remains essentially constant; swelling occurs in the ground substance and leads to increased spatial separation of the collagen fibrils.[53] Those regions that are devoid of collagen fibers are often referred to as stromal 'lakes' (Fig. 5.1, *C*). It is theorized that if a stromal lake reaches a size comparable to half the wavelength of light, scattering increases markedly, leading to a loss of corneal transparency.[20] Loss of light transmittance increases with the amount of corneal swelling.

Following debridement of the overlying epithelium during refractive surgical procedures, keratocytes in the underlying corneal stroma are stimulated to undergo programmed cell death or 'apoptosis.'[54] Keratocyte apoptosis seems to be a benign response thought to have evolved to protect the cornea from further inflammation and the subsequent loss of transparency. These cells are simply replaced following re-epithelialization, probably by replication and migration of keratocytes from the debridement margin.[55,56] There is little or no expression of fibrotic markers.[57]

The cornea is remarkably resistant to stimuli that would initiate a fibrotic repair response in other tissues. These features of cornea may have evolved to limit undesirable changes in tissue structure due to normal renewal or repair processes, much as corneal immune privilege protects it against damaging inflammatory reactions.[58] These phenomena have collectively been termed 'corneal constancy.'[59]

When damage to the cornea penetrates the basement membrane and into the stroma, stromal cells transition into repair phenotypes under the influence of cytokines released by the corneal epithelium.[57,59,60] Keratocytes transformed to the repair or 'activated' phenotype exhibit many morphologic characteristics of fibroblasts, including a fusiform shape, multiple nucleoli, and a lack of cytoplasmic granules. A battery of new genes is activated, including genes that encode cell:matrix adhesion molecules, repair-type extracellular matrix components, and proteinases such as the matrix metalloproteinases.[61,62] As wound healing progresses, a subset of repair fibroblasts assumes properties that are characteristic of myofibroblasts, defined by their larger appearance and expression of alpha-smooth muscle actin.[60,63] Corneal myofibroblasts are responsible for wound contraction as well as for extracellular matrix deposition and organization during corneal repair.

Much of the synthetic activity of the repair cell is involved with the production of an opaque, repair-type extracellular matrix. The composition of this matrix is very different from that of the normal, uninjured stroma. This difference in composition, as well as the disorganized manner of repair tissue deposition, contributes to its opacity.[64] A major change is the appearance of fibronectin, much of which is synthesized by the repair fibroblast.[65] Tenascin is also synthesized in the repair tissue, but not in normal stroma.[66] The ratio of collagen types synthesized by the repair fibroblast is different from the types found in the normal stromal extracellular matrix.[67] Synthesis of keratan sulfate proteoglycan is downregulated, while synthesis of decorin sulfate proteoglycan is induced.[68] The reason for this change is not known, but might represent an alternation in the biosynthetic pathway, possibly through new expression of a specific glycosyltransferase enzyme.

Because of the opacity of repair tissue, refractive surgical procedures aim to limit the wound healing response.[69] Laser surface ablation procedures accomplish this by minimizing the amount of tissue damage. Flap-creating procedures such as LASIK minimize the epithelial-stromal interaction that mediates fibrosis. In such minimal wound healing situations, repair tissue deposition is very low and does not appear to be a major factor in the subsequent 'haze' or translucency that can develop in the cornea following surgery. In this case, cells may be the most important reason for loss of transparency. Indeed, the cells that migrate into the wound bed in corneal wounds are highly reflective when viewed by in vivo confocal microscopy.[70] The molecular changes responsible for this acquisition of light-scattering properties are not known. Possible molecular contributors are the repair-type cytoskeleton with its highly developed stress fibers, or the pericellular extracellular matrix. Another mechanism might lie in reduction in the levels of a newly discovered class of molecules called 'corneal crystallins.' These are taxon-specific, multifunctional proteins that accumulate to very high levels in corneal cells.[71] Aldehyde dehydrogenase 3 (ALDH3) and transketolase (TKT) are the main water-soluble proteins in the corneal stromal keratocytes of most mammals.[72] These proteins at high concentrations may contribute to the transparent state of the cornea by destructively interfering with scattered light through short-range physical interactions, similar to the lens crystallins.[73] Transformation of keratocytes to the repair phenotype in culture is accompanied by loss of crystallins in cell culture.[74,75] In a rabbit wound healing model, crystallin loss correlates with loss of cell transparency.[60] However, ALDH3A1-deficient mice appear indistinguishable from wild-type corneas, and are transparent as determined by light and slit-lamp microscopy.[76] It remains to be seen whether subtle changes in clarity occur that are difficult to measure and perhaps more likely to be manifest in stress conditions. However, the corneal crystallins may probably serve other functions that could preserve corneal clarity, for example protecting tissue against oxidative stress, as occurs in the lens.[77] In fact, a recent publication indicates that ALDH promotes survival of corneal epithelial cells in the face of reactive oxygen species (ROS) and DNA damaging agents.[78]

Recently, a role was proposed for bone marrow-derived stem cells in tissue regeneration. It was suggested that these cells have the potential to form new tissue cells, especially after injury.[79,80] Bone marrow-derived stem cells might either transdifferentiate into corneal cells (such as corneal keratocytes) or, more likely, fuse with existing cells to form a multinucleated cell. Studies are currently ongoing in multiple laboratories to examine their hypotheses and the results promise to be very interesting.

MACROSCOPIC ORGANIZATION

EMBRYONIC DEVELOPMENT

Between the fifth and seventh week of human embryogenesis a series of important developmental events in the corneal stroma occur. By this time the lens vesicle has pinched away from the surface ectoderm and cells of the limbal periocular mesenchyme, a secondary mesenchyme (i.e. a mesodermal area infiltrated by neural crest cells), begin to migrate anteriorly and inward in three waves to fill the void. There are two somewhat contradictory theories on the order of the migration of cells. Both theories concur that the first wave of cells migrates between the surface ectoderm and the lens to form the corneal and trabecular endothelium. They, however, differ on the destiny of the second and third wave of cells. In one theory the second wave of cells migrates between the primitive corneal epithelium and endothelium to give rise to the keratocytes with the third wave giving rise to the stroma of the iris between the endothelium and lens.[81–83] Tripathi and Tripathi proposed the reverse.[84] The presence of the lens appears to be essential during the migration of these periocular mesenchymal cells in the differentiation of the corneal stroma.[85,86]

From the second and into the third month, differentiation of the corneal stroma continues. The stroma increases from ~5 to 8 rows of cells to 15 and now contains collagen fibers, particularly type I and type III. The stroma spreads toward the sclera and the central stroma is more attenuated compared to the more confluent peripheral posterior layers. Lying in parallel to the corneal epithelium, the anterior stromal cells tend to be more round in shape compared to the spindle-shaped posterior cells.[87–89] The arrangement of the fibroblast (predecessors of the keratocytes) coincides with the synthesis of glycosaminoglycans, such as keratan sulfate, which regulates the spacing of the collagen fibers,[90] hence transparency. At this stage the cornea is hydrophilic and translucent due to the high water content.[88] Sensory nerve fibers can be observed, with innervation beginning at 3 months reaching into the epithelium by 5 months of age.[91]

At 4 months the cornea continues to differentiate and mature. Although the stromal region is greater than 15 layers thick and of equal thickness throughout, the corneal diameter has increased due to longer collagen fibrils, and the demarcation between the stroma and sclera is more distinct. There are fewer mesenchymal cells and more flattened keratocyte type cells and an abundance of parallel collagen lamellae.[88,89] From here on the differentiation of the cornea continues at a slower rate. Into the fifth month the Bowman's layer abutting the corneal basement membrane becomes visible at the ultrastructural level. The keratocytes at this stage of development also exhibit an increased level of lysosomal enzyme activity indicative of a potential involvement in collagen and glycosaminoglycans turnover rate.[92]

The eyelids open at about 6 months and morphological changes involving stromal thickness and cellularity occur. As observed in many vertebrate animals, the stroma increases in thickness just prior to eyelid opening with thinning after opening. Also, the density of stromal cells appears to decrease.[93,94] It is uncertain if the number of cell decreases or if the density shift is due to the shift in volume. This swelling and thinning may be related to sulfation of lumican, a major keratan sulfate proteoglycan in the stroma. Synthesis of keratan sulfate increases water absorption and consequently swelling and maturation of the endothelium, the corneal pumping station, leads to a thinning. It should also be noted that

between the period of eye opening and birth the number of proliferating cells in the stroma drops precipitously. The remaining stromal cells express little or no cyclins or cyclin-dependent kinase inhibitors, suggesting an exit from the cell cycle into G0, which is supported by the ability to stimulate these cells to proliferate.[55,95]

By the seventh month the cornea is well developed. The diameter of the cornea will have increased from 4.2 mm at 4 months to 9.3 mm at term. After birth in the first postnatal month the cornea has a steep curvature which decreases over the next 6 months until finally stabilizing.[96]

SHAPE

The cornea has a dual role of providing protection to trauma and infection as well as maintaining transparency and structural integrity to refract light into the eye and to maintain the eyeball's shape under the action of the intraocular pressure. The bulk of the cornea is formed by the lamellar stroma, which in the human adult is approximately 450–550 μm thick centrally and consists predominantly of flattened, stacked, collagenous lamellae (200–250 layers) oriented parallel to the corneal surface. The stroma is considerably thicker in the periphery (550–750 μm). Because of its features, the stroma is the layer that provides the cornea with its shape and mechanical properties. The adult human cornea is smaller in the vertical diameter (9–11 mm) than in the horizontal diameter (11–12 mm). The shape of the anterior corneal surface is convex and aspheric. The central 3-mm optical zone radius where the surface is almost spherical is between 7.5 and 8.0 mm, with the peripheral corneal curvature being less marked. The posterior surface overall has a shorter radius of curvature. Corneal shape varies between individuals. An interesting side note is that right and left corneas are structurally distinct, although both seem to exhibit a degree of midline symmetry that might help to explain the topographical enantiomorphism exhibited by fellow corneas.[97]

PHYSICAL STRENGTH

Human corneal tissue is a complex viscoelastic structure. The cornea is able to recover its original shape after stress is removed, but the relaxation path is different from the deformation path. This property is referred to as hysteresis and is due to the ability of the tissue to absorb and dissipate energy. The tensile strength of the cornea is dependent on its collagen content. The stroma thus provides the majority of the cornea's tensile strength. The exact mechanism responsible for the maintenance of the corneal shape, however, is not known.

The orientation of successive fibril layers throughout the entire cornea is an important factor determining the mechanical properties of the cornea. There is a difference between the arrangement of the lamellae in the anterior third of the cornea and that in the posterior two-thirds.[98] In the mid- and posterior stroma, collagen lamellae tend to be arranged parallel to the surface, and fibrils in one lamella run at approximately right angles to those in the adjacent lamellae in the superior–inferior and nasal–temporal directions preferentially (Figs 5.4, *A* and *C* and 5.5).[99,100] It has been suggested that these collagen lamellae patterns exist to withstand the stress exerted on the cornea by the ocular motor muscles, thereby helping to preserve corneal shape.[99,100] In the anterior one-third of the stroma, collagen lamellae run in more random directions and branching of the lamellae in this superficial region (100–120 μm thick) has been described in both the vertical and horizontal planes with fibrils interdigitating from one lamella to the next, sometimes weaving between three lamellar layers (Fig. 5.4, *B* and *C*).[98] Some stromal interweaving in the horizontal plane also occurs in the deeper lamellae.

In corneal edema, swelling is lowest in the most anterior part of the stroma and even extreme swelling has little effect on corneal curvature. The proteoglycan ratio in the corneal stroma is related to stromal hydration and water distribution. In the posterior part keratan sulfate, a more hydrophilic proteoglycan, is prevalent; whereas in the anterior part dermatan sulfate, a much less hydrophilic proteoglycan, is prevalent. Müller et al suggest that the tightly interwoven anterior lamellae, which restrain corneal swelling, might also account for the maintenance of corneal curvature.[101] Given the importance of this site, a question about corneal stability arises concerning excimer laser refractive surgery in which this part of the stroma is either ablated (photorefractive keratectomy) or intersected (keratomileusis). Furthermore, a proportion of the anterior lamellae inserts into Bowman's layer. Interestingly, Bowman's layer is not present in all animals[102] and its removal does not measurably alter the mechanical properties of the cornea.[103] Thus, while there are speculations as to the purpose for Bowman's layer, its function remains unclear.

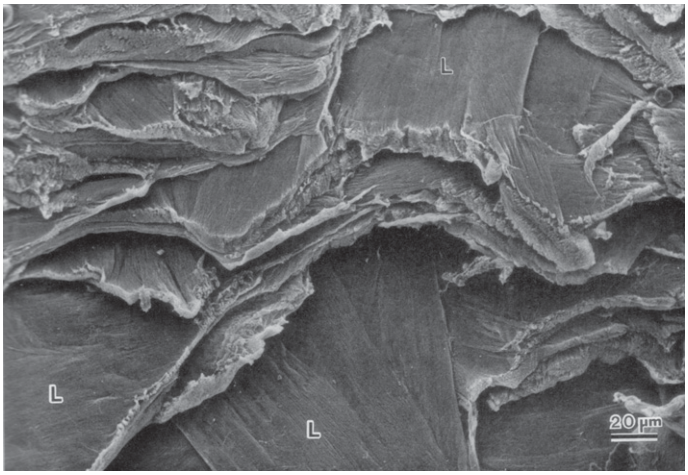
The physical strength can be compromised in different corneal diseases, which results in anomalies of corneal shape, and thereby on the eye's refractive status (Table 5.1). Corneal thinning is a hallmark of noninflammatory ectatic disorders. The orthogonal arrangement of the collagen fibrils is profoundly altered in keratoconus with a loss, rather than a compaction, of collagen, which is responsible for the clinical thinning.[104] Both the thinning and altered collagen arrangement can account for the biomechanical instability of the tissue, and lead to corneal protrusion.

BIOMECHANICAL RESPONSE TO EXCIMER LASER REFRACTIVE SURGERY

Although thinning of the cornea is associated with protrusion and consequent increase in curvature in noninflammatory ectatic disorders such as keratoconus, the opposite response occurs when the normal cornea is intentionally thinned by removing tissue in a specific pattern via laser refractive surgery. In this case, the central cornea flattens biomechanically due to alteration of the structure by ablation of central portions of tension-bearing lamellae. Preoperatively, the normal cornea can be considered analogous to a series of rubber bands, stacked one on top of the next, with water-soaked sponges in between each layer. The rubber bands represent corneal lamellae, and the sponges represent ground substance or matrix. The rubber bands are stretched due to loading by the intraocular pressure, and the water held in the sponges is 'squeezed' out by the

Table 5.1

Corneal thickening	Corneal edema
Corneal thinning	Ectatic disorders
Noninflammatory	Keratoconus
	Pellucid marginal degeneration
	Keratoglobus
	Posterior keratoconus
	Post-LASIK keratectasia



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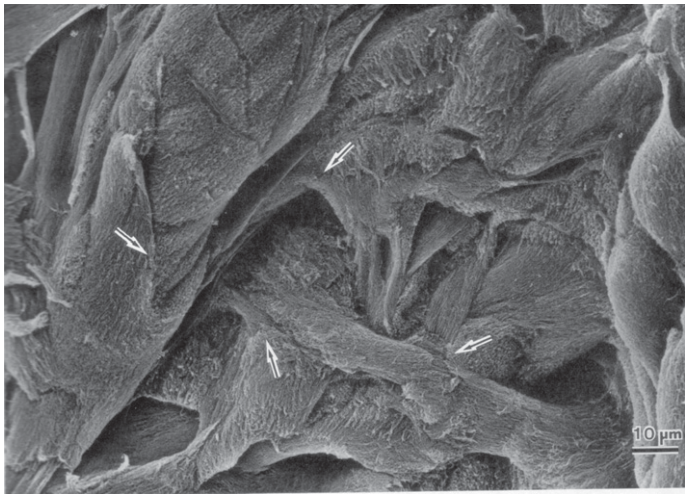

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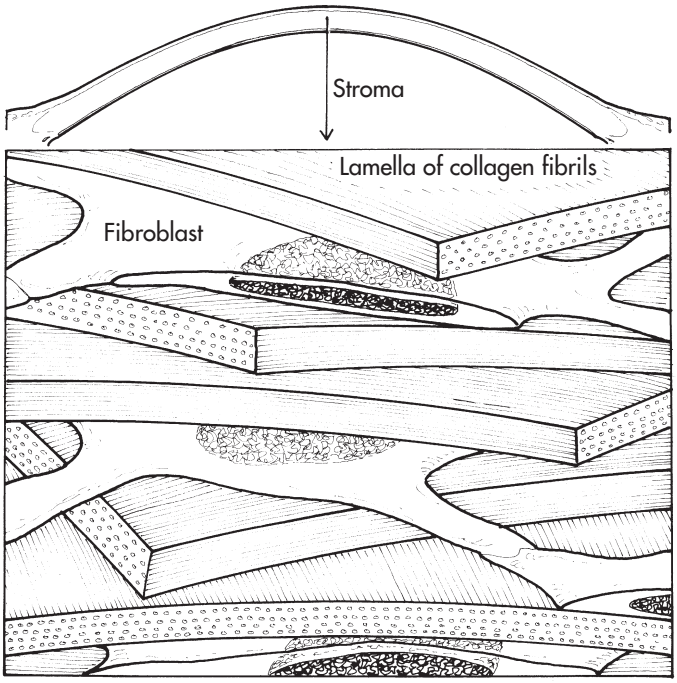

C

Figure 5.4. Orientation of the collagen lamellae in the corneal stroma. *A,* EM image (×1100) showing the arrangement of the lamellae in the posterior two-thirds of the cornea shows the orderly pattern of collagen orientation within each stromal lamella and the relationships between successive lamellae (L, lamellae); *B,* EM image (×580) showing the arrangement of the lamellae in the anterior third of the cornea. Note the branching and interlacing pattern of collagen lamellae. *C,* Schematic of *A* and *B.* (Figures 5.4, *A* and *B* are from Ushiki and Komai. The three-dimensional organization of collagen fibrils in the human cornea and sclera. Invest Ophthalmol Vis Sci 1991.)

constant tension in the rubber bands. Thus, the normal corneal state of relative dehydration is enhanced by the tension carried in the lamellae, unless the swelling forces are altered by pathology or surgery (Fig. 5.6, *A*). In laser refractive surgery, the lamellae are severed in a circumferential pattern, with the deepest ablation in the center for a myopic procedure and deepest ablation in the paracentral region for a hyperopic procedure. Once the central lamellae are ablated, the tension in the remaining peripheral lamellar segments is dramatically reduced, much like cutting through layers of rubber bands in the analogous model. The relaxed rubber bands can no longer hold the water out of the sponges, and the sponges expand as they imbibe water. However, unlike the stacked rubber bands, the cornea has a complex interweaving collagen microstructure. As the lamellar segments remaining in the peripheral cornea relax when the central cornea is ablated, the swelling forces are regionally altered, causing the peripheral cornea to swell and thicken.[105] This is illustrated schematically in Fig. 5.6, *B*. This is a similar mechanism to that which causes the central cornea to flatten between opposing arcuate incisions in the peripheral cornea, which are used to treat astigmatism. The incisions are placed 180° apart in the meridian of greatest curvature, causing that meridian to flatten, even without the removal of tissue. Thus, any procedure which severs corneal lamellae in an arcuate or circumferential pattern will cause the central cornea to flatten and the peripheral cornea to thicken. The biomechanical central flattening is in synchrony with the ablation pattern in a myopic procedure, and opposes it in a hyperopic procedure where the goal is to increase central curvature. Figure 5.7 is a series of topographic maps from a patient who received a myopic LASIK procedure. The preoperative pachymetry and tangential curvature are given in Fig. 5.7, *A* and *B*. The corresponding postoperative maps are given in Fig. 5.7, *C* and *D*, which illustrates the typical paracentral steepening that is characteristic of myopic refractive surgery. The pachymetric and tangential curvature difference maps are given in Fig. 5.7, *E* and *F*. The central cornea shows a reduction in thickness in the pachymetric difference map, which is expected in a myopic procedure. However,

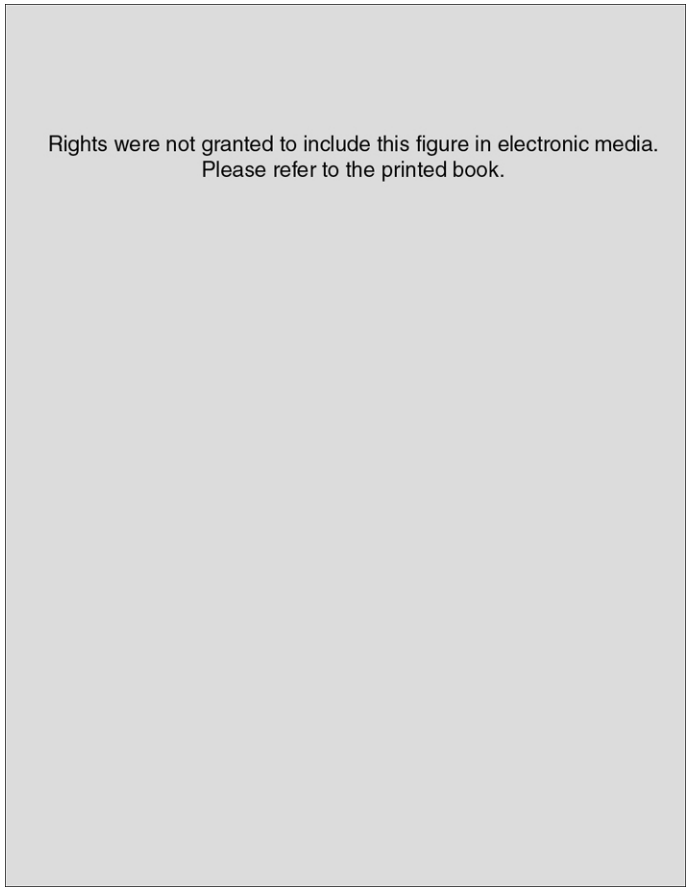

Figure 5.5. Electron micrograph (×32 000) of the posterior stroma shows strictly alternating cross-sectioned and longitudinal sectioned collagen bundles. (K, keratocyte). (This figure is also taken from Komai Y, Ushiki T. The three-dimensional organization of collagen fibrils in the human cornea and sclera. Invest Ophthalmol Vis Sci 1991 July; 32(8): 2244–2258.)

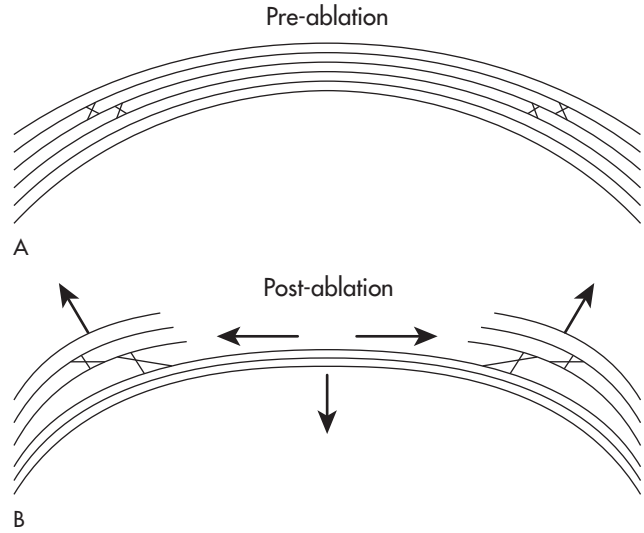

Figure 5.6. Schematic illustration of the change in corneal structure between the preoperative normal state (*A*) and the postablative state (*B*). Once the central portions of the tension-bearing lamellae are removed via ablation, the remaining peripheral lamellar segments relax and the peripheral cornea imbibes water causing it to expand. Due to the complex interweaving microstructure, the peripheral swelling generates a force on the underlying layers causing the central cornea to flatten.

the peripheral cornea shows an increase in thickness within the transition zone, where tissue was actually ablated. This is consistent with the model presented in Fig. 5.6, *B*. The peripheral thickening in laser refractive surgery is associated with an increase in curvature, which is evident in the tangential difference map. This paracentral steepening contributes to biomechanical spherical aberration induction after myopic excimer refractive surgery.

In rare cases, loss of structural stability may occur following laser refractive surgery. This results in further corneal thinning and consequent steepening, characteristic features of iatrogenic ectasia. This biomechanical decompensation response is similar to that seen in keratoconus. Iatrogenic ectasia has been reported more often in LASIK than in PRK, and greater risk has been associated with enhancements, low residual stromal bed thickness, and preoperative curvature anomalies, as well as other factors.[106,107] However, postoperative ectasia has also occurred in the absence of these risk factors. The exact mechanism remains unknown. The widely accepted threshold for residual stromal bed thickness after the creation of a flap and subsequent ablation is 250–300 μm in LASIK, and 400 μm of total corneal thickness in surface ablation. Yet, a series of 'ultrathin' corneas after surface ablation has been reported with a final total corneal thickness less than the accepted threshold without the occurrence of ectasia over 5 years of follow-up.[108] Some of these eyes had a total corneal thickness of less than 300 μm without the occurrence of ectasia. The hypothesis for the long-term stability of these ultrathin corneas was that a wide 10 mm ablation zone was used in a phototherapeutic pattern, which more evenly distributed the stress in the cornea and avoided the stress concentration of a small diameter, thin zone. Therefore, the risk for developing iatrogenic ectasia is multidimensional. It is also possible that an as yet unidentified risk factor exists related to preoperative biomechanical properties that might indicate a weaker cornea. The ability to readily measure biomechanical properties in vivo would allow further study of this rare complication.

MEASUREMENT OF CORNEAL BIOMECHANICAL PROPERTIES IN VIVO

Until the introduction of the ocular response analyzer (ORA) in 2005,[109] no clinical technique existed to measure corneal biomechanical properties in the living eye. The ORA is similar to a noncontact tonometer in that a controlled stream of air is used to rapidly deform the cornea to a flattened state of applanation. This inward applanation event is detected by an electro-optical system composed of an infrared emitter aligned with the cornea such that when applanation occurs, the light becomes focused on an infrared detector creating a spike in the measured signal. The air stream produced by the ORA, however, continues to increase past applanation to a state of corneal concavity where the air pressure peaks. As the air pressure subsequently decreases, the cornea passes through a second applanation event in the outward direction, as the cornea recovers its original shape. If the cornea were purely elastic, the air pressure at which both the inward and outward applanation events occur would be equal. However, due to the viscoelastic nature of the cornea, some of the energy is absorbed or dissipated, and the air pressure at which the second applanation event occurs is less than that of the first applanation event. The difference between the two air pressures is termed 'corneal hysteresis', and is a marker for the viscoelastic properties of the cornea.

In an elastic material, the response of the material is dependent only on the magnitude of the applied force. In a viscous substance,

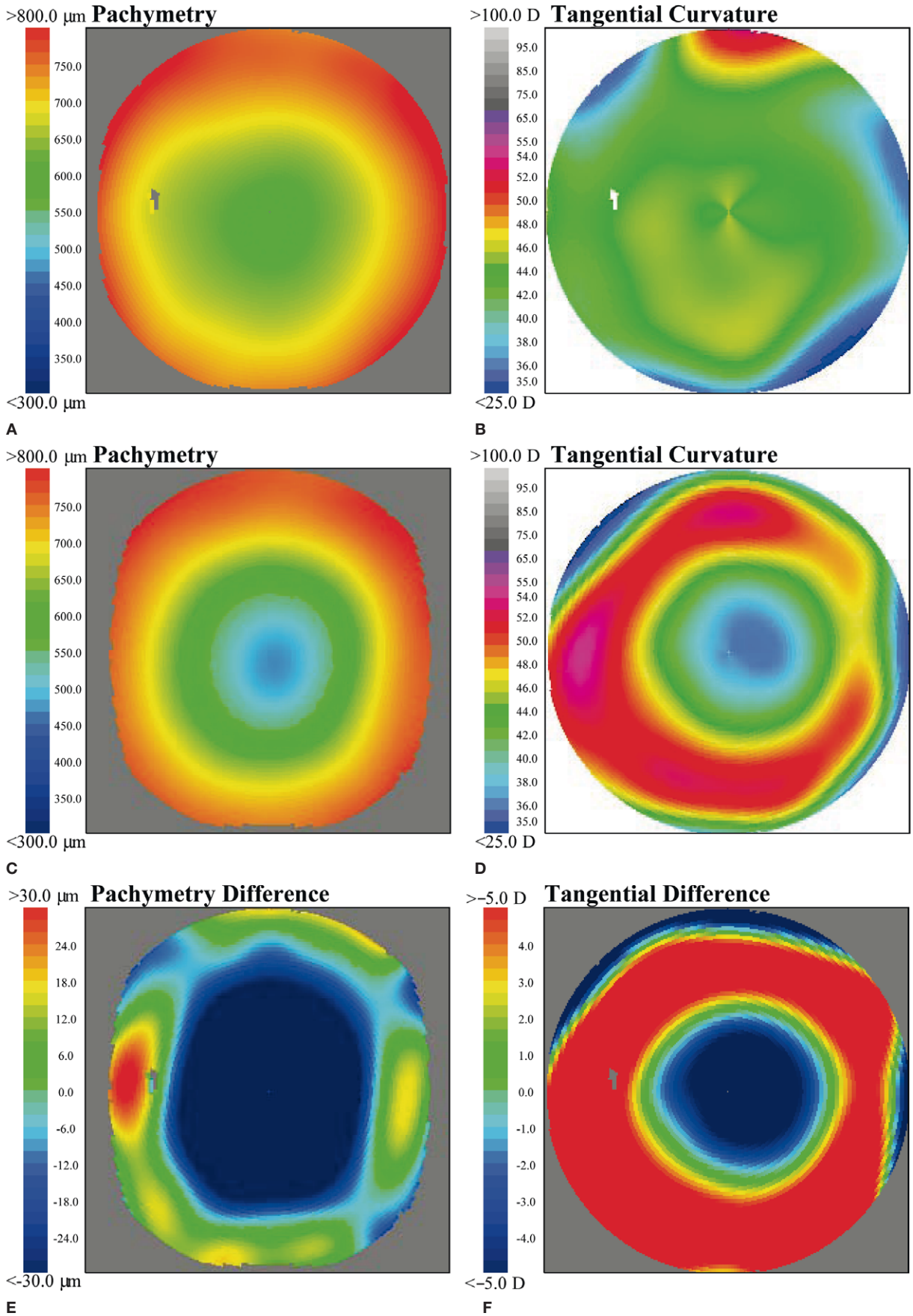

Figure 5.7. Topographic maps from a patient who received a conventional myopic LASIK procedure. The full diameter of the maps is 9 mm. *A,* Preoperative pachymetry map. *B,* Preoperative tangential curvature map. *C,* Postoperative pachymetry map. *D,* Postoperative tangential curvature map. *E,* Pachymetric difference map which shows a central decrease in thickness across the optical zone and a peripheral increase in thickness within the transition zone where ablation occurred. *F,* Tangential curvature difference map that shows a central decrease in curvature, along with biomechanically driven paracentral and peripheral increases in curvature (From Cynthia Roberts).

the response is dependent not only on the magnitude of the applied force, but also on the rate at which the force is applied. In other words, viscosity implies a delayed or time-dependent response. However, it is important to remember that in a viscoelastic material like the cornea, the resulting hysteresis is influenced by both the viscous and elastic components. Two corneas with the same level of hysteresis may be different in terms of elasticity and viscosity.

Corneal hysteresis is positively correlated with corneal thickness,[110] which indicates that a thicker cornea dissipates or absorbs more energy than a thinner cornea. This may be due to increased collagen content in a thicker cornea. However, the viscoelastic response of the cornea may be altered by pathology or surgery. Patients with keratoconus or Fuchs' dystrophy have been reported to have corneal hysteresis lower than that of normal eyes,[109] despite the vastly different corneal states. Keratoconic eyes are thinner than normal due to loss of collagen, and corneas with Fuchs' dystrophy are thicker than normal due to edema. It is interesting to note that thick normal corneas tend to have higher hysteresis, and thick edematous corneas tend to have lower than normal hysteresis. It is unlikely that the elastic and viscous components in keratoconic and Fuchs' corneas are similar, even with similar values of low hysteresis, due to the distinct structural characteristics. Further research is needed.

Excimer laser refractive surgery not only alters corneal thickness and curvature, it also modifies corneal biomechanical properties. Corneal hysteresis is significantly reduced after both surface ablation and LASIK.[111] The reduction in hysteresis is not predicted by the change in corneal thickness, and therefore may be attributed to a fundamental change in viscoelastic properties. The long-term effects of this modification in corneal properties are not yet known.

Early evidence indicates that corneal hysteresis correlates with visual field loss in glaucoma.[112] However, the nature of the association between properties of the cornea and damage at the back of the eye is not yet known. Understanding the importance of corneal biomechanical properties for diagnosis and treatment in disease states is in its infancy, due to recent development of the ability to measure corneal biomechanical properties in vivo.

Mechanical properties of the stroma account for the transparency, shape, and physical strength of the cornea. Corneal biomechanics can be altered in corneal diseases injury, and corneal surgery. Whereas most medical and surgical treatments of the cornea are geared toward the restoration of corneal transparency or shape, refractive surgery for the transparent cornea designed to change its shape has recently been introduced. The long-term stability and predictability of corneal refractive procedures have now become more prominent concerns. A better understanding of the corneal biomechanical response is essential, in addition to corneal pathology, for screening potential refractive surgery candidates, predicting corneal behavior, and achieving optimal visual performance.

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6 Stromal wound healing

Trevor Sherwin, Colin R. Green

The cornea has been described as an evolutionary compromise due to the diversity of the functional demands placed upon it. In order to fulfill these demands the cornea must remain transparent, refract light, contain the intraocular pressure, and act as a barrier to protect the eye from the surrounding environs, with each of these functions being provided by the highly specialized substructural organization.[1]

The stroma or substantia propria forms approximately 90% of the 600-μm thick cornea and is predominantly composed of an extracellular matrix arranged in lamellae running parallel to the corneal surface (Fig. 6.1). Interlaced within the matrix lamellae are layers of keratocytes whose primary role is to maintain the stroma. These cells are critical in the process of wound healing.

THE CORNEAL STROMA IN HOMEOSTASIS

MATRIX COMPONENTS

The cornea is mainly composed of an extracellular matrix with the two major constituents being collagen and proteoglycan. There are 19 known collagen types and the cornea expresses 10 of these plus some spliced variants[2] with type I collagen and type V collagen being the most abundant.[3] Two classes of proteoglycan are found within the stroma, those with keratan sulfate side chains (lumican, keratocan, and mimecan) and those with dermatan sulfate side chains (decorin).[2] The normally acellular Bowman's layer is a specialized condensation of the anterior stroma that contains type III collagen in addition to types I and V.[4]

KERATOCYTES

The keratocytes within the stroma appear sparse when examined within anteroposterior sections[3] (Fig. 6.1). However, labeling the cells of the cornea with a fixable live cell dye enables the cellular components of the stroma to be seen more clearly even within anteroposterior sections[5] (Fig. 6.2). 'En face' images of keratocytes reveal the highly connected nature of the cell syncitium and there are differences in cellular appearance depending upon their position in the anterior, mid-, or posterior stroma. These differences between the three keratocyte subpopulations identified are clearly illustrated in comparable high-resolution three-dimensional reconstructions of cells from each region (Fig. 6.3). Large, variably shaped, and orientated cell bodies and numerous short cell processes characterize anterior keratocytes. Together they form a variety of cell process to cell process, cell process to cell body, and cell body to cell body contacts that dominate the anterior stroma. In the central stroma, where cell density is clearly lower, cell bodies also show variable shape and orientation, and maintain some cell body to cell body contacts. However, continuity with adjacent keratocytes is largely maintained through an attenuated network of cell process to cell process contacts. The cell bodies of posterior keratocytes appear 'swollen' when compared to anterior and central keratocytes. They are fringed by a number of short cell processes and flat extensions of cytoplasm, which form thin fenestrated areas adjacent to parts of the cell body.[5]

NERVE ARCHITECTURE

The cornea is densely innervated by sensory fibers from the ophthalmic branch of the trigeminal nerve, which responds to mechanical, thermal, and chemical stimulation of the cornea. Individual nerve cells communicate via a range of both classical and peptidergic neurotransmitters. In the human cornea, many radially oriented nerve bundles enter the cornea via the sclera in the 9–3 h direction, bend 90° and pass through Bowman's layer (Fig. 6.4, *A*), then bend 90° again, before ramifying and ending within the epithelium as free nerve endings (mostly C-fibers). Corneal nerve architecture in humans has been studied using light and electron microscopy.[6–8] As elegant as these studies were, the intrinsic limitations of corneal tissue obtained from cadavers or enucleated eyes and the fragile nature of corneal nerves was illustrated by the fact that significant degeneration of sub-basal nerve bundles occurred within 13.5 h of death.[7] However, the advent of the in vivo confocal microscope led to the visualization of stromal and sub-basal nerves in living subjects (Fig. 6.4, *B* and *C*). Most recently, this technique has been utilized to map large areas of the sub-basal nerve plexus of the central and mid-peripheral human cornea in health[9] (Fig. 6.5) and disease.[10]

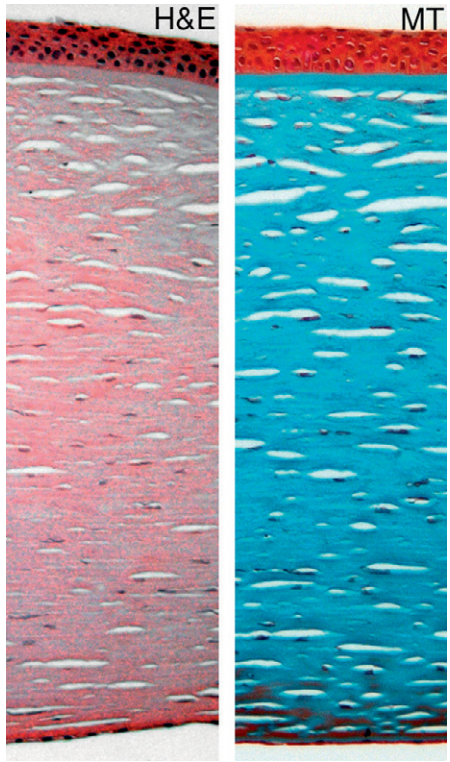


Figure 6.1. Classical hematoxylin and eosin stain (H&E) of an anteroposterior section of the human cornea showing the distinct layers that comprise this tissue. The epithelium consists of five to seven cell layers. The stroma, between Bowman's layer underlying the epithelium and Descemet's membrane above the single cell layer endothelium, makes up about 90% of the 600-mm thick cornea. Masson's trichrome (MT) illustrates that the blue stained stroma is predominantly composed of collagen. Stromal keratocyte density is seen to be greatest in the anterior stroma. The spaces evident within the stroma are a preparation artifact, but serve to illustrate the layered structure of the collagen lamellae.

STROMAL HEALING

CELLULAR RESPONSE

The response to any injury, which includes corneal surgery, involves four phases: (1) the removal of damaged tissue, (2) a proliferative and migratory phase, (3) a phase of repair and replacement, and (4) termination of the wound-healing process. The primary cellular change in response to injury or a surgical incision is the spreading death of keratocytes immediately adjacent to the wound site through apoptosis. Apoptosis is the programmed death of cells occurring without significant release of intracellular components that might damage the surrounding tissue. Apoptosis of keratocytes peaks at about 4 h but the effects may last up to 1 week after the incision. The loss of keratocytes from the stroma by these two processes can lead to an acellular zone that extends 200–300 μm from the incision.[3]

The subsequent cellular response is the appearance of inflammatory cells at the anterior end of the incision. These inflammatory cells, in or near vascular regions of the cornea, include macrophages, T cells, and polymorphonuclear cells that migrate into the corneal stroma from the limbal vessels, or it has been proposed possibly from the tear film.[11] Author citations differ as to the timing of the appearance of the inflammatory cells varying from 3.5 to 12 h.[3,11] However, infiltration already begins to resolve by 48 h.[3] These cells probably function in clearing the stroma of the apoptotic bodies and other cellular material left behind by the die back of keratocytes.[11]

Within 6 h after injury subtle changes are occurring in the keratocytes which border the acellular zone. The cells appear to increase in size mirrored by an increase in the number of phagosomes and vesicles and both the number and size of the nucleoli.[3] Most ribosomal RNA genes are located in specialized regions of chromosomes associated with the nucleolus, thus these changes are consistent with increased protein translation. The cytoskeleton is remodeled as the keratocytes appear to transform into fibroblasts with stress fibers containing actin (Fig. 6.6), nonmuscle myosin, and α-actinin becoming visible and the cell morphology changes into a more fusiform shape.[12,13] These repair cells migrate into the acellular zone within 24 h after insult and reach the edge of the incision by day 2. At approximately 72 h after injury the fibroblasts that have reached the wound edge begin to proliferate such that a fibrotic network of cells form parallel to the cut surface.[3]

Depending on the type of wound, myofibroblasts may appear characterized by the expression of α smooth muscle actin (α-SMA) and increased levels of cadherins and transforming growth factor β (TGF-beta) receptors. These cells are usually larger and contain more stress fibers and focal adhesions than fibroblasts.[14] The appearance of α-SMA is thought to impart greater contractile properties on the myofibroblast cells[15] and expression of α-SMA is concurrent with wound contraction. Myofibroblasts appear first under the epithelium[13,15] and then spread backwards to engulf the whole region under repair, tending to occur in highly fibrotic wound types associated with significant extracellular matrix deposition and extensive tissue contraction (Fig. 6.7).[16] The appearance of myofibroblasts within the cornea and their subsequent contraction are associated with opacity during repair.[17,18] As the wound is resolved the loss of myofibroblast markers within stromal cells is seen, followed by the loss of fibroblast markers. Cell numbers begin to decline and return to normal between 3 and 6 days post injury and gradually the cells at the wound site return to normal morphology and number.[3] From this point remodeling of the cornea begins to produce a mature and more functional scar.[14]

CYTOKINES

The cytokine family comprises several subclasses, including growth factors, interleukins, colony-stimulating factors, and interferons, and is responsible for a variety of biological responses, including cell growth, differentiation, inflammation, and wound healing. Cytokines are expressed by a mixture of diverse immune and non-immune cell types. These factors are ubiquitous throughout the human body tissues and have a plethora of roles that include extracellular matrix production, extracellular matrix degradation, and chemotaxis.[19]

The release of cytokines in response to a corneal wound is detected within minutes with the key regulator being interleukin-1 (IL-1). The release of IL-1 and tissue necrosis factor α (TNF-α) from compromised epithelial cells after injury has been implicated in the keratocyte apoptosis that follows.[20,11] However, the interactions are complex as IL-1 has also been shown to initiate increased keratinocyte growth factor (KGF) and hepatocyte growth factor (HGF) in the stroma and the keratocytes, now competent for IL-1 production, enter a self-perpetuating loop modulating this growth factor production.[3,20]

The response of the keratocytes at the periphery of the acellular zone following apoptosis, to transform and migrate and then to

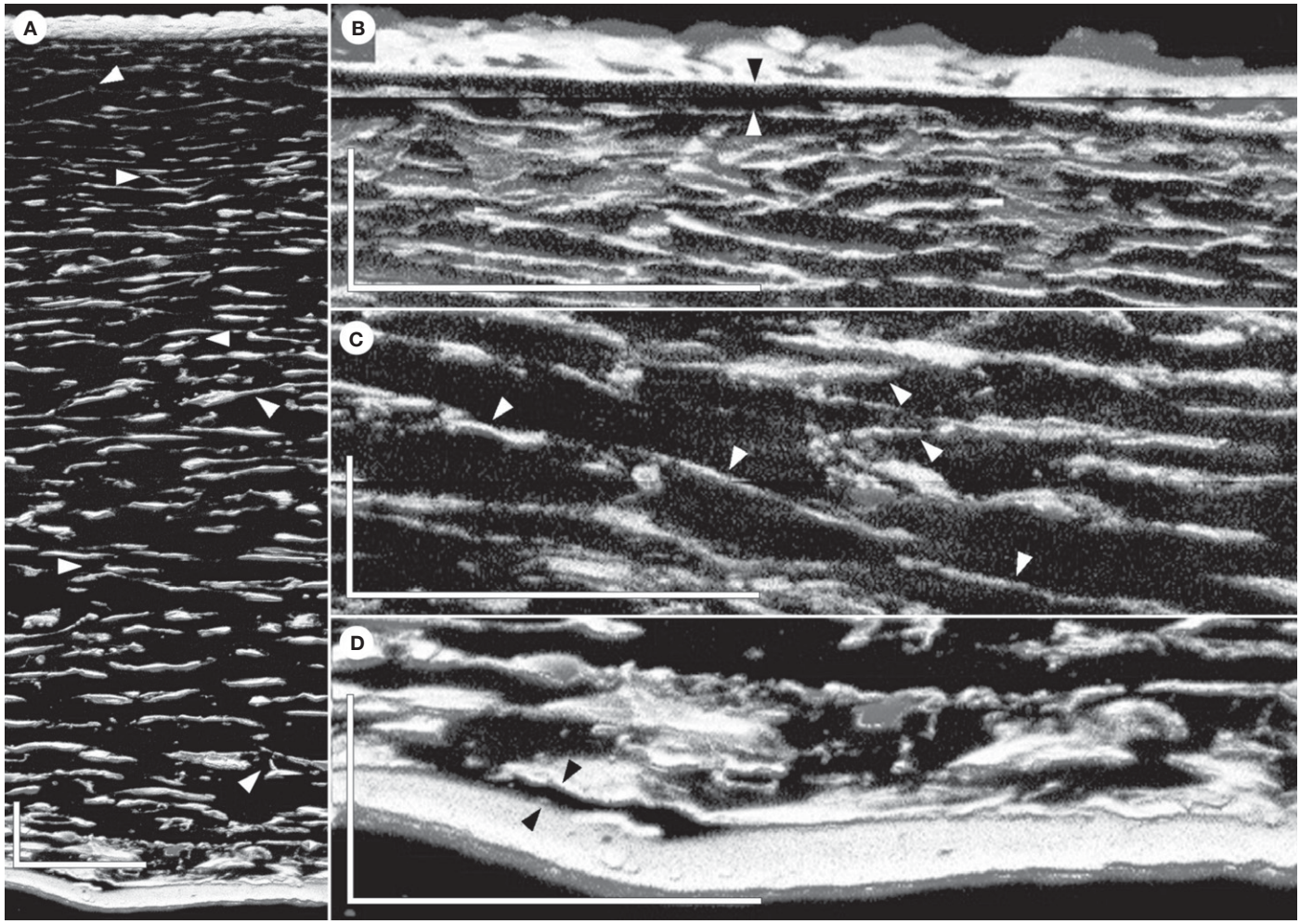


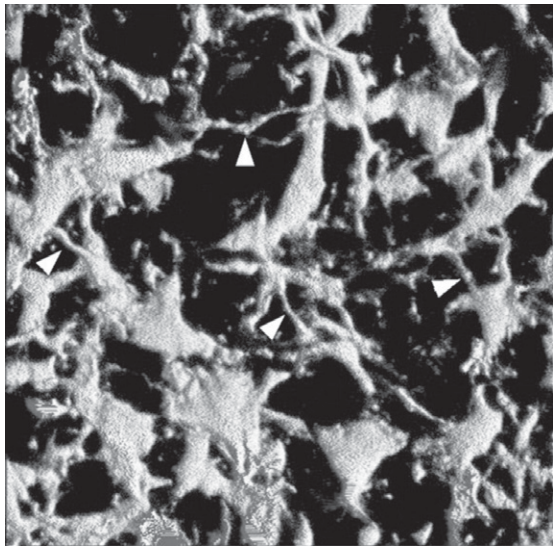
Figure 6.2. *A,* Human cornea visualized using a live cell tracker dye (CMFDA) in an anteroposterior direction. The light colored cells appear in layers interspersed with extracellular matrix (unstained), but processes appear to run between layers linking them (arrow heads). *B, C,* and *D:* higher magnification images at the anterior (*B*), mid (*C*), and posterior (*D*) levels of the stroma. Cell density is higher at the anterior level but the keratocytes here are finer in structure. Arrow heads in *B* indicate Bowman's layer. Arrow heads in *C* indicate cell to cell contacts between keratocytes and arrow heads in *D* indicate an extracellular matrix between a stromal keratocyte and Descemet's membrane. Note that Descemet's membrane shows positively with the cell tracker dye but is an acellular structure.[5] (Reprinted courtesy of Clinical and Experimental Ophthalmology.)

proliferate, is stimulated by the release of platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-beta) from the epithelium into the stroma.[3,11] PDGF along with epidermal growth factor (EGF) and insulin-like growth factor (IGF) have been implicated in the inhibition of apoptosis once healing is under way.[20,21] A significant increase in TGF-beta binding is initially observed at the wound margin, playing an important role in modulating the inflammatory response and in providing the stimulus for fibroblasts at low cell density to transform into myofibroblasts.[22] This latter transformation is enhanced with the interaction of PDGF.[23] Later in the healing cascade, fibroblast growth factor (FGF) has been observed to play a role in the latter stages of wound closure. In culture FGF has been shown to induce the conversion of myofibroblasts to fibroblasts,[22] a function seemingly supported by the fact that FGF inhibits TGF-beta expression,[24] which drives the transformation in the reverse direction. Whilst the above data seem to indicate specific roles for specific cytokines in corneal wound healing, the interactions between growth factors and cell, and growth factor to growth factor inevitably means that the right combination of factors needs to be expressed with spatial and temporal coordination to ensure correct wound healing.

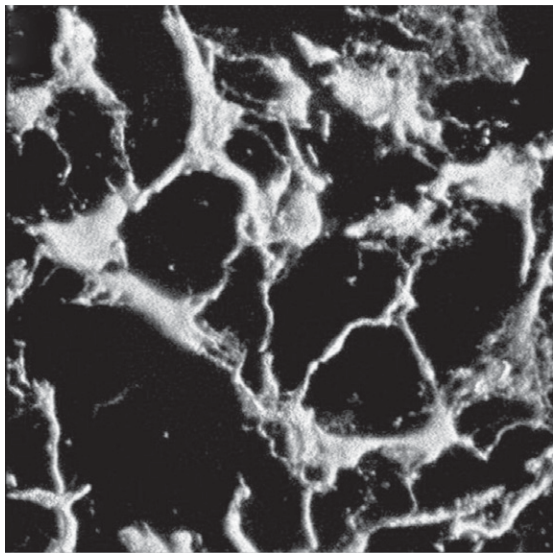
Several trophic factors have been identified within the human cornea, the most prominent of which is nerve growth factor (NGF), which has been shown to be essential in neuronal regeneration after injury.[25,26] However, NGF has also been shown to play roles in cell proliferation, migration, and differentiation in non-neural cells.[27–29] Indeed, topical NGF has been applied with success in human chronic corneal epithelial defects such as immune or neurotrophic ulcers[30,31] and been shown to accelerate the healing at the surgical incision site after cataract surgery.[32] Whilst this indicates a direct role for NGF in corneal wound healing by exerting an effect upon the non-neuronal cells, the relationship between the abundant corneal nerves, the non-neuronal cells with which they interact and NGF remains to be elucidated.

REMODELING OF EXTRACELLULAR MATRIX

Corneal wounds that enter the stroma require not only deposition of new matrix components but also the removal of old damaged matrix components and then extensive remodeling of corneal repair tissue. Initial phases of wound healing which involve the removal of damaged stroma is orchestrated by the plasminogen-activator/



A



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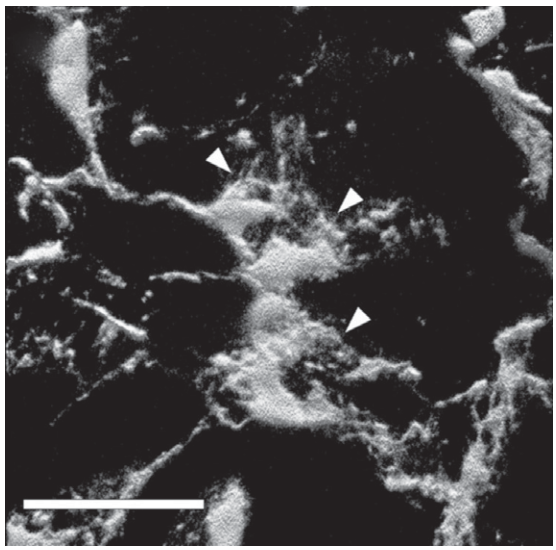

C

Figure 6.3. A detailed view of keratocytes in anterior (*A*), mid (*B*), and posterior (*C*) stroma shown using live cell tracker dye (CMFDA). Arrow heads in *A* clearly show fine cellular processes linking keratocytes and indicating that the tissue behaves as a syncitium. In *B* the mid-stroma is seen to be more sparsely populated. In *C* stromal keratocytes appear to form more cell body to cell body contacts, with arrow heads indicating fine fenestrae on the cell bodies.[5] (Reprinted courtesy of Clinical and Experimental Ophthalmology.)

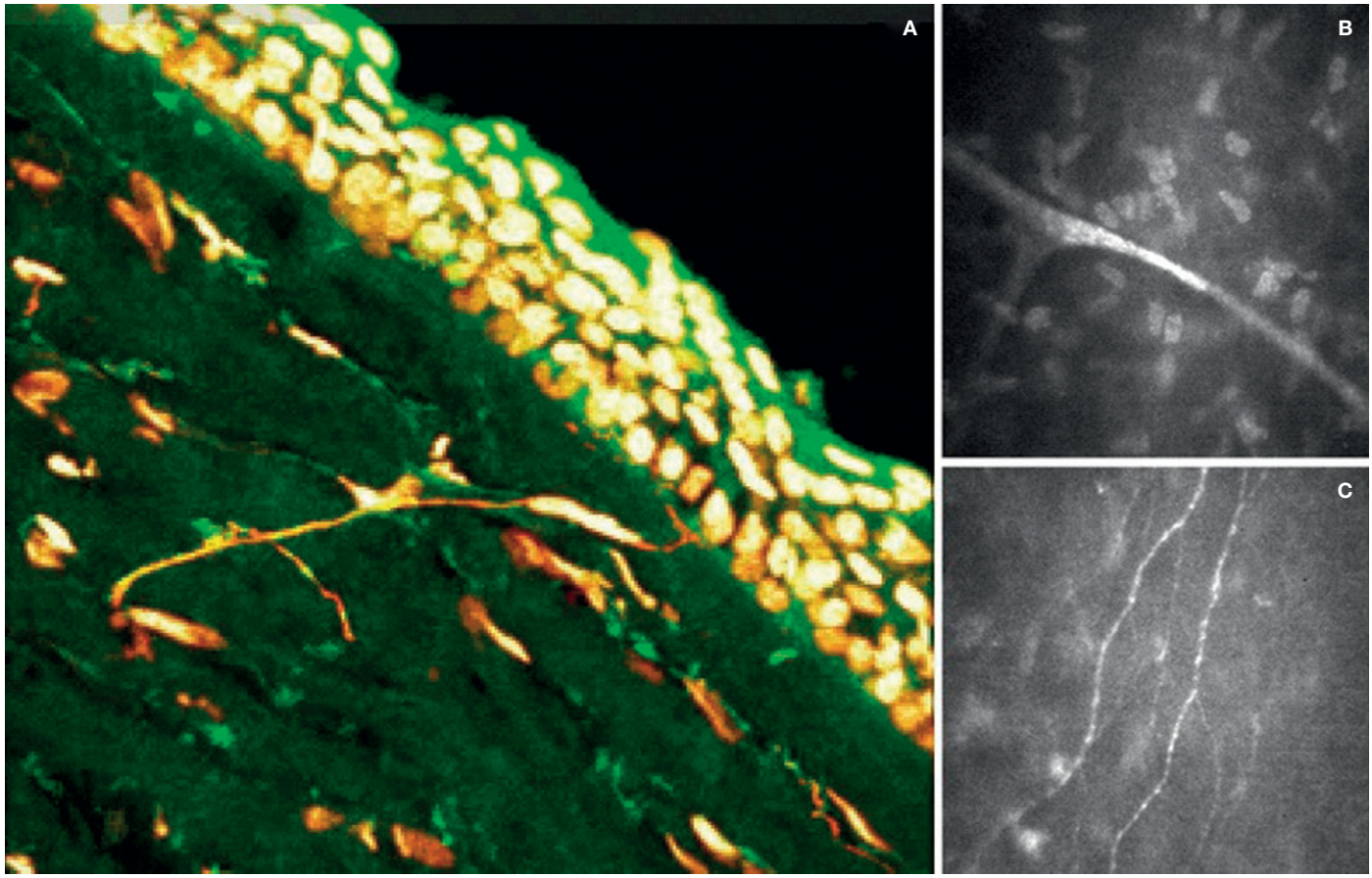

Figure 6.4. *A,* Immunofluorescence detection of stromal nerves and cell nuclei shows a nerve approaching and crossing Bowman's membrane before spreading along the basal layers of the epithelium. The nuclei of several stromal keratocytes can be seen in association with the nerve before it contacts the epithelium. Stromal nerves may provide a direct route of communication between keratocytes and epithelium. *B,* In vivo confocal microscopy of stromal nerves also shows association of keratocytes with the nerve axons. These axons give rise to the nerve fibers which form the sub-basal nerve plexus shown by in vivo confocal microscopy (*C*).

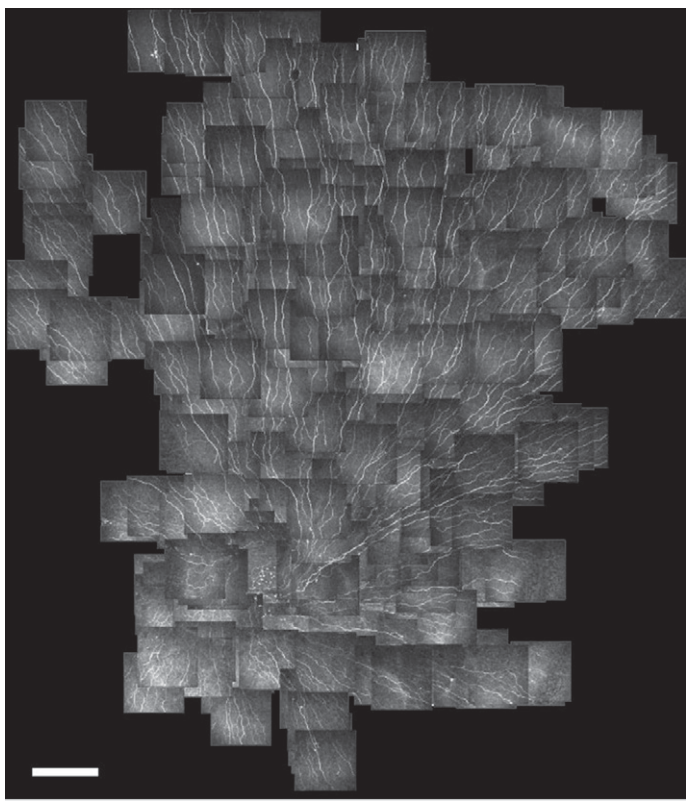

Figure 6.5. A montage of 315 in vivo confocal images depicting the architecture of the sub-basal nerve plexus of a single subject over the central and near peripheral cornea. Images were captured using the HRT II fitted with the Rostock corneal module. Scale bar, 400 μm.

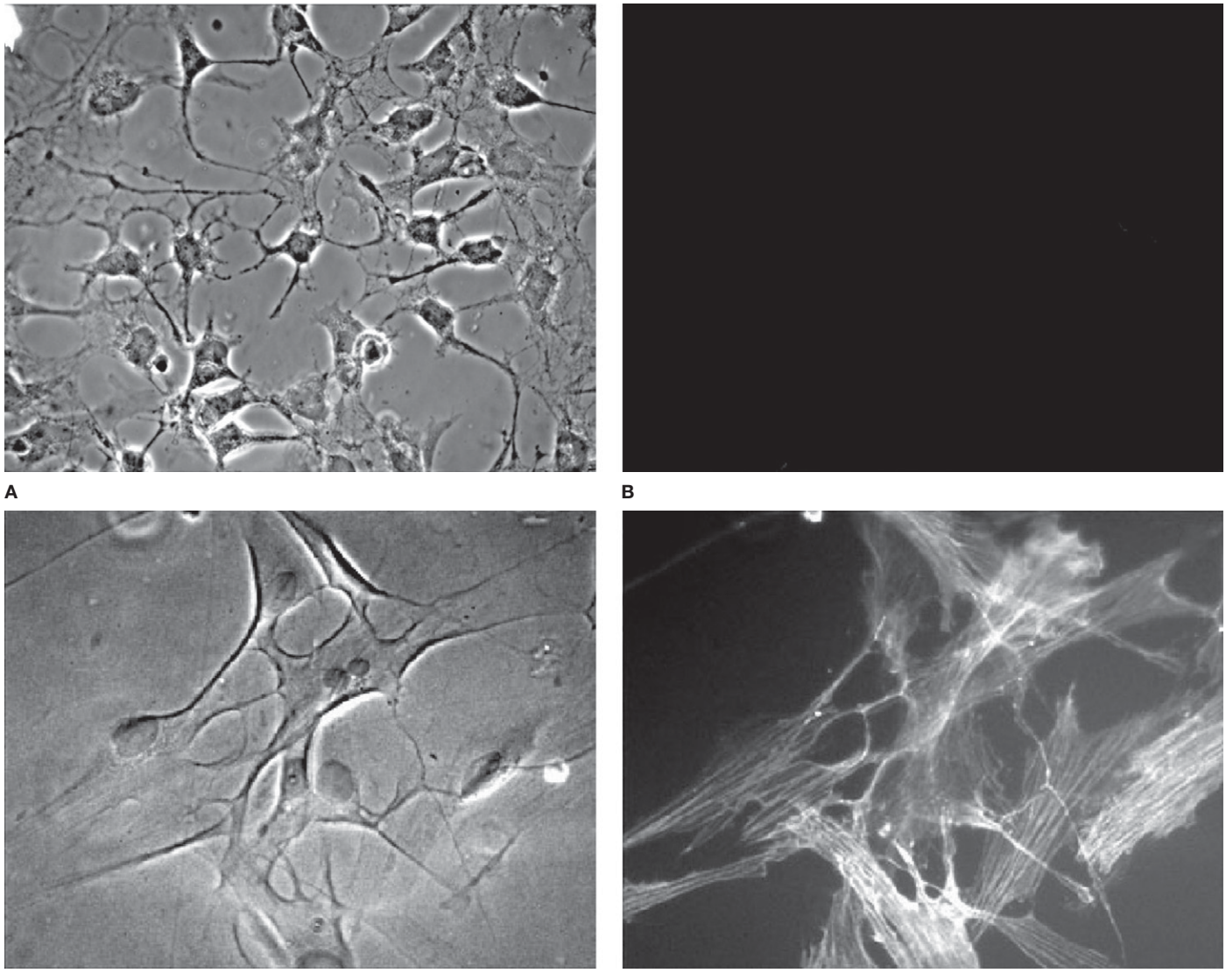

Figure 6.6. *A,* Human stromal keratocytes in culture retain their in vivo morphology with fine processes linking cells. *B,* Immunohistochemical labeling indicates that these cells are devoid of filamentous actin. Upon insult (serum addition) the keratocytes undertake a fibroblastic morphology (*C*) and have now assembled actin stress filaments in their cytoplasm (*D*).

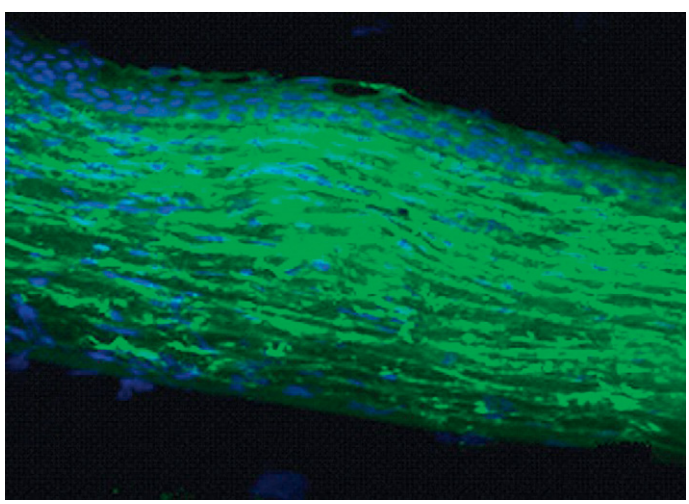

Figure 6.7. Alpha smooth muscle actin labeling myofibroblasts in the peripheral stroma of a laser-ablated rat cornea. The smooth muscle actin appears green with cell nuclei highlighted in blue. Even though the PRK ablation was in the central region of the cornea, keratocyte differentiation has occurred though the full thickness of the cornea peripheral to the wound site and the cornea has swollen to double its normal thickness.

plasmin system[33,34] and by matrix metalloproteinases.[35] Members of the family of zinc-containing endo-peptidases, the matrix metalloproteinases (MMPs), which are expressed at very low levels in normal tissue, have been implicated in the turnover of matrix components in corneal wound healing. The expression of MMPs is upregulated in response to inflammation and during remodeling of tissues in response to cytokines and growth factors.[36]

Only one MMP has been shown to be present in the intact normal cornea, namely MMP2, also known as gelatinase A, as these proteolytic enzymes were first named after the substrates that they cleaved. This enzyme is capable of cleaving fibronectin, denatured collagens, and basement membrane components, and has been detected in normal human corneal stroma. The origin of MMP2 in the stroma appears to occur in the most part by diffusion from the aqueous humor[37] but as little tissue remodeling is required in the quiet cornea the metalloproteinase is in its pro-enzyme form and associated with a specific inhibitor for MMP2, namely tissue inhibitor metalloproteinase 2 (TIMP2).

Studies comparing expression of MMPs in the stroma of corneal wound models compared with unwounded cornea found MMP 1 (collagenase), MMP3 (stromelysin-1), and MMP9 (gelatinase B) were all present 24 h after the wound was created but still absent from the unwounded cornea. MMP2 levels had significantly increased and now the enzyme was in an active form. Other studies have demonstrated MMP expression during the time course of repair tissue deposition and subsequent long-term remodeling.[38,39] The expression pattern of all four MMPs follows similar kinetics. For example, MMP1 increases 1.4-fold between 1 and 4 weeks after insult while cell numbers rise 4.5-fold. Between 4 and 8 weeks after injury, the MMP1 level drops 4.2-fold while cell number decreases by only 1.8-fold up to week 10. This shows that MMP1 levels are not related to stromal cell numbers but are being regulated temporally. Of interest is the fact that nonsteroidal anti-inflammatory drugs (NSAIDs) do not downregulate MMP gene expression, with MMPs 1 and 8 being expressed in increasing amounts in ulcerative keratolysis from topical NSAID use.[40] In photorefractive keratectomy (PRK) treatment, a fast wound-healing process was found to be associated with very high levels of MMP8 and membrane type 1-MMP (MT1-MMP)[36] and their activation, suggesting a role for MMP8 and MT1-MMP in the corneal wound healing cascade. In skin wounds the activation of MMP2 has been correlated with the expression of MT1-MMP,[41] which could signal a joint role in corneal wound healing.

EXTRACELLULAR MATRIX MOLECULES

The stromal fibroblasts and myofibroblasts are responsible for stromal remodeling after wounding through the production and resorption of collagen and the production of glycosaminoglycans.[2,36] The provisional corneal wound matrix produced is rich in fibronectin and chondroitin sulfate, which enhances the migration of repair fibroblasts into the wound area.[42] In contrast to the upregulation of chondroitin sulfate proteoglycan is the decrease seen in the levels of keratan sulfate proteoglycan in the wounded stroma.[43] The deposition of fibronectin in the provisional matrix is mirrored by the repair fibroblasts turning on the synthesis of the $\alpha 5$ integrin chain to form the $\alpha 5\beta 1$ integrin heterodimer, classically defined as the fibronectin receptor. It has been proposed that acquisition of this receptor allows focal adhesions to fibronectin and thus may contribute to the ability of the fibroblast to migrate on the fibronectin-rich provisional matrix.[44] Using in vitro models of human corneal fibroblasts in collagen gels, it has also been demonstrated that the presence of fibronectin or vitronectin was required for contraction of the collagen gels.[45] Molecules which are normally present only in the basement membrane also seem to be deposited within the provisional stromal matrix, including type IV collagen, type VII collagen, and laminin.[2] After formation of the provisional matrix the remodeling phase begins as the initial provisional matrix that results in scarring is gradually replaced with matrix that will be more functional in terms of optical quality. This matrix contains type I and type III collagen that were not part of the provisional matrix. Thus, it is suggested that the provisional matrix, which is rich in fibronectin and chondroitin, promotes the entry of migrating repair fibroblasts into the wound site and also may promote the contractile functions of the myofibroblast aiding in pulling wound edges together. Upon reversion to normal keratocyte phenotype the scar tissue is gradually remodeled over a period of years in an attempt to restore optical quality.

COMPARISON WITH SKIN WOUND HEALING

The tissue model used for many wound-healing studies has been the skin. Due to the similarities between skin and cornea—both are composed of a collagenous stroma with the corneal stroma being the equivalent of the dermis in skin, and both are overlaid with a squamous epithelium—it is not surprising that the knowledge gained from skin wound healing has largely proved directly transferable to the cornea, the most significant difference being the limited number of cell layers (five to seven) in the corneal epithelium. The corneal keratocytes and skin fibroblasts play similar roles, and undergo similar phenotypic changes during wound repair to close the wound (differentiating into myofibroblasts) or to lay down scar tissue. Many of the cytokines involved in wound repair are duplicated, such as TGF-beta3 which has been the focus of therapeutic intervention in both tissues. However, there are also differences in the wound healing process that exist both due to anatomical differences and also probably due to the need to maintain the function of the cornea, especially its transparency. One major factor contributing to corneal transparency is the precision with which the stromal matrix is ordered. First, the collagen fibrils are composed of heterodimers of type I and type V collagens, which allows a very narrow fiber diameter. Second, type VI collagen is present within the cornea at unprecedented levels. This type of collagen is not located within the fibrils themselves, but instead forms thin filaments with a 100-nm periodicity.[46,47] These type VI collagen filaments have been shown to run alongside and between the collagen fibrils[48] and are thought to interact with stromal proteoglycans within the interfibrillar matrix to determine the interfibrillar distance of the collagen fibrils.[49] The emergence of new collagen types such as type XII collagen that has been shown to be present in the quiescent stroma may play a role in the arrangement and assembly of the collagen fibrils.

SURGICAL WOUNDS: HEALING AND VISUAL OUTCOMES

SUTURED AND UNSUTURED WOUNDS

Penetrating keratoplasty is historically the oldest, the most common, and the most successful form of transplant procedure performed

worldwide. Two forms of suturing are used to secure the tissue in place, continuous and interrupted, and surgeons variously use one or both. The presence of sutures within a surgical corneal wound provides several beneficial functions. Firstly, the suture brings together the edges of the wound, eliminating empty space, thus minimizing the distance that repopulating cells (fibroblasts) must travel. Secondly, the suture limits epithelial ingrowth and thirdly it provides immediate tensile strength. Finally, sutures act as an inflammatory stimulus for leucocytes and macrophages which assist healing and also provide substrata along which these cells may move.[50] Modern cataract surgery now routinely uses the corneal step method, which uses intraocular pressure to seal the unsutured wound and the corneal flap created during LASIK refractive surgery also remains unsutured.

Comparative studies on deep sutured and unsutured wounds in a primate corneal model and observation of human tissue postmortem that had undergone previous surgery revealed some interesting findings.

Sutured wounds were found to (1) lack epithelial plugs, (2) exhibit more complete healing, (3) display substantial sub-epithelial fibroplasia with a hypertrophic scar, and (4) display fibroblasts and lamellae that spanned across the wound. Similar wounds that were left unsutured displayed (1) prominent, chronic epithelial plugs (Fig. 6.8), (2) less complete healing, (3) a lack of sub-epithelial fibroplasia, and (4) fibroblasts and lamellae that ran parallel to the wound edge.[51]

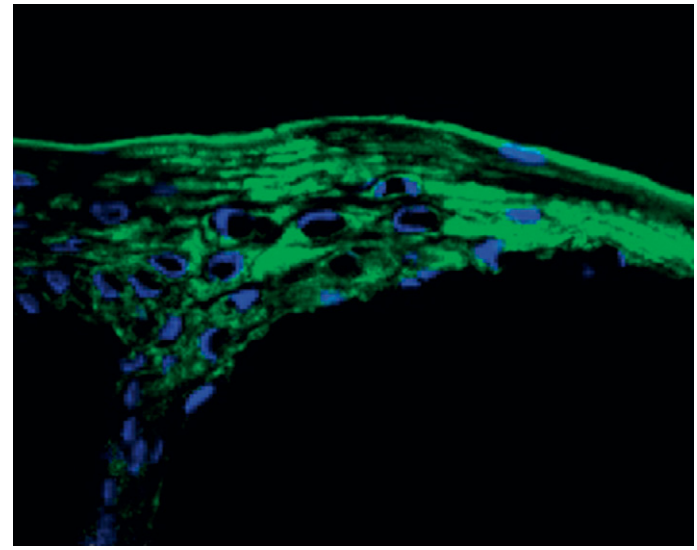

Figure 6.8. The formation of an epithelial plug, which serves to fill unwanted tissue gaps and provide a smooth ocular surface, is a common postsurgical occurrence of unsutured corneal wounds. The figure depicts an in vitro model of unsutured corneal wounds that forms perfect epithelial plugs, seen here immunolabeled for keratins 3 and 12 (green) and counterstained with DAPI to show nuclei (blue).

PENETRATING KERATOPLASTY

The healing of a human corneal wound does not occur by the reanastomosing of the cut ends of collagen lamellae within the stroma. Rather, healing occurs by the deposition of a provisional matrix within the wound site, which intercalates with the existing lamellae.[2] Thus the physical architecture of the wound in penetrating keratoplasty (or any other incision for that matter) will play a role in the healing process. Often the donor and recipient corneas are not cut so that the edges lie at 90° to the cut surface but rather to form a trapezoid with the longer of the parallel sides at the corneal surface (Fig. 6.9). The recovery of tensile strength within the wound has been shown to be slow in animal models, with tensile strength being 8, 36, and 50% of normal at days 10, 40, and 100, respectively. However, in humans the recovery is even slower with 50% of normal corneal tensile strength being reached between 2 and 3 years postoperatively.[52]

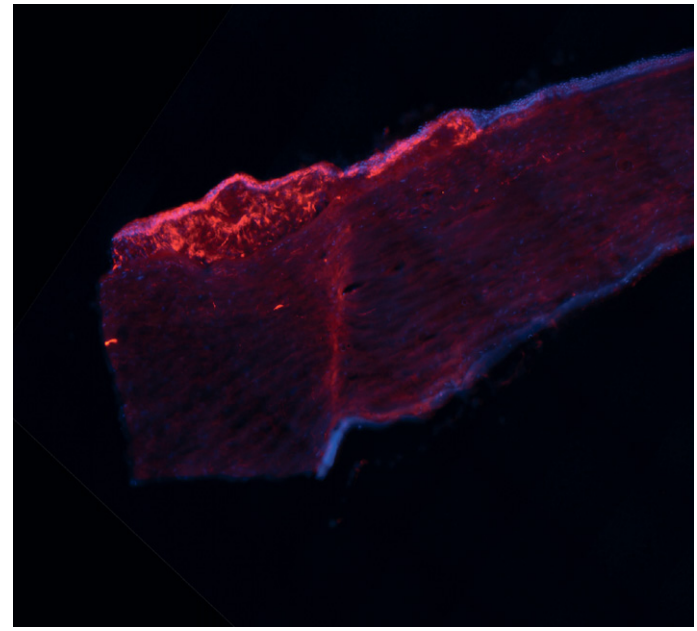

Figure 6.9. The host–graft junction of a cornea from a 70-year-old female grafted 10 years previously for keratoconus, and now being regrafted for progressive astigmatism. The graft had no previous history of rejection and exhibited no vascularization. The grafted cornea, fixed, frozen, and crysectioned, has been stained for actin and counterstained with DAPI to show the nuclei. Of interest is (1) the host–graft junction interface which is not perpendicular to the corneal surface, (2) the presence of actin positive cells (fibroblasts) at the interface 10 years post-graft, and (3) the disrupted nature of the epithelium from the recipient spilling across the junction to involve the epithelium on the graft.

REFRACTIVE SURGERY

The cellular response to refractive surgical techniques, PRK and LASIK have been analyzed in a rabbit model.[53] This study found that there was increased keratocyte apoptosis, keratocyte proliferation, and myofibroblast generation in PRK for high myopia in comparison with LASIK for high myopia or PRK for moderate myopia. In LASIK eyes, keratocyte apoptosis and proliferation occurred within the stroma above and below the lamellar interface of the flap. In contrast, in corneas after PRK procedures, keratocyte apoptosis was observed in the anterior stroma with proliferation occurring in the posterior and peripheral stroma. No generation of myofibroblasts was observed in the central cornea of eyes after LASIK for high myopia or PRK for moderate myopia. The authors suggested that the proximity of the stromal cellular processes to the overlying epithelium in PRK treatment facilitates the generation of

myofibroblasts and other healing processes. Further noted was the agreement of the above rabbit data with the low incidence of haze noted in LASIK or low myopia PRK treated human corneas.[54–56]

A recent study examined corneal wound healing after LASIK where the corneal flap was created using a conventional mechanical microkeratome versus a femtosecond laser.[57] The study found no difference in keratocyte activation or migration between the two techniques, but the authors did note a modulation of wound healing at the flap edge. It was noted that the flap edge produced by the femtosecond laser was more defined than the edge produced by the mechanical microtome, the latter of which also showed epithelial cell invasion rather than the epithelial plug seen in the femtosecond laser flap. At the 2-month examination of the microkeratome group, the epithelial cells had disappeared, leaving an irregular zone of fibrotic wound healing. In the femtosecond laser group at the 2-month examination, the stroma adjacent to the flap was hyperreflective, suggestive of a wound healing process, but no activated or abnormally large keratocytes were present. The authors suggested that the more abundant fibrotic tissue in the femtosecond laser group was due to the precision cutting of the laser. In the microkeratome flap the cut edge resembles an incision wound, producing tighter fitting edges on contact, whereas the femtosecond laser flap produces a gap which is filled by an epithelial plug producing a greater interaction between epithelium and stroma, thus producing greater scarring. The femtosecond laser is said to create greater corneal stromal inflammation than the mechanical microtome up to 24 h postoperative, but a stronger flap adhesion.[58]

EMERGING AND FUTURE TECHNOLOGIES

STEM CELLS FOR STROMAL REPAIR

Pluripotent stem cells provide a source of cells for corneal stroma repair and engineering in vivo. They undergo asymmetric differentiation to reproduce themselves and progenitor cell offspring with high fidelity and potency. They usually reside in protective niches such as hematopoietic stem cells in the bone marrow, or limbal epithelial stem cells in the palisades of Vogt at the limbal rim (see Ch. 12.6 for further details on epithelial stem cells). Although still poorly understood, both limbal epithelial stem cells[59] and stromal stem cells[60] express putative stem cell markers such as ABCG2, p63, and PAX6, and lower levels of the gap junction protein connexin.[43] Stromal stem cells have only recently been identified,[60] residing near the highly vascularized limbal rim. As with limbal epithelial stem cells, they are label retaining owing to a slow cell cycle time and can therefore be isolated in a fluorescent activated cell sorter as a specific side population.

Autologous stem cell transplantation has proven to be a very effective surgical procedure for the restoration of badly damaged ocular surfaces.[61] Harvesting sufficient numbers of cells can result in deficiency in the donor eye[62] but may in the future be overcome by culturing holoclone balls providing a source of pluripotent cells for transplantation. The success rate for allogenic transplantation for bilateral injury or disease remains low despite the administration of immunosuppressants[63,64] but provides promise for the future, not only the cornea, but also for other tissues. Limbal epithelial stem cells transplanted into damaged retina are able to differentiate into a neuronal phenotype[65] and may play a role in stromal repair where epithelial–keratocyte interactions are important.[20] Stromal stem cells are also pluripotent, for example expressing cartilage-specific markers such as cartilage-oligomatrix protein, aggrecan and type II collagen under chondrogenic conditions, and glial fibrillary acidic protein, neurofilament protein and beta-tubulin II when grown in neurogenic culture medium.[60] Although hematopoietic stem cells may provide a source of keratocytes for stromal repair,[66] the stromal stem cells appear to be the first to be identified with truly keratocyte progenitor potential providing a possible resource for stroma cell-based therapy and tissue engineering.

GENE THERAPY AND GENE REGULATION

By 2005 technological advances had enabled more than 300 phase I and II gene-based clinical trials, but few have been applied to the cornea.[67] Yet the cornea is ideally suited for gene regulation, being readily accessible and immune-privileged. Wound healing with growth factors, for example, has had limited benefit owing to the vast soup of factors involved (over 3500 genes are significantly altered when a tissue is damaged[68]). The length of delivery, timing of application, and expense of production are important, but an overriding factor is the effective delivery of factors with sufficient bioavailability. Gene therapy and gene regulation protocols (ranging from transient antisense or RNAi strategies to stable viral transfections) offer a possible solution. Originally developed to correct heritable gene defects,[69,70] gene therapy is defined as a treatment based upon introduction of genetic material to provide therapeutic benefit, directly by the expression of a gene product, or indirectly by inducing translation of an antagonist or modifier product. In its wider sense, 'gene therapy' may include regulation of gene products at the mRNA level (antisense genes, RNAi, siRNA, antisense oligonucleotides, morpholinos, deoxyribozymes) although most of these do not necessarily involve stable transfection of genetic material. Methods of gene delivery may involve liposomes, electroporation, direct injection, coated particle bombardment, or viral techniques (such as viral vectors, recombinant adenoviruses, and retroviruses—for full review see ref. 71). Gene therapy has the potential to reverse myofibroblast differentiation using FGF-1 or FGF-2[22] or to inhibit the expression of TGF-beta to reduce postoperative scarring and PRK-induced corneal haze.[72] A plasmid vector-encoding tissue plasminogen activator (tPA) has shown promise in reducing fibrin formation, the biologically active tPA being detected for 4 days after vector application[73] and gene transfer of a TGF-beta type II receptor to block TGF-beta activity has inhibited corneal opacification, edema, and angiogenesis.[74] For disease conditions such as keratoconus, a strong increase in the Sp3 short isoform and a lack of the Sp3 activator long isoform causes a total absence of the nerve growth factor (NGF) receptor TrkA (and decreased levels of NGF itself along with reduced p75 neurotrophic receptor levels).[75] The possibility exists for future gene therapy for diseases of this type.

COMPONENT SURGERY AND CORNEAL ENGINEERING

Penetrating keratoplasty is the current treatment of choice for irreparably damaged corneas. The success rate is high owing to the low incidence of immunogenic rejection although once rejection does occur, secondary procedures are inevitably less successful. Furthermore, with alkali burns, immunological disorders, severe dry eye, stem cell deficiency, vascularization, ocular diseases such as Stevens–Johnson syndrome or neurotrophic scars secondary to herpes zoster ophthalmicus, penetrating keratoplasty may not be tolerated. Recent trends to replace only the essential tissues or cells, termed 'component surgery', help to reduce the risk of rejection and

may yield better refractive outcomes. Where surgery is required to repair stromal dystrophies, damage to the endothelium can be avoided reducing the risk of complications. Component surgery may include the epithelium, epithelial or stromal stem cells, portions of the stroma itself, or the endothelium. Tissue components may be transplanted as sheets using carriers or scaffolds, or as lamella sections (for review see ref. 76). Several procedures such as amniotic membrane carriers for the epithelium, endothelial lamella keratoplasty, and deep lamella keratoplasty are already in clinical practice. Epithelial sheet transplant has proven successful for burns, ocular surface diseases such as Stevens–Johnson syndrome, and ocular cicatricial pemphigoid.[77] Epithelial sheets are most commonly grown on amniotic membranes in air–liquid interface cultures using 3T3 feeder cells and are then applied to provide stromal covering and repair. These epithelia become multilayered and show differentiation through the layers, including expression of epithelial markers such as keratins 3 and 12.[78,79] Polymers and extracellular matrices have also been used; whether all of these cultured epithelial sheets contain cells with stem-like properties remains unresolved. In lamellar keratoplasties irregularities in the surface being grafted onto can leave haze, and keratomes that create lamellar flaps or caps are favored. Deep lamellar excisions to the level of Descemet's membrane is a relatively newer procedure[80] although perforation of Descemet's membrane remains the most common complication, occurring in approximately 30% of cases.[76] For endokeratoplasty, inclusion of Descemet's membrane and some deep stroma preserves the anterior corneal curvature reducing changes in astigmatism or refraction. Again, use of a microkeratome to prepare both host and donor tissues creates a smooth interface with better outcomes.[81]

Penetrating keratoplasty or component surgery are, however, both limited by the availability of suitable donor tissue with waiting lists exceeding 2 years now common in the USA.[82] This issue is further exacerbated by diseases such as HIV and hepatitis C, and by the increased use of LASIK corrective surgery, which renders the cornea unsuitable for grafting.[83] The development of keratoprostheses and tissue-engineered corneas has been rapid, especially since 2000.[84] The highly organized stroma, with over 300 highly ordered layers, represents a special challenge if the transparency of the cornea is to be maintained. Synthetic materials are readily available, have good optical properties, reduce the risk of disease transfer, and no postoperative remodeling is required.[85] However, biodegradable polymers are generally not suitable if they are to retain transparency,[86] and artificial materials must also be nontoxic, oxygen and nutrient permeable, and must avoid triggering an immune or inflammatory response that could lead to biodegradation, calcification or tissue melting.[85,87] Some keratoprostheses have now been in use since the 1990s (such as the Dohlman–Doane keratoprosthesis[88]) but complications are not unusual with artificial devices, including glaucoma, retroprosthetic membrane, melting, retinal detachment, and endophthalmitis.[89] As a result, there is a growing interest in cell-based engineered tissue replacements that mimic the structure and functions of the natural cornea. It is expected that cell-based engineering will ultimately lead to corneal substitutes that will play an important role in corneal healing and stromal repair. As noted above, the recent discovery of stromal stem cells[60] and the pluripotency of limbal epithelial stem cells offers numerous possibilities for tissue engineering, including autologous tissue engineering, provided the correct substrate and medium is provided. The multiple use of limbal rims returned from transplant surgery is especially appealing provided suitable matrices can be identified for cell population from the limbal rim. Currently, natural biopolymer hydrogels such as those based upon alginate, chitosan, agarose, and collagen are favored and have been shown to support three-dimensional growth of cells.[84] Since 85% of the stroma is extracellular matrix, the majority of studies have used gels based upon these components (primarily type I collagen, chondroitin sulfate, and heparin sulfate). One of the limiting factors has been the mechanical properties of the matrices used, with higher collagen concentrations and cross-linking techniques used to improve these.[82] Possibly owing to the poor mechanical properties of bioengineered corneas or corneal tissue for stromal wound repair, few tissue-engineered cornea research groups are seeking clinical application.[84] However, the potential of stem cell research coupled with advances in gene therapy, tissue engineering, and advanced corneal surgery provides a positive future for the corneal surgeon.

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7 Corneal endothelium: structure and function in health and disease

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INTRODUCTION

The cornea covers the anterior one-sixth of the circumference of the globe. It is a clear, transparent, avascular structure richly supplied with sensory nerves in the anterior third of the corneal stroma. In fact, the corneal sensory nerve endings are found in the epithelium and they subserve touch and pain sensations. There are no lymph vessels or other channels for bulk fluid flow. The interface between the corneal tear film and the ambient atmosphere provides roughly two-thirds of the refractive power of the human eye. It, therefore, is a common point where medical (e.g. contact lenses) or surgical (e.g. laser in situ keratomileusis (LASIK) or surface ablation) interventions are performed to improve refractive errors. Much of its oxygen requirement for metabolic activities comes from the atmospheric oxygen dissolved in the tear film.[1] When the eyelids are closed, oxygen can also enter the tear film from the superficial conjunctival capillaries. Most nutrients such as carbohydrates, vitamins, amino acids, and other substrates are primarily delivered to the cornea through the leaky corneal endothelial barrier with a minor contribution from the vascular arcades of the limbus. Certain growth factors, immune constituents, or other substrates, like retinol (prevents epithelial keratinization), are secreted by the lacrimal gland and delivered to the cornea by the tears. Carbon dioxide and other metabolic end products are removed across the corneal endothelium to the aqueous humor, by the tear film, or through the limbal capillaries. The cornea itself is resilient, yet is described as viscoelastic in its response to stretching forces. Due to its avascular nature, the human cornea heals in a limited primitive fashion to injury,[2] albeit epithelial–stromal interactions and fibrous metaplasia of the corneal endothelial cells will result in localized areas of stronger fibrotic wound healing.

Although other cell types do exist in the cornea, like Langerhans and dendritic bone marrow-derived immune cells, trigeminal nerve dendrites, Schwann cells, and histiocytes, the human cornea is primarily composed of three cell types: epithelial cells, stromal keratocytes, and endothelial cells.[1] They all can replicate under mitosis, but they vary significantly in their in vivo self-mitotic capacity (proliferative capacity) with epithelial cells being the most renewable, stromal keratocytes being in the middle, and endothelial cells being the least renewable. This fact is seen clinically when epithelial cells can completely regenerate after injury (e.g. corneal abrasions) or can develop into cancer (e.g. squamous cell cancers that originate from limbal progenitor cells, or stem cells, at the Pallisades of Vogt), while endothelial cells are most commonly involved in age-related (e.g. Fuchs' dystrophy) or injury-related disease (e.g. pseudophakic bullous keratopathy), ultimately resulting in corneal edema and bullous keratopathy.

The limited proliferative capacity of human corneal endothelial cells apparently is only an in vivo phenomenon as endothelial cells can proliferate quite well in ex vivo cell culture conditions.[3–5] The in vivo mitotic quiescence of human corneal endothelium has been found to be predominantly due to cell contact inhibition, in part through the activity of p27.[3] This results in corneal endothelial cells being arrested in the G1-phase of the cell cycle.[4] High aqueous humor concentrations of TGF-beta2 along with age-related cellular senescence and lack of an injury-inducible cytokine-stimulating pathway are secondary fail-safe mechanisms that also suppress in vivo endothelial cell proliferation if cell-to-cell contact is compromised (e.g. endothelial cell damage).[3,4]

The purpose of this chapter is to describe the structure and function of the corneal endothelium in health and disease. Moreover, common potential endothelial stressors will be discussed, such as contact lenses and commonly practiced surgical procedures.

MICROSCOPIC ANATOMY, ULTRASTRUCTURE, AND PHYSIOLOGY

EMBRYOLOGY TO BIRTH

Although embryologic eye development begins at 4–5 weeks of gestation (27–36 days) during lens vesicle formation, the development of the corneal endothelium only occurs by the end of this time period when the first wave of neural crest-derived mesodermal cells begin to extend beneath the corneal epithelial cells from the

limbus at around 5 weeks of gestation (33 days). These cells form the primitive endothelium, which is initially composed of two-cell layers. By 8 weeks of gestation, a monolayer of cells is formed that starts to produce Descemet's membrane. The epithelium and endothelium remain closely opposed until 7 weeks of gestation (49 days) when a second wave of mesoderm begins to grow centrally from the limbus between the epithelium and endothelium producing the corneal stroma. By the third month of gestation, Descemet's membrane can be clearly recognized on histologic sections. By the seventh month of gestation, the cornea resembles that of the adult in most structural characteristics other than size. At birth in the full-term infant, the horizontal diameter of the cornea is only around 9.8 mm (surface area 102 mm^2), or approximately 75–80% of that of an adult human cornea (note that the posterior segment is <50% of adult size at birth). Additionally, at birth, the cross-sectional thickness of the epithelium averages 50 μm, the Bowman's layer averages 10 μm, the central cellular corneal stroma averages 450 μm, Descemet's membrane averages 4 μm, and the endothelium averages 5 μm thick.

INFANCY TO ADULTHOOD

The endothelium of the infant cornea is composed of a single layer of approximately 500 000 neural crest-derived cells, each measuring around 5 μm in thickness by 20 μm in diameter, covering a surface area of 250 μm^2.[6,7] The cells lie on the posterior surface of the cornea and form an irregular polygonal mosaic. The tangential appearance of each corneal endothelial cell is uniquely irregular, usually uniform in size to one another, and typically six-sided hexagons (which is the most energy efficient and optimal shape to cover a surface without leaving gaps).[8] They abut one another in an interdigitating fashion with a 2–4-nm wide extracellular space between each other. The extracellular space is known to contain discontinuous apical tight junctions (macula occludens) and lateral gap junctions (Fig. 7.1), thereby forming an incomplete barrier to the diffusion of small molecules. As corneal endothelial cells have numerous cytoplasmic organelles, particularly mitochondria, they have been studied and found to have the second highest aerobic metabolic rate of all cells in the eye next to retinal photoreceptors.[6] At birth, the central endothelial cell density of the cornea is around 5000 cells/mm^2.[7] Because the corneal endothelium has a very limited in vivo regenerative capacity (endothelial cells are currently hypothesized to proliferate—particularly in the corneal periphery near Schwalbe's line—at too low a rate to adequately replace dying cells) and because aging results in progressive cellular senescence, particularly in the central regions of the cornea in part through the activity of the cyclin-dependent kinase inhibitor p21, there is a well-documented decline in central endothelial cell density with age that typically involves two phases: a rapid and a slow component (Fig. 7.2).[4,5,7–9] During infancy, the cornea continues to grow over the first 2 years of life reaching adult size at 2 years of age with an average horizontal diameter of 11.7 mm (surface area 138 mm^2). It changes very little in size, shape, and optical properties thereafter. The only significant structure in the cornea that continues to grow after age 2 is Descemet's membrane as it gradually increases an additional 6–11 μm in thickness from birth to death. Due to corneal growth and age-related or developmentally selective cell death, during the fast component, the central endothelial cell density decreases exponentially to about 3500 cells/mm^2 by age 5 and 3000 cells/mm^2 by age 14–20.[8,9] Thereafter, a slow component occurs where central endothelial cell density decreases to a linear steady rate of 0.3–0.6% per year, resulting in cell density measurement around 2500 cells/mm^2 in late adulthood.[7–9] Because the corneal endothelium maintains its continuity by migration and expansion of surviving cells, it is not surprising that the percentage of hexagonal cells decreases (pleomorphism) and the coefficient of variation of cell area increases (polymegathism) with age.[8]

It is important when reviewing this information to realize that these are average central corneal endothelial cell counts from predominantly Caucasian US populations. Several studies reveal that important racial and geographic differences exist as Japanese, Filipino, and Chinese corneas have been found to have higher cell density measurements than Caucasians, while Indian corneas have lower cell densities (Table 7.1).[10–13] It is hypothesized that this range of central cell densities may be predominantly due to differences in corneal diameter and endothelial surface area between these groups (e.g. Japanese, Caucasian, and Indian horizontal corneal diameters averaged 11.2, 11.7, and 12.0 mm, respectively), but genetic and environmental factors are also a possibility. Additionally, this data applies only to central corneal endothelial counts

Table 7.1 Comparison of Endothelial Cell Density in Indian, American, Chinese, Filipino, and Japanese Populations

	INDIAN[a]		AMERICAN[b]		CHINESE[c]		FILIPINO[d]		JAPANESE[b]	
Age groups (years)	No. of eyes	Cell density (cells/mm^2)	No. of eyes	Cell density (cells/mm^2)	No. of eyes	Cell density (cells/mm^2)	No. of eyes	Cell density (cells/mm^2)	No. of eyes	Cell density (cells/mm^2)
20–30	104	2782 ± 250	11	2977 ± 324	100	2988 ± 243	114	2949 ± 270	18	3893 ± 259
31–40	96	2634 ± 288	6	2739 ± 208	100	2920 ± 325	112	2946 ± 296	10	3688 ± 245
41–50	97	2408 ± 274	11	2619 ± 321	97	2935 ± 285	112	2761 ± 333	10	3749 ± 407
51–60	98	2438 ± 309	13	2625 ± 172	97	2810 ± 321	102	2555 ± 178	10	3386 ± 455
61–70	88	2431 ± 357	8	2684 ± 384	90	2739 ± 316	114	2731 ± 299	6	3307 ± 330
>70	54	2360 ± 357	15	2431 ± 339	83	2778 ± 365	86	2846 ± 467	15	3289 ± 313

[a] Rao SK, et al. Corneal endothelial cell density and morphology in normal Indian eyes. Cornea 2000; 19: 820–823.

[b] Matsuda M, et al. Comparison of the corneal endothelium in an American and a Japanese population. Arch Ophthalmol 1985; 103: 68–70.

[c] Yunliang S, et al. Corneal endothelial cell density and morphology in healthy Chinese eyes. Cornea 2007; 26: 130–132.

[d] Padilla MDB, et al. Corneal endothelial cell density and morphology in normal Filipino eyes. Cornea 2004; 23: 129–135.

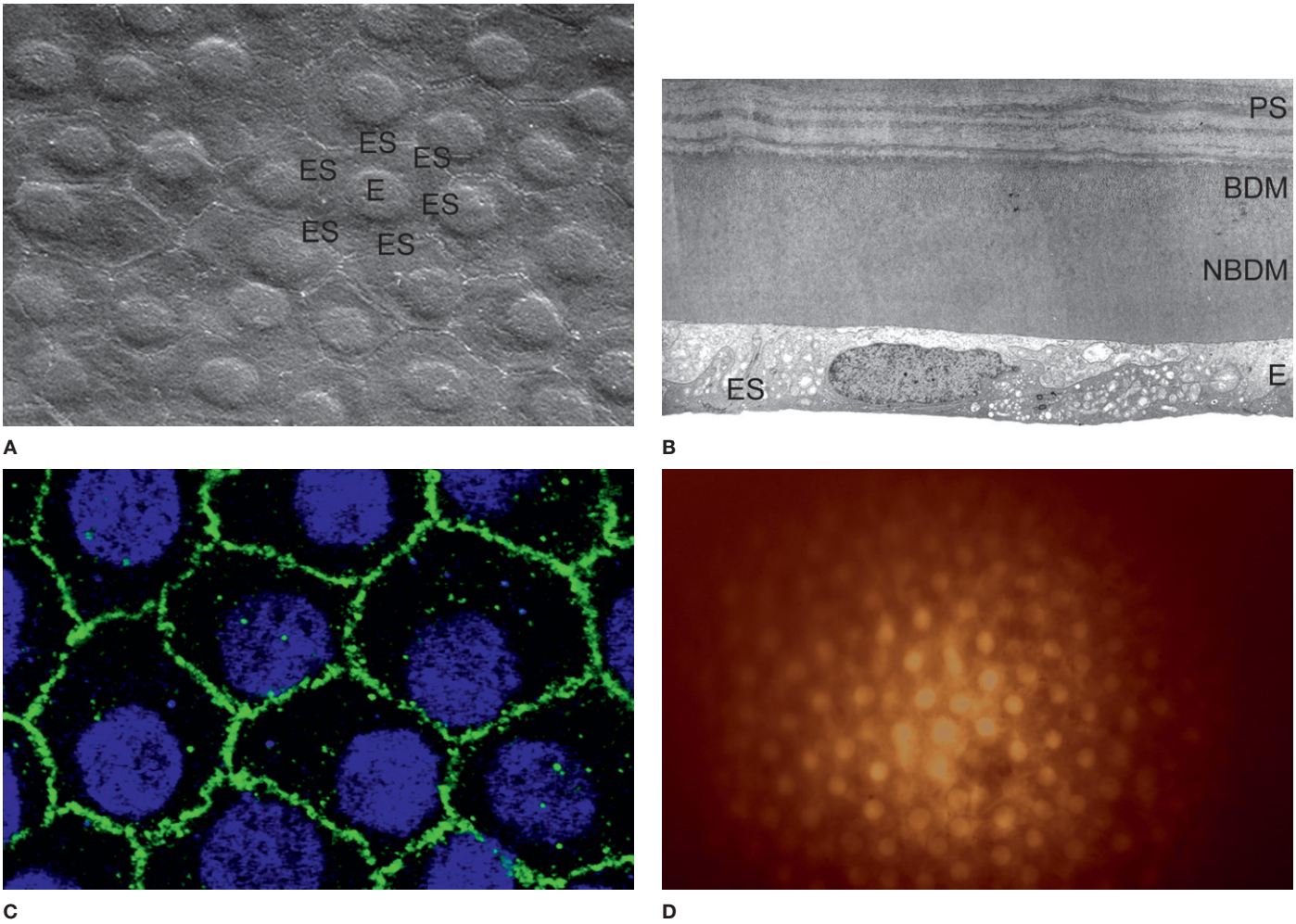


Figure 7.1. *A,* Scanning electron micrograph (×1000) on the posterior surface of the corneal endothelium from a 65-year-old patient with healthy eyes. Note how the hexagonal endothelial cells form a uniform monolayer with small 2–4-nm extracellular spaces between adjacent endothelial cells. E, endothelial cells; ES, extracellular space. *B,* Transmission electron micrograph (×4750) of the posterior corneal stroma, Descemet's membrane, and corneal endothelium from a 65-year-old patient with healthy eyes. PS, posterior stroma; BDM, banded portion of Descemet's membrane; NBDM, nonbanded portion of Descemet's membrane; E, endothelial cells; ES, extracellular space. *C,* Immunofluorescence confocal microscopy illustrating labeling of junctional adhesion molecule A (JAM-A) in corneal endothelial cell junctions (green). Nuclei are counterstained with TO-PRO 3 (blue). The photomicrograph (×2000) highlights tight junctional complexes (green). (From Kenneth J Mandell, MD, PhD). *D,* Photomicrograph (×400) of fluorescein-dye spreading between many adjacent endothelial cells in a human cornea, which demonstrates the intimate importance of gap junctions in how endothelial cells communicate with one another. (From Mitchell A Watsky, PhD).

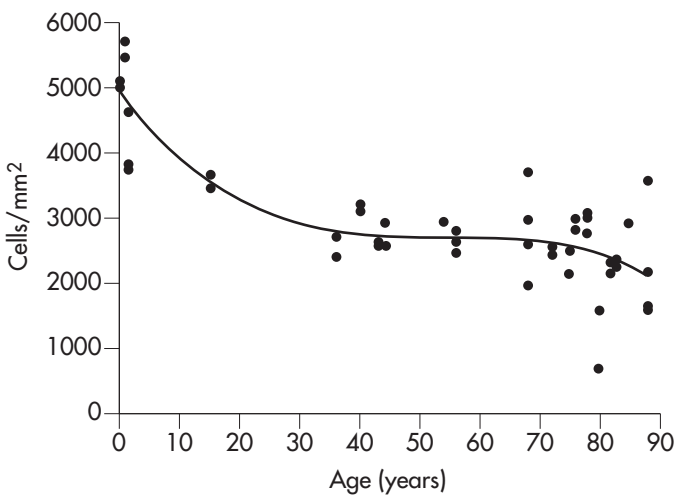


Figure 7.2. Scatterplot with best fit curve showing the average central corneal endothelial cell density for normal, healthy eyes of different ages. (From Williams KK, Noe RL, Grossniklaus HE, et al. Correlation of histologic corneal endothelial cell counts with specular microscopic cell density. Arch Ophthalmol 1992; 110: 1146–1149.)

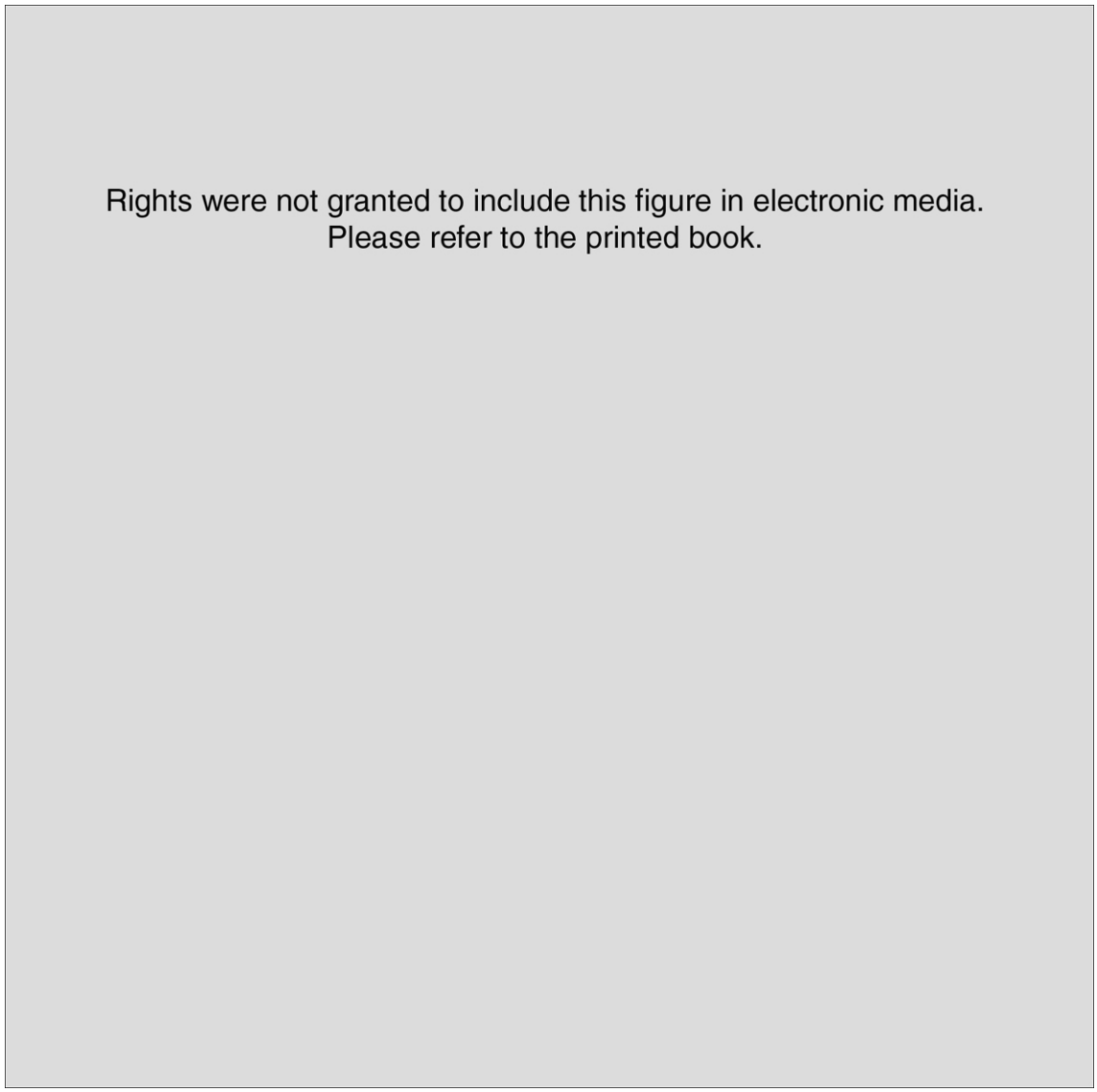


Figure 7.3. Diagram (*A*) and graph (*B*) illustrating the central, paracentral, and peripheral corneal endothelial cell densities in healthy, normal subjects. (From Rangaswamy NV, Zhou W, Harwerth RS, Frishman LJ. Effect of experimental glaucoma in primates on oscillatory potentials of the slow sequence mfERG. Inv Ophthalmol Vis Sci 2006; 47: 753–767).

since recent work has shown that higher endothelial cell densities can typically be found in more peripheral aspects of the cornea (Fig. 7.3).[14] Therefore, it appears that corneal endothelial cell numbers decrease on average about 50% from birth to death in normal subjects. Because corneal decompensation typically doesn't occur until central density values approach 500 cells/mm^2 (90% decrease in endothelium from birth or 80% decrease from healthy adulthood level), there appears to be plenty of cellular reserve potential remaining after an average human lifespan of 75–80 years of life.[8,9] Estimates suggest that healthy, normal human corneal endothelium should maintain corneal clarity up to a minimum of 224–277 years of life, if humans lived that long.[9]

The primary function of the corneal endothelium is to maintain the deturgescence and clarity of the cornea through a barrier function and a pump-leak mechanism first described by David Maurice.[15] Secondarily, it is also known to secrete an anteriorly located basement membrane called Descemet's membrane and a posterior located glycocalyx layer.[1]

BARRIER FUNCTION

The barrier function of the endothelium is dependent upon having a sufficient number of corneal endothelial cells to cover the posterior surface of the cornea and having integrity of endothelial cellular tight junctions, which are present in the extracellular spaces between endothelial cells (Fig. 7.4). Clinically, the barrier function of the cornea can be assessed by the use of the specular microscope or the confocal microscope (endothelial cell density), and fluorophotometry (permeability). In healthy human corneas, this barrier prevents the bulk flow of fluid from the aqueous humor to the corneal stroma, but does allow moderate diffusion of nutrients, water, and other metabolites to cross into the stroma through the 2–4-nm wide extracellular spaces. The leaky endothelial barrier may initially seem inefficient, but when one considers that most nutrients for all layers of the cornea come from the aqueous humor, some limited leakiness of the monolayer is reasonable. Additionally, despite the normal loss of endothelial cells that occurs with age,

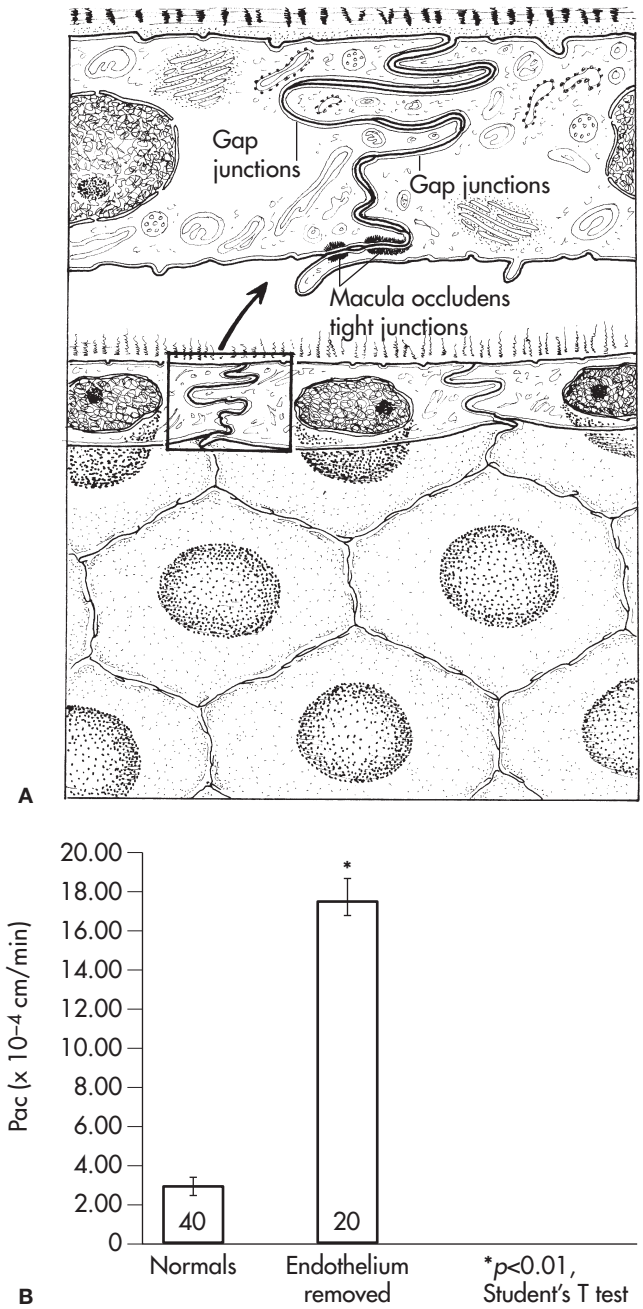


Figure 7.4. Diagram (*A*) and graph (*B*) illustrating the normal barrier function of corneal endothelium, which is due to endothelial cells covering the posterior corneal surface without gaps and the focal, tight junctions (macula occludens). The bar graph in *B* shows the normal permeability of human endothelial monolayer to carboxyfluorescein compared to that without endothelium, which resulted in a six-fold increase in permeability. (From Watsky MA, McDermott ML, Edelhauser HF. In vitro corneal endothelial permeability in rabbit and human: the effects of age, cataract surgery, and diabetes. Exp Eye Res 1989; 49: 751–767 with permission from Elsevier.)

there appears to be no appreciable increase in the permeability of normal, healthy aged corneas.[16] Only when the endothelium is severely reduced in cell density (central endothelial cell density = 2000 cells/mm^2), is acutely damaged, and/or has disrupted cell junctions, does its permeability increase (up to a maximum six-fold increase in permeability to carboxyfluorescein (12.85×10^{-4} cm/min) compared to normal (2.26×10^{-4} cm/min)).[16] Studies have inferred that during the fifth month of gestation the tight junctions completely form and the endothelial barrier is established.[17]

A number of factors have been known to acutely affect the barrier function of the endothelium, including the following: reversible disruption of cell junctions (calcium-free solutions or glutathione-restricted solutions); mechanical damage (e.g. trauma, IOL insertion); surgical instrument trauma; or chemical injury (e.g. non-physiologic or toxic intraocular solutions, preservatives). Fortunately, the remaining viable cells are able to migrate, re-cover the posterior corneal surface by spreading out over a larger surface area, and re-establish the intercellular cell junctions. Thus, the barrier function of the corneal endothelium is efficiently restored.

PUMP-LEAK MECHANISM

The classic temperature reversal studies provided the first evidence that the maintenance of corneal transparency was metabolically dependent.[18] Corneal thickness was found to increase when intact eyes were refrigerated. This effect was observed to reverse (i.e. the tissue thinned) when the tissue was re-warmed (temperature reversal). Subsequent in vitro corneal perfusion studies demonstrated that temperature reversal still occurred in the absence of the corneal epithelium, implicating active metabolically dependent processes in the corneal endothelium as mediating corneal deturgescence.[1] Subsequent studies demonstrated that transporters, located primarily in the endothelial cell's lateral cell membrane, effected the transport of ions—principally sodium (NA^+) and bicarbonate (HCO^{3-})—out of the stroma and into the aqueous humor. An osmotic gradient is created and water is thus osmotically drawn from the stroma into the aqueous humor.[19] It is important to note that this osmotic gradient occurs only if the endothelial barrier is maintained. A transport protein found to be essential to endothelial 'pump function' is Na^+/K^+-ATPase (Fig. 7.5).[20,21] Subsequently, the number and density of Na^+/K^+-ATPase sites have also been quantified using [3H]-ouabain.[21] These studies have shown that approximately 3 million Na^+/K^+-ATPase sites are present in the lateral membrane of a single endothelial cell. This corresponds to an average pump site density of 4.4 trillion sites/mm^2 along the lateral plasma membrane wall of an intact endothelium.[22] In rabbit corneas, studies have demonstrated that only by 5–7 months of gestation does the density of Na^+/K^+-ATPase sites increase to adult levels so that the cornea becomes dehydrated and transparent.[23] Clinically, the metabolic pump of the corneal endothelium can be assessed in vivo using pachymetry to measure how quickly the corneal thickness recovers after being purposefully swollen by wearing an oxygen-impermeable contact lens. A number of factors are known to alter endothelial pump function: pharmacologic inhibition of Na/K-ATPase (e.g. ouabain), decreased temperature, lack of bicarbonate or carbonic anhydrase inhibitors, and a chronic reduction in endothelial cell numbers from mechanical injury, chemical injury, or disease states. Fortunately, with regard to the latter, physiologic compensatory mechanisms prevent corneal edema from occurring to a certain degree when central endothelial cell densities are between 2000 and 750 cells/mm^2. This occurs by either increasing the activity of pump sites already present, which requires more ATP production by the cell, and/or by increasing the total number and density of pump sites on the lateral membranes of endothelial cells (Fig. 7.6).[22] A similar phenomenon occurs in the proximal tubule cells of the human kidney to adjust for an increased salt load. In Fuchs' endothelial dystrophy, for example, the cornea has been found to remain clear

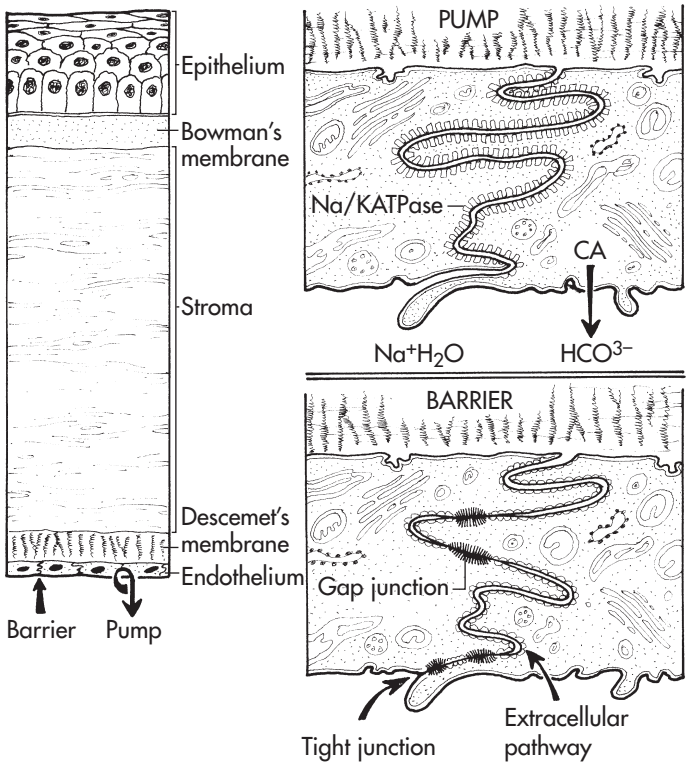


Figure 7.5. Diagram illustrating the opposing forces of the corneal endothelial barrier and metabolic pump. When the leak rate equals metabolic pump rate, the corneal stroma is 78% hydrated and the corneal thickness is maintained. (From Waring GO, et al. The corneal endothelium. Normal and pathologic structure and function. Ophthalmology 1982; 89: 531 © Elsevier 1982.)

and of normal thickness despite having very low endothelial cell counts and increased endothelial monolayer permeability to fluorescein (5.30×10^{-4} cm/min).[21] Apparently, this occurs because the metabolic activity and density of the Na^+/K^+ pump sites increase to compensate for the increased permeability.[24] The point at which compensatory mechanisms appear to ultimately fail is when the central endothelial cell density reaches 500 cells/mm^2 or less (range of 750–250 cells/mm^2) (Fig. 7.6).[7,25] At this low cell count, the permeability has greatly increased to such a point that the endothelial cells, which are spread so thin, do not have enough room on their lateral cell membranes for more metabolic pump sites and all the current pumps are maximally active. Therefore, the metabolic pump fails to balance the leak and corneal edema results. A summary of the entire corneal endothelial cell transport system was most recently reviewed by Bonanno.[26]

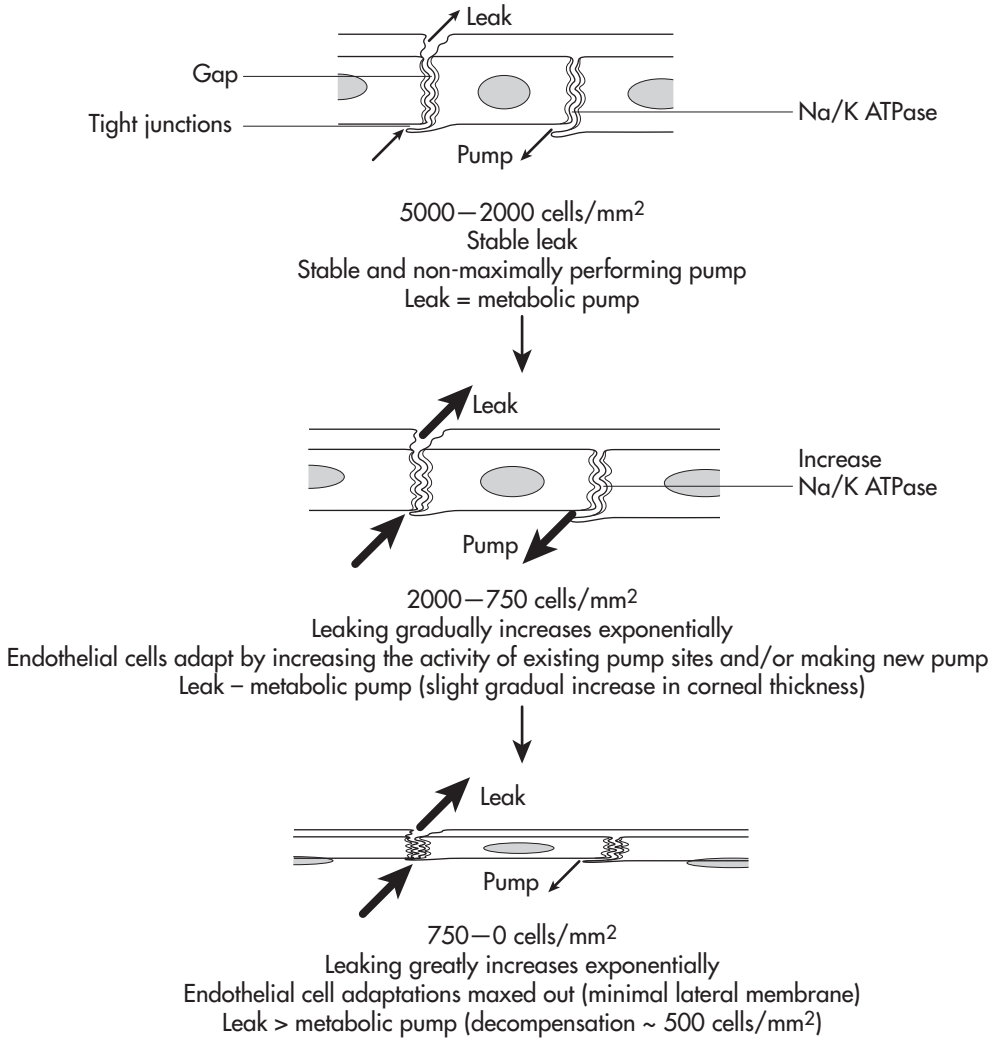
When the corneal endothelial barrier and metabolic pump are functioning normally, the corneal stroma has a total Na^+ concentration of 179 mEq/L (134.4 mEq/L free and 44.6 mEq/L bound to stromal PGs), while the aqueous humor has a total Na^+ concentration of 142.9 mEq/L (all free).[27] Therefore, after accounting for chloride activity and stromal imbibition pressure, an osmotic gradient of +30.4 mmHg exists causing water to diffuse from the stroma to the aqueous humor (Fig. 7.7). Additionally, the corneal endothelial cells contain high concentrations of carbonic anhydrase, which forms HCO^{3-} (bicarbonate) from metabolic CO^{2-}. The HCO^{3-} diffuses down its concentration gradient into the extracellular space or across the membrane to the aqueous humor via the Cl^-/HCO^{3-} exchanger[28] or through Cl^- (anion) channels.[29,30] Bicarbonate can also enter the cells via a Na^+/HCO^{3-} co-transporter,[31] and the intracellular pH can be regulated, at least in part, by a basal Na^+/H^+ exchanger.[32] Endothelial Cl^- transport occurs through both transporters and channels, with Cl^- entering the cell from the stroma via a basal $Na^+/K^+/2Cl^-$ transporter and the HCO^{3-}/Cl^- exchanger, and exiting into the aqueous humor via apical anion channels.[31–33]

ENDOTHELIAL CELL BASEMENT MEMBRANE AND GLYCOCALYX

A secondary function of endothelium is its ability to secrete an extracellular matrix. The secreted and deposited extracellular matrix along the basal surface of the endothelium forms Descemet's membrane (Fig. 7.1, *B*) and is essentially a life-long accumulated basement membrane of the endothelial cells. Although some collagen fibrils from the posterior stroma are embedded in the Descemet's membrane, it really has no major junctional or adhesional complexes to the posterior stroma other than a small 0.5 μm thick layer of fibronectin. Descemet's membrane is highly elastic and relatively strong since it is primarily composed of collagen (type IV and VIII) and glycoproteins (fibronectin, laminin, thrombospondin). At birth, it averages 4 μm thick. On electron microscopy, the fetal Descemet's membrane is composed of many wide-spaced, 110-nm banded collagen fibrils.[34] After birth, collagen is gradually added to this initial fetal layer throughout life, being notably different from the fetal layer as it is nonbanded and contains small diameter collagen fibrils that arrange into a lattice matrix.[34] Typically, the Descemet's membrane at the end of a normal human lifespan (75–80 years of age) measures around 10–15 μm thick (4-μm thick banded layer and a 6–11-μm thick nonbanded layer). With disease (e.g. Fuchs' dystrophy) or injury (e.g. trauma or surgery), the Descemet's membrane may become focally or diffusely thicker than normal from abnormal collagen deposition. This newly deposited abnormal collagen is called the posterior collagenous layer of the Descemet's membrane and is classified into one of three types: banded, fibrillar, or fibrocellular.[35] Presumably, this posterior collagenous layer is deposited because endothelial cells become stressed. Finally, the endothelium is also known to secrete a 0.72 ± 0.02 μm (mean ± SE) thick glycocalyx layer on its apical surface (Fig. 7.8).[7] Functionally, the glycocalyx layer appears to protect the endothelium, particularly in regard to anterior segment surgery.

WOUND HEALING

Because the primary role of the corneal endothelium is to maintain proper stromal hydration, the recovery of an intact and functional endothelial cell monolayer is essential to the maintenance of corneal transparency. As mentioned previously, corneal endothelial wound healing occurs predominantly by cell migration and enlargement rather than by cellular proliferation because of in vivo mitotic quiescent mechanisms.[5] Thus, injury to the central endothelium results in decreased cell densities, both in the central and the peripheral cornea.[36–38] The percentage of endothelial cells that are hexagonal (pleomorphism) is reduced (normal is >50%) and the coefficient of variation in cell size (polymegathism) is increased (normal is less than 45%).[36–38] In the rabbit, where wound healing is accompanied by both endothelial cell migration and near complete cellular reconstitution (i.e. proliferation), these parameters shift toward preoperative values during the time course of wound healing. In cat corneas, where minimal cell division occurs following endothelial wounding, cell density remains depressed; a similar situation occurs in the human cornea.



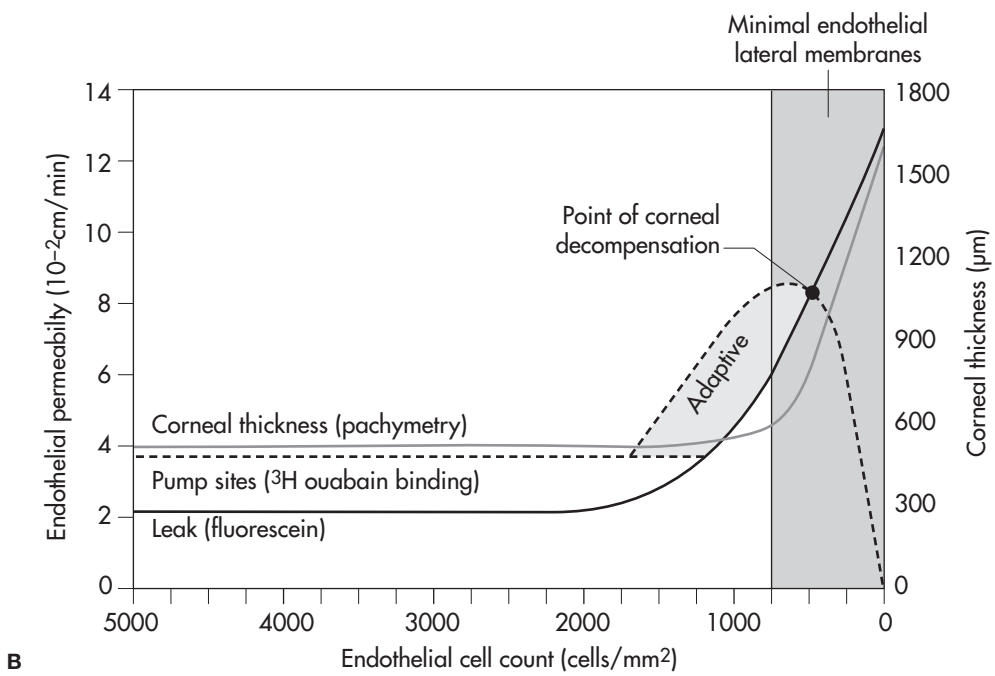


Figure 7.6. Diagram (*A*) and graph (*B*) illustrating the relationship between central endothelial cell density, barrier function, pump sites, and pachymetry. Note that the number of pump sites are not all maximally used in the normal state (5000–2000 cells/mm^2). With increased leaking (2000–750 cells/mm^2), there is an adaptive phase in which the endothelial cells can maximally use all the pump sites or form more pump sites to offset the leak up to a point. When the surface area of the lateral membranes of endothelial cells progressively becomes too small (750–0 cells/mm^2), these adaptations max out and eventually decline. The point where endothelial cell pump site adaptations crosses permeability (500 cells/mm^2) is typically when corneal decompensation occurs. (From Dawson DG, et al. Physiology of the eye and visual system: cornea and sclera. In: Duane's Foundation of Clinical Ophthalmology on CD-ROM. 2006; vol. 2c. 4: 1–76.)

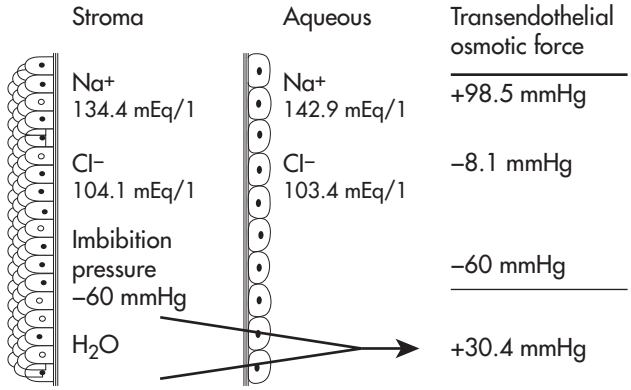


Figure 7.7. Diagram illustrating the total transendothelial osmotic force due to Na^+ activity, Cl^- activity, and imbibition pressure. Although the Na^+ activity within the aqueous humor is greater than that within the stroma (142.9 vs 134.4 mEq/L, $p < 0.05$), using a reflection coefficient of 0.6, the calculated osmotic force due to Na^+ is 98.5 mmHg. Similar calculations for Cl^- and imbibition pressure result in osmotic forces of –8.1 and –60 mmHg, respectively. The sum of these forces results in a total osmotic force of +30.4 mmHg, which ultimately results in deturgescence of the cornea. (From Stiemke MM, et al. Na^+ activity in the aqueous humor and corneal stroma of the rabbit. J Exp Eye Res 1992; 55: 425–433 with permission from Elsevier.)

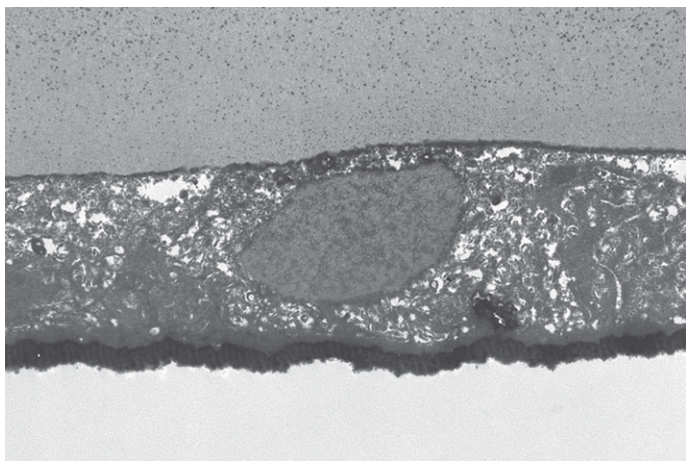


Figure 7.8. Transmission electron micrograph (×7300) using a special mucin preserving stain (2.5% glutaraldehyde with 0.1 M sodium cacodylate HCl and 0.5% cetylpyridinium chloride) demonstrates the natural 0.72 μm thick glycocalyx layer covering the apical surface of human endothelial cells. (From Deepta Ghate, MD.)

Several studies have examined endothelial cell function following wound healing. Yee and co-workers examined the permeability characteristics of the endothelium over the time course of wound healing, while incorporating a ouabain binding analysis to quantitate endothelial Na^+/K^+ ATPase pump site densities.[38] Based on these studies, it was concluded that the rabbit corneal endothelium following a transcorneal freeze injury heals in three stages. Stage one (0–3 days) is characterized by an initial coverage of the wound by pleomorphic spindle-shaped cells that form a functional, but incomplete barrier that have minimal pump site densities. In stage two (4–7 days), the endothelial cells assume a flattened configuration, have an irregular polygonal shape, and establish normal pump site density and barrier function. During this stage, corneal thickness was observed to show its most rapid rate of normalization. Stage three (8–30 days) is characterized by a remodeling of the endothelial cell monolayer. During the final stages of wound healing, cell rearrangement can occur (exchange of neighbors among cells by sliding past one another).

Endothelial wound healing in the cat cornea is slower and less complete in terms of returning to preoperative values than rabbits. Ling and co-workers found that removal of the central 6 mm of cat corneal endothelium resulted in stromal swelling that returned to preoperative values only by 35 days after wounding.[39] Central endothelial cell density decreased 25% at 4 weeks after wounding, and the coefficient of variation increased to 60%. In a separate study, it was found that permanent stromal swelling occurred in the cat when cell density was reduced to below 40–45% of control values.[40]

Human corneal endothelium appears to heal even slower and to a less complete extent compared to that of both the cat and rabbit. With aging, the number of replication-competent endothelial cells decreases and the number of senescent cells increases, particularly in the center of the cornea.[5] It is hypothesized that this increased central cellular senescence explains why age-related endothelial cell disease is primarily found in humans. Fortunately, humans can also tolerate more total cell loss than animals as chronic stromal swelling only occurs when cell density is reduced around approximately 80% of normal.

CORNEAL EDEMA

The Donnan effect states that the swelling pressure in a charged gel, like the corneal stroma, results from ionic imbalances. The fixed negative, or anionic, charges on corneal stromal proteoglycan GAG side-chains (one carboxylic acid and one sulfate ester side chain per disaccharide repeat on a dermatan sulfate GAG polymer, and one or two sulfate ester side chains per disaccharide repeat on a keratan sulfate GAG polymer) have a central role in this effect. The anti-parallel GAG duplexes (tertiary structure) produce long-range electrostatic repulsive forces that induce an expansive force termed swelling pressure (SP). Because the corneal stroma also has cohesive and tensile strengths that resist expansion, the normal SP of the non-edematous corneal stroma is around 55 mmHg.[41,42] If the stroma is further compressed (e.g. increasing IOP or mechanical applanation) or expanded (e.g. corneal edema), the SP will correspondingly increase or decrease. Conversely, the negatively charged GAG side-chains also form a double-folded helix in aqueous solution (secondary structure) that attracts and binds Na^+ cations, which results in an osmotic effect leading to the diffusion and subsequent absorption of water by proteoglycans via bound Na^+ cations. Thus, the central corneal thickness is maintained around its average value of 540 to 550 μm (based on ultrasound pachymetry) because the fixed negatively charged proteoglycans induce a constant swelling pressure through anionic repulsive forces, and because the hydration level of corneal stroma is constantly maintained at 78% water because corneal stromal proteoglycans imbibe water through cationic attractive forces.[43] Under normal circumstances, the negative pressure drawing fluid into the cornea, called the imbibition pressure (IP) of the corneal stroma, is approximately –40 mmHg.[44] This implies that the negative charges on corneal proteoglycans are only about one-quarter (~27 %) saturated, or bound, with Na^+ and water, and that the remaining unbound proportion is still available to bind more Na^+ and absorb more water if given either a compromised endothelium or epithelium, or both. Normally, the highly impermeable epithelium and mildly impermeable endothelium keep the diffusion of electrolytes and fluid flow in the stroma to such a low level (resistance to diffusion of electrolytes and fluid flow = epithelium (2000) >> endothelium (10) > stroma (1)) that the endothelial

cell metabolic pump can maintain stromal hydration in the normal range of 78%. Although IP = SP when corneas are in the ex vivo state, IP is actually lower than SP in the in vivo state because of the hydrostatic pressure induced by intraocular pressure (IOP), which now must be accounted for. This is best represented by the equation IP = IOP − SP[44] and explains why the hydration level of a patient's cornea is not only dependent on having normal barrier functions, but also on having a normal IOP. Therefore, a loss of corneal barrier function, an IOP ≥55 mmHg, or a combination of the two results in corneal edema.[45]

Corneal edema is a term often used loosely and nonspecifically by clinicians, but literally refers to a cornea that is more hydrated than normal, or >78% water. The topic of corneal edema is important for clinicians to understand because it affects the architecture and function of the corneal epithelium and stroma. Epithelial edema clinically causes a hazy microcystic appearance to occur in the epithelium in mild to moderate cases, significantly decreasing vision and increasing glare. It also can cause the development of large painful, sub-epithelial bullae in severe cases. These changes correlate histopathologically with hydropic basal epithelial cell degenerative changes and the development of extracellular subepithelial fluid filled spaces (e.g. cysts and bullae). Interestingly, if bullae are chronically present, a fibrocollagenous degenerative pannus often times will form in the subepithelial space, decreasing vision further but markedly reducing the pain. In comparison, corneal stromal edema clinically appears as a painless, hazy, thickening of the corneal stroma, resulting in a mild to moderate reduction in visual acuity and an increase in glare. At the same time, Descemet's membrane folds commonly appear on the posterior surface of the cornea. Histopathologically, these changes correlate with the light microscopic findings of thickening of the corneal stroma in the posterior cross-sectional direction with loss of the normally present artifacteous stromal clefting.[46] Ultrastructural and biochemical studies have further shown that stromal edema causes an increase in the distance and disruption of spatial order between collagen fibrils,[45] a decrease in the refractive index of the extracellular matrix,[47] hydropic degenerative changes or cell lysis in the resident keratocyte population,[48] and a loss of proteoglycans.[49] Although various proportions of the two types of negatively charged proteoglycan may account for the higher hydration levels in the posterior stroma compared to the anterior stroma,[50,51] it appears that the directional orientation of the collagen fibrils and degree of lamellar interweaving has the greatest influence on the amount of regional stromal thickening, or swelling, as a result of increased hydration levels. Because the collagenous architecture of the corneal stroma (i.e. limbus to limbus directional orientation of collagen fibrils) highly resists circumferential expansion, only anterior–posterior expansion occurs in the human cornea, mostly in the posterior direction. This occurs because most of the collagen fibrils in the anterior third of the corneal stroma are obliquely oriented and, perhaps most importantly, extensive lamellar interweaving occurs in the anterior third of the corneal stroma, whereas weak bridging filaments (i.e. type VI and FACIT collagens) occur diffusely throughout the entire corneal stroma. Furthermore, the lamellar interweaving explains why the anterior third of the cornea mildly swells and actually maintains the anterior corneal curvature even when the remaining stroma swells up to three times its normal thickness.[48] Because fibrotic corneal scars have random directionally oriented collagen fibrils, they also have been found to resist swelling under edematous conditions.[52]

Therefore, although it is commonly stated that corneal thickness and interfibrillar spacing increase in a linear fashion to the hydration level of the corneal stroma,[42,46] one needs to know that this relationship mainly applies to the posterior two-thirds of the corneal stroma. Finally, while both epithelial and stromal edema commonly co-exist together, there are two notable exceptions. As the epithelium lacks fixed negatively charged proteoglycans and has much weaker cohesive and tensile strength values than the corneal stroma, its state of hydration is mainly dictated by IOP levels.[53] Conversely, because collagen fibrils in corneal stroma are anchored at the limbus for 360°, they exert increasing or decreasing cohesive strength on the corneal stroma (i.e. compression of stromal tissue) as the IOP elevates above or decreases below normal, respectively. This results in the transmission of stromal edema to the epithelial surface in cases of high IOP or to the stroma in cases of low IOP. Therefore, if IOP is ≥55 mmHg with normal endothelial barrier and pump function, epithelial edema usually occurs by itself, or if endothelial cell dysfunction and hypotony (IOP ~0 mmHg) occur together, then stromal edema occurs alone (Fig. 7.9).

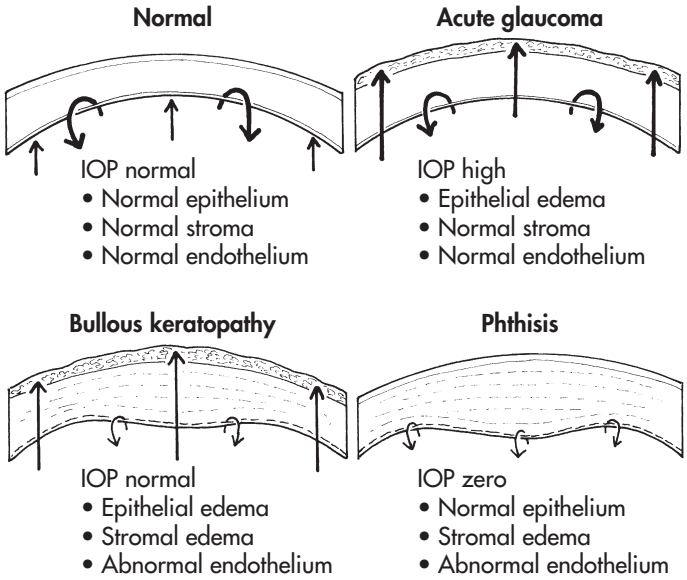


Figure 7.9. Diagram demonstrating the delicate balance between stromal swelling pressure, endothelial pump function, and intraocular pressure. Usually if endothelial cell pump function fails and IOP remains normal, both stromal and epithelial edema occurs (lower left). Only when IOP increases above the swelling pressure of the stroma and the endothelium functions normally do we see epithelial cell edema alone (upper right) and only when IOP is zero and the endothelium functions abnormally do we see stromal edema alone (lower right). (From Hatton MP, et al. Corneal oedema in ocular hypotony. Exp Eye Res 2004; 78: 549–552 with permission from Elsevier.)

INJURY

There are many exogenous stresses that could potentially damage the corneal endothelium over a person's lifetime (Fig. 7.10). Perhaps the most common interventions that might stress a person's cornea are contact lens wear, excimer laser-based keratorefractive surgery (LASIK, PRK), and intraocular surgery (cataract surgery, refractive IOL surgery, corneal transplantation).

CONTACT LENSES

Contact lens wear does not cause loss of endothelial cell density, but it can cause acute reversible corneal edema and can also potentially cause chronic signs of endothelial cell stress (increased polymegathism and decreased pleomorphism).[6,54] The corneal endothelium

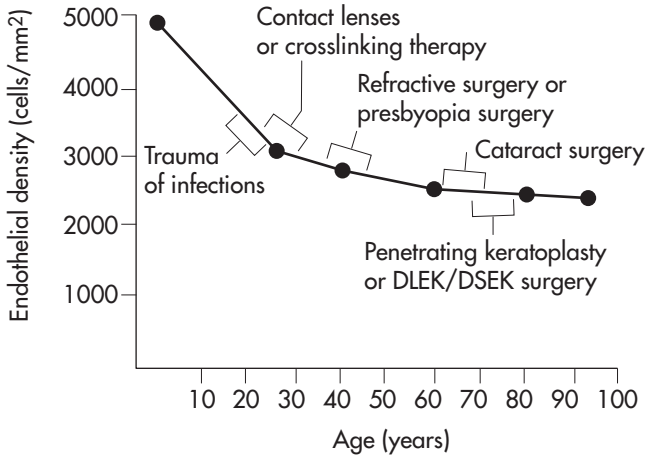


Figure 7.10. Graph demonstrating the normal decrease in endothelial cell density that occurs with aging. Located along the line graph are major endothelial cell stressors that commonly may occur in a person's lifetime, which may decrease the cell density loss greater than normal.

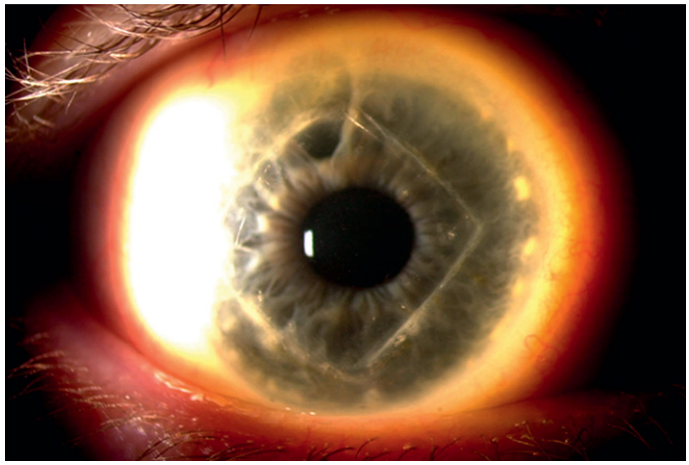
utilizes the same carbohydrate metabolic pathways as the corneal epithelium. However, the transport function of the endothelial cell requires oxidative activity that is five to six times that of epithelial cell.[55] Atmospheric oxygen is the primary source of oxygen to the endothelium. Interruption of this oxygen supply by low oxygen transmissibility contact lenses or a low oxygen environment will result in a shift to anaerobic metabolism, a concurrent increase in stromal lactic acid and CO_2, and a drop in stromal pH.[56] In addition, hypoxia can stimulate epithelial production of 12(R)HETE, a potent inhibitor of the endothelial Na^+/K^+ ATPase.[57,58] Acute reversible clinical changes observed with hypoxia include stromal swelling, endothelial dysfunction, and endothelial blebbing. Chronic hypoxia can eventually lead to irreversible endothelial polymegathism and pleomorphism. In fact, Polse and co-workers have shown that chronic corneal hypoxia in humans alters the endothelium's ability to reverse induced swelling.[59]

SURGICAL INJURY

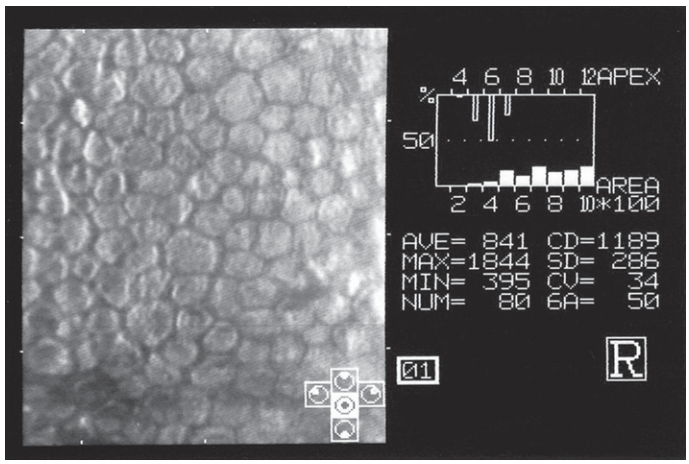
Excimer laser-based keratorefractive surgery has been found to induce acute, temporary endothelial cell stress (increased polymegathism and decreased pleomorphism) and loss of barrier function if performed on a cornea with a residual corneal thickness of 200 μm, presumably because of the shockwave produced by the laser ablation.[7] Otherwise, no long-term endothelial cell effects have been linked to laser refractive surgery.[7]

By comparison, all intraocular surgeries have been found to cause varying degrees of both acute and, more importantly, long-term damage to corneal endothelium. Modern small incision cataract surgery (Kelman phacoemulsification (KPE) + various foldable IOLs) is the preferred technique in the USA, Europe, and other more developed countries as randomized studies have shown that it results in better clinical outcomes compared to larger incision techniques, like extracapsular cataract extraction.[60] However, KPE does cause significant endothelial cell injury due to a number of factors, such as corneal distortion, ricocheting of nuclear fragments, intraocular lens or intraocular instrument contact, and release of free radicals.[61] A recent randomized controlled trial showed that KPE caused an exponential reduction in central endothelial cell density up to 1 year after surgery with endothelial cell density loss averaging 10.5%.[61] However, no significant changes in polymegathism or pleomorphism were found.[61] This fast component period of cell loss is statistically similar to that observed following extracapsular cataract extraction (ECCE), another common alternative technique used for performing cataract surgery (particularly in third world countries), which results in a 9.1% reduction in endothelial cell density at 1 year after surgery.[61] Capsule rupture with vitreous loss, hard cataracts, and age at the time of surgery are factors that have been shown to significantly increase endothelial cell loss rates (Fig. 7.10).[61] Long-term slow component cell loss data is currently unknown for KPE, whereas ECCE data shows that a 2.5% per year linear rate of cell loss occurs from 1 to 10 years after surgery.[9,54,61,62] Recent data on the two phakic refractive IOL procedures commercially available in the USA, Verisyse (Ophthec, distributed by Advanced Medical Optics) and the foldable Visian ICL (Staar Surgical), show less acute component damage than standard cataract surgery (Verisyse causes around 7% cell density loss and Visian ICL around 3% cell density loss at 1 year after surgery).[63] However, just like with ECCE, a chronic, slow component that is four- to nine-fold higher than normal cell loss has been observed over a 5-year postoperative time point (Verisyse causes on average 2.7% cell density loss per year and Visian ICL 2.5% cell density loss per year between 1 and 5 years after surgery).[63]

Corneal transplantation surgery, or penetrating keratoplasties (PK), has been found to cause the greatest long-term decrease in central endothelial cell densities of all the commonly performed intraocular anterior segment surgical procedures (Fig. 7.11), perhaps because of the peripheral loss of stem-like cells or the loss of the peripheral storage zone of higher cell densities.[64] Long-term longitudinal studies up to 20 years after surgery show that endothelial cell loss after corneal transplantation occurs in two phases: a fast and a slow component.[65] During the fast component, the central endothelial cell density decreases exponentially with 36.7% cell loss at 1 year and 8.4% cell loss per year up to 5 years after surgery.[60] Thereafter, a slow component occurs where central endothelial cell density decreases at a linear steady rate of 4.2% per year.[65] Concurrently, polymegathism gradually increases and pleomorphism gradually decreases throughout the longitudinal follow-up period. Over the last 9 years, corneal transplantation surgical procedures have significantly changed the way most clinicians manage corneal endothelial cell disorders as posterior lamellar keratoplasty techniques have evolved to selectively replace the corneal endothelium. Posterior lamellar keratoplasty (PLK), deep lamellar endothelial keratoplasty (DLEK), Descemet's stripping endothelial keratoplasty (DSEK), and Descemet's membrane endothelial keratoplasty (DMEK) are the current options in this group of surgeries being performed to date.[66,67] Currently, the simplest and most effective technique is DSEK surgery, which seems to be preferred by patients compared to more traditional full-thickness PK surgery.[68,69] It is important to mention that the preferred approach of DSEK may be supplanted soon by another technique, so this chapter may not be up to date by the time it is published. Despite this possibility, one of the major concerns with DSEK surgery, probably second only to the high dislocation rate found with this surgery, is how the endothelium survives long term in these grafts. The fact that surgeons commonly fold the DSEK grafts and insert them through small incisions using various grasping forceps, and that air is used to keep the graft in place for 1 hour to 1–2 days in duration after the surgery would make one think that it damages the corneal endothelium much more than routine PK surgery (Fig. 7.12). In fact, many posters studying corneal endothelial cell loss after foldable posterior lamellar keratoplasty techniques including DSEK surgery at the 2006 and 2007



A



B

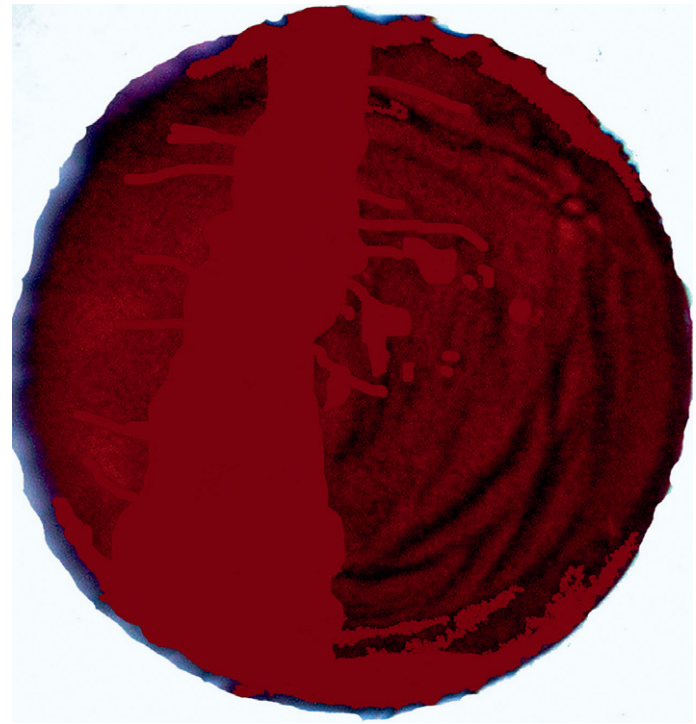
Figure 7.11. Slit-lamp photograph (*A*) and specular micrograph (*B*) of one of Dr Castroviejo's patients 42 years after his square penetrating keratoplasty surgery. The central endothelial cell density is 1189, CV is 34, and the percentage of hexagons is 50.

ARVO meetings showed greater rates of cell loss than that observed after penetrating keratoplasty.[70–73] A recent published study from one experienced surgeon's practice also supports this as the acute endothelial cell density decrease one year after DSEK was 40%.[74]

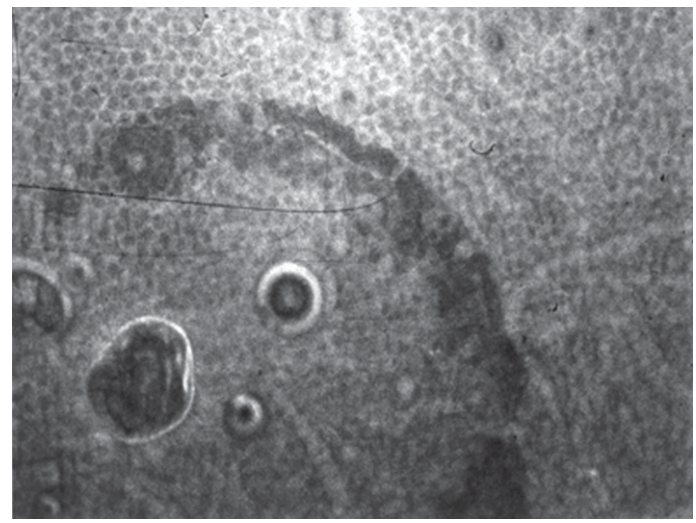
Finally, there are other surgical adjuvants or new procedures on the horizon that could affect the corneal endothelium. The surgical adjuvant that is most concerning is that of topical mitomycin C (MMC), which is applied after excimer laser-based keratorefractive surface surgery to prevent or treat subepithelial scarring. Currently, there appears to be no evidence of endothelial cell toxicity if a single local application of MMC is used at a concentration of 0.02–0.002% for an exposure duration of 12 s to 2 min.[75,76] The newest procedure that is most concerning is that of corneal collagen crosslinking with riboflavin and UVA light, which is one of the most promising treatment options for corneal ectasia. Currently, no evidence of endothelial cell damage has been found, but most of the studies to date are only preliminary, small in number, and are under strict research protocols.[77]

PHARMACOLOGIC TOXICITY

In addition to surgical injury, the corneal endothelium can also be influenced by pharmacologic toxicity.[7,78] Past studies that helped guide the development of intraocular irrigating solutions found that the best solutions were those that were most similar to aqueous humor in composition (Table 7.2). BSS Plus (Alcon Laboratories, Ft Worth, TX, USA) is currently the most physiologically compatible intraocular irrigants for intraocular surgery. BSS is probably the



A



B

Figure 7.12. *A,* Flat mount of an 8-mm diameter DSEK graft stained with 1% Alizarin red after trephination, viscoelastic placement on the endothelium with subsequent folding and insertion through a 5-mm wound using MacPherson forceps into an eye bank globe. Notice that 40% of endothelial cells were acutely damaged (lighter red) from this manipulation. In our experiments, the range of endothelial cell death was 30–70% using this identical DSEK insertion technique. *B,* Specular photomicrograph (×250) showing air bubble damage to the human corneal endothelium, which was mounted in an in vitro specular microscope and the endothelium was perfused with BSS Plus. The damaged area (dark area) from the air bubble shows a ring of endothelial damage. This bubble damage can occur within minutes.

Table 7.2 Composition of aqueous humor compared to various intraocular irrigating solutions

Ingredient	Human aqueous humor	BSS Plus	BSS
Sodium	162.9	160.0	155.7
Potassium	2.2–3.9	5.0	10.1
Calcium	1.8	1.0	3.3
Magnesium	1.1	1.0	1.5
Chloride	131.6	130.0	128.9
Bicarbonate	20.15	25.0	—
Phosphate	0.62	3.0	—
Lactate	2.5–4.5	—	—
Glucose	2.7–3.7	5.0	—
Ascorbate	1.06	—	—
Glutathione	0.002–0.010	0.3	—
Citrate	—	—	5.8
Acetate	—	—	28.6
pH	7.38	7.6	7.4
Osmolarity (mOsm)	304	305	298
Protein	0.135–0.237	—	—

[a] All concentrations are expressed in millimoles per liter or millequivalents per liter of solution.

Table 7.3 Causes of toxic anterior segment syndrome

1) Irrigating solutions or viscoelastic devices
   - Incomplete chemical composition
   - Incorrect pH (<6.7 or >8.1)
   - Incorrect osmolality (<270 mOsm or >350 mOsm)
   - Preservatives or additives (e.g. antibiotics, dilating medications)
2) Ophthalmic instrument contaminants
   - Detergent residues (ultrasonic, soaps, enzymatic cleaners)
   - Bacterial LPS or other endotoxin residues
   - Metal ion residues (copper and iron)
   - Denatured viscoelastics?
3) Ocular medications
   - Incorrect drug concentration
   - Incorrect pH (<6.7 or >8.1)
   - Incorrect osmolality (<270 mOsm or >350 mOsm)
   - Vehicle with wrong pH or osmolality
   - Preservatives in medication solution
4) Contaminated water sources
   - Water baths
   - Autoclave reservoirs
   - Non-sterile or non-pyrogen-free water
5) Intraocular lenses
   - Polishing compounds
   - Cleaning and sterilizing compounds

next best alternative. Overall, it became apparent that the main ingredients needed in intraocular solutions to be biologically compatible are essential ions, glucose as an energy source, bicarbonate as a buffer, and glutathione. It was also found during this time period of studying ophthalmic irrigants that intraocular tissues, particularly the corneal endothelium, had a relatively narrow physiologic range with which it stays healthy—a pH between 6.7 to 8.1 and an osmolality between 270 and 350 mOsm. Furthermore, any medications used intraocularly need to be at a nontoxic concentration and to contain no preservatives.

Pharmacologic toxicity to the anterior segment tissues of the eye, including the corneal endothelium, has recently become better understood through the discovery of a condition known as toxic anterior segment syndrome (TASS).[78] TASS is a sterile postoperative inflammatory reaction caused by a noninfectious substance that enters the anterior segment, resulting in toxic damage to intraocular tissues (i.e. cells and extracellular matrix). Most severe cases result in a 50% loss of central endothelial cell density or more. The process typically starts 12–48 h after cataract or anterior segment surgery, is limited to the anterior segment of the eye, is always Gram stain and culture negative, and usually improves with steroid treatment. The primary differential diagnosis is infectious endophthalmitis. Review of the literature indicates that possible causes of TASS include intraocular solutions with an inappropriate chemical composition, concentration, pH, or osmolality; preservatives; denatured ophthalmic viscosurgical devices; enzymatic detergents; bacterial endotoxin; oxidized metal deposits and residues; and factors related to intraocular lenses such as residues from polishing or sterilizing compounds (Table 7.3).[78] Therefore, as TASS is an environmental and toxic control issue, it has made anterior segment surgeons and surgical staff more aware that the health of the corneal endothelium requires a thorough understanding of all medications and fluids used during surgery. Additionally, it has helped all involved in intraocular surgery understand the importance of proper cleaning and sterilization of intraocular instruments since most cases of TASS appear to be directly caused by retained detergents or contaminated water sources.

In summary, although born with a substantial reserve of extra corneal endothelial cells for maintenance of normal corneal hydration and function, normal growth, development, and aging to an average lifespan of 75–80 years of age reduces one's endothelial cell numbers on average by 50%. Compounded to this normal decline are other exogenous stressors that could potentially damage the endothelial monolayer further so that it reaches another 80% reduction in cell numbers, which is the level (central cell density of 500 cells/mm^2) associated with the development of corneal edema and loss of transparency. Perhaps the most concerning of these stressors are trauma, infections, keratoplasty procedures, intraocular surgery when very young in age, and TASS.

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8 The keratometer in the diagnosis of corneal disease

Peter C. Donshik, William Ehlers

The keratometer, or ophthalmometer, is not a new instrument. Since it was first developed by Herman von Helmholtz in 1854, significant improvements have been made. Today, several companies manufacture these machines, such as the Haag-Streit Ophthalmometer (Lagomarsino Medical, Inc, Ft Lauderdale, FL), the keratometer from Bausch & Lomb (Buffalo, NY), and the CLC Ophthalmometer by A 0 Reichert Scientific Instruments (Buffalo, NY). In addition, over the last few years the keratometer has been automated. The nomenclature associated with this instrument is confusing. Helmholtz used the term 'ophthalmometer', which is the generic name for this instrument. However, this term is not accurate because it implies a measurement of the entire eye, not just the cornea. Bausch & Lomb introduced the term 'keratometer' as its trade name for the instrument that was designed to measure the curvature of the central cornea, and it is the term most commonly used today.[1]

The keratometer measures the central 2–4 mm of the anterior curvature of the cornea, commonly referred to as the corneal cap. The measurements, known as K readings, are expressed in either diopters or millimeters of radius. From an optical perspective, the cornea is similar to a convex mirror. The mires of the keratometer form an image that is reflected from the anterior corneal surface. This image is virtual, small, and erect. Using equations based on the theory of reflection from a convex mirror, one can determine the radius of curvature of this anterior corneal surface. By aligning the mires of the keratometer, which are the targets that are reflected from the anterior corneal surface, one obtains the K readings in both the flat and steep meridians of the cornea.[2] This gives an objective measurement of the corneal astigmatism and power. The target image differs depending on which keratometer is used.

TYPES OF KERATOMETERS

With the Bausch & Lomb keratometer, the operator sees three reflected images, or mires, each consisting of a circle with a plus sign at the 3 o'clock and 9 o'clock positions, and a minus sign at the 12 o'clock and 6 o'clock positions (Fig. 8.1). The lower right-hand circle is the 'central' circle, which is the image of the reflected mires from the cornea. The image is reflected from approximately the central 3.2 mm of the cornea. However, this can range from 2.6 to 3.7 mm, depending on the steepness or flatness of corneal curvature.[1] This reading represents the distance between the two reflective points that the keratometer is measuring from the corneal surface. The assumption is that the curvature between these two points is spherical. This is not always the case and can lead to errors in measuring the corneal surface. However, the quality of the image that one obtains can also identify a steep or flat cornea. For example, a steep cornea gives a smaller image than a flat cornea. With the Haag-Streit keratometer, there are two images of different colors with a horizontal line through their centers (Fig. 8.2). Multiple steps are required to obtain the K readings. The operator aligns the two front surfaces of each image in first horizontal and then the vertical meridians to obtain the K readings of the corneal surface. Likewise, the operator can also obtain information about the corneal surface from the quality of the boxes and the mires. The boxes will be somewhat smaller in a very steep cornea and larger in a flat cornea. In the last 20 years, several intraoperative keratometers have been developed. The main rational for the development of these instruments was to help control surgically induced astigmatism during cataract and corneal transplant surgery. Although some are still available and may be helpful during corneal transplant surgery, the popularity of small incision cataract surgery, with minimal surgically induced astigmatism, has obviated the need for these devices.

USING THE KERATOMETER

The keratometer is very helpful in identifying and verifying corneal astigmatism. The difference between the measurements of the horizontal and vertical meridians indicates the amount of regular corneal astigmatism. In the presence of regular astigmatism, the plus and minus mires of the Bausch & Lomb, or the horizontal and vertical mires of the Haag-Streit, easily align themselves in the vertical and horizontal meridians. If the flattest meridian is within 30° of 180°, then the corneal astigmatism is considered to be with the rule, whereas if the flattest meridian is 30° of 90°, then the corneal astigmatism is against the rule. In the presence of irregular astigmatism, the operator, using the Bausch & Lomb keratometer, is unable to align the horizontal and vertical meridians

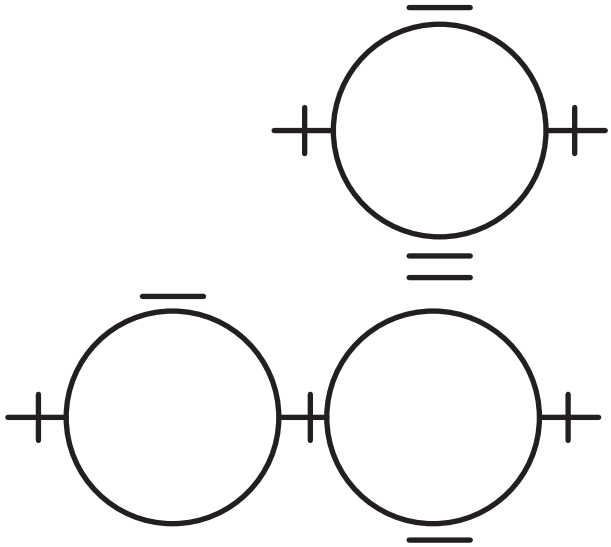

Figure 8.1. The reflected images (mires) of the Bausch & Lomb keratometer.

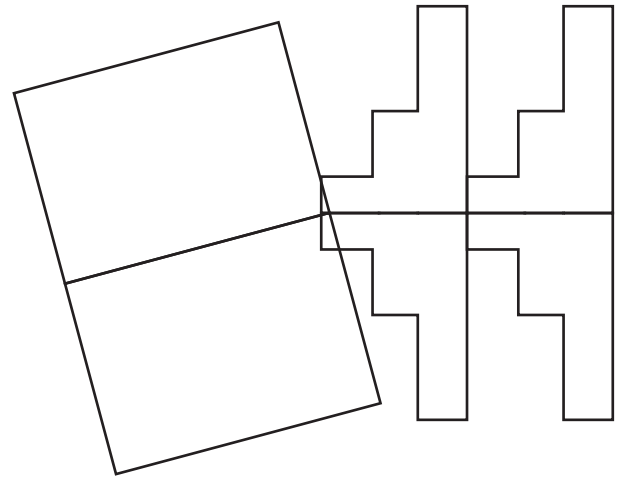

Figure 8.3. The Haag-Streit keratometer showing irregular astigmatism with the inability to line up the two image boxes. (From Leibowitz HM. Corneal Disorders: Clinical Diagnosis and Management. Philadelphia: WB Saunders; 1984. © Elsevier 1984.)

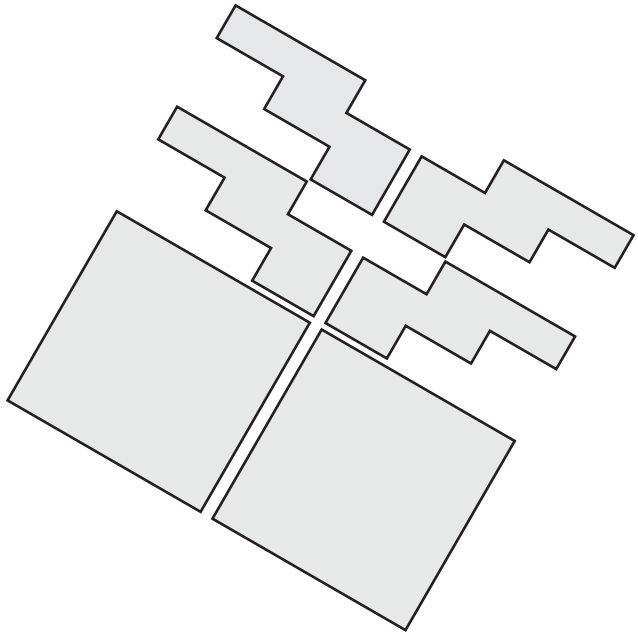

Figure 8.2. The Haag-Streit keratometer showing the two images with horizontal lines through the center.

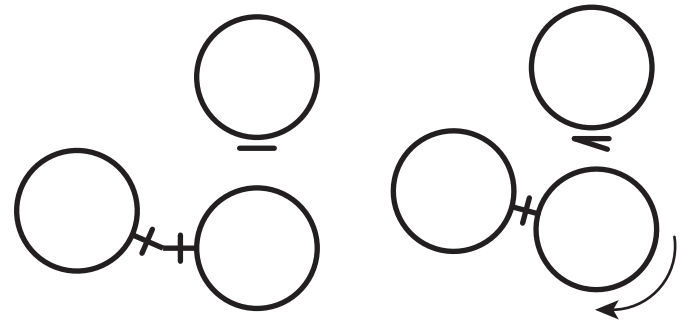

Figure 8.4. Inability to align the plus and minus mires with the Bausch & Lomb keratometer in keratoconus. (From Leibowitz HM. Corneal Disorders: Clinical Diagnosis and Management. Philadelphia: WB Saunders; 1984. © Elsevier 1984.)

simultaneously. With the Haag-Streit keratometer, the alignment of the front surfaces of the two images is slightly ajar. As the irregular astigmatism increases, the operator sees distortion of the boxes and has greater difficulty in aligning the flat surfaces of each of the target boxes. This instrument is very sensitive and can detect the slightest presence of irregular astigmatism. The ability to detect minimal amounts of irregular astigmatism may be very important in the evaluation of the refractive surgical patient. In keratoconus, a lack of parallelism of the mires of the Haag-Streit keratometer with distortion of the size of the two box images is seen (Fig. 8.3). With the Bausch & Lomb keratometer, there is an inability to line up the plus and minus mires (Fig. 8.4). Also, the plus mires may jump from one side to the other when alignment is attempted (Fig. 8.5), and often the circles can be irregular or blurry.[3]

In patients with tear film deficiency, the practitioner can see abnormalities on the corneal surface.[4] The mires of the keratometer become distorted as dry spots occur on the corneal surface. Immediately after the blink, the mires are sharp, but as the tears begin to break up, the mires are distorted. In patients with dry eye who have rapid breakup of the tear film, one can easily visualize this irregularity during the course of obtaining the K readings of the cornea. The amount of mire distortion is a good measure of the severity of the corneal surface. The keratometer is invaluable in the fitting of contact lenses.[2] It helps the contact lens fitter to decide on the appropriate back and central optical radius of the contact lens, to monitor changes in the central cornea with contact lens wear, to evaluate the quality of the soft contact lens front surface, and to check the radii of curvature of the contact lens before dispensing it to the patient. In both soft and rigid contact lens fitting, the keratometer provides baseline information on the corneal curvature. The practitioner can then determine by repeated keratometry studies whether the contact lens, either soft or rigid, is affecting the corneal curvature or causing corneal molding.[5] With rigid contact lens fitting, the keratometry readings obtained provide a starting point for determining the base curve of the rigid lens that is applicable to that patient's cornea. In soft contact lens fitting, keratom-

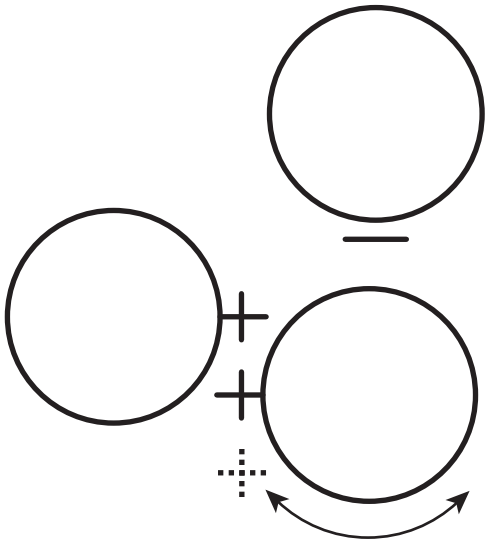

Figure 8.5. The plus mire jumping from each side as the operator tries to align the plus mires of each of the two circles. (From Leibowitz HM. Corneal Disorders: Clinical Diagnosis and Management. Philadelphia: WB Saunders; 1984. © Elsevier 1984.)

etry can demonstrate the corneal surface characteristics of the soft lens by the quality and stability of the mires.[5]

When observing patients with both soft and rigid contact lenses, comparisons of keratometry readings made on successive visits provide valuable means of detecting corneal changes secondary to the contact lens. If the contact lens is deforming the cornea, then the mire images will be distorted. This can vary from mild distortions, as in irregular astigmatism, to severe distortion, as in keratoconus. Keratometry taken on the front surface of a soft contact lens can reveal the quality of the contact lens surface. If the contact lens becomes coated, mire images will appear indistinct. In refractive surgery, the keratometry is helpful in the pre-evaluation in determining the presence of irregular astigmatism. The K readings are important in determining keratome selection and settings. Preoperative keratometric readings are often used to predict the expected corneal curvature following the refractive procedure. While the acceptable range of postoperative corneal curvature values will vary from surgeon to surgeon, most refractive surgeons feel comfortable with a postoperative corneal curvature between 38 and 50 D. Outside this range abnormalities in the cornea's optical performance can degrade visual results.

Studies have found that following refractive surgery the mean subjective refraction decreased more than the mean corneal dioptic power measured with either videokeratoscope or manual keratometry.[6] The central corneal power as measured by the keratometer as well as by video keratoscopes is thus erroneously higher than the actual central corneal power.[7,8] This can have an adverse effect on the determination of IOL power when cataract surgery is considered. Various formulas and methods have been developed to improve the accuracy of IOL power calculation in postrefractive patients.[8,9]

LIMITATIONS

There are limitations of the keratometer of which one must be aware. The keratometer only measures a small area of the cornea, approximately 2.6–3.7 mm, and thus does not give an accurate picture of the peripheral cornea. However, with certain adaptations, such as the topogrameter or by having the patient look up, down, or to the side, one can determine certain peripheral corneal values.[1] In addition, it is important to understand that the measurements obtained are taken along the visual axis, rather than the geometric axis. The visual axis is usually nasal compared with the geometric axis, and thus the curvature of the visual axis may be slightly flatter compared with the geometric axis. If, in taking the measurement, the eye rotates so that the mires do not have a perpendicular incident to the eye, abnormal readings of the corneal surface can be obtained. Highly myopic corneas and highly astigmatic corneas can yield incorrect values. However, in our experience, the amount of astigmatism in the axis obtained with the keratometer is very similar and consistent when compared with the computerized topography studies available.

CONCLUSIONS

In summary, the keratometer is a relatively inexpensive instrument that can easily be used by all eye care personnel. The operator can verify the amount of corneal astigmatism present, can determine whether the surface is regular or irregular, and can identify possible abnormalities, such as dry eye surface characteristics. In addition, it provides valuable information for contact lens fitting and follow-up care. It is helpful in determining the presence of regular or irregular astigmatism and the presence of corneal astigmatism and residual astigmatism.

In the presence of more sophisticated computerized corneal measuring instruments, the keratometer, even with its limitations, still remains an instrument that is important for all eye care practitioners.

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9 Corneal structure and function: Placido-based corneal topography

Stephen D. Klyce, Tetsuro Oshika

Corneal topography analysis has become the standard of care for the anterior segment specialist. Accurate analysis of corneal shape has become particularly indispensable for refractive surgeons as a method for preoperative screening, surgical planning, assessment of surgical outcomes, detection and management of complications, and the development and refinement of surgical techniques. Other important applications are in the fields of contact lens fitting, evaluation of intraocular surgery such as cataract surgery, postoperative management of keratoplasty, and diagnosis as well as monitoring of keratoconus and other corneal ectatic noninflammatory diseases. This chapter reviews the basic concepts of Placido disk-based corneal topography.

PRINCIPLES OF THE PLACIDO DISK CORNEAL TOPOGRAPHER

Modern corneal topography was first developed using Placido disk technology,[1] and this approach has been recognized as the most widely accepted, used, and understood. The Placido target is a series of concentric illuminated rings (mires) that are reflected by the convex, mirror-like corneal surface and are imaged, along with the cornea, by a video camera (Fig. 9.1). The number of mires projected onto the cornea varies with the model; in general, closely spaced mires with a large area of coverage are desirable. Close spacing with a small diameter central mire will permit the highest spatial resolution; however, the more closely the mires are spaced, the sooner will large corneal irregularities merge adjacent mires and make analysis inaccurate. Since the detection of subtle surface distortions is paramount for the early detection and diagnosis of corneal pathology, the fine mire Placido disk may be optimal. Area of coverage becomes important for contact lens fitting as many contact lenses ride on the peripheral cornea. Good area coverage is also needed to detect keratoconus when it involves the peripheral, usually inferior, cornea. Variations in mire geometry are shown in Figure 9.1.

The two-dimensional digital image of the eye with the reflected mires is stored in computer memory and analyzed to reconstruct the three-dimensional corneal shape. The size and distortion of ring patterns are the basis for the calculation. The ring location relative to the center of the pattern determines radial distance, and the size of rings and the spacing between rings determine the local radius of curvature. Closely spaced rings indicate higher corneal powers, and widely spaced rings represent lower powers. Corneal powers are calculated for 6000–23 000 points with topography units. There are several algorithms used for reconstructing corneal shape from the mire positions; the arc-step method is generally agreed to be the most accurate.

The dioptric power of the cornea is derived from the local radii of curvature using one or more methods. Axial power is calculated using a fixed center of curvature on the corneal topographer axis for calculating the power at all points along semimeridians on the corneal surface:

$$P_{\text{axial}} = (n' - 1) / r_{\text{axial}} \quad (1)$$

where $n' = 1.3375$ (the keratometric index of refraction) and r_{axial} is the distance from the corneal surface to a point of intersection on the corneal topographer axis. The n' is not a true refractive index of the cornea, but an approximated index to yield the total corneal power as a single refracting surface by compensating for the negative power of the posterior surface.

Axial power tends to have a spherical bias because each curvature measured is referred to the optical axis. For aspherical surfaces, this bias gives an accuracy better than 0.25 D in the central cornea, but this can fall to 3 D in the periphery by comparison to 'instantaneous power.'[2]

The 'instantaneous power' is calculated based on a floating center of curvature by means of a standard mathematical method for determining the local radius of curvature:

$$P_{\text{inst}} = (n' - 1)/r_{\text{inst}} \quad (2)$$

where again, $n' = 1.3375$ and r_{inst} is the radius of curvature for any given point on the cornea. Calculations have less spherical bias because curvature is calculated without reference to the reference axis or the overall shape of the cornea. However, the method is more sensitive to small measurement error than the axial power calculation, which can introduce unwanted 'noise' artifact in the color-coded map.

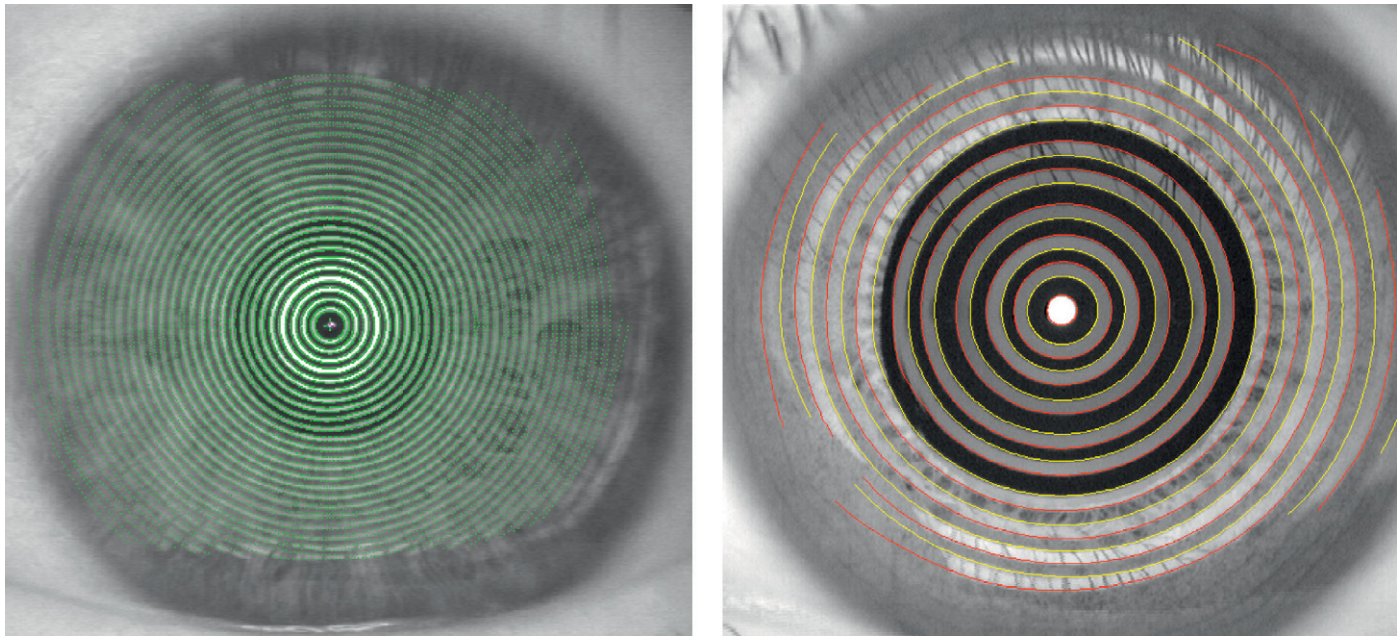

Figure 9.1. Placido mire patterns differ among corneal topographers. The pattern generated by the fine mire cone projector of the Nidek Magellan topographer is shown on the left, while the wide mire pattern made with the Nidek OPD-Scan is shown on the right.

For the central paraxial rays where the sagittal depth is approximately proportional to the curvature, paraxial power formulas can be used. Outside the central region, however, the assumptions used in Equations (1) and (2) are not necessarily valid.[3] The appropriate equation for the 'refractive power (secondary focal point power)' for the incoming parallel rays is given as:

$$P_{\text{ref}} = n/f \tag{3}$$

$$f = z + y/\tan(\theta_i - \theta_r) \tag{4}$$

where f is the distance from the vertex normal to the secondary focal point (where the refracted ray intersects the videokeratoscopic axis) located in the image space, z is the dimension along the videokeratoscopic axis from the vertex normal to the surface point, and θ_i and θ_r are the angles of incidence and refraction, respectively. It should be noted that in order to successfully calculate corneal power using the focal length method, the local shape or slope of the cornea must be known beforehand in order to calculate the angles of incidence and refraction.

No unanimous opinion has been reached regarding which of these three methods is the best for displaying corneal power (Fig. 9.2). The axial power formula produces inaccurate refractive power values for peripheral portions of the cornea as it does not encompass the effects of spherical aberration. However, the method does have the advantage of providing maps that are very simple to interpret for the clinician and values that are directly comparable to keratometry. The instantaneous power formula attempts to offer a more realistic representation of the peripheral corneal topography by determining corneal power from the local slope. This method produces significantly better estimates of the peripheral corneal power than the axial power formula. However, repeatability is less and noise is greater than the axial power measurement, since the instantaneous value is a conversion from the axial value based on a second derivative.[4,5] The refractive power (secondary focal length power) analysis is theoretically valid and provides realistic values for corneal power in the periphery, but the refractive power map is less familiar to clinicians and not easy to interpret. In addition, although the refractive power map shows the residual corneal spherical aberration in the periphery, it cannot show how much of this is further compensated by the shape and the radial refractive index gradients present in lens of the eye, since this information is not available on a per patient basis unless aberrometry is simultaneously employed.

DISPLAY FORMAT

COLOR-CODED MAP: SCALING

The color-coded contour map of corneal surface power has been adopted as a standard presentation scheme in corneal topography.[6] The color-coded contour map markedly facilitates the viewer's interpretation through the association of power with color and recognition of pathology with the patterns formed by the map contours. Warm colors—red and orange—are used to represent relatively higher powers (steeper curvatures), green and yellow are used for powers associated with normal corneas, and cool colors—hues of blue—are used to denote relatively lower powers (flatter curvatures). This concept, along with standard scales, provides an intuitive basis for the interpretation of corneal topography.

The use of a standardized and fixed color scale for routine clinical examinations is important for consistent and correct evaluation of corneal topography. Scales that adapt themselves to the range of powers on an individual cornea can lead to confusion (Fig. 9.3). A physiological asymmetry or astigmatism may be amplified by an adaptable scale and possibly lead to misdiagnosis as pathological. Alternatively, a cornea with substantial irregular astigmatism can be made to look less abnormal with an adaptable scale.

Initially, a standardized absolute scale was proposed,[6] ranging from 9.0 to 101.5 D with the central portion of the range in 1.5-D

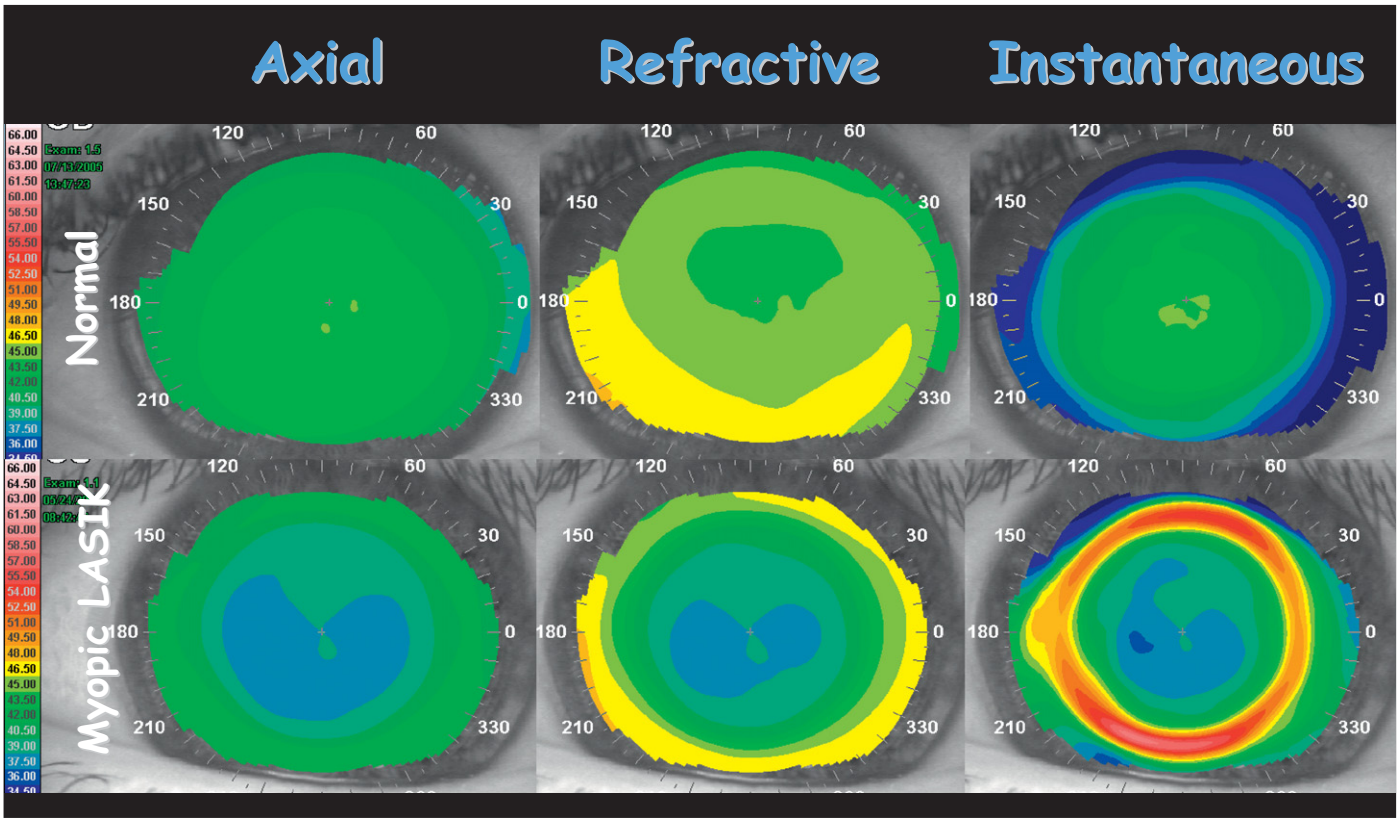

Figure 9.2. Corneal topography displayed with different power calculation methods. Upper row is a normal cornea. Lower row is a cornea following the LASIK procedure for the correction of myopia. Left-hand column uses the axial power method; central column uses the refractive power calculation; while the right-hand column uses the 'instantaneous power' (also called tangential) calculation (see text for details). Note that using the axial power method, both normal and LASIK cornea display the sense of corneal shape—the normal cornea is uniform in the center and flattens toward the limbus; the LASIK treated cornea has been flattened in the center. Note the 'red ring' illustrated with the instantaneous power method with the LASIK cornea. This is an example of the usefulness of that power method as the red ring (not seen with the axial method) is known to be responsible for night vision complaints in some patients.

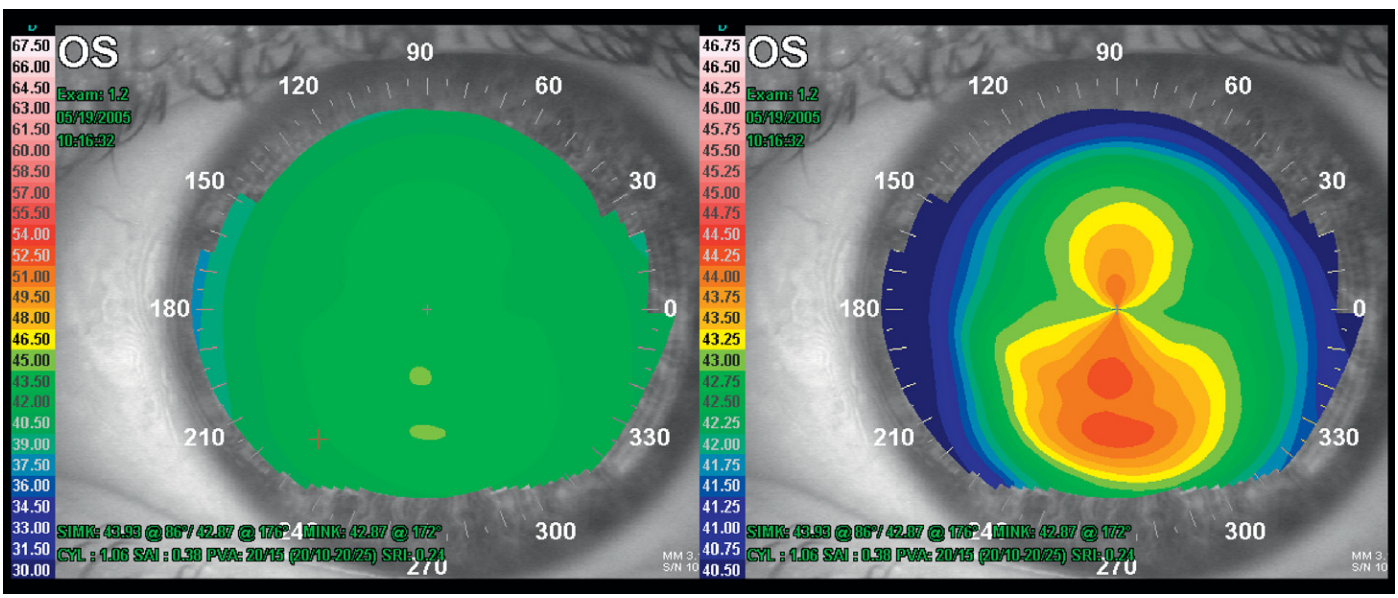

Figure 9.3. Corneal topography scales that are fixed and of a proper dioptric interval are important to establish consistent interpretation. The cornea illustrated above has a minor amount of asymmetry, but is otherwise normal. It has that appearance with the Smolek/Klyce scale used on the top left display, but the same cornea looks pathologic (keratoconus?) with a 0.25-D scale often used in corneal topography.

steps, and the extreme limits of the range in 5.0-D steps. While this range covered the entire corneal power spectrum seen in corneal practice, salient topographic features were occasionally lost within the 5-D intervals, particularly at the low end of the scale. Hence, this was modified to the so-called Klyce/Wilson scale,[7] which ranges from 28.0 to 65.5 D in equal 1.5-D intervals. It has been argued that the 1.5-D interval between contours is so wide that irregularities in corneal topography may be masked. However, it has been demonstrated that the 1.5-D scale could detect all the topographic characteristics sensed by a more sensitive 1.0-D scale in a consecutive series of patients that included contact lens wearing corneas, early to moderate and advanced keratoconus, penetrating keratoplasties, extracapsular cataract extraction, excimer laser photorefractive keratotomy, radial keratotomy, aphakic epikeratophakia, and myopic epikeratophakia.[7]

The corneal topographers currently on the market have their own standard color scales and the actual power values, intervals, and colors used differ from machine to machine. Presentation of data in varying or nonstandard formats inhibits easy interpretation and precludes comparison from one machine to another. One absolute color scale should be common to all devices as a standard feature, independent of technology. If all topography machines provided the same data using the same color scale, the resulting consistency would greatly facilitate interpretation.[8]

ELEVATION MAP

With the expanding application of the new forms of refractive surgery, especially LASIK and new forms of surface ablation, increasing attention is directed toward a topographic map which depicts the corneal shape in terms of height, as well as curvature and power. There is a claim that the elevation map is the true representation of corneal topography as opposed to a derivative form. The elevation map could be highly useful in contact lens fitting and keratoconus shape analysis. In Placido disk systems, the corneal height is calculated from the curvature, while in the non-Placido disk system height information is first obtained and then the curvature is derived.

Although the idea of comparing corneal height before and after refractive surgery appears interesting, there are several difficulties in doing so with sufficient reproducibility. Firstly, alignment of the two elevation data sets for comparison is challenging, in that a stable reference zone must be identified where the elevation has not been altered by the surgery. The corneal apex is inappropriate. Secondly, geometric elevation is relatively insensitive to optically significant surface features, and thus all systems that use the elevation actually must display a map of the relative change in elevation by subtracting a spherical component from the data. There are currently no standards for the best-fit sphere component to be subtracted. Thirdly, standardization of the color-code remains to be established. If color is standardized to the elevation relative to a mean sphere, the scale will not be consistent from map to map where the mean sphere varies from eye to eye. This is similar to the comparison difficulty that occurs with the adaptable scale for the dioptric map.

Another potential problem is the inherent discrepancy in the way the elevation and dioptric maps are interpreted. Since many of us are familiar with the Placido disk system and the dioptric map which has been in use for a decade, reading the newer elevation map requires a learning curve. The slope (or power) and elevation are rarely synonymous. The fact that cool colors indicate an area of lower power in the dioptric map vs. a depressed area in the elevation map may be somewhat incomprehensible. In astigmatic keratotomy, the incisions are always made in the steeper meridian. On a power map, the incision is placed in the axis of warm colors. On an elevation map, it would be placed in the axis of cool colors (the area of depression).

QUANTITATIVE INDEXES

The color-coded map is a qualitative display of the data, which is designed to allow rapid and easy pattern recognition. On the other hand, there have been several means to mathematically analyze the data so that the information is represented as quantitative indexes (Fig. 9.4). These indexes can be compared to a normal range, or grouped to summarize the topography of several patients, as in clinical studies.

Simulated keratometry (Sim K) is a relatively simple corneal index that is equivalent to the conventional keratometer readings, and is offered by all topography devices. The indexes first incorporated in TMS system include the surface asymmetry index (SAI), which measures the difference in corneal power at each ring and compares symmetry, and the surface regularity index (SRI), which represents local fluctuations in the central corneal power.[9,10] The potential visual acuity (PVA) is an estimation of predicted visual acuity based on SRI. The Holladay diagnostic summary display of EyeSys system also provides several numeric indexes, such as asphericity values (Q), regular astigmatism (Reg Astig), corneal uniformity index (CU), and vertical and horizontal pupil decentration data.[11]

The numerical approach has been also extended for the quantitative method of differential diagnosis. This was first done by Rabinowitz and McDonnell, who examined central corneal powers and inferior to superior midperipheral power differences obtained from corneal topography examinations in order to detect keratoconus.[12] In a system designed to detect and discriminate keratoconus from other clinical situations, eight topographic indexes were evaluated:[13] Sim K1 and K2, SAI, the differential sector index (DSI), opposite sector index (OSI), the center surround index (CSI), the irregular astigmatism index (IAI), and the analyzed area (AA). The analysis yielded the keratoconus prediction index (KPI), which could detect keratoconus with very high sensitivity and specificity among corneas of various entities, i.e. normals, keratoconus, regular astigmatism, keratoplasty, epikeratoplasty, photorefractive keratectomy, radial keratotomy, contact lens-induced warpage, astigmatic keratotomy, scarred corneas, postretinal detachment surgery, postcataract surgery, and keratomileusis.[13] This approach has been extended to use neural networks[14] and to simultaneously classify normal, astigmat, keratoconus suspect, keratoconus, pellucid marginal degeneration, penetrating keratoplasty, myopic refractive surgery, and hyperopic refractive surgery.[15] This automated classification of corneal topography (Fig. 9.5) is a very useful tool as a screening of refractive surgery candidates as well as a tool with which to explore the natural history of keratoconus and other corneal conditions.

Other applications of quantitative indexes of corneal topography are the assessment of refractive surgical results, including the quantitative analysis of irregular astigmatism, central islands following excimer laser photorefractive keratectomy, and decentration of refractive surgeries.[16,17] Other approaches, such as decomposition of topographic data using the Fourier series[18,19] or the Zernike polynomials,[20] are useful to investigate the optical quality of the cornea after ocular surgery or trauma (Fig. 9.6).

Figure 9.4. Statistics derived from corneal topography can be useful to differentiate specific shortcomings of individual corneas. In the illustration, the right column lists statistics developed from analysis of the topographies shown in the left column. On the top row is a normal topography while the bottom row is a decentered radial keratotomy procedure. Each of the statistics are color coded so that those within the range for a normal population are green, those two to three standard deviations from the mean of normals are colored yellow, while those more than three standard deviations from the normal are indicated in red. See text for further details.

LIMITATIONS

Corneal topography has become an integral part of refractive surgery and diagnosis of corneal diseases. As with many clinical tests, however, topography has limitations and can provide misinformation if intentionally or unintentionally abused. For example, topography devices, including the Placido disk system, can be sensitive to alignment and focusing errors.[21–23] Inadequately compensated focus and/or alignment has been found in the past to produce artifactual information. Tear film breakup can be a source of artifacts if a prolonged fixed gaze is requested by the operator; the effect is usually poor tracking with missing data and a map with the appearance of irregular astigmatism. In routine clinical settings, both keratometry and corneal topography are best done as the first procedure, before instillation of topical medication, intraocular pressure measurement, refraction, or external examination, to preserve the normal corneal tear film. It should be noted that precise and meaningful analyses are only possible when data acquisition is proper; correct operation of the topographer and patient cooperation are all important.

CONCLUSION

Corneal topography has established its unique role in ophthalmology as a noninvasive, qualitative, as well as quantitative measurement tool which processes huge amounts of data to be viewed and utilized in various forms. It is said that this technology is one of the most important diagnostic advances in recent years. The development and evolution of modern refractive surgery seem to have been the wind that fanned the rapid growth of corneal topography, and vice versa.

Corneal topography is a continuously evolving technology which has yet to achieve its final form. Several important issues remain to be further elucidated, and new technologies are on the horizon. The exciting fields in the future include real-time topographic analysis in the operating room, more robust and device-independent expert systems for classification of corneal topography, and further analyses of the correlations between optical quality of the cornea and corneal shape. The advancements in topographic technology will play ever-expanding roles in adding to our knowledge and understanding of the most powerful refractive surface in the eye, the cornea.

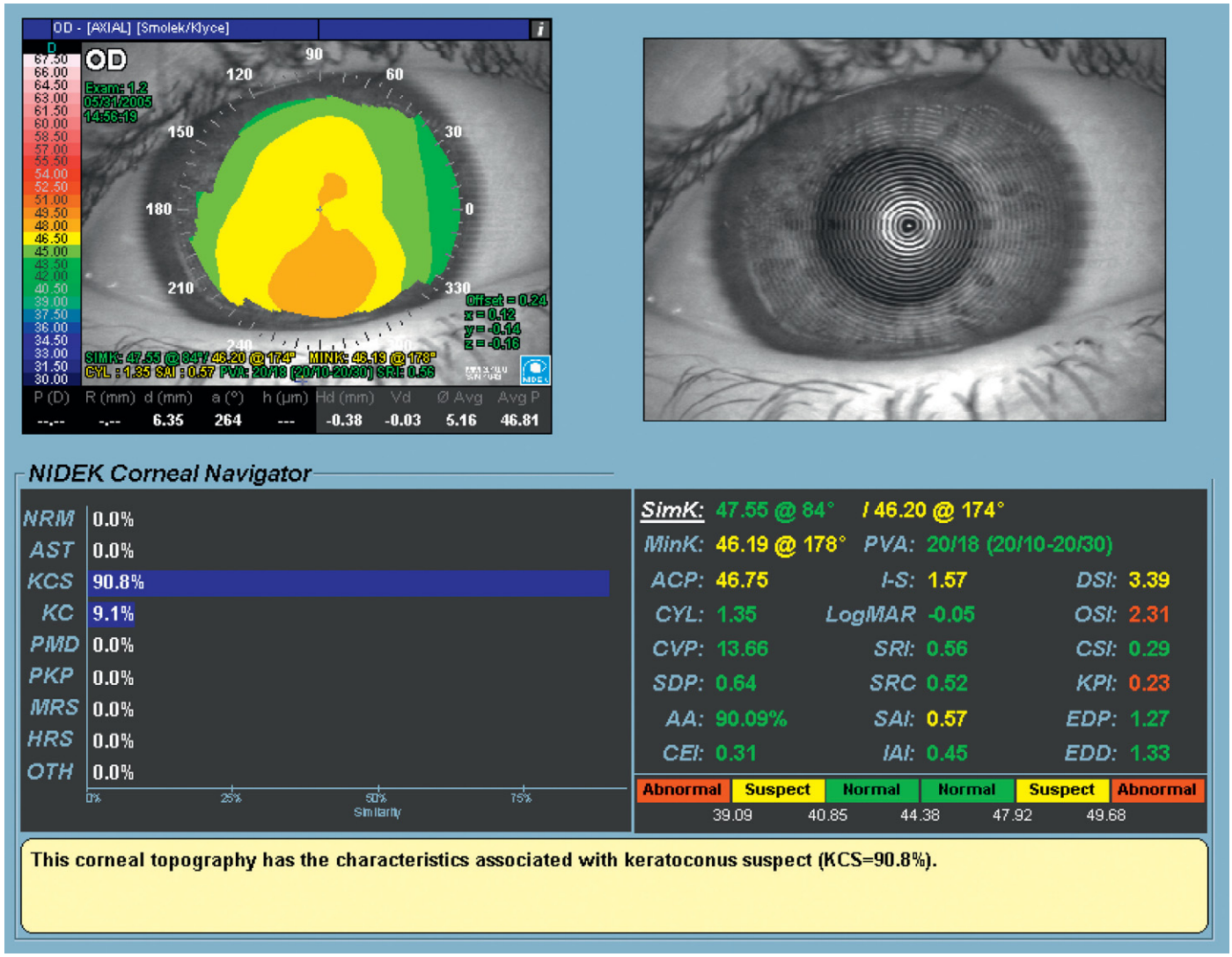

Figure 9.5. An example of the Nidek Magellan Navigator (corneal navigator) program, which classifies several categories of corneal topography. This cornea has the features consistent with a suspect keratoconus (KCS) cornea and is on the borderline for classification of clinical keratoconus (KC).

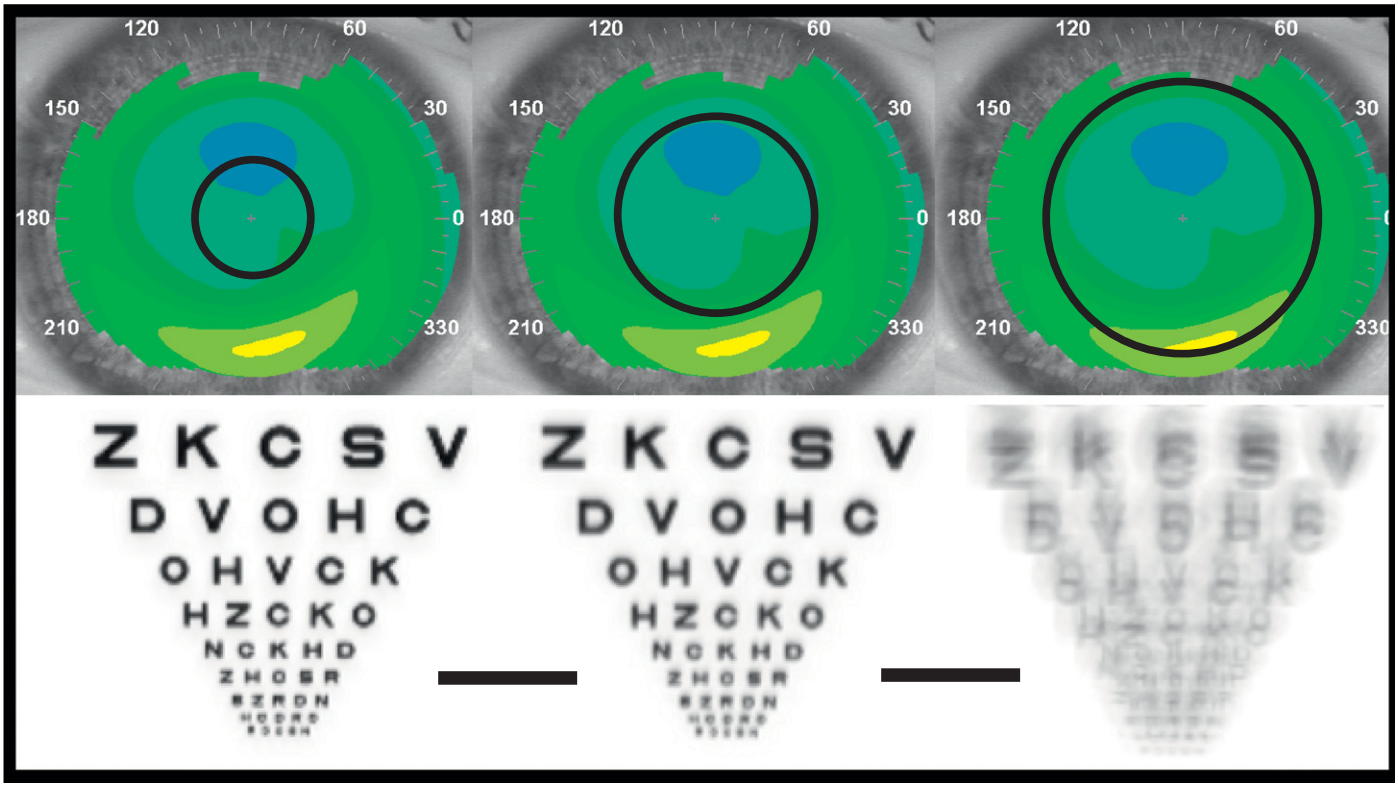

Figure 9.6. Using Zernike analysis to demonstrate corneal optical performance. The cornea received LASIK for myopia. Illustrated is a standard eye chart viewed with the aberrations contained within a 3-mm pupil (top left), 5-mm pupil (top center), and 7-mm pupil (top right). Note that the cornea has 20/20 potential for the 3-mm and 5-mm pupils, but when the pupil is expanded to 7 mm, vision falls to 20/60 (top row of letters on this chart). This demonstrates the need for large, well-centered treatment zones with refractive surgery which should avoid potential night vision complaints.

ACKNOWLEDGMENTS

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10 Corneal tomography and anterior chamber imaging

Catherine E. Wheeldon, Charles N.J. McGhee

INTRODUCTION

The word 'topography', derived from the Greek words *topos* meaning 'place' and *graphien* meaning 'to write', can be defined as the science of describing, or representing, the features of a particular place in detail. The similarly sounding, but differing, tomography is derived from the Greek *tomos* meaning 'a section' and herein lies the essential distinction between topography and tomography: the former is a two-dimensional representation of the anterior corneal surface, the latter a three-dimensional representation (or section) of the cornea and anterior segment. Thus, a contemporary computerized tomographer may also be a corneal topographer but the reverse is not necessarily true.

As detailed in earlier chapters, although Christopher Scheiner (1619) was the first to document attempts to measure the anterior corneal curvature, and Helmholtz introduced the concept of ophthalmometry (keratometry) in 1856, it was not until 1880 that Placido's disk of alternating white and black circles with a central perforation enabled qualitative assessment of more than four points of the central corneal surface. Surprisingly, despite the development of several techniques, the quantitative clinical potential of the Placido disk was not realizable until the development of the personal computer and video frame grabbers 100 years later—in the mid-1980s. Since the late 1980s the most widely established computerized video-keratography systems have been based on Placido disk technology. Through a set of complex algorithms, quantitative assessment and virtual reconstruction of the curvature of the corneal surface is possible. However, such Placido-based curvature topography does not directly measure true elevation topography nor provide a three-dimensional reconstruction of corneal thickness or the anterior chamber. The first widely commercially available corneal tomographer was the Orbtek Orbscan slit-scanning device launched in 1995, more recently (2002) the Oculus Pentacam tomography device has attracted considerable clinical interest.

The first system to use elevation topography to establish the true anterior corneal surface shape was the no longer available PAR Corneal Topography System (PAR Vision Systems Corp.) using the principle of triangulation. However, when the Orbscan (Orbtek, Inc.) was introduced into clinical practice in 1995 it provided a new paradigm for corneal analysis. Using eye tracking with scanning-slit or parallelepiped methodology, and the principle of measuring the dimensions of a slit-scanning beam projected onto the cornea, it can assess both the anterior and posterior surfaces of the cornea, as well as the anterior surfaces of the lens and iris.[1]

This chapter deals in some detail with the more widely available contemporary corneal/anterior segment tomography units—the slit-scanning Orbscan II and the rotational Scheimpflug-based Oculus Pentacam system. It will also outline the more established method of ultrasound pachymetry and specialized anterior segment tomographic applications of ultrasound biomicroscopy (UBM) and optical coherence tomography (OCT).

ORBSCAN II SLIT SCANNING TOPOGRAPHY

More than 100 scientific publications have documented the significant advantages and modest limitations of Orbscan tomography since its clinical launch a decade ago.[1] The original Orbscan was designed to acquire elevation information directly, but important curvature information can also be derived from this. However, the later development of the Orbscan II (Orbtek, Inc.) following the incorporation of the slit-scanning technique with a Placido disk attachment meant that curvature information could be derived directly (Fig. 10.1). The most recent model, the Orbscan IIz (Bausch & Lomb), is integrated with a Shack-Hartmann aberrometer in the Zyoptix workstation where information from both examinations can be transferred for direct treatment with the Bausch & Lomb Technolas excimer laser systems.

The Orbscan II and IIz devices incorporate both a Placido disk and a slit-scanning technique using white light, enabling both two-dimensional anterior corneal topography and three-dimensional corneal and anterior segment tomography (Fig. 10.2). During the data acquisition phase with the Orbscan IIz, the Placido disk is illuminated and the reflection of its mires from the anterior corneal surface is stored. Following this, 40 slits, 20 from left and 20 from right, 12.5-mm high and 0.3-mm wide, are projected onto the cornea at an angle 45° to the instrument axis. The appearance of the backscattered light from these slits is recorded as a two-

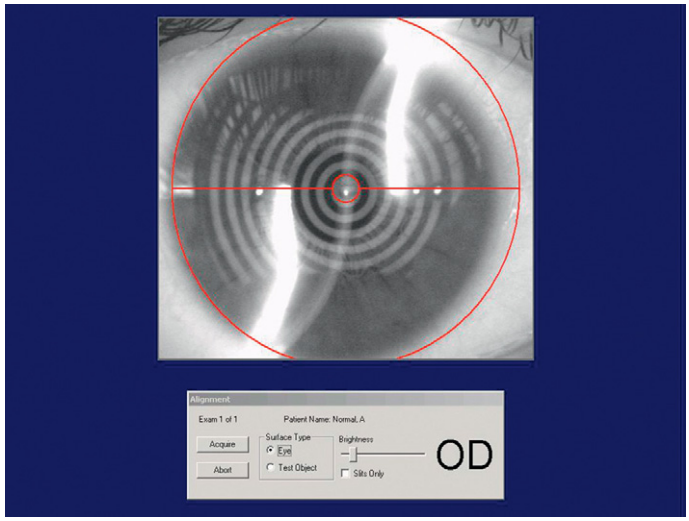
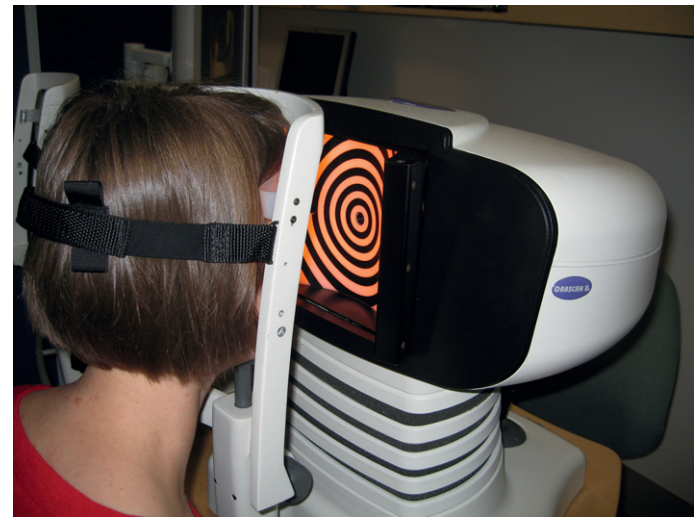


Figure 10.1. Screen image of Orbscan II showing the combination of Placido and scanning slit mires (overlapping centrally).

A



B

Figure 10.2. Orbscan II: Patient's view (*A*) and patient position (*B*) during scan. The data calculated on internal surfaces of the eye are not as precise as the anterior surface, as it is measured indirectly. These surfaces are calculated from the previously generated anterior topographic representations of elevation and curvature which will therefore exert an influence on the measurements.[2]

dimensional image by the digital video camera in the device. The acquisition is rejected if there is excessive movement or incomplete images, and the examiner is prompted to reacquire the data. By detecting the anterior edge of each slit and the edge of the reflected mires from the Placido disk, using the principles of triangulation, the system creates an elevation topographic representation and curvature reconstruction of the anterior surface of the cornea. Further processing of the collected data enables the system to then digitally recreate the posterior cornea, anterior iris, and lens.

This noncontact examination process takes a few seconds and relies on the subject placing their chin on the chin rest, and maintaining steady fixation on the center of the fixation target while not blinking. The processing phase, of up to 9000 data points from each assessment, takes approximately 30 s and following this a total of more than 30 anterior segment topo/tomographic maps can be created. The more practical display options tend to include axial and tangential keratometric curvatures, pachymetry, and anterior and posterior floating best-fit sphere (BFS) (Fig. 10.3).

The most established method of depicting the anterior corneal surface topography is the curvature or keratometric (dioptric) power map. Technically, since the relationship between power and radius of curvature is nonlinear, dioptre scales should be used only to describe the refractive power of the cornea and not its curvature. Axial topography is presented from the radius of curvature measurement by analyzing the reflection of the Placido disk to provide the normal to the surface, and then relating this to the instrument axis. If adjacent data are collated these will then reveal local curvature change or tangential topography. While derivations on axial curvature can describe how the cornea performs in a 'global' refractive sense, tangential curvature can better represent the 'local' shape of the anterior corneal surface (see Ch. 9 for further details).

In analyzing the anterior and posterior surface of the cornea, Orbscan can also provide total optical power (TOP) maps, a measure of the optical focusing capacity of the cornea. TOP maps have shown an encouraging correlation with manifest refraction when compared to anterior axial maps for detecting the refractive change postmyopic LASIK.[3]

True corneal elevation data are relatively insensitive to optically significant surface components; therefore, for the presentation of elevation topography the Orbscan uses a BFS technique, i.e. a sphere whose radius of curvature and position relative to the instrument axis can be altered to best fit the surface being measured. This allows small deviations in the surface shape to become more apparent (Fig. 10.4). The default floating BFS offers a useful means of analyzing the surface profile of the entire area measured. The BFS can be constrained in various means to highlight particular examination features. For example, limiting the radius of curvature of two separate anterior elevation maps to the same value might aid in the understanding of their topography, or fixing the virtual center of the BFS to the instrument axis to monitor for progression in keratoconus by preventing the floating BFS fitting off center, which could otherwise normalize the appearance of the maps.[4]

It is important to note that not all Orbscan acquisitions provide a complete map due to the effect of eyelids, reflections, etc. If peripheral, typically flatter, data are missing a BFS will have a decreased radius of curvature to best fit the steeper, more central

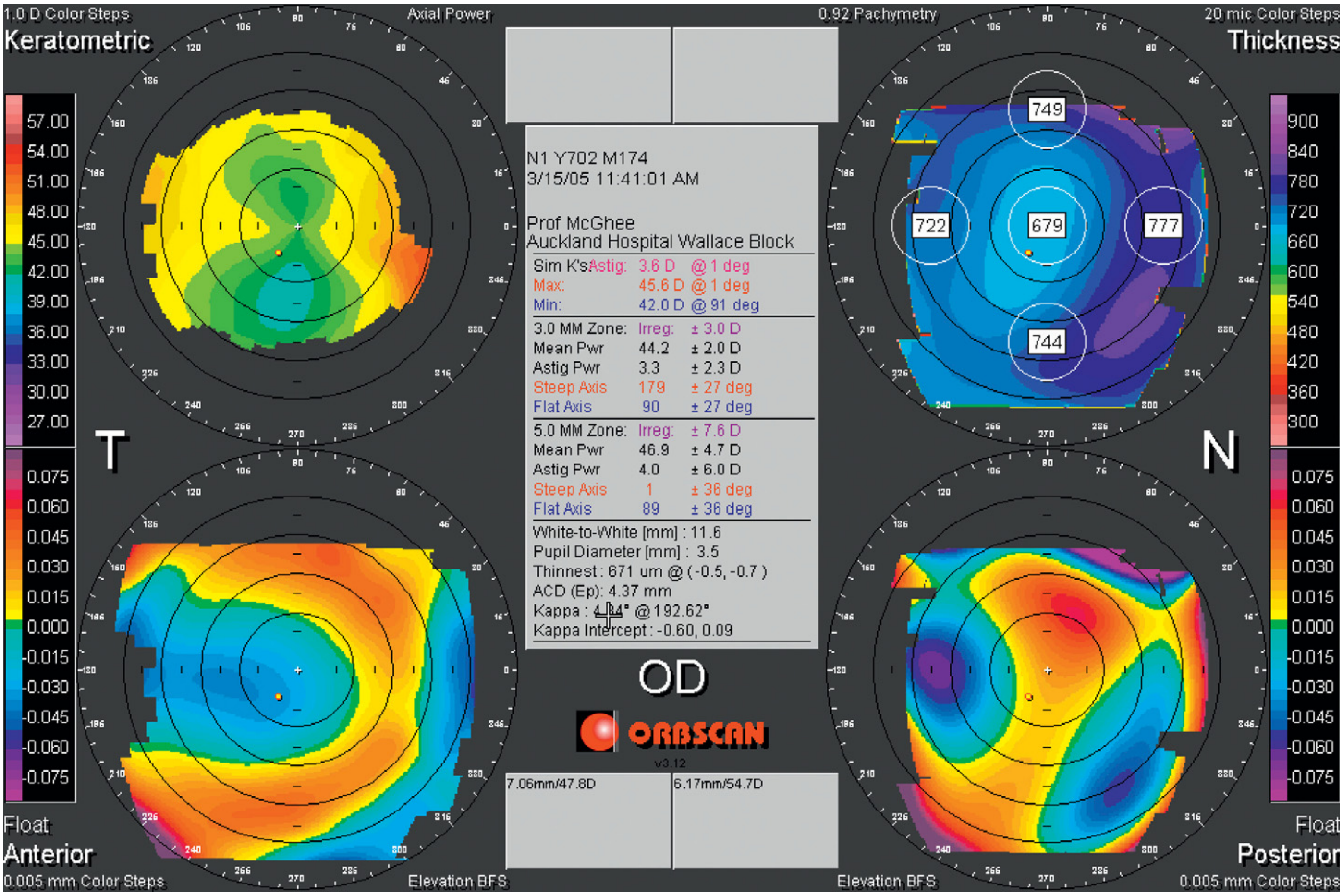


Figure 10.3. Orbscan II quad-map of a cornea with early Fuchs endothelial dystrophy. Clockwise from top left this display presents: *A,* a keratometric or power map in dioptres; *B,* a wide-field pachymetry map in micrometers (679 µm centrally); *C,* an anterior elevation map in microns relative to a BFS; *D,* a posterior elevation map in microns relative to a BFS.

region that will imply deceptive values and induce inconsistency. The development of any classification scheme must therefore be restricted to a specific zone of consistent complete data coverage between maps.

In an independent study, the Orbscan II demonstrated extreme accuracy in measuring the anterior surface using a variety of test surfaces, although the authors cautioned that no direct comparison can be made to the cornea in vivo.[5] The repeatability of Orbscan II slit-scanning topography for measuring anterior elevation in human corneas has been shown to be approximately 2 µm, decreasing towards the more peripheral cornea.[6,7] However, to date, no peer-reviewed publication has presented a reproducible technique to establish the accuracy of the Orbscan posterior surface elevation measurement and thereby the absolute accuracy of pachymetry maps.

The repeatability of early morning or peripheral measurements of pachymetry by Orbscan II is poorer than that of central measurements (±3.0 µm SD), which produce results generally comparable to ultrasound.[8,9] However, since the initial scientific publications it has become apparent that in normal corneas the Orbscan consistently produces pachymetry measurements thicker than ultrasound, by approximately 30 µm.[10–12] Possible explanations of this phenomenon include compression of the cornea or probe misalignment with ultrasound, or Orbscan measurement including the tear film and mucus layer. Owing to the concern that in LASIK patients the pachymetry may be measured thicker than with ultrasound, creating the impression that the maximum safe ablation depth for LASIK patients is greater than genuinely acceptable, the manufacturers introduced a correction factor to more closely align the results from Orbscan and ultrasound pachymetry. This correction factor is known as the 'acoustic factor' and reduces the entire Orbscan pachymetry map by 8%. Obviously, the use of a single correction factor across the entire cornea and different populations must be accepted with significant reservations when a constant linear relationship between ultrasound and Orbscan pachymetry has not been proven.[11] This disparity is compounded when considering corneal tomography that deviates from normal, such as post-LASIK. Studies that compare Orbscan and ultrasound pachymetry post-LASIK show, in contrast to the trend in normal corneas, that Orbscan has a general tendency to underestimate corneal thickness.[11,13,14] Moreover, the introduction of an acoustic correction factor of 8% induces further reduction in Orbscan pachymetry and therefore greater reduction when compared to ultrasound. Postoperative ultrasound pachymetry has been demonstrated to correlate well with preoperative predicted values, whereas Orbscan measures postoperatively have been reported to be approximately 40 µm less than predicted.[13] This would suggest that the inconsistency lies with the Orbscan measurement rather than with that of the ultrasound. Indeed, the presence of clinically significant haze is associated with an underestimation of corneal thickness,[15] and more recently the authors have demonstrated a

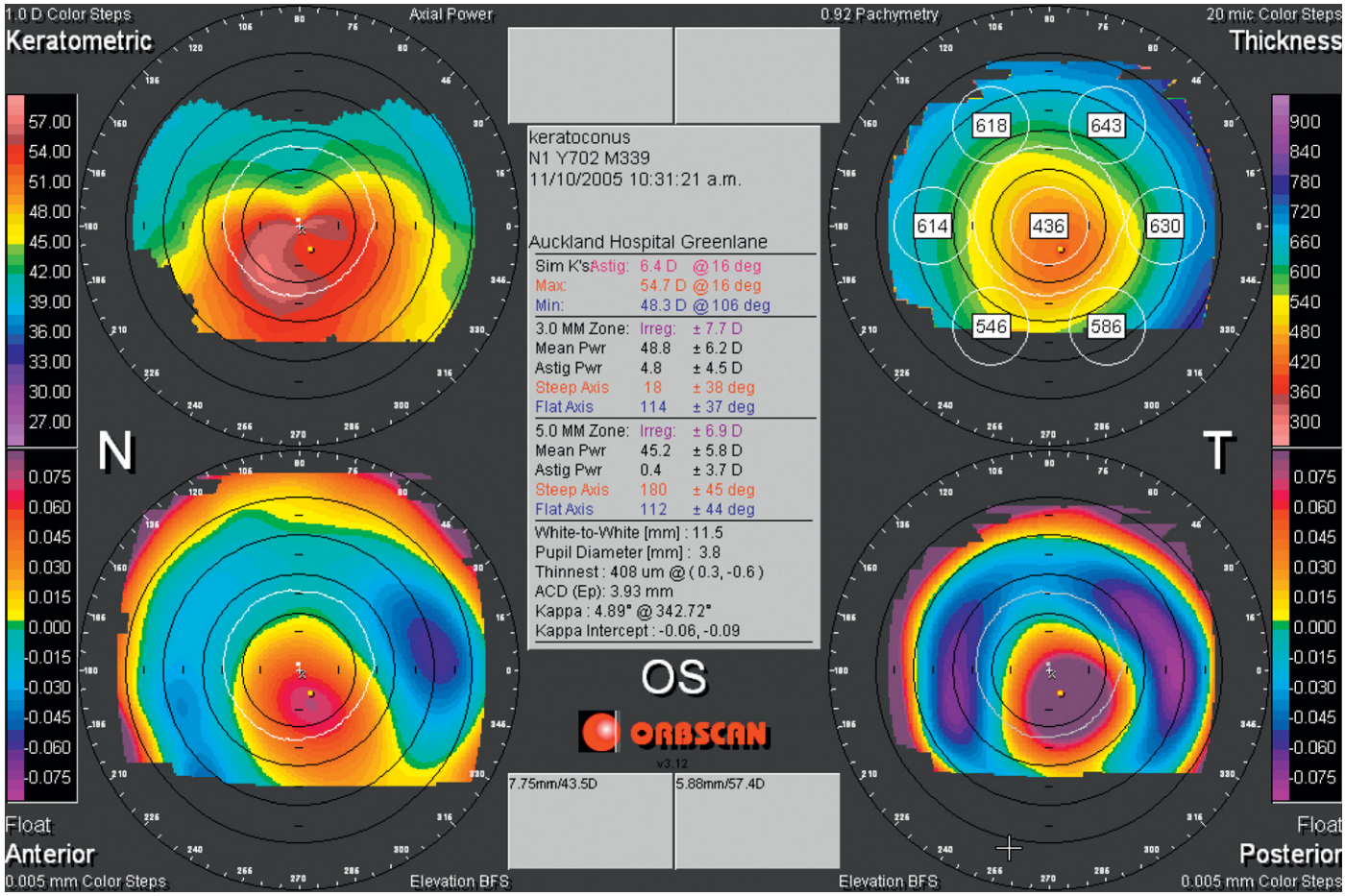


Figure 10.4. Orbscan II quad-map of cornea showing keratoconus. Clockwise from top left: *A,* the keratometric axial power map highlights a large inferior, oval cone with simulated K values of 54.7 and 48.3 D at 106°; *B,* the thickness map reveals significant central thinning with a value of 436 μm; *C,* the anterior elevation map highlights central elevation of greater than 60 μm relative to the BFS, of more than 75 μm; *D,* the posterior elevation map shows central protrusion, relative to the BFS, of more than 75 μm.

similar association with subclinical interface haze following LASIK (unpublished data).

When measuring anterior chamber depth (ACD) in phakic and pseudophakic eyes, the Orbscan appears to have good repeatability and the mean values correlate well with ultrasound A-scan.[16–18] Orbscan measurements also appear similar to those of the intraocular lens (IOL) master (Carl Zeiss Meditec) in the determination of ACD, but not as reliable as the IOL master in measurement of white-to-white corneal diameter.[19,20]

A significant observation highlighted by Orbscan tomography in eyes following laser keratorefractive surgery is the (apparent) anterior shift of the posterior corneal surface. Significant debate continues as to whether this is a genuine physical corneal ectasia or largely an optical phenomenon, although a number of large studies have generally suggested that this phenomenon does occur[21–23] even though the magnitude of the ectasia may be artifactually increased. It has been postulated that removal of tissue from the central cornea coupled with a superficial LASIK flap weakens the integral mechanical structure of the cornea and under the effect of intraocular pressure (IOP) causes a forward protrusion or true keratectasia. The mild regression seen in a significant number of eyes after LASIK could be partly explained by a genuine shift, or keratectasia of the cornea, which would effectively increase the axial length of the eye. However, many inconsistencies between studies prevent a resolute answer to this question, and it should be remembered that all evidence is based on the yet to be independently confirmed premise that Orbscan can accurately measure the posterior surface of the cornea after refractive surgery. Interestingly, the authors have recently reported a paradoxical reduction in ACD associated with apparent keratectasia following successful LASIK procedures, which tends to suggest this forward ectasia is at least partly artifact.[4]

OCULUS PENTACAM

The Oculus Pentacam (Oculus Inc., Germany) system is a multifunctional tool that images the cornea and anterior segment. Using a rotating Scheimpflug camera and a monochromatic light source (blue LED at 475 nm) that rotate together around the optical axis of the eye, multiple images are taken of the anterior segment from the anterior corneal surface to the posterior surface of the crystalline lens (Fig. 10.5). These measurements are subsequently used to generate three-dimensional images and animations from which data can be calculated and analyzed. This information can be used for a broad range of clinical applications. At the time of writing, the Pentacam has only been widely available in clinical practice for approximately 3 years and therefore the evidence base, in relation to the advantages and potential limitations of this system, is limited to a little over 20 peer-reviewed scientific publications.

In practice, the operator visualizes a real-time image of the patient's eye on a computer screen and can manually focus and align the image, with the machine identifying the corneal apex,

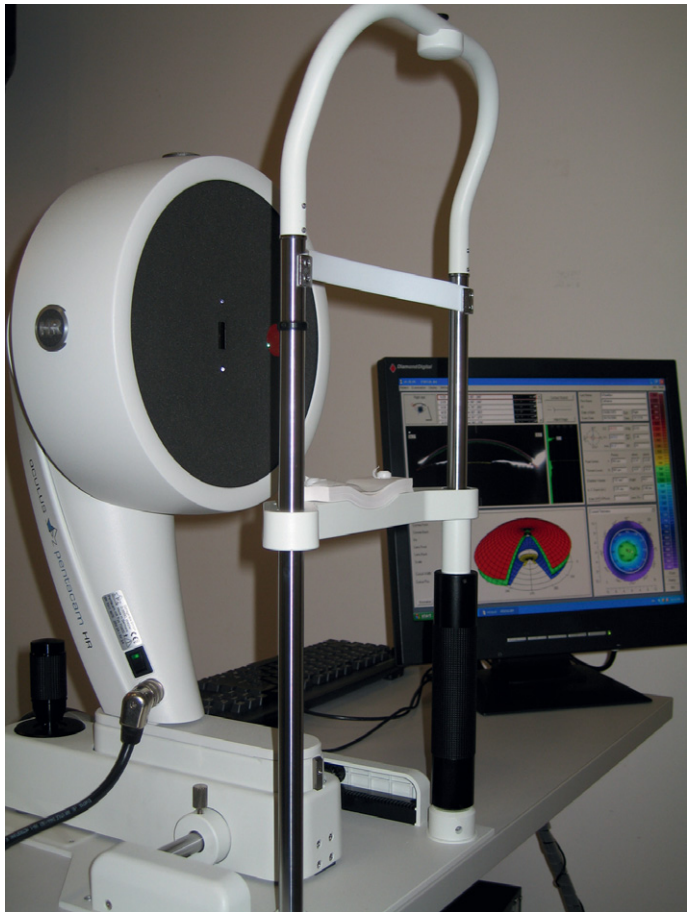


Figure 10.5. Oculus Pentacam Scheimpflug tomography device.

pupil edge and center in real time. Arrows that guide the operator's alignment in the horizontal, vertical, and antero-posterior axes are displayed on the screen. An automatic release mode can be used for the machine to automatically perform the scan on achieving the correct focus and alignment with the corneal apex. This noncontact measurement process takes less than 2 s to rotate 180°, and in this time performs up to 50 single captures depending on the function mode. Each capture consists of 500 true elevation points so a total of up to 25 000 height values are detected and processed into a three-dimensional mathematical model of the anterior segment. According to the manufacturer the condition of the tear film has no effect on measurements. Minute eye movements are captured by a second camera and automatically corrected simultaneously. The quality factor (QF) takes into account possible measurement confounders from blinking or extraneous light influences so users can easily determine whether an examination should be repeated. A QF > 95% indicates a reliable examination.

There are five evaluation modes: Scheimpflug tomography, pachymetry (including adjustment for IOP), three-dimensional anterior chamber analysis (chamber depth, angle and volume, including a manual measuring function for any location in the anterior chamber), densitometry of the lens, and corneal topography (including anterior and posterior corneal surface as well as keratometry) (Fig. 10.6). Comparison screens allow the user to obtain the optimal impression of any general changes, the difference between examinations shown as color maps, as well as numerical values. In axial terms, imaging is limited to the posterior capsule of the lens. Being optically based and imaging the eye from several angles, theoretically data can often be captured from behind a modest opacity or through corneal haze.

The Pentacam software generates a full-color-coded pachymetry map from limbus to limbus (potentially) and also highlights the thinnest part of the cornea (Fig. 10.7). Any point on the cornea can then be manually located onscreen to determine the precise corneal thickness at that point. This mode is particularly useful in refractive surgery, especially for evaluating patients seeking re-treatment, to determine if there is sufficient residual stromal tissue to allow a safe enhancement procedure. In glaucoma patients, the pachymetry-based IOP correction function allows the operator to enter the tonometrically measured eye pressure and, on selecting a formula for IOP correction, the Pentacam, like the Orbscan system, will calculate the patients 'corrected IOP' based on the measured corneal thickness.

A study comparing central corneal thickness (CCT) measured by the Pentacam and ultrasound pachymetry demonstrated that on average the Pentacam yielded slightly, but systematically, thinner values for CCT.[24] Similar results have been reported when comparing the Pentacam with both ultrasound pachymetry and Orbscan scanning-slit corneal topography.[25] In keratoconus it has been suggested that caution is needed when using data on corneal thickness interchangeably between the Pentacam, ultrasound pachymetry and noncontact specular microscope as significant differences between the measurements from these instruments have been shown.[26]

As an objective, noncontact measurement of CCT the Pentacam has been reported as yielding excellent intraoperator repeatability, and interoperator reproducibility, in the region of 0.84–1.1%, respectively.[27,28] The Pentacam might provide further insight into the presence of post-LASIK 'ectasia' that has been documented when assessing corneal thickness with the Orbscan, which as previously noted underestimates corneal thickness compared to ultrasound. Recent reports of change in the posterior corneal surface after refractive surgery suggest that contrary to previous studies, posterior 'ectatic' changes are not routinely identified after LASIK surgery.[29]

In addition to information about the central ACD, the Pentacam also measures depth at the periphery, an application which is useful for the suitable selection, surgical planning, and follow up of cases of phakic IOL implantation. Interestingly, in phakic eyes ACD measurements with the Pentacam, ultrasound A-scan, and Orbscan have been shown to be similar.[30,31]

The Pentacam can also evaluate safety distances between the posterior surface of a phakic IOL implant and the crystalline lens and from the anterior optic surface of an anterior chamber IOL to the corneal endothelium. The latter may be regarded as the most critical distance for determining endothelial safety.

In glaucoma patients, it is claimed that the Pentacam can be used to follow changes in anterior chamber angle, depth, and volume dimensions in response to surgical or pharmacological intervention. Additionally, users have claimed that the device can image the filtration bleb following glaucoma surgery and visualize the position of glaucoma drainage implants in the anterior chamber. However, anterior chamber dimensions measured by the Pentacam suggested that ACD and anterior chamber angle only correlate moderately and that ACD is only minimally correlated with the potential risk of developing angle-closure glaucoma.[32]

The use of Scheimpflug photography to quantify cataract has previously been well established using systems such as the Nidek EAS-1000 system,[33] and in addition to other functions the Pentacam lens densitometry function should enable quantification of lens density and the differentiation of various forms of cataract. The

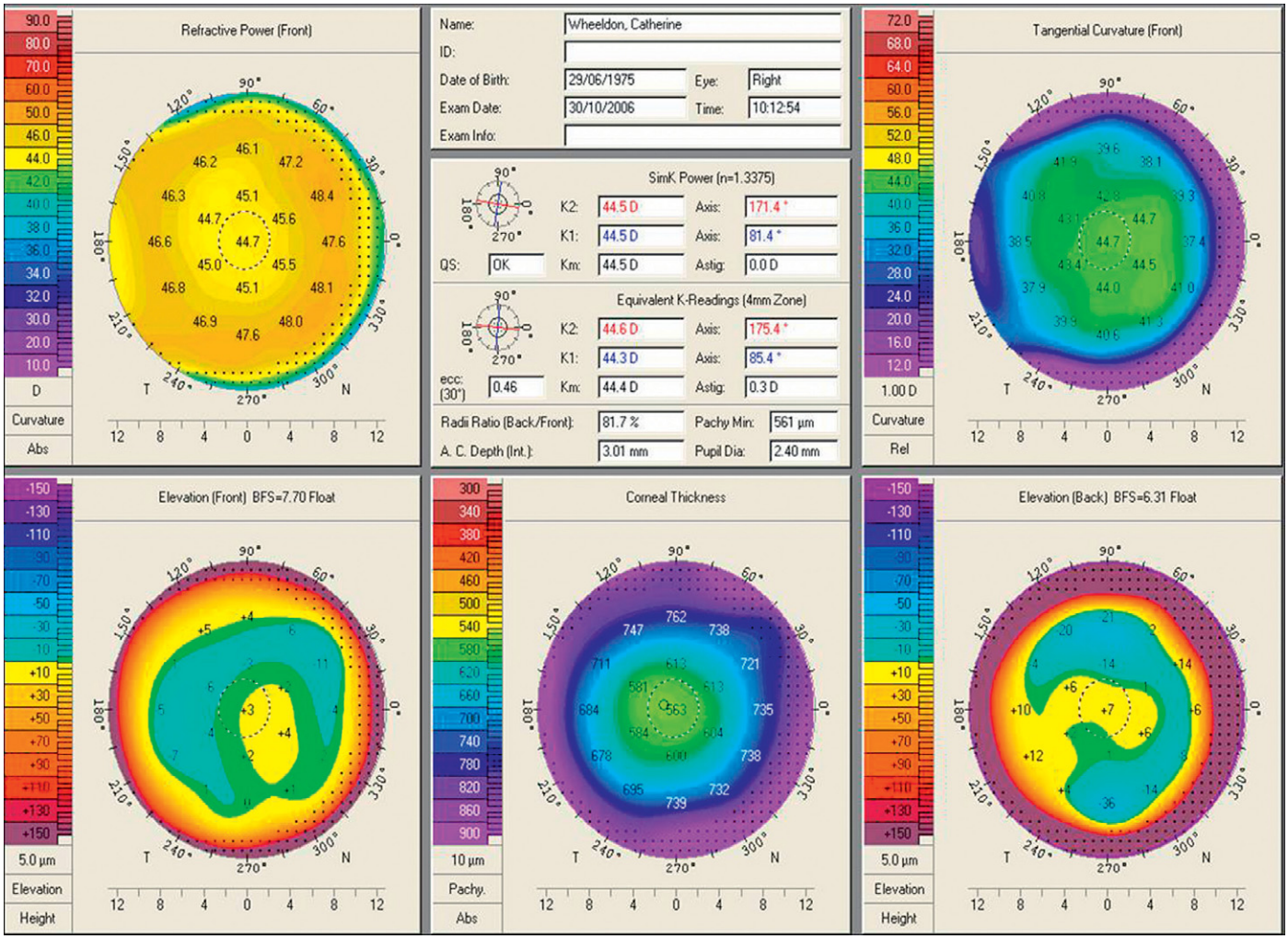


Figure 10.6. Oculus Pentacam maps of a normal cornea with SimK values 44.5 and 44.5 D at 81.4° and CCT of 563 µm. From left to right the six screens provide: top row: *A,* refractive power (front); *B,* patient bio-data and summary statistics; *C,* tangential curvature (front); bottom row: *D,* front elevation map; *E,* corneal thickness map; *F,* back elevation map (*D* and *F* are presented in respect to the BFS).

precise monitoring of cataract progression can be documented over time as well as the quantitative status of the crystalline lens following phakic IOL refractive surgery. The density of the lens is standardized from 0 to 100, where 0 shows no clouding and 100 represents a completely opaque lens. It is important to note that maximum pupil dilation is needed in order to fully visualize the posterior surface of the crystalline lens for thickness measurements, the edges of implanted IOLs, or the location and extent of opacification of the anterior and posterior capsule.

The Pentacam software enables a 'true net power' map, similar to the Orbscan TOP map, to be calculated and displayed. This takes into consideration the posterior surface of the cornea, potentially providing the basis of a more accurate calculation of refractive power of the cornea compared to Placido-based systems. The obvious potential for improving the predictability of pseudophakic IOL power calculation using the Pentacam's true net power map, in a growing population of cataract patients with a history of refractive surgery, is encouraging.

In the wider field of corneal disease, serial studies can be used to document and evaluate the progression of conditions such as keratoconus, pterygium, and Terrien's disease. The interfaces between corneal graft and host tissues and implanted intracorneal ring segments can be visualized. The 12.0-mm diameter topography map may be useful in guiding decisions about suture removal post-penetrating keratoplasty compared to the 9.0–10.0 mm zone of placido-based instruments.

ALTERNATIVE MEASUREMENT OF PACHYMETRY

Accurate corneal pachymetry plays an important role in several areas of ophthalmology. It can be regarded as an indirect correlation to the physiological condition of the corneal endothelium and may be useful in the diagnosis and management of conditions such as Fuchs corneal dystrophy and keratoconus.[34] Pachymetry is also vitally important in the avoidance of complications such as corneal ectasia in keratorefractive surgery. Recent evidence of the link between decreased IOP measurement readings and apparently decreased CCT have also highlighted its integral role in the early diagnosis and management of glaucoma.[35–37]

Ideally, a pachymeter should be safe to use, noninvasive, reliable, and provide accurate reproducible results. There are many different ways of measuring CCT thickness, including those techniques highlighted in the preceding sections, i.e. Orbscan and Pentacam tomography. However, pachymetry can also be usefully assessed by OCT, UBM, in vivo confocal microscopy, and ultrasound pachymetry—the

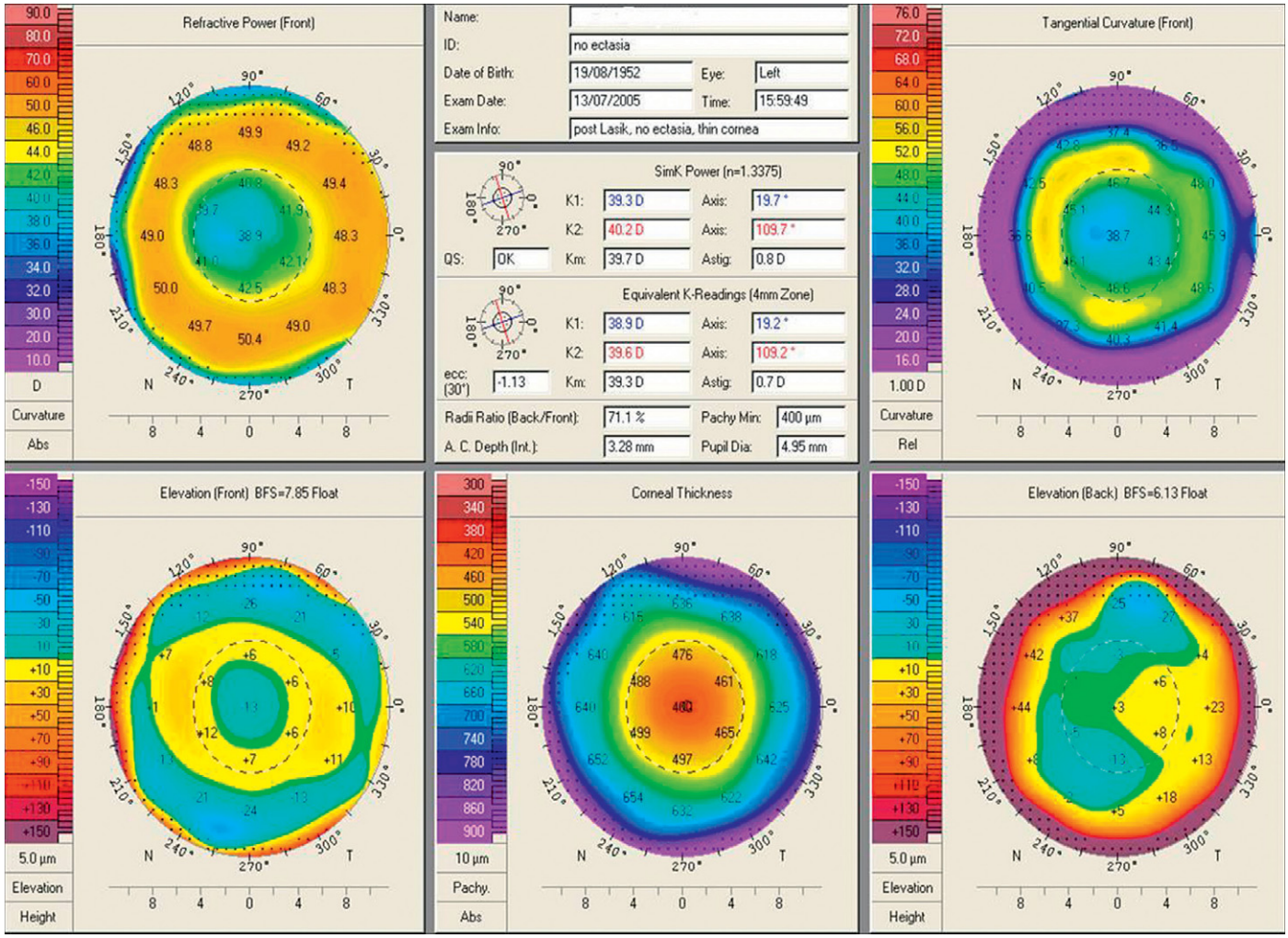


Figure 10.7. Oculus Pentacam maps of a post-LASIK cornea. Top row left to right: *A,* a central area of reduced refractive power; *B,* summary statistics highlighting SimK of 39.3 and 40.2 D at 109.7°; *C,* a more complex appearance of reduction in central and mid-peripheral tangential curvature. Bottom row, left to right: *D,* relative anterior central 'flattening' on front elevation map; *E,* a reduced CCT (minimum of 400 µm); *F,* no suggestion of ectasia on the posterior elevation map.

latter has historically been used most commonly and is often regarded as the gold standard.

ULTRASOUND PACHYMETRY

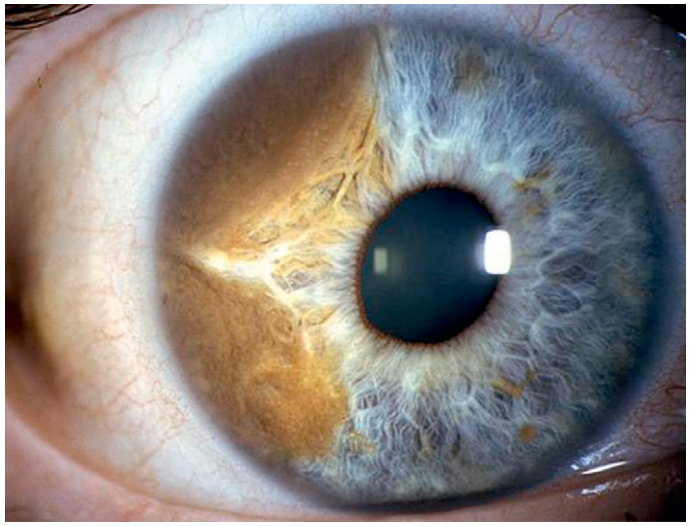
In use, the ultrasound probe is applied perpendicularly to the anesthetized cornea and an ultrasonic pulse is generated by the stimulation of a Piezoelectric crystal by an electromagnetic pulser. This ultrasonic pulse is reflected by Descemet's membrane back through the cornea and stimulates the crystal to generate an electronic pulse. From the time it takes for the ultrasonic pulse to travel through the cornea and back the corneal thickness can be calculated. The formula used to calculate this relies on a measurement of 1640 m/s for the speed of sound in the cornea:

corneal thickness = (total travel time × speed of sound in cornea)/2

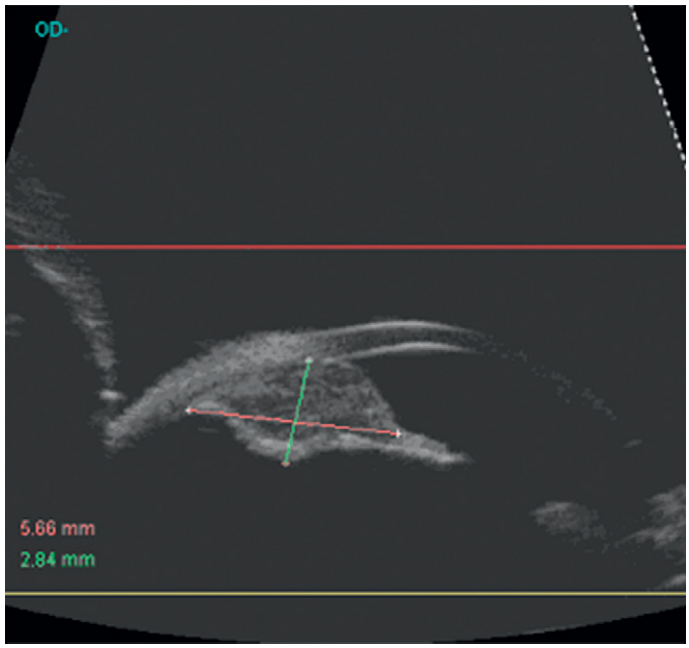
The pachymeter usually analyzes a series of around 100 measurements at each site and can store multiple readings from different locations on the cornea. Hand-held ultrasound pachymeters offer the advantage of relative ease of use, portability, and low cost. In general, ultrasound pachymetry has been shown to have a reasonable degree of intraoperator, interoperator, and inter-instrument reproducibility.[9,38,39] However, limitations of this system include difficulties in alignment and centration with consequent off-center placement of the probe yielding thicker measurements, the lack of a fixation light for gaze control, and the variability of sound speed in wet and dry tissues. In addition, relying on corneal contact necessitates the administration of a topical anesthetic, risk of epithelial damage, possible transmission of infection, and may yield slightly thinner readings as a result of unavoidable tissue indentation.

ULTRASOUND BIOMICROSCOPY

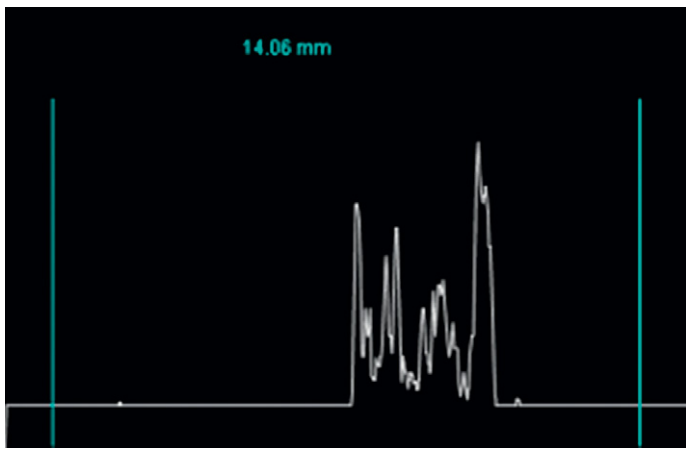
Ultrasound biomicroscopy provides high resolution, in vivo contact imaging of the anterior segment. Structures in the posterior chamber hidden from clinical observation can be assessed, and the relationship between tissues and their architecture in disease can be studied. The technology is based on 50–100 MHz transducers incorporated into a B-mode clinical scanner.[40] The resolution and depth of penetration are moderated by transducer frequency. Lower frequency transducers provide greater depth of penetration with less resolution, whereas higher frequency devices provide better resolution of more superficial structures. Commercially available units operate at



A



B



C

Figure 10.8. Clinical photograph (A) and high-frequency UBM image (B, C) of a large iris melanoma with dimensions of 5.66 mm × 2.84 mm, closely juxtaposed to the posterior cornea (courtesy of Dr Peter Hadden).

Figure 10.9. The Visante OCT (Carl Zeiss, Meditec) in use.

up to 50 MHz, providing a penetration depth and tissue resolution of approximately 5.0 mm and 50 µm, respectively. Generating a 5.0 × 5.0 mm field of view, consisting of 256 A-scans, at a scan rate of 8 frames/s, the UBM provides a dynamic image of the anterior segment. When gathering quantitative information it is important to consider the effect that room illumination, fixation, and accommodation can have on anterior segment anatomy.

UBM is an effective tool in both the diagnosis and management of anterior segment tumors. Tumor size can be measured and extent of invasion determined (Fig. 10.8). However, in terms of corneal pachymetry per se, UBM is significantly more expensive but no more accurate than standard ultrasound pachymetry.[41]

ANTERIOR SEGMENT OPTICAL COHERENCE TOMOGRAPHY

The anterior segment OCT is a noncontact, high-resolution tomographic and biomicroscopic device aimed at in vivo imaging and measurement of anterior chamber structures such as the anterior chamber angle, depth, corneal diameter, and corneal and LASIK flap thickness (Fig. 10.9). Anterior segment OCT has only been available over the last 5–6 years and therefore the published evidence base is still relatively limited though growing quickly.

The OCT acquires and analyzes cross-sectional tomograms of the anterior segment using low coherence interferometry to obtain high-resolution images. Coherent light is sent along two optical paths, the sample path into the eye and the reference path of the interferometer. The typical light source is a 1310 nm, infrared, super-luminescent light-emitting diode that employs a wavelength that has limited penetration in the eye. Light returned from the sample and reference paths are combined at the photodetector. The strength of the combined returned signal is a measure of the reflectance of a small volume of tissue at that specific location. In a similar fashion to ultrasound A-scan, by changing the optical length of the reference path at each scanning spot the axial depth of the tissue reflectivity signal can be determined. By laterally moving the scanning spot across the eye, the OCT acquires multiple A-scans that can be aligned to construct two-dimensional images analogous to an ultrasound B-scan. The anterior segment OCT typically performs 4000 scans per second with a scan width of 1.0–16.0 mm, scan depth of 1.0–8.0 mm, and axial resolution of 15 µm.

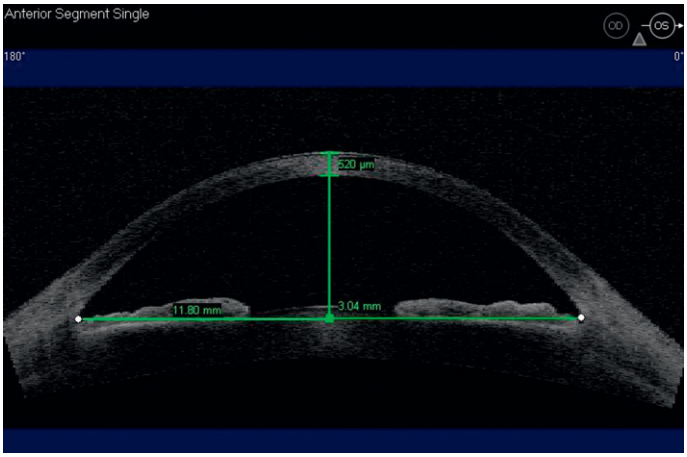


Figure 10.10. Anterior segment OCT of the cornea, iris, angle, and limbal region highlighting corneal pachymetry, angle to angle, and ACD measurements.

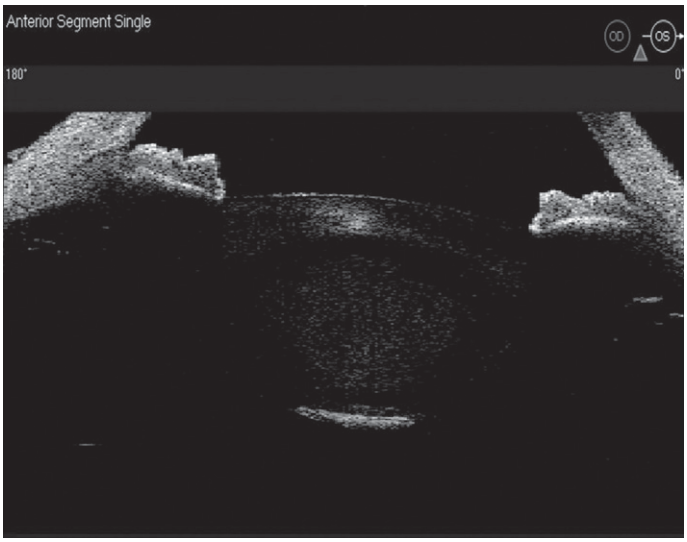


Figure 10.11. Anterior segment OCT image of an eye highlighting a dilated pupil and a posterior subcapsular cataract.

Potential applications of OCT in anterior chamber imaging include corneal pachymetry, LASIK flap thickness measurement, narrow angle glaucoma screening, internal angle-to-angle dimensions, and ACD (Fig. 10.10). As the infrared light beam is stopped by iris pigment a satisfactory view of structures behind the epithelial pigment layer of the iris is not usually possible, and usually only the central, anterior portion of the lens is seen (Fig. 10.11).

The in vivo analysis of the eye is a quick, noncontact procedure that provides data of high spatial resolution with no mechanical distortion of tissue, within a few seconds of alignment having been achieved. During the procedure the subject fixates on an optical target. The targets focus can be adjusted with positive and negative lenses to compensate for the subject's spherical ametropia and thus allow acquisition of images of the un-accommodated eye. It is also possible to defocus the target with negative lenses to induce physiological accommodation in the eye.

The OCT central and peripheral corneal pachymetry map consists of eight radial lines, 10 mm in length, each containing 128 axial scans. Measurements can be made of LASIK flap and bed thickness (Fig. 10.12). This allows comparison of predicted and achieved flap

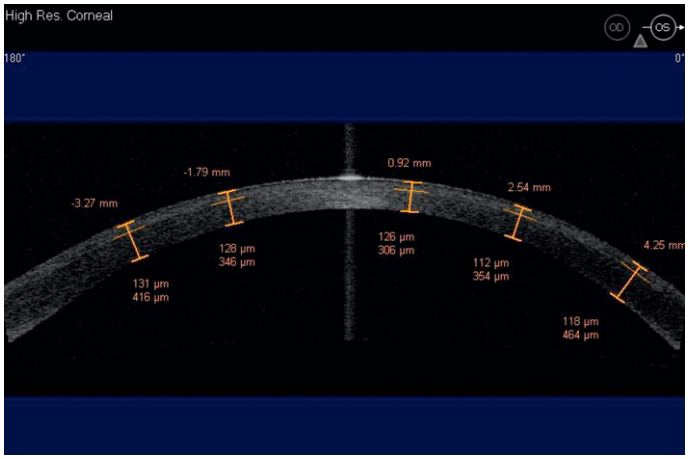


Figure 10.12. Anterior segment OCT image post-LASIK highlighting the LASIK flap dimensions.

thickness and ablation depths, and is therefore a useful guide to the feasibility of secondary procedures. Flap architecture can be viewed, and, being noncontact, assessment can be carried out immediately after corneal surgery. Difference maps can be used to monitor for the progression of corneal conditions such as Fuchs endothelial dystrophy. Measurements of CCT have been shown to have good repeatability with results equivalent to ultrasound pachymetry in eyes before and after LASIK.[42] In contrast, repeatability in measurements of corneal epithelial thickness has shown to be poor.[43]

In refractive surgery, eyes with high ametropia are often not suitable for corneal refractive laser ablation because of the combined risks of induced ectasia and optical aberrations. Clear lens extraction can be an alternative but this is associated with loss of accommodation and the risk of retinal detachment. In certain patients the use of phakic IOLs may be an option. The use of these IOLs relies on accurate sizing in order to avoid complications such as pupil ovalization, iritis, and iris atrophy that can occur if the IOL is too large, or endothelial damage and peripheral anterior synechiae if the IOL is too small and becomes mobile. Traditionally, external 'white-to-white' corneal diameter measurement has served as a guide to anterior chamber width; however, external measurements can be biased by anatomical variations, vascular pannus, and arcus senilis, and thus external landmarks may not correlate well with internal landmarks. The OCT is claimed to assess true anterior chamber dimensions including depth, angle size, and angle-to-angle measurements that can be used in the evaluation of suitability for phakic IOL surgery. Additionally, postoperatively the distances between implanted phakic IOLs and the corneal endothelium and anterior lens capsule can be measured and monitored. Reproducible OCT anterior chamber biometry has been demonstrated but with a high variation between users.[44] This could be partially addressed by the incorporation of automated software for biometric measurements within the OCT to eliminate human error.

Anterior segment imaging allows evaluation and assessment of corneal pathology such as keratoconus, and the outcome of penetrating and lamellar keratoplasty.

CONCLUSION

Corneal analysis has come a long way since the advent of the keratometer and Placido's disk. Largely due to computer processing we can now measure thousands of corneal data points and analyze

them in seconds rather than the hours, or even days, it would have taken only 25 years ago. As this brief overview highlights, true corneal tomography is now available in a number of systems with applications that can be tailored for the precise needs of the corneal and the refractive surgeon.

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11 Confocal microscopy of the cornea

Matthew Giegengack, William D. Mathers

Confocal microscopy is a technique that continues to gain utility in both clinical and experimental ophthalmology. Increasing numbers of ophthalmology centers are employing this exciting technology. Confocal microscopy has many advantages over other modalities of examination. It has the distinct advantage over traditional laboratory light and electron microscopes of being usable with living tissue. Compared with other in vivo techniques (slit-lamp biomicroscopy, spectroscopy, etc.), it provides both higher resolution and, perhaps more importantly, the ability to produce optical sections of the tissue being examined.

As the confocal becomes more popular, the number of papers on its use continues to increase. The subject has become prohibitively broad for an all-encompassing review. This chapter provides an explanation of the theory behind confocal microscopy. Clinically proven applications of the confocal are detailed. A sampling of some of the research previously and currently underway is also included. Many clinical photos are included so that the reader gets a sense of the power of the technology in its present uses as well as to stimulate ideas for future investigations.

PRINCIPLE OF CONFOCAL MICROSCOPY

In 1955, Marvin Minsky[1] constructed the first microscope based on the confocal principle. In all types of light microscopy, the specimen to be examined is illuminated by a light source and the light from that specimen is then collected and magnified by an objective lens. The modification of this basic design, which defines confocal microscopy, is best understood with a diagram. Figure 11.1 is a depiction of a confocal microscope in its simplest form, similar to the microscope first designed by Minsky.[1]

A point source of light is created by shining a light through a pinhole P1. The light from this point source is then collected by a converging lens L1 and focused to a point X in the specimen. The light from the specimen is then collected by a second lens L2 and focused on the detector. L2 is placed in such a way that its focal point is at point X. In order to discriminate against light not originating at point X, a second pinhole P2 is placed in front of the detector. L1 and L2 (the light source and the objective lens) are therefore confocal, hence the name.[2]

This design allows for better transverse resolution than nonconfocal microscopy for a given wavelength of illumination. It also has enhanced axial resolution, as light from above and below point X do not reach the detector (note the blue rays in the diagram originating from a point deeper within the specimen than point X). The confocal described above would deliver excellent resolution of the specimen at point X at a set depth within the specimen as dictated by the focal lengths of the illumination and the objective lens. By moving the specimen in front of the microscope, multiple point Xs could be combined to provide an image of an optical section at that depth (as depicted in the diagram by the vertical line through the point X). Moving the specimen toward or away from the microscope would provide an image of an optical section at a different depth within the specimen. However, it is often difficult to move the specimen in a controlled manner (especially a living patient). Alternatively, the light source and objective can be scanned across (or moved closer to) the specimen.[2]

Different methods for scanning the light source across the specimen have been designed. The most common method employs a Nipkow disk. The Nipkow disk is a thin disk with multiple pinpoint holes (Fig. 11.2). Light from the source is directed through these holes to make multiple point sources; each of these point sources is focused to a point in the specimen. The reflected light from each focal point in the specimen is then refocused on the disk and either directed through the same hole that the illumination came from or through a corresponding hole on the other half of the disk. The disk is then rotated so that many points of the focal plain can be sampled quickly. Nipkow disk-based confocal microscopes have several variables that determine image quality. The size of the holes on the disk determines the resolution. The smaller the hole, the higher the resolution. This comes at a cost, the smaller the hole the less light transmitted, and consequently brighter illumination is required to obtain adequate contrast. Resolution is further affected by the power of the objective lens, higher power lenses having greater resolution. The rate at which the disk rotates determines the speed at which a complete image can be obtained. The faster the speed, the more forgiving the microscope is of patient movement. However, at faster speeds the alignment of the microscope parts is more difficult to maintain.[2]

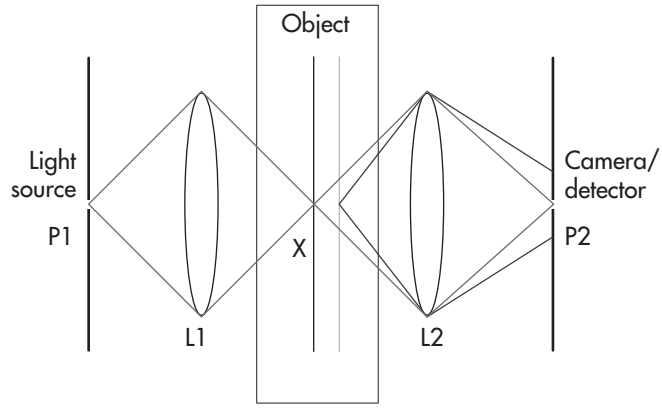

Figure 11.1. A depiction of a confocal microscope in its simplest form, similar to the microscope first designed by Minsky.

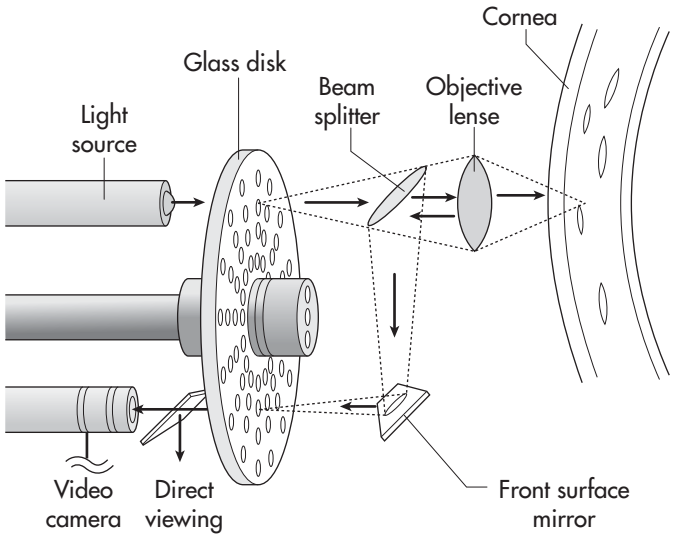

Figure 11.2. The Nipkow disk is a thin disk with multiple pinpoint holes.

A further modification of the confocal microscope has been developed by converting the scanning spot to a scanning slit.[3] Expansion of the field in one dimension decreases the confocal properties of the microscope but permits better transmittance and more rapid image capture.

One aspect of the confocal microscope not yet discussed is that of the detector or camera. Although confocal microscopy increases resolution, it does so at the expense of the brightness of the field. When images are stationary, the low light levels can be compensated for by longer exposure times with cooled CCD cameras, which can achieve startling resolution under very dim illumination. In vivo confocal microscopy is, however, significantly impaired by movement of the tissue being observed. Although normal eye motion does not appear to be significant when viewed without magnification, at a magnification of ×400, the surface of the eye moves considerably even when fixated on a small target. The eye is actually never stationary while awake. The rapidity of this motion must be compensated for by relatively short image acquisition times to avoid blur. Real-time video imaging requires 30 frames per second, limiting the amount of time available for any frame to 30 ms. This time is not sufficiently rapid to stop eye motion. The

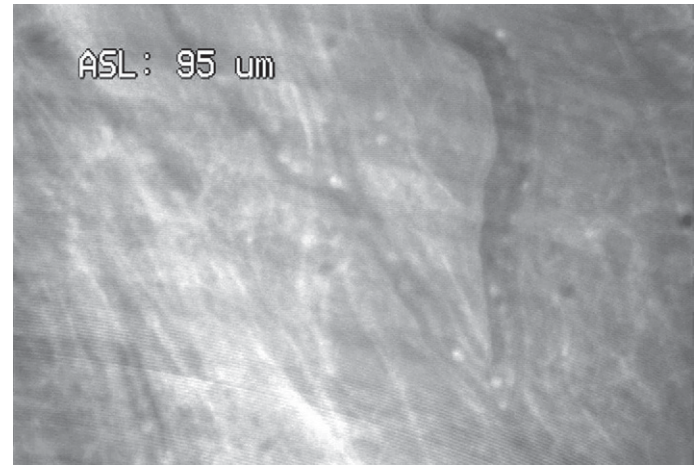

Figure 11.3. Vessels within the stroma of conjunctiva are also clearly visible.

low light level inherent with confocal microscopy imposes a severe limitation on exposure. One answer to this dilemma is pulsed light. The instrument devised by Koester[4] uses this solution effectively. Another method uses an intensified camera for image capture; however, the image intensification process induces some loss of resolution. Fortunately, camera technology continues to improve rapidly, and advances can be expected to aid image quality.

NORMAL MORPHOLOGY

Both the bulbar and the palpebral conjunctiva can be examined with the confocal. Bulbar conjunctival epithelial cells are slightly smaller than their palpebral counterparts. Goblet cells are present in greater numbers on the palpebral conjunctiva, and appear as larger cells amidst the epithelium. Vessels within the stroma of conjunctiva are also clearly visible (Fig. 11.3). It is further possible to image individual cells within the blood flow. The Palisades of Vogt are readily seen in the basal layer of the conjunctiva at the limbus. Conjunctiva-associated lymphatic tissue in the form of subepithelial follicles can also be imaged.[5]

The surface of tear film can be visualized with confocal microscopy using a standard ×5 or ×10 dry microscope objective.[6] Interference patterns from the lipid layer generate sharply demarcated interference patterns, which indicate lipid thickness (Fig. 11.4). White light illumination and color camera capture reveal the full spectrum of interference colors as seen by other systems for lipid interference imaging.[7,8]

The thickness of the tear film can be estimated with confocal microscopy, as demonstrated by Prydal and Dilly.[9] By correlating interference patterns with measurements taken on thin plastic films, they estimated the thickness of the water layer to be 45 μm in humans and several other animal species.[10] This measurement was thicker than the previous estimates, indicating a much greater tear volume than obtained with fluorophotometry.

Confocal microscopy of the epithelium represents one of the most important areas of investigation.[11] The surface of the epithelium can easily be seen and is especially vivid in patients following corneal transplantation for reasons that are not understood (Fig. 11.5). The dimensions of the epithelial cells and the size and position of the nucleus can be measured. Following desquamation, the smaller cells underneath are revealed. The depth encoder available for some confocal microscopes can measure the thickness of the epithelial

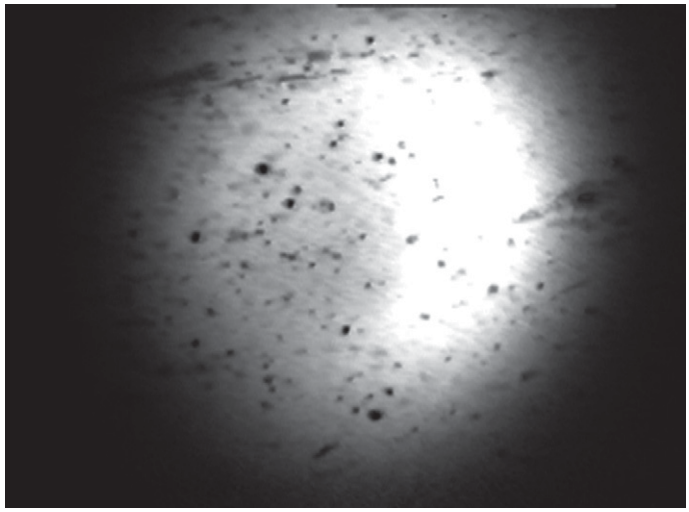

Figure 11.4. Interference patterns from the lipid layer generate sharply demarcated interference patterns, which indicate lipid thickness.

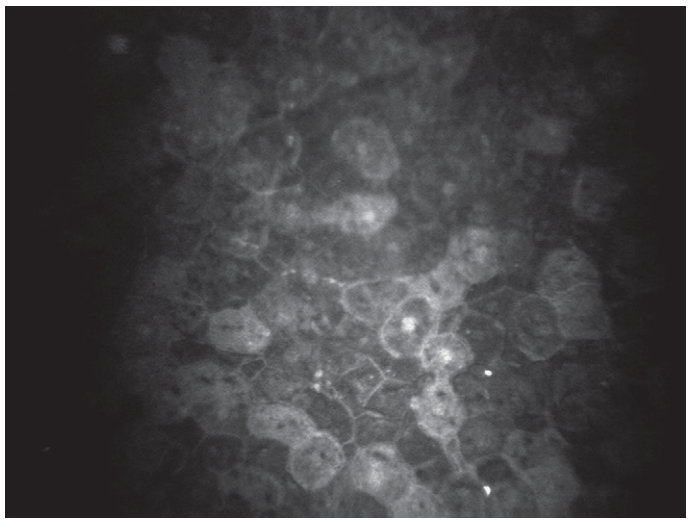

Figure 11.5. The surface of the epithelium can easily be seen and is especially vivid in patients following corneal transplantation for reasons that are not understood.

Figure 11.6. In inflamed conjunctiva, Langerhan's cells may sometimes be seen as dendritic reflective cells in the limbal and conjunctival epithelium.

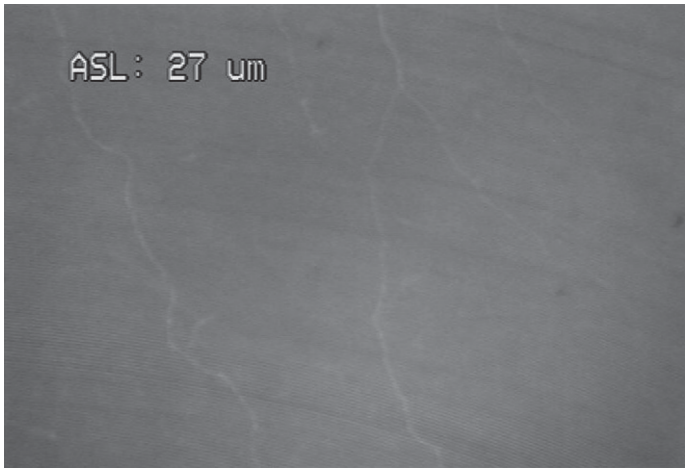

Figure 11.7. Corneal nerves underneath Bowman's layer are easily seen as long branching structures with a width of approximately 5 μm.

cells as well.[12] In inflamed conjunctiva, Langerhan's cells may sometimes be seen as dendritic reflective cells in the limbal and conjunctival epithelium (Fig. 11.6). They are also frequently seen in the cornea epithelium, near the limbus or diffusely following viral infection.

Bowman's layer can be visualized in some patients.[13] It is often seen as a wavy and irregular layer with crevices and folds. The details of Bowman's layer are often less easily visualized than other structures in the cornea.

Corneal nerves underneath Bowman's layer are easily seen as long branching structures with a width of approximately 5 μm (Fig. 11.7). The sites where these nerves pierce Bowman's layer and enter the epithelium appear to be stationary, enabling observation of the distal growth of corneal nerves in the epithelium. Corneal nerves in the epithelium itself are considerably smaller than the subepithelial nerve plexus and are much less easily seen.[14]

Corneal stroma consists of a relatively dense meshwork of keratocytes that have relatively long and thick processes in contact with many other keratocytes in the vicinity.[11] These thin processes are not seen with in vivo confocal microscopy but have been demonstrated with laser scanning confocal microscopy in vitro.[15,16] The relative density of keratocyte cell bodies can be estimated and demonstrated with three-dimensional reconstructions of stacked optical sections.[17]

The endothelium can be seen in detail over a relatively wide area using confocal microscopy even when the stroma is not completely clear (Fig. 11.8).[11] Details of the endothelial cells are similar to those seen in high-quality specular microscopy.

The normal trabecular meshwork has not been visualized with in vivo confocal microscopy. The confocal microscope can be used to focus through the trabecular meshwork area; however, Schlemm's canal is not identifiable. The vascular supply to the limbus is easily visualized, but individual trabecular meshwork cells cannot be identified.

CLINICAL APPLICATIONS

ACANTHAMOEBA KERATITIS

The most significant clinical application of confocal microscopy has been the identification of organisms causing keratitis, particularly

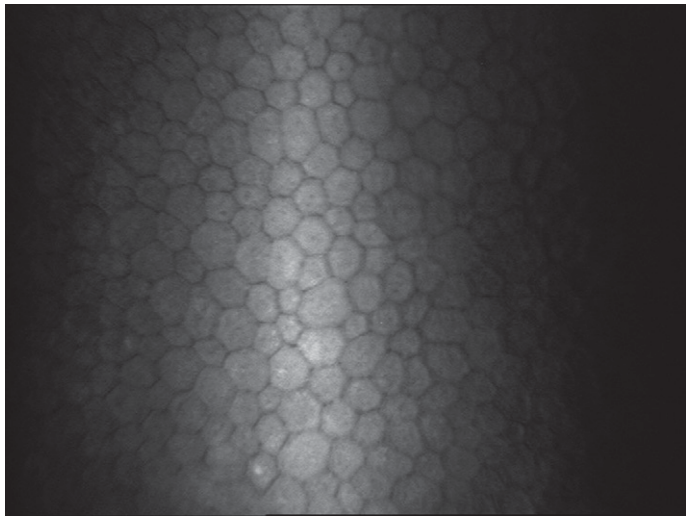

Figure 11.8. The endothelium can be seen in detail over a relatively wide area using confocal microscopy even when the stroma is not completely clear. (From Cavanagh HD, et al. Clinical and diagnostic use of in vivo confocal microscopy in patients with corneal disease. Ophthalmology 1993; 100: 1444. © Elsevier 1993.)

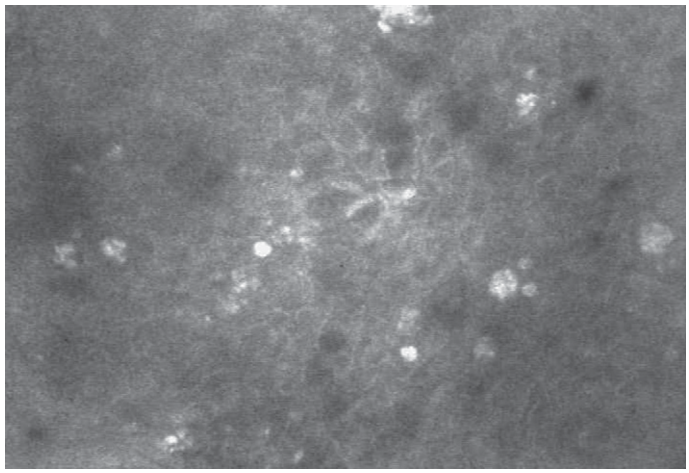

Figure 11.9. The most significant clinical application of confocal microscopy has been the identification of organisms causing keratitis, particularly Acanthamoeba.

Acanthamoeba (Fig. 11.9). Chew and co-workers[18] first reported in vitro identification of *Acanthamoeba keratitis* in a rabbit. In 1994, Auran and co-workers[19] reported the first case in a human using confocal microscopy. That single case report identified a 26-µm diameter organism in the anterior stroma subsequently confirmed histopathologically. Cavanagh and co-workers[11] reported a similar appearance in an animal model. Pfister and co-workers[20] reported a single case in a human.

Winchester and co-workers[21] reported eight cases of human Acanthamoeba keratitis identified with confocal microscopy; in each case, the highly reflective ovoid organisms were 10–25 µm in diameter located in the deep epithelium. Many other investigators have since demonstrated the utility of identifying Acanthamoeba in the corneas of patients with suspected Acanthamoeba keratitis and using the instrument to follow the course of the disease. A larger series demonstrated that the disease is more common than previously estimated.[22] Most cases do not have the previously reported association with contact lens use. Many cases are, however, associated with herpes simplex keratitis, and both infections may be present in the same person.[23] Acanthamoeba organisms have been demonstrated within an active dendrite (Fig. 11.10). Although internal details of Acanthamoeba organisms can be visualized with confocal microscopy, the instrument does not reveal sufficient detail to enable the diagnosis to be made with certainty based on confocal findings alone. Most physicians still use epithelial or stromal biopsy or culture to make a definitive diagnosis.

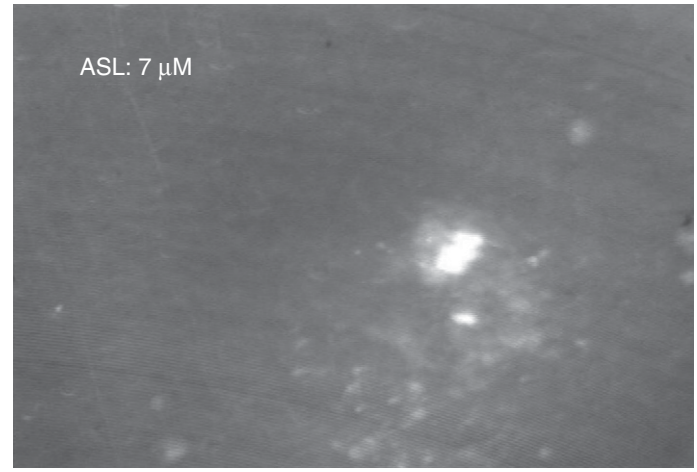

Figure 11.10. Acanthamoeba organisms have been demonstrated within an active dendrite.

Acanthamoeba keratitis often requires months of topical medication, and it can be difficult to evaluate when the organism has been eradicated.[24–26] Confocal microscopy has made a major contribution in the ability to identify when an organism has been eradicated since repeated examinations can easily be performed.

FUNGAL KERATITIS

The diagnosis of fungal keratitis is another problem that has been aided by confocal microscopy.[18,27] Branching hyphae in the deep epithelium and stroma are relatively easy to identify, which enables treatment to begin much sooner. Yeasts, such as Candida, which usually do not form branching filaments, are much more difficult to diagnose because they cannot reliably be discriminated from inflammatory cells. As with Acanthamoeba, the efficacy of treatment can be followed with repeated examinations.

BACTERIAL KERATITIS

Bacterial keratitis is much more difficult to identify with confocal microscopy. Although the theoretical limit of resolution for the instrument is actually better than standard white light microscopy of fixed specimens, the practical application with video capture using intensified CCD cameras, rapid motion of an in vivo subject, and low light conditions make the practical resolution approximately 1 to 2 µm. Because most bacteria are 0.5 µ in length or less, it is generally impossible to see individual bacteria in the cornea. Some organisms, however, are much larger, approaching the 2-µm range. These organisms probably can be identified with confocal microscopy, as reported by Kaufman and co-workers.[28] The inflammatory component, consisting of lymphocytes, macrophages, and polymorphonuclear leukocytes, is readily identified in the area of the keratitis. Dense infiltrates induce considerable light scattering and reduce the visibility of deeper structures.

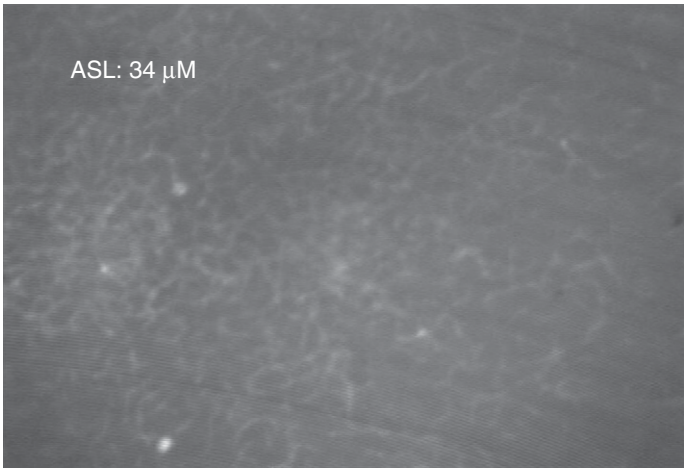

Figure 11.11. Dendritic cells are found to intertwine with the subepithelial nerve plexus to make a web-like pattern.

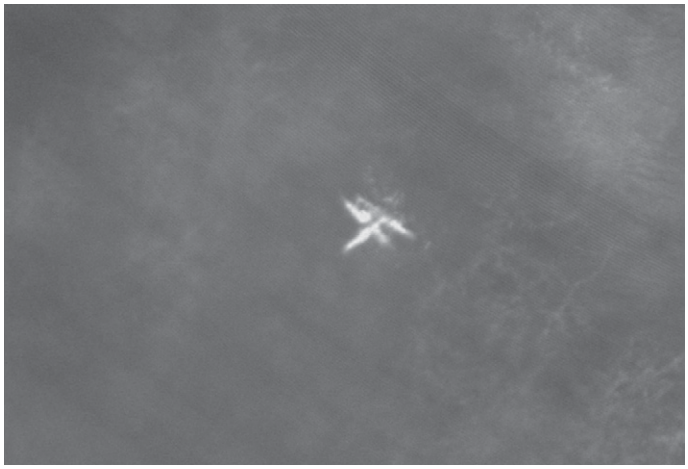

Figure 11.12. Bacteria can form crystalline-like patterns or amorphous shapes as they colonize the cornea, particularly following topical steroid use in corneal transplants. (From Wilhelmus KR, Robinson NM. Infectious crystalline keratopathy caused by *Candida albicans*. Am J Ophthalmol 1991; 112: 322. © Elsevier 1991.)

Microsporida may also be identified with confocal microscopy as a series of small cellular structures and spheroid clumps in the deep epithelium and anterior stroma. The appearance is quite characteristic and can be confirmed with biopsy.[29]

VIRAL KERATITIS

Viral keratitis (herpes keratitis and epidemic keratoconjunctivitis) has a characteristic appearance on confocal that can be used to aid in the diagnosis. Dendritic cells are found to intertwine with the subepithelial nerve plexus to make a web-like pattern (Fig. 11.11). As the infection runs its course, these dendritic cells decrease in density. This can be followed clinically as sign of recovery.[30]

CRYSTALLINE KERATOPATHY

Crystalline keratopathy is a bacterial phenomenon that is highly invisible with confocal examination.[31,32] Bacteria can form crystalline-like patterns or amorphous shapes as they colonize the cornea, particularly following topical steroid use in corneal transplants (Fig. 11.12).[33] The most common organism causing this phenomenon is *Streptococcus viridans*, although many others, including fungi, also produce this pattern. The crystals are very easily seen with confocal microscopy and often are quite dramatic.[32] They may, however, be confused with deposits of cholesterol or other substances. This discrimination is particularly important because often it is very difficult to obtain a sample of the organisms when they are located only in deeper structures. Often, there is no active infection or epithelial defect on the ocular surface. Prolonged application of an appropriate antibiotic therapy can result in complete eradication of the organism if the diagnosis is made early; otherwise, corneal retransplantation is often necessary.

DRY EYE SYNDROME/MEIBOMIAN GLAND DYSFUNCTION

The appearance of the lipid layer can be correlated with tear film function and disease states.[34] In seborrheic meibomian gland dysfunction with excess lipid production, large amounts of lipid are usually expressible from the meibomian gland orifices. Confocal microscopy of meibomian gland dysfunction shows large areas of linear interference layers and pools of lipid. When meibomian glands are expressed and the lipid viewed immediately after expression, this seborrheic pattern becomes more obvious as the lipid layer thickens.

Patients with dry eye often have increased amounts of debris in their tear film and relatively thin lipid layers. Sometimes they show a reticulated pattern of fine lines quite dissimilar from the appearance of seborrheic meibomian gland dysfunction. Normal eyes often have a very thin lipid layer (100 μm) despite low evaporation rates; thus it would appear that meibomian gland function can be normal with low evaporation without having a thick lipid layer. Patients with obstructive meibomian gland dysfunction and diminished amounts of lipid or those with very thick meibomian secretions display increased amounts of debris in the tear film and a very thin lipid layer.[34]

CORNEAL DEPOSITS

Confocal microscopy is not required to identify most foreign material, as the foreign material is large enough to be seen with slit-lamp microscopy. It may aid, however, in the identification of material such as ciprofloxacin deposits.[35] Their appearance as small, uniform crystals with confocal microscopy is characteristic, as is the appearance of amiodarone, in which many spheres 5–30 μm in diameter are dispersed through the deep epithelium without evidence of inflammation. Iron deposits are 8–10 μm, more densely packed, and uniform in size (Fig. 11.13).

CONTACT LENS WEAR

The confocal microscope has been used to identify corneal changes that occur in contact lens wearers. Eckard and co-workers used the confocal to quantify changes to the corneal epithelium. Cell bodies of superficial cells were smaller and consequently more dense. Corneal epithelial thickness was decreased in the periphery. Hollingsworth and Efron[35a] demonstrated an increase in microdot opacities (thought to be lipofuscin) in rigid gas permeable lens wearers relative to controls. Hamrah and co-workers[35b] found increased Langerhan cell density in both the central and peripheral cornea in contact lens wearers relative to controls. The clinical significance of these corneal changes is not known.[36]

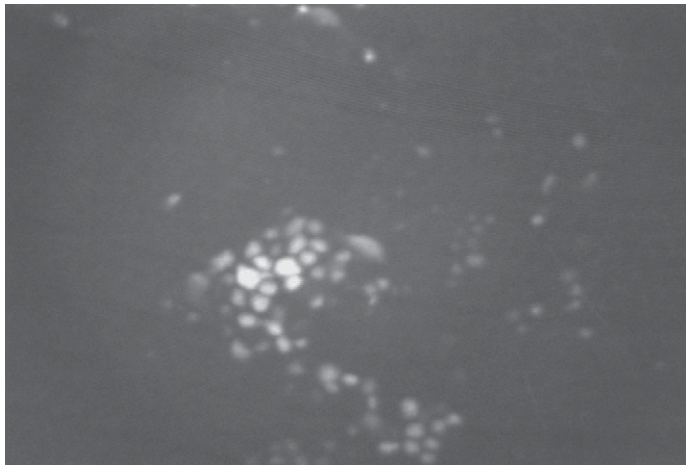

Figure 11.13. Iron deposits are 8 to 10 μ, more densely packed, and uniform in size. (From Wilhelmus KR, Robinson NM. Infectious crystalline keratopathy caused by *Candida albicans*. Am J Ophthalmol 1991; 112: 322. © Elsevier 1991.)

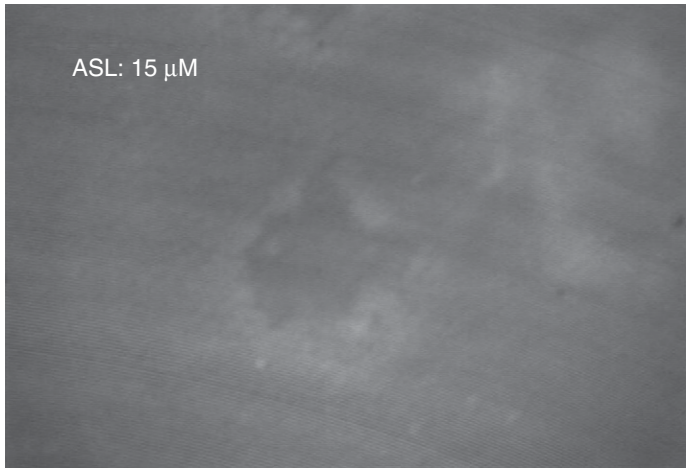

Figure 11.14. The redundant basement membrane is also identifiable with confocal microscopy as wavy semitransparent material without evidence of inflammation.

CORNEAL DYSTROPHIES

The normal basement membrane between the epithelium and Bowman's layer is not identifiable with confocal microscopy. Basement membrane dystrophy (also referred to as map, dot, fingerprint dystrophy, or recurrent erosion syndrome) has a thickened, irregular basement membrane and epithelial microcysts usually identifiable with slit-lamp microscopy. The redundant basement membrane is also identifiable with confocal microscopy as wavy semitransparent material without evidence of inflammation (Fig. 11.14). Additional basement membrane material may form large cysts within the epithelium, forming irregular patterns and whorls.

Meesman's epithelial dystrophy can appear as whitish, moderately reflective, spherical deposits 20 to 50 μ in diameter, interspersed with cysts in the midepithelium. The cysts can be as large as 200 μ in diameter and contain degraded basement membrane material. It is important to distinguish this from Acanthamoeba keratitis, in which the organisms are smaller, are more uniform in size, and show internal structure. With Meesman's dystrophy, there is also an absence of inflammatory cells and bilateral symmetry.

The deposits in lattice, granular, and Avellino dystrophies are less sharply demarcated than expected from slit-lamp microscopy.[11]

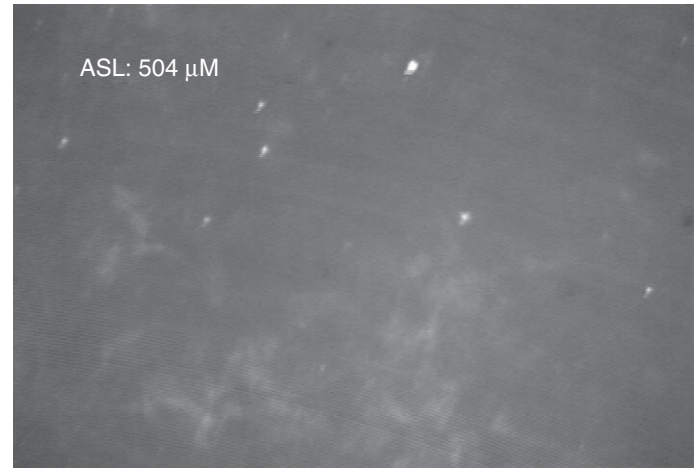

Figure 11.15. In posterior polymorphous dystrophy, normal epithelium is interspersed with nests of abnormal cells, forming irregular patterns.

Amorphous material without characteristic shape or reflective quality can be seen in the stroma. Macular dystrophy also shows deposition of reflective material in the anterior and midstroma.

In Fuchs' endothelial dystrophy, guttata can be identified in the endothelium and, when epithelial edema is present, hollow cysts in the basal epithelium 100 to 200 μ in diameter.[37] The stroma does not have a characteristic appearance.

In posterior polymorphous dystrophy, normal epithelium is interspersed with nests of abnormal cells, forming irregular patterns (Fig. 11.15). The demarcation between the dystrophic and normal cells is usually distinct.

Examination of Fleck dystrophy reveals small, discrete, amorphous shapes in the deep stroma. These shapes have the semblance of large keratocytes, suggesting that this may in fact be what they are. There is an absence of inflammation, and the other keratocytes otherwise appear normal.

CORNEAL GRAFT REJECTION

Confocal microscopy has been used to investigate corneal graft rejection.[38] In rabbits, corneal transplant rejection appears as inflammation in the graft and is especially pronounced around sutures. This application has not been useful to evaluate corneal graft rejection in humans as the response appears to be relatively nonspecific and can be easily evaluated with other modalities.

WOUND HEALING

Confocal microscopy is particularly useful to investigate wound healing.[39] The cell migration and general reparative process can be studied in vivo with repeated observations to assess the progress over time.[40,41] Keratocyte infiltration and wound gape have been measured following radial keratotomy type wounds.[42,43] Epithelial and endothelial migration following various types of injury have also been assessed.[44]

REFRACTIVE SURGERY

The effects of photoablative keratectomy have also been investigated and the resulting epithelial and stromal thickness changes measured.[45] Confocal microscopy is uniquely suited to measuring

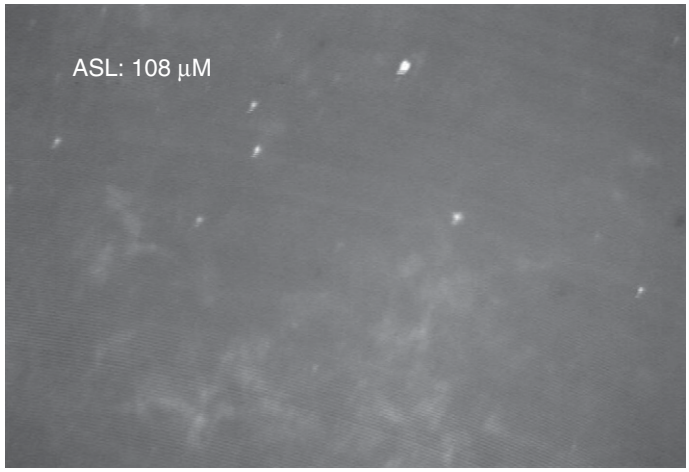

Figure 11.16. Confocal microscopy can also be used to accurately assess flap depth. Cuts made with the microkeratome leave behind microscopic metal fragments.

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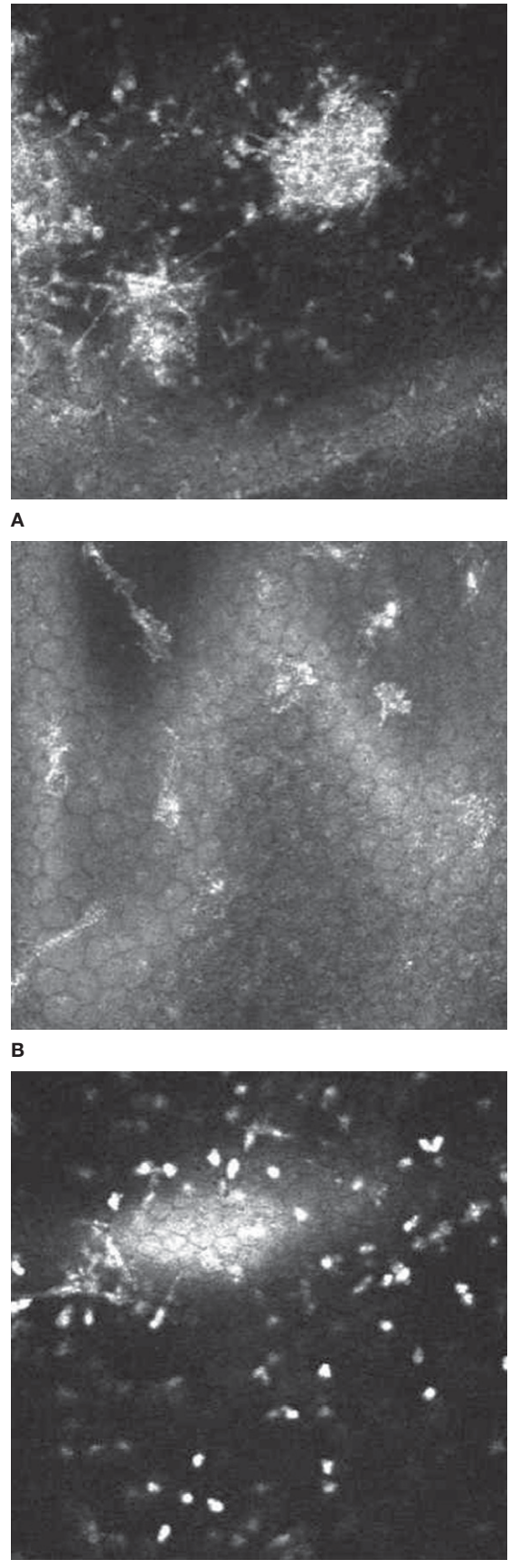
Figure 11.17. In cases of known scleritis an increased number of rolling leukocytes is seen along the vessel walls relative to controls and allergic patients. (From Lim L, Hoang L, Wong T, Mathers WD, Rosenbaum JT. Intravital microscopy of leukocyte-endothelial dynamics using the Heidelberg confocal laser microscope on patients with scleritis and allergic conjunctivitis. Mol Vis 2006 Oct 26; 12: 1302–1305.)

epithelial thickness following photorefractive keratectomy. Epithelial thickness has been shown to decrease following photoablation, and the effect appears to persist.[12] Following photorefractive keratectomy, keratocytes appear activated and fewer in number with increased haze in the area of ablation.[12,45] Over 6 months, they return to a more normal appearance and density. Preliminary studies have been done on the keratocyte density following in situ keratomileusis, but the technique has not been used to full advantage as yet.[46]

Confocal microscopy can also be used to accurately assess flap depth. Cuts made with the microkeratome leave behind microscopic



A

B

C

Figure 11.18. At least six different morphologies of keratic precipitates have been differentiated based on their confocal appearance. (From Wertheim MS, Mathers WD, Planck SJ, et al. In vivo confocal microscopy of keratic precipitates. Arch Ophthalmol 2004 Dec; 122(12): 1773–1781.)

metal fragments (Fig. 11.16). These fragments are easily detectable in the interface with the confocal. The flap thickness and residual stromal thickness can be determined, thereby aiding in surgical planning if retreatment is necessary. The interface created by the femtosecond laser is less easy to find.[12]

SCLERITIS/UVEITIS

Conjunctival and scleral vessels are easily examined with the confocal microscope. In cases of known scleritis, an increased number of rolling leukocytes is seen along the vessel walls relative to controls and allergic patients (Fig. 11.17).[47] Keratic precipitates are readily visible with confocal microscopy. At least six different morphologies of keratic precipitates have been differentiated based on their confocal appearance (Fig. 11.18).[48] It is promising that the keratic precipitate morphology may aid in diagnosing the etiology of the underlying inflammation.

FUTURE STUDIES

Confocal microscopy extends our vision beyond that achieved with current magnification. It is hardware and software dependent, and advances will rely on future improvements in camera technology and computer power. Limitations now imposed by low light levels and the need for rapid multiple image acquisition are the next obstacles to overcome. Current levels of computational power have improved to such an extent that high-resolution images can be captured in real-time, digitized, and stored without excessive expense. Problems with digital image storage will continue; however, continual improvements in disk storage should keep up with demand. As processing power continues to evolve, video resolution can be increased correspondingly. Eventually, very high-resolution video will be captured in real time without destructive compression.

Another technique of considerable future importance is the use of fluorescein markers for identification of pathogens and physiologic and biologic processes. Confocal microscopy can be modified to incorporate filters for fluorescent microscopy. This application has already been reported in preliminary animal studies. Current methods and low light conditions still limit this application; however, these difficulties can and should be overcome. Eventually, confocal microscopy may represent a method of diagnosing a wide variety of pathogens and biologic conditions in the cornea rapidly, safely, and with minimal expense.

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12 Specular microscopy

Ronald A. Laing

A primary concern in evaluating corneal tissue before surgery or before its use as donor tissue in penetrating keratoplasty is the condition of the corneal endothelium, the region of the cornea that is primarily responsible for the maintenance of normal corneal thickness, turgor, and transparency. Through changes in cell morphologic characteristics, the corneal endothelium reflects stresses and strains that have been placed on the cornea. Thus, any morphologic changes seen in the endothelium are indicative of the current status of the endothelium and its functional reserve, the ability of the endothelium to respond favorably to unexpected stress.

Specular microscopy is a method of evaluation that allows, in either a clinical or eye bank setting, for the direct observation of the corneal endothelium. Other tissues that may be seen with the specular microscope include the corneal epithelium, the cells of the crystalline lens, various types of ocular debris, inflammatory cells, and optically reflecting structures. The optical principles of specular microscopy[1] and the evaluation of corneal endothelium using specular microscopy[2] have been described. Also, several reviews of the general field of ocular specular microscopy have been published.[3–5] In many respects, the information obtained in specular microscopy of the corneal endothelium is similar to that received from scanning electron microscopy, but specular microscopy has the distinct advantage of allowing the observation to occur in the living cornea without inflicting any damage to the cornea. If desired, serial observations may be made to observe morphologic changes over time in the same cornea. In addition, the specular microscope allows for the observation of reflecting structures within the cells that cannot be discerned with scanning electron microscopy.

The importance of determining the viability and functional reserve of the corneal endothelium before penetrating keratoplasty makes specular microscopy a valuable tool as a noninvasive, nondamaging method of endothelial cell evaluation.[6–9] Combining the specular microscope, either a clinical specular microscope or an eye bank specular microscope, with appropriate computer and software enables rapid quantitative and statistical analysis of the state of the corneal endothelium, instant photographs and reports, and the ability to send photographs, endothelial analysis data, and other data over the Internet to other physicians or to centralized analysis centers.

PRINCIPLES OF SPECULAR MICROSCOPY

The specular microscope is an optical reflection microscope that reflects a slit of light from the cornea and allows observation of this specularly reflected beam. In this context, the term 'specular reflection' refers to the situation where, as with a mirror, the angle the reflected beam of light makes with the reflecting surface is equal to the angle that the incident light beam makes with the reflecting surface.

Because of its design, the specular microscope does not allow nonspecular light rays to be observed, so that the image that is seen is attributable solely to the specularly reflected light rays.

Figure 12.1 shows a simplified optical design of the specular microscope. As is seen in Figure 12.1, a projected slit is focused onto the posterior endothelial surface by an objective lens. The light that is reflected from this surface is collected by the same objective lens and is focused onto a focus plane, generally either a film plane or sensor of a video camera, or it may be directly observed by the examiner. An image of the posterior surface is seen at the focus plane and is directly viewed, captured on photographic film, or displayed on a video monitor screen. By focusing the specular microscope at places other than the posterior corneal surface, one may observe various other reflective surfaces. For example, by focusing the instrument on a plane within the stroma, one may detect the presence of ghost vessels, typically seen as linear refractile structures, nerve fibers, and so forth.

In the normal endothelial image, one sees the cells as having dark cell borders and bright cell surfaces. The reason for this appearance is illustrated in Figure 12.2, which shows the nature of the specular reflection from various types of endothelial surfaces: smooth, rough, wavy, and with excrescences, respectively. In each case, the ray indicated as 1 reflects from a 'flat' portion of the surface and is specularly reflected directly into the objective lens, thus causing the surface to appear as a bright structure to the observer. The rays indicated as 2 are specularly reflected from a curved part of the

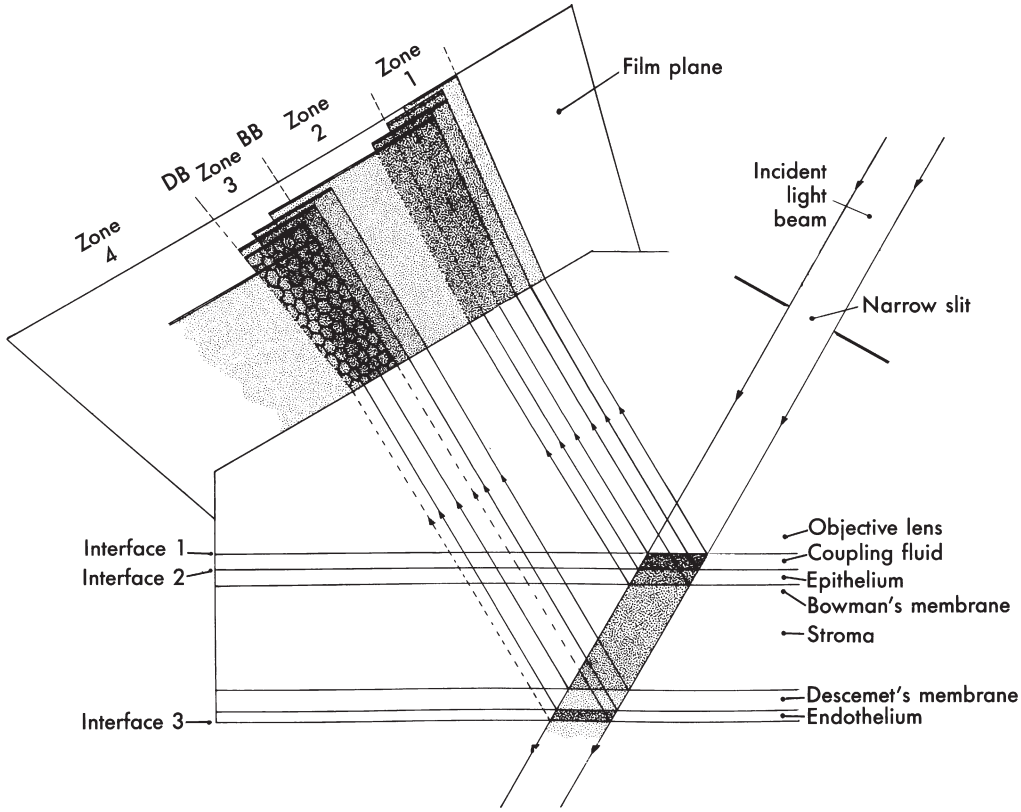

Figure 12.1. Optical principles of the eye bank specular microscope. A slit of light is focused onto the surface of interest (normally posterior endothelial surface). Specularly (mirror-like) reflected light rays are focused onto the film plane. In general, image at the film plane can be viewed with a viewing ocular lens or seen on a real-time video monitor.

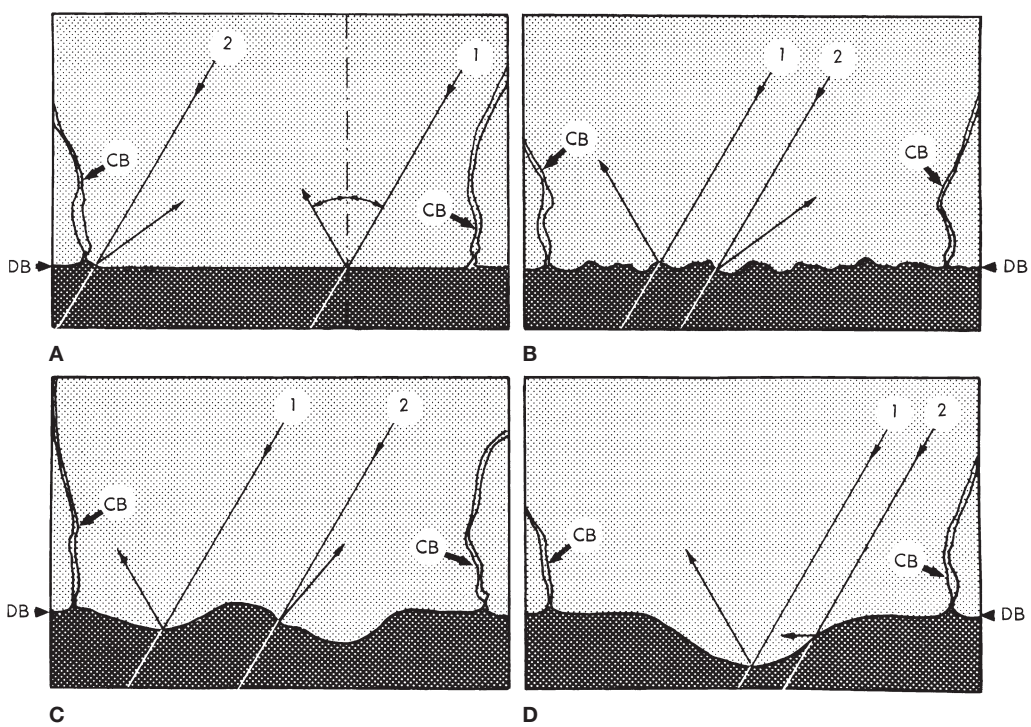

Figure 12.2. Nature of specular reflection from various types of posterior endothelial surfaces. Surfaces shown are: *A,* smooth; *B,* rough; *C,* wavy; and *D,* a posterior endothelial surface containing an excrescence. In each figure, cell boundary is denoted by CB; ray denoted as 1 is collected by objective lens of specular microscope and results in a bright area on film, whereas ray denoted as 2 is not collected by objective lens and result is a dark region on film plane. DB, dark boundary as seen on specular micrographs.

surface and as such are not collected by the objective lens. Therefore curved surfaces, such as the cell borders, the sides of rough areas, and the sides of an excrescence, appear dark to the observer. Thus in specular microscopy, the normal endothelial cell having a smooth surface appears as a bright circle surrounded by a dark border. If, instead of a smooth surface, the cell has a rough surface, the inside of the cell will have a granular appearance with the spacing between the granular dark regions being indicative of the degree of the roughness of the surface. As may be seen in the Figure 12.2, *D*, isolated corneal guttae appear as roundish dark structures with a central bright spot, which marks the apex of the excrescence.

CLINICAL AND EYE BANK SPECULAR MICROSCOPES

Depending on the objective lens used, the specular microscope may be either a contact microscope, in which the front of the objective lens touches the cornea, or a noncontact microscope, in which there is an air space between the front of the objective lens and the cornea. As is true of all optical microscopes, the resolution (sharpness) of the image and the optical sectioning ability depend on the numerical aperture (NA) of the objective lens. Contact specular microscopes generally have objective lenses with an NA that is higher than that of noncontact instruments such that the image quality obtained is somewhat better with contact instruments.

Clinical contact specular microscopes somewhat inhibit eye motion, thus reducing motion artifacts in the image. Contact instruments also enable stromal, epithelial, and lens epithelial cells to be observed and generally give a readout of the corneal thickness. In the past few years, several noncontact instruments have been developed that have the advantage of not having to touch the cornea. A typical clinical noncontact specular microscope that was recently developed is shown in Figure 12.3.

Eye bank contact specular microscopes can and have been used for observation of the corneal endothelium in the whole globe. However, most modern eye banks prefer to observe the cornea after it has been excised and placed in storage media. In such cases, contact objective lenses cannot be used because the cornea cannot physically be placed in contact with the objective lens. Again, the resolution and optical sectioning ability of the eye bank specular microscope depend on the NA of the noncontact objective lens, and these can often be improved for older instruments by changing the objective lens to one of the newer designs that are now available. Eye bank specular microscopes used for observing the cornea in eye bank storage chambers have been popular, and observation in chambers remains the most common method of endothelial observation. A typical eye bank specular microscope for observing the cornea in storage chambers is shown in Figure 12.4. This and similar instruments allow observation of the corneal endothelium, epithelium, and stroma either in whole globes (using a contact objective lens) or in excised corneas in storage chambers (using a noncontact objective lens). The instrument shown allows the cornea to be tilted about its center of curvature, allowing observation of the peripheral and the central endothelium. Because the optics head is mounted to a rigid column, a variety of cameras may be attached to the unit without concern for the weight of the camera. Often, both direct observations and documentation of the image on film or display of the image on a video monitor are used concomitantly. Recently there has been renewed interest in observing the cornea in the vials in which storage media is supplied.

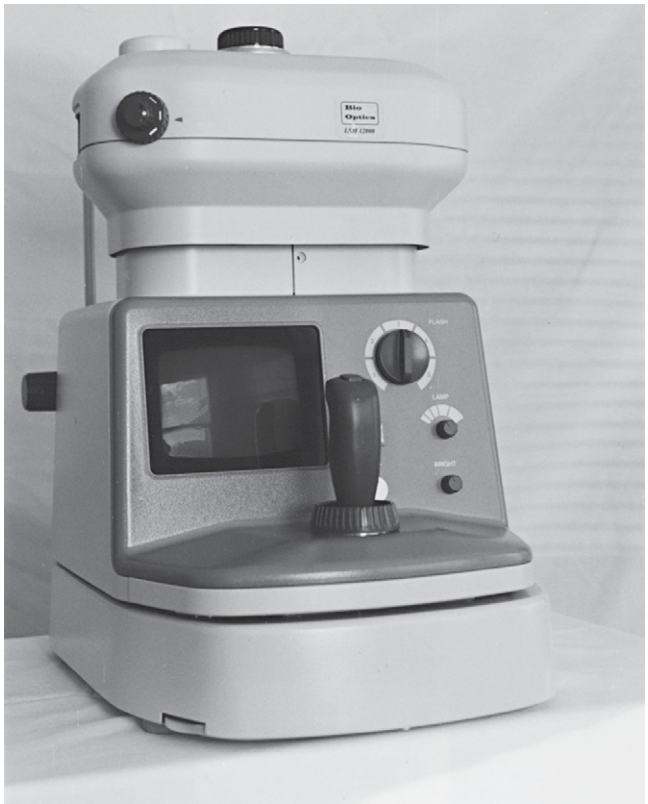

Figure 12.3. Typical modern clinical noncontact specular microscope. This instrument, the LSM-12000, allows both video and 35-mm film images of the corneal endothelium to be obtained. (Courtesy of Bio-Optics, Inc., Portland, OR.)

TECHNIQUES OF EYE BANK SPECULAR MICROSCOPY

Most eye banks store corneas at 4°C either in special plastic eye bank chambers or in glass vials. At this temperature, the endothelial fluid pump is relatively inactive, the cornea is somewhat edematous, and the endothelial surface has lost its normal smoothness. For most corneas, the endothelium is not easily seen at 4°C and must be warmed to 25°C for observation. Figure 12.5, *A* shows the appearance of the corneal endothelium at 4°C, and Figure 12.5, *B* shows the corneal endothelium after warming to room temperature. Note that there is a noticeable abnormality in the appearance of the endothelial cells of the cornea at 4°C, yet the cells appear normal after warming to room temperature. The warming time required to obtain a good endothelial image can be highly variable, ranging from 45 min to more than 2 h. The reasons for this variability are currently unknown. As the cornea warms to room temperature, the endothelial pump becomes reactivated, pumps fluid out of the swollen stroma, and restores the corneal endothelium to its normally smooth shape. In the absence of epithelial trauma resulting from the excision process, corneas having a shorter warming time may be expected to have a more active endothelial pump than those having a longer warming time and thus are 'better' corneas. However, the barrier function of the corneal epithelium is extremely sensitive to manipulation during excision so that there may be differences in the 'leakiness' to fluid of the epithelium of different donor corneas. The cycle of cooling, warming, and recooling of donor corneas has been shown to have no adverse effects on the

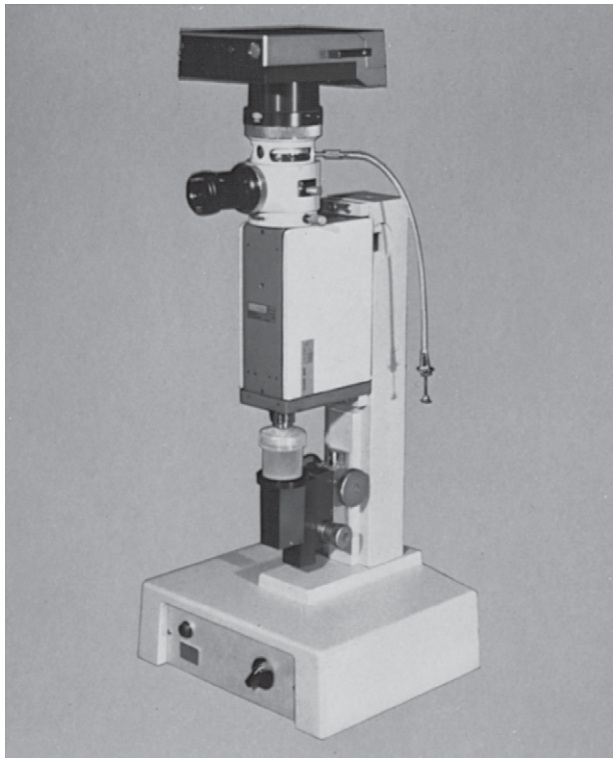

Figure 12.4. Eye bank specular microscope. Various magnifications and modes of operation are possible when objective or ocular lens are changed. As well as high-resolution direct observation, this instrument allows for real-time viewing on a video monitor, hard-copy documentation on 35-mm, Polaroid, or other film type, and recording of image obtained on videotape. This instrument also has capability of direct input of image into a computerized morphometric analysis system. (Courtesy of Bio-Optics, Inc., Portland, OR.)

metabolic or morphometric parameters of the cornea, even when warmed and cooled each day for 7 days.[10]

TECHNIQUES OF CLINICAL SPECULAR MICROSCOPY

In clinical specular microscopy, the technique used depends on the particular instrument that is used. In all cases, however, the basic technique is to align the instrument to the patient's eye so that the conditions for specular imaging are obtained.

NECESSARY CONDITIONS FOR NORMAL OBSERVATION OF THE CORNEAL ENDOTHELIUM

As with any microscope, the endothelium being observed must be at the correct distance from the objective lens (the working distance) so that its image is in focus on the focus plane of the specular microscope. In addition, to see sharp cell borders, the corneal endothelium must satisfy the conditions of specular imaging as described above. For eye bank specular microscopes and clinical contact specular microscopes, this essentially requires that the region of the endothelium being observed be perpendicular to the optic axis of the objective lens. For clinical noncontact instruments, this essentially requires that the region of the endothelium being observed be perpendicular to the line bisecting the optic axis of the illuminating objective and the optic axis of the light-collecting objective.

As one progressively focuses the specular microscope toward the endothelial surface and beyond it, there is light reflected back into the specular microscope that is minimal when the focus point is far from the endothelial–fluid interface and is maximal at this interface. The corneal endothelium is located at the point of maximum reflected light level. It is unlikely, however, that the image seen will resemble, at least to the inexperienced user, anything remotely similar to the appearance of the endothelial cells in the photographs in this book. At this point, the cell borders may not be visible because the conditions necessary to see the specular image have not yet been met. With practice, the nonspecular image is easy to recognize as an amorphous, low-contrast image that moves as the chamber or vial (for the eye bank specular microscope) or the microscope itself (for the clinical specular microscope) is moved laterally. To visualize the cell borders, the instrument must be aligned so as to observe the specular image as described in the previous paragraph. When this is completed, the cell borders become apparent, and the normal corneal endothelial image can be seen.

FACTORS AFFECTING IMAGE QUALITY

A variety of factors affect the quality of the image seen with the specular microscope including the NA of the objective lens. Advances in the design and manufacture of objective lenses in the past few years have made possible lenses that give considerably improved image quality as compared with lenses manufactured some years ago. In addition, it is very important that the front surface of the objective lens be clean. A slight oily film, possibly resulting from someone rubbing their finger across the lens to wipe off dust or from mascara, on the front of a clinical objective lens can degrade the image considerably. For eye bank specular microscopes, the condition of the plastic or glass between the corneal endothelium and the objective lens is very important. Optical distortions in these materials can adversely affect the image quality. Such distortions may arise in the manufacturing process or be the result of heat changes in the plastic top of eye bank chambers because of heat shrinking the protective seal onto the chamber. It is important to cover the specular microscope with a dust cover when it is not in use to minimize the possibility that the lenses become contaminated and dirty. A regular cleaning and alignment of the specular microscope by the factory every 2 to 3 years may be appropriate to ensure that the specular microscope is giving the best possible images.

IMAGE CAPTURE, STORAGE, AND ANALYSIS

In past years most corneal endothelial images were captured on photographic film and analysis was performed on enlargements from the photographic negatives. The film and the enlargements can be easily stored to provide documentation of the endothelial image should this subsequently be required for legal or other reasons. Although photographic film is still used in some clinics, most specular microscopes sold today capture video images that can be instantly seen on a video monitor screen; and with the availability of the personal computer and frame grabbers, computerized image capture, image enhancement, and image analysis systems have been developed.[7] One such system that has been available and in wide use for many years is the Bambi endothelial evaluation system (Bio-Optics, Inc., Portland, OR), which is now only a Windows-based systems, as shown in Figure 12.6. The latest system,

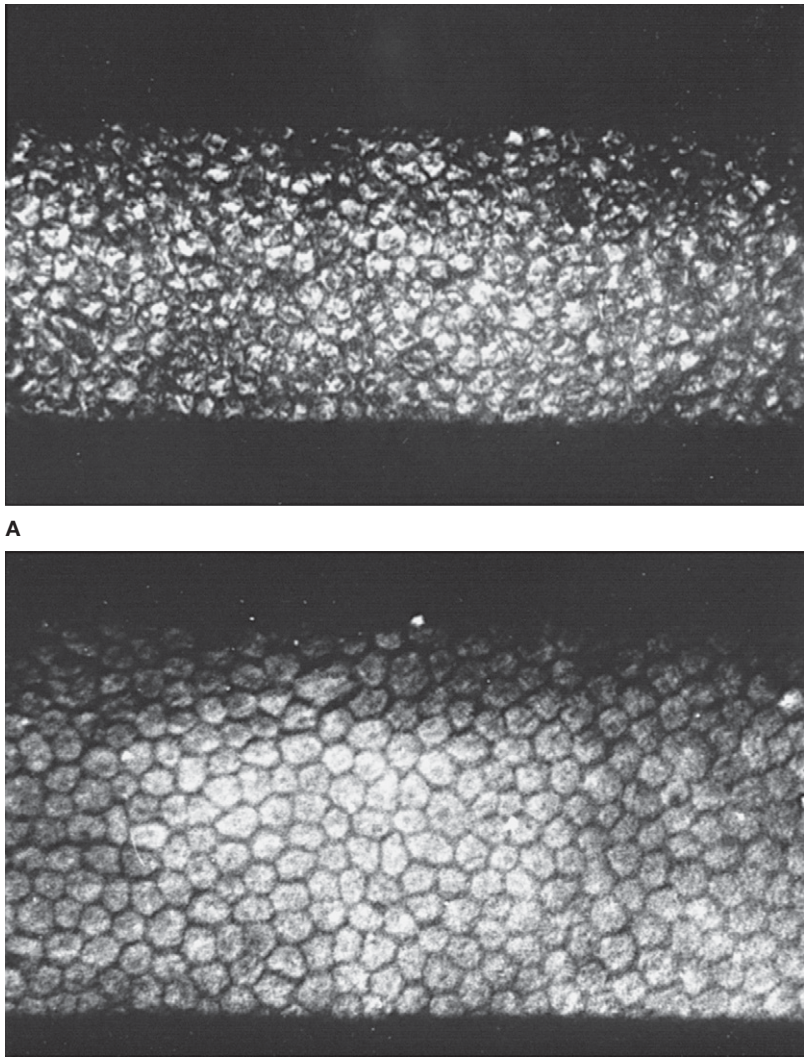

Figure 12.5. Appearance of corneal endothelium at different temperatures: *A,* 4°C; *B,* room temperature.

A

B

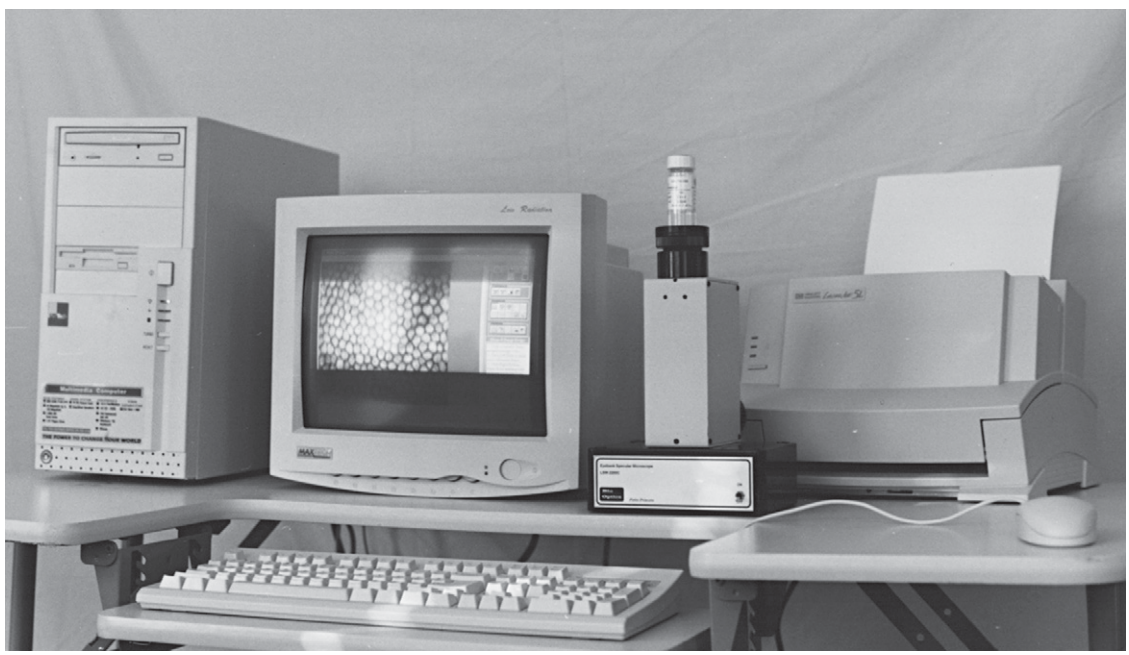

Figure 12.6. Bambi 97 computerized system for endothelial image documentation and analysis. This system captures and digitizes the endothelial image. The normally low-contrast image can then be contrast enhanced and analyzed to obtain the cell count and other morphometric parameters characterizing the corneal endothelium. The endothelial image can be printed out on a laser printer, stored on computer disk, and sent via the Internet to another location. A database is maintained of images and numerical and clinical (or eye bank) data. Letters and reports can be generated containing the image obtained. (Courtesy of Bio-Optics, Inc., Portland, OR.)

Bambi 2500, allows direct video input of the endothelial image from the video specular microscope or, alternatively, by scanning 35-mm negatives or enlargements. This system enables the user to enhance the normally low-contrast endothelial image rapidly, and to obtain the cell count and other morphometric data from the image. Determination of such evaluation parameters as cell density, degree of pleomorphism, and polymegathism is easy and fast. The image can be stored digitally on the local computer or sent to a server so that the endothelial image can be viewed in any other computer. Letters and reports that can include the endothelial image can also be generated with this system. The images and screen displays can be sent to other programs, such as Microsoft PowerPoint, for presentations. The data obtained are stored in a database that is expandable to allow the user to add additional data or to merge into an existing database. Such a computerized analysis system speeds up the entire process of specular microscopic endothelial evaluation and provides additional information not obtainable by manual methods of evaluation.

If the images are stored along with the morphometric data, then after a sufficiently large database is obtained, these data can be analyzed to obtain information concerning such things as possible risk factors and contraindications for procedures and to compare the relative efficacy and safety of new procedures.

QUALITATIVE EVALUATION OF THE CORNEAL ENDOTHELIUM

The specular microscopic image of a young, normal endothelium is shown in Figure 12.7. The cells are similar in size and shape, with no abnormally dark or bright structures being apparent and no evidence of inflammatory cells or adherent debris. The cell density is between 2000 and 3500 cells/mm^2 on the corneal surface. This is an ideal image of the endothelium of a donor cornea. In practice, the appearance of the endothelium of most donor corneas cannot be expected to be this good. In the older cornea and in corneas that have undergone various types of prior trauma or disease, the endothelium has a much different appearance. For the donor cornea, factors contributing to a change from normal include time from death to preservation, whether the eyelids were closed after death, whether any light ice packs were applied to the lids of the donor, trauma inflicted on the donor, trauma resulting from the excision procedure, and so forth. For the clinical cornea, factors contributing to changes from normal appearance include trauma, exposure to environmental pollutants, corneal dystrophies, and so forth.

Ideally one would prefer that a corneal endothelium, either from a donor cornea or a patient's cornea, has endothelial cells that are uniform in size, shape, and appearance. In practice, however, a variety of cell sizes (polymegathism) and shapes (pleomorphism) and abnormally bright or dark structures are encountered (Figs 12.8–12.10).

For corneas that are in the process of healing or recovering from certain types of stress, the processes of cellular coalescence[11–13] and cellular mitosis[14] can occur. In the first case, the coalescing endothelial cells appear as shown in Figure 12.11. In this process, a common cell border between two cells disappears, and the two cells fuse into a single cell. Although it is not presently known if this would contraindicate the use of the cornea in transplant, prudence dictates that, as long as other suitable tissue is available, corneas exhibiting such cells should not be considered for use in penetrating keratoplasty. It has been reported that corneas with considerable polymegathism or pleomorphism have an increased incidence of postoperative decompensation[15] and have a reduced functional reserve.[16] These studies indicate that donor corneas with such findings should not be used in transplant surgery. These findings in the clinical environment would indicate that one should be cautious with any ocular procedures performed on such a patient.

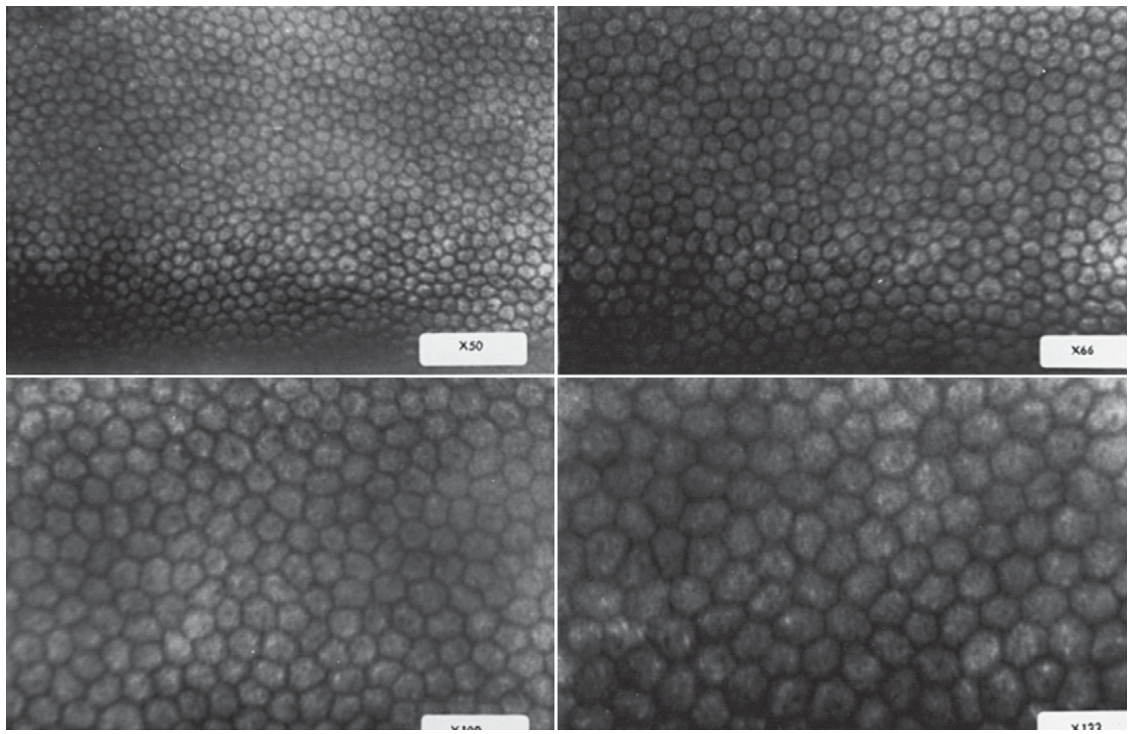

Figure 12.7. Appearance of young, normal endothelium at room temperature viewed at different magnifications. Cells are hexagonal and uniform in size and appearance.

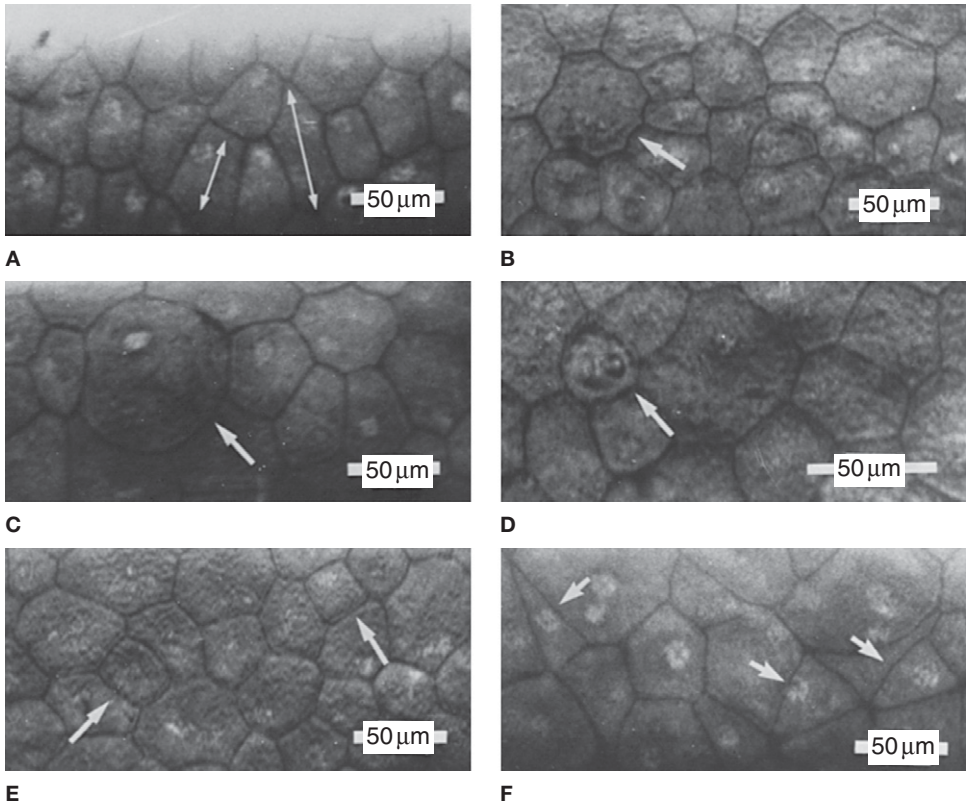

Figure 12.8. Various abnormal endothelial cell shapes, arrows: *A,* stretched; *B,* scalloped; *C,* large; rounded; *D,* small, rounded; *E,* square; *F,* triangular.

As shown in Figure 12.12, one may observe corneal guttata on examination with the specular microscope. Cornea guttata has been reported to reduce endothelial function or functional reserve,[17,18] and for this reason any cornea showing significant guttae should not be considered as acceptable for use in transplant surgery and should be treated gently during ocular surgery.

Bacteria and inflammatory cells are easily seen under the specular microscope. Bacteria are observed as small, bright twinkling objects whose shape and position rapidly change. Inflammatory cells have a similar appearance but are slower in their motions than bacteria. The presence of either bacteria or inflammatory cells (see Fig. 12.9, *H*) probably indicates contamination of either the storage media or the cornea, and as such would contraindicate the use of such a cornea for transplantation.

Other abnormal appearances are indicative of disease states (Figs 12.13 and 12.14) when seen under the specular microscope. Such corneas should not be considered for transplantation use.

QUANTITATIVE EVALUATION OF THE CORNEAL ENDOTHELIUM

A variety of methods have been developed to obtain quantitative information about the state of the corneal endothelium. In early studies, what became known as fixed frame cell counting was used. This method was subsequently modified to allow fixed frame cell counting to be done on a computer, generally with a mouse being used to draw the frame and to mark the cells. This method was shown to have very large and unpredictable errors unless the number of cells completely inside the frame was very large in comparison to the number of 'border cells', i.e. those cells that were cut by one of the borders of the frame.[19] Since this is seldom the case, fixed frame cell counting should seldom be used these days.

A method of eliminating the 'border errors', i.e. those errors due to not knowing how much of the area of the border cells were inside, or outside, the frame was solved by the variable frame cell counting method[19] in which a frame border is traced around a group of cells such that all cells inside the frame are whole cells—the frame does not cut any of the cells in the group. The number of cells inside the frame is divided by the area of the frame to determine the cell count. With the use of personal computers and endothelial images on monitor screens, this method became easy to implement since the frame could be drawn with a mouse and the cells inside the frame could be marked and counted by clicking the mouse when the cursor was inside the frame. The variable frame cell counting method remains the most accurate and reliable semiautomated method for obtaining a cell count. It does not, however, provide information about the distribution of cell sizes in the sample being studied and the method is tedious to perform if the number of cells in the sample is large. To reduce the time required and tedium of drawing a frame and marking the cells, as well as to be able to obtain statistical information about the cell sample, several methods for automated cell counting and analysis have been developed. As might be expected, some give more accurate and reliable results than others. Probably the most difficult aspect of developing an automated method is the complex nature of the endothelial image. When looked at casually, the cells all seem to have clean, dark, and unbroken borders. If looked at more closely, that is far from the case for most endothelial images. Some borders have 'missing border points' and/or places where a clear border between two apparently adjacent cells is unclear. This problem essentially eliminates the use of many of the standard automated image analysis methods that programmers are familiar with. In some cases, a 'medical' decision has to be made as to whether or not an elongated cell with a faint or partially missing interior border is one large and irregular cell, a coalescing cell,[11–13] or two individual cells. This

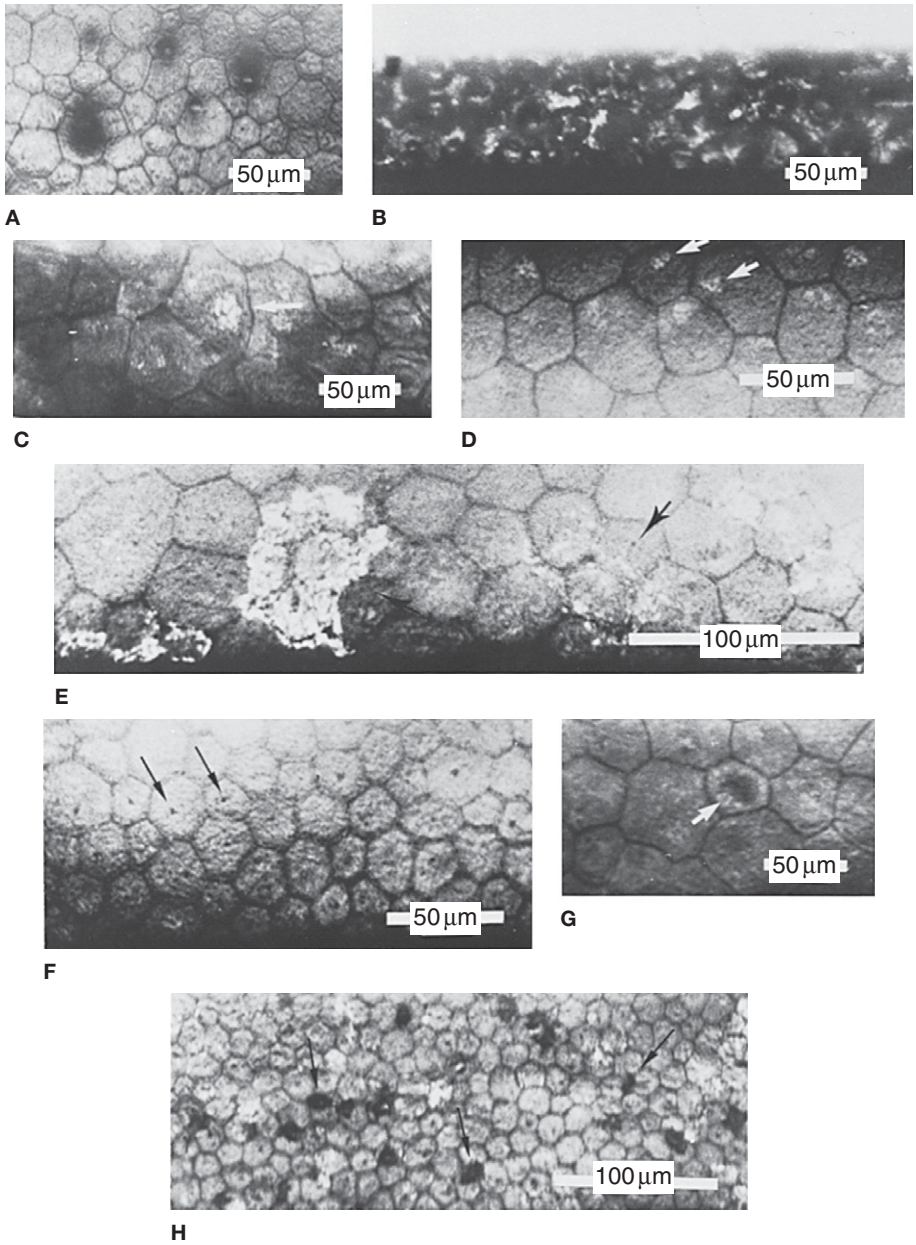

Figure 12.9. Various abnormal intracellular and intercellular structures: *A,* isolated smooth excrescences (cornea guttata); *B,* multiple coalesced guttae; *C,* pigment deposits and linear structures; *D,* bright structures (presumably nuclei); *E,* adherent pigment deposits; *F,* central cilia; *G,* large, dark structure; *H,* inflammatory cells.

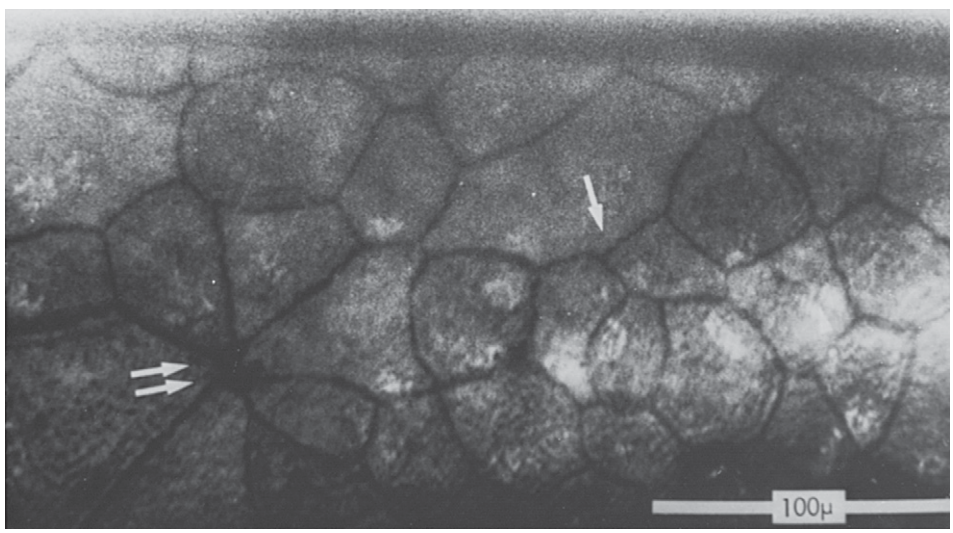

Figure 12.10. Abnormal corneal endothelium showing a 'reformation figure' (double arrow) believed to be indicative of endothelial repair by sloughing and cell sliding. Also seen is a cluster of 'smaller' cells (single arrow), probably resulting from mitosis. Large, multisided cells seen are believed to have resulted from coalescence of cells.

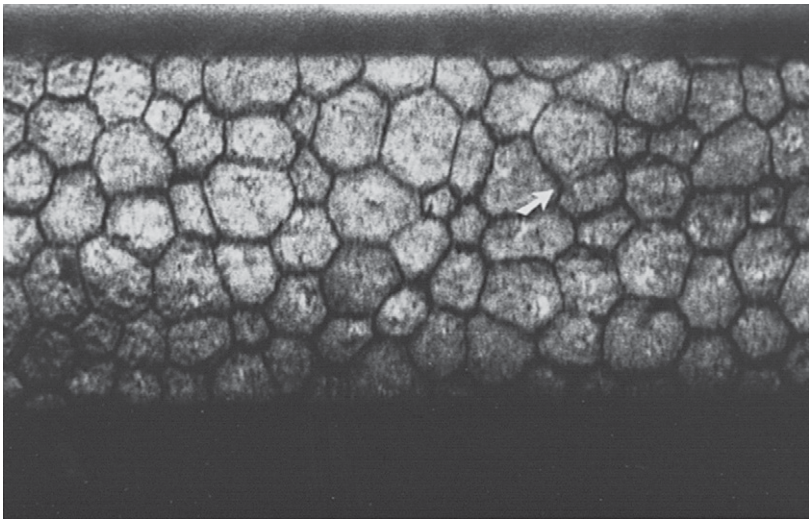

Figure 12.11. Abnormal corneal endothelium showing endothelial cells in the process of 'healing', or recovering from stress, by process of cell coalescence. The cell border (arrow) was seen to disappear over time. Endothelium exhibits pronounced polymegathism and pleomorphism.

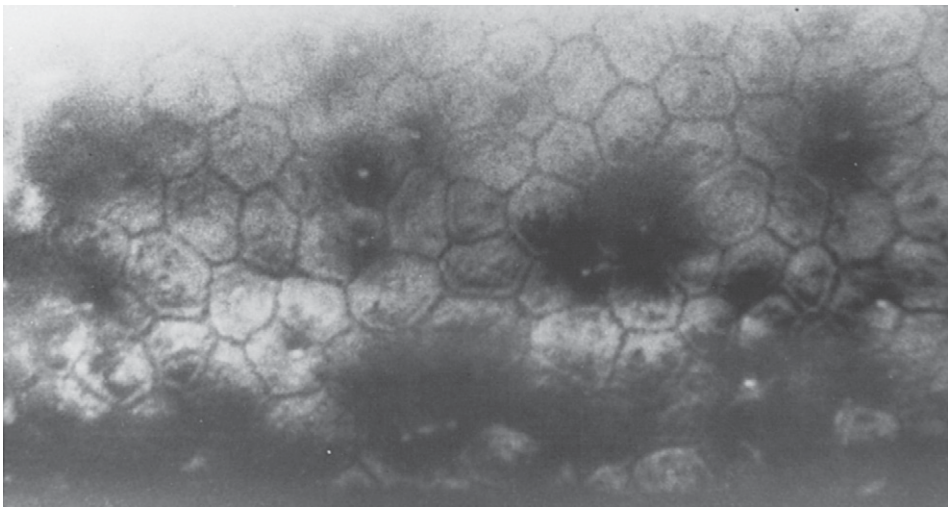

Figure 12.12. Abnormal appearance of corneal endothelium resultant from Fuchs' dystrophy. Notice guttae, seen as irregular, dark patches.

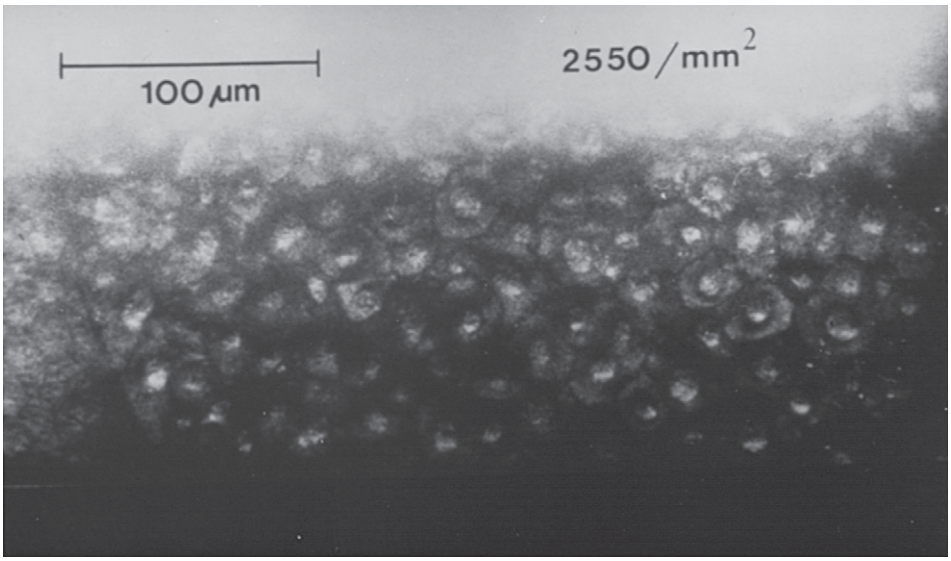

Figure 12.13. Abnormal appearance of corneal endothelium as seen in patients with posterior polymorphous dystrophy.

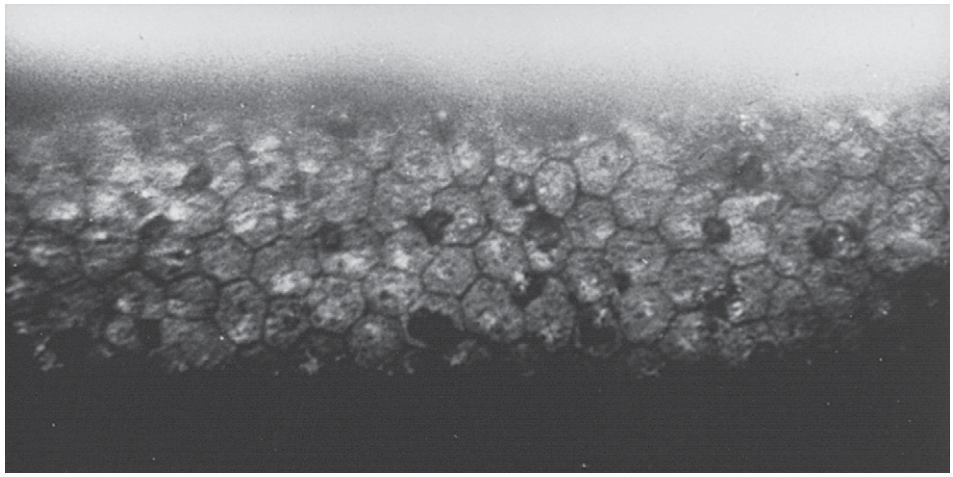

Figure 12.14. Effects of heterochromic cyclitis on corneal endothelium as seen in a specular photomicrograph.

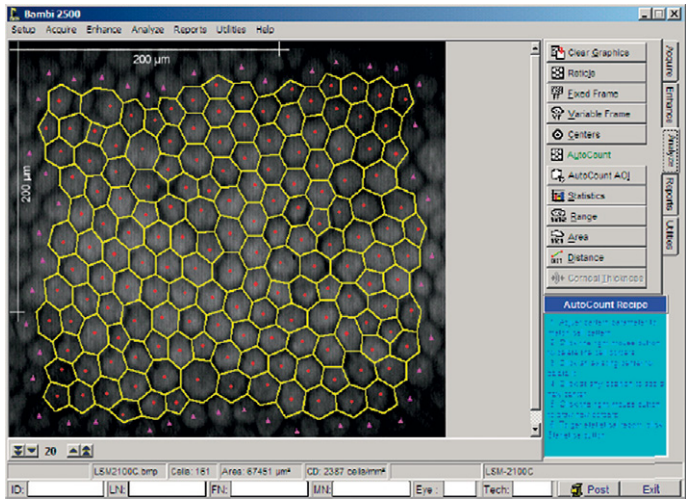

Figure 12.15. Screen shot of the results of Bio-Optics automated cell count and analysis program, AutoCount, in which a cell count of 2367 cells/mm2 for a sample of 161 cells was obtained in less than 1 s. (Courtesy of Bio-Optics, Inc., Portland, OR.)

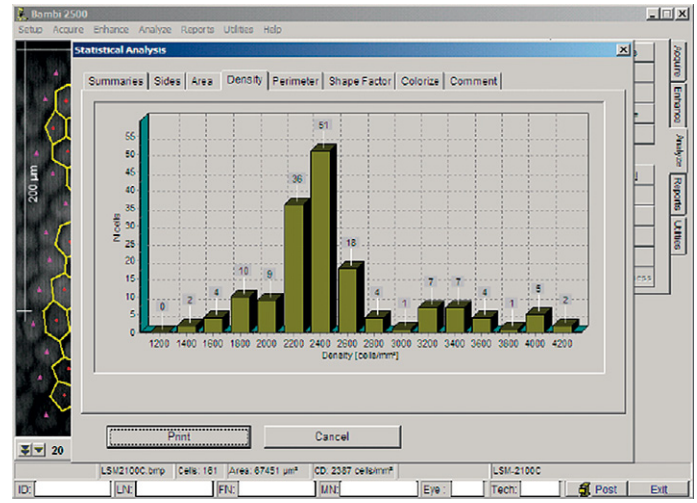

Figure 12.16. Screen shot showing the cell density histogram from the image shown in the previous figure. (Courtesy of Bio-Optics, Inc., Portland, OR.)

decision should be made by a trained medical professional and should not be determined a priori by a programmer who generally has minimal understanding of the complexity of the corneal endothelial image. One of the fully automated methods for endothelial cell analysis is the AutoCount program used in Bambi 2500. Figure 12.15 shows a screen shot of what is displayed for a typical endothelial image from the Bio-Optics LSM2100C Eye Bank Specular Microscope. A total of about 200 cells were marked, the red round marks denoting cells 'inside' the variable cell count frame, and the purple triangular marks denoting cells 'outside' the frame and thus not counted in the determination of cell count. The AutoCount program marked the 200 cells and drew the cell borders in less than 1 s. To mark 200 cells manually and then draw an external border around a group of 150 cells takes about 100 s, or more. In practice, the accuracy with which the cells are marked should always be checked, and corrected if necessary, to make sure that there is one, and only one, mark per cell. With AutoCount this might take an additional 3–5 s after which time an accurate cell count is calculated and displayed, again in less than 1 s.

If accurate statistical information is desired about the endothelial mosaic, then there must not only be one, and only one, mark per cell but the marks must be in the centers of the cells. This should always be checked. With AutoCount it is easy to eliminate a mark that is in the wrong place and add one that is correctly in the center of the cell. Again the time taken to do a recount is less than 1 s. A variety of statistical information and reports can also be obtained. Figure 12.16 shows a screen shot of a cell density histogram showing that the distribution is quasi-normal but with a rather long tail at the higher density levels. Figure 12.17 is a screen shot showing a 'colorized' view of the endothelial image with 'normal' cells being colored gray, cells 'larger' than normal being colored red, and cells 'smaller' than normal being colored blue. Such displays are useful in studying localized trauma of the corneal endothelium.

As instrumentation improves and images with larger numbers of cells are obtained, the automated cell counting and analysis programs become even more valuable. Figure 12.18 is a screen shot of an image obtained with the Bio-Optics LSM2200C/E2 Eye Bank Specular Microscope. AutoCount marked almost 700 cells, 491 of them being 'inside' cells, drew the cell borders, and calculated the statistical parameters of the image in less than 1 s. To mark this number of cells manually would take about 7 min and it is doubtful that anyone would want to do this more than a few times before

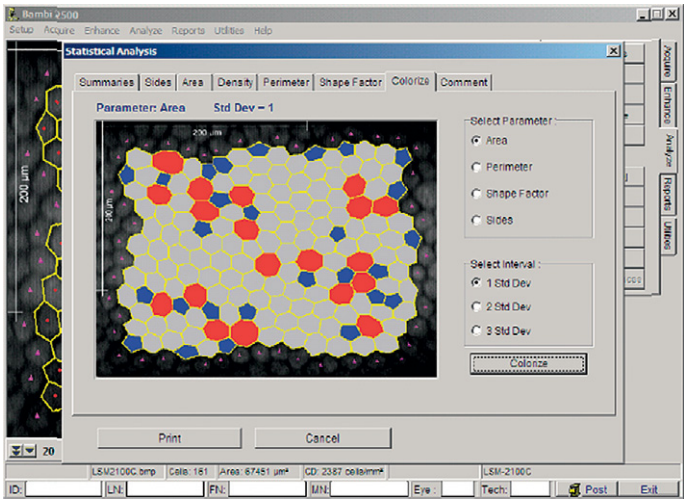

Figure 12.17. Screen shot showing a 'colorized' image from the image shown in the previous figure. (Courtesy of Bio-Optics, Inc., Portland, OR.)

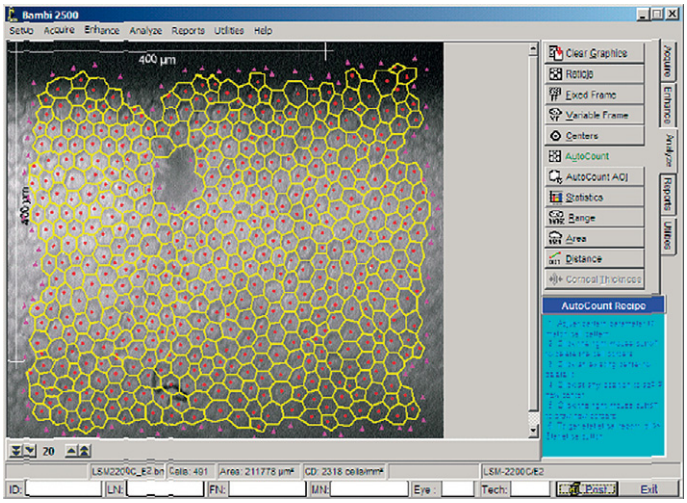

Figure 12.18. Screen shot showing the results of Bio-Optics AutoCount program in which a cell count of 2316 cells/mm^2 for a sample of 491 cells was obtained in less than 1 s. (Courtesy of Bio-Optics, Inc., Portland, OR.)

finding another line of work. This figure also shows two things that any automated, semiautomated, or manual method of cell counting must do if it is to give accurate and valid cell counts. In the upper left of the image is an area in which cell borders cannot be seen. In AutoCount this area is excluded from the frame area that is used. In the past, this has sometimes not been appreciated and has resulted in many invalid cell counts being calculated and used. Whatever method is used to obtain a cell count, any area in which cell borders cannot be seen must be excluded from the analysis used or else the cell count will be too small and invalid. The second thing shown in Figure 12.18 is the black object, probably due to a piece of lint on the image sensor. In this case this artifact did not interfere with the cell borders being seen and drawn automatically, and any automated cell counting system used should also have the feature of not giving invalid results due to lint, dust, or similar image artifacts.

Whatever automated cell counting and analysis system is used, it is important that the user has a way of checking to determine the accuracy of the analysis. Although computers can do numerical calculations very rapidly and accurately, all automated analysis programs, by necessity, make assumptions about the nature of the endothelial pattern being analyzed. If the assumptions made by the programmer are correct for the endothelium being analyzed then the cell count will be correct. If they are not, then the cell count will be incorrect and invalid. The user should always have a way of seeing the intermediate results from the computer and have a way of correcting them so as to get a valid count. Of concern in cell counting and analysis is the question as to whether enough cells have been counted to obtain a valid number. The conventional wisdom has long been that 100 cells are needed to reduce the errors of the counting method used to an acceptable value. As discussed above, the counting errors depend upon the method used, the fixed frame method having much larger counting errors than the variable frame, and AutoCount methods, for the same number of cells counted. Another issue is whether or not the number of cells in the image analyzed is sufficient to characterize that part of the endothelium that is of interest, i.e. the central endothelium, the superior endothelium, the entire endothelium, etc. The Bio-Optics MICS (Multiple Image Cell Statistics) program enables data from multiple images to be merged and analyzed as a whole and provides statistical parameters of the multi-image sample. A recent program, Cells Analyzer[20] also provides this ability and also calculates the statistical significance of the sample. Although for general clinical or eye bank use such programs may not be necessary, they are essential for research applications in which detailed endothelial changes with time and/or treatment are needed.

EVALUATION CRITERIA

The presence of an abnormal, or 'bad-looking', corneal endothelium most likely indicates that the cornea is functionally deficient and compromised. Such characteristics of an abnormal endothelium, as seen by specular microscopy, are:

1. An endothelial cell density less than 1500 cells/mm^2. (In general, corneas whose only flaw is a low cell density still present the risk of a continued cell loss,[21] which could ultimately lead to a density low enough for corneal decompensation.)
2. Severe polymegathism or pleomorphism of the endothelial cell pattern.
3. Presence of corneal guttata.
4. Presence of many abnormally shaped cells, such as those seen in coalescence.
5. Abnormal single-cell defects.
6. Extensive areas of severe edema.
7. Presence of inflammatory cells or bacteria on the endothelium.
8. Presence of ghost vessels in the stroma.

The age of the cornea appears to be of secondary importance in determining the health and functional reserve of the tissue. An older cornea having a high endothelial cell count, low degrees of polymegathism and of pleomorphism, and a normal overall appearance is most likely functionally superior to that of a younger cornea that has a lower cell density or exhibits an abnormal appearance. Specular microscopy, especially when used with computerized morphometric analysis, proves to be extremely useful in the evaluation of corneas from older patients because it allows for the determination of suitability of the tissue for ophthalmic procedures or for use

in transplantation, rather than an arbitrary decision based on age alone.

ANTICIPATED CHANGES

At the time of writing (December 2006), the current specular microscopes available generally use video cameras or Charge Coupled Device (CCD) sensors that output a standard video signal. The cell counting and analysis systems input this video signal via a cable that leads to a computer frame grabber. Standard video signals are constrained to have only 480 vertical lines (in the USA) and this standard limits the resolution of current endothelial images. Such images characteristically have a resolution of about 0.25 megapixels (MP). At the present time there is considerable activity in the development of high definition television, with 1080 vertical lines and in digital camera sensors with resolutions of up to 12 MP. It can be expected that such technology will be utilized by the major manufacturers of specular microscopes and cell counting and analysis systems in the near future. Another activity that can be expected to alter our field is the rapid expansion of WiFi and WiMax networks around the world. By the publication date of this book, it may well be that higher resolution images will be obtained on very high-resolution sensors and sent wirelessly to a server and/or notebook computer for cell counting and analysis and perhaps even to a counting and analysis center in a different part of the country. Although the instrumentation may be better, the underlying accuracy and validity of the obtained cell counts and analysis will still be limited by the complex nature of the corneal endothelial image, and the skill and knowledge of the user in understanding what is seen in those images and how to correct for possible incorrect assumptions made by the computer software.

SUMMARY

The specular microscope is a valuable tool for use in the evaluation of the corneal endothelium. In the eye bank, specular microscopy can be used to identify corneas that are functionally deficient or that have a marginal functional reserve so that such corneas are not used for human transplantation. Specular microscopy can thus help to improve the quality of the tissue used in penetrating keratoplasty and to reduce the number of grafts that fail. In the clinic, specular microscopy can be used to evaluate the function and functional reserve of the cornea, as a tool in diagnosing various corneal disease states, to demonstrate that no untoward trauma has resulted from an ocular procedure, and to observe and better understand the wound healing process after surgery.

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13 Tonometry and biomechanical analysis

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INTRODUCTION

Ophthalmologists have long appreciated that the inherent properties of the cornea—such as curvature, astigmatism, rigidity, and hydration—can affect the quality and accuracy of intraocular pressure (IOP) measurements using Goldmann applanation tonometry (GAT). Goldmann tonometry is a static measurement calculating IOP, using the Imbert Fick Principle, from the force applied during a steady-state applanation of the cornea.[1] Goldmann applanation assumes that the cornea has a standard thickness and behaves biomechanically as an infinitely thin and perfectly flexible membrane. In reality, Goldmann IOP measurements are filtered through the viscoelastic characteristics of the cornea, influenced by inter-individual corneal variations, and can be substantially affected by corneal surgery.

In 1975, Ehlers et al[2] showed that eyes with thinner corneas had lower Goldmann pressures compared to manometry, while thicker corneas had higher GAT IOP than manometric reading in the same eyes. Recently, the relationship between central corneal pachymetry (CCT) and GAT IOP measurement has been highlighted by the Ocular Hypertension Treatment Study,[3] which showed an inverse correlation between CCT and the risk for developing glaucomatous damage. Several investigators have suggested linear algorithms to 'correct' Goldmann IOP measurements based upon CCT.[4] However, the basis for linear correction of IOP is fraught with potential error, as there is only a weak correlation between GAT and CCT (R^2 = 0.06 to 0.17) in normal eyes.[4,5]

Corneal biomechanics reflects more than central pachymetry. For example, GAT generally decreases following a number of surgeries (i.e. radial keratotomy and hyperopic laser in situ keratomileusis (LASIK)) where there is little change in CCT but profound changes in corneal rigidity.[6–9] Attempts at linear 'correction' of Goldmann tonometry based on CCT can, in fact, be in the wrong direction in select cases.[10,11] More accurate measurement of IOP, in theory, requires instruments that perform dynamic, rather than static, applanation measurements and therefore assess and compensate for corneal biomechanics. This is particularly important in eyes with altered structure and biomechanical properties, such as those with corneal ectasias (keratoconus and pellucid marginal degeneration), Fuchs' dystrophy, or following incisional or ablative corneal surgery.[12] We review below the definitions of biomechanical metrics and their impact on tonometry—a subject that encompasses the effects of corneal hydration, regional pachymetry, viscoelasticity, and other inherent corneal characteristics that may not yet be fully defined.

GENERAL PRINCIPLES OF CORNEAL STRUCTURE

The structural characteristics of the cornea facilitate its essential functions, specifically to serve as both a transparent barrier and the predominant refractive element of the eye. Given the integral relationship between form and visual function, the biological and mechanical responses of the cornea to surgical interventions impact its optical performance.[13,14] While major advances have occurred in the refinement and standardization of corneal surgical techniques, our ability to compensate for individual biological responses to surgery remains limited and can influence the predictability and stability of visual outcomes after corneal surgery. Further understanding of these factors provides the basis for improving outcomes and reducing complications of corneal surgery, by identifying individual response outliers and developing strategies for regulating or compensating for these biomechanical features.[15]

The cornea is a complex composite (of collagen, proteoglycans, water, and salts) with nonlinear elastic and viscoelastic properties. It is characterized by important local variation in organization in central versus peripheral and anterior versus posterior architecture. Swelling studies have shown that the interlamellar adhesive strength of the central cornea depends upon proteoglycan bonding, whereas branching and interlacing of lamellae provides additional adhesive strength peripherally (Table 13.1).[16] Changes in the proteoglycan matrix may explain the increased pliability of the central cornea in keratoconus and may potentially impact the corneal response to keratorefractive surgery, contact lens wear, and tonometric testing.[17] The anterior-most stromal lamellae have oblique branching and interweaving fibers that insert into Bowman's layer.[18] Because of these features, the anterior stroma swells less and is about 25% stiffer than its posterior counterpart.[19] These findings suggest that

peripheral and/or posterior incisional surgery may have less of a profound impact on corneal biomechanics than anterior, central surgery. Mathematical modeling of such a complex system is therefore quite difficult, but begins with identification of intrinsic properties of corneal tissue, as described below (Table 13.2).

METRICS OF CORNEAL BIOMECHANICAL PROPERTIES

Elasticity (Young's modulus, E) is an indicator of material stiffness, with a higher modulus corresponding to a stiffer material. Elasticity can be calculated by determining the stress applied to a material (force per unit cross-sectional area) divided by the resultant strain (i.e. change in the material's length divided by the unit starting length). This ratio of stress to strain (i.e. elasticity), measured in Pascals, can be thought of as a measure of the material's resistance to a change in length. For example, a metallic rod would have a higher modulus than a wooden rod (Fig. 13.1). A perfectly elastic material returns to its original form when an external stress is withdrawn in a completely reversible and symmetric manner, i.e. along the same stress–strain pathway.[20] Elasticity is traditionally measured *ex vivo* with an extensiometer that records the force generation required during steady axial elongation of a tissue sample. The slope of stress (force per unit cross-sectional area, measured in Pascals) over strain (the change in length divided by the starting length) is calculated for a representative portion of the curve. A linear approximation can be obtained from the instantaneous slope of the stress–strain curve (tangent modulus) or as a chord between two points on the curve (secant modulus). Whereas *ex vivo* dissection of strips of human cornea and application of weights to cause elongation has allowed the estimation of regional strain characteristics, such *in vitro* modeling has been difficult to translate into *in vitro* correlates.[21–24] Other methods, such as electronic speckle pattern interferometry and dynamic corneal imaging following indentation,[12,25] may be better suited for *in vitro* studies of corneal biomechanics and elasticity. These will be discussed in detail in a later section.

Viscoelasticity extends the biomechanical response of biological tissues into complex mathematical descriptions of viscous fluids, where responses are time and rate dependant.[26] Viscoelastic materials return to their pre-stress shape via different stress–strain pathways that depend upon loading rates. Viscoelastic properties can be described through metrics of hysteresis, stress relaxation, and creep. Viscoelastic creep is a time-dependent elongation of tissue (or increasing strain) that occurs under a sustained or constant stress

Table 13.1 Local Variation in Corneal Lamellar Ultrastructure

Collagen Lamellae in the Peripheral Cornea:
Greater number
Greater branching and interlacing
Circumferential orientation
Greater resistance to swelling
Collagen Lamellae in the Anterior Cornea:
Anterior strands insert into Bowman's layer
Greater proteoglycan bonding centrally
Greater stiffness than posterior cornea

Table 13.2 Descriptors of Corneal Biomechanical Properties

Elasticity (also known as the Young's modulus, modulus of elasticity, or elastic modulus): A measure of the stiffness of a given material, defined as the ratio of the rate of change of stress with strain and can be measured as the instantaneous slope of a stress–strain curve.
Stress: Force per unit cross-sectional area, measured in Pascals.
Strain: The change in length of a material divided by its original length. Strain is positive if the material has gained length during the application of an external force or tension, but can be negative if it has reduced length (compression) during this process. Strain has no units of measure but can be expressed as a percentage.
Viscoelasticity: Property of a material that has the ability to store energy of deformation and in which the application of a stress gives rise to a strain that approaches its equilibrium value slowly.
Hysteresis: In general terms, hysteresis refers to the lag between making a change, such as increasing or decreasing power, and the response or effect of that change. Using the Ocular Response Analyzer ORA, corneal hysteresis is the difference between intraocular pressure measured during the two applanation events produced by compression of the cornea with a collimated air pulse (CH = P1 – P2).
ORA corneal resistance factor: An ocular response analyzer metric that is derived as a linear combination of P1 and P2 to maximally correlate to central pachymetry.
Creep: A situation where there is a slow change in the dimensions of a material from prolonged stress, such that application of a step constant stress causes increasing strain.
Stress relaxation: A situation in which strain is held constant while a slow, quantifiable time-dependant decrease in stress is observed.
Shear strength: The maximum stress which a material can withstand without rupture or splitting into two parts that slide past each other.
Ocular rigidity: A measure of the resistance which the eye exerts to distending forces, described by pressure–volume calculations that relate the change in intraocular pressure to the change in intraocular volume.
Ocular pulse amplitude: The difference in intraocular pressure between systole and diastole (IOP systolic – IOP diastolic) measured by the Pascal Dynamic Contour Tonometer. This may be a marker for ocular rigidity.

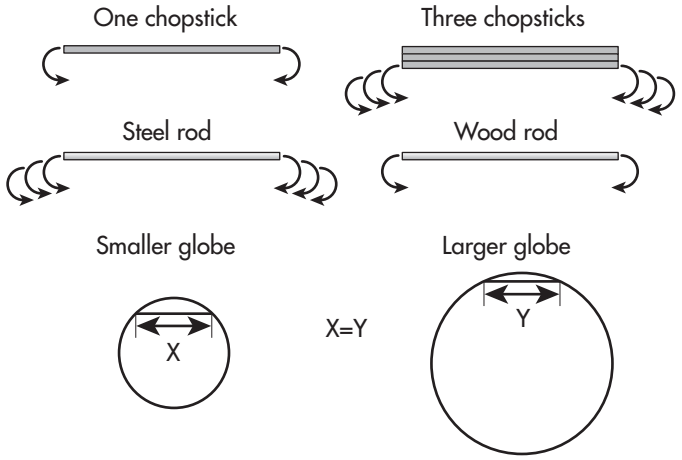

Figure 13.1. The influence of structural and material properties on the ability to deform the cornea. Bending a single chopstick is usually easy. However, bending three of the same type of chopsticks at once is much more difficult (top row). Hence, a larger deformation will be generated for thinner corneas given the same applied force. This partially explains the underestimation of IOP in eyes with thinner corneas. In contrast, it requires greater pressure to applanate or indent a thicker cornea, which contributes to overestimation of IOP in eyes with thicker corneas. Similarly, much more force is required to bend a steel rod than a wooden rod of the same dimensions (middle row). The difference in this case is the elastic properties of the material, specifically Young's modulus. Steel has a much higher Young's modulus (w200 000 MPa) than wood (w10 000 MPa); therefore, if all other parameters are the same, it is much harder to deform a steel structure than a wooden structure. Corneal curvature is another variable that can affect the accuracy of IOP measurement, possibly because of the difference in the volume of the displaced fluid after a given area is flattened (bottom row).[47]

(such as IOP).[26] The effect of creep is a reduction in effective tissue stiffness, which can lead to a decrease in resistance to stretch. Creep may be a precursor to ectasia, where stressed collagen fibrils undergo a pathologic weakening without an initial change in length. Once the collagen fibrils are weakened, a gradual stretching then occurs under constant stress or IOP. Viscoelastic stress relaxation refers to a situation where strain is increased then held constant (no more tissue elongation) while a slow but quantifiable time-dependent relaxation of the load is observed (Fig. 13.2).

Hysteresis, in general, is a property of physical and biological systems that do not instantly follow the forces applied to them but react slowly or do not return completely to their original state.[26] Hysteresis describes a lag between making a change, such as increasing or decreasing power, and the response or effect of that change. Whereas a rubber band can be described as elastic because it springs back to its original shape at the same rate as when it is stretched, a putty exhibiting viscoelastic behavior quickly assumes a new shape when pushed upon but will not immediately return to its original shape when the mechanical pressure is released. In broad terms, corneal hysteresis can be thought of as a metric of the ability of the cornea to absorb energy.

Volumetric distension experiments provide a measure of whole globe stiffness, or ocular rigidity. The slope of a pressure–volume curve can be recorded during such experiments. Ocular rigidity is nonlinearly dependent upon IOP and has been shown to increase with age.[27] The utility of metrics describing ocular rigidity may be limited with respect to their impact on the understanding of corneal surgery, given the contributory role of the scleral and uveal tissue to ocular rigidity.

New techniques for in vivo measurement of corneal biomechanical properties and intraocular pressure

While ex vivo diagnostic techniques, such as extensiometry, have provided valuable information on the biomechanical nature of normal and pathological corneas,[28] a new era is dawning in biomechanical research with the development of techniques to measure structural and biomechanical properties in vivo. Imaging of the cornea can now be performed by confocal microscopy, very high frequency ultrasound,[29] optical coherence technology, and holographic interferometry.[30,31] Dynamic corneal imaging uses stepwise central indentation of the cornea and computer analysis of videokeratography images during indentation to assess corneal elastic properties in vivo.[25]

Alternative techniques that dynamically derive IOP from corneal movement in response to a rapid air pulse stimulus simultaneously assess and compensate (to varying degrees) for the effect of the cornea's viscous and elastic qualities on IOP measurement. The Ocular Response Analyzer (ORA; Fig. 13.3, Reichert Ophthalmic Instruments, Depew, New York, USA)[12] utilizes a metered collimated air pulse to applanate the cornea and an infrared electro-optical system to record inward and outward applanation events. The air-pulse deforms the cornea through an initial applanation event (peak 1), then beyond into concavity and then gradually subsides, allowing the cornea to rebound through a second applanation (peak 2). Corneal hysteresis (CH; Fig. 13.4) is defined as the difference between the applanation pressure at peak 1 (P1) and peak 2 (P2), so that CH = P1 − P2. Whereas corneal hysteresis may reflect mostly corneal viscosity, corneal resistance factor (CRF, defined as a linear combination of P1 and P2, weighted for P1 and maximal correlated to CCT) may predominantly quantify corneal rigidity. The ORA provides an IOP-G (Goldmann-equivalent) IOP reading, based upon a linear regression formula compared to GAT, and an IOP-CC (corneal compensated) IOP, based upon a regression ($P2 - 0.43 \times P1$) of measurements from normal and postrefractive surgery patients.

Pascal Dynamic Contour Tonometry (PDCT; Swiss Microtechnology AG, Port, Switzerland) employs a concave tip (Fig. 13.5) to 'contour match', rather than applanate, a convex segment of the central cornea and thus may be relatively independent of the effects of CCT or surgical intervention on IOP assessment.[32–34] The instrument dynamically records over 100 IOP measurements per second, measuring IOP fluctuations throughout the cardiac cycle and digitally displaying the average diastolic IOP. Ocular pulse amplitude (OPA), the difference in IOP between systole and diastole (IOP systolic – IOP diastolic), is also reported and may be a marker for overall ocular rigidity,[27] although it is also affected by ocular blood flow.

Another dynamic or rebound tonometer (RBT; Tiolat Oy, Helsinki, Finland) comprises an assembly of two coils coaxial to a probe shaft that bounce a magnetized probe off the cornea and detect the deceleration of the probe caused by the eye. A change in voltage at the two ends of the coil generates a magnetic field, which is detected by the tonometer sensor. The inverse of the probe's deceleration speed seems to correlate with the IOP.[35] Clinical evaluation demonstrated that RBT gives higher IOP readings than GAT and is also dependent upon CCT.[36]

The Proview (Bausch & Lomb, Rochester, New York, USA) eye-pressure monitor is based on the principle that pressure applied to

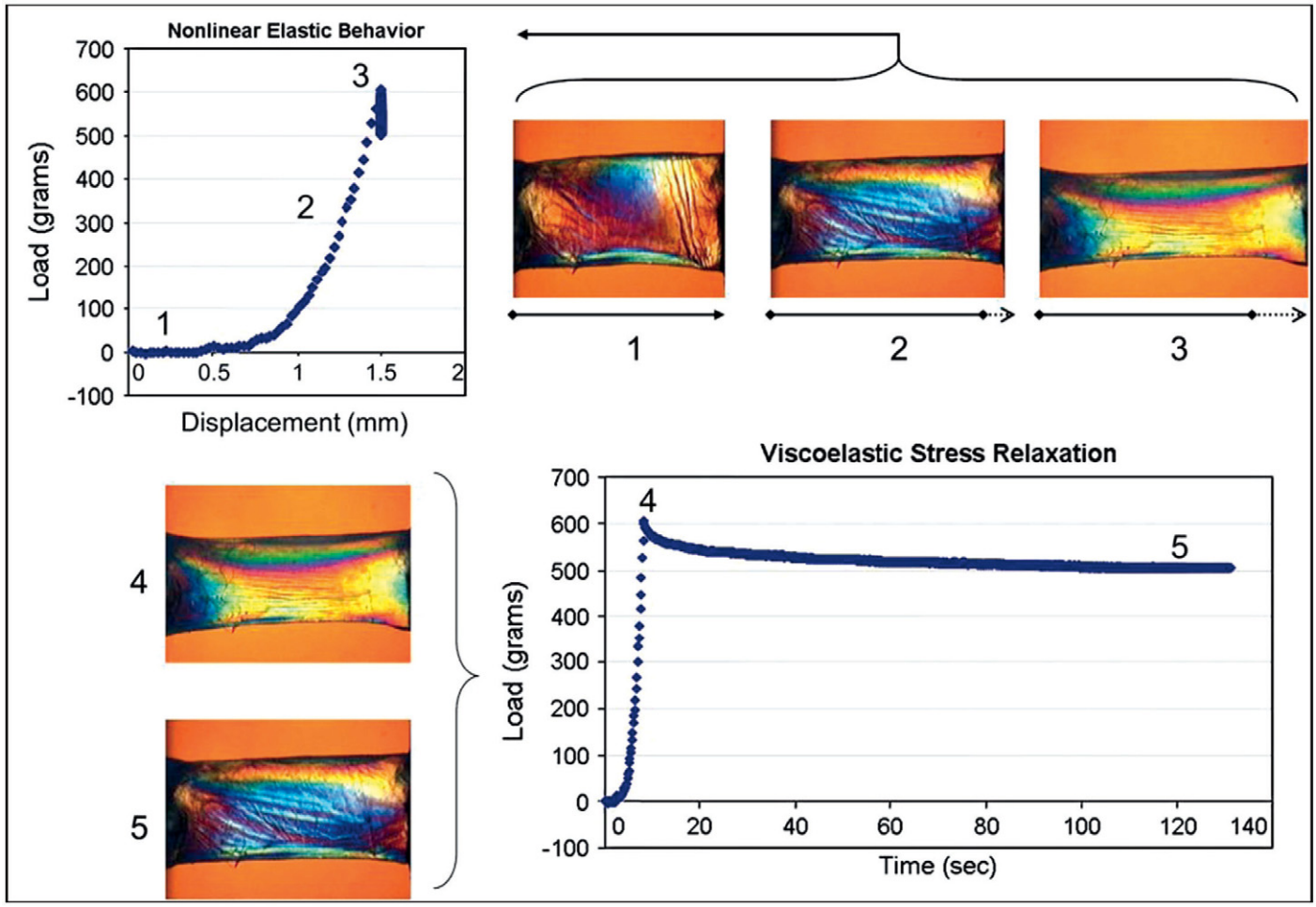

Figure 13.2. Experiments illustrating elastic and viscoelastic properties in a 7-mm, full-thickness horizontal corneal strip from a 63-year-old donor. Elliptical polarization allows visualization of nonhomogeneous internal stresses. Progressive stretching of the sample (1, 2, and 3) and measurement of the induced load (stress) allows calculation of the elastic (Young's) modulus from the slope of the stress–strain relationship. The relationship is nonlinear. A second experiment in which a constant displacement is imposed in the same sample demonstrates time-dependent stress relaxation, a viscoelastic property of biological soft tissues (4 and 5).[20]

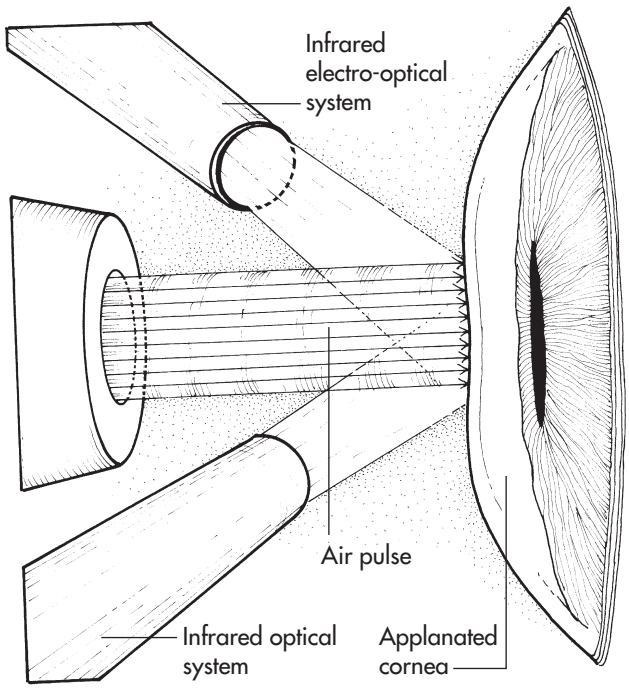

Figure 13.3. The Ocular Response Analyzer utilizes a collimated air pulse to applanate the cornea. Courtesy of D. Taylor, Reichert, Inc.

the sclera generates a self-perceptible visual phenomenon, known as a phosphene spot. The threshold pressure for creating a phosphene spot may be used to estimate IOP. The tip of the tonometer is pressed against the closed eyelid, and the pressure is recorded when the patient detects the phosphene. The Proview method may be useful for patients with corneal abnormalities that may interfere with accurate pressure measurements and may avoid artifact related to corneal thickness. The accuracy of the instrument in the clinical setting requires further investigation.[37–40]

BIOMECHANICS AND INTRAOCULAR PRESSURE

It appears that corneal shape is not determined on a random basis, but results from a steady-state balance between the biomechanical properties of the cornea and IOP.[41] The cornea assumes the shape for which its potential energy content is minimal (i.e. for which its stromal fibrils are in a relatively relaxed state) as a function of variables such as tissue elasticity, thickness, fibril length, and rate of change of IOP. Physiologic corneal stresses (such as from normal blinking or diurnal variation in IOP) and nonphysiologic corneal stresses (such as from forceful lid closure or rubbing) may potentially impact the corneal shape. However, normal corneas have been found to show low extensibility, measured by changes in anterior

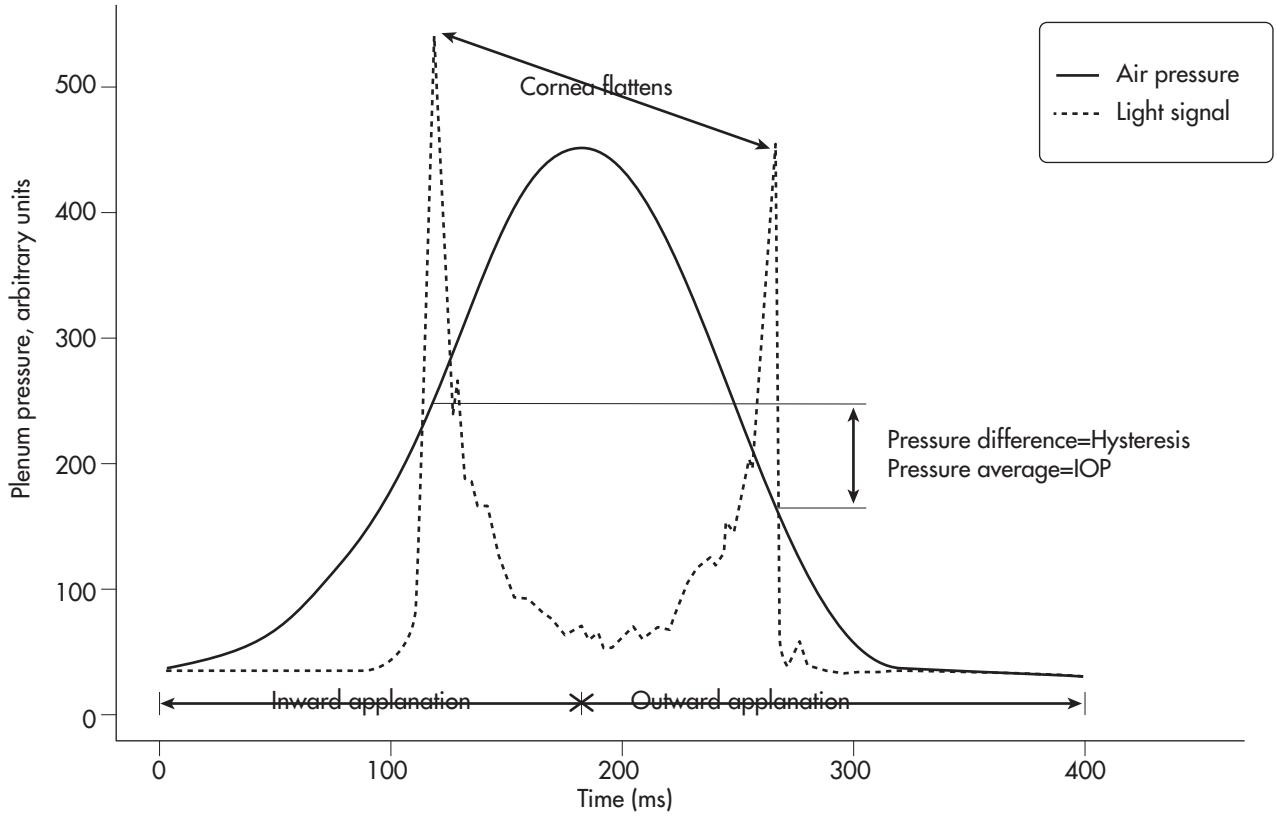

Figure 13.4. The waveform generated from the Ocular Response Analyzer identifies the pressure difference, or hysteresis, during inward (peak 1) and outward (peak 2) applanation events during noncontact tonometry.[49]

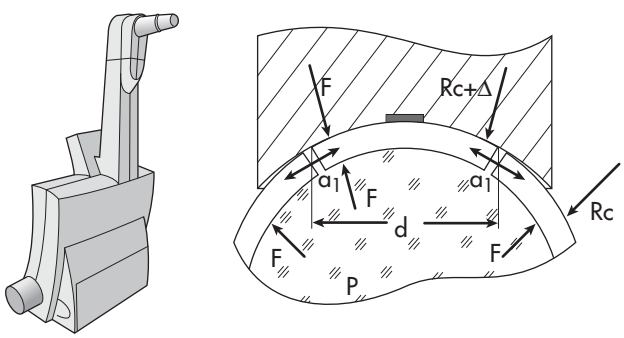

Figure 13.5. The Pascal Dynamic Tonometer utilizes 'contour-matching' to measure intraocular pressure via a microchip at the tonometer tip.

surface sagittal height, for a wide range of physiologic conditions in order to maintain refractive stability, even with marked elevations in IOP.[20] Conversely, when corneal biomechanical properties are altered via incisional surgery such as radial keratotomy, diurnal variation in IOP can lead to fluctuation in corneal refractive power by greater than 1 D.[20]

Increasing attention has focused on the impact of corneal parameters, particularly central corneal thickness, on the measurement of IOP.[4] IOP measurements have been demonstrated to vary with CCT using the Goldmann applanation,[42] pneumotonometry,[43] and noncontact tonometry.[44] The deformation of the cornea during applanation is determined by an interaction of the external applied force with the intrinsic properties of the cornea. With the same applied force, a larger deformation will be produced for less rigid corneas. This partially explains the underestimation of IOP in eyes with thinner corneas. In contrast, it requires greater force to applanate a more rigid cornea, partially explaining the overestimation of IOP in eyes with thicker corneas. The clinical implications of this observation are seen in the classification of patients as normals, ocular hypertensives, or with low-tension glaucoma. A number of studies have found a significant difference in the mean CCT of these three groups. After adjustment of GAT by regression algorithms for CCT, several studies have suggested that a third of low-tension glaucoma eyes can be reclassified as having primary open angle glaucoma. With similar adjustment factors, 30–65% of ocular hypertension eyes can be reclassified as normal.[45,46] It is possible that a larger percentage of misclassification errors may be found if biomechanical metrics other than CCT are also taken into account and properties are also taken into account when correcting GAT IOP measurements.

It is clear that tonometry is affected by biomechanical properties not fully measured by CCT. Liu and Roberts[47] attempted quantitatively to analyze the influence of corneal biomechanical properties on GAT IOP measurements through a mathematical model. The authors analyzed the separate influence of CCT, radius of curvature, and modulus of elasticity on IOP measurements obtained by applanation tonometry. They demonstrated a nonlinear relationship between CCT and IOP, and between corneal radius of curvature and IOP readings. Steeper curvature has a more significant impact on IOP accuracy than a flatter curvature. Theoretically, the steeper the corneal curvature, the more the cornea must be indented to produce the standard area of applanation. Therefore, more force must be applied, increasing the indicated value of IOP. This may have important implications in differences in the IOP measurement error after hyperopic photoablation than following myopic keratorefractive surgery. Furthermore, Liu and Roberts concluded, based upon their

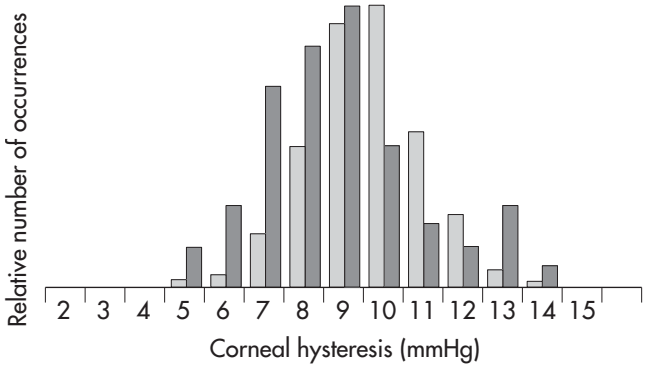

Figure 13.6. Distribution of hysteresis values in 339 normal (pale gray) and 60 keratoconic (dark gray) eyes. Mean hysteresis for normal and keratoconic eyes was 9.6 and 8.1 mmHg, respectively.[12]

mathematical model of tonometry, that variations of the elasticity of the cornea within a range predicted to occur in a normal population would result in an error of IOP measurement even higher than the one induced only by variations in corneal thickness.

Using the Ocular Response Analyzer, CH has been reported to range from 5.0 to 18.7 mmHg in normal eyes, with a mean hysteresis of 9.6 to 12.7 mmHg.[11,12,48] Hysteresis values did not show a statistical difference in a cohort of 21 normal patients between right and left eyes, with a mean difference of 0.4 mmHg ($p > 0.08$).[48] CH appears to be relatively insensitive to diurnal effects, although intrasubject variations have been observed. The correlations of CCT with CH and CRF were 0.59 and 0.62, respectively, in one study of normal eyes.[11] Lower hysteresis has been associated with visual field progression in a glaucomatous population.[49]

Martinez-de-la-Casa et al,[50] in a study of 48 eyes, showed that both IOP-G ($r = 0.460$, $p = 0.001$) and IOP-CC ($r = 0.442$, $p = 0.001$) correlated significantly with CCT, but not with corneal curvature or refraction. Pepose et al,[11] in a cohort of preoperative LASIK patients, confirmed a statistically significant correlation between IOP-G and CCT ($r = 0.322$, $p < 0.01$), although they suggested a nonlinear relationship. They did not find, however, a significant association between IOP-CC and CCT. Similarly, Medeiros and Weinreb,[51] in a univariable regression, did not find a significant correlation of IOP-CC to CCT ($p = 0.106$), corneal curvature ($p = 0.112$), or axial length ($p = 0.117$). IOP-CC measurements, in their cohort, were significantly associated with age ($p = 0.044$). Patients with thicker corneas tended to have higher GAT measurements compared with IOP-CC, whereas with thinner corneas had lower GAT readings than IOP-CC. In a multiple regression model, GAT, CCT, and corneal curvature each positively correlated with CRF.

Corneas with keratoconus (Fig. 13.6), Fuchs' dystrophy and postrefractive surgery demonstrate a general decrease in corneal hysteresis compared to corneas in normal eyes.[12] The low corneal hysteresis in the Fuchs' eyes is seen despite unusually thick, but edematous, corneas. However, the large 95% confidence interval of corneal hysteresis seen in normal controls has considerable overlap with diseased and postsurgical corneas, limiting its diagnostic value as a single metric in individual cases. What may turn out to allow better diagnostic differentiation are the significant changes seen in applanation waveform in diseased or postsurgical corneas. Keratoconic and post-LASIK corneas appear to have similar applanation signal morphology, indicating reduced or low corneal viscoelastic properties in both cases (Fig. 13.7). Investigations to quantify morphologic characteristics of the ORA waveform are now underway

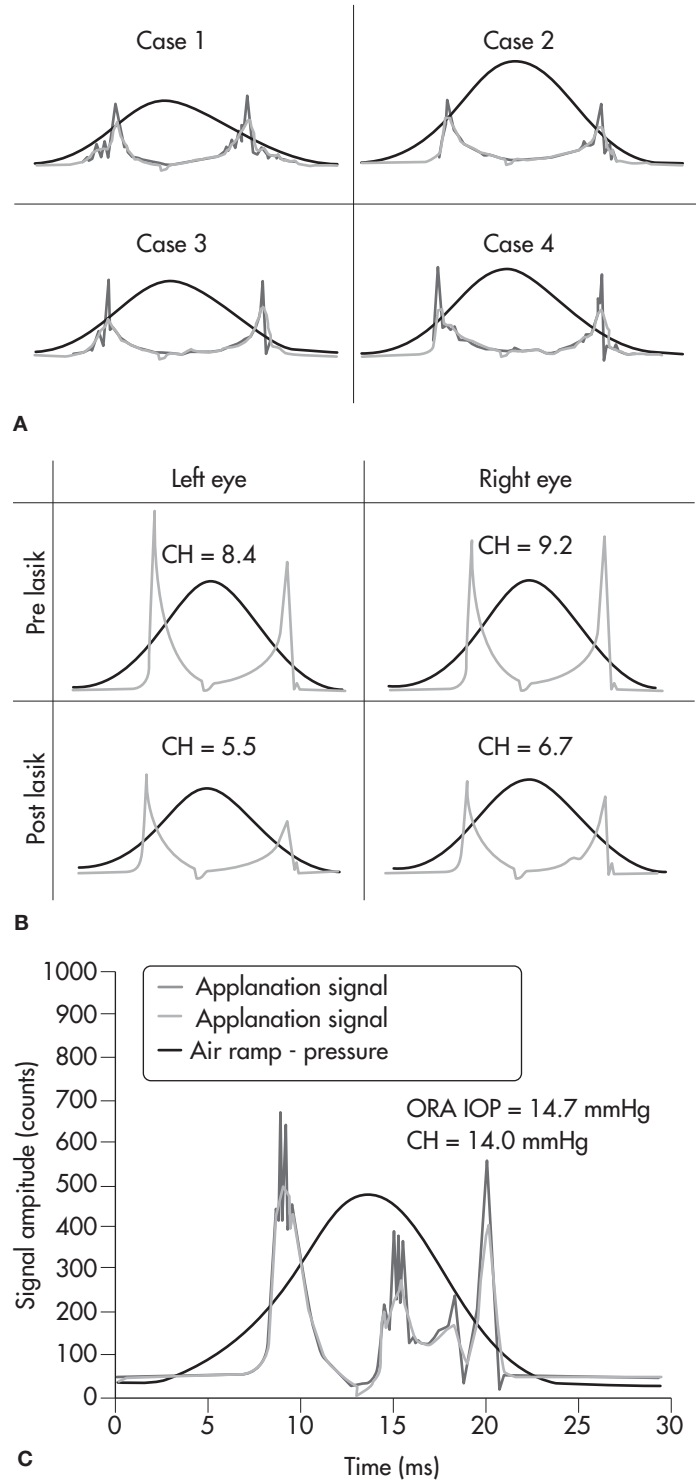

Figure 13.7. ORA applanation signal in keratoconic and post-LASIK eyes shows depressed applanation peak amplitudes and altered applanation peak widths: *A,* Case 1–4 are from keratoconic eyes; *B,* pre- and post-LASIK waveforms show a decrease in hysteresis postoperatively, along with reduced applanation peak amplitudes; *C,* waveform post penetrating keratoplasty shows marked alternation in the applanation signal, with increased noise during the applanation events.[12]

that attempt to extract additional corneal biomechanical information. Corneal hysteresis may be useful as a qualification factor for LASIK in corneas that have similar CCT but display significantly different waveform properties. Thus, the ORA waveform, along with the derived biomechanical metrics of corneal hysteresis and resistance factor, may provide a more complete characterization of corneal biomechanical properties than corneal thickness alone and is perhaps a better tool for assessing refractive surgery qualification and outcomes.

Corneal biomechanical properties appear to have only a limited effect on PDCT measurements. Several investigators have shown that PDCT IOP does not significantly correlate with CCT, including after keratorefractive laser surgery, and are higher than with GAT (as well as ORA).[11] A possible explanation for this is that the PDCT was calibrated against a manometrically controlled pressure standard. Manometric studies by Feltgen et al[52] indicate that the Goldmann IOP measurement averages 1.2 mmHg lower than manometry in human eyes in vivo. The OPA is a parameter affected by both ocular rigidity and ocular blood flow. Ocular rigidity has been reported to be reduced in enucleated pig eyes following corneal ablation (Pallikaris IG—ESCRS presentation, Lisbon, Portugal, 2005). In human patients, OPA was not significantly affected by LASIK, although it is unclear how potential changes in ocular rigidity or blood flow impact OPA measurements following photoablation *in vivo*.

CONCLUSION

A review of the biomechanical features of the cornea reveals complex interactions that influence the measurement of IOP. Dynamic tonometers may provide multiple metrics that may be combined with advanced structural and functional diagnostic imaging techniques to develop mathematical models of the viscoelastic features of the normal and postsurgical cornea during IOP measurement. As our understanding of these processes improves, so will our ability to offer rational interventions and strategies for further improving the predictability of keratorefractive surgery and may lead to a paradigm shift in the management of glaucoma.

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14 Anesthesia for corneal surgery

Jerry G. Ford, John W. Reed

Prior to the 19th century, the only anesthetic available was a drink of brandy or a bullet to bite, making ocular surgery quite difficult. After the introduction of ether and nitrous oxide as general anesthetics in the mid-19th century, ocular surgery became much less stressful, but severe coughing and vomiting upon awakening caused many postoperative complications. A major breakthrough came in 1884 with the introduction of topical cocaine by Koller, and by the turn of the century ophthalmologists were primarily using repeated applications of topical cocaine as anesthesia for ocular surgery.[1] By the 1930s and 1940s in the USA, retrobulbar anesthesia was replacing topical anesthesia as the preferred method of anesthesia.[2] Recently, much has been written about returning to the use of topical anesthesia alone for many types of ocular surgery.

The decision to use general, local, or topical anesthesia is based upon many factors: the age, health, anxiety level, and cooperative ability of the patient; the technical difficulty and duration of the surgery to be performed; and the setting in which the procedure is to be performed. The surgeon's experience with one type of anesthesia or another also is a factor in the decision-making process. This chapter discusses the different types of anesthetic agents and modes of delivery for surgical procedures of the cornea.

GENERAL ANESTHESIA

General anesthesia has the benefit of complete immobility of the patient as well as complete anesthesia. This benefit allows for a more relaxed pace and eliminates stressful situations, such as when a patient suffers anxiety from being under sterile drapes, becomes restless with a lengthy procedure, or continues to blink with incomplete lid akinesia, thereby creating posterior pressure on the globe during 'open sky' procedures.

The disadvantages of general anesthesia include increased turnover time; increased labor and overall costs;[3] risk of intraoperative contamination of the operative field with nasal secretions;[4] increased incidence of postoperative nausea, sore throat,[5] and urinary retention;[3] slower recovery time; and, possibly, an increased physiologic stress to patients with systemic disease.[3]

General anesthesia is commonly achieved by a combination of different agents, such as inhalation anesthetics, narcotics, sedative-hypnotics, and muscle relaxants. Varying amounts of each agent can be individualized to fit the particular situation. The minimum alveolar concentration (the minimum concentration of anesthetic that allows complete anesthesia in 50% of patients) of some common inhalation anesthetics is listed in Table 14.1.

General anesthesia may result in greater physiologic stress to the patient. Studies have shown that patients undergoing ocular surgery under general anesthesia have higher plasma adrenalin, cortisol, and glucose levels than those being managed under local anesthesia.[6] The metabolic control of blood glucose of noninsulin-dependent diabetic patients undergoing cataract surgery has been shown to be better when local rather than general anesthesia is used.[7] One study of healthy, elderly patients undergoing cataract surgery who were randomly assigned to receive general or local anesthesia showed a greater incidence of transient hypoxia and more marked fluctuations of blood pressure and heart rate in the general anesthesia group, but there were no differences in significant adverse events or cognitive function 3 months later.[3] In addition, studies of patients with cardiovascular disease undergoing carotid endarterectomy or peripheral vascular bypass surgery randomly assigned to receive local or general anesthesia have shown no significant difference in (or even a reduced incidence of) adverse outcomes in patients in the general anesthesia groups.[8,9] In healthy patients, general anesthesia appears to have no greater risk than local anesthesia, but when systemic disease is present, the risk versus method of anesthesia choice is less clear.

LOCAL ANESTHESIA

Table 14.2 compares ester and amide injectable anesthetic agents, including onset and duration of action, dosages, and toxicity. The ester agents are of lower toxicity, but their short duration of action limits their use in ophthalmic surgical procedures. The amides (e.g. lidocaine and bupivacaine) have a longer duration of activity and are used very commonly in ophthalmic procedures, but they have greater toxicity. Central nervous system (CNS) toxicity, which is generally seen first, is manifested initially by CNS stimulation followed by CNS depression. However, with bupivacaine, CNS depression may occur without signs of excitation. Stimulation of the CNS

may be manifested by restlessness, apprehension, euphoria, tremors, twitching, and seizures. Hypotension, severe respiratory depression, and stupor may follow, representing depression of the CNS. Cardiovascular effects are seen with high systemic concentrations. Effects on the heart include a decrease in electrical excitability, conduction rate, and force of contraction. Early signs of cardiovascular involvement include hypertension, tachycardia, and arrhythmias. Later signs include bradycardia and hypotension.[2,10]

Hypersensitivity reactions to the local anesthetics are infrequent. Sensitivity to the amide-linked agents has been reported to be rare.[11] However, type IV hypersensitivity reactions to any of the local anesthetic agents can occur, ranging from contact dermatitis to an anaphylactic reaction with hives and angioneurotic edema. Cross-sensitivity does not exist between the amide and ester groups.[10]

MODES OF DELIVERY

Subconjunctival anesthesia is obtained using a syringe with a 26- or 30-gauge needle for injection of 2% lidocaine with or without epinephrine or 0.75% bupivacaine just beneath the conjunctiva (Fig. 14.1). This approach provides excellent anesthesia for procedures such as removal of conjunctival or corneal intraepithelial neoplasia as well as small pterygia, conjunctival biopsy, or other similar procedures. Globe penetration may occur with this route of delivery.

Intracone (retrobulbar) injection is a safe and effective method for excellent ocular anesthesia and akinesia. It was first described by Knapp[12] in 1884, but it did not gain widespread use until the 1930s and 1940s.[2] The technique described by Atkinson[13] in 1948, with a few modifications, has become the most commonly used technique for local anesthesia in ophthalmic surgery[2] (Fig. 14.2). The needle is introduced through the skin at the inferotemporal orbit with the globe positioned upward and inward, thereby moving the inferior oblique muscle out of the way; as described by

Table 14.1 Minimum Alveolar Concentrations of Inhalation Anesthetics

Anesthetic	Minimum Alveolar Concentration (%)
Halothane	0.75
Methoxyflurane	0.16
Enflurane	1.68
Nitrous oxide	105 ± 35
Fluroxene	3.4
Isoflurane	1.15

From Gravlee GP. General anesthetics. In: Tolmie JD, Birch AA, eds. Anesthesia for the Uninterested. Rockville, MD: Aspen Publishers; 1986.

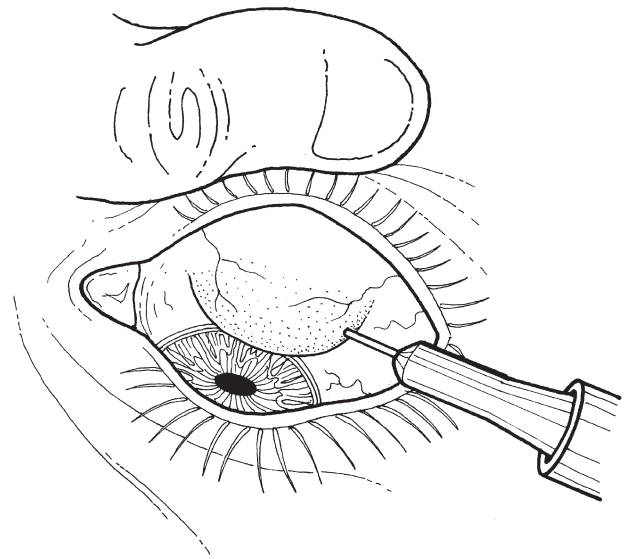


Figure 14.1. The superior conjunctiva is injected with a 25-gauge needle.

Table 14.2 Local Anesthetics

	Concentration (%)	Onset (min)	Duration (h)	MAXIMUM DOSE (mg/kg)	MAXIMUM DOSE (Total mg)	Toxicity
Ester group						
Procaine	1–2	2–8	0.5–1.0	10–15*	1000	Low to moderate
Chloroprocaine	1–2	2–12	0.5–1.2	10–20*	1000	Low
Amide group						
Lidocaine	0.5–2	4–6 2–3[a]	1.0–1.5 7[a]	3–4 500	300	Moderate
Bupivacaine	0.25–0.75	5–30	3–12	2–3	200	Moderate
Mepivacaine	1–2	3–5	2–3	7–8	550	Moderate
Prilocaine	1–3	3–8	1.5–3.0	8–10	600	Moderate
Etidocaine	0.5–1	3–5	≥5	4 5.5[a]	300 400[a]	Moderate Moderate

From Crandall DC. Pharmacology of ocular anesthetics. In: Tasman W, Jaeger EA, eds. Biomedical Foundations of Ophthalmology. Philadelphia: Lippincott-Raven; 1995.

[a] With epinephrine.

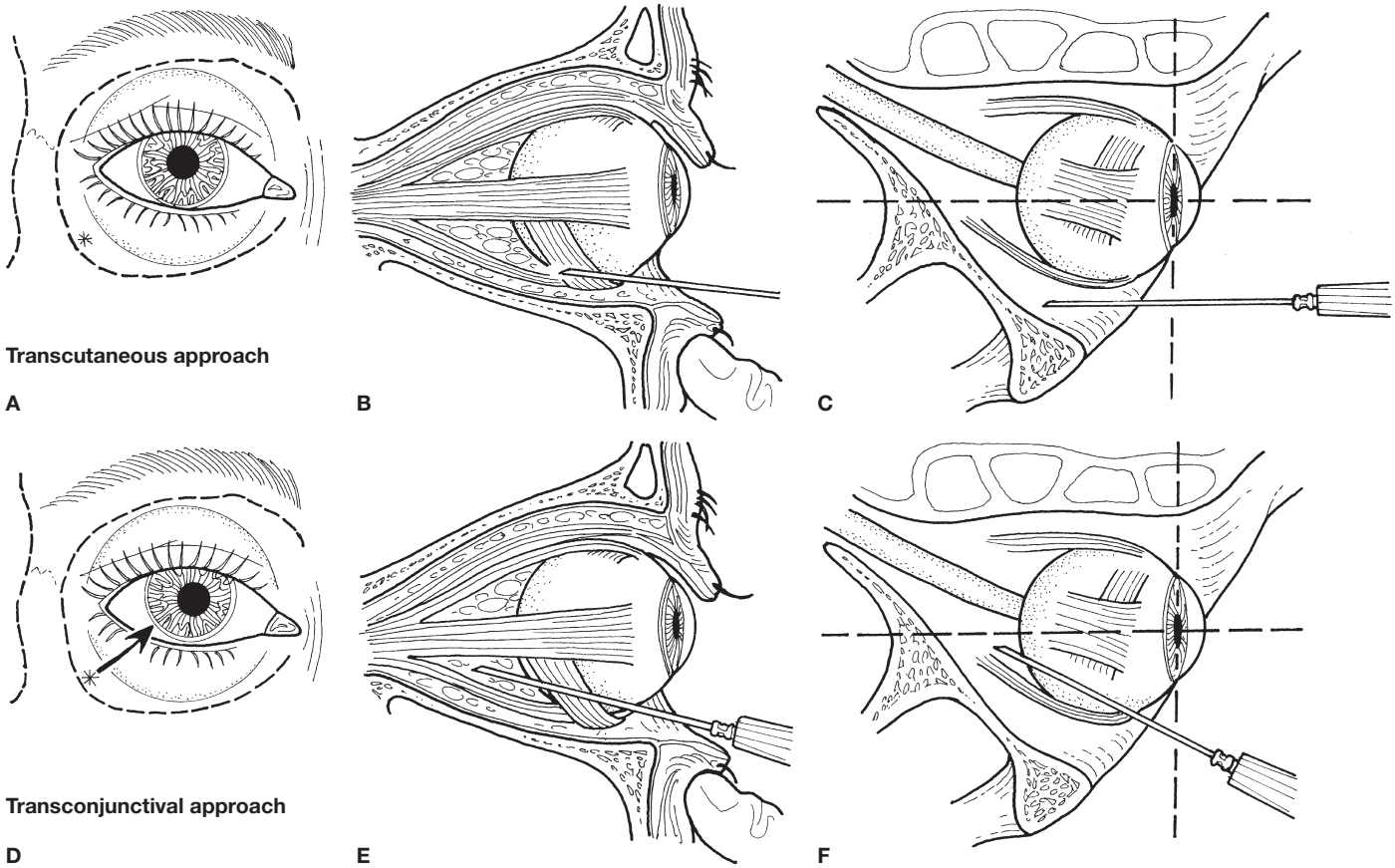


Figure 14.2. Inferotemporal intracone (retrobulbar) block. *A* and *D,* Views from front; *B* and *E,* views from lateral side; *C* and *F,* views from above (27-gauge, 31-mm sharp disposable needle). The asterisk (*) represents the injection site. The figure represents the transcutaneous (*A–C*) and transconjunctival (*D–F*) approaches. The approaches are similar except the lower lid is retracted in the transconjunctival method. The globe is in primary gaze. The needle tip enters at the lower temporal orbit rim, slightly up from the orbit floor *(A)* and very close to the bone. The needle track passes initially backwards in the sagittal plane *(C)* and parallel to the orbit floor; that is, with a 10° elevation from the transverse plane *(B)* until the midshaft of the needle has reached the plane of the iris and the needle tip has passed the globe equator *(B, C).* (If the needle were advanced further in the sagittal plane, contact with the lateral wall of the orbit would occur.) Following this step, the needle is directed with medial and slightly upward components *(D)* aiming for an imaginary point behind the globe on the axis formed by the pupil and the macula, so that the needle tip approaches but does not pass the midsagittal plane of the globe *(F)*. The needle enters the intracone space by passing through the intermuscular septum just inferior to the lower border of the lateral rectus muscle *(E).* The globe is observed continuously during needle placement to detect globe rotation that would indicate engagement of the sclera by the needle tip. During needle placement, continuing observation of the relationship between the needle/hub junction and the plane of the iris establishes an appropriate depth of orbit insertion *(E, F).* In a globe with normal axial length, as illustrated, when the needle/hub junction has reached the plane of the iris, the tip of the needle lies 5–7 mm beyond the hind surface of the globe *(E, F)*. After test aspiration, up to 4 mL of anesthetic solution is injected very slowly.

Atkinson, the needle is then directed to the orbital apex. Other authors fear that this technique puts the needle in close approximation to the optic nerve, posterior portion of the eye, and ophthalmic artery, and therefore recommend that the needle be directed to the inferior part of the superior orbital fissure.[14,15] To minimize complications, a blunt retrobulbar needle no longer than 35 mm has been recommended,[16,17] although many ophthalmologists use a sharp 25-gauge, 32-mm (1.25-inch) needle. The most common complication is retrobulbar hemorrhage, with an incidence of 0 to 1% with a blunt needle and as high as 5% with a sharp needle.[2,18] Other complications include perforation of the globe.[19] Various studies have shown an incidence of ocular penetration of less than 0.1% for eyes with an axial length of less than 26 mm and an incidence of less than 1% for eyes with an axial length of greater than 26 mm.[20] Optic nerve injury,[16] retinal vascular occlusion,[21,22] and strabismus[23] are other reported complications. Injection into the subdural space has been hypothesized as the mechanism causing contralateral amaurosis, brainstem anesthesia with apnea, and cranial nerve palsies[24–28] and has been demonstrated to occur following the injection of radio-opaque dye during positive-contrast orbitography.[29] Wittpenn and co-workers,[30] in a prospective study comparing 2 or 4% lidocaine with 0.75% bupivacaine in 3123 retrobulbar injections, found that 4% lidocaine had a significantly higher incidence of respiratory arrest (0.79% vs 0.09%). They hypothesized, as an alternative theory to direct injection into the optic nerve sheath, that the total amount of anesthetic agent placed in the retrobulbar space was an important risk factor for respiratory arrest. Systemic absorption via intrarterial injection is another theory proposed to explain these CNS and cardiovascular problems.[2]

Peribulbar injection was introduced as a method to achieve anesthesia and akinesia with less risk than that from retrobulbar injection.[31] The first stage of the technique, using 1% lidocaine with epinephrine, began as a 0.5-mL subcutaneous injection just above the inferior orbital rim and a finger-breadth distance from the

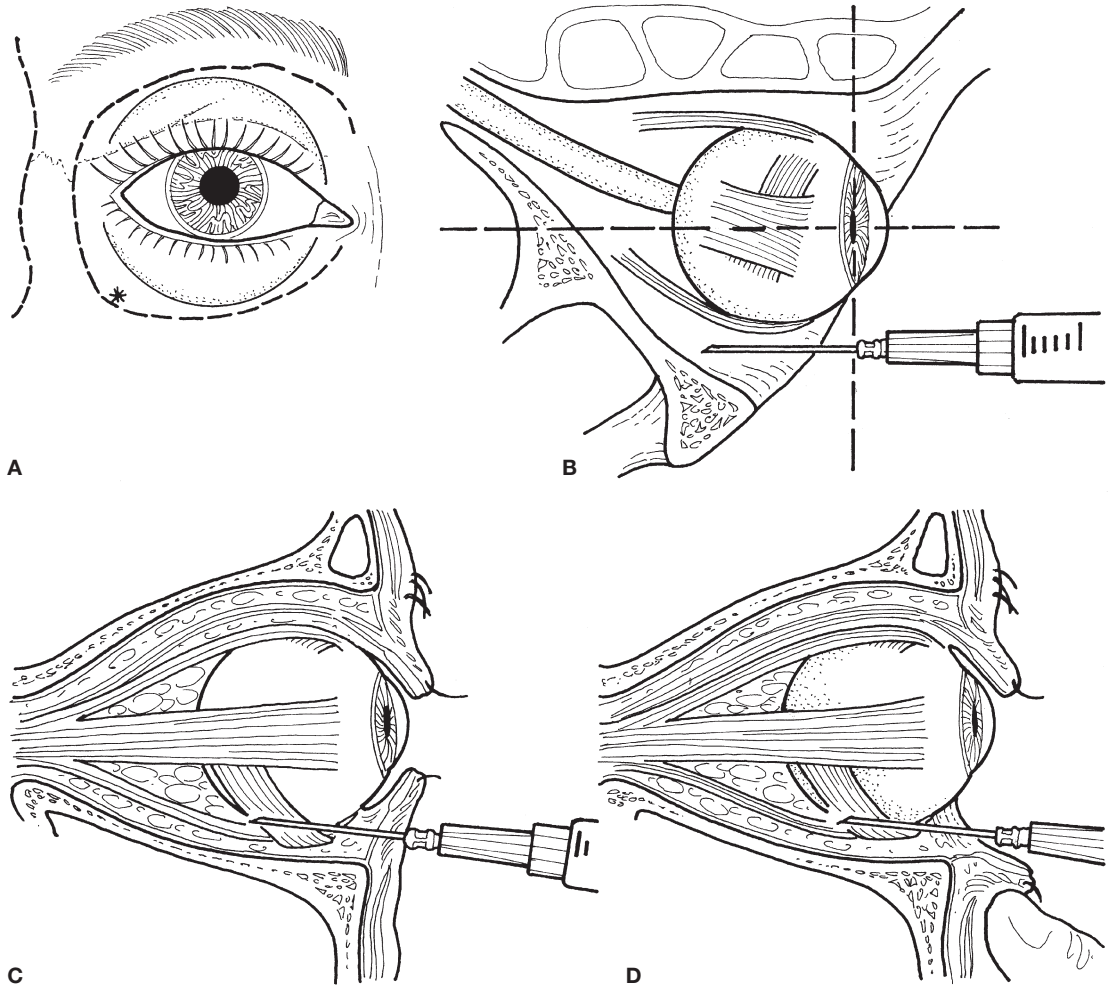


Figure 14.3. Inferotemporal pericone (peribulbar) injection. *A,* View from front; *B,* view from above; *C,* view from lateral side (transcutaneous injection); *D,* view from lateral side (transconjunctival injection). The globe is in primary gaze and the asterisk (*) is the injection site. A 27-gauge, 20–25-mm sharp disposable needle enters the orbit at the junction of its floor with the lateral wall *(A)* and very close to the bony rim. The needle passes backwards in a sagittal plane *(B)* and parallel to the orbit floor *(C, D),* passing the globe equator to a depth controlled by observing the needle/hub junction reach the plane of the iris *(B).* After test aspiration, up to 10 mL of anesthetic solution may be injected slowly (single needle technique) or up to 5 mL (if combined with complemental pericone block). The technique is equally applicable to the transcutaneous *(C)* or transconjunctival *(D)* route.

lateral canthus, followed by 0.5-mL injection into the orbicularis muscle and 1-mL injection into the anterior orbit. A similar injection was given just inferior to the supraorbital notch. The second stage included use of an Atkinson 23-gauge, 32-mm (1.25-inch) blunt retrobulbar needle to inject a 1-mL mixture of 0.75% bupivacaine and 1% lidocaine into the anterior orbit and an additional 1 to 2 mL at the equator of the globe as the needle was directed along the inferior orbit. Then, just below the supraorbital notch, the same amount was deposited into the anterior orbit and adjacent to the equator of the globe. Others have reported variations of this technique, including using a 25- or 26-gauge, 16-mm (0.5-inch) needle to deliver 5–7 mL of anesthetic in the inferotemporal orbit with sufficient pressure being placed on the syringe to place the needle at or behind the equator of the globe[32] (Fig. 14.3).

Peribulbar block appears to be as effective or better than retrobulbar block in achieving anesthesia and akinesia.[33,34] The complications of this technique are the same as retrobulbar block,[19,20,35] but because the needle is placed in a more anterior location, the complication rate may be lower.[31,36,37]

Sub-Tenon's infiltration, a mode of obtaining complete ocular anesthesia and akinesia without risk of globe perforation or other risks of retrobulbar injections, has been reintroduced (Fig. 14.4). This goal is achieved through a small conjunctival incision, by blunt dissection into one quadrant to obtain access below Tenon's layer for direct instillation of anesthetic agent as described by Turnbull[38] in 1884. Stevens[39] reported a variation of this technique that uses a blunt-tipped cannula to inject into sub-Tenon's space by way of a small conjunctival incision in the inferior nasal quadrant, thereby avoiding the inferior temporal vortex vein. Reported complications of the latter technique have included excessive chemosis or subconjunctival hemorrhage obscuring the operative site, and inefficient anesthesia if the anesthetic agent is not delivered far enough posteriorly.[39,40]

Retrobulbar and peribulbar blocks and sub-Tenon's infiltration allow for excellent anesthesia and akinesia with little risk. Under these conditions, procedures such as removing recurrent or large pterygia with or without conjunctival autograft; limbal cell harvesting or transplantation or other similar, extensive surface procedures; and lamellar keratoplasty can be performed. During 'open sky' procedures, such as corneal transplantation with or without cataract extraction or intraocular lens (IOL) exchange during local anesthesia, lid akinesia is desirable to prevent pressure from lid

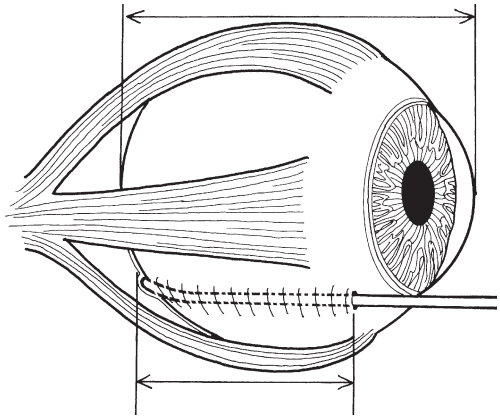


Figure 14.4. Schematic diagram of the path of the Southampton cannula, following the contour of the globe, to deliver anesthetic solution posterior to the equator.

blinks on the globe, which can create a risk of protrusion of intraocular contents. Reports have indicated that the peribulbar or retrobulbar block achieves effective lid akinesia by diffusion of anesthetic, especially with the use of hyaluronidase and orbital decompression devices.[41] However, some surgeons prefer to use an additional block to assure akinesia of the lids.

Several techniques have been described to achieve lid akinesia by way of anesthetizing the branches of the facial nerve at various locations. O'Brien[42] described a technique to block the temporofacial division of the facial nerve. In this block, the zygomatic arch is located with the index finger and followed along the underside of the arch backward to a point just in front of the tragus of the ear. At this location, the index finger is directly over the condyloid process of the mandible, which can be felt sliding back and forth as the patient opens and closes the mouth. A needle 1.5 cm in length is passed down to the anterior portion of the condyloid process, and 1–2 mL of local anesthetic is injected. The disadvantages of this type of block are the temporofacial branch of the facial nerve can be missed; the lower branches that supply the lips and face may be blocked, producing an undesirable and often prolonged facial paralysis; and the patient experiences a significant amount of discomfort if no sedation is used.[13] Other variations aimed at blocking the facial nerve at a more proximal location have been reported. The modified O'Brien block places the needle along the posterior portion of the mandible just below the condyle.[43] Wright[44] and, later, Nadbath and Rehman[45] described blocking the facial nerve as it emerged from the stylomastoid foramen. In addition to the undesirable effect of a total facial paresis that may last for several days, this type of block may also block the glossopharyngeal, vagus, and spinal accessory nerves where they exit the closely located jugular foramen, leading to significant respiratory and swallowing difficulties.[46–49]

van Lint[50] described a technique to block the more terminal branches of the facial nerve, thereby avoiding the total facial block encountered if the trunk of the nerve was blocked. In his description of the technique, a needle is introduced at the imaginary intersection of a horizontal line extending from the lowest part of the inferior margin of the orbit and a vertical line from the most temporal part of the lateral margin of the orbit. The needle is advanced as far as the bone and directed inward and slightly downward into the deep tissues just below the orbital margin. Anesthetic is injected while the needle is withdrawn until it reaches the entry site of the skin. Without being removed, the needle is then directed in a similar manner upward and inward near the orbital margin close to the bone.

Atkinson[13] described the disadvantages of this block: ballooning or edema of the lids may be produced; more of the anesthetic solution is required than for a proximal block, thereby increasing the risk of a toxic reaction to the anesthetic; and patient discomfort is great. He recommended inserting a 23-gauge, 3.5-cm long, blunt-tipped needle, at a location at the lower edge of the zygomatic bone about 1 cm posterior to the intersection of a vertical line drawn from the lateral margin of the orbit and a horizontal line drawn along the lower edge of the zygomatic bone. The injection is made along the lower edge of the zygomatic bone and upward across the zygomatic arch close to the bone.

One last technique involves injecting the anesthetic solution directly into the center of the lids beneath the orbicularis. One study measuring the force of lid closure and electromyographic activity of the orbicularis muscles compared these techniques and showed that the lid block and the O'Brien blocks were the most effective in producing akinesia of the lid.[41]

TOPICAL ANESTHESIA

As mentioned earlier in this chapter, the use of topical anesthesia appears to be increasing in frequency as the anesthesia method of choice for anterior segment surgery. Using it in combination with intravenous sedation creates a viable option to other anesthesia choices. The advantages include less cost, quicker turnover times, and a way to avoid the risks associated with local injections or general anesthestics.

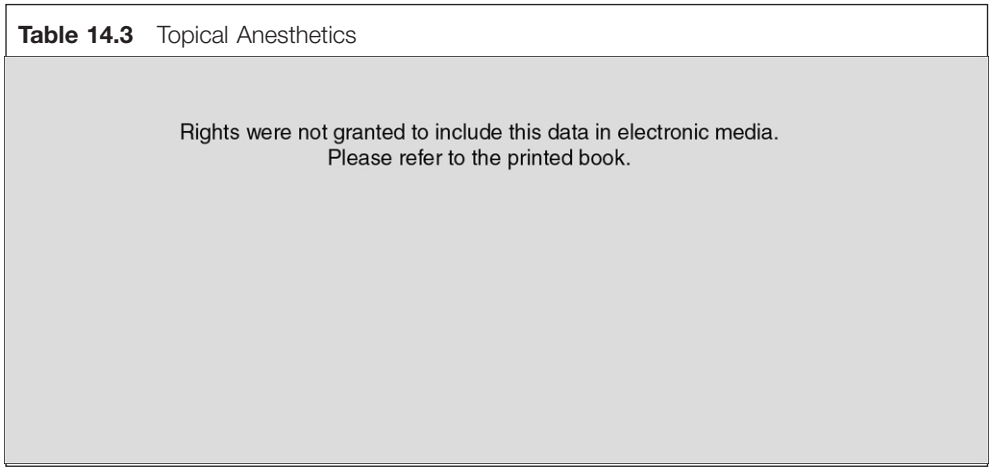
Procedures that are commonly performed under topical anesthesia include: corneal scraping and biopsies, removal of conjunctival and corneal foreign bodies, epithelial debridement, superficial keratectomy, phototherapeutic keratectomy, corneal micropuncture, and corneal refractive surgeries (photorefractive keratectomy, laser assisted in-situ keratomileusis, and astigmatic keratotomy).

Some procedures, historically, have been done primarily under local block or general anesthesia. But, recently, for reasons mentioned above, surgeons are doing these procedures more frequently using topical anesthetics combined with intracameral lidocaine and intravenous sedation. These procedures include repair of corneal lacerations, exchange or reposition of an IOL, placement of a phakic IOL, placement of secondary IOL including iris-fixated IOLs, and endothelial keratoplasty procedures such as deep lamellar endothelial keratoplasty (DLEK), Descemet's-stripping endothelial keratoplasty (DSEK), and Descemet's-stripping automated endothelial keratoplasty (DSAEK).

Penetrating keratoplasty with or without other anterior segments procedures such as cataract extraction and IOL implantation most often are done under local anesthetic injection or under general anesthesia. However, under certain situations where these anesthesia options are not possible or less desirable, penetrating keratoplasty can be done under topical anesthesia.[51,52]

A complication of topical anesthesia is the lack of effective anesthesia with patient pain or the presence of patient anxiety (with or without adequate anesthesia). One can try to avoid the latter by appropriate patient selection and supplementing the topical anesthesia with intracameral preservative-free lidocaine when possible and intravenous sedation. In some cases, it may be necessary to switch to one of the other modalities of anesthesia described above in this chapter.

Table 14.3 Topical Anesthetics



From Crandall DC. Pharmacology of ocular anesthetics. In: Tasman W, Jaeger EA, eds. Biomedical foundations of opththalmology. Philadelphia: Lippincott-Raven; 1995 and Liu JC, Steinemann TL, McDonald MB, et al. Topical bupivacaine and proparacaine: a comparison of toxicity, onset of action, and duration of action. Cornea 1993; 12: 228.

Table 14.3 lists some commonly used topical anesthetics, times of onset, and durations of activity. These agents have a very quick onset of activity with excellent corneal anesthesia. However, the duration of activity is relatively brief.

These agents have toxic effects, especially locally on the corneal epithelium. A few drops of these agents can cause a significant epithelial disturbance and inhibition of epithelial healing.[53] One study comparing rabbit corneal epithelial toxicity of topical bupivacaine and proparacaine showed that with just a few drops, both caused epithelial toxicity, and proparacaine delayed epithelial healing in comparison to a saline control.[54] Data on tetracaine or cocaine were not included, but significant epithelial haze and irregularity can be seen shortly after application of these agents. Long-term abuse of these agents is known to cause severe surface disturbance with large epithelial defects, stromal infiltrates, and endothelial changes. Local allergic response of the lids and conjunctiva is possible, and systemic anaphylactic reactions occur, but they are less common.[53]

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15 Corneal and conjunctival foreign bodies

Marc R. Criden, Steven E. Katz, Richard G. Lembach

Ocular surface foreign bodies are a common cause of patient visits to the emergency room and the ophthalmologist. The cornea is highly innervated by sensory branches of the fifth cranial nerve. A foreign body that lies embedded in the corneal stroma with disruption of the overlying epithelium will be aggravated with each blink response, thus prompting the patient to seek out medical care. Even if the foreign body is no longer present the foreign body sensation persists.

This chapter discusses protective mechanisms of the ocular adnexae, presentation of the corneal and conjunctival foreign bodies, their evaluation and management. A high degree of suspicion should always be maintained for the possibility of an eye wall rupture, intraocular and orbital foreign bodies associated with high velocity force.

PROTECTIVE MECHANISMS

The eyelids and ocular adnexae form a physical barrier for the ocular surface and contribute to a number of protective mechanisms against corneal and conjunctival foreign bodies, including blinking and tear film composition.

Spontaneous blinking (i.e. without an apparent external stimulus) occurs approximately 15 times per minute in adult humans.[1] Reflex blinking is initiated by corneal or conjunctival contact. The afferent arm of the blink reflex is the ophthalmic division of the fifth cranial nerve. First-order neurons synapse in the ipsilateral chief sensory nucleus in the pontine tegmentum. Second-order neurons then project to the nucleus of the facial motor nerve bilaterally. The seventh cranial nerve innervates the orbicularis oculi muscle to complete the reflex arc. Stimulation of either ocular surface thus leads to a bilateral blink response with increased lacrimal gland secretion and tear production.

Tear drainage is predominately driven by contraction of the orbicularis oculi muscle that occurs with blinking. The tear pump mechanism is described by Doane[2] as follows: positive pressure created within the nasolacrimal sac on blinking forces tears to drain into the nose, and negative pressure within the nasolacrimal sac as the lids open draws tears from the ocular surface into the lacrimal punctae. Rewetting of the ocular surface occurs with each blink. Surface foreign bodies caught in the precorneal tear film will lead to increased blink rate and reflex tearing, which will wash the foreign body out of the eye or into the inferior cul-de-sac.

Loss of these and other protective mechanisms predisposes to corneal and conjunctival foreign bodies and their sequelae. Proptosis and eyelid retraction, such as seen in thyroid-related orbitopathy, lead to increased exposure of the ocular surface. Lack of Bell's phenomenon may occur as an idiopathic phenomenon or may be due to inferior rectus muscle restriction in thyroid orbitopathy. Hypesthesia in the first division of the fifth cranial nerve due to herpes simplex keratitis, chronic contact lens wear, and dry eye syndromes may be associated with diminished tearing. Bell's palsy and eyelid malpositions such as entropion or ectropion decrease the tear pump function. Penetrating trauma may bypass all of the protective mechanisms.

HISTORY

Common conjunctival and corneal foreign bodies include loose eyelashes, wind-blown debris, or insects and organic foreign bodies frequently found in gardeners, farmers, and campers, and may be associated with fungal infection. Projectile foreign bodies may occur in relation to shattered glass (i.e. motor vehicle accident), use of tools (i.e. hammering, grinding metal on metal, sawing, or drilling) or explosion (Fig. 15.1). High-velocity metallic foreign bodies of this nature are often sterile due to high temperature at time of fragmentation.

In these cases, a detailed history of the materials involved may be important factors. For example, composition, shape, likelihood of single or multiple pieces, proximity of the point of impact to the globe, energy transferred to the projectile, and the angle of incidence are all relevant details of the history of injury. Foreign bodies may be inert (i.e. glass, gold, and silver) or may be associated with higher likelihood of toxicity (i.e. iron and copper) or infection (i.e. organic matter, eyelashes, and insects). It is important to note whether the incident was work related and whether alcohol was involved.[3] The presence of discomfort, including the time of onset, character, location, and exacerbating factors should be noted. For example, increased discomfort with blinking may indicate a

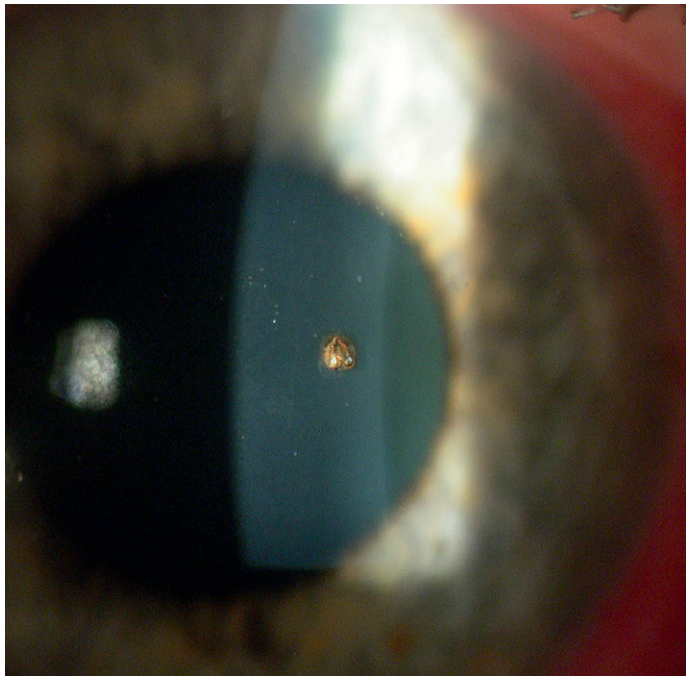

Figure 15.1 Central, superficial metallic foreign body (*photo courtesy of Ayad A. Farjo, M.D.*).

superior tarsal foreign body. Other complications may include redness, itching, tearing, photophobia, or decreased vision.

EXAMINATION

The importance of documenting initial visual acuity cannot be overstated. When the vision is significantly decreased out of proportion to the clinical findings suspicion is raised of occult corneoscleral or orbital penetrating injury. Slit-lamp exam using an angled beam is ideal for the evaluation and removal or corneal foreign bodies because of the ease in delineating depth of penetration. Surgical loupes, which provide ×2.5 to ×3.5 magnification, may be adequate when a slit lamp is not available. Confocal microscopy has also been utilized to detect small foreign bodies with or without infiltrates. This may be a useful tool to identify subtle inflammatory reactions and to monitor resolution.[4] The dimensions of the overlying epithelial defect noted with fluorescein stain should be measured for future evaluation of the rate of healing. Patients with delayed presentation may exhibit concomitant stromal infiltration, which may persist even after foreign body removal. Cells in the anterior chamber may occur as a traumatic iritis, in relation to a sterile or infectious corneal stromal infiltrate or in association with intraocular penetration, and may progress to form a frank hypopyon. A small gross or microscopic hyphema may indicate possible occult ocular perforation.

A high suspicion for intraocular or intraorbital foreign body should be maintained in the appropriate clinical setting, such as a high-velocity injury. A standardized classification system of ocular trauma terminology was published in 1996.[5] Common signs of globe perforation are broad and listed in Table 15.1.

Fluorescein dye 2% may be instilled to assess wound leakage under a blue light (positive Seidel's sign); however, small or shelved wound edges may be self-sealing, and the lack of aqueous leak and a formed anterior chamber does not guarantee against eye wall rupture. A self-sealing corneal laceration may be able to maintain normal or even elevated intraocular pressure (Fig. 15.2). The anterior chamber depth should also be compared to the fellow uninjured eye.

Once a ruptured globe is suspected, further evaluation and exploration should take place in the operating room after appropriate radiologic evaluation, if indicated. A metal shield is taped securely over the eye. Pain and nausea are controlled to avoid eyelid squeezing and emesis, which may cause extrusion of intraocular contents. Prophylactic antibiotic (cefazolin 1 g intravenously) should be given, and the tetanus prophylaxis status assessed and updated. The patient should be maintained without oral intake, and anesthesia should be consulted. Any preoperative studies (e.g. blood count,

Table 15.1 Signs of Globe Rupture

Identifiable entrance site (corneal or scleral laceration)
Prolapse of intraocular contents (uvea)
Peaking of the pupil or altered pupil size
Lens displacement or extrusion
Visualization of intraocular foreign body
Hemorrhagic chemosis
Anterior chamber or vitreous heme
Shallowing of anterior chamber
Hypotony
Traumatic cataract
Decreased vision

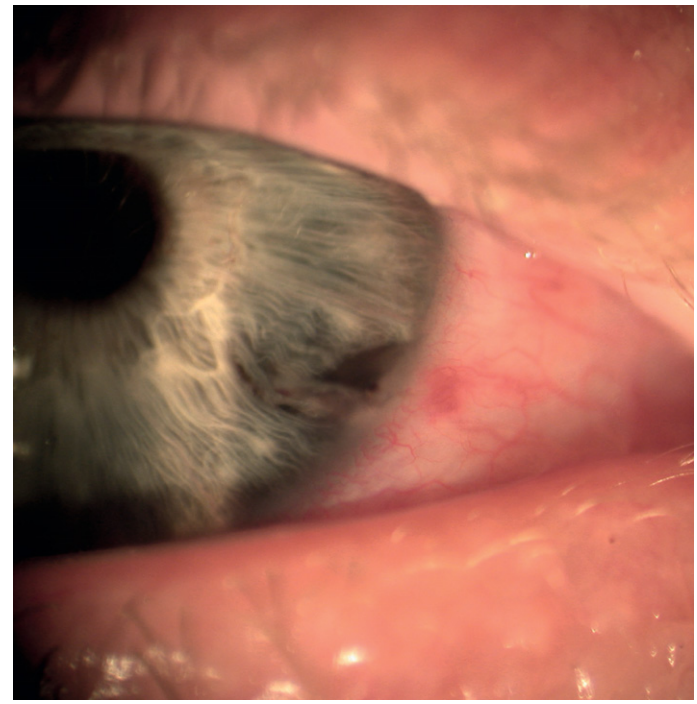

Figure 15.2 Self-sealing peripheral corneal laceration with iris defect and retained metallic intraocular foreign body in vitreous cavity (*photo courtesy of Ayad A. Farjo, M.D.*).

electrolytes, EKG, and chest X-ray) should be ordered as soon as possible in preparation for surgery.

TREATMENT OF CONJUNCTIVAL FOREIGN BODIES AND LACERATIONS

Conjunctival foreign bodies may occur in a tarsal, forniceal, or bulbar location. Upper tarsal conjunctival foreign bodies may be associated with linear abrasions (i.e. vertical tracks best noted with fluoroscein staining) in the upper cornea and should be suspected in this setting. The upper eyelid should be everted after instillation of topical anesthetic, and the foreign body removed with a moist cotton-tipped applicator or jeweler's forceps. The upper lid should not be everted, however, if there is any suspicion of a globe rupture as this complication may increase intraocular pressure and cause extrusion of intraocular contents. Upper lid eversion may be achieved by pulling the lashes and lid margin superiorly over a cotton-tipped applicator placed centrally in the eyelid crease.

The superior and inferior fornices should be thoroughly examined with appropriate light and magnification. Contact lenses are commonly dislocated into the superior fornix and are generally retrieved without difficulty. They may become embedded into the conjunctiva and can be associated with chronic foreign body inflammation[6] and infection. Nicolitz and Flanagan[7] reported a 26-year-old woman with a hard contact lens embedded in the supratarsal space, who presented with a progressively enlarging anterior orbital mass lesion. Instillation of fluorescein dye will concentrate in a soft contact lens making visualization easier when a retained contact lens is suspected but not found. Elderly patients wearing aphakic contact lenses are vulnerable to this problem due to loss of orbital fat, deep-set globes, and lax lids.

Conjunctival lacerations may be obvious by direct visualization or detection of prolapsed Tenon's fascia, orbital fat, or exposed sclera. Bloody chemosis may obscure visualization of these details.

Signs of an orbital foreign body may include globe displacement, dysesthesia in the V1 or V2 distribution of the trigeminal nerve, abnormality of ocular ductions, or new onset of manifest deviation, ptosis, and conjunctival laceration. If the globe appears formed with no other evidence of ocular penetration, the conjunctiva can be explored under topical anesthesia in a cooperative patient. If there is any historical or clinical suspicion of an ocular or orbital foreign body, appropriate imaging studies should be obtained.

A computed tomography (CT) scan of the orbits with axial and coronal cuts of 3 mm or less is ideal in the setting of trauma. A CT scan is readily available, requires less scanning time per image than magnetic resonance imaging (MRI), provides a safer option when metallic foreign bodies are suspected, and offers better bony visualization. An MRI is contraindicated as the primary imaging modality in the setting of trauma until the presence of ferrous foreign bodies has been excluded. Posterior segment hemorrhage, vitreous space distortion, and lens disruption identified on a CT scan correlate with poor visual or anatomic outcomes. MRI may be superior in detecting nonmetallic foreign bodies, such as wood.[8] Although ultrasound has been successfully used in ocular[9] and orbital trauma, its routine use is not advocated in this setting. Pressure from the probe on the eye may be uncomfortable for the patient, and posterior pressure may lead to extrusion of intraocular contents if the globe is ruptured. The necessary ultrasound equipment is generally not available in the emergency room and an experienced ultrasonographer may not be readily available during the off hours when these patients frequently present.

In the absence of ocular or orbital penetration, most conjunctival lacerations do not require surgical repair. Larger conjunctival lacerations can be closed with 8-0 polyglycan sutures. With cooperative patients, this may be accomplished in a treatment room rather than an operating room by using topical viscous lidocaine anesthetic. When opposing the conjunctival edges, care should be taken to avoid incarcerating Tenon's fascia, which may lead to formation of Tenon's cysts. Tenon's fascia can be closed as a separate layer; however, it is generally much easier to partially excise this tissue when it has prolapsed anteriorly through the conjunctival wound. Topical antibiotic drops, such as a broad spectrum fluoroquinolone, or ointment with follow-up at 3 to 5 days is generally adequate in these circumstances.

TREATMENT OF SUPERFICIAL CORNEAL FOREIGN BODIES

Placement of a topical anesthetic reduces discomfort and blepharospasm and allows easier evaluation and treatment. Foreign bodies that lay on the epithelium or are loosely embedded may be gently removed with a moistened cotton-tipped applicator or a jeweler's forceps after applying topical anesthetic. When the foreign body is firmly embedded in the corneal stroma, an 18- or 21-gauge needle can be placed on a 1- or 3-mL syringe for stability. The beveled needle tip should face away from the surface of the cornea. The tip can be advanced beneath the anterior projection of the foreign body and gently teased from the stroma back through the entrance site. Once the foreign body has been dislodged it can be removed with a moistened cotton-tipped applicator. A wire speculum may be advantageous if the patient is not too blepharospastic or if an assistant is not available to hold open the upper lid.

It is often useful to give the patient a fixation target for the opposite eye, particularly when the foreign body is in the visual axis. The operating hand can be rested on the patient's zygoma for support. The upper eyelid is elevated to prevent blinking. The physician should inform the patient in advance of the steps to be taken and give reassurance that the needle will not enter the eye. However, it is a good practice to avoid showing the needle to the patient, if possible.

Most epithelial defects associated with foreign body removal will heal within 24 to 48 h. If the epithelial defect is small, topical antibiotic drops may be used and the patient re-evaluated the following day. Pressure patching is generally unnecessary and may be associated with increased discomfort and delayed epithelial healing. Larger (>50%) or poorly healing epithelial defects may benefit from a bandage contact lens with a topical antibiotic plus a nonsteroidal anti-inflammatory.[10] The presence of a stromal infiltrate will deter epithelial healing and should be treated aggressively with topical antibiotics to avoid progression to a nonhealing corneal ulcer.

Routine bacterial cultures of corneal foreign bodies without stromal infiltrate are unnecessary. DeBroff and co-workers[11] cultured 63 consecutive corneal foreign bodies and found that nine (14.3%) were positive for bacteria. In this study, the most common bacteria cultured was coagulase-negative *Staphylococcus*, which is commonly found as normal flora of the ocular adnexa. When a corneal ulcer is present, however, cultures for aerobes, anaerobes, and fungi should be considered especially if organic matter is involved.

Ferrous foreign bodies may be associated with a rust ring as soon as 3–4 h after the injury. Rust rings may be removed on the initial

visit with the use of a battery powered burr[12]; however, they are often more easily removed 24–48 h later when the surrounding corneal tissue has softened. They can gently be lifted off with a disposable needle. The burr often leaves a larger defect than necessary, and Liston and co-workers[13] found a trend toward deeper corneal stromal damage when using an electric burr drill versus a small gauge hypodermic needle in a rabbit model. Removal of most of the rust ring allows the epithelium to heal over; however, the importance of removing all of the rust has been overstated. A minimally noticeable scar by slit-lamp, which is usually off-axis, will generally have less visual significance than an overzealous attempt to remove the complete rust ring with a burr.

The use of topical anesthetics outside the office is contraindicated due to delayed healing, epithelial erosion, development of neurotrophic keratitis, and a secondary bacterial infection. Similarly, topical corticosteroid medications are contraindicated in the setting of an epithelial defect as they may predispose to a secondary infection. When an element of traumatic iritis is present, a short acting topical cycloplegic (i.e. cyclopentolate 1%) may be used and a topical corticosteroid added if necessary after the epithelial defect has healed. With an epithelial defect, steroids may be used judiciously in conjunction with a broad spectrum antibiotic only if there is no suspicion of fungus or infiltrate.

Patients should be advised that discomfort will return as the topical anesthetic wears off. Reassurance regarding the rate of healing is important for their peace of mind. Analgesia with extra-strength acetaminophen is generally adequate; however, the use of ketorolac, acetaminophen with codeine, oxycodone, or sleeping medications may be indicated on a short-term basis when large epithelial defects are present. Topical diclofenac has been reported to relieve pain associated with corneal rust rings in a prospective, double-blind, placebo controlled clinical trial.[14]

Fluoroquinolone antibiotics have been the mainstay of antimicrobial treatments for several years. Second-generation quinolones such as ciprofloxacin and ofloxacin are still frequently used and are effective agents. However, many organisms have developed resistance against these agents. The advent of fourth-generation fluoroquinolones (gatifloxacin and moxifloxacin) has expanded the spectrum of coverage against both gram-positive and gram-negative organisms and atypical bacteria.[15] These also demonstrate superior corneal penetration and should represent first-line agents for both prophylaxis and treatment of corneal ulcers and endophthalmitis.

Corneal wound healing and speed of re-epithelialization are essential to decreasing risk of infection and visual outcome. Rapid corneal healing also reduces the risk of stromal scarring, haze, or irregular astigmatism. Post-surgical management often includes steroids that may impair the healing process and their use should be monitored closely.

TREATMENT OF DEEP CORNEAL FOREIGN BODIES

Buried corneal stromal foreign bodies may be left in place if small and inert (i.e. without keratitis). Shattered glass often leaves multiple inert intrastromal fragments that are well tolerated by the cornea and may be observed. Attempted removal of deep fragments may result in unnecessary stromal scarring. Only an ophthalmologist in a controlled setting should remove foreign bodies that lie close to Descemet's membrane. Aggressive attempts at removal with inappropriate instrumentation or inadequate visualization may cause posterior migration of the foreign body, which may penetrate Descemet's membrane and convert a corneal foreign body into an intraocular foreign body.

Foreign bodies that are suspected to penetrate into the anterior chamber should be removed under the operating microscope in which corneal sutures may be placed to close an aqueous leak if necessary. Small leaks are often self-sealing or may be amenable to placement of a bandage contact lens with an adjunctive aqueous suppressant. Cyanoacrylate glue may also be used to close small corneal leaks. Meskin and co-workers recently described the feasibility and effectiveness of 2-octyl-cyanoacrylate glue as a temporary wound barrier following clear corneal cataract surgery.[16] This method was found easy to use, effective, and demonstrated a favorable side-effect profile. A hand-held magnet may also be useful in removing some intrastromal foreign bodies.

Inflammation in response to insect hairs is referred to as ophthalmia nodosa. The more common offenders are caterpillar and tarantula hairs that are blown into the eye or transferred by direct contact. These hairs frequently possess barbs that lodge into the corneal stroma. Repeated blinking, worsened by irritation, may force these hairs further into the cornea and, ultimately, into the anterior chamber.[17]

Within the stroma, these hairs may be surrounded by nummular infiltrates and there may be a profound anterior chamber reaction. A conjunctival nodule may also be present, although these hairs may be very difficult to visualize in this location. Attempts should be made to carefully remove visible, exposed hairs but this is often limited due to their fragility. The inflammatory response responds well to steroids and should be accompanied by a topical antibiotic. Steroids should be continued for several months and tapered slowly.[18]

Fiberglass particles are also a relatively common cause of corneal abrasion and source of corneal foreign body. These fine fibers easily penetrate the cornea and may be embedded within the corneal stroma or work themselves into the anterior chamber. They are often difficult to visualize and break easily when attempting to remove them. Fiberglass is relatively inert but may harbor a variety of bacteria. If the fiberglass particles cannot be removed then bacterial cultures should be obtained followed by broad spectrum antibiotic coverage and close monitoring for infectious keratitis or endophthalmitis.

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16 Conjunctival and corneal cultures, resections, and biopsies

Sarah M. Nehls, Neal P. Barney

CORNEAL CULTURES

Infectious keratitis is a sight-threatening condition that requires urgent diagnosis and management. Identification of the organism responsible for infection by corneal scraping for culture and smears is important in guiding effective antimicrobial treatment and for tracking the epidemiology of infectious keratitis. Small, peripheral corneal ulcers are sometimes treated empirically, without culture, at the discretion of the treating physician. Larger, central, sight-threatening lesions and those with atypical features or a lack of response to empiric therapy should be cultured.

Most corneal cultures can be taken with the patient sitting at the slit-lamp microscope. For more extensive sample collections or to facilitate cooperation, the patient may also be positioned supine under a microscope. The eye should be anesthetized with topical proparacaine hydrochloride 0.5% drops and all necessary media and glass slides should be available for immediate plating or smears. A sterile Kimura platinum spatula, a 15-blade scalpel or a calcium alginate swab moistened with sterile broth can be used to scrape the cornea at the leading edge of the corneal ulcer.[1,2] Care should be taken to avoid contact with eyelid skin, lashes, or conjunctiva in order to avoid contamination of the sample. An increase in the size of the corneal epithelial defect is an expected outcome at the end of the procedure.

The samples are immediately inoculated onto agar plates and smeared on to glass microscope slides. Several samples may need to be collected to allow for the complete spectrum of culture plates and smears required for diagnosis. A platinum spatula can be flame sterilized by a Bunsen burner; alternatively a fresh spatula, blade, or swab can be used for each sample taken. All plates and slides should be carefully labeled with the patient's name, medical record number, date, and site of collection.

In some clinical settings it may be difficult to maintain appropriate culture media so the use of transport media such as Amies media without charcoal may be considered. The microbiology lab will plate the cultures upon receiving the sample. No difference in recovery rates for bacterial and fungal organisms was found for samples plated as long as 24 h after collection with Amies transport media.[3]

Cytology is often invaluable for rapid identification of the class of organism causing a corneal infection. Corneal samples smeared on to glass slides are transported to the laboratory where they are air dried, fixed, stained, and examined under the microscope. Gram stain is used to identify bacterial organisms. Giemsa stain or a 10% potassium hydroxide (KOH) wet mount is useful in diagnosing fungal pathogens. Atypical mycobacteriae can be seen with a Ziehl–Neelsen acid-fast stain. Giemsa, acridine orange, and calcofluor white stains are useful in detecting acanthamoebae (Table 16.1).[4,5] Herpes simplex virus (HSV) keratitis can be confirmed by finding multinucleated giant cells on Giemsa stain.[6] Smears can also be prepared for an immunofluorescence assay (IFA) to evaluate for the presence of HSV.

The identification of organisms causing bacterial keratitis is achieved by plating specimens on 5% sheep's blood, and chocolate agars. Most bacterial species will grow on blood agar; chocolate agar is needed for growth of *Haemophilus*, *Neisseria*, and nutritionally variant *Streptococcus* species. Fungal organisms can also grow on blood and chocolate agars or more specific fungal culture plates such as Sabouraud's agar can be used.[7] Atypical mycobacteria will grow on blood agar, Lowenstein–Jensen media, and Middlebrook 7H11 media.[8–10] Acanthamoeba should be plated on non-nutrient agar with an overlay of live *Escherichia coli*.[5] For the isolation of more unusual organisms such as fungi, atypical mycobacteriae and acanthamoebae, the microbiology lab should be contacted to establish the preferred culture media and means of plating.

Samples collected for analysis of HSV keratitis should be placed in viral transport media to be transported to the lab for cell culture (Table 16.1). Traditional cell culture has the disadvantage of a slow rate of detection. Faster detection rates can be achieved with a combination of an IFA and polymerase chain reaction (PCR) detection of HSV DNA.[6] Calcium alginate swabs should not be used for PCR specimen collection because of an inhibitory response; collection by a platinum spatula or Dacron swab is preferred.[11]

The overall yield of corneal cultures ranges from 38 to 67%.[3,7,12–15] If antimicrobial therapy is initiated prior to cultures, there does not appear to be a significant difference in rates of organism identification but a delay in pathogen recovery is more likely to occur.[13,16]

Table 16.1 Culture media and smears for identification of corneal pathogens

Organism	Culture Media	Smear
Bacteria	5% sheep's blood agar, chocolate agar	Gram stain
Fungi	5% sheep's blood agar, chocolate agar, Sabourand agar	Giemsa stain, 10% KOH wet mount
Atypical mycobacteria	5% sheep's blood agar, Lowenstein Jensen media, Middlebrook 7H11 media	Gram stain, Ziehl–Neelsen stain
Acanthamoeba	Non-nutrient agar with *E. coli* overlay	Giemsa stain, acridine orange stain, calcofluor white stain
Herpes simplex virus	Viral transport media for cell culture	Giemsa stain, immunofluorescence assay

The patient should be started on broad spectrum antibacterial therapy while awaiting culture results. Therapy can then be tailored as the specific infectious organism and panel of antimicrobial sensitivities are identified.

CONJUNCTIVAL CULTURES

Culture of the conjunctiva is an important procedure in the clinical setting of microbial conjunctivitis. Identification of causative pathogens, designing specific treatment plans, determination of the efficacy of treatment, or persistence of infection despite treatment is reason to perform conjunctival cultures. Because several classes of organisms may infect the conjunctiva, knowledge of modalities to identify these infecting agents requires review.

Bacterial conjunctivitis is most suspected when symptoms of gluey or sticky lids present with signs of purulent discharge.[17] Cultures to isolate bacteria are taken directly from the conjunctiva. The physician prepares the patient by describing the planned procedure. Topical proparacaine 1% may be instilled. The inferior lid is rolled away from or lowered from the globe and the sample is obtained by applying a premoistened swab into the fornix with both a sliding and rotating motion. The swab is then placed in transport media or may be plated directly to various media (reviewed in culture of cornea). The swab may be moistened with the sterile liquid transport media or both for culture. Care is taken to avoid swab contact with the lid margins to assure inoculation of organisms only from the conjunction. The swab may be that supplied with the transport media, a sterile cotton swab, or calcium alginate swab. Calcium alginate and cotton swabs have been demonstrated to inhibit recovery of different organisms.[18] It is believed that the glue used for the various swabs may be toxic to either the organisms directly or the cells in culture that are to be inoculated as in the case of *Chlamydia* culture. Transportation of the collected specimen should be directed to the laboratory immediately for processing.

Viral conjunctivitis more likely is bilateral, typically has a watery discharge or increased tearing, and may have associated sore throat and preauricular adenopathy. Cultures may be obtained in the same manner as for suspected bacterial conjunctivitis but transported in different media. Sodium chloride moistened cotton-tipped swabs gave better yield topical of virus detection than commercial viral transport media.[19] The use of topical anesthetic enhanced viral recovery rate. Cell culture for virus detection is viewed as the standard but may take 4–7 days to show the cytopathic effect. Quantitative polymerase chain reaction has been shown to be more sensitive in direct comparisons. Availability may be limited in some regions.

Chlamydia conjunctivitis is a chronic, follicular conjunctivitis in adults. Laboratory diagnosis relies on both microscopic slide evaluation and specimen submission for culture or molecular diagnostic evaluation. Collection of a specimen for microscopic evaluation differs slightly from other causes of conjunctivitis. When *Chlamydia* is suspected, the upper or lower tarsal conjunctiva should be scraped with a Kimura spatula or blunt end of a #15 blade. The slides may be air dry. Detection may be made with the use of Giemsa stain for basophilic cytoplasmic inclusions or with direct immunofluorescence. A swab for culture should be placed in appropriate *Chlamydia* transport media. Viral transport media may contain antibiotics that could reduce the likelihood of positive culture results. Positive growth of clinical specimen from adult inclusion conjunctivitis occurs in a lower percentage of patients than from neonates. Finally, serology may prove useful in identifying a patient with *Chlamydia* but would not be helpful unless clinical findings support the presence of active infection.

Neonatal conjunctivitis requires preparation of both slides and culture for suspected organisms most associated with this condition: *Chlamydia* and *Neisseria*. Ordinarily a scraping of the conjunctiva is appropriate to create slides for evaluation. Since cooperation of the infant is unlikely, one must minimize the risk to the patient. If necessary, use a swab of the conjunctiva to collect a specimen for slide preparation. As mentioned above, be sure to include a chocolate agar plate when *Neisseria* is suspected.

BIOPSY

Diagnostic conjunctival biopsy may be performed as an outpatient procedure. In general, the procedure poses such small risk to the patient that, with rare exception, a cooperative patient may undergo the procedure in the office minor operating room. Excisional conjunctival biopsy may be performed in the minor operating room or an outpatient surgical center depending on the extent of tissue removal and need for adjunctive procedures at the time of the biopsy. Indications for conjunctival biopsy include unknown lesions that are threatening vision or causing chronic irritation or lesions that may indicate systemic disease. Conjunctival biopsy may be used to determine the presence of a malignancy.

Anesthesia may be topical alone in a few patients, but some require subconjunctival injection of anesthetic. Depending on the nature of the procedure and expected duration of the procedure, retrobulbar anesthesia may be indicated. Topical anesthesia may be proparacaine 0.5%, tetracaine 0.5%, or lidocaine 2% gel. If concern is for effectiveness, a cotton-tipped applicator soaked in either anesthetic may be applied and held directly over the area of planned

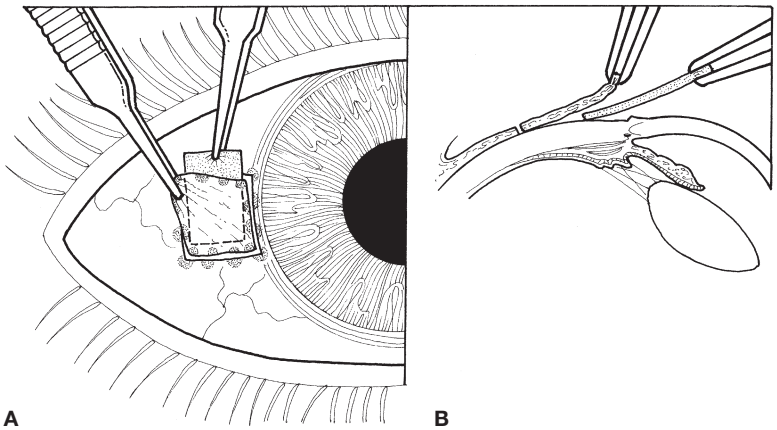

Figure 16.1. Conjunctival biopsy. *A,* The previously marked margins have been incised and the tissue to be removed has been undermined. Filter paper placement on the globe surface and gentle insertion beneath the specimen are performed as the tissue is drawn out to the filter paper. *B,* Cross-sectional view of the technique shows filter paper insertion beneath the excised tissue.

biopsy. If this approach is elected, care should be taken to avoid abrasion to the cornea and avoid abrasion or crushing injury to the area of pathology. Artifactual changes in the specimen may impact correct histologic diagnosis.

Subconjunctival anesthesia is useful in procedures requiring large biopsies or biopsies that require adjunctive treatment (e.g. cryotherapy). Retrobulbar anesthesia may be necessary for long procedures or procedures that require akinesia and traction sutures for appropriate eye positioning. Regardless of anesthesia type, topical phenylephrine 2.5% given as preoperative drops may reduce bleeding.

Appropriate movement of a specimen biopsy from the operating room to the pathology laboratory should first be planned with the pathologist. For most conjunctival specimens, immediate fixation in formalin is appropriate and easy. Specimen orientation may be assisted by immediately placing the biopsy on filter paper with the epithelial side facing up. The combined specimen and filter paper is then placed in formalin. A nonabsorbable suture may be placed in the specimen to assist the pathologist in orientation during the embedding process. If the differential diagnosis necessitates tissue collection for frozen sections or immunohistochemistry of nonfixed specimens, the following methods ensure adequate preservation of histologic architecture: In the operating room, the specimen is placed in a small (2-mL) freezing vial, sealed tightly, and immediately placed in liquid nitrogen to snap freeze the specimen. This frozen tissue should then be embedded in optimal cutting temperature compound and stored at −70°C until sectioned for staining. Discussion with the pathologist can also be helpful to insure the optimal method of tissue preservation and transportation for the suspected diagnosis.

Preparation of the site should include antiseptic cleansing of the skin and placement of a sterile drape. The operating microscope is preferred, but loupes may be used. If the area for excision needs to be demarcated, a hand-held disposable cautery or, preferably, a sterile marking pen can be used. Any lid speculum is acceptable. A nontoothed, serrated forceps is used to elevate normal conjunctiva within 1–3 mm of the lesion, and Westcott or Vannas scissors are used to incise the conjunctiva. It should be undermined without regrasping if possible. The predetermined margins are incised, and the specimen slid onto the precut filter paper with the epithelium remaining facing up (Fig. 16.1). Cautery of bleeding is at the discretion of the surgeon. It is usually not necessary to reapproximate the margins of the incised conjunctiva to cover the defect regardless of the size of the biopsy. Instillation of antibiotic ointment, such as erythromycin or bacitracin ophthalmic ointment, and placement of a pressure patch for 4–24 h are appropriate. Antibiotic ointment is applied three times daily for 1 week, during which the patient may experience blood-tinged tears. Control of pain may warrant the use of acetaminophen (325 mg)–codeine (15 mg) combination tablets every 4–6 h as needed.

TRAUMA

Conjunctival trauma may be blunt or sharp. It may be the result of a foreign body injury. The history surrounding the injury is most important in guiding the examination to determine the likelihood of deeper penetrating injury of the globe. Blunt injury may result in chemosis, subconjunctival hemorrhage, subconjunctival air, or a ruptured globe. Chemosis is a nonspecific reaction with swelling of the conjunctiva to irritating stimuli. It is usually self-limited, painless, and nonthreatening to vision. Regardless of the nature of the injury, focal hemorrhagic chemosis may be a sign of underlying scleral rupture. Treatment of uncomplicated chemosis is supportive alone (e.g. ice to the closed eye). If the chemosis is so large as to be exposed, antibiotic ointment should be applied three times daily until resolution. Subconjunctival hemorrhages also are self-limited. They require no treatment, and the patient should be reassured that they will resolve in 3 weeks.[20]

Conjunctival foreign bodies may be single or multiple, inert or reactive, and grossly evident or occult. The history of the exposure should alert the examiner to the likelihood of a foreign body. The examiner should determine the material, the speed of travel at impact, and the use of any protective eyewear during the incident. Examination should include double eversion of the upper lid, fluorescein staining, and direct observation of the conjunctiva. Superficial foreign bodies may be removed with forceps following use of topical proparacaine 0.5%. Subconjunctival foreign bodies may not generate much inflammatory reaction and remain present for many years without sequelae. Others may cause granuloma, cysts, or membrane formation, requiring removal.[21]

Lacerations of the conjunctiva are usually found on the bulbar conjunctiva and occur from a shearing force or sharp injury. Conjunctiva laceration combined with underlying scleral laceration would occur with penetrating injury. Maintaining a high index of suspicion for concurrent scleral laceration will help reduce oversight of this severe type of injury.[22]

Examination should include determination of best corrected visual acuity (pinhole is acceptable), motility tests, pupil examination, evaluation of muscle balance, slit-lamp examination, dilated funduscopic examination, and intraocular pressure measurement.

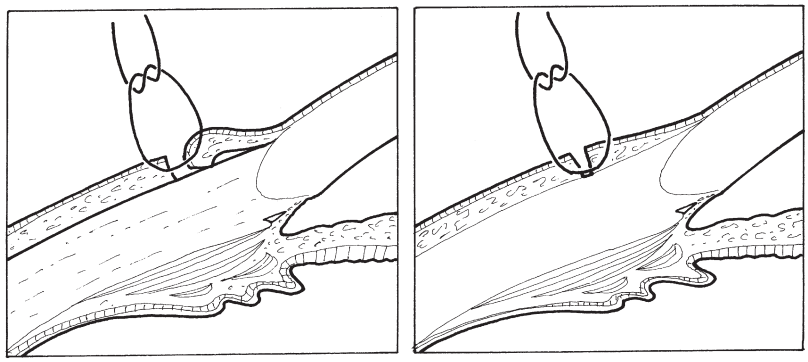

Figure 16.2. Conjunctival laceration repair using nonabsorbable suture. *A,* Care should be taken not to leave an inverted edge of conjunctiva as shown. *B,* Careful apposition of conjunctival edges and placement of a nonabsorbable suture are shown.

All portions of the examination requiring any diagnostic drop medications should be deferred until assessment of the presence or absence of scleral involvement is accomplished. The extent of any scleral injury may be greater than the conjunctival laceration.

If visual acuity is not compromised and the history does not suggest perforation, careful slit-lamp examination alone may verify if an intact globe is present. Injuries suspicious for concurrent scleral laceration but without slit-lamp evidence of hemorrhagic chemosis, pigmented tissue showing, or low intraocular pressure may be explored in the minor operating room. Exploration in the major operating room is indicated under general anesthesia if the likelihood of penetrating injury exists.

Minor operating room exploration would require topical anesthesia with tetracaine 0.5%, a lid speculum, nontoothed forceps, optional wound repair instruments, and the operating room microscope. The cut ends of the conjunctiva may be gently elevated off the globe to determine their fullest extent. The edges of the lacerated conjunctiva may be inverted. Careful observation for evidence of uveal or vitreous tissue beneath these elevated conjunctival edges should be performed.

All conjunctival lacerations with concurrent penetrating trauma should be closed at the time of surgery. The decision to close conjunctival lacerations with no concurrent penetrating injury depends on length of laceration, location, size of conjunctival defect, and involvement of Tenon's capsule. In general, lacerations smaller than 1 cm do not require repair. Epithelial closure will likely occur in 1–3 days, and even large epithelial defects (e.g. those in an avulsion) will re-epithelialize in 1 week. Lacerations in the fornix generally have good apposition and do not require sutures.

Anesthesia for laceration repair may need to be subconjunctival and not topical alone. Repair of the laceration should be in two layers if Tenon's capsule is involved. Incorporation of the injured Tenon's capsule in the conjunctiva laceration closure should be avoided as this approach may cause cyst formation, significant scarring, or contracture of the conjunctiva and reduce its mobility. Absorbable suture (e.g. 6-0 to 8-0 polyglactin 910) should be used to close Tenon's capsule. An absorbable or nonabsorbable suture may be used to close conjunctiva. If 6-0 to 8-0 polyglactin 910 is used, it should be placed so the knot is buried beneath the conjunctiva. The physician should be sure to evert the edge of the conjunctiva and pass the needle from the underside out and then from the outerside in on the opposite side of the wound. Based on the surgeon's preference, a running suture (in the same manner) or interrupted suture is then completed. Nonabsorbable suture is preferred by some but is limited by the need to remove it after healing has occurred. The knot should be placed so that it is exposed for easy removal (Fig. 16.2). Again, a running or interrupted suture is sufficient. Antibiotic ointment and a pressure patch, if necessary, are indicated for 24 h regardless if exploration is accomplished with or without repair. Antibiotic ointment should be used twice daily for 1 week following injury.

Complications include missed foreign body, missed scleral laceration, infection, inclusion cyst, pyogenic granuloma, and fibrosis. Infection in a wound of this highly vascularized tissue is very rare. A plain radiograph of the face can be used to rule out a metallic foreign body. Fibrosis may be severe with motility disturbance.

CONJUNCTIVAL RESECTION OR RECESSION

Conjunctival resections are performed usually to remove diseased tissue. Vision-threatening peripheral corneal disease is often associated with disease of the limbal conjunctiva. Corneal epithelial stem cells are located at the limbus.[23] The limbal conjunctiva contains Langerhan's cells, complement components, immunoglobulin, and mast cells and is considered to be an immune reactive site. The small vessel configuration of the limbal region makes the area predisposed to immune complex deposition.[24] Thus, cellular proliferation diseases (e.g. conjunctival intraepithelial neoplasia) and inflammatory diseases (e.g. peripheral ulcerative keratitis) are associated with changes in the limbal conjunctiva. Tabbara and co-workers[25] showed that conjunctival resection would reduce peripheral corneal infiltration of white blood cells in rabbits immunized by intravenous administration of antigen. Eiferman and coworkers[26] used conjunctiva resected from patients with rheumatoid arthritis and peripheral ulcerative keratitis to induce collagenolysis in vitro. With this background, it is not surprising that indications for conjunctival resections include reports of its use for Mooren's ulcer,[27] superior limbic keratoconjunctivitis,[28,29] peripheral ulcerative keratitis,[30–32] sebaceous adenocarcinoma,[33,34] Kaposi's sarcoma,[35] and conjunctival intraepithelial neoplasia.[36,37]

In the literature, conjunctival recessions are performed almost exclusively concurrent with or subsequent to strabismus surgery. However, a conjunctival recession may be used by some surgeons for any or all of the indications listed for conjunctival resection.

TECHNIQUE

Conjunctival resections may be performed in the minor operating room using local anesthesia as long as no scleral tissue inlay or tectonic grafting is planned. If these more involved procedures are planned, they are best performed in the major operating room with adequate intravenous sedation and a retrobulbar or peribulbar block. Local anesthesia should include subconjunctival injection of

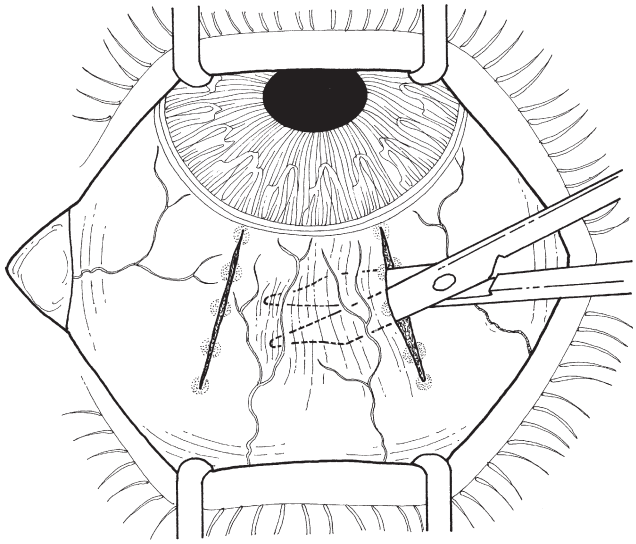

Figure 16.3. In conjunctival biopsy, the margins of the area to be excised are marked. Undermining of the entire area is accomplished before the limbal and posterior margins of resection are incised.

lidocaine 2% with or without epinephrine 1 : 100 000. The usually inflamed tissue, particularly if near the limbus will require more than topical anesthesia alone. If distinct margins of resection are to be adhered to, they should be marked with a sterile marking pen prior to subconjunctival anesthesia. An aseptic cleansing of the skin should be performed, and a sterile field established. An operating room microscope is required because resection of the conjunctiva is occasionally accompanied by lamellar dissection of underlying sclera. Anticipation of the specimen fixation and transport is the same as described for conjunctival biopsy.

Using blunt-tipped, serrated forceps, the physician elevates the conjunctival from the globe at a location posterior to the main pathology but at the anticipated margin of resection. After incising through conjunctiva and undermining the demarcated area, the physician should work toward the limbus and posteriorly until the area to be resected is free of underlying attachments (Fig. 16.3). Attempts to regrasp should be as infrequent as possible. The excision is completed by cutting along the previously designated margins. Bleeding may be controlled with wet field or thermal cautery. Attempts to reapproximate the cut edges of conjunctiva may be undertaken but are not necessary. Depending on the indication for surgical resection, adjunctive medications (e.g. mitomycin C) may be given or adjunctive treatment (e.g. freezing the cut edge of conjunctiva) may be performed.

Subconjunctival injection of gentamicin 20 mg or cefazolin 50 mg may be given at the end of the case. Antibiotic ointment application with a pressure patch for 4–24 h may be appropriate. Follow-up until complete conjunctival closure occurs is appropriate, as is antibiotic ointment three times daily.

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17 Epithelial debridement and superficial keratectomy

Tina C. Lucas-Glass, Christopher J. Rapuano

Stripping or curettage of the corneal epithelium for treatment of map-dot-fingerprint dystrophy was noted to be therapeutically effective as early as 1965 in a report by Guerry[1] and by Wolter and Fralick[2] in 1966. Today, the terms 'epithelial debridement' and 'superficial keratectomy' can be used interchangeably with corneal stripping and curettage. However, epithelial debridement and superficial keratectomy are often incorrectly used interchangeably. Epithelial debridement is defined as surgical removal of just the corneal epithelium. Bowman's layer remains undisturbed with this procedure. Superficial keratectomy is a nonspecific term. Its more widely accepted definition is surgical removal of 'corneal epithelium plus subepithelial fibrous, fibrovascular, or otherwise dystrophic tissue',[3] typically with Bowman's layer and superficial stroma. The procedure is performed without tissue replacement. A new, but not necessarily superior, procedure that has similar indications to epithelial debridement and superficial keratectomy is excimer laser phototherapeutic keratectomy (PTK). PTK, also referred to as laser superficial keratectomy, involves the use of an excimer laser to ablate abnormal tissue in the anterior portion of the cornea.

INDICATIONS FOR EPITHELIAL DEBRIDEMENT

The most common indications for epithelial debridement are as follows:

1. For tissue diagnosis:
   Microbiology
   Histopathology
2. To speed resolution of a superficial corneal epithelial infection by debulking infected tissue (in combination with antimicrobial therapy):
   Herpes simplex virus epithelial keratitis
   Acanthamoeba keratitis[4,5]
   Fungal keratitis
3. For excision of dystrophic corneal epithelium and Bowman's membrane:
   Reis-Bücklers' dystrophy
   Map-dot-fingerprint dystrophy
   Post-traumatic and idiopathic recurrent erosion
4. For the removal of band keratopathy (in combination with a calcium chelating agent)
5. For treatment of epithelial ingrowth after laser in situ keratomileusis (LASIK)[6]
6. To remove epithelial edema for corneal clarity during vitrectomy and scleral buckling surgery
7. For debridement of vernal shield ulcers[7]

SURGICAL TECHNIQUE FOR EPITHELIAL DEBRIDEMENT

Prior to epithelial debridement, the patient should be informed that the procedure may need to be repeated in the future. Under topical anesthesia, an eyelid speculum is placed in the eye. Depending on the comfort of the surgeon and the cooperation of the patient, the procedure may be performed at the slit lamp or using an operating microscope. Epithelial debridement can be performed with a sterile cotton-tipped applicator, a dry cellulose sponge, a blunt spatula (e.g. Kimura), or a sharp rounded-end blade (e.g. #64 Beaver blade, Rudolph Beaver, Waltham, and Mass). Without exerting significant posterior pressure, the epithelium can be removed with gentle sweeps of the instrument of choice across the corneal surface (Fig. 17.1). If a sharp blade is used, great care must be taken to avoid cutting into superficial stroma. Fluorescein drops can be instilled on the surface to identify areas of persistent epithelium. When epithelial removal is complete, the denuded surface can be polished with a cellulose sponge. Patients can expect moderate to severe pain until the epithelial defect heals.

Often there are residual epithelial basement membrane complexes adherent to Bowman's layer, which may or may not be readily visible at the slit lamp or operating microscope. A diamond burr can be used to polish Bowman's membrane and remove these tenacious adhesions safely and effectively.[8] A large, round diamond burr (4–5 mm in diameter) is best (Fig. 17.2). A gentle circular motion is used to buff the de-epithelialized cornea for approximately 5–20 s, depending on the extent of the pathology. In an efficacy study by Sridhar and co-workers,[9] diamond burr treatment was shown to have advantages over PTK in the treatment of recurrent corneal erosions.

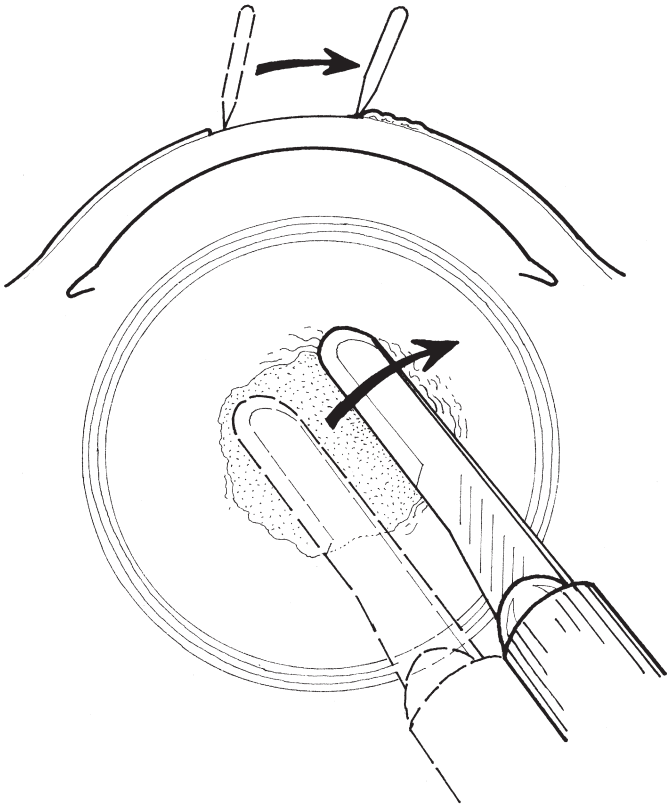


Figure 17.1. Epithelial debridement. A sharp rounded-end blade is used to sweep across the cornea, removing the epithelium without cutting into the stroma. The motion of the blade is sideways, perpendicular to the orientation of the blade.

A

B

Figure 17.2. Diamond burr. *A,* A 5-mm diamond burr; *B,* the diamond burr seated in the hand-held battery operated handle.

INDICATIONS FOR SUPERFICIAL KERATECTOMY

Superficial keratectomy shares several indications with epithelial debridement.[3] The indications for a superficial keratectomy are as follows:

1. For tissue diagnosis:
   Microbiology
   Histopathology
2. For removal of hyperplastic, degenerative, necrotic, or scarred tissue:
   Salzmann's nodular degeneration
   Spheroidal degeneration
   Calcific band keratopathy (after or in conjunction with calcium chelation)
   Pterygium
   Corneal dermoid
   Keratoconus nodule
   Superficial corneal scar
   Peripheral hypertrophic subepithelial degeneration[10]
3. For excision of retained corneal foreign material
4. For removal of corneal haze after photorefractive keratectomy[11]
5. For excision of dystrophic tissue:
   Reis-Bücklers' dystrophy
   Map-dot-fingerprint dystrophy[12]
   Post-traumatic and idiopathic recurrent erosion
   Anterior stromal dystrophies (e.g. lattice and granular dystrophies)
6. For recurrent dystrophies in corneal grafts:
   Reis-Bücklers' dystrophy[13]
   Granular dystrophy[14]
   Lattice dystrophy

SURGICAL TECHNIQUE FOR SUPERFICIAL KERATECTOMY

As with epithelial debridement, the patient undergoing superficial keratectomy should be informed that this procedure may need to be repeated. The patient should know that until re-epithelialization occurs, there is often a significant amount of discomfort. Depending on the comfort of the surgeon and the cooperation of the patient, this procedure can be done under topical or peri- or retrobulbar anesthesia. The operating microscope is used, and an eyelid speculum is placed in the eye. Corneal epithelium over the involved area can be removed with a dry cellulose sponge. For blunt dissection of hyperplastic lesions, a plane is established between the fibrous membrane and normal Bowman's membrane with fine-toothed forceps and a cellulose sponge or a sharp rounded-end blade. The forceps are used to fixate tissue and stabilize the eye while the sponge or blade pushes (not cuts) between the lesion and Bowman's layer to create a plane (Fig. 17.3). Once a plane is established, blunt dissection can be completed with a cyclodialysis spatula, a cellulose sponge, or the blade in a noncutting fashion. With the forceps, epithelium, basement membrane, and fibrous membranes can often be peeled in one continuous sheet (Fig. 17.4). As the pathology is often diffuse and contiguous with the limbus, the abnormal tissue must be separated from the peripheral corneal and limbal tissue. The central sheet can often be torn away from the peripheral remnants in an epithelial-rhexis fashion using the toothed forceps and a circular pulling motion (Fig. 17.5). Occasionally, if the membrane resists tearing, it needs to be cut away from the limbus with a sharp blade or fine scissors.

When a smooth plane cannot be easily established, sharp dissection may be required. In this case, the goal is to create a lamellar plane with toothed forceps and a sharp rounded-end blade. It is critical to dissect in one plane to minimize corneal irregularity and scarring and to decrease the risk of perforation. A microkeratome has also been used to create a smooth plane. This technique involves applying a suction fixation ring to raise the intraocular pressure to over 65 mmHg and using a flat oscillating blade to shave off the

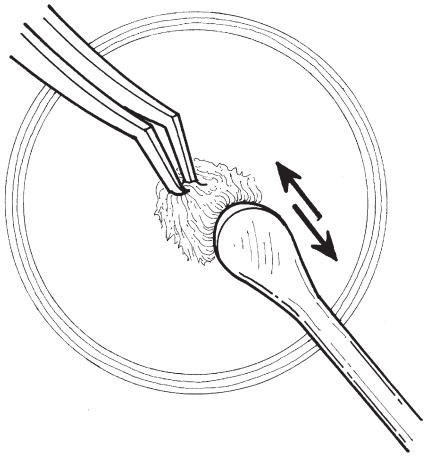


Figure 17.3. Superficial keratectomy. A blunt or sharp rounded-end instrument is used in a front-to-back pushing motion to create a plane between the lesion and Bowman's layer. The lesion is being stabilized with fine-toothed forceps.

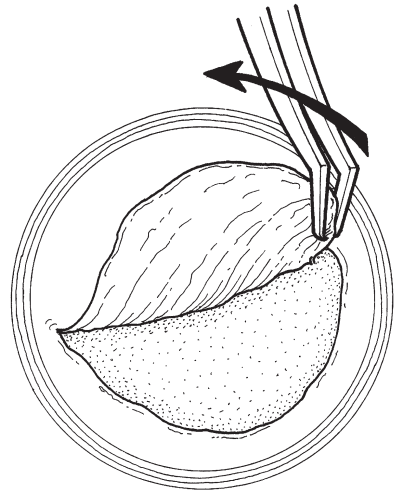
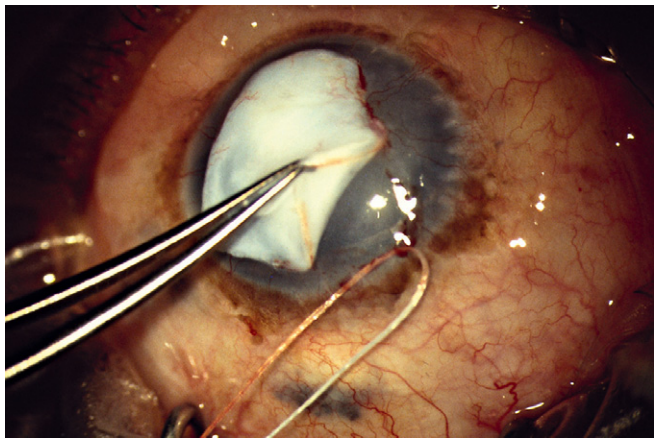
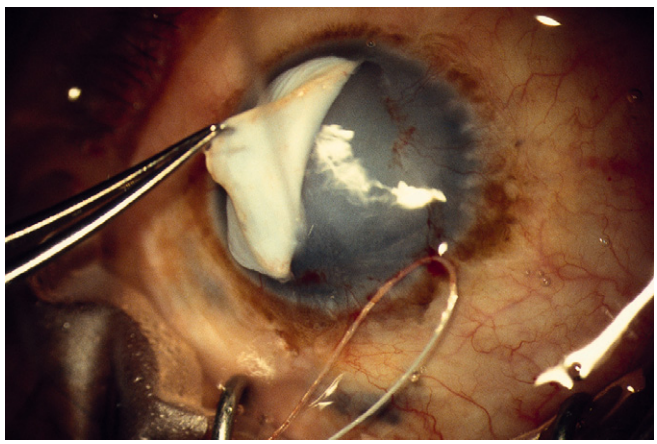


Figure 17.5. Peeling of a superficial corneal lesion. Frequently a dense subepithelial membrane can be peeled off Bowman's layer. Where it is contiguous with the peripheral cornea and limbus, the membrane can often be separated in an epithelial-rhexis fashion.

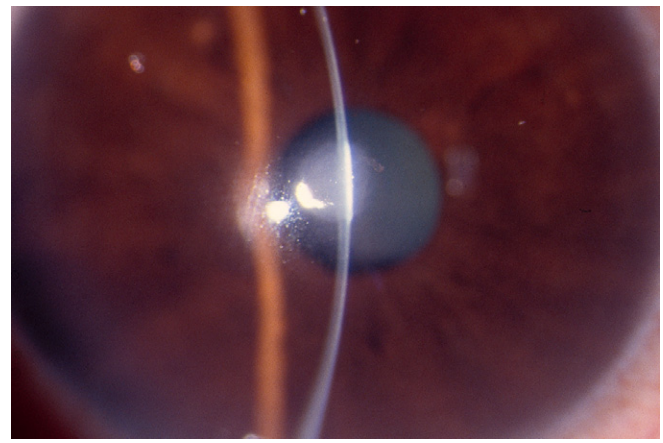


A



B

Figure 17.4. *A,* A large elevated degenerative nodular membrane lesion is peeled off the cornea. *B,* As blunt dissection and peeling are used to remove the lesion, the remaining Bowman's layer is smooth and relatively clear.



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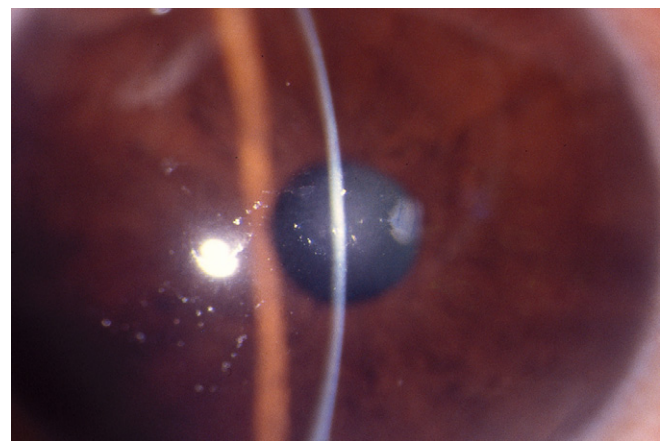

B

Figure 17.6. *A,* An elevated Salzmann's nodule causing poor visual acuity prior to superficial keratectomy. *B,* Two-day postoperative photo reveals a smooth corneal surface with mild residual anterior stromal haze, yielding significantly improved vision.

anterior cornea. A diamond burr can be used to treat areas of persistent corneal irregularity.

POSTOPERATIVE MANAGEMENT

Postoperative care after epithelial debridement and superficial keratectomy is similar. At the conclusion of surgery, a topical antibiotic and a cycloplegic agent should be instilled in the eye. A pressure patch or bandage soft contact lens may also be used. Otherwise frequent instillation of topical antibiotic ointment is preferred. The patient should be followed closely until re-epithelialization is complete. Topical nonsteroidal anti-inflammatory drugs may help to control pain. A topical corticosteroid–antibiotic drop may be beneficial after the procedure, especially if there is significant corneal inflammation. Depending on the size of the epithelial defect, re-epithelialization usually occurs within 2 to 7 days (Fig. 17.6). Close follow-up is required until re-epithelialization is complete, as these eyes are at risk for persistent defects and infection. Once re-epithelialized, the medications can be tapered and discontinued. For treatment of many conditions, and especially recurrent erosions, lubrication therapy with artificial tears, hypertonic solutions, or ointments should be instituted once re-epithelialization is complete.

RESULTS

Buxton and Fox[15] reported a series of 13 eyes with epithelial basement membrane dystrophy treated with epithelial debridement and soft bandage contact lenses. Of these patients, 84.7% were relieved of symptoms during a follow-up period ranging from 6 weeks to 48 months. One patient had two subsequent attacks of erosive symptoms which were managed with lubricants. Three corneas that had not received paralimbal diamond burr treatment developed peripheral erosions. All patients had a smooth corneal surface and tear film by 6 to 12 weeks postoperatively. Buxton and Constad[16,17] extended their initial series to 33 cases of symptomatic epithelial basement membrane dystrophy. In this report, the follow-up period ranged from 2 months to 7 years. Of these patients, 100% were relieved of preoperative symptoms after epithelial debridement. Only 3% showed evidence of recurrence of the epithelial basement membrane dystrophy.

Perhaps the biggest criticism of epithelial debridement and superficial keratectomy is the length of the postoperative recovery period. When compared to anterior stromal micropuncture, Rubinfeld and co-workers[18] thought that epithelial debridement was relatively safe and effective, was more technically difficult, resulted in more postoperative pain, and had a longer recovery time. Despite these drawbacks, epithelial debridement was thought to be the best treatment for diffuse map-dot-fingerprint dystrophy with spontaneous, bilateral, multiple erosions.

Diamond burr polishing of Bowman's membrane has been used as a supplement to simple epithelial debridement. Lance and co-workers[19] noted significantly more rapid healing in rabbit corneas when diamond polishing was combined with debridement.

Soong and co-workers[20] reported great success using diamond burr polishing of Bowman's membrane to treat recurrent erosion syndrome in 54 eyes of 47 patients with 3 to 53 months of follow-up.

In this era of laser treatments, diamond burr polishing still is a reliable, inexpensive procedure for recurrent erosions. Sridhar and co-workers[9] compared the efficacy of PTK to epithelial debridement and diamond burr polishing of Bowman's membrane in a total of 42 eyes of 39 patients. Their study compared these procedures in the treatment of recurrent corneal erosions associated with anterior basement membrane dystrophy. They found no statistically significant difference in haze and recurrence of erosions.

A statistically significant improvement in visual acuity after epithelial debridement and diamond burr polishing was noted in 13 eyes of 10 patients by Tzelikis and co-workers.[8] These patients were followed for an average of 21.8 months in this retrospective study.

SUMMARY

Epithelial debridement and superficial keratectomy, although different procedures, share similar indications and postoperative care. They are relatively safe and effective procedures for several epithelial and anterior corneal abnormalities.

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18 Corneal micropuncture in recurrent erosion syndromes

Roy Scott Rubinfeld

Commonly encountered in ophthalmic practice, recurrent erosion syndrome is a painful, often frightening, and sometimes incapacitating condition for many patients worldwide. In this syndrome, as implied by its name, corneal epithelial cells erode, resulting in denuded areas on the corneal surface. These areas then re-epithelialize, and the process recurs when the epithelial cells slough again at a later time. Erosions are characteristically episodic in nature, with many patients free of symptoms other than perhaps a mild ocular foreign body sensation or vague 'awareness' of the affected eye between erosions. This sensation of awareness can be most noticeable in dry, cold, or windy environments. Most erosions occur during the evening or early morning hours and are described as an abrupt 'ripping' or 'tearing' sensation generally followed immediately by sharp pain, a marked foreign body sensation, epiphora, photophobia, visual disturbances, and often lid swelling.

These attacks may vary greatly in pattern and intensity. Some patients have mild symptoms every few months or years, and some experience severe, incapacitating, frequent erosions causing pain and other symptoms lasting for hours or days at a time. In some patients with recurrent erosion, the epithelial defects never fully close, and loose sheets of epithelium slide over the surface of the eye with each blink. These patients experience constant pain and can be some of the most distraught individuals encountered in clinical practice.

The unpredictable nature of recurrent erosions often heightens patient anxiety. For active people, the knowledge that, on any given day, they may suddenly experience acute pain and be unable to work or participate in normal activities for hours or days at a time can be extremely disturbing. It is not uncommon for patients with severe erosions to begin displaying signs of depression and anxiety disorders. Since most erosions occur during sleep or on awakening, some patients come to fear falling asleep and experience varying degrees of insomnia. The resulting disruption in normal sleep patterns may exacerbate the patient's psychologic stress as well as their experience of the symptoms. Anxiety may even make erosions more frequent by causing patients to open their eyes more quickly on awakening and by inducing more rapid eye movements as well as interfering with normal blinking and tear production.

PATHOPHYSIOLOGY

The pathophysiology of recurrent erosion syndrome is only partially understood. Normal adhesion of the corneal epithelium depends primarily on structures known as attachment complexes, which are composed of elements from the basal epithelial cell, basement membrane, Bowman's layer, and corneal stroma. Through electron microscopic and immunohistochemical staining methods, these elements are thought to include hemidesmosomes, basal lamina, lamina densa, lamina lucida, anchoring fibrils, laminin, fibronectin, and types IV and VII collagen.

Abnormalities of epithelial adhesion resulting in recurrent erosion can be associated with previous traumatic abrasions or with corneal dystrophies. In the case of erosions associated with previous trauma, superficial injury to the cornea may damage the basement membrane. Some corneas appear unable to re-form normal attachment complexes, resulting in recurrent erosions occurring up to many years after the original injury.

Many ophthalmic or systemic diseases are associated with an increased incidence of recurrent erosions. A partial list of these includes lattice, Reis-Bücklers', macular, granular, and Meesmann's dystrophies; diabetes mellitus; and bullous keratopathy. Anterior basement (Cogan's or map-dot) corneal dystrophy is the dystrophy most commonly responsible for recurrent corneal erosion. Basement membrane abnormalities, including reduplication of basement membrane within the epithelium (maps) and cystic degeneration of cells (microcysts), have been reported to be present in 6–42% of the general population.[1,2]

DIAGNOSIS

For clinicians familiar with the common features of recurrent erosion syndrome, a patient with a history of previous trauma to the involved eye, episodes of pain on awakening, and a ragged, grayish-staining area of epithelium (Fig. 18.1) constitutes little or no diagnostic challenge. The diagnosis of recurrent erosion syndrome in more subtle cases, however, can be quite difficult.

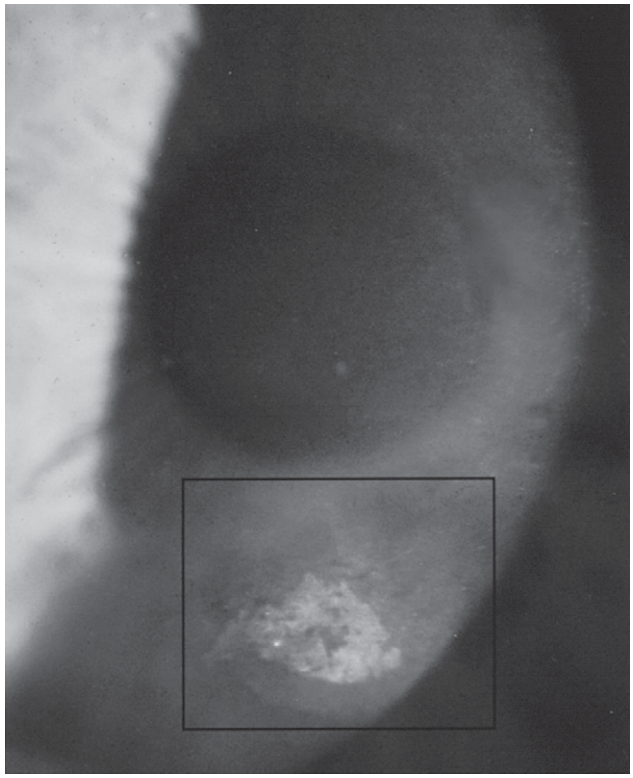

Figure 18.1. Slit-lamp appearance of active recurrent erosion showing ragged, edematous, disrupted gray epithelium (box). Note that the area of erosion is surrounded by apparently intact but also edematous grayish epithelium. (Courtesy of Peter R Laibson, MD; from Rubinfeld RS. Recurrent corneal erosion. In: Roy FH, ed. Master Techniques in Ophthalmic Surgery. Baltimore: Williams & Wilkins; 1995.)

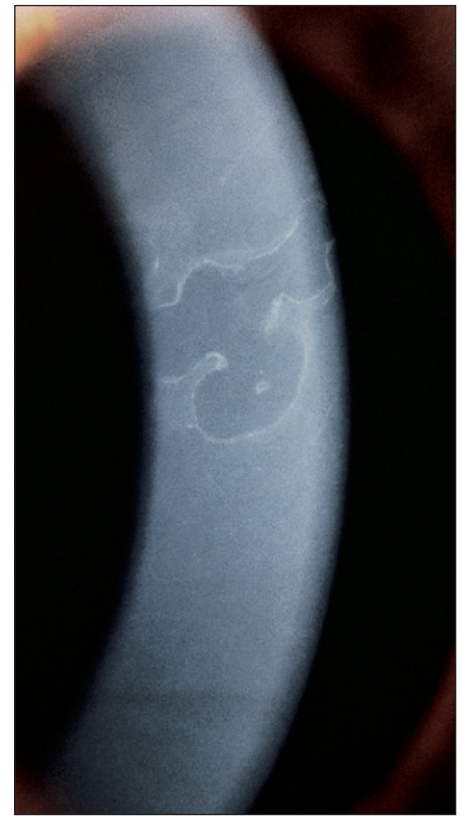

Figure 18.2. Broad beam slit-lamp appearance of anterior basement membrane lines present in recurrent erosion patient. This pathology was much less obvious using standard narrow slit-beam illumination. (From Krachmer et al. Cornea, 2nd edn 2005, Elsevier, Chapter 91. © Elsevier 2005.)

The clinician should carefully inquire about trauma to the involved eye. Often the patient will describe previous milder episodes of erosion, which helps support the diagnosis. Keen slit-lamp examination is often required to find subtle signs of erosion. Several different examination techniques can be helpful in this situation. Broad, angled slit-beam examination of both eyes before and after instillation of fluorescein (Figs 18.2 and 18.3) should be performed as well as a retro-illumination examination of the cornea with dilation of the pupil to discern signs of basement membrane dystrophy or sites of previous erosion. This careful examination may not only confirm the diagnosis but may also indicate which areas will need to be treated. Gentle pressure applied to the cornea through the eyelid may demonstrate wrinkling of loosely adherent epithelium. A fine slit-beam examination may reveal subtle, residual brown granularity of the stroma (brawny edema), which persists briefly after restoration of epithelial integrity.

Sometimes even the best observer will discern no visible corneal abnormalities on slit-lamp examination because the epithelial defect has resolved in the time between the occurrence of the erosion and the examination of the patient. In this situation the clinician should be especially careful not to label the distraught patient with complaints of eye pain and no visible signs of disease as 'functional' or 'psychoneurotic.' Clinicians should remember that recurrent erosion patients often display signs of anxiety and depression, as previously described. In these situations when the diagnosis is in question, the patient should be instructed to return for examination immediately after the next episode of pain without allowing time for the epithelium to heal and cover the erosion. Usually this approach will not only confirm the diagnosis but will help in choosing the correct treatment as well as the areas to be treated.

MEDICAL TREATMENT

For decades, recurrent erosion syndrome remained one of the more frustrating ophthalmologic problems encountered in clinical practice because of its occasional resistance to available treatments and prolonged course. Today, new therapies and a rational stepwise approach to management of erosions provide opportunities to convert distraught individuals suffering from persistent recurrent erosion into some of the most grateful patients in a clinician's practice.

TOPICAL AGENTS

A mainstay of medical treatment that remains effective to this day for the vast majority of patients with corneal erosions involves the long-term nightly use of hyperosmotic lubricating ointments. The rationale for this treatment derives from the concept of nocturnal relative hypotonicity of the preocular tear film. At night, with the eyes closed, tear evaporation is reduced. The resultant lowered concentration of dissolved salts in the tears is postulated to shift the osmotic gradients, resulting in a relative increase in corneal epithelial edema and consequent reduction in epithelial adhesion. The vehicle (e.g. petrolatum) serves also to prevent erosions by keeping the eye lubricated during rapid eye movements or while opening the eyes in the morning. Hyperosmotic eyedrops during the daytime are sometimes added to this approach in an effort to minimize epithelial edema during waking hours as well, thus allowing re-formation of more normal attachment complexes. These agents must be used consistently for at least 6–12 months after the patient's last erosion, since it often takes this much time for re-

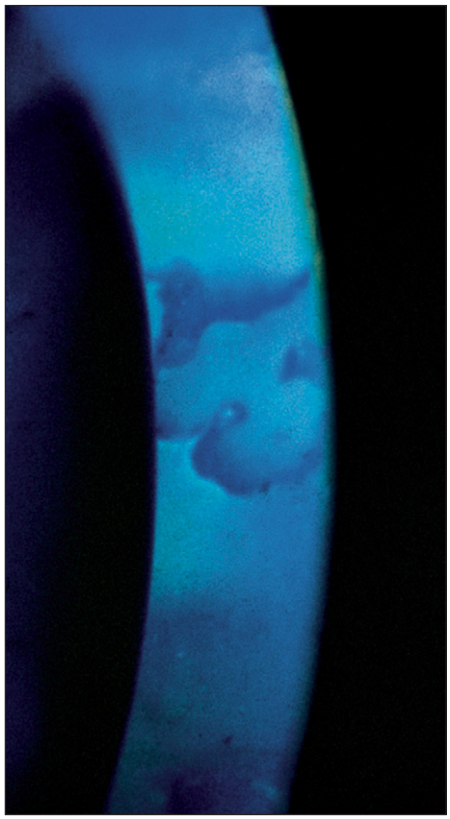

Figure 18.3. Slit-lamp appearance of the same patient's eye as in Figure 18.2 in which visualization of the basement membrane lines is enhanced with a tear film thickly stained with fluorescein. (From Krachmer et al. Cornea, 2nd edn 2005, Elsevier, Chapter 91. © Elsevier 2005.)

formation of normal attachment complexes. Unfortunately, patients frequently decide to stop the use of these topical agents soon after the erosions resolve, only to have a recurrence, which may prolong the time required for the attachment complexes to re-form. It is essential to query and educate patients in this regard. Some clinicians use only bland lubricants without a hyperosmotic component, but this approach may be less effective. Currently available hyperosmotic ointments include sodium chloride 5% (Muro-128, Bausch & Lomb) and sulfacetamide 10% (Bleph-10, AK-Sulf).

In addition to the hyperosmotic agents that are now available, other topical preparations may be of value in treating some patients with recurrent erosions. Some promising results have been reported in early studies using topical osmotic colloidal solutions[3] and clinical trials are now underway to further evaluate these preparations. Topical autologous serum eyedrops[4] as well as numerous investigational trophic growth factors may be demonstrated to be effective in treating some erosion patients, especially in patients with more severe types of epitheliopathy, such as those associated with long-term diabetes or neurotrophic keratitis.

Some investigators[5] have suggested that topical corticosteroids combined with oral doxycycline may help treat recurrent erosions by inhibition of matrix metalloproteinase-9. The use of topical steroids in the treatment of recurrent erosion must, however, be weighed against the potential risks of infection, cataract, and intraocular pressure elevation.

PATCHING AND BANDAGE LENSES

Patching during acute erosions in conjunction with lubricant/antibiotic agents is another effective treatment that helps to resolve the acute erosion in the vast majority of patients. Bandage contact lenses may be helpful in the case of acute erosions, but there may be an increased risk of microbial keratitis associated with their use.[6,7] In addition, they are often not effective in preventing further erosions except in cases where abnormalities in lid anatomy play a significant causative role in the erosions. Patching acute erosions and the consistent long-term nightly use of hyperosmotic ointments effectively resolve recurrent erosion syndrome for the vast majority of patients.

In addition to lid abnormalities or corneal inflammation, patients with recurrent erosions may be found, on careful examination, to have other concomitant ophthalmic diseases. Conditions such as dry eye syndrome or meibomian gland dysfunction blepharitis should be treated aggressively with frequent nonpreserved tear supplements or systemic tetracycline (such as doxycycline 50 or 100 mg orally each day), respectively.

SURGICAL TREATMENT

For patients in whom consistent, aggressive medical management fails to resolve the erosions, there exist several effective surgical options. The indication for surgical intervention is any situation in which aggressive medical management does not improve the symptoms and signs of erosions, and when the patient's continued pain and epithelial defects interfere with normal activities. The presence of recurring epithelial defects may result in infectious keratitis. This risk of infection, in conjunction with the prospect of continued patient disability and pain, generally overshadows the limited risks of appropriate surgical treatment of recalcitrant recurrent erosions. The choice of surgical approach is determined by the frequency and severity of erosions, the presence of concomitant dystrophies or other diseases, the etiology and location of the erosions, and the patient's needs and desires (Table 18.1).

DEBRIDEMENT AND SUPERFICIAL KERATECTOMY

Historically, debridement[8,9] and then superficial keratectomy[10] were the first surgical approaches to the treatment of resistant corneal erosions, and these procedures remain in use today. Debridement may be useful for removing a localized area of very loosely adherent 'floppy' sheet of epithelium in a limited number of erosion patients (Fig. 18.4). This technique requires only a cotton swab or blunt instrument and can be performed at the slit lamp with topical anesthesia. The suboptimal efficacy and limitations of this procedure derive from the fact that no significant modifications to enhance epithelial adhesion are made in Bowman's layer or other deeper corneal structures. A more aggressive approach, generally requiring the use of an operating microscope, is that of a large superficial epithelial keratectomy. This technique is much more likely to benefit recurrent erosion patients. The optimum candidate for this procedure has spontaneous multiple erosions in different areas of the cornea, no history of trauma, and severe basement membrane dystrophy, resulting in poor vision and large areas of loosely adherent irregular epithelium. After subconjunctival, peribulbar, or retrobulbar injections of a local anesthetic agent (or, in some highly cooperative patients, the use of topical anesthetic agents) a lid speculum is inserted to hold the eye open. A superficial plane of dissection using a blade or spatula is established in the perilimbal area. Leaving approximately 1 mm of intact perilimbal epithelium, the rest of the epithelium and its basement membrane, if possible, are lifted and dissected free. An attempt should be made

Table 18.1 Surgical therapies for recurrent erosion syndromes

Procedure	ASP (ER)	Epithelial Keratectomy	Debridement	Excimer PTK	YAG Procedures
Optimum candidate	Localized erosions with or without mild to moderate ABM dystrophy	Erosions in multiple areas, moderate to severe ABM, with decreased VA; loose sheet of floppy epithelium	Single area of erosion with localized loose sheets of epithelium	Erosions in multiple areas, moderate to severe ABM, with decreased VA, loose sheets of epithelium with refractive error	Unclear
Availability	Worldwide	May require operating microscope and diamond burr apparatus	Worldwide	Limited	Moderately limited
Cost	Very inexpensive	Moderate	Very inexpensive	Extremely expensive	Moderately expensive
Debridement required with	–	+	+	+	Debridement required only for older technique
Efficacy reports	Excellent	Excellent	Limited	Mixed	Some early encouraging reports

ABM, anterior basement membrane; ASP, anterior stromal puncture; ER, epithelial reinforcement; PTK, phototherapeutic keratectomy; VA, visual acuity; YAG, yttrium–aluminum–garnet.

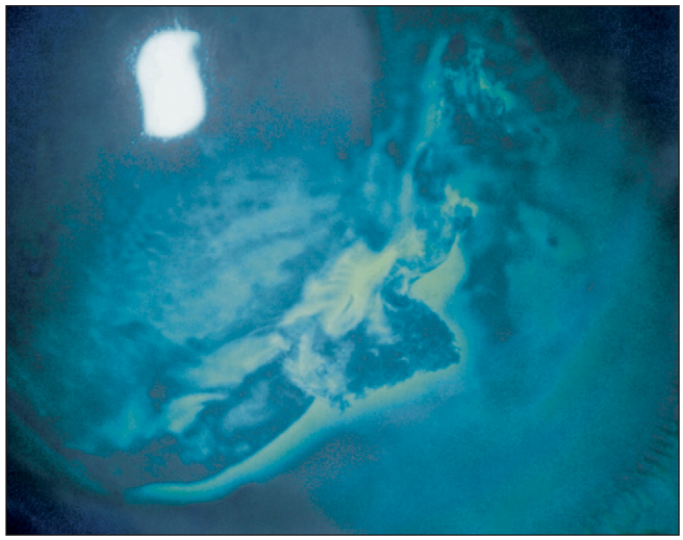

Figure 18.4. Slit-lamp appearance of loosely adherent sheet of floppy epithelium in a recurrent erosion patient. This sheet slid back and forth across the cornea with each blink. Note that fluorescein staining of the tear film helps make the loose epithelium more visible. (From Krachmer et al. Cornea, 2nd edn, 2005, Elsevier, Chapter 91. © Elsevier 2005.)

to peel and dissect away the epithelium in a continuous sheet. Persistent epithelial fragments may be visualized by instilling fluorescein. Bowman's layer should not be incised but should be scraped with a blade oriented perpendicular to the surface of the cornea, taking care not to produce linear scars in Bowman's layer. Alternatively, a diamond burr may be used to gently polish Bowman's layer to enhance epithelial adhesion as described by Forstot et al.[11] Preoperatively, the instillation of several drops of topical nonsteroidal anti-inflammatory agents such as bromfenac (Xibrom), ketorolac tromethamine (Acular), or diclofenac (Voltaren) generally helps greatly with pain management in patients undergoing debridement or superficial epithelial keratectomy procedures. Postoperatively the use of these drops, in conjunction with a well-fitted bandage contact lens for up to 3–5 days, usually improves patient comfort during the early postoperative period. More recently a technique known as alcohol delamination of the corneal epithelium[12] has been proposed to improve the efficacy of debridement in the treatment of recurrent erosions.

ANTERIOR STROMAL PUNCTURE (EPITHELIAL REINFORCEMENT, CORNEAL MICROPUNCTURE)

In 1986 McLean et al[13] described a significant innovation in the surgical management of resistant corneal erosions, which they termed 'anterior stromal puncture.' This highly effective office technique involved the use of a straight 20-gauge needle to make multiple shallow penetrations through the epithelium into anterior corneal stroma to improve epithelial adhesion, apparently by forming tiny scarring attachments similar to the metalworking technique of spot welding. Laibson[14] and co-workers expressed concerns about the possibility of corneal perforation with a straight needle, and several perforations have been reported using a 20-gauge needle.[15] Despite a high level of surgeon's skill, these perforations may occur because of the natural tendency for many patients undergoing stromal puncture to slowly back away from the slit lamp during the procedure and then jerk forward unpredictably once they realize their head position is wrong.

Concerns regarding this possibility of perforation, as well as questions regarding depth of penetration, the possibility of excessive scarring, and the reproducibility of results with stromal puncture, prompted the design of a disposable, inexpensive, specialized instrument for use in corneal micropuncture.[16] In histopathologic studies of cadavers and in clinical trials, this instrument has been

Figure 18.5. Hematoxylin and eosin-stained human cadaver eye after stromal puncture with conventional straight needle. The mean penetration depth with this technique was 208 μm (original magnification ×50). (From Krachmer et al. Cornea, 2nd edn, 2005, Elsevier, Chapter 91. © Elsevier 2005.)

Figure 18.6. Hematoxylin and eosin-stained histopathology slide of human cadaver eye after stromal puncture with a standardized specially designed needle. Mean penetration with this needle was 108 μm (Original magnification ×50). (From Rubinfeld RS, MacRae SM, Laibson PR, et al. Successful treatment of recurrent corneal erosion with Nd:YAG anterior stromal pressure. Am J Ophthalmol 1991; 111: 252–254. © Elsevier 1991.)

shown to produce consistent, shallow penetrations (Figs 18.5 and 18.6), minimal scarring (Figs 18.7 and 18.8), and virtually eliminated the possibility of perforation while retaining the high success rate of anterior stromal puncture with a straight needle.[15,16]

Anterior stromal puncture or micropuncture is an office procedure performed conveniently at the slit lamp under topical anesthetic. When discussing this procedure with patients, the term 'epithelial reinforcement' may be substituted for 'stromal puncture' to allay patient anxiety (Lindstrom, personal communication). In my experience, for most patients the use of the word 'puncture' is the most frightening aspect of this technique. Before the procedure (CPT Code 65600), the chart should be reviewed and drawings of previous erosions studied to determine the area to be treated. A careful preoperative slit-lamp examination should also include retro-illumination. Epithelial reinforcement may be performed either between erosive episodes or through loose, irregular epithelium during an active erosion without the need for debridement. Topical nonsteroidal drops such as ketorolac, diclofenac or bromfenac should be instilled every 10–15 min, starting 30 min to 1 h before the procedure to aid in postoperative pain management. In addition, several drops of a fluoroquinolone, or other broad-spectrum antibiotic, may be used preoperatively to reduce the likelihood of infection by decreasing the bacterial population of the external eye.

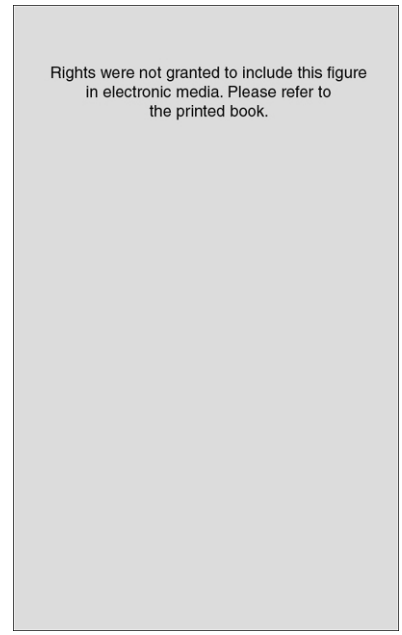

Figure 18.7. Slit-lamp photograph showing corneal scarring 3 months after anterior stromal puncture with a 25-gauge straight needle. This scarring faded slowly, becoming nearly invisible by 2 years after surgery. (From Rubinfeld RS, Laibson PR, Cohen EJ, et al. Anterior stromal puncture for recurrent erosion: further experience in new instrumentation. Ophthalmic Surg 1990; 21: 318–326.)

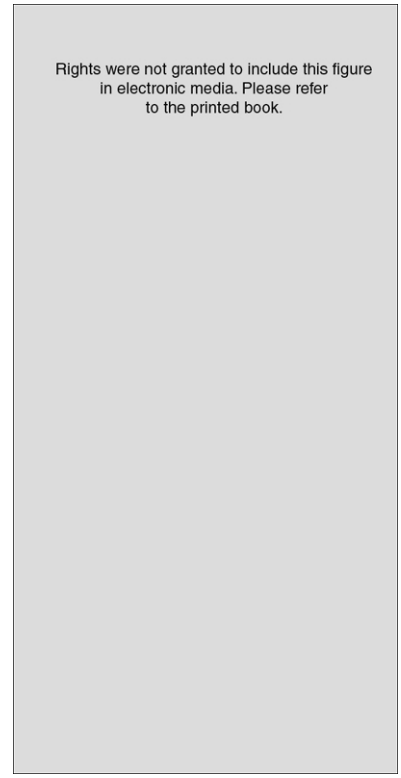

Figure 18.8. Slit-lamp photograph showing minimal corneal scarring only 2 weeks after anterior stromal puncture with a standardized, specially designed needle. This haze resolved completely by 2 months after surgery and was no longer visible by slit-lamp examination. (From Rubinfeld RS, Laibson PR, Cohen EJ, et al. Anterior stromal puncture for recurrent erosion: further experience in new instrumentation. Ophthalmic Surg 1990; 21: 318–326.)

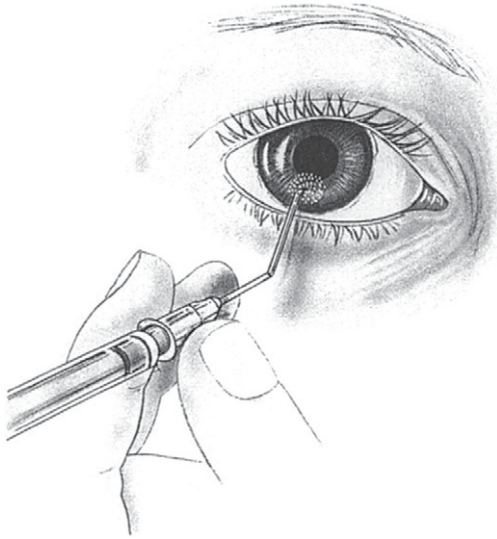

Figure 18.9. Epithelial reinforcement technique (stromal puncture). The two preset bends in the standardized needle prevent the patient from visualizing the needle tip and shaft, thereby reducing patient anxiety. (From Rubinfeld RS. Recurrent corneal erosion. In: Roy FH, ed. Master Techniques in Ophthalmic Surgery. Baltimore: Williams & Wilkins; 1995.)

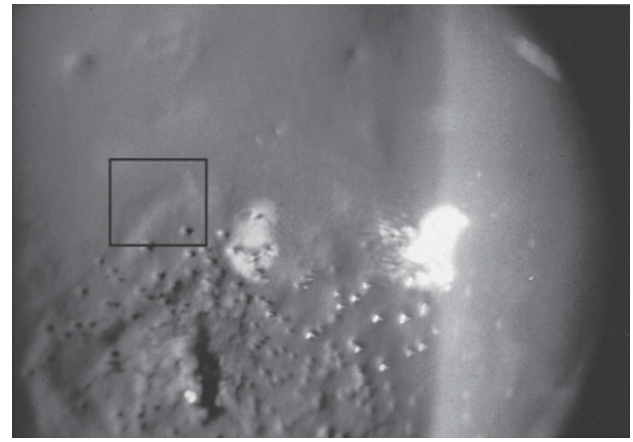

Figure 18.10. Retro-illumination slit-lamp photograph taken immediately after anterior stromal puncture. Note that the area of anterior basement membrane abnormality (box) extends beyond the limits of the treated fluorescein-stained erosive epithelium. (Reproduced from Rubinfeld RS, Laibson PR, Cohen EJ, et al. Anterior stromal puncture for recurrent erosion: further experience and new instrumentation. Ophthalmic Surg 1990; 21: 318–326, by kind permission of Slack Inc.)

Fortunately, however, infections after epithelial reinforcement (stromal puncture) are extremely rare.

Fluorescein, along with several drops of topical anesthetic, should be applied to help visualize the puncture marks. The patient is admonished not to move or blink without warning the surgeon and is assured that the procedure itself is completely painless because of the use of the topical anesthetic. A drop of anesthetic in the nonoperative eye may help to control the urge to blink during the procedure. The standardized disposable stromal puncture needle* is mounted on a tuberculin syringe. The angled tip of the needle is kept perpendicular to the surface of the cornea and a few punctures are made. It is helpful to pause at this point to confirm for the patient that the procedure is truly painless. Patient anxiety will thereby be lessened and cooperation enhanced. Generally, the design of the needle prohibits the patient from even visualizing the device during the procedure, which also helps allay patient anxiety (Fig. 18.9).

Closely placed, generally nonconfluent punctures should cover the entire erosive area and should also include 1–2 mm of apparently normal margins outside the visible limits of the erosive area. Treatment of these apparently normal margins is necessary because the loose epithelium usually extends beyond the visible limits of the erosion, as can sometimes be demonstrated by retro-illumination (Fig. 18.10). Treatment within the pupillary space should be minimized if possible, although in our experience subjective and objective glare testing has revealed no problems in patients who have been treated with the standardized needle in the pupillary space.[16] A topical antibiotic drop or ointment such as tobramycin ointment or fluoroquinolone drops, a cycloplegic agent such as scopolamine 0.25%, and more topical nonsteroidal drops are instilled postoperatively. A hydrophilic bandage lens can be applied and left in place for 1–2 days, but this may increase the risks of postoperative infection and, in the author's experience, this has not improved postoperative comfort significantly. Patients may use the topical nonsteroidal agent up to three times daily as needed for pain over the next 2–3 days. Alternatively, the eye may be patched without a bandage lens after the nonsteroidal and antibiotic drops or ointments are instilled. Oral oxycodone or codeine-acetaminophen tablets or a systemic nonsteroidal agent should be prescribed. Once re-epithelialization has occurred, hyperosmotic ointments are used three or four times daily to lubricate and protect the delicate healing epithelial tissue for several weeks postoperatively. Hyperosmotic ointments should then consistently be used at bedtime for 6–12 months (and occasionally longer) after stromal puncture while attachment complexes and other ultrastructural components are re-forming to achieve maximal epithelial adhesion.

Postoperatively, following micropuncture, it is not uncommon for patients to experience a foreign body sensation and occasionally some subtle discomfort on awakening in the morning or at other times when the eye is poorly lubricated. Also, patients often experience an 'awareness' of the eye for many months or more after their erosions resolve. As with most erosion patients, this is particularly noticeable on exposure to wind or dry air currents. In our experience with several years' follow-up, a single anterior stromal puncture (epithelial reinforcement) procedure is effective approximately 80% of the time in selected recurrent erosion patients (Laibson, personal communication).[17] Treatment failure generally tends to occur when the surgeon treats too small an area, and erosions then develop outside of the treated area (Fig. 18.11). A second, larger treatment can often resolve the erosions in patients in whom the initial epithelial reinforcement procedure was unsuccessful. The optimum candidate for anterior stromal puncture or epithelial reinforcement is the patient with a single persistent area of erosion associated with previous trauma or minimal anterior basement membrane dystrophy.

A technique dubbed 'pancorneal puncture' by MacRae, in which large areas of the cornea are treated in patients with moderate

*Available from Sharpoint Surgical Specialties Corporation, Reading, PA (order number 3800) 1.800.523.3332 www.surgicalspecialties.com (or www.angiotech.com) or Bausch & Lomb/Storz, Rochester, NY (Stromal Puncture Cannula) 1.800.338.2020 (order number E7185) www.storz.com.

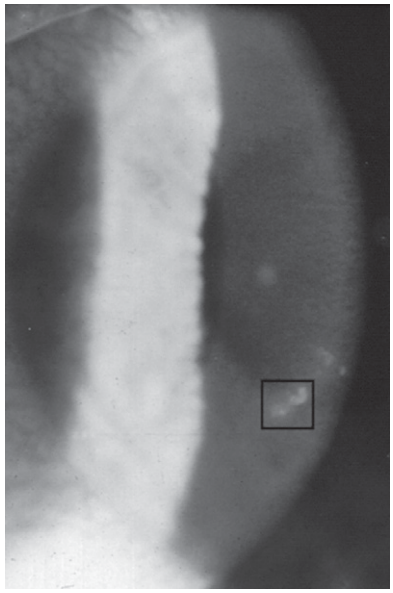

Figure 18.11. Slit-lamp photograph of small erosion (box) that occurred 4 days after stromal puncture in an untreated area adjacent to the original erosion. This is the same patient as shown in Figure 18.10. (Reproduced from Rubinfeld RS, Laibson PR, Cohen EJ, et al. Anterior stromal puncture for recurrent erosion: further experience and new instrumentation. Ophthalmic Surg 1990; 21: 318–326, by kind permission of Slack, Inc.)

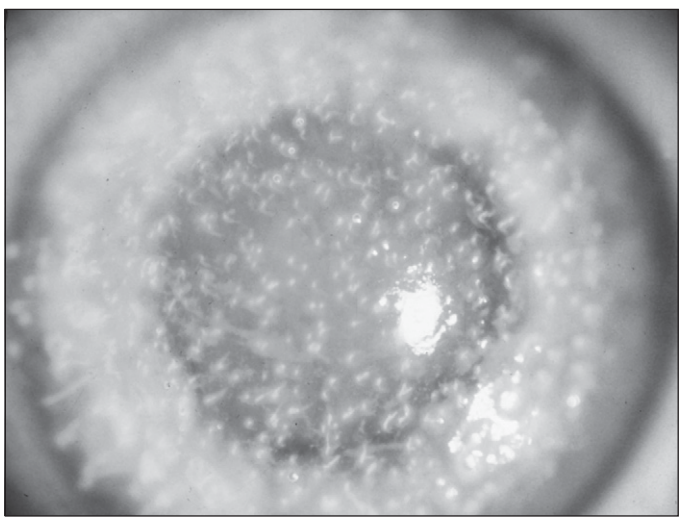

Figure 18.12. Slit-lamp photograph taken immediately after epithelial reinforcement in a patient with moderate degrees of diffuse basement membrane dystrophy and multiple recurrent corneal erosions. This technique has been dubbed 'pancorneal puncture.' (From Krachmer et al. Cornea, 2nd edn, 2005, Elsevier, Chapter 91. © Elsevier 2005.)

amounts of basement membrane dystrophy, can be quite effective (Figs 18.12 and 18.13). Patients with severe basement membrane dystrophy, however, with consequent loss of visual acuity and numerous spontaneous, multifocal erosions are better candidates for superficial keratectomy than anterior stromal puncture.

Although the efficacy of anterior stromal puncture has been established, the mechanism of action of this technique has not been fully elucidated. It has been postulated that multiple plugs of epithelium fill the puncture sites and function as a series of 'spot welds,' focally binding the loosened sheets of corneal epithelium to the underlying edematous stroma until more normal ultrastructural

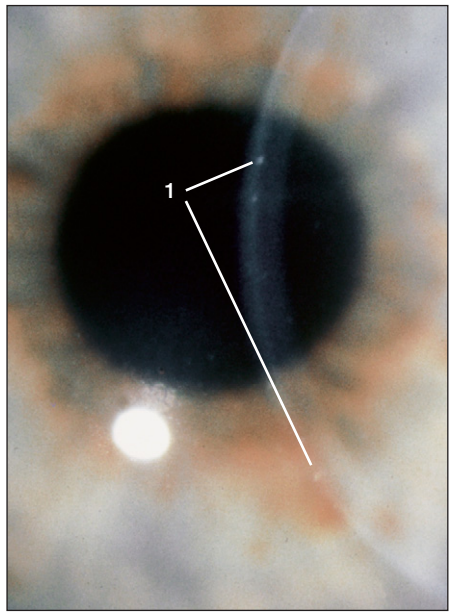

Figure 18.13. Slit-lamp photograph of the same patient as in Figure 18.12 taken 2 months after pancorneal puncture treatment. The patient is completely free of erosions at this point and remains so throughout 2 years of follow-up. Note that almost no scarring (1) is visible. (From Krachmer et al. Cornea, 2nd edn, 2005, Elsevier, Chapter 91. © Elsevier 2005.)

architecture and attachment complexes can form.[15,18] Katsev et al[19] describe a case of stromal puncture in which punctures of 0.1 mm depth caused a fibrotic reaction and new basement membrane formed as well. Hsu et al[20] performed electron microscopic and immunohistochemical studies of stromal puncture in human corneas with bullous keratopathy. Fibronectin, type IV collagen, and laminin were found within the puncture sites and in the reactive subepithelial pannus adjacent to the puncture site. They postulated that stimulation of production of these extracellular matrix proteins may be important in the attachment of epithelial cells to the underlying connective tissue. Epithelial–stromal reactions in the development of subepithelial fibrosis may also play a role in re-establishing epithelial attachment.

Encouraged by the success of anterior stromal puncture in recurrent erosion patients without corneal dystrophies and in those with basement membrane dystrophy, some surgeons have used this technique on patients whose corneal erosions are associated with bullous keratopathy. Although corneal stromal edema is generally well tolerated, rupture of epithelial bullae and the resulting corneal erosions in these patients can be very painful. For some of these bullous keratopathy patients with erosions, who are poor candidates for penetrating keratoplasty because of poor visual potential or medical contraindications, stromal puncture has been shown to be a useful treatment.[15,17,20,21] Epithelial reinforcement can also be used to control painful erosions in patients with bullous keratopathy, who are awaiting corneal transplantation. The optimum candidates for this type of treatment are those whose bullae are localized[20,21] and not diffusely distributed throughout the cornea (Figs 18.14 and 18.15).

YAG LASER PROCEDURES

Several investigators have suggested the use of YAG laser treatments for resistant corneal erosions. Geggel[22] initially proposed a technique in which epithelial debridement was performed and then

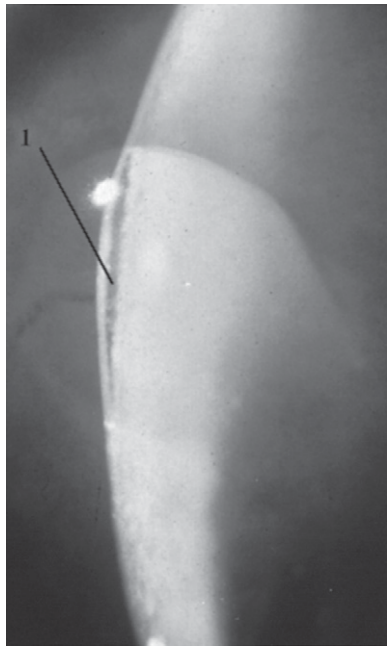

Figure 18.14. Slit-lamp photograph of patient with bullous keratopathy and secondary painful corneal erosions. Note bullous elevation of the corneal epithelium (1). (Reproduced from Hsu JK, Rubinfeld RS, Barry P, et al. Anterior stromal puncture. Immunohistochemical studies in human corneas. Arch Ophthalmol 1993; 111: 1057–1063. © 1993 American Medical Association.)

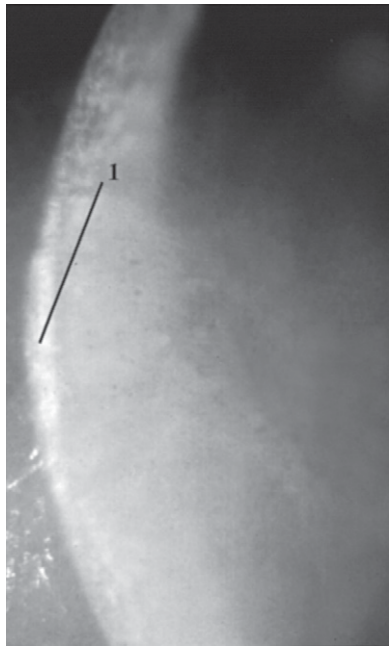

Figure 18.15. Slit-lamp photograph of the same patient as in Figure 18.14, 8 months after anterior stromal puncture treatment. This patient remained free of any further painful corneal erosions for over 4 years of follow-up. Note the resolution of the subepithelial bullae and the formation of subepithelial fibrosis/pannus (1). (Reproduced from Hsu JK, Rubinfeld RS, Barry P, et al. Anterior stromal puncture. Immunohistochemical studies in human corneas. Arch Ophthalmol 1993; 111: 1057–1063. © 1993 American Medical Association.)

photodisruption of the anterior corneal stroma was induced with the YAG laser. Katz et al[23] reported modifying the procedure so that debridement was not necessary. They renamed this technique Nd:YAG laser photo-induced adhesion. Extensive experience and long-term follow-up are not available with these techniques, and they involve more expensive technology than stromal puncture.[16] However, these approaches, especially the technique that eliminates the need for debridement, may have some role in the treatment of patients with resistant corneal erosions.

EXCIMER PHOTOTHERAPEUTIC KERATECTOMY

The ArFl excimer laser has been used to treat patients with recurrent corneal erosions.[24–26] This application of the excimer laser is covered more extensively in Chapters 19 and 20. However, a limited discussion of this approach is appropriate here. Phototherapeutic keratectomy (PTK) using the excimer laser involves treating Bowman's layer or anterior stroma, resulting in an ultramicroscopically modified, roughened surface to anchor the corneal epithelium (Stein, unpublished). This approach involves extremely expensive technology, and clinical experience and long-term follow-up data are limited. Also, surgical technique and success rates vary widely with individual surgeons, patient characteristics, and laser techniques. One group of investigators[29] has, in fact, reported that symptoms of recurrent erosion were more common and more pronounced in patients who had PRK than in patients who had LASIK for the correction of myopia.

The patient's epithelium is usually removed mechanically by scraping with a spatula or blade, since using the laser to ablate the epithelium in patients with severe basement membrane dystrophy can induce irregularities in the deeper corneal tissues. Development of better coupling or masking agents may eliminate this problem in the future. Once the epithelium is removed, the laser is used to treat or 'dust' Bowman's layer.

Excimer PTK usually results in a postoperative refractive shift toward hyperopia. In patients with myopia and corneal erosions associated with marked basement membrane dystrophy the excimer laser can be used to perform a combined PTK and photorefractive keratectomy (PRK) procedure. In this case, the PRK parameters and techniques are determined in part by the patient's preoperative refractive status. Combining PTK and PRK can reduce or eliminate ametropia, improve the best corrected vision by reducing the surface irregularity of the dystrophic epithelium, and resolve the recurrent corneal erosions. Postoperatively, bandage contact lenses along with topical nonsteroidal agents and antibiotics are generally used.

Despite questions regarding cost, refractive shift, long-term success rates, and wide variation in technique, excimer PTK may be an important treatment for recurrent erosions, especially in patients whose corneal erosions are associated with marked basement membrane dystrophy and ametropia. In addition, patients with corneal erosions caused by other corneal dystrophies, such as superficial variant of granular dystrophy, Reis-Bücklers' dystrophy, and other similar conditions involving the anterior cornea may be excellent candidates for excimer PTK.

DISCLAIMER

The author has no proprietary interest in any of the devices or techniques described herein.

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19 Phototherapeutic keratectomy: indications, contraindications, and preoperative evaluation

Liane M. Clamen, Waleed Mahran, Dimitri T. Azar

In 1981, the US Air Force School of Aerospace Medicine first began researching the effects of the 193-nm argon fluoride (ArF) excimer laser on the eye.[1] Trokel and co-workers[2] in New York then found that the excimer laser could produce precise corneal ablations in bovine eyes; in 1983, they published the first article to describe the surgical potential of excimer photoablation. By 1985, Seiler performed the first excimer laser phototherapeutic keratectomy in a sighted eye.[3] In the spring of 1995, the US Food and Drug Administration issued premarket approval of the Summit (Waltham, MA) and VISX (Santa Clara, CA) lasers for phototherapeutic keratectomy.

The popularity of PTK for treatment of corneal opacities and irregularities stems from the fact that the 193-nm ArF excimer laser emits pulses of light that ablate the cornea with submicrometer precision and with minimal damage to adjacent tissue.[4] The high-energy ultraviolet light emitted by the laser allows for accurate control of the depth and shape of tissue removal. By removing precise amounts of superficial corneal stroma, PTK leaves an optically smooth surface with reformation of basement membrane complexes and minimal corneal scarring.[2,4–8] Phototherapeutic keratectomy has various advantages over manual keratectomy surgery. Manual keratectomy with diamond and steel blades produces more irregular and diffuse tissue damage when compared to a 193-nm ArF excimer laser. Although manual keratectomy cannot create a clear boundary between the treated and untreated area at the histologic level, PTK can produce an exact histologic border.[2] Patients who are successfully treated with PTK can postpone or avoid more invasive techniques, such as surgical keratoplasty.

INDICATIONS

Many cases of visual loss resulting from corneal pathologic conditions can be corrected with corneal keratoplasty. However, corneal transplantation carries the risk of rejection, graft failure, endophthalmitis, dramatic postgraft astigmatism, and expulsive choroidal hemorrhage. In addition, the initial corneal infection or dystrophy may recur in the graft. Of the more than 34 000 corneal transplants performed each year in the USA, as many as 10% produce poor results.[9–11] In some circumstances, PTK is a less expensive, easier, and more effective method than corneal keratoplasty. The efficacy of PTK varies widely, depending on both the underlying diagnosis and the preoperative condition of the cornea.

A multicenter trial that reviewed the results of PTK treatment in 232 eyes concluded that the best candidate eyes are those with superficial corneal opacities and without significant corneal thinning.[12] In eyes with a central corneal thickness of less than 400 µm or an opacity deeper than the anterior 100 µm of the corneal stroma, there is an increased likelihood that PTK will cause complications. In these eyes, PTK may create an exceptionally thin cornea, thereby causing regular and irregular astigmatism, postoperative haze, a hyperopic shift, or a combination thereof.[12] Similarly, Marshall and co-workers[13] noted endothelial cell loss after PTK when the remaining unablated stromal thickness is 40 µm or less. It is not known, however, if similar endothelial loss would occur with equally deep mechanical lamellar dissection. The results of reports on PTK for various indications are summarized in Table 19.1.

RECURRENT CORNEAL EROSIONS

For patients with recurrent corneal erosions recalcitrant to conventional treatments, surgical options include manual epithelial debridement, anterior stromal puncture, and phototherapeutic keratectomy. Because the treatment depth of excimer laser photoablation is relatively shallow (5–10 µm) and usually limited to Bowman's layer, corneal wound healing is faster and significant postoperative hyperopic shift is absent (Table 19.2).

One disadvantage of PTK is postoperative pain caused by epithelial removal. Ardjomand and co-workers introduced a modified technique to reduce the immediate pain from removal of the epithelium after PTK in the treatment of recurrent corneal erosion. PTK with an epithelial flap or epithelial reflap similar to laser-assisted subepithelial keratectomy (LASEK), in which the peeled epithelium is placed back on the stroma, may result in faster postoperative visual rehabilitation and reduction of ocular pain in the immediate postoperative period. The relatively weak adherence of the epithelium to the stroma makes ethanol treatment before epithelial peeling unnecessary.[14]

Table 19.1 Phototherapeutic keratectomy in corneal disease

Pathologic Condition	Schwind	Technolas	Nidek	VISX	Summit	Meditec	Taunton	No. Eyes	Follow-up (months)	Success Rate (%)	References
Recurrent epithelial erosions	+	–	+	+	+	+	+	318	19.6	75.6	34,60–68,51
Cornea dystrophies											
Reis–Bücklers'	–	+	–	+	+	–	+	52	8.55	100	4,42,51,50,66,67,69–74
Lattice	–	+	–	+	+	–	–	37	14.75	89	4,32,42,51,71,74,75
Granular	–	+	–	+	+	–	+	37	11.8	78	4,28,32,33,42,66,67,71,73,74,75
Salzmann nodular	–	+	–	+	+	–	+	39	8.6	85	4,33,51,66,76,77
Map-dot-fingerprint	–	–	–	+	+	–	–	10	5.2	100	51–74
Schnyder's	–	–	–	+	+	–	–	6	6.0	67	66,67,74
Avellino	–	–	–	–	–	+	–	1	12.0	100	79
Gelatinous droplike	–	–	–	–	+	–	–	1	4.0	100	80
Meesmann's	–	–	–	+	+	–	–	2	9.0	100	74
Fuchs' endothelial	–	–	–	+	+	–	–	1	9.0	100	74
Corneal scars											
Postinfectious	–	–	–	+	+	–	+	12	8.5	50	32,33,73,
Post-traumatic	–	–	–	+	+	–	+	23	11.1	61	32–34,65–67
Herpetic	–	–	–	+	+	–	+	24	15.0	71	33,35,89
Trachomatous	–	–	–	–	+	–	–	3	6.0	67	90
Pterygium	–	–	–	+	+	–	+	10	11.2	80	33,34,51,66,67,73
Stevens–Johnson syndrome	–	–	–	–	+	–	–	3	11.7	67	34
Contact lens wear related	–	–	–	+	+	–	–	2	3.0	50	51,67
Unknown cause	–	–	–	+	+	–	–	12	14.6	50	4,46,51,67,91
Cornea irregularities											
Band keratopathy	–	+	–	+	+	–	+	169	14.7	83	32–34,40,42,51,73
Apical scars in keratoconus	–	–	–	+	+	–	–	21	9.7	81	33,34,66,67,92,93
Cornea Intraepithelial dysplasia	–	–	–	–	–	–	–	1	26.0	100	94

Modified from Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Table 19.2 Recurrent corneal erosions

Study	Laser	No. Eyes	Phototherapeutic Keratectomy	Follow-up (months)	SUCCESS AFTER TREATMENTS: Initial	SUCCESS AFTER TREATMENTS: Retreatment
Jain[60]	NIDEK	77	Epithelial debridement and 30-μm PTK	24	53 (69%)	
Ohman[61]	Summit/VISX	76	Epithelial debridement and 3-μm or 5–20-μm PTK through intact epithelium	16.3	56 (74%)	70 (92%)
Dausch[62]	Meditec (800 mJ/cm^2)	74	1–3-μm PTK at epithelial defect sites 30–40-μm PTK at marginal epithelium	21.1	55 (74%)	—
Fagerholm[34]	Summit	37	Epithelial debridement and 3-μm PTK	11.8	31 (84%)	37 (100%)
Holzer[63]	Schwind	25	Epithelial debridement and 18.82-μm PTK	15.5	20 (80%)	1 (84%)
Chow[64]	Schwind	13	Epithelial debridement and 4.6-μm PTK	49.5	11 (84.6%)	
Forster[65]	Summit	9	Epithelial debridement and 3–4-μm PTK	6.0	8 (89%)	—
Rapuano[66,67]	VISX	3	—	9.0	3 (100%)	—
John[68]	Summit	2	Epithelial debridement and 3–4-μm PTK			—
Sher[33]	Taunton	1	Epithelial debridement and 30-μm PTK (simultaneous corneal scar removal)	10.0	1 (100%)	—
Hersh[51]	Summit	1	Epithelial debridement and 3.8-μm PTK	4.0	1 (100%)	—

Modified from Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Kim and co-workers evaluated the use of multifocal PTK for the treatment of indolent and persistent epithelial defect (PED) in 15 eyes. Ablation was performed along the sites surrounding the epithelial defect until a smooth corneal ablative bed was achieved. The ablation depth was less than 45 μm at each site to prevent going beyond Bowman's membrane. Re-epithelialization occurred in 13 eyes within 7 days. It required 11 and 12 days in 2 eyes. One case developed an epithelial defect in a different site on the cornea 3 months after surgery and was subsequently retreated.[15] Successful retreatment with PTK has been employed for patients with persistent macroerosions who have failed primary phototherapeutic keratectomy.[16]

BULLOUS KERATOPATHY

Two studies have evaluated the role of PTK in bullous keratopathy (BK). Maini and co-workers[17] studied the efficacy of PTK for pain relief for patients with painful BK and poor visual potential. Lin and co-workers[18] evaluated the therapeutic effects of PTK combined with therapeutic contact lens for painful recurrent corneal erosions secondary to BK not suitable for penetrating keratoplasty. Both studies concluded that PTK can be a useful therapeutic measure in painful BK. Deep PTK appears to be more successful in pain management than superficial treatment.

CORNEAL DYSTROPHIES

Corneal dystrophies are a group of hereditary disorders that affect the central part of both corneas and are not associated with inflammation or systemic disease. Typically, the disorders show autosomal dominant inheritance with variable expressivity, early onset (present in the first few decades of life), and either stationary or slow progression. Corneal dystrophies may involve any of the five layers of the cornea. Phototherapeutic keratectomy is most effective for superficial corneal dystrophies that involve the epithelium, the epithelial basement membrane, and Bowman's layer. For these conditions, PTK may obviate the need for conventional invasive surgery such as lamellar and penetrating keratoplasty. Such traditional surgeries may be necessary in cases of deep stromal dystrophies, however, for which PTK is less effective.[19,20]

Dystrophies of the epithelium and basement membrane: Superficial corneal lesions of the epithelium and epithelial basement membrane include juvenile hereditary epithelial (Meesmann's) dystrophy and map-dot-fingerprint (Cogan's) dystrophy. Phototherapeutic keratectomy ablation to a depth of 3–4 μm has been shown to be an effective treatment for these conditions.[19] Although a high success rate for PTK has been reported in the management of superficial corneal dystrophies, PTK is usually unnecessary.[9–12,21] Most often, the decreased visual acuity accompanying these dystrophies is the result of an irregular epithelium over the pupil. Because corneal scraping should be sufficient to remove the irregular epithelium, PTK should be reserved for recalcitrant eyes.[12,19]

Reis–Bücklers' dystrophy of Bowman's layer: First defined by Reis in 1917,[22] Reis–Bücklers' dystrophy was later described in more detail by Bücklers.[23] Reis–Bücklers' dystrophy is a bilateral disorder with deposits limited to Bowman's layer, leading to episodes of ocular irritation, photophobia, and watering. After the third decade of life the attacks become less frequent, but visual acuity decreases as scar tissue replaces Bowman's layer. The decrease in visual acuity is secondary to both the diffuse, subepithelial opacification and the irregular corneal surface.[19,24]

Although advanced cases of Reis–Bücklers' dystrophy can be treated with lamellar or penetrating keratoplasty, the dystrophy often recurs in the grafts, requiring repeat grafting. However, nine

Table 19.3 Reis–bücklers' dystrophy

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

recently published studies have independently documented the high success rate for PTK in the treatment of Reis–Bücklers' dystrophy (Table 19.3). Typically, laser stromal treatment does not exceed 15–20 μm.[19]

Stromal dystrophies: Although phototherapeutic keratectomy is an excellent treatment for dystrophies of the superficial cornea, it has a lower success rate with the deeper, stromal dystrophies.

Granular dystrophy: Treatment options for late-stage granular dystrophy include lamellar keratectomy or PTK. One problem with transplantation is that recurrences often occur in the grafts, sometimes as early as 1 year after surgery.[25,26] The success rate of PTK for the treatment of granular dystrophy is variable (Table 19.4). Note that recurrent granular dystrophy in a graft is another indication for PTK, and that just as granular dystrophy may recur after a surgical keratectomy, it can also recur after PTK treatment.[27,28]

Macular dystrophy: Macular dystrophy is a bilateral, symmetric autosomal recessive disorder, presenting in the first decade, that results in opacities which can affect stroma, Descemet's membrane, and corneal endothelium. The distribution of opacities thus makes the efficacy of PTK questionable.

Hafner and co-workers investigated the functional and morphological long-term outcome of PTK in macular corneal dystrophy in 10 patients. They concluded that PTK may be a reasonable treatment option in a case of superficially accentuated plaque-like stromal deposits in the central cornea, increasing BSCVA moderately for a limited period of time. Despite possible complications, primary PK still appears to be the definitive therapeutic option for patients with macular corneal dystrophy.[29]

Lattice dystrophy: In the early stages, lattice dystrophy can present as dots and branching lattice lines in the anterior axial stroma or as a diffuse haze in the center of the cornea. Over time, the faint central haze becomes more dense and eventually leads to reduced visual acuity.[19] Recurrent erosions can become a prominent feature.

PTK is a very successful method of treating lattice dystrophy (Table 19.5). As with granular dystrophy, lattice dystrophy often

Table 19.4 Granular dystrophy

Study	Laser	No. Eyes	Phototherapeutic Keratectomy	Follow-up (months)	Success rate (%)	HYPEROPIC SHIFTS Eyes (%)	Range (D)
Rapuano[71]	VISX	9	Transepithelial approach PTK (90–122 μm)	1.8	89		
Rapuano[66,67]	VISX	6	Epithelial debridement/ablation	8.3	83	66	0.62–2.0
Stewart[42]	Technolas	5	Mechanical epithelial debridement	22.3	80		
Orndahl[74]	Summit	4	Fluorescence-guided epithelial ablation PTK (45 μm)	12.0	75	—	Up to 2.0
Stark[4]	VISX	4	PTK standard taper/modified taper	—	75	—	—
Hahn[73]	Summit	2	Hydroxymethylcellulose (1.0%) Mechanical epithelial debridement PTK (40 μm) focal technique	8.3	66	66	Up to 2.0
Sher[33]	Taunton	2	Mechanical epithelial debridement PTK (5 μm) (Combined 'myopic and hyperopic' cut) PTK disciform/elliptical	6.0	0	100	0.3–1.1
Nassaralla[75]	VISX	2	Epithelial debridement/ablation PTK (110 μm) disciform	42.0	100	—	—
Dogru[28]	Nidek	2	transepithelial ablation PTK (120–130 μm)	15	100	50	1.0
Campos[32]	VISX	1	Epithelial debridement PTK (110 μm) disciform	24.0	100	—	—

Modified from Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Table 19.5 Lattice dystrophy

Study	Laser	No. Eyes	Phototherapeutic Keratectomy	Follow-up (months)	Success rate (%)	HYPEROPIC SHIFTS Eyes (%)	Range (D)
Orndahl[74]	Summit VISX	11	Fluorescence-guided epithelial ablation PTK (45 μm)	12	90	—	Up to 2.0
Stark[4]	VISX	11	PTK standard/modified taper	—	90	—	—
Stewart[42]	Technolas	5	Mechanical epithelial debridement PTK (7–137 μm)	22.3	100		
Rapuano[71]	VISX	5	Transepithelial approach PTK (84–130 μm)	1.8	80		
Campos[32]	VISX	2	Mechanical epithelial debridement PTK (100–110 μm); disciform	10	100	100	3.0–8.2
Nassaralla[75]	VISX	2	Epithelial debridement/ablation PTK (125 μm)	53.5	100	50	8.0
Hersh[51]	Summit	1	Hydroxymethylcellulose (1.0%) Epithelial debridement/ablation PTK smoothing technique	4	100	0	—

Modified from Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

recurs after corneal transplantation. Fortunately, PTK can be particularly valuable in patients who have recurrent lattice dystrophy in the graft because these recurrences tend to be relatively superficial.

Schnyder's dystrophy: Central crystalline dystrophy of Schnyder is characterized by bilateral central corneal opacities that generally occur in early life, sometimes as early as 2 months of age. A slowly progressive autosomal dominant disease, Schnyder's dystrophy may often go unnoticed, but it may cause a moderate reduction of visual acuity. The yellow-white opacity of Schnyder's dystrophy primarily involves Bowman's layer and the anterior stroma; frequently, it extends into the deeper layers. The epithelium and intervening stroma are usually clear, but punctate white opacities may be scattered in the stroma.[19]

In cases of decreased visual acuity, PTK can be used to remove the central opacities only if they are superficial.[30] There have been very few reports of eyes with Schnyder's dystrophy that have been treated with PTK (see Table 19.1). In instances when PTK fails to improve the vision, penetrating or lamellar keratoplasty can be performed.

CORNEAL SCARS

Phototherapeutic keratectomy treatment of corneal scars that are limited to the superficial stroma produces significant improvement of visual function.[4,12] Visual improvement after phototherapeutic keratectomy of deeper corneal scars is less likely to occur for the following reasons: (1) the scar may ablate at a different rate than the adjacent normal stroma and (2) this irregular ablation, along with the presence of calcified or cartilaginous tissue, may result in postoperative irregular astigmatism.[21]

Post-traumatic scars: Although there has not been a large cohort of reported cases of post-traumatic scars that have been treated with PTK, some investigators have described the results of such treatment (Table 19.6). In general, PTK should be avoided if the scar is of full thickness, but may be attempted if the scar is superficial.

Postinfectious and postherpetic scars: Although most investigators agree that PTK should not be used in the treatment of active infectious keratitis (see later discussion), there is still some controversy over the success of PTK in treating postinfectious scars. Perhaps the controversy stems from the variable success rate in PTK treatment of postinfectious and postherpetic scars (Table 19.7). Migden and co-workers[31] reported significant visual improvement in none of the five postinfectious eyes at 3 months follow-up after treatment with PTK. Campos and co-workers[32] found significant improvement in two of six eyes with postinfectious scars.

Some investigators have attempted to use PTK to treat both postinfectious scars and postherpetic scars. Sher and co-workers[33] reported significant visual improvement in three of five eyes with postinfectious scars, but in only one of four eyes with scars resulting from herpes simplex virus (HSV) infection. Fagerholm and co-workers[34] reported a 73% success rate (22 of 30 eyes) with scars secondary to infection, and an 80% success rate (12 of 15 eyes) with scars secondary to HSV infection. Eyes with scars from HSV keratitis are at risk for recurrence of HSV keratitis after PTK.[35] It is still unknown, however, whether PTK increases the incidence of recurrences of HSV or whether patients would experience the same frequency of recurrences without PTK treatment.[34] Nonetheless, with the variable success rates for postherpetic scars, many investigators believe that the risk of recurrence in herpetic disease outweighs the potential benefits of treating herpetic scars with phototherapeutic keratectomy, unless the alternative is penetrating keratoplasty.[4,32,35,36]

Postpterygium scars: After pterygium surgery, superficial corneal scars may remain on the eye, occasionally causing irregular astigmatism and opacification. Because the postpterygium scars are usually superficial, PTK is often a successful treatment (Table 19.8). Using PTK during the primary surgical excision of the pterygium may be more complicated because of the presence of corneal swelling and intraoperative bleeding. Walkow and co-workers investigated the long-term functional results of the combination of PTK and local mitomycin C therapy after bare sclera technique pterygium excision. They found that this technique led to improvements in visual acuity, low recurrence rate, and minimal complications.[37]

CORNEAL IRREGULARITIES

Band keratopathy: Band keratopathy is a degenerative condition characterized by the gradual development of a gray-white opacity of the superficial cornea. Calcium is deposited in the basement membrane, Bowman's layer, and anterior stromal lamellae. When the pathologic condition extends over the visual axis, patients may complain of glare and decreased visual acuity. In addition, considerable ocular irritation and discomfort arises if the epithelial surface is breached.[38]

Treatment of primary band keratopathy typically involves removing the opaque calcium deposits by manual debridement combined

Table 19.6 Post-traumatic scar

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Please refer to the printed book.

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Table 19.7 Postinfectious scars and postherpetic scars

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Please refer to the printed book.

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Table 19.8 Post-pterygium scar

Rights were not granted to include this data in electronic media.
Please refer to the printed book.

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

with a chelating agent such as ethylenediaminetetraacetic acid (EDTA).[4,32,33,36,39] Some investigators have attempted to treat band keratopathy with PTK (Table 19.9). O'Brart and co-workers[40] report a high success rate of 91% in treating band keratopathy (113 of 122 eyes improved after PTK). Others have had less positive results. Maloney and co-workers[12] performed PTK on 21 eyes with band keratopathy and recorded a mean improvement in vision of only 0.1 line. Stewart and co-worker[41] found that BCSVA was improved or unchanged in 18/33 eyes (55%), while there was loss of one or more lines of acuity in 15/33 (45%). They suggested that these poor results are the result of coexisting ocular disease, which often accompanies calcific band keratopathy. Sher and co-workers[33] and Campos and co-workers[32] also had little success with PTK for the treatment of band keratopathy. One possible reason for the poor results is that calcium does not ablate at the same rate as corneal stroma. Because of this difference, there is a high risk of obtaining a severely irregular corneal surface after treatment with PTK. Thus, it is best to remove the superficial calcium first with a calcium chelating agent such as EDTA and later, if necessary, PTK can be used to treat any residual corneal opacification.[36,42]

SALZMANN'S NODULAR DEGENERATION

Salzmann's nodular degeneration is characterized by degeneration of the superficial cornea. In Salzmann's degeneration, the combination of corneal nodules, corneal surface irregularities, and

Table 19.9 Band keratopathy

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

Table 19.10 Salzmann's nodular degeneration

From Azar DT, Jain S, Stark W. Phototherapeutic keratectomy. In: Azar DT, ed. Refractive Surgery. Connecticut: Appleton and Lange; 1996.

associated refractive error may lead to visual impairment. The preferred treatment is mechanical debridement. However, if this cannot be achieved or if there are remaining opacities or elevations after the superficial corneal debridement, then laser treatment can be useful. By filling in depressed areas so that nearby elevated areas can be treated further, masking agents are useful in creating a smooth corneal surface.[43]

When the pathologic condition secondary to Salzmann's nodular degeneration involves the anterior one-third of the cornea, PTK is generally effective in establishing a uniform, smooth surface and in removing opacities causing optical degradation, while minimizing any induced refractive change.[44] Elevated corneal opacities, such as Salzmann's nodular degeneration, often have good results after treatment with PTK (Table 19.10), but the condition may recur.[12]

Corneo-conjunctival carcinoma

Spadea and co-workers[45] evaluated the use of PTK in the treatment of recurrent intraepithelial corneo-conjunctival carcinoma. They found that PTK was very effective in destroying dysplastic superficial corneo-conjunctival cells, preventing a recurrence of the tumor and resulting in a clear cornea, normal corneal topography, and visual acuity of 20/20 with correction. The laser ablation was very superficial and the Bowman's layer only partially ablated. They concluded that PTK could be considered a minimally invasive, effective, and safe treatment for recurrent corneal in situ carcinoma.

CONTRAINDICATIONS

HYPEROPIA

Phototherapeutic keratectomy can create a significant hyperopic shift as a result of associated corneal flattening. Four potential mechanisms for the hyperopic shift include: (1) greater degrees of epithelial hyperplasia and tear film thickness at the edge of ablation; (2) greater ablation in the center of the area of the corneal pathologic condition thins progressively toward the visual axis; (3) increased shielding of the stroma toward the edge of the ablated zone by the ablation products (plume); and (4) the oblique angle of incident radiation falls on the more peripheral cornea, causing a decreased peripheral ablation.[21,46,47]

One may attempt to minimize undesired hyperopic shifts through careful planning before surgery and through periodic slit-lamp examination during the procedure.[38] In addition, the use of appropriate masking agents may minimize the hyperopic shift.[21] Other strategies for minimizing hyperopic shifts include Stark's modified taper technique[4] or Sher's method of using the laser system to cut a secondary hyperopic correction ('combined' ablation).[21,33] However, in patients who already have a considerable degree of hyperopia, it may be best to avoid PTK.

CORNEAL THICKNESS

As noted later, when PTK treatment leaves a thin cornea, laser-induced scarring may significantly limit visual improvement and corneal instability may ensue. One may choose to exclude eyes with central corneal thickness less than 400 µm or an opacity deeper than the anterior 100 µm of the corneal stroma.[12] Typically, eyes with a predicted postoperative corneal thickness less than 250 µm are less likely to have good results from PTK, and this may also be used as a criteria for exclusion from treatment.[39]

OTHER OCULAR AND SYSTEMIC CONTRAINDICATIONS

It has been suggested that scarring resulting from adenoviral epidemic keratoconjunctivitis should only be treated after the keratitis has been quiescent. At this time, the eye should be treated as gently and lightly as possible because continued corneal remodeling and possible antigen–antibody reaction reactivation may cause new scarring.[48] Uncontrolled uveitis, severe blepharitis, and lagophthalmos are also contraindications to PTK under many protocols. Systemic contraindications to phototherapeutic keratectomy include immunosuppression, collagen vascular disorders, and other problems that affect healing.

RELATIVE CONTRAINDICATIONS

INFECTIOUS KERATITIS

There are a variety of reasons why the treatment of active infectious keratitis has been discouraged. First, one must be concerned with the potential dissemination of microorganisms during or after PTK treatment. Second, stromal involvement in most corneal infections extends deeper than the clinically visible lesion; PTK would not be effective in treating mid- or deep stromal infiltrates because tissue penetration depth of 193-nm radiation is 1 µm at most.[43] Lin and co-workers,[49] however, showed different results. They evaluated the efficacy of using PTK in the treatment of superficial keratomycosis in nine patients and concluded that PTK can shorten treatment time, hasten re-epithelialization, and restore reasonably good vision. PTK can be a valuable therapeutic alternative for superficial keratomycosis, especially in instances where there is poor response to treatment by topical antifungal agents alone.

LONG-STANDING POST-TRAUMATIC AND DEEP STROMAL SCARS

Although the success rate of PTK treatment of post-traumatic scars averages approximately 60%, PTK has been less successful in the treatment of post-traumatic scars in the superficial stroma that are long standing. These scars may prove resistant to ablation.[50] The use of surface-modulating agents or the 'smoothing' technique may make it easier to ablate these scars. The smoothing technique involves gently rotating the head under the laser beam to blend the edges of the irregularities. In addition, further irregularities can be avoided by maintaining the corneal surface meticulously clear of debris and cellular remnants. Deep corneal scars should not be treated with PTK because of the untoward effects of corneal thinning that may result from such treatments.

BAND KERATOPATHY

As noted above, the standard treatment for the removal of band keratopathy is debridement with a chelating agent such as EDTA combined with manual debridement. Although some investigators have experienced success in treating band keratopathy with PTK alone, one should use caution. First, patients with band keratopathy often have coexisting ocular disease. Band keratopathy is often associated with juvenile rheumatoid arthritis, and it has been described in long-standing inflammatory conditions of the eye. Second, because calcium does not ablate at the same rate as corneal stroma, PTK can create an irregular corneal surface when used to treat band keratopathy. As previously discussed, if one uses PTK to treat band keratopathy, it is best to apply EDTA on the eye first to remove the superficial calcium.[27]

RECURRENT EROSIONS

As noted above, PTK has a success rate of 77% in the treatment of recurrent corneal erosions. One hypothesis for this high success rate is that by smoothing the subepithelial corneal surface, PTK creates a substrate conducive to epithelial migration and adhesion.[51] Although PTK is useful for recalcitrant recurrent epithelial erosions, conservative methods should continue to be the first line of treatment because most patients with recurrent corneal erosions experience relief of symptoms with such methods. Current treatments include manual epithelial debridement, anterior stromal puncture, and bandage contact lenses.

PREOPERATIVE EVALUATION

The preoperative evaluation should include a thorough history of systemic and ocular problems so that patients with contraindications to the procedure are identified. A complete preoperative exam should also include best spectacle-corrected and -uncorrected Snellen acuity. In addition, best spectacle-corrected acuity should be compared with the visual potential, which may be evaluated with a pinhole, hard contact lens, and potential acuity meter. One should

also perform intraocular pressure measurements, manifest refraction, keratometry, dilated fundus examination, a visual fields test, and a test of extraocular movements. A slit-lamp microscopy examination is necessary to determine the type, depth, and extent of the corneal pathologic condition. To devise the best treatment plan, it is important to determine the type of pathologic condition before surgery. For example, disorders such as Salzmann's nodular degeneration can usually be scraped mechanically off Bowman's layer before determining if excimer laser therapy is then necessary to remove residual nodules and smooth the surface. The depth of the corneal pathologic condition is important to determine in a preoperative evaluation because the best candidates for excimer laser PTK are those whose pathologic condition is limited to the anterior 20% of the cornea. Candidates with very deep corneal damage are less likely to benefit from PTK. Finally, optical pachymetry or ultrasonic biomicroscopy can be used to measure the depth of the intended treatment.

To ensure optimal performance, the excimer laser must be finely tuned and calibrated before each treatment. Because the excimer laser beam is not adjusted during surgery, its overall operation must be confirmed before surgery by ablating a standard treatment into a calibration plate test block made of a material such as polymethylmethacrylate (PMMA). Using nomograms, the exact corneal ablation rate is calculated and entered into the laser computer program. The plane of the corneal surface is measured before treatment by focusing the microscope at high magnification. This step is important because a suboptimal outcome may result from poor centration of laser treatment.

WOUND HEALING

THE HEALING RESPONSE

Wound healing after PTK is similar in type and rate to healing after surgical keratectomy. In a review of rabbit corneas that underwent either excimer laser photoablation or lamellar keratectomy, Tuft and co-workers[52] found no quantitative difference in the synthesis of new connective tissue over a wound made by the laser or the lamellar keratectomy. Like the type of healing, the rate of healing is similar for laser and surgical keratectomy. Microscopic observation of monkey corneas showed that re-epithelialization occurred within 24 to 48 h after PTK, or at approximately the same rate of healing recorded in monkeys that underwent surgical keratectomies.[7]

In a recent study of human eyes that underwent PTK, re-epithelialization occurred in 59% of eyes within 1 week, and in 93% of eyes within 2 weeks. The remaining two eyes re-epithelialized completely in 3 and 4 weeks, respectively, after receiving bandage contact lenses.[4] Some studies have noted that a pseudomembrane forms over the ablated zone almost immediately after surgery. This pseudomembrane seals the exposed surface and confers enough stability to serve as a template to help hyperplastic migrating epithelial cells fill in the wound and achieve an orderly and smooth re-epithelialization.[7,53,54]

Although re-epithelialization after PTK typically occurs within the first week, anchorage of the epithelium to the stroma is not achieved until 1 to 3 months later. It takes that amount of time for the adhesion structures of the new epithelium (hemidesmosomes, basal lamina, and anchoring fibrils) to be deposited adequately on the underlying stroma.[5,53] Interestingly, the synthesis of stromal connective tissue does not begin until epithelial cells have regrown over the wound. It is proposed that epithelial cells exert a stimulatory influence on keratocytes during stromal wound healing.[52]

To evaluate the effect of intraoperative mitomycin C (MMC) on corneal light scattering after PTK, Jain and co-workers performed PTK in 24 rabbit eyes followed by application of MMC in different ways and concentrations. Corneal light scattering was measured weekly from 1 to 6 weeks, at 10 weeks, and at 8 and 13 months using a scatterometer which measures back-scattered light from a defined region of the cornea under standardized illumination conditions. They found that controlled application of 0.5 mg/mL MMC in the corneal midperiphery transiently reduces corneal light scattering after excimer keratectomy.[55]

In a recent study, Ayres and co-workers,[56] performed to determine the safety and efficacy of the use of intraoperative MMC during PTK for anterior corneal disease, showed that MMC is safe for intraoperative use during PTK, does not appear to inhibit epithelial healing, and may help prevent recurrent anterior corneal disease.

THE EFFECT OF DEPTH OF ABLATION ON WOUND HEALING

In animal models, it appears that the depth of laser ablation plays a role in the healing process. It is important to know how deeply one can ablate the cornea and still achieve complete remodeling. Tuft and co-workers[52] found that although the processes of epithelial hyperplasia and stromal collagen synthesis work together to restore the original corneal surface contour of shallow wounds in rabbits (15 µm), remodeling of deeper wounds (50 and 75 µm) is incomplete, leaving a residual depression in the surface that persists 6 months after surgery. After performing laser refractive keratectomy on rabbit corneas, Goodman and co-workers[6] also concluded that for ablations less than 50 µm, no scarring, collagen regrowth, or epithelial hyperplasia was observed. Faktorovich and co-workers[57] reported that 100 µm PTK ablation resulted in significantly more corneal scarring than the 15 µm PTK ablation, even though there was no difference in the pattern of TGF and bFGF expression after deep and shallow ablations through immunohistochemical analysis.

In humans undergoing corneal ablations deeper than 50 µm, laser-induced scarring may significantly limit visual improvement. Wu and co-workers[8] report four cases of anterior stromal scarring after PTK ablation to a central depth of 50–113 µm. In these four cases, visual acuity was so poor that a keratoplasty was eventually necessary. The authors studied the changes in the corneas of these four patients at 6 to 15 months after excimer laser PTK ablation, but the cohort was small and a few similarities were found. They did note slightly more scarring in the more central aspect of the ablated areas, and they postulated that this might be the result of the delayed re-epithelialization of the central zones.

Although the US Food and Drug Administration-approved indications allow for ablations of up to 33% of the corneal thickness, deep ablations can cause severe corneal flattening or irregularity, or both. The best results from PTK occur when the pathologic condition is limited to the top 10 to 20% of the corneal stroma.[27]

After PTK, the cornea may develop subepithelial haze for 3 to 6 months after surgery.[52] Haze may be the result of light scattering by 'activated' keratocytes in the wound. Another cause of haze is the deposition of new, irregular collagen fibers.[13,52,54,58] Postoperative treatment with steroids can help decrease the thickness of the subepithelial layer of collagen and the density of subepithelial scarring.[52] How corticosteroids achieve these results is not fully understood. However, the postulated mechanisms of action include the following: steroids reduce DNA synthesis and collagen deposition in activated fibroblasts, and steroids prevent the recruitment

of lymphocytes and macrophages.[59] The benefits of continued steroid use may be outweighed by potential side effects, such as steroid responsiveness.[21]

CONCLUSIONS

Phototherapeutic keratectomy is often an effective alternative to penetrating keratoplasty. It is faster and less expensive than surgery, and it allows one to avoid the risks of surgical complications and of graft rejection. As PTK techniques improve and we advance our understanding of the subtleties of PTK methods and of wound healing, perhaps we will increase the efficacy of PTK and expand the applications of this technique. It is the authors' hope that, in the future, we will also decrease the number of post-PTK complications and diminish the number of cases that are contraindicated for phototherapeutic keratectomy.

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20 Phototherapeutic keratectomy: operative techniques and complications

Timothy B. Cavanaugh

Treatment for anterior corneal pathologic conditions has progressed beyond the standard techniques of superficial keratectomy, lamellar keratoplasty, and penetrating keratoplasty. Mechanical superficial keratectomy usually involves removal of the epithelium and the area affected by the anterior corneal pathologic condition with a surgical microblade such as a no. 64 Beaver blade. Although the blade is a very effective tool for epithelial debridement, removal of subepithelial or anterior stromal lesions in this manner can result in a rough surface with irregular astigmatism that prevents optimal visual acuity. If the media is clear, alternative treatment has traditionally been hard contact lenses, but this is not possible in all patients, especially the elderly. For pathologic surfaces combined with media opacity, lamellar or penetrating keratoplasty have been the treatment of choice. It is well known, however, that keratoplasties can be plagued with both operative and postoperative complications, not to mention asymmetric or irregular astigmatism after keratoplasty, necessitating hard contact lenses.

Given the aforementioned problems with standard surgical techniques, a powerful new procedure to treat anterior corneal disease was developed that provides superior results with less cost, risk, and morbidity. Since the advent of excimer laser phototherapeutic keratectomy (PTK), the excimer laser has been shown not only to remove anterior corneal pathologic material in a precise, controlled fashion, but also to leave behind a remarkably smooth stromal surface. It is the smoothness of the stromal surface that enhances corneal clarity and promotes uniform re-epithelialization with reformation of basement membrane complexes, even in the absence of Bowman's layer.[1–3] The PTK-treated stromal surface not only can prevent corneal erosion, but also yields the quality refractive surface necessary for good visual acuity.[4–7] The excimer laser is the best corneal polishing tool that has been developed to date. The diamond burr is sometimes used to polish the corneal surface after blade mechanical keratectomy, but the smoothness of the resultant surface is clearly inferior to the surface achieved with excimer PTK.[8] Phototherapeutic keratectomy has a distinct advantage over mechanical superficial keratectomy in that topically applied masking agents may be used during broad-beam laser ablation in PTK to provide a smoothing effect in the pathologic area.[4,5]

BACKGROUND

In the USA in 1988, investigational clinical trials of PTK involving humans began under the close guidance of the US Food and Drug Administration (FDA) and two laser manufacturers, Summit Technology, Inc. (Waltham, MA) and VISX (Sunnyvale, CA). The author's research site was involved in the Summit study, which consisted of 13 centers across the country with a total of 249 eyes treated by PTK during the entire clinical trial. All patients were over 21 years of age and were categorized into one of the three treatment groups: corneal scars, irregular astigmatism, and recurrent corneal erosion. The VISX study consisted of 17 investigational sites, with a total of 271 patients treated. The VISX study included four categories of patients: corneal opacities, irregular corneal surface, superficial infectious keratitis resistant to medical therapy, and postsurgical refractive abnormalities. The clinical trial successfully proved the efficacy and safety of PTK with both machines; thus, the procedure gained FDA approval for the Summit laser in the spring of 1995 and for the VISX laser later the same year.

Phototherapeutic keratectomy has an uncanny ability to rid the anterior cornea of pathologic material in a relatively noninvasive manner with low attendant surgical risk to the patient. Many of the potential PTK candidates would have been forced to consider either lamellar or penetrating keratoplasty before the advent of this exciting new laser technology. There are nearly 32 000 corneal transplants performed in the USA each year, and converting a fraction of eligible patients to PTK achieves significant savings in cost to patients and payers, not to mention greatly reduced surgical risk and potential morbidity. Furthermore, failure of PTK to provide adequate visual recovery does not preclude the possibility of keratoplasty at a later date.

PATIENT SELECTION

Consistent success in PTK depends on careful patient selection (see Ch. 19 for indications and contraindications). Even state-of-the-art laser technology is prone to complications if the operation is performed incorrectly or on a poor surgical candidate. Candidates for

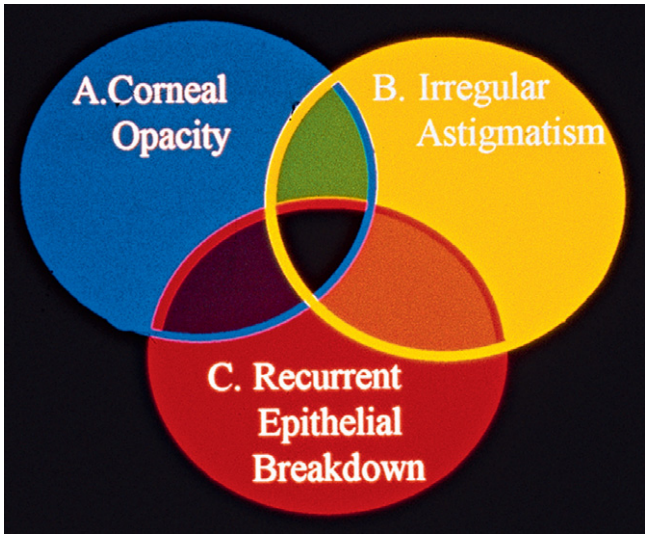


Figure 20.1. Diagram depicting overlap of indications for phototherapeutic keratectomy.

BOX 20.1 IDEAL PATIENT CRITERIA FOR PHOTOTHERAPEUTIC KERATECTOMY

- Significant visual compromise
- Pathologic condition in anterior third of cornea
- Elevated or flat opacity
- Myopic
- Under consideration for corneal transplant
- Realistic patient expectations for surgical outcome
- Quiet, uninflamed eye
- Recurrent erosion that has failed medical therapy

PTK fall into three general categories: corneal opacities, irregular astigmatism, and recurrent corneal erosion. Overlap between two or three categories in a single patient is not uncommon (Fig. 20.1). The ideal condition for PTK is an elevated anterior corneal opacity in proximity to the visual axis, which causes decreased visual acuity and irregular astigmatism in a myopic eye (Box 20.1).[4]

Special caution should be exercised when considering treatment of herpetic corneal scars with PTK[9] (Box 20.2). Often herpes simplex virus (HSV) scars are flat or depressed and associated with tissue loss that makes treatment difficult and can leave the patient with significant residual irregular astigmatism, large hyperopic shifts, or both. In addition, reactivation of HSV keratitis has been reported after PTK, and such patients must be well informed about the potential risks.[10,11] The author's recommendation is to pretreat HSV patients with oral antiviral agents (acyclovir 400–800 mg five times daily or famciclovir 500 mg thrice daily) for 2–4 weeks before surgery and for 4–12 weeks after surgery on a tapering dose. This regimen is similar to what the author uses in penetrating keratoplasties on HSV patients and to date no HSV recurrences with PTK have been seen using this methor.

INDICATIONS FOR PHOTOTHERAPEUTIC KERATECTOMY

Patients undergoing PTK typically fall into one of three categories. There are a wide variety of causes of corneal opacities and irregular surfaces that are amenable to treatment using PTK (Box 20.3). The list is self-explanatory, but one must remember to consider the patient selection criteria and various surgical techniques along with these indications to maximize positive results.[12–24] Although some of the listed dystrophies are stromal, PTK can fully treat the anterior varieties and partially treat those that extend deeper into the stroma by smoothing the corneal surface and lightening the amount of opacification.

Painful recurrent corneal erosion or nonhealing epithelial defects have traditionally been treatment challenges and a source of considerable distress to patients. Excimer PTK has a definite role in treating a variety of epithelial adherence problems (Box 20.4). Although the mechanism for the re-establishment of epithelial basement membrane complexes with PTK is poorly understood, its remarkable effectiveness in treating recurrent corneal erosion syndrome recalcitrant to medical and standard surgical therapies has been well documented.[1,2,25–30] Candidates with corneal erosion should try (and fail) medical therapy with lubricants, hyperosmotics, and bandage contact lenses, as well as surgical adjuncts such as epithelial debridement, before considering PTK. Some surgeons advocate the use of stromal micropuncture or diamond burr superficial keratectomy first, but it is the author's bias that PTK is superior to both.

BOX 20.2 RELATIVE CONTRAINDICATIONS FOR PHOTOTHERAPEUTIC KERATECTOMY

- Pathologic condition deeper than one-third of depth
- Tissue loss or depressed opacity
- Thin preoperative cornea
- Active ocular inflammation, i.e. uveitis
- Hyperopic refractive error
- Severe blepharitis
- Lagophthalmos or poorly controlled dry eye
- Collagen vascular diseases, i.e. rheumatoid arthritis
- Immunosuppression
- Unrealistic expectations for surgical outcome
- Herpes simplex keratitis

BOX 20.3 INDICATIONS FOR PHOTOTHERAPEUTIC KERATECTOMY: CORNEAL OPACITY AND IRREGULAR ASTIGMATISM GROUP

- Anterior corneal dystrophies[12]
- Anterior membrane dystrophy
- Reis-Bückler's dystrophy[13,14]
- Lattice dystrophy
- Granular dystrophy
- Macular dystrophy[15]
- Schnyder's crystalline dystrophy
- Meesmann's dystrophy
- Recurrent dystrophies after keratoplasty[16]
- Anterior corneal scars, postinfectious or post-traumatic[17,18]
- Salzmann's nodular degeneration[19]
- Band keratopathy
- Postpterygium scars
- Keratoconus apical scars[20,21]
- Shield ulcers and corneal plaques in vernal keratoconjunctivitis[22]
- Recurrent corneal intraepithelial dysplasia[23]
- Infectious crystalline keratopathy[24]

BOX 20.4 INDICATIONS FOR PHOTOTHERAPEUTIC KERATECTOMY: CORNEAL EROSION AND PERSISTENT EPITHELIAL DEFECT GROUP

- Recurrent erosion syndrome secondary to basement membrane dystrophy[25–28]
- Traumatic recurrent erosion syndrome
- Idiopathic recurrent erosion syndrome
- Bullous keratopathy-associated recurrent erosion[29,30]
- Neurotrophic keratopathy
- Nonhealing epithelial defects after keratoplasty

Little or no scarring results from PTK in contrast to micropuncture, the very mechanism of which depends on the inducement of stromal scars; micropuncture overlying the visual axis in same eyes may be problematic.

The success of PTK in the treatment of long-standing neurotrophic or similar epithelial defects is also a mystery. It is postulated that the laser smoothens the damaged Bowman's membrane or anterior stroma to provide better substrate for epithelial adherence. For these patients, the author strongly recommends the concurrent use of adjunctive therapy with bandage contact lenses or lateral tarsorraphies.

SURGICAL TECHNIQUE

BASIC CONCEPTS

Phototherapeutic keratectomy can be one of the most challenging surgical procedures to perform correctly. PTK has been described as one of the most 'artistic' surgical procedures, with each cornea representing a different 'canvas' on which the surgeon applies the masking agent ('paint') with the laser beam ('brush'). It involves a thorough understanding of each patient's disease process, topography, and refractive needs, as well as the nuances of the excimer beam parameters and techniques. Careful attention should be given to hand position, head movement, epithelial debridement, transepithelial ablation, use of masking agents, and polishing. The excimer computer-controlled software can lull the surgeon into a false sense of security, but, unlike its PRK counterpart, the PTK technique is very surgeon dependent and will vary with the type of corneal pathologic condition.

The initial lasers used in the USA for PTK were manufactured by Summit Technology, VISX, and Chiron Technolas. The techniques for the Summit and VISX lasers were essentially identical in that both used a stationary broad beam of variable diameter with patient head movement to provide the necessary polishing motion. The Technolas laser used a joystick to move the beam, which allowed for more precision when targeting the pathologic areas. The author's initial experience was on the Summit Omnimed, Apex, and Apex Plus excimer lasers, and the description of the surgical technique reflects the suggested technique for these machines. In addition, the procedure described is the author's bias, and it should be noted that technique can vary between surgeons and also between laser systems.

PREOPERATIVE EVALUATION

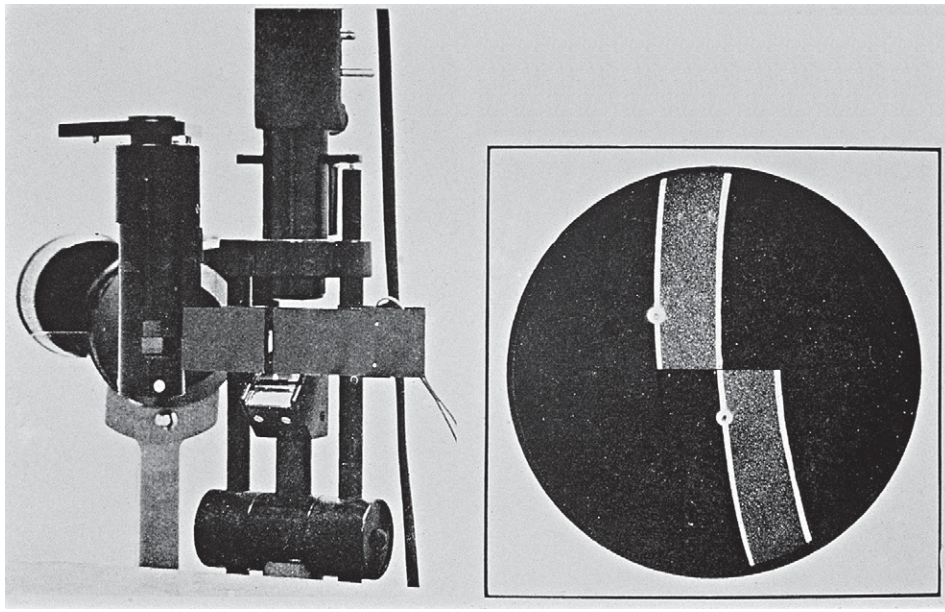
Preoperative evaluations should be performed no longer than 90 days before surgery. Visual acuity with and without correction, phoropter refraction, intraocular pressure, careful slit-lamp examination, and dilated fundus examination should all be performed. Irregular astigmatism and surface profile should be evaluated by keratometry, corneoscopy, computerized corneal topography, or a combination thereof. Standard keratometry is often suboptimal because of the limited surface area evaluated; placido disc-type evaluations are generally superior in finding distortion in the central two or three mires. Although corneal topography provides the greatest amount of detail, the color maps can sometimes be overinterpreted by the computer's smoothing software and can be potentially misleading to the surgeon. Because of this, the author always recommends comparison of the color map with the clinical appearance and the placido disc image for surgical planning. The degree of irregular astigmatism from corneal epithelial irregularity can be quite striking, with as high as 3 D measured by placido disc topography measurement. Slit-lamp photographs to document preoperative clinical appearance for comparison with postoperative photographs may be indicated.

The potential for improvement in visual acuity from elimination of the irregular astigmatism or paraaxial opacification is estimated by pinhole vision, potential acuity meter, and/or gas-permeable contact lens over-refraction. If the corneal opacity is axial, a gas-permeable contact lens over-refraction may still improve the visual acuity solely from its smoothing effect. Decreased visual acuity from a corneal stromal opacity is measured objectively in comparison with the patient's visual loss tolerance and lifestyle; from this data a risk-benefit assessment is made, as one may do in the case of cataract. Photophobia and glare in the setting of anterior stromal opacity are assessed subjectively by symptoms and objectively by the decreased visual acuity caused by the opacity. Brightness acuity testing can be a useful adjunct to quantify the degree of degradation of visual acuity. Preoperative corneal thickness is measured by ultrasonic pachymetry, and the depth of the pathologic condition can be measured by optical pachymetry (Fig. 20.2, *A* and *B*).[31] Full informed consent outlining potential risks and benefits is obtained. Careful discussion of potential refractive error shifts and the potential need for later corneal transplant is mandatory.

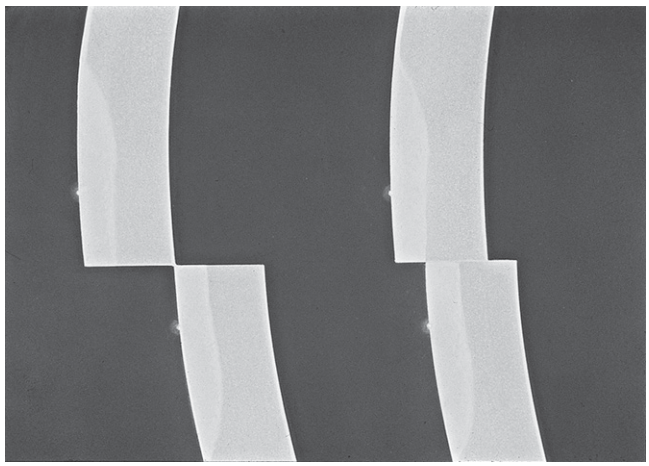
The recurrent erosion patient workup varies only slightly. The use of a cellulose Weck-cel microsurgical sponge at the slit lamp may be extremely helpful in determining the presence of loosely adherent epithelium (Fig. 20.3). The sponge is gently rubbed over areas of suspicion, causing the loosely adherent epithelium to detach and wrinkle into folds while tightly adherent epithelium remains undisturbed. Drawings documenting the exact location of abnormal epithelial adherence should be used as guides during surgery.

LASER PARAMETERS

After the excimer laser is appropriately calibrated, the surgeon should verify that the parameters of fluence, repetition rate, ablation rate, and ablation diameter are appropriate for the desired PTK treatment. The desired fluence and ablation and repetition rates are usually standardized according to the type of excimer laser used and not to the corneal diagnosis necessitating PTK. The ablation diameter may be set or varied throughout the session, according to type, size, depth, and location of the corneal pathologic area. For example, the surgeon may select an ablation diameter of 6 mm, which provides a wide treatment of the entire cornea, for a patient with anterior basement membrane dystrophy with recurrent erosion syndrome. Conversely, for an elevated isolated scar, the surgeon



A



B

Figure 20.2. *A,* Optical pachymeter measuring thickness of normal cornea. (Courtesy of WJ Stark, MD.)
B, View of corneal scar through optical pachymeter and judgment of scar depth.

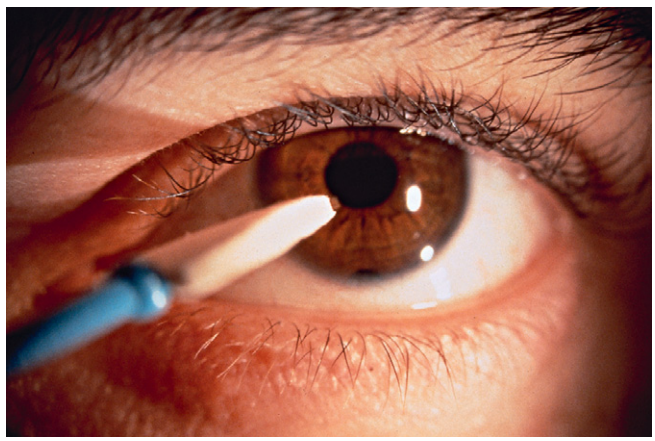
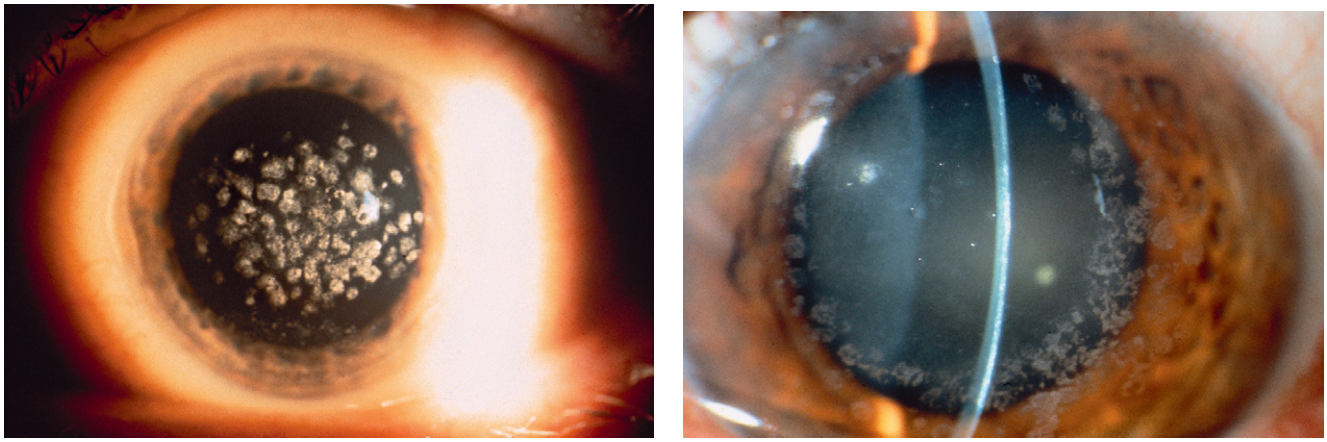


Figure 20.3. Cellulose sponge test used to assess adherence of corneal epithelium in patients with recurrent erosion.

may use successively larger ablation diameters to flatten the elevated peak of the scar. Novice PTK surgeons can make the mistake of using ablation zones that are too small. This is usually performed with the intent of targeting localized pathologic areas but often results in a poor outcome because of rapid ablation and the creation of holes or divots in a cornea with irregular astigmatism. It is far better to use the largest-diameter beam possible to polish while isolating localized pathologic areas with masking agents.

PREOPERATIVE PREPARATION

With good patient education and expectations, preoperative sedation is usually unnecessary. Thirty minutes before surgery, the eye is anesthetized with topical tetracaine, repeated every 10 min. All patients should be examined at the slit lamp immediately before placement in the operative chair so the surgeon has a clear view of the pathologic areas and treatment plan. The patient is then reclined supine in the operative chair and a betadine preparation is applied, followed by a wire-lid speculum. An eye patch is placed over the nonoperative eye to encourage fixation only with the operative eye. The patient is then placed under the laser operating microscope and instructions are given. Visualization and familiarization with the



A B

Figure 20.4. *A,* Preoperative photograph of patient with anterior granular dystrophy. *B,* Postoperative photograph of granular dystrophy patient treated with 'point and shoot' phototherapeutic keratectomy technique. (Courtesy of WJ Stark, MD.)

fixation beam in the laser are achieved, and the patient is instructed to maintain this fixation throughout the procedure. The aiming beam is focused on the central cornea, and the pass-through beams are visualized on either side of the pupil. The snapping sound and smell of the laser are discussed, followed by a trial run of a few sample pulses of the laser. Encourage the patient to relax their shoulders and neck, and explain how you will be moving their head from side to side or around in small circles in a polishing fashion.

EPITHELIUM REMOVAL

Corneal epithelium removal is typically performed with a no. 64 or similar Beaver blade, but a blunt spatula, rotating brush, or alcohol may be used as well. In patients with recurrent erosion, all loose epithelia are first removed with a cellulose sponge. The Merocel sponge (Xomed Surgical Products, Inc., Jacksonville, FL) is preferred because it does not leave any fibers on the corneal surface. The epithelium may come off in incomplete sheets, so debridement should be complete, extending to the level of Bowman's layer. The no. 64 Beaver blade should be used (at an angle of 45° so that the blade scrapes but does not cut corneal tissue) to debride a wider margin, usually resulting in an approximately round corneal epithelial defect measuring about 7–9 mm. The Merocel sponge is then used to remove final epithelial remnants and dry the surface for visual inspection. In treatment of opacities, the edge of epithelial removal should *never* be in the visual axis to prevent a ridge in the line of vision; an additional margin of epithelium is often removed to prevent this.

In some cases, transepithelial ablation with the laser is preferable to mechanical removal. Subepithelial scar tissue should always be removed manually if possible, but in cases of significant surface irregularity caused by anterior stromal lesions, it may be best to ablate directly through corneal epithelium, taking advantage of the uncanny natural smoothing or masking ability of the laser. Determining an endpoint can be very challenging. Transepithelial ablation should be performed in a darkened room with a large-diameter ablation zone. Intact epithelium autofluoresces a light purple hue with laser beam interaction, but this hue changes to a dark purple/black when ablation begins to break through the epithelial layer. Ideally, the breakthrough spots should correspond to the elevated pathologic areas visualized before surgery at the slit lamp. Corneal epithelium and stroma ablate at slightly different rates, so one must be careful to pay special attention to the endpoint when epithelium and stroma are being ablated simultaneously.

MECHANICAL REMOVAL OF PATHOLOGIC AREAS

One of the first mistakes made by early PTK surgeons in the clinical trials was to attempt removal of all pathologic areas with the excimer laser. Although the effect looked quite dramatic, the resultant surfaces were often not as smooth as desired, and excessive laser pulses resulted in thinner postoperative corneas and large hyperopic shifts. This PTK method has been termed the *point and shoot* method and has since been abandoned for more advanced techniques (Fig. 20.4).[5] The current recommended method is the *debride and polish* technique, which has proven quite effective (Fig. 20.5).[5] This technique uses mechanical keratectomy with the no. 64 Beaver blade to remove cleanly a corneal nodule or elevated corneal pathologic areas in which clear cleavage planes exist between it and the stromal lamellae. Surprisingly, dense and large pathologic areas can be removed manually, leaving a smoother underlying surface. Usually this tissue is subepithelial in nature, but occasionally anterior stromal lesions can be cleanly removed also. The excimer laser is then used as a final polishing tool to achieve as pristine a surface as possible (Fig. 20.6). Calcific band keratopathy should always be chelated with disodium ethylenediaminetetraacetic acid (EDTA) and scraped, leaving PTK to treat only the rough underlying exposed stroma. Finally, depressed corneal pathologic areas where there is absence of tissue are not improved with mechanical keratectomy and should be treated with laser only, with strong consideration given to using the transepithelial approach.

LASER ABLATION

Hand position

The surgeon's hands are positioned with the palms covering the patient's ears, the fingers relatively straight and in contact with the patient's cheeks, and the fingertips slightly bent around the angle of the mandible (Fig. 20.7). The surgeon may need to resist bending the fingers too much, as this may increase the patient's discomfort

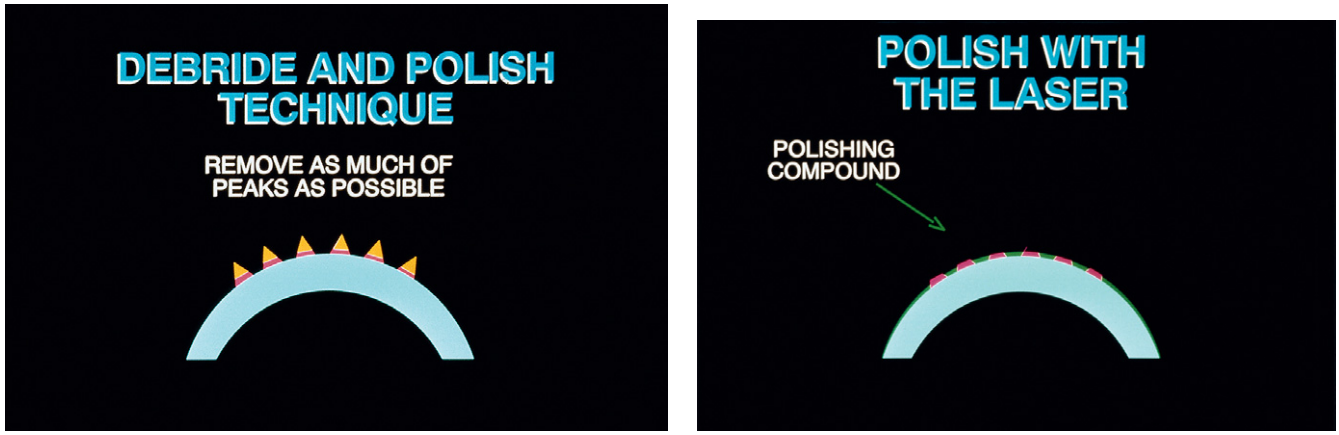


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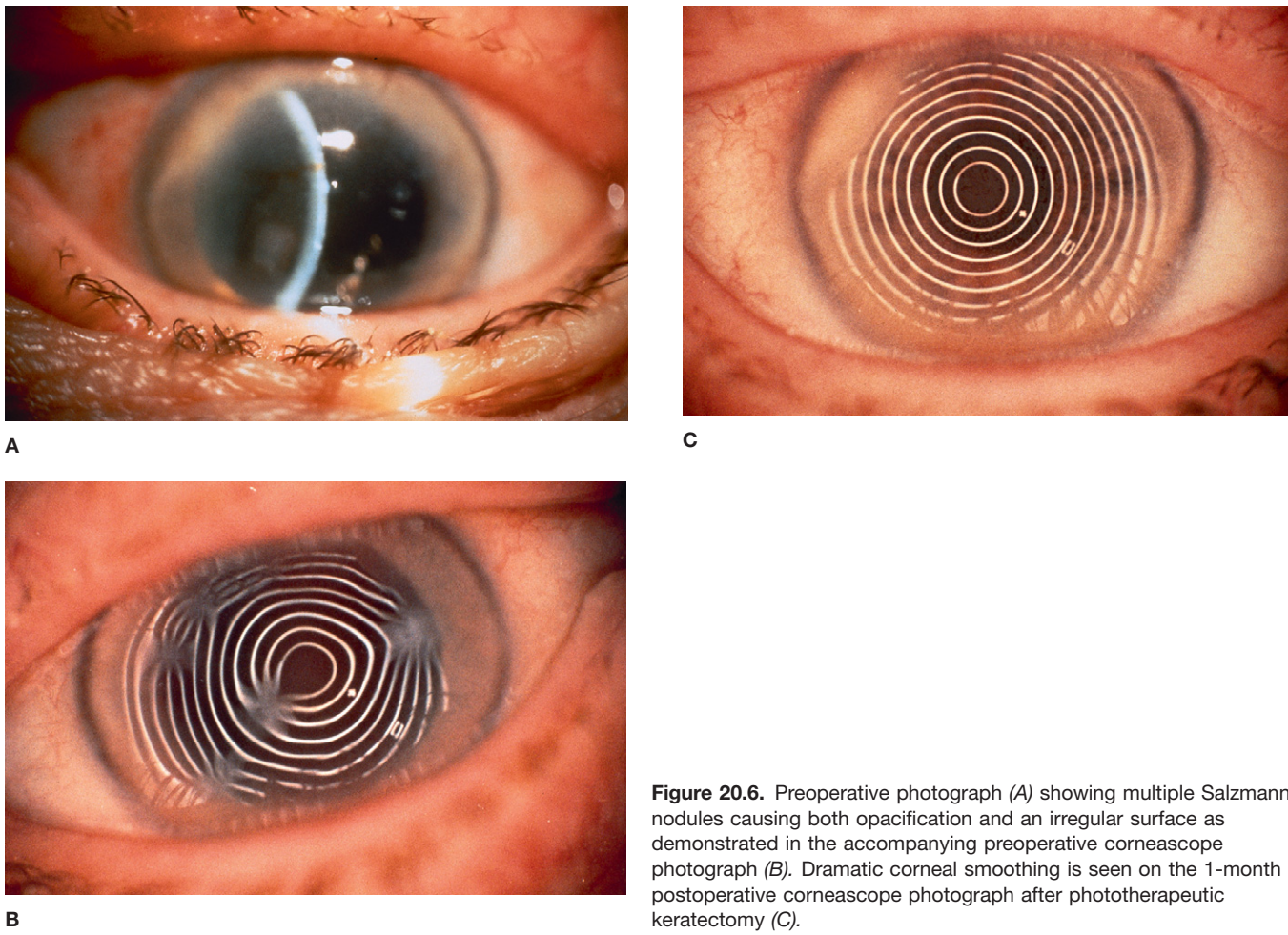
Figure 20.5. *A,* The debride portion of the 'debride and polish' technique involves removal of largely elevated pathologic areas manually with a blade. *B,* The final polish is performed with laser phototherapeutic keratectomy using a masking agent to aid in smoothing.



A C B

Figure 20.6. Preoperative photograph *(A)* showing multiple Salzmann's nodules causing both opacification and an irregular surface as demonstrated in the accompanying preoperative corneascope photograph *(B).* Dramatic corneal smoothing is seen on the 1-month postoperative corneascope photograph after phototherapeutic keratectomy *(C).*

and cause the neck to stiffen. A relaxed grip will facilitate smooth movements of the patient's head.

Head movement

Appropriate movement of the patient's head will facilitate corneal polishing maneuvers with PTK. When head movement is desired, the surgeon should initiate head movement before depressing the foot pedal so that the desired degree of excursion is being attained *before* the photoablating begins. This familiarizes the patient with the concept of circular head movement while maintaining fixation on the green target light in the laser. Practice movement should always be conducted before initiating laser treatment.

Masking agents

In recurrent erosion cases, a masking agent is rarely used and the laser is applied directly to the affected Bowman's layer. For other

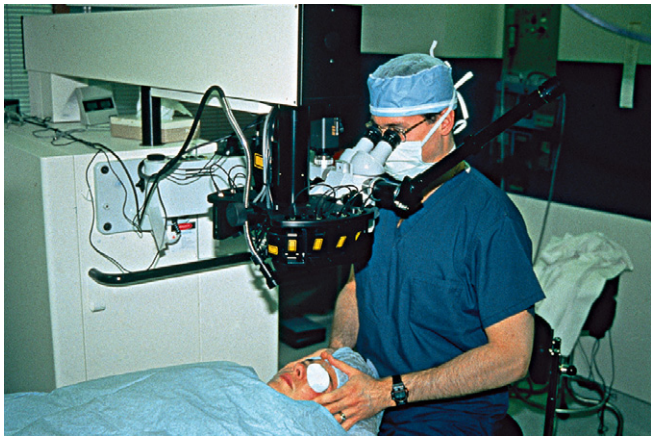


Figure 20.7. Photograph of proper surgeon hand placement for phototherapeutic keratectomy. Note thumbs on forehead and fingers lightly cupped on side of face and curved toward mandible.

cases, after mechanical removal of epithelium and any subepithelial scar tissue, the surgeon should assess the resulting corneal surface. If the surface is relatively smooth, the surgeon may then elect to proceed with PTK without a masking agent. In most cases, however, the resultant surface is sufficiently irregular to warrant further smoothing adjuncts such as masking agents. When an excimer laser beam encounters an irregular corneal surface profile, it will ablate and remove the corneal tissue, but the pattern of the irregularity is preserved and etched into deeper corneal layers (Fig. 20.8).[4] Masking agents are variable viscosity solutions of carboxymethylcellulose or similar substances that may be applied to an irregular corneal surface and act to regularize the 'peaks and valleys', so the excimer laser beam encounters a fairly smooth corneal surface. The masking agent will fill the corneal tissue valleys to the level of the tissue peaks. The excimer beam can then simultaneously ablate the corneal tissue peaks while the valleys are prevented from deepening.[4] The masking agents are typically used after corneal epithelial removal (Fig. 20.9).

Various masking agents tried over the years with varying degrees of success include Tears Natural II (Alcon Laboratories, Inc., Fort Worth, TX),[32] polyvinyl alcohol, 1% hydroxypropyl methylcellu-

A B

Figure 20.8. *A* and *B,* Diagrams demonstrating how the excimer laser will ablate an irregular surface deeper into the tissue without the use of a smoothing agent. Reproduced with permission from Durrie DS, Schumer JD, Cavanaugh TB. Phototherapeutic keratectomy: the Summit experience. In: Salz JJ, McDonnell PJ, McDonald MB, eds. Corneal Laser Surgery. St Louis, 1995, Elsevier. © Elsevier 1995.

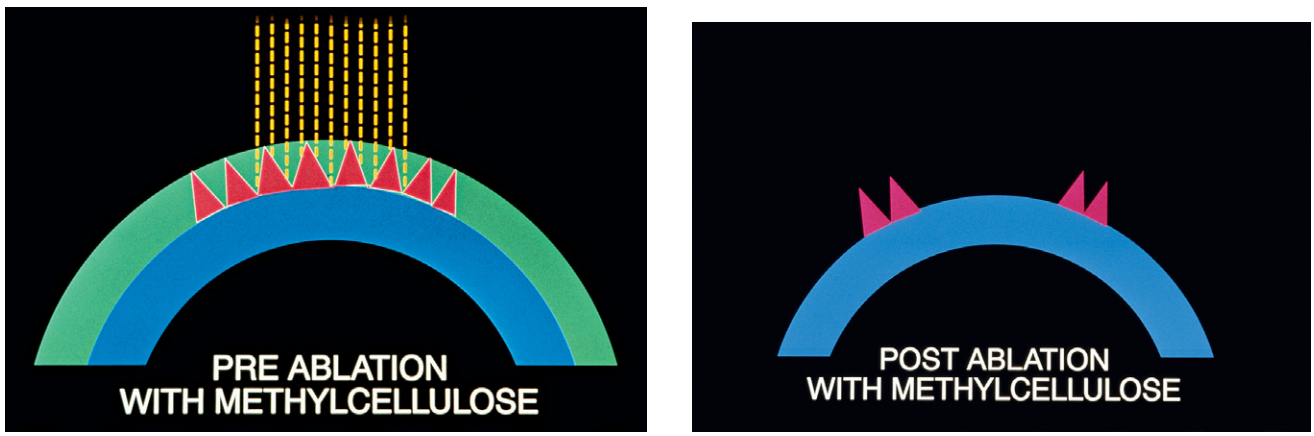


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Figure 20.9. Diagrams demonstrating how a masking agent can dramatically smooth an irregular corneal surface in phototherapeutic keratectomy. Reproduced with permission from Durrie DS, Schumer JD, Cavanaugh TB. Phototherapeutic keratectomy: the Summit experience. In: Salz JJ, McDonnell PJ, McDonald MB, eds. Corneal Laser Surgery. St Louis, 1995, Elsevier. © Elsevier 1995.

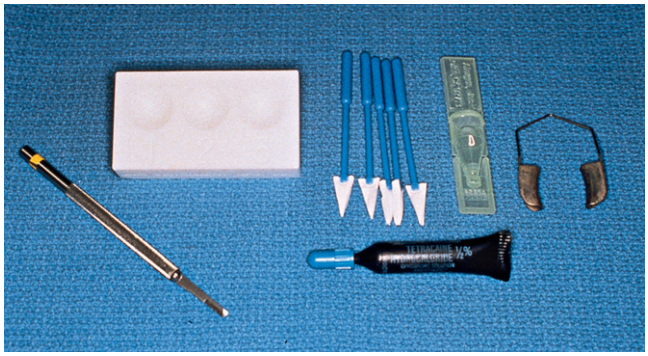

Figure 20.10. Surgical field for phototherapeutic keratectomy with three-well reservoir for different viscosity masking agents, murocel sponges, methylcellulose, wire-lid speculum, no. 64 Beaver blade, and tetracaine.

lose,[33] Healon (AMO, Inc., Santa Ana, CA),[34] carboxymethycellulose, and Unisol.[32] The most common masking agent for PTK procedures is carboxymethylcellulose. A highly viscous agent does not cover uniformly and can become clumped during ablation. A low-viscosity solution tends to run off quickly or be knocked aside by the laser impact, thereby exposing both peaks and valleys.

The author prefers to use different viscosity solutions based on the task at hand. The surgical field has a triple-well container with three different concentrations of carboxymethylcellulose: 1.0% (Celluvisc), 2.0% (Goniosol), and balanced salt solution used to dilute the Celluvisc or Goniosol (Fig. 20.10).[4] A thicker masking agent is used initially to flatten highly elevated peaks. As the treatment continues and the surface becomes progressively smoother, the thinner agents are used. The carboxymethylcellulose 1% solution is the workhorse masking agent, because it is viscous enough to fill the corneal tissue valleys and remain, yet liquid enough to flow relatively easily. The masking agent is applied with a cellulose sponge dipped into the well like a paintbrush; the excess is removed with a dry sponge. As soon as the surgeon is satisfied with the smoothness of the confluent layer of masking agent, PTK commences. Short sessions of PTK ablation are interrupted by wiping the masking agent off and drying the corneal surface for close inspection. The entire process is repeated multiple times using decreasing viscosities until the surface is sufficiently smooth on final inspection. It is impossible to fill every valley and selectively ablate each and every corneal tissue peak, but with successive cycles of masking and photoablating, the opacity diminishes and the stromal tissue becomes more regular. With experience, the PTK surgeon acquires better judgment and 'touch'. For a typical single PTK treatment, the surgeon executes rapid, efficient sequences of masking agent application, cellulose sponge blotting, and excimer laser photoablation. Phototherapeutic keratectomy is an artistic procedure, and deciding how much to mask and which concentrations to use depends on the surgeon's judgment.

Laser treatment

The laser aiming beams should be focused on the cornea before application of masking agents because the viscous fluid sometimes blurs the beam image. The aiming beam should then be focused more anteriorly to compensate for the thickness of the methylcellulose before commencing ablation. The laser is armed with from 25 to 100 pulses, and the optical zone diameter is selected, usually 5–6.5 mm.[4] With a masking agent in place, the author does not recommend applying more than 100 pulses before reassessing the confluency of the methylcellulose layer, the smoothness of the underlying corneal surface, and the need for an additional agent. The PTK pulses are applied while rotating the patient's head in a small circular motion to facilitate a polishing or 'spray painting' technique. The entire area of corneal epithelial debridement is treated with PTK, and the ablating area should overlap the undebrided epithelium by a small amount.

For the patient with corneal surface irregularity, the surgeon must rely on both visual and audible cues, termed the *sight and sound technique*, as PTK progresses.[4] Ablation on the masking agent will turn it blue/white as the excimer laser beam photoablates the carboxymethylcellulose, and this is accompanied by a rapid soft audible ticking sound. When the excimer beam contacts unprotected cornea, the fluorescence is a darker blue/purple and the sound changes to a louder snapping or popping sound. The corneal tissue appears as lakes of white-blue flashes interspersed with dark peaks of exposed corneal tissue. If the photoablation produces an entirely white-blue area without gaps, only the masking agent and no corneal tissue peaks are being photoablated. Ideally, the darker areas will correspond to the areas of elevation that were noted on the preoperative slit-lamp examination, signifying that these areas are successfully, selectively ablated. The force of the beam impact moves the masking agent and changes the sight and sound during ablation. If the patterns seen and heard deviate from what is expected based on the pathologic condition, the ablation should be stopped and the surface reassessed. The first set of pulses with masking agent produces the greatest masking agent flash, the quietest pop, and the least obvious smoothing effect because the corneal tissue peaks are narrow near the apex and the most viscous masking agent is used in the early stages of the operation. As the surface is polished, the less viscous agents applied in smaller amounts result in less flash, louder sound, and more rapid ablation of corneal tissue. Be careful not to induce an irregular corneal surface by ablating through clumped methylcellulose (this occurs if the masking agent is applied too thickly or if the surgeon fails to stop and reassess frequently).

The optical zone diameter can be incrementally increased or decreased by programming the desired value with each set of 25–100 pulses. The choice of optical zone diameter, when to increase it, the number of pulses within a set, and the total number of sets are determined by the surgeon with experience and are part of the art of PTK. Twenty-five to one hundred pulses per set before assessment of effect is a good, conservative benchmark for providing a demonstrable effect and forces frequent assessment of decreased opacification and increased smoothness, while minimizing the tendency to overtreat. After one or two short treatment sessions, the surgeon should consider taking the patient to the slit lamp for a more thorough assessment of the depth of treatment and of the remaining pathologic areas. Phototherapeutic keratectomy can be thought of as multiple small surgeries combined into one session. One should always be cognizant of the total number of pulses given and the depth achieved, because the laser ablates approximately 0.25 μm per pulse. The last set of pulses is usually performed at an optic zone diameter of 6 mm with wide rotational movement for a generalized polishing, nonrefractive effect.

Phototherapeutic keratectomy endpoint

The endpoint of the PTK session itself requires judgment. If the opacity is clear and the cornea is smooth, the session is finished. If the opacity is cleared and the cornea is slightly rough, a final polish with carboxymethylcellulose is often used. It may be impossible to

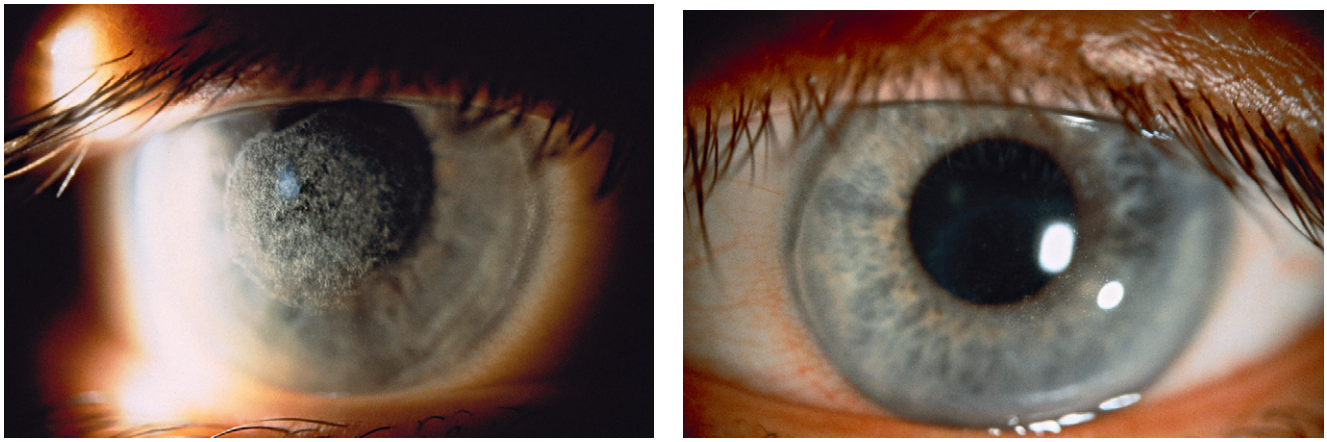

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Figure 20.11. *A,* Significant corneal opacification causing visual loss to 20/80 in this preoperative photograph of a patient with Schnyder crystalline dystrophy. *B,* Significant corneal clearing and improvement in vision to 20/25 in this 1-month postoperative phototherapeutic keratectomy photograph.

completely remove the opacity, but partial removal may be sufficient to improve the visual acuity markedly. Because the hydration state of the cornea is not as critical as with photorefractive keratectomy, the surgeon may move the patient between sessions of PTK to a slit lamp to judge the decrease in the opacity. The same principle applies with regard to titrating the final corneal smoothness; one should perform enough PTK until the best smoothing agent can provide the final uniformity restoration. The principal rule of PTK is that an undertreatment is better than overtreatment, an intuitively obvious concept that is easy to forget when one is actually treating the pathologic condition. An undertreated patient can return for additional treatment. With proper technique, the results can be rather dramatic, as demonstrated by the patient in Figure 20.11. Figure 20.12 demonstrates the smoothing ability of PTK in a patient with a visually significant pericentral corneal scar with severe irregular astigmatism. The application of mitomycin-C in concentrations of 0.02 or 0.002% for varying intervals from 10 to 120 s after the ablation may become a method to help minimize postoperative haze.

POSTOPERATIVE CARE

Simply stated, the postoperative care involves three phases:
1. Managing the epithelial defect and preventing infection;
2. Controlling wound healing to prevent scarring; and
3. Fine tuning refractive error.

The author's postoperative regimen after PTK includes immediate administration of a single drop of topical antibiotic (ofloxacin 0.3% or trimethoprim/polymyxin) and a topical nonsteroidal agent (diclofenac 0.5%). A disposable bandage soft contact lens is placed and the fit confirmed while the patient remains supine. Typically, a loose-fitting lens with a flat base curve (9.1 or 9.3) allows for tightening of the lens with hydration over the next few days. Oral pain medications such as meperidine 50 mg with promethazine 25 mg or Tylenol with codeine can be taken every 4–6 h as needed for pain, and the patient is cautioned to minimize activity.

The patient is seen on postoperative day 1 and every 2–3 days until the epithelial defect heals, at which time the bandage soft contact lens is removed. Recently, the author has removed the bandage lens at day 3 because lens tightening occurs and the relative hypoxia causes discomfort and delays re-epithelialization. Topical antibiotic is given four times daily along with the topical nonsteroidal agent until the epithelial defect heals. Patients are instructed to use diclofenac only as needed for pain because it has been shown to delay epithelialization. In the authors' experience, 70–80% of patients experience re-epithelialization by the third postoperative day, but this varies greatly depending on a host of factors, including the size of the original epithelial defect induced at the time of surgery. For patients with recurrent erosion whose PTK did not extend too deeply, no topical steroid is used because greater than trace reticular healing haze is rare. For patients with scars or deeper treatments, postoperative reticular haze is commonly seen and a course of topical fluorometholone 0.1% is prescribed, starting at four times daily and tapered according to need. Most patients experience complete epithelialization by 1 week after surgery, and the next follow-up should be at 1 month, with further visits at the surgeon's discretion. Final refractions are performed no earlier than the 1-month visit to allow for wound healing, stromal remodeling, changes in epithelial thickness, and astigmatism shifts, which all affect the final refractive result. If a patient has significant healing haze at the 1-month visit, final refraction should be delayed, because this is indicative of ongoing healing activity that will shift the refraction.

SIDE EFFECTS AND COMPLICATIONS

REFRACTIVE SHIFTS

The principal side effect of PTK appears to be a flattening of the central cornea with induced hyperopia of varying degrees.[35] Proper technique, an appropriate use of masking agents, and a conservative surgical mindset can minimize the amount of induced hyperopia. If the patients are well informed about the progression of hyperopia and accept the methods of treatment, such as contact lenses, then hyperopic patients can be good candidates as well. Conversely, excessive ablation of peripheral corneal pathologic areas can result in a myopic shift resulting from relative steepening of the central cornea induced by flattening of the periphery. If the surgeon realizes that undertreatment is better than overtreatment and that the cornea need not be completely clear or smooth on completion of PTK, this complication is alleviated to a large degree.

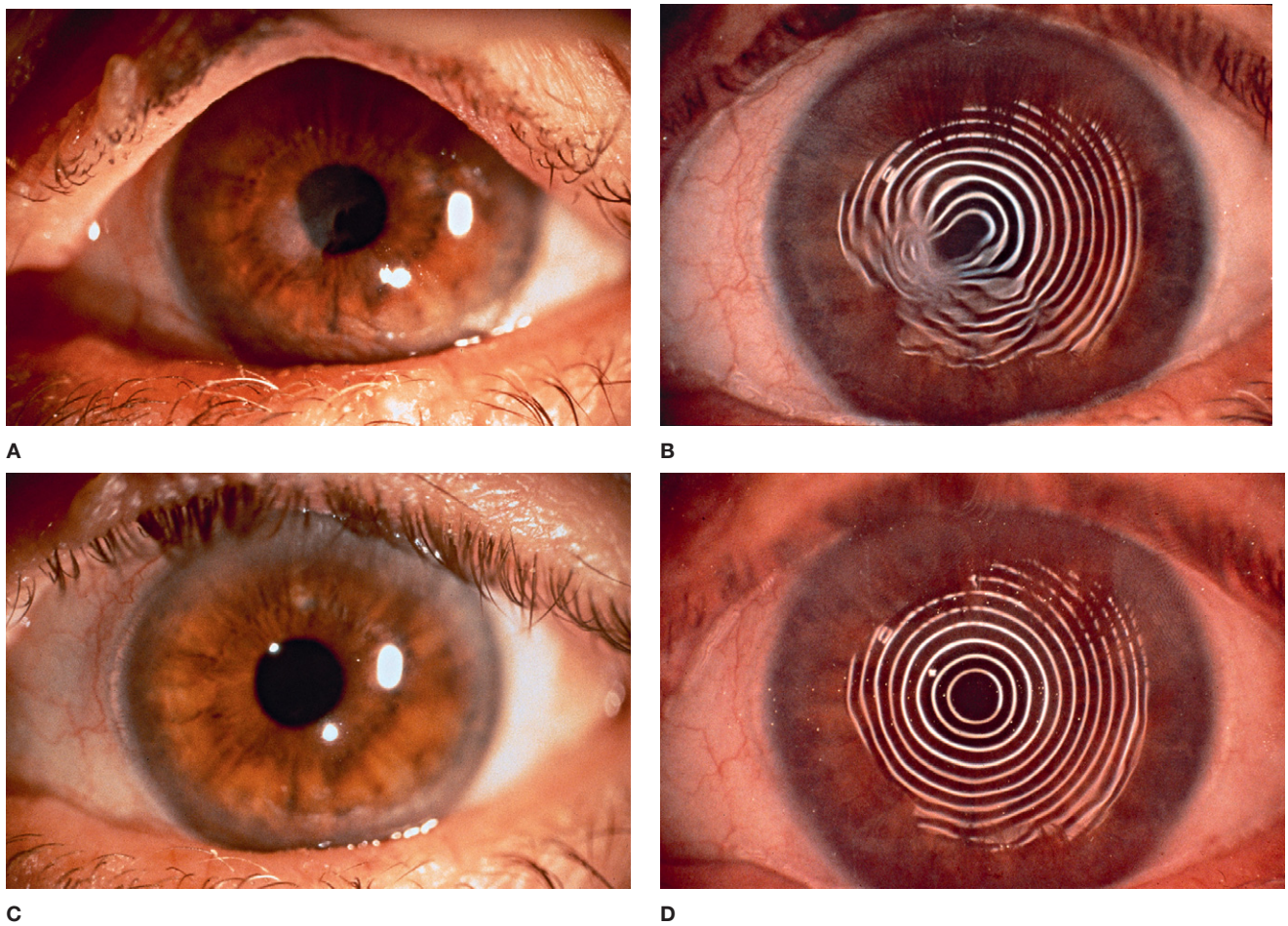

Figure 20.12. *A,* Photograph showing preoperative view of a visually significant pericentral anterior stromal corneal scar with best corrected acuity of 20/200. *B,* Preoperative corneascope shows impressive distortion of the surface profile. After phototherapeutic keratectomy there is dramatic clearing of the opacity *(C)* and improvement in the smoothness of the corneal surface *(D)* with enhanced best corrected vision to 20/30.

PAIN

Postoperative pain may be severe during the first 24–48 h but dissipates rapidly when the epithelium heals. During the clinical trials, only patching and oral pain medications were allowed after surgery; needless to say, postoperative pain was significant. Since PTK approval, good pain control has been achieved with the use of postoperative bandage soft contact lenses, diclofenac 0.5%, and oral meperidine 50 mg with promethazine 25 mg every 4–6 h. Most patients experience only burning and irritation rather than frank pain. Cycloplegics are of questionable value for patients with severe pain after PTK.

DELAYED EPITHELIALIZATION

Although most PTK patients experience complete re-epithelialization between days 3 and 7, delayed wound healing can occur. Chamon and coworkers[36] reported delayed epithelialization requiring 3–4 weeks for complete healing in two patients with morbidity factors such as Salzmann's nodular degeneration and significant alcohol intake. The patients who most commonly experience prolonged re-epithelialization are those with band keratopathy (PTK with mechanical superficial keratectomy and calcium EDTA chelation), severe dry eyes, and Salzmann's nodular degeneration. The routine use of bandage contact lenses has aided epithelialization in most cases, but lens hydration and tightening can occur in the first few postoperative days, which delays healing because of corneal hypoxia. Adjunctive therapy such as a temporary lateral tarsorraphy with or without inferior punctal occlusion (silicone plug or cautery) has been extremely beneficial in recalcitrant cases.

INFECTION

Postoperative infection is rare and occurs with the same frequency as in any eye with a large corneal abrasion. The author managed one pericentral staphylococcal ulcer at his center that responded to topical ofloxacin without adverse outcome. Infections can be prevented by treating adenexal infections such as blepharitis before surgery, using sterile operative technique, using postoperative antibiotics, and closely monitoring until complete re-epithelialization occurs. Although not a primary infection, reactivation of herpes simplex keratitis has been reported after PTK and steps to prevent recurrence should be undertaken.[37,38] Herpes simplex virus scars are a *relative* contraindication for PTK because the scars are flat or depressed and associated with tissue loss, which makes treatment difficult and can leave the patient with significant residual irregular astigmatism, large hyperopic shifts, or both. In addition, reactivation of HSV keratitis has been reported after PTK.[39,40] There has been

some success in treatment of herpetic corneal scars with PTK, but these patients must be well informed.[41] The author's recommendation is to pretreat HSV patients with oral antiviral agents (acyclovir 400–800 mg five times daily or famciclovir 500 mg thrice daily) for 2–4 weeks before surgery and for 4–12 weeks after surgery on a tapering dose. This regimen is similar to what the author uses in penetrating keratoplasties on HSV patients and to date has not seen any HSV recurrences with PTK.

STROMAL HAZE AND SCARRING

After PTK, most corneas are either clear or have trace to 1+ reticular haze that is not visually significant and clears within 3–6 months. Prompt treatment with topical steroids can minimize the severity and course of haze. Visually significant scarring as a result of PTK is rare. Significant residual scarring is more common when scars are too deep to ablate fully. Treatment depth should not exceed 160–170 µm, assuming an average central corneal thickness of 500 µm. A good rule of thumb in thinner corneas is to always leave *at least* 250 µm of corneal thickness after PTK; treatment deeper than that can result in significant scarring, instability, and possible ectasia over time. Patients with suboptimal visual function resulting from residual scarring or irregular astigmatism 3–6 months after full healing may benefit from either lamellar or penetrating keratoplasty.

CORNEAL GRAFT REJECTION

In some cases, patients who have had previous penetrating keratoplasty are candidates for PTK. This is most commonly seen when dystrophies recur after grafts. Caution is advised in this group because corneal graft rejection after PTK has been reported by both Hersh and coworkers[42] and Epstein and Robin.[43] As with any rejection episode, prompt aggressive immunosuppressive therapy can lead to successful reversal. Pretreatment with topical steroids may be prudent, but they should be discontinued after surgery until complete re-epithelialization occurs to avoid infection, delayed epithelial healing, or corneal melting. Corticosteroids should be restarted as soon as possible after re-epithelialization to prevent rejection. In addition, graft patients typically have more postoperative haze requiring steroid therapy for rapid resolution.

TREATMENT FAILURE AND NEED FOR SUBSEQUENT PENETRATING KERATOPLASTY

Phototherapeutic keratectomy was originally intended to obviate the need for keratoplasty in a certain number of patients, but it is not always successful. It is reasonable to attempt PTK in lieu of transplant if there is a reasonable chance for PTK success. Patients with corneal scars should be well informed before surgery of the possible need for subsequent keratoplasty, and this should not necessarily be viewed as a complication.

OUTCOMES

The author's site was one of the clinical investigative centers for Summit Technology's Food and Drug Administration clinical PTK trial involving 249 patients with variable pathologic conditions (Table 20.1). Good improvements in best corrected visual acuities (BCVAs) were achieved (Table 20.2 and Fig. 20.13). Most patients in the corneal opacity and irregular surface groups had substantial

Table 20.1 Corneal diseases treated with phototherapeutic keratectomy in the Summit technology clinical trial

Condition	Number of Procedures
Anterior basement membrane disease	13
Band keratopathy	24
Corneal dystrophies	30
Corneal scars and/or irregularities	78
Pterygium	10
Recurrent epithelial breakdown	42
Salzmann's nodules	52
Total procedures	249

Table 20.2 Change in best corrected visual acuity after phototherapeutic keratectomy in the Summit clinical trial

Condition	Improved[a] (%)	Unchanged (%)	Decreased[a] (%)
Corneal opacity	77	5	18
Irregular surfaces	70	8	22
Epithelial breakdown	36	46	8

[a] Improved or decreased represents at least one line of vision.

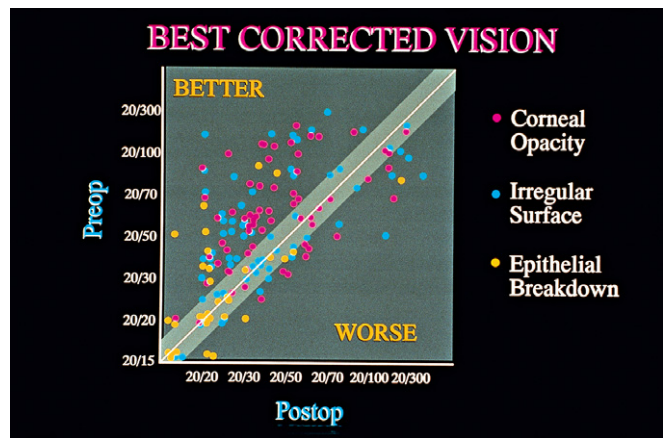

Figure 20.13. Scatter plot of patients gaining or losing vision as a result of phototherapeutic keratectomy in the Summit clinical trial.

improvement in acuity; unfortunately, there was also a loss of at least one line of vision in 18–22% of these patients. As anticipated, most patients in the recurrent erosion group (42%) had no change in vision, because the goal of surgery was to relieve pain rather than to improve vision. Corneal cylinder reductions are shown in Table 20.3.

The success of PTK is largely measured by improvement in BCVA. Maloney and coworkers[44] reported that 45% of their patients had an improvement in best corrected spectacle acuity at 12 and 24 months, whereas 9 and 8% of treated eyes lost two or more lines of vision at 12 months and 24 months, respectively. Sher and coworkers[45] reported similar results, with 48% of patients improving

Table 20.3 Comparison of preoperative and postoperative levels of astigmatism with phototherapeutic keratectomy for all three treatment groups in the summit clinical trial

Condition	Preoperative Average (D)	Postoperative Average (D)
Corneal opacity	–1.84	–1.69
Irregular surface	–2.33	–1.63
Epithelial breakdown	–0.98	–0.97

two or more lines of vision after PTK and 15% worsening two or more lines. Azar and coworkers[46] reported the average improvement in BCVA to be 1.8 lines; 10% of patients lost two or more lines of BCVA and 45% gained two or more lines. These results were confirmed in other studies as well.[36,38]

The outcome of PTK is also dependent on the underlying corneal pathologic condition. Maloney and coworkers[44] showed that treatment was most effective in eyes with hereditary corneal dystrophies, Salzmann's nodular degeneration and corneal scars. Eyes with calcific band keratopathy appeared to improve the least. This study confirmed the results of both Chamon and coworkers[36] and Campos and coworkers.[38] Reis-Bücklers' dystrophy has also been successfully treated with PTK.[47,48] Fagerholm and coworkers[49] successfully treated 37 of 37 patients with recurrent corneal erosions with no further recurrences reported at 1 year, and 28 of 30 patients with a history of a postinfectious corneal scar also had successful treatment outcomes.[19] Goldstein and coworkers[50] successfully treated two of three patients with corneal scarring from trachoma. Other studies, however, have not reported as much success with regard to treatment of corneal scars.[38] Dausch and coworkers[51] reported a 74% success rate in the treatment of recurrent corneal erosion with PTK. Cameron and coworkers[52] successfully treated three eyes with shield ulcers and corneal plaques secondary to vernal keratoconjunctivitis. In general, patients with more superficial corneal pathologic conditions (anterior 100 μm), regardless of the underlying cause, tend to have better outcomes after PTK. Those patients with deeper stromal involvement or calcific band keratopathy tend to have poorer visual outcomes.[36,38,44,45]

Changes in refractive error are common after PTK. Postoperative-induced hyperopia is directly related to the number of stromal pulses.[36,49] Maloney and coworkers[44] reported 41 and 48% of patients with a hyperopic shift of 1 D or more at 12 and 24 months, respectively. Previous studies have reported hyperopic shifts in 50–81% of treated eyes.[36,38,45] This finding is not surprising because removal of central corneal tissue during PTK lessens the corneal curvature. Treatment of deeper stromal lesions can be expected to produce more postoperative hyperopia. Astigmatism may change after PTK, with 30–50% of treated eyes developing an increase in astigmatism of 1 D or more.[38,44] Stability of both the mean refraction and the mean best spectacle corrected visual acuity has been shown to occur at the third postoperative month.[44]

FUTURE ADVANCES

The technique and understanding of the procedural nuances of PTK have come a long way since the inception of the clinical trials. Second- and third-generation lasers are equipped with devices such as joysticks and tracking systems that may improve technique and results, and future technologic advances may exponentially improve outcomes in the years to come.

Improvements in masking agents and techniques will be a key to better success in patients with corneal scars and irregular astigmatism. Work has already begun in at least three clinical centers on different variations of collagen-based masking agents.[53–55] A collagen polymer gel can be applied to a rough corneal surface, and a hard contact lens of a predetermined curvature can be placed on the gel. When the gel polymerizes to its more solid state, the contact lens is removed and the smooth curvature of the lens is transferred to the corneal surface. Because the gel is made of collagen similar to corneal collagen, theoretically it will ablate at the same rate as cornea, thereby leaving a perfectly smooth corneal surface of the same curvature as the lens. With this technique, there is potential to tailor the postoperative refractive effect based on the curve of the lens selected and the resulting keratometric profile.

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21 Pterygium

Christopher Y. Chow, Steven P. Dunn, David G. Heidemann

INTRODUCTION

Pterygia are common fibrovascular lesions of the bulbar conjunctiva and cornea. Their triangular shape, reminding some of a bird wing, accounts for the name, which originates from the Greek word *pterygos*, meaning wing. Ancient medical texts dating back over 3000 years discuss the clinical presentation and treatment of pterygia. The passage of time has improved our understanding of their pathogenesis and treatment, but has not diminished their importance or, by best estimates, their frequency. They continue to be a source of local irritation, cosmetic aggravation, or visual loss from a patient perspective and, frequently, a source of frustration for the physician due to their proclivity to recur after removal.

CLINICAL APPEARANCE AND ANATOMY

Pterygia typically develop in the interpalpebral space, with a significantly greater number occurring medially than temporally. Those developing inferiorly and superiorly may be reactive in nature, overgrowing a previous area of limbal irritation or inflammation. Many are bilateral, although their rate of growth and central extent are often quite asymmetric. The degree of elevation varies considerably depending on the amount of fibrovascular proliferation. Cystic spaces are not uncommon and may occasionally account for relatively rapid enlargement of these lesions (Fig. 21.1).

Anatomically, the pterygium can be divided into different parts. The *body* extends from the limbus over the bulbar surface and often incorporates the semilunar fold and caruncle proximally when medially situated. The *neck* is the narrowed portion of tissue overlying the limbus and extending onto the peripheral cornea. The most central extension of fibrovascular tissue is the *head*. A white-gray avascular subepithelial 'cap' (Ilots of Fuch's, Fuch's Islands) is frequently present with a subtle red-brown iron line (Stocker line) occasionally being present along its central edge (Fig. 21.2). *Double pterygium* describes a situation in which there are two pterygia present in one eye, one nasally and one temporally (Fig. 21.3).

A *recurrent pterygium* is one that develops after removal of a true pterygium. It is often more adherent to the underlying limbus and anterior stroma (Fig. 21.4). The majority of recurrences develop within 6 months of the primary surgery and are more common in young patients, individuals who have had a high level of sunlight or ultraviolet exposure, and those who have had an aggressive, inflammatory growth pattern.[1,2]

Pseudopterygia are differentiated from true pterygia (as described above) by the former's lack of adherence to the limbus. Pseudopterygia bridge this area, allowing a muscle hook or similar instrument to be easily passed beneath it. Many of these result from limbal or corneal inflammation secondary to trauma or chemical insult (Fig. 21.5). Thinning beneath a pseudopterygium can present problems at surgery if not recognized or anticipated preoperatively.

PRESENTATION

The vast majority of pterygia develop gradually and quietly over an extended period of time. As a result, they do not attract much attention. The age of earliest development has not been studied; however, pterygia typically become clinically evident between the ages of 20 and 50 years. Pterygia are uncommon in children. While the majority of cases are sporadic, there have been a number of pedigrees reported in which the frequency suggests a hereditary factor.[3–5]

Most patients first notice their pterygia when looking in the mirror, although some are brought to their attention by friends or family. Occasionally, localized drying or surface irregularity may result in a foreign body sensation or focal injection. A small percentage of patients will present with complaints of blurred vision, which may be related to either overgrowth of the visual axis by the pterygium (advanced) or, more commonly, the development of secondary astigmatism. Since the astigmatism develops insidiously, it is usually attributed initially to normal refractive changes rather than to the progressing pterygium. The amount of astigmatism is related to the length, width, and elevation of the pterygium, with reports reaching as high as 9 D (Fig. 21.6).[6,7] Given the fact that most pterygia occur in the horizontal meridian, contraction of the fibrovascular tissue more commonly results in flattening between 3 and 9 o'clock and with-the-rule astigmatism. One study found that 61% of patients demonstrated with-the-rule

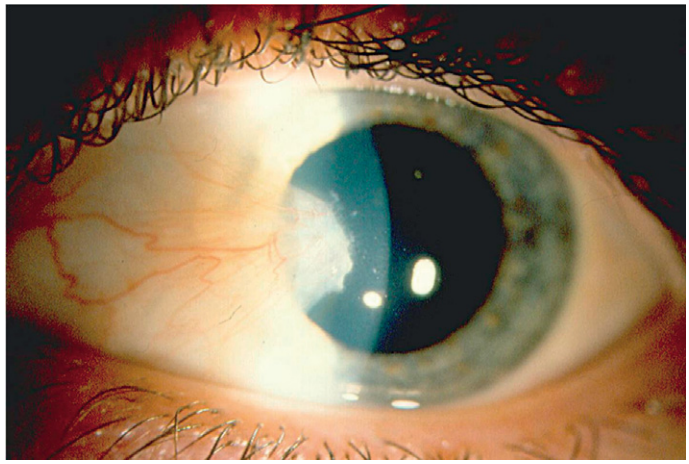

Figure 21.1. Pterygium.

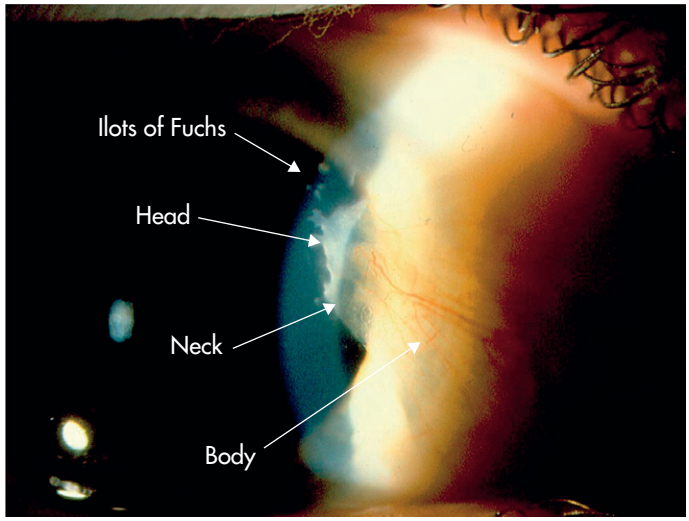

Figure 21.2. Anatomy of a pterygium.

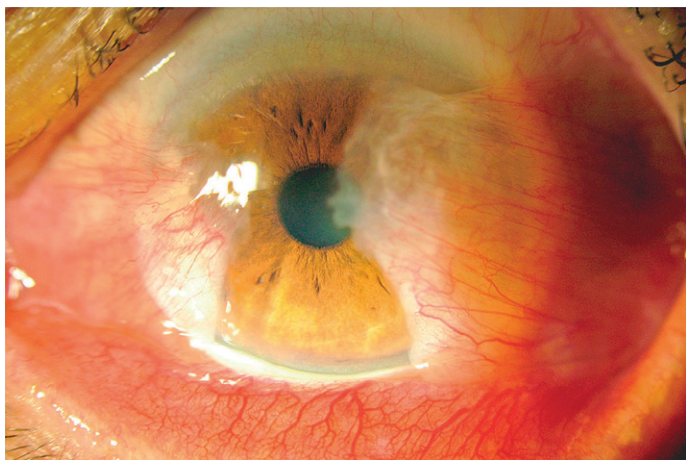

Figure 21.3. Double pterygium.

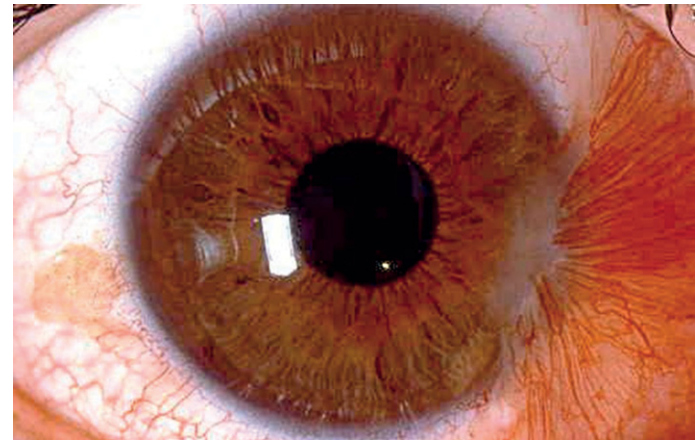

Figure 21.4. Recurrent pterygium. Note the broad base, vascular injection, and ongoing inflammation 6 months after primary surgery.

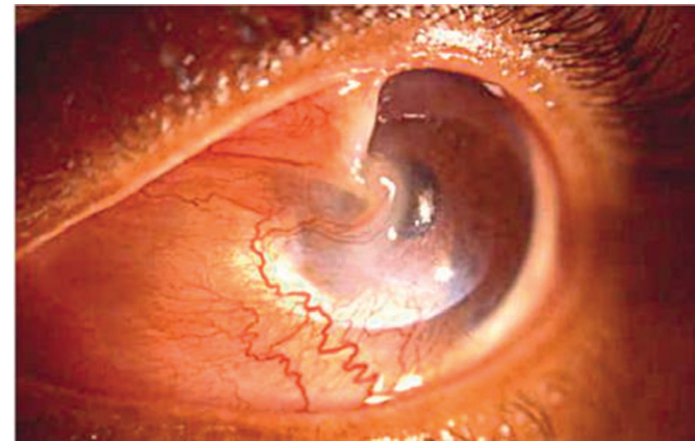

Figure 21.5. Superior psuedopterygium with symblepharon.

astigmatism, 31% against-the-rule astigmatism, and 8% no astigmatism.[8] The amount of astigmatism may be dynamic, varying with the field of gaze.[9] Surgical excision of the pterygium characteristically results in a dramatic reduction in secondary astigmatism when it is significant. Decreased contrast sensitivity and increased glare sensitivity may also be seen in pterygia patients.[10] Diplopia can occasionally develop with large or recurrent pterygia and may vary with eye position.

DIFFERENTIAL DIAGNOSIS

The characteristic appearance and presentation of most pterygia make this lesion reasonably easy to diagnose clinically. Pinguecula, Terrien's marginal degeneration, leukoplakia, papillomas, and conjunctival/corneal intraepithelial neoplasia may masquerade or accompany pterygia. Punctate staining with lissamine green or rose bengal, as well as the presence of a scalloped or fimbriated central edge, brings into question the true nature of any lesion. When there is doubt as to the diagnosis, an excisional biopsy is the wisest course.

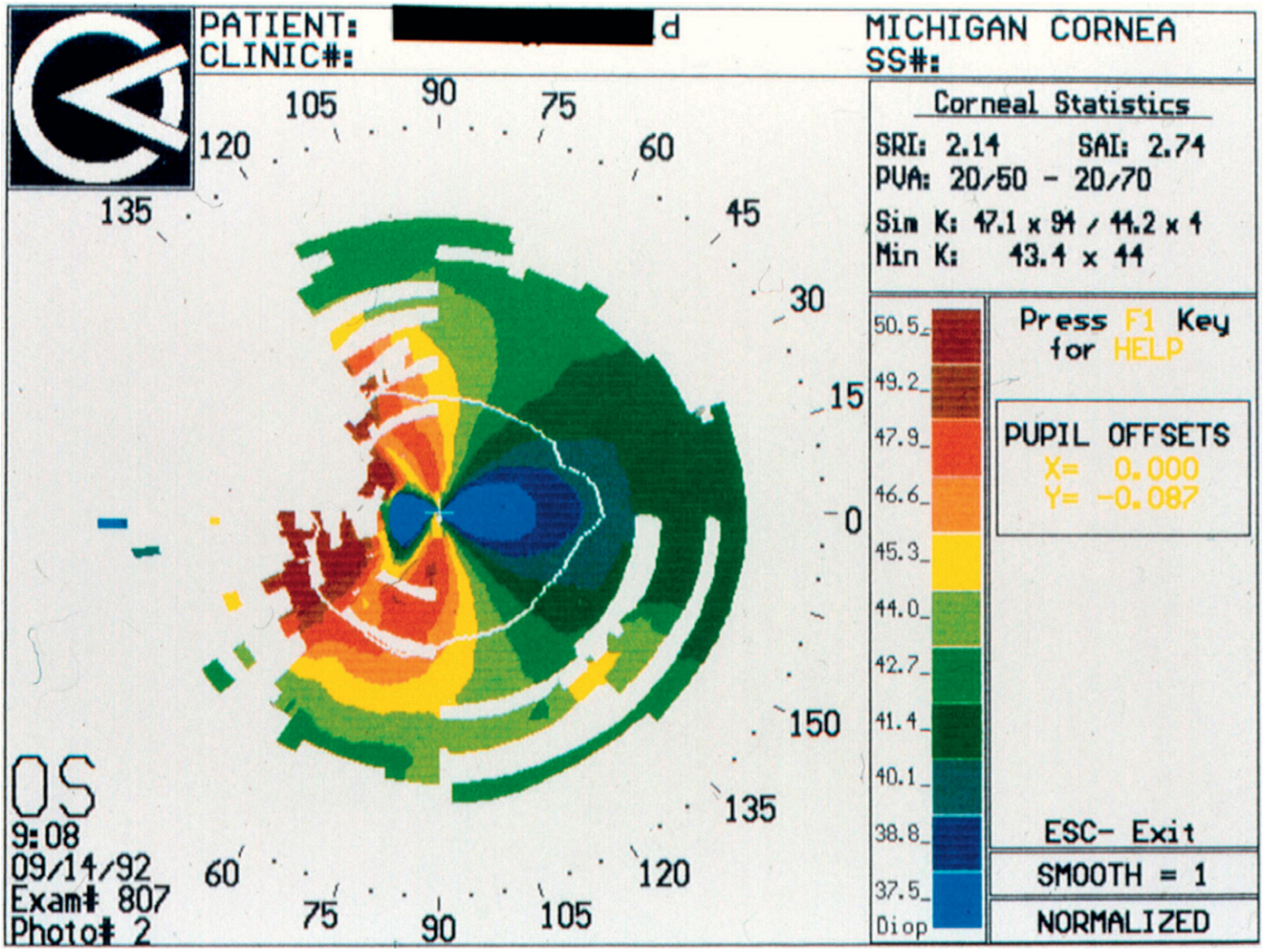

Figure 21.6. Topographic changes induced by a pterygium.

PREVALENCE AND PATHOGENESIS

An extensive review of the world's literature shows considerable variation in published prevalence rates. Factors that influence these figures relate in large part to the characteristics of the particular population being evaluated, i.e. rural vs. urban, tropical vs. temperate climate, public vs. private hospital, or clinic-based vs. a general population sampling. Age-, lifestyle-, and gender-associated occupational roles in different cultures also influence these figures.

A significant relationship between cumulative sun exposure (an indirect measure of UV exposure) and age was noted in a study from rural Indonesia, which showed an overall prevalence rate of 10.0%, with the age group of 21–29 years having a prevalence of 2.9% as compared with 17.3% in the group of 50 years or older.[11] The Australian Blue Mountain Eye Study found an overall prevalence of 7.3%; 11% of men and 4.5% of women had pterygia. A population-based study in rural southern China showed a prevalence of 33.01% in individuals aged 50 years or older. In this cohort, there was a significantly higher prevalence in females (35.70%) than in males (29.70%).[12] A population-based study of residents of the Australian state of Victoria looked at clusters of patients from three settings: urban, nursing home, and rural. Pterygium was present in 1.2% of patients from the urban setting, 1.7% of the nursing home residents, and 6.7% of the rural residents.[13] The Barbados Eye Study looked at prevalence rates in a random sampling of 4700 patients aged 40–84 years. They found a prevalence rate of 23.4% in the island's black population, a prevalence of 23.7% in the mixed population, and 10.2% in the white population.[14] A West Malaysia study also found racial differences, with a greater prevalence in individuals of Chinese descent as compared to those of Malaysian and Indian descent.[15]

Despite the varying prevalence rates reported, a number of risk factors keep reoccurring in studies where multivariant analysis has been preformed.[11,12] These include occupation, particularly when involving extended periods of work outdoors and progressive age (cumulative sun exposure). Ultraviolet exposure seems to be a critical factor in these situations, with the prevalence of pterygia clearly being higher in regions that straddle the equator.[16,17] The question has been raised as to whether excessive sun exposure during certain periods of life (i.e. early childhood) has a disproportionate influence on the risk of subsequent pterygium development.[18] Risk factors that are less well substantiated

are the influence of race, dust/grit exposure, gender, smoking, and ethanol intake.

HISTOPATHOLOGY

Histopathologically, a primary pterygium involves the conjunctival and corneal epithelium, and their associated subepithelial layers. The epithelium undergoes changes characterized by acanthosis, parakeratosis, and hyperkeratosis.[19] The basal epithelium has a distorted orientation, and immunohistochemical staining has demonstrated alterations within the limbal basal stem cells.[20,21] Austin et al described the subepithelial changes as (1) hyalinization of the subepithelial connective tissue of the substantia propria, (2) diffuse or lobular collections of eosinophilic granular material with an associated increase in the number of fibroblasts and other cells, (3) an increased number of thickened and tortuous fibers that stain strongly with elastin stains immediately adjacent to and beneath the hyalinized region ('elastotic material'), and (4) concretions within the hyalinized and granular areas that may show either eosinophilia or basophilia.[22] A fibrovascular layer develops beneath the epithelium and is separated from the sclera and prevented from adhering to it by the presence of the episclera. Activated fibroblasts, mast cells, and lymphocytes are found within this layer in quantities significantly greater than in the normal conjunctival substantia propria. Extension of activated fibroblasts onto the cornea leads to fragmentation and destruction of Bowman's layer. In some cases, the superficial stroma immediately beneath the pterygium may also become involved.[23,24]

The term 'elastotic degeneration' is frequently used in association with pterygia. It was originally applied because fibrillary material within the specimens stained with Weigert's and Verhoff's elastic tissue stain. One unexplained finding was the observation that this material showed no evidence of elastolysis when incubated with the enzyme elastase.[25] Subsequent studies have indicated that this material is composed of newly synthesized elastic fiber precursors and immature or aberrant elastic fibers that are not cleaved by elastase.[21] Elastase only works on mature elastic fibers.[26] The origin of this material is still unclear; however, radiation-activated fibroblasts are known to produce elastic fiber precursors in the skin and may do the same in pterygium.[21]

The molecular composition of pterygium tissue and the immunologic significance of various findings have attracted increasing attention. The findings, however, have yet to be fully understood. Raman spectral analysis as well as immunohistochemistry have demonstrated the presence of increased elastoid fibers, lymphocytes, contractile myofibroblasts, and mast cells as compared with normal bulbar conjunctiva.[27] The detection of T-lymphocyte infiltration and ICAM-1 and HLA-DR expression in pterygium epithelium (typically absent in normal conjunctiva) strongly supports the suggestion that cellular immunity plays a role in pterygium formation. The level of HLA-DR expression appears related to the density of T4 cells, especially CD4 lymphocytes.[28,29]

Activated fibroblasts within the pterygium produce elevated MMP-1, MMP-2, and MMP-9 expression, which probably are the agents responsible for the dissolution of Bowman's layer. Overexpression of MMP-1 and MMP-3 in dermal fibroblasts has been linked with UV exposure and may play a similar role in pterygium.[30] The increased expression of insulin-like growth factor-binding protein mRNA and protein in pterygium fibroblasts is strong evidence to support the transformed phenotype of these cells and helps explain why there is increased growth of fibrovascular tissue.[31] Increased levels of VEGF in pterygium tissue, together with the abundance of von-Willebrand factor-stained new vessels, indicate activation of angiogenesis.[32] Understanding the role these molecules play may lead to novel therapies (i.e. MMP blocking agents and VEGF inhibitors) aimed at reducing the progressive nature of pterygia.

MANAGEMENT—MEDICAL

Treatment of a pterygium is determined by the amount of irritation or inflammation it induces, its effect on vision, its cosmetic appearance, and the actual or perceived threat of extension into the central cornea. Patient and physician factors influence how aggressively medical treatment is pursued and at what point surgery is advocated.

Irritation and inflammation, when not self-limiting, can often be treated with ocular lubricants or intermittent topical NSAIDs, cyclosporin, or steroids. The judicious use of topical vasoconstrictors may be helpful for patients who are bothered by occasional segmental hyperemia. Some patients experience recurrent episodes due to repeated exposure to environmental or work-associated stimuli. Reducing exposure by the use of a brimmed hat, UV-blocking sunglasses, or wrap-around moisture chamber glasses (i.e. 7 Eye®, Wiley X®, and Bugz®) may be helpful in some of these cases.

Glasses can be used to correct mild to moderate amounts of astigmatism. Rigid gas-permeable contact lenses are not very useful in the management of astigmatism in patients with pterygia because of lens decentration and edge-related mechanical irritation. Scleral lenses are a theoretical option, but one rarely pursued because of availability, cost, and handling difficulties.

MANAGEMENT—SURGICAL

INDICATIONS FOR SURGERY

Surgical intervention for pterygium is indicated in a number of circumstances. These include obstruction of vision secondary to encroachment of the pterygium into the visual axis, loss of vision secondary to induced irregular astigmatism, the threat of vision loss due to progressive growth of the pterygium toward the central cornea, restriction of ocular motility with secondary binocular diplopia, and atypical appearance of a pterygium suggestive of possible malignancy. Removal of the pterygium may also be warranted in cases of significant irritation, discomfort, and burning refractory to medical treatment if the symptoms are clearly thought to be related to the pterygium and not to other coincidental conditions such as blepharitis, dry eye, or allergic conjunctivitis. A pterygium that interferes with contact lens wear, cataract surgery, or corneal refractive surgery may also benefit from or require removal. Finally, patients often desire removal of pterygia for cosmetic reasons. This may be an acceptable indication for surgery following a careful discussion of benefits and risks, including the possibilities of postoperative redness, scarring, and recurrence of the pterygium.

SURGICAL MANAGEMENT OF PTERYGIUM

A number of techniques are available for surgical management of pterygia. All methods generally begin with excision and removal of the pterygium from the globe. These techniques then vary in their

handling of the conjunctival defect and in the adjunctive measures taken in an attempt to achieve a safe, cosmetically acceptable, and recurrence-free procedure. Unfortunately, even with the large number of treatment options developed over the centuries, none have completely satisfied that criteria. Even in the modern medical literature, attempts to ascertain the procedures most likely to result in an optimal outcome are hampered by a number of factors including limitations in study design, a range of geographic locations with differing levels of ultraviolet exposure, poorly described and dissimilar patient populations, variations in management technique, small patient numbers, limited durations of follow-up, and inconsistent definitions of recurrences.

Excision of pterygium

Historically, some surgical efforts attempted to redirect the head of the pterygium away from the cornea and into the adjacent inferior fornix, into the adjacent upper fornix, or into both fornices after splitting of the pterygium head.[33,34] These procedures resulted in poor cosmetic outcomes and high recurrence rates. As a result, the vast majority of modern surgical techniques involve excision of the pterygium head and body, rather than redirection. A description of the basic surgical approach for pterygium excision follows.

Topical and subconjunctival anesthesia may be adequate for excision of small pterygia with either the 'bare sclera' technique, where the conjunctival and corneal defects are left to re-epithelialize postoperatively without surgical closure, or a very simple closure. However, for the majority of procedures with extended conjunctival dissection, creation of conjunctival flaps, conjunctival autografting, or transplantation of an amniotic membrane, peri- or retrobulbar anesthesia will allow for more careful dissection, better control of globe positioning, better hemostasis, more precise suturing and closure, etc.

Once adequate anesthesia is obtained, a lid speculum is utilized for optimal exposure of the globe. Traction sutures are placed superiorly and inferiorly either in the peripheral cornea or in the anterior sclera to facilitate positioning of the globe. Several drops of 1:1000 epinephrine or 2.5% phenylephrine may be topically applied to the pterygium to aid in hemostasis. The conjunctival aspect of the pterygium may be marked with gentian violet to guide excision. Most surgeons remove the head of the pterygium first, usually beginning at the apex. This may be performed by lifting the head of the pterygium with fine forceps and then dissecting the pterygium off the underlying corneal stroma with a sharp, rounded blade. Alternatively, techniques have been described in which the pterygium head is avulsed from the cornea by passing a suture, a pair of forceps, or a scissor underneath and through the neck of the pterygium to then shear the pterygium head off the cornea.[35,36] With any method, it is important to excise the soft tissue of the pterygium only and to avoid dissection into the corneal stroma as much as possible.

After excision of the pterygium head, the body of the pterygium can be excised with Wescott scissors following the previously placed gentian violet marks. Some surgeons advocate a subconjunctival injection of balanced salt solution to balloon the conjunctiva for easier excision. Anteriorly, underlying Tenon's capsule and episclera are dissected and removed down to bare sclera. With certain pterygia, these tissues may be quite thick and vascular. More posteriorly, care must be taken to avoid injury to the underlying rectus muscle which may be difficult to identify, particularly if there is significant fibrovascular scarring as is often the case with recurrent pterygia. Bleeding may be profuse, and hemostasis is obtained with wet-field cautery as necessary. The cornea, limbus, and exposed sclera are then smoothed by scraping with the edge of a blade or by polishing with a diamond-dusted burr. Again, care should be taken during this step to avoid excessive removal of corneal stroma or scleral tissue.

Bare sclera technique

The simplest method for managing the bulbar conjunctival/scleral defect after excision of a pterygium is to let the surrounding conjunctiva migrate over the area of exposed sclera on its own, hence the name 'bare sclera' technique. This is the quickest option for completing the surgery, the one most amenable to in-office surgery with topical or subconjunctival anesthesia and a method that can be completed without an operating microscope. For a period of time, this was a popular technique for pterygium surgery. However, a number of studies have shown high recurrence rates with the bare sclera technique, with one study that combined bare sclera excision with excimer laser smoothing of the corneal surface having a recurrence rate of 91%.[37,38] Meta-analysis found that the odds of recurrence with the bare sclera technique are six times higher than that for conjunctival autografting and 25 times higher than that for adjunctive mitomycin C, both of which are discussed below.[39] Many recurrences with the bare sclera technique are rapidly progressive and significantly inflamed and can result in a larger pterygium than the primary one. Consequently, it is preferable to attempt to reduce the risk of recurrence by performing some type of closure over the bared sclera or including an adjunct such as mitomycin C or beta irradiation. A number of investigators have utilized combinations of more than one type of closure or adjunct.

Simple conjunctival closure

This technique involves suturing the superior and inferior cut conjunctival edges together to close the scleral defect following pterygium excision. Undermining of the bulbar conjunctiva adjacent to the defect is required to facilitate closure. While this may be an acceptable procedure for smaller primary pterygia, caution must be exercised in attempting simple conjunctival closure with larger pterygia. If the pterygium body is entirely excised resulting in a large initial conjunctival defect, attempted closure may result in forniceal foreshortening or increased likelihood of wound dehiscence due to the tension required to bring the cut conjunctival edges together. Alternatively, to allow for closure of the conjunctival defect from a large pterygium, a portion of its body may have to be left behind. In either case, the chances of increased postoperative inflammation, scarring, granuloma formation, and recurrence of the pterygium would be higher. There are few published reports discussing simple conjunctival closure after pterygium excision. The published results of this technique in these few studies have been variable, with recurrence rates ranging from 2 to 88%.[40,41]

Conjunctival flaps

Conjunctival flaps have been employed to close the pterygium site for decades. These have most commonly been sliding, rotational, or pedicle-type flaps. The use of a conjunctival 'z-plasty,' where normal conjunctiva is rotated into a limbal position while the pterygium body is rotated toward the bulbar conjunctiva, has been described.[42] The reported recurrence rates following various conjunctival flap procedures have ranged from 1 to 5%.[37] Two relatively large series utilized a sliding conjunctival flap with recurrence rates of 3.2% in 258 eyes[43] and 1.6% in 913 patients.[44]

Conjunctival grafts

The technique of conjunctival autografting involves closure of the conjunctival defect following pterygium excision with a free conjunctival graft harvested from another area of the globe. This technique has been popular due to a relatively low recurrence rate and general lack of sight-threatening complications. Conjunctival autografting also has the advantages of a more normal anatomic and physiologic reconstruction of the surgical area and potentially a better cosmetic result than other surgical methods (Fig. 21.7). Disadvantages of this technique include greater disruption to the ocular surface, prolonged surgical time, and increased patient discomfort.

The basic procedure for conjunctival autograft transplantation was introduced by Kenyon et al in 1985.[45] With this technique, the head and body of the pterygium are excised as described previously. The posterior cut conjunctival edges may be partially closed. The residual conjunctival defect is then measured with calipers. The traction sutures are used to rotate the globe downward to expose the superotemporal bulbar conjunctiva. Gentian violet is used to outline the conjunctiva to be harvested according to the previous measurements and general shape of the surgical defect. The limbal edge of the graft should be denoted with specific marks so that this edge can be subsequently easily identified. The conjunctival autograft is then harvested by undermining and careful dissection with blunt Wescott scissors. Better results are achieved by removing only a thin layer of tissue and leaving Tenon's capsule behind. This step may be aided by ballooning of the conjunctiva with a subconjunctival injection of balanced salt saline. The eye is then rotated with the traction sutures to expose the area of the pterygium excision. The free conjunctival autograft is then positioned over the area of bare sclera, being careful to maintain the limbus-to-limbus and epithelial-side-up orientations. The autograft is then sutured to the underlying sclera at the limbus and to the cut conjunctival edges with 10-0 nylon and/or 8-0 or 9-0 Vicryl sutures. In general, the graft harvest site does not require closure and will re-epithelialize on its own. Postoperatively, topical steroids and antibiotics are employed, initially at a rate of 4–8 times a day, and tapering over 4–8 weeks depending on the degree of inflammation and postoperative course.

Recently, fibrin tissue adhesive has been utilized as an alternative to sutures to secure the conjunctival graft. The use of fibrin glue has been reported to result in reduced surgical time and better postoperative patient comfort with comparable recurrence rates to sutured conjunctival autografts (Fig. 21.8).[46,47]

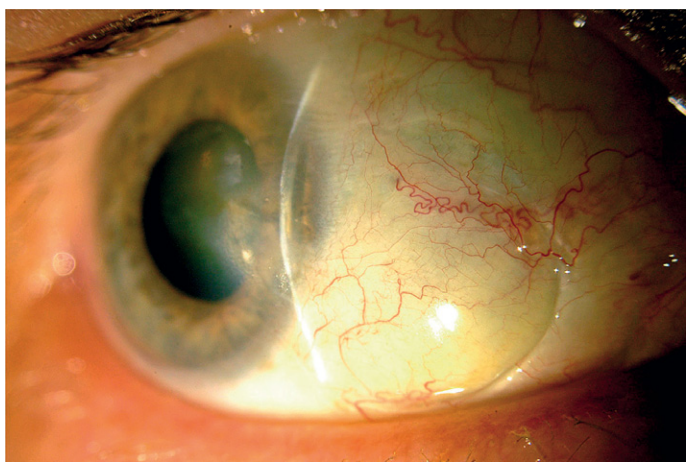

Figure 21.7. Appearance of well-healed conjunctival autograft.

Kenyon et al reported a recurrence rate of 5.3% after 57 conjunctival autograft procedures in their original publication.[45] While the majority of subsequent papers have found recurrence rates of under 10%,[48,49] several reported higher rates, even for primary lesions.[50,51]

Some investigators have emphasized the importance of including limbal tissue in the conjunctival autograft. It has been postulated that a pterygium represents a local stem cell deficiency and that the transplantation of healthy limbal tissue with corneal epithelial stem cells could act as a barrier, preventing recurrence. The technique of transplanting a limbal-conjunctival autograft is similar to that for the conjunctival autograft, except that the graft includes limbal epithelium with or without 0.5 mm of peripheral lamellar superficial cornea. Limbal-conjunctival autografts have had low, but variable, recurrence rates for primary and recurrent pterygia ranging up to 14.6%.[52–54] One report found that this technique may be superior to conjunctival autografting without limbal tissue in cases of recurrent pterygia.[52] Limbal allografts, as opposed to autografts without inclusion of limbal tissue, have also been successfully utilized for treatment of recurrent pterygia.[55] This method, however, requires donor tissue and introduces the potential complication of graft rejection.

Other variations on conjunctival autografts have included harvesting of the autograft from the inferior bulbar conjunctiva[56] and rotational autografts.[57]

Amniotic membrane transplantation

The amniotic membrane is the thin, innermost layer of the placenta. It is comprised of an avascular stroma and a basement membrane. Amniotic membrane components have been demonstrated to have anti-inflammatory and antifibroblastic activity, properties that make it a suitable, and perhaps excellent, tissue for use in pterygium surgery. In addition, it contains growth factors, has antimicrobial properties, is nonimmunogenic, and is readily available. Amniotic membrane is available commercially as both frozen and dehydrated lyophilized tissue.

Amniotic membrane may be used in a manner similar to that of a conjunctival graft. It is generally placed on the ocular surface with the stromal side down and the basement membrane side up. The stromal surface can be identified by a 'sticky' interaction when contacted by a surgical sponge. The amniotic membrane transplant can be cut and shaped as needed and then sutured to the sclera, conjunctiva, and cornea with 10-0 nylon or with 8-0 or 9-0 Vicryl sutures. Amniotic membrane transplantation may be especially useful when it would be difficult to harvest enough conjunctival autograft tissue to close the scleral defect such as in cases of very large or double pterygia. Amniotic membrane can also be utilized to spare the superior bulbar conjunctiva for possible future trabeculectomy or implant surgery in glaucoma patients.

In the modern era of pterygium surgery, Prabhasawat et al first reported on the use of human amniotic membrane grafts.[48] They found a recurrence rate of 10.9% with amniotic membrane transplantation following surgery for primary pterygia. Other studies have found recurrence rates of 3.8–15.4% for primary growths.[49,58] Prabhasawat et al found a much higher recurrence rate of 37.5% for amniotic membrane transplantation when utilized for recurrent pterygia, more than four times their recurrence rate for conjunctival autografts of 9.1%. For recurrent pterygia, others have combined amniotic membrane transplantation with a limbal autograft[59] and

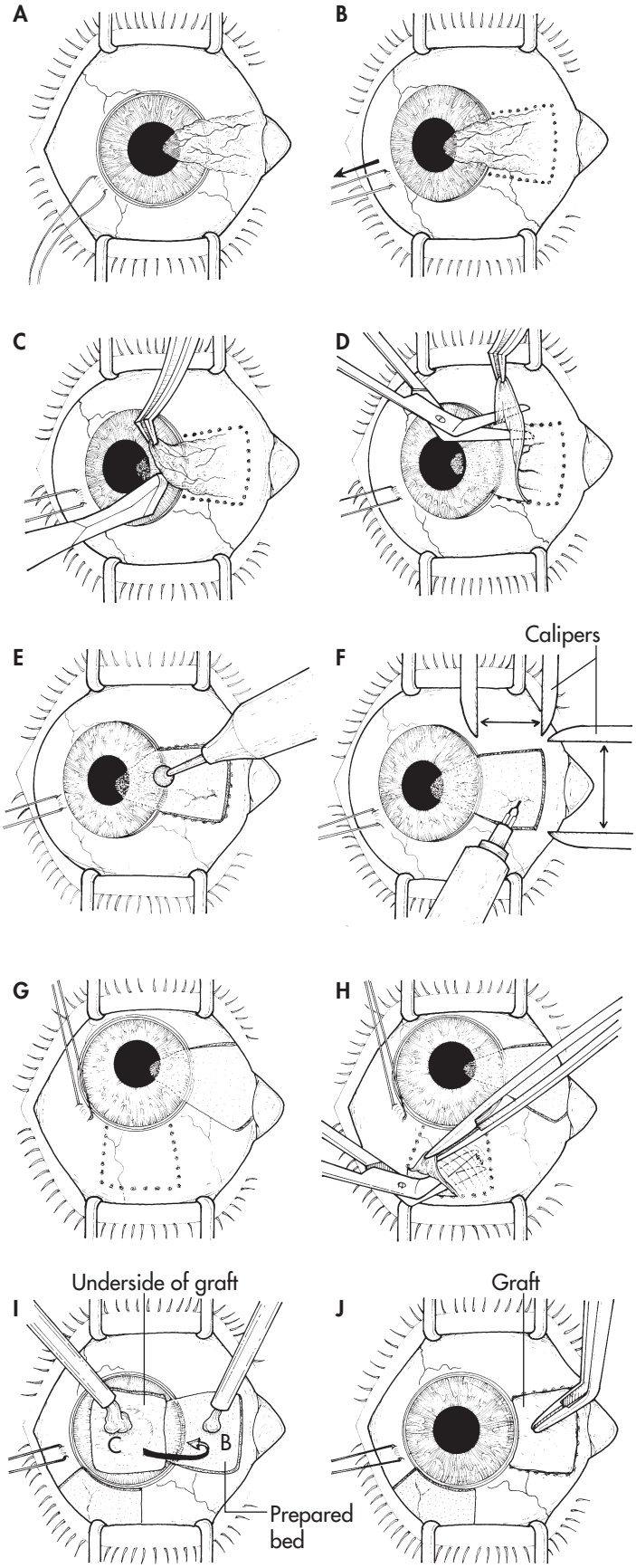

Figure 21.8. Pterygium surgery—basic technique. (*A*) A traction suture is placed at 2 o'clock and the eye is rotated temporally (*B*). The margins of the pterygium are marked off. (*C*) A superficial keratectomy using a 57 Beaver blade or similar is performed starting central to the 'cap' and working peripherally to the limbal region. (*D*) The body of the pterygium is undermined with scissors and the pterygium is excised along the previously placed marks (*B*). (*E*) A diamond burr or rounded microblade is used to smooth the corneal and limbal area if rough or irregular. (*F*) Excess episcleral tissue is removed from along the cut edge of the conjunctiva. Cautery is used to establish hemostasis. The conjunctival defect is measured. (*G*) The eye is rotated downward using the traction suture and the measurements transferred onto the superior bulbar surface. (*H*) The autograft is harvested by careful removal of the conjunctival epithelium. Injecting saline with epinephrine beneath the epithelium can be helpful. (*I*) Flip the autograft over onto the cornea: apply one part (usually the thicker, fibrin component) to the inner surface of the autograft and the second part (usually the thinner component) to the exposed sclera medially. (*J*) Mate the two surfaces, smooth out the conjunctival layer, and allow the two to set.

also with both a limbal allograft and an intraoperative mitomycin C[55] with no recurrences in those series.

Ang and colleagues recently reported on the use of ex vivo cultured autologous conjunctival epithelial sheets grown on amniotic membrane for transplantation following pterygium excision.[60] This technique resulted in faster epithelialization and more rapid healing and resolution of inflammation compared to transplantation of amniotic membrane alone. However, this procedure requires a conjunctival biopsy several weeks prior to surgery and also calls for tissue culture facilities and techniques that are probably not readily available to the vast majority of ophthalmic surgeons.

In addition to conjunctiva and amniotic membrane, investigators have reported on the utilization of mucous membranes, split thickness skin, and processed pericardium to close scleral defects following pterygium excision.[61–63]

Lamellar keratoplasty

Recurrent pterygia with significant underlying corneal thinning from previous surgery may necessitate lamellar keratoplasty to improve and restore the structural integrity of the cornea and globe. Some have also suggested that lamellar keratoplasty itself may aid in prevention of pterygium recurrence.[64] The results with various lamellar keratoplasty techniques have varied widely, with recurrence rates ranging from 0 to 100%.[65–67] Disadvantages of lamellar keratoplasty include increased difficulty of surgery, prolonged surgical time, and the requirement for donor tissue. It is now generally employed only in cases where augmentation or restoration of corneal or globe integrity is essential.

Surgical complications

Complications during or following pterygium surgery are not common and are generally not sight or globe threatening. Intraoperative complications include perforation of the cornea or sclera with the traction sutures, excessive removal of corneal stromal tissue, perforation when removing recurrent pterygia if there is marked or unrecognized underlying thinning, improper orientation of a transplanted conjunctival graft or amniotic membrane, excessive bleeding, and injury to an underlying rectus muscle. In general, these complications can be prevented with careful preparation and meticulous surgical technique.

When discussing postoperative complications of pterygium surgery, one must always begin with recurrence of the pterygium, a frequent source of frustration for both the patient and the surgeon. The majority of recurrences will be relatively small and quiet. However, at times the recurrence can be far more aggressive and rapidly progressive, resulting in a recurrent pterygium which may be more inflamed, larger, and thicker than the primary one. Surgery for recurrent pterygia may be difficult, potentially complicated by profuse bleeding, corneal thinning, scarring, fornix loss and symblepharon formation, and injury to the rectus muscles. The majority of recurrences appear in the first year following surgery.[68,69] Risk factors for recurrences may include younger patients[41] and pterygium morphology which includes loss of transparency and fleshiness.[70] The level of surgeon experience and skill also has an impact on recurrence rates.[69]

Other postoperative complications include wound dehiscences, graft chemosis, dellen formation, persistent epithelial defects, formation of conjunctival granulomas or epithelial inclusion cysts, astigmatism, forniceal foreshortening and symblepharon formation, ptosis, poor cosmesis and scarring and subconjunctival fibrosis involving a rectus muscle that restricts eye movement. Scleral necrosis has been reported following all types of pterygium surgery, with rates being higher following use of certain adjuncts as discussed in the following sections.[71]

Adjunctive therapy

A number of adjuncts have been developed for pterygium surgery in an effort to reduce the incidence of recurrences. The most commonly used adjunctive therapies have included radiation and various chemotherapies. These may have a role, particularly in cases of recurrent pterygia where significant inflammation and increased risk of yet another recurrence may be anticipated.

Radiation therapy

Numerous investigators have looked at the use of beta irradiation after bare sclera removal of a pterygium. The most common agent used is strontium-90. Beta irradiation works to reduce recurrence rates by inhibition of mitosis in rapidly dividing cells such as fibroblasts and vascular endothelial cells. Use of this type of radiation is advantageous because the energy is delivered in a depth-dose pattern, as the delivered dose drops to 19% at 2 mm tissue depth and 1% at 5 mm tissue depth.[72] This is important in limiting radiation delivered to deeper structures, such as the crystalline lens.

There is currently no consensus as to the total dosage required and the need for fractionation. Most recent protocols involve a dose between 1000 and 3000 rad, which have been given either as a single intraoperative dose or in fractionated doses over several weeks. If radiation therapy is to become a commonly used adjunct, it would seem that delivery at the time of surgery would permit the best control of treatment and the least inconvenience for the patient.

Recurrence rates following pterygium excision with adjunctive beta irradiation have varied widely. Studies involving radiotherapy have been many, more than 50 since the mid-1900s, and have been difficult to compare due to differences in dosage and delivery regimens, as well as variations in study populations and duration of follow-up. The recurrence rate is most commonly in the 5–13% range for primary pterygia, and there have been reports that demonstrate reduced recurrence rates in irradiated patients compared to nonirradiated controls.[73–76]

While the recurrence rates with the use of radiation therapy are low, there remains significant concern over potential complications. It is well known that radiation therapy leads to cataract formation in a dose-dependent manner. Other complications include keratoconjunctivitis sicca, corneal ulceration, symblepharon formation, ptosis, episcleritis, and iritis. Of greatest concern is the incidence of corneal and scleral necrosis (Fig. 21.9), which may become secondarily infected and lead to frank endophthalmitis. This incidence is not trivial as, in one study involving 63 eyes which had received a radiation dose of 750–5200 rads (mean 3475 rads), 51 (81%) developed scleral ulceration and 4 (6.4%) developed *Pseudomonas endophthalmitis*.[77] Because many of the complications developing following radiation therapy have a delayed onset, averaging 14.45 years in one study,[78] any report looking at this procedure would ideally include 15 or 20 years of follow-up. A report with less than this duration of follow-up could under-report the true complication rate. With the published rates of potential late, serious complications, this procedure, as we know it now, may be difficult to justify for a disease such as a pterygium.

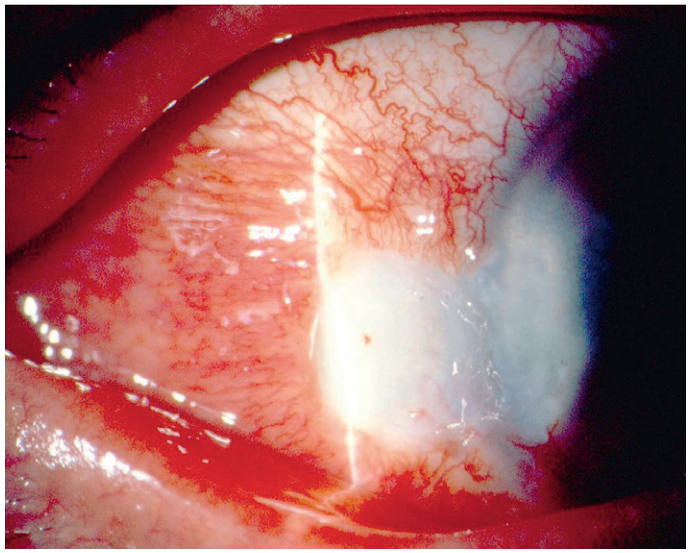

Figure 21.9. Scleral melt following pterygium surgery.

Chemotherapy

Thiotepa

Thiotepa is an alkylating agent that interferes with mitosis in rapidly proliferating tissues. It is believed to reduce pterygium recurrence by inhibiting vascular endothelial proliferation. Its first use in pterygium surgery was reported in 1962 by Meacham.[79] This agent is most commonly used at a dilution of 1:2000 or 1:5000, which the patient administers topically every 3 h for 6–8 weeks following bare scleral excision of a pterygium. The recurrence rates reported in a number of studies, primarily from the 1960s and 1970s, were quite good, ranging from 0 to 16%.[80] Several studies demonstrated significant reductions in the rate of recurrence in thiotepa-treated patients when compared to that in a control group.[81,82] Use of this agent, however, has been limited by side effects, primarily poliosis and permanent periorbital skin depigmentation, especially in darkly pigmented patients.[83] Other complications have included allergic reactions, conjunctival pigment deposition, chronic conjunctivitis, and scleral ulceration.

Mitomycin C

Mitomycin C is an antibiotic that has antineoplastic and antimetabolite properties. Mitomycin C inhibits DNA replication, having the greatest antiproliferative effect on cells with the highest rate of mitosis. In pterygium surgery, as in glaucoma-filtering surgery, it is thought to aid in the procedure by inhibiting episcleral fibroblast proliferation, reducing fibrovascular regrowth and scarring. It was first described as an adjunct for pterygium surgery in 1963 by Kunimoto and Mori in Japan.[84] Since that time, and especially in the last several decades, there has been great interest in the use of this agent. While there have been reports of injection of mitomycin C into the pterygium 1 month before surgical excision,[85,86] the majority of studies have utilized this agent postoperatively or intraoperatively.

Postoperative use of mitomycin C has been reported for both primary and recurrent pterygium. Typically, a dose of 0.4 or 0.2 mg/mL is applied topically two to four times a day for 4 days to 2 weeks after surgery. The majority of studies have demonstrated the effectiveness of mitomycin C in the reduction of the recurrence rate. Singh et al treated patients with 1.0 mg/mL mitomycin C eyedrops, 0.4 mg/mL mitomycin C eyedrops, and placebo four times daily for 2 weeks following excisional surgery. The recurrence rate after 5 months was 2.3% in the 44 patients in the mitomycin groups and 89% in the placebo group.[87] Another study utilized 0.2 mg/mL mitomycin C drops bid for 5 days postoperatively and found a recurrence rate of 9.4% compared to 25.9% in a group that had undergone conjunctival autografting.[88] These rates have been thought to be somewhat better than those with radiation therapy and comparable to conjunctival autografting.[89]

Although postoperative use of mitomycin C has been described as a safe adjunct,[90] other reports have been published that raise concerns as to the potential risks of this therapy. Complications reported include wound dehiscence, secondary glaucoma, corneal edema, corneal ulceration and perforation, scleral ulceration, necrotizing scleritis, iritis, sudden-onset mature cataract, scleral calcification, photophobia, and pain. Rubinfeld found a high incidence of serious complications in patients who had associated ocular surface disease and suggested that topical mitomycin is contraindicated in patients with dry eyes, blepharitis, atopic keratoconjunctivitis, and herpes keratitis.[91] Hayasaka et al reported four cases of scleral ulceration with calcific plaque formation, which occurred between 18 and 25 years after the use of topical mitomycin drops following simple pterygium excision.[92] Those patients required scleral patch grafting. One additional concern with mitomycin C utilized in a topical postoperative fashion is the potential for prolonged use or misuse by patients, which may lead to a greater incidence of complications. As was the case with radiation therapy, additional long-term studies are needed to determine the true complication rate and safety profile with the use of adjunctive mitomycin C.

Mitomycin C has also been utilized as an intraoperative application during pterygium surgery. This method of use has been employed as an attempt to decrease ocular morbidity and to eliminate the potential for patient noncompliance. Many surgeons are comfortable with this technique, as mitomycin C is now routinely used intraoperatively during glaucoma-filtering surgery. Although the published reports utilize a wide range of treatment protocols, intraoperative application of mitomycin C appears to be an effective adjunct for pterygium surgery. The majority of studies have utilized concentrations of 0.2 or 0.4 mg/mL applied directly to the exposed bare sclera for 2–5 min following pterygium excision. Recurrence rates using intraoperative mitomycin have been comparable to those using postoperative mitomycin drops, generally under 10% for primary pterygia and under 20% for recurrent pterygia.[93,94] One study did compare three groups, conjunctival autografting, postoperative mitomycin C (0.2 mg/mL q.i.d. for 1 week), and intraoperative mitomycin C (0.4 mg/mL for 3 min), and found recurrence rates of 22.2, 21.1, and 10.5%, respectively.[95] Recurrence rates may be somewhat lower for recurrent pterygia with intraoperative mitomycin than with limbal-conjunctival autografts.[53] Another study compared the use of intraoperative mitomycin C plus a conjunctival autograft with the bare sclera technique alone, with adjunctive mitomycin C alone, and with a conjunctival autograft alone. This report found the combined technique to be the best in preventing recurrence with no recurrences in 30 patients compared to 14 out of 30 (46.6%) for the bare sclera group, 2 out of 30 (6.6%) in the mitomycin C alone group, and 4 out of 30 (13.3%) in the conjunctival autograft alone group.[96]

Reported complications following intraoperative use of topical mitomycin C include scleral melting, corneal thinning and perfora-

tion, punctate keratitis, and subjective complaints of pain and photophobia. Three patients with scleral or limbal melting following pterygium surgery with intraoperative mitomycin C 0.02% for 3 min, each ultimately requiring tectonic corneal or conjunctival grafting, have been reported.[97] Lower concentrations of mitomycin C may reduce the rate of complications. Others have looked at mitomycin C application times as short as 30 s.[94] Finally, most surgeons now routinely close the scleral defect with conjunctiva following application of mitomycin C to reduce the rate of complications.[98–100] Certainly, additional long-term studies are necessary to establish the complication rate and safety of intraoperative mitomycin C. Patients undergoing adjunctive mitomycin C for their pterygium surgery should be carefully screened and monitored long term.

5-Fluorouracil

A few investigators have also utilized 5-fluorouracil (5-FU), another antifibrotic agent that inhibits DNA synthesis, as a surgical adjunct. One initial study found it to be ineffective when applied intraoperatively at 10 mg/mL for 5 min with a bare sclera technique.[101] The recurrence rate in that series was 60%. A pilot study looked at utilizing 5-FU injections directly into the head of early pterygium recurrences and found that the recurrence process was arrested in five out of six patients.[102] A subsequent study included 39 patients who received intralesional injections of 5-FU for impending recurrent pterygia (fibrovascular tissue in the area of recent pterygium surgery without corneal involvement) and found that this intervention reduced the rate of actual recurrence to 7.7% compared to 31.4% in the control group.[103] 5-Fluorouracil has also been employed as a 3-min intraoperative application with pterygium surgery in 28 patients with a 25% recurrence rate.[104] The results in these few studies suggest that further investigation of the role of 5-FU in pterygium patients may be warranted.

CONCLUSION

Pterygia are common lesions that can be a source of patient complaints, and ocular and visual morbidity. Our understanding of their etiology and pathogenesis has improved in the last few decades. An array of options exists for the management of pterygia. Despite this, the ideal and perfect method, one that is easy to perform, results in a good cosmetic outcome, and is risk free and recurrence free, has yet to be established. Our present options are good and consist primarily of surgical excision with conjunctival flap or autograft closure of the surgical defect. Amniotic membrane grafts or adjunctive mitomycin C may be utilized in certain carefully selected cases. As our understanding of the etiology and pathophysiology of pterygia and their recurrence process advances, refinements to present techniques and novel techniques will emerge to further our ability to manage these lesions successfully.

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22 Tissue adhesives

Erich H.P. Braun

INTRODUCTION

The use of tissue adhesives in ocular surgery was first reported in 1963 by Refojo et al and Webster et al for the management of corneal perforations.[1,2] Since then cyanoacrylate-based adhesives have become a standard adjunctive therapy for anterior segment surgery and treatment. Over the last several years, human fibrin-based tissue adhesives have also proved to be advantageous in many areas of ocular surgery. Currently, all adhesives used in ophthalmology are considered 'off-label' applications.

Tissue adhesives may be used as structural fillers or tissue scaffolding in place of or in addition to sutures and donor transplant materials. They are readily available, quickly and easily applied, and relatively inexpensive. They have been used primarily to seal small corneal perforations or progressive thinning as well as adjuncts for pterygium surgery.[3] Tissue adhesives also have the advantage of reducing operating time, temporizing a corneal perforation to permit more optimal planned surgery, reducing pain and surgical risks for the patient, reducing the need for donor tissue, improving visual prognosis, and allowing more flexibility for surgeons without immediate access to operating rooms. The cyanoacrylate adhesives have especially been shown to have bacteriostatic properties, reducing the risk of corneal melting, and the need for penetrating keratoplasty or conjunctival flap procedures.[4–8]

CYANOACRYLATE ADHESIVES

Cyanoacrylate tissue adhesives (CTAs) are rapidly polymerizing synthetic monomer compounds, which achieve very high tensile strength after setting. They polymerize on contact with basic fluids such as water or blood, forming a solid adherent plaque within seconds. Bonding to biological materials occurs during polymerization in the presence of minimal fluid. They may form a barrier to both bacteria as well as collagenase-secreting inflammatory cells from the tear film and stroma.[9] CTAs resist biodegradation but they may cause local foreign body inflammation with neovascularization and tissue necrosis.

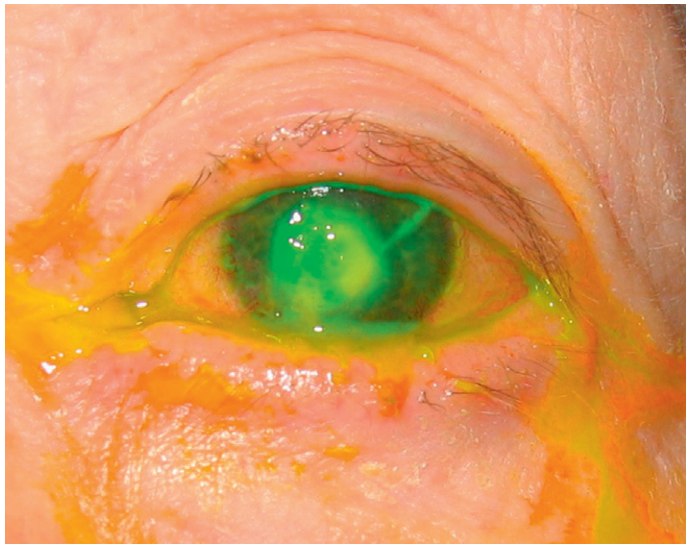
HISTORY AND MECHANISM OF CTAs

The family of cyanoacrylate glues include methyl 2-cyanoacrylate, the first commercially available CTA, followed by *n*-butyl (Isodent™, Indermil™), *n*-heptyl (Histoacryl™), and octyl derivatives (Dermabond™). While approved for dental and dermatologic applications, no cyanoacrylate glue has yet been approved for ophthalmic applications. The various cyanoacrylates bond rapidly in an exothermic reaction via polymerization of liquid monomers in the presence of anions thereby forming a solid polymer. Polymerization entails two steps: first, isocyanate reacts with water and forms a carbamic acid component that rapidly decomposes to carbon dioxide and the corresponding amine, then the amine reacts with residual isocyanate groups, cross-linking the adhesive through substituted urea groups.

INDICATIONS FOR CTAs

Use of CTAs in treatment of corneal perforations and progressive corneal thinning has been well documented. Therapeutic success has been demonstrated in thinning secondary to bacterial keratitis, sterile ulcerative keratitis, neurotrophic ulcers, stromal melts, fungal keratitis, keratitis sicca, herpes keratitis, and other surface diseases.[10–12] Early treatment of corneal thinning may prevent progression to perforation by creating a barrier between the cornea and inflammatory cells and collagenase-secreting cells in the tear film.[6,7,9] Cases of peripheral corneal ulceration or perforation demonstrated resolution with good visual outcome solely with the application of CTA. CTAs also have a role as a temporizing measure until a definitive procedure such as penetrating keratoplasty or conjunctival flap can be performed (Fig. 22.1). Use of CTAs for corneal perforations or progressive thinning may decrease the rate of penetrating keratoplasty, conjunctival flap surgery, and enucleation.[5,6,13]

CTAs leave a hard, non-absorbable, impermeable foreign body, which limits its applications in ophthalmic surgery. They have been used successfully for leaking glaucoma blebs,[14,15] scleral reinforcement,[16] temporary tarsorraphies,[17,18] and blepharoplasty.[19,20]



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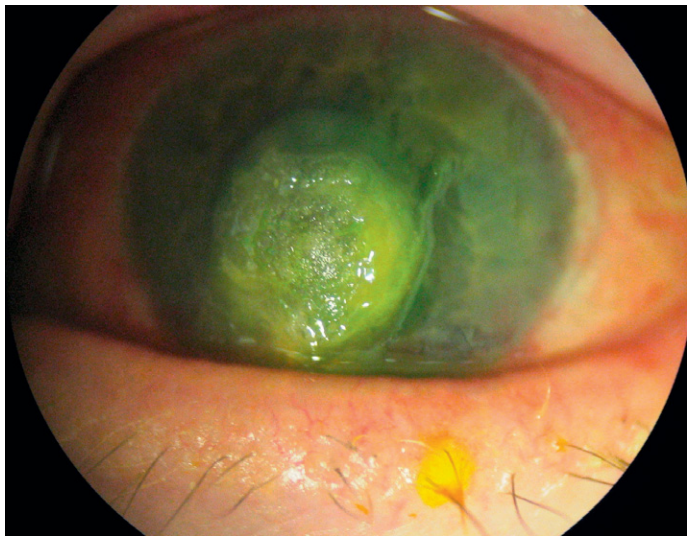

B

Figure 22.1. *A*, Seidel-positive corneal perforation due to pseudomonas ulcer with flat anterior chamber and lenticular-corneal touch. *B*, Following cyanoacrylate adhesive application, the perforation is sealed and the anterior chamber has reformed.

Applications in glaucoma, strabismus, retinal detachment surgery and punctual occlusion have also been published.[21,22]

APPLICATION METHOD FOR CTAS

Corneal application of CTAs for thinning or perforation is complicated by the rapid polymerization and low viscosity of the glue and the need for a clean and dry substrate on which to adhere. CTAs can be applied successfully using one of two methods: the 'drop' method involves direct application with a dropper or small syringe while the 'disk' method uses a plastic disk to apply the glue. Corneal thinning and small perforations may be treated at the slit lamp but larger perforations are easier to treat with the patient supine. Perforations larger than 2–3 mm or with significant surrounding necrotic tissue may not be amenable to adhesive repair.

A lid speculum is required to keep the area dry and avoid an inadvertent tarsorraphy. It is critical to prepare the surface well by debriding necrotic tissue and surrounding epithelium and then drying the area well. After the glue has set and before application of a bandage contact lens, it is important to gently retract the glue to ensure that appropriate adhesion has been achieved. If the adhesion is inadequate, removal of the glue and re-application is recommended. If the iris or lens is plugging a corneal perforation, we recommend taking the patient to the operating room. Introduction of air and or a small amount of viscoelastic agent can be used to push the iris or lens away from the perforation before gluing to avoid incorporation in the wound.[5,23,24] A free tissue patch or loose supporting reticulum of 10-0 nylon suture may also facilitate closure of larger defects.[13,25]

After application, the patient is placed on prophylactic antibiotic drops, with or without additional topical steroid. Topical aqueous suppressants may also be indicated to encourage retention of the adhesive. The patient is followed on a regular basis to ensure adequate repair and to monitor the adhesive status, intraocular pressure, anterior chamber depth, and chance of secondary infection. The risk of subsequent infections, estimated to be 9%, is likely due to the severity of the disease in the eye as well as the extended use of a therapeutic contact lens.[6,26] The duration of the glue for corneal perforations may vary from one day to over 2 years (mean 45–72 days).[6,27,28] The glue will typically be displaced as the epithelium and stroma grow under the glue.[1,29]

For the 'drop' method of application, use a tuberculin syringe with a short 30-gauge needle, draw up a small amount of CTA. Dry the surface immediately before applying the glue and apply only the smallest drop of glue possible. Application of multiple thin layers of glue may be necessary to cover the defect. Avoid using a single large drop as this will not adhere as well, takes longer to cure, may detach earlier, and will be more uncomfortable for the patient. Apply a soft bandage contact lens and re-examine to ensure the integrity of the repair and the fit of the contact lens (Fig. 22.2).

The 'disk' method of application uses small trephine, cut a 2–3 mm disk of sterile plastic drape. Apply a small amount of ophthalmic ointment or gel on the stick-end of a sterile cotton applicator and seat the disk on the gel. Place a small drop of CTA on top of the disk. Dry the surface and immediately cover the defect with the glue-disk. Once the glue has cured, apply a soft bandage contact lens directly over the plastic disk and re-examine to ensure the integrity of the repair and the fit of the contact lens (Fig. 22.3).[1,29]

HUMAN FIBRIN ADHESIVES

Human fibrin adhesives (HFAs) have become increasingly popular adjuncts to various ophthalmic surgeries. They may be used in place of CTAs in the treatment of progressive corneal thinning and small perforations, potentially resulting in less corneal and conjunctival inflammatory reaction. They are biodegradable into nontoxic metabolites and may be used underneath biologic surfaces such as conjunctival autografts, which may promote faster re-epithelialization. However, they have less tensile strength and require more complex preparation and longer cure times. HFAs also have the potential to transmit infection from the donor-derived thrombin and fibrinogen. Additional uses of fibrin glues in ophthalmic surgery include minimizing sutures in recurrent pterygium surgery, forniceal reconstruction, conjunctival and amniotic membrane transplantation, and lamellar corneal grafting.[30–35]

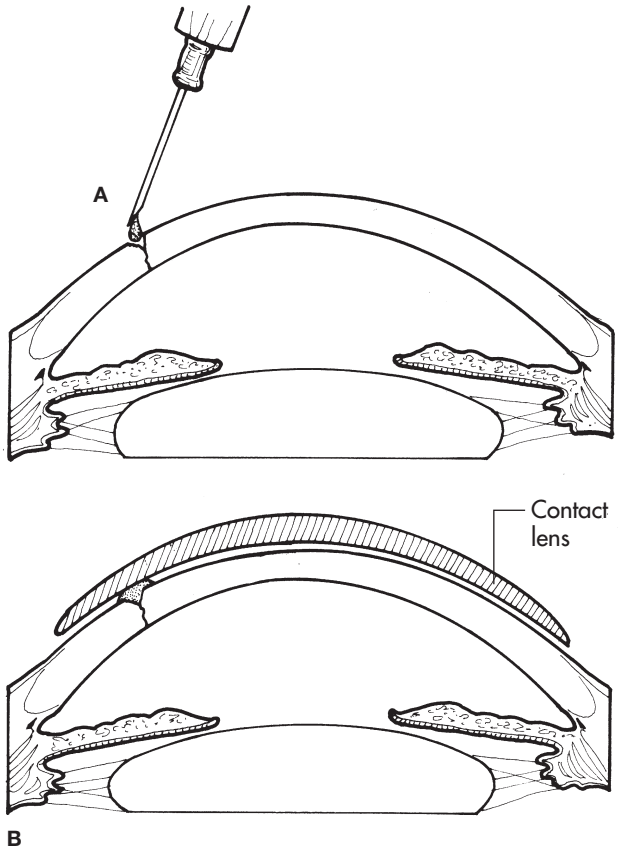

Figure 22.2. Technique for direct application of cyanoacrylate cornea glue. *A*, Once the area is prepared, a micropipette or 3 mL TB (tuberculin) syringe with a 30-G needle is partially filled with glue. After drying the area carefully, a tiny drop of cyanoacrylate glue is placed directly on the cornea (Pearl: Warmth from fingers on the syringe will expand air in the syringe to elicit the smallest drop of glue). *B*, Allow to dry then repeat to cover the wound and place a contact lens over the glue.

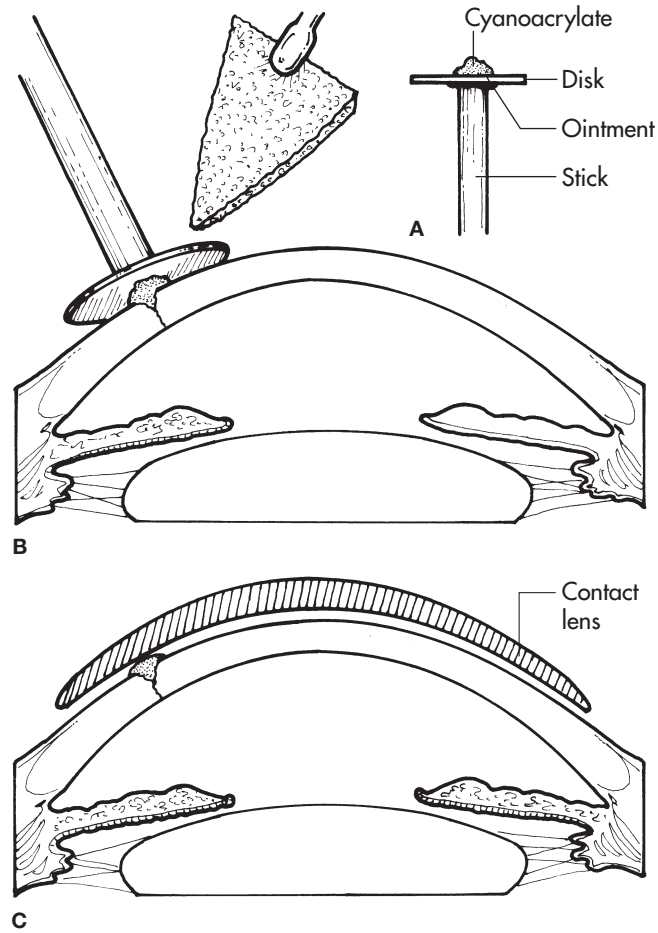

Figure 22.3. Technique for cyanoacrylate cornea glue with a plastic disk. *A*, Prepare the area carefully debriding the wound and drying with an absorbent spear. A trace of antibiotic ointment is placed on the stick-end of a cotton swab and a sterile plastic disk is applied. A small drop of cyanoacrylate glue is then placed on the disk. *B*, After drying the site carefully, the glue and disk are then applied to the corneal perforation. *C*, A contact lens is applied over the glue/disk.

HISTORY AND MECHANISM

Fibrin-based adhesives were first introduced in the 1970s in Europe for use in hemostasis. Introduced as bovine-derived products, they evolved with the use of human-derived thrombin to improve allergic tolerance and aprotinin to retard lysis of the fibrin clot, gaining acceptance especially in the general and vascular surgery fields.[36] One commercial preparation, Tisseel VH Fibrin Sealant (Baxter AG, Vienna, Austria) was approved by the US Food and Drug Administration only for hemostasis in some general and cardiovascular surgery procedures. Application in ophthalmic procedures represents an off-label use.

While single donor and autologous fibrin glue preparations are available, they still require the use of exogenous thrombin.[37] These preparations require significant additional preparation time and result in a lower concentration of fibrin, reducing the tensile strength of the fibrin clot.[36,38]

The Tisseel VH preparation forms a firm, clear, gelatinous fibrin clot when pooled human fibrinogen, plasminogen, fibronectin, and factor XIII in a bovine aprotinin solution is combined with human thrombin initiating the final stage of the coagulation cascade. Once mixed, thrombin cleaves fibrinogen into fibrin, then factor XIII crosslinks the fibrin to form a fibrin clot. Both fibrin and fibronectin are able to crosslink with tissue collagen to adhere the clot to surfaces such as corneal stroma. The bovine aprotinin acts as a fibrinolysis inhibitor to resist degradation of the clot.[39]

APPLICATION METHOD FOR HFAs

A typical HFA system requires a fibrin solution to mix with an activating solution such as thrombin immediately prior to application. The Tisseel kit has duel syringes with linked plungers and a common mixing hub (Duploject) that mixes and ejects equal volumes of the two solutions. For multiple applications, the two syringes may be separated to allow mixing on the field and to avoid clogging of the applicator tip. Alternatively, each solution may be applied to opposite sides of the tissue to be glued to better control glue distribution and to postpone activation until the two sides are apposed.[8,40]

HFAs may be used much like the CTAs with several modifications. HFAs require additional time to prepare as they must be reconstituted, warmed, and transferred to a delivery device. The HFAs do

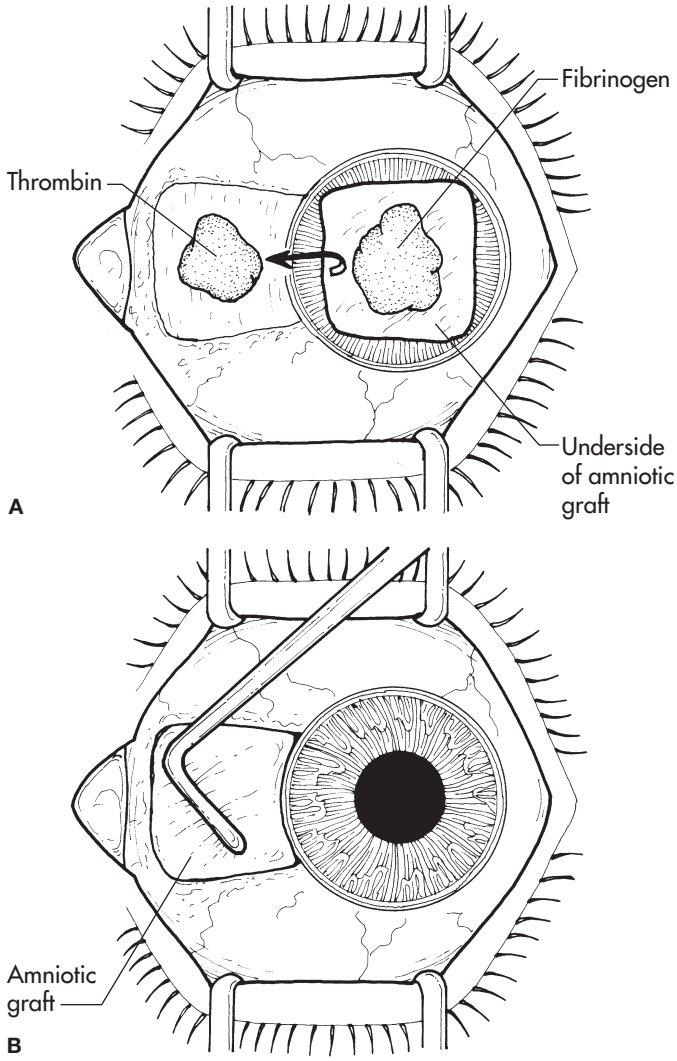

Figure 22.4. Technique for application of fibrin-based adhesive. *A*, Reconstitute the adhesive early in the surgery. After removing the pterygium and preparing the surface, the conjunctival or amniotic graft is placed base-up on the cornea. Thrombin is spread over the bare sclera and fibrinogen is placed on the base of the graft. *B*, The graft is then placed base-down on the site, smoothed with a muscle hook, and allowed to set. The graft may be trimmed with scissors if any tags remain.

not harden as quickly as CTAs, allowing for some manipulation after application. The speed of HFA congealing can be manipulated by diluting the thrombin component prior to mixing. Typical setting times allow HFAs to be manipulated, smoothed, or wiped off in the first 30–60 s to achieve a better seal.

For conjunctival or corneal repairs, the HFA and any adjunctive materials such as donor lamellar grafts, conjunctival flaps, or amniotic membrane should be prepared prior to application of the glue. Non-corneal grafts may be trimmed after bonding. After drying the two surfaces, apply a thin layer of adhesive and appose the surfaces with minimal tension or manipulation. The surface may be gently stroked with a smooth instrument or wet cellulose sponge to remove excess glue and adjust the overlying tissue (Fig. 22.4).[41] Allow several minutes for the HFA to form a firm adhesive clot. For corneal applications, a bandage contact lens may be necessary to protect the repair from mechanical disruption.[42]

Autologous HFAs have been prepared and used with success though they lack the strength and durability of the commercial HFA due to their lower fibrinogen content.[43] The duration of HFA on eyes in vivo is typically less than 2 weeks.[30,43,44] Postoperative application of aprotinin drops may be used to slow lysis of the clot.[42]

IMMUNOLOGIC RISKS OF HFA

Current commercial sources of HFA use human thrombin and fibrinogen and still use bovine aprotinin thereby carrying a risk of antigenic response or transmissible infectious agents such as viruses or prions.[36,45,46] In particular, parvovirus B19 (HPV B19) is difficult to remove or inactivate. Human infection has been reported after the use of fibrin glue in cardiothoracic surgery.[47,48] However, the risks are thought to be low and no reports of HFA-related viral infections have yet been reported following ocular surgery applications.

INDICATIONS FOR HFAs

HFAs have been used for corneal perforations and thinning with or without amniotic membrane.[29,31,32] Of note, in a prospective randomized study, Sharma et al compared HFA to CTA in treating corneal perforations. While both adhesives performed well in closing the perforations, HFA-treated patients developed less giant papillary conjunctivitis and deep stromal vascularization compared to CTA-treated patients.[30] HFAs have become increasingly popular for pterygium surgery with conjunctival or amniotic membrane graft. The surgery is faster with improved hemostasis and the graft can be secured with few or no sutures (Figs 22.5 and 22.6).

Postoperative discomfort and inflammation is also diminished and the risk of pterygium recurrence may be lower than with sutures.[40,49–51]

HFAs have also been used for other conjunctival closures,[52–54] limbal stem cell transplants,[55] lamellar keratoplasty and amniotic membrane patch,[35] prevention of recurrent epithelial ingrowth after LASIK surgery,[56] glaucoma surgery and bleb repair,[57–59] scleral ulcers,[60] blepharoplasty,[61] and anterior segment reconstructive surgery.[33]

THE FUTURE OF OCULAR ADHESIVES

While CTAs and HFAs have become increasingly popular surgical adjuncts, some of their surgical characteristics and potential infectious issues limit broader use. Modifications of current HFAs include use of recombinant protein components, antibiotic-, growth factor-, or stem cell-infused preparations, and platelet gels. Novel adhesives under investigation include a photo-polymerized hyaluronic acid compound,[62] a poly-ethylene glycol hydrogel,[63] a porous poly (L-lactic-*co*-glycolic acid) scaffold with a laser-activated serum albumin solder[64] and a riboflavin-fibrinogen compound,[65] chondroitin sulfate aldehyde,[66] and biodendrimer compounds.[67] These new compounds offer additional desirable qualities in a tissue adhesive—flexibility, absorbability, biocompatibility, durability, adhesion strength, ease of application, and a lower risk of infection and inflammation.

Tissue adhesives play an essential and expanding role in state-of-the-art anterior segment surgery and ophthalmic care.

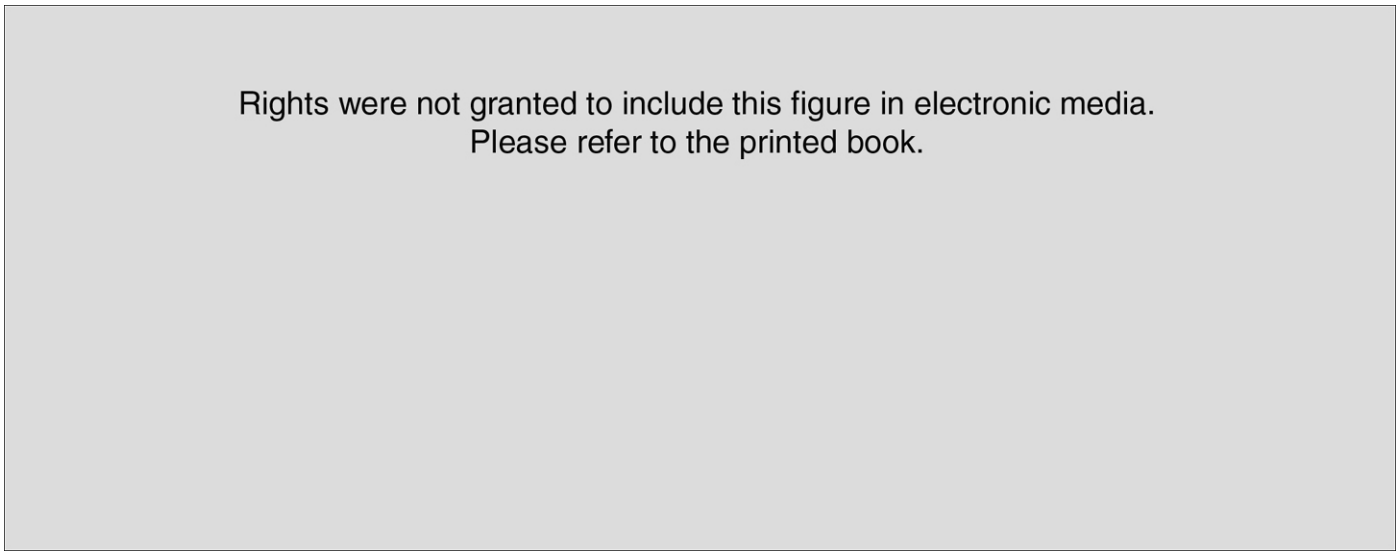

Figure 22.5. *A*, Primary pterygium. *B*, Following excision and repair with fibrin-based adhesive and amniotic membrane. Photograph credit: Dr Scheffer Tseng (Ocular Surface Center, Ocular Surface Research & Education Foundation; Miami, FL).

Figure 22.6. *A*, *C*, Recurrent pterygium. *B*, *D*, Following excision and repair with fibrin-based adhesive and amniotic membrane. Photograph credit: Dr Scheffer Tseng (Ocular Surface Center, Ocular Surface Research & Education Foundation; Miami, FL).

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23 Conjunctival flaps and amniotic membrane transplantation

Christopher I. Zoumalan, Glenn C. Cockerham, C. Stephen Foster

The beneficial effects of covering a diseased or damaged cornea with vascularized autologous conjunctiva were noted in the latter half of the 19th century. Schoeler in Berlin described a conjunctival flap in 1877, but Kuhnt popularized the concept in 1884.[1] Byers[1] listed uses for flaps in cataract surgery, eviscerations, and corneoscleral lacerations in 1912. In the same year, Van Lint proposed placement of conjunctiva over cataract incisions to retard infection and expedite healing.[2] In 1927, Green[3] advocated surgical duplication of 'nature's third process of repair,' or wound healing by conjunctival in-growth, as beneficial for various corneal ulcerations, including herpetic and Mooren's ulcers, and for perforations. In 1954, Haik[4] described his wartime experience with fornix conjunctival flaps in severely injured eyes, noting that such flaps, although temporary, were expeditious. In 1958, Gundersen[5] published a technique for fashioning a thin flap by dissecting conjunctiva from underlying Tenon's fascia, thereby describing the operation, which, because of its success, remains in use today. Prior to that publication, conjunctival flaps were purse-string flaps drawn over to a corneal sector after complete peritomy or advancement flaps (hood flaps) of conjunctiva and Tenon's capsule. Purse-string flaps retracted in a few days, whereas hood flaps could last a few months.[5] Gundersen's technique of removing Tenon's fascia reduced flap contractility, allowing permanent coverage of diseased corneas.

Tissue adhesives, bandage contact lenses, amniotic membranes, and improved antibiotic, antifungal, and antiviral therapy offer alternatives for management of corneal injury and disease not available to previous generations of surgeons. Such new alternatives in ocular surface disease management have decreased the indications for Gundersen conjunctival flaps; however, flaps remain appropriate and reliable therapy in selected cases.[6] Unfortunately, fewer ophthalmologists are performing and learning the procedure, and conjunctival flaps may not be performed, even when appropriate, because of surgeon inexperience. Gundersen flaps may be a temporizing measure, followed by penetrating keratoplasty at a later date, or they may be definitive therapy for chronic conditions. In addition to the total conjunctival or hood flap, described by Gundersen to cover the entire cornea, partial flaps are designed to cover a specific sector. Partial advancement flaps are created by undermining perilimbal conjunctiva to cover an adjacent peripheral corneal abnormality. They offer the advantage, unlike a Gundersen flap, of better visualization of the anterior chamber, accurate intraocular pressure (IOP) measurements, and suitability in patients with short fornices.[7] Racquet flaps are produced by rotating, or swinging, a flap of limbal conjunctiva onto the cornea.[8] Bucket handle flaps can be used to provide a richly vascularized bed to central corneal areas without the extensive dissection necessary for total flaps.[9]

Thick flaps, with the inclusion of Tenon's capsule, are commonly used in treating corneal disorders with stromal loss. Gundersen modified his own procedure by using thick conjunctival flaps in the treatment of bullous keratopathy. More recently, Khodadoust and Quinter have successfully used thick partial conjunctival flaps with Tenon's capsule in treating deeper corneal ulcers and perforations.[7] In instances of severe loss of stromal tissue, as seen in peripheral mycotic corneal abscesses, Sanitato et al have advocated the use of thick conjunctival flaps with a keratectomy.[10] Geria and associates have been successful in using thick conjunctival flaps with the use of deep, localized keratectomy in four patients with infected corneal grafts.[11]

The exact mechanism for the success of conjunctival flaps remains unclear. In general, prompt relief of ocular pain is achieved after flap placement.[12–14] Refractory ulcerations and necrotic areas heal with scar formation, and inflammation subsides. Earlier, surgeons speculated on the restorative capacity of full-thickness flaps and ascribed it to the introduction of blood vessels and a protective layer to corneal tissue.[1] Gundersen,[5] in his original article, hypothesized that a thin flap provides protection from tears and irritants and places a highly vascular membrane supplying blood factors in contact with damaged or infected cornea. Later authors have suggested that a vascular conjunctival flap expedites processing of bacterial antigens, allows neutralization of proteases, and provides a source of viable fibroblasts for wound repair.[15] A conjunctival flap provides some degree of tectonic support in thin corneas, although a flap as sole management is contraindicated in actual corneal perforation.[6,16]

Disadvantages of total conjunctival flaps include impairment of vision and a diminished view of the anterior chamber and intraocular contents. In general, conjunctival flaps are performed in poorly sighted eyes for which no visual rehabilitation is planned.

Intraocular pressure measurement by applanation tonometry will be affected.[17]

INDICATIONS

Indications for conjunctival flaps are listed in Table 23.1.

INFECTIOUS ULCERATIVE DISORDERS

Herpetic keratitis

Progressive or necrotizing herpetic stromal keratitis remains a difficult management dilemma. Surgeons used conjunctival flaps as a reliable way to arrest inflammation and to provide relief from pain in the era before topical and systemic antiviral therapy. In a series of patients reported by Wiedman and Gundersen[2] in 1968, 60 of 177 conjunctival flaps were performed for chronic herpetic keratitis. Flaps remain useful in cases of herpetic ulcerative stromal disease refractory to intensive medical management. Herpes simplex and herpes zoster accounted for 11 of 33 cases requiring conjunctival flap in a published review by Insler and Pechous.[18] In a series of 122 consecutive partial and complete conjunctival flaps performed over 8 years, Paton and Milauskas[19] reported 36 involved eyes with herpetic keratitis. Only four eyes had postoperative persistence of keratitis, two of which had incomplete coverage caused by buttonholes. In a series of 14 conjunctival flaps published by Brown and associates,[20] 9 were indicated for herpetic keratouveitis (7 with herpes simplex and 2 with herpes zoster). All patients had persistent epithelial defects (PEDs) with significant ocular inflammation. Various modalities had been used, including multiple medications, bandage contact lenses, and tissue adhesives. All eyes were comfortable by 1 week after flap placement. No patient had recurrence or deeper inflammation with a follow-up of 1–6 years. Additionally, there was a significant reduction in office visits and use of medications after the procedure.[20]

Most recently, Alino and associates performed a significant percentage of conjunctival flaps (26%) on patients with herpetic corneal disease in their study group of 61 eyes in 1998.[21] None had recurrence, and flap retraction was the only reported postoperative complication, which ranged from an average of 8% in full conjunctival flaps to an average of 23% in the partial conjunctival flap group. These percentages should be similar in theory, but gravity and mechanical effects on the horizontal partial flaps may have predisposed them to more retraction than expected.[21]

Table 23.1 Indications for conjunctival flap

Refractory infectious ulcerations
Herpetic
Fungal
Bacterial *(Pseudomonas)*
Parasitic
Ocular surface disorders with persistent epithelial defect
Neurotrophic ulcer
Dry eye conditions
Exposure keratopathy
Keratoconjunctivitis sicca
Bullous keratopathy
Refractory stromal thinning
Peripheral ulcerative keratitis (PUK)
Mooren's ulcer
Tectonic support

Fungal keratitis

In cases of peripheral fungal keratitis unresponsive to medication, debridement of necrotic material and lamellar keratoplasty in conjunction with a partial inlay conjunctival flap have been suggested to halt progression. Sanitato et al reported resolution in three cases of keratomycosis managed in this manner.[10] The authors suggested that saprophytic fungi do not survive in a well-vascularized cornea. Additionally, Townsend[22] proposed that conjunctival flaps permit access of the cell-mediated immune system to intracorneal fungal elements. The timing of the procedure is important. Intensive medical management should be attempted for 1 week. Progression or lack of response is an indication for surgery in order to avoid the formation of a corneal or anterior chamber abscess.[22] Penetrating keratoplasty is the treatment of choice for central, progressive fungal ulcers.[10,22]

Bacterial keratitis

Pseudomonas species may produce rapid dissolution of corneal tissue, leading to descemetocele formation or perforation. Intensive topical and subconjunctival antibiotics are first-line management. In cases of progressive pseudomonal ulceration refractory to medical management, conjunctival flaps have demonstrated utility (Fig. 23.1). Buxton and Fox[15] reported resolution in three of four cases of culture-proven *Pseudomonas* managed in this manner; failure in one case was attributed to scleral involvement at the time of surgery. Indications for surgical intervention were extension of the abscess to three-quarters corneal depth or three-quarters of the total corneal area.

Parasitic keratitis

Early identification and treatment of *Acanthamoeba* keratitis are the keys to successful medical management. However, it often presents clinically similarly to bacterial and herpetic keratitis, thus delaying diagnosis. The use of conjunctival flap with combined lamellar keratoplasty has been shown to arrest inflammation in cases where medical therapy provided little benefit.[23]

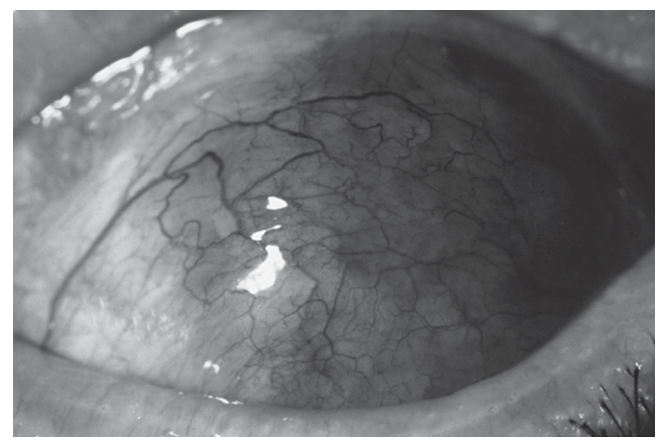

Figure 23.1. A Gundersen flap. This 79-year-old man had recurrent culture-proven *Pseudomonas* corneal ulcers with hand motion vision. Within several weeks of surgery, the eye was quiet and comfortable.

OCULAR SURFACE DISORDERS

Persistent epithelial defects or painful recurrent erosions from a variety of causes that are unresponsive to lubrication, bandage contact lenses, and tarsorrhaphy may require a conjunctival flap. Specific molecules, including topical fibronectin, autologous serum factors, nerve growth factor, and substance P, may accelerate epithelial healing.[24–31] In corneas unresponsive to other measures, replacement of damaged corneal epithelium by conjunctiva may stabilize the surface, prevent further erosions, and arrest stromal melting. Lugo and Arentsen[32] performed a total conjunctival flap in seven patients with neurotrophic ulcerations resistant to lubricants, patching, and contact lenses. Corneal anesthesia was secondary to herpes zoster ophthalmicus in six patients and trigeminal nerve injury in one patient. The neurotrophic ulcer resolved in all patients after flap placement, with thinning and clearing of the flap within 3 months.

Epithelial breakdown despite aggressive medical management may occur in dry eye syndromes from a variety of causes. Exposure keratopathy was listed as the diagnosis in 16% of the conjunctival grafts from 1974 to 1980 reported by Hirst et al.[33] Conjunctival flaps may be the only useful alternative if lubricants, punctal occlusion, therapeutic contact lenses, and tarsorrhaphy are not effective in preventing stromal loss.[13] Portnoy et al[34] prevented further corneal thinning in two children with lagophthalmos and exposure keratopathy by placement of partial inferior conjunctival flaps.

Bullous keratopathy of varied etiology has been successfully treated with conjunctival flaps, with relief of pain and cessation of recurrent erosion.[35] Gundersen reported success using thick conjunctival flaps (including Tenon's capsule) with a lamellar keratectomy to treat bullous keratopathy.[36] However, recent authors have also found success in using a thin conjunctival flap alone.[19,21]

STROMAL THINNING DISORDERS

Since the advent of tissue adhesives, conjunctival flaps have assumed a lesser role in the management of stromal thinning disorders. From 1960 to 1974, conjunctival flaps were used in 37% of cases of corneal thinning or perforation in a series reported by Hirst et al[33] but only in 10% of such cases from 1974 to 1980 after tissue adhesives were introduced.[37] Similarly, conjunctival flaps were used and in 8.6% of 58 eyes treated between 1978 and 1982 by Arentsen et al.[6]

Flaps have been successfully used as adjunctive care in cases of rheumatoid arthritis, systemic lupus erythematosus, and Mooren's ulcer.[18] Filipec[13] recommended flaps for progressive marginal ulcerations threatening global integrity. Conjunctival flaps may be used as adjuncts to lamellar or full-thickness grafts in melting disorders to stabilize the surface and prevent lytic destruction of the grafts.[16] Despite their reinforcing ability, conjunctival flaps should not be considered sole management for corneal perforations. A flap will help the anterior chamber to reform, but leakage of aqueous is common.[22] The perforated eye may develop endophthalmitis or secondary angle closure.[38]

MISCELLANEOUS

Conjunctival flaps may be an alternative to enucleation in the blind and painful eye. In phthisical eyes, a conjunctival flap provides a strong bed for a cosmetic shell.[22] It allows for good retention of the globe with acceptable cosmesis. The flap can also provide a suitable surface for the placement of a cosmetic scleral shell or painted contact lens.

SURGICAL TECHNIQUE

TOTAL ADVANCEMENT FLAP (AFTER GUNDERSEN)

The technique of fashioning a thin flap was first described by Gundersen[5] in 1958. Since then, numerous modifications have been proposed.[19,39–41] The basic procedure is as follows:

1. Local anesthesia is achieved with lid block and retrobulbar or peribulbar injection.
2. A lid speculum is placed.
3. All of the corneal epithelium is removed with a blade. This technique allows flap adherence and prevents epithelial cyst formation. Any necrotic tissue is also removed. A superficial keratectomy is unnecessary.
4. A complete 360° peritomy is made. Hemostasis is obtained as needed by cautery.
5. A traction suture of 6-0 silk is placed through the superior cornea at the limbus, and the eye is rotated downward. Alternatively, a traction suture may be placed through the superior rectus to infraduct the eye (Fig. 23.2).
6. The area to be dissected may be marked with a surgical marking pen. Enough conjunctiva must be mobilized to cover the cornea without tension or traction on the flap. The vertical height of the flap should be 16–18 mm above the superior limbus, allowing 1.5 mm of conjunctiva for each millimeter of cornea to be covered. Superior tarsal conjunctiva may be used if necessary, although this increases the possibility of postoperative ptosis. The horizontal extent of the flap should be 15–20 mm.
7. Conjunctiva is separated from Tenon's capsule by a subconjunctival injection of balanced salt solution, 2% lidocaine with 1 : 100 000 epinephrine, or air. The needle is inserted outside of the intended dissection area to avoid a perforation in the flap.
8. The superior edge of the flap is incised horizontally. An assistant provides exposure by elevating the flap with smooth forceps. Fascial tags and connections are removed from the

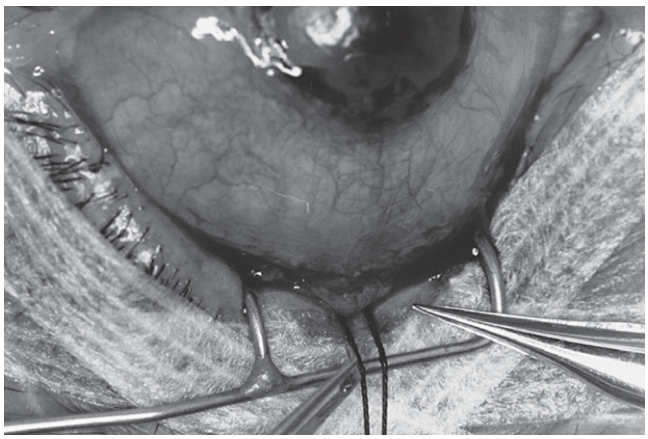

Figure 23.2. Creation of a Gundersen flap: surgeon's view. The superior bulbar conjunctiva is exposed. A 4-0 silk traction suture has been placed through the superior rectus, and the eye is infraducted. (Photograph courtesy of Jonathan H Talamo, MD.)

underside of conjunctiva by blunt dissection with a moist cotton-tip applicator, or by spreading and cutting with blunt scissors, until the superior half of the limbus is reached. The flap should be kept moist with saline irrigation (Fig. 23.3).

9. The conjunctival flap is then pulled down to cover the entire corneal surface. Sufficient tissue must be available to cover without stretch or tension (Fig. 23.4).
10. The inferior edge of the flap is secured to the inferior limbus incision using 10-0 nylon sutures (mattress or interrupted), incorporating episclera into the bite. Episcleral anchoring is important to prevent retraction of the suture line over the cornea. Care must be taken to approximate the cut conjunctival edges, to avoid epithelium implantation into the wound. The superior flap margin is secured with 10-0 nylon sutures to episclera. The superior defect is left bare to re-epithelialize (Fig. 23.5).
11. If a buttonhole occurs, it should be repaired with 10-0 nylon on a tapered vascular needle. If one occurs near the medial or lateral edge of the flap, it may be possible to undermine enough additional conjunctiva to place the defect in an area away from the corneal surface.
12. It is preferable to have an intact corneal covering. There is generally not enough inferior bulbar conjunctiva to perform a total flap. However, if a superior flap cannot be mobilized sufficiently to completely cover, then the inferior edge of the flap may be sutured into the cornea. Alternatively, inferior bulbar conjunctiva may be mobilized and sutured to the superior flap along the cornea.
13. Antibiotic ointment and a pressure patch are applied. The sutures may be removed in 1 month.

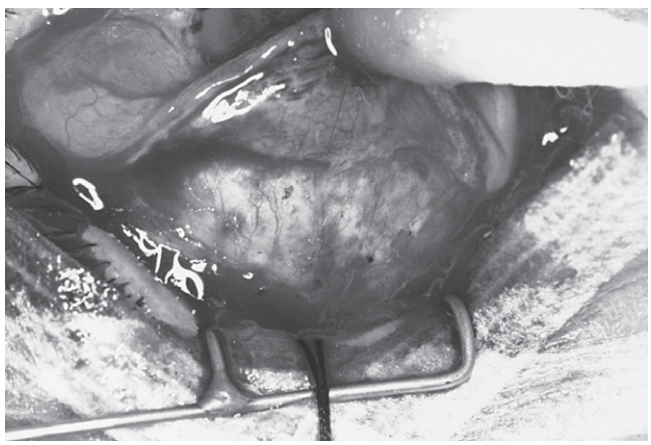

Figure 23.3. The conjunctival flap has been dissected free of fascial attachments down to the superior limbus. A moist cotton-tipped applicator is used for retraction. (Photograph courtesy of Jonathan H Talamo, MD.)

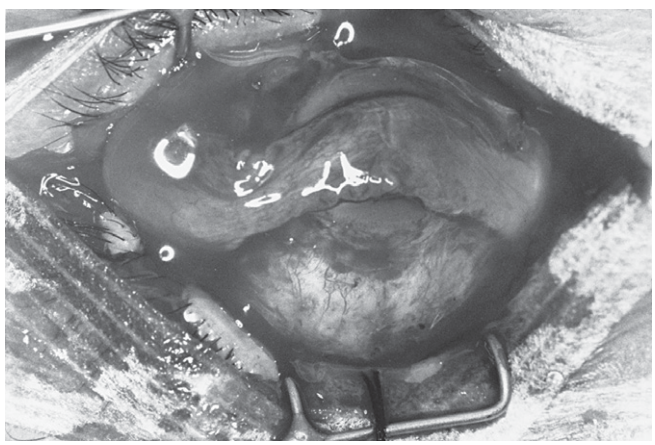

Figure 23.4. Dissection of a flap and 360° peritomy are completed. Sufficient conjunctiva is available to cover the cornea without tension. All corneal epithelium has been removed mechanically. (Photograph courtesy of Jonathan H Talamo, MD.)

PARTIAL ADVANCEMENT FLAP[10,41]

1. A lid block with retrobulbar or peribulbar anesthesia is obtained, with supplementation with topical anesthetics as needed.
2. A lid speculum is placed.
3. Corneal epithelium in the area to be treated is removed with a surgical blade (Fig. 23.6, *A*).
4. If necrotic tissue is present, a lamellar keratectomy is performed to remove as much of this tissue as possible. This dissection should be extended to the limbus.
5. In noninfectious cases of peripheral thinning with threatened perforation, a conjunctival flap may be used in conjunction with a scleral or corneal patch graft.
6. A limbal peritomy is made, extending one clock hour to either side of the area to be covered. A fornix-based conjunctival flap is created by sharp and blunt dissection, undermining conjunctiva and releasing Tenon's capsule with blunt scissors (Fig. 23.6, *B*). Enough conjunctiva is mobilized to completely cover the area of concern without tension.
7. The flap is secured to the corneal bed with interrupted 10-0 nylon sutures. Care should be taken to avoid the visual axis with central sutures (Fig. 23.6, *C*).
8. An antibiotic ointment and pressure patch are placed on the eye. Sutures may be removed in several weeks.
9. A partial 'bridge' flap may be constructed inferiorly for exposure or neurotrophic ulceration using the technique described above. An inferior relaxing incision in the mid-peripheral bulbar conjunctiva allows greater mobility of the bridge. Viability must be maintained by wide vascularized horizontal margins (Fig. 23.6, *D* and *E*).

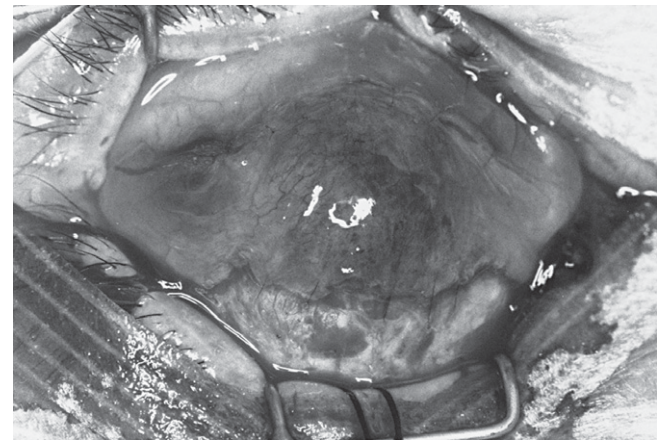

Figure 23.5. Suturing of a flap is completed. 10-0 nylon sutures are used to secure the inferior flap edge to episclera, then to the apposing conjunctival edge. The superior flap edge is also secured to episclera. The superior bulbar area is left bare to re-epithelialize. (Photograph courtesy of Jonathan H Talamo, MD.)

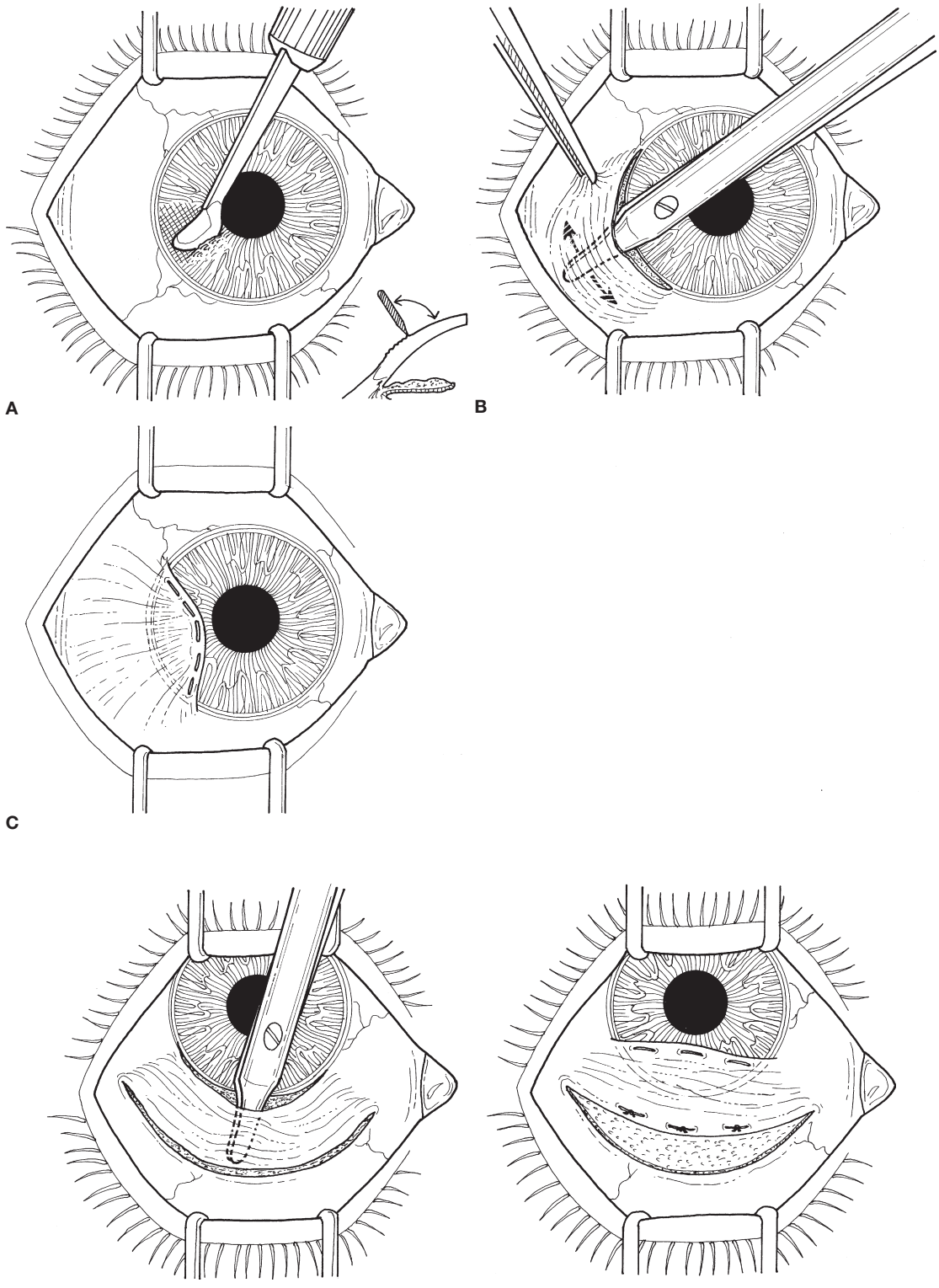

Figure 23.6. A partial conjunctival flap: surgeon's view. *A*, A surgical blade is used to remove epithelium and necrotic tissue. If necessary, a lamellar keratectomy and patch graft are performed. *B*, A fornix-based conjunctival flap is created beginning with a peritomy and bluntly dissected deep and wide enough to cover the abnormal area. Smooth forceps are used to elevate the flap. *C*, The partial flap is advanced over the area without tension and secured, avoiding suture placement in the visual axis. *D* and *E*, A partial 'bridge' flap may be constructed inferiorly for exposure or neurotrophic ulceration using the technique described in *A* through *C*. A relaxing incision in the mid-peripheral bulbar conjunctiva allows greater mobility of the bridge. Viability is maintained by wide horizontal margins.

Table 23.2 Complications of conjunctival flap

Buttonhole
Flap retraction
Epithelial cyst formation
Ptosis
Recurrence, with or without erosion

COMPLICATIONS

Potential postoperative complications are listed in Table 23.2. A fenestration of the conjunctival flap, or buttonhole, will almost certainly enlarge, and this complication will defeat the purpose of the flap. Repair of the tear with 10-0 nylon on a tapered vascular needle should be attempted. It may be possible to position a buttonhole away from the corneal surface by undermining additional conjunctiva laterally or nasally.

Retraction of a flap results from tension placed on the inferior anastomosis and subsequent tearing away of the suture line. This complication usually occurs within 2 months of surgery.[19] Alino and associates identified retraction in 11.4% of 61 eyes, all of which occurred by 1 month after surgery.[21] Retraction can be avoided by securely attaching the flap to the underlying episclera without tension. In most instances, retraction can be managed by observation if enough flap coverage is sufficient to suppress the inflammatory process. Adequate mobilization and dissection of the flap, with secure anchoring of sutures to episclera, are preventative. Reoperation may not be necessary, as several weeks of flap coverage may suffice to quiet an inflammatory process.

Cyst formation may occur from inadequate removal of corneal epithelium, or from inclusion of conjunctival epithelium in the wound. Cysts are usually located at the limbus.[19] They may be multiple and as large as one-third of the corneal circumference.[36] If cysts are problematic, they may be excised. Needle decompression of a cyst is a temporary solution.

Postoperative ptosis of 1–3 mm has been noted.[19] This complication is the result of downward traction on the superior fornix and may be an unavoidable consequence of mobilizing enough conjunctiva to cover the cornea. An additional small amount of ptosis is generally well tolerated in patients with long-standing ptosis from chronically inflamed, painful eyes.[19] Müeller's muscle should be avoided in dissections high in the superior fornix.

Recurrence of culture-proven herpes simplex type 1 in a conjunctival flap has been reported 2 years postoperatively.[42] Corneal recurrences with involvement of the overlying flap have been reported in two cases; one resolved with topical antivirals and corticosteroids, and the other required penetrating keratoplasty for perforation.[43] Erosion of conjunctival flaps has been reported in cases of chronic herpetic keratitis and Mooren's ulcer.[19]

AMNIOTIC MEMBRANE TRANSPLANTATION

Amniotic membrane is a fetal tissue derived from placenta that is beneficial in the corneal and conjunctival reconstruction of various ocular surface disorders. Davis first described the use of amniotic membrane in skin transplantation in 1910.[44] Since then it has been used in tissue regeneration for a variety of cutaneous and mucosal lesions. De Rotth in 1940 and Sorsby and Symons in 1946 were the first to use amniotic membranes in ocular surface reconstruction.[45,46] Difficulties in tissue processing and preservation limited its availability. Kim and Tseng introduced amniotic membrane to ophthalmology in 1995 with better tissue techniques.[47] Amniotic membrane dissolves slowly and produces local anti-inflammatory, antiangiogenic, and antifibrotic effects. It promotes epithelial regeneration through growth factors and prevention of apoptosis. Anatomically, amniotic membrane is the innermost layer of the fetal membrane, consisting of a single layer of epithelial cells attached to a thick basement membrane maintained structurally by an underlying avascular stromal matrix.[48–50]

Table 23.3 Current uses of amniotic membrane transplantation in ocular surface disorders

Conjunctival lesions
Pterygium
Intraepithelial tumors/lesions
Cicatricial ocular disorders
Symblepharon
Limbal stem cell deficiency
Scleromalacia
Corneal reconstruction
Corneal ulcers
Nontraumatic perforations
Bullous keratopathy
Persistent epithelial defects

INDICATIONS

Amniotic membrane can be used as a graft (with basement membrane side facing up) or as a protective patch (with basement membrane down). Grafts are generally used to cover nonhealing ulcerations or postsurgical tissue defects. Several layers of amniotic membrane tissue, up to three or four, may be used at a time to cover the bed of an ulcer. The goal is to maintain appropriate wound coverage while stimulating epithelial growth over the amniotic membrane. Amniotic membrane patches are effective in persistent corneal epithelial defects, where it protects the cornea from the mechanical forces of blinking and exposure, thus allowing epithelial growth and adhesion. Table 23.3 effectively summarizes the current uses of amniotic membrane transplantation in ocular surface disorders.

Amniotic membrane has traditionally been sutured into place, but recent research has shown promise in placing sutureless amniotic membrane onto the ocular surface. Fibrin adhesives produce adequate adhesion of amniotic membrane onto the corneal surface in rabbit models.[51] It has also shown excellent results in adherence onto bare sclera and healing in a patient who underwent an excision of an atypical conjunctival melanosis.[52]

CONJUNCTIVAL GRAFTS

Amniotic membrane has been shown to be a suitable alternative to conjunctival autografts in extensive resections of conjunctival

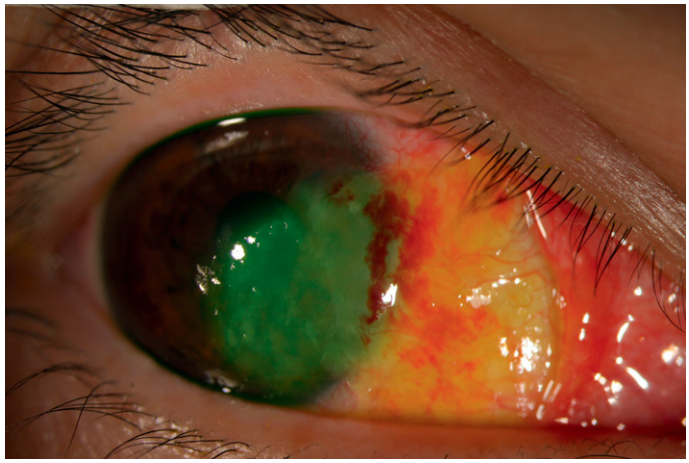

Figure 23.7. Amniotic membrane graft sutured over a nasal pterygium excision site of a right eye. Fluorescein staining highlights the corneal epithelial defect. Photograph was taken on postoperative day 1. (Photograph courtesy of Christopher N Ta, MD.)

lesions such as pterygia, tumors, intraepithelial lesions, symblepharon, and scleromalacia.[48,53–57] It may be employed when insufficient or inadequate host conjunctiva is available for autografting, as occurs in scarring from prior surgeries, injury, pemphigoid, or autoimmune disease.

PTERYGIUM

The use of amniotic membrane in primary pterygium excision has repeatedly shown similar results to conjunctival autografts, ranging from 3.0 to 15% recurrence rates. Equivalent recurrence rates with the two techniques have been reported for recurrent pterygia (38–95%).[53,54,58–61] Amniotic grafts can provide a bed for epithelial regeneration in cases of large pterygium excision (Fig. 23.7). Amniotic membrane transplantation does not require the use of adjunctive therapies, as often seen with conjunctival autografts, such as beta radiation and mitomycin C, thus avoiding the risk of scleral necrosis and perforation.

TUMORS AND INTRAEPITHELIAL LESIONS

Amniotic membrane transplantation has been used successfully in the treatment of ocular surface neoplasias including conjunctival intraepithelial neoplasia, primary acquired melanosis, and malignant melanoma. It has a significant advantage by allowing regeneration of healthy epithelium within large areas without the use of adjunctive cryotherapy. A recent study by Espana and associates showed complete epithelial healing in all 16 patients who underwent single-layer amniotic membrane grafts for large neoplastic lesions up to 20 mm in diameter.[62]

CICATRICIAL OCULAR SURFACE DISEASES

Cicatricial disease can result from chemical/thermal burns, Stevens–Johnson's syndrome, and ocular cicatricial pemphigoid. Amniotic membrane serves an important role in restoring healthier ocular surface in cicatricial surface diseases. It has properties to repopulate the diseased ocular surface and permit healing to occur.[55,63] Amniotic membrane has been successfully used in patients with conjunctival and corneal stem cell dysfunction and deficiency in conjunction with limbal stem transplantation. However, amniotic membrane alone will not restore normal corneal epithelial phenotype in limbal stem cell deficiency. Amniotic membrane grafts have been shown to be helpful in patients with severe cicatricial ocular surface diseases, including chemical/thermal burns, Stevens–Johnson's syndrome, and ocular cicatricial pemphigoid. Early surgical intervention may arrest progression of ocular surface inflammation.[64,65] Amniotic membrane has shown good results in restoring a deep fornix after symblepharon lysis in 12 of 17 eyes.[53] However, inadequate lubrication is a significant risk factor for surgical failure in such populations. Patients with severe dry eyes (Schirmer's value less than 5 mm in 15 min) have shown to respond poorly to amniotic membrane grafts.[66,67] Early surgical intervention with adequate lubrication or sufficient tear film production will ultimately provide suitable factors for healing.

CORNEAL GRAFTS

Corneal ulcers and perforations

Amniotic membrane grafts are a suitable alternative in treating nontraumatic corneal perforations. Usually one or more layers have been used for the treatment of corneal ulcers and subsequent perforations. Solomon and associates reported a successful outcome in 28 of 34 patient eyes (82.3%) with deep ulcers and descemetoceles.[68] Similarly, Rodriguez-Ares and associates reported successful long-term outcomes in corneal perforations (less than 1.5 mm in diameter) in 11 of 15 eyes (73%).[69] Fibrin glue with multilayer amniotic membrane has been proposed as an alternative to treating larger corneal perforations. Hick and associates reported an overall success in 13 of 14 eyes (92.9%) with perforations up to 3 mm in diameter, with the combined use of fibrin glue and amniotic membrane.[70]

Bullous keratopathy

Amniotic membrane provides symptomatic relief in patients with bullous keratopathy, especially in cases of intractable pain, poor visual potential, and/or when penetrating keratoplasty is not indicated. Loose epithelium within the affected area is first completely debrided and an amniotic membrane graft subsequently placed. Gris and associates reported complete epithelialization in all five patient eyes with bullous keratopathy within the first 16 days after the transplantation.[71] Espana and associates also showed long-term success in 17 of 18 eyes and significant immediate pain relief in over 88% of the patients.[72]

Persistent epithelial defects

Persistent epithelial defect may occur in neurotrophic keratopathy, exposure keratopathy, and scarring disorders such as chemical or thermal burns, Stevens–Johnson's syndrome, and ocular cicatricial pemphigoid. Currently accepted treatments include topical lubricants, topical and systemic anti-inflammatory medications, punctal plugs, bandage contact lens, conjunctival flap, amniotic membrane transplantation, and tarsorrhaphy.[47–50,58] Amniotic membrane is a relatively simple option after medical therapy has failed. Long-term healing of PED after amniotic membrane placement was reported in 82% of patients in a study by Prabhasawat and associates; the study included corneas with and without stromal thinning and perforation.[58] The mean healing time was 2.1 weeks, with significantly shorter times in eyes that underwent multilayer amniotic membrane versus single-layer transplantation.

AMNIOTIC MEMBRANE TRANSPLANTATION SURGICAL PROCEDURE

1. Local anesthesia is achieved with lid block and retrobulbar or peribulbar injection.
2. A lid speculum is placed.
3. Conjunctiva is incised horizontally along the diseased surface area. If Tenon's fascia is disease free, the conjunctiva is undermined from Tenon's fascia to allow the tissue to retract to its normal anatomical position. The adjacent extraocular muscles are identified and hooked. If there is diseased conjunctiva near the muscle insertions, carefully blunt dissect the abnormal tissue around the muscle sheaths. Use cautery for hemostasis of the exposed sclera.
4. If cornea is involved, the affected corneal epithelium is removed with a blade. This technique allows better graft adherence.
5. An amniotic graft is prepared from the preserved membranes, by measuring it to be approximately 20% larger than the corresponding area of conjunctival and/or corneal defect. Care must be taken to provide sufficient tissue to cover the area without stretch or tension.
6. If the amniotic membrane's function is to serve as a graft, it should be placed basement membrane side up on the scleral and/or corneal surface and secured to the conjunctival edge with 8-0 vicryl sutures, incorporating episclera into the suture bite. If the amniotic membrane's function is to serve as a patch, it should be placed basement membrane side down (stromal matrix side up) on the scleral and/or corneal surface and secured to the conjunctival edge with 8-0 vicryl sutures, incorporating episclera into the suture bite. Episcleral anchoring is important to help prevent any graft or patch retraction.
7. Antibiotic ointment and a pressure patch are applied overnight. The sutures can be removed in several weeks.

SUMMARY

Surgeons have used autologous conjunctival tissue to stabilize inflamed, infected, or thinned corneas for over a century. Early full-thickness flaps were temporary, retracting in days to weeks. Gundersen described a permanent flap, using thin conjunctiva from which underlying Tenon's fascia had been removed. Therapeutic Gundersen-style conjunctival flaps have been supplanted in many instances by bandage contact lenses, tissue adhesives, and improved topical antibiotic and antiviral therapy. Although less commonly used today, conjunctival flaps have demonstrated utility in selected conditions. Conjunctival flaps may arrest progressive inflammatory and ulcerative conditions and control chronic ocular pain; thus they remain an important procedure in the anterior segment surgeon's armamentarium.

Amniotic membrane is a useful adjunct in ocular surface reconstruction. Although temporary, its antiangiogenic and anti-inflammatory environment promote regeneration of epithelium. It is advantageous in covering surface defects too large for conjunctival flaps. Advancements in understanding the biology of corneal thinning and wound repair will hopefully lead to additional refinements in the medical and surgical management of these potentially blinding conditions.

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24 Central corneal thinning and perforation

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Many ocular conditions predispose the cornea to thinning and possible perforation. These conditions range from chronic, indolent circumstances associated often with long-standing ocular or systemic problems to more acute and rapidly progressing processes. Common to them all are persistent corneal epithelial defects,[1–4] stromal dehydration with associated thinning, and often Descemet's membrane rupture and global collapse. Although the rapidity of the process varies from one condition to the next and the speed of the therapeutic response may often vary as well, the ultimate result of inadequately treated corneal thinning and perforation is devastating to the eye. The persistent loss of the integrity of the anterior chamber in an eye that is leaking aqueous through a corneal perforation can—and probably will—result in anterior synechiae and secondary glaucoma, cataract formation, and possible endophthalmitis. Prompt measures to seal the perforation, even if only temporarily in preparation for a more definitive treatment, must be instituted as quickly as possible.

FACTORS LEADING TO LOSS OF CORNEAL EPITHELIAL INTEGRITY

The factors that can lead to the loss of corneal epithelial integrity and subsequent potential for corneal perforation have been summarized by Doughman.[2]

INFECTION

Although some bacterial organisms can invade the intact corneal epithelium, such as *Neisseria gonorrhoeae,* Koch–Weeks bacillus, and *Corynebacterium diphtheriae,* most other bacteria, fungi, and viruses require a defect in the surface for entry.[6–17] Once established in the corneal stroma, these organisms create a necrotic process that can ultimately lead to loss of stromal mass with perforation. In addition to the destructive nature of the organism itself, the surrounding regenerating epithelial cells and the polymorphonuclear leukocytes called forth by the severe inflammatory reaction then liberate proteolytic enzymes, which further damage the collagen matrix and hasten the corneal dissolution. Herpes simplex corneal infections, because of the often severe inflammation and the high frequency of recurrences, seem to be ideally suited for the creation of the string of events that may culminate in corneal perforation (Fig. 24.1).[6,8,18,19]

In herpes zoster ophthalmia, the corneal hypesthesia often seen may lead to a persistent epithelial defect and a subsequent corneal perforation from the trophic (sterile) process, the active viral necrosis,[6] or both. Secondary keratoconus with a Fleischer ring pattern has been reported following trachomatous infections as well.[20]

XEROSIS

Many systemic and local ocular conditions result in corneal desiccation caused by inadequate mucus and water components in the tear film. Diseases such as rheumatoid arthritis, erythema multiforme, epidermolysis bullosa, vitamin A and B complex deficiencies, and others are often associated with chronic epithelial abnormalities and persistent healing defects.[5,14,21–30] Inadequate corneal fibroplasia and vascularization are also characteristic and retard corneal stromal healing. When combined with persistent epithelial defects, conditions are ripe for corneal perforation in these patients.

Localized specific ocular diseases (e.g. Mooren's corneal ulceration,[31–33] Terrien's marginal dystrophy, and severe cases of keratitis sicca[34,35]) can, for reasons still unknown, lead to severe corneal stromal melting and perforation, often in the corneal periphery. These mainly peripheral corneal conditions are discussed in Chapter 25.

The topical use of corticosteroids for treating corneal disease, particularly when there is an epithelial defect, has led to melting of the corneal stroma and subsequent perforation.[18,36] The mechanism by which this effect occurs is not fully understood, but corticosteroids probably act by perpetuating the lytic action of the proteolytic enzyme collagenase, which is produced in various corneal conditions rather than by a direct alteration of the collagen molecule.[37] Conditions in which production may occur include corneal infections, such as *Pseudomonas aeruginosa* or herpes simplex neuroparalytic keratopathy, the ulcers of alkali-burned corneas, the ulcers of patients with rheumatoid arthritis or Stevens–Johnson syndrome, and the corneal graft wounds of patients with collagen diseases, alkali burns, Stevens–Johnson syndrome, or ocular pemphigoid.

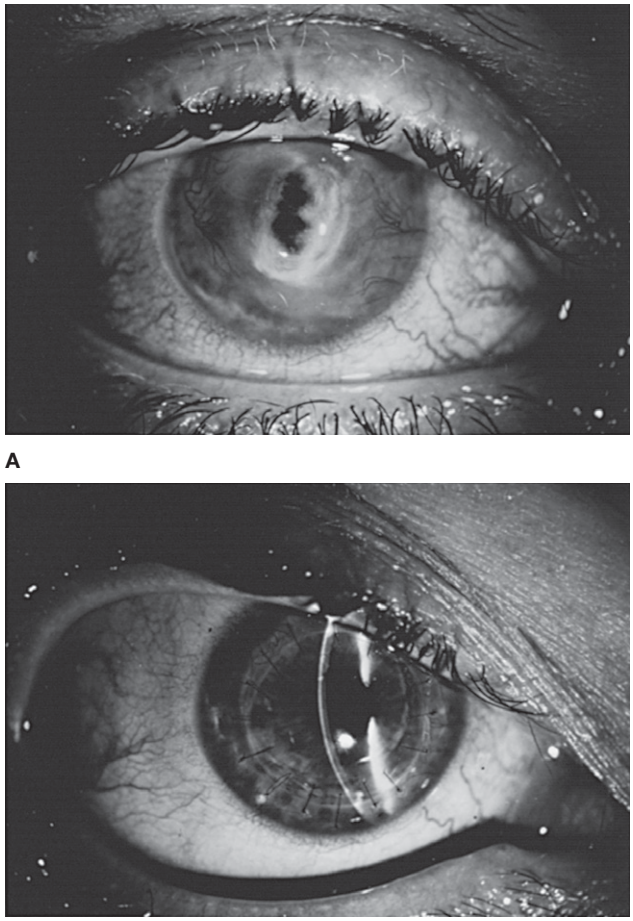


Figure 24.1. *A*, Corneal perforation caused by stromal herpes simplex keratitis in a 28-year-old woman. *B*, The same eye 6 months postoperatively. Eleven years later, the graft remained crystal clear and vision was corrected to 20/20.

Corneal ulcers seen in rheumatoid arthritis are often central as well.[38–40] The systemic use of the antigout medicine colchicine has been shown to possibly delay epithelial healing of wounds in the cornea. Cessation of this systemic medication should therefore be considered if its use is associated with a nonhealing corneal ulcer.[41]

TRAUMA

Incidental corneal trauma, such as an abrasion or, more seriously, penetrating or perforating corneal laceration, can result in situations similar to the cases discussed. Incidental trauma requires the same vigorous therapeutic intervention.[3,4,42–45]

Superficial corneal abrasions, especially linear types such as a corneal scratch from the edge of a piece of paper or a baby's fingernail, can cause destruction of the hemidesmosome bonding of the basal epithelium to the underlying basement membrane.[3,4,46] This event can lead to recurrent, nonhealing, epithelial defects with ultimate stromal melting. The failure of prompt hemidesmosome reformation may be attributable to localized basement membrane injury, or it can be associated with systemic conditions such as diabetes mellitus, severe malnutrition, and other metabolic derangements.

Corneal ulcerations can also occur after cataract and intraocular lens surgery, especially if there is an associated dry eye condition.[47]

CHEMICAL INJURY

The classic chemical injury that frequently leads to persistent epithelial defects with associated stromal melting, defective fibroplasia, and vascularization is the alkali-burned cornea. The result of increased collagenase activity, severe ischemia from the destructive effect of the burn on the limbal vessels, and the alteration in the fibroplastic response of these corneas often leads to corneal melting and perforation with perhaps the worst prognosis for treatment of all corneal perforations.[1,37,48–58]

SPONTANEOUS PERFORATION

Rarely, spontaneous corneal perforation can be seen. In immunologically incompetent individuals (e.g. patients with acquired immunodeficiency syndrome), spontaneous corneal perforation has been reported with molluscum contagiosum infections of the eyelid and conjunctiva.[59] Advanced degenerative corneal conditions, such as keratoconus, posterior keratoconus, Ehlers–Danlos syndrome,[60] and that following refractive procedures (e.g. repeated radial keratotomy operations)[5] and posterior polymorphic corneal dysgenesis[17,61] have all resulted in extreme thinning and occasional corneal perforation. Premature infants may spontaneously undergo corneal perforation following epithelial defects and infiltration.[62] Advanced climatic keratopathy may go on to spontaneous perforation after corneal dissolution and secondary infection.[16] Finally, one case was reported of spontaneous corneal perforation after extracapsular cataract surgery in a patient with rheumatoid arthritis.[47]

DIAGNOSIS

In the initial examination of the cornea, the surgeon must decide (1) whether or not an epithelial defect is present, (2) the extent of stromal thinning, and (3) whether or not corneal perforation has occurred. When fluorescein pools over the thinned area rather than staining Bowman's membrane and when the eye is not inflamed, the likely diagnosis is dellen (saucer-shaped excavation of dehydrated corneal stroma) rather than a more worrisome form of corneal thinning. Often the limbal area near the thinned portion is elevated, causing problems with corneal wetting. The thinning may respond only to hydration and removal of the contiguous elevated area.[2]

If a true epithelial defect is seen with associated stromal thinning and loss of tissue, the surgeon needs to observe for white blood cell infiltration beneath the ulcer. When the involved tissue and surrounding area appear whitish grey or creamy yellow, the surgeon should assume that the tissue is infected, as well as edematous. Appropriate corneal scrapings should be obtained directly over and adjacent to the stromal infiltrate for Gram's, periodic acid-Schiff, or other fungal stains and smears plated for bacterial (aerobic and anaerobic), viral, and fungal cultures.

When frank perforation is observed, the surgeon must determine the size of the opening. If the perforation site is large (over 2 mm), the treatment may be different from what it would be if it were small (less than 2 mm). Pre-existing conditions, such as viral infections, corneal trauma with vegetable matter, prior topical use of corticosteroid medication, generalized predisposing local or systemic problems, corneal exposure, or dry eye conditions, may indicate the source of the presenting problem.

The examination is completed when the visual acuity and intraocular pressure measurements are recorded. A careful examination

is then made for evidence of anterior synechiae formation or central iris adherence (leukoma), hypopyon or hyphema, cataract formation, or signs of an intraocular foreign body. Trauma associated with corneal perforation indicates the possibility of a penetrating foreign body, and orbital X-ray examination, ocular computed tomography scans, and B-scan ultrasonography are then appropriate.

TREATMENT

The specific treatment of epithelial defects (ulcers) is dependent on the presence or absence of perforation, concomitant infection, size of the perforation, and possible association with an autoimmune disease process (Table 24.1).

A. *The following recommendations are for epithelial defects with stromal thinning only:*

1. Topical antibiotics even if there is no infiltrate present.[2]
2. With infiltration, specific antibacterial, antiviral, or antifungal treatment combined with frequent debridement, after initial scrapings for stains and cultures.
3. Corneal lubrication (artificial tears, bland ointment, punctal occlusion, or all) in cases of dehydration (dellen) or associated corneal drying.
4. Avoidance of topical corticosteroids to prevent stromal melting.
5. With or without collagenase inhibitors (acetyl-cysteine drops 10–20%).
6. Lid closure with tape, eye pad, or possible temporary tarsorrhaphy surgically or with glue[63,64] if exposure, corneal drying, or both are present and nonresponsive to local lubrication measures, including drops and ointments. No patching has also been recommended[65] in cases of small noninfected corneal abrasions.
7. Extended-wear therapeutic standard soft lens fitting if it is preferable to lid closure (8.0–8.7-mm lenses are adequate for most cases).
8. Anterior stromal puncture (needle or laser) or epithelial debridement for resistant recurrent erosion syndrome epithelial defects.
9. Conjunctival flap placement for unresponsive ulcers.
10. Glued-on hard contact lens, if severe healing problems (i.e. alkali burn).[66]
11. Amniotic membrane transplantation for persistent epithelial defects with sterile ulceration possibly helpful.[67,68]

B. *The following recommendations are for noninfected epithelial defect with corneal perforation:*

1. Antibiotic coverage with topical solutions.
2. Orally or topically given carbonic anhydrase inhibitors optional because decreased aqueous flow may help in sealing.

Table 24.1 Treatment options for corneal thinning and perforation

Epithelial Defect (Stromal Thinning Only)	Noninfected Epithelial Defect (With Corneal Perforation)	Infected Epithelial Defect (With ≤2 mm Corneal Perforation)	Infected Epithelial Defect (With ≥3 mm Corneal Perforation)
Topical antibiotics associated with debridement as needed	Topical antibiotics	Debridement	Debridement
Corneal lubrication if evidence of dehydration	Oral or topical carbonic anhydrase inhibitors	Topical or subconjunctival antibiotics	Topical or subconjunctival antibiotics
No corticosteroids	Collagenase inhibitors (optional)	Oral or topical carbonic anhydrase inhibitors	Collagenase inhibitors (optional)
Collagenase inhibitors (optional)	Short trial pressure patch with or without soft contact lens	Collagenase inhibitors (optional)	No pressure dressing, soft contact lens, and conjunctival flap
Possible lid closure and/or punctal occlusion	Tissue adhesive glue or fibrin sealant	After 24–48 h of antibiotics, soft contact lens (with or without a patch over eye)	Tissue adhesive or fibrin sealant (with or without patch graft or soft contact lens)
Extended-wear contact lens	Partial conjunctival flap	Tissue adhesive glue or fibrin sealant	'Blow-out' patch graft
Conjunctival flap or glued-on hard contact lens (temporary)	'Blow-out' corneal patch graft	Conjunctival flap (partial after glue removed)	Delay of penetrating keratoplasty
Amniotic membrane transplantation	If associated with autoimmune disease (i.e. rheumatoid arthritis and Sjögren's disease) consider topical corticosteroids, short-term cytotoxic agents, or autogenous periosteal or split-thickness dermal graft	'Blow-out' patch graft	

3. Topical collagenase inhibitors optional.
4. Short trial (6–8 h) with pressure dressings if opening 1 mm or less in an attempt to reform anterior chamber and prevent anterior synechiae formation until more definitive treatment is instituted.
5. Soft contact lens with pressure dressing if defect is 1 mm or less.
6. Tissue-adhesive glue or fibrin sealant[69–72] with or without soft contact lens.
7. Partial conjunctival flap for small opening if glue not successful or unavailable with the anterior chamber depth always being left observable.
8. 'Blow-out' corneal patch graft if no reformation by other methods by 24 h.

C. *If corneal perforation is associated with autoimmune disease, the surgeon should consider:*

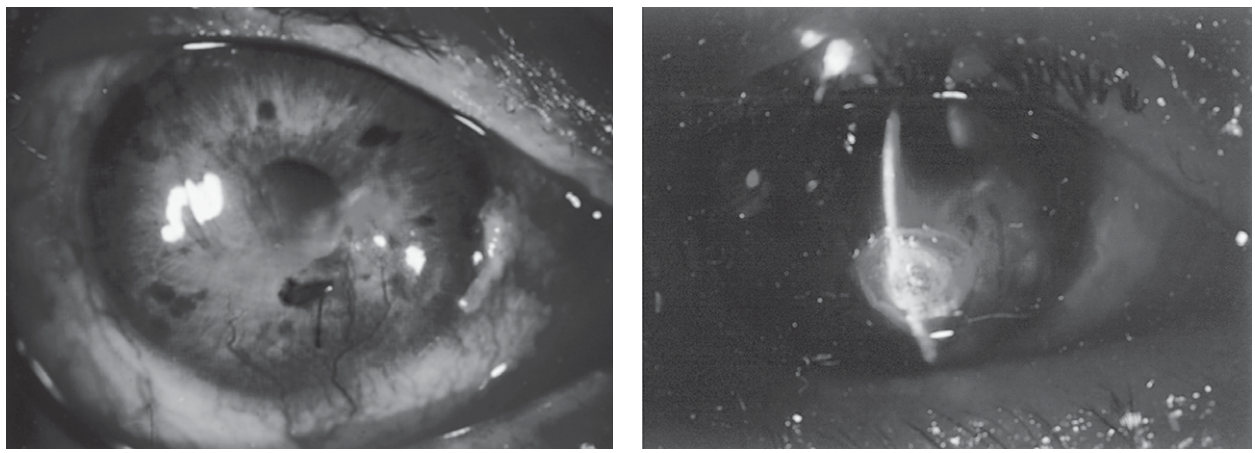
1. topical corticosteroids for 1–3 days depending on response;
2. cytotoxic agents (cyclophosphamide or azathioprine 50–100 mg/day, with dose adjustment depending on local and systemic effect);
3. autogenous periosteal graft or split-thickness dermal graft in face of significant thinning and failure of above methods to heal area.[32,73]

D. *The following recommendations are for an infected epithelial defect with 2 mm or less corneal perforation:*

1. Debridement of necrotic material.
2. Apply appropriate topical anti-infective agent or agents.
3. Subconjunctival antibiotics every other day, optional.
4. Carbonic anhydrase inhibitor, optional.
5. Topical collagenase inhibitors or thiol-based peptides,[52,53,74] optional.
6. Avoid patching an infected eye.
7. After 24–48 h of anti-infective therapy, a soft contact lens with or without a pressure dressing may be tried (allows observation and continued topical medication).
8. Tissue-adhesive glue or fibrin sealant with or without corneal patch and soft contact lens (Fig. 24.2).
9. Partial conjunctival flap after careful removal of all previously placed glue.
10. 'Blow-out' corneal patch graft if no chamber reformation is effected by other methods within 24 h (Fig. 24.3).

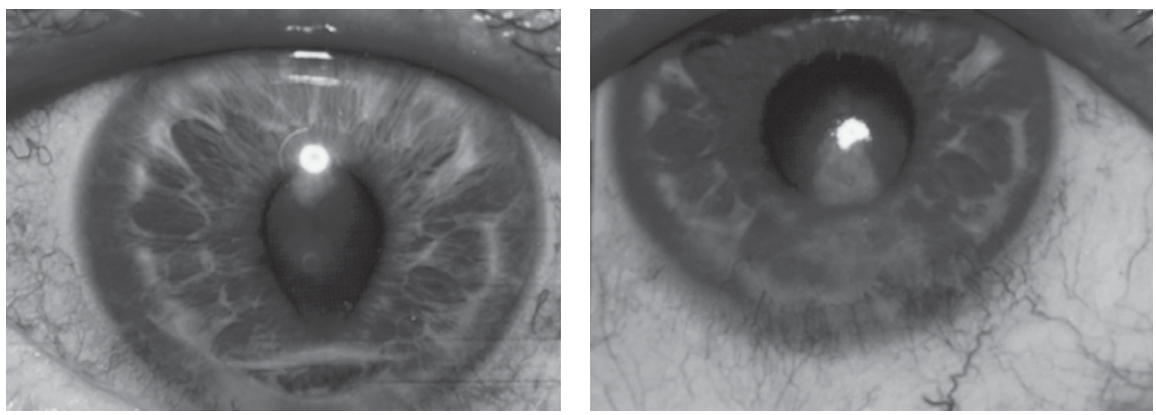
E. *The following recommendations are for an infected epithelial defect with 3 mm or more corneal perforation:*

1. Debride necrotic material.
2. Apply appropriate topical anti-infective agent or agents; subconjunctival antibiotics optional.



A B

Figure 24.2. *A*, Corneal perforation (beneath pigment) associated with herpes simplex keratitis. *B*, Corneal perforation in the same eye 24 h after sealing with cyanoacrylate tissue adhesive.



A B

Figure 24.3. *A*, Rheumatoid corneal melt with iris prolapse. Notice the quiet, noninflamed nature of eye. *B*, Healed corneal patch graft in the same patient.

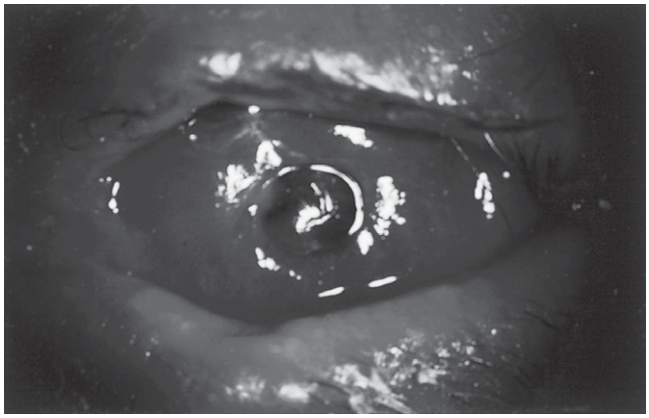


Figure 24.4. Herpes simplex perforation through center of the conjunctival flap. Total flap placement must be avoided in large corneal perforations (over 1–2 mm).

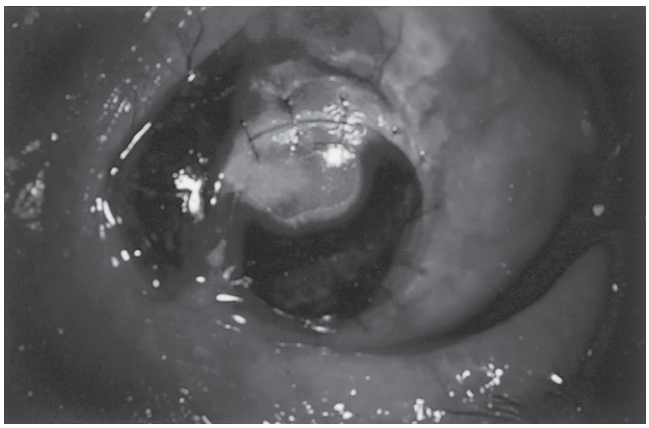


Figure 24.5. Recurrence of epithelial herpes simplex infection in penetrating corneal graft. Many corneal grafts fail if performed on inflamed or infected corneal ulcerations.

3. Collagenase inhibitors optional.
4. Avoid pressure bandage, soft contact lens, or conjunctival flap (Fig. 24.4).
5. Tissue-adhesive glue or fibrin sealant with or without corneal or scleral patch and with or without soft contact lens.
6. 'Blow-out' patch graft if anterior chamber is not easily reformed after glue. Carefully remove all glue placed previously before positioning patch graft because glue-degradation products cause necrosis of overlying patch graft.
7. Avoid penetrating corneal graft in an inflamed, infected eye as initial therapy (Fig. 24.5). Spread of infection to donor graft along with failure is common. Use only as the last resort.[75]

SPECIFIC THERAPEUTIC MEASURES

The treatment of recurrent corneal erosion by anterior stromal puncture and the technique for performing a conjunctival flap are reviewed elsewhere in this text.

GLUING TECHNIQUE FOR CORNEAL PERFORATION

Tissue-adhesive glue

In the past almost 30 years since Refojo and coworkers[76] reported the initial use of cyanoacrylate glue on a human eye, many other articles have followed, finding uses for glue involving every area of the eye from the treatment of corneal perforations to leaking filtering blebs, lid abnormalities, and even choroidal perforations. In the past, the most popular tissue adhesives used in ophthalmic care have included the *N*-heptyl octyl and isobutyl cyanoacrylate monomers. Bucrylate, the brand name of isobutyl cyanoacrylate, has been, in the past, available from Ethicon (Somerville, NJ). Isobutyl (Histacryl) and *N*-butyl (Histacryl-*N*-blue) has come from Germany via Tri Hawk International (Montreal, Canada). The *N*-butyl cyanoacrylate glue (Nexacryl) is now being manufactured by Closure Medical Corporation (Raleigh, NC). Patients who require the glue application can be referred to a center that has a tissue-adhesive investigational device status or can be treated with glue not yet approved by the Food and Drug Administration (FDA), possibly obtained from a local veterinary clinic or from the Veterinary Products Laboratories (Phoenix, AZ) (phone 888 241–9545). Because no tissue glue has been approved by the FDA, there are none currently available to the human ophthalmic community directly. Nexacryl has received an orphan device status to treat 'corneal melting' as there are no FDA-approved products presently available.

Reports have appeared in the literature extolling the virtues of cyanoacrylate tissue adhesive (CATA) as the first-line treatment to close leaking corneal wounds and to thereby restore temporarily or even permanently the integrity of the anterior chamber.[19,29,30,76–82] As a simple office procedure, the gluing of corneal wound leaks can quickly restore a deep anterior chamber with normal intraocular pressure until a more definitive corneal procedure can be done.

By rapid polymerization of carbon molecules, the adhesive readily sets up on contact with dry non-necrotic tissue and bonds firmly with the cornea until the natural scarring process of the cornea can take over in a few days to 1 or more weeks. Later, the degradation of the polymer will occur with cleavage of its carbon-to-carbon backbone and release of formaldehyde and other products.[79,83] These toxic by-products have led to stringent criteria for the use of this product and the reluctance of the FDA to approve it for general use. In truth, however, there has not been good evidence showing any deleterious ocular effects from these toxic by-products, and the inflammation observed with their use is probably more related to a foreign body reaction.[80]

The degree of reaction to the glue may be related to the amount used and to the specific monomer used, with perhaps less reaction being observed with higher monomers.[80,84]

The actual technique for applying the glue varies among corneal surgeons,[29,76,80,81,85] but certain basic principles apply. A common method is illustrated in Figure 24.6, *A*. Alternately, after topical anesthesia, the wet area of application can be blotted to remove any excess fluid, and necrotic tissue is debrided prior to glue application. The adhesive can then be directly applied to the perforation site in a drop-wise fashion using a sterile, tuberculin syringe and a 25–27-gauge needle so as to lightly coat and not entirely fill the defect (Fig. 24.6, *B*).[86,87] Another method for glue application involves the aerosolization of the glue and its application by a fine mist spray. This approach has only been attempted in cadaver eyes, and the initial results appear promising.[85] Although techniques for applying glue (see Fig. 24.6, *A* and *B*) vary, the following general principles apply:

1. Topical anesthesia is used, with a lid speculum being optional but also useful.
2. All necrotic tissue and epithelium are removed around the perforation site for at least 2 mm.

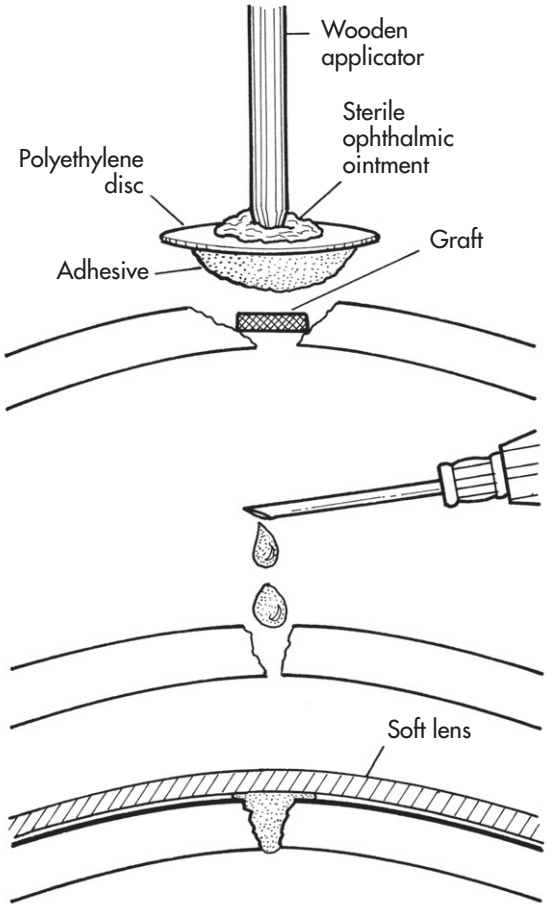


Figure 24.6. *A*, Method for sealing corneal perforation using a lamellar donor graft and cyanoacrylate tissue glue. *B*, Alternative method for glue application using tuberculin syringe and a 25- to 27-gauge needle to fill the defect.

3. The area is thoroughly dried with cellulose sponges because the polymerization of the glue occurs more efficiently without moisture.
4. Often optional, a lamellar piece of fresh or glycerin-preserved cornea or sclera is created and free-hand cut to fill the defect.
5. A small polyethylene disc having a 3–4 mm diameter is cut and affixed to the blunt end of a wooden applicator stick with a small amount of sterile ophthalmic ointment.
6. A tiny drop of the cyanoacrylate glue is placed on the face of the disc, and the disc–glue combination is pressed onto the once again dried perforation site and held in place for 1–2 min while polymerization occurs.
7. Often optional, a soft contact lens is fitted over the corneal glue site with a small air bubble maintained to demonstrate vaulting. This contact lens acts to separate the lids from the often heaped-up and hardened glue that can appear around the edges of the disc, which is otherwise quite irritating to the eyelid.
8. If the chamber does not deepen, the area is not sealed and the procedure can be repeated immediately.
9. If the gluing procedure is not successful and a lamellar patch graft with or without a partial conjunctival flap is contemplated, all the previously placed glue must be carefully removed just before placement of the patch graft. If this removal is not done, the underlying glue may cause considerable inflammation and necrosis of the overlying tissue with continued leaking of the site (Fig. 24.7).

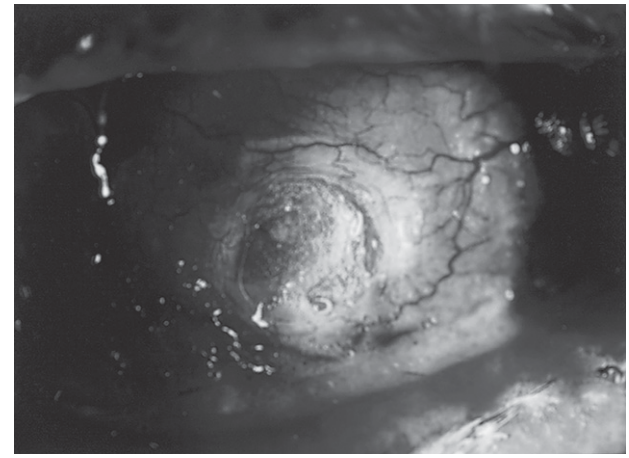


Figure 24.7. Necrosis of conjunctival flap 3 weeks after placement over tissue adhesive used to seal perforation. Toxic breakdown products of glue cause severe necrosis of overlying tissue (conjunctival flap or corneal patch graft). All glue should be meticulously removed before placement of tissue over the perforation site.

Fibrin tissue glue

Fibrin tissue glue has these components: human fibrinogen concentrate, bovine fibrinolysis inhibitor, human freeze-dried thrombin, and calcium chloride solution.[64] By mimicking the body's own response to injury, fibrin creates a clot that allows tissues to stick together. Within 3–5 min of delivery a coagulum forms, with 70% of its ultimate strength derived in the first 10 min and full strength developed by 2 h.[88] Fibrinogen converts to fibrin strands, which bind collagen together into a clot-like structure. In order to minimize the risk of pathogen transmission, the fibrinogen is vapor heated and freeze dried in its commercial preparation.[72]

METHOD OF APPLICATION OF FIBRIN GLUE

Prior to mixing, the components are placed for 10 min in a 37°C water bath. To avoid premature coagulation, the fibrinogen and thrombin are separately placed into each side of a double-barreled syringe, allowing their mixing only when the two components come together in a common cannula on injection at the surgical site. The glue rapidly solidifies at the treatment area and forms an opalescent gel solid, which fades with time. The fibrin complex acts to provide a smooth surface for epithelial overgrowth and stable matrix for later scar formation. The incorporation of the fibrin plug under the epithelium and into the corneal stroma provides an additional tectonic benefit for the weakened cornea.[64] Individual techniques notwithstanding, the following is a general method for fibrin glue placement:

1. Prepare the fibrin glue according to kit instructions.
2. After applying topical anesthesia, remove the epithelium around the involved area to better demarcate the level of the stroma involved.
3. Remove loose debris and dry the area to be treated thoroughly with cellulose sponges.
4. Apply fibrin glue with the fine cannula provided, which both mixes and delivers material to the treatment site.

5. Place the drop solution only to the anterior-most level of the stroma, which will thereby underfill the ulcer and allow transverse horizontal re-epithelialization.
6. The immediate post-treatment placement of a soft bandage lens to be used for the next 2–3 weeks aids in both supporting the plug and allowing the epithelial regrowth to proceed more easily.[64]

Fibrin glues are currently available commercially from these sources: Beriplast Fibrin Sealant (Nycomed, Roskilde, Denmark), Hemaseel Fibrin Sealant (Haemacure Corporation, Sarasota, FL, USA), and Tiseel VH Fibrin Sealant (Baxter, Deerfield, IL, USA).[72]

ADVANTAGES OF FIBRIN GLUE AS A TISSUE SEALANT

Fibrin glue in the operating room is more quickly applied than multiple suture placement[88] and may permit more rapid healing than CATA. There is less corneal vascularization than with CATA.[89] Its placement is quite easy and can be performed by most ophthalmologists in a simple setting.[64] The fibrin material does not foam up, thereby allowing better judgment on application height; it lies flat once applied and is better biologically incorporated, thus promoting more rapid re-epithelialization.[64] Finally, because it is biodegradable and flexible, it can be placed more easily beneath tissues with less inflammatory response and less discomfort to the patient both during and after treatment.[72]

DISADVANTAGES OF FIBRIN TISSUE GLUE AS A SEALANT

Fibrin requires a significantly longer time for adhesive plug formation than CATA.[89] CATA may be better for perforations that are smaller than 2 mm, as it adheres more strongly to stromal elements than fibrin.[64] Fibrin's low inflammation-inducing property may be a disadvantage if vascularization is desired in order to hasten wound healing.[72] Autologous fibrin glue must be used to limit the potential transmission of diseases such as those caused by prions and viral particles.[72] Other disadvantages of fibrin glue are its relatively short life of less than 2 weeks, which may require repeated applications, and its being a somewhat more expensive treatment if it is required to be used repeatedly.[72,88]

TECHNIQUE FOR LAMELLAR 'BLOW-OUT' PATCH GRAFTING

If a corneal perforation of greater than 2–3 mm is present, the site should be repaired with a small lamellar or full-thickness graft (Fig. 24.8). An alternative method of converting the circular defect to an elliptical one, which is then sutured and glued, has also been reported.[90] Penetrating keratoplasty is to be avoided because these grafts do poorly in inflamed, often infected, and hypotonous eyes.[75] The technique itself varies, but general principles apply.[2]

Preparation of recipient perforation:

1. Local anesthesia is preferred, but care must be taken to minimize ocular squeezing during the placement of the lid and retrobulbar block.
2. A lid speculum is placed.
3. The epithelium and necrotic tissue are carefully removed for 2–3 mm outside the perforation site, and an application of cyanoacrylate glue can be made in the usual manner to seal the perforation (see Fig. 24.8, *A*).
4. After the glue has been placed, a paracentesis can be made, and balanced saline solution, hyaluronate, or both are injected into the anterior chamber to restore normal depth and pressure.
5. Small 'sizing' corneal trephines are gently placed over the perforation site so as to leave a small cuff of normal tissue about the central inflamed core (Fig. 24.8, *B*). Usually a 3- or 4-mm trephine will suffice.
6. A mark is made with a trephine, and the resulting circle is deepened with a razor blade or diamond knife to one-half to two-thirds the corneal depth (Fig. 24.8, *B*). The usual spinning trephination is more difficult because of the ocular hypotony.
7. The area of clear cornea inside the ring is dissected off to about one-half the corneal depth with a #6600 Beaver lamellar or comparable blade (Fig. 24.8, *C*). Air can be injected into the recipient stroma around a descemetocele to temporarily thicken the stromal bed and to facilitate the deep lamellar dissection without perforation.[91]

Preparation of donor:

1. A donor whole eye—fresh, frozen, or glycerin preserved—is inflated to normal or just above normal intraocular pressure and is placed in a donor eye holder.

TECHNIQUE FOR CREATING A LAMELLAR DONOR BUTTON

1. The epithelium of the donor is removed and a one-half corneal-depth trephination (0.3–0.4 mm) is made with a 6–8-mm corneal trephine (Fig. 24.8, *D*).
2. Using a lamellar dissector, a two-thirds corneal-depth incision is created over 80% of the button, with care being taken to allow a small area of nonseparated cornea to remain at the distal edge of the dissection so that the button created remains hinged along this remaining area (Fig. 24.8, *E*). The proximal edge of the button is sutured back to the edge of the adjoining corneal surface with one to three interrupted 10-0 nylon sutures (Fig. 24.8, *F*). The hinge on one side and the interrupted sutures on the opposite result in a firm seating of the lamellar button once again on its bed. This approach prevents graft rotation on subsequent trephination of the button to be used in creating the patch graft.
3. The appropriately sized trephine, determined on prior inspection of the recipient eye, is then used to create the exact-sized button for the patch graft (Fig. 24.8, *F*).
4. The donor button thus created is placed over the recipient site and affixed with multiple interrupted sutures, a short running 10-0 nylon suture, or Figure 24.8 mattress sutures with buried knots (Figs 24.8, *G* and 24.9, *A*).
5. Often optional, a soft contact lens may be used to promote re-epithelialization, and appropriate antibiotics and cycloplegic drops are administered.
6. Corneal sutures are removed 1–3 months after surgery (Fig. 24.9, *B*).
7. Some surgeons prefer a full-thickness corneal button to use as the donor. In this case, it is appropriate simply to create a 3–4-mm full-thickness button with a corneal punch as described above.

8. The use of donor, preserved keratoconus corneas has been recently described as useful in therapeutic corneal patching in fungal ulcers with perforation.[92]

AMNIOTIC MEMBRANE TRANSPLANATION

Amniotic membrane is the innermost layer of fetal membranes. It is comprised of stromal matrix, a thick collagen layer, and an overlying basement membrane with a single layer of epithelium. It has a combination of antiadhesive effects, bacteriostatic properties, and wound-protective abilities, and its surgical use allows both the reduction of pain and the enhancement of tissue epithelialization. It has a lack of immunogenicity and has been used as a surgical material for several decades.[93]

MECHANISM OF ACTION OF THE AMNIOTIC MEMBRANE GRAFT

The presence of normal corneal substrate is critical to normal epithelial differentiation and proliferation. The corneal basement membrane acts to facilitate the migration of epithelial cells and reinforce the adhesions of basal epithelial cells, and helps to promote epithelial differentiation while preventing epithelial apoptosis. The amniotic membrane also acts as a transplanted basement membrane, which serves as a healthy substrate 'scaffolding' allowing proper re-epithelialization. In addition, the membrane provides various growth factors such as basic fibroblastic growth factor, hepatocyte growth factor, and transforming growth factor β, which can stimulate epithelialization. The tissue can act as a 'bandage lens' promoting healing while simultaneously acting to inhibit protease activity. Through its antifibrotic effect it induces a downregulation of the transforming growth factor β's signaling and thereby reduces the fibroblastic activation seen in wound healing. Finally, amniotic membrane material can serve as a barrier that separates two potentially sticky surfaces, and its relatively avascular nature is believed to inhibit the incursion of new blood vessel growth.[94]

CONDITIONS WHICH MAY BENEFIT FROM AMNIOTIC MEMBRANE GRAFTS

Amniotic membrane grafts have been found to be useful in a variety of anterior segment conditions including: Mooren's ulcers;[95] severe

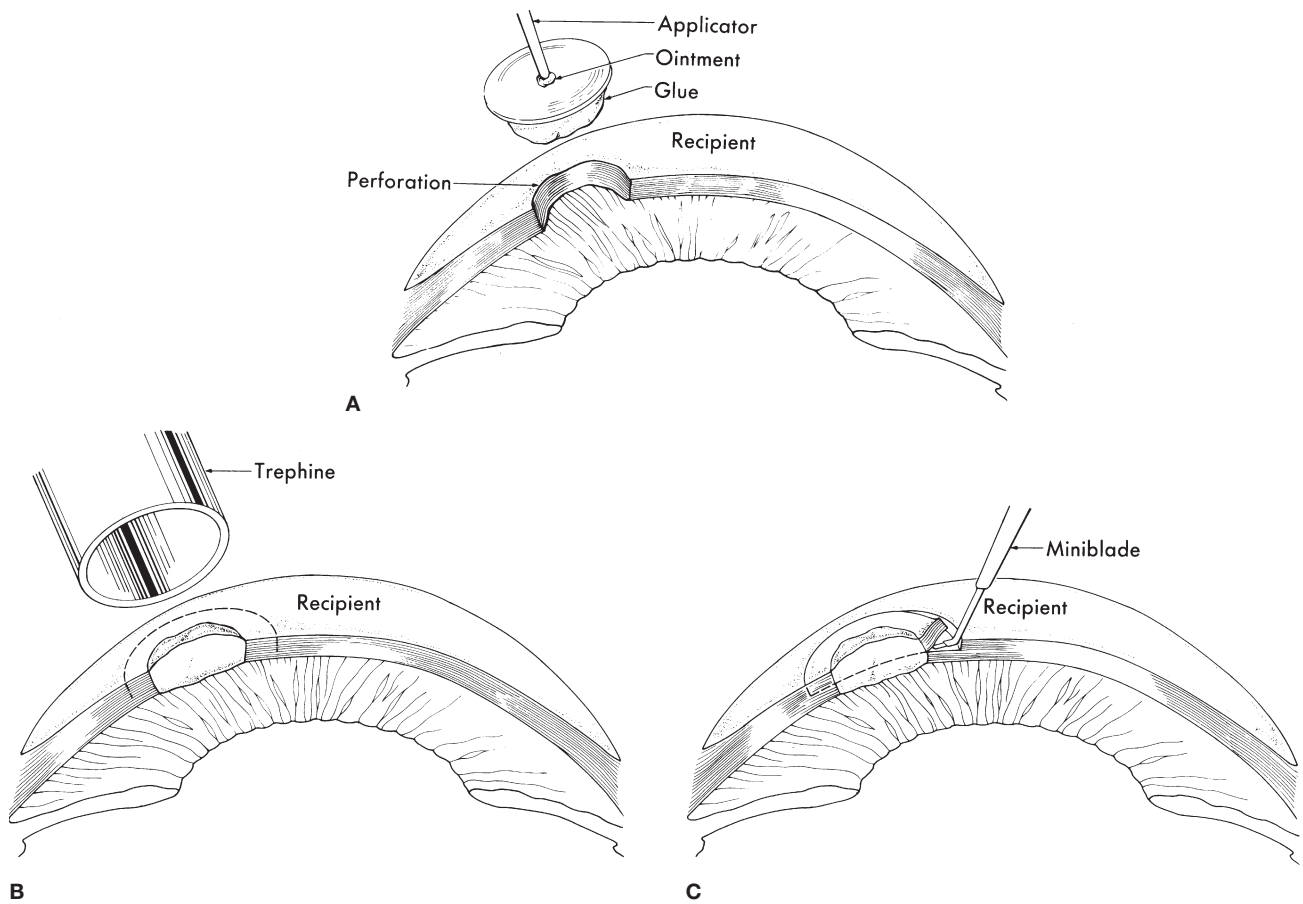


Figure 24.8. Lamellar keratoplasty principles used in creating a 'blow-out' patch graft for sealing a corneal perforation. *A*, Cyanoacrylate adhesive on a rounded plastic drape before application over the perforation site. Sodium hyaluronate can be used to push back adherent iris if necessary. *B*, Recipient perforation 'plugged' with glue. Sizing trephine outlines a one-half to two-thirds depth incision in normal cornea surrounding the perforation. *C*, No. 6600 lamellar blade dissection inside the trephine mark creates a bed for the 'patch' graft. Notice the perpendicular wall, which facilitates suturing of the button into the recipient bed. *D*, Trephination of donor cornea in the same general area as the recipient hole, outlining an incision of 0.3–0.4-mm depth. In some cases, full-thickness donor buttons trephined from the anterior corneal surface are satisfactory and will ultimately thin down and conform to recipient bed thickness. *E*, One method for dissecting donor lamellar graft in deep stromal plane. *F*, After reanchoring of dissected lamellar button with suture, a properly sized trephine creates the exact button desired. *G*, Donor cornea is sutured into the perforation with 10-0 interrupted nylon. Knots should be trimmed short or buried.

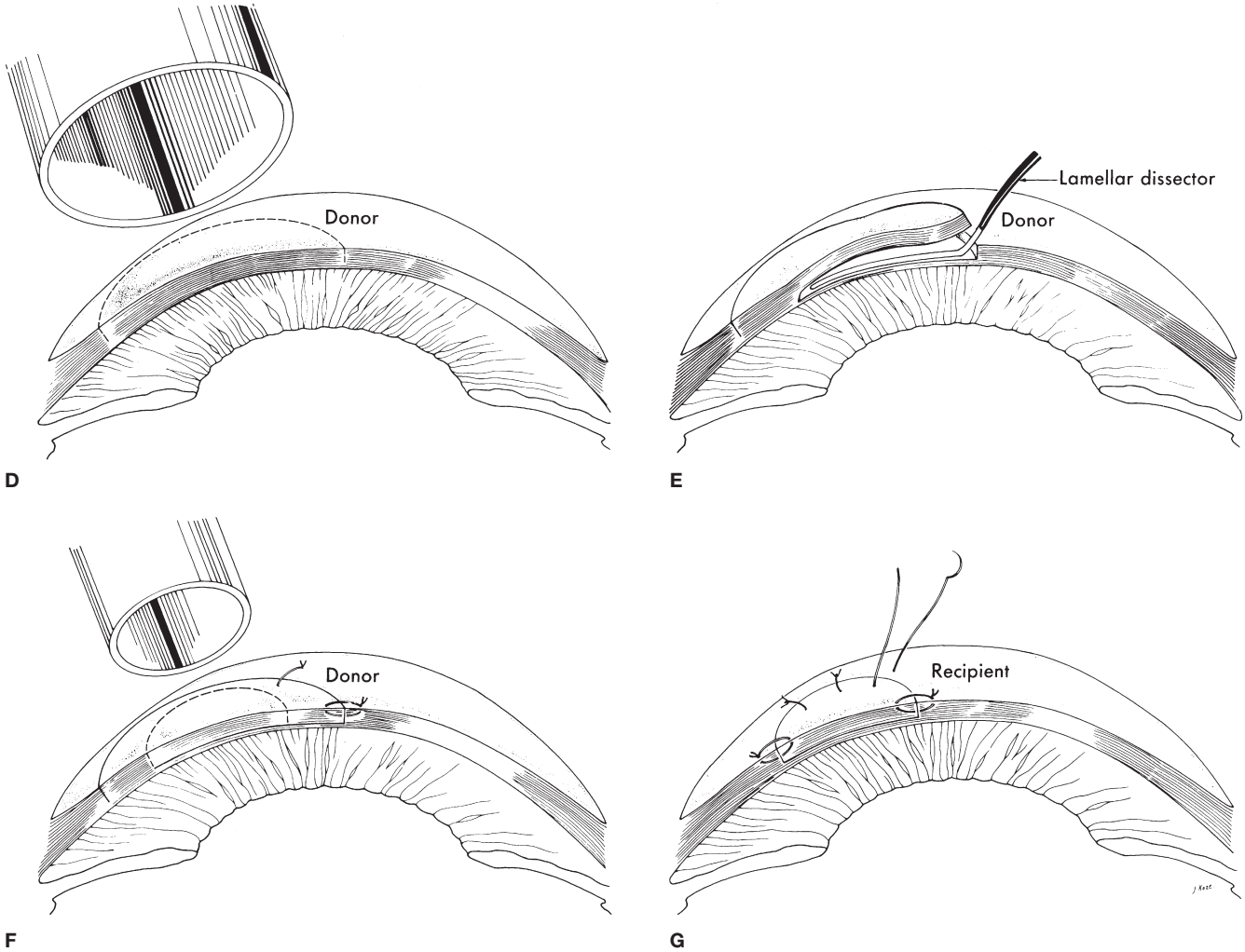


Figure 24.8. Continued

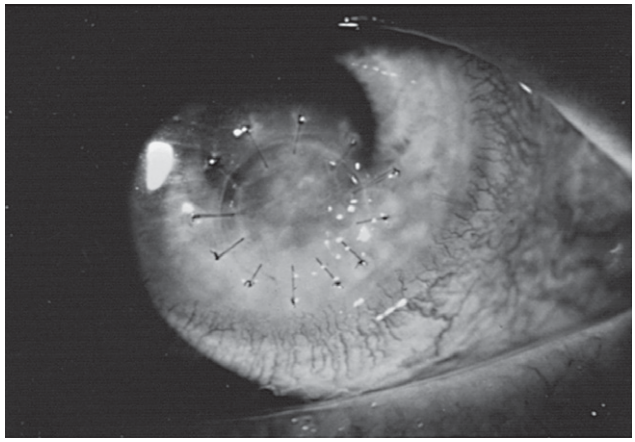
neurotrophic corneal ulcers;[96] persistent corneal epithelial defects;[68] as an adjunct in corneal and conjunctival surface reconstruction procedures;[96] as an alternative to conjunctival flaps, botulinum toxin injection or tarsorrhaphy;[94] as a substitute for transconjunctival grafting in pterygium surgery;[94] in combination with limbal stem cell transplantation in diffuse limbal stem cell deficiency states such as with Stevens-Johnson syndrome, advanced ocular pemphigoid, or chemical and thermal burns;[94,97,98] symblepharon;[93] nonhealing corneal ulcers;[99] nontraumatic corneal perforations and descemetoceles;[100] perforations of the cornea in hypovitamin A states;[101] severe and nonresponding corneoscleral and/or corneal ulcers;[102] corneal surface disorders in patients with Grave's disease;[103] and in acute ulcerative and necrotizing herpetic keratitis.[104]

PREPARATION OF PRESERVED HUMAN AMNIOTIC MEMBRANE FOR GRAFTING

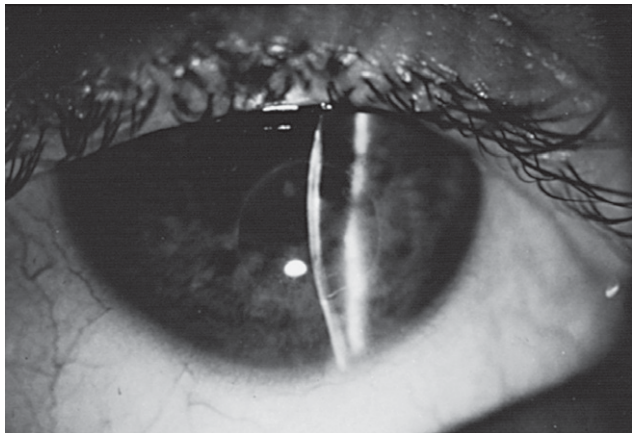
The membrane is screened for HIV infectivity, both types 1 and 2, human T-lymphoma virus type 1, hepatitis B and C viruses, and syphilis both at the time of caesarean delivery and at 6 months postpartum.[96] The harvested amniotic membrane is next flattened onto nitrocellulose paper, with the epithelium/basement membrane oriented surface up. It is stored in a sterile plastic vial at −80°C. When needed for use, it is defrosted by warming the container at room temperature for 10 min. The tissue is then rinsed three times in plain saline and then once in saline containing 100 mg dibekacin sulfate.[94] Celgene Cellular Therapeutics offers a packaged dehydrated human amniotic membrane allograft called Acelagraft. While this is a simple alternative to the preparation of the membrane, the major disadvantages are poor availability and high cost.

TECHNIQUE FOR PERFORMING AN AMNIOTIC MEMBRANE GRAFT FOR A PERSISTENT CORNEAL EPITHELIAL DEFECT OR ULCERATION

Debride the base of the ulcer or defect and the loose epithelium around the edge of the ulcer. Separate, with blunt forceps, the underlying chorion from the amniotic membrane or purchase prepared dehydrated or frozen amniotic membrane. Spread the membrane on the eye surface and cut it slightly larger than the area needed to be covered. The membrane is always placed with the epithelial side up and the mesenchymal surface in contact with the eye to facilitate adherence of the membrane to the ocular surface. Use 10-0 sutures to attach the membrane to corneal tissue and 9-0 Vicryl sutures to attach the membrane to the episcleral/conjunctival surface. After membrane suturing is complete, place a bandage contact lens, and apply antibiotic and steroid drops. Sutures can be removed approximately 3 weeks post-op.[94]



A



B

Figure 24.9. *A*, Lamellar patch graft anchored with 10-0 interrupted nylon sutures for rheumatoid patient with corneal melt (early in postoperative course). *B*, The same eye after healing and suture removal.

ADVANTAGES OF USING AMNIOTIC MEMBRANE GRAFTS

Amniotic membrane material contains both biological growth factors and anti-inflammatory factors.[64] The membrane is easily obtained and plentiful;[94] and can be preserved at –80°C for several months.[94] It does not express HLA-A, B, or DR antigens and is therefore not host rejected.[94] It may contain antimicrobial properties with a reduced risk of post-op infections.[94] Its antifibroblastic and cell migration/growth activities are helpful in complication-free healing.[94] Since the membrane heals rapidly and becomes transparent in a few weeks, vision recovery is sooner. The graft's relative avascularity also achieves greater cosmesis in comparison to conjunctival graft's more opaque appearance.[68]

DISADVANTAGES OF AMNIOTIC MEMBRANE GRAFTS

Amniotic membrane materials are not always available at all treatment centers worldwide. Cryopreservation technology and tissue banking facilities are required. Sutures are needed to hold tissue in place; as the grafted material can become unstable, tear and be dislodged, or can disintegrate before epithelialization has taken place. Experience is required for proper orientation of both the smooth epithelial and the sticky mesenchymal sides against the ocular surface.[64,94]

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25 Peripheral corneal disease with thinning

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Peripheral corneal ulcers and thinning disorders are unusual diseases that may be difficult to treat but rarely require surgical intervention. The mainstay of therapy for Mooren's ulcer is medical, with surgical intervention treatment only in the event of perforation or threatened perforation. Terrien's marginal degeneration and pellucid marginal degeneration may require surgical therapy to improve visual acuity or reinforce the cornea in the presence of severe thinning.

MOOREN'S ULCER

Mooren's ulcer is a chronic, painful, and devastating peripheral keratitis, rare in the USA but more common in developing countries. It was first described by Mooren in 1867.[1] The lesion begins with a steep, undermined, and occasionally infiltrated leading border and characteristically is confined to the periphery of the cornea in the early stages, but it relentlessly progresses, circumferentially and centripetally, to involve the whole cornea and occasionally the adjacent sclera.[2] With progression, the entire cornea may become thin, vascularized, and opaque. It is bilateral in 25% of cases but does not necessarily develop simultaneously. An interval of several years may lapse between the involvement of the first and the second eyes.[3,4]

CLINICAL DESCRIPTION OF PERIPHERAL CORNEAL DISEASE WITH THINNING

Patients with Mooren's ulcer usually complain of tearing, photophobia, and redness of the eye, but severe pain is typically the main symptom. Visual acuity can be decreased because of irregular astigmatism from peripheral corneal thinning or extension of the ulcer into the pupillary area. On examination, the disease may begin as one or two patches of grey infiltrate near the margin of the cornea, which slowly spread, coalesce, and eventually break down to form a shallow furrow. It may also begin as a narrow grey infiltrate near the limbus, which in a few weeks breaks down to form a marginal ulcer. The ulcer spreads around the periphery, toward the center of the cornea and occasionally into the sclera. The ulcer spreads slowly, undermining the corneal epithelium and the superficial lamellae so that a grey, infiltrated, overhanging edge is formed. This edge is characteristic of Mooren's ulcer.[5]

Wood and Kaufman[2] divided Mooren's ulcer into two groups. The first is a limited type that is unilateral, occurs in older male patients, does not have a racial predilection, and responds to conservative measures.[6] The second is a progressive type, most commonly occurring bilaterally in young black patients between 20 and 30 years of age and frequently involving the sclera as well as the peripheral cornea.[7] It is associated with severe pain and has a poor prognosis because it does not respond well to therapy, and one-third eventually develop corneal perforations.

HISTOPATHOLOGY

Histopathologic examination of the conjunctiva adjacent to the lesion shows numerous plasma cells, lymphocytes, and mast cells in various stages of degranulation. The corneal stroma, as well as the conjunctiva, is infiltrated with inflammatory cells, such as lymphocytes and neutrophils, that appear to be actively releasing their granules and forming phagocytic vacuoles.[8] The leading edge of the ulcer is infiltrated with leukocytes. The epithelium and Bowman's membrane overlying the lesion are destroyed, and in some cases all that is eventually left is Descemet's membrane. When the cornea is healed, conjunctival epithelium and vessels cover the most posterior corneal lamellae.

ETIOLOGY

The disease can be divided into two groups: primary and secondary. The most common of these groups is primary or idiopathic. The ulcer usually occurs without any precipitating cause and can manifest itself in either a limited or a relentless form. The secondary form, or Mooren's-like ulcers, occurs after various insults to the cornea, including cataract surgery,[9–11] penetrating keratoplasty,[12,13] corneal injuries such as foreign bodies or alkali burns,[2] and herpes zoster ophthalmicus.[10–14] Most secondary cases are unilateral and clinically behave like a limited form and generally respond well to therapy.

An association with Mooren's ulcer and chronic hepatitis C virus (HCV) has been described.[15–17] In these cases, the corneal disease

improved after treatment of the systemic disease. However, when a study in India compared 21 patients with Mooren's ulcer to 44 controls, none of the patients were hepatitis C positive, while one of the controls was. There was also no statistically significant difference in seropositivity rates for rheumatoid factor, ANCA, and antinuclear antibodies, but history of trauma, surgery, or infection was reported 3.4 times more frequently in patients with Mooren's ulcer.[18] Another study at Nehru Hospital examined 50 patients with chronic HCV infection and found that none of them had any evidence of Mooren's ulcer, suggesting that screening of HCV patients for Mooren's ulcer is unnecessary.[19] This agrees with the low estimated frequency of Mooren's ulcer in HCV patients—1 : 10 000 by Wilson et al.[17] The same team is investigating the possibility that HCV-associated flaviviruses are involved in Mooren's ulcer pathogenesis.[20]

In the past, Mooren's ulcer has been related to metabolic disorder and malnutrition, trophic disturbances involving the trigeminal nerve, deficiency of vitamin B1, and ancylostomiasis.[21] An Association with hookworm infection in patients from Sierra Leone was proposed in 1963[22] but could not be confirmed due to high rate of this parasitic infestation in the study population. Both patients and controls had the parasite and antibodies to it, although Mooren's ulcer patients had significantly higher titers.[23]

The etiology of Mooren's ulcer is unknown, but evidence suggests an autoimmune basis. Supporting evidence includes the presence of plasma cells and lymphocytes in the conjunctiva adjacent to the ulcer;[24] circulating antibodies to conjunctival and corneal epithelium in the serum of patients with Mooren's ulcer;[25–27] an elevation of serum levels of immunoglobulin (Ig)A, IgG, IgM, and C3;[25,26,28] lymphocytes sensitized to saline-soluble cornea antigen;[8] increased antibody levels to a cornea-specific stromal protein antigen;[29] increased helper T cell to suppressor T cell ratio;[28,30] and favorable response to immunosuppressive agents in some patients.[6,28] A unique cornea-associated protein that is present in the cornea and is the target of autoantibodies from patients with Mooren's ulcer was isolated and sequenced.[29,31] This Ca-binding protein, termed calgranulin C, is identical to a neutrophil protein found on the surface of filarial nematodes.[32] Calgranulins are a family of Zn- and Ca-binding proteins secreted by neutrophils, monocytes, and other immune cells. Calgranulin C absorbs on the surface of a parasite and has filaricidal and filaristatic activities.[33] Recognition of this complex on a filarial nematode is suspected to lead to autoimmunity to the cornea in patients with persistent parasitic infection resulting in Mooren's ulcer.

Mooren's ulcer may represent a final common pathway to a variety of insults to the cornea in susceptible patients. Trauma or infection may alter normal corneal antigens, which may lead to an autoimmune response. The cornea is further damaged, liberating more altered corneal antigens that aggravate and perpetuate the process until the corneal stroma is completely destroyed.[34]

DIFFERENTIAL DIAGNOSIS

Mooren's ulcer is a rare disease.[35] The differential diagnosis includes other inflammatory or noninflammatory causes of peripheral thinning, such as catarrhal ulcer, collagen vascular disease, and Terrien's degeneration. Terrien's degeneration[36] is a noninflammatory peripheral corneal thinning disorder that is usually superior, bilateral, and not associated with significant pain or inflammation unless there is an associated episcleritis or superficial scleritis. The corneal epithelium remains intact, and the disease progresses slowly circumferentially but does not involve the central cornea. Peripheral marginal keratitis (catarrhal ulcer), seen in association with staphylococcal blepharitis, can also demonstrate peripheral infiltrates. In these patients, the infiltrate is usually unilateral and separated from the limbus by a lucid interval, the pain is not severe, and the course is benign and self-limited.

Collagen vascular diseases, such as rheumatoid arthritis, polyarteritis nodosa, Wegener's granulomatosis, and systemic lupus erythematosus,[37] may also be associated with peripheral-corneal infiltrates and ulcers with features that resemble Mooren's ulcer, and an associated scleritis may be present.[38–43]

Scleritis is a well-recognized complication of rheumatoid arthritis.[40,42] The scleritis can spread into and involve the adjacent cornea as a sclerokeratitis, which may be associated with marginal thinning. However, a characteristic marginal corneal ulcer has been described in patients having rheumatoid arthritis with or without scleritis. The characteristic marginal furrows of rheumatoid arthritis were observed in patients who had the disease for at least 5 years. The marginal furrows were located approximately 1 mm within the limbus and usually in the inferior cornea, usually bilateral. It could be superficial and nonprogressive, or it could progress to epithelial breakdown, marked stromal thinning with descemetocele formation, and finally perforation. Usually, there was minimal inflammation and vascularization unless the lesion perforated. The marginal furrows may encircle the cornea, and bilateral involvement may be found. Occasionally, the entire superficial part of the remaining central island of corneal stroma may slough away.

To make the distinction between all these diseases, history and serologic testing may be indicated. Foster[30] recommends that all Mooren's ulcer patients need to undergo a general history, a medical examination, and laboratory studies that should include complete and differential blood cell counts, platelet counts, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibodies, chest X-ray examination, liver enzymes, Venereal Disease Research Laboratory, fluorescent treponemal antibody absorption test, blood urea nitrogen, serum protein electrophoresis, and urinalysis.

THERAPY

Currently, a stepladder approach to therapy is recommended.[6] The objective of the therapy is to stop the progression of the ulcerative process and promote the re-epithelialization of the ulcerated area. Symptoms of pain and photophobia and inflammatory signs of conjunctiva hyperemia and edema generally disappear shortly after healing is complete. Brown and Mondino[6] suggest a stepladder approach that includes topical corticosteroids, conjunctival resection, and systemic immunosuppressives. Table 25.1 summarizes results using this approach in 44 eyes of 28 patients. Most of the cases (31 of 44 eyes) healed with this regimen. Other surgical treatments are possible, but their indications are rare and specific.

Topical corticosteroids

Initially, patients with Mooren's ulcer are treated with topical corticosteroids, usually prednisolone acetate 1% every hour, as long as there is no sign or danger of imminent perforation. If the ulcer heals completely, the frequency of topical drops can be slowly tapered. Aggressive therapy with topical corticosteroids may be effective in unilateral and bilateral nonsimultaneous cases but not in bilateral simultaneous cases. Patients with Mooren's ulcer are treated with topical antibiotics to prevent secondary bacterial infection. Cycloplegics can be administered to control the pain from spasm of the

Table 25.1 Treatment results for mooren's ulcer

	Topical Corticosteroid[a]	Conjunctival Excision[a]	Immunosuppression[a]	Total[a]
Unilateral	8/12	3/4	0/1	11/12
Bilateral nonsimultaneous	3/6	3/3	—	6/6
Bilateral simultaneous	4/22	2/15	8/16	14/26
Total	15/40	8/22	8/17	31/44

[a] Number of eyes healed/number of eyes treated with each treatment.

ciliary body. Topical corticosteroids must be used with extreme caution in patients having rheumatoid arthritis associated with corneal ulcers.

A novel experimental therapy of noninfectious corneal ulcers utilizing lecithinated superoxide dismutase in a form of topical drops has been described in a study on 19 eyes with corneal ulcers, 6 of them being Mooren's ulcer.[44] Superoxide dismutase reduces reactive oxygen metabolites produced by polymorphonuclear leukocytes to hydrogen peroxide, thus limiting tissue destruction by these toxic mediators of polymorphonuclear neutrophilic leukocyte (PMN) function. Dismutase therapy has been also successfully used in limiting hypoxic damage of muscle and lung tissue. In this study, Mooren's patients who failed topical corticosteroid therapy had an average 71.5% reduction of epithelial defect in 2 weeks of dismutase application, and some healed completely after 5 weeks of therapy.

Conjunctival resection

If there is an incomplete or absent response to topical corticosteroids, conjunctival excision may be performed adjacent to the ulcer.[45,46] After the topical application of proparacaine hydrochloride 0.5% for anesthesia (sometimes patients may require subconjunctival or retrobulbar anesthesia) and phenylephrine hydrochloride 2.5% for vasoconstriction, the conjunctiva is incised approximately 3 mm from the corneoscleral limbus and adjacent to the ulcer. The conjunctiva is dissected to the corneoscleral limbus and excised. The epithelium in the bed of the ulcer and less than 0.2 mm of corneal epithelium central to the ulcer are removed by simple debridement. Postoperatively, topical corticosteroids and antibiotics are continued. The procedure can be repeated if necessary. Conjunctival resection may be beneficial to patients with peripheral corneal ulcers associated with collagen vascular disease. Pathological examination of tissue excised in six bilateral Mooren's ulcer cases showed intact epithelium and basal membrane but edematous stroma with mixed cellular infiltration primarily of plasma cells and lymphocytes, with few neutrophils, mast cells, and eosinophils.[47] Hyperemia and hemorrhagic infiltration were present, but vessels showed no signs of necrotizing vasculitis. Aviel[48] describes a surgical technique with cryotherapy and peritomy in patients with Mooren's ulcer, and his results may have a similar effect to conjunctival excision.

Systemic immunosuppressives

Sometimes, patients with bilateral and progressive disease are very difficult to treat, and conjunctival excision does not result in total healing of the ulcer. In these cases, immunosuppressive therapy is considered and the supervision of an internist or oncologist is needed.

The most common immunosuppressive drugs used are cyclosphosphamide (2 mg/kg/day) and azathioprine (2 mg/kg/day) with or without prednisone (1 mg/kg/day). Alternatively, other medications could be used, such as methotrexate (7.5–15 mg/week). Some authors treat Mooren's ulcer with systemic and topical cyclosporin A (0.5%) and report favorable results.[49–51] The efficacy of topical cyclosporin is attributed to local depression of the ocular immunopathologic reaction.[51]

If healing does not occur after 1 or 2 months, immunosuppressive therapy is slowly decreased and then discontinued. On the other hand, if some healing is observed, the medication is continued until complete healing and then for an additional month after which the dosages are slowly decreased. During treatment, dosages of the medication are titrated to maintain a hemoglobin level of 10 g/100 mL or more, a white blood cell count of more than 3000 cells/mm with at least 1500 neutrophils/mm, and a platelet count of more than 100 000 platelets/mm. A complete blood cell count, including platelet count, is obtained for each patient taking cyclosphosphamide or azathioprine weekly for the first month of therapy, twice each month for 2 months, and once each month thereafter if hematologic findings are stable.

The peripheral corneal ulcers associated with collagen vascular diseases may also respond to systemic immunosuppressives.[41] Therapy for corneal ulceration and scleritis in patients with collagen vascular diseases should focus initially on the management of the systemic disease. Medical and rheumatologic consultation is important because of the increased mortality in patients without proper treatment. Systemic immunosuppressive agents, including corticosteroids, have been proven effective in the treatment of scleritis and ulcerative keratitis. Moreover, cytotoxic agents may improve long-term survival.

Interferon-α2b

Recently, an association has been reported between Mooren's ulcer and hepatitis C infection.[15–17] In some cases, a bilateral ulcer that did not respond to any form of conventional therapy demonstrated a marked improvement after treatment with systemic interferon-α2b for the chronic active hepatitis. In another example, the corneal disease improved after 6 weeks of interferon-α2b treatment, abruptly worsened when interferon was discontinued, and improved again when the medication was reinstituted.

Surgical procedures

An overall schematic plan for the surgical treatment of peripheral corneal perforations is presented in Figure 25.1.

Tissue adhesive

Some patients progress to corneal perforation. If the perforation is less than 1 mm in size, the best treatment is the tissue adhesive, isobutyl-cyanoacrylate (see Fig. 25.1, *A*). The adhesion is formed by polymerization of d-alkyl-2-cyanoacrylate monomers. This

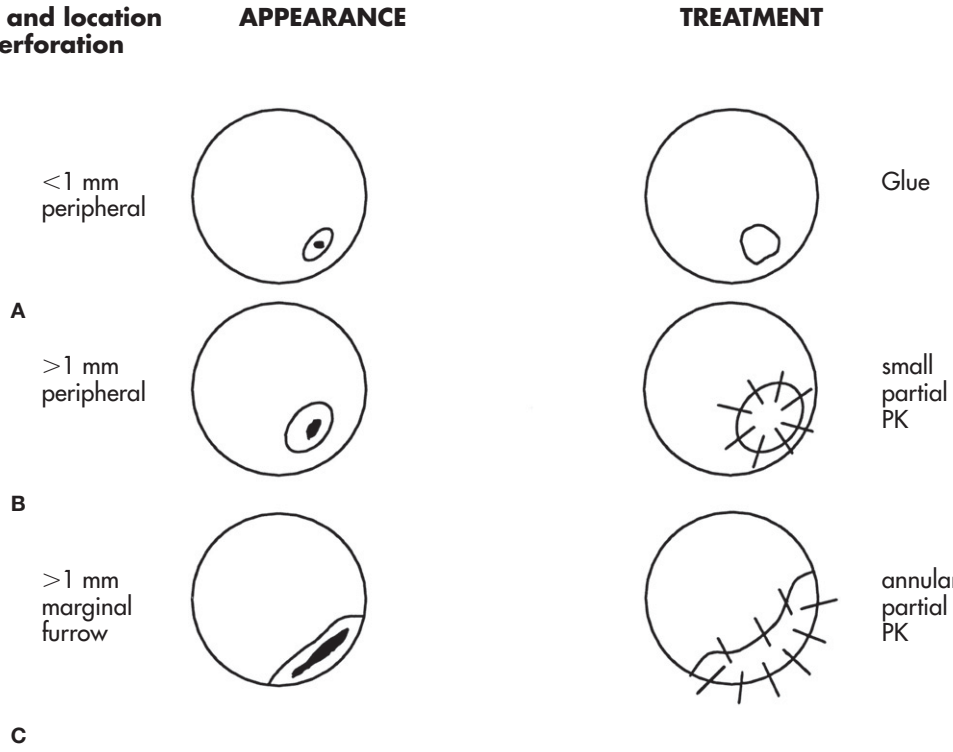


Figure 25.1. Diagrammatic approach to the treatment of peripheral corneal perforations. The area in the figures represents the ulcer bed, and the black area within represents the perforation. *A*, For peripheral perforations 1 mm and less, tissue adhesive is the first line of treatment. *B*, If tissue adhesive fails or the perforation is greater than 1 mm, a small partial peripheral penetrating keratoplasty may be performed. *C*, In cases of marginal ulcerations and perforations, an annular peripheral penetrating keratoplasty is often necessary.

monomer is an electronegative liquid that, in the presence of anions, polymerizes and becomes a solid adhesive. Animal and human studies show that if the application is done at an early stage, before perforation, prompt arrest of the ulceration may occur by preventing the migration of polymorphonuclear leukocytes into the ulcerated area.[52,53]

Several methods of application have been described; because the adhesive rapidly polymerizes on contact with water, it must be applied carefully on a dry surface to minimize formation of a large, elevated, rough mass. One technique that maximizes the chances of obtaining a smooth surface is to apply the adhesive using a small polyurethane disc, which may even be cut from surgical drape material. Then a small drop of adhesive is placed on the other side of the disc and held upright. The area of perforation or ulceration is de-epithelialized and dried. The adhesive and disc are then applied to the area. The eye is irrigated with balanced salt solution to completely polymerize the adhesive. The disc overlying the adhesive minimizes the chances for a rough surface.

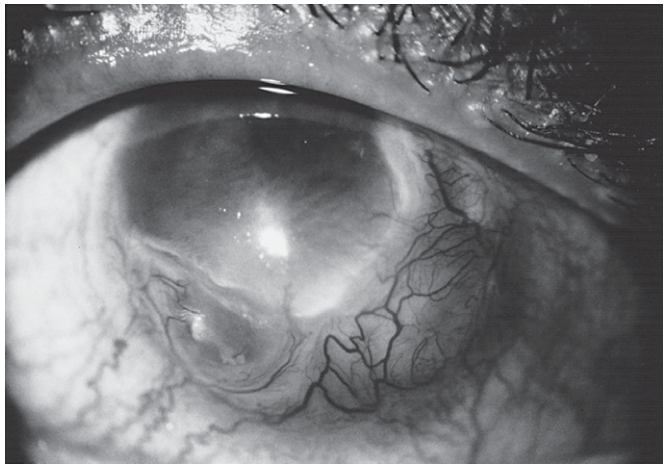
Keratoplasty

When a perforation is too large for tissue adhesive to seal the leak, some type of patch graft may be necessary (see Fig. 25.1, *B, C*). This patch may range from a tapered plug of corneal tissue to a peripheral penetrating keratoplasty.[54] A small piece of corneal tissue is fashioned into a tapering plug to fill the defect. The anterior chamber can be filled with sodium hyaluronate or similar viscous substance to protect and cushion the corneal endothelium. The margins of the perforation site should be cleaned of any necrotic material and epithelial tissue. The plug is placed in the perforation site and sutured into place with interrupted 10-0 nylon suture. When suturing to the thin peripheral cornea, the bite should be through and through and extend into adjacent sclera.

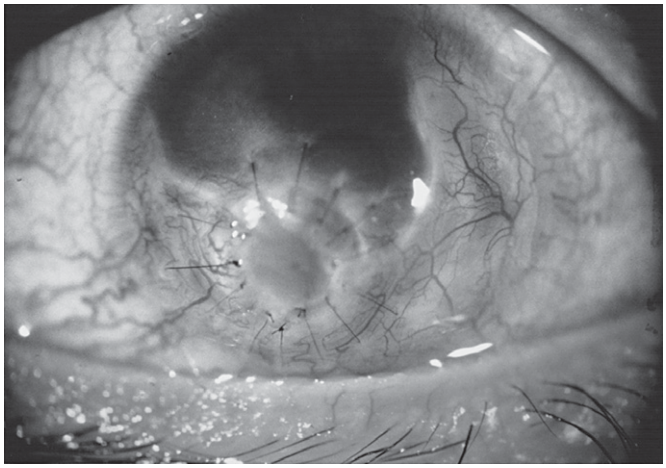
In cases of larger peripheral perforations, a partial penetrating keratoplasty may be performed (Fig. 25.2, *A–C*). This procedure is performed by marking the area around the perforation with a trephine of appropriate size. Next, the perforation site is entered with one blade of the corneal scissors. The cornea is incised and then excised along the trephine mark. A button of larger size is then sutured into place using interrupted 10-0 nylon suture. Penetrating keratoplasty has also been described in patients with healed Mooren's ulcers, but the results are generally poor. Penetrating keratoplasty may be complicated by the recurrence and extension of the disease process into the donor tissue with resultant necrosis and sloughing. In Mooren's ulcer, penetrating keratoplasty may restore some vision in a healed and quiet eye with an opaque or scarred cornea (Fig. 25.3, *A* and *E*). When the cornea is not perforated, a crescentic annular lamellar graft is rarely used in cases of peripheral corneal thinning. In these cases, the area of the recipient cornea to be repaired is marked using trephines. The edge of the marked cornea is lifted, and a lamellar dissection is then performed. The donor cornea is then trephined and placed into the recipient bed and sutured in place with interrupted 10-0 nylon (Fig. 25.4, *B*).

AMNIOTIC MEMBRANE TRANSPLANTATION

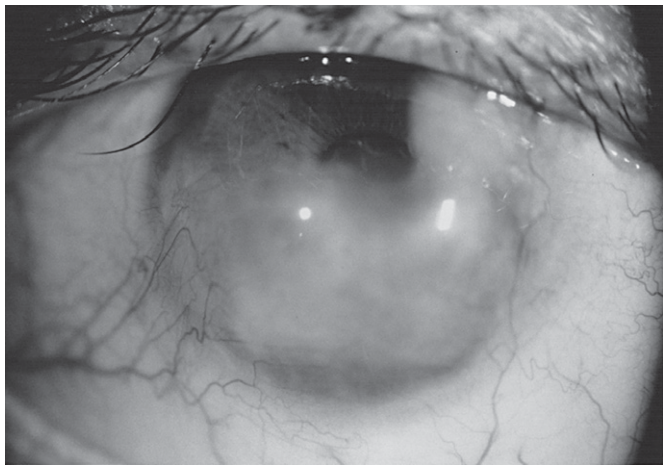
An alternative treatment for reconstruction of ocular surface and corneal stroma damaged by an immunologic process involves the use of amniotic membrane (AM). Although exact mechanisms of its function are not clear, AM has been shown to possess anti-inflammatory and anti-immunogenic qualities and may be a substrate for stromal reconstruction due to abundance of collagen IV and fibroblasts in this tissue.[55] A few authors attempted to limit Mooren's ulcer progression as well as reconstruct damaged cornea with single- and multilayer AM transplantation. The former method involves placing an AM stromal side down onto the ulcerated defect and securing it with sutures.[56–58] Multilayer AM fragments can be



A

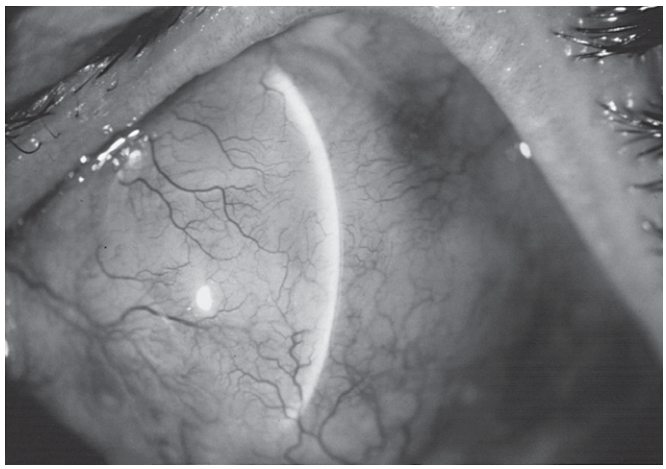


B



C

Figure 25.2. *A*, A typical bilateral Mooren's ulcer, which progressed despite intensive medical treatment to peripheral corneal perforation. *B*, Surgical treatment with small partial penetrating keratoplasty in the area of perforation. *C*, Long-term follow-up showing the disease in a quiescent stage.



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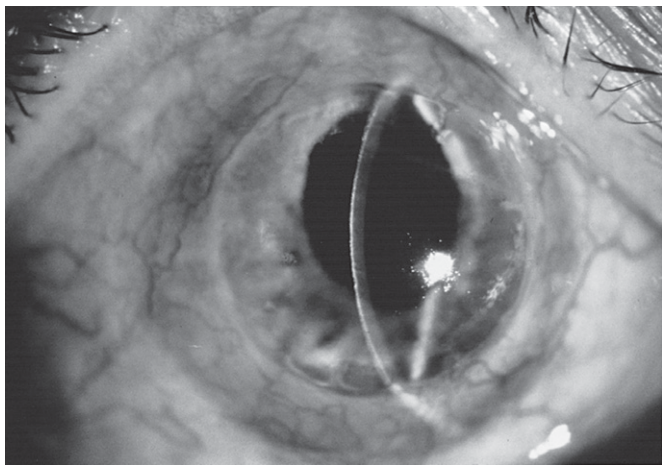
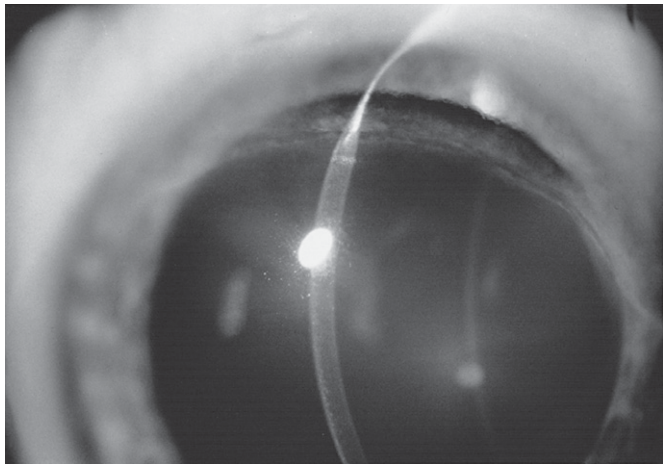


B

Figure 25.3. An end-stage case of Mooren's ulcer. *A*, Advanced corneal destruction with thin cornea and vascularization. *B*, The cornea several weeks after a central penetrating keratoplasty to restore ocular integrity.



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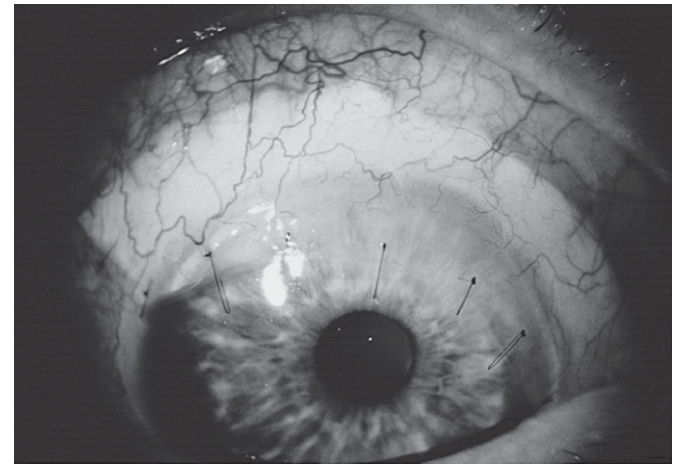

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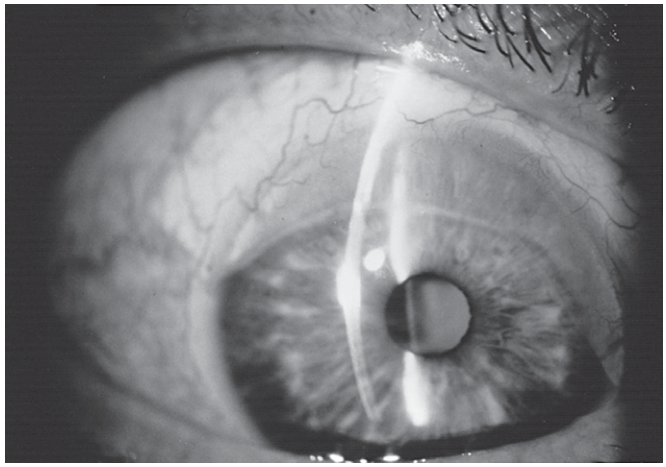

C

Figure 25.4. *A*, Preoperative photograph of Terrien's marginal degeneration with severe superior peripheral thinning. *B*, Early postoperative result of crescentic lamellar keratoplasty to treat severe thinning in Terrien's marginal degeneration. *C*, Long-term postoperative result of crescentic lamellar keratoplasty. (Courtesy of Thomas H. Pettit, MD, Los Angeles, CA.)

placed into a stromal ulcer defect to facilitate fibroblast migration and proliferation, as well as to provide a matrix for healing. This is then covered with a single-layer AM suture stromal side down. In summary, AM transplantation may be a promising anti-inflammatory treatment for Mooren's ulcer, but currently clinical data are limited and require further investigation.

OTHER SURGICAL PROCEDURES

Mooren's ulcer has been treated with keratoepithelioplasty.[59] In this procedure, donor corneal lenticules are sutured into the scleral bed after conjunctival excision. Corticosteroids are administrated postoperatively for more than 6 months. The use of an autogenous periosteal graft has been reported for the treatment of scleral thinning after lamellar keratectomy.[60]

When all fails, and the ulcerative process has progressed to the extent that only a central island of residual stroma remains, Brown and Mondino[6] recommend excision of the island to prevent central ulceration, accelerate epithelial healing, and resolve pain. The corneal stroma is probably the target of the destruction in Mooren's ulcer because once the stroma is totally destroyed or removed by excision, ulceration and associated inflammation stop and central transparency remains to allow some vision.

CONJUNCTIVAL FLAP

There are still occasions when medical and surgical therapy fail and the patient experiences pain from recurrent epithelial breakdown with stromal ulceration. A conjunctival flap will often provide comfort, reduce the ocular inflammation, and promote healing in these patients. It is especially useful for elderly, debilitated patients for whom prolonged hospitalization and medical therapy may not be warranted.

CATARACT SURGERY

After complete control of inflammation has been established, patients with Mooren's ulcer can undergo cataract extraction. Two small studies indicate that visual outcomes are usually good and ulceration is not exacerbated.[61,62]

TERRIEN'S MARGINAL DEGENERATION

Terrien's marginal degeneration is a chronic progressive thinning of the peripheral cornea associated with vascularization and lipid deposition. Two-thirds of the patients are males and are 40 years or older. The age at onset, however, ranges from 10 to 70 years. The disease is usually bilateral but may initially present in one eye.[63] As the disease progresses, marked astigmatism and severe peripheral corneal thinning often develop. The risk of spontaneous or traumatic corneal rupture is high.[64] Surgical intervention is required to correct visually disabling astigmatism, prevent impending perforation, and treat frank perforation.

CLINICAL FINDINGS

Terrien's marginal degeneration usually begins superonasally with peripheral, fine, yellow-white punctuate stromal opacities. A lucid zone separates the opacities from the limbus. With time, the opacities coalesce into a line similar to arcus senilis, superficial vessels advance into the line from the limbus, and the intervening stroma gradually thins (see Fig. 25.4, *A*).[63] The thinning slowly spreads circumferentially and in rare cases centrally.[65] In the advanced stages, localized areas of ectasia develop along the course of corneal thinning. Circumferential ectasia is rare.[64] Epithelium remains intact throughout the course of the disease.

The disease process is extremely slow, often taking 30 years. Vision gradually deteriorates because of increasing against-the-rule astigmatism. Perforation occurs in 15% of the reported cases and can be either spontaneous or following minor trauma.[64] Spontaneous breaks in Descemet's membrane have been reported as well. The overlying Bowman's layer remained intact, resulting in corneal intralamellar dissection and corneal cysts.[66,67] Occasionally, intracorneal aqueous pockets become continuous with subconjunctival space and result in filtering blebs with hypotony.[67] In two of the five reported cases, intracorneal cysts resolved spontaneously. The remaining three required surgical intervention.

Pseudopterygia occur in 20% of patients with Terrien's marginal degeneration. The pseudopterygia characteristically occur in positions other than 9 o'clock and 3 o'clock and grow onto the cornea at an oblique angle. They may occur in the early stages of the disease when thinning is subtle.[65]

Most patients with Terrien's lack significant inflammatory signs and symptoms. Austin and Brown,[64] however, reported six patients with recurrent, disabling ocular pain associated with episcleritis or superficial scleritis. Most of the patients were young females. None demonstrated progression of the corneal changes during the 6 years of follow-up.

HISTOPATHOLOGY

Histopathologic reports of corneal specimens from patients with Terrien's marginal degeneration reveal the following findings. The epithelium, except for the basal layer, is intact. Basal epithelial cells are degenerated. Bowman's layer and anterior stromal lamella are lost and replaced by vascularized loose connective tissue. The vessels originate at the limbus, advance centrally within the superficial connective tissue, loop at the central margin of the furrow, and migrate back to the limbus passing just anterior to Descemet's membrane.[68]

The remaining stromal lamella is compressed, and lipid deposition is evident. Lipid deposition is most prominent anterior to the vascular arcades. Histiocytes line the blood vessels and are laden with the phagocytosed lipid, corneal collagen, and ground substance. There is evidence of high lysosomal activity within the histiocytes, consistent with an ongoing degradation of corneal tissue.[68] Tear fluid in patients with Terrien's degeneration has a three-fold higher level of lysosomal enzymes than the tear fluid collected from age-matched controls.[69]

Descemet's membrane is usually intact but is either thickened or thinned. Several reports describe the presence of healed ruptures of Descemet's membrane. The endothelium is intact and is either normal or attenuated.[68,70]

PATHOGENESIS

The cause of Terrien's marginal thinning remains unknown. Its bilaterality, extremely slow progression, lack of significant clinical and histologic inflammation, and lipid deposition suggest a degenerative process in most cases. Association of Terrien's with posterior polymorphous dystrophy,[71] keratoconus,[72] and erythema elevatum diutinum[73] has been described in isolated cases.

Recurrent bouts of episcleritis and scleritis associated with Terrien's in the six patients described by Austin and Brown[64] suggest an inflammatory mechanism in a subset of patients. Iwamoto et al[74] distinguished two forms of Terrien's degeneration based on histopathology: quiescent and inflammatory. The inflammatory form was characterized by perivascular lymphocytic and neutrophilic infiltration, vascular occlusion, and fibrinoid necrosis. Austin and Brown,[64] however, disputed the existence of the inflammatory form of the disease, stating that the authors' clinical photographs and their description of central progression with epithelial breakdown were more consistent with Mooren's ulcer than with Terrien's degeneration.

DIFFERENTIAL DIAGNOSIS

Several conditions may clinically mimic some of the features of Terrien's disease. Arcus senilis may mimic the peripheral opacification associated with early stages of Terrien's disease. Arcus senilis, however, is characterized by both superior and inferior peripheral corneal opacification, absence of vascularization, and lack of corneal thinning. Peripheral corneal thinning is seen in collagen vascular diseases, gutter or furrow degeneration, pellucid marginal degeneration, and Mooren's ulcer. The symptomatology, morphology, and associated systemic findings should distinguish these conditions from Terrien's marginal degeneration.

Corneal thinning seen in collagen vascular diseases, such as rheumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa, and relapsing polychondritis, is usually associated with systemic findings of arthritis, renal and sinus abnormalities, or vasculitis. Rheumatoid factor, or antineutrophil cytoplasmic antibody, or antinuclear antibody levels are usually elevated. Gutter or furrow degeneration lacks vascularization. Peripheral corneal thinning associated with pellucid marginal degeneration is inferior and lacks lipid deposition and vascularization. The most common disease that can mimic Terrien's disease is a healed Mooren's ulcer. Both lack systemic findings. Mooren's ulcer may be either bilateral or unilateral, whereas Terrien's is usually bilateral. An

active Mooren's ulcer is usually associated with pain and conjunctival inflammation, whereas Terrien's is usually painless and uninflamed.

An epithelial defect is usually present at the central edge of an active Mooren's ulcer, whereas the epithelium is intact in Terrien's marginal degeneration. Mooren's ulcer has an overhanging central edge, and inflammatory infiltrate may be present. Lipid is absent. Terrien's has a gradually sloping central edge with lipid deposition. Peripheral cornea may be vascularized in both conditions. Mooren's ulcer usually spreads rapidly, both circumferentially and centrally. Terrien's degeneration progresses slowly and circumferentially. Pathogenesis of Terrien's is unknown, but it is probably a degenerative process. Mooren's ulcer is probably an autoimmune process.

TREATMENT

Spectacles and contact lenses are used to correct astigmatism in mild cases of Terrien's marginal degeneration. When astigmatism becomes so extreme that optical means fail to correct the reduced vision or when thinning becomes so severe that corneal perforation occurs or is threatened, a reconstructive keratoplasty is performed (Fig. 25.4, *A–C*).

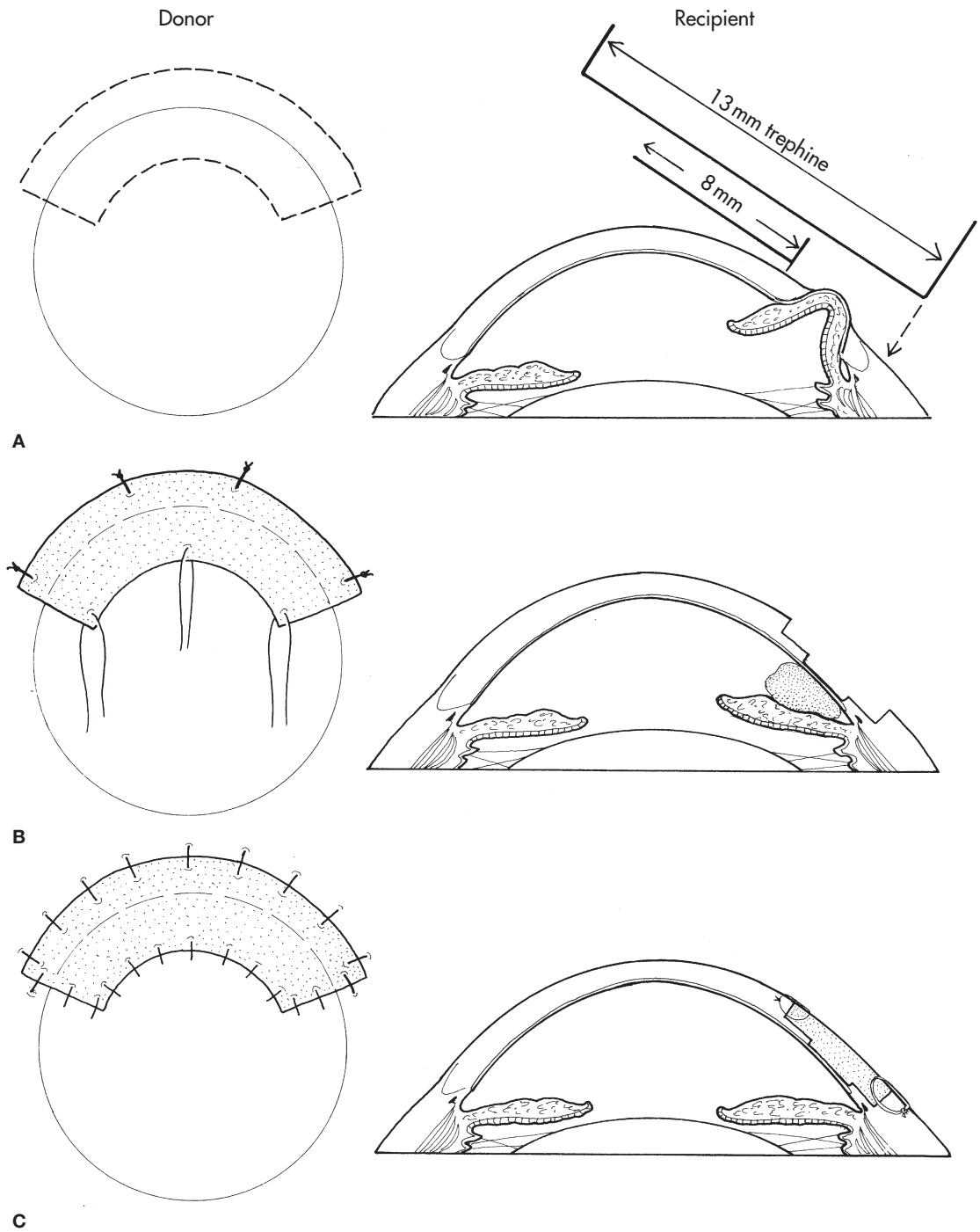

Figure 25.5. *A*, Smaller and larger trephines used to make initial incisions surrounding perforated area. *B*, Note perpendicular margins in the recipient bed from trephine and knife dissection. The iris was repositioned by viscoelastic. *C*, A crescentic piece is anchored using multiple interrupted sutures.

The most common technique for corneal reconstruction in Terrien's marginal thinning is crescentic lamellar or full-thickness keratoplasty. Lamellar keratoplasty is performed as follows. The center of the cornea is marked. A trephine is then used to outline the curvature of the inner edge of corneal thinning (Fig. 25.5, *A*). A blade is then used to deepen the trephine groove and to shelve the outer edge of the thinned cornea toward the limbus. Lamellar dissection of the cornea posterior to the trephine groove is performed, and the shelved outer edge of the thinned area is excised, leaving a crescent-shaped recipient bed (see Fig. 25.5, *B*).[75] The width of the bed is measured. A corneal crescent corresponding to the recipient bed is excised from the donor cornea either free-hand or using two trephines (Fig. 25.6). A large trephine can be used to separate the corneal donor button from the scleral rim. A smaller trephine is then used to excise a central button, leaving a corneal rim corresponding in width to the width of the recipient bed. Descemet's membrane is stripped, and the donor crescent is sutured to the recipient bed (see Fig. 25.5, *C*). A variation on this technique, called by the authors 'compressive C-shaped lamellar keratoplasty', utilizes a donor crescent that is 0.25–0.5 mm narrower than the recipient bed.[76] In combination with tight 9.0 sutures, this produces less progressive ectasia and against-the-rule astigmatism in the postoperative period, according to the authors.

Full-thickness crescentic keratoplasty can be performed as above, except that the thinned cornea is removed entirely and the Descemet's membrane of the donor is retained.[77] Caldwell and coworkers[78] described an alternative technique for restoring cornea in patients with Terrien's marginal thinning. An incision is made into the stroma down to Descemet's membrane along the anterior edge of the thinned cornea using a diamond knife set to a depth determined by preoperative pachymetry. A lamellar blunt dissection is performed to the level of Descemet's membrane toward the limbus. Corneal crescent superficial to Descemet's is then excised, and the wound edges approximated with sutures. This technique can be coupled with simultaneous cataract extraction. Corneal incision is made at the degeneration furrow, cataract extraction is performed, and the incision reapproximated to the limbus under keratoscopic control to reduce corneal torricity.[79]

PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration is a bilateral, inferior corneal thinning disorder characterized by a narrow band of thinning (1–2 mm) of the inferior cornea running parallel to the limbus (Fig. 25.7). The thinned cornea is clear, and the cornea above and below the thinned cornea is of normal thickness. The cornea protrudes above the area of thinning, resulting in high regular and irregular astigmatism. Spontaneous perforation and hydrops have been described.[80,81]

Pellucid marginal degeneration is usually detected between the second and fifth decades of life. There is no sex predilection, and there is no evidence for hereditary transmission, although moderate or high astigmatism has been found in family members.[82]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of pellucid marginal degeneration includes other corneal thinning disorders, such as Terrien's degeneration, keratoconus, and Mooren's ulcer. Unlike pellucid degeneration, Terrien's degeneration affects both the superior and the inferior cornea and has vascularization and lipid deposition. In active Mooren's ulcer and other peripheral ulcerative disorders, the epithelium overlying the area of thinning is usually not intact. Healed peripheral ulcers are vascularized and scarred. The thinned cornea in pellucid marginal degeneration remains clear with epithelium intact. In contrast to keratoconus, patients with pellucid marginal degeneration have no iron ring, no Vogt striae, and no central corneal thinning or scarring of the protruding cornea. The corneal protrusion is located above rather than in the area of thinning.

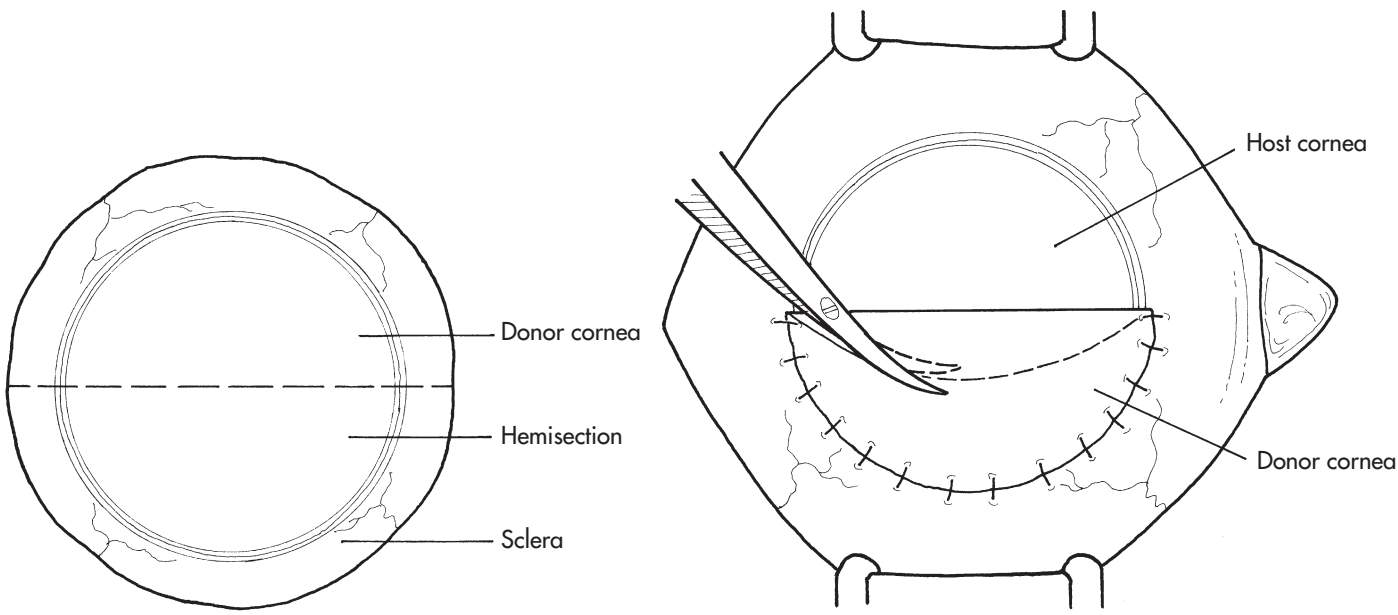

Figure 25.6. A demonstration of free-hand scissors dissection of a donor corneal crescentic piece matching the trephined recipient bed (trephines can be used to accomplish the same shape).

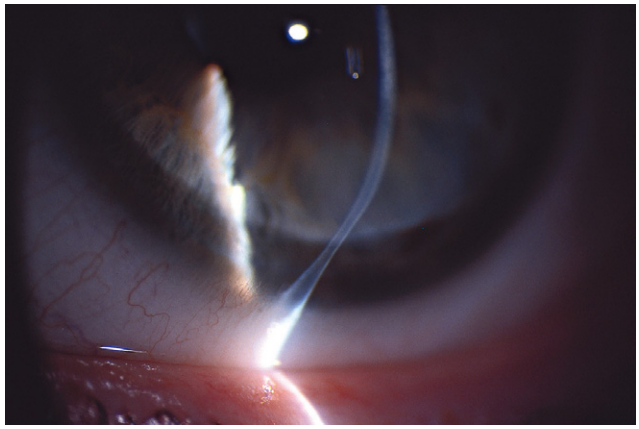

Figure 25.7. Slit-lamp photograph of pellucid marginal degeneration with a thinned area 2–3 mm from the interior limbus. Note near-normal thickness closer to the limbus. (Photo courtesy of FS Brightbill, MD.)

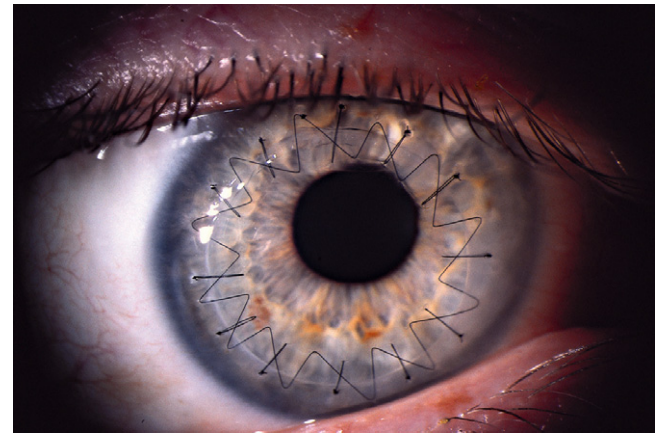

Figure 25.9. 1986 slit-lamp photograph after wedge resection of a thinned area inferiorly in a 30-year-old male with pellucid marginal degeneration. Over the next 10 years, thinning in the same area recurred with high astigmatism, necessitating a penetrating keratoplasty. (Photo courtesy of FS Brightbill, MD.)

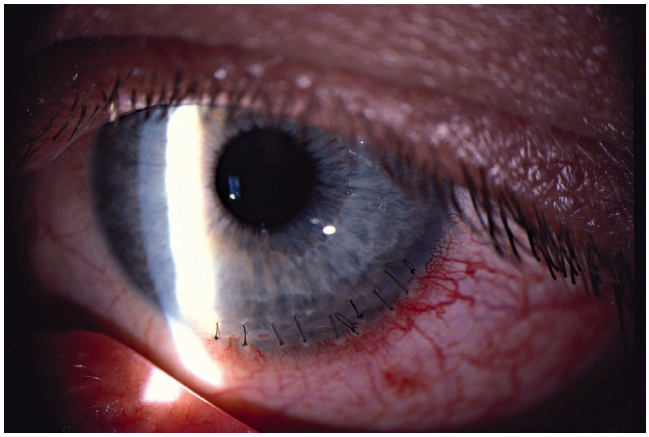

Figure 25.8. The same eye as in Figure 25.9 with inferiorly decentered 8.5 mm penetrating keratoplasty. (Photo courtesy of FS Brightbill, MD.)

TREATMENT

Spectacle correction of pellucid marginal degeneration is usually inadequate because of the high astigmatism. Contact lenses initially offer good optical correction but are difficult to fit as the disease progresses. The cornea is flat centrally and steep peripherally, so the lenses are difficult to center and tend to lift off.

Surgical correction of pellucid marginal degeneration includes diathermy, thermokeratoplasty, crescentic wedge resection, lamellar keratoplasty, and penetrating keratoplasty (Fig. 25.8). If the area of thinning is less than 2 mm, wedge resection (Fig. 25.9) or crescentic lamellar or penetrating keratoplasty can be performed.[83,84] MacLean et al. report that full excision of thinned tissue is often possible with mean residual astigmatism of 1.4 D, but long-term astigmatic drift increases it to 2.1 D over 55–138 months.[83] If the area of thinning is large (i.e. >2–3 mm), large, eccentric keratoplasty can be performed. However, the risk of rejection and graft vascularization is higher because of the close proximity of the graft to the limbus. A better alternative may be a total lamellar keratoplasty followed by a smaller, central penetrating keratoplasty. Duran et al[85] have also described a technique for crescentic resection of the thin peripheral area to treat pellucid marginal degeneration. A combination technique described by Rasheed and Rabinowitz[86] for advanced pellucid degeneration includes a simultaneous inferior lamellar keratoplasty with a central full-thickness penetrating keratoplasty (PKP). Inferior ectatic cornea is initially reinforced by a lamellar graft, which is then trephined and a 7.5-mm graft is sutured centrally. Simultaneous technique allows for relatively rapid visual rehabilitation, and reinforcement of the inferior cornea helps minimize astigmatism.

A more conservative tissue-saving approach to early and moderate pellucid marginal degeneration involves reinforcement of ectatic corneal stroma with intrastromal rings and segments, such as Intacs and Ferrara rings. Initially developed for mild myopia and demonstrated to be effective in keratoconus,[87] these inserts can be used to minimize regular and irregular astigmatism by supporting weakened collagen fibrils. The segments are usually implanted through a temporal incision, one inferiorly and the second superiorly.[88–90] The inferior 0.25 or 0.45 mm segment is inserted through the thinnest part of the cornea or just above it providing reinforcement and a barrier minimizing irregular astigmatism induced by the ectatic band just below it. Dissecting the channels for the inserts through such thin tissue is prone to error, and femtosecond laser has been successfully used to precisely place the channels.[91] Overall, this reversible procedure may provide a safe approach to stabilize progressively degenerating corneas.

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26 Epithelial transplantation for the management of severe ocular surface disease

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Severe ocular surface disease is a clinical term for conditions that result from injury or disease of the limbal stem cells, the source for normal corneal epithelium, or the conjunctiva, with its mucin-secreting goblet cells, which are vital for normal tear film physiology. Patients with severe ocular surface disease are some of the most challenging to manage in ophthalmology. Conventional management techniques, including superficial keratectomy, penetrating or lamellar keratoplasty, and tarsorrhaphy, are generally unsuccessful because they fail to correct the underlying deficiency of normal conjunctival or corneal cells. Epithelial transplantation procedures have significantly improved the success rate of the management of these patients.

OCULAR SURFACE ANATOMY

The ocular surface is comprised of the tear film and the epithelium of the cornea and conjunctiva. Stratified, nonkeratinized epithelium covers the entire cornea, as well as the bulbar and palpebral conjunctiva. The corneal epithelium is constantly being sloughed and renewed. The proliferating cells responsible for the renewal of the corneal epithelium are stem cells and transient amplifying cells, located in the basal epithelial layers at the limbus.[1–7] Stem cells are long lived and demonstrate a capability to divide in an asymmetric manner.[3,5,6] This asymmetric cell division allows one of the daughter cells to remain a stem cell while the other differentiates to become a transient amplifying cell. The transient amplifying cell then differentiates into postmitotic cells and finally into terminally differentiated cells. Both the postmitotic cells and the terminally differentiated cells are incapable of cell division.[5] Schermer et al[2] proposed the cell proliferation scheme for the cornea as follows (Fig. 26.1): limbal basal epithelium (stem cells) to basal corneal epithelium (transient amplifying cells) and to suprabasal corneal epithelium (terminally differentiated cells), which is mature corneal epithelium. The normal conjunctival epithelium contains goblet cells. These cells are unicellular, mucin-secreting glands that account for approximately 5–10% of the total number of basal cells. The function of the mucin secreted by the goblet cells is to coat the surface of the epithelium. Mucin, which is extremely hydrophilic, allows the otherwise hydrophobic epithelium to be wettable. Mucin also maintains the stability of the tear film. The location of stem cells for conjunctival goblet and nongoblet epithelial cells is not known, although it is postulated that the forniceal zone is the most likely location for this stem cell population.[8]

ETIOLOGIES OF STEM CELL DEFICIENCY

Profound morbidity can result from conditions that severely compromise the ocular surface caused by damage or injury of the limbal stem cells or conjunctiva. Corneal disease can include development of chronic abnormal epithelium, neovascularization, scarring, ulceration, and possible perforation. Conjunctival sequelae include inflammation, scarring, and aqueous tear, as well as mucin deficiency. Pain and loss of vision are common complications in severe cases.

A stable ocular surface depends upon the proper functioning of the limbal stem cells. A limited number of disorders have been described that lead to ocular surface instability from abnormal stem cell function (Table 26.1). Aniridia is a primary stem cell disorder that appears to result from a deficiency in the development or maintenance of limbal stem cells.[9–11] Secondary disorders of limbal stem cells are more common. In chemical and thermal burns, there is direct injury to the limbal stem cells as well as to the corneal and conjunctival epithelium, including the goblet cells. Most damage and loss of stem cells occurs at the time of the initial injury, with further gradual attrition resulting from the chronic anterior segment inflammation, which often follows. Stevens–Johnson syndrome (SJS) and ocular cicatricial pemphigoid (OCP) are diseases primarily of the conjunctiva. They may result in severe inflammation, with conjunctival scarring, goblet cell depletion, aqueous tear deficiency, and the eventual loss of limbal stem cells.[12] Multiple surgical procedures or chronic use of toxic topical medications can also result in limbal stem cell deficiency. The authors proposed the term 'iatrogenic limbal stem cell deficiency' as a descriptor for patients with ocular surface disease from this mechanism.[13] Corneal intraepithelial neoplasia is a less common cause of limbal stem cell deficiency.[14] Corneal intraepithelial neoplasia almost always originates at the limbus and probably causes stem cell deficiency because of replacement of healthy stem cells with neoplastic cells. Severe

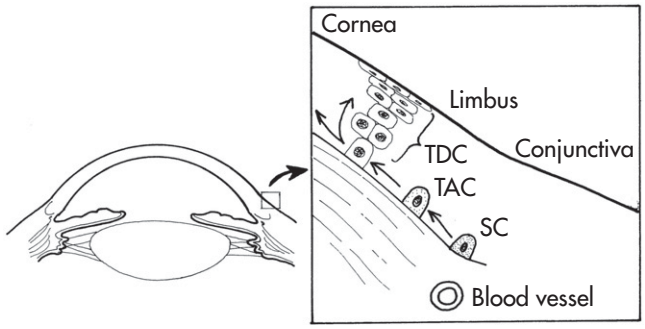


Figure 26.1. Schematic representation of limbal stem cells (SC). These cells are located at the basal epithelium of the limbus and give rise to transient amplifying cells (TAC) of the basal corneal epithelium and to terminally differentiated cells (TDC), which compose the suprabasal corneal epithelium.

contact lens-induced keratopathy is another category of stem cell-related ocular surface disease. The stem cells are injured as the result of chronic trauma to the limbus from the contact lens;[15] chronic hypoxia probably also plays a role.

CLASSIFICATION OF EPITHELIAL TRANSPLANTATION PROCEDURES FOR SEVERE OCULAR SURFACE DISEASE

A previous article reviewed in detail the history of epithelial transplantation procedures in the management of severe ocular surface disease.[16] Confusion arises when reviewing reports of these procedures because the use of terminology has been inconsistent; multiple terms have been used by different authors to describe the same technique, while the same term has been used for more than one technique. Therefore, a standardization of the classification of epithelial transplantation procedures for ocular surface disease has been proposed[17] (Table 26.2). All of the procedures share the common goal of transplantation of a new source of epithelium for a diseased ocular surface. Although the different techniques have similar goals, they vary based on the source of the donor tissue and whether the procedure is primarily a conjunctival or a limbal transplantation. Limbal transplantation procedures also vary depending on the carrier tissue used for the transfer of the limbal stem cells. Carrier tissue is needed in limbal transplantation because it is not technically possible to transfer limbal stem cells alone.

The source of donor tissue for epithelial transplantation can be the fellow eye (autograft), cadaveric whole globe (allograft), cadaveric corneoscleral rim (allograft), or a living relative (allograft). Conjunctival transplants transfer only conjunctiva. Limbal transplants, on the other hand, use either conjunctiva or cornea as a carrier tissue for the fragile limbal stem cells. Based on the source of donor tissue, the carrier tissue used, and whether the procedure is a conjunctival transplant or a limbal transplant, the following classification of surgical procedures for epithelial transplantation for ocular surface disease was devised. A conjunctival autograft (CAU) uses tissue from the fellow eye. A conjunctival allograft can use donor tissue from a cadaver or living relative and be designated as a cadaveric conjunctival allograft or living related conjunctival allograft. Limbal transplantation procedures can be subdivided based on the donor and the carrier tissues. A conjunctival limbal autograft (CLAU) uses tissue from the fellow eye, and conjunctiva is the carrier. A cadaveric conjunctival limbal allograft

Table 26.1 Ocular surface disease with limbal stem cell deficiency

Category	Disease	Pathogenesis of Limbal Deficiency
Congenital	Aniridia Ectodermal dysplasia	Abnormal development or maintenance of limbal stem cells
Trauma/toxic	Chemical and thermal burns Contact lens wear	Direct injury to limbal stem cells. hypoxia, mechanical trauma, and chemical toxicity
Inflammatory	Stevens–Johnson syndrome Ocular cicatricial pemphigoid Atopic keratoconjunctivitis	Inflammatory destruction of limbal stem cells
Iatrogenic limbal stem cell deficiency	Surgery Antimetabolites/ antifibrotics (e.g. mitomycin-C)	Excision or mechanical destruction of limbal stem cells and/or chronic exposure to toxic medications with damage to stem cells
Neoplasia	Squamous cell carcinoma	Replacement of normal limbal stem cells with neoplastic cells

Table 26.2 Classification for epithelial transplantation procedures for ocular surface disease

Procedure	Donor Source	Transplanted Tissue
CLAU	Fellow eye	Limbus and conjunctiva
lr-CLAL	Living donor or cadaver	Limbus and conjunctiva
KLAL	Cadaver	Limbus and cornea
Ex vivo cultured epithelium	Autologous, living donor, or cadaver	Limbus, conjunctiva, or oral mucosa

CLAU, conjunctival limbal autograft; lr-CLAL, living-related conjunctival limbal allograft; KLAL, keratolimbal allograft.

(CLAL) uses a cadaveric donor for conjunctiva and limbus. A living-related conjunctival limbal allograft (Lr-CLAL) is a procedure in which a living relative donates conjunctiva and limbal tissue. Finally, a keratolimbal allograft (KLAL) uses a cadaveric donor, transferring the limbal stem cells via peripheral cornea and sclera (i.e. limbus).

RECOMMENDATIONS FOR EPITHELIAL TRANSPLANTATION PROCEDURES

Indications for epithelial transplantation include cicatrizing conjunctival disease and limbal deficiency. Patients with limbal deficiency may benefit from epithelial transplantation to manage a persistent epithelial defect of the cornea, to improve decreased vision caused by an irregular epithelial surface, or to stabilize the ocular surface prior to keratoplasty.

The first consideration is whether the condition is unilateral or bilateral (Fig. 26.2). If unilateral, the autograft procedures hold the best prognosis because they eliminate the issue of immune rejection. If the condition results from a unilateral limbal deficiency, then the procedure of choice is a CLAU. However, the patients with the greatest need are usually those with bilateral disease. These patients require an allograft to manage ocular surface disease caused by limbal stem cell and/or conjunctival deficiency. The clinician may choose from three procedures to restore the ocular surface: CLAL, KLAL, or a combination of both.

CLAL allograft tissue may be obtained from either a cadaver or a living relative. The cadaveric CLAL procedure has only two published cases and appears to have significant disadvantages when compared to Lr-CLAL and KLAL: (1) cadaveric conjunctival tissue is difficult to handle and often is not available on donor globes, (2) the survival of cadaveric conjunctiva on whole globes in storage media has not been documented, and (3) the survival of this tissue post-transplantation has not been studied. Therefore, at this time, the only tissue sources for bilateral ocular surface disease are the Lr-CLAL and cadaveric KLAL.

To determine which epithelial transplantation procedure to perform for the patient with bilateral severe ocular surface disease, an assessment must be made of whether the cause is primarily limbal stem cell deficiency or combined limbal stem cell and conjunctival deficiency. For patients with conjunctival and limbal deficiency, if a living-related donor is willing and available, Lr-CLAL should be the first procedure considered. This recommendation is based on published studies. Human leukocyte antigen (HLA) matching and ABO typing may be useful in determining the best living-related donor match. The results of allograft procedures that include conjunctiva (living-related conjunctival allograft and Lr-CLAL) appear to have better outcomes than the results of published KLAL studies in the subgroup of patients with combined limbal and conjunctival deficiency.

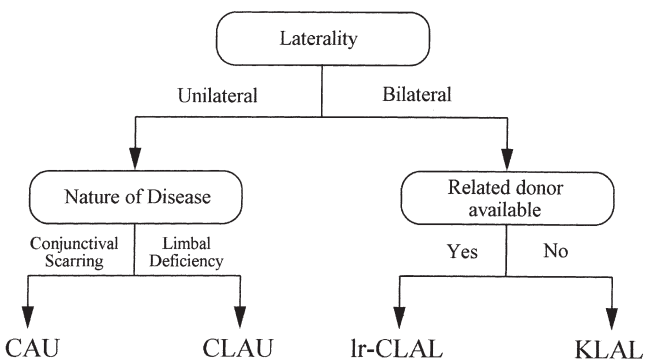


Figure 26.2. Recommendation for epithelial transplantation procedures. CAU, conjunctival autograft; CLAU, conjunctival limbal autograft; Lr-CLAL, living-related conjunctival limbal allograft; KLAL, keratolimbal allograft.

However, in cases of limbal stem cell deficiency without conjunctival deficiency (e.g. aniridia), Lr-CLAL does not appear to have a better success rate when compared with KLAL. In fact, patients with aniridia keratopathy benefit dramatically from KLAL. This technique offers one clear distinct advantage over other limbal stem cell techniques: three separate 180° segments of limbal tissue are used, thereby offering 150% more limbal stem cells.[18] Other advantages of KLAL include the ready availability of tissue for all recipients, elimination of surgery on a healthy living relative, and the fact that it is an avascular transplant, which may reduce the risk of rejection.

In patients with severe ocular surface disease with concomitant conjunctival and limbal stem cell deficiency, a living-related conjunctival allograft may not always provide adequate number of stem cells, and therefore the patient may be at risk of developing conjunctival in-growth in the large 'gap' areas nasally and temporally. Therefore, these patients may benefit from a combined KLAL and CLAL.

PREOPERATIVE CONSIDERATIONS

Ocular adnexa and anterior segment structures of patients with severe ocular surface disease must be carefully examined. Abnormal globe-to-eyelid anatomy can lead to chronic exposure, chronic inflammation, and direct corneal trauma. Significant abnormalities such as entropion or ectropion, trichiasis or distichiasis, and palpebral conjunctival keratinization should be corrected prior to epithelial transplantation. Patients with aqueous tear deficiency usually require permanent punctal occlusion. If lagophthalmos or poor lid closure exists, lateral tarsorrhaphy at the time of surgery should be considered. In patients with severe conjunctival deficiency and obliteration of the fornices, an autologous graft from the oral or nasal mucosa may be necessary to reconstruct the fornix prior to considering limbal transplantation.

It is also crucial to inquire about any past history of glaucoma and to look for evidence during the physical examination. Glaucoma should be managed aggressively because chronic glaucoma is a major risk factor for long-term poor visual functioning in patients who otherwise undergo successful limbal stem cell grafting.

SURGICAL TECHNIQUES

CONJUNCTIVAL-LIMBAL AUTOGRAFTS

Donor tissue selection

In considering a CLAL for unilateral ocular surface disease, the vital criterion for tissue selection is that the donor eye be free from any condition that may predispose it to later development of limbal stem cell deficiency, such as long-term contact lens use, multiple prior surgeries, or glaucoma (in which conjunctival surgery could jeopardize the success of later filtering surgery if needed). If any contraindications exist, then a Lr-CLAL is advised if a related donor is available, or a KLAL if no related donor is available.

Anesthesia

The procedure involves both eyes. If the patient is healthy and can safely tolerate general anesthesia, this method is usually preferred because it eliminates time constraints of local anesthesia and reduces patient anxiety over a bilateral procedure. When necessary, local anesthesia can be used with a peri- or retrobulbar block with or without a cranial nerve VII block (O'Brien) for the recipient eye and a topical or subconjunctival anesthesia for the donor eye.

Preparation of the recipient eye

Any speculum providing adequate exposure is used. A lateral canthotomy is sometimes necessary to increase exposure. If symblepharon formation has occurred and limits exposure of the ocular surface, conjunctival adhesions can be released at the limbus. A 360° limbal peritomy is performed, and conjunctiva is resected posteriorly 2–3 mm with Wescott scissors. It is important to remove this tissue from the limbus because the new source of epithelium must repopulate the ocular surface prior to reinvasion by the fibrovascular tissue of the conjunctiva. Extensive bleeding can occur because of neovascularization of the injured eye's surface. If bleeding interferes with visualization, one quadrant at a time can be operated on to control bleeding. Topical epinephrine (1 : 10 000 dilution) and thrombin applied with surgical spears are useful adjuncts to wet-field cautery. Once the limbal conjunctival tissue is excised, the recipient CLAUs are prepared (Fig. 26.3, *A*). The grafts will be centered at the 12 and 6 o'clock meridians and will measure approximately 8 mm horizontally by 5 mm vertically (no more than three clock hours each).

Next, abnormal corneal epithelium and fibrovascular pannus are removed by superficial dissection (Fig. 26.3, *B*). Various approaches can be useful. Blunt dissection with a cellulose sponge may work. If a dissection plane is established, forceps can sometimes be used to peel the abnormal tissue off in a sheet. However, sharp dissection is often needed in areas to find an adequate tissue plane to create a smooth ocular surface. A No. 64 Beaver blade can be used for this maneuver. Care is given to avoid cutting deep into stroma because of the risk of corneal perforation and postoperative optical distortion from surface irregularity. Bleeding is often encountered with the removal of corneal surface pannus, and topical epinephrine and thrombin can be used on this tissue as well. When hemostasis is achieved, the surface is moistened, the speculum removed, and the eyelids are closed while the autografts are being harvested from the other eye.

Harvesting the donor tissue

The speculum is placed in the fellow eye. The two CLAUs are taken from the corresponding 12 and 6 o'clock positions. A gentian violet surgical marking pen is used to mark the conjunctival portions of the grafts with the same 5 mm vertical by 8 mm horizontal dimensions. The conjunctiva can be elevated with a subconjunctival

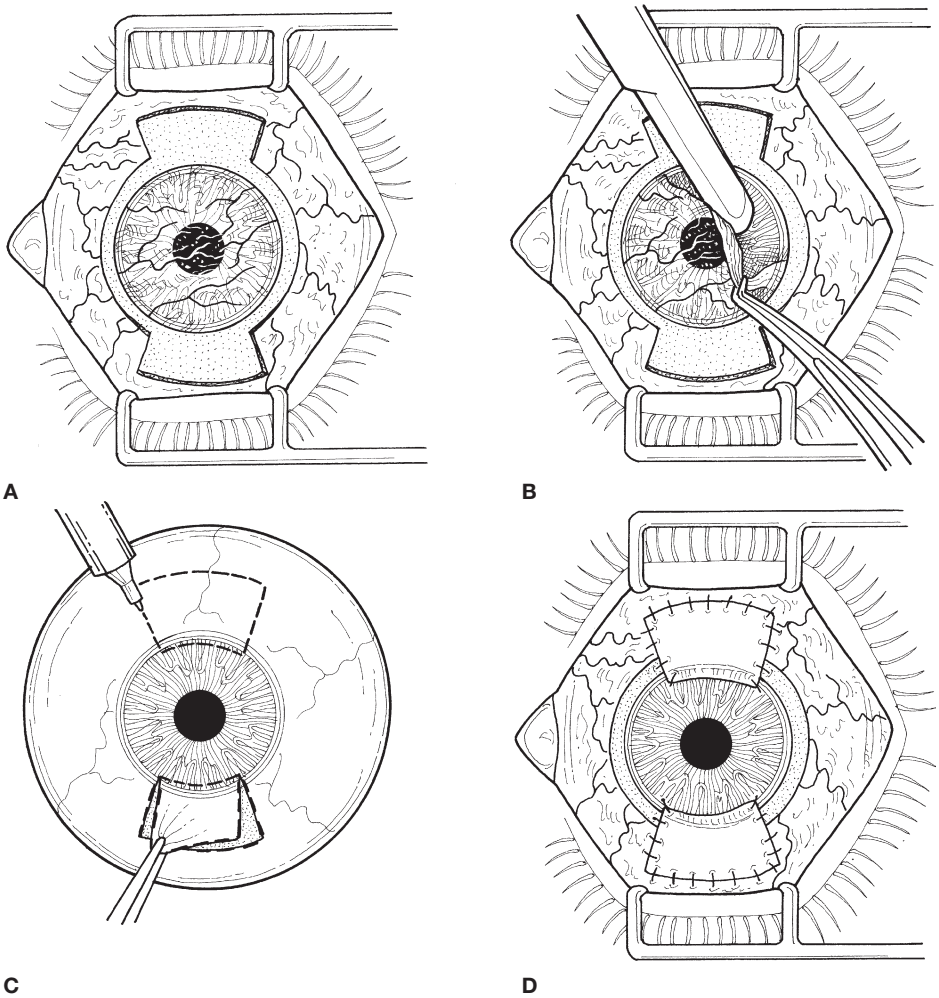


Figure 26.3. Technique for conjunctival limbal autograft or allograft transplantation. *A*, Recipient eye preparation. A 360° limbal peritomy is performed with removal of 2–3 mm of bulbar conjunctiva. *B*, Abnormal corneal epithelium and fibrovascular pannus are removed by superficial dissection using necessary techniques (peeling, blunt dissection, and sharp dissection). *C*, Donor tissue harvesting. Conjunctival dimensions of the grafts are marked with a gentian violet marking pen. The corneal epithelial extent of the graft is also marked 1 mm beyond the peripheral corneal vascular arcades with a blade. Harvesting begins with the bulbar conjunctival portion and proceeds anteriorly. *D*, The conjunctival limbal grafts are transferred to their corresponding anatomic positions on the recipient eye and secured with multiple interrupted 10-0 nylon sutures.

injection of balanced salt solution. Wescott scissors are used to begin the dissection by incising along the lateral borders, with complete undermining between the lateral edges if possible before cutting along the posterior edge (Fig. 26.3, *C*). This sequence helps keep the tissue on-stretch. The gentian violet markings should be included in the graft to help delineate the epithelial surface from the undersurface. Nontoothed forceps are recommended to help avoid button holes and tears through the conjunctiva.

Once the lateral and posterior edges are free, the conjunctiva is reflected anteriorly over the cornea, and blunt dissection is continued anteriorly. When the point of conjunctival insertion at the limbus is reached, further blunt dissection should be performed with a dull scarifier (e.g. Tooke blade) into the peripheral cornea approximately 1 mm beyond the peripheral corneal vascular arcades. The desired corneal epithelial extent of the dissection should be lightly marked with any type of blade from the corneal side. This maneuver is essentially a superficial epithelial keratectomy of peripheral limbus and cornea and not a lamellar dissection into stroma or sclera. It is also extremely important to carry the dissection onto the peripheral cornea and to avoid prematurely excising the piece of tissue without the stem cells. Once the tissue is free, it is transferred epithelial side upward to a Petri dish and covered with corneal storage media (or balanced salt solution if the former is unavailable). The donor sites are left open to heal.

Placement of the donor tissue

Each autograft is sutured into its anatomically correct position (limbus to limbus) with multiple interrupted 10-0 nylon sutures (Fig. 26.3, *D*). Some surgeons prefer nylon over polyglactin because it causes less postoperative inflammation. The corners are secured first, and then sufficient additional sutures are placed in between to prevent postoperative dehiscence. The sutures are placed first through the conjunctival graft, then through the recipient episcleral tissue, and finally through the recipient conjunctiva. The sutures are tied and cut on the knot, but the knots are not buried because the bites are short and attempts to bury them often result in the sutures being pulled out accidentally. The sutures can be left for many months. Some loosen and fall out on their own; others that loosen or cause irritation can be removed at the slit lamp, preferably after 2 weeks. During the suturing, the autograft epithelium should be protected from desiccation and trauma with balanced salt solution and a viscoelastic material. At the conclusion of the operation, an antibiotic-corticosteroid ointment is placed in the inferior cul-de-sac of the recipient eye and a drop of antibiotic-corticosteroid solution is placed in the donor eye. A patch and protective shield is placed over the recipient eye until the patient is seen the next day.

Postoperative care

The donor eye is treated with the antibiotic-corticosteroid drops three to four times daily until re-epithelialization is complete and inflammation has subsided. The donor eye should be followed until the donor sites are completely epithelialized (usually 1–2 weeks). A rare complication of this technique is the occurrence of a pyogenic granuloma at an autograft harvest site. The recipient eye is treated with a low-toxicity antibiotic once or twice daily as prophylaxis during re-epithelialization. Topical corticosteroids are used three or four times daily for inflammation. It is important to avoid overtreatment with topical corticosteroids because they can inhibit mitosis and retard epithelialization. If significant inflammation occurs in the immediate postoperative period, oral corticosteroids should be considered. In addition to controlling postoperative inflammation and preventing rejection of the allograft tissue, management of the ocular surface is the other key factor. All patients are instructed to use nonpreserved artificial tears every 1–2 h. Punctal occlusion, tarsorrhaphy, and use of a bandage soft contact lens are other interventions commonly used as needed.

Results

Several reports document the benefits of CLAU. In a series pterygium, or conjunctival intraepithelial neoplasia of 21 eyes, comprised mostly of unilateral chemical burns, 20 eyes achieved a stable corneal epithelium and 17 had significantly improved visual acuity.[6] Similarly, Dua and Azuara-Blanco attained successful epithelialization in six eyes with persistent epithelial defects from stem cell failure resulting from several causes including chemical injury, pterygium, or conjunctival intraepithelial neoplasia.[19]

CLAU has been used in combination with deep lamellar keratoplasty in a reported series of 39 patients with unilateral advanced chemical injuries.[20] In addition to conjunctival limbal tissue, conjunctival autografts were also harvested from the healthy fellow eyes to allow encircling of the recipient limbus. All of the eyes achieved a stable ocular surface.

A modification of CLAU involving the harvesting and repositioning of stem cells from a single eye sectoral stem cell deficiency has been reported with good results.[21] Attractive features of this procedure are the elimination of the need to perform surgery on a patient's unaffected eye and the ability to treat patients with only one eye. A major concern regarding this procedure is the risk of inducing further stem cell dysfunction in the diseased eye. In the future, ex vivo stem cell expansion may allow for further utilization of this procedure.

LIVING-RELATED CONJUNCTIVAL LIMBAL ALLOGRAFTS

Donor tissue selection

The related donor should be screened for potential blood-borne diseases including human immunodeficiency virus-1 and -2 and hepatitis B and C. These tests are the standard serologic screening required by the Eye Bank Association of America for tissue used for keratoplasty (including KLAL). Human leukocyte antigen typing is performed to find the best match if there are multiple siblings, but it is not necessary if a parent acts as the donor. The authors consider a three antigen match to be acceptable and this should be the case with donated tissue from either biological parent.

Anesthesia

In most cases, the authors use a peri- or retrobulbar injection for harvesting from the donor relative. A combination of topical and subconjunctival anesthesia is an alternative under selected circumstances. The recipient patient's eye is anesthetized with a peri- or retrobulbar injection, or occasionally general anesthesia is used if necessary.

Harvesting the donor tissue from the relative

Most surgeons will not have the luxury of running two operating rooms simultaneously. Therefore, the authors recommend harvesting from the donor first and transplanting to the recipient afterward. The procedure is identical to that of the CLAU section and is as follows:

1. Mark the donor conjunctival sites with a surgical marking pen, each three clock hours wide, centered at the 12 and 6

o'clock limbal positions and extending 5 mm posteriorly (Fig. 26.3, *C*).
2. Elevate the first site with a subconjunctival injection of balanced salt solution.
3. Begin the excision along the lateral edges, undermining the graft completely if possible with blunt dissection before cutting the posterior edge.
4. Reflect the tissue anteriorly over the cornea and continue the dissection into the peripheral cornea 1 mm past the peripheral vascular arcade with a blunt scarifier. This maneuver is a superficial epithelial keratectomy of peripheral cornea and limbus and not a lamellar dissection into stroma or sclera.
5. Place the tissue into a sterile Petri dish containing either corneal storage media or balanced salt solution and cover.
6. Repeat for the second site.
7. Antibiotic–corticosteroid ointment is placed in the inferior cul-de-sac, and the eye is patched until the patient is seen the next day.

Preparation of the recipient eye and placement of the donor tissue

These steps are described in detail in the discussion of CLAU and are summarized as follows:

1. Perform a lateral canthotomy if needed for exposure.
2. Perform a 360° limbal peritomy and remove 2–3 mm of conjunctiva (Fig. 26.3, *A*).
3. Achieve hemostasis with cautery. Use of topical epinephrine (1 : 10 000 dilution) and thrombin may be helpful.
4. Prepare the recipient graft sites to match the dimensions of the harvested tissue.
5. Carefully remove abnormal corneal epithelium and fibrovascular pannus with blunt and sharp dissection (Fig. 26.3, *B*).
6. Orient the first CLAU in its anatomic position and secure with interrupted 10-0 nylon sutures. Protect the graft from trauma and desiccation with viscoelastic and balanced salt solution while suturing. Cut the sutures on the knot and do not rotate to avoid accidental removal (Fig. 26.3, *D*). Repeat with the second graft.
7. Antibiotic–corticosteroid ointment is placed in the inferior cul-de-sac, and a patch and shield is placed over the eye until the patient is seen the following day.

Postoperative care

Topical medications for both the donor and the recipient are discussed in the CLAU section. Systemic immunosuppression consisting of oral prednisone, cyclosporin A (CsA) or tacrolimus, and azathioprine or mycophenolate mofetil is started on the day of surgery for allograft patients if no contraindication exists. Table 26.3 summarizes the dosing regimen. A thorough discussion of the postoperative monitoring for the various immunosuppressive medications can be found in Chapter 62 on immunosuppression after high-risk keratoplasty.

Results

Daya and Ilari performed lr-CLAL on 10 eyes with SJS, ectodermal dysplasia, chemical injury, OCP, and atopic keratoconjunctivitis.[22] HLA typing was done and systemic cyclosporin was given. Eight eyes achieved a stable corneal epithelium (80%), with a mean follow-up of 26 months. Both primary failures were in patients with SJS. Similarly, Kwitko et al reported on 12 eyes with SJS, toxic epidermal necrolysis (Lyell's syndrome), and chemical and thermal burns who underwent lr-CLAL. At 17 months, 11 of those eyes had a stable ocular surface and improved vision (92%).[23] Interestingly, in these patients systemic cyclosporin was not given and HLA typing was performed retrospectively. Samson and coworkers reported that only half (50%) of 10 eyes with SJS were successfully re-epithelialized after lr-CLAL with a follow-up of at least 2 years.[24] No systemic immunosuppression was utilized postoperatively, however. Similarly, Rao et al reported that all nine eyes with chemical burns and SJS that underwent lr-CLAL without postoperative systemic immunosuppression obtained initial successful restoration of corneal epithelium but subsequently developed corneal vascularization.[25] The authors concluded that lack of immunosuppression, incomplete encircling of the limbus, and HLA mismatch were potential explanations for failure. We believe that systemic and topical immunosuppression are essential for long-term graft survival.

KERATOLIMBAL ALLOGRAFTS

Donor tissue selection

To obtain appropriate tissue for performing a KLAL, the surgeon needs to communicate with the eye banks of potential supply to inform and educate them of the special requirements of this procedure, which is not commonly performed. If the eye bank is unaware of preferred differences in the age of the donor and preparation techniques, it will be impossible to obtain optimal tissue prepared in the desired fashion.

For routine penetrating keratoplasty, most surgeons avoid using tissue from infant donors (usually less than 4 years of age) because of the difficulty of working with the tissue. Its flaccid nature and its tendency to stretch postoperatively lead to unpredictable results. Eye banks are aware of this problem and thus do not routinely pursue such tissue. In performing a KLAL, the pliability of the tissue has not been an issue. More importantly, tissue from young children results in rapid re-epithelialization (5–7 days) of the recipient's cornea. It is intuitive that the limbal stem cells of infants and children would be the most active and vital. Thus, the authors prefer to use the youngest tissue possible, including neonatal. As an upper age limit, the authors have avoided using tissue from donors greater than 50 years of age. The authors inform their local eye bank when they have a patient on the waiting list for a KLAL so that they will accept infant tissue that they otherwise would decline. Additionally, both eyes of the donor should be obtained to provide sufficient tissue for the procedure.

When the eye bank is aware of the availability of appropriate tissue for a KLAL, contact is made with the potential recipient to confirm the pending procedure. Once tissue is obtained, the KLAL should be performed as soon as possible in an effort to maximize the viability of the limbal stem cells, preferably within 72 h of the donor's death. Thus, the patient is often asked to complete a preoperative evaluation even before final clearance of the donor tissue. If patients are coming from any considerable distance away, they need to be appropriately advised in advance on how to manage the logistics of such a short notice for their surgery.

Donor tissue preparation

As with the donor criteria, there are several variations from standard tissue harvesting techniques of which a prospective eye bank supplier needs to be informed. (1) Normally the emphasis during tissue harvesting is to avoid damaging the corneal endothelium and stroma, with less regard for the epithelium; in these cases,

the limbal tissue and epithelium need to be carefully protected from both trauma and desiccation. The authors want the entire corneal epithelium to appear as normal as possible to serve as an indirect sign that the limbal stem cells have hopefully undergone minimal harm. (2) Whereas most of the conjunctiva is normally removed during the harvesting procedure, the authors ask for a peripheral skirt of 3–4 mm to be left if possible. This step helps minimize damage to the limbal area, and it allows for some goblet cells to be included in the transplantation. (3) A 4–5-mm scleral rim should be included in the resection from the globe. (4) Finally, both donor eyes are needed to provide sufficient tissue for the procedure.

Anesthesia

Either peri- or retrobulbar anesthetic with a cranial nerve VII (O'Brien) block or general anesthesia is administered.

Preparation of the recipient eye

Exposure is often difficult in these patients because of superior and inferior symblepharon. A speculum is inserted, and a lateral canthotomy is performed if necessary. The initial incision is a limbal peritomy for 360°. In most patients with severe ocular surface disease, significant bleeding is encountered during the peritomy, which may necessitate resecting one quadrant at a time. Hemostasis is maintained with topical epinephrine (1 : 10 000 dilution), thrombin, and wet-field cautery. In areas of symblepharon, conjunctival tissue is first recessed at the limbus and then undermined to allow the conjunctival tissue to fall back, not only to create a new fornix but to supply tissue for a new palpebral surface as well. If the initial dissection was made at the fornix and the symblepharon simply excised, there would be a broad area of epithelial defect on the palpebral conjunctival side, leading to further symblepharon formation. Therefore, the symblepharon are actually used to help reconstruct the fornix and provide the epithelium of the palpebral surface. Care is taken to avoid damaging the superior or inferior rectus muscles in areas of broad symblepharon.

The conjunctiva is resected 4–5 mm from the limbus to expose an adequately sized bed of denuded sclera on which to position the KLAL tissue. Abnormal fibrovascular pannus and epithelium, which are typically present, are next removed from the surface of the cornea. Blunt dissection with a cellulose sponge is used initially, although often semisharp dissection with a rounded steel blade is needed to create a smooth surface. Care is taken to ensure that the dissection continue in a lamellar fashion, remaining anterior, and that the deep layers of the corneal stroma are not disturbed. The purpose of this dissection is removal of the abnormal fibrovascular conjunctivalized surface that has replaced normal corneal epithelium. Topical epinephrine and thrombin can be used to control bleeding during this step as needed.

Harvesting of the limbal tissue

The purpose of performing a KLAL is to provide healthy limbal stem cells to the recipient limbus. Because the stem cells lie in a narrow, fragile portion of the limbus, they must be delivered attached to a more robust carrier tissue. Using peripheral corneoscleral tissue allows for safe transfer and secure attachment of the stem cells to the recipient limbus. A recent corneoscleral crescent technique is a modification of the procedure first described by Tsubota and coworkers in 1995.[26] Unlike a lenticule technique,[27] in which a whole globe is needed, this technique uses a corneoscleral rim preserved in corneal storage media at 4°C (Fig. 26.4, *A*). The central cornea of the corneoscleral rim is excised with a 7.5-mm trephine. The authors use two donor corneas (for three available keratolimbal halves) with an Iowa cutting press and place the tissue epithelial-side down in the standard fashion used for cutting a corneal button for routine keratoplasty. This approach does not cause any apparent

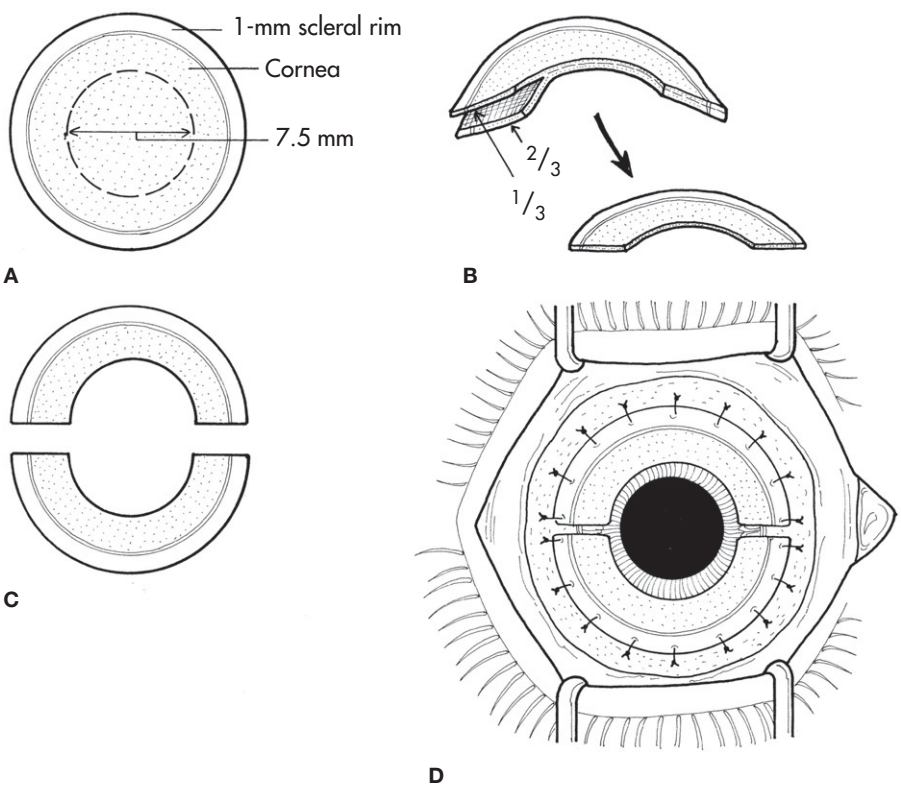


Figure 26.4. Technique for KLAL transplantation. *A*, Donor corneoscleral rim with central 7.5 mm of cornea removed using a trephine. *B*, Remaining corneoscleral rim is cut into equal halves, forming two crescents (total of four crescents from two donor eyes). *C*, Each corneoscleral crescent undergoes lamellar dissection to remove between half and two-thirds the posterior tissue. *D*, Three KLAL crescents are sutured to the recipient eye with the anterior corneal edges overlying the recipient limbus.

harm to the limbal stem cells. The corneal buttons are placed back into storage media for potential later use (e.g. if a combined penetrating keratoplasty and KLAL are planned). The remaining corneoscleral rims are sectioned into equal halves (Fig. 26.4, *B*). Scissors are used to dissect the excess peripheral scleral tissue, leaving approximately 1 mm of sclera peripheral to the limbus. The posterior half to two-thirds of each hemisection is removed by lamellar dissection using a super-sharp rounded steel crescent blade (Fig. 26.4, *C*). This step usually requires an assistant to help stabilize the tissue with forceps under the operating microscope. Aldave and Wong have reported a technique where the donor tissue is glued to a disposable acrylic sphere using cyanoacrylate.[28] Other techniques using an artificial anterior chamber to facilitate donor harvesting have been reported.[29,30] The dissection removes the posterior sclera and posterior stroma, including Descemet's membrane and endothelium. If the graft is too thick, there is greater likelihood that, once transplanted, the friction of the eyelids closing over the surface will impede re-epithelialization. The posterior tissue is discarded, and the second corneoscleral donor rim is prepared in the same fashion. The four pieces are then placed epithelial-side up in storage media solution while awaiting placement.

Two eyes are required to have sufficient tissue to place around the recipient limbus without gaps. Previously, tissue from only one eye was used, with resultant small gaps at the 3 and 9 o'clock limbal positions; conjunctivalization frequently occurred across the gaps, even if filled with lamellar sections from the remaining corneal button. These gaps are largest when using tissue from an infant eye because of the smaller limbal circumference. To eliminate gaps, corneoscleral rims from a pair of eyes are always needed. Using our current technique, a total of three crescents are used for each eye. Many surgeons, especially in areas where donor tissue is more scarce, use just one complete corneal scleral rim.[31]

Placement of the donor tissue

The crescents are next placed on the recipient eye with the anterior corneal edges overlying the recipient limbus (Fig. 26.4, *D*). The two anterior corners of a crescent are secured first at the limbus with interrupted 10-0 nylon sutures. The corneal edge of the KLAL should lie flush on the recipient cornea. Then the two posterior corners are sutured. An additional suture or two can be placed along the posterior edge if needed for security. Additional crescents are placed end-to-end in the same fashion until the entire circumference of recipient limbus is covered by healthy donor stem cell tissue. During suturing the authors place viscoelastic material on the KLAL tissue to protect the epithelium, and a balanced salt solution prevents desiccation. If there is a functioning bleb from a prior glaucoma filtering surgery, a gap can be left to preserve the bleb. In situations in which a seton drainage device has been placed, or is anticipated, the limbus can be covered with the new graft tissue without interfering with the success of these glaucoma procedures. It is not necessary to suture the free edges of the recessed recipient conjunctiva to the posterior edges of the segments. The patient's conjunctiva usually retracts minimally and adheres to the edges on its own accord. Recently, we have had success with using fibrin tissue adhesives (Tisseel) to adhere the corneoscleral rims to the host scleral surface. Sutures are still used on the corneal side to close the gaps. This has reduced the operating time and has reduced ocular discomfort postoperatively. At the conclusion of the procedure, an antibiotic-corticosteroid ointment is placed in the inferior cul-de-sac and the eye is patched until the patient is seen the next day.

Postoperative care

The postoperative regimen is essentially the same for Lr-CLAL recipients (Table 26.3). Patients use a topical antibiotic until the corneal and conjunctival epithelial defects are healed. Complete epithelialization usually occurs over 1–3 weeks. Topical corticosteroids are used three or four times daily for inflammation with overtreatment avoided to minimize retarding epithelialization. Patients are maintained on a tapering dose of topical corticosteroids indefinitely. Most patients receive oral prednisone 1 mg/kg/day, with a slow taper generally over 3–6 months. Systemic immunosuppression with CsA (Neoral) or tacrolimus (Prograf) and azathioprine (Imuran) or mycophenolate mofetil (Cellcept) are also begun postoperatively. In addition, topical CsA 0.05% (Restasis) is used four times a day indefinitely. All patients are instructed to use nonpreserved artificial tears on a frequent basis. Punctal occlusion and lateral tarsorrhaphy are additional steps to maximize surface lubrication. A therapeutic contact lens can be placed if a patient experiences significant discomfort or cessation of epithelial healing.

Table 26.3 Immunosuppressive regimen after keratolimbal allograft transplantation

Agent	Dosage and Duration	Monitoring
Corticosteroids		
Topical	q.i.d.–q.d., indefinitely	IOP, epithelial healing
Oral	1 mg/kg/day, taper over 6 months	BP, serum glucose, weight, gastritis, bone density, and lipids
Cyclosporin A		
Topical	0.05% q.i.d., indefinitely	Epithelial toxicity
Oral[a]	3 mg/kg/day, 12–18 months	Serum level 100–150 ng/dL, creatinine, BP, lipids, LFTs minerals, urinalysis, and CBC
OR		
Tacrolimus[a]	1–4 mg b.i.d., 12–18 months	Serum level 8–10 ng/mL for 3 months, then 5–8 ng/mL, creatinine, BP, lipids, LFTs minerals, urinalysis, and CBC
OR		
Azathioprine[a]	100 mg/day, 12–18 months	CBC and LFTs
Mycophenolate[a]	500 mg b.i.d., 12–18 months	CBC, chemistries, and LFTs

[a] Only one of these two agents is used.

IOP, intraocular pressure; BP, blood pressure; LFT, liver function test; CBC, complete blood count.

Results

In a recent review of our KLAL results in 31 eyes with aniridia, a stable ocular surface was achieved in 74% of cases and 7 out of 10 subsequent penetrating keratoplasties were successful.[18] Systemic immunosuppression appeared to be a crucial determinant of success in that series. We previously reported a similar ocular surface restoration rate of 72% in a series of patients with SJS.[16] Tsubota and coworkers published a series of 43 eyes with SJS or OCP that underwent KLAL.[32] They achieved a successful epithelialization in 51% of eyes transplanting entire circular corneoscleral rims and using oral cyclosporin for immunosuppression. Dua and Azuara-Blanco performed KLAL with only one donor cornea on six eyes using tacrolimus for systemic immunosuppression.[19] Five of those eyes had a successful outcome. The corneoscleral rim was obtained by lamellar dissection on a whole globe. In order to cover 360° of limbus in that series both the cadaveric corneal tissue and the CLAL from the recipient's fellow eye (a KLAL–CLAU hybrid) were performed. Not all studies, however, have demonstrated the same long-term success. Solomon and coworkers reported on 39 eyes that underwent KLAL for several diagnoses including chemical injuries (16 eyes) and SJS (9 eyes).[33] Twenty-four of these eyes underwent a penetrating keratoplasty, at the same time or at a later procedure. In their report, 77% of patients had a stable ocular surface at 1 year, but this fell to 24% at 5 years. Long-term survival of donor tissue in the recipient eye has been demonstrated conclusively after KLAL when adequate systemic immunosuppression is used.[34]

COMBINED LIVING-RELATED CLALs AND KLALs

In a select group of patients who have concomitant conjunctival and limbal stem cell deficiency, a combined lr-CLAL and KLAL may provide a better alternative for reconstructing the ocular surface. Specifically, patients with SJS and OCP who have a living relative donor may benefit the most from the added conjunctival tissue while having the maximum number of limbal stem cells transplanted. Specifically in these patients, the conjunctival loss contributes significantly to the ocular surface pathology. Severe symblepharon, forniceal loss, and trichiasis present mechanical barriers to successful stem cell transplantation. Additionally, the associated loss of goblet cells results in disruption of the mucin layer of the tear film.

The preoperative considerations previously discussed for KLAL and lr-CLAL apply to these patients. Typically, patients requiring the combined procedure have the most extensive ocular surface disease. Reconstruction of the ocular surface in these patients often requires restoration of the conjunctival fornices and lid procedures that are best performed with the assistance of an oculoplastic surgeon. In the most severe cases, mucous membrane grafting is appropriate, which may require the services of an otolaryngologist to harvest nasal mucosa from the inferior turbinate. Thorough evaluation by each subspecialist is required before proceeding with the surgery.

Surgical technique

The living-related tissue is harvested as described for lr-CLAL and stored in storage medium. A single corneoscleral rim is processed as previously described for the KLAL procedure and placed in storage medium. The second corneoscleral rim is not required because the superior and inferior aspects of the recipient limbus will receive the lr-CLAL tissue. Attention is then turned to the recipient eye, and all symblepharon and surface scarring are lysed to create space for new fornices. An encircling limbal peritomy is performed in areas where conjunctiva is present. Conjunctival preservation is essential whenever possible. A superficial keratectomy is performed to remove abnormal epithelium and fibrovascular pannus. Meticulous hemostasis is maintained with gentle cautery. When needed, the palpebral surfaces of the lids are resurfaced with mucous membranes. The CLALs are then positioned and secured at the 12 and 6 o'clock positions (Fig. 26.5). Interrupted 10-0 nylon sutures are used to secure the lateral and posterior aspects of the grafts. The cadaveric tissue is then positioned at the temporal and nasal limbus. The arrangement of the tissue must be planned to avoid gap areas between the allografts. The keratolimbal tissue is secured with 10-0 nylon sutures as previously described. Occasionally, a symblepharon ring is used to maintain the fornices while the ocular surface re-epithelializes. The results of our preliminary experience with combined CLAL–KLAL have been encouraging.[31] We have seen better results with this procedure in patients with severe conjunctival and limbal deficiency than with KLAL alone.

EX VIVO STEM CELL EXPANSION

A primary limitation of stem cell transplantation has been rejection. CLAU avoids rejection but is limited to a small percentage of patients in need of stem cell replacement. The ability to reliably harvest small numbers of stem cells from patients with bilateral stem cell failure, culture these cells in vitro, and transplant them back to the patient will revolutionize stem cell transplantation. While cost and technical difficulties currently limit the availability of this procedure, several researchers have demonstrated the feasibility of ex vivo stem cell expansion.

In 1996, Torfi et al reported on transplantation of ex vivo cultivated corneal epithelium, with a successful outcome in three of four

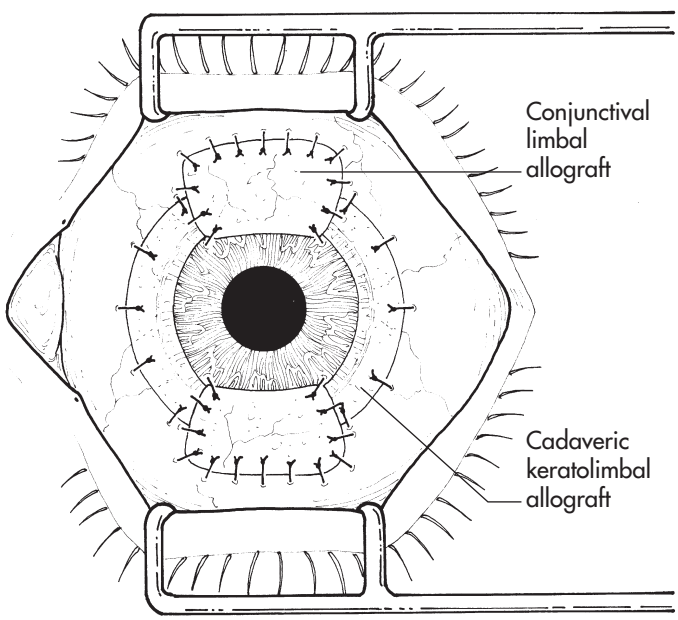


Figure 26.5. Technique for combined keratolimbal allograft (KLAL) and conjunctival limbal allograft (CLAL) transplantation. The CLAL are harvested as before (Fig. 26.3), and the KLALs are prepared from cadaveric tissue as shown in Figure 26.4. The CLAL tissues are placed in the superior and inferior quadrants, while the KLAL grafts are secured to the nasal and temporal limbus.

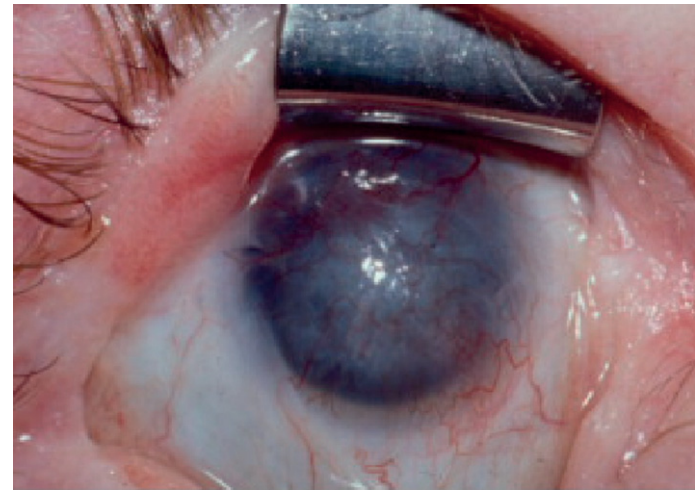
cases.[35] Similarly, Pellegrini and coworkers reported long-term stabilization of two eyes with unilateral alkali burns following transplantation of autologous corneal epithelium that was grown in vitro from a 1 mm biopsy from the healthy fellow eye.[36] Tsai and coworkers have demonstrated the benefits of amniotic membrane as a substrate on which to cultivate and transplant limbal epithelium. In their report, success was attained in six of six stem cell-deficient eyes that received expanded tissue from the fellow eyes.[37] Expanded stem cell allografts have also been described. Schwab and coworkers published studies on a series of 14 eyes, 10 of which received autologous expanded tissue harvested from the fellow eye and 4 of which received allogeneic tissue, with success in 10 of the eyes.[38] Koizumi and coworkers transplanted allogeneic corneal epithelial material, which had been expanded on an amniotic membrane substrate, cocultured with a layer of fibroblasts and subjected to air lifting, which is believed to promote formation of tight junctions.[39,40] All patients received systemic immunosuppression and all eyes had a stable ocular surface 1 year after surgery, except for three eyes that experienced rejection. Repeating the same procedure yielded a satisfactory outcome in those three eyes. In a final series of 13 eyes reported on by Shimazaki et al, limbal epithelium of cadaveric ($n = 7$) or living-related origin was cultivated on amniotic membrane and transplanted. Corneal epithelialization was achieved in only six of those eyes.[41] Recently, several groups have reported the successful use of cultured oral mucosal epithelial cells for reconstruction of the corneal surface.[42] This could be a very useful technique for patients with bilateral total limbal stem cell deficiency. In particular, by using autologous cells, the need for immunosuppression is negated. Further studies are needed to demonstrate the long-term results of this procedure.

PENETRATING KERATOPLASTY POSTEPITHELIAL TRANSPLANTATION SURGERY

In rare circumstances, namely significant corneal thinning with risk of perforation, penetrating keratoplasty is performed concomitantly with one of the above epithelial transplantation procedures. Otherwise, the authors prefer to wait at least 3 months for the ocular surface to appear stable before proceeding with additional surgeries, particularly penetrating keratoplasty. A relatively fresh donor cornea with near-perfect epithelium should be selected. Care is taken during the surgery to minimize trauma and desiccation of the limbal grafts already in place. Specifically, viscoelastic is used to cover the limbal grafts at all times. It is best to trephine the host immediately anterior to the limbal grafts and prevent any gap areas between the limbal graft and the penetrating corneal graft.

SUMMARY

Improvement in epithelial transplantation continues to progress. The role of systemic immunosuppression has been firmly established with the importance of triple therapy including steroids, a calcineurin inhibitor (cyclosporin or tacrolimus), and an antimetabolite (azathioprine or mycophenolate). The techniques discussed in this chapter represent significant advancement in the management of these very difficult groups of patients with severe ocular surface disease caused by limbal stem cell or conjunctival deficiency (Fig. 26.6).



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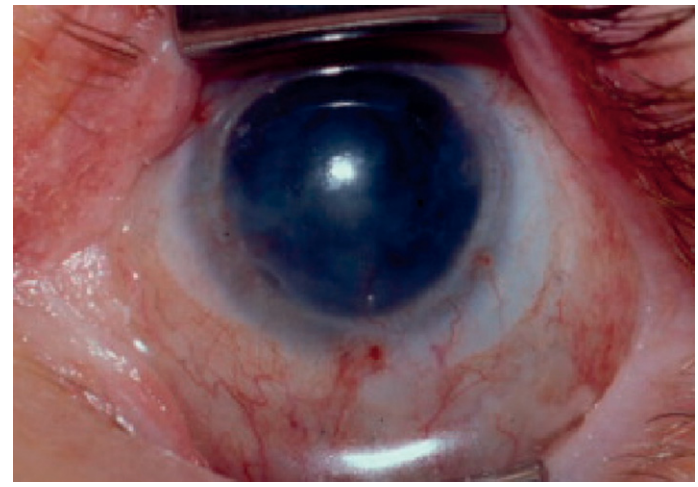

B

Figure 26.6. Preoperative (A) and postoperative (B) appearance of a patient with limbal stem cell deficiency due to Stevens–Johnson syndrome who underwent KLAL.

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27 Autologous conjunctival and scleral grafts

David W. Vastine

The use of autologous conjunctival grafting for reconstruction of the ocular surface was first introduced by Thoft.[1,2] Subsequent to his report, the use of autologous conjunctival grafting for the reconstruction of the periocular mucous membrane for multiple disorders including pterygium was reported by Vastine et al.[3] Autologous conjunctival grafts have been most frequently used for surface reconstruction following excision of primary or recurrent pterygium.[3,4] Similar surgical techniques can be used for surface mucous membrane grafting for symblepharon and ankyloblepharon from various causes.[3,5] Contralateral or ipsilateral donor sites have been recommended in surface mucous membrane reconstruction following scarring from traumatic injury, chemical burns, or severe cicatricial mucous membrane infections or disorders. The use of contralateral donor sites is essential in unilateral disease in which the recipient eye has had severe injury with no residual conjunctiva or the conjunctival stem cells have been obliterated, as in mitomycin toxicity or severe chemical injury. The theory and use of stem cell grafts are discussed elsewhere in this text.

INDICATIONS

Autologous grafting has been used for reconstruction after resection of tumors, cicatricial entropion, thermal and chemical injuries, and postsurgical cicatricial strabismus and in complex plastic reconstruction of the lids and conjunctiva. In severe bilateral injuries, donor heterologous conjunctiva has been shown to be effective in monkeys[6] but has not been used widely in humans because the prompt procurement and preservation of cadaver tissue is difficult. Alternatives such as donor corneal peripheral epithelioplasty for stem cells, amniotic mucous membrane, buccal mucous membrane, and hard palate mucosa have been used with varying degrees of success. None of these techniques has proven as satisfactory as conjunctiva in restoring the most natural cosmetic or functional result. As in any procedure, exacting technique and attention to detail in the reconstructive process are essential for good function and cosmesis after the surgery.

THEORETICAL CONSIDERATIONS

The theory of the procedure is based on the use of normal undisturbed conjunctival mucous membrane with its intact superficial vascular network and healthy surface cells to provide a source of normal goblet, columnar surface, and stem cells for resurfacing an injured membrane. Through careful observation after grafting, the surgeon can watch the migration of the normal cells as they spread over the abnormal surface and displace the cells that have filled the defect by transformation from the epithelial cells of the lid margins. The migration patterns can be outlined with fluorescein, and the abnormal cells frequently pick up rose bengal stain. The most dramatic effect of the conjunctival grafts is their minimalization of graft shrinkage, which is frequently seen after buccal mucous membrane grafts or after allowing the natural reparative processes to close a surface wound by secondary intention (e.g. after the bare scleral procedures for excision of pterygium or large tumors of the conjunctiva). The resultant pseudopterygium can be very dramatic in its appearance and alteration of function, leading to diplopia and restrictive strabismus (Fig. 27.1). Thin conjunctival patch grafts rapidly revascularize, thus limiting the stimulus for subepithelial fibrosis and shrinkage of the graft and surrounding tissues. The normal surface cells spread into areas lacking normal surface cells, thus reducing the stimulus for inflammation and scarring (Figs 27.2 and 27.3).

RESULTS

Most importantly, since previously reported in 1982,[3] this technique has been used for reconstruction of patients with symblepharon, ankyloblepharon, chemical burns, mitomycin toxicity, post-traumatic and postsurgical scarring and fibrosis, resection of primary and secondary pterygium, and tumor resection with plastic reconstruction. There have been no complications with this procedure over the past 17 years. As with many procedures, the confidence and familiarity with the procedure is a big factor in its use and success. The success rates have been well established with repair after primary or secondary pterygium.[3,4,7–10] The main controversy remains between the use of excision with primary closure by flap rotation or autologous conjunctival grafts and simple bare scleral excision with adjunctive therapy such as β-radiation or mitomycin-C.[11,12] The best cosmetic results with the lowest recurrence rates are achieved with the grafting techniques. Unlike β-radiation or mitomycin application, there are no short-term complications of scleral necrosis or long-term complications due to late infectious scleritis

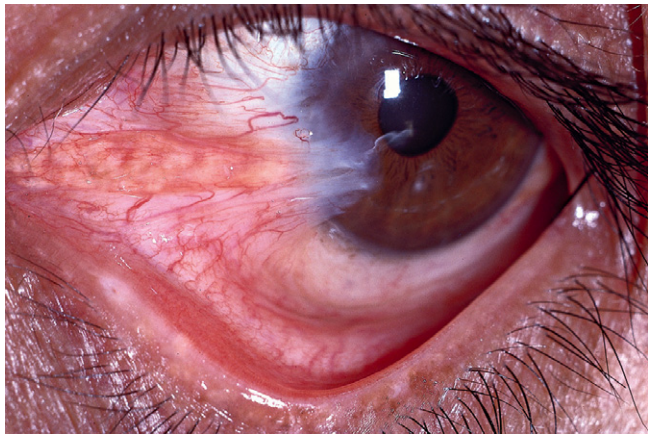


Figure 27.1. Medial symblepharon after pterygium excision with restriction and diplopia prior to reconstruction with an autologous conjunctival graft.

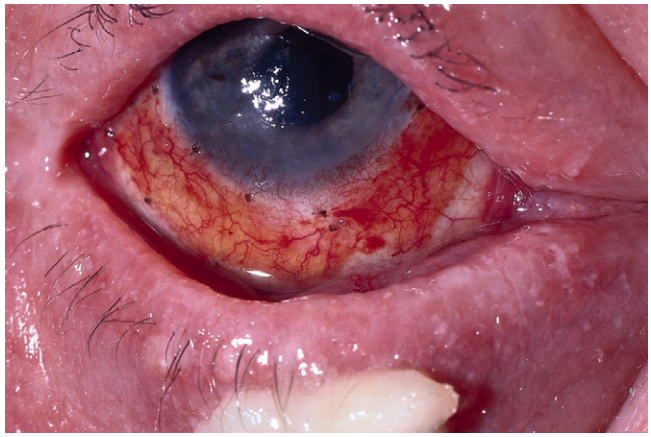


Figure 27.2. Multiple sutured small patch grafts are seen resurfacing the entire inferior bulbar conjunctiva in a patient with severe ocular shrinkage secondary to chronic atopic disease. The pseudopterygium is extensive with a mattress suture over the bolster and through the lid to redirect the scar tissue immediately postoperatively.

or cataract.[13,14] Severe surface disease with scleral necrosis has occurred with the use of mitomycin-C, which is an unnecessary risk to take with a readily available nontoxic surgical alternative.[15]

SURGICAL CONSIDERATIONS

No attempt at surgical repair should be initiated until the acute process or trauma has been controlled and is quiet for at least 6 months. The surgical approach to reconstruction can use simple conventional techniques in mild cases. Conjunctival Z-plasty and other simple conjunctival procedures may be helpful in the less severe cases. Advanced scarring and tissue destruction will require extensive reconstruction with free autologous conjunctival mucous membrane grafts. Surgical intervention should not be attempted until any acute inflammatory process has been controlled. Procedures done in the presence of aggressive inflammation and necrosis may result in failure of the graft or unsatisfactory results. However, in some cases, such as chemical injury in which lack of adequate stem cells results in progressive disease, it is necessary to intervene to prevent further damage. This case also occurs in mitomycin toxicity, in which progressive scleral necrosis and ischemic scleritis will not be controlled without intervention.

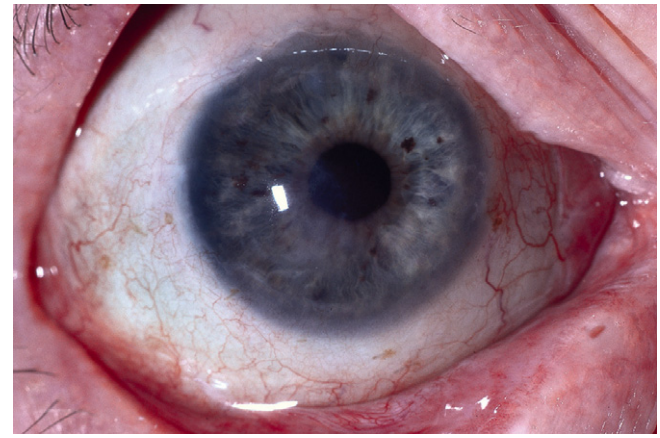


Figure 27.3. Seven months postoperatively, the grafts cannot be distinguished with a normal inferior fornix. A quiet eye is maintained with fluorometholone drops once a day and sodium cromolyn to control chronic atopic disease.

TECHNIQUES OF AUTOLOGOUS CONJUNCTIVAL TRANSPLANTATION

The procedure for successful grafting begins with a careful and full dissection and excision of the diseased portion of the eye. It is important to remove all the subepithelial fibrosis and recess as much of the remaining normal conjunctiva as possible to create a deep and healthy fornix. In most cases, there is sufficient virgin bulbar conjunctiva under the upper lid in the same or contralateral eye for proper reconstruction. In desperate cases, patches of conjunctiva can be sutured in the most critical areas around the corneal limbus, and the transplanted cells will migrate over the areas of bare sclera to fill in defects and create an intact mucous membrane layer with minimal resultant foreshortening of the fornix. It is important to save and reposition as much of the normal conjunctival membrane around the areas of pathology as possible without compromising the adequate resection of the diseased tissue. The first step is to prepare the recipient site to receive the graft. The excessive scar tissue must be excised, and any bleeding in the recipient bed must be controlled by bipolar cautery. Part of this process may require separation of the lids (ankyloblepharon) (Fig. 27.4, *A*). The recipient site is measured to establish the size of the donor graft required. The use of the binocular operating microscope is recommended for all of these procedures to achieve precise control and evaluation of the normal and abnormal anatomy. Anterior limbal 7-0 black silk sutures are placed to move the eye in all directions to assure lysis or remove any restrictive adhesions, to provide adequate surgical exposure, to allow resection of all submucosal scar, and to assure full mobility of the globe (Fig. 27.4, *B* and 27.5). Subepithelial resection of the excessive thickened Tenon's fascia is important to help debulk the recipient site and allow enhanced acceptance and adherence of the donor graft (Fig. 27.5). This approach also improves the final cosmetic and functional result. In advanced cases of foreshortening of the fornix, the remaining bulbar conjunctiva may be used to provide a palpebral conjunctival surface and create a new fornix with a through-the-lid mattress bolster suture. The bulbar conjunctiva is provided with the donor autologous conjunctival graft (Fig. 27.6; see also Fig. 27.2).

The preparation of the donor conjunctival graft from the ipsilateral or contralateral donor site is also done under microscopic control. The procedure includes the placement of a 7-0 black silk

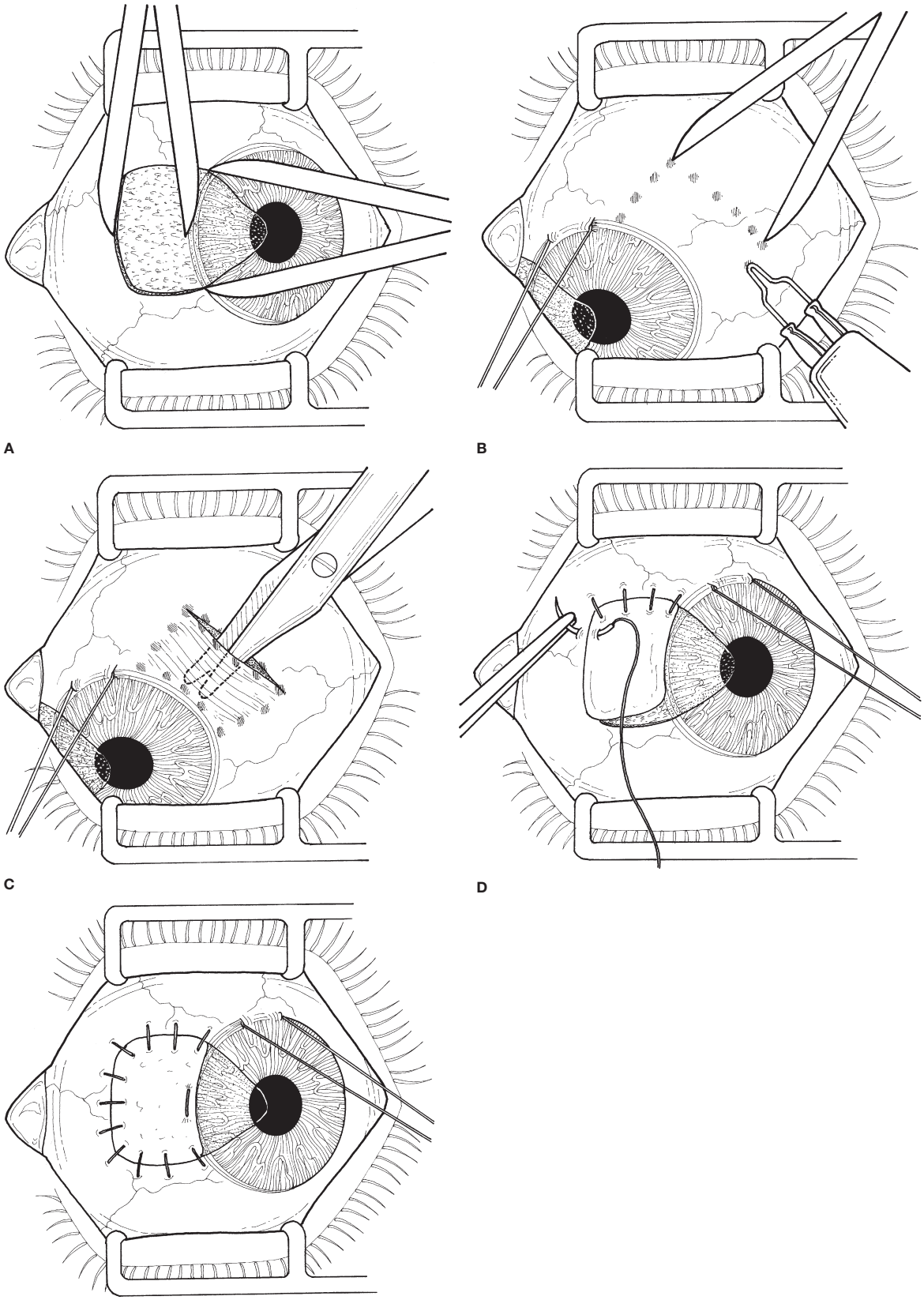


Figure 27.4. Autologous conjunctival grafting. *A*, After resection of the pterygium or symblepharon, the defect is measured with calipers to establish an exact match from the donor site. *B*, A 7-0 black silk suture is placed at the superior limbus to manipulate the globe and expose the superior bulbar conjunctiva, which is marked with a cautery to assure proper size and configuration of the donor graft. *C*, Fine-tipped Wescott or Vannas scissors are used to gently separate the conjunctiva and the underlying connective tissue, making the graft as thin as possible. *D* and *E*, The donor graft is slid into place and oriented properly to fill the defect. If a small defect remains, the adjacent conjunctiva may be undermined and slid in to fill the defect with primary closure.

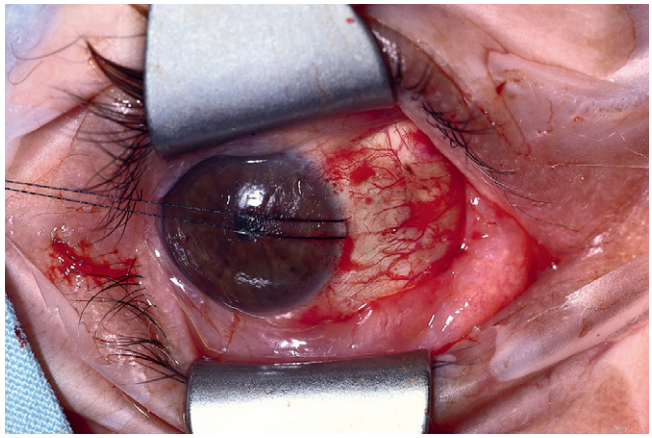


Figure 27.5. An intraoperative photograph shows the placement of a limbal-based black silk suture used for manipulation and control of the eye during surgery. Note the extensive resection of scarred conjunctival tissue required to get free mobility of the globe.

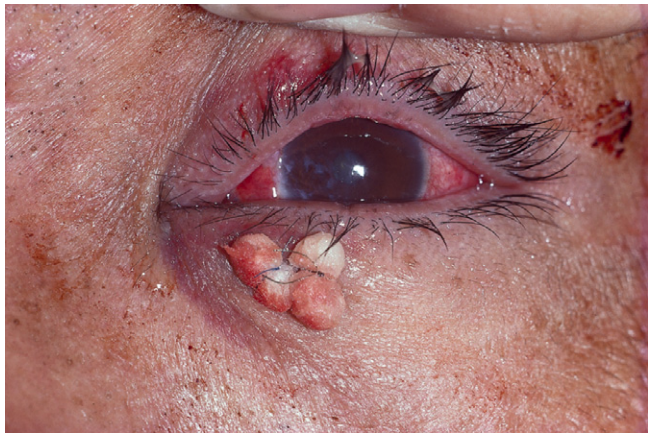


Figure 27.6. The appearance of a patient on the first postoperative day after his fifth surgery for recurrent pterygium and his first conjunctival graft. Because of obliteration of the inferior fornix, the pterygium was transposed and used to create a new inferior fornix held in position with a through-the-lid bolster.

suture at the superior temporal limbus, and the eye is displaced inferiorly and nasally, exposing the superior bulbar conjunctiva. The dimensions of the patch graft are marked with gentle bipolar cautery (see Fig. 27.4, *B* and *C*). A subconjunctival injection of 1% lidocaine with 1/100 000 epinephrine is given with a 30-gauge needle just under the mucosal surface. This injection is used to separate the surface mucous membrane from underlying Tenon's fascia. Careful dissection of the donor patches are done with Vannas or sharp, pointed Westcott scissors. Care is taken to avoid button-holing the patch or leaving too much underlying connective tissue (see Fig. 27.4, *C*). The graft may or may not include the limbal stem cells, depending on the needs of the recipient eye. The donor site is left bare and is not closed. Experience has shown that the donor site will re-epithelialize without significant shrinkage and can be used again for additional grafts in special circumstances. There have been no reported complications noted at the donor site.

The graft is transferred to the recipient site with care to prevent eversion. The most useful technique is to place it on a segment of plastic drape, sliding it on and off to maintain proper orientation. The donor patch is transferred to the recipient site and sutured into

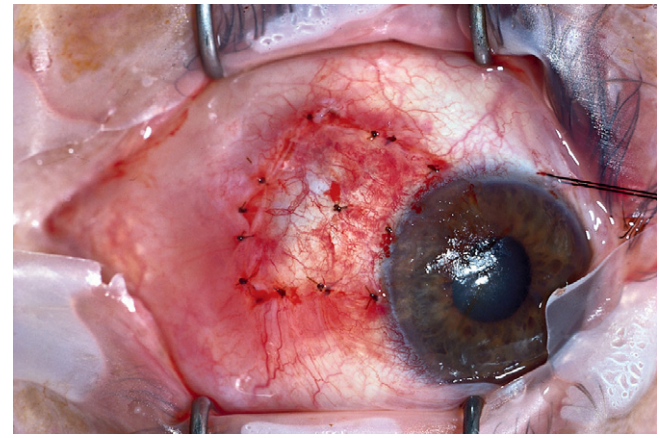


Figure 27.7. The intraoperative appearance of a small thin graft secured with multiple interrupted sutures.

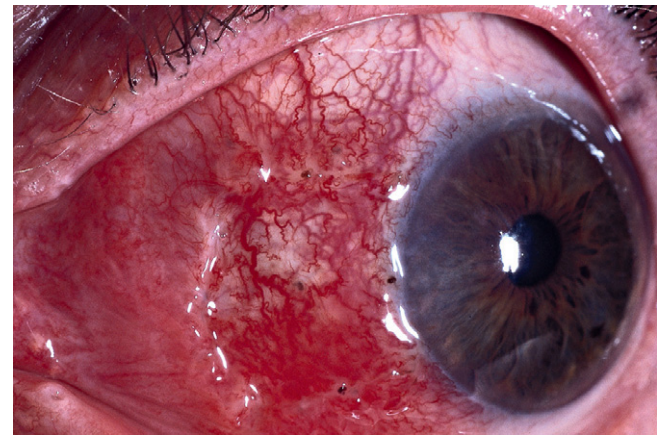


Figure 27.8. Typical postoperative chemosis and hyperemia are noted immediately after grafting.

place with multiple interrupted sutures. If some of the tissue at the recipient site has been rotated into the fornix, it can be secured with a through-the-lid double-armed mattress suture with a bolster. The donor patch is sutured to the underlying connective tissue and episclera with a 10-0 nylon (see Fig. 27.4, *D* and *E*). The suture of choice was 8-0 chromic collagen, which is no longer available. Monofilament nylon is superior to the current 8-0 or 9-0 monofilament polyglactin 910 suture, which may also be used (Fig. 27.7). The mechanical irritation and perisuture necrosis caused by the polyglactin 910 is not ideal and may cause excessive inflammation and graft reaction. The grafts that are well secured have remained stable during the revascularization process.

Postoperatively, the grafts appear edematous and avascular with no flow in the vessels for the first 3–5 days. The grafts will begin to revascularize and will become edematous and hemorrhagic in appearance for about 2 weeks (Fig. 27.8). Over 7–10 days, the patches become well adhered. Within the next 2–3 months, the patches assume a normal appearance (Fig. 27.9). During the post-operative period, topical antibiotic and corticosteroid drops are used initially from four to eight times daily and gradually tapered, depending on the degree of postoperative reaction.

ALTERNATIVE PROCEDURES

Alternative tissues have been used in cases in which no normal conjunctival cells exist (e.g. bilateral chemical burns). Prior to the

Figure 27.9. The same patient as in Figure 27.8, 1 year after surgery, with a quiet normal appearance at the recipient site.

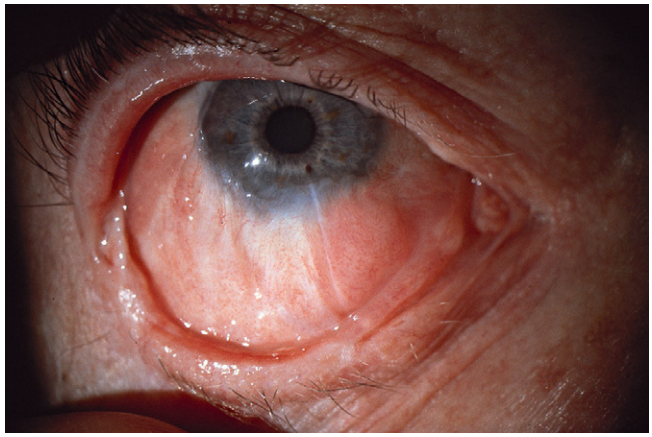


Figure 27.10. A buccal mucous membrane graft with thickened appearance and abnormal vascular pattern gives unsatisfactory cosmetic and functional results.

use of autologous conjunctival grafting, mucous membrane of the mouth has been the most commonly used source. The lack of a vascular tree and the need to revascularize result in shrinkage of these grafts, with an unsightly cosmetic appearance. In some cases, complete shrinkage and replacement of the graft can occur. The surgical procurement of buccal or labial mucous membrane is much more cumbersome, requires a dermatome, and does not supply a source of conjunctival stem cells for cellular transformation. The subsequent physiology of the tear film is not satisfactory in these patients. After complete healing, a partial-thickness buccal mucous membrane graft is more likely to shrink and may be cosmetically and functionally less satisfactory than autologous conjunctiva (Fig. 27.10). These grafts will frequently shrink despite the use of conformers, symblepharon rings, and stents to limit shrinkage and destruction of the grafts.[16]

Prior to using autologous conjunctiva for recurrent pterygium, lamellar keratoplasty[17] was advocated to prevent aggressive recurrence after multiple attempts at resection but is rarely used today. The author has not used either heterologous conjunctival grafts or amniotic membrane grafts. There are clear indications for these grafts, but the need for these extreme techniques is fortunately rare. The use of autologous conjunctival grafting has shown little evidence of postgraft shrinkage and resistance to fibrosis due in part to the supportive vascular network transplanted into the defect.

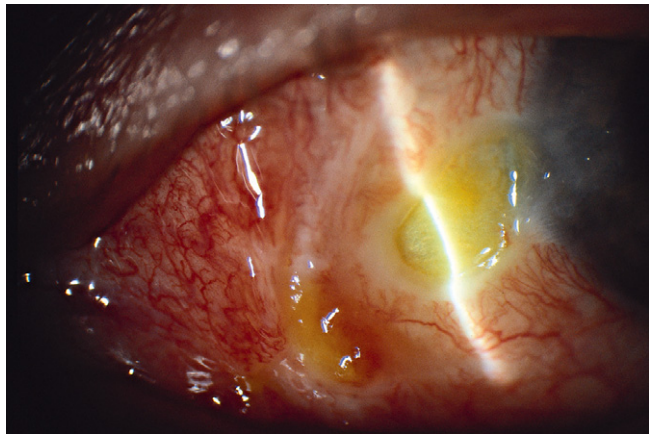


Figure 27.11. Localized scleral thinning, melt, and ischemia with surrounding conjunctival hyperemia and chemosis following simple excision of a pterygium with the application of β-radiation.

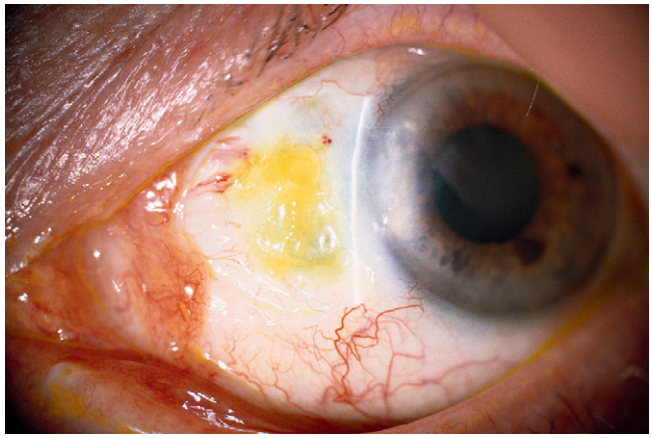


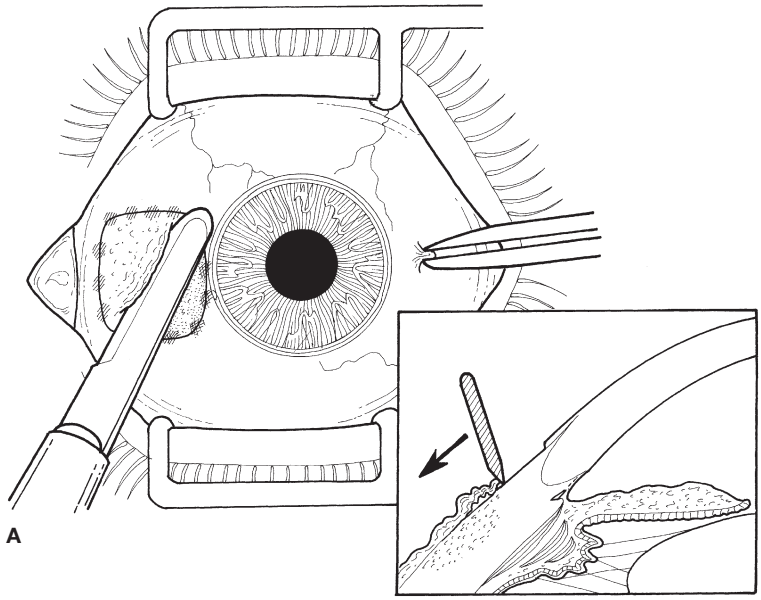
Figure 27.12. Scleral necrosis using mitomycin-C topical treatment after bare scleral excision of a recurrent pterygium. There is also mild corneal thinning. In some patients, there is extensive corneal surface abnormality due to lack of normal stem cells.

RESULTS

The results of several published studies[3,4,7,10] have shown conjunctival grafting to be the safest and the most effective technique for surface restoration after excision of recurrent pterygium. The recurrence rate with the autografting technique ranges from as low as 2% to as high as 16–25% in primary and recurrent pterygia. It appears as if the prospective studies show the best results, and the recurrence rate depends on a varying definition of recurrence. The results are compatible with those of studies showing a less than 6% recurrence for primary and recurrent pterygium combined. Meticulous surgical technique plays a vital role in the outcome of the procedure. The complications of scleral necrosis and ischemic scleritis have not been reported.

AUTOLOGOUS SCLERAL GRAFTS FOR RECONSTRUCTION

The complications of noninfectious and infectious scleritis after the use of β-radiation[13,14] and mitomycin[15] present challenges in restoring the ocular surface. Mitomycin toxicity offers the additional challenge of destruction of the surface stem cells and lack



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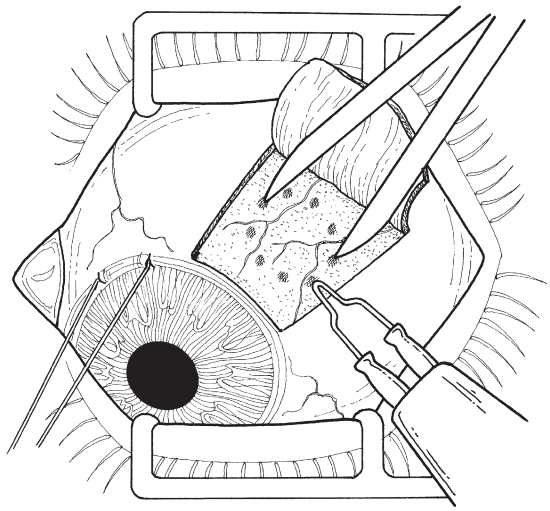

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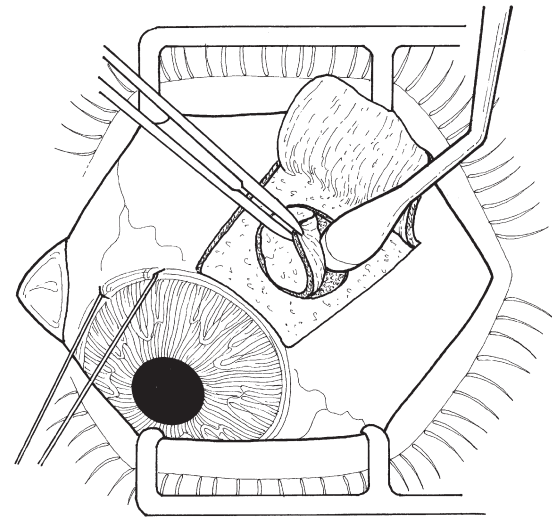

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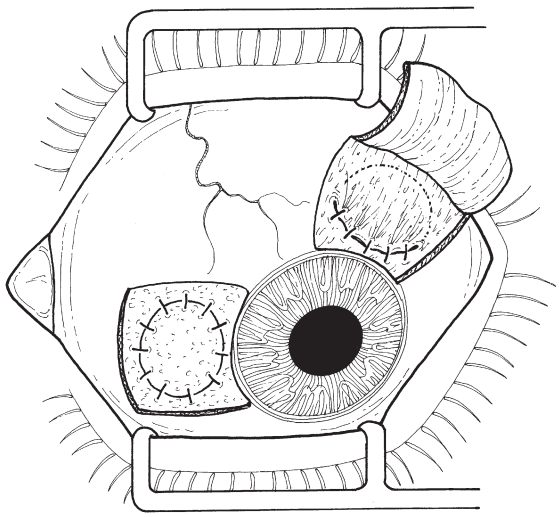

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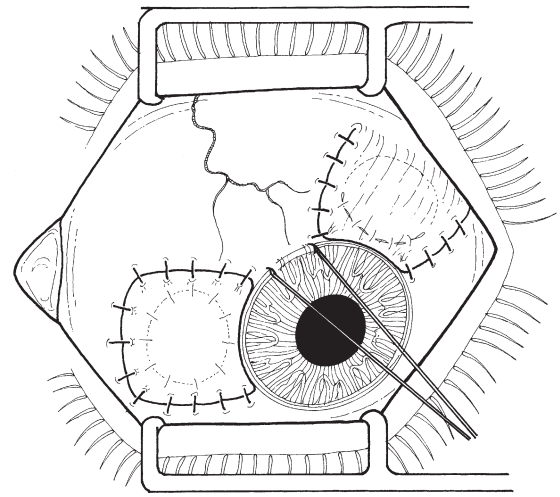

F

Figure 27.13. Autologous scleral grafting in combination with contralateral autologous conjunctival graft to repair scleral necrosis. *A* and *B*, The diseased and ischemic conjunctiva is removed to a healthy recipient bed, and the underlying necrotic sclera is removed with a #69 Beaver blade. *C*, The eye is displaced inferiorly, and the conjunctiva is reflected with sharp dissection leaving the superior bulbar sclera exposed. The scleral patch is outlined with a caliper and a cautery, but the episcleral vessels are not treated with cautery. *D*, The sclera is incised with a diamond knife to approximately one-half thickness, and the scleral flap is dissected with a spatula knife and removed and transferred to the donor site. *E*, The donor site is closed carefully with adjacent Tenon's fascia sutured to the donor site with 7-0 polyglactin 910, and the conjunctiva is closed carefully with 10-0 nylon as it has poor healing secondary to mitomycin-C toxicity. The scleral graft is transferred and positioned to fill the defect and sutured into place with interrupted 10-0 nylon. *F*, The contralateral autologous conjunctival graft is sutured into place with primary anastomosis to healthy recipient conjunctiva surrounding the original area of resection. 10-0 nylon suture is also used to close the conjunctival graft.

of the ability of the surface to restore the persistent defect and stop the progression of ischemic necrosis of the sclera. These patients have consistent pain and discomfort with no response to topical noncorticosteroidal anti-inflammatory drops as well as topical corticosteroids.

THEORETICAL CONSIDERATION

Previous reports had documented the failure of ipsilateral conjunctival grafts in repair of this complication.[15] This finding was the result of failure of the stem cells to repopulate the normal cell structure. In addition, transplantation of healthy mucous membrane over a large ischemic area results in lack of revascularization of the graft and eventual graft failure.

In response to this challenge in 1993, reports were published about the successful use of autologous scleral patch grafting with contralateral autologous conjunctival grafting to restore ocular integrity in these complicated patients.[18] The rationale for the procedure relates to the effects of the use of mitomycin, which is strictly surface toxic in the areas of intact conjunctiva. The ischemic necrosis caused in the area of pterygium resection from β-radiation or mitomycin continues to break down, causing severe pain and chronic discomfort (Figs 27.11 and 27.12). Donor scleral grafts or periosteal grafts have been successfully used in scleral necrosis in patients with rheumatoid arthritis. The advantages of fresh autologous sclera with an intact episcleral vascular network are ease of procurement, ready availability, and low risk of infection. Periosteum is difficult to harvest from the patients' pretibium and is difficult to work with in comparison with autologous sclera.

TECHNIQUE OF AUTOLOGOUS SCLERA GRAFTING

The repair begins with debridement of the area of necrosis and removal of dead tissue from the defect (Fig. 27.13, *A* and *B*). The defect is measured, and the shape of the defect is outlined. Attention is drawn to the superior and temporal quadrant. 7-0 black silk limbal suture is placed in the superior corneal limbus. A limbal incision is made, and a fornix-based conjunctival flap is elevated from the sclera. Minimal cautery is used to preserve the intact episcleral vessels. A caliper is used to outline the pattern of the scleral defect with a light bipolar cautery (Fig. 27.13, *C*). An incision is made with a diamond knife to approximately one-half thickness of the sclera. Using a spatulated angulated blade, the scleral graft is elevated similar to the technique of creating a trabeculectomy sclera flap and undermined throughout the area of the donor graft. (Fig. 27.13, *D*). A Vannas scissors is used to remove the scleral patch. The graft is transferred to the recipient site and sutured into place with multiple interrupted 10-0 nylon sutures. The donor site is closed by drawing Tenon's fascia into the defect and suturing it in place with interrupted 10-0 nylon sutures. The conjunctival flap is closed over the scleral defect with nonadsorbable sutures (Fig. 27.13, *E*). The recipient site is covered with a contralateral, healthy, free autologous conjunctival graft. Care is taken to attach the graft to areas of undisturbed conjunctiva with relatively normal vasculature (Fig. 27.13, *F*). The technique used is as described previously.

OUTCOME

The combined technique has been used in four patients with mitomycin scleral necrosis with successful results on long-term follow-up in all cases[19] (Figs 27.14 and 27.15). The scleral grafts have remained stable, and the superficial scleral vasculature recanalizes and provides a stable patch. The contralateral conjunctival patch graft protects and supports the donor scleral graft and supplies healthy stem cells for stabilizing the conjunctival surface. In these cases, it is essential to harvest the limbal cells from the donor conjunctiva. Healthy corneal epithelial cells are imported as well and will correct the chronic epitheliopathy seen in severe toxicity after mitomycin application. There have been no complications noted at the donor site in any of the patients (Fig. 27.16).

CONCLUSION

The use of natural tissues with no additive chemical or radiation for reconstruction is a safe, effective, and nontoxic technique for preservation and reconstruction of the ocular surface mucous membrane in multiple conditions without significant complications.

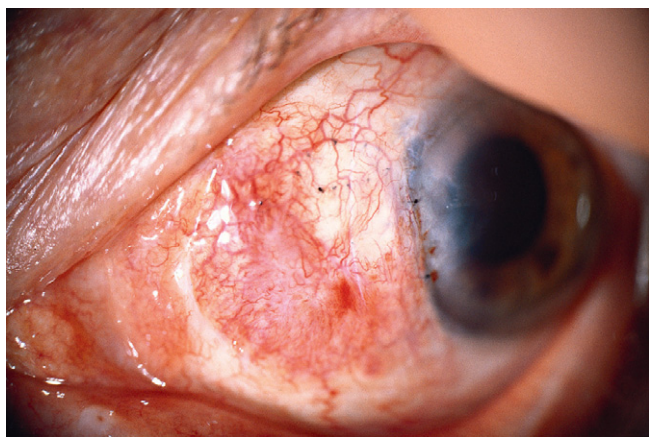

Figure 27.14. The postoperative appearance of the patient in Figure 27.12, 6 weeks after the combined grafts, shows vascularization of the conjunctival and scleral graft.

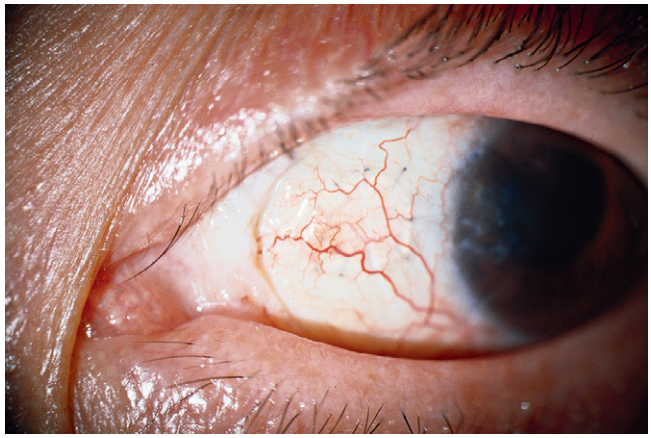

Figure 27.15. The postoperative appearance of the same eye 1 month after the combined graft; a distinct vessel is feeding the donor episcleral vessels through the vessels of the donor conjunctival autologous graft.

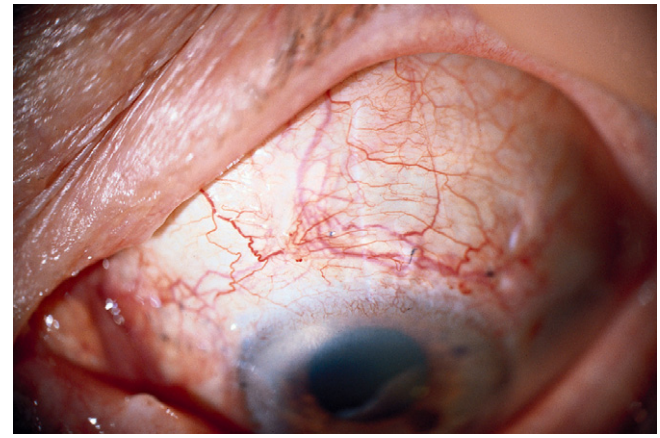

Figure 27.16. The appearance of the scleral donor site 6 weeks after surgery shows no signs of wound breakdown or thinning of the sclera.

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28 Surgery of limbal dermoids

David B. Glasser

Epibulbar limbal dermoids are choristomas: benign congenital growths of abnormally located tissue. To be histopathologically classified as a dermoid, a choristoma must contain epithelial elements in the form of hair follicles and sebaceous glands (pilosebaceous apparati). Dermoids are usually covered by keratinized stratified squamous epithelium and may contain other elements of ectodermal and mesodermal origin. These elements can include nerve, brain, lacrimal, adipose, and fibrous connective tissue, sweat glands, cartilage, bone; teeth, and blood vessels.

Choristomas comprise 22–33% of all surgically excised epibulbar tumors in children, with 48–58% of these lesions being classified as dermoids. Other epibulbar choristomas, which differ from dermoids by lacking pilosebaceous apparati, include dermolipomas (24–30%), ectopic lacrimal gland (18%), complex choristomas (6%), dermis-like choristomas (6%), osseous choristomas (2%), and simple choristomas (2%). The incidence of epibulbar choristomas is between 1/10 000 and 3/10 000.[1–3]

The pathogenesis of choristoma formation is uncertain, with theories dating back to the 19th century. Sequestration of dermal tissue in underlying layers during embryogenesis has been previously thought to account for choristoma formation. Duke-Elder[4] theorizes that the extent of a choristoma depends on the time during embryogenesis at which the malformation occurs. If it occurs prior to development of the lens, corneal tissue is replaced by fibrofatty growth, and the anterior chamber, iris, and lens are absent. If the malformation occurs during lens formation, the entire cornea is involved, but an ill-formed lens and rudimentary anterior chamber and iris structures are present.[4] Choristomas are thought to arise from metaplastic transformation of mesoblasts between the rim of the optic nerve and surface ectoderm during early development of the embryo. Most choristomas occur sporadically and are not inherited, although there have been reports of familial cases.[3] A rare syndrome of autosomal dominantly inherited bilateral dermoids forming a ring around the limbus with corneal and conjunctival extension has been described,[5] as has an X-linked form of bilateral corneal dermis-like choristomas.[6]

Epibulbar choristomas can be seen in association with Goldenhar syndrome (oculoauriculovertebral dysplasia) and the linear epidermal nevus syndrome. The classic findings in Goldenhar syndrome include preauricular fistulae, preauricular appendages, and epibulbar dermoids. Approximately 30% of patients with Goldenhar syndrome have epibulbar dermoids. Other reported ocular findings in Goldenhar syndrome include orbital or lid choristomas, lid, brow, or uveal colobomas, optic nerve hypoplasia, pseudopapilledema, peripapillary hypopigmentation, aniridia, iris heterochromia, microphthalmos and partial cryptophthalmos, lacrimal drainage abnormalities, Duane syndrome, neuropathies involving the third, fifth, or seventh cranial nerves, cataract, and retinal vascular tortuosity.[3] The epidermal nevus syndrome is manifested by dermatologic, skeletal, neurologic, and vascular disorders. The skin lesions that lend the disorder its name are linear epidermal nevi, which are congenital linear papules with increased pigmentation and variable hyperkeratosis. They usually do not cross the midline and have a predilection for the head and face. Lesions containing many sebaceous glands are called *sebaceous nevi* and, unlike linear epidermal nevi, are known to undergo malignant transformation. Epibulbar choristomas associated with the linear epidermal nevus syndrome are typically complex choristomas and are frequently bilateral and extensive. Other ocular findings may include choristomas of the lid or choroids, colobomas of the lid, optic nerve, or choroids, epidermal nevus of the lid, micro- or macrophthalmia, nystagmus, ophthalmoplegia, cortical blindness, and cataract.[3]

CLINICAL APPEARANCE

Typical epibulbar dermoids are solid round or oval raised dome-like lesions fixed to underlying tissue. They are usually well defined, are yellow, white, or pink, and may be hard, rubbery, or soft (Fig. 28.1). Fine hairs may be present on the surface. Multiple or bilateral lesions may be seen but are not typical. Epibulbar dermoids are located most commonly at the limbus (63–67%) or the conjunctiva (20–33%) or on the cornea (17%). Limbal dermoids are located temporally in 84–94% of patients, most often inferotemporally.[1,2] A ring of lipid is usually present in the cornea, separated from the anterior edge of the dermoid by a clear zone. In several series, 43–76% of patients with a single limbal dermoid demonstrated corneal astigmatism greater than 1 D in the affected eye, with central corneal flattening in the axis of the lesion.[7–12] In one small series,

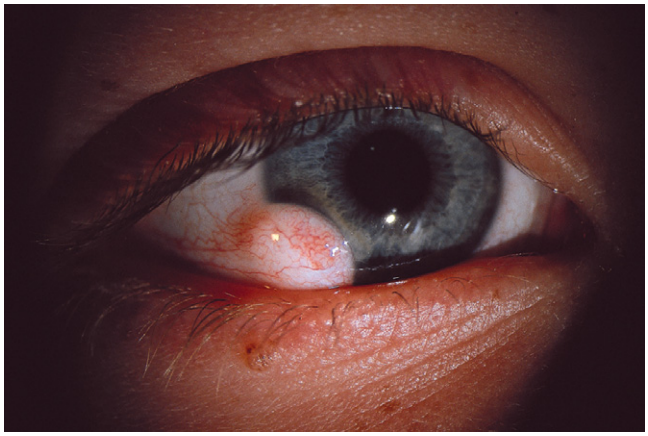


Figure 28.1. A 7-year-old female with classical limbal dermoid. The patient desired cosmetic improvement. (Photo courtesy of FS Brightbill, Madison, WI.)

4 out of 10 patients demonstrated over 6 D of astigmatism.[11] The astigmatic error may induce amblyopia.

Limbal dermoids may vary in size from a few millimeters to a large mass filling the epibulbar area.[1,2,13] Growth can occur but is uncommon except at puberty, when the lesions are more likely to increase in size and develop more hairs. Mann[3] classified limbal dermoids into three grades based on anatomic involvement. Grade I lesions are epibulbar limbal dermoids with superficial corneal involvement and are the most common. Grade II dermoids affect the full thickness of the cornea, although Descemet's membrane and the endothelium may be uninvolved. The entire cornea and all anterior chamber structures are replaced in grade III lesions, which are rare.

SURGICAL MANAGEMENT

The most common primary indication for surgical removal of a limbal dermoid is reconstructive. The distinction is made between reconstructive and cosmetic surgery to emphasize that surgery is being performed to correct an abnormal growth, not an essentially normal tissue. There are additional medical indications. High degrees of astigmatism may lead to amblyopia, the lipid ring or the lesion itself may encroach on the visual axis, a large or elevated tumor may produce irritation from mass effect, drying and superficial keratitis or dellen formation may occur secondary to interference with tear flow, blinking, or lid closure, the hairs may produce irritation or keratitis, and a thinned area may perforate. Amblyopia therapy may be considered prior to surgical intervention if the visual axis is clear.

Simple excision (shaving or shelling out) and excision with peripheral lamellar keratoplasty are the two most commonly used techniques for removal of grade I limbal dermoids. The surgeon should carefully consider the possible need for donor tissue based on the preoperative examination. Small limbal dermoids can occasionally extend full thickness. The extent or depth of a lesion may be difficult to determine preoperatively, particularly if the dermoid covers a large portion of the central cornea. Careful examination through clear areas of cornea with the globe rotated may reveal intraocular involvement. Preoperative gonioscopy is helpful in determining whether a full-thickness procedure will be necessary. Ultrasound biomicroscopy prior to surgery may be able to reveal the extent of these lesions.[14,15]

SIMPLE EXCISION

General anesthesia is usually necessary in this pediatric age group, although retro- or peribulbar anesthesia may be used if the patient can cooperate. Scissors are used to perform a conjunctival peritomy around the dermoid. The lesion may then be shaved off or shelled out with a straight or angled blade. Sharp dissection is begun on the scleral border of the dermoid and carried forward into the cornea in one plane. A lamellar blade (Martinez, Troutman) and a pushing rather than a cutting motion make it easier to maintain a single plane of dissection within the cornea. The cornea is kept dry, and gentle traction is used to pull upward on the free edge of the tumor. A two-thirds depth excision is usually sufficient to completely remove the dermoid. Hemostasis is achieved with cautery. If the conjunctival defect is large, surrounding tissue is mobilized with blunt dissection and the defect is closed with absorbable sutures or fibrin glue. The eye is patched with antibiotic and corticosteroid ointment.

Follow-up is performed on the first postoperative day and frequently until the corneal and conjunctival epithelium have healed. Topical antibiotics are continued until epithelial healing is achieved. Topical corticosteroids are continued until inflammation has subsided. In one small series of 10 cases, epithelial healing was complete in 1–39 days (mean, 16.2 days). An epithelial defect persisted for 2 weeks or more in 4 out of 10 patients. Cosmetic appearance was improved, and the visual axis remained clear in all 10 patients. However, peripheral corneal vascularization and scarring were noted in seven cases.[8] Simple excision usually has little or no effect on the astigmatic error that accompanies a dermoid.[8,9] Therefore, amblyopia therapy may be necessary after surgery.

EXCISION WITH PERIPHERAL LAMELLAR KERATOPLASTY

Excision with lamellar keratoplasty is more complex and lengthier than simple excision. In addition, it necessitates suture removal, usually under anesthesia, 1–3 months after surgery. However, some corneal surgeons believe that lamellar keratoplasty is preferable to simple excision. The presence of a graft may produce a more satisfactory cosmetic result, with less scarring and vascularization than simple excision. Tight suturing of a lamellar graft can also steepen the cornea, thereby reducing the central corneal flattening and astigmatism in the axis of the dermoid. Published reports on astigmatism reduction after dermoid excision with lamellar keratoplasty have demonstrated variable results. Some indicate a significant reduction in astigmatism, particularly for those patients with greater than 6 D of astigmatism prior to surgery.[7,11] Others report no significant change[10] or a variable response with increased, decreased, and unchanged astigmatism in subgroups of those treated.[12]

General, retrobulbar, or peribulbar anesthesia is used, depending on the age and cooperation of the patient. Because the extent and depth of the lesion are not always known with certainty, the dermoid should be excised and the host bed prepared prior to preparation of the donor. A conjunctival peritomy surrounding the conjunctival side of the lesion is performed with scissors (Fig. 28.2, *A*). The smallest trephine that will completely surround the lesion is chosen and used to make a partial-thickness cut (Fig. 28.2, *B*). A razor or diamond knife is used to carry the dissection deeper, if necessary, until clear corneal stroma is reached. The vertical edges of the dissection should be kept perpendicular to facilitate donor tissue placement. A lamellar dissection is then performed beneath

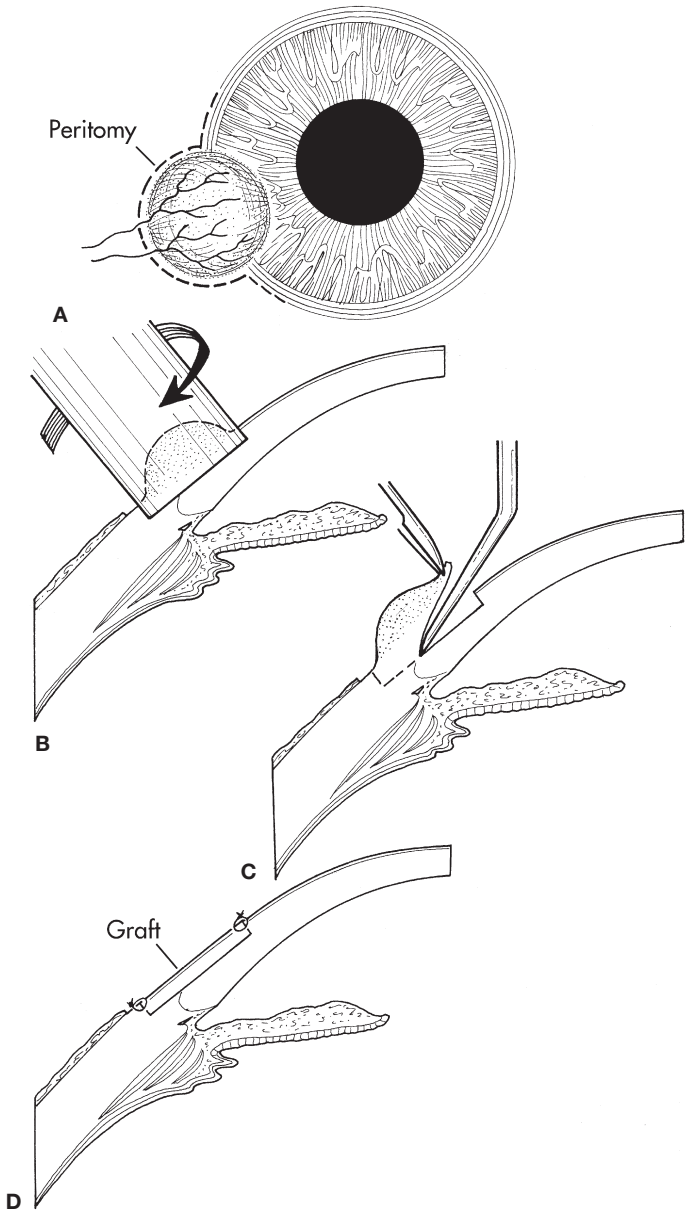


Figure 28.2. *A*, A conjunctival limbal peritomy is used to expose dermoid. *B*, The smallest trephine that will completely surround the lesion is used to make a partial-thickness cut. *C*, Lamellar dissection is performed for dermoids with deeper stromal opacification. Note that the perpendicular margins of the bed offer the best suture placement. *D*, A partial-thickness donor button cut slightly larger than recipient defect is anchored with interrupted sutures.

the dermoid, beginning on the corneal side of the lesion and carried across the limbus into the sclera (Fig. 28.2, *C*). A lamellar dissection spatula (Martinez, Troutman) and a pushing rather than a cutting motion make it easier to maintain a single plane of dissection within the cornea. The field is kept dry, and gentle traction is used to pull upward on the free edge of the tumor during the dissection. The dissection can be carried slightly beyond the edge of the bed to allow for easier placement of a swollen donor and reconstruction of a perpendicular wound if the edges become distorted during dissection. If deeper opacities remain, a deeper plane is created with the trephine, and the dissection is repeated. The dermoid should be completely removed at its peripheral boundaries because the abnormal tissue is too soft to hold sutures. Hemostasis is achieved with cautery. The donor is then sewn into the recipient bed with interrupted or running 10-0 nylon sutures (Figs 28.2, *D* and 28.3, *A* and *B*). If the graft is large, a paracentesis may be necessary to allow good wound apposition. The eye is patched with antibiotic and corticosteroid ointment.

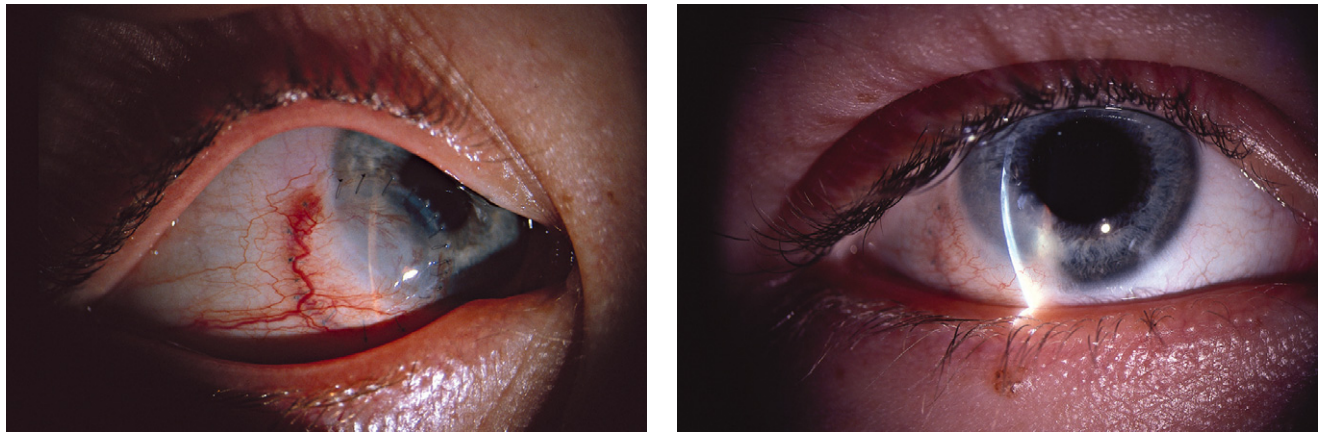
Preparation of the donor tissue is accomplished most easily if a whole globe is available. The donor eye is tightly wrapped in gauze. Intraocular pressure is elevated by manually compressing the globe or by placing a hemostat on the gauze. A razor or diamond knife is used to make a small incision at the limbus to the necessary depth. The donor should be slightly thicker than the depth of the recipient bed, as the initial swelling of the donor will disappear. If the donor is thinner than the recipient bed, the area will be depressed postoperatively. A Martinez lamellar dissection spatula is introduced into the incision so that it is parallel to the surface of the cornea. The end of the instrument should be directed slightly upward, as it is used to create a lamellar dissection of the entire donor cornea. A back-and-forth pushing and rotating motion is used. Care is taken to maintain a constant plane without pushing posteriorly. A trephine is then used to cut through the donor cornea. Unlike punching a donor button from the endothelial to the epithelial surface, which produces a graft that is approximately 0.2 mm smaller than the size of the trephine, this technique produces a donor button equal in diameter to the size of the trephine blade used. For small lesions, the same size trephine should be used for the recipient and the donor. When the recipient bed is 6 mm or greater, the donor should be oversized by 0.20–0.25 mm. If the donor is harvested from the limbus, the curvature of the donor will more closely match that of the host. Proper anatomic alignment using limbal tissue may produce a better cosmetic result,[16] but most patients achieve good cosmesis even when central corneal tissue is used for grafting.[10,11] Inclusion of sclera in the donor requires lamellar dissection of the donor beyond the limbus prior to trephination of the donor button.

Preparation of donor material from a corneoscleral rim can be accomplished with slightly greater difficulty. An orbital implant is tightly wrapped with gauze, and a hemostat used to maintain tight application of the gauze to the sphere. The corneoscleral rim is then anchored to the gauze with interrupted 5-0 sutures. The limbus is incised to the necessary depth, and the lamellar dissection is carried out as described above. If a microkeratome and artificial anterior chamber are available, and the donor rim is of sufficient diameter for mounting on the artificial anterior chamber, it is fairly simple to obtain a lamellar graft from a corneoscleral rim.

Postoperative care includes topical antibiotics until epithelial healing is achieved and topical corticosteroids until inflammation has resolved. The patch is removed on the first postoperative day, and frequent follow-up is maintained until epithelial healing is complete. Healing may be delayed in patients with Goldenhar's syndrome who have decreased corneal sensation or dry eye. Amblyopia therapy is instituted where appropriate if significant astigmatism is present. Sutures are removed in 1–3 months, or sooner if they become loose, collect mucus, or develop suture abscesses. If the patient is cooperative, suture removal can be accomplished at the slit lamp with topical anesthesia. Otherwise, general anesthesia is necessary.

PENETRATING KERATOPLASTY

Grades II and III dermoids involving the full thickness of the cornea or anterior segment and perforations that occur during dissection



A B

Figure 28.3. *A*, A 2-month postlamellar corneal graft is placed over the corneal limbus in the same eye as in Figure 28.1. Note the buried nylon sutures are 360°. *B*, The same eye 9 months postoperatively with some residual deep corneal opacity. (Photos courtesy of FS Brightbill, Madison, WI.)

of the recipient bed require penetrating keratoplasty or anterior segment reconstruction. Penetrating keratoplasties in children have a guarded prognosis because of accompanying amblyopia and the high incidence of graft rejection. A second full-thickness procedure is often necessary because the initial graft, whether lamellar or full thickness, commonly opacifies. If a grade II or III dermoid requires greater than a 7-mm graft, a planned two-stage procedure may be preferred. First, the external bulk of the tumor is excised and a large lamellar keratoplasty is placed in the bed. A freehand dissection may be necessary if the dermoid is too large for a trephine to encompass it. Several months later, when the lamellar graft has healed, a smaller central penetrating graft with excision of residual internal tumor can be done to establish a clear visual axis. This two-stage technique reduces the risk of anterior synechiae, vascularization, and rejection associated with large penetrating grafts.[17] The details of penetrating keratoplasty are covered in greater depth elsewhere in this text.

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29 Tarsorrhaphy and lacrimal occlusion

Alon Kahana, Mark J. Lucarelli

Corneal desiccation can be vision and eye threatening. The etiology may be inadequate hydration, inadequate coverage, or both. Inadequate hydration is often referred to as 'dry eyes' and its symptoms often, but not always, manifest as foreign body sensation, ocular irritation, and decreased vision. Since other ocular diseases share these symptoms, a careful ocular examination is essential for proper diagnosis and treatment. For example, blepharitis, keratoconjunctivitis, pterygia, and ocular foreign bodies comprise a portion of the differential diagnosis for 'dry eyes'. Valuable portions of the examination include fluorescein and/or rose bengal staining, Schirmer basal tear production test, tear breakup time, and tear meniscus height, as these tests can be extremely helpful for diagnosis and follow-up assessments.

Corneal desiccation can also result from inadequate coverage by the eyelids, leading to corneal exposure and accelerated evaporation of the protective tear film. Inadequate coverage can result from eyelid malposition (e.g. ectropion or entropion), as well as lagophthalmos or poor blink. Hence, inadequate coverage may be related to cicatricial eyelid changes and facial nerve injury, as well as to central nervous system injuries and postoperative changes.

The medical treatment of corneal desiccation includes artificial tears as well as lubricating gels and ointments. For certain etiologies and patients, topical cyclosporin 0.05% (Restasis, Allergan, Inc.) may be helpful. It is important to keep in mind that the goals of therapy are to not only improve discomfort and blurred vision but also prevent ocular surface infections, scarring, and permanent loss of vision.

The neurotrophic cornea can present a particular challenge because lack of corneal sensation can also interfere with the tear secretion pathway, as well as diminish the protective blink reflexes. Hence, an aggressive and comprehensive treatment approach is often necessary to avoid vision-threatening complications.[1]

When medical therapy measures prove to be inadequate, more invasive interventions are often required. These may include temporary measures, such as punctal occlusion or temporary eyelid closure (through a temporary tarsorrhaphy), or permanent measures, such as punctal ablation or permanent transposition tarsorrhaphy. The most useful 'permanent' techniques are often reversible, providing the treating surgeons with maximum flexibility in the care of their patients.

LACRIMAL OUTFLOW: PUNCTAL AND CANALICULAR OCCLUSION

Corneal hydration and protection can be achieved through increased lubrication or decreased evaporation. Hence, an important therapeutic strategy to corneal desiccation involves occlusion of the lacrimal drainage system in order to decrease tear outflow and provide additional ocular surface hydration. Three general approaches can be used: temporary, reversible, or permanent occlusion of the lacrimal drainage system. Often, the treatment approach follows the same progression: temporary occlusion is tested using absorbable punctal plugs. If symptomatic relief and objective improvement are achieved, reversible long-term occlusion is attempted with a nonabsorbable device. In situations where lacrimal outflow occlusion achieves symptomatic resolution but requires frequent replacement or causes ocular irritation, permanent surgical occlusion using a puncto- or canaliculodestructive procedure may be cautiously considered.[2]

PUNCTAL AND CANALICULAR PLUGS

Occlusion of lacrimal outflow is a hallmark of treatment for moderate to severe corneal desiccation. Since the first description of punctal plugs by Freeman,[3] punctal and canalicular plugs have been shown to be effective in treating moderate to severe dry eye conditions.[4–11] Unfortunately, punctal plug placement has often been treated as even less than the minor procedure that it is.[12] Since lacrimal occlusion may be associated with complications, some of which may be quite significant, educating the patient about the risks, benefits, and alternatives to treatment would be appropriate.[13–23] Informed consent should be obtained prior to undertaking the occlusive measures. A careful ophthalmic examination with quantifiable measures (e.g. Schirmer test, corneal staining, tear lake height, fluorescein dye disappearance test, etc.) will facilitate determination of efficacy in follow-up visits.

A perfect occluder of the lacrimal drainage system would be easy to fit, simple to insert, and nonirritating, provide complete occlusion, last as long as needed, and be straightforward to remove. Alas, such a plug has not yet been devised. However, the modern clinician currently has a multitude of options from which to choose, each with its own advantages and disadvantages.

Temporary punctal plugs are made of a variety of absorbable materials, such as collagen, hydroxypropyl cellulose, gelatin, and catgut, and, after placement in the punctum, can last for approximately a week. These plugs are often used to test the efficacy and tolerability of punctal occlusion in the treatment of the patient's symptoms. A more durable but absorbable punctal occlusion can be achieved with plugs made of synthetic absorbable material (polycaprolactone or PCL), which can last 2–6 months (e.g. DuraPlug, Eagle Vision).

GRADED PUNCTOCANALICULAR OCCLUSION

On many occasions, a stepwise lacrimal occlusion is undertaken, and occlusion of only one canaliculus may produce sufficient relief. One functional punctocanalicular system appears to be sufficient for draining basal tearing but may not be sufficient for draining reflex tearing.[24,25] Many ophthalmologists, when choosing to occlude only one punctocanalicular system, preferentially choose to occlude the inferior one because of its accessibility.[7] However, several experimental studies suggest that the upper and lower canaliculi drain fairly equivalent volumes of tears.[25–29]

The choice of which punctum to occlude should take into account the ease of performing the occlusion procedure and the relative risk of failure. With punctal plugs, one common cause of failure is plug extrusion. Several studies have shown that an upper punctal plug is more likely to extrude than a lower punctal plug.[4,6] This may be related to the challenge of properly fitting the superior punctum or to an increase in ocular irritation associated with a punctal plug that moves across the ocular surface thousands of times per day. Another possible explanation is simply that the upper lid punctum moves much more than the lower lid punctum.

It has also been argued that after plug extrusion, a second plug may be even more likely to extrude.[4,6] One possible explanation is that by evaluating patients who have already experienced punctal extrusions, the authors may have selected for puncta that are larger, more flexible, and harder to fit. These individuals may also experience plug-related discomfort, leading to eyelid rubbing, which can result in recurrent plug extrusion. Another possibility is that overdilation of the punctum at the time of plug insertion caused trauma to the punctal annulus, which would result in a poor punctal plug fit on subsequent insertions.

The need for long-term but reversible punctal or canalicular occlusion led to the development of a variety of nonabsorbable plugs that fit snugly into the ampula or canaliculus. These fall into two general categories: punctal plugs and intracanalicular plugs. Punctal plugs are made of synthetic materials (e.g. silicone or polyethylene) and fit on the punctum (Fig. 29.1). The advantages of the punctal plug are simple placement, easy monitoring, and usually straightforward reversibility. The disadvantages include a high extrusion rate and occasional ocular irritation and epiphora.[4,6] Extrusion often results from a poorly fitting plug, although patients can also dislodge a well-fitting plug by rubbing.

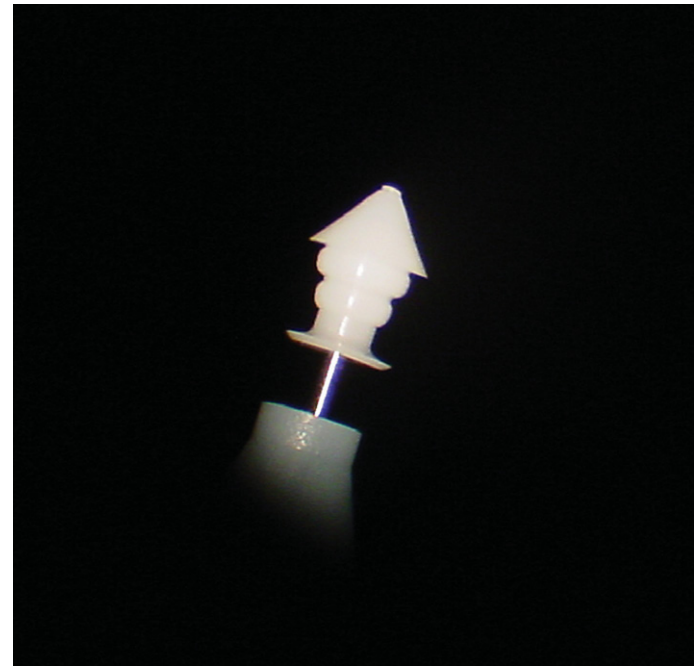
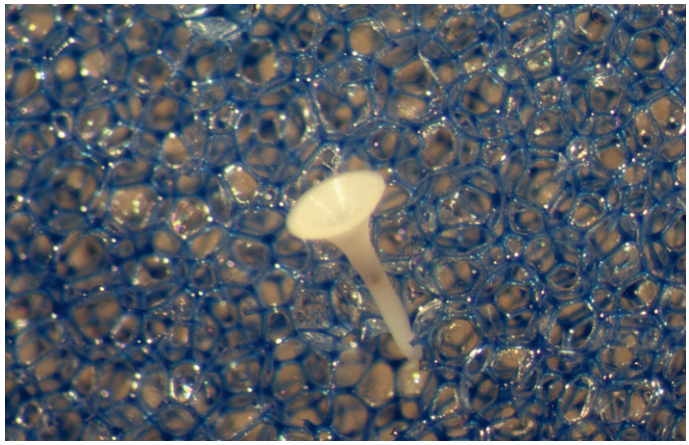


Figure 29.1. The Freeman-style silicone punctal plug (photo courtesy of Ayad A. Farjo, MD).

INTRACANALICULAR OCCLUSION

The use of intracanalicular plugs is controversial. The Herrick plug (Lacrimedics, Inc.) is made of silicone and is designed for permanent placement inside the horizontal section of the canaliculus (Fig. 29.2, *A*). It is simple to place and can provide effective lacrimal occlusion,[5] but can be difficult to monitor and can cause complications such as granuloma formation, infection, scarring, and nasolacrimal duct obstruction with dacryocystitis[13,30,31] (Fig. 29.2, *B*). In theory, the Herrick plug was designed to be easily irrigated out of the canaliculus. However, several published studies have noted the unpredictability of Herrick plug removal. A recently introduced modified Herrick plug, the opaque Herrick plug (Lacrimedics, Inc.), may make it easier to monitor plug placement but does not address the other issues associated with the original Herrick intracanalicular plug. A dissolvable version of the opaque Herrick plug, made of polydioxanone, is now available and is designed to last approximately 6 months. At the time of writing, no comparative studies have been published regarding long-term efficacy and safety. It is interesting to note that an article was published by Dr Herrick describing his preferred techniques for canalicular reconstruction after canalicular scarring related to a Herrick plug.[32]

The SmartPlug (Medennium, Inc.) is a thermosensitive acrylic plug that changes its shape at body temperature to fit into and completely occlude the ampula and canaliculus. Specifically, it expands when warm and contracts when cold. The SmartPlug is simple to insert, but also difficult to monitor. It was designed to be a 'one-size-fits-all' plug that would not need to be fitted and would be easier to remove by irrigating the canaliculus with cold water. It can be useful in patients for whom Freeman-style punctal plugs are not a good option.[8] However, over the short time period of SmartPlug availability, a similar series of untoward side effects that have been reported with the Herrick plug are beginning to be reported to occur with the SmartPlug. As with the Herrick plug, the location of the SmartPlug can be more difficult to confirm (especially when the canaliculus is only partially occluded), and the plug



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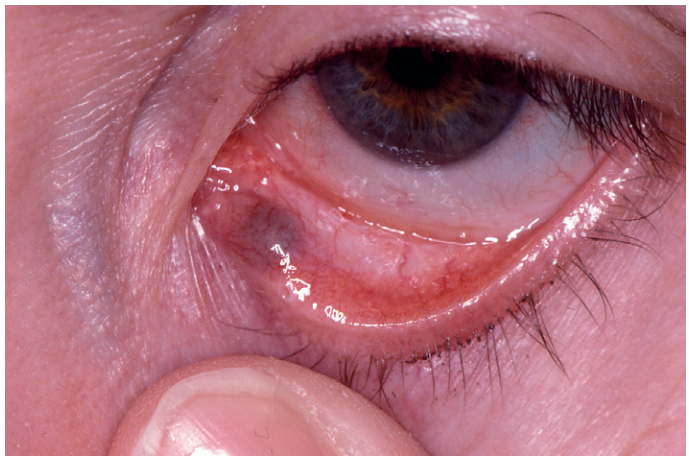


B

Figure 29.2. Intracanalicular plugs. *A*, The Herrick-style intracanalicular plug. *B*, Canalicular damage requiring surgical intervention. The plug in *A* was retrieved.

can either migrate when it should not or fail to get flushed out of the canaliculus when a reversal of the procedure is desired.[14,33] When the need for reversal arises, failure may lead to infections, surgery for canalicular reconstruction, and dacryocystorhinostomy (DCR).[14] Nevertheless, the SmartPlug may be the only good option in patients with stenotic puncta (under 0.3 mm) who require lacrimal outflow occlusion.

Given the difficulty of monitoring lacrimal occlusion with an intracanalicular plug, along with the somewhat higher rate of complications with such plugs, our bias is for using well-fitting Freeman-style silicone punctal plugs such as the Eagle plugs (Eagle Vision, Memphis, TN). While these plugs are not complication free, they are simple to fit and insert, easy to remove, and straightforward to monitor, and rarely migrate deep into the canaliculus. The exceptions are patients who report significant ocular irritation with Freeman-type plugs or patients whose stenotic puncta are too small for any commercially available punctal plugs. For these patients, other measures should be considered.

PUNCTAL PLUG INSERTION

Insertion of a synthetic plug into the ampula is done at the slit lamp (Fig. 29.3). First, the ocular surface is anesthetized with a topical anesthetic such as proparacaine. It is often useful to also treat the punctum directly with a topical anesthetic by applying proparacaine to a cotton-tipped swab, placing it between the upper and lower puncta next to the caruncle, and asking patients to close their eyes for 1–2 min. This can achieve excellent short-term anesthesia and comfort.[34] Next, the correct plug size is chosen using a punctal gauging instrument. The end point should be a snug fit that requires some gentle pressure for insertion and removal, causing slight expansion of the punctal tissues. When a perfect fit cannot be obtained, a slightly larger plug may be preferable to one that is too small.[4,6,21] Care must be taken not to overly stretch the punctal annulus, since such trauma may dramatically increase the risk of punctal migration or extrusion. The punctum should then be dilated very slightly using a punctal dilator. Dilation allows the correct size plug to be inserted, with the punctal tissues closing around the plug to form a good seal. We favor a reusable and autoclavable stainless steel dilator (such as the Wilder or the Hosford from Storz, Inc.) over the relatively blunt, plastic disposable dilator often provided with Freeman-type plugs. The plug is then inserted with the provided applicator or a generic applicator.

The end point should be a fit that is flush with the lid margin surface (Fig. 29.3, *C*). If the plug is too small, it could easily migrate and lodge in the ampula or fall out of the punctum, whereas if the plug is too large, it will distort the punctal anatomy and cause discomfort and possible annulus damage and punctal stretching. Removal is usually easy, using toothed or non-toothed forceps to grasp the flange of the plug and remove it.

The disadvantages of Freeman-style plugs include a high extrusion rate and occasional ocular irritation. Extrusion often results from a poorly fitting plug, although patients can also dislodge a well-fitting plug by rubbing. Techniques have been published for suture anchoring of punctal plugs,[35] but with a good fit and control of rubbing, punctal plugs should remain effective for a significant duration without additional surgical steps.

PERMANENT PUNCTAL/ CANALICULAR OCCLUSION

A variety of surgical techniques have been devised for permanently blocking tear drainage through the lacrimal drainage system. These include punctal ablation with cautery or Argon laser,[36,37] canalicular ligature,[38] canalicular excision,[39] punctal tarsorrhaphy, and punctal patch (for a review, see ref. 2). All the techniques share as a basic principle the introduction into the lacrimal drainage apparatus of a discontinuity that would block outflow. The most common techniques are punctal ablation with thermal cautery, electrocautery (diathermy), or argon laser. In recalcitrant cases, where punctal continuity is re-established, a combination of punctal ablation and canalicular ligature may offer the simplest and most efficacious outcome (Charleux 1978, as described in ref. 2).

Punctal ablation can be most easily performed with a battery-operated thermal cautery unit according to previously published methods.[40] A local anesthetic should first be injected so that discomfort will not limit the appropriate treatment needed for punctal ablation. Pressure anesthesia may also be effective.[34] The ocular surface is anesthetized with proparacaine and a lubricated corneal protective shield may be placed. The looped tip should be inserted deep into the punctum to the full depth of the ampula and vertical canaliculus before the cautery unit is activated (Fig. 29.4). The tip should be rocked and rotated inside the punctum so that the entire circumference of the punctum and vertical canaliculus are treated.

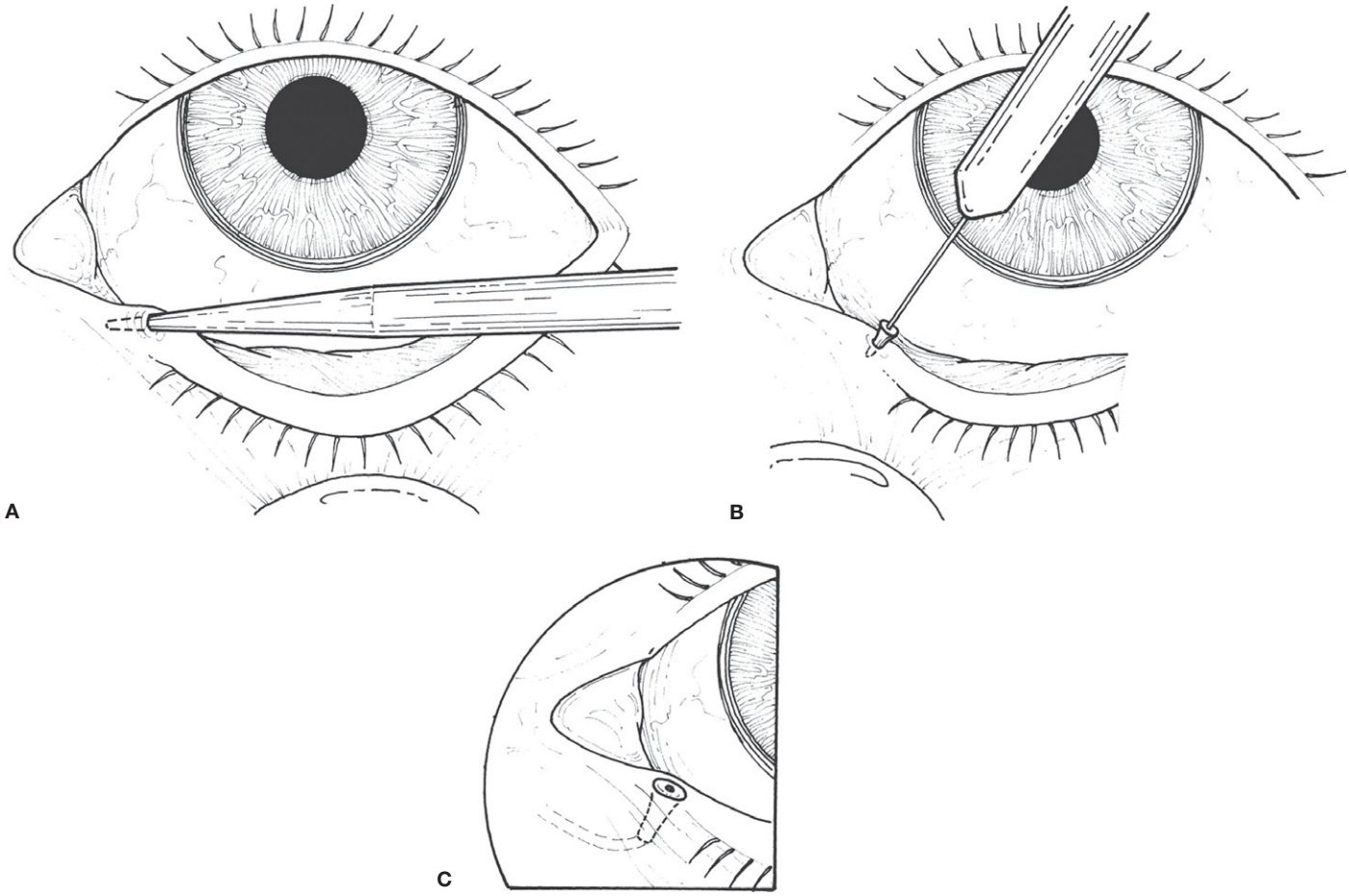


Figure 29.3. Punctal plug insertion. After punctal sizing, the punctum is gently dilated (*A*), and the plug is inserted (*B*). Following insertion, the plug should be flush with the lid margin (*C*).

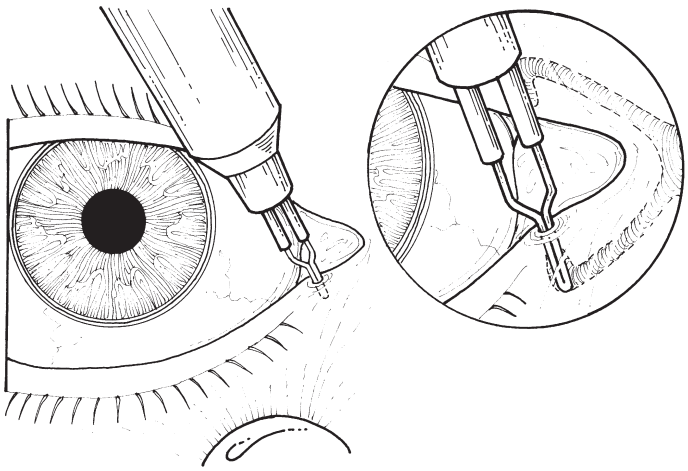


Figure 29.4. Thermal cautery of the punctum. The cold tip is placed deep into the punctum. After activation, blanching of the surrounding tissues indicates sufficient treatment. The tip should be turned around in the punctum and removed while still hot.

The tip should be removed while still hot so that adherent epithelium will be removed. Permanent adhesion and scarring require the removal of the epithelium; otherwise, the canalicular mucosa can heal and recannulate the punctum. Tissue swelling is typically sufficient to oppose the raw surfaces to create scarring and punctal closure. On occasion, placement of a simple interrupted absorbable suture through the cauterized punctum helps to achieve the required apposition.

Care should be taken throughout the procedure to avoid injury to the globe and adjacent tissues, especially during insertion, removal, and movement of the hot tip (a protective shield is particularly helpful in this regard). Punctal ablation with electrocautery can employ a partially insulated tip that will properly treat the deep vertical canaliculus and ampula while leaving the punctal opening intact.[2] Argon laser-assisted punctal ablation techniques vary, but a general guideline is to use 100–200 μm spots and start at 200 mW over 0.1–1.0 s. When the patient is lightly pigmented, dying the punctal epithelium with a marking pen[41] or a drop of blood from the anesthetic injection site[42] will facilitate absorption of the laser power. The power should then be titrated to effect, typically to significantly higher power settings. Initial spots should surround the punctum to contract and delineate it. Further surrounding of the punctum with laser burns will leave the punctal tissues elevated and isolated. Finally, laser burns should be applied directly to the punctum. Charring must be removed with forceps or cotton-tipped swabs before continuing. Sufficient laser burns should be applied to cause contracture and closure of the punctum. Variations on this technique have been described.[2]

Finally, canalicular excision and punctal ligature are two surgical techniques that obtain punctocanalicular destruction under direct visualization. Methods for each have been described,[38,39] but the underlying principle remains the introduction of permanent and complete scarring into the lacrimal drainage system.

TARSORRHAPHY

Tarsorrhaphy, or surgical closure of the eyelids, is an extremely powerful surgical tool for the protection of the cornea and ocular surface.[43] It has very few contraindications and can generally be reversed. Suture tarsorrhaphies can be performed at the bedside with local anesthesia under most circumstances. The indications include paralytic lagophthalmos from facial cranial nerve (VII) damage,[44–46] cicatricial lagophthalmos,[47–51] postsurgical lagophthalmos and exposure,[52,53] poor blink reflexes and incomplete blink, dry eyes (including keratoconjunctivitis sicca and filamentary keratitis), neurotrophic and congenital neurogenic keratopathies,[54–56] and nonhealing sterile keratopathies with thinning.[57,58] Lateral tarsorrhaphies have even been employed for the treatment of floppy eyelid syndrome.[59] Tarsorrhaphy can be performed for short-term efficacy, lasting days to several weeks, or as a permanent (but still reversible) protective measure that uses epithelialization and scar formation to maintain lid margin adhesion.

An assessment of the indication for a tarsorrhaphy must include an eye examination, with a careful evaluation of the cornea. The presence of an active ocular infection is generally a contraindication for a complete tarsorrhaphy. In the infrequent instance in which a complete tarsorrhaphy may be necessary, a comprehensive eye examination would be indicated prior to placement of the tarsorrhaphy.

The choice of temporary vs. permanent tarsorrhaphy is not always clear cut. The so-called 'permanent' tarsorrhaphy can still be divided with relative ease, although it would require a local anesthetic and careful technique to avoid untoward sequelae. Conversely, temporary suture tarsorrhaphies can often be effective for as long as 3 months, providing an easily reversible lid closure technique that can be a useful alternative to the more invasive 'permanent' transposition tarsorrhaphy. At the time of surgical planning, the predicted period needed for lid closure must be assessed. When in doubt, a temporary suture tarsorrhaphy can be placed, using an easily reversible technique that would allow for periodic opening of the lids for ocular examination, followed by reclosure of the lids if needed.

To enhance effective duration, 4-0 polypropylene suture is employed, and the lid is divided into medial, central, and lateral thirds, each supported by a dedicated tarsorrhaphy suture and two bolsters (see description below). Some surgeons prefer silk, but in our experience, silk causes more local inflammation and irritation and hence cannot be kept in place as long as nonreactive synthetic sutures such as polypropylene or nylon.

Occasionally, a tarsorrhaphy is required for a child of amblyogenic age. In such children, amblyopia may develop rapidly, and comanagement with an experienced pediatric ophthalmologist is essential.

SIMPLE TEMPORARY SUTURE TARSORRHAPHY TECHNIQUE

The simple suture tarsorrhaphy involves approximation of the eyelids with a permanent suture over a bolster, to protect the eyelid margin tissues. A double-armed 5-0 polypropylene suture is often used, unless the tarsorrhaphy is needed for over 4 weeks, in which case a 4-0 double-armed polypropylene suture is used. The polypropylene suture is very well tolerated and maintains tensile strength, allowing the suture tarsorrhaphy to remain in place for up to several months. Another commonly used suture is 4-0 silk, although local tissue reaction may limit the tolerated duration and require earlier removal.

Many different materials can be used for bolsters. However, for simplicity, sterility, and availability, the silicone tubing from a butterfly phlebotomy needle kit is a superior choice (such kits are available with differing needle gauges, but the tubing is typically the same). After the tubing is cut into small segments that are 2–3 mm long (Fig. 29.5, *A*), a needle is threaded through a tubing segment. Both needles are then passed through skin and tarsus and out through the gray line of the lower lid (Fig. 29.5, *B*), and then through the gray line of the upper lid and then out through skin 3 mm above the lashes (Fig. 29.5, *C*). Care must be taken to avoid injury to the globe during needle passage. Everting the lid margin with Adson forceps while the needle is passed can be helpful in this regard. One needle is then threaded through a second 3-mm silicone bolster, and the suture is tied tightly (Fig. 29.5, *D*). Tying the suture over the upper lid may prevent suture-related irritation caused by tissue crowding in the lower lid area. As many as three such sutures can easily be placed to achieve anywhere from a localized lid closure to a complete closure. Additional sutures also allow the tarsorrhaphy to remain effective for significantly more time.

ABSORBABLE TEMPORARY SUTURE TARSORRHAPHY TECHNIQUE

Occasionally, a temporary tarsorrhaphy is indicated where a patient may find it difficult to present for tarsorrhaphy removal.[60,61] In such a situation, a 4-0 chromic gut suture can be used to approximate the lateral eyelid margins without a bolster. Care must be taken not to overtighten the suture. An ophthalmic ointment is prescribed to help with the timely absorption of the suture. When placing central eyelid tarsorrhaphies, this technique should be avoided, since the suture may irritate the cornea during the absorption process as the eyelid margins separate.

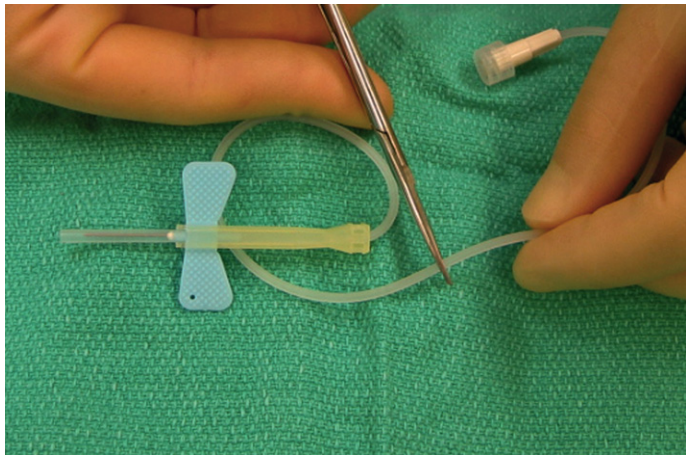
An alternative technique for short-term tarsorrhaphy is the use of cyanoacrylate glue (e.g. Dermabond, Ethicon, Inc.).[62–68] However, the duration of action may be less predictable, and glue may come in contact with the ocular surface, resulting in irritation. Nevertheless, this can be a useful technique in selected cases.

REVERSIBLE KNOT TEMPORARY SUTURE TARSORRHAPHY TECHNIQUE

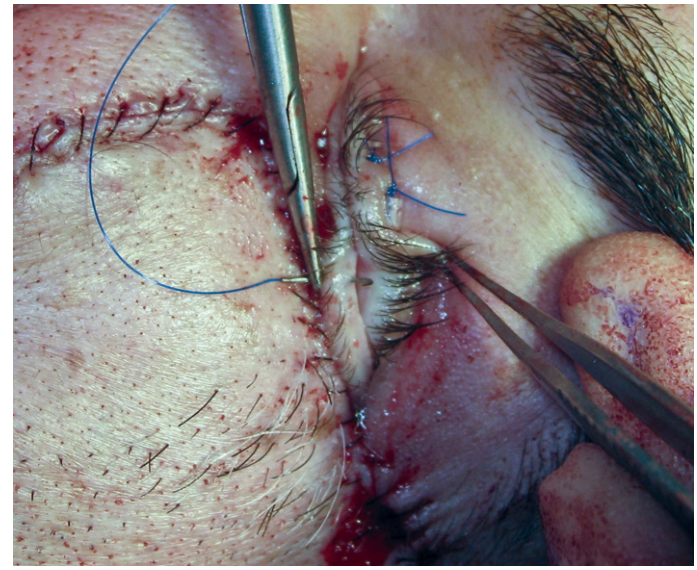
When a tarsorrhaphy is required along with frequent ocular examinations, as is often the case with corneal thinning, a simple technical variation can be performed.[69,70] Each bolster can be sutured to the eyelid with partial-thickness tarsal bites, using 5-0 polypropylene or nylon suture. Protective corneal shields may be used when making the partial thickness tarsal passes. A 4-0 nylon, polypropylene, or silk suture can then be threaded through the bolsters, pulled, and tied to approximate the lids. This suture can then be cut in subsequent office visits, the lids separated for a complete ocular examination, and then a new suture threaded through the bolsters for reclosure of the lids.

SURGICAL APPOSITION AND TRANSPOSITION TARSORRHAPHY TECHNIQUES

The indications for a permanent tarsorrhaphy are varied but have the following in common: chronic exposure keratopathy that cannot be effectively treated with enhancement of lubrication (in



A



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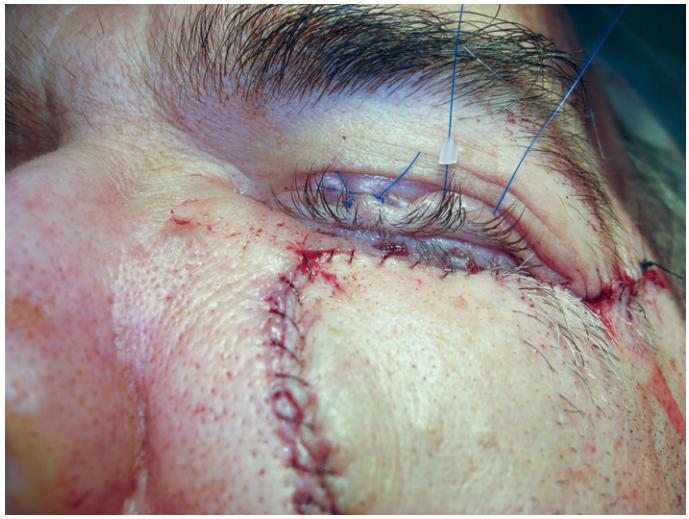

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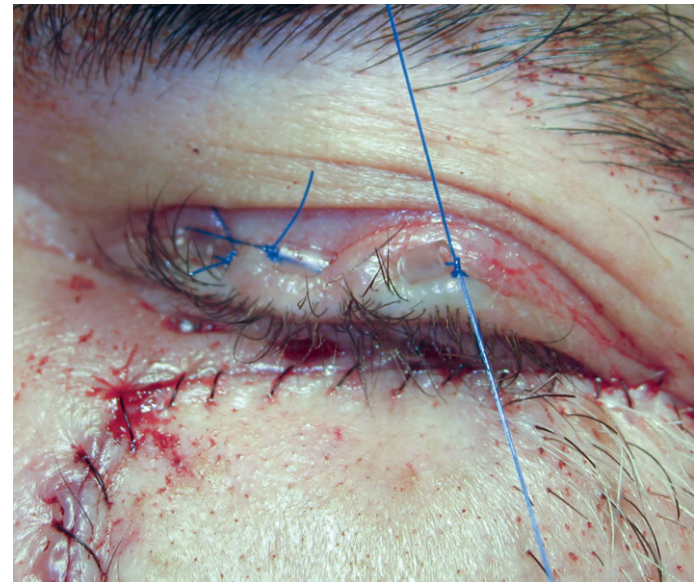

D

Figure 29.5. The temporary suture tarsorrhaphy using double-armed 4-0 polypropylene suture and tubing from a butterfly needle kit. *A*, The tubing is cut into small segments for bolsters. One needle is threaded through a bolster. *B*, Each needle is then passed in a partial thickness fashion through skin and tarsus, exiting at the gray line. *C*, Needle passage through upper lid margin and threading of the second silicone bolster. *D*, The sutures are tied to provide good lid margin apposition.

the form of lubricating preparation or punctal occlusion) or with the placement of a gold weight for paralytic lagophthalmos. The cosmetic and psychological aspects of a permanent tarsorrhaphy must be addressed preoperatively. At times, placement of a temporary tarsorrhaphy allows the patient to properly evaluate the effectiveness of the procedure before committing to a permanent tarsorrhaphy.

The technique, in its standard form, has been well described in numerous publications. Briefly, the anterior and posterior lamellae are split with a #11 Bard-Parker blade. The segments of the lid margins where adhesion is desired are de-epithelialized to expose raw edges on both the upper and the lower lids. The lash line and lateral commissure are spared. For apposition tarsorrhaphy, the anterior and posterior lamellae are then sutured using 4-0 chromic gut or 6-0 polyglactic acid (Vicryl) sutures, keeping the knots away from the ocular surface.

The 'tongue-in-groove' transposition technique provides a stronger adhesion but may be more challenging to reverse. Following splitting of the anterior and posterior lamellae and removal of the posterior lamellar epithelium, a short segment of inferior tarsus is removed, and the upper lid tarsus is fashioned for transposition into the newly created tarsal notch (Fig. 29.6). The epithelium of the anterior lamella is left undisturbed. A double-armed 4-0 chromic gut suture or 6-0 polyglactic acid suture can be used to attach the tarsal edges, using partial-thickness tarsal passes to reduce ocular irritation during the healing process.

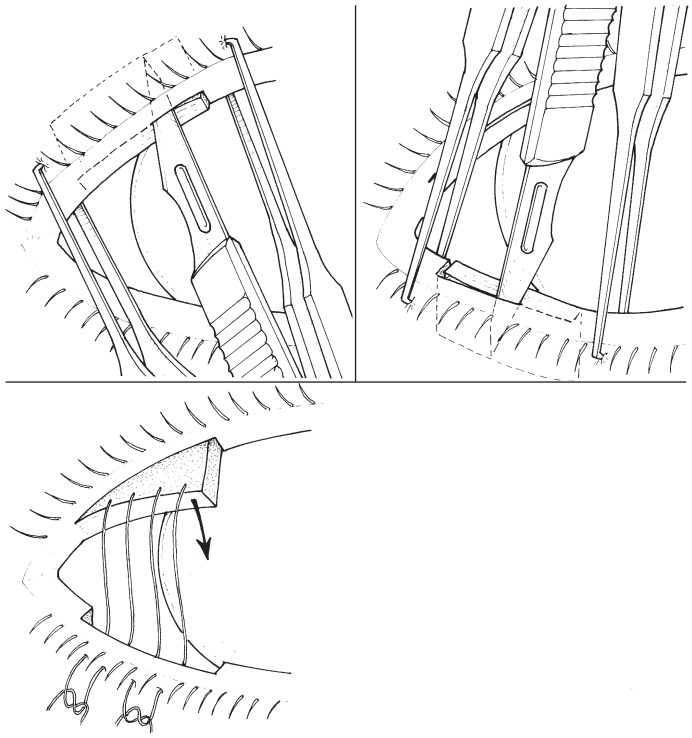

Figure 29.6. Tarsal transposition tarsorrhaphy. After splitting the lid margins and removing the margin epithelia, a back-cut helps create an upper lid tarsal tongue. A small amount of superior tarsus is removed from the lower lid to create the groove. The upper-lid tarsal tongue is sutured to the lower-lid tarsal groove employing either simple interrupted technique using 6-0 polyglactic acid sutures (Vicryl) or horizontal mattress technique using 4-0 chromic gut sutures. Partial thickness tarsal bites are employed to avoid ocular surface irritation. Comment: The depiction of the horizontal mattress sutures in the drawing is only meant to provide a general idea for the location of the sutures, and not a definitive illustration.

Reversal of a 'permanent' tarsorrhaphy can be performed in the office or the operating room. First, a local anesthetic is injected into both sides of the opposed lid margins, taking great care to avoid injury to the eye. A topical anesthetic drop is placed at the medial commissure and allowed to seep onto the ocular surface. A narrow malleable retractor can be placed over the ocular surface and under the opposed eyelid margins to provide protection to the ocular surface. A straight iris scissors or a #15 Bard-Parker blade is used to divide the tarsorrhaphy between the upper and lower lash lines. An ocular protective shield is then placed over the corneal surface, and minimal pinpoint cautery is used for hemostasis. No char should be left on the lid margin surface in order to avoid ocular irritation. Cautery-induced tissue contracture should be minimized. Gentle pressure for a few minutes with gauze over the closed eyelids will stop most bleeding. The possibility of lid margin abnormalities should be discussed prior to division of the tarsorrhaphy, and preferably even before the tarsorrhaphy procedure is performed.

SUMMARY

Corneal desiccation can be vision and eye threatening. Judicious use of lubrication and temporary or permanent lacrimal occlusion can be of great benefit to ocular surface health. Partial or complete closure of the lids with a temporary or permanent tarsorrhaphy can provide a powerful protective measure, although these procedures will often interfere with vision. Overall, these are important tools in the armamentarium of the ophthalmologist.

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30 Aphakic and pseudophakic eyes

Alan Sugar

Pseudophakic bullous keratopathy (PBK) and aphakic bullous keratopathy (ABK) were the leading indications for penetrating keratoplasty for the last two decades of the 20th century.[1,2] Recently, these indications have declined slightly.[3] PBK, often in eyes with concurrent Fuchs' dystrophy, still accounts for a significant proportion of penetrating corneal grafts for endothelial disease. Newer posterior lamellar techniques of endothelial keratoplasty (EK) are increasing rapidly in frequency and are done primarily in pseudophakic eyes.[4,5] When aphakic and pseudophakic eyes are considered for keratoplasty, the noncorneal pathology is often greater than in most phakic eyes, requiring that other sequelae of the previous cataract surgery be evaluated. Thorough preoperative evaluation of these eyes can help to prevent intra- and postoperative problems. The resulting refinement of surgical planning and technique can decrease the risk of disappointment for both the patient and the surgeon.

HISTORY

Taking a careful history is a mandatory component of any preoperative evaluation. Such problems as amblyopia, previous retinal disease, and glaucoma or optic neuropathy may be known to the patient but may not be apparent on clinical examination of eyes with edematous or opaque corneas. A probing history of the course of the loss of vision is often helpful in determining whether the visual loss is related solely to the corneal disease. Knowledge of changes in vision throughout the day is often helpful in the evaluation of patients with corneal edema, especially when a patient who is being examined late in the day has good vision, despite a claim of poor vision much of the time. Information on past contact lens experience may be helpful in planning for possible future lens use. Increasingly, past refractive surgery is relevant. Past laser refractive surgery may not affect penetrating keratoplasty outcomes but will affect the refractive outcome of EK. Details of past trauma and its sequelae should also be sought. It is often useful to know about past and present use of corticosteroids and other anti-inflammatory agents, both to assess their need and avoid flare of inflammation with discontinuance, and to anticipate corticosteroid-induced ocular hypertension.

Any evaluation of history should also include an assessment of the patient's activities, employment, and avocations, and the effect of the visual loss on these. Without this information, the relation of current visual loss to visual needs, which provides the critical input into equations for deciding the indications for surgery, cannot be assessed. Formal methods of measuring vision-related 'quality of life,' such as the VF-14 test, have been used to appraise outcomes after keratoplasty and are likely to find a greater role in routine patient evaluation in the future.[6,7]

Detailed information on the best visual acuity that was obtained after the previous cataract surgery is often crucial. A history of visual loss from macular degeneration or cystoid macular edema (CME) may not contraindicate keratoplasty, but it is helpful in the prognostication of visual outcomes.

Perhaps the most crucial historical factor involves detailed information on the previous cataract surgery, including techniques used in cataract removal, status of the posterior capsule and zonules, and intra- and postoperative complications. If possible, the previous operative notes should be reviewed.[8] The type, power, configuration, and placement of the intraocular lens should be obtained from the records or from the intraocular lens (IOL) registration card given to most patients.

As in all ocular surgery, a history of general medical problems is helpful in planning for pre- and postoperative care and anesthesia. Management of systemic medications is imperative in the elderly aphakic and pseudophakic population that is generally undergoing keratoplasty.

VISUAL FUNCTION ASSESSMENT

Assessment of best-corrected visual acuity and potential visual acuity may be critical in decision-making for keratoplasty. Keratometry often makes accurate refraction easier, especially if corneal opacity limits retinoscopy, which it usually does in eyes being considered for corneal grafting. All experienced corneal surgeons have had the experience of greatly improving the vision of a patient who was referred for keratoplasty by using careful refraction rather than surgery. Although it is often less helpful for

refraction, computerized videokeratography may confirm irregularity of the cornea that is not readily apparent on slit-lamp examination or with the use of keratometry. In many cases, a rigid contact lens gives unexpectedly good vision and, even if not practical for use in a given patient, may help in determining the potential postoperative acuity.[9] A pinhole likewise may be helpful in estimating visual potential in eyes with milder opacity.

Glare testing has been used widely in the evaluation of cataract patients to demonstrate that visual function may be severely limited in some lighting situations, even though visual acuity using high-contrast letters in a dimly lit examining room may be quite good.[10] Likewise, contrast sensitivity testing may document symptomatic decreased visual function that is not well judged using standard visual acuity testing. Contrast sensitivity is decreased in the presence of CME, even when visual acuity is good.[11] Contrast sensitivity testing in patients with corneal disease has been limited.[12] The combination of glare and contrast testing approaches evaluation of 'real-world' visual function.[10] When patients already have documented poor visual acuity, these tests may have negligible added value.

When opacity of the cornea does not permit direct measurement of potential acuity, possible visual function must be inferred by indirect means. A relative afferent pupillary defect may be detected by the swinging flashlight test if the pupil can be seen, or by the reverse test in the opposite eye. Such a defect may indicate asymmetric glaucoma, other optic nerve disease, or retinal disease and is a certain sign that the corneal problem does not account fully for the visual defect.

TESTS OF RETINAL FUNCTION

Various entoptic phenomena have been used to assess retinal function behind opacities in the ocular media.[13] Light perception and projection should be tested routinely in eyes with very poor acuity. Occasionally, the bright light of the indirect ophthalmoscope must be used to obtain a response, in which case the prognosis is obviously very poor; keratoplasty may be precluded unless possibly when both eyes are similarly involved. Accurate light projection is not a guarantee of good retinal status, and poor projection may occur despite a normal retina and optic nerve, when corneal opacity is severe. Two-point light differentiation and color perception are likewise of limited predictive value.

Entoptic images, visual images originating within the eye, may be of some use in the estimation of gross visual potential. A light moving over the closed lid will cast retinal vascular shadows that are detectable by most patients with normal retinas. When this pattern is discerned, there is likely to be at least perifoveal function. Detection of the normal avascular zone indicates that the fovea may be functioning. The blue-field entoptic phenomenon allows assessment of the ability of the patient, while looking into a bright blue light, to detect white blood cells passing through perifoveal capillaries. This is a moderately good predictor of macular function in patients with anterior segment opacities, although it is not widely used.[14]

Laser interferometric visual acuity testing was developed to evaluate potential acuity in patients with cataract and other media opacities. It has been shown to be of value in patients with corneal opacity, but less so than in cataract patients.[15,16] This technique requires an adequate pathway for two laser beams to enter the pupil and is therefore limited in eyes with severe corneal opacity. Laser interferometry has a tendency to overestimate acuity in eyes with amblyopia, macular degeneration, or CME. White-light interferometers, such as the Lotmar Visometer (Haag-Streit, Waldwick, NJ) and the IRAS Visometer (Randwal, Southbridge, MA), use similar principles and are moderately accurate at predicting postoperative vision in patients with lens opacities, although the utility of the findings in cataract patients is limited because of the high success rate and the validity in corneal disease has not been evaluated.[17] These methods are all limited in eyes with severe opacities. False-negative responses (poor test results with good postoperative vision) are frequent, but a positive response is usually significant.

The potential acuity meter (PAM) of Guyton and Minkowski projects a visual acuity chart through a very small aerial aperature.[18] Like the interferometers, it requires at least a pinhole-sized clear pathway to allow the beam to focus on the retina. It is of less value in predicting outcomes before keratoplasty than before cataract surgery.[18] The accuracy of PAM can be increased significantly in patients with keratopathy if a hard contact lens is placed on the cornea during testing.[19] In cataract cases, the PAM tends to underpredict potential visual acuity.[20] Unfortunately, this method may give falsely optimistic readings in eyes with CME, a frequent comorbidity in eyes with bullous keratopathy.[18]

Electrophysiologic testing to predict potential visual acuity is rarely useful. Electroretinography occasionally may be helpful to rule out gross retinal damage in children, or when the tests discussed above are not helpful. The bright-flash electroretinogram (ERG) gives a response despite most dense media opacities and can be performed trans-sclerally to bypass the media.[21] The visually evoked response (VER) can be used to measure central retinal function but does poorly in eyes without clear media.[22]

Visual field testing is important in the evaluation of visual function, especially when there is a history of glaucoma or optic nerve disease and the fundus cannot be well seen. Although formal testing often is not feasible, a hand-held light can be used to estimate grossly the fields of eyes with vision of only hand motions or light perception. This penlight field can usually detect hemianopsia or a temporal island of advanced glaucoma. Diffuse preoperative field constriction, however, is not a reliable predictor of postoperative field restriction.

RETINAL STRUCTURE EVALUATION

Preoperative detection of retinal detachment is of particular concern in aphakic and pseudophakic eyes with opaque corneas, particularly when the original procedure was complicated by vitreous loss or nucleus dislocation. The presence of a long-standing detachment may contraindicate keratoplasty, but a more recent detachment may be an indication for a temporary keratoprosthesis (TKP) for combined keratoplasty and pars plana vitrectomy.[23] The visual function tests discussed earlier may suggest the presence of retinal detachment or macular disease. Indirect ophthalmoscopy should be performed, to the extent possible, on all prekeratoplasty eyes. Contact B-scan ultrasonography can be performed easily and rapidly as a screening procedure for retinal detachment, vitreous hemorrhage, and intraocular tumor. When a detachment or vitreous hemorrhage is found, a combined retinal–corneal procedure may be planned. A TKP, such as that of Landers or Eckardt[23] is inserted after corneal trephination, allowing a full range of posterior segment procedures followed by TKP removal and corneal donor grafting.

SCREENING FOR CYSTOID MACULAR EDEMA

Cystoid macular edema is a major problem, both pre- and postoperatively, in eyes with aphakic and PBK.[24] Cystoid macular edema was a great problem with several of the iris-supported and closed-loop anterior chamber IOLs used in the 1970s and 1980s, which are no longer implanted. Even with current cataract and IOL techniques, complicated cases, including capsule rupture, vitreous loss, and nucleus loss into the vitreous, are associated with CME.[25] In many such eyes developing late bullous keratopathy, there is associated late-onset CME. Together, this has been called the corneal–retinal syndrome.

Careful slit-lamp examination for vitreous in the anterior segment helps to determine the need for anterior vitrectomy, itself a risk for CME, at keratoplasty. Fluorescein angiography usually cannot be performed in eyes with significant corneal edema, but fluorescein angioscopy with the indirect ophthalmoscope and a blue filter often allows visualization of late cystoid macular pooling of dye. The presence of CME is the most frequent vision-threatening complication of pseudophakic keratoplasty, occurring in about one-third of eyes and accounting for up to two-thirds of those with poor vision.[24] CME in this setting can clear gradually over a period of 2 or more years.[26] Preoperative knowledge of CME can help to prevent disappointment and limit the tendency to blame poor vision related to earlier procedures on the keratoplasty.

CORNEAL EXAMINATION

Obviously, slit-lamp examination is the essential feature of the diagnostic evaluation. Careful attention should be paid to the status of the lids, conjunctiva, tear film, and cornea, as in any preoperative eye. Good lid apposition is necessary to avoid epithelial healing problems from exposure, entropion, or trichiasis. Blepharitis should be treated preoperatively. Conjunctival scarring increases the risk of graft surface problems, especially when it is a sign of mucus membrane pemphigoid.

Most aphakic and pseudophakic grafts are for bullous keratopathy. Because the severity of corneal edema may vary with humidity and time of day, the edema noted on examination late in the day may not appear to be adequate to warrant keratoplasty. Repeat examination early in the day, when edema is more likely to be maximal, may be helpful in explaining patient symptoms. Serial pachymetry may be of some use in documenting progression. Specular microscopy is not usually necessary but may be useful in predicting endothelial failure. An endothelial density of <500 cells/mm^2 suggests imminent decompensation.

Documentation of the slit-lamp examination should include variations in corneal thickness, extent and depth of vascularization, and location of opacities and edema. The colored-pencil drawing system described by Waring and Laibson is useful.[27] Anterior chamber depth, peripheral anterior synechiae, posterior synechiae, and the position, type, and stability of the intraocular lens, vitreous, and capsule are important to observe preoperatively.

Routine considerations for all corneal grafts should not be neglected. One of the most important of these is intraocular pressure. There is a high prevalence of glaucoma in eyes with PBK; about one-third are using glaucoma medications at the time of grafting.[24] Intraocular pressure should be controlled before keratoplasty, if possible, or a combined trabeculectomy or drainage device insertion should be considered.[28] The presence of uncontrolled glaucoma or a drainage tube is considered to be a strong risk factor for graft failure.[29,30]

EVALUATION OF THE INTRAOCULAR LENS

In the pseudophakic eye about to undergo keratoplasty, special attention should be paid to the IOL itself and to its relationship with surrounding structures. The presence, extent, and clarity of the capsule should be noted, as should the status of the iris. Gonioscopy should be performed when possible. New imaging modalities including ultrasound biomicroscopy, very-high-frequency ultrasound (Artemis), and anterior-segment optical coherence tomography (OCT, Zeiss) should be considered.[31–33]

The type of IOL present is still very important, although the population of patients with undesirable past IOL types is disappearing gradually. The approach to management of the original IOL was influenced by poor long-term results in eyes with iris-supported and closed-loop anterior chamber lenses. Clinical outcomes support the replacement of essentially all lenses other than stable posterior chamber lenses or well-positioned, semiflexible, one-piece Kelman-style anterior chamber lenses. Phakic intraocular lenses may be associated with endothelial damage in some cases and may require removal, usually before frank corneal decompensation.[34]

In aphakic eyes, it is usually reasonable to insert a secondary IOL. Scleral sutured or iris suture posterior chamber lenses, Artisan iris-claw lenses, and open-looped Kelman-style anterior chamber lenses are all reasonable options. Preoperative planning for IOL power includes axial length measurement and estimation of postoperative corneal curvature.[35]

CONCLUSIONS

The evaluation and preparation of the aphakic or pseudophakic eye and patient for keratoplasty include all of the considerations given to phakic eyes, with the addition of detailed assessment of the effects of the previous surgery. Corneal surgeons must be concerned about posterior segment complications that may affect postoperative visual function and anterior segment alterations that may affect the surgical approach. Often the most critical special consideration is the plan for an original IOL or its replacement. Improvements in cataract surgery and IOLs have made this a less critical issue in most eyes, but individualization and patient involvement in planning remain important for successful keratoplasty and visual outcomes.

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31 Herpetic eye disease: ocular herpes simplex and herpes zoster

Jeffrey Day Lanier

Herpes simplex keratitis became the leading infectious cause of loss of vision in the USA within 6 years after the introduction of topical steroids in 1950, as was reported by Thygeson et al.[1] A simple clinical classification and description of ocular herpes simplex disease follows.

OCULAR HERPES SIMPLEX DISEASE

PRIMARY OCULAR HERPES SIMPLEX

Primary ocular herpes simplex infection occurs as the first encounter with the herpes simplex virus. It differs from recurrent ocular herpes simplex infections in that primary ocular herpes simplex infection may be unilateral or bilateral; it may or may not be associated with skin lesions; a tender, palpable preauricular node; a follicular conjunctival response; a membranous conjunctival response; or a transient mild epithelial keratitis. Primary ocular herpes simplex may be difficult to differentiate clinically from adenoviral keratoconjunctivitis, if there are no skin lesions. The duration of the infection is usually 1–4 weeks; it rarely has any significant sequelae such as visual loss due to corneal scarring. Exceptions to this natural course usually are seen in immunologically compromised patients.

RECURRENT OCULAR HERPES SIMPLEX

Epithelial herpes simplex keratitis

Epithelial herpes simplex keratitis is the most common form of recurrent ocular herpes simplex. It is usually mild and presents with few symptoms, and it rarely leaves any significant sequelae. The usual healing time for the epithelial lesion is 1–4 weeks; however, this healing time may vary within the same person from one recurrence to another. Topical antiviral medication may or may not shorten the healing time. Various combinations of antiviral agents and physicochemical techniques have been evaluated over many years.[2] Even though there are several clinical appearances of epithelial herpes simplex keratitis, the classical forms in order of development and severity include *punctate*, *dendritic*, and *geographic*. A granular subepithelial opacity may accompany the epithelial keratitis and usually fades with time.

Stromal herpes simplex keratitis

Stromal herpes simplex keratitis is the potential blinding stage of ocular herpes simplex disease when residual corneal opacities occur. There are many clinical appearances of stromal herpes simplex keratitis, but most fall into three basic categories of *disciform*, *infiltrative*, and *infiltrative necrotizing*. Marginal herpes simplex keratitis[3] is epithelial, stromal, or both. It is given a special recognition and description because of the danger of misdiagnosing this form as staphylococcal hypersensitivity marginal infiltrates (catarrhal ulcers).

Disciform herpes simplex keratitis

Disciform stromal herpes simplex keratitis presents as a localized annular stromal edema with minimal white blood cell (WBC) infiltration. There may or may not be keratitic precipitates (KP) on the endothelium (endotheliitis), but there are very few, if any, WBCs in the anterior chamber (AC). The natural healing course for disciform stromal herpes simplex keratitis is 2–6 months. Before 1950, disciform stromal herpes simplex keratitis rarely left significant corneal opacities.[4] However, the natural course of healing and residual sequelae are difficult to assess today because most patients with disciform stromal herpes simplex keratitis are treated with topical steroids.

Infiltrative herpes simplex keratitis

Infiltrative stromal herpes simplex keratitis presents with WBC stromal infiltration, with or without stromal edema. Again, there may or may not be KP on the endothelium (endotheliitis), but there are very few, if any, WBCs in the AC. The conjunctival hyperemia usually is localized as a ciliary injection. There is rarely a severe generalized conjunctival hyperemia as is seen commonly in bacterial and fungal keratitis. Corneal stromal WBC infiltrates vary in intensity, but they usually display a granular pattern that is seen best by retroillumination. This granular pattern is rarely seen in bacterial and fungal keratitis. Only in the severe forms of infiltrative stromal herpes simplex keratitis do the WBCs coalesce to form a

dense stromal infiltrate, which resembles the typical bacterial and fungal keratitis. The natural healing course for infiltrative stromal herpes simplex keratitis is 2–6 months. Before 1950, this form of stromal herpes simplex keratitis was rarely, if ever, seen.[4] Today, it is the most common form of herpes simplex keratitis that leads to corneal opacities and reduced vision.

INFILTRATIVE NECROTIZING HERPES SIMPLEX KERATITIS

Infiltrative necrotizing stromal herpes simplex keratitis presents as a severe WBC infiltrative keratitis with stromal tissue loss that may progress to a descemetocele or a perforation. This stage of stromal herpes simplex keratitis is likely to have a significant AC cellular response; therefore, it may be difficult to differentiate clinically between a bacterial and a fungal infection, and a corneal smear and culture are indicated. The natural course of healing for infiltrative necrotizing herpes simplex keratitis is at least 2–6 months. This is the stage of stromal herpes simplex keratitis for which a conjunctival flap may be indicated most strongly. Amniotic membrane transplantation has been shown to be helpful in herpes simplex necrotizing keratitis in mice.[5] Residual visual compromise is the usual result of infiltrative necrotizing herpes simplex keratitis.

HERPES SIMPLEX KERATOUVEITIS

Herpes simplex keratouveitis presents as a uveitis with varying degrees of keratitis, ranging from very mild to very severe. A significant AC cellular reaction is necessary to meet the criteria for herpes simplex keratouveitis. The Herpes Eye Disease Study (HEDS)[6] defined herpes simplex keratouveitis as having '11 or more AC cells in a slit-lamp beam that is 1 mm high and 0.5 mm wide, with the illuminating arm of the slit lamp at an angle of 45° to the viewing arm.' Herpes simplex keratouveitis is relatively rare, as is indicated by the fact that only 50 out of 104 patients needed for statistical purposes could be recruited from eight clinical centers over 4 years.[6] The fact that herpes simplex keratitis usually has a minimal AC cell reaction (fewer than 10 cells in a 1-mm beam), except in the keratouveitis and infiltrative necrotizing forms, is a very important clinical observation. Disciform and infiltrative stromal herpes simplex keratitis may have KPs on the endothelium (endotheliitis) but rarely do they demonstrate an AC cell reaction of greater than 10 cells in a 1-mm beam. Bacterial keratitis and fungal keratitis with the same degree of corneal involvement routinely have a more significant AC cell reaction. The natural healing course for herpes simplex keratouveitis is at least 2–6 months, and the visual sequelae vary with the severity and duration of the inflammation.

PREOPERATIVE CONSIDERATIONS

Cessation of inflammation

A common denominator that prevails in reported cases of keratoplasty for herpetic disease is that of increased success when the eye is free of inflammation for an extended period of time.[7–10] This may be the single most important variable in the determination of success or failure. The eye should be free of inflammation without the use of steroids for a period of at least 6 months.[10] It may be very difficult to reduce and stop the use of topical steroids if they have been used in stromal herpes simplex keratitis. The most common regimen is to taper steroid usage slowly by decreasing the frequency first, and then decreasing the concentration and frequency. As the frequency and concentration are decreased, ocular inflammation usually increases. Seldom does an eye remain noninflamed with steroid reduction. It is important that patients understand this fact when they are tapering steroids. Allowing the eye to retain some inflammation may be necessary to eventually obtain a noninflamed eye, without the use of topical steroids.

Vascularization

Stromal invasion of vessels is common in infiltrative and necrotizing stromal herpes simplex keratitis. It may be that the natural immunologic inflammatory response is necessary if the stromal herpes simplex keratitis is to be healed (Figs 31.1 and 31.2). The corneal vessels usually become attenuated or they become ghost vessels (Fig. 31.3) after healing takes place, which generally takes 2–6 months without topical steroids. Control of corneal vascularization before penetrating keratoplasty is performed has been attempted by various means over the years, but the benefit has never been shown. Most corneal surgeons simply control bleeding at the time of surgery using light cautery or irrigation. Further attenuation of vessels in the peripheral recipient corneal continues to occur post keratoplasty (Fig. 31.4). Preoperative recipient bed vascularization is generally thought to be a significant risk factor for homograft

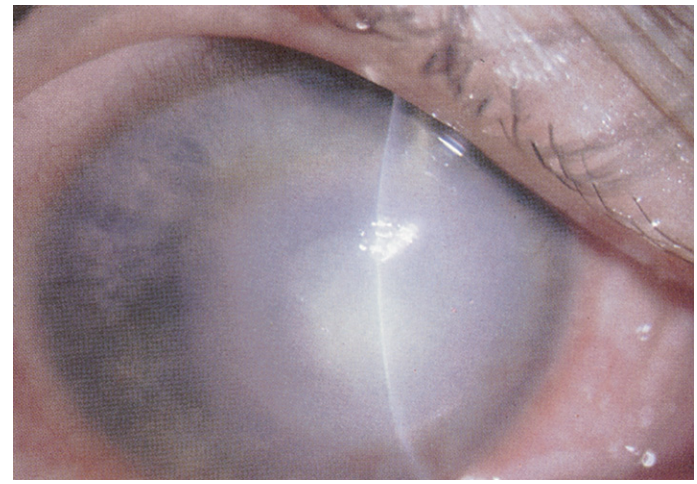

Figure 31.1. Infiltrative stromal herpes simplex keratitis.

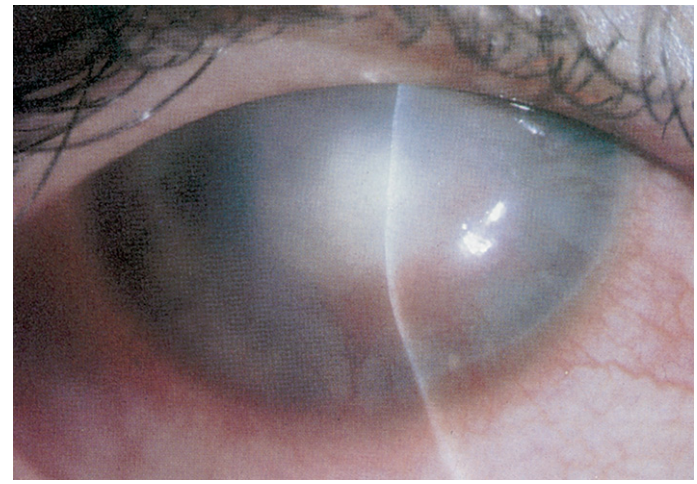

Figure 31.2. Inflammatory invasion of vessels to heal the stromal herpes simplex keratitis.

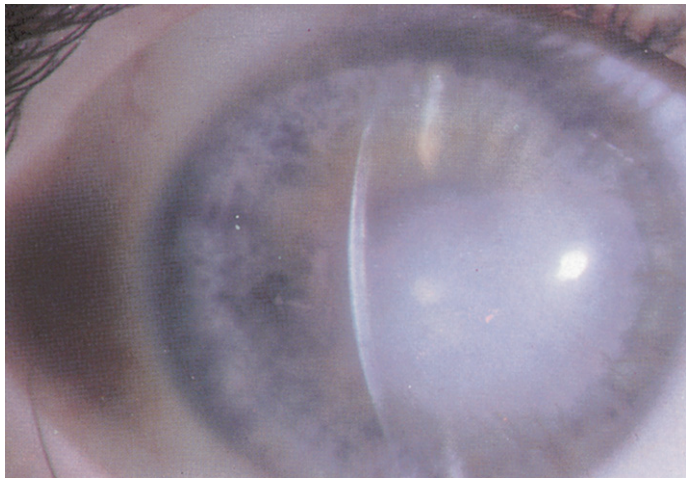

Figure 31.3. Same eye 6 months after discontinuation of topical steroids. Healing has occurred, the eye is quiet, and the vessels have become attenuated.

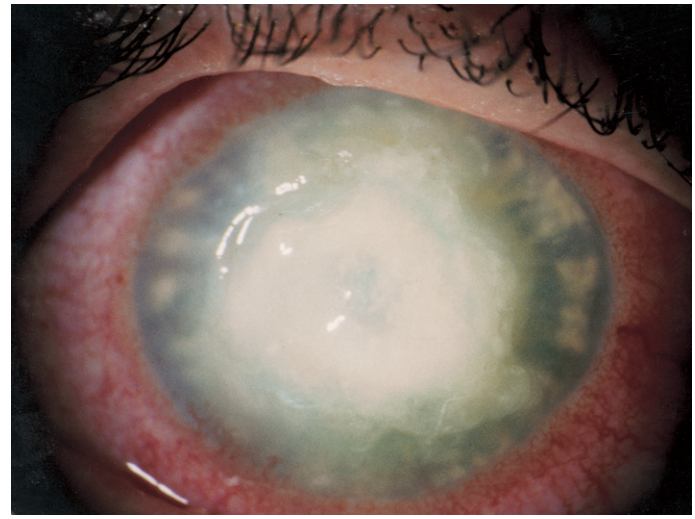

Figure 31.5. Stromal infiltrative necrotizing herpes simplex keratitis with descemetocele.

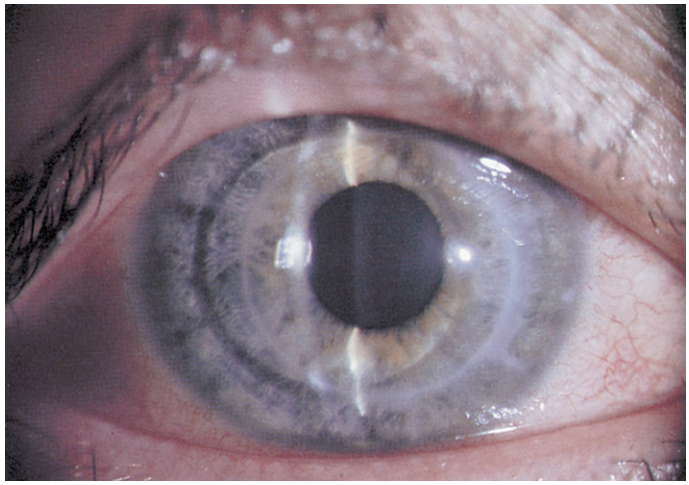

Figure 31.4. Same eye 15 years after keratoplasty with further attenuation of peripheral recipient vessels.

reaction in both herpetic[7,9,11] and nonherpetic[12–14] corneal transplantation. Others did not find vascularization to be statistically significant for increased homograft reaction in herpes simplex keratitis,[15] herpes zoster keratitis,[16] or corneal transplantation in general.[17]

Corneal sensation

Corneal sensation commonly is diminished by chronic stromal herpes simplex keratitis. This decreased sensation can range from minimal to totally absent, and the duration can be short to permanent. If sensation is diminished severely, neurotrophic keratitis may occur, resulting in poor healing of the overlying corneal epithelium.[9,18] A preoperative return of corneal sensation is not a prerequisite for keratoplasty. The return of corneal sensation may take years to occur, if it returns at all.

Topical antiviral drugs

The only stage of ocular herpes simplex keratitis for which topical antivirals have been shown to be of help is active epithelial herpes simplex keratitis. Topical antiviral drugs frequently are used in conjunction with topical steroids. This concept stems primarily from two early studies: one using 5-iodo-2 deoxyuridine (IDU)[19] and the other using trifluridine (Viroptic®).[20] No recent well-designed, well-controlled studies have been done to concur with this concept. The *Physicians' Desk Reference* states: 'Viroptic® has not been shown to be effective in the prophylaxis of herpes simplex virus keratoconjunctivitis and epithelial keratitis by well-controlled clinical trials. . . . Continuous administration of Viroptic® for periods exceeding 21 days should be avoided because of potential toxicity.'[21]

Systemic antiviral drugs

No antiviral, either topical or systemic, has been shown to be effective in the treatment of active stromal herpes simplex keratitis. The Herpetic Eye Disease Study showed no statistically or clinically significant beneficial effect of oral acyclovir.[6] Oral acyclovir also showed no benefit in preventing stromal herpes simplex keratitis or iritis when used in patients with epithelial herpes simplex keratitis.[22]

Conjunctival flap

Stromal infiltrative necrotizing herpes simplex keratitis can result in severe stromal tissue loss and perforation. Topical steroids may have little, no, or an adverse effect on the necrotizing process. A conjunctival flap should be considered *before* perforation occurs (Figs 31.5 and 31.6). Gundersen[23] described the surgical technique that is most commonly used today. This modality of surgical treatment should always be considered in the treatment of stromal infiltrative necrotizing herpes simplex keratitis, as well as with other types of refractory herpes simplex keratitis. The conjunctival flap can be used as a temporary measure (8–12 months); it may be removed before or at the time of keratoplasty. The conjunctival flap can also remain in place permanently. Amniotic membrane transplantation has been shown to be helpful in herpes simplex necrotizing keratitis in mice.[5]

Corneal perforation

Corneal surgery should be avoided when active inflammation is present with herpes simplex keratitis.[7,9,10,15,18,24] Unfortunately, infiltrative necrotizing stromal herpes simplex keratitis may lead to corneal perforation that requires some type of intervention. The integrity of the AC must be re-established. A conjunctival flap or

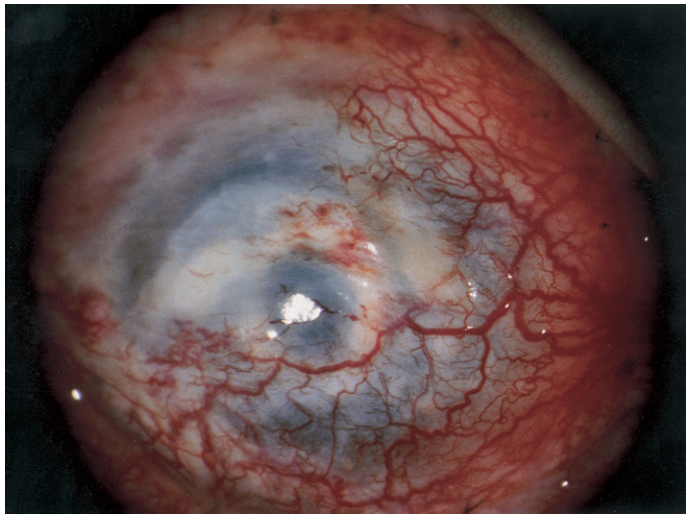

Figure 31.6. Two weeks post Gundersen conjunctival flap. The active inflammation has subsided and the necrotic process ceased. The eye is quiet and comfortable.

amniotic membrane will not do this. When the diameter of perforation is less than 2 mm, a therapeutic soft contact lens with pupil dilation, with or without tissue adhesive, may allow the AC to reform, with eventual healing of the corneal perforation. If this is not accomplished, or if the perforation is greater than 2 mm, surgical intervention must be undertaken. Both penetrating[10] and lamellar[9] keratoplasties have been advocated. Severe inflammation and perforation result in a much more difficult surgical procedure and adverse outcome.

OPERATIVE CONSIDERATIONS

Most corneal surgeons do not alter their surgical technique specifically for corneal scarring caused by previous herpetic keratitis. An exception is the use of interrupted stitches in vascularized and edematous corneas,[8,25] where rapid healing and loosening permit selective suture removal. Rapid loosening of stitches will occur routinely, regardless of stitch technique, if they are placed in fibrovascular or edematous recipient tissue. To minimize this loosening of stitches, longer bites that are tied with increased tension should be made. All stitches that become loose should be removed.

A basic principle in corneal transplant surgery is to sew into the healthiest recipient tissue possible. This principle is important when one is determining graft size and centration. When extremely thin or necrotic recipient tissue is present, large-diameter or eccentric grafts may be necessary.

POSTOPERATIVE CONSIDERATIONS

The postoperative course of keratoplasty for herpetic keratitis can be extremely variable.

TOPICAL STEROIDS

Titrating topical steroids that are given to control postoperative inflammation is necessary. The inflammation may be minimal or extensive. Some have reported an increase in the incidence of recurrent herpes simplex keratitis with the use of high-dosage steroids,[7] whereas others have reported no such increase.[15]

TOPICAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) have undergone few clinical or investigative studies concerning herpes simplex keratitis, with or without keratoplasty. No well-designed study has proved their efficacy.

TOPICAL ANTIVIRAL DRUGS

The same concepts that were discussed in the section on preoperative considerations, regarding the concomitant use of antiviral medications with topical steroids, apply postoperatively. The literature does not support the theoretical postulation that the use of topical antiviral medications reduces the incidence of recurrent herpes simplex in postoperative keratoplasty;[11,15,18] it also provides no support for the theory that the use of high doses of topical steroids increases the incidence of recurrent herpes simplex in postoperative keratoplasty.[7,15] Topical antiviral drugs may delay wound healing,[18,26] and their use may lead to epithelial toxicity and persistent epithelial defects.[9,26]

SYSTEMIC ANTIVIRAL DRUGS

A herpetic eye disease study showed no statistically or clinically significant beneficial effect of oral acyclovir in active stromal herpes simplex keratitis.[6] Another herpetic eye disease study also showed no benefit of oral acyclovir in the prevention of herpes simplex stromal keratitis or keratouveitis in patients with epithelial herpes simplex keratitis.[22]

The frequency of genital herpes simplex type 2 recurrences has been shown to be decreased as long as the patient is taking acyclovir.[27,28] Once the oral acyclovir was discontinued, recurrences returned to the pretreatment frequency, and some patients reported unusually severe symptoms with the first post-treatment recurrence.[27] Similar findings in ocular herpes simplex keratitis were reported in a retrospective, uncontrolled study of 27 patients in which (1) disease recurrence seems to be reduced while the patients are maintained on a long-term prophylactic dose of oral acyclovir and (2) severe recurrences occurred in three patients when oral acyclovir was reduced or stopped.[29] Acyclovir-resistant herpes simplex strains emerge during treatment and are associated with prolonged infections in immunosuppressed patients.[30] Resistant strains are isolated from healthy patients who experience recurrences while they are taking oral acyclovir for long-term suppression.[31] Acyclovir-resistant herpes simplex keratouveitis that occurs after penetrating keratoplasty has also been reported.[32]

Later studies have indicated that oral acyclovir may be beneficial in the prophylaxis of recurrent herpes simplex infection in patients with and without grafts.[33–35] A follow-up herpetic eye disease study demonstrated that a 12-month suppressive oral acyclovir therapy reduced the rate of epithelial and stromal herpes simplex keratitis.[36] This study was designed with immunocompetent patients who had not undergone penetrating keratoplasty. Oral acyclovir's benefit was greatest for patients who had experienced prior stromal herpes simplex keratitis.[36] A recent study suggests that oral acyclovir effectively prevents herpes-related recurrences after penetrating keratoplasty in herpetic eye disease.[37] Others have indicated that a double-drug regimen with mycophenolate mofetil and acyclovir helps prevent both allograft rejection and herpes simplex recurrence following corneal transplantation.[38,39]

GRAFT REACTION VERSUS RECURRENCE OF HERPES SIMPLEX KERATITIS

The major complications of keratoplasty in eyes with scars caused by herpes simplex are (1) recurrent herpes simplex keratitis and (2) endothelial graft reaction. Graft failure is more likely to be caused by endothelial graft reaction than by recurrent herpes simplex keratitis.[8,40,41] Corneal graft reaction has been reported to be as high as 71%[9] and 79%,[7] whereas others have reported a much lower incidence of 20.6%.[15] The postoperative recurrence rate of herpes simplex keratitis varies with the duration of follow-up time and the criteria for diagnosis. The range of reported recurrence is from 6 to 47%, and it can occur immediately postoperatively or years later.[7,9,11,18] A recurrence of herpes simplex keratitis within a graft does not necessarily result in an opaque graft. Central scars or completely opaque grafts have been reported to occur in only 23.8% of herpetic recurrences.[18]

Differentiating the two problems diagnostically can be very difficult, but careful observation of clinical signs may be helpful. Recurrent herpes simplex keratitis can occur after a graft reaction, or a graft reaction may develop after the patient experiences recurrent herpes simplex keratitis, within a few days of initial onset of either.

The most specific clinical sign of recurrent herpes simplex keratitis is a classical herpetic epithelial dendrite, which can be appreciated best by staining with fluorescein or rose bengal. However, any epithelial defect can heal in a dendritic shape and mimic a herpetic dendrite. Cultures usually are positive in active epithelial herpes simplex keratitis. The first recurrence within a graft has been reported to be epithelial in 74.7% of patients, and it occurs at the line of union between the graft and the recipient in 61.5% of cases.[18] With both geographic and chronic epithelial defects, it is difficult clinically to assess the cause. Herpetic cultures should be considered to differentiate from poor epithelial healing in that the cornea is in a neurotrophic state. Topical antivirals are toxic and should be avoided unless there is an active epithelial herpes simplex keratitis. Most active cases of epithelial herpes simplex keratitis heal within 1–4 weeks. Topical antivirals should be used no longer than 21 days in the treatment of epithelial herpes simplex keratitis so that epithelial toxicity is avoided.[21] Topical steroids should be avoided in the presence of active epithelial herpes simplex keratitis, even if topical antivirals are used concomitantly.

Recurrent stromal herpes simplex keratitis is a much more serious postoperative complication than is graft reaction. The recurrence can occur at any location in the graft; it usually presents as an infiltrative stromal herpes simplex keratitis, with or without KP on the endothelium (endotheliitis). Herpetic cultures are usually negative in active stromal herpes simplex keratitis. The stromal infiltrates of WBCs can appear in the more common focal, irregular, coalescing granular pattern that is seen best by retroillumination, or they may occur as the less common dense stromal WBC infiltrates that mimic bacterial or fungal stromal keratitis. The natural healing course of stromal herpes simplex keratitis within a corneal graft is 2–6 months. If there is no favorable healing response within 1–2 weeks, and if there is no associated active epithelial herpetic keratitis, topical steroids commonly are used to suppress the natural inflammatory response. Titrating and tapering the frequency and concentration of topical steroids requires careful observation for months to years, with possible rebound inflammation as the topical steroids are reduced.

Compared with recurrent herpes simplex keratitis, graft reaction usually is associated with a more evenly distributed stromal edema with no significant WBC stromal infiltrates. The inferior cornea is the most common site of initial involvement, but the graft reaction may advance superiorly with time. A Khodadoust keratic precipitate line is pathognomonic of an endothelial graft reaction, but evenly distributed KP may also be found.

Even though corneal scarring caused by herpes keratitis is not the most favorable indication for successful keratoplasty, when surgery is performed in inflammation-free eyes and postoperative complications are anticipated and treated quickly, clear grafts with good visual rehabilitation can be obtained in 75[18] to 80%[15] of patients.

OCULAR HERPES ZOSTER DISEASE

There are many differences between ocular herpes simplex and ocular herpes zoster disease, but one of the most important is that herpes zoster does not recur within the same dermatome once the inflammatory response is allowed to clear totally without the suppression of topical steroids, which usually requires 2–6 months. Recurrent herpes zoster within the same dermatome has yet to be documented.[42] Recurrent herpes zoster in different dermatomes, bilateral herpes zoster, and disseminated herpes zoster are extremely rare and occur in immunocompromised hosts.[43,44] Herpes simplex can mimic herpes zoster, which is referred to as pseudozoster. Misdiagnosis of pseudozoster (herpes simplex) for herpes zoster can result in the false impression of recurrent herpes zoster.[42] Rebound inflammation, which may occur as topical steroids are decreased or discontinued, has also been interpreted as recurrent herpes zoster. Among patients in whom herpes zoster keratitis was determined to be completely free of inflammation and topical steroids had been stopped for at least 6 months, recurrence has never been documented by laboratory confirmation.[42] The clinical signs and symptoms listed in Table 31.1 help to differentiate herpes zoster from pseudozoster (herpes simplex), but laboratory confirmation is necessary for definitive diagnosis of the specific infectious agent.

Table 31.1 Differentiating features of herpes simplex (pseudozoster) and herpes zoster disease

Herpes Simplex (Pseudozoster)	Herpes Zoster
1. Incomplete dermatomal distribution	1. More complete dermatomal distribution
2. Less pain	2. More pain
3. Rarely scars the skin	3. Frequently scars the skin
4. Postherpetic neuralgia rare	4. Postherpetic neuralgia common over age 50 years
5. Iris atrophy very rare, except in keratouveitis	5. Iris atrophy more common, and usually in a sectoral pattern
6. Rarely bilateral	6. Very rarely bilateral
7. Often recurs	7. Recurrence has yet to be documented
8. Corneal hypesthesia	8. Corneal hypesthesia

The fact that herpes zoster does not recur within the same dermatome is a great advantage in keratoplasty. Recurrence of herpes simplex within the graft is a major complication that is eliminated in the treatment of herpes zoster if the eye is allowed to become inflammation free for at least 6 months while the patient is off topical steroids.

A more severe loss of corneal sensation is more likely to occur in herpes zoster keratitis. This loss of corneal sensation may result in poor epithelial healing more frequently in keratoplasty for herpes zoster than for herpes simplex.

Keratoplasty that is undertaken to treat herpes zoster ophthalmicus corneal scarring is relatively rare.[45,46] Two recent reports have shown good results, with clear grafts in 7 of 9 patients (78%)[16] and in 10 of 12 patients (83%).[47]

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32 Preoperative tests and evaluations

Robert E. Brass, Frederick S. Brightbill

PREOPERATIVE EVALUATION FOR KERATOPLASTY

The success of any surgery, especially keratoplasty, depends on a thorough preoperative evaluation. A complete ocular and systemic history will help the surgeon to anticipate and avoid problems during and after the procedure. The ocular history often indicates the level of visual acuity that can be expected after keratoplasty and the likelihood of graft survival. This not only helps the surgeon in preoperative planning but also helps to give the patient realistic expectations. For example, a patient with a failed graft secondary to uncontrolled glaucoma has a different prognosis than a patient who is undergoing a primary keratoplasty for Fuchs' endothelial dystrophy. Systemic history is important in determining the overall health of the patient. This helps guide the physician in determining the type of anesthesia to be used, as well as the overall feasibility of performing the proposed procedure. The slit-lamp examination, combined with other forms of ocular diagnosis, provides the cornerstone of diagnosis and management. Proper patient selection, preparation, and evaluation maximize the potential for a favorable outcome.

COMPONENTS OF PREOPERATIVE EVALUATION

Medical history

When obtaining the patient's history and review of systems, the first goal is to determine whether the patient has the ability to undergo the proposed operative procedure. In considering local anesthesia, for example, a patient must be able to lie flat for the duration of the procedure, and comfortable being semiconscious for the surgery. This ability could be compromised by pulmonary, musculoskeletal, or cardiac abnormalities. General anesthesia may be warranted if severe arthritis makes it impossible for the patient to remain comfortably in one position for an extended period of time. The surgeon must ultimately decide whether the patient's surgery can be performed under local monitored anesthesia or general endotracheal intubation anesthesia. Pre-existing medical problems such as hypertension and diabetes should be stabilized in concert with the patient's primary-care physician before the keratoplasty is undertaken. Because preoperative anxiety is common, patients should be advised to take their normal dose of antihypertensive medication on the morning of surgery. Insulin-dependent diabetic patients should undergo surgery early in the day if possible, and one-half their normal dose should be administered before surgery, with the other half given postoperatively along with breakfast. Allergies to such medications as antibiotics, systemic medications, and anesthetics should be questioned directly, noted in the chart, and reviewed so that subsequent complications may be avoided. The presence of cardiopulmonary disease should be noted, in that it may limit the postoperative use of β-blockers. Patients may be allergic to the preservative in topical medications rather than to the drug itself. In such cases, skin testing can identify allergies to preservatives, before an entire class of medications is excluded.

Patients taking aspirin, nonsteroidal anti-inflammatory drugs, and other medications that interfere with blood coagulability deserve special preoperative consideration. It has been traditional practice to discontinue aspirin and nonsteroidal drugs 15 days before surgery, and discontinue Plavix® or Coumadin® 5 days before surgery. This is always done in consultation with the prescribing physician. Relative safety has been demonstrated in patients undergoing intraocular procedures who have continued to take medications that affect their coagulation. McCormack and coworkers[1] demonstrated that procedures such as extracapsular cataract extraction with intraocular lens implantation, vitreoretinal procedures, and trabeculectomy surgery all could be performed safely without changing the anticoagulation status of the patient. Gainey and coworkers[2] concluded, 'If anticoagulants are necessary for a patient's well-being, they should not be discontinued for cataract surgery.' When prothrombin times are in reasonably good range, the authors have had good success with simply discontinuing anticoagulation 48 h before keratoplasty and resuming treatment on the first postoperative day. If temporary cessation of anticoagulation is deemed inadvisable, patients on Coumadin® (warfarin) may require heparinization 24–48 h postoperatively.

Another goal for the clinician in obtaining a patient's medical history should be to understand the patient's social and family support systems. The outcome of the operative procedure will rely

in large part on the patient's compliance with postoperative medication and follow-up appointments. The patient's compliance with preoperative appointments and testing is a fair indication of postoperative compliance. Even compliant patients may be physically unable to self-administer topical eye medications. In such cases, family and local medical support (e.g. a visiting nurse) should be arranged before surgery is performed. History of substance abuse or abrupt changes in family conditions should be identified because they may interfere with patient follow-up and could be a relative contraindication to surgery, at least until conditions stabilize.

Ocular history

Understanding the pathophysiology of a patient's current status is essential when one is contemplating keratoplasty. The nature of the patient's ocular complaints can guide the physician during the ocular examination and can help lead to an accurate prognosis. For example, confirmation of good visual acuity in the affected eye before development of the current condition carries a better prognosis (i.e. good acuity post cataract surgery in eyes later developing pseudophakic bullous keratopathy) than does the presence of a corneal scar since childhood that has resulted in amblyopia. However, a patient with a failed corneal graft secondary to uncontrolled glaucoma may have a poor prognosis, even though good visual acuity was once present. Patients should be questioned about the onset of the visual disturbance—whether it was preceded by a previous intraocular procedure or infection, or whether it simply deteriorated over time. The presence of pain should be noted and its occurrence and severity should be quantified. Changes in quality of vision as the day progresses should also be ascertained. For example, in Fuchs' dystrophy, vision is often worse immediately upon awakening, with gradual improvement noted as the day progresses.

When they are available, old records are invaluable; they can alert the physician to potential operative problems and can confirm important information such as previous best-corrected visual acuity, past intraocular pressure control, and previous intraocular lens powers. Patients often carry intraocular lens identification cards that are useful in computing the replacement intraocular lens power. A history should be ascertained of previous ophthalmic surgical procedures such as cataract extraction, filtering procedures, or neodymium: yttrium-aluminum-garnet (Nd:YAG) laser for posterior capsular opacification. Knowledge of complications that developed during the preceding procedure helps to prevent potential surprises during keratoplasty.

OPERATIVE EVALUATION FOR KERATOPLASTY

Numerous factors affect the optimal timing of keratoplasty. The patient's subjective complaints and ability to perform daily activities are very important in the evaluation of a candidate for surgery and the relative urgency for the procedure. An active 55-year-old woman with painful bullae and decreased vision secondary to Fuchs' endothelial dystrophy and a 24-year-old keratoconus patient with an enlarging cone, diplopia, contact lens intolerance, and difficulty with night vision both may be in greater need of intervention than an 80-year-old patient with painless pseudophakic bullous keratopathy who is functioning well in her home environment with 20/100 visual acuity. The rheumatoid patient with acute corneal melting and impending perforation may require emergency patch grafting. At times, the status of the other eye must also be considered. A patient with pseudophakic bullous keratopathy in one eye and poor visual acuity and the same closed-loop anterior chamber lens in the other eye is in greater need of keratoplasty than is the keratoconus patient with asymmetric involvement and good contact lens tolerance.

The presence of glaucoma must be evaluated carefully, and the condition must be controlled before keratoplasty is performed. Elevated postoperative pressure can have deleterious effects on graft survival[3] and will ultimately lead to graft failure. Investigators have demonstrated that elevated intraocular pressure leads to thinning of the corneal endothelium, morphologic signs of damage, and decreased endothelial cell count.[4,5]

A corneal leukoma in the visual axis has important implications that are worthy of consideration. Was it the result of bacterial keratitis in a soft contact lens wearer, or was it of viral origin (e.g. herpes simplex, with increased potential for graft rejection), perhaps requiring a topical antiviral agent or oral acyclovir[6–8] post keratoplasty? Obviously, the prognosis for a successful outcome is linked inexorably to a thorough knowledge of the patient's preoperative history.

PHYSICAL EXAMINATION OF PATIENT DURING KERATOPLASTY EVALUATION

COMPONENTS OF PHYSICAL EXAMINATION

Visual acuity assessment

Good history taking should confirm when a patient's past visual acuity was better and what the best-corrected visual acuity is. Amblyopia secondary to anisometropia, strabismus, or corneal scarring during childhood should be ruled out, and visual acuity should be tested using standard Snellen testing. If the patient cannot read the chart at a distance of 20 ft (6 m), additional acuity task results such as counting fingers and detecting hand motions must be documented, along with data indicating the presence or absence of light perception. One of the most important acuity factors involves carefully testing the eye for light projection. In eyes with corneal opacity and light perception vision, the patient's ability to discern the direction from which a light is projected is an important indicator of retinal and optic nerve function. A patient with good retinal function should be able to appreciate in all quadrants the light emitted from a standard muscle lamp (Fig. 32.1). In some eyes with severe central visual loss, use of light emitted from the indirect ophthalmoscope may be required before the patient can determine its direction. Testing visual acuity in a darkened room to compensate for light scattering and glare may also be beneficial. Careful examination for afferent papillary defect as well as color discrimination can be helpful in identifying optic nerve pathology.

The importance of a good refraction cannot be overemphasized. In keratoconus, for example, in which retinoscopy is impossible because of scissoring light reflexes, one must consider checking keratometry and manifesting the patient by dialing in the high astigmatic components (i.e. +3.00 first at 90°, then 180°, and refining), then progressively changing the sphere. It is also helpful to test for visual acuity with a rigid, gas-permeable lens on the eye after topical anesthetic has been instilled. Even if a contact lens is not practical for long-term management, it often can eliminate irregular corneal astigmatism and provide an indication of better-corrected visual acuity and visual potential. Pinhole visual acuity, potential acuity meter, and glare testing in our experience have

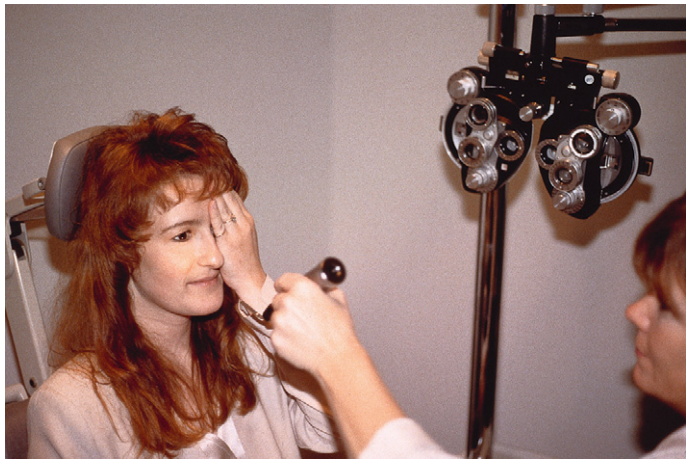


Figure 32.1. Evaluation of light projection. Note the patient looking straight ahead with the other eye completely covered.

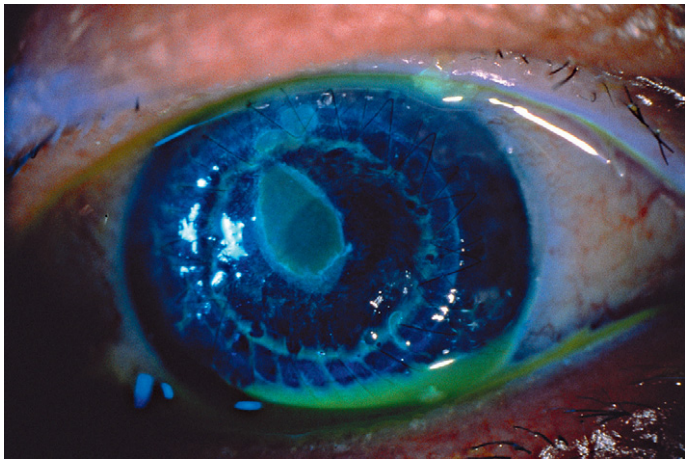


Figure 32.2. Nonhealing epithelial defect in corneal graft of a patient with dry eye.

limited value in predicting best visual acuity, probably because of severe light scattering that results from corneal pathology. One study suggests that it is beneficial to place a hard contact lens over the cornea before performing potential acuity meter testing.[9]

In eyes with corneal edema in which improvement in visual acuity post keratoplasty is questionable, it is worthwhile to attempt to improve acuity and to facilitate retinal viewing by using a topical glycerin that is instilled after topical anesthesia is administered; then, wait 20–30 min for corneal clearing. Epithelial debridement and intravenous fluorescein study may also be used preoperatively for evaluating pre-existing cystoid macular edema.[10]

External examination

The bony structures of the orbit and the prominence of the brow should be evaluated, especially if the patient has deep-set eyes or abnormally thin palpebral fissures, so that the patient's head position during surgery can be planned and an appropriate lid speculum can be chosen. If the patient has active acne rosacea with staphylococcal blepharitis, appropriate treatment should be instituted before the procedure is performed. Herpes zoster, trauma, or radiation may account for lid scarring or neurotrophic keratitis, and ultimate graft failure.

Slit-lamp examination

Lids, lashes, and lacrimal gland

Lid diseases such as blepharitis or meibomitis should be identified and controlled before keratoplasty is performed. If the patient has an ectropion, an entropion, or trichiasis, all of which can lead to epithelial scarring, permanent correction, usually surgical, is advised before keratoplasty is undertaken. Mild spastic entropion is frequently subclinical until the time of surgery; it should be treated rapidly when it is noted postoperatively.

Normal tear production is crucial to graft re-epithelialization; therefore, tear film abnormalities and dryness must be noted during the preoperative examination. Fluorescein and/or rose bengal and Schirmer testing indicate the extent of dryness and epitheliopathy. When there is significant evidence of dryness, consideration should be given to partial or complete punctal occlusion preoperatively, or at the time of keratoplasty, sometimes in combination with partial medial or lateral tarsorrhaphy (particularly when exposure keratitis is suspected).

Conjunctiva and limbus

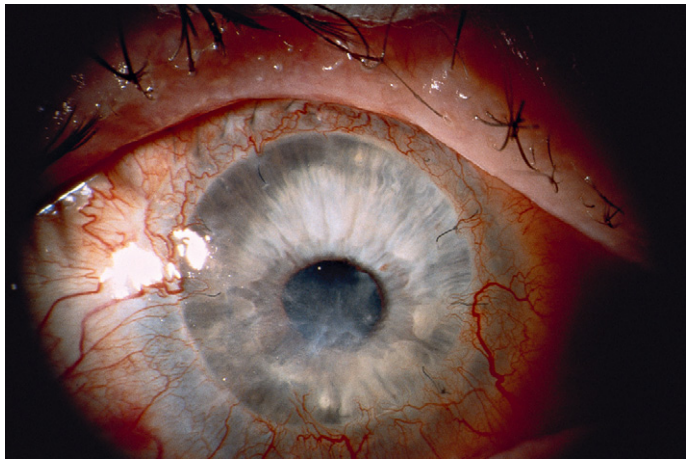
Patients with a history of Stevens–Johnson syndrome, ocular cicatricial pemphigoid, or chemical burn should be examined for scarring and symblepharon; these patients are at significant risk of dry eyes, nonhealing epithelial defects (Fig. 32.2), and postoperative infection because the normal external immune defense mechanisms of immunoglobin A and lysozyme are compromised. Procedures such as punctal occlusion, conjunctival transplant, and limbal stem cell transplantation,[11–13] when performed before keratoplasty, may increase the prognosis for graft survival in these high-risk patients (Fig. 32.3, *A* and *B*). On the day of surgery, the patient should be evaluated for blepharitis and conjunctivitis. If these are detected, the surgery should be canceled and then undertaken only after treatment is provided and complete resolution is attained.

Cornea

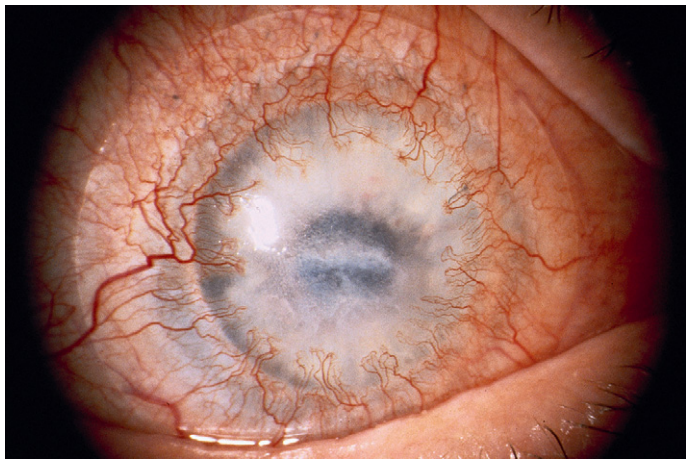
The causes of corneal opacification that require transplant can be divided broadly into ectatic and stromal dystrophies (keratoconus, lattice, granular, or macular dystrophy), postinfectious corneal scarring with or without corneal vascularization (bacterial or viral ulcers), endothelial dysfunction with secondary stromal and/or epithelial edema (Fuchs' dystrophy), and endothelial degeneration (pseudophakic bullous keratopathy). Table 32.1 provides a general outline of these causes and their prognosis for graft survival.

The diameter of the graft is determined in part by the diameter of the corneal irregularity and its proximity to the central visual axis. If possible, the diameter of the cone in keratoconus should be surrounded completely by the trephine so as to avoid thick-to-thin-edge suturing and progressive postoperative recipient bed thinning. Cone diameter is determined best using direct ophthalmoscopic viewing at +6.00 D following maximum mydriasis, or by viewing the Fleischer ring intraoperatively. The Fleischer ring can be seen well at the slit lamp using the cobalt blue light. Preoperative sketching is also of value. Leukomas do not necessarily need to be totally surrounded, except in scars caused by herpes simplex virus in which removal of latent virus would seem desirable.

The Oculus Pentacam® is an anterior segment and corneal imaging device that uses a rotating Scheimpflug camera, which provides Scheimpflug imaging of the cornea, topography, pachymetry, tomography, and keratometric power deviation. This new technology is useful in diagnosing and following progression of



A



B

Figure 32.3. *A*, Corneal graft in patient with severely dry eyes secondary to sulfuric acid burns. Photograph shows early vascularization and clouding 15 months after corneal transplantation. *B*, Photograph of the same eye 2.5 years later. The patient had numerous bouts with persistent epithelial defects. This patient may have benefited from limbal transplantation before penetrating keratoplasty.

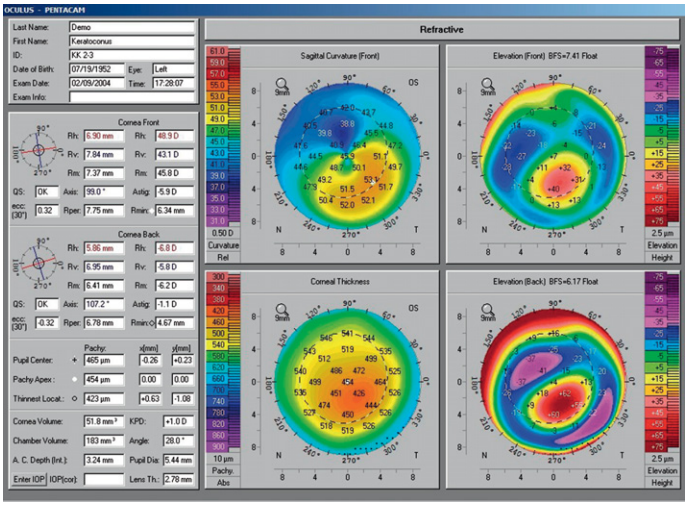
leukomas, Fuchs' dystrophy, keratoconus, and other corneal pathology that commonly leads to keratoplasty. This technology is also beneficial in postoperative care (Fig. 32.4, *A* and *B*). Optical coherence tomography is also available for corneal and anterior segment imaging. It can help to characterize corneal opacities, measure LASIK flap thicknesses, and give accurate anterior chamber angle measurements.

The condition of the host graft bed, its corneal thickness, and peripheral thinning must be assessed. Ultrasonic pachymetry should be performed to quantify thinning or thickening of the cornea. The presence of corneal vascularity dictates the graft sizing and suturing technique that best minimize the propensity toward vascularization of the graft and possible rejection. In eyes with a postinfectious leukoma without vascularization, or in corneal edema secondary to either Fuchs' or bullous keratopathy, the central visual axis should be the center of the donor button, with average diameters ranging from 7.5 to 8.5 mm. A diameter of 8 mm is usually a good average size for trephination, but, when overall corneal diameter is large, the surgeon should consider larger graft sizes. In most of the authors' patients, the donor cornea is oversized by 0.25 mm. In the keratoconus patient, to avoid inducing increased myopia, some

Table 32.1 Causes of corneal opacification and their prognoses for graft survival

Excellent Prognosis	*Diagnosis*
90% or more	Keratoconus
	Central Fuchs' dystrophy (early)
	Granular dystrophy
	Central or paracentral inactive scars
	Rotating grafts or autografts
Very Good Prognosis	*Diagnosis*
80 to 90%	Advanced Fuchs' dystrophy
	Pseudophakic bullous keratopathy
	Aphakic bullous keratopathy
	Inactive herpes simplex keratitis
	Macular dystrophy
	Interstitial keratitis
	Iridocorneal endothelial syndromes
Fair Prognosis	*Diagnosis*
50 to 80%	Active bacterial keratitis
	Active herpes simplex keratitis
	Congenital hereditary endothelial dystrophy and breaks in Descemet's membrane associated with birth trauma
	Active fungal keratitis
	Mild chemical burns
	Moderate keratitis sicca
	Lattice dystrophy
	Congenital glaucoma
Poor Prognosis	*Diagnosis*
0 to 50%	Severe chemical burns
	Radiation burns
	Ocular pemphigoid
	Stevens-Johnson syndrome
	Neuroparalytic disease
	Epithelial downgrowth
	Anterior chamber cleavage syndromes
	Multiple graft failures

This table is meant only as a guideline. The prognosis for each group is worsened by the presence of elevated intraocular pressure, intraocular inflammation, lid and conjunctival defects, and other ocular surface disorders. Failed grafts generally are considered to possess the prognosis for the group of their primary diagnosis, or slightly less. (From Brightbill FS, Corneal Surgery: Theory, Technique, and Tissue, ed 2, St Louis, 1993, Mosby.)



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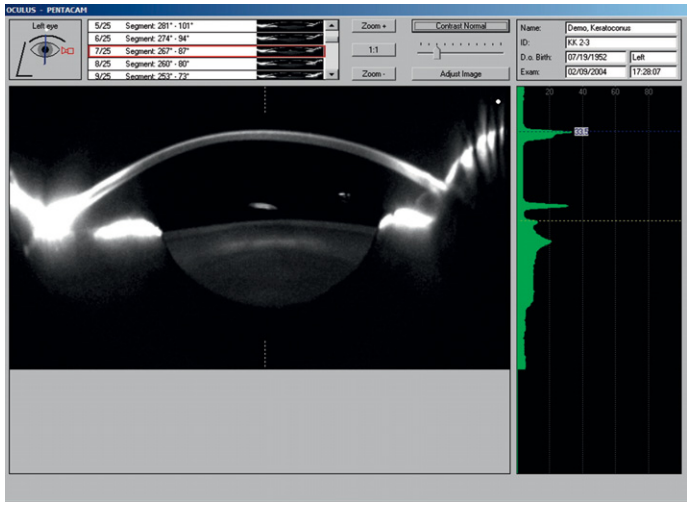


B

Figure 32.4. *A*, Pentacam® images showing topography, anterior elevation, corneal thickness, and posterior elevation. Note the decentered apex and the positive corneal elevation in the area of corneal thinning on both anterior and posterior elevation maps. *B*, Scheimpflug image showing the irregular contour of the keratoconic eye in the accompanying figure. Note the thinning of the cornea, and the irregular curvature.

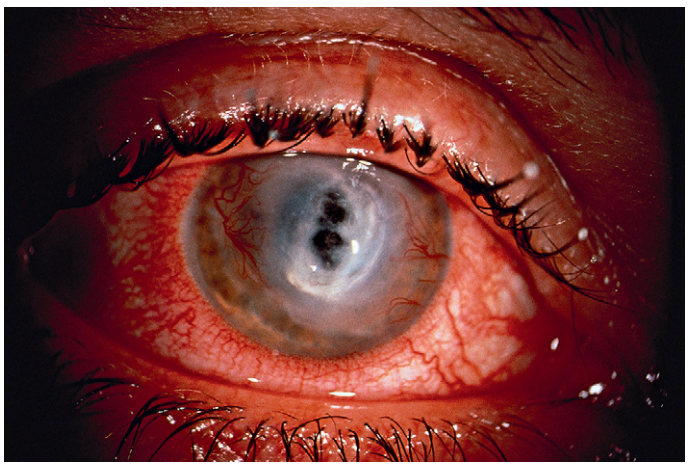
surgeons will not oversize the donor button, and they even may use a smaller donor cornea.[14,15] In patients with postinfectious scarring with thinning and vascularization, or displaced corneal ectasia as in pellucid marginal degeneration, sizing and placement of the graft may be less straightforward, and some decentering may be required. The surgeon must decide the optimal sizing of the graft while avoiding areas of vascularization and peripheral thinning. Interrupted sutures may be indicated to allow for selective suture removal if the areas of vascularization become aggravated by the sutures (Fig. 32.5, *A* and *B*). In cases of corneal edema, an increased depth of trephination and deep suturing into the host bed to allow Descemet's membrane-to-Descemet's membrane graft–host approximation are important.

Anterior segment/iris

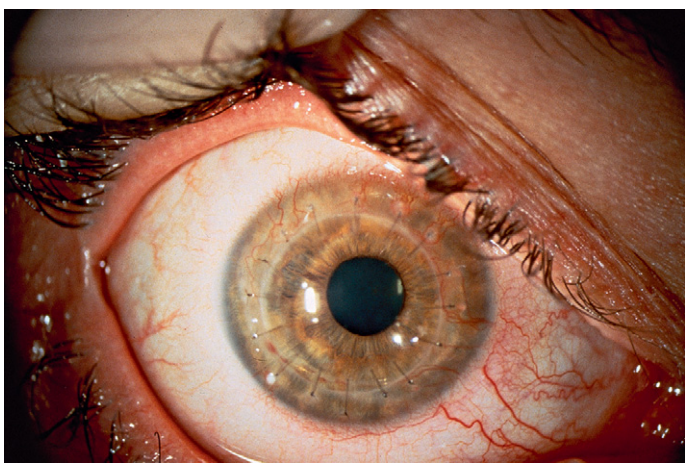
An anterior chamber lens must be identified as either an open- or a closed-loop lens. Iris-supported and closed-loop anterior chamber lenses should be replaced as should any open-loop anterior chamber lens when movement is suspected (Fig. 32.6, *A* and *B*).[16,17] Gonioscopy should be used to examine iridocorneal adhesions and peripheral iridectomies and to locate the positions of lens haptics if an anterior chamber lens is present. Ultrasound biomicroscopy reportedly aids in the evaluation of iris, lens, iridocorneal adhesions, and peripheral anterior synechiae in the cornea, with dense corneal scarring precluding direct visualization.[18] If the anterior chamber lens must be replaced, the patient's anterior chamber anatomy (i.e. the locations of posterior and anterior synechiae and of the residual lens capsule) will play a role in deciding the appropriate lens replacement type.

A thorough evaluation of the iris is important. The presence of rubeosis, fibrovascular membranes obscuring the pupil, and the locations of peripheral iridectomies must be noted. If the pupil can be visualized well, as mentioned previously, the presence or absence of a relative afferent pupillary defect should be documented. The presence of color visual perception also helps to rule out optic nerve damage.

During the ocular examination, it is perhaps most important to rule out active inflammation. In cases of elective transplantation, a

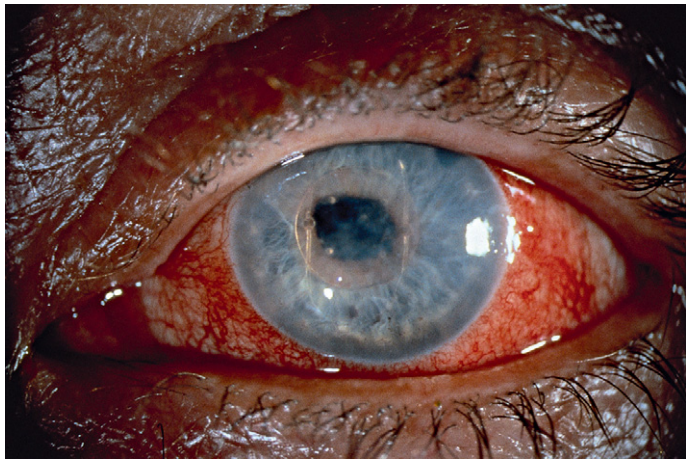


A



B

Figure 32.5. *A*, Stromal necrotizing keratitis secondary to herpes simplex infection, with descemetocele and deep vascularization. *B*, The same eye 6 months after penetrating keratoplasty, demonstrating crystal clear graft with interrupted suture placement. Note the absence of vessels in the donor tissue.



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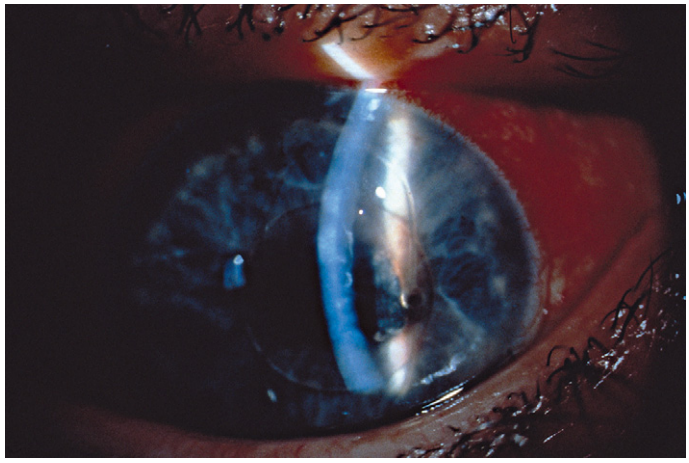

B

Figure 32.6. *A*, A patient with iris-supported lens and pseudophakic bullous keratopathy. *B*, Magnified slit-beam view of same eye, demonstrating stromal edema.

quiet, noninflamed eye offers the best chance for a favorable outcome. Ciliary flush, keratitic or intraocular lens precipitates, anterior synechiae, and iridocorneal adhesions all are signs of past or present inflammation, and they should be noted.

Lens

Before keratoplasty is performed, the patient's lens should be examined using the slit-lamp microscope. The lens may have weakened zonules, and it may exhibit phacodonesis. In many elderly patients, especially those with Fuchs' dystrophy, the lens may exhibit early cataractous changes that may signal the need for a combined keratoplasty and cataract extraction. It is the authors' belief that keratoplasty, perhaps aided by high-dose postoperative corticosteroids, is frequently a cataractogenic procedure. Triple procedures were routinely performed when even minimal lens opacities were present, to obviate the need for future cataract extraction, which may damage the endothelium and threaten the integrity of the graft. In a recent study, patients with Fuchs' corneal dystrophy with corneal pachymetry measurements less than 640 µm maintained useful vision after cataract surgery and were able to avoid keratoplasty.[19] With modern, less endothelial toxic cataract extraction techniques, the keratoplasty surgeon may be able to avoid the need for a triple procedure in Fuchs' dystrophy patients, depending on the preoperative lens opacity and corneal thickness. New techniques for endothelial transplantation without the need for penetrating keratoplasty will also affect the decision regarding the performance of triple procedures in the future.[20,21] Patients with chronic luetic inactive interstitial keratitis and scarring frequently do not present to the corneal surgeon until progressive cataract occurs, which necessitates a combined procedure.

In the treatment of eyes that have undergone previous cataract extraction, knowledge of intraocular lens design (anterior chamber, iris supported, or posterior chamber) or aphakia is critical to effective operative planning. The type of lens that was implanted will dictate whether it should be replaced. Important questions to answer include: is there a clear, intact posterior capsule, and has Nd:YAG capsulotomy been performed?

Intraocular pressure

The presence of borderline controlled or uncontrolled glaucoma is a contraindication to keratoplasty. Accurate applanation pressures in corneas with epithelial edema are difficult to obtain, and attempts may generate falsely low readings; the use of a Tono-Pen (Mentor Ophthalmics, Santa Barbara, CA), a pneumotonometer, or a MacKay-Marg tonometer is more accurate.[22,23] Intraocular pressure should be no higher than the low 20s with no more than two topical medications; otherwise, primary filtering or combined filtering and penetrating keratoplasty should be considered. Because all keratoplasty patients receive intraoperative viscoelastics to coat donor endothelium, to aid in the control of bleeding, and to help prevent synechiae,[24] eyes with pre-existent glaucoma usually require immediate postoperative oral ocular hypotensives and topical aqueous inhibitors to control intraocular pressure. The use of a lower-viscosity viscoelastic such as Healon® and its removal or dilution with balanced salt solution in the anterior chamber before final button placement and suturing are recommended. The long-term use of topical corticosteroids to prevent rejection may lead to steroid-induced glaucoma and requires careful intraocular pressure monitoring for the entire postoperative period. In our experience, long-standing chronic glaucoma with intraocular pressures in the low to mid-20s is a common cause of slow graft failure.

Retina/vitreous

Evaluations of both retinal function and the vitreous are required to ensure that decreased vision is secondary to problems with the cornea alone. Macular degeneration, cystoid macular edema, macular holes, and an opaque or hazy vitreous among other maladies are all conditions that do not improve after the keratoplasty procedure. Knowledge of such conditions before keratoplasty helps in prognostication; such information can often be obtained in examination of old records and discussions with the referring ophthalmologist. In cases in which there is a question, potential acuity meter testing, laser inferometry, or electrophysiologic testing may be tried, but these have limited sensitivity. If the retina and vitreous cannot be visualized using direct or indirect ophthalmoscopy, ultrasonography should be undertaken to rule out a retinal detachment, a retinal mass, or vitreous hemorrhage.

COMMUNICATION BETWEEN PHYSICIAN AND PATIENT WHEN EVALUATION IS COMPLETE

The keratoplasty patient is entering into a lifelong doctor–patient relationship—sound preoperative planning and open communication will help to make this relationship a fruitful one. The risks of

the procedure, the long healing time, the need for antiglaucoma treatment, and rejection rates should be addressed. The patient should be given realistic expectations for potential visual acuity and the time it may take to reach that acuity. The possible use of a contact lens, relaxing incisions, or wedge resection to reach best visual acuity should be understood by the patient before the procedure to ensure patient satisfaction in the postoperative period.

The procedure should be explained clearly using handouts, models, and/or videotapes as indicated. The authors' videotape, 'Patient Eye View,' is available through the Eyebank of Wisconsin, Inc.; it offers previous recipients' evaluations of their surgery, pre- and postoperative instructions, and education on drop instillation, eye care, and signs of rejection.

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33 Gross and slit-lamp examination of the donor eye

William J. Reinhart

The majority of corneal transplant surgeons are no longer intimately involved with all aspects of eye banking. The surgeon places a request for tissue with an eye bank expecting that high-quality corneal transplant tissue will be procured, processed, and delivered to the operating room on schedule. Corneal transplant surgeons can request that limbal conjunctiva be retained for keratolimbal autografts; that the eye bank leave an adequate scleral rim diameter on the excised corneoscleral donor tissue, permitting the use of artificial anterior chambers for the preparation of lamellar endothelial donor grafts; and that accurate endothelial cell evaluation through slit-lamp biomicroscopy and specular microscopy has been performed prior to tissue being offered for transplantation.

Eye bank personnel have become increasingly professionalized, partly in response to the increased regulation by government agencies such as the Food and Drug Administration in the USA and as documented by training and certification through local, state, and national organizations. The main objective, of course, is to ensure that the recipient of corneal donor transplant tissue can expect that the donor cornea will function in an expected optical and physiologic manner and that the donor will not be the source of any potentially transmissible disease. The self-regulation of eye banks through national organizations, such as the Eye Bank Association of America (EBAA), provides additional assurance of quality and safety to transplant surgeons and the public.

Unlike many manufactured items, a donor cornea supplied by an eye bank to a corneal transplant surgeon has no warranty or guarantee. Indeed, most eye banks print a disclaimer on the donor information form, which states that the using ophthalmic surgeon is ultimately responsible for evaluating the donor tissue and determining its suitability for use. Most receiving surgeons, however, do not have access to a slit lamp in the operating room. The surgeon can only view the tissue in its storage chamber against background light to rule out gross infiltrates and under the objective of the operating microscope. Since most operating microscopes have coaxial illumination and do not have a slit-lamp attachment, this type of evaluation is not very satisfactory. This less-than-ideal examination would not usually allow the surgeon to detect a donor Descemet's membrane detachment or a low endothelial cell count. The tissue evaluation by the eye bank is, therefore, the only relevant one for most surgeons. It is also a given that the most diligent surgeon cannot examine a donor eye or excised corneal sclera rim and determine if the donor may have been septic or infected with a transmissible fatal virus (e.g. rabies or Creutzfeldt–Jakob disease), that antibiotics had not been added to the excised corneoscleral rim storage media, that storage and shipping conditions were less than optimal, etc. The surgeon's review of the donor information form is useful, therefore, only if all of the appropriate information has been actively sought and recorded by eye bank personnel. The using surgeon must trust the care, precision, and thoroughness of the eye bank team. This has been the goal of the Medical Advisory Board and the Accreditation Board of the EBAA in the USA to make sure that this trust is well placed.[1] Eye Bank organizations in other countries or regions play a similar role.

All eye banks certified by the EBAA must have an extensive procedure manual. The procedure manual must contain standard operating procedures (SOPs) for all aspects of operations of the individual eye bank. This includes operations such as 'potential donor screening,' 'procurement,' 'processing and preservation,' and 'evaluation.' Within these operations would be found SOPs for various procedures such as whole-eye enucleation, in situ corneal excision, whole-eye slit-lamp examination, laboratory corneal excision, slit-lamp biomicroscopy of the excised cornea scleral rim, endothelial specular microscopy of the excised corneal scleral rim, etc. Each procedure is a detailed document containing the purpose, responsibility, scope, definition, references, materials and equipment, policy, and the procedure written in such detailed fashion that a competent technician could ideally perform the procedure using only the manual as a guide. Such documents can be obtained on request from most EBAA-certified eye banks.[2]

PROCUREMENT

Donor corneal tissue may be obtained and stored before transplantation using the following techniques:

1. In situ corneoscleral rim excision with immediate transfer into storage media

2. Whole-globe enucleation with moist chamber storage
3. Whole-globe enucleation followed by laboratory corneoscleral rim excision with transfer to the following:
   a. Media for hypothermic storage at 4°C
      (1) Short term (e.g. M-K medium)[3]
      (2) Intermediate term (e.g. Optisol GS)[4–9]
   b. Media for organ culture at 30°C to 37°C[10–13]
   c. Cryopreservation[14–16]

All methods require a careful examination of the donor as well as an in situ examination of the donor eye and the orbit. When tissue has then been transported to the laboratory, an examination of the donor globe or excised corneoscleral rim, including a detailed slit-lamp examination and any additional studies such as endothelial specular microscopy, should then be recorded on an evaluation form prior to offering the tissue to a requesting surgeon.[17]

Whole-globe enucleation has long been the standard procurement procedure for donor eye tissue. However, with the increased number of well-trained eye bank technicians, in situ corneoscleral rim excision is becoming more common. In situ corneoscleral excision, rather than enucleation, often creates less friction with morticians since cosmetic restoration is less of an issue and is also sometimes more acceptable to donor families. The time from procurement to storage of the excised corneoscleral rim in preservation media, especially if the procurement site is in a location remote from the eye bank laboratory, is also significantly decreased if in situ excision is performed. The increased use of in situ corneoscleral rim excision does have some disadvantages. Most eye banks do not provide portable slit lamps for in situ evaluation of the anterior segment. If the donor tissue is judged unacceptable for transplantation on the basis of a slit-lamp examination of the whole globe in the laboratory, then the eye bank saves the cost of the preservation media, as well as the cost of a corneal storage viewing chamber(s) that would have been used if an in situ excision had been performed. The whole globes judged unacceptable for transplantation because of scars, corneal guttata, etc., which would not have been detected during an in situ evaluation, can also be offered for research protocols or practice surgery, an option not available if an in situ excision had been performed. Corneoscleral rims removed from whole globes in the laboratory also allow use of the posterior part of the globe for scleral preservation for transplantation, or for research protocols that only require the posterior globe, whereas an in situ excision obviously leaves the posterior part of the eye with the donor.

PHYSICAL EXAMINATION OF THE BODY

The eye bank technician must first ensure that the donor has been identified, that consent for tissue donation has been obtained, that eye and medical history screening has been performed and the appropriate forms filled out, and that the location for tissue procurement is appropriate. Screening for behavioral and medical high-risk factors by physical examination of the body is required. The technician should don personal protective equipment such as a gown, examination gloves, protective eyewear and a surgical cap. Visual inspection from donor head to toes involves looking for needle tracks, injection sites, and scars in all areas for evidence of IV drug abuse or high-risk behavior, paying close attention to the following areas: tattoo areas and/or skin lesions, brachial/radial veins and arteries, hands, and feet including the area in between the webs of the toes and fingers, external jugular, abdomen, thigh, calf, forearm, and upper arms. The rectal area should be examined for physical evidence of anal intercourse including perianal condyloma. The male and female genitalia should be examined for physical evidence of risk of sexually transmitted diseases such as genital ulcerative disease, herpes, syphilis, and chancres. All tattoos should be evaluated for possible age and origin. Evidence of acupuncture or body piercing, including pierced genitalia, should be evaluated. Comprehensive examples detailing some sexually transmitted diseases, homemade tattoos, and other pathology and their appearance are available for view by watching the EBAA—Physical Inspection CD-ROM.[18]

IN SITU EXAMINATION OF THE EYE AND ORBIT

The eye bank technician should perform a careful inspection of the orbital area of the donor. Examination of the periorbital and orbital tissues in cases involving facial trauma (e.g. vehicular accidents and homicide) may indicate how severely the eye itself may have been traumatized before death. The lids, lashes, and periorbital tissues should be carefully examined for signs of infection, such as styes, skin pustules, or accumulation of mucopurulent material on the lid margins and lashes from conjunctivitis. Details of the gross examination may help explain asymmetric findings on later slit-lamp examination and should be carefully recorded. Obviously, examination of the enucleated eye or excised corneoscleral rim in the laboratory cannot reveal any of these associated findings, which can be detected only by direct examination of the donor. The eye bank technician must be diligent, therefore, in seeking and recording this information.

When an enucleation is performed, in situ examination of the anterior segment of the eye is less important because careful gross and slit-lamp examinations are performed in the laboratory. However, a careful in situ gross examination may allow the enucleator to supply an educated guess as to the suitability of tissue for transplantation. For in situ corneoscleral rim excisions, however, a careful gross examination is very important. Since few eye banks include a portable slit lamp for in situ examination in their protocol, the technician must be adept at a careful penlight examination for two major reasons: (1) There may be important conditions involving the eye that could not be detected by laboratory examination of the excised corneal scleral rim alone. Some examples might include an eye that has undergone anterior segment surgery, such as cataract surgery, cataract intraocular lens implant surgery, and laser surgery involving the iris. Other conditions that might affect donor suitability (e.g. scleral rupture and congenital anomalies of the iris or lens) cannot be detected on subsequent laboratory examination of the excised corneoscleral rim. In addition, tumors of the anterior segment of the eye that would preclude transplantation must be identified.[19] (2) An evaluation of the degree of stromal folds and stromal edema can be more precisely assessed before placement in storage media containing osmotic agents, such as dextran, which decreases the stromal hydration of a previously swollen cornea. If an in situ gross evaluation of the eye raises any questions about transplant suitability, and if consent allows for either whole-globe enucleation or in situ excision, a whole-globe enucleation may be the safer choice since a more detailed slit-lamp evaluation can be conducted in the laboratory.

GROSS EXAMINATION

IN SITU

A penlight with fresh batteries is used to provide oblique illumination of the donor eye so that the technician, without magnification, can detect the following:

1. Epithelial edema (haze) and epithelial defects (exposure, trauma, and foreign bodies)
2. Stromal opacities:
   a. Arcus senilis
   b. Central corneal stromal scars
   c. Nonulcerated anterior stromal infiltrates
   d. Microbial infiltrates
3. Estimate of stromal edema:
   a. Clarity of cornea
   b. Number and severity of deep stromal folds (light, obvious, and heavy striae)
4. Keratitic precipitates
5. Abnormal corneal shape:
   a. Keratoconus
   b. Microcornea or megalocornea
6. Condition of the anterior chamber
   a. Formed, shallow, or flat
   b. Evidence of gross blood
   c. Abnormal anterior segment anatomy:
      (1) Congenital
      (2) Acquired (e.g. from intraocular surgery)
   d. Haziness of aqueous humor
7. Any evidence of corneal, lens, or other anterior segment eye surgery or injury

ENUCLEATED EYE

The examination is conducted in the same manner as described for the in situ examination except that the external posterior area of the globe can also be examined for abnormalities such as previous retinal detachment surgery. In addition, evidence of poor enucleation technique as manifested by traumatic corneal epithelial abrasions, retention of excessive orbital tissue, or lacerations of the globe may alert the laboratory to the possibility of a poorly trained enucleator. An excessive amount of corneal stromal edema may be explained if a globe has been improperly transported immersed in saline solution and may not necessarily negate use of the eye if adequate endothelial function can be inferred (e.g. through the use of specular microscopy).

SLIT-LAMP EXAMINATION

A careful slit-lamp examination of the donor globe or excised corneoscleral rim is the sine qua non quality control of a first-class eye bank before the release of tissue to the accepting surgeon. The major skill that eludes many technicians is the ability to adequately evaluate the corneal endothelium. The improved optics of a corneal storage viewing chamber will allow even the neophyte, however, to rapidly acquire the ability to evaluate the corneal endothelial cell layer in its entirety, which in turn will improve the detection of abnormalities that may require interpretation by the medical director. With acquired experience, the technician feels more confident in evaluating the corneal endothelium of whole globes or excised corneoscleral rims stored in bottles in which the optics and view make endothelial evaluation much more difficult even for the experienced technician or surgeon.

WHOLE-GLOBE EXAMINATION

1. Remove the eye jar lid and place it upside down in a sterile area such as a laminar flow hood or an ultraviolet lamp tissue transfer hood if the whole eye is to be shipped in the same container. Decant any excessive fluid from the jar and then clamp the jar in a viewing brace attached to the slit lamp. The eye in its holding cage should be brought forward using a sterile hemostat, sterile forceps, or sterile cotton-tipped applicators.
2. Using low magnification and either the diffuse illumination provided by a filter or a wide slit-lamp beam angled at 45°, examine the anterior globe. Major defects, which might be missed at higher magnification, are more easily identified at low magnification and then subsequently studied using higher magnification. In general, after an overall view of the eye has been obtained, the examination should proceed in a systematic fashion from the corneal epithelium back to the anterior surface of the iris, using first a broad and then a more narrowed slit beam for each aspect of the examination.
3. Adjust the microscope head and the slit beam so that they are almost coaxial, creating retroillumination which, with searching, may reveal defects or opacities in the stroma that may not have been noticed with an oblique slit.

Corneal epithelium

Microcystic edema, abrasions, and retained foreign bodies should be identified. Nonvital epithelium may have lost its adhesion to the underlying stroma and may have been rubbed off by lid action. If the epithelium is missing, it is necessary to carefully rule out stromal injury. Foreign bodies embedded in the epithelium should be carefully examined with a narrow slit beam to determine if they have penetrated into the corneal stroma. The interpalpebral area of the corneal epithelium, which may have been exposed before and after death, should be carefully examined for the presence of missing epithelium (Fig. 33.1), underlying evidence of stromal

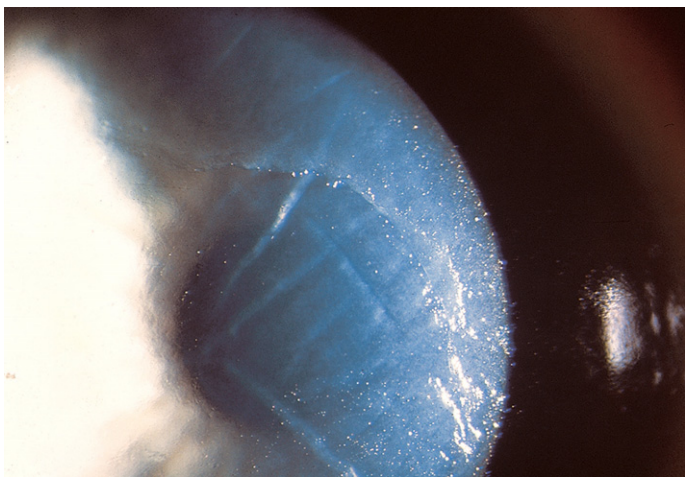
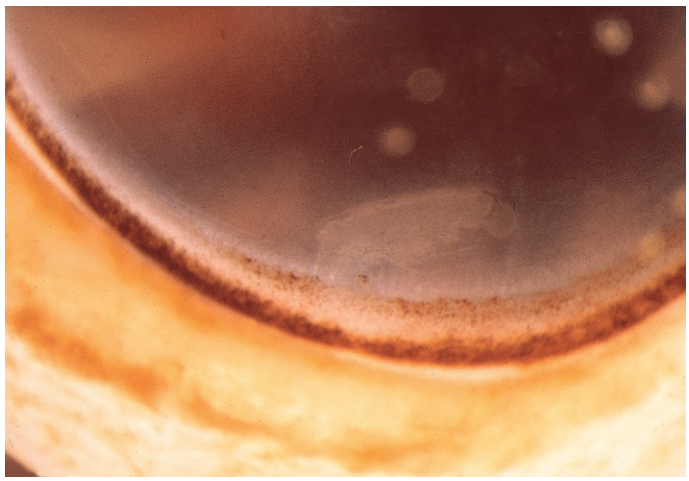


Figure 33.1. Edges of epithelial defect as shown in broad slit illumination. Mild stromal corneal folds also visible.

opacification, or inflammatory infiltrate. It is not always possible to distinguish between stromal scars, noninfectious stromal infiltrates and microbial infiltrates. In general, stromal scars have a more slate gray appearance without adjacent stromal edema, whereas microbial infiltrates have more discrete borders, adjacent stromal edema, and a white or yellowish white appearance. If the stromal opacity involves the central cornea, the cornea should not be offered for transplantation, whereas marginal opacities are primarily of concern if microbial infection cannot be ruled out. Unless it is obviously an inactive stromal scar, the medical director and using surgeon should make the final decision regarding acceptability for transplantation.

Corneal stroma

Major stromal opacities are identified with the gross examination, low-magnification scan, and retroillumination. Higher magnification using a narrow slit beam is used to define the extent, depth, location and appearance of stromal opacities in an attempt to characterize them as congenital or acquired inactive scars or as inflammatory infiltrates (Fig. 33.2, *A* and *B*). Corneal stromal folds are associated with stromal edema. There is a complex interaction between the barrier and pump function of the corneal endothelium that determines the degree of stromal hydration.[20] At 4°C, the pumping action of the endothelium ceases and the normal cornea swells. The anatomy of the cornea is such that most of the increased stromal hydration is accompanied by increased thickening of the cornea toward the endothelial cell layer, throwing the elastic Descemet's membrane into folds, which in turn lead to folds in the deeper corneal stroma. Thus, the number and severity of stromal folds depend on factors such as ante mortem endothelial function, traumatic disruption of the barrier function of the endothelium, and postmortem conditions such as temperature, elapsed time from death, and the integrity and hydration of the overlying corneal epithelium. An appreciation for what is normal helps the technician identify tissue that may have been improperly labeled by an outlying collection station or induces suspicion that the estimated time of death to examination time may be longer than indicated.



A

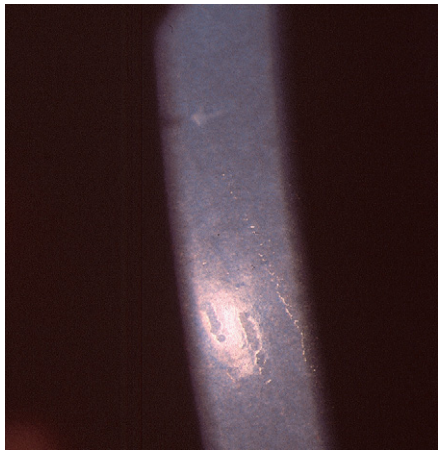
B

Figure 33.2. *A*, Oval anterior stromal infiltrate in excised corneoscleral rim. *B*, Appearance of anterior stromal infiltrate as shown in Figure 33.2, *A* examined with narrow slit.

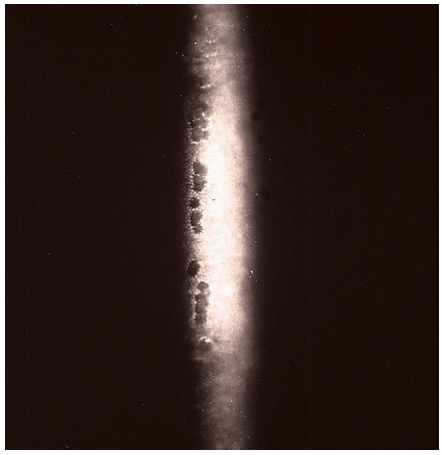
Corneal endothelium

The use of the slit-lamp technique of specular reflection for examination of the corneal endothelium in the whole globe is a skill acquired with practice and experience. The beginning eye bank technician can rapidly acquire experience by examining live subjects,[21] particularly those with Fuchs' endothelial dystrophy. The experience the technician gains in identifying the abnormal endothelial appearance of these eyes becomes invaluable when later attempting in vitro endothelial assessment in the eye bank laboratory. If the epithelial surface is dried out or irregular, placing a drop or two of an antibiotic solution on the anterior surface of the enucleated eye improves viewing conditions. The slit lamp is the most efficient and rapid means for the technician to determine the quality of the endothelial layer with respect to density of cells, the degree of cell uniformity, the intactness of the endothelial sheet and Descemet's membrane, and the detection of cornea guttata, endothelial vesicles, Descemet's tears, and stress fractures in the endothelial sheet from the trauma of excision (Fig. 33.3, *A* and *B*).

In general, eye banks do not determine the refractive status of the donor cornea, except in a research protocol, because it is not clear how that information would be used. Acquired disorders of corneal shape (e.g. keratoconus in its earlier stages) can be almost impossible for the eye bank technician to detect in the laboratory, although central cornea stromal thinning, deep stromal striae, and stromal scars should all be diligently sought on slit-lamp examination. A donor history of contact lens wear should prompt an even more exhaustive search for such slit-lamp signs of keratoconus. Of more concern is the increased prevalence of donors who may have undergone refractive corneal surgery with procedures such as radial keratotomy, epikeratoplasty, keratomileusis, LASIK, and excimer laser photorefractive ablation. The incisional scars of radial keratotomy, epikeratoplasty, and keratomileusis are usually visible on slit-lamp examination, although the change in corneal contour may be much more subtle. However, the anterior stromal scarring from laser ablation surgery and the very faint circular anterior stromal scars of LASIK surgery may be almost undetectable by ophthalmologists using the slit lamp to examine the eye in vivo, and so it is unlikely that an eye bank technician will be able to detect all such cases in the laboratory.[22,23] A donor history of refractive corneal surgery or keratoconus remains the most reliable means for screening out eye donors with abnormally shaped corneas. It is possible that topography techniques for either the in situ cornea or the excised corneoscleral rim can be adapted to screen for undesirable refractive properties of the donor cornea.[24–26] Viewing the excised corneoscleral rim in a viewing chamber against a light background using the unaided eye or low-power slit-lamp examination may be



A



B

Figure 33.3. *A*, Slit-lamp appearance of stressline-induced pseudoguttate excrescences. *B*, Higher magnification view of stressline-induced pseudoguttate excrescences.

used to detect unrecognized stromal opacities or the unequal transmission of light caused by corneal refractive procedures. Additional techniques for detecting corneas that have had refractive surgery such as LASIK or photoablation surface surgery have been evaluated, but there is yet no foolproof method for identifying such corneas.[27–29]

Anterior chamber

A crystalline-appearing aqueous in the anterior chamber may indicate that the eye has been frozen, and it should not be offered for use. The iris should be evaluated for evidence of prior trauma, laser surgery, intraocular surgery, or iris tumors. The presence or absence of the crystalline lens should be determined, and an intraocular lens implant, if present, should be identified.

Excised corneoscleral rim

Short-term storage containers are usually provided either as glass bottles or as a plastic viewing chamber, each holding approximately 20 mL of storage medium. Before corneoscleral rim excision and transfer, the expiration date and the clarity and color of the manufactured corneal storage media should be confirmed on slit-lamp examination. If there is an excessive amount of ciliary body debris in the medium after transfer of the excised corneoscleral rim, the

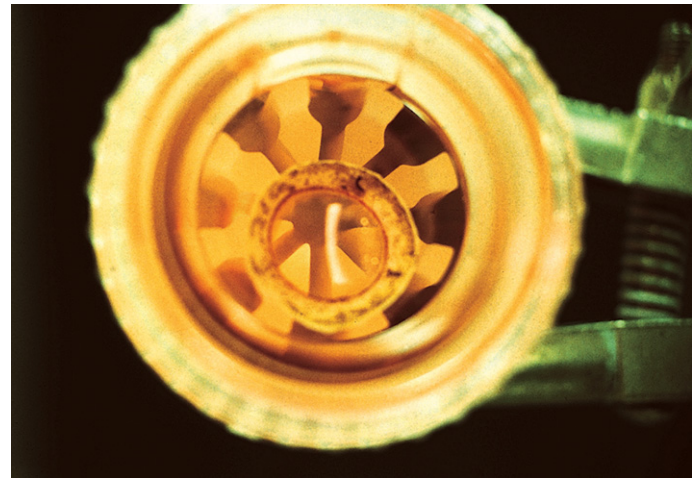


Figure 33.4. Excised corneoscleral rim in a corneal storage viewing chamber.

corneoscleral rim should be transferred to a new storage container. In a humid environment, condensation of moisture on the walls of the container may prevent adequate viewing if the container has been refrigerated. The glass vials may be clamped so that the cornea may be viewed through the bottom directly with a viewing mirror. Many technicians and surgeons prefer a corneal viewing chamber because the superior optical qualities allow more precise evaluation of the donor cornea, especially the corneal endothelium (Fig. 33.4).

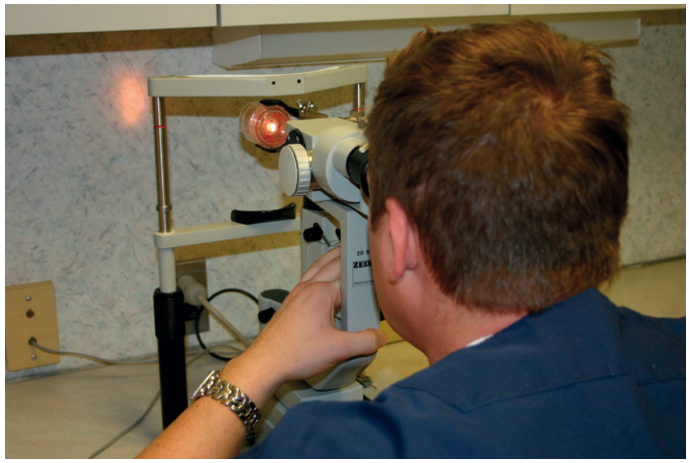
The slit-lamp evaluation of the excised corneoscleral rim proceeds in the same fashion as described for the whole globe beginning with the epithelium and scanning back to the endothelium. If the same technician has performed the whole-eye slit-lamp examination and corneoscleral rim excision, the major effort is directed at detecting any evidence of epithelial or endothelial trauma as a result of the excision. Particular attention should be directed toward detection of Descemet's membrane detachments, which may be too small to be of any significance but should be pointed out to the accepting surgeon (Fig. 33.5, *A* and *B*).

EVALUATION FORM

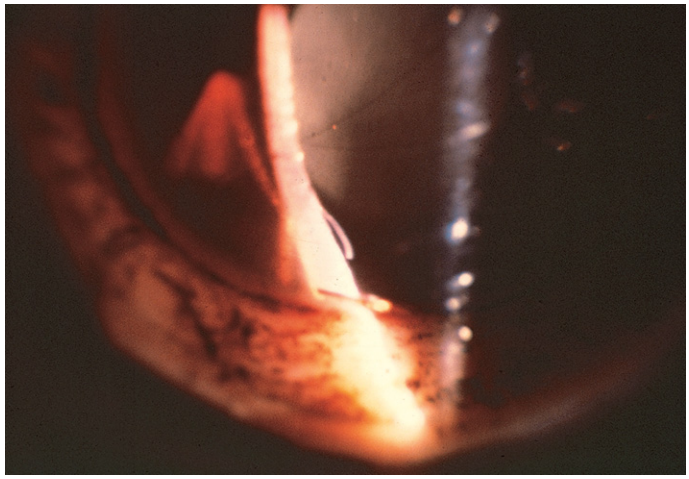
Finally, a laboratory pro forma should be completed, detailing the findings noted.[17] Details regarding time of death, time of death to refrigeration, time of enucleation, transport time, warming time in the laboratory for specular microscopy or slit-lamp examination, and endothelial cell density determinations with an estimation of variation in cell shape (pleomorphism) and size (polymegathism) should be recorded on the donor information form along with the name of the examining technician or medical director and forwarded with the tissue to the receiving surgeon.

SPECULAR MICROSCOPY

Specular microscopy is very appealing to eye bank technicians because it allows for a seemingly precise determination of endothelial cell density and allows cornea guttata to be easily identified (Fig. 33.6). However, the area of the central corneal endothelium in a typical 8–8.5 mm donor button is much larger than any area that can be sampled by the specular microscope even with multiple-field examinations.[30] In addition, there may be a significant amount of rewarming time needed to allow viewing of the corneal endothelial



A



B

Figure 33.5. *A*, Slit-lamp evaluation of an excised corneoscleral rim in a corneal storage viewing chamber. *B*, Detached Descemet's membrane in excised corneoscleral rim. (Courtesy G. Rowell, Kansas City Eye Bank, Kansas City, MO.)

Figure 33.6. Specular microscopy examination of the endothelium of an excised corneoscleral rim in a corneal storage viewing chamber.

mosaic. A careful slit-lamp examination remains the most important means for assessing the overall character of the endothelial cell layer, and specular microscopy should be regarded as a supplementary tool. However, many eye banks and corneal transplant surgeons consider specular microscopy to be an essential part of donor corneal evaluation. In addition, specular microscopy may increase the willingness of surgeons to accept tissue from older donors and is required by the EBAA if the donor eye has had anterior segment surgery.[31,32] Standardization of endothelial cell density determinations is an issue for eye banks.[33,34]

Because many eye banks have a significant turnover in part-time personnel, the publications listed in the bibliography[35–38] are particularly didactic for the novice and can be recommended as permanent additions to the eye bank laboratory library.

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34 Tissue typing and matching

Bonnie C. Weston

INTRODUCTION

Corneal transplantation has undergone numerous changes since Zirm performed the first successful human penetrating keratoplasty in 1905.[1] Incredibly, the graft remained clear, possibly due to the use of a human donor cornea from an enucleated eye. Although most early cases were not this successful, over time the procedure grew increasingly more predictable due to better operative techniques, instrumentation and suture material. Eventually, there was enough demand for tissue that Townley Paton opened the New York Eye Bank in 1959.[2] With the introduction of McCarey–Kaufman medium in 1974, tissue could be kept viable for days, making keratoplasty an elective procedure. These improvements have almost eliminated primary graft failure, and the most common reason for a failed graft is now immunologic rejection.[3] In turn, as techniques and medications improve, a greater number of high-risk transplants are being performed today. This has led to increased interest in the nature of corneal graft rejection and how it is affected by the donor tissue itself.

BASIC TRANSPLANTATION IMMUNOLOGY

When an animal receives a solid tissue allograft, unless the donor and recipient are genetically identical the tissue is recognized by the immune system as non-self. A process called rejection ensues, which involves the formation of specific antibodies and lymphocytes directed against the tissue. The cellular antigens causing this response are determined by a group of genes called the major histocompatibility complex, or MHC. In humans, these genes are called the human leukocyte antigens or HLA genes. The HLA system is a multigene family consisting of more than 10 loci coded on the short arm of chromosome 6.[4]

There are two major subclasses of HLA genes. HLA Class I comprises the HLA-A, HLA-B, and HLA-C loci. The antigens produced by these genes are found on almost all nucleated cells. These are transmembrane glycoproteins consisting of a small beta2 microglobulin associated with a heavy chain which has three globular domains on its extracellular portion. These domains are recognized by cytotoxic (CD8-positive) T cells.[5] HLA-A and HLA-B are considered the classical transplantation antigens. HLA-C is expressed at much lower levels and is not thought to play a role in rejection. HLA Class II includes the HLA-DP, HLA-DQ, and HLA-DR loci. The antigens these genes produce are found only on immune cells that cooperate with or present antigen to T helper cells. This includes B lymphocytes, monocytes, macrophages, and activated T cells as well as dendritic cells and Langerhans cells. Each molecule consists of two glycoprotein chains, both having an extracellular immunoglobulin-like domain. HLA Class II antigens are recognized by CD4-positive T cells. They are required for antigen presentation to Class II-restricted T cells, and thus they control the level of the immune response.[6]

The HLA system is important in solid tissue transplant rejection. Despite extensive study, rejection is still poorly understood for all types of organ transplants. Briefly, the immune response has two portions: the afferent arc and the efferent arc. There are multiple pathways for activation of both parts of the response. Sensitization of the host to the graft is initiated when dendritic cells, which display both Class I and II antigens, present antigen to recipient T helper cells.[7] The interaction causes release of lymphokines, which induce the formation of specific cytotoxic T cells and stimulate B cells to produce serum antibodies against the donor tissue. In transplant rejection, most of the damage is a result of cellular immunity, rather than serum antibodies.

HLA typing of donors was initially performed on serum with the microlymphocytotoxicity assay. Very small amounts of both lymphocytes to be typed and antisera of known HLA specificity are mixed and observed for cell viability. The test is done in a large microtiter tray to allow for the large number of known HLA alleles.[8] Due to some inaccuracy of this technique particularly for Class II antigens and cadaver blood samples, newer techniques were developed. Molecular typing with polymerase chain reaction (PCR) can detect much smaller DNA variations and is considerably more accurate than serology.[9] It has also led to a large increase in the number of known alleles at each locus. Molecular typing has since become the standard for HLA-DR typing.

IMMUNOLOGY OF CORNEAL TRANSPLANTATION

Corneal transplants represent a unique case immunologically. As corneal transplantation improved technically in the early 20th century, it was recognized that donor corneal tissue did not always opacify with time. Autografts were used if possible, as it was observed that they did well. Postoperative rejection was recognized as a distinct entity, differing from other types of graft failure, by Paufique and colleagues in 1948.[10] It was further described by Maumenee[11] and other authors. The phrase 'immune privilege' was introduced to describe the lower frequency and severity of corneal transplant rejection compared with other solid tissue transplants.[12] Multiple theories were proposed to explain this, but in 1948 Medawar provided evidence that it is primarily due to the lack of direct vascular supply,[13] and this has been supported by subsequent research. In addition, there are no lymphatic channels in the cornea. Combined, this delays both the afferent and the efferent arc of the immune response. It has also been proposed that anterior chamber-associated immune deviation (ACAID) plays a role in the low rate of rejection. However, this usually leads to suppression of delayed-type hypersensitivity, which does not appear to play a major role in experimental models of graft rejection.[14] More recently, there is evidence that the lack of antigen-presenting (Langerhans) cells in the central cornea may be an important reason for the low immunogenicity of the cornea.[15]

Despite these advantages, rejection does occur in a significant percentage of grafts. Rejection rates have declined from a high of 60% in early reports[16] to between 10 and 20% for most authors, but some of these are irreversible. The cornea expresses HLA antigens as well as minor histocompatibility antigens. HLA Class I antigens have been demonstrated in the corneal epithelium, stroma, and endothelium.[17] Class II antigens have been found in Langerhans cells within the epithelium, and many other corneal cells can be induced to express them in the setting of inflammation.[18] It is not known whether sensitization occurs in the recipient bed or the graft tissue, but Langerhans cells are a key component of the response. The activated T helper cells produce lymphokines that induce the formation of T lymphocytes targeted against the donor tissue. The mechanism of graft rejection must be extrapolated from experimental models and chronically rejected grafts. In corneal transplants, as in other transplants, cell-mediated immunity is thought to be most important.[19] However, humoral immunity probably plays a role in the tissue damage.

RESEARCH STUDIES ON HLA MATCHING

Tissue matching for keratoplasty was proposed on the basis of positive results for renal transplantation. The Collaborative Transplant Study was able to demonstrate increased survival for both new kidney grafts and regrafts. The improvement in transplant half-life was also significant.[20] If HLA matching of corneas were to decrease the incidence of rejection, it would be a goal worth pursuing. Rejection can lead to graft opacification and loss of vision, vascularization of the host bed, and sensitization of the host to foreign antigen. Irreversible rejection with loss of vision occurs in some patients, requiring repeat transplantation. If this could be prevented, the risk and cost of further surgery could be avoided in these patients.

HLA matching in corneal transplantation has been studied since the 1970s but remains controversial. Some early papers failed to show a benefit for HLA matching[21–23] but just as many demonstrated increased graft survival. Batchelor et al showed better graft survival with increasing number of HLA-A and HLA-B matches.[24] Ehlers and Kissmeyer-Nielsen[25] as well as Gibbs et al[26] showed that matching two or more HLA-A and HLA-B alleles led to a lower rate of graft loss due to rejection. Unfortunately, most early studies were retrospective, small and uncontrolled. Often these high-risk patients had very high failure rates due to other causes of graft failure, which tended to confound the results.

To address this, a number of small prospective studies followed, which again showed a benefit to HLA-A and HLA-B matching.[27–29] Boisjoly et al added HLA-DR matching to their protocol, which suggested a benefit to matching in high-risk transplants.[30] In 1985, a much larger, multicenter study, the Collaborative Cornea Transplantation Study (CCTS), was designed to clarify whether tissue typing is beneficial in high-risk keratoplasty. It was a double-blind prospective study, which investigated the role of crossmatching and HLA matching in graft survival.[31] In the Antigen Matching Study, patients received either a high antigen-matched (3–4 HLA-A or HLA-B or 2 HLA-DR), medium-matched, or unmatched cornea. At 3 years, the rates of graft rejection and survival were similar for both high and low HLA-A- and HLA-B-matched groups and for high and low HLA-DR-matched groups. In the crossmatching study, patients who had lymphocytotoxic antibodies on entering the study received either a negatively or a positively crossmatched cornea. After 2 years, both groups had a similar rate of graft rejection and survival.

The CCTS also investigated the importance of ABO blood group. The results showed similar rejection rates for ABO-compatible and ABO-incompatible corneas, but a higher failure rate from rejection for the incompatible group.

The results of the CCTS were not expected and were analyzed extensively. The most plausible explanation for the lack of effect is that the intense postoperative steroid regimen and follow-up schedule negated any benefit of tissue matching. There is a similar precedent in the solid organ transplant literature, where success can be heavily dependent on postoperative immunosuppression protocols. Recent evaluation of heart[32] and liver[33] transplants still does not support HLA matching, and thus allocation is often determined by need and tissue viability factors. It has also been suggested that studies carried out on homogeneous populations differ significantly from those done in the USA, where the ethnically diverse patients are not adequately matched by matching only major histocompatibility antigens. Minor histocompatibility antigens are expressed in the cornea[34] and can induce graft rejection experimentally even when major histocompatibility antigens are matched.[35] In addition, the HLA-DR testing in the CCTS was performed with serology, which has since been replaced by DNA techniques due to poor accuracy in cadaver blood samples. Later, repeat HLA typing of CCTS samples showed poor agreement with the original data.[36] A simulation by Volker-Dieben et al discusses the effect of errors in HLA typing on statistical results and demonstrates that even small errors in HLA typing can cause the effect of matching to be lost.[37]

Since the CCTS, the results of the crossmatch study have been upheld by Borderie et al. They followed 100 keratoplasties over 5 years. Twenty-eight percent of recipients had donor-specific anti-corneal stroma antibodies, but this did not affect rejection rate.[38] Roy et al were able to show a benefit to matching Lewis blood group antigens, but not ABO group antigens in unvascularized recipients.[39]

Not only high-risk patients have been shown to benefit from tissue matching. In 1990, Boisjoly et al were able to show a benefi-

cial effect of HLA matching (A, B, and DR) for low-risk patients.[40] In over 400 normal-risk patients controlled for other variables, Reinhard and coworkers were able to show that recipients matched for HLA-A, HLA-B, and HLA-DR had a rejection-free survival of 92% at 4 years versus 66%[41] for unmatched recipients. However, only combined matching was beneficial in this group.

The question of tissue typing is still a subject of study around the globe. Some of these studies were done in more localized areas in Europe and involved fewer surgeons, centralized testing, and more homogeneous populations. More recent studies also have the advantage of newer technology for tissue typing and matching. The majority have continued to show a benefit for HLA Class I matching. Volker-Dieben and colleagues performed a large study in the Netherlands. HLA Class I matching was performed prospectively and HLA-DR typing performed retrospectively on 1681 recipients done by one surgeon and typed serologically by one laboratory. Graft survival was significantly better in HLA-AB- and HLA-DR-matched grafts.[42] A small group of grafts was typed retrospectively using corneal tissue and DNA techniques by Bartels et al, and, again, HLA typing at the A, B, and DR loci improved graft survival.[43] Using DNA typing, Morita et al from Japan found a lower risk of rejection in grafts matched for HLA-A and HLA-DPB1[44] but not for HLA-B, HLA-DRB1, or HLA-DQB1.

The role of HLA Class II matching is less clear. A significant study, the Corneal Transplant Follow-up Study, examined data about 2777 grafts registered with the UK Transplant Support Service between July 1987 and June 1991. Vail and coworkers found that while there was a higher risk of rejection with a poor HLA Class I mismatch, those mismatched at HLA-DR had a lower rejection rate.[45] It is plausible that HLA Class II matching could lead to a higher risk of rejection because these molecules are necessary for antigen presentation. More efficient activity of antigen-presenting cells could possibly enhance the immune response in some cases.

CURRENT PRACTICE AND FUTURE TRENDS

In the USA, tissue typing is not routinely carried out for corneal grafts (personal communication, EBAA). The most significant reason is that the CCTS, which was carried out in North America, did not show a benefit to HLA typing. The time required to match donor and recipient is significant in a system that relies on liquid tissue preservation medium that lasts for 7–10 days; many surgeons are concerned about using tissue near the end of this period when it has suffered more potential oxidative damage or contamination. As well, the substantial increase in waiting time for the patient to find a tissue match is also a detriment in the USA, where waiting time for corneal transplantation is relatively short. However, as healthcare costs increase in the USA, services may be rationed and waiting times may increase. As well, the savings in repeat transplantation outweigh the cost of HLA typing. A few surgeons do wait for an HLA-matched donor for high-risk keratoplasty patients who have had multiple failed grafts. These are usually located through the Multiple Organ Retrieval Program.

In contrast, most eye banks in Europe use organ culture to sustain donor corneas.[46] This can maintain corneal viability for 4 weeks or more, which affords more time for tissue matching and locating the proper recipient. Approximately 50% of European eye banks perform tissue matching on a regular basis, for a small percentage of high-risk keratoplasty patients. Two German eye banks match all donors and recipients (personal communications, 2007). Although the wait for an HLA match can be significant, the lower number of failed grafts as a result of matching prevents these patients returning to the already long waiting list. Recently, more emphasis is being placed on the length of the wait and the ability to estimate it for patients.[47] This wait can approach years, and, for some patients with rare HLA types, a good match may never be found. The number of known alleles for each HLA locus has increased tremendously since the introduction of molecular tissue typing, increasing the difficulty of finding a good match. Recently, the concept of acceptable HLA mismatch has been introduced. Patients with certain HLA phenotypes mount stronger immune responses. Based on HLA phenotype, certain HLA mismatches may be well tolerated whereas others will be more immunogenic.[48] A computer algorithm, called HLAMatchmaker, examines the exposed portions of the HLA molecules and matches amino acid triplet sequences rather than entire HLA alleles. This allows matching without extensive serum screening.[49] When used to match a group of normal-risk keratoplasty patients, those with lower than 13 triplet-string mismatches (equivalent to 1 HLA allele mismatch) had a better graft survival than those with more. The advantage is a reduced waiting time for matched tissue, as more potential donors are identified with this method.[50]

SUMMARY

Graft rejection is now the leading cause of corneal transplant failure. Since tissue type plays an integral role in the immune response to allografts, tissue typing and matching would seem to be beneficial. However, studies have not shown this to be the case in all settings. As our limited understanding of the histocompatibility system grows, the reasons for this may become more clear. There is evidence that improved immunosuppression reduces the need for accurate tissue typing, which in turn may allow increased use of statistical tools to optimize acceptable mismatches. The rising cost of healthcare dictates that efficient allocation of resources be a priority in the future. Graft rejection leads to significant cost to society in terms of tissue preparation, surgical cost, and lost productivity for the patient. Minimizing this complication should be a priority for all transplant surgeons.

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35 Corneal trephines, cutting blocks and artificial anterior chambers

Thomas John

INTRODUCTION

This is a very exciting time in the world of human corneal replacement surgery. There appears to be a tsunamic trend that is gradually gaining in momentum and driving the surgical techniques of corneal transplant surgery from full-thickness penetrating keratoplasty (PKP) toward sutureless corneal transplantation, with all its advantages of an intact host cornea without the full-thickness corneal wound and the absence of surgically induced corneal astigmatism. Further, the continued improvements and refinements in the surgical techniques bring sutureless corneal transplantation to the front stage. The new terminology introduced by the author, namely, selective tissue corneal transplantation (STCT), is defined as the selective removal of the diseased portion of the patient's cornea and its replacement with anatomically similar healthy donor corneal tissue.[1–3] With STCT, for endothelial decompensation, posterior lamellar keratoplasty (PLK) is performed, namely, descemetorhexis with endokeratoplasty (DXEK), while in corneal stromal and/or epithelial diseases with healthy endothelium, requiring surgery, an anterior lamellar keratoplasty (ALK) is performed.[2]

Whether it is PKP, which is the current gold standard of corneal transplantation (at the time of writing this chapter), or the sutureless (no corneal sutures) corneal transplantation, the need for trephines, cutting blocks, and artificial anterior chambers (AACs) continues to exist. These instruments transcend the borders and are useful for both techniques of corneal transplantation. This chapter will describe these surgical instruments and their surgical applications.

CORNEAL TREPHINES

The word 'trephine' refers to a circular or cylindrical saw,[4] a surgical instrument for cutting out circular sections, as of corneal tissue or bone.[5] By definition the use of laser technology, such as the femtosecond laser, to perform PKP is not to be considered a trephine and will not be covered in this chapter.

Trephine blades are used on both the donor and the recipient corneal tissue. It is used for both PKP and PLK procedures such as DXEK. These trephines can be broadly divided into two groups, namely those with suction and the others without suction. Although, historically, there are several types and models of trephine blades developed during the evolutionary stages of corneal transplantation, this chapter will mainly focus on the current trephines that are more popular and widely used among the corneal surgeons worldwide.

SUCTIONLESS TREPHINE

Suctionless trephines consist of a cylindrical metal blade that is sharp on one end and blunt on the other end (Fig. 35.1). These blades are used between two fingers of the surgeon, usually the thumb and index finger, and rotated in clockwise–counterclockwise directions to cut the recipient corneal tissue. It can be used on both the donor and the recipient corneas. On the donor corneal tissue, such trephines are used to cut the cornea from the endothelial side using a guillotine-type corneal punch. However, these trephine blades can also be used to cut the donor corneal disc from the epithelial side using an AAC (see below under AAC). When cutting the donor cornea from the corneal surface, the use of the trephine blade is terminated upon entry into the AAC and the rest of the cut is carried out using corneal microscissors. It is important to continually protect the donor corneal endothelium during the preparation of the donor corneal disk.

Although these suctionless trephines can be successfully used even on irregular, scarred host corneas, where suction trephines may fail to establish good suction, it is essential to remain perpendicular to the central cornea during the trephination. Maintaining a perpendicular orientation by viewing through the central opening in the trephine blade, while cutting the recipient cornea, will help minimize faulty angulation of the trephine and thus decrease the chances of an irregular cut-edge of the recipient cornea. A similar approach should be taken when trephining the donor corneal tissue from the epithelial side using an AAC. However, when trephining the donor corneal tissue from the endothelial side, it is helpful to use a guillotine-type corneal punch to obtain a more uniform cut-edge in the donor corneal disk. The wound edges, the cut-margin of the donor and recipient corneas, and the differences in the diameter of the donor corneal disk and the recipient corneal opening created with the trephination process

Figure 35.1. Photograph displaying multiple, suctionless trephine blades of varying diameters. (Photograph courtesy of Katena Products, Inc., Denville, NJ.)

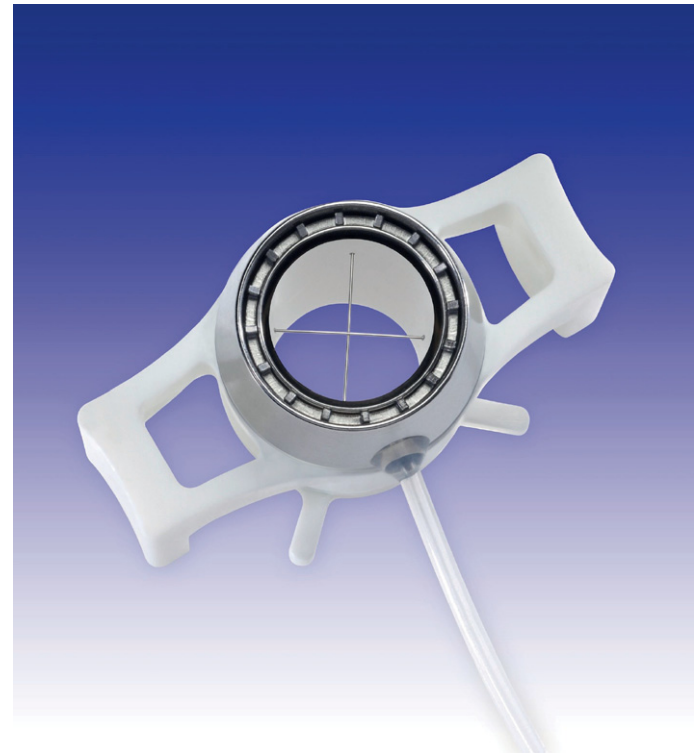

Figure 35.2. Barron radial vacuum trephine. (Photograph courtesy of Katena Products, Inc., Denville, NJ.)

will all play a role in the surgically induced postoperative corneal astigmatism.

These suctionless trephines can also be used with a handle. The handle is inserted into the blade opening from the end that is blunt, and the handle is tightened and then rotated to carry out the trephination. However, when a handle is used with these trephines, the central viewing of the cornea is no longer possible.

These disposable, individually packaged, sterile, donor trephine blades are distributed by the manufacturers for a single-time use. They are available in increments of either 0.25 or 0.5 mm, and the range of diameters will vary depending on the manufacturer.

SUCTION TREPHINES

Suction trephines are held in place by the vacuum and steadied by the surgeon's fingers during the trephination of the corneal tissue. Examples of suction trephines currently in use by corneal surgeons include the Barron radial vacuum trephine (Katena Products, Inc., Denville, NJ) (Fig. 35.2) and the Hanna trephine (Moria S.A., Antony, France) (Fig. 35.3).

CUTTING BLOCKS

Cutting blocks are used to prepare the donor corneal tissue for both PKP and DXEK. Similar to the trephines, the cutting blocks are also available with and without a vacuum device. The vacuum cutting blocks have the added advantage of holding the donor corneal tissue while the trephine makes the circular cut on the donor cornea. The cutting blocks are also available as a punch, where the trephine blade makes a vertical guillotine-type cut on the donor cornea. Figure 35.4 shows a Barron vacuum punch (Katena Products, Inc., Denville, NJ) that can be used on the donor corneal tissue.

Figure 35.3. Hanna trephine. (Courtesy of Moria SA, Antony, France.)

ARTIFICIAL ANTERIOR CHAMBERS

The creation of an AAC[6] is a major milestone in the field of corneal surgery. The pre-AAC era dealt with using whole globes or a corneoscleral button that was wrapped tightly around a glass orbital implant for the lamellar graft dissection.[7] These AACs are used for both LKP and PKP. For PKP, the AAC is used to trephine the donor

Figure 35.4. Barron vacuum punch. (Photograph courtesy of Katena Products, Inc., Denville, NJ.)

cornea from the epithelial side such that a similar corneal circular cut is made both on the donor and on the recipient cornea if the same-diameter trephine blade is used.

The AAC was first described by Ward and Nesburn in 1976.[6] They described a way to trephine the donor cornea from the anterior surface when the donor corneal-scleral tissue (DCST) was mounted on an instrument that formed a seal around the scleral rim of the excised donor cornea, allowing the endothelium to be supported physically by the liquid storage medium.[6] Hence, the AAC protected the donor endothelial cells from damage as if they were still in the intact globe.[6] Since the initial description, various modifications and improvements in the AAC have been made, giving ophthalmic surgeons the ability to trephine to any desired donor corneal depth.[7–21] For lamellar corneal surgery, AACs may be utilized for both manual and automated lamellar dissection of the donor cornea using a microkeratome and the Moria ALTK system (Moria SA, Antony, France).

This chapter describes the various AACs that are currently available in the USA at the time of this writing.

SURGICAL OBJECTIVE

Lamellar corneal surgery

The surgical objective is to obtain a lamellar corneal disc of the desired thickness and diameter, an even surface with a uniplanar cut to augment the donor–host corneal interface, ease of operation, and avoidance of disc perforation.

Full-thickness PKP

The AAC is used to prepare the donor corneal disk, with the trephine cut being made from the corneal surface and protecting the donor endothelium within the AAC.

TYPES OF AAC

1. Reusable AAC
2. Disposable AAC

Reusable AAC

Reusable AAC, as the name suggests, can be used repeatedly provided care is taken not to damage the AAC unit by improper handling.

Types:

1. Moria AAC (manual), and Moria ALTK system (automated with microkeratome)
2. Bausch & Lomb (B&L) AAC (manual)

Moria AAC

The Moria unit for lamellar surgical procedures is called the ALTK system. It utilizes the Evolution3 console (Moria, Inc.) that is fully compatible with all Moria microkeratomes including the LSK, M2, and the CB units. However, currently, Moria is distributing only the CB unit with the Moria ALTK system, and it works very well with this AAC. The Evolution3 console has built-in safety features and provides ease of use for the surgeon and operating room staff. It runs on wall current and has a battery back-up for uninterrupted use. It has two high pumps that provide a quick and stable vacuum for the procedure.

The Moria ALTK system can be used for ALK (extraocular procedure) or for deep lamellar endothelial keratoplasty (DLEK) or for DXEK (intraocular procedures).

The DCST can be used for ALK using, preferably, the automated technique for the best interface (with microkeratome use) or alternatively if the ALTK system is not available in the operating room; then, the Moria AAC can be used for manual dissection of the donor lamellar disc. When using the AAC with manual dissection, the partial-thickness anterior lamellar dissection of the donor cornea can be performed after partial trephination to the desired depth using the Moria AAC and the Hanna trephine (Moria, Inc.) that is set to the required depth in microns. The Hanna trephine (Moria, Inc.) seats well on the Moria AAC and allows for stable partial-thickness trephination of the donor cornea from the epithelial side. This is followed by manual lamellar dissection of the donor corneal tissue. The same trephine with the same blade can be used on the recipient cornea for the same-diameter disc resection as that of the donor lamellar disc. Unlike the Moria ALTK system, with the Moria AAC there is no control of the amount of corneal tissue that is exposed within the ring. Hence, the diameter of tissue resection is determined by the diameter of the blade in the Hanna trephine. The Barron vacuum trephine does not seat optimally on the Moria AAC and hence proper trephination cannot be carried out with the Barron trephine in a Moria AAC.

For automated donor corneal lamellar disc, the Moria ALTK system is used, which utilizes both the Evolution3 console and the microkeratome described above. The Moria ALTK system utilizes a different design for its AAC (Fig. 35.5). This AAC has the capability of raising or lowering the mounted donor corneoscleral button (Fig. 35.5), thus altering the final diameter of the resected donor tissue. The diameter can be approximated by using the applanating lenses. The diameter by measurement on the donor cornea does not necessarily match exactly with the final resected donor lamellar disc. Hence, it may be better to resect the donor tissue first before using the microkeratome on the recipient cornea.

The Moria ALTK system consists of an artificial chamber that has a central post on which the donor corneoscleral button is placed with the endothelial side down, after applying viscoelastic material on the receptacle and the metallic rim and injecting corneal storage media (Optisol GS, Bausch & Lomb Surgical, Irvine, CA) from the donor corneal vial. Next the encasing cylindrical unit with the

Figure 35.5. The Moria ALTK system utilizes an AAC that has the capability of raising or lowering the mounted donor corneoscleral button, thus altering the final diameter of the resected donor tissue. (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

Figure 35.6. Moria ALTK system showing sequential assembly for the Moria LSK microkeratome (left) and the Moria CB microkeratome (right). (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

central opening for the cornea is moved into place, such that the three posts descend into the corresponding slots in the base of the AAC unit, taking care to maintain the central position of the donor cornea. Turning this encasing unit in a clockwise fashion locks it in place, and the donor corneoscleral button is now firmly mounted on to this AAC, with uniform pressure being applied to 360° of the scleral rim. The surgeon then titrates the intraocular pressure by injecting additional fluid from the attached syringe into the chamber and locking the valve if the pressure is low, or alternatively aspirating fluid from the chamber if the intra-chamber pressure is too high. The pressure can be checked by finger palpation or by using a Barraquer tonometer as needed. Next, depending on whether an LSK or CB microkeratome is used with this unit (currently only CB heads are distributed by Moria for the ALTK system), the appropriate ring is chosen and screwed on to the unit. The amount of corneal tissue being exposed is then adjusted by turning the rings and raising or lowering the central post (Fig. 35.5). The applanation lenses provide an estimate of the diameter to be resected, ranging from 6 to 11 mm. Figure 35.6 is a composite showing the set-up for the LSK microkeratome on the left and for a CB unit on the right. The LSK microkeratome or a CB microkeratome (Fig. 35.7) can be used to complete the lamellar excision of the donor corneal disc.

In summary, the three steps to the use of Moria ALTK system are as follows (Fig. 35.8):

1. The donor cornea is sealed within the AAC, and the intra-chamber pressure is adjusted to the required level.
2. The surgeon selects the desired diameter of the cut.
3. Lastly, perform the donor corneal resection.

The ALTK's adjustability and versatility reduce the incidence of induced corneal astigmatism. In this system the high-speed, high-power turbine (30000 cuts/min) creates a smooth keratectomy for a seamless-edge margin. The single-piece construction of the microkeratome heads are precalibrated for various depths of cut (130–400 μm).

Moria AAC for PKP

The Moria AAC is used to mount the donor corneoscleral rim with viscoelastic protection of the donor corneal endothelium. The intra-

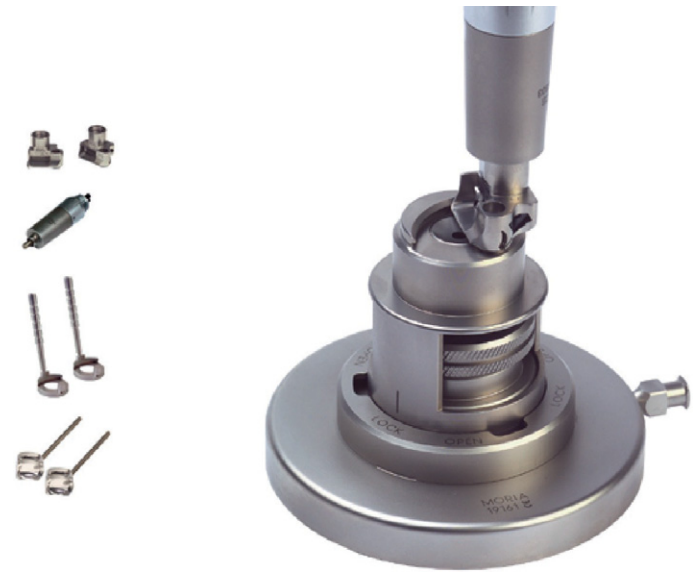

Figure 35.7. Moria CB microkeratome being used with the Moria ALTK system. (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

chamber pressure is increased and checked with digital palpation (see above). Next, the Hanna trephine (Moria, Inc.) is used to make the full-thickness cut of the donor corneal tissue from the epithelial side. The Hanna trephine (Moria, Inc.) seats well on the Moria AAC. The same trephine with the same blade can be used on the recipient cornea for the PKP procedure. Alternatively, different-diameter trephine blades can be used on the donor and recipient cornea depending on the surgeon's preference.

Bausch & Lomb AAC

The B&L AAC (Fig. 35.9) can be used for manual dissection of the donor lamellar corneal disc. It is not designed for use with a microkeratome. The B&L AAC can be used for both PLK and ALK.

1 2 3

Figure 35.8. The three steps to the use of Moria ALTK system: (1) the donor cornea is sealed within the AAC, and the intra-chamber pressure is adjusted to the required level; (2) surgeon selects the desired diameter of the cut; and (3) performs the donor corneal resection. (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

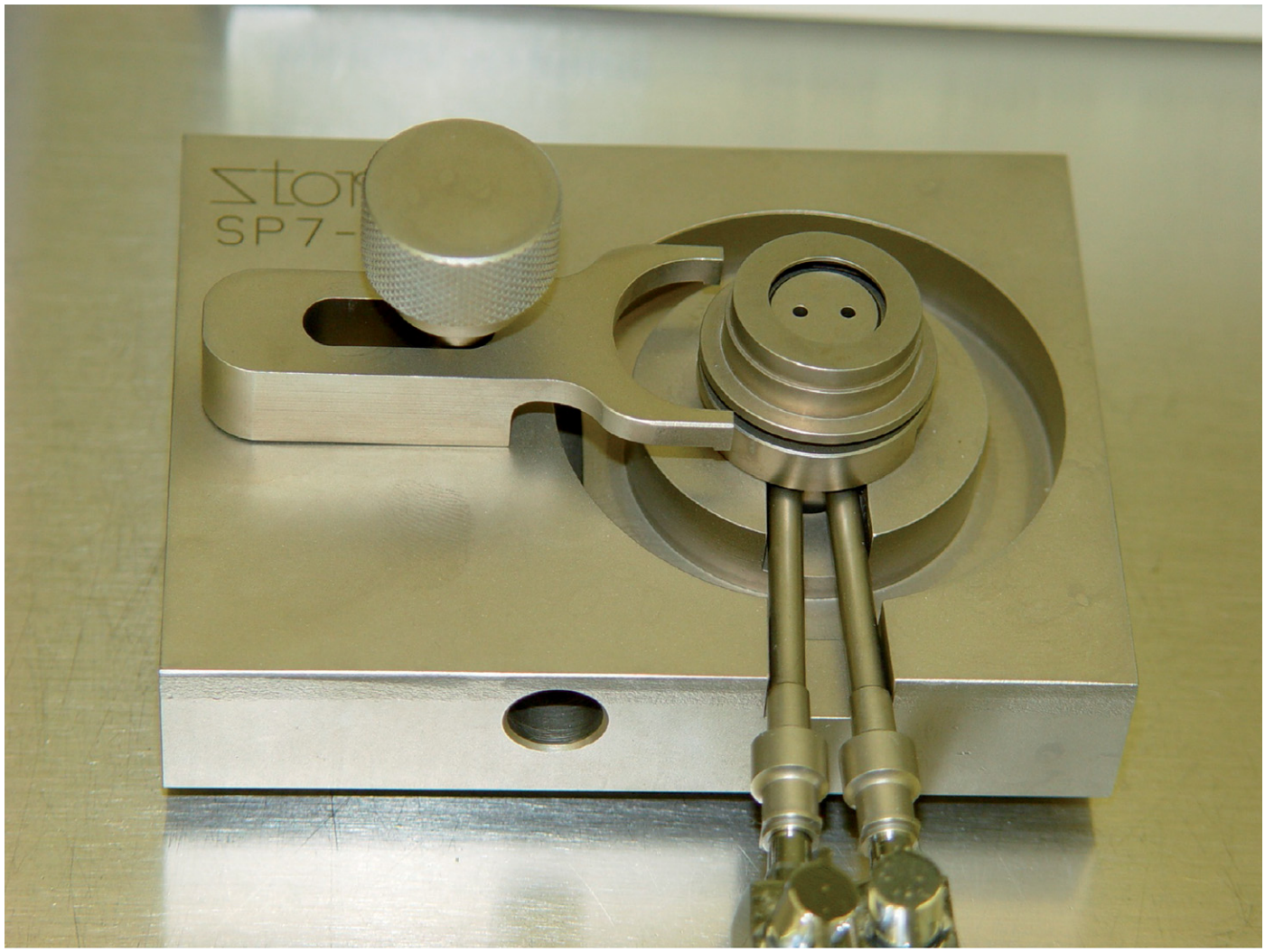

Figure 35.9. Bausch & Lomb AAC (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

It consists of a solid metallic rectangular base with a central post on which the donor corneoscleral rim is placed with the endothelial side down, after applying viscoelastic material and fluid from the donor corneal vial. The central post has two openings for egress of fluid used to alter the intra-chamber pressure. The metallic base has a circular space surrounding the central post for collecting the fluid that egresses out of the two openings in the central post. Two metallic channels are attached to the central post on one end and to metallic valves on the other end where corneal storage media (Optisol GS, Bausch & Lomb Surgical, Irvine, CA) can be attached. Once the donor corneoscleral rim is placed on the central post and the intra-chamber space is primed with corneal storage media (Optisol GS, Bausch & Lomb Surgical, Irvine, CA), the circular fixation ring is placed over the donor corneoscleral rim and the C-arm is moved forward such that it is above the flange of the fixation ring. Once the C-arm is in its extended position, the screw is tightened and this fixates the donor cornea within the B&L AAC. The intra-chamber pressure is optimized by injecting fluid from the attached syringe and closing the valve to maintain the chamber pressure. The unit is now ready for lamellar dissection or for full-thickness cut. Unlike the Moria AAC where the fixation pressure on the donor corneoscleral rim is applied 360° directly from the top, in the B&L AAC the C-arm applies pressure only on the proximal 180° of the flange of the fixation ring, which in turn transmits the pressure to the scleral rim.

A Barron radial vacuum trephine (Katena, Inc.) of the desired diameter is placed on the moistened, epithelial surface of the donor cornea, and suction is applied to fixate the trephine. Partial-thickness trephination to the desired corneal depth is followed by lamellar dissection of the donor cornea to obtain a lamellar donor corneal disc. With the full-thickness cut, once the chamber is entered the trephine is removed and the circular cut can be completed with corneal microscissors.

Disposable AAC

Barron disposable AAC (Katena, Inc., Denville, NJ, USA)

The Barron AAC (Figs 35.10 and 35.11) is sterile, disposable, and comprises three pieces: a base with tissue pedestal, a tissue retainer, and a locking ring. The base has two parts with silicone tubing: in-line pinch clamps and female luer-lock connectors. Either port may be used to inject or aspirate balanced salt solution (BSS) and solution from the donor corneal vial, namely, corneal storage media (Optisol GS, Bausch & Lomb Surgical, Irvine, CA) viscoelastic, or air.

This AAC is a companion to the disposable Barron radial vacuum trephine. This AAC allows for trephination from the epithelial side. It is designed to hold a donor cornea (14–18 mm) on a bed of viscoelastic. The bright blue color of the unit provides a high-contrast background to view the donor cornea.

USEFUL SURGICAL SUGGESTIONS AND AVOIDING COMPLICATIONS

1. The corneoscleral rim that is obtained from the eye bank should have adequate scleral rim 360° (see below) for proper housing and fixation within the AAC of any kind. If the scleral rim is short on any one side, this will lead to tissue slippage, loss of intra-chamber pressure, fluid leakage from the unit with inability to perform an adequate lamellar dissection of the donor cornea, and a suboptimal full-thickness cut of the donor cornea.

Figure 35.10. Barron disposable AAC (Katena, Inc.). (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

Figure 35.11. Barron disposable AAC (Katena, Inc.). (Reproduced with permission from Jaypee Brothers Medical Publishers (P) Ltd.)

2. If possible, the surgeon should have a back-up cornea available in the event of inadvertent damage to the first donor.
3. First dissect the donor cornea before operating on the recipient cornea.
4. If general anesthesia is used for surgery, the donor cornea can be prepared even before the patient is anesthetized. This will reduce the total time that the patient is under general anesthesia. Additionally, it will ascertain that a suitable lamellar corneal disc for LKP or full-thickness disc for PKP is ready for use even before the patient is anesthetized.
5. If there is tissue slippage and significant loss of intra-chamber pressure, then it may be advisable to abandon the lamellar dissection and use the back-up cornea. Dissecting without proper stabilization of the donor cornea within the AAC can result in multiplanar lamellar dissection, uneven interface, and, more importantly, possible perforation of the lamellar disc.
6. If using the Moria ALTK system, check the blade and the microkeratome head before use and lubricate with BSS to limit any mechanical epithelial damage to the donor cornea. However, in LKP procedures, the surgeon often will remove the epithelium prior to the microkeratome cut.
7. If using the Moria ALTK system, the surgeon should have prior experience with its use (e.g. LASIK surgery) or be trained and be familiar with its use for the donor cornea.
8. The Barron radial vacuum trephine usually does not fit on a Moria AAC, and hence use the appropriate matching units to facilitate and complete the procedure. A Hanna trephine will fit the Moria AAC and can be used routinely for this purpose.
9. The depth of cut on the Hanna trephine can be set in microns. With the Barron radial vacuum trephine, the depth is set by the number of quarter turns on its post.
10. For LKP, suitable lamellar dissection blades and knives should be available for the procedure.
11. In manual dissection, maintain a uniplanar lamellar dissection, by staying in the same plane of dissection until the disc is fully excised. This will help in attaining a better donor–host interface.
12. The intra-chamber pressure should always be checked before any trephination or lamellar dissection of the donor cornea. Adjust the intra-chamber pressure as needed by injecting or aspirating fluid via the attached syringe.
13. Maintain the intra-chamber pressure by closing the valve or applying the clamps provided with the unit.
14. The intra-chamber pressure may be checked digitally or with the Barraquer tonometer. Inadequate intra-chamber pressure will result in potential complications with the donor corneal tissue.

RESULTS AND CONCLUSIONS

We compared three AACs to determine the optimal sizes of DCST.[22] Twenty DCSTs were evaluated. The AACs tested were Bausch & Lomb, Moria AAC, and Moria ALTK. Twenty DCSTs were evaluated. The scleral skirt was measured from the limbus to the cut edge at four cardinal points (mean rim size 3.14 ± 0.61 mm; range 2.07–4.19). Donor corneoscelar tissues were mounted in the AACs; a target pressure of 65 mmHg was set using Barraquer tonometer. Tissue slippage with seal rupture before reaching the target pressure was considered a failure. The mean scleral rim sizes that maintained a seal and failed to maintain a seal, respectively, were 3.4 ± 0.7 mm (range 2.1–4.2) and 2.99 ± 0.51 mm (range 2.13–3.5). Using Optimal Data Analysis (ODA) techniques, we found that the DCST should have a minimal scleral skirt of 3.6 mm for successful use in an AAC for lamellar or PKP (epithelial approach).[22]

In summary, the currently available trephines, cutting blocks, and AACs greatly facilitate and improve the surgical outcomes for both full-thickness PKP procedures and lamellar grafts, namely both ALK and PLK surgeries. The introduction of the AACs into the field of corneal surgery has advanced the success rate of lamellar corneal surgery. Eye bank awareness and standardization of the required scleral rim size for lamellar corneal surgery are essential for successful outcome of the donor corneal tissue dissection and transplantation.

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36 Viscoelastic materials

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Author Past Editions Jeremy E. Levenson

Viscoelastic materials (now referred to as ophthalmic viscosurgical devices, OVDs) have added a new dimension to corneal surgery. Although originally introduced into anterior segment surgery as a means of protecting the corneal endothelium during intraocular lens implantation,[1] these materials have now found an ever-expanding role in corneal transplantation. They offer an exquisite tool for both coating and protecting surfaces, for separating tissue spaces, and for avoiding adhesions after surgery. These features make OVDs an indispensable tool in the modern corneal surgeon's armamentarium, because they assist in the surgeon's overall goal of maximizing the survival of donor graft endothelium.

PROPERTIES OF VISCOELASTICS

Fechner[2] listed the following necessary characteristics of suitable OVDs:

1. Inert and isosmotic, sterile, nonpyrogenic, and nonantigenic.
2. Free of corpuscular elements (clumps) and optically clear.
3. Viscous enough to satisfy clinical needs.
4. Hydrophilic and able to be diluted so that most of the material can be irrigated out of the eye at the end of the operation and that the remains can leave the anterior chamber through the natural outflow channels.

Viscosity measures the resistance to flow of a solution. OVDs have a high internal friction caused by molecular attraction. At rest the long molecular chains coil on themselves. These spheroidal-shaped molecules resist movement when a force is applied. The degree of viscosity is a function of concentration, molecular weight, and the size of the flexible coils of the polymer in solution. Viscosity is the property of a viscoelastic that allows it to maintain space against vitreous (posterior) pressure. The viscosity of OVDs also varies with the rate of movement of the material, known as shear rate. In most cases, the viscosity decreases as the shear rate increases. Some viscoelastics, such as chondroitin sulfate, maintain nearly the same viscosity despite having varying degrees of force applied to them.

Pseudoplasticity is the ability of an OVD to transform, when under pressure, from a semisolid (gel) to a liquid state. As a force is applied, the spheroidal molecules unfold and, as soon as the initial resistance (viscosity) is overcome, the OVD flows with increasing speed as the shear rate increases. The pseudoplasticity of OVDs, like sodium hyaluronate, allows them to be injected through relatively small cannulas.

Viscoelasticity is the ability of a solution, once deformed, to return to its original shape, that is for the unfolded molecules to assume their spheroidal shape. Molecules with longer chains have greater elasticity than shorter-chained molecules. *It is the interaction of viscosity, plasticity, and elasticity that make OVDs such useful surgical tools for tissue manipulation.*

Cohesiveness is a measure of the degree to which a material adheres together. Highly elastic OVDs with a high molecular weight and large intertwined molecules are more cohesive. Cohesiveness is advantageous when attempting to irrigate an OVD from the anterior chamber during keratoplasty. Solutions of smaller molecules, such as chondroitin sulfate, are less cohesive and are often referred to as dispersive viscoelastics. As a mass, they tend to fracture easily, making them difficult to irrigate from the eye. The preference of cohesive or dispersive properties depends on the particular surgical application.

Coatability, that is the ability of an OVD to coat a solid, is a function of its surface tension and the contact angle formed by a drop of the substance on a flat surface. Solutions with low surface tension (Viscoat, Alcon) coat intraocular structures and surgical instruments better than high-surface-tension substances (Healon, AMO). Coating of tissue can be protective so long as the coating substance is not toxic. A low surface tension, however, results in a tendency for bubbles to form and can make the OVD difficult to irrigate from the eye.

The properties described above affect the clinical behavior of an OVD in terms of endothelial protection, tendency to increase intraocular pressure, ease of removal, space maintenance, coating ability, and flow characteristics (Table 36.1).[3–5] An ideal OVD would maintain space well, protect the corneal endothelium, and remain in the eye during surgery, yet be easy to remove at the conclusion of surgery. No one material is universally ideal. The unique properties of each material make it more or less suitable for a particular surgical application.

Table 36.1 Clinical properties of some viscoelastics (best to worst: 4 to 1)

	NaH	NaH (High MW)	NaH/CDS	HMPC
Chamber maintenance	3	4	3	1
Intraocular lens/tissue coating	1	1	3	3
Ease of insertion	3	3	2	1
Ease of removal	4	3	1	2
Intraocular pressure rise	4	4	4	4
Endothelial protection	3	3	4	2
Optical clarity	4	4	3	4

NaH, sodium hyaluronate; CDS, chondroitin sulfate; HPMC, hydroxypropyl methylcellulose; MW, molecular weight.

From Arshinoff SA, Jafari M. New classification of ophthalmic viscosurgical devices (Table 4). J Cataract Refract Surg 2005 Nov; 31(11): 2167–2171.

OPHTHALMIC VISCOSURGICAL DEVICE COMPONENTS

SODIUM HYALURONATE

Sodium hyaluronate was introduced into ophthalmic surgery as a vitreous substitute.[6] It is a polysaccharide with a high molecular weight composed of repeating disaccharide units of sodium glucuronate and N-acetylglucosamine. Sodium hyaluronate is found ubiquitously throughout the body and is present in high concentrations in the vitreous humor. It is obtained from several sources, including the dermis of rooster combs, umbilical cords, and cultures of streptococci. Each commercial preparation has the same structure but may vary in molecular weight, concentration, and shear rate.

Sodium hyaluronate has the highest molecular weight—in excess of 1 million—of the available OVD molecules. It is relatively viscous and pseudoplastic, allowing for good space maintenance and ease of both injection and removal. It is nonantigenic, nontoxic, and relatively noninflammatory and does not interfere with wound healing. Some studies indicate that it may actually facilitate wound healing through the modulation of various inflammatory cells.[6] The disadvantages are its low coating ability, tendency to elevate intraocular pressure, need for refrigeration, and high drag force on removal, which can damage endothelium.[7,8] All the viscoelastic materials tend to elevate intraocular pressure. Sodium hyaluronate elevates intraocular pressure as much as other viscoelastic materials and by some accounts more so.[9,10] Sodium hyaluronate has gained widespread acceptance by corneal surgeons, as attested by the many published reports of its use in corneal transplantation.[11–16]

The first commercially available OVD was sodium hyaluronate (Healon, AMO), introduced in 1980; it remains the standard by which newer materials are judged. Currently, there are several formulations of sodium hyaluronate (Table 36.2).

CHONDROITIN SULFATE

Chondroitin sulfate is a polysaccharide found naturally in harder connective tissue of the body, such as cartilage and the cornea, where it is bound to a protein as a proteoglycan. Unlike sodium hyaluronate, it is sulfated, resulting in an extra negative charge. This negative charge allows chondroitin sulfate to coat the positively charged tissue, intraocular lenses and surgical instruments more effectively and thus decrease the electrostatic interaction between the implant, instruments and endothelium.[17,18] Its safety and efficacy have been documented for the human eye.[19] It has a molecular weight of approximately 22 500 Da and is extracted from shark fin cartilage.

Chondroitin sulfate 20% was initially used successfully in coating intraocular lenses but, because of its low viscosity, was poor in space maintenance.[18] Increasing the concentration to 50% resulted in a hyperosmotic solution that caused endothelial dehydration and damage.[18,20] A 1 : 3 mixture of 4% chondroitin sulfate derived from shark fin cartilage and 3% sodium hyaluronate (Viscoat, Alcon) seeks to combine the advantageous properties of each individual material.

METHYLCELLULOSE

Methylcellulose 1% was introduced into anterior segment surgery by Fechner[21] as a coating for intraocular lenses. A 2% solution was found to be more effective in space maintenance[2] and is available as Ocucoat (Bausch & Lomb). The main ingredient is a highly purified brand of hydroxypropyl methylcellulose (HPMC) derived from wood pulp. Although the human enzyme systems supposedly cannot metabolize methylcellulose, this does not appear to be of any clinical significance when used in small quantities in the eye. It has been used in many combination cataract extraction and lens implantation operations without deleterious results.[2,22,23] The use of methylcellulose in keratoplasty with equally satisfactory results has also been reported.[16]

Methylcellulose has a low surface tension and contact angle, which increases coating ability, but has a lack of elasticity, which makes it more 'viscoadherent' than viscoelastic. It has been shown not to damage the endothelium.[20] Other advantages are its availability, ability to be autoclaved, low cost and ability to be stored and shipped at room temperature. Disadvantages include poor pseudoplasticity requiring a large cannula, difficulty in removal, and poorer space maintenance.

AIR

Intraocular air has some of the features of an OVD and, before the introduction of sodium hyaluronate, air was used to move tissues and separate spaces within the anterior chamber. It can be sterilized

Table 36.2 Properties of some viscoelastic materials

Company/Product	Chemical (%)	Molecular Weight (d, avg)	Viscosity (Centipoises)	Osmolality (mOsm/L)	Source
Alcon					
Viscoat	3 NaH/4 CDS	600 000	40 000	325	BF
					SH
Provisc	1 NaH	2 400 000	39 000		BF
Discovisc	17 mg NaH/40 mg CDS	1 700 000	75 000	298	BF/SH
Allergan					
AMO IVISC	1 NaH	5 000 000	140 000	310	RC
AMO	1.4 NaH	5 000 000	430 000	310	RC
IVISC+					
AMO	3 NaH	500 000	40 000	310	RC
Vitrax					
Chiron					
Amvisc	1.2 NaH	2 000 000	40 000	318	RC
Amvisc Plus	1.6 NaH	2 000 000	55 000	340	RC
Mentor					
Optimize	3 NaH	700 000	50 000		
Pharmacia & Upjohn					
Healon	1 NaH	4 000 000	200 000	302	RC
Healon GV	1.4 NaH	5 000 000	2 000 000	310	RC
Healon 5	2.3% NaH	4 000 000	7 000 000	320	RC
Shah & Shah					
Visilon	2 HPMC		4100	285	WP
Storz					
Ocucoat	2 HPMC	86 000	4000	285	WP

NaH, sodium hyaluronate; CDS, chondroitin sulfate; HPMC, hydroxypropyl methylcellulose; BF, bacterial fermentation; SH, shark fin; RC, rooster combs; WP, wood pulp.

when it is passed through a millipore filter. However, air passes much more readily through a partially sutured wound and cannot maintain the anterior chamber against even moderate posterior pressure. It has been shown to have at least a slightly detrimental effect on the endothelium.[24–26] Although potential uses for air during corneal transplantation are discussed in this chapter, its use has been largely superseded by other OVDs.

COMMERCIAL VISCOELASTICS AND CLASSIFICATION

Each commercial preparation varies in (1) the chemical properties of molecular structure, molecular weight, concentration, pH, buffering agent, and osmolality and (2) the rheologic properties of viscosity, pseudoplasticity, viscoelasticity, and surface tension.[3,4,27] OVDs can be classified by material, viscosity, or cohesion dispersion. Previously there was a high correlation between viscosity and cohesiveness. With the introduction of several viscoadaptive OVDs, a new classification system that takes into account both viscosity and cohesion is necessary, as these two characteristics are not always correlated. Such a system of classification was proposed by Arshinoff and Jafari, which creates six classes of viscoelastics (see Table 36.3).[28]

HIGH-VISCOSITY COHESIVES

Healon (AMO) was the first commercially available viscoelastic, and its introduction revolutionized anterior segment surgery. Healon is a cohesive, high-molecular-weight and high-viscosity sodium hyaluronate derived primarily from rooster combs.

Provisc (Alcon) is a highly purified sodium hyaluronate obtained from fermentation and prepared to a specific target viscosity. It is equally useful and as safe as other sodium hyaluronate products derived from rooster comb dermis.[29]

Table 36.3 Viscoelastic materials

Zero-Shezr Viscosity Range	Cohesive OVDsCDI 30 (%asp/mm Hg)	Dispersive OVDsCDI 30 (%asp/mm Hg)
$7–18 \times 10^6$ (ten millions)	I. Viscoadaptives	I. Ultra high viscosity dispersives
	Healon5	None
	iVisc (MicroVisc) Phaco	
	BD MultiVisc	
	II. Higher viscosity cohesives	II. Higher viscosity dispersives
$1–5 \times 10^6$ (millions)	A. Super viscous cohesives	A. Super viscous dispersives
	Healon GV	None
	iVisc (MicroVisc, HyVisc) Plus	
	BD Visc	
$10^5–10^6$ (hundred thousands)	B. Viscous cohesives	B. Viscous dispersives
	Healon	DisCoVisc
	iVisc (MicroVisc, HyVisc)	
	Viscorneal Plus	
	Provisc	
	Opegan Hi	
	Viscorneal	
	Biolon Prime	
	Biolon	
	Amvisc Plus	
	Amvisc	
	Coese	
	Biocorneal	
	III. Lower viscosity cohesives	III. Lower viscosity dispersives
10^4-10^5 (ten thousands)	A. Medium viscosity cohesives	A. Medium viscosity dispersives
	None	Viscozt
		Biovisc
		Rayvisc
		Opelead
		Vitrax
		Cellugel
10^3-10^4 (thousands)	B. Very low viscosity cohesives	B. Very low viscosity dispersives
	None	Opegan
		OccuCoat, ICell, Ocuvis, Vislon, Hymecel, Adatocel, Celoftal (HPMCs)

CDIZ cohesion-dispersion index (% aspirated/mm Hg); OVDsZ ophthalmic viscosurgical devices.

Healon GV (AMO) has a high viscosity because of its higher concentration (1.4%) and higher molecular weight (5 million), making it more efficient at maintaining space.[30] However, the difficulty in removing this agent from the anterior chamber during keratoplasty combined with its high viscosity increases the possibility of serious postoperative glaucoma.[31] Consequently, it should probably be used during keratoplasty only under unusual circumstances.

Amvisc and Amvisc Plus (Bausch & Lomb Surgical) are both sodium hyaluronate products. Amvisc plus has a higher viscosity for improved space maintenance.

LOWER-VISCOSITY DISPERSIVES

Viscoat (Alcon) is a 1:3 mixture of 4% chondroitin sulfate derived from shark fin cartilage and 3% sodium hyaluronate that seeks to

combine the advantageous properties of each individual material. Viscoat is a dispersive viscoelastic that readily coats intraocular structures and remains in the eye.

Vitrax (AMO) is a low-molecular-weight, high concentration of sodium hyaluronate, dispersive OVD. AMO vitrax does not require refrigeration, which may be an advantage.

Ocucoat (Bausch & Lomb) is a preparation of 2% HPMC. Ocucoat has excellent coating ability and very little pseudoplasticity.

Cellugel (Alcon) is a preparation of 2% HPMC. Cellugel has a higher molecular weight than Ocucoat, which results in a greater viscosity and an improved ability to maintain space.

HIGH-VISCOSITY COHESIVE VISCOADAPTIVES

Healon 5 (AMO) is a viscoadaptive agent that seeks to combine cohesive and dispersive properties. It consists of 2.3% hyaluronic acid. It has a very high zero shear viscosity and pseudoplasticity. However, unlike other hyaluronic acid-based viscoelastics, under higher flow rates Healon 5 fractures, allowing it to remain in the eye during phacoemulsification. By using appropriate aspiration techniques, it can still be effectively removed from the eye.

HIGH-VISCOSITY DISPERSIVE VISCOADAPTIVES

Discovisc (Alcon) is a mixture of sodium hyaluronate and chondtroitin sulfate. This OVD has a high viscosity but also has dispersive qualities. This allows it to coat intraocular structures and remain in the eye during phacoemulsification, but it is easier to remove at the conclusion of the case with irrigation.[32]

OTHER VISCOELASTIC AGENTS

Other viscoelastic agents are available, and new agents are being tested or will be developed in the future. An understanding of their physical properties, as outlined above, will permit a good prediction as to their behavior during keratoplasty.

SURGICAL APPLICATIONS OF OPHTHALMIC VISCOSURGICAL DEVICES

An ideal OVD for penetrating keratoplasty would protect the new donor endothelium, maintain the space between the donor tissue and the rest of the anterior segment, and either be able to be left in place at the end of surgery without producing a rise in intraocular pressure or be easily irrigated from the eye.

Although the use of several OVDs in corneal transplant surgery has been reported in the literature, cohesive sodium hyaluronate-based agents such as Provisc or Healon appear to be the agents of choice for corneal transplantation. Their high viscosity provides good space maintenance, and there pseudoplasticity allows them to be introduced through a small cannula. Their cohesiveness aids in removal from the anterior chamber. The superior endothelial coating provided by other OVDs is not as great an advantage as with cataract surgery, because as soon as the donor corneal button is placed in the recipient bed, additional manipulation in the anterior chamber is minimal. However, one retrospective study by Miyata et al suggested that the placement of Viscoat on the corneal donor during and after trephination, along with the use of Healon to maintain the chamber intraoperatively, resulted in less endothelial cell loss than the use of Healon alone to coat the donor endothelium over a 12-month follow-up period.[33] The following potential application for these materials during surgery are based on published reports and on our experience and are summarized in Box 36.1.

BOX 36.1 APPLICATIONS OF VISCOELASTIC MATERIAL IN CORNEAL SURGERY

- Fill anterior chamber of whole donor globe to facilitate trephination
- Fill anterior chamber of recipient globe to prevent tissue damage and loss of aqueous fluid
- Firm whole eye before lamellar dissection
- Coat donor button to retard swelling
- Synechiolysis
- Tamponade hemorrhage
- Fill anterior chamber before placing donor cornea to protect endothelium, to prevent donor from falling into vitreous and to aid in suture placement
- Leave in eye after surgery to help avoid synechiae and prevent keratolenticular touch
- Aid in placement of posterior or anterior chamber intraocular lens
- Tamponade vitreous
- Assist in sealing corneal perforations by reforming anterior chamber before tissue adhesive is applied
- Protect epithelium while suturing

TREPHINATION AND PREPARATION OF DONOR CORNEAL BUTTON

Although it is much less common to trephine the donor button from a fresh, whole eye since the onset of widespread use of preservation media, an OVD can assist in the maneuver. Filling the anterior chamber with an OVD (less ideally, air) through a paracentesis opening allows more complete trephination without involving the underlying intraocular tissues. Alternatively, placing an OVD in the anterior chamber through the wound after initial trephination assists in the final cutting of the donor button with corneal scissors or a diamond knife.[16] In a like manner, an OVD can be used to firm up a whole eye before a lamellar corneal button is dissected.

Before the donor button is punched out from the endothelial surface of an excised cornea, an OVD used to coat the barrel of the trephine after the obturator has been retracted 4–5 mm from the cutting edge of the blade provides a protective cushion and a coating for the endothelium (Fig. 36.1).[34] If an OVD has not been used on the trephine, it can be placed directly on the donor button after punching and before placing balanced saline solution (Fig. 36.2). The viscoelastic material retards swelling of the button and thus assists in approximating tissues accurately during the suturing procedure, particularly if there has been a significant delay while the recipient eye is prepared.

TREPHINATION OF RECIPIENT EYE

After the initial trephination and just after the anterior chamber is entered, an OVD can be placed through the wound (Fig. 36.3). By helping to maintain the anterior chamber, the material also helps in making completion of the excision of the recipient button with scissors or a diamond blade easier and safer by offering some

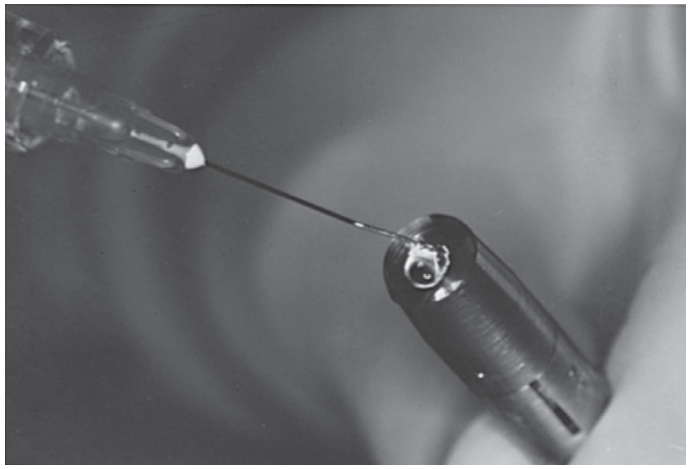

Figure 36.1. Viscoelastic material is placed in a barrel of trephine.

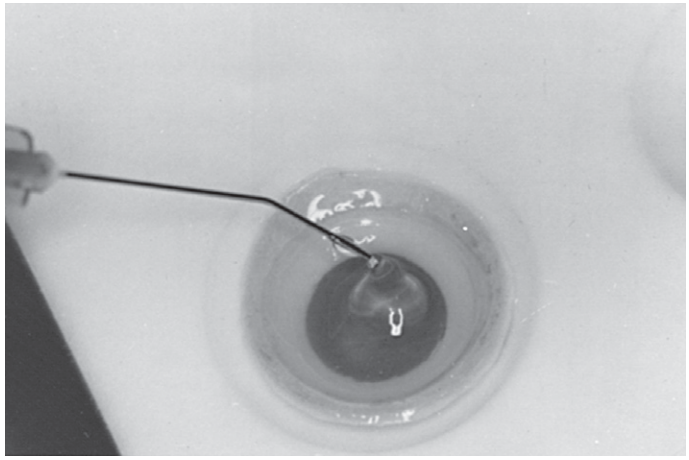

Figure 36.2. Donor button is protected by a cutting block with a layer of viscoelastic.

Figure 36.3. Viscoelastic is injected through a small anterior chamber entry point after initial trephination.

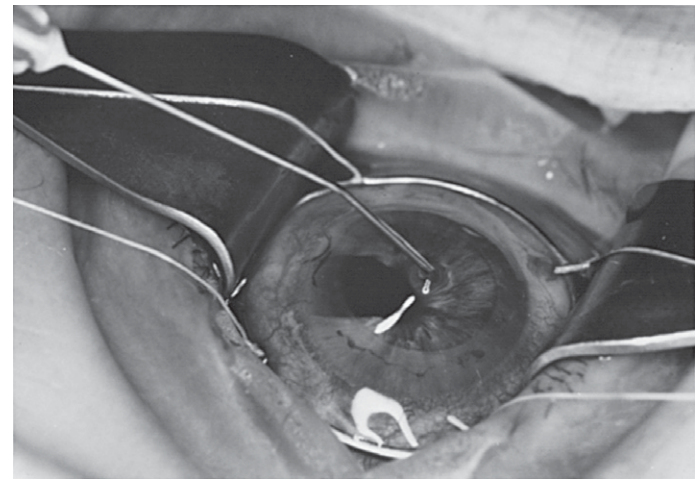

Figure 36.4. Anterior chamber is filled with viscoelastic before the placement of a donor button in the recipient bed.

protection to the underlying iris and lens. Such a technique is particularly helpful in cases such as keratoconus, where the floppy cornea tends to collapse posteriorly, distorting the wound.

Gruber et al[35] have recommended filling the entire anterior chamber through a paracentesis opening before trephination. With the chamber filled with an OVD, it is much safer to perform a through-and-through, 360° trephination with less risk of damaging the underlying tissues.

A relative disadvantage in placing an OVD in the anterior chamber at this stage of the procedure arises in an aphakic eye where it is not certain beforehand that a vitrectomy will be necessary. In general, formed vitreous can be distinguished from a viscoelastic by the tendency of the former to adhere to a cellulose sponge producing signs of traction, whereas the latter drops away. With an OVD present, a small prolapsing vitreal strand in the anterior chamber may be hidden, giving the false impression that a partial vitrectomy is not needed.

PHAKIC GRAFTS

Studies have shown that the manipulation of the donor button during suturing and the rubbing of the button against the iris diaphragm cause endothelial cell loss, especially in phakic grafts.[35,37] Filling the anterior chamber with an OVD before placement of the donor button in the recipient bed (Fig. 36.4) has a beneficial effect on postsurgical graft edema and therefore presumably on endothelial survival.[11–16] An OVD material tends to stabilize the donor button, making suturing easier and preventing contact with the iris.

PSEUDOPHAKIC GRAFTS

Corneal transplantation over a previously implanted intraocular lens, particularly of the anterior chamber variety, requires special precautions, because even transient contact between a polymethylmethacrylate lens and the posterior surface of the graft produces immediate damage to the endothelium because of the adherence of the cell membranes to the plastic.[38,39] In the past, the use of various transanterior chamber struts and stay sutures to hold the intraocular lens posteriorly and to allow an air bubble to be maintained between the lens and the endothelium of the graft proved helpful in these cases.[40] A much simpler and more effective method involves coating the lens with a layer of an OVD before placement of the donor button in the recipient bed (Fig. 36.5).[14–16]

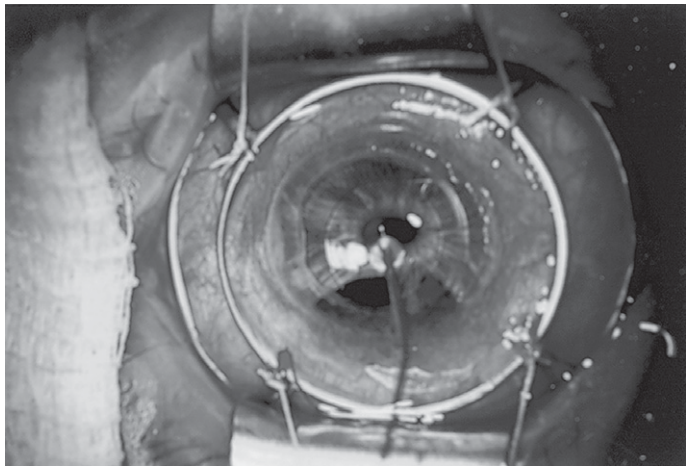

Figure 36.5. The anterior chamber of the intraocular lens is coated with viscoelastic before suturing in the donor button.

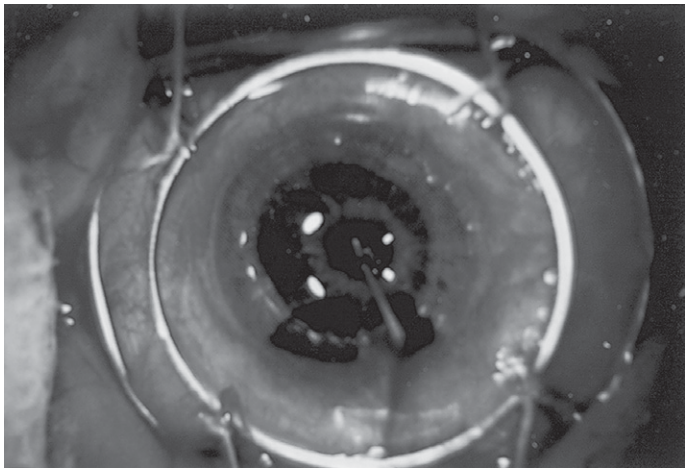

Figure 36.6. Viscoelastic is placed over the pupil and iridectomy sites.

Alpar[11,41] showed that the use of sodium hyaluronate in pseudophakic corneal transplants produced thinner grafts with less cell loss when compared with a control group in which air and balanced saline solution were used. In the author's experience, an OVD placed over an intraocular lens has allowed successful corneal transplantation even when the anterior chamber has collapsed because of posterior pressure, a situation that may otherwise require removal of the implant if an OVD had not been used.

TRIPLE PROCEDURES

Cataract extraction with intraocular lens implantation at the time of corneal transplantation can be facilitated by an OVD, both to protect the graft from the lens after it is in place and to assist with the lens implantation itself. As in a standard cataract operation, in-the-bag placement of an intraocular lens at the time of keratoplasty is greatly facilitated by use of a capsulorrhexis procedure to perform the anterior capsulotomy. If the opening cannot be made large enough to allow expression of the nucleus safely, an open sky emulsification can be performed. An OVD can be helpful in assisting in removal of the nuclear fragments after the nucleus has been fractured into smaller pieces. After removal of the nucleus and cortical cleanup, an OVD can be used to elevate the anterior capsular flaps, facilitating in-the-bag insertion of the posterior chamber lens. If sulcus fixation is considered desirable, or if too much posterior pressure causing anterior displacement of the posterior capsule makes sulcus fixation the safest alternative, an OVD can be used as a tool to separate the iris from the posterior capsule. This makes lens insertion easier and safer. Other uses in cataract extraction are reviewed elsewhere and include tamponading breaks in the posterior capsule before placing an intraocular lens, removal of intraocular lenses, preventing and repositioning iris prolapse, hydrodelineation of nucleus and cortex, keeping the pupil dilated, and repositioning or repairing a detachment of Descemet's membrane.[42,43]

APHAKIC KERATOPLASTY WITH AND WITHOUT SECONDARY LENS IMPLANTATION

In aphakic keratoplasty with an intact, posteriorly positioned vitreous face, placement of an OVD in the anterior chamber either before trephination through a paracentesis opening or just after trephination helps to reduce the chances of vitreous prolapse and the need for an anterior vitrectomy. When an anterior vitrectomy has been performed, an OVD can be placed over the pupil and iridectomy sites (Fig. 36.6). The weight and viscosity of the material act like a cork in a bottle, pushing back and keeping the vitreous posterior to the iris, thus preventing a stray strand of vitreous from prolapsing into the anterior chamber and possibly adhering to the wound during suturing of the graft. An air bubble in the anterior chamber can be used for the same purpose. However, care must be taken because accidentally trapping a large air bubble in the posterior chamber behind a constricted pupil can make adequate reformation of the anterior chamber impossible.

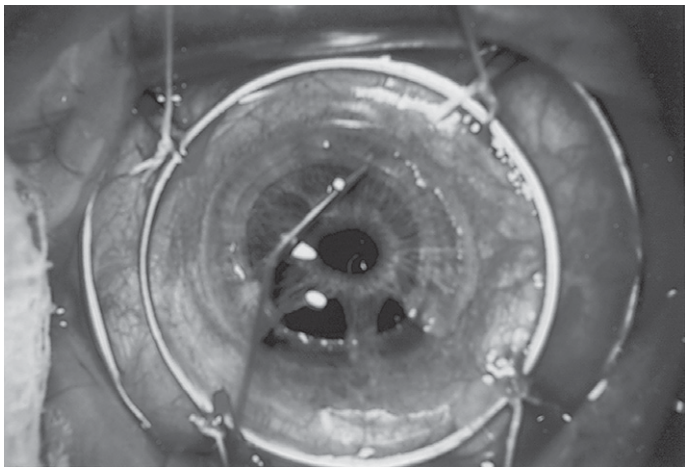

Figure 36.7. Viscoelastic is placed into the chamber angle.

If secondary lens implantation is performed, an OVD in the posterior chamber helps prevent vitreous prolapse and traction during the maneuvers necessary in the placement of an anterior chamber lens through the central trephine opening. A small amount of an OVD placed in the chamber angle assists in the proper placement of the 'feet' of the anterior chamber lens to prevent entrapment of the iris with consequent pupillary distortion (Fig. 36.7). Placing an OVD in the posterior chamber is also helpful before suturing in a posterior chamber lens to avoid vitreous traction and prolapse. A layer of the material should also be placed over the implant before placement and suturing of the donor button.

SPECIAL SITUATIONS

An OVD can be helpful in several special situations that may arise during the operative procedure. Bleeding may occur in such situations as lysing synechiae or removing an intraocular lens, particularly a flexible anterior chamber lens whose haptics have become enmeshed in fibrous adhesions. OVDs tend to localize blood in the angle and keep it from passing through the pupil into the vitreous in aphakic eyes. They also appear to tamponade oozing from capillaries, although it is not effective against more pronounced bleeding.[43,44] Such bleeding should be controlled before an OVD is introduced because the presence of blood mixed with sodium hyaluronate in the anterior chamber is prolonged.

When anterior synechiae to the wound are noted after suturing of the graft and filling of the anterior chamber with balanced saline solution, it is important to release these adhesions before surgery is finished because they may be progressive and lead to compromise of the angle. A fine cyclodialysis spatula or a cannula attached to a syringe filled with balanced saline solution or air can be used to sweep away the synechiae, but this is not without some risk to the endothelium of the graft and to the lens. A much more elegant method is to use an OVD introduced through the wound or through a paracentesis opening as a tool to push the iris away from the back of the cornea.

A situation that involves elements of both the aforementioned problems and where an OVD may make the difference between successful surgery and a disaster arises when a graft is placed on an inflamed eye. The irides of such eyes tend to ooze blood and, more significantly, fibrin, which causes the iris to adhere to the peripheral area of the cornea. If not released, these adhesions lead to difficulty in controlling glaucoma. An OVD can be used to separate the 'sticky' iris from the corneal rim and reform the angle before placement of the donor button in the recipient bed. Although not completely effective, a layer of such a material between the iris and the cornea in the immediate postoperative period may decrease the incidence of late-forming anterior synechiae. Usually, it is best to leave the material in the eye at the end of surgery and deal with any secondary glaucoma medically.

An OVD combined with a cyanoacrylate tissue adhesive can be used to restore the anterior chamber after a corneal perforation.[45] Introducing the OVD through a paracentesis tract, if possible, or directly through the wound allows repositioning of the iris, releasing of anterior synechiae, and the reformation of the anterior chamber. After removal of any excess material appearing about the surface of the cornea, which would interfere with adherence, the opening is sealed with a tissue adhesive. Maguen et al[46] used this technique to obtain normotensive eyes after perforation. A primary corneal transplant can then be safely performed, giving a better tectonic result and shorter visual rehabilitation. A lamellar graft at this point is another option.[47] Other uses of OVDs in anterior segment trauma have been reviewed[48] and include restoring the pressure and shape of the globe, evacuating hyphemas, removing foreign bodies, controlling bleeding, and manipulating tissues to restore anatomy.

OPHTHALMIC VISCOSURGICAL DEVICES IN LAMELLAR GRAFTS

Several papers have described the use of an OVD such as Healon to separate Descemet's membrane from the overlying stroma in deep anterior lamellar keratoplasty. The maintenance of the space overlying Descemet's membrane with an OVD reduces the risk and anterior chamber entry.[49,50] Prolonged detachment of Descemet's membrane resulting in need for penetrating keratoplasty has been described as a complication of this technique with OVD retention.[51] The use of air has also been described to separate Descemet's membrane from the overlying stroma.[52]

PREPARATION OF TISSUE WITH INTRALASE FOR POSTERIOR LAMELLAR KERATOPLASTY

An OVD can be used when preparing the donor disk in a hand dissected posterior lamellar keratoplasty (PLK). When preparing a donor button Descemet's stripping automated endothelial keratoplasty (DSAEK) with the femtosecond laser from the endothelial side, the use of an OVD to protect the endothelium from being damaged by the applanation process was described by Sikder and Snyder.[53] They utilized Ocucoat, Viscoat, and Healon in the study.

PROTECTION OF EPITHELIUM

Placement of an OVD on the donor button during suturing is very effective in protecting the epithelium (Fig. 36.8). Although it may make suture material more difficult to manipulate and may decrease visualization, it relieves the need for constant irrigation of the donor button with balanced saline solution, which can be traumatic to the epithelium.

GENERAL PRINCIPLES AND TECHNIQUES

Materials with less elasticity, such as Viscoat, require a larger cannula (such as = 25 gauge) for injection. These are generally supplied commercially with the material. Only syringes with a Luer-Lok system should be used to avoid the cannula being inadvertently propelled into the eye. The material should be flowing and all air bubbles expressed from the syringe before entry into the eye. A slow injection tends to avoid trapping air, fluid or debris. If an air bubble is desired, it should be placed anterior to the material. Intraocular medications should be instilled posterior to the viscoelastic material to minimize endothelial toxicity. Avoid over-

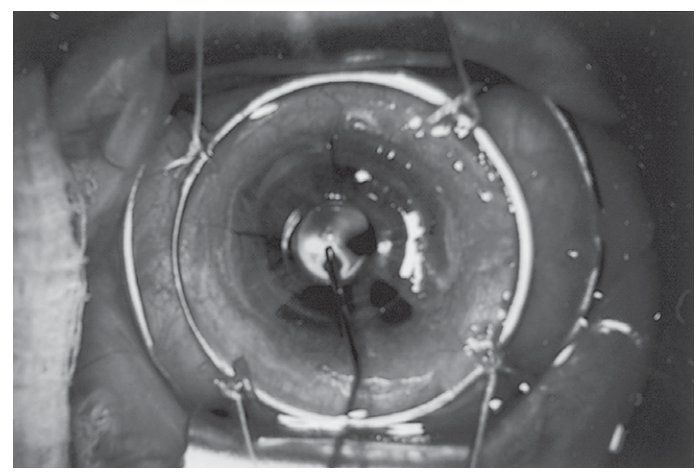

Figure 36.8. The donor epithelium is coated for protection during suturing.

filling the eye and placing the viscoelastic where it cannot be removed easily.

POSTOPERATIVE COMPLICATIONS AND REMOVAL OF OPHTHALMIC VISCOSURGICAL DEVICES

The major complication from the use of OVDs is the development of postoperative intraocular pressure rise.[14,15] The mechanism is complex and related to decreased outflow facility.[6] It may be modulated by individual variations in trabecular pore size and charge, by the amount of fibrin and inflammatory debris present that are pushed into the trabecular meshwork, or by simple mechanical blockage.[4]

Clinically, intraocular pressure peaks at 4–7 h and generally returns to preoperative levels by 24 h.[6,20,54] Alpar[11] reported an average pressure rise of 10 mmHg in a group of cases in which sodium hyaluronate had been used when compared with a control group. This amount of intraocular pressure elevation is fairly typical for most OVDs. The literature comparing the relative pressure elevating effect of all the available OVDs conflicts somewhat.[9,10] The variability of the reported results probably reflects differences in case selection, aggressiveness of agent removal, time interval at which the initial pressure measurement is taken, and other factors. The best consensus seems to be that despite their differences in physical properties, most of the available OVDs have a similar likelihood of causing elevated intraocular pressure.[55] In those studies where a difference has been reported, the higher molecular weight agents, such as Healon[56] and Healon GV,[57] have caused a greater and longer sustained pressure rise in some patients. In a study by Burke et al comparing IOP rise at 4, 10, 24, and 72 h in patients undergoing PKP with Healon or Viscoat, both groups had a similar rise in IOP at 4 and 10 h, with the Healon group continuing to have an IOP rise at 24 h, while the Viscoat group had returned to baseline. Both groups were at baseline after 72 h.[58]

The volume of an OVD left in the eye appears to be one of the factors that influence the postoperative pressure response. If 0.3 mL of sodium hyaluronate or less are used in the anterior chamber, the occurrence of postoperative pressure elevation is rare. As a general rule, the smallest amount of an OVD possible, consistent with clinical objectives, should be used. In a phakic patient for whom coating of the iris is the only objective, as little as 0.1 mL of OVD may be all that is needed. In addition, excessive sodium hyaluronate in the anterior chamber can give the false impression of a watertight wound closure with the result that, after surgery, an unappreciated wound leak is found.[59]

Another factor influencing the postoperative response of an eye to an OVD is the preoperative status of its outflow capacity. An eye with diminished outflow and pressure problems before surgery is very likely to have postoperative pressure problems even without the use of such a material. Such patients and all in whom an OVD is not removed, unless medically contraindicated, should be given an oral carbonic anhydrase inhibitor prophylactically in the immediate postoperative period and have their intraocular pressures closely monitored. This can blunt but may not eliminate the increased intraocular pressure.[60] Using topical hypotensives alone or in addition to a carbonic anhydrase inhibitor may provide equal or superior blunting of intraocular pressure elevation.[61]

Removal of OVDs at the end of surgery is technically more difficult after keratoplasty than after cataract surgery. However, in cases where relatively large amounts have been used, it is advisable to remove at least some of the material. Removing an OVD may only reduce or shorten the rise in intraocular pressure and not eliminate it.[22] The earlier in the suturing process this can be carried out, the easier it is to remove the material. In cases where there is relatively little posterior pressure, after the anterior chamber is stabilized with four to six cardinal sutures, a cannula with balanced saline solution placed deep into the chamber in each of the quadrants while the wound is slightly separated allows a good proportion of the material to be irrigated from the eye. Cohesives such as Healon and Provisc are more easily removed than other less cohesive materials such as Viscoat and Ocucoat, which require direct aspiration at the site of the OVD.[62] Placement of an air bubble in the anterior chamber before tying a running suture has been suggested as a way of pushing an OVD into the chamber angle from where it can be directly aspirated.[35] The air bubble can then be replaced with balanced saline solution. Maneuvers to remove an OVD should not be too vigorous, especially with the more viscous materials such as sodium hyaluronate, so as to avoid shear stress on the endothelium.[8]

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37 Sutures and suturing technique

David H. Haight

The goals of modern penetrating keratoplasty are to achieve a clear graft and to minimize postoperative refractive error. Attention to the details of adequate wound closure are also imperative to achieve the best possible wound strength to guard against postsurgical wound rupture and also to attempt to minimize postoperative epithelial down-growth syndrome.[1] The long-term survival of graft clarity is dependent on factors such as preoperative pathology, the quality and viability of donor tissue, and postoperative events, all of which are to some extent beyond the control of the surgeon. However, minimizing postoperative refractive error is within the scope of the surgeon's control, provided attention is paid to proper surgical technique and postoperative manipulation. Large ametropias, often including high degrees of astigmatism, have historically plagued otherwise successful transplant surgery. Contributing factors include distortions induced by fixation rings, mismatches between donor and recipient trephinations induced either by poor trephine technique or by recipient pathology (e.g. keratoconus), undetected astigmatism in the donor cornea, irregularities induced by suture technique or removal practices, and other postoperative events such as trauma, infection, or graft reaction. For example, de Toledo and colleagues have reported on a series of successful keratoplasties for keratoconus and found that, despite retention of clear grafts and an initial period of stabilization of astigmatism, there was a late increase in astigmatism from year 10 and beyond. The authors attributed this to progressive disease in the host cornea and noted a correlation, on slit-lamp biomicroscopy, of a peripheral crescent-shaped thinning at the graft–host junction.[2] The roles of trephination technique and suture removal are discussed in other chapters. The following pages address the role of suture materials, pattern of placement, and intra- and postoperative adjustment techniques in the quest for emmetropia.

SUTURE MATERIALS

Before the introduction of nylon in the 1970s, braided silk was commonly used for both cataract and keratoplasty closure. However, the rapid degradation and high tissue reactivity of silk makes it unacceptable for modern keratoplasty. It does, however, have an ancillary role as a material for securing scleral support rings. Absorbable sutures are also unsuitable because of their loss of tensile strength long before healing of the keratoplasty wound occurs. Tissue adhesives, although often used for temporary closure of perforating injury, or melts have not yet been adequately developed for long-term keratoplasty closure. Likewise, staples, which have become routine in other surgical closures, have thus far been unsuitable for keratoplasty. Hence, wound closure must be effected using nonabsorbable monofilament threads.

NYLON

Soon after its introduction to ophthalmic surgery, nylon became the suture of choice for keratoplasty closure. The monofilament thread passes easily through corneal stroma and incites very little tissue reaction. The tensile strength is maintained for more than 1 year, thus allowing ample time for wound healing to occur. Nylon does not absorb, but over a period of years it undergoes a gradual hydrolysis that causes late relaxation of tension and eventually breakage of threads. It is therefore not a permanent suture and, because of the possibility of broken strands precipitating an infection or graft reaction, it is preferable to remove nylon sutures at an appropriate postoperative interval.[3,4] Nylon possesses a moderate amount of elasticity, which must be considered when tensioning and tying the material. It can be stretched up to 25% of its original length.[5] Sutures that appear tight visually may actually have inadequate tension to appose the wound, whereas over-tightening can produce an excessively flat wound with a drum head configuration and possible 'cheesewiring' of the nylon through the stroma. The latter is a result of the postsurgical contraction of the overstretched nylon. Some degree of experience is needed to obtain a feel for the correct amount of tension required for wound closure, particularly when a continuous suture is used.

Notwithstanding the idiosyncrasies of elasticity and hydrolysis, nylon remains the most widely used material for keratoplasty closure. Most commonly, the 10-0 size is used because it offers the best compromise between ease of placement and tensile strength. The 9-0 nylon is generally too large for efficient placement and manipulation, whereas 11-0 nylon lacks the strength to effect wound closure adequately by itself. The 11-0 nylon is used in

combination with other sutures, particularly 10-0 nylon, where its role is to assist in long-term wound stability.

POLYPROPYLENE

Polypropylene is a nonabsorbable material that does not undergo the process of hydrolysis. It also possesses high tensile strength and elicits very little tissue reaction. It has been successfully used for years as a haptic material for intraocular lenses, and its introduction in the 10-0 size prompted an investigation of its use for keratoplasty. In practice, polypropylene has been difficult to handle; it is negatively impacted by elasticity and can stretch up to 38% of its original length.[5] It is also quite stiff and can easily become kinked. The problems of over- or under-tensioning, as seen with nylon, exist to a greater extent with polypropylene. Given enough patience and practice, results have been reported to be good because of the low reactivity, high tensile strength, and permanence of this thread.[6] However, it is rarely used alone in keratoplasty closure. Some surgeons do use it in a continuous pattern in combination with interrupted 10-0 nylon. In this application, the nylon sutures are selectively removed to modify postoperative astigmatism while the polypropylene maintains permanent wound support. Perhaps the most important roles of polypropylene in keratoplasty are adjunctive. Its permanence and biocompatibility make it the suture of choice for iris repair and the scleral or iris fixation of posterior chamber intraocular lenses in the absence of capsular support.[7] In the latter application, long transchamber needles, both curved and straight, are armed with 10-0 polypropylene (e.g. Alcon's SC-1, SC-5, and AUM-5/SC-5 combination and Ethicon's CIF-4, STC-6, and CTC-6/CS160-6 combination).

POLYESTER

The quest for a permanent and nonelastic suture for keratoplasty led to the development of monofilament 10-0 and 11-0 polyester threads. Braided polyester materials had been previously used with good success in strabismus and retinal surgery, and the introduction of monofilament threads over 15 years ago immediately attracted the attention of corneal surgeons. Monofilament polyester is truly nonabsorbable and is inelastic, with a stretch factor of only 1%.[5] In theory it could be placed with the desired wound tension, and as soon as the tension is set and stabilizes in the corneal tissue, the corneal curvature and refraction should be permanent for the life of the graft. Thus, intraoperative or early postoperative adjustment could control astigmatism and potentially eliminate the need for suture removal or secondary astigmatic procedures. Likewise, the permanence of the thread could decrease the number of postoperative visits and avoid the infection, infiltrates, graft rejections, and refractive shifts associated with late hydrolysis of nylon. These potential benefits have led to the exploration of polyester in both running and interrupted patterns either alone or in combination with nylon for both keratoplasty and wedge resections.

The experience with polyester has fallen short of expectations. Although the material has maintained its tensile strength in situ for up to 4 years, numerous problems have been reported. Because of its inelasticity, handling is difficult and intraoperative breakage is common for those accustomed to nylon. Additionally, the lack of elasticity demands precise tensioning; slightly loose sutures result in wound leaks, and tight sutures cause cheesewiring. Although these problems can be seen with nylon and polypropylene, their elasticity leaves a greater margin for error. Also, there have been numerous reports of sterile infiltrates surrounding the threads. In one series of 14 grafts using 11-0 Mersilene, Frucht-Perry[8] reported some scarring in all cases and excessive amounts in 11 of the 14. The cause of the reaction may be particulate material attracted to the polyester during surgery, and strict avoidance of foreign body adherence may decrease the incidence of such reactions.[9] Adjustment of a continuous polyester suture after surgery is also difficult with numerous complications, including loose or broken loops, neovascularization, and wound leaks.[10] The difficulties of handling and tissue complications have caused many surgeons to abandon the material altogether. In a recent study, Bartels and coworkers compared complication rates for a polyester suture (Mersilene) with nylon.[11] The study confirmed an increased rate of early complications with the Mersilene compared to nylon including infiltrates, scarring along the suture line, and cheesewiring. However, at 2 years and beyond, the complications associated with suture retention actually decreased with Mersilene as compared to nylon. Therefore, for those surgeons who prefer to leave sutures in place with the hope of avoiding late changes in refraction, polyester remains the suture of choice. Its use, however, demands careful intraoperative manipulation in a particle-free field with precise control of wound tension and little or no postoperative adjustment.

NEEDLES

To commence our discussion of needles in keratoplasty, a review of basic nomenclature is in order.

The *point* is the sharp, penetrating end of the needle.

The *swage* is the back end of the needle to which suture material is attached.

The *length* is the total distance from point to swage before bending.

The *chord* is the straight-line distance from point to swage after bending.

The *diameter* is the diameter of the original wire from which the needle is made. Historically, this has been measured in mils (1 mil = 0.001 inches). Recently, most manufacturers have adopted millimeters as the standard. Typical wire sizes for keratoplasty are 6 or 4 mil (0.15 and 0.12 mm).

The *curvature* is that portion of a circle to which the needle is bent (e.g. one-half of a circle = 180°).

Regular cutting refers to a needle whose cross section is a face-down triangle.

Reverse cutting refers to a needle whose cross section is an apex-down triangle.

A *spatulated* needle is one with a flattened, reverse cutting point, with the third cutting edge on the bottom removed (also known as *side cutting*).

A *tapered* needle is one with a circular cross section tapering evenly to a point.

Various needle and point configurations are illustrated in Figures 37.1–37.3. The needles of choice for keratoplasty are small in diameter, ranging from 0.15 to 0.10 mm. They should also be of the reverse-cutting, spatulated type. This flattened configuration easily splits the corneal lamellae and is minimally traumatic. Additionally, the small wire size permits easy passage and leaves smaller needle tracts that are less prone to leakage. Ethicon's CS design features a concave spatula configuration that displaces more mass in a horizontal direction and produces a wide, thinner tissue tract. Alcon's A and S series needles feature a deeper triangular cross section,

creating a more radially symmetric cross section to the tract, which is advantageous for suture burial. The N series apogee needles from Alcon offer an extremely flattened spatula that is perhaps best used when shallow bites are required, such as in lamellar procedures or in secondary suture placement when there is a need to avoid preexistent deeper sutures. Alcon's C series is an earlier spatulated design, which is generally less suited for keratoplasty because of its tendency to lose both sharpness and curvature on multiple passes. Both Ethicon CS and Alcon A needles work quite well for keratoplasty, and personal preference ultimately directs the choice of needle for each surgeon.

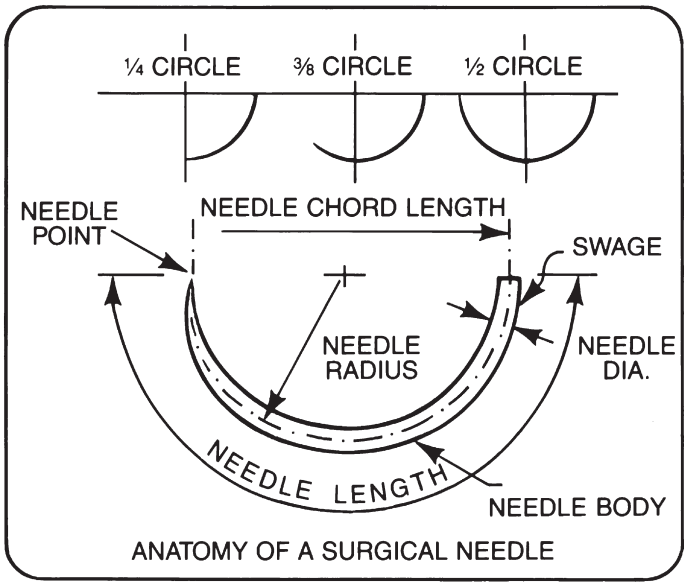


Figure 37.1. Anatomy of a surgical needle. (Courtesy of Ethicon, Inc, Somerville, NJ.)

FULL-CURVE NEEDLES

Full-curve needles (Fig. 37.4, *A*) are the most frequently used in ocular surgery. The bevel of the needle is circular with a curvature of 140–180°. The bite produced is somewhat long and shallow. The main advantage of this needle is the ease of handling and familiarity afforded by virtue of its use in most anterior segment procedures. This has made it a logical choice for both beginning and experienced corneal surgeons. It is the needle of choice for those who use an intentionally nonradial suture pattern. Efficient suture placement begins with proper placement of the needle in the needle holder. Ideally, the needle should be grasped in an area about one-quarter to no more than one-third of the distance from the swaged area to the point. Additionally, the needle should be grasped as close as feasible to the tip of the needle holder, while still maintaining an adequate grasp upon the needle. This positioning will allow the maximum length of the needle to be passed through both the donor and the recipient sides of the corneal tissue and will also prevent the tip of the needle holder from impinging on the corneal tissue during passage. This positioning is illustrated in Figure 37.5, *A*. If the needle is grasped close to the midpoint of the body and/or too far back in the jaws of the needle holder then there will be insufficient length to make an efficient pass across both sides of the wound, and, additionally, the end of the needle holder may physically interfere with the passage of the needle. This inappropriate positioning is illustrated in Figure 37.5, *B*. The needle is manipulated by first grasping the tissue with a toothed forceps and elevating it with a slight backward bend. The point of the needle is driven into the tissue immediately behind the forceps. Passage through the tissue is completed with either a pronation of the wrist if a standard curved needle holder is used or by twirling the fingers for a round-bodied, straight-jawed needle holder. Care must be taken, however, to achieve adequately deep bites, especially in the presence of edematous tissue where a bite that seems deep

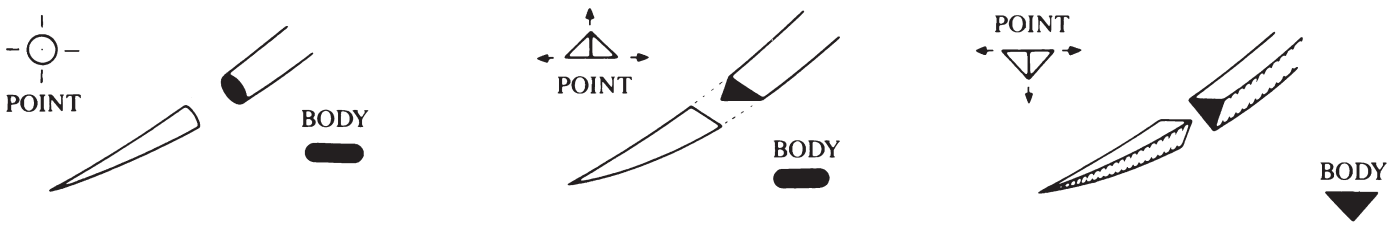


Figure 37.2. Geometry of stainless steel surgical needles. (Courtesy of Ethicon, Inc, Somerville, NJ.)

Figure 37.3. Concave spatula (CS) design of Ethicon surgical needle. (Courtesy of Ethicon, Inc, Somerville, NJ.)

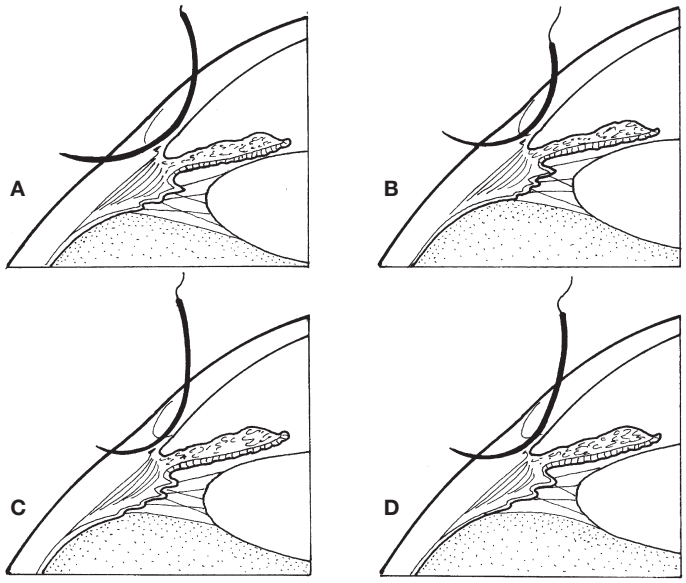


Figure 37.4. Examples of curvature of surgical needles. *A*, Full-curve needle. *B*, Minicurve needle. *C*, Bicurve needle. *D*, Compound curve needle. (Courtesy of Ethicon, Inc, Somerville, NJ.)

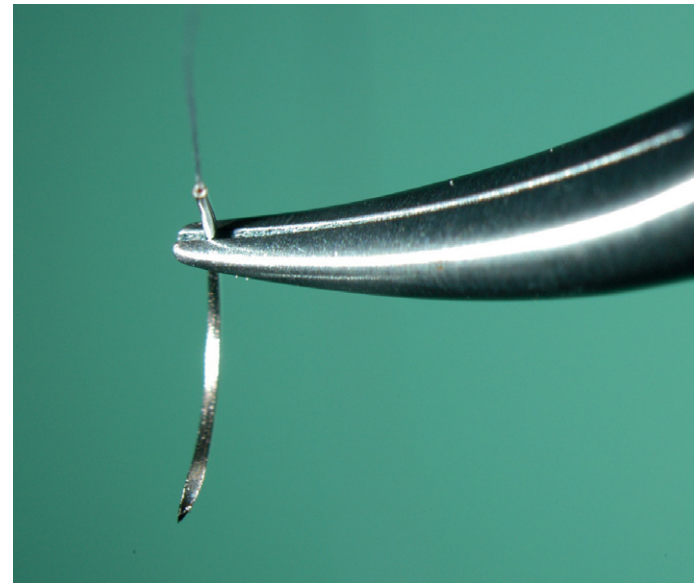
may actually penetrate only half thickness. Failure to take deep, equal bites on both sides of the wound can result in a lambda effect or a posterior wound gape (Fig. 37.6). This wound configuration can cause late slippage, excessive astigmatism, or even frank wound dehiscence. With the full-curve needle, deeper bites must be obtained at the expense of increasing the length of the tract. This in turn causes a reduction of the optical zone of the graft and allows for greater tissue compression, resulting in undesirable distortions when the suture is tensioned. The exact length and depth of the bite are a function of the curvature and length of the needle. Short, deep bites result from short chord lengths and larger curvatures, and longer, shallower bites are associated with large chord lengths and smaller curvatures. Examples of full-curve needles include Ethicon's CS-160-6, Alcon's AU-5, and US Surgical's SE-160-6.

MINICURVE

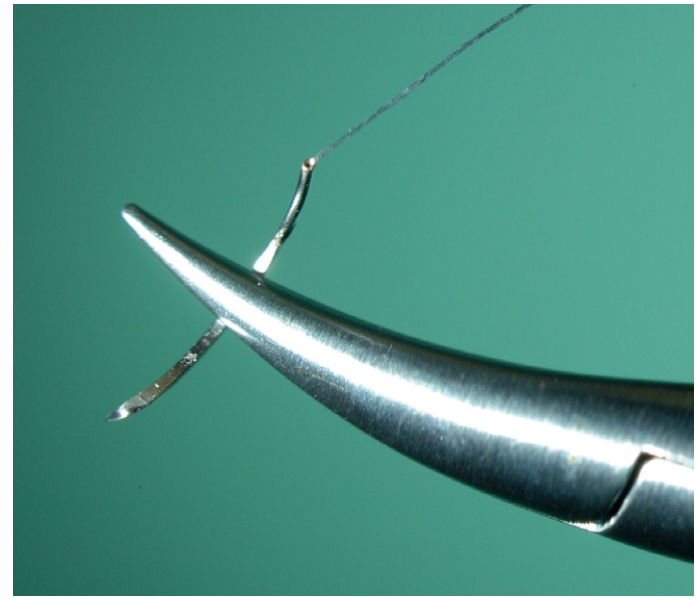
The minicurve needles (see Fig. 37.4, *B*) were developed to facilitate shorter and deeper bites. Like the full-curve needles, they have a continuous, nonchanging radius and their curvature is specified in degrees. However, their total length, chord length, and radius of curvature are all significantly smaller than their full-curve counterparts. This allows for a deeper bite while traversing less distance across the wound. In theory, this should afford better wound closure while avoiding excessively long suture bites. In practice, the small size and tight radii make handling difficult, and they are not commonly used as a primary needle for keratoplasty. They may, however, be useful when suture placement must take place in a confined space such as in repair of corneal lacerations, suturing of keratotomy incisions, or adding additional sutures to a previously sutured wound. Examples include Ethicon's CS-M-6 and Alcon's AUM-5.

BICURVE

The bicurve needle (Fig. 37.4, *C*) is another design aimed at achieving short, deep bites while improving on the handling of mini-curve



A



B

Figure 37.5. *A*, Shows the proper positioning of the needle in the jaws of the needle holder. *B*, Shows poor positioning of the needle in the jaws of the needle holder, with the needle being held too close to the mid-position of the body and too far from the tip of the jaws of the needle holder.

designs. Sometimes dubbed a 'fishhook,' this needle features an average to flat radius from the swage to the mid-portion and a steeper radius from the mid-portion to the point.

The initial flat portion toward the swage facilitates handling, and the tighter radius toward the tip permits rapid turnout after a deep bite is achieved. In practice, these needles allow for more efficient placement of deep or penetrating bites equidistant from both sides of the wound without requiring excessively long bites. The short bite avoids compromise of the optical zone, and the depth provides more secure closure. These needles are best driven with a short, straight-jawed needle holder. The technique involves grasping the flatter portion of the needle, placing the point perpendicular to the corneal surface, driving the needle down to the desired depth, and

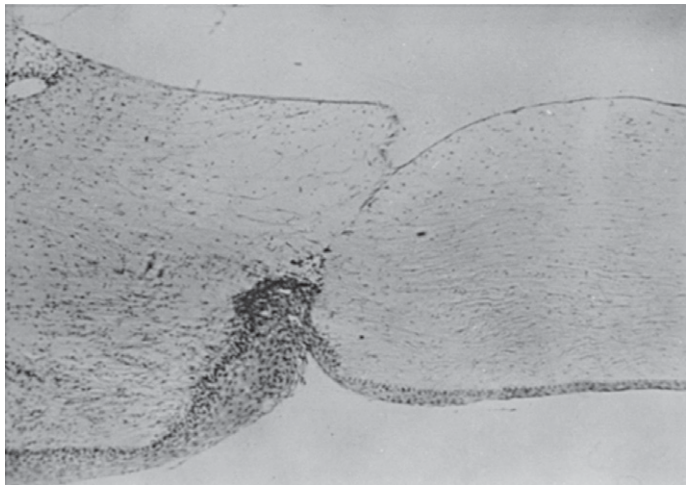


Figure 37.6. Posterior wound gape or lambda effect. Sutures placed at level of Descemet's membrane migrate anteriorly within a few days and therefore result in a posterior wound gape.

then rotating the point out by rolling the needle holder in the fingertips. This manipulation is substantially different from that used for full-curve needles but is easily learned and affords efficient, reproducible closures. Examples of the bicurve include Ethicon's CS-B-6 and Alcon's AU-6 and AU-8.

COMPOUND CURVE

The compound curve needle is a further development of the bicurve design. This needle has an initial flat curve changing to a steep curve at the midpoint and ending in a sharp, straight point. The straight point further facilitates initial entrance and penetration to desired depth, while rapid turnout is assured by the steep curve immediately behind the point. Examples of this needle are Ethicon's CS-C-6, TG6-C, and US Surgical's SE-CC-6. Needle geometry is shown in Figure 37.4, *D*.

Ultimately, the choice of needle is a matter of individual preference, but certain principles must be observed. Suture bites must be of sufficient depth to afford secure closure without posterior wound gape. This is especially important if secondary astigmatism surgery such as wedge resections or relaxing incisions are required. The effective 'optical zone' of the corneal graft with sutures in place is a diameter that lies somewhat inside the ring defined by the ends of the suture bites on the donor side. Excessively long bites shrink this optical zone and degrade the optics of the new cornea and thus the potential vision of the patient. Additionally, the tensioned long bites will have a more profound effect on tissue compression and can lead to excessive and unequal tension across the wound. Therefore, shorter and deeper bites are preferable; the author's preference is for full-thickness suturing with compound, curve-needle design. Selected needles for keratoplasty from Alcon, Ethicon, and US Surgical are listed in Table 37.1.

SUTURE TECHNIQUES

As soon as the surgeon has determined the appropriate needle and suture material to use, the strategy for wound closure must be selected. Each strategy has certain attendant features that must be properly managed both during and after surgery to achieve a successful result. Common goals for all techniques involve secure closure without over-ride or posterior wound gape, control of astigmatism and overall curvature, avoidance of tissue distortion that could decrease sutures in acuity, and prompt redressing of suture-related tissue complications.

The first decision that must be made regards the use of a ring for scleral support. At one time it was routine to use such a ring in all keratoplasty cases. The ring can maintain scleral rigidity and contour after excision of the recipient button, especially in aphakic eyes that have undergone vitrectomy. However, the ring itself can distort the scleral and corneal shape, thereby leading to irregular trephination and an ill-fitting donor button. If a ring is used, it should be sutured with care equal to the keratoplasty itself. Interrupted sutures are less desirable because of the greater risk of unequal tension, causing distortion. A running suture of six episcleral bites evenly spaced with even and light tensioning should be used. 8-0 or 9-0 silk armed with a circle spatulated needle is effective for this purpose. With the rising popularity of limbal-suction trephines such as the Krumeich and Hanna systems, which preclude the use of a scleral ring, many keratoplasties are now successfully performed without any scleral support. Thus far, there are no comparative studies that demonstrate deleterious effects attributable to the absence of scleral support, and the use of a ring in keratoplasty may be regarded as an optional step.

Trephination technique is another factor that impacts wound closure. This subject is discussed in Chapter 16, but it should be mentioned here that the type of trephine used and the graft–host disparity selected bear on wound closure. Most manual trephines require some oversizing of the donor to obtain a good fit and postoperative keratometry in the average range.[12] Limbal suction trephines such as the Hanna or Krumeich generally use the same size for donor and recipient to achieve emmetropia.[13] Special situations such as keratoconus also call for same sizing or undersizing the donor to modulate postoperative keratometry.[14] Conversely, in cases of a shallow anterior chamber, oversizing may be appropriate. The amount of tensioning required varies according to these factors; in general, same- or smaller-size buttons need tighter closure than oversize buttons. In this respect, one size (tension) definitely does not fit all. Appropriate tension for an oversize button may lead to wound leaks in a same or undersize situation, whereas sufficient tension to close a same-size keratoplasty can lead to excessive wound compression in oversize buttons. Thus, care must be taken to learn the specific cutting characteristics of each trephine. Another area in which trephination may affect the corneal power and regularity of post-keratoplasty astigmatism has been pointed out by Seitz and coworkers. Their study included 489 eyes with sutures in and 308 eyes with all sutures out, for a variety of pathology, including Fuchs and stromal dystrophies and aphakic and pseudophakic bullous keratopathy. The study included grafts done with diameters of 8.0, 7.5, and 7.0 mm with a graft oversize of 0.1 mm with trephinations performed by a Meditec Excimer Laser. They concluded that small graft diameters resulted in overall flatter K-readings and also greater corneal irregularity as evidenced by corneal topography, whereas larger grafts tended to have steeper overall keratometry and lower degrees of topographic irregularity. However, there was no significant difference with respect to the overall magnitude of the astigmatism among the different graft sizes.[15]

INITIAL GRAFT PLACEMENT AND SUTURING

The process of wound closure begins with the placement of the donor button over the recipient bed. The ideal of a perfectly round

Table 37.1 Selected sutures for keratoplasty

Manufacturer	Needle	Curvature	Chord (mm)	Length (mm)	Wire (mm)	Radius (mm)	Suture
Alcon	AU-5	180°	4.01	5.51	0.15	1.98	10-0 Nylon
							10-0 Polypropylene
	AU-8	Bicurve	3.71	4.83	0.15	1.51/2.79	10-0 Nylon
	AUM-5	180°	3.00	4.22	0.15	1.52	10-0 Nylon
	SU-5	180°	4.01	5.51	0.15	1.98	10-0 Nylon
							10-0 Polyester
	AU-18	Bicurve	3.71	4.83	0.10	1.52/2.79	11-0 Polyester
							10-0 Polyester
Ethicon	CS160-6	160°	3.91	5.33	0.15	2.00	10-0 Nylon
							11-0 Nylon
							10-0 Mersilene
							11-0 Mersilene
							10-0 Prolene
	CS-M-6	160°	3.00	4.27	0.15	1.52	10-0 Nylon
	CS-B-6	Bicurve	NA	4.83	0.15	1.39/2.54	10-0 Nylon
							10-0 Mersilene
							11-0 Mersilene
	CS-C-6	Compound curve	NA	4.83	0.15	1.39/2.54	10-0 Nylon[a]
	TG6-C	Compound curve	NA	4.83	0.15	1.40/2.54	10-0 Nylon
	TG6-S	Bicurve	NA	4.83	0.15	1.39/2.54	10-0 Nylon
US surgical	SE-160-6	160°	3.96	6.00	0.15	2.02	10-0 Nylon
							10-0 Polypropylene
							10-0 Polyester
	SE-CC-6	Compound curve	3.71	5.00	0.15	1.5/2.8	10-0 Nylon

[a]Available only in 6″ length.

NA, not applicable.

button and bed are seldom realized. Therefore, it is important to place the button so as to optimize the fit. The use of a surgical keratometer to identify the placement that maximizes sphericity has been shown to lead to lower sutures-out astigmatism.[16] To effect this, the donor button is rotated in the recipient bed while simultaneously regarding tissue apposition and keratometric reflex. The end point for rotation of the button should be the position that yields the most spherical reflex from the keratometer (Fig. 37.7, *A*). Suturing should begin with the cornea in this position. The sutures should be passed using a small-toothed (0.12 mm) or cupped forceps to hold the button securely. The needle should be driven directly behind the fixation point, with care taken to achieve deep or penetrating bites. The exact entry point varies with the geometry of the needle but will be approximately 0.75 mm from the wound edge. The spacing should be equal on both the donor and the recipient sides unless contraindicated by local tissue factors.

Suturing of the cornea begins with placement of interrupted cardinal stitches. The first pass should be made with care not to displace the position of the cornea. A double fixation forceps such as the Polack or Bores will hold the button securely while preventing any rotation (see Fig. 37.7, *A*). The needle should be driven directly behind the fixation point. The first suture is then tensioned and tied. The location of the first cardinal is not critical, although most surgeons begin at the 12 o'clock position. Placement of the second cardinal is critical because it in effect divides the cornea into two halves that must be equidistant from the recipient bed. The bite must be 180° away from the first, and during placement the alignment of the button to the bed must be observed (Fig. 37.7, *B* and *C*). If an oversize button is used, the overlap must be equal on both sides; conversely, for an undersized button, the space or gap must be equal. The second suture should be tied with the same tension as the first cardinal. Next, additional cardinals are added, as a minimum of two additional bites are made, each 90° away from the first two, yielding four total sutures. These sutures stabilize the button, but there can be large gaps between them that make accurate closure difficult. Therefore, six or eight cardinals are preferable, and they should be spaced evenly and tensioned equally. The cornea is now ready for definitive closure.

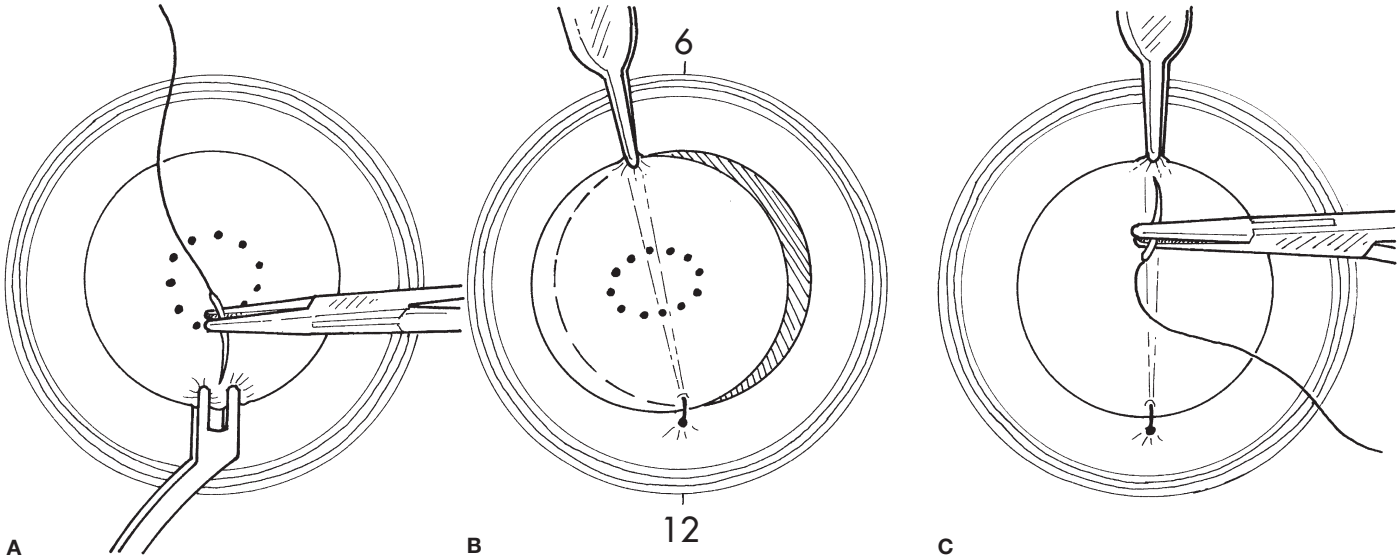


Figure 37.7. *A*, The cornea has been rotated to achieve a 'best fit,' and the first cardinal will be placed. The cornea is securely held with a double fixation forceps and the needle is driven immediately behind the forceps. *B*, The cornea is being aligned for the second cardinal. The button must be manipulated to divide the tissue precisely on both sides. *C*, The button is properly aligned, and the second suture bite is driven behind the fixation forceps.

THE SLIP KNOT

Precise control of wound tension is a key element in successful keratoplasty, and the usefulness of a slip knot for this purpose has previously been reported.[17] The slip knot offers several advantages, including exquisite control of suture tension, the ability to hold that tension temporarily while other adjustments are made followed by re-tensioning, and smaller knot size that facilitates burial. The slip knot is also helpful in ancillary procedures including placement of additional sutures for astigmatism control, relaxing incisions with compression sutures, and wedge resections. Therefore, a brief description of the tie may prove useful. There are several versions of the tie, and it is beyond the scope of this chapter to describe them all. Thus, the discussion is limited to the single slip knot with parallel sutures method (Fig. 37.8).

This knot is begun by placing the short and long sutures parallel to each other on the tissue surface (Fig. 37.8, *A*). The surgeon may wish to fixate the short end with the straight forceps held in the nondominant hand. The curved forceps are first placed over the two parallel sutures. These forceps are then sequentially brought under (Fig. 37.8, *B*) and over (Fig. 37.8, *C*) both sutures. The straight forceps are used to place the short suture into the grasp of the curved forceps (Fig. 37.8, *D*). The curved forceps are brought through the loops formed by the parallel sutures (Fig. 37.8, *E*). Again, this maneuver may be facilitated by fixing the long suture with the straight forceps. The loop is closed by pulling on the long end. This step should be performed before tensioning the suture to allow proper sliding of the suture and to minimize knot size. The suture can be tightened by pulling on the long end and loosened by pulling on the short end (Fig. 37.8, *F* and *G*). This adjustment may be performed multiple times if needed to achieve the desired suture tension. The knot is then secured with two single throws.

KNOT BURIAL

Knots of permanent sutures should always be buried and should be left in the donor button. All suture materials can incite some tissue reaction, and knots, because of their bulk, do so to a greater extent. Burying knots on the recipient side places them closer to limbal vessels and increases the risk of vascularization at the site with the attendant problems of graft rejection or suture abscess. Burial of interrupted sutures is accomplished by grasping the suture 1 mm behind the knot, elevating slightly, and moving the loop briskly in a radial direction toward the donor. If resistance is met, a toothed forceps can apply countertraction to the donor edge. A small amount of viscoelastic may also help lubricate passage of the knot. The use of the slip knot also aids burial because of its smaller size. The knot should be left in anterior stroma to facilitate later removal. The technique for burial of the knot of a continuous suture is slightly different. First, enough slack must be generated behind the knot to permit advancement into the cornea. A forceps is used to lift and slightly advance loops beginning about four to five loops behind the knot. The slack should be carried to the loop just beyond the burial site, so there is no tension immediately on either side of knot. The suture loop is then grasped with tying forceps on both sides of the knot and advanced into the cornea with a simultaneous push and pull motion. Because in this pattern the suture may not be crossing the cornea radially, it is helpful to lift and straighten the loop just behind the knot to prevent it from having to turn as it enters the cornea. This maneuver keeps the forces acting along the direction of travel and decreases the chance of suture breakage.

SUTURE PATTERNS

The preceding sections described the basics of anchoring the donor button in place with cardinal and mid-cardinal interrupted sutures. As soon as this is carried out, the anterior chamber should be reformed with saline or viscoelastic, with the latter used particularly if an intraocular lens is present to protect against inadvertent endothelial damage. A small amount of viscoelastic placed on the surface of the button helps preserve the epithelium to improve a keratometric reflex for later suture adjustment. Wound closure is then completed with one of a number of patterns. The following sections present some of the pros and cons of each technique.

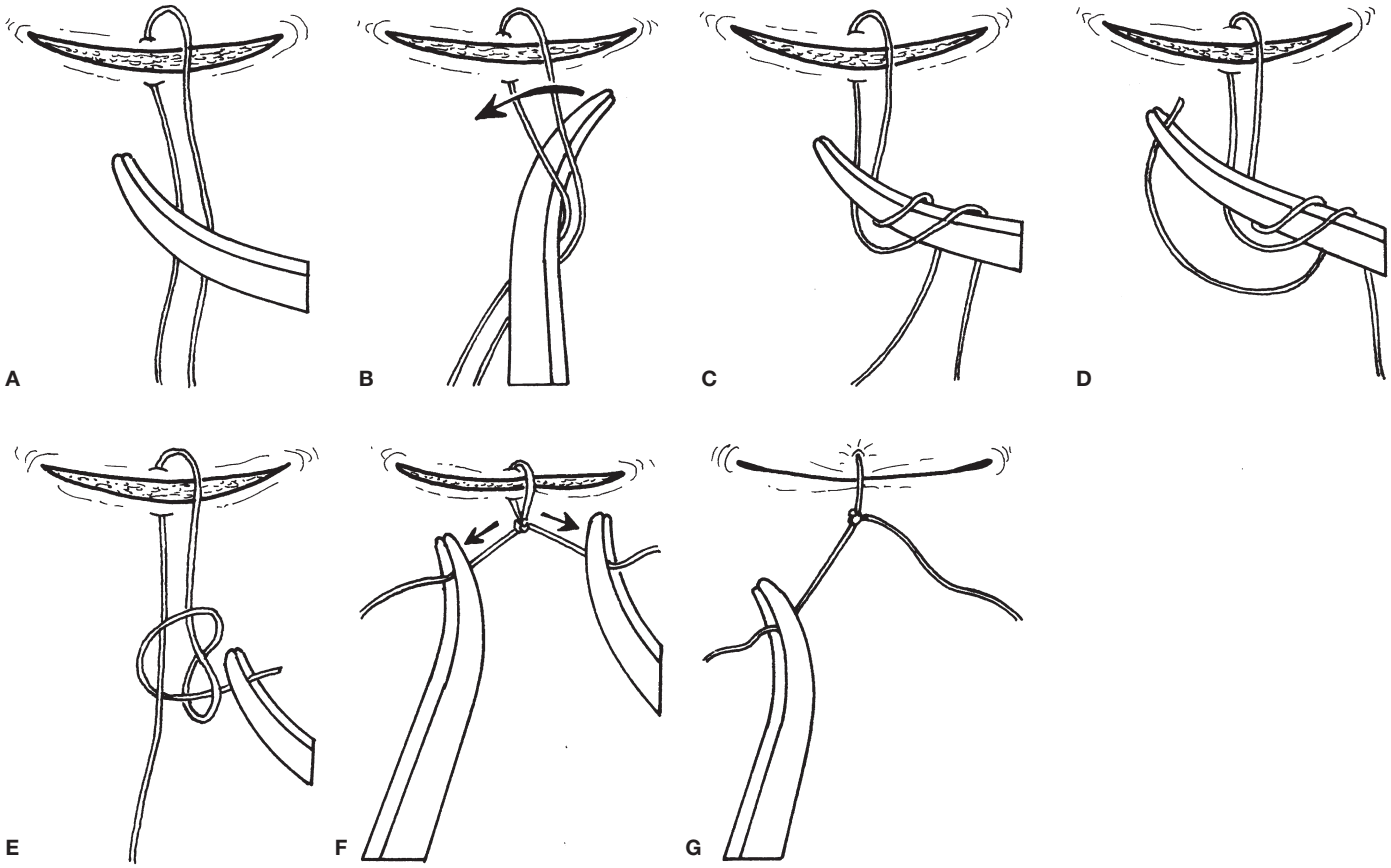


Figure 37.8. The drawings show the sequential steps for tying the 'parallel sutures' type of slip knot.

SINGLE CONTINUOUS TECHNIQUE: RADIAL PLACEMENT

The single continuous technique with radial placement (Fig. 37.9, *A*) uses a single suture of 20–24 bites to close the wound. Placing more than this number of bites or placing the bites too close to the limbus is associated with an increase in corneal neovascularization and should be avoided.[18] The pattern may be started anywhere, but the 6 or 12 o'clock positions are most common. The bites are made radially across the wound with equal spacing between bites and equal bite lengths. Deep or full-thickness bites should be taken. Initially, the donor edge is held with the toothed forceps, and the needle is driven into the cornea immediately behind. The forceps may then be moved to the recipient side to apply counterpressure at the planned site of egress of the needle. Usually, the needle need not be regrasped, but if a long bite is required or if facial features make access difficult, the needle may be passed first through the donor, drawn out of the wound, regrasped, and then passed through the recipient bed. Because the wound is not closed until the last bite is taken and the suture tied, periodic reformation of the anterior chamber is required. Viscoelastic may help maintain the chamber better, but complete filling is not desirable because of difficulty in subsequent removal, leading to postoperative pressure increases. It is preferable to use small amounts in the periphery to push back the iris where needed and rely on saline as the primary fluid for chamber maintenance. If the suture breaks during passage, a new needle may be spliced on using the slip knot. The knot does not compromise the tensile strength of the suture and may be left as part of the continuous suture; however, it must be buried. Alternatively, a very long section of new suture may be spliced on and then pulled backward loop by loop to the beginning of the pattern until the original suture and splice are removed. On completion of the pattern, the suture should be tied with a slip knot and tensioned. Tensioning should take place after the chamber is fully reformed with saline. Tensioning a flat chamber can lead to an excessively tight suture with a distorted drumhead configuration. It may be useful to use a hand-over-hand technique where one forceps holds the distal loop and maintains tension while the other pulls up slack on the proximal loop. This is then repeated loop by loop until the starting point is reached. Adequate tension should be just enough to approximate wound edges and prevent leakage. As soon as this is achieved, the knot is secured with two additional throws and buried in the donor cornea. The cardinal sutures are generally loose by this point and should be removed. The application of liquid fluorescein helps in identifying any wound leaks. It is not uncommon to see leaks through suture tracks if penetrating bites are used; these need no action and usually seal within 24 h. If the leak persists beyond 24 h then the application of a bandage contact lens, collagen shield, or patching, may be helpful. If the leak persists beyond 2–3 days, despite the implementation of these measures, there is some risk of development of a permanent fistula. Persistent leaking loops must be resutured because they may act as a site for epithelial down-growth.

The single continuous technique is easily and rapidly placed. Other advantages include the ease of intra- and postoperative suture adjustment to modulate astigmatism. Also there is usually only one knot present, and this minimizes the chance of vascularization of the graft. On the negative side, because only one

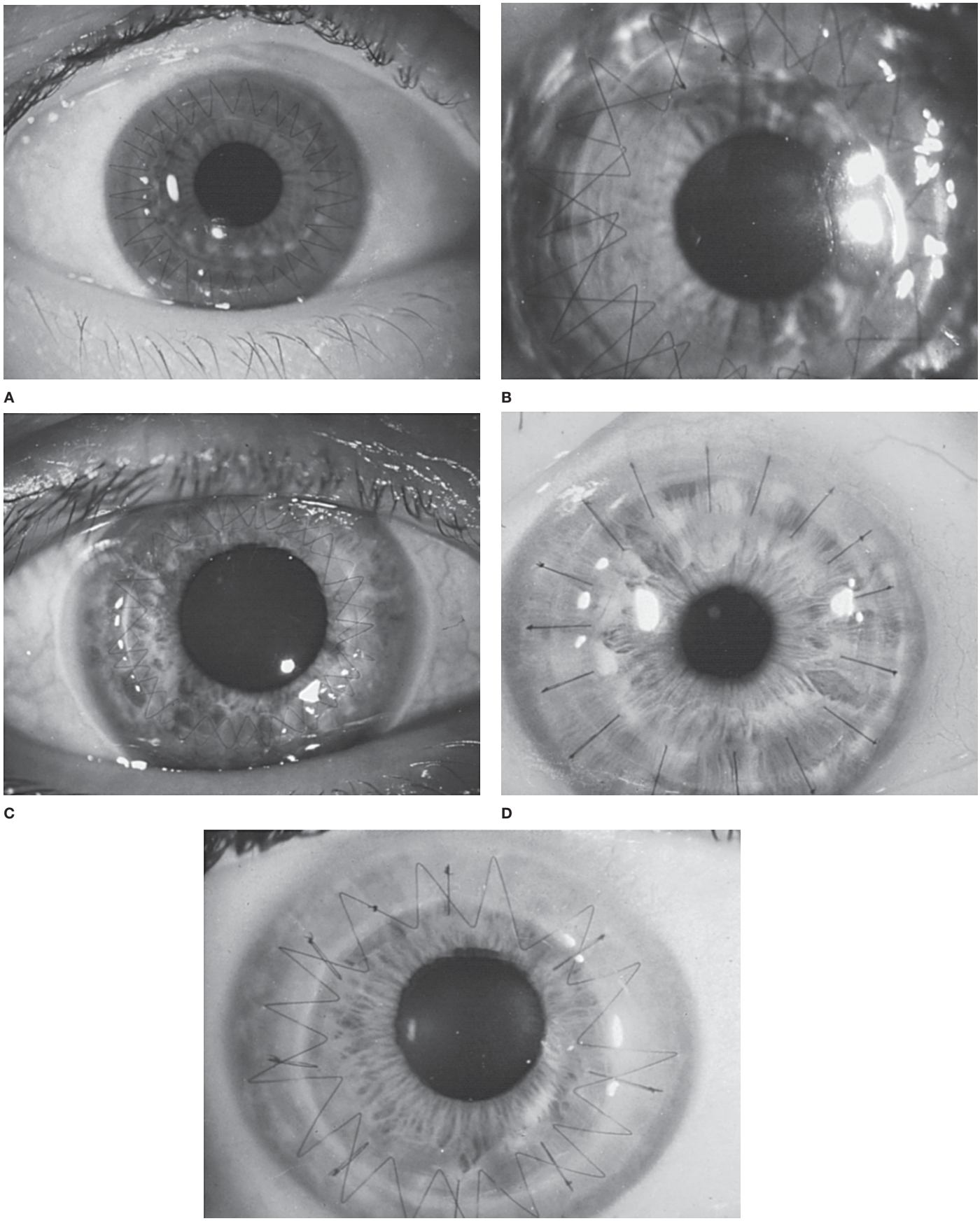


Figure 37.9. *A*, Single continuous, no torque. *B*, Double continuous torque–antitorque pattern. *C*, Double continuous, 10-0 and 11-0 nylon placed in same clockwise direction. *D*, All interrupted pattern. *E*, Combination interrupted and single continuous sutures.

needle is used for many bites, the point may become dull and in some cases must be replaced by attaching a new needle to the distal end of the suture. Also the wound is not fully secure or the chamber continuously formed until the completion of the pattern, thereby leaving the eye vulnerable in the event of any medical misadventures. After surgery, any trauma or severe tissue reaction or infection involving the solo suture may require surgical repair. A recent review of this technique revealed an average sutures-out astigmatism of 3–4 D with an average keratometry of 45 D.[19] Other studies have reported late and/or sutures-out astigmatism in the range of 3–5 D.[20–24] Another potential advantage of the single running technique versus all interrupted sutures was demonstrated in a cadaver study by Au and coworkers.[25] In this cadaver eye study, the water tightness of wound integrity in keratoplasty was evaluated by hydrostatically increasing the intraocular pressure. The results indicated that either a single running technique or a combined running and interrupted pattern produced a more secure closure than interrupted sutures alone. While there is no comparable human study, the conclusions drawn from the cadaver study do follow the logic that the continuous pattern with its suture loops overlapping the cornea between bites would provide a more secure closure. Another benefit to the single continuous was outlined by Filatov and coworkers, who compared a single continuous pattern versus a combined continuous and interrupted pattern. Although they noted no difference in the final postoperative astigmatism out to 4 years, they did observe that the single continuous pattern yielded a more rapid visual rehabilitation and less early astigmatism.[21] Furthermore, Ramirez and coworkers compared a single continuous suture versus a double running technique and concluded that the single running technique with postoperative adjustments produce less keratometric astigmatism during the first year, when sutures were still in place.[22]

SINGLE CONTINUOUS TECHNIQUE: NO TORQUE PLACEMENT

A disadvantage of the single continuous technique is that the portion of the suture that crosses over the top of the wound imparts a torque to the wound when tensioning is performed. This torque may be released when the suture is removed or breaks and may account for the late changes in astigmatism that can be seen.[26] To circumvent this torsion, some surgeons use a continuous, no-torque pattern. The classic no-torque pattern used in lamellar refractive keratoplasty is comprised of eight bites placed across the wound at 45° from the radial direction and angled in the direction of suture advancement. This placement creates a series of isosceles triangles that theoretically negates torsion. This pattern has been adopted for keratoplasty by a few surgeons by increasing the number of bites to 20–24 required for wound closure. The 45° angulation requires a greater overall length for each bite to bring the point out at an adequate distance from the wound on the recipient side, thus necessitating a full-curve needle and ample suture length. Otherwise, placement and adjustment are similar to radial single continuous patterns. Several publications have shown favorable results using this technique.[27,28] Another interesting observation was made by Sharma and coworkers, who found that the antitorque suturing pattern tended to produce a high proportion of prolate topographic maps postoperatively.[29] As the normal corneal contour is prolate, it would seem that obtaining a prolate pattern post keratoplasty would be optically desirable, but more studies will be required to establish the superiority of this suturing technique to that of other patterns in producing this type of topography.

Vajpayee and colleagues have also described an 'antitorque' pattern of continuous suturing.[30] The authors describe the antitorque pattern as being one in which the suture bites are again angled across the wound instead of being radial to it. In contradistinction to the no-torque placement described above, the angulation of the pass is made in the opposite direction of the advancement of the suture. For example, if a suture pattern is being advanced in a clockwise direction and a bite is taken through the donor button at the 12 o'clock position, the pass would be angled backward toward 11 o'clock instead of forward toward 1 o'clock, as would be the case in the no-torque pattern. Vajpayee and colleagues performed 53 keratoplasties and divided them roughly equally into three groups: one using the classic radial or torque placement, another the antitorque placement, and finally the no-torque pattern. The study concluded that at 3 and 6 months postoperatively there was no significant difference in astigmatism among the three groups. This study went on to mention that postoperative suture adjustment was helpful in reducing postoperative astigmatism in all three groups. Thus, the literature is unclear as to whether the no-torque or antitorque placement is actually better than the radial placement.

DOUBLE CONTINUOUS TORQUE–ANTITORQUE TECHNIQUE

Another approach to circumvent wound torsion is the double continuous torque–antitorque placement (Fig. 37.9, *B*). The first suture is placed with radial bites proceeding in a clockwise direction. After this suture is tensioned and tied, a second suture of the same size and material is run in a counterclockwise direction. The bites of the second suture fall between and parallel the direction of the bites of the first suture. When the second suture is tensioned, the torque it imparts compensates for that of the first suture, thus leaving only radial forces acting across the wound. Each suture is comprised of 12–14 equally spaced bites. The overall effect is a tighter, more secure wound closure with the added safety factor of two sutures.[31] Additionally, the first suture usually results in a closed chamber, thus facilitating placement of the second suture. Dolorico and coworkers have reported that, using this technique, they were able to achieve a mean postoperative manifest cylinder of 3.42 D within the 1–3 month post suture-removal period and that this astigmatism remained stable for follow-up ranging from 18 to 66 months.[32] Spadea and coworkers compared a single continuous versus a double continuous suture pattern, employing each technique in approximately 35 keratoplasties. With all sutures out at about 3 years, each group averaged approximately 3.5 D of astigmatism, and there was no statistically significant difference between the groups. However, the double running group appeared to have a faster restoration of visual function due to earlier stability of the astigmatism.[23] Solano and coworkers also compared a single continuous versus double continuous suture pattern and found that following suture removal there was no statistical difference between the techniques with respect to either mean keratometry or mean astigmatism, which in this study was 4.6 D for the double running group and 5.2 D for the single running group.[24] Thus, this technique has demonstrated advantages of a more secure wound closure, good control of postoperative astigmatism, and the possibility of earlier stability of the astigmatism versus a single continuous approach but has not been demonstrated to show a lower overall sutures-out

astigmatism. Disadvantages include a somewhat longer closure time and greater difficulty in both intra- and postoperative suture adjustment because of the necessity of simultaneous manipulation of two sutures in close proximity traveling in opposite directions.

DOUBLE CONTINUOUS-SAME DIRECTION TECHNIQUE

In the double continuous-same direction technique (Fig. 37.9, *C*), both sutures are placed with radial bites and proceed in the same direction. The goal is not to achieve a torque-free wound but to use different materials. Usually, one suture is 10-0 nylon and the second may be 11-0 nylon, polypropylene, or polyester. Ten to sixteen bites of 10-0 nylon are placed, tensioned, and tied. The 11-0 is then placed between the 10-0 bites. The 10-0 nylon is placed with deeper bites and is tensioned to close the wound. The second suture is placed more superficially and tensioned just enough to take up slack. The 10-0 nylon supplies the bulk of the support for initial wound healing. However, as previously noted, a tight 10-0 nylon may distort the cornea or produce excessive astigmatism. With this pattern, the 10-0 nylon may be removed as early as 2–3 months after surgery in the expectation that the 11-0 nylon will maintain wound support and provide a better optical surface. Thus, the overall goal of this technique is to produce faster visual rehabilitation; if the 11-0 nylon is a permanent suture, the refraction could be stable as early as a few months after surgery. Disadvantages include a slightly longer surgical time and difficulty in performing suture adjustment.

INTERRUPTED TECHNIQUE

Some surgeons prefer closing the wound with 16–24 radial interrupted sutures (Fig. 37.9, *D*). This may be the best technique for pediatric grafts where wound healing is rapid, for heavily vascularized corneas, or for corneas with segmental vascularization in which differential suture removal may be required. The closure may be more rapid, especially if the cardinal sutures can be maintained; the speed can also recommend this approach for patients who cannot remain long in the surgical position. Because of multiplicity of sutures, wound security in the presence of accidental suture breakage is the greatest of the aforementioned techniques. Postoperative astigmatism may be controlled via selective suture removal. However, intraoperative astigmatism is more difficult to modulate, and the unsupported tissue between bites leads to less even distribution of tension across the wound. The multiple knots increase the risk of vascularization, and removal may be difficult and may subject the patient to multiple periods of change in refraction. Nevertheless, Murta and coworkers have reported that an all interrupted closure compared to a single continuous closure resulted in lower post-keratoplasty astigmatism at 6- and 12-month postoperative intervals. There was, however, no statistically significant difference at 24 months post surgery. This allowed them to conclude that the interrupted pattern allowed better early control of postsurgical astigmatism and a more rapid recovery of vision.[33]

INTERRUPTED AND CONTINUOUS COMBINATION TECHNIQUE

The interrupted and continuous combination technique (Fig. 37.9, *E*) attempts to marry the benefits of selective postoperative suture removal afforded by the interrupted technique with the long-term support offered by a single continuous technique. Eight to twelve interrupted sutures are placed first, followed by a 12–16 bite running. The interrupted sutures stabilize the cornea, maintain the anterior chamber early, and facilitate placement of the continuous sutures. All bites are radial, and the continuous sutures bisect the interrupted sutures. A variety of materials and sizes may be used. Most commonly, the interrupted sutures are 10-0 nylon, and the running sutures may be 10-0 or 11-0 nylon, polypropylene, or polyester. In theory, the interrupted sutures are removed early to achieve a minimal astigmatism, while the continuous sutures maintain the wound. This approach is most valid when polyester or polypropylene is used for the continuous sutures because they may be left in place permanently. If nylon is used for the continuous sutures, late breakage can cause refractive shifts. Earlier reports showed good results with low sutures-out astigmatism,[34] but the more recent popularity of suture adjustment may point to decreasing usefulness of this technique. Filatov and coworkers[21] compared the sutures-in and sutures-out astigmatism with single continuous to continuous–interrupted combinations. They found the sutures-in astigmatism was lower in the continuous cases, but final sutures-out astigmatism was similar for both. Thus, the continuous offered a more rapid rehabilitation when compared to the combined technique. Karabatsas and coworkers also compared a combined technique to a single continuous with postoperative adjustment and also concluded that there was no significant difference at 3, 6, 9, or 12 months post surgery between either of the groups.[20] Dursun and coworkers reported on attempts to use the combined technique to control astigmatism as well as postoperative myopia and anisometropia.[35] In this technique, 92 keratoplasties were performed using 12 interrupted 10-0 nylon sutures and a tight 12-bite continuous suture. This was then followed by selective removal of the interrupted sutures. In this particular study, however, the use of the tighter continuous sutures and selected removal of fewer interrupted sutures resulted in an actual increase in final postoperative astigmatism and had no significant impact on the final spherical equivalent. In a review of factors associated with graft failure, Vail and coworkers found an increased risk with the combined continuous–interrupted pattern.[36]

SUTURE ADJUSTMENT

INTRAOPERATIVE SUTURE ADJUSTMENT

The final element in wound closure should be the minimization of astigmatism by suture adjustment. As described earlier, the donor button should be placed under keratometric control. A variety of surgical keratometers ranging from small disposable units to sophisticated qualitative and quantitative devices are available. They share a common principle of operation. A light is projected onto the wound surface, and its reflex is altered by the corneal curvature. An initially circular image appears elliptical in the presence of an astigmatic surface, with the short axis of the ellipse corresponding to the steeper meridian. When a continuous suture is used, it should be adjusted after tensioning and tying to yield a more spherical reflex (Fig. 37.10). Before starting, the chamber should be filled, cardinal sutures and scleral rings removed, and any viscoelastic rinsed from the field. The net effect is redistribution of tension from the steep meridian to the flat meridian. One or both sides of the suture may be adjusted as needed. This process may be used for single and double continuous patterns. Keratometric control may also be used with interrupted patterns but is more difficult. In these

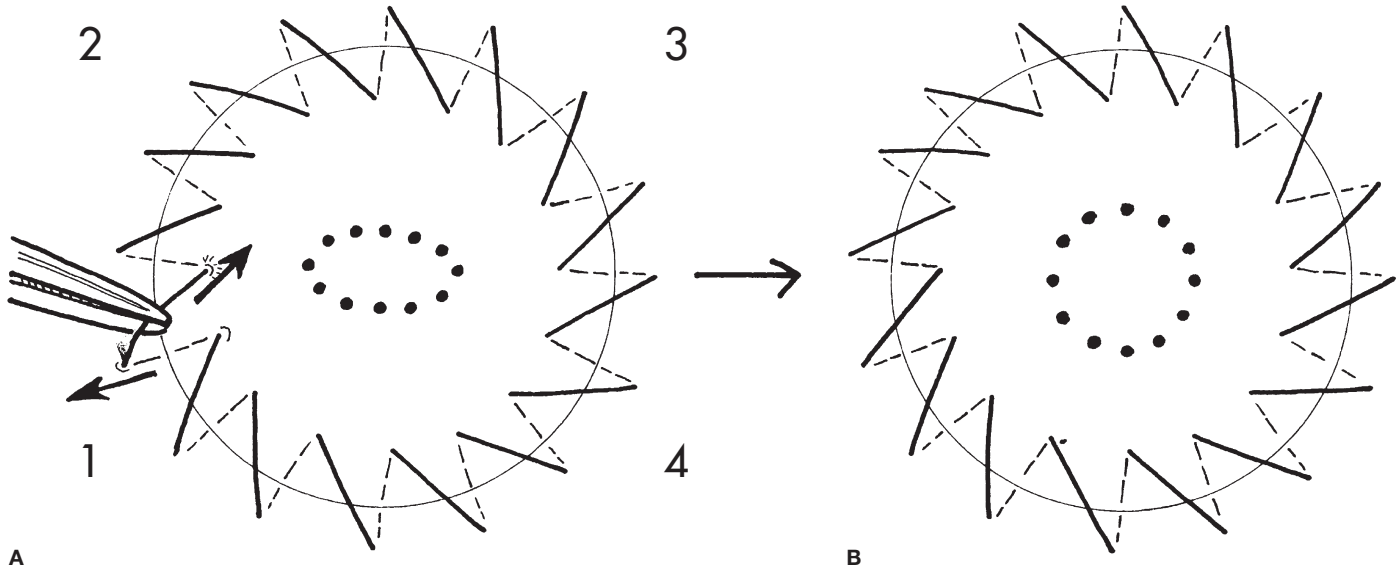


Figure 37.10. *A*, A large, with-the-rule astigmatism is shown by the oval keratometric reflex with short axis from 6 to 12 o'clock. This is adjusted by successively pulling each loop across the wound and advancing from position 1 to position 2. The slack generated is then distributed among the loops from position 2 to position 3. If needed, tightening can be performed from position 3 to position 4, and the slack distributed from position 4 to position 1. The end result will be a circular reflex as shown in *B*.

cases, sutures must be added or replaced with varying tension to influence the keratometric reflex. In all cases, the final integrity of the wound must be confirmed.

Serdarevic et al performed a randomized trial comparing long-term effects of intraoperative adjustment with no adjustment.[28] The intraoperatively adjusted group had less astigmatism, more regular topography, and better best spectacle corrective acuity than the control group. Shimazaki and coworkers corroborated this result in their analysis of 53 patients undergoing keratoplasty with a continuous suture technique, who had either intra- or postoperative adjustment at varying time periods. They concluded that intraoperative suture adjustment significantly reduced final astigmatism and, in some cases, eliminated the need for further postoperative manipulation.[37] Thus, a relatively rapid and easily performed step can significantly improve postoperative results.

POSTOPERATIVE SUTURE ADJUSTMENT

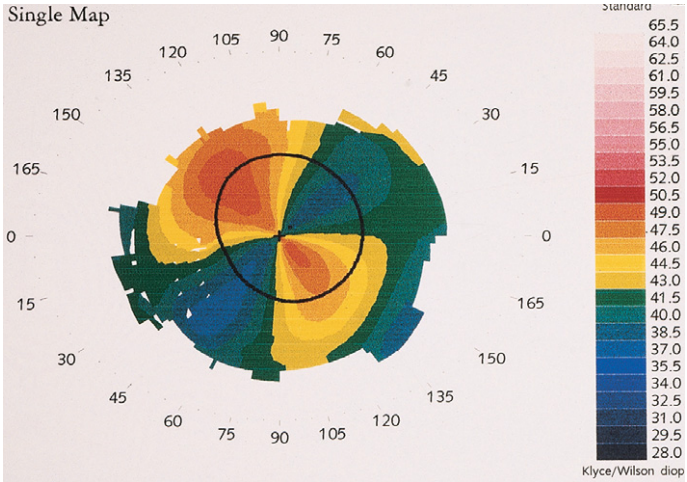
Despite efforts at intraoperative adjustment, some astigmatism may still be present in the postoperative period. In general, a cylinder of greater than 3–5 D can be a visual impediment for the patient and should be addressed. Clinical keratometry has been the mainstay for identifying astigmatism and is still useful. However, photokeratoscopy and computerized topography yield additional information including identifying tight sutures and asymmetric astigmatism. These instruments should be used if available. Postoperative adjustment is carried out much in the same manner as described for intraoperative adjustments and has been shown to be effective in numerous studies.[38–40] It may be performed as early as readable keratometry or topography can be obtained and is most effective in the first 3 months after surgery, although later adjustments may still be fruitful.[37]

The suture may be adjusted at the slit lamp using a Tennant tying forceps after administration of topical anesthetic. If feasible, somewhat better control is afforded by a surgical microscope and keratometer with the patient in a supine position. Frequently, the epithelium has closed over the loops and must be broken before adjustment. This is accomplished with a small-diameter spatula such as the Johnson. The spatula is gently inserted under each loop and swept back and forth to break the epithelium. This should be performed in sequence for all loops. The adjustment is limited by the position of the knot. Unlike the intraoperative scenario, it is best not to externalize the knot because reburial may be quite difficult. After adjustment, appropriate antibiotic and corticosteroid coverage should be used as prophylaxis against either infection or graft reaction. This technique is effective in reducing both sutures-in and ultimate sutures-out astigmatism.[41] It may be used for both single and double continuous patterns but is more easily effected with the single continuous technique. Compared with selective removal of interrupted sutures, which is done sequentially over many months, this approach affords more effective and rapid stabilization of vision because usually only one adjustment is required.[42] An example of topography of an adjusted cornea is shown in Figure 37.11, *A* to *C*.

An additional technique for modulating postoperative astigmatism was proposed by Buzard.[43] Based on examination of keratoscope mires, it may be possible to identify flat meridians of 'microdehiscence' of the wound that are causing astigmatism. By placing additional interrupted sutures under keratometric control, the wound is strengthened and the surface is made more spherical. If performed early in the healing phase, the effect can persist even after suture removal. Additional sutures can be effective even in the absence of demonstrable microdehiscences and can be adjunctive to suture adjustment.

SUMMARY

This chapter has presented information on commonly used suture materials and needle types for keratoplasty closure and comments regarding their effective use. Additionally, the pros and cons of the different types of suture patterns have also been reviewed. Ultimately, each surgeon must decide which combination of suture



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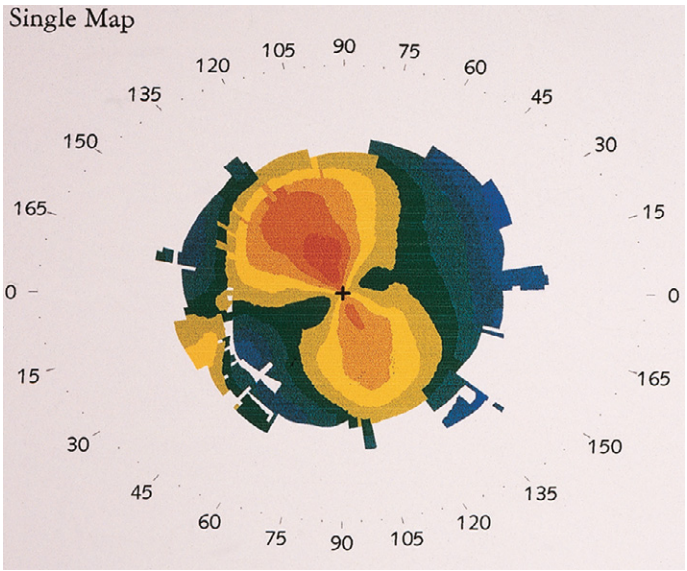

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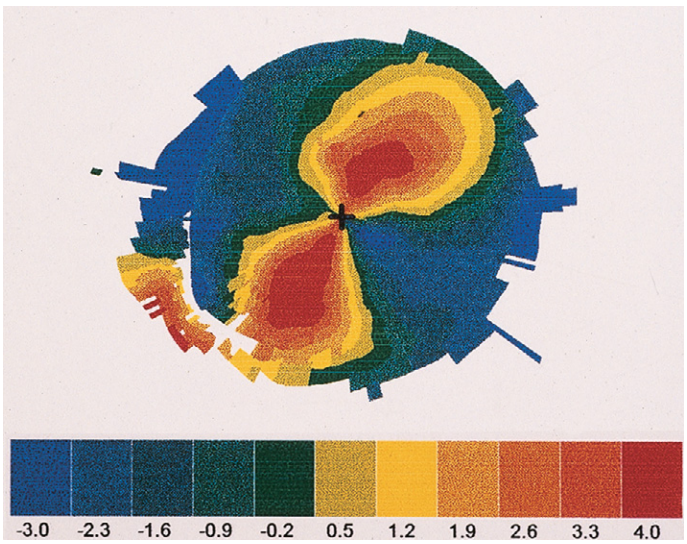

C

Figure 37.11. A, Topography of a cornea 2 months after keratoplasty with a steep astigmatic band at 130°. Sim K is 48.52 × 132/38.23 × 42. The suture was adjusted with some limitation imposed by the buried knot. **B**, Post-adjustment topography. The steep axis is shifted slightly to 120° and the Sim K is reduced to 47.78 × 121/42.03 × 31. **C**, A digital subtraction of the preadjustment from postadjustment maps shows the steepening of the flat axis *(red colors)* that has resulted from the adjustment. Note the scale in **C** is not diopters of curvature but rather diopters of keratometric change. Difference = A − B.

material, needle design, and suture pattern will best serve the goals of effective keratoplasty closure. Although this chapter has referenced numerous articles reflecting the experience of a variety of corneal surgeons with the differing techniques, it should be noted that no closure technique may be definitively cited as optimal. In fact, in a recent review article Frost and coauthors reviewed 27 randomized trials of differing penetrating keratoplasty techniques.[44] The authors concluded that among the trials reviewed there was little convincing evidence to demonstrate the superiority of one suturing pattern over another for an effective control of final sutures-out astigmatism. It will take yet further studies on larger numbers of keratoplasties before a definitive best technique may be identified.

In the final analysis, even if an optically clear graft is to be obtained but functional acuity is prevented by high astigmatism not readily correctable by spectacles or contact lenses, it may be appropriate to perform a repeat keratoplasty operation, and such operations have been noted to be accomplished with some success.[45]

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38 Indications and contraindications for anterior lamellar keratoplasty

Sanjay V. Patel, H. Kaz Soong

INTRODUCTION

Although the first human lamellar keratoplasty (LKP) was performed in the 19th century,[1] the surgery never gained immense popularity or prevalence because it eventually was superseded by the technically easier penetrating keratoplasty (PKP) in the latter half of the 20th century. With improved methods of corneal preservation and increasingly successful outcomes of PKP,[2] lamellar grafting became relegated to the removal of superficial central lesions in the cornea and to tectonic repair. In this chapter, 'LKP' will refer to traditional, anterior lamellar corneal transplantation. Posterior lamellar transplantation (DLEK, DSEK, and DSAEK), a more recent development, is discussed in a subsequent chapter.

In LKP, only the anterior part of the cornea is transplanted, leaving the recipient posterior stroma, Descemet's membrane, and endothelium intact. Although technically more demanding than PKP, lamellar grafting has several advantages. The wound strength in lamellar grafts is considerably superior to that of PKP, because recipient Descemet's membrane and deep stroma are left intact. The entire lamellar interface between donor and recipient cornea comprises the graft–host junction in LKP, whereas in PKP it is limited to the extremely weak peripheral trephination wound. Accordingly, PKP wounds are much more susceptible to dehiscence, occasionally with devastating clinical consequences. LKP is in essence an extraocular procedure, and therefore it is less likely to cause glaucoma, cataract, uveitis, cystoid macular edema, retinal detachment, infectious endophthalmitis, expulsive choroidal hemorrhage, and phthisis bulbi. Since the endothelium is not transplanted in LKP, donor corneal requirements are not as stringent as in PKP. Eye bank tissue with unhealthy endothelium or with preservation times in excess of 2 weeks may thus be used in LKP. It is a practical and perhaps safer alternative to PKP in regions of the world not served by eye banks and without easy patient access to postoperative care.

PKP may have certain advantages relative to LKP. One limitation of LKP is that the lamellar interface is a source of light scattering, optical attenuation, and wavefront aberrations,[3] all contributing to reduced visual acuity. Lamellar interfaces are a frequent nidus for (1) centripetal in-growth of blood vessels from the periphery of vascularized recipient corneas, (2) lipid deposition, (3) leukocyte migration (diffuse lamellar keratitis), and (4) entrapment of blood or particulate debris, such as fibers from cotton-tipped applicators, lint from cloth drapes or gauze pads, secretions from meibomian glands, and powder from gloves. When the forward-bulging cornea in advanced keratoconus is flattened by the donor lamellar overlay, visually significant folds in the recipient side of the interface may result. If the lamellar dissection is insufficiently deep, the residual stromal opacities may preclude visual improvement. If a tear or hole is present in host Descemet's membrane, it is not uncommon for a 'double anterior chamber' or 'pseudochamber' to result from aqueous humor gaining access into the lamellar interface.[4] From a technical standpoint, LKP is more time consuming and difficult than full-thickness keratoplasty and generally does not have as good a visual result as PKP. With improvements in microkeratome technology[5–7] and the advent of the clinical femtosecond laser,[8] however, LKP is undergoing a renaissance and resurgence. These newer technical innovations have aided in both the improvement of the lamellar interface smoothness and the reduction of the technical difficulty of LKP (Fig. 38.1).

Broadly, preoperative criteria for LKP include adequate recipient corneal endothelial function, a healthy ocular surface, and anterior corneal opacity/disease that spares Descemet's membrane. If possible, ocular surface disorders, such as dry eye, trichiasis, meibomian gland disease, entropion and ectropion, lagophthalmos, limbal stem-cell insufficiency, and pemphigoid should be eliminated or at least aggressively treated prior to LKP. Lamellar transplantation is advantageous in patients with poor compliance and patients who are young and physically active and therefore at greater risk of postoperative trauma.

LKP is used for both optical and tectonic indications: (1) optical LKP for improving vision in patients with anterior corneal opacities or irregular astigmatism from surface pathology and (2) tectonic LKP for reinforcement of structural integrity in corneas weakened and distorted by thinning, perforation, or descemetocele. LKP may also be used for a combination of optical and tectonic indications. Prior to performing PKP on a very thin cornea, LKP could be done first to restore a normal corneal thickness to allow safer and easier suturing of the future penetrating graft.[9,10] Lamellar grafting should generally be avoided in the removal of malignant corneal tumors

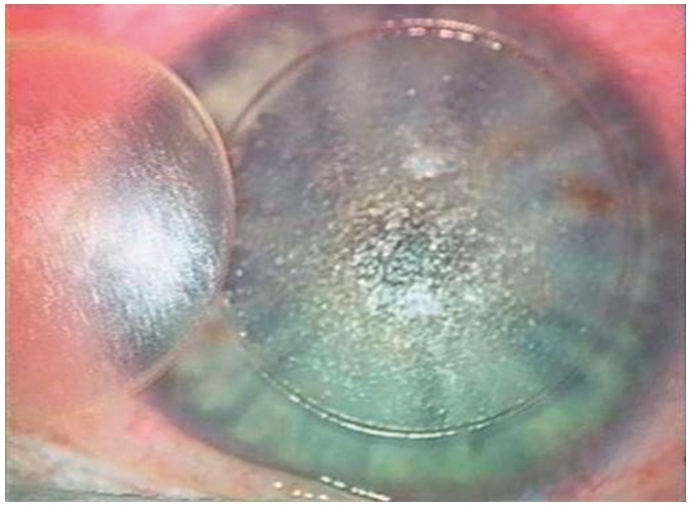

Figure 38.1. Recipient lamellar bed produced by femtosecond laser. (Reproduced with permission from Tibor Juhasz, PhD.)

or deep corneal infections, as the possibility of subtotal extirpation or recurrent disease exists.

OPTICAL INDICATIONS

Clinical indications for optical LKP may vary among regions of the world, reflecting the differences in the relative prevalence of endemic corneal diseases. For example, there are noticeable dissimilarities in preoperative indications for LKP between India (Table 38.1)[11,12] and the USA (Table 38.2).[13]

Although dystrophies of Bowman's layer and anterior stroma are common indications for optical LKP in the USA (Table 38.2), LKP may also be considered in some cases of macular and lattice dystrophies if the deep stroma is mostly or entirely spared.[11] Corneal dystrophies recur frequently in grafts,[13] usually more so in the anterior stroma;[14] thus, LKP is a favorable option to PKP, because the procedure could be repeated multiple times without violating the intraocular anatomy.[13,15]

LKP may be preferred over PKP in aniridic keratopathy, because of the high incidence of intraocular complications, such as glaucoma, endothelial rejection, and cataract with full-thickness keratoplasty.[16,17] Combination of LKP with limbal stem-cell transplantation may improve its long-term survival, corneal graft clarity, and visual prognosis.

Corneal scars or leukomas in the anterior corneal stroma, usually resulting from infection or trauma, may be successfully treated with LKP. Corneal scars that result from infection account for a large proportion of LKPs in the developing world,[11,12] and many of these infections may be directly or indirectly related to trachoma.[12] Most scars from infectious keratitis can be successfully treated with LKP, but scars from Herpes simplex keratitis carry a risk of recurrent disease, corneal melting, and subsequent graft failure. Of the four LKPs done for scars resulting from herpetic infection in our series,[13] two grafts failed after severe stromal ulceration. One ulcer began as a nonhealing epithelial defect 3 months after surgery, while the other developed dendritic keratitis 9 years postoperatively.

Lamellar transplantation in keratoconus may be done for both optical (Fig. 38.2, *A* and *B*) and tectonic indications. The main purpose of LKP in keratoconus is to flatten the cone and to reduce the irregular distortion, but a secondary benefit is the removal of

Table 38.1 Clinical indications for optical LKP in India

Diagnosis	No. of Eyes (Total = 138)	% of Total
Climatic droplet keratopathy	62	45
Infectious keratitis scarring	31	22.5
Band-shaped keratopathy	6	4.3
Herpetic scars	6	4.3
Salzmann nodular degeneration	3	2.2
Lattice corneal dystrophy	6	4.3
Macular corneal dystrophy	3	2.2
Traumatic corneal scars	3	2.2
Dermoid	3	2.2
Amyloid	1	0.7
Regraft	2	1.4
Not mentioned	12	8.7

Table reproduced from Saini et al[11] with permission of *Cornea*.

Table 38.2 Clinical indications for optical LKP in the USA

Preoperative Diagnosis	No. of Eyes (No. of Patients)
Dystrophy	14 (5)
Granular	8 (3)
Reis–Buckler	6 (2)
Aniridic keratopathy	10 (9)
Scar	9 (9)
Herpes simplex	4 (4)
Herpes zoster	2 (2)
Bacterial corneal ulcer	2 (2)
Foreign body injury	1 (1)
Keratoconus	7 (6)[a]
Atopic keratopathy (with anterior corneal haze and vessels)	3 (2)
Interstitial keratitis	3 (2)
Contact lens keratopathy (with anterior corneal haze and vessels)	3 (1)
Corneal dermoid	1 (1)
Hot gunpowder burn	1 (1)
Salzmann nodular degeneration	1 (1)
Total	52 (37)

[a] Five patients had Down's syndrome.

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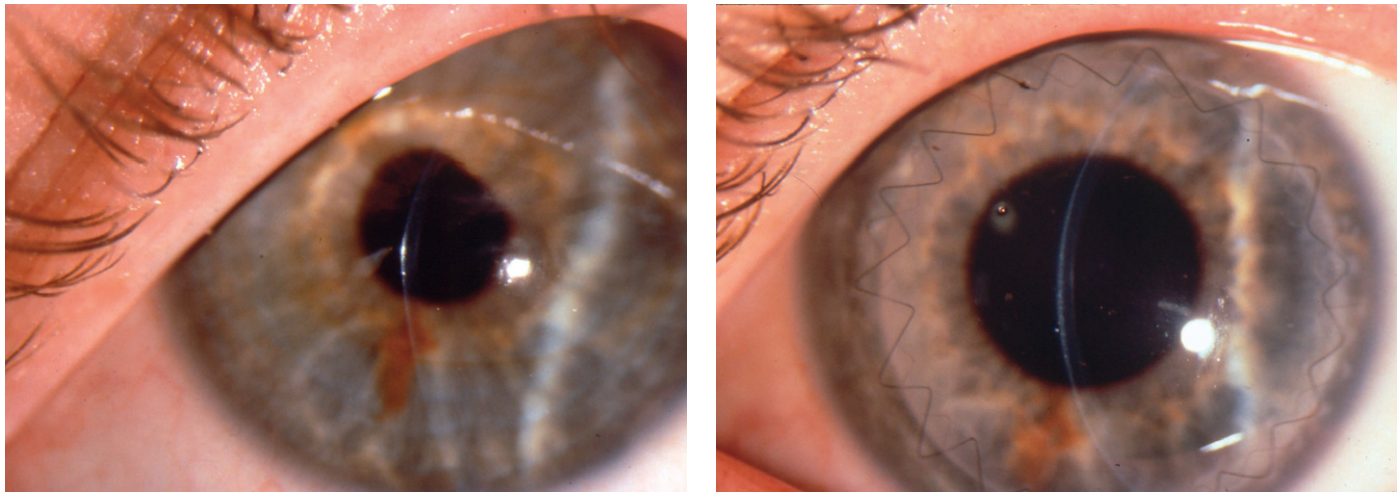

A B

Figure 38.2. Optical LKP for keratoconus: *A*, preoperative; *B*, postoperative.

stromal scars from the visual axis. Contact lens fitting and tolerance are also improved. As many keratoconus patients tend to be young, physically active, and prone to trauma, LKP may be a safer alternative to PKP. LKP is the procedure of choice for patients with Down's syndrome in whom eye rubbing and self-induced trauma may preclude PKP.[18,19] In our series, five of the six patients who underwent optical LKP for keratoconus had Down's syndrome.[13] The visual results in LKP for keratoconus are, however, not as good as in PKP,[2,20,21] especially when deep stromal scars are present. Consequently, some surgeons advocate deep dissection to Descemet's membrane (deep anterior LKP) for the surgical treatment of keratoconus.[22–28] To facilitate the baring of Descemet's membrane in these procedures, lamellar injection of air (big-bubble),[28] fluid,[24] or viscoelastic may be employed to physically separate the membrane from posterior stroma.

Degenerations of the anterior cornea comprise another relatively frequent indication for optical LKP, especially in the developing world.[11,12] Climatic droplet keratopathy accounted for 45% of LKPs at one referral center in India.[11] Although Salzmann's nodular degeneration[11–13] and band keratopathy[11–13] may also be treated by LKP, simple peeling of the nodules or chemical chelation of the calcium, with or without diamond drill polishing of the Bowman's layer, is usually sufficient and may preclude the necessity for transplantation. Other indications for optical LKP include chemical burns,[12] pterygia over the central visual axis,[12,29] and benign superficial tumors, such as dermoids.[12,13]

TECTONIC INDICATIONS

LKP in the surgical management of acute corneal ulceration, with or without perforation, is sometimes called patch grafting. When urgent reparative or reconstructive surgery must be performed à chaud in these acutely inflamed eyes, LKP is safer than a more invasive procedure such as PKP. A reconstructive patch graft serves as a temporary stop-gap measure to stabilize the globe, allowing it time to quiet down before a vision-restoring PKP is performed at a later time. Tectonic LKPs are thus helpful in the treatment of corneal melts, not only by providing structural support, but also by buying precious time until systemic immunosuppressive therapy has a chance to arrest the underlying collagenolytic activity. Tectonic lamellar grafts are structurally superior to cyanoacrylate tissue adhesive or amniotic membrane inlays and overlays and are definitely the therapy of choice in large (>1 mm) corneal ulcerations or perforations. Furthermore, in central corneal ulcers or perforations, LKPs usually do not obscure the visual axis as much as opaque cyanoacrylate tissue adhesives or amniotic membrane. Lamellar transplantation may also help resolve inflammatory keratitis that is refractory to medical therapy by debriding necrotic tissue that contains inflammatory cells, toxic debris, and collagenolytic compounds. Less invasive corneal surgery, such as tarsorrhaphies and conjunctival flaps, may also be considered. Whenever possible, therapeutic LKP should be delayed for as long as possible, unless the corneal disease appears to be worsening despite maximal medical therapy and the integrity of the globe is threatened.

Inflammatory corneal ulceration with underlying systemic autoimmune disease is a frequent indication for tectonic LKP, accounting for 50 out of 80 cases in our series.[4] Of the systemic diseases associated with sterile ulcerative keratitis requiring tectonic lamellar grafting, rheumatoid arthritis is the most common in our experience (Table 38.3). Autoimmune systemic diseases are frequently associated with severe keratoconjunctivitis sicca, and accordingly attention should also be directed toward aggressive control of the dryness through the use of artificial tears, ointments, cyclosporin, and punctal occlusion. Tectonic lamellar grafting is successful in the long term only if the underlying immunological disease is adequately controlled through the use of systemic medical therapy. Good systemic control of the disease is necessary not only for the successful salvage of the globe and the preservation of vision,[4] but also for reducing patient mortality associated with systemic vasculitis.[30] Tectonic LKP in the treatment of peripheral ulcerative keratitis[4] often requires technically difficult freehand, eccentric, crescentic, or fan-shaped (Fig. 38.3) lamellar dissections.[31]

Infectious corneal ulceration accounts for 18.8% of the tectonic lamellar grafts in our series,[4] with bacterial and herpetic infections predominating (Table 38.3). Fungal infections have traditionally been considered a contraindication for lamellar procedures,[32–34] because of the depth of penetration of organisms in the cornea.[35] Although PKP is usually preferred in fungal keratitis, LKP may be done if there is a reasonable chance that all infected corneal tissue could be extirpated.[35]

Noninflammatory indications for tectonic LKP include keratoconus,[18,19] pellucid marginal degeneration,[36] keratoglobus,[9] and

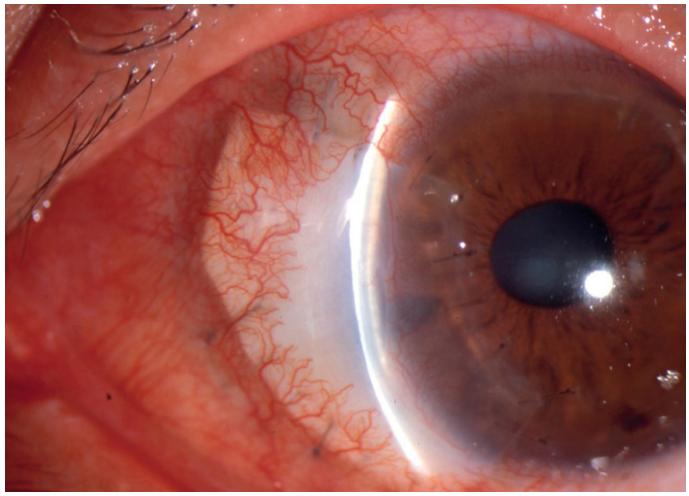

Figure 38.3. Fan-shaped, freehand peripheral LKP with attached scleral patch graft.

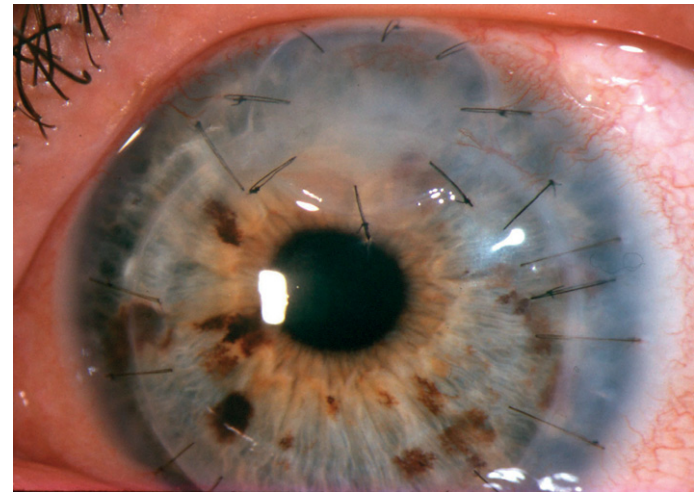

Figure 38.4. Smaller snowman (piggyback) lamellar patch graft used to seal focal corneal melt with perforation at graft–host junction of PKP.

Table 38.3 Clinical indications for reconstructive lamellar patch graft

Preoperative clinical diagnosis	No. of cases (No. of patients)
Systemic autoimmune disease	50 (36)
Rheumatoid arthritis	37 (26)
Systemic lupus erythematosus	6 (4)
Ocular cicatricial pemphigoid	4 (4)
Stevens–Johnson syndrome	3 (2)
Infection	15 (14)
Bacterial corneal ulcer	6 (6)
Herpes simplex	6 (5)
Herpes zoster	3 (3)
Neurotrophic keratitis	3 (3)
Mooren's ulcer	4 (4)
Radiation keratitis	2 (1)
Foreign body injury to cornea	2 (2)
Corneal melt after pterygium excision	1 (1)
Alkali burn	1 (1)
Exposure keratopathy	1 (1)
Idiopathic	1 (1)
Total	80 (64)

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Terrien's marginal degeneration.[37] Lamellar grafting in these diseases may improve vision by restoring a more normal, less astigmatic corneal contour.[13,38] LKP may also be used, as mentioned previously, as the initial step to structurally reinforce a thin cornea prior to PKP.[9,10]

Other indications for tectonic lamellar grafting include the reinforcement of an excessively thin cornea after excision of a deep dermoid[12,13,39] and for the removal of other benign neoplasms.[12] Rarer indications include neurotrophic, exposure, and radiation keratopathies (Table 38.3). Small, tectonic lamellar ('snowman' or 'piggyback') grafts are also used to repair focal sterile ulcerations or perforations at the graft–host junction in PKP (Fig. 38.4).[40] The use of these small piggyback grafts preserves the central portion of the PKP and is also a safer alternative to an oversize PKP, which carries an increased risk of rejection, glaucoma, and cystoid macular edema.[41,42]

SUMMARY

The success of optical LKP has varied in the past, but the procedure is a good alternative in select cases and possesses numerous advantages over PKP. Although it is a safer alternative to PKP, it is limited by vision-reducing interface problems and by being a more technically challenging procedure. The visual results of LKP may be improved by deep LKP baring recipient Descemet's membrane and the use of a mechanical microkeratome or femtosecond laser for cutting the lamellar button in both donor and recipient corneas. Tectonic LKP is an effective procedure for reinforcing and repairing the integrity of the eye damaged by corneal melting. It is less invasive than PKP and is the preferred keratoplasty method in acutely inflamed and unstable eyes. It also provides structural support while allowing systemic immunosuppressive therapy time to take effect and for the eye to become quiescent before future vision-restoring surgery.

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39 Epikeratoplasty

Ayad A. Farjo, Michael D. Wagoner

INTRODUCTION

Epikeratoplasty (EKP) is a form of onlay lamellar keratoplasty (LKP) in which a lens made of human corneal tissue is sutured onto the anterior surface of the cornea to change the anterior curvature and refractive properties of the cornea.[1] It was originally introduced by Dr Herbert Kaufman at the Jackson Memorial Lecture at the American Academy of Ophthalmology[1] as an extension of the pioneering work of Joaquin Barraquer[2] in the development of keratophakia for aphakia and keratomileusis for myopia.

The objective of EKP is to provide the refractive benefits of keratophakia and keratomileusis with less cost, less technical complexity, fewer complications, and without requiring dissection and removal of a portion of the central cornea.[2] To accomplish this, Kaufman recommended suturing of cornea donor tissue that was commercially prepared by cryolathing to a prespecified dioptric power onto a recipient eye from which the central epithelium had been removed but Bowman's layer had been left undisturbed (Fig. 39.1, *A* and *B*).[1] The use of commercially prepared EKP 'lenticules' eliminates the need for the operating surgeon to purchase the expensive equipment required to perform the technically difficult cryolathing procedure. The elimination of central corneal dissection step greatly reduces the complexity of the procedure, along with the risks of complications such as interface opacification and stromal scarring. Finally, EKP is potentially reversible because the central cornea is not disturbed by the procedure. The use of a commercially prepared lenticule of precise power (or 'living contact lens') and the utilization of a surgical technique that provides for 'complete reversibility' in a worst-case scenario resulted in optimistic claims that EKP would become the ideal refractive surgical procedure for the correction of both myopia and hyperopia.

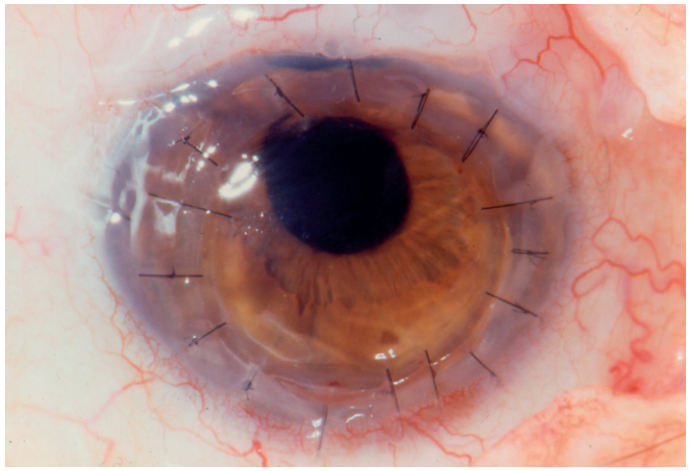
INDICATIONS

Epikeratoplasty was originally introduced for contact lens-intolerant, monocularly aphakic adults, in whom secondary intraocular lens implantation was contraindicated.[1,3,4] The indications were later expanded to include the correction of keratoconus,[5,6] pediatric aphakia (Fig. 39.2),[7,8] and myopia.[9] Between 1985 and 1988, a nationwide study was conducted by 234 'general ophthalmologists,' who had received an intensive 2-day training course, to evaluate the use of EKP for all four indications in preparation for market approval by the US Food and Drug Administration (FDA).[10–14]

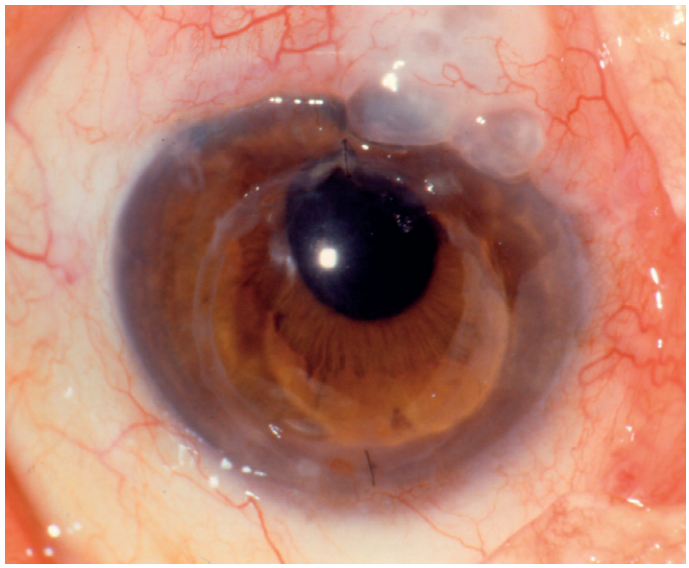
The original optimism after the introduction of EKP was not fully realized in the original clinical trials or subsequent studies. As a result of data generated from a nationwide study, the FDA did not approve the use of EKP for myopia due to poor predictability and an unacceptably high rate of refractive regression.[10] Although FDA approval was obtained for use of EKP for adult aphakia, the advent of improved anterior chamber intraocular lens designs and the development of techniques for intraocular lens fixation in the absence of capsular support provided a more simple solution for the treatment of adult aphakia.[15] Secondary intraocular lens placement with anterior chamber, iris-sutured posterior chamber, or scleral-sutured posterior chamber intraocular lenses is associated with more rapid visual rehabilitation, better visual acuity, better contrast sensitivity, and superior refractive accuracy than EKP and has led to abandonment of this procedure for adult aphakia.[14,16,17] Despite FDA approval for pediatric aphakia, favorable results with pediatric intraocular lenses, as well as increasing acceptance of intraocular lens insertion in children offered an attractive alternative to EKP in children.[18,19] Today, the excellent safety record of secondary intraocular lenses[19] has largely eliminated the need for aphakic EKP. The only remaining FDA-approved use of EKP that is currently used is for the treatment of contact lens-intolerant keratoconus and for tectonic reinforcement of the globe for corneal thinning disorders, such as keratoglobus, Terrien's marginal degeneration, and pellucid marginal degeneration. [11,20–26]

Epikeratoplasty for keratoconus

Lamellar keratoplasty has long been used to reinforce thin, ectatic corneas in eyes with keratoconus and other corneal thinning disorders (Fig. 39.3). Compared with penetrating keratoplasty (PKP), LKP is an extraocular procedure that reduces or eliminates many of the serious complications of intraocular surgery such as expulsive hemorrhage or endophthalmitis. By preserving the recipient endothelium, which is almost invariably normal in young patients with keratoconus, the likelihood of maintaining normal corneal hydra-



A



B

Figure 39.1. Clear EKP 1 month (*A*) and 1 year (*B*) after transplantation. The surgical procedure has not affected a well-functioning filtering bleb superiorly.

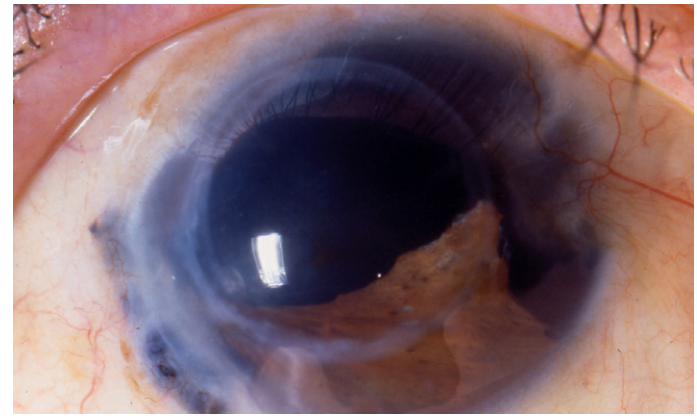


Figure 39.2. Six year postoperative appearance of an EKP for traumatic pediatric aphakia.

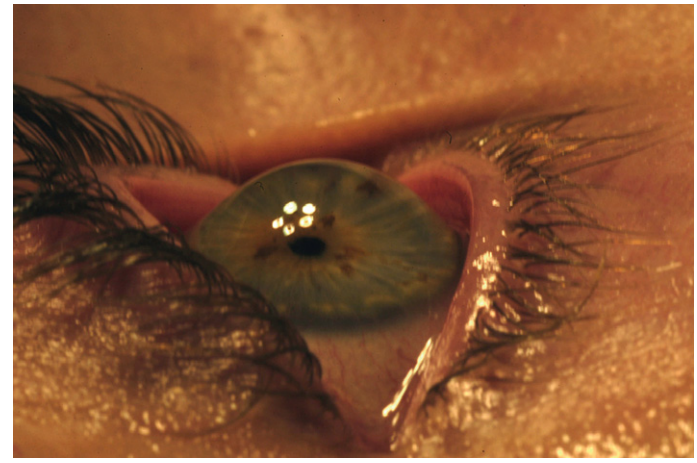


Figure 39.3. Intraoperative view of an eye undergoing EKP for keratoglobus.

tion and clarity for many decades is much higher after LKP than with PKP. In addition, the risk of endothelial rejection, which is seen in 8–39% of PKP for keratoconus, is eliminated.[27–29] While the risk of stromal rejection is probably identical with PKP and LKP, this complication is far less serious than endothelial rejection.[30] Despite the potential advantages of LKP, it was largely abandoned due to the superior visual results of PKP for keratoconus,[29] especially since overall graft survival remains high after PKP despite the incidence of endothelial graft rejection episodes.[27,31,32]

As originally described, EKP was best suited for keratoconus patients with poor spectacle acuity, absence of scarring in the visual axis, best-corrected visual acuity with a hard contact lens of 20/40 or better, and contact lens intolerance.[11] Because of the flattening and slight shift of the position of the cone, EKP was not recommended in eyes with paracentral scars within 1 mm of the visual axis.[11] Exceptions were made in cases such as Down's syndrome, where the advantages of an extraocular procedure outweighed the disadvantages of a 'less than perfect' visual result following EKP in eyes with mild to moderate central corneal scarring. Similar reasoning was applied to a large population with keratoconus in Saudi Arabia in which concerns about postoperative compliance and access to follow-up care were felt to offer a significant risk of graft failure due to neglected endothelial rejection episodes.[20] While some observers felt that better results could be obtained with cones less than 60 D in steepness,[16,21] this observation was not supported by later studies.[20]

Epikeratoplasty may be performed as part of a 'staged' tectonic procedure (T-EKP) in the treatment of corneal thinning disorders such as keratoglobus, pellucid marginal degeneration, or Terrien's marginal degeneration.[25,26] Large custom-made lenticules, up to 12.5 diameters and approximately 300 µm in thickness, may be ordered and used to reinforce the entire cornea in the first stage. If the postoperative improvement in corneal contour results in acceptable visual acuity with spectacles or a contact lens, no additional therapy is needed. If the visual acuity remains inadequate, a central PKP can be performed to complete visual rehabilitation. The reinforcement of peripheral corneal tissue by EKP greatly facilitates proper suturing of the donor cornea.

SURGICAL TECHNIQUE

Epikeratoplasty lenticules are prepared from corneal tissue that meets the criteria of the Eye Bank Association of America for trans-

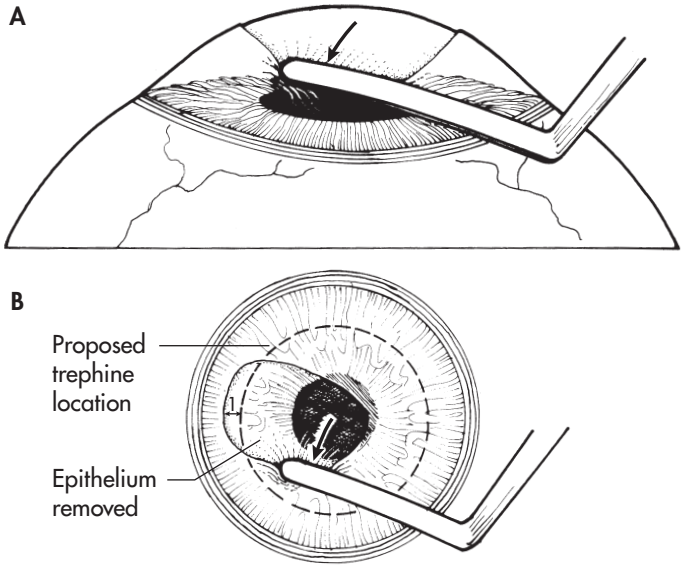


Figure 39.4. Technique for epithelial removal, side view (*A*) and surgeon's view (*B*), with blunt debridement with a spatula or blade.

plantation but does not qualify for use for PKP due to factors such as poor endothelial cell counts, long death-to-preservation times, or excessive length of time in storage media. Originally, corneal tissue was cryolathed and lyophilized prior to shipment to the operating surgeon. Today, fresh corneal stromal tissue is cut to a specific thickness and diameter, as requested by the operating surgeon, by participating eye banks and provided in standard storage media utilizing the same protocol that is used for other eye bank tissue. For treatment of keratoconus, donor stroma with a diameter of 9.0 mm and a thickness of approximately 225 µm is recommended. In the absence of prepared lenticules, alternatives include manual dissection of a donor anterior stromal disc using an artificial anterior chamber or using pre-cut corneal tissue originally intended for endothelial transplantation.

Epikeratoplasty may be performed with general anesthesia, retrobulbar or peribulbar anesthesia, or topical anesthesia (in extremely cooperative adults). The central corneal epithelium is debrided at least 1.0–1.5 mm beyond the edge of the anticipated trephination with a dull spatula, facilitated by topically applied 4% cocaine, if necessary (Fig. 39.4, *A* and *B*). Although 20% ethanol can also be used to remove the epithelium, its use should be judicious, as it has been suggested to contribute to poor postoperative epithelial healing. All epithelium should be removed from the surgical field and fornices to prevent accidental retention of epithelial nests in the interface during lenticular suturing.

After epithelial removal, an 8.5 mm (or one that is 0.5 mm less in size than the donor size requested by the surgeon) manual or Hessburg–Barron trephine is centered on the visual axis and trephination is performed approximately 225–250 µm into the corneal stroma (Fig. 39.5). Many surgeons perform a 0.5-mm annular keratectomy on the axial side of the trephine incision to facilitate suturing of the lenticule, although this is not mandatory (Fig. 39.6, *A* and *B*).

If lyophilized tissue is used, the lenticule is rehydrated for 20 min in balanced salt solution containing antibiotics. If fresh corneal donor tissue is used, it is transferred directly to the recipient eye from the donor storage media. Edge-to-edge approximation of the donor tissue and the recipient cornea should be performed with

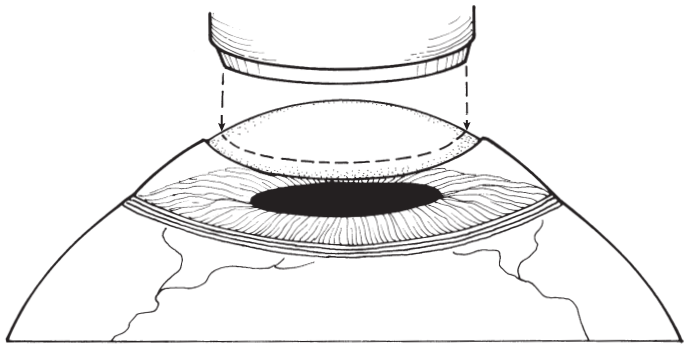


Figure 39.5. Partial thickness trephination can be accomplished with a manual or vacuum-assisted trephine.

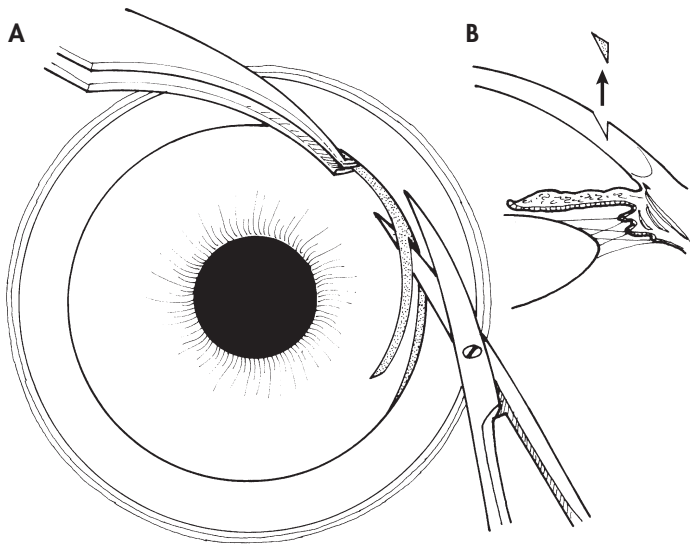


Figure 39.6. An optional partial-thickness annular keratectomy of the host cornea, side view (*A*) and surgeon's view (*B*), can facilitate suturing of the donor lenticule.

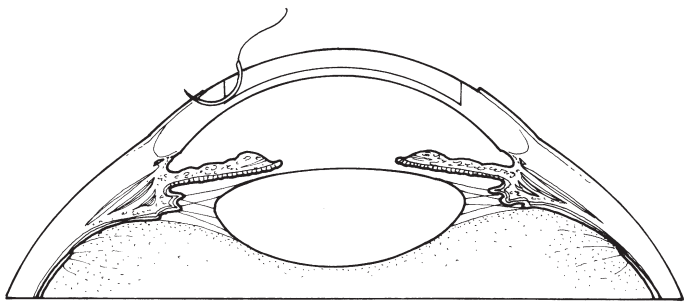


Figure 39.7. Edge-to-edge donor to host approximation is essential to a successful outcome. Care should be taken to avoid donor override of the host that may delay epithelialization.

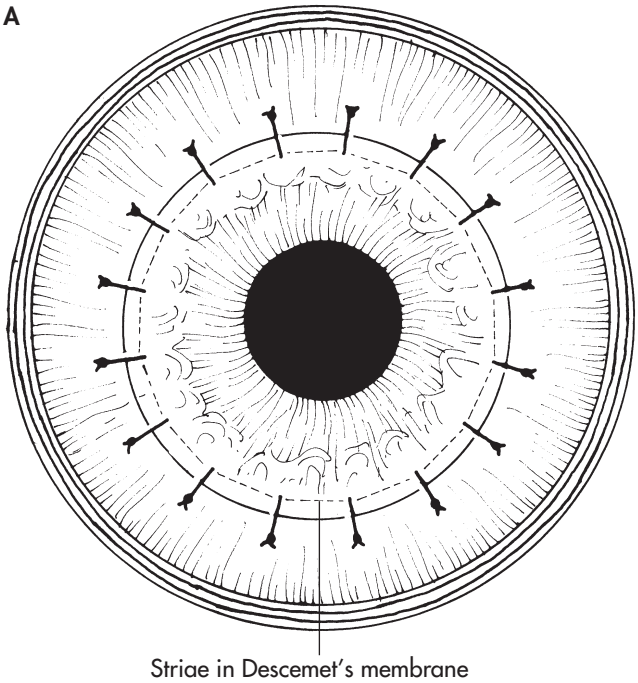
suture placement as posterior as possible in the donor tissue without inadvertent through-and-through bites and at the base of the recipient trephination groove (Fig. 39.7). A total of 16 or 24 sutures-interrupted 10-0 nylon sutures are placed, after which all knots should be rotated and buried. To obtain maximum flattening of the cone, some surgeons utilize a 9-0 silk suture for the four cardinal sutures and replace them with 10-0 nylon sutures at the conclusion of the case. Cardinal sutures should be tied as securely as possible

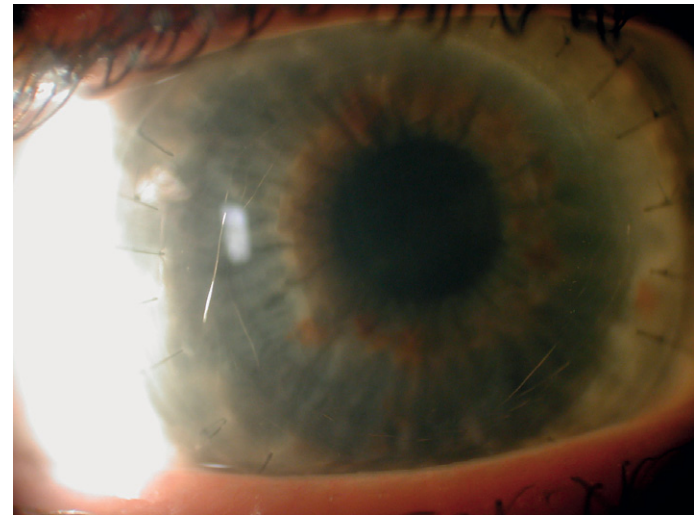
while the assistant flattens the cone with a flat spatula. Alternatively, or additionally, to aid in flattening the cone, an anterior chamber paracentesis can be performed to remove aqueous humor and lower the intraocular pressure. Concentric folds should be present in Descemet's membrane at the conclusion of the procedure, indicating that the cone has been flattened significantly (Fig. 39.8, *A–C*). These vanish after suture removal and have no permanent effect on visual outcome.

POSTOPERATIVE CARE

The success of EKP for keratoconus is highly dependent upon facilitating prompt re-epithelialization of the donor tissue and control of inflammation to prevent premature suture and interface vascularization. To facilitate re-epithelialization, most surgeons use bandage soft contact lenses or pressure patching. In the past, when lyophilized donor tissue was used, delayed re-epithelialization was

A





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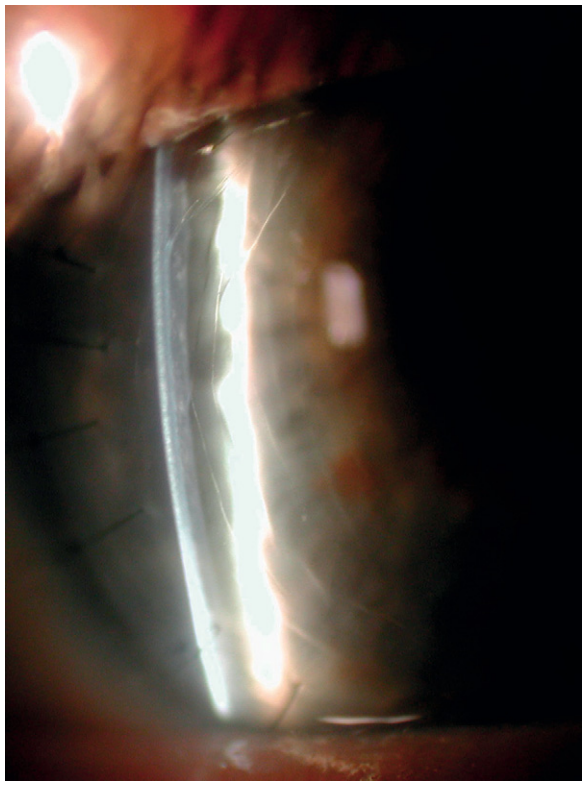
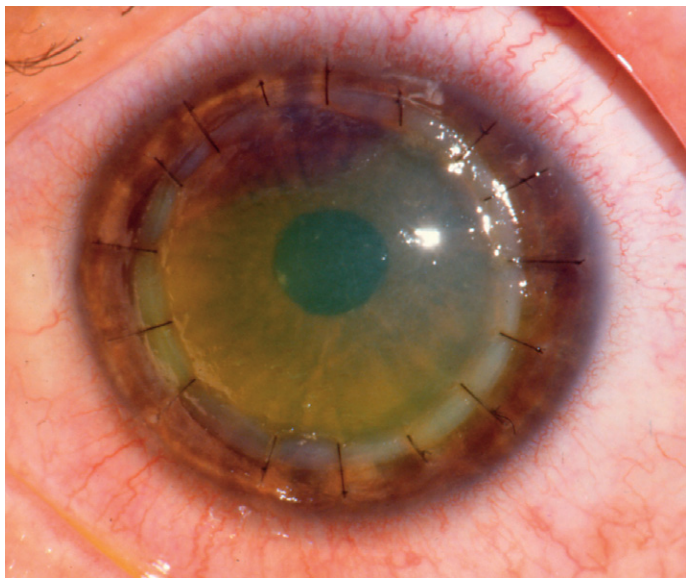


C

Figure 39.8. Appropriately tightened sutures will result in concentric striae (*A–C*).

common. Loss of graft clarity almost invariably occurred when epithelial defects persisted for more than 2 weeks with lyophilized issue, often in association with sterile corneal ulceration due to the lack of viable keratocytes essential for proper wound repair in the donor tissue (Fig. 39.9, *A–C*).[33] Removal of the lenticule was essential in such cases to restore the original status of the recipient cornea and prevent permanent scarring and visual loss.[34] One study demonstrated that placement of a temporary tarsorrhaphy at the conclusion of the surgical procedure reduced the mean time of re-epithelialization to 4.61 days, compared to 8.03 days with pressure patching ($p < 0.01$) and 13.2 days with bandage soft contact lenses ($p < 0.005$).[35] Since delayed re-epithelialization of 2 weeks or more is often associated with irreversible loss of lyophilized lenticular clarity, prophylactic placement of a temporary suture tarsorrhaphy at the conclusion of every EKP procedure became routine practice for many clinicians.[35] Today, persistent epithelial defects after EKP are unusual due to the use of fresh corneal donor tissue, so it is acceptable practice to utilize pressure patching or bandage soft contact lenses in the early postoperative period and to reserve temporary tarsorrhaphy for those cases in which re-epithelialization is delayed beyond the first week or in cases where delayed healing is expected. Topical prophylactic antibiotics should be utilized until re-epithelialization is complete. Removal of the EKP lenticule is occasionally necessary in the early postoperative period due to loss of graft clarity or sterile ulceration due to persistent epithelial defects (Fig. 39.10, *A* and *B*) or due to secondary microbial keratitis.[33,34,36,37]

Proper suture management is essential to achieve the desired result. Maintenance of tight corneal sutures for a minimum of 3 months, and preferably at least 6 months, is necessary to achieve maximum permanent corneal flattening and reduction of irregular astigmatism. Topical corticosteroids should be used to prevent



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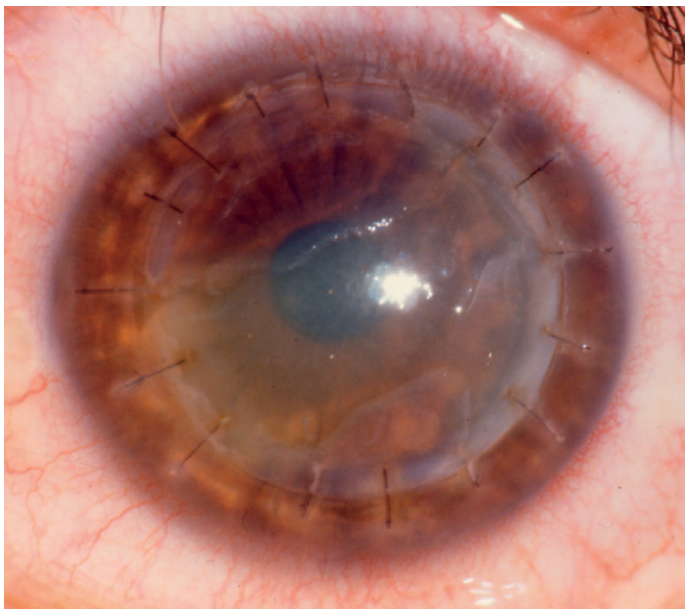

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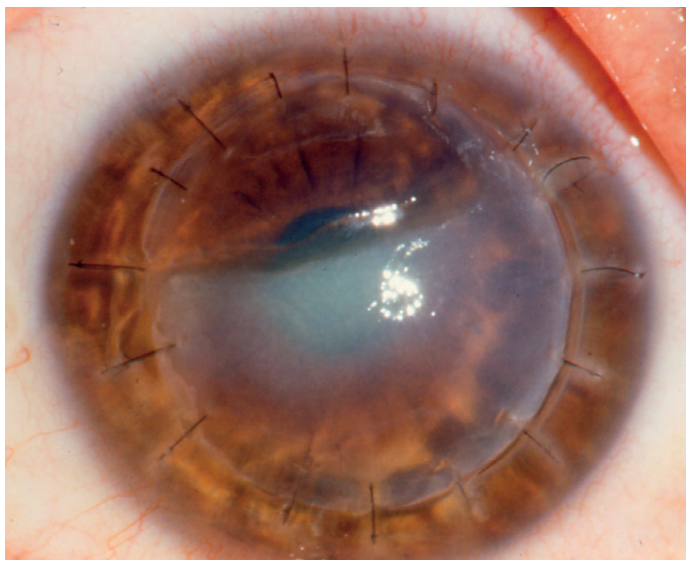
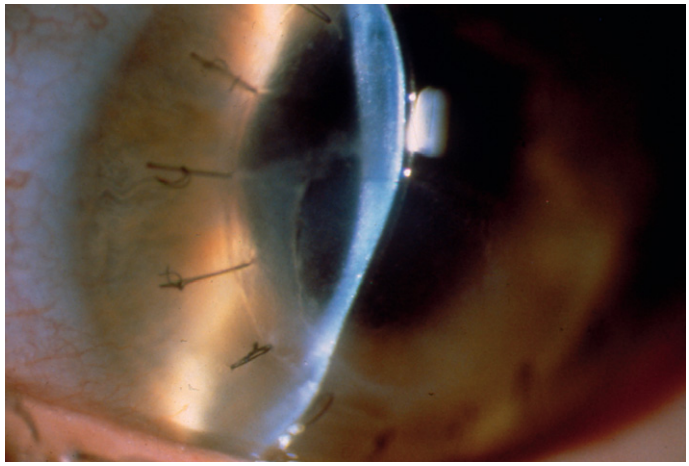


C

Figure 39.9. *A*, Persistent corneal epithelial defect after EKP. *B*, Two weeks later the defect is epithelializing, but *C*, by 1 month the lenticule has failed and retracted from 2:00 to 5:00.



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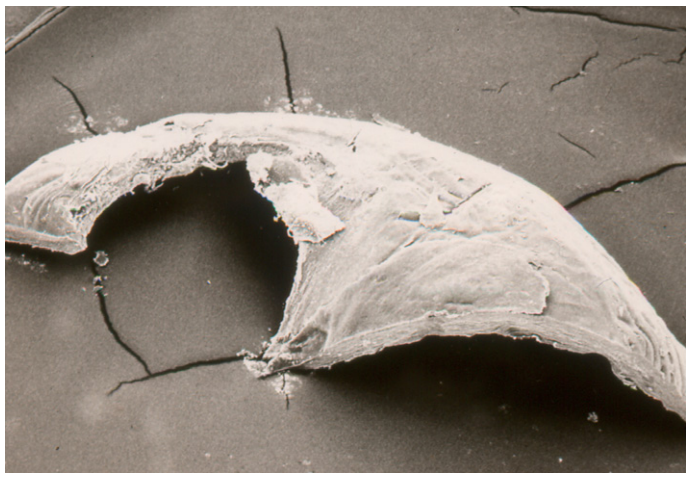
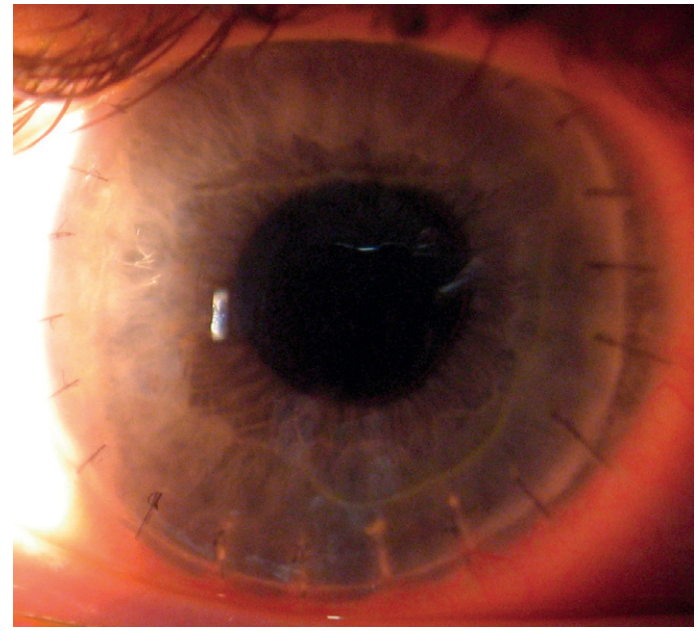


B

Figure 39.10. Sterile ulceration of EKP lenticule (*A*) with accompanying scanning electron micrograph (*B*) after removal of the donor tissue.

premature suture vascularization and loosening as well as epithelial and/or stromal rejection (Fig. 39.11, *A* and *B*). A reasonable regimen is prednisolone acetate 1.0% four times daily for 2 weeks, three times daily for 2 weeks, twice daily for 3 months, and once daily for 3 months. Loosened sutures should be removed to prevent vascularization (Fig. 39.12) and secondary microbial keratitis as well to avoid compromising the prognosis for future potential LKP or PKP. Suture removal should always be performed so that the knot exits from the host corneal side of the wound to avoid dehiscence of the wound. If the lenticule does dehisce during suture removal, it is important to tuck the lens back into position either at the slit lamp or in the minor treatment room. If the edge of the lenticule does not remain in proper position, it is essential to resuture the wound to avoid compromising the surgical result. Sutures that are removed within the first month should be replaced to prevent development of irregular astigmatism in the meridian of suture removal even if the graft appears to be in proper position, unless there is significant neovascularization or keratitis in the area of suture removal.

Removal of the lenticule may be necessary in the late postoperative course due to suboptimal visual acuity related to persistent irregular astigmatism, poor lenticular clarity, or interface haze or opacification (Fig. 39.13). If PKP is planned, it is best to combine



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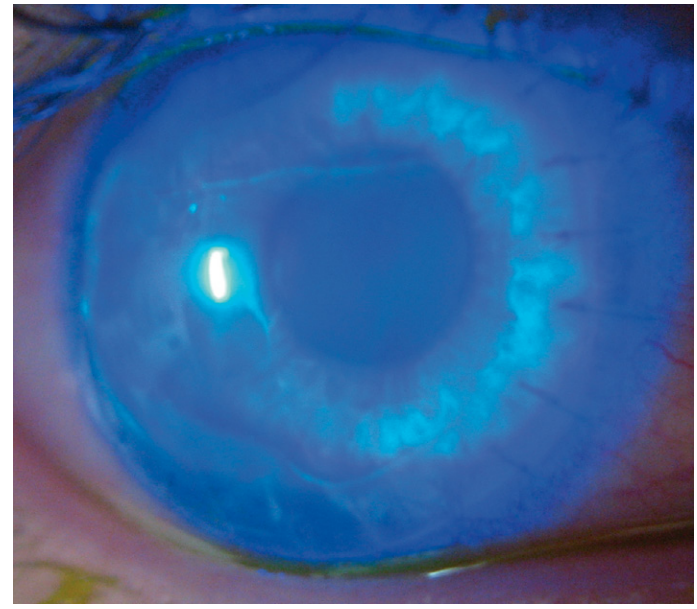


B

Figure 39.11. *A* and *B*, Central ring-shaped epithelial rejection line with prominently inflamed sutures inferiorly. Prompt steroid therapy, with removal of inflamed sutures if possible, is imperative.

it with EKP removal in a single procedure. The most efficient method of removing the lenticule at the time of a combined procedure is simple trephination of the central cornea. Anecdotally, the prognosis of PKP does not seem to be compromised by prior EKP, but there are insufficient data in the literature to firmly support this observation.

RESULTS

When EKP was introduced, there was optimism that it would provide visual results comparable to PKP and fewer complications than LKP. Unfortunately, the results of the initial nationwide study and

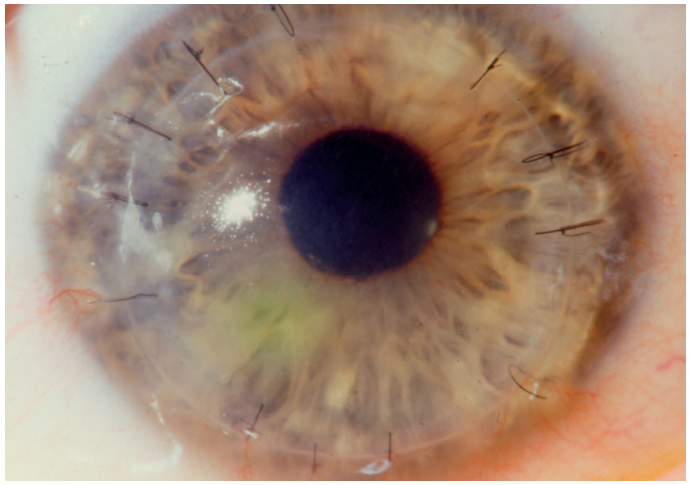


Figure 39.12. Loosened sutures (at 4:30 and 8:30) are a nidus for neovascularization and can lead to infection. These should be removed whenever identified.

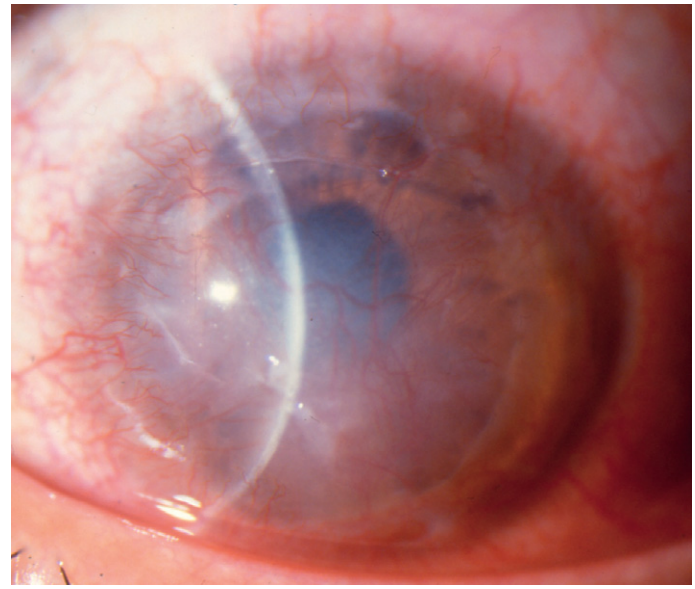
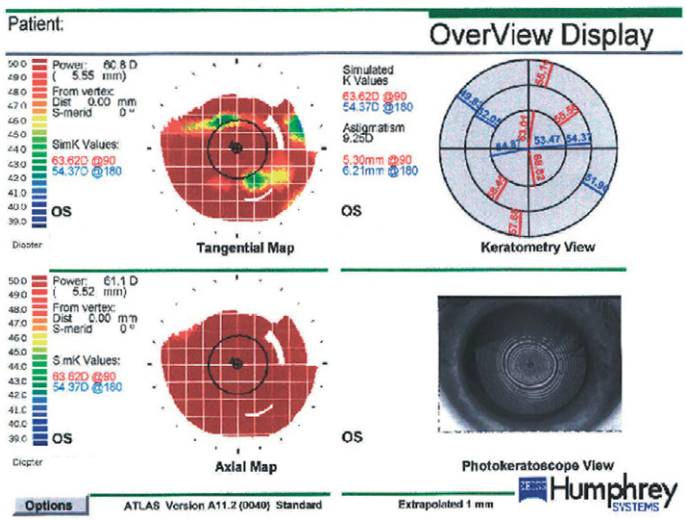


Figure 39.13. Failure of EKP in a noncompliant patient who did not use topical steroids or have sutures removed in a timely fashion.



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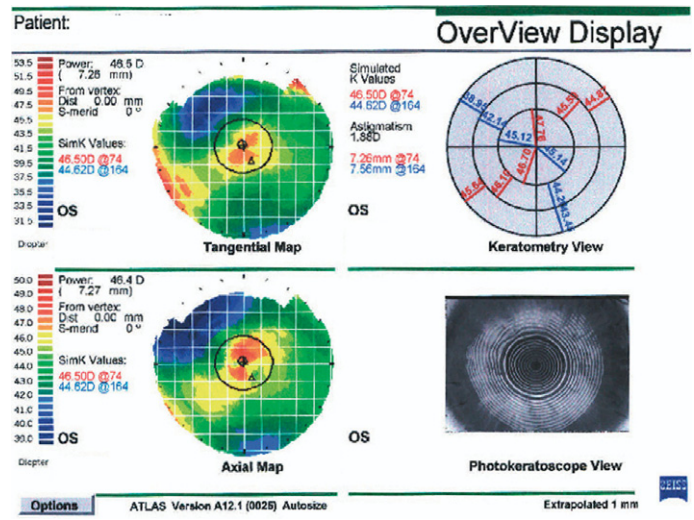

B

Figure 39.14. *A*, Preoperative and *B*, postoperative topography of a patient who underwent EKP. Note the significant central flattening and reduction of corneal astigmatism.

subsequent studies confirmed that EKP does not meet these expectations.[11,20–24]

The nationwide study of EKP for keratoconus reported satisfactory results of 82 cases in which more than 30 days of follow-up was available following suture removal.[11] Uncorrected visual acuity improved in all but two patients. Whereas only 9% of eyes had an uncorrected visual acuity of 20/100 or better preoperatively, 64% had an uncorrected visual acuity of 20/100 or better postoperatively. All but two patients achieved a best-corrected visual acuity within one line of the preoperative best-corrected contact lens visual acuity. In most cases, the reduction in irregular astigmatism permitted this outcome to be achieved with spectacle correction (Fig. 39.14, *A* and *B*). For patients who chose to continue contact lens wear, the flattening of the cone permitted more satisfactory fitting, comfort, and wearing time.

Several other investigators have compared the results with EKP and PKP in small, nonrandomized series. Fronterre and Portesani reported similar mean uncorrected visual acuity (20/63 vs. 20/52), spectacle-corrected visual acuity (20/23 vs. 20/22), and contact lens-corrected visual acuity (20/21 vs. 20/20) in a comparison of EKP and PKP, respectively.[23] Steinert and Wagoner reported a mean best-corrected spectacle acuity of 20/32 vs. 20/27 after 2 years with EKP and PKP, respectively, although no eyes with EKP achieved 20/20 acuity.[21] Goosey and associates observed that while 93% of eyes achieve best-corrected acuity of 20/40 or better after either EKP or PKP, only 23% with EKP obtained 20/20 vision, compared to 73% with PKP.[24] Contrast sensitivity is reduced with or without glare after EKP when compared with both rigid gas-permeable hard contact lenses and PKP.[38]

The largest comparative study came from Saudi Arabia where 161 eyes with keratoconus treated with EKP at the King Khaled Eye Specialist Hospital (KKESH) in Riyadh were compared to 443 eyes treated contemporaneously with PKP at the same institution by the same surgeons.[20] A minimum of 24 months of follow-up was available, with a mean follow-up period of 54 months for EKP and 52 months for PKP. Among patients who chose either spectacle or contact lens rehabilitation, the median visual acuity was 20/50 for 77 eyes treated with EKP compared to 20/30 for 209 eyes treated with PKP ($p = 0.0003$). Over 75% of eyes achieved a best-corrected visual acuity of 20/40 or better after PKP, compared to only 25% after EKP. Among patients who did not choose to use optical correction postoperatively, the median visual acuity was 20/60 in 84 eyes treated with EKP and 234 eyes treated with PKP. The large series of patients treated with EKP was generated, in part, because of logistical concerns about the ability of many of the patients to have access to prompt intervention for graft-related complications, due to long distances required to travel to the tertiary eye care facility in Riyadh. Despite logistical concerns that previously existed about access to postoperative care and patient compliance, the prognosis for PKP in the latter group was found to be excellent, with a high rate of clear grafts and an acceptably low complication rate.[31]

SUMMARY

There has been limited enthusiasm about utilizing EKP as an alternative to PKP in eyes with keratoconus because of statistically significant poorer visual results.[20] Deep anterior lamellar keratoplasty (DALK) has become the alternative procedure of choice for eyes with scarring in the visual axis for which PKP is undesirable or contraindicated.[39] Visual outcomes comparable to those achieved with PKP may be possible with DALK due to the virtual elimination of interface scarring that often occurs after LKP. Epikeratoplasty may still be considered as an option if there are concerns about self-induced trauma from rubbing (e.g. Down's syndrome) or external trauma related to professional or athletic activities, especially if the alternative is withholding surgical therapy. Although both LKP and DALK maintain some extraocular advantages of EKP, they can make the eye more vulnerable to trauma, although not to the same degree as PKP, thereby preserving a limited role of EKP for this indication. From a surgical standpoint, EKP is also technically easier than DALK.[40] Finally, for contact lens-intolerant patients with clear corneas and mild to moderate keratoconus, intracorneal ring segments may supplant EKP due to acceptable visual results and greater likelihood of achieving complete reversibility in failed cases.[41,42]

Originally, EKP was expected to become the treatment of choice in countries without eye bank programs because of logistical difficulties in obtaining donor tissue before the expiration of donor endothelial viability and concerns about access of many patients to prompt and reliable postoperative care. The current use of donor storage media with donor endothelial viability of up to 2 weeks[43–45] has made it possible for countries, such as Saudi Arabia, that obtain donor tissue from abroad to offer patients a prognosis for graft survival that is comparable to that obtained in Western countries, despite the difference in media storage time.[29,31,45] The alternative use of EKP because of concerns about patient compliance and access for follow-up care remains applicable in some areas.

FUTURE DIRECTIONS

SYNTHETIC EPIKERATOPLASTY

Synthetic epikeratoplasty (S-EKP) is an investigative procedure whereby a biocompatible synthetic lenticule is attached to the anterior surface of a de-epithelialized recipient cornea in a manner identical to that described for EKP.[46–48] The impetus to develop S-EKP originated from a desire to overcome the shortcomings of the use of fresh or lyophilized donor tissue for EKP, while retaining the benefits of providing a potentially reversible extraocular procedure. Whether using fresh corneal tissue, lyophilized corneal tissue, or synthetic tissue, an ideal donor lenticule must (1) be readily available, (2) be of predictable size and dioptric power, (3) have optical clarity, (4) support epithelial migration and adhesion, (5) be permeable to solute, and (6) resist enzymatic digestion.

The anticipated success of EKP as a refractive procedure raised concerns about potentially compromising the availability of donor tissue for patients needing optical or therapeutic keratoplasty. This concern was partially offset by the requirement that tissue used for EKP should be unsuitable for corneal transplantation, but this did not address the issue that the potential demand for hundreds of thousands of donor corneas per year would impose upon eye bank networks. Successful development of an S-EKP lenticule offers the potential for a limitless supply of lenticules, thereby eliminating concerns related to both ethics and supply of donor tissue for the procedure.

Collagen-containing or collagen-derived materials and copolymers consisting of 2-hydroxyethyl methacrylate (HEMA) and collagen are good candidates for biomaterials for S-EKP.[46] Both materials are biocompatible, are adequately permeable to aqueous nutrients and metabolites, and can be accurately cut to precise diameters, thickness, and dioptric power. Reliable in situ excimer modulation is theoretically feasible with either material, since haze and collagen remodeling would not be expected in an acellular matrix. Lenticules containing type I, III, or IV collagen offer the advantage of good potential for epithelial migration and adhesion, but the disadvantage of susceptibility to enzymatic degradation by naturally occurring collagenase. Copolymers containing HEMA have better resistance to enzymatic degradation, but potential problems supporting epithelial migration and adhesion.

Thompson and coworkers reported limited in vivo success with S-EKP in nonhuman primates.[46–48] S-EKP lenticules were prepared with type IV collagen extracted from the supernatant of human placenta that was cross-linked with glutaraldehyde. Lenticules were 7.5 mm in diameter and 250 μm thick, and had an optical power ranging from +10.00 to −10.00 D. In vitro studies demonstrated that these synthetic lenticules were capable of supporting epithelial spreading and attachment. In vivo studies were performed on seven eyes of seven monkeys who were selected as an experimental model due to similarity of rhesus monkey eyes to human eyes. Failure of re-epithelialization in the first four eyes with lenticular loss due to expulsion or erosion was attributed to eye rubbing. Success of re-epithelialization in the last three eyes was attributed to hand restraints that were used for the first 7 postoperative days. Among the three eyes with successful re-epithelialization, two had focal erosions at 4 months, while one remained stable until the animal was sacrificed 42 months postoperatively. Histopathological examinations demonstrated evidence of formation of satisfactory

hemidesmosomes, anchoring fibril components, and new basement membrane.

As with EKP, other advances in the treatment of keratoconus and refractive disorders of the eye has dampened the enthusiasm for further development and implementation of S-EKP in humans. Sufficient fresh corneal donor tissue is available for the rather limited indications of EKP for KC, and most of the shortcomings of the procedure related to the use of lyophilized tissue have been eliminated. The advent of modern, reliable, and relatively simple and safe keratorefractive procedures,[49,50] and the availability of safe intraocular lenses and implantation techniques for all age groups[15,18,19] make further development of S-EKP for the correction of ametropia in humans unlikely to occur in the foreseeable future.

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40 Deep anterior lamellar keratoplasty

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The goals of corneal transplantation are to provide corneal clarity with minimal irregularity to permit good vision indefinitely. Penetrating keratoplasty (PKP) may be complicated by endothelial graft rejection and failure, with poor prognoses for regrafts.[1] Lamellar keratoplasty or partial-thickness corneal grafting retains the patient's own endothelial layer, eliminating corneal blindness from allograft rejection. The procedure does, however, require some technical skill to obtain consistently good outcomes. Several advances in technique, combined with improvements in instrumentation, have made the procedure a worthwhile consideration in those with a normal endothelium.

HISTORICAL PERSPECTIVE

The concept of creating a lamellar corneal dissection leaving Descemet's membrane was first postulated by Von Walther in 1830 and further advocated by his student Muhlbauer in 1840.[2] During the late 19th century and first half of the 20th century, Von Hippel, Dürr, De Wecker, Füchs, Filatov, and Paufique all performed lamellar grafts and developed surgical techniques.[3] Deep dissection into the recipient cornea was pioneered by Hallermann in 1959 using full-thickness donor material.[4–6] The motivation to develop and perform lamellar techniques was to avoid penetration of the eye rather than endothelial preservation, of which there was little understanding at the time. Better outcomes were observed with deep dissection, and several hypotheses to account for this observation were proposed. These included McCulloch's theory that deep dissection left minimal host edematous tissue posterior to the graft[7] and the Descemet's membrane (DM) on the donor would act as a barrier to aqueous influx. Deep anterior lamellar grafts were performed with full-thickness donor tissue in conditions including bullous keratopathy!

Stocker suggested that the outcomes of deep anterior lamellar grafts with full-thickness donors were better as 'Descemet's membrane provides a smoother line of separation between donor and recipient, which may encourage the formation of thin solid connective tissue barrier which acts as a barrier to aqueous humor.'[7] Malbran and Stefani in1972 described better results by peeling off stroma from Descemet's centrally.[8] In the same year, Anwar described deep dissection under direct visualization. He found that deeper dissection down to DM level created a very smooth surface.[9] Anwar used full-thickness donor tissue but stripped off Descemet's membrane before transplantation and demonstrated less inflammation and interface scarring. This was supported by histopathologic evidence by Morrison and Swan.[10] Archila in 1984 described a new technique of injecting intrastromal air to facilitate deep lamellar dissection.[11–16] Hydrodelamination of Descemet's membrane was later introduced by Sugita and Kondo (1997),[17] with many adopters of the technique.[15,18,19] Hirano et al, however, demonstrated that delamination does not in fact take place at the Descemet's–stroma interface as initially thought but rather between the anterior and posterior banded zones of Descemet's membrane, reducing the tensile strength of the remaining tissue even further.[20] Melles et al described a novel method to aid deep dissection by injecting air into the anterior chamber to optically delineate Descemet's membrane.[21,22] Finally, in 2002, Anwar and Teichmann introduced the 'big bubble' technique to separate DM by injecting air close to deep stroma.[23,24] The surfaces produced with this technique provide a smooth interface with good early visual outcomes.

PRE-DESCEMET'S AND DESCEMET'S DISSECTION

The variety of techniques developed has now culminated in two possible levels of dissection for deep anterior lamellar keratoplasty (DALK), namely pre-Descemet's, where a small amount of posterior stroma is left on the recipient, and Descemet's, where the membrane is exposed with no residual stroma. The accomplishment of this dissection depends on whether manual dissection is performed or a delamination using either water or air. Although exposure of Descemet's possibly provides the best chance of visual outcome, a small amount of residual posterior stroma does provide more tensile strength, reducing complications, and is unlikely to significantly affect visual outcome. An alternative is a combination of pre-Descemet's dissection peripherally and peeling of stroma centrally to the level of Descemet's membrane as advocated by Malbran.[6] Ultimately, surgeons should select the technique that they are most comfortable with and that is reproducible in their own hands.

INDICATIONS

The indication for DALK is in all cases where the endothelium is normal and where pathology involves deep layers of the corneal stroma. Such indications include keratoconus ocular surface disease and corneal perforations.[25,26]

Outcomes of DALK are often related to the underlying diagnosis and indication for surgery. A proposed classification is to use the indication for performing the procedure and broadly divided into visual, tectonic, ocular surface disease, and miscellaneous (Table 40.1). Ocular surface disease is a special category in that factors that contribute to graft failure include persistent inflammation and corneal necrolysis from persistent epithelial defects. Graft survival was found to be better in those that had a lamellar graft rather than penetrating grafts in association with keratolimbal stem cell transplantation.[38] This categorization enables appropriate comparison of outcomes among authors.

SURGICAL PLANNING

Careful planning is necessary along with appropriate patient counseling. A useful list of questions for surgeons to ask themselves includes: (1) Is the endothelium normal? (2) What level does the pathology extend to and might it involve Descemet's membrane? (3) Will leaving minimal posterior stroma affect visual outcome? (4) What dimensions are required and is dissection technically possible? (5) Are there any issues that may influence the choice of technique, such as previous history of hydrops and a break in Descemet's membrane that might make a delamination technique a relative contraindication? (6) Finally, which dissection technique should be used?

Table 40.1 Indications for lamellar keratoplasty

Visual (optical)
• Keratoconus
• Corneal stromal dystrophies
• Corneal stromal degenerations
• Deep corneal scarring (traumatic, post infection, and other stromal scars)
Tectonic
• Corneal ectasia (focal such as pellucid marginal degeneration, diffuse, or post full-thickness grafting)[4,27]
• Corneal melt (autoimmune,[28,29] neurotrophic, or infectious[30,31])
• Traumatic corneal perforation[32–34]
• Peripheral corneal thinning (Mooren's ulcer, Terrien's marginal degeneration,[35] collagen disease, and other autoimmune diseases)
Ocular surface disease
• Stevens–Johnson syndrome (SJS)
• Chemical or thermal burns
• Ectodermal dysplasia
• Ehler–Danlos syndrome
• Corneal stromal scarring or thinning from an ocular surface disease
Miscellaneous
• Postexcision of corneal lesions (pterygium,[36] dermoid,[37] and tumors)

PATIENT COUNSELING

Patients must be counseled regarding the procedure, with special emphasis on the technical challenges and the possibility of a macroperforation and conversion to PKP. It is probably wise to include the possibility of conversion in the consent form. Other complications, including a double anterior chamber and early intervention and injection of air or isoexpansile gas, should also be conveyed. This is often balanced out by detailing the advantages of the procedure, including the safety of a relatively closed system and the reduced long-term risk of visual loss from rejection. Patients should understand the need for spectacles or contact lenses following surgery and possibly even refractive surgery for high levels of astigmatism.

ANESTHESIA CONSIDERATIONS

Lamellar keratoplasty can and often is performed under local anesthetic; however, monitoring by an anesthesiologist or designate is advised. General anesthesia is useful for a surgeon learning the technique; however, as air may be used in the anterior chamber, the anesthetist must be informed that no nitrous oxide should be used, as this will result in expansion of the air bubble within the eye. The latter may have unexpected and serious consequences, including high pressure and loss of vision.

SURGICAL TECHNIQUES

Vertical trephination and peripheral undermining in the recipient helps good graft–host apposition, accommodation of a thicker donor, and avoidance of graft slippage after suture removal. This improves the visual and refractive outcomes by reducing astigmatic error. Dissection should be as deep and smooth as possible, close to Descemet's membrane to minimize the risk of interface haze and reduced vision due to bed irregularity and consequent irregular astigmatism.[39]

A variety of surgical techniques will be described, commencing with ones that involve dissection and classified as pre-Descemet's followed by others that involve delamination and exposure of Descemet's membrane.

DIRECT DISSECTION

This technique involves initially performing a partial-thickness trephination in the recipient. The corneal stroma is then dissected using a lamellar spatula or crescent knife under direct visualization. Once accomplished, a full- or partial-thickness donor is sutured in place. This technique can be used in situations where the eye is soft, such as a perforation. The disadvantages of this technique include unreliable depth of dissection and possible tilt with a thicker area of remaining stroma on one side of the donor compared to the other, resulting in high levels of astigmatism. Irregularity of the host bed may also be translated to the anterior surface and compromise

vision. The incidence of interface haze can also be high, resulting in reduced vision.

MELLES TECHNIQUE

Melles and coworkers described a technique to visualize the depth of lamellar dissection in DALK. The technique involves exchanging the aqueous with air through a long paracentesis, creating an optical air–endothelium interface.[21] This interface acts as a convex mirror, reflecting back the posterior stroma and instrument to the viewer. A limbal incision is made, and Melles' red dissector (DORC Instruments, Rotterdam, Netherlands) is used to advance posteriorly. A black band is visualized in front of the dissecting instrument, which represents twice the residual posterior stroma (Fig. 40.1). As the instrument advances posteriorly, the black band disappears rapidly and wrinkles become apparent in Descemet's membrane. At this point, the correct depth has been reached close to Descemet's membrane and the red dissector is exchanged for the silver dissector to separate the tissue further through the limbal incision. A longer and more curved blue dissector is used to dissect the cornea in the far periphery opposite the incision. The whole cornea is dissected and, once accomplished, air is partially removed from the anterior chamber and viscoelastic is injected into the lamellar plane to push the posterior lamellar layer posteriorly.[40,41] Trephination is then performed anteriorly, perforating the anterior cornea. The anterior recipient tissue is removed, and the viscoelastic removed by irrigation followed by suture of a full donor with Descemet's membrane removed (see Donor preparation, below).

This technique has the advantage of being reproducible; however, dissection of the whole cornea is unnecessary. Additionally, with such a large area of dissection, tears in Descemet's membrane can occur diagonally opposite to the limbal incision or possibly involve the cone if excessively steep.

The author (SMD) has modified Melles' technique (Fig. 40.2, *A–D*) and commences by performing partial-thickness trephination to 75% depth. A paracentesis is created peripheral to the trephined area for air injection. Dissection takes place using Melles' optical delineation technique in the area central to the trephination along with some peripheral undermining. The anterior lamellar tissue is removed with curved corneal scissors with the bevel angled outward in order to avoid a ledge, and the donor is then sutured. The greatest advantage of this technique is its reproducibility. Deep dissection can be achieved in almost all corneas whether or not there has been previous hydrops. The author has also used this technique to perform lamellar keratoplasty on eyes with previous PKPs that have developed thinning in peripheral host tissue from residual keratoconus. The rationale is to add tissue to the host, permitting a future smaller graft centrally. In six of seven cases performed, no further graft was required, with all patients gaining vision (Fig. 40.3). One case obtained good vision (20/30) for 2 years and then developed endothelial decompensation.

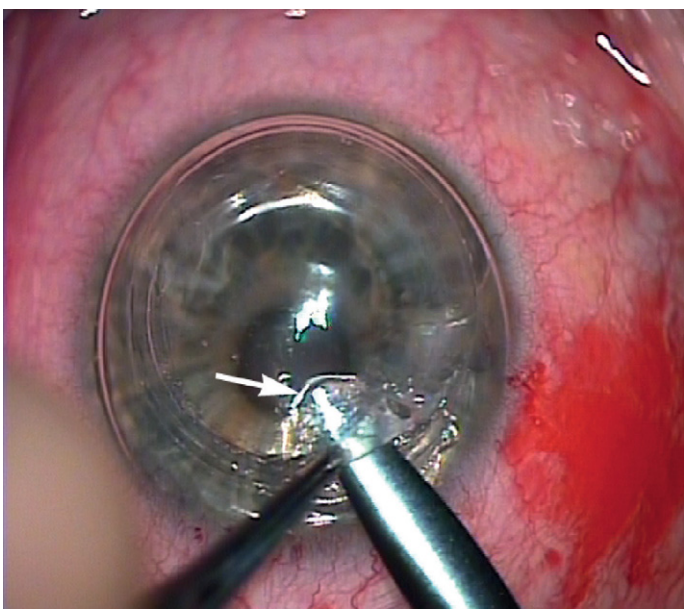


Figure 40.1. Author's modification of Melles technique, using a partial-thickness trephination to commence dissection. Arrow illustrates the 'black band,' representing twice the residual posterior stroma.

FERRARA'S CIRCULAR RING TECHNIQUE

A more recently described technique by Ferrara uses a wider channeling ring similar to that used for implantation of intracorneal ring segments. The curved blade has an eyelet at its tip through which a 6-0 monofilament nylon suture is passed. A mark is placed on the cornea, and the corneal thickness is measured at the point of incision. A micrometer diamond knife is set to 90% and a vertical incision made. A pocketing knife is used to create space posteriorly to allow entry of the curved blade with suture attached. The ends of the suture are held outside the incision with enough slack to allow the blade to rotate. The blade is slowly rotated in the corneal stroma 360° until the tip reaches the radial incision. The leading end of the suture is then removed through the incision. The two ends of the suture are now held, one that remained outside at the entry point and the other passed through the corneal channel and retrieved at the incision. The two ends of the suture are then pulled gradually toward the incision, acting like a cheesewire and creating an ultra-smooth dissection through the cornea. Once the suture is pulled out of the corneal stroma, trephination is performed and an appropriate-sized full-thickness donor is sutured in place.[42]

INTRASTROMAL AIR INJECTION

Archila, Price, and Chau described injection of air into the corneal stroma to opacify and thicken the cornea to facilitate dissection and identification of Descemet's membrane.[11,12,16] As corneal thickness increases the margin of error improves. Furthermore, any tissue left behind subsequently thins out following absorption of air. The technique involves injection of air in the midperiphery of the cornea using a 26-guage needle. This turns the cornea white. A partial trephination is performed and followed by lamellar dissection as close as possible to Descemet's membrane. Once the correct depth is achieved, a blunt spatula is used to complete the dissection of stroma. A paracentesis is usually performed after the injection of air to decrease intraocular pressure, especially if air has entered the anterior chamber as often occurs, possibly through the trabecular meshwork.[12] Occasionally injected air accumulates as a bubble in between stroma and Descemet's; this observation furthered the development of the 'big bubble' technique of Anwar.

A disadvantage is that this technique is not possible in corneas that have had previous breaks in Descemet's membrane. Additionally, dissection can be difficult to accomplish successfully through a scarred opaque cornea or with opacification created by stromal air.

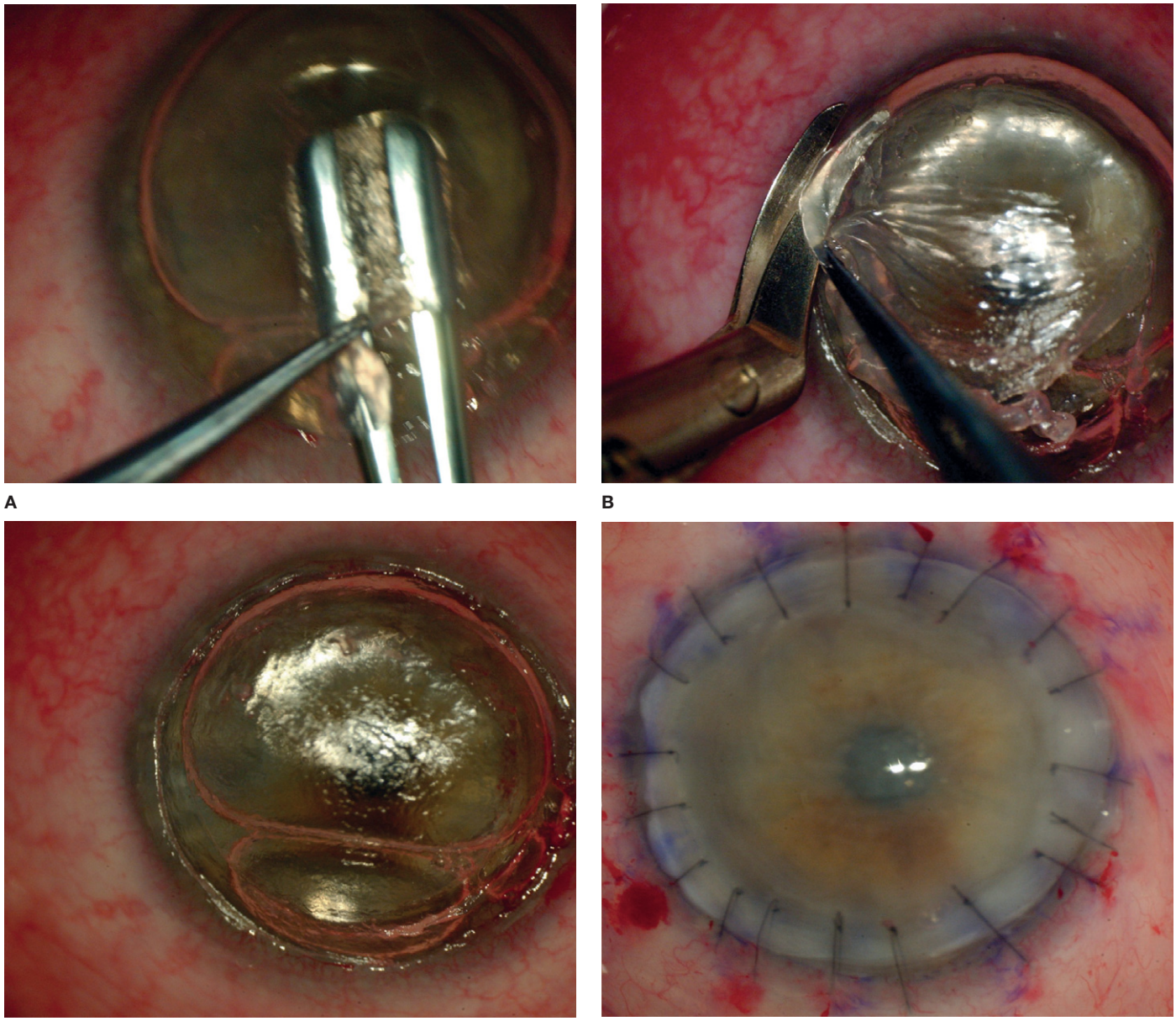


Figure 40.2. Large 10 mm DALK. Following optical delineation of Descemet's membrane, *A*, dissection performed using Daya Lamellar Separators (Duckworth & Kent, Herts, UK), *B*, removal of anterior lamellar tissue using curved corneal scissors, *C*, exposed posterior lamellar bed, and *D*, graft sutured in place.

AIR DISSECTION OR 'BIG BUBBLE' TECHNIQUE OF ANWAR

The occasional observation of a big bubble in the stroma after intrastromal injection led Anwar to develop a technique to achieve the big bubble more consistently.[9,23,24,43] The technique has the advantage of exposing Descemet's free of overlying stroma. A partial-thickness trephination is performed aiming at 60–80% depth. A 27- or 30-gauge bent needle, bevel down and attached to a syringe filled with air, is introduced deep in the stroma (about 3–4 mm from entry site) and air is injected (Fig. 40.4, *A*). In most cases, the air forms a big bubble between Descemet's membrane and the stroma. The bubble is a sharply defined whitish semiopaque disc (Fig. 40.4, *B*). A paracentesis is performed outside the area of trephination to allow the eye to be softened if necessary. Partial anterior dissection is performed, leaving a thin layer over the big bubble. A final dissection removing the remaining anterior lamellar tissue is performed with a protective spatula in the space immediately anterior to Descemet's membrane (Fig. 40.4, *C* and *D*). This portion of the procedure is potentially hazardous, as the fragile Descemet's membrane can easily tear if it comes into contact with any sharp-edged instrument or barb from a damaged instrument.

A disadvantage of this technique is that a big bubble is not always achieved. If this occurs, further air injections can be considered at sites where the cornea is still clear. Should this also not be successful (9% in Anwar's hands[23,24]), then anterior lamellar dissection will need to be carried out similar to the intrastromal air injection technique described above. While the technique is rapid when successful, it is limited to those who have not had previous injury to Descemet's membrane (laceration or hydrops). In the case

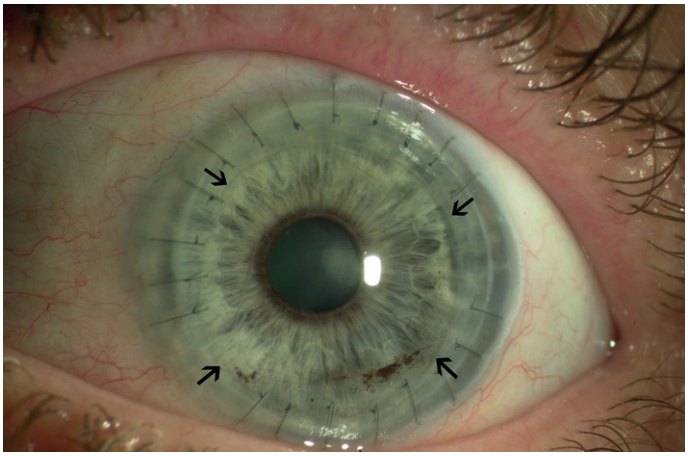


Figure 40.3. Large lamellar graft on a previously grafted (PKP) keratoconus eye with severe corneal thinning peripheral to the graft. Arrows indicate the edges of the retained posterior aspect of the old PKP.

of a previous Descemet's tear, injection of air could lead to dehiscence of the previous wound and perforation.

HYDRODELAMINATION

This technique was originally described by Sugita and Kondo[17] and involved injection of balanced saline solution into the deep stroma to swell stromal collagen fibers, thus thickening the cornea and facilitating deep dissection. Like stromal injection of air, the technique reduces the risk of DM perforation. Unlike air, which opacifies all tissue, scarred stroma does not easily swell and is relatively easy to differentiate from normal clear corneal stroma, enabling a dissection sufficient to resect corneal pathology. Panda and Singh compared the results of hydrodelamination with other techniques (air injection, viscoelastic dissection, and dry dissection) and found this technique to be less time-consuming and easier to perform, although visual and refractive outcomes were similar in all groups.[15]

VISCOELASTIC DISSECTION

In 1999, Manche et al utilized the observation of Descemet's membrane detachment after inadvertent injection of viscoelastic material in the cornea to design intentional DM detachment by injecting viscoelastic material in the deep corneal stroma.[41] Later, Melles et al described a quicker method using viscoelastic but optically defining Descemet's membrane using air in the anterior chamber as described above. When the 30 G needle is at the correct position, viscoelastic material is injected into the cornea to separate Descemet's membrane.[2,40,41,44,45] The stroma is excised and the interface is washed before suturing the donor cornea. It is important to remove all viscoelastic material, reducing the possibility of entrapment of material at the interface and a persistent double anterior chamber.[45] This method, however, has a high rate of perforation (25%).[40]

MISCELLANEOUS AND ADJUNCTIVE TECHNIQUES

Microkeratome-assisted deep lamellar keratoplasty has been previously described by Azar et al.[46] A microkeratome is used to create a hinged anterior stromal flap in the host cornea. This is followed by a manual deep lamellar stromal dissection and resection of diseased tissue. The donor graft is prepared in a similar fashion on an artificial anterior chamber. The donor button is then grafted, and the flap is repositioned and sutured. While there is a theoretical advantage of this technique in the ability to correct postoperative refractive error by lifting the flap and applying excimer laser treatment, it requires the use of expensive technology, and no studies have been performed to demonstrate any major advantage over other techniques.

Malbran's peeling technique,[6,47] described in 1972, pays attention to the visual axis, exposing Descemet's membrane centrally and leaving posterior stroma in the periphery, providing a clearer axis and thus better acuity. The technique can be used in situations where very large grafts are required for conditions such as keratoglobus.

DONOR PREPARATION

The donor can be created using a regular donor punch cutting from the endothelial side down. In keratoconus, using the same size helps to flatten the cornea and reduce myopia. Ideally, both the recipient and the donor surfaces should be as smooth as possible, and this can be accomplished by peeling Descemet's membrane. Removal can be accomplished by simply peeling Descemet's membrane using dry surgical spears on the edge of the posterior surface of the donor. Once the membrane edge starts to peel, complete dissection can be accomplished with nontoothed forceps or dry spear sponges (Fig. 40.5). To facilitate identification of Descemet's membrane Trypan blue can be used to stain the surface, and this can be useful in young donor tissue where Descemet's membrane is thinner.

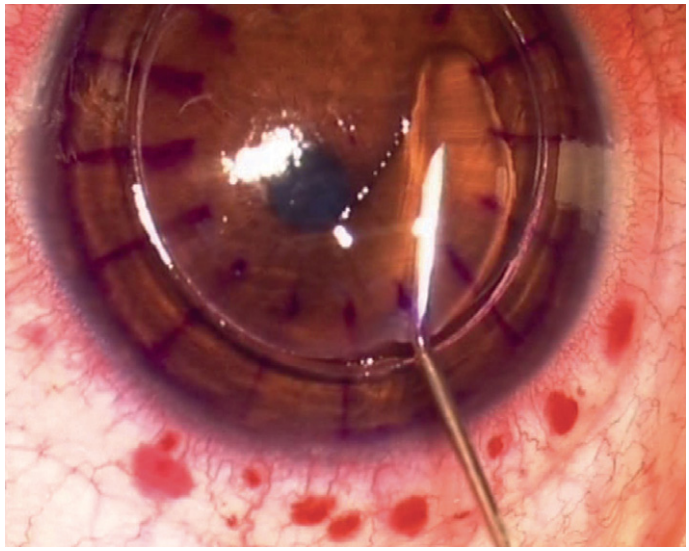
COMPLICATIONS—INTRAOPERATIVE

MICROPERFORATION

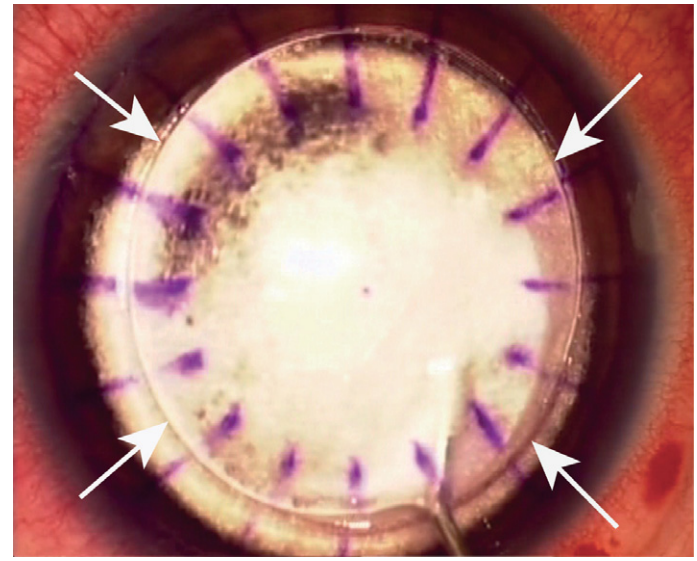
Inadvertent penetration of Descemet's membrane often occurs during the process of dissection. This can also result from shear forces on an old scar or from the edge of a dissecting instrument. This is usually evident by sudden softening of the eye and the excursion of fluid or air into the interface. Should this occur, it is best to reform the anterior chamber with air and continue to dissect the cornea at a site remote from the area of perforation, leaving this to the end. Leaving a small amount of stromal tissue above the area of perforation (if in the periphery) helps minimize chamber collapse after removal of the anterior lamellar tissue. The occurrence of microperforation can be as high as 39%[11,16,17,22,48] and can occur in the best surgical hands. To minimize the chances of a postoperative double anterior chamber, leaving an air bubble is useful, as is positioning the patient in a supine position in the initial postoperative period.

MACROPERFORATION

This typically occurs at the site opposite the point of entry. In very steep keratoconic eyes, to avoid this complication, the author suggests leaving the dissection of the apex and the area opposite till later. Progressive dissection can be accomplished by sequentially cutting the recipient along the line of trephination, enabling access for dissection of the remaining cornea. Central dissection can be



A



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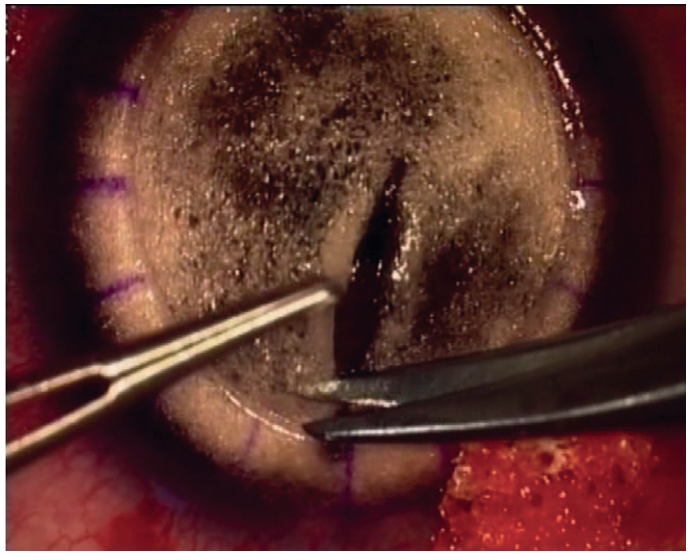

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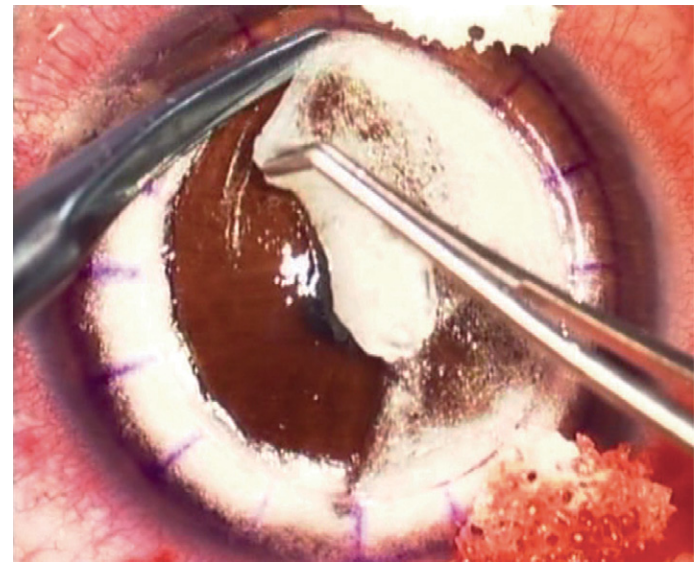

D

Figure 40.4. Big bubble technique of Anwar and Teichmann. *A*, A bent 27-gauge needle with the bevel down is inserted into the stroma in the mid periphery. *B*, Air is injected and a 'big bubble' is visible with edges outlined by arrows. *C*, Following removal of an anterior stromal layer, an incision is made to the big bubble. *D*, The remaining stroma is removed with curved corneal scissors. (Images courtesy of Mohamed Anwar.)

accomplished more reliably under direct visualization. Should a macroperforation occur, the situation is still retrievable if most of the cornea has been dissected. An air bubble can be used to position the posterior lamellar layer against the anterior donor. If this cannot be performed, then conversion to a PKP may be necessary.

PUPILLARY BLOCK GLAUCOMA

This can occur whenever air is left in the anterior chamber. The air bubble can block the pupil, leading to posterior accumulation of aqueous and angle closure. This is best avoided by pupil dilation whenever air is used or by limiting the size of the air bubble and also periodically examining the eye in the hours immediately after surgery. One consequence of transient high pressure is Urrett–Zavalier syndrome,[49] where the pupil can become atonic and dilated.

COMPLICATIONS—POSTOPERATIVE

DOUBLE ANTERIOR CHAMBER

This is a result of a microperforation or from sutures that have been passed through the posterior host cornea, providing a channel for aqueous to enter the interface[50] (Figs 40.6 and 40.7). Another cause is entrapped viscoelastic material at the interface if viscoelastic, when used, is not sufficiently irrigated from the host bed. Varying rates of double anterior chambers have been reported with up to 30% of cases in one report.[17] Spontaneous resolution usually does occur; however, healing may be accelerated by injecting intracameral air or isoexpansile gas (e.g. sulfa-hexafluoride, SF6) and drainage of interface fluid through the graft host incision. This can be accomplished at the slit lamp through a paracentesis

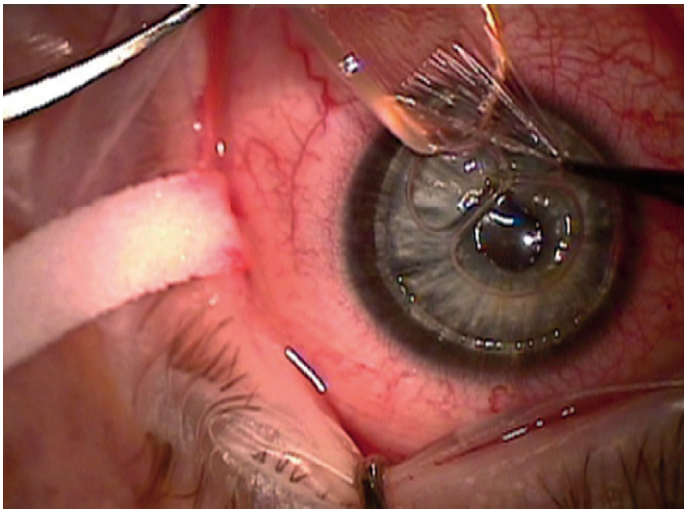

Figure 40.5. Following punch trephination removal of Descemet's membrane with fine nontoothed forceps after the edge is identified.

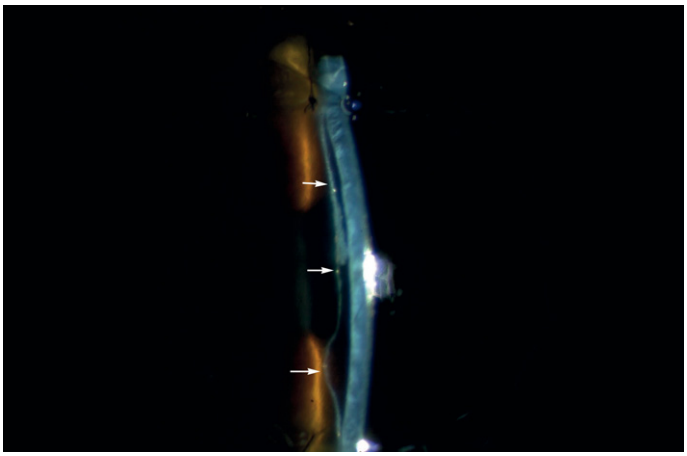

Figure 40.6. Double anterior chamber, arrows showing the posterior lamellar layer dislocated from the donor, day 1 postoperatively.

incision. Early management may decrease the chance of interface haze.

FOLDS AND WRINKLES

Descemet's folds and wrinkles often occur secondary to compression at the interface in cases where there is a disparity between the posterior lamellar surface area and donor cornea as in keratoconus. The wrinkles are typically concentric and outside the visual axis, and have no visual consequence (Fig. 40.8). Sometimes folds occur in the visual axis and these can be induced by sutures. These are best identified at the time of surgery using air in the anterior chamber. If not related to sutures, the folds can be removed by using closed forceps at the graft–host wound to pull the posterior lamellae peripherally. Should folds persist, they are likely to affect vision; however, we have observed them to disappear over several years.

EPITHELIAL, SUBEPITHELIAL OR STROMAL REJECTION

Allograft tissue can reject at different levels anatomically with the exception of endothelium. Stromal, epithelial, or subepithelial graft

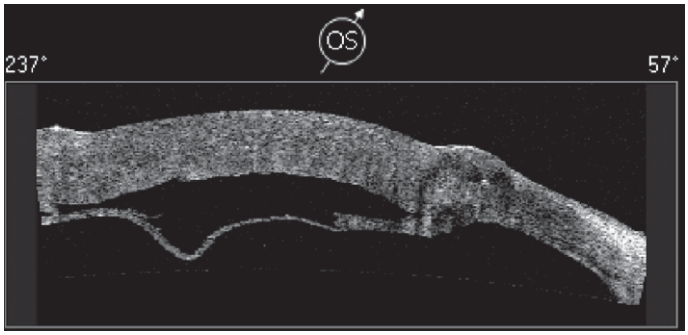

Figure 40.7. Visante (Zeiss-Meditec, Jena, Germany) ocular coherence tomography (OCT) image of an eye with a double anterior chamber prior to injection of air.

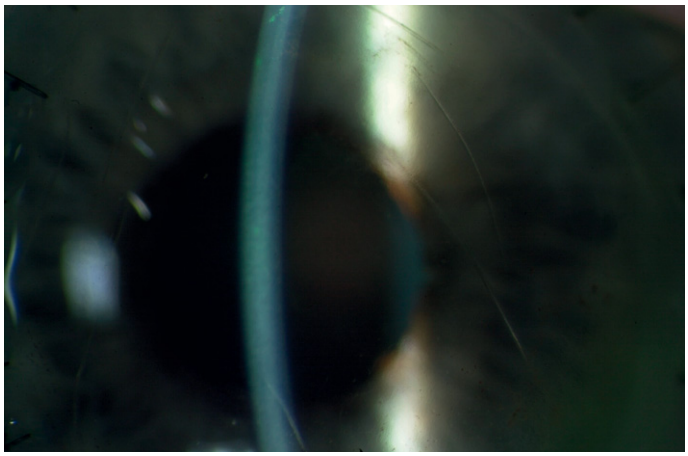

Figure 40.8. Descemet's membrane compression folds, concentric superiorly.

rejections have been reported,[51,52] and the time to rejection can vary. Epithelial rejection manifesting as an advancing line of edema often inferiorly usually occurs in the first year. Subepithelial infiltrates indicating subepithelial rejection also often occur in the first year and like epithelial rejection can be treated with increased frequency of topical steroids. Stromal rejection (Fig. 40.9) is rare (1.4%[53] and 1.9%[39]) and manifests as stromal edema along with vascularization, later clearing and leaving ghost vessels. Stromal rejection can occur at any time. Al Torbak et al reported a case of stromal rejection 16 months after DALK for keratoconus in a 13-year-old girl,[51] and Watson et al reported this as late as 41 months.[52]

POSTOPERATIVE CARE

SHORT TERM

Management of a DALK in the immediate postoperative period includes topical steroids and a broad-spectrum antibiotic. Specific therapy may be required depending on the underlying diagnoses. Where a lamellar graft is performed for herpes simplex, prophylactic indefinite use of acyclovir 400 mg twice daily is advised. Steroid use can be reduced earlier than for a PKP; however, rejection can occur as indicated above and patients must be informed to return if symptoms or signs of redness, sensitivity to light, visual loss, or pain (RSVP) occur. In the context of ocular surface disease, rapid epithelialization is the goal and all measures to achieve this must be undertaken to preserve graft clarity and integrity.

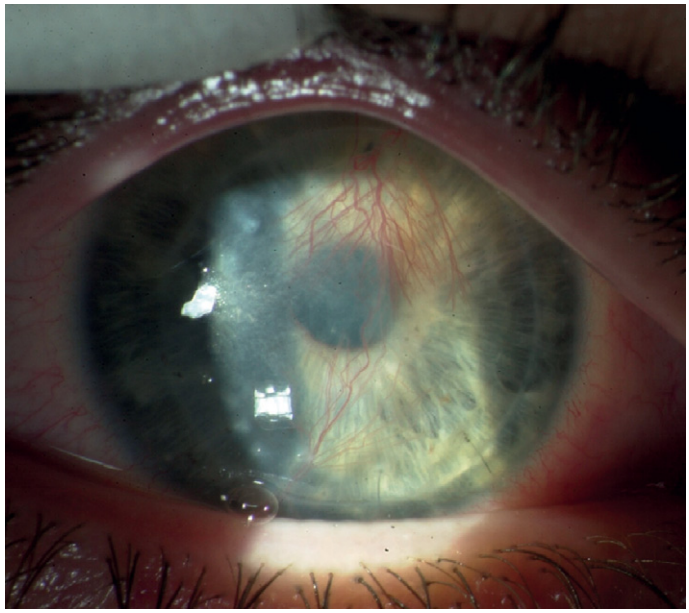

Figure 40.9. Stromal rejection of donor 12 months after DALK.

Figure 40.10. Visante OCT image of a well-apposed DALK. Note the thin dimensions of the posterior lamellar layer (arrowheads).

SUTURES

Sutures can be removed as early as 9 months, depending on how aggressively the wound has healed and how quickly steroids have been tapered. The author prefers to leave sutures in for at least 18 months if possible and until a strong fibrous ring at the interface is observed. This decreases the chances of graft dehiscence and high astigmatism.

VISUAL REHABILITATION

Visual rehabilitation can take a year or longer; however, patients, especially those with keratoconus, notice a dramatic improvement quite early from corneal flattening and reduction of myopia alone. In the authors' own series of 119 eyes who received grafts for visual rehabilitation, at last follow-up the spherical equivalent was –0.96 D. Spectacle correction and sometimes contact lenses are needed. Laser refractive surgery can also reduce anisometropia and high astigmatism. Once all sutures have been removed and vision rehabilitation accomplished, patients in low-risk categories can often be discharged from care altogether.

OUTCOMES

ENDOTHELIAL CELL LOSS

Several reports have demonstrated normal endothelial cell counts in recipients of DALK.[54–57] The progressive decline in endothelial cell density that is seen following PKP does not occur at the same rate in DALK. The percentage of endothelial loss after DALK varies from 10 to 25% depending on the surgical technique.[17,54,55] Long-term (10 years or more) outcomes in terms of endothelial cell counts are not available for DALK. The initial drop in endothelial cell count after PKP is up to 33% at 2 years and 50% after 5 years. Cell loss in PKP continues at a rate of 4.2% 5–10 years postoperatively.[58] In DALK by comparison, endothelial cell loss is 11% at 6 months, 2% at 1 year, and 1.2% at 2 years.[55] As the cells are not allogeneic, it is expected that cell loss will in time decline to reach the physiologic rate of normal adult human eyes (0.6 ± 0.5%).[55,59,60] Complications, especially those needing surgical intervention or manipulation of the graft, might adversely affect the cell count; however, Sugita and Kondo[17] found that the difference in cell count between those who developed a double anterior chamber requiring intervention and a group of uncomplicated cases was not statistically significant at 12 months postoperatively.

VISUAL OUTCOMES

There is usually a significant improvement in the visual acuity after a year.[16–18,48,61] Soong et al reported that 79% of patients required at least 1 year to achieve vision of 20/50 and that there was progressive improvement in visual acuity with time.[39] Limitations to visual improvement can be from interface haze causing light scatter. Folds in Descemet's membrane can also have an effect. Compression folds occur because of disparity between the posterior lamellae and the graft. The folds are typically concentric and outside the visual axis in keratoconus. Smoothness of the interface may also have an influence, and, as posterior lamellae are less compact, the deeper the dissection, the less the impact of irregularity (Fig. 40.10). Visual outcomes vary from report to another (Table 40.2). However, best visual results have been documented using the big bubble technique, supporting the concept that smoother is better.

REFRACTIVE OUTCOMES

Postoperative astigmatism influences visual rehabilitation with DALK. Lamellar grafts are sutured with 10-0 nylon, and a variety of suture patterns can be used. Uninterrupted (running) sutures facilitate adjustment to minimize any induced astigmatism. On the other hand, interrupted sutures allow for selective removal of sutures. The magnitude of residual astigmatism ranges from 2.00 to 4.00 D in most studies (Table 40.3), easily correctible with spectacles. Irregular astigmatism can occur, and contact lenses may be necessary for visual rehabilitation.

COMPARISON TO PKP

Penetrating keratoplasty and DALK result in comparable visual and refractive outcomes (Tables 40.2 and 40.3).[62] Deep anterior lamellar keratoplasty is more advantageous in high-risk situations, including

Table 40.2 Comparison of reported best-corrected visual acuity after deep anterior lamellar keratoplasty and penetrating keratoplasty in different studies

Study	No. of Eyes	BCVA ≥ 20/40	BCVA ≥ 20/30
Deep anterior lamellar keratoplasty for keratoconus			
Daya et al (unpublished)	50	74.2%	56%
Sugita and Kondo[17]	113	62.8%	N/A
Coombes et al[61]	37	80%	64%
Amayem and Anwar[18]	24	87.5%[a]	95.8%[b]
Watson et al[19]	25	87.5%	N/A
Anwar and Teichmann[23]	181	89%	27%
Fogla and Padmanabhan[56]	13	92.3%	84.6%
Funnel et al[62]	20	89%	78%
Penetrating keratoplasty for keratoconus			
Buzard and Fundingsland[63]	104	88%	88%
Lim et al[64]	93	87%	N/A
Watson et al[19]	22	95%	N/A
Funnel et al[62]	20	85%	N/A

[a] At 6 months.

[b] At 1 year.

Table 40.3 Comparison of different reports of astigmatism after deep anterior lamellar keratoplasty and penetrating keratoplasty

Study	Mean Astigmatism
Deep anterior lamellar keratoplasty	
Daya et al (unpublished)	3.36 D (SD ± 2.81)
Anwar and Teichmann[23]	3.25 D (1.75–8.00 D)
Watson et al[19]	4.00 D (–5.40, –2.00)[a]
Panda et al[57]	83% had astigmatism <3 D
Funnel et al[62]	3.10 D (SD ± .70)
Coombes et al[61]	3.85 D (SD ± .87)
Amayem and Anwar[18]	2.54 D (–1.0 to –4.00)
Fogla and Padmanabhan[56]	2.57 D (0 to –4.00)
Tsubota et al[48]	3.20 D (SD ± .30)
Penetrating keratoplasty	
Buzard and Fundingsland[63]	1.70 D (SD ± 3.10)
Watson et al[19]	3.25 D (–4.50, –2.25)[a]
Panda et al[57]	33.3% had astigmatism <3 D
Funnel et al[62]	5.00 D (SD ± 3.50)

[a] Median (interquartile range).

young recipients, large grafts, and highly vascularized corneas and in those who are mentally subnormal such as Down's syndrome.

Intraoperative complications that threaten vision are less likely to occur in DALK, as the procedure is essentially in a closed system. Risks of expulsive choroidal hemorrhage and infection are theoretically lower.

Postoperative care requires less use of topical steroids, thus reducing the likelihood of developing steroid-related glaucoma or cataract. There is also no need to use systemic immunosuppression following anterior lamellar keratoplasty. Retaining host endothelium eliminates the risk of endothelial graft rejection responsible for graft failure following PKP.[51,65,66] Epithelial, subepithelial, or stromal rejection has been observed; however, it is less intense and easily treatable.[51,52,62,65] Follow-up can thus be less frequent; however, patients need to be cautioned about the possibility of problems and must return to the transplant center immediately should these occur.

Visual outcomes have been reported to be better in full-thickness grafting.[39,66] However, recent studies have demonstrated comparable visual outcomes of DALK to PK.[56,62,67] Visual recovery, however, tends to take longer with DALK. Although glare test results at 6 months favor PKP, the difference is not statistically significant.[67] Guell and coworkers also reported better visual quality in eyes with a PKP in an intraindividual study comparing PKP to DALK.[68] Snellen acuities, however, have been reported to be comparable, and the impact of this difference in visual quality patients who have had very poor vision requires further evaluation.

A further advantage of DALK is the ability to perform very large limbal to limbal grafts in keratoglobus and even in those who have previously had a PKP and developed a thin residual periphery. This provides some comfort in being able to accomplish a large graft without the increased risk of visual loss through immunological rejection as might occur following a large PKP.

Finally, DALK has great application in developing countries where there is considerable shortage of corneal material. Outdated material not suitable for PKP can be used for lamellar techniques in this environment. Freeze-dried methods[12] enable long-term storage of lamellar tissue, which can be effectively used in this setting.

There is increased interest in deep anterior lamellar techniques. Regrafting following failed PKP is becoming a more common indication and, considering the poorer prognosis of regrafts, DALK for long-term visual rehabilitation is a more desirable option and should be considered whenever the endothelium of the recipient is normal.

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41 Indications and contraindications of penetrating keratoplasty

John E. Sutphin

Penetrating keratoplasty (PKP) is the most frequent and most successful organ or tissue transplant, with the exception of blood transfusions, performed in the USA. Table 41.1 indicates the relative frequencies of transplantations for 2006. These statistics refer to allografts or homografts, which are transplants from one member of a species to another. Penetrating keratoplasties may also be isografts using a donor from the fellow eye (autograft) or by rotating the transplant within the same eye (rotating autograft) or, less frequently, from a genetically identical twin. Xenografts are transplants between species and have not been done since the advent of transplant in the 19th century.

The exponential growth in the frequency of PKP is due to two principal developments. Prior to the mid-1930s, corneal transplant was reported infrequently and in small numbers because the requirement for diseased eyes with clear corneas as sources of tissue limited the availability of the operation. During the 1930s, Filatov in Odessa, Russia, popularized the use of cadaveric donors. The use of refrigerated donor eyes was expanded by the organization of eye banks with the first American bank established by R. Townley Paton in 1944 in New York City as the Eye Bank for Sight. The Eye Bank Association of America (EBAA) was organized in 1961 and reported 2000 transplants done that year. In 2006, the EBAA reported about 77 135 corneas donated and 45 035 transplanted.[1] The majority, 79%, were used for PKP, 13% for endothelial keratoplasty, 0.2% for anterior lamellar keratoplasty, and 0.0030% for keratolimbal allograft.[1] The second major contribution to this rapid growth has been the availability of preservation media, allowing for the maintenance of the donor cornea for periods up to 1 week with satisfactory clinical results.[1a] The first description of preservation was by Magitot in 1911,[2] but the modern era began with the use of McCarey–Kaufman media described in 1974.[3] There have been numerous improvements in the technology and technique of PKP since Zirm's first patient in 1905, but there have been no major changes in the underlying principles.[4]

INDICATIONS

Indications for a procedure are the reasons making that surgery particularly desirable for the condition to be treated. The decision to perform the surgery balances benefit versus risk in the specific patient. This section will cover the general benefits of corneal transplantation, including the common diagnoses for which it is performed.

Indications for keratoplasty fall into four broad categories:[5,6]

1. Optical: Prime purpose is to improve visual acuity.
2. Tectonic: Prime purpose is to restore altered corneal structure, including extreme thinning, perforation, and traumatic loss of tissue.
3. Therapeutic: Prime purpose is to relieve pain, to remove tissue for progressive keratitis after failure of specific antimicrobial or anti-inflammatory therapy or as an adjunct to other surgery, such as temporary keratoprosthesis and pars plana vitrectomy for ocular trauma.
4. Cosmetic: Prime purpose is to restore a normal appearance to an eye with limited vision potential.

Optical or visual indications for transplantation have become the principal reason, accounting for 74% of 5281 transplants in the Australian Graft Registry.[7] Therapeutic indications, primarily pain relief, were one of the immediate reasons for grafting in 20%; tectonic indications were listed in 3%; and cosmesis was included as an indication in 3%. Figures 41.1–41.4 show examples of the general indications. In the first series of transplants reported by Elschnig, 35 out of 174 (20%) of the grafts were for staphylomas or frank corneal perforations (tectonic).[8] With the advent of more specific diagnoses as the indication, the general indications are not always reported in large series.[9–12] Typically, a transplant done for visual reasons will have salutary effects to restore the appearance of the eye or to reduce comorbidity such as pain. But more importantly, transplants done to preserve the globe both tectonically and therapeutically will often have the benefit of improved clarity and subsequently improved visual acuity. Eighty per cent of all transplants showed at least one Snellen level of improvement, but only 66% of patients over 80 years old achieved improved postoperative vision.[7] Therapeutic keratoplasties will often have secondary effects of restoring a more normal appearance.

Optical indications for PKP generally follow the same guidelines as cataract surgery. There is no absolute level of vision below which

Table 41.1 USA transplant statistics

Tissue/Organ	Initial Year	Number in 2006
Cornea	1905	45 035
Kidney	1954	13 616
Heart	1967	2 276
Liver	1967	7 304
Pancreas	1969	2 027
Lung	1981	1 330

Source: United Network for Organ Sharing Facts and Statistics compiled for the National Organ Procurement and Transplantation Network under contract with the United States Department of Health and Human Services.

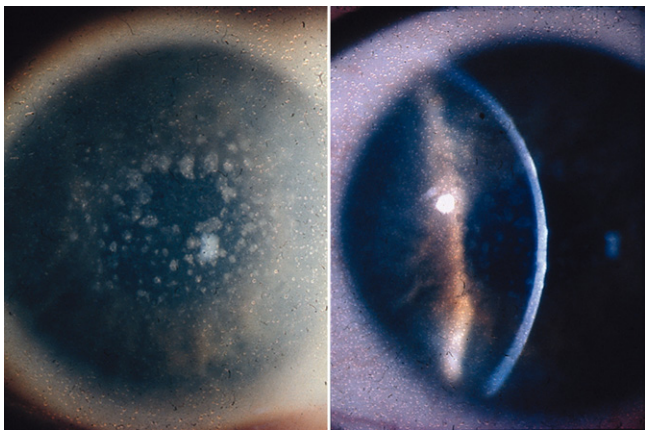


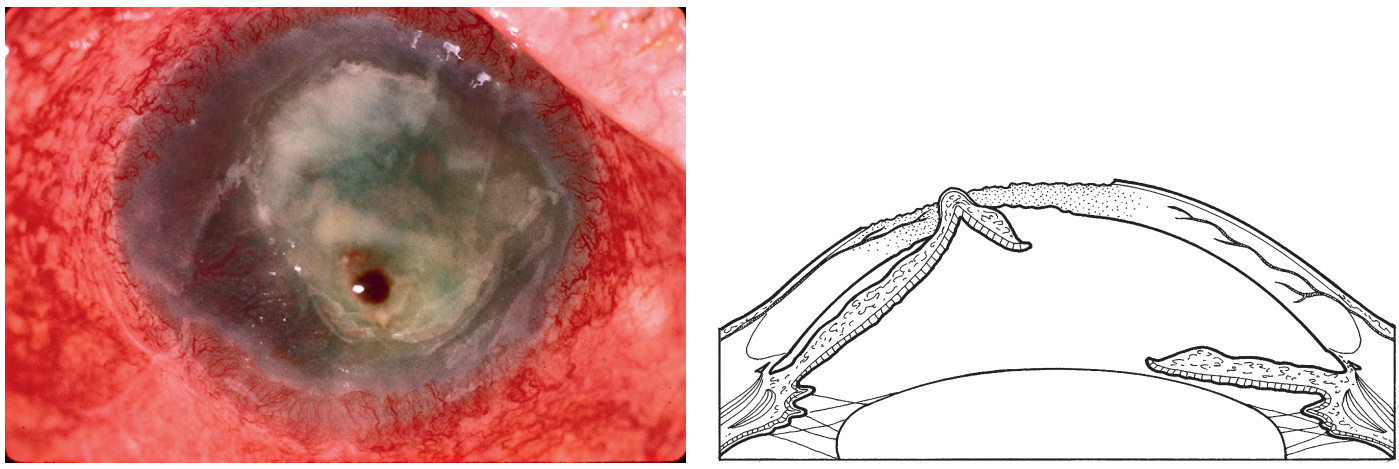
Figure 41.1. Optical Indication for PKP. This montage shows two views of an eye of a patient with macular corneal dystrophy and decreased vision from opacity and irregular astigmatism.

a patient requires cataract surgery. The indication for surgery is based on the patient's visual function and visual needs, intrinsic disease of the lens, or need for visualizing the fundus. Recently, there has been clarification of the indications in cataract surgery by several national organizations.[13] If both eyes are impaired by the underlying disease and the recipient is an acceptable candidate, then the indication for surgery is usually unequivocal. However, with the advent of managed care and the economic considerations of third parties, all indications for surgery have come under increasing scrutiny. Javitt and others showed the correlation between improved quality of life and improved visual function in a prospective nationwide trial of 1021 patients with cataract and other degenerative eye diseases measuring visual, social, and psychological endpoints.[14,15] Others have also shown unequivocally the benefit of improved visual function in improving the overall health of the elderly.[16–20]

Although PKP shares visual indications with cataract surgery, the prognosis for corrected visual acuity is less. The Australian Graft Registry reports, in a series of 5281 records, overall 1-year survival of 94% and 5-year survival of 74% with best Snellen vision of 20/40 in 48% of recipients.[7] Fifty-nine per cent had acuities of 20/60 or better and 24% were worse than 20/200. Better visual outcomes occur when indications are limited to dystrophies (20/40 in 66% with Fuchs' dystrophy[21] and 20/40 in 83% with keratoconus).[7]

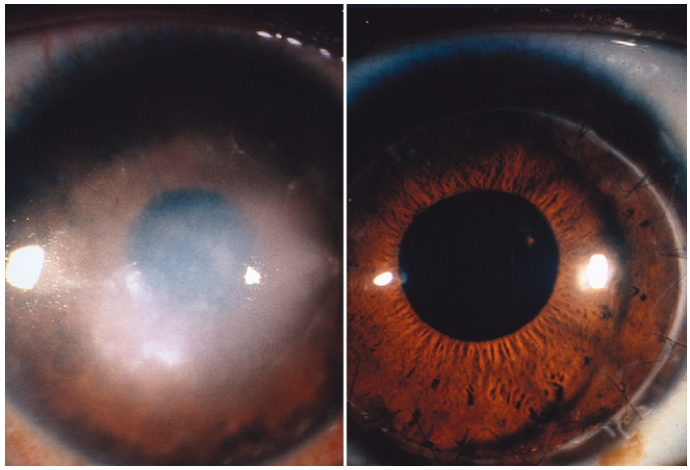
Patients' perceptions of the value of PKP to themselves was rated in a smaller series showing 75% of patients had overall satisfaction with the operation and results. Satisfaction was associated with better vision in the grafted eye versus the other eye, clarity of the graft, and improvement in lifestyle. Dissatisfaction was primarily related to graft failure or problems with contact lens wear.[22]

In unilateral cases or in the case of the second eye after successful first eye transplant, there is more controversy regarding the positive impact of surgery. Javitt and others confirmed the value of second eye surgery for cataract in a preliminary study but that study did not look at individual patient outcomes.[14] In a subsequent study, the value of second eye surgery for cataract was confirmed with a 61% increase in the VF-14 (a validated measure of visual function), a 27% decline in trouble with vision, and a 24% improvement in satisfaction with vision.[23] These find-

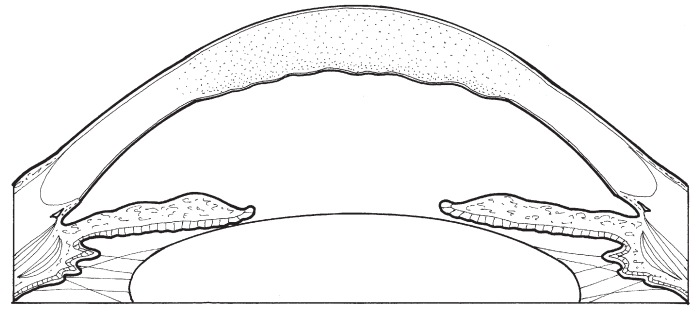


A B

Figure 41.2. *A*, Tectonic indication for PKP. This patient has chronic herpes simplex keratitis with an area of thinning and descemetocele formation, with iris lining the descemetocele. Transplantation is needed to restore ocular integrity. *B*, Same patient as Figure 41.1, *A* with a central and side view to illustrate the zone of thinning and anterior synechiae to the descemetocele.



A



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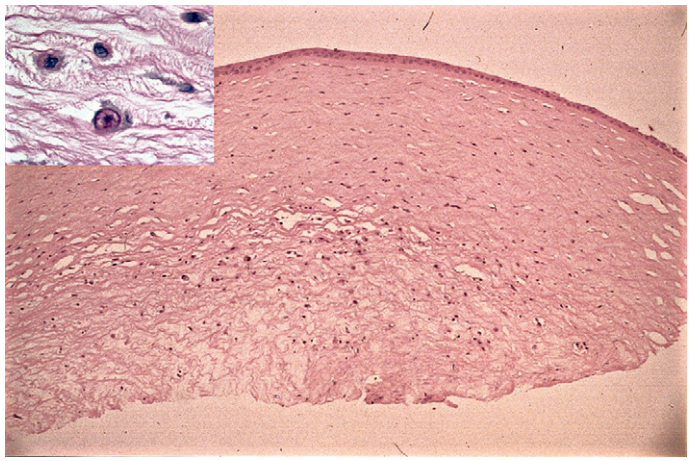


C

Figure 41.3. *A*, Therapeutic indication for PKP. This montage shows a preoperative image of a patient with persisting inflammation despite 6 months of treatment for *Acanthamoeba* keratitis. The image on the right shows the clear corneal transplant. *B*, Same cornea as in *A*. The ongoing inflammatory nature of the infection required a therapeutic transplant to reduce the load of organisms and allow the immune system to contain any residual infection from the amoeba. *C*, Corneal button from *A*. The relative absence of *Acanthamoeba* in the anterior stroma with an intact epithelium and a concentration of trophozoites and cysts in the deep stroma suggest poor drug penetration. There is artifactual loss of Descemet's membrane. The inset shows *Acanthamoeba* cysts and macrophages.

ings are generalizable to the situation involving corneal transplant, although there is a longer rehabilitation involved with corneal transplants.

Indication for the second eye to receive a transplant involves assessing the specific risk of a second graft. Early work indicated a possible trend toward more rejections in keratoconus patients who underwent surgery in the second eye.[24–32] Others have found no change in risk to either eye.[33–37] Two large graft registries have recently reported, using multivariate analysis, an increased survival of the second eye graft.[38,39] One center did report an increased risk for rejection and failure in the first eye,[39] but the risk to both eyes fell the longer the time between surgeries, with best survival if there was no rejection for 3 years in the first eye prior to surgery on the second. The explanation for increased survival in the second eye is unclear, and possibilities can be proposed: patient selection bias and underlying good prognosis for many bilateral conditions (corneal dystrophies), negative bias in avoiding second eye surgery with poor outcome in the first eye, patient education and experience with medications, use of steroid in second eye and not first at time of second surgery, immune modulation following first eye, or relative anergy in patients who accept one graft without rejection.[39] At this time, second eye surgery indicated by the patient's visual requirements is not contraindicated by the risk of rejection with proper education and management, including topical steroids in both eyes perioperatively.

Therapeutic and tectonic reasons for doing surgery are almost always imperative and are not subject to the same controversy. Therapeutic indications may be involved in the rare circumstance where visualization of the posterior segment is required, for example following temporary keratoprosthesis for complicated retinal detachment repair including pars plana vitrectomy or to allow for photocoagulation of diabetic retinopathy. Alternatives to corneal transplant should be sought where applicable. Hard or soft contact lenses may be used in circumstances of irregular astigmatism for thin scars subject to glare and photophobia. Lamellar keratoplasty or use of tissue glues may be appropriate in the management for tectonic indications. Limbal autografting or allografting may be appropriate for primary restoration of the ocular surface or as preparation for subsequent PKP.[40] Optical iridectomy for Peters anomaly or other central scarring may provide better long-term visual results for PKP with poor prognosis.[41] Corneal tattooing has been used to improve cosmesis as well as to reduce glare and pho-

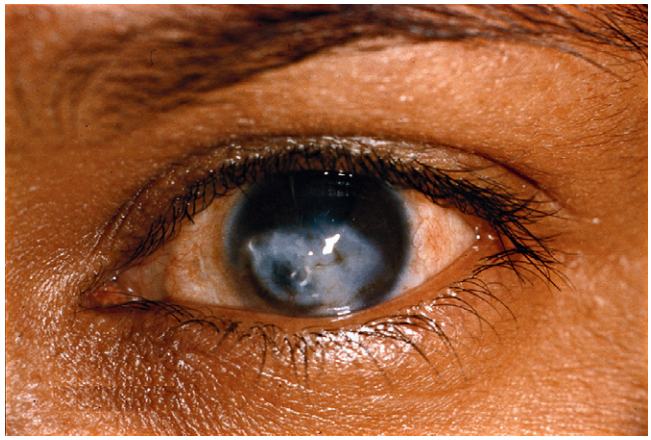


Figure 41.4. Optical indication for PKP. This young Asian female with a history of a fork injury to the left eye at the age of 2 years for which she received minimal medical intervention desires improvement in her appearance. Improvement in vision from corneal transplant is unlikely due to amblyopia.

tophobia from corneal scarring. Tarsorrhaphy and conjunctival flaps can be successful in treating persistent corneal ulceration. Pharmacological means have also been used, including metalloproteinase inhibitors, growth factors, antivirals, and oral antibiotics, such as tetracycline, with varying degrees of success.

Transplants done for cosmetic reasons are very rare with the advent of the Narcissus Foundation Program to provide painted soft contact lenses and other sources of tinted contact lenses or painted cosmetic shells. Although rare, cosmesis may still be justifiable in circumstances where the cornea is white from a long-standing injury and vision potential is limited by amblyopia.

RECIPIENT DIAGNOSIS

In 1994, the EBAA introduced a grouping of recipient diagnosis in order to improve the tracking of the indications of keratoplasty.[12] The intent was to identify trends early to allow for planning at the level of the EBAA and to direct research to appropriate areas. Table 41.2 lists the diagnoses as updated by Lindquist at the Annual Meeting of the Eye Bank Association, Santa Barbara, CA (personal communication, 1996). Many patients fall into more than one category, and it is difficult for surgeons to know precisely which is the principal indication. A prime example is pseudophakic bullous keratopathy in the presence of Fuchs' corneal dystrophy. The EBAA indicates that such a patient should be coded with Fuchs' dystrophy.

Medical advances leading to the aging of the population and the advent of intraocular lenses, which led to a rapid rise in the performance of cataract surgery, have led to changes in the indications for transplant. In the 1950s, the more common indications for grafting were regrafts, herpetic scarring, and keratoconus.[9–10] Indeed, until Max Fine reported success in 49 eyes at the Corneal World Congress in 1964, PKP was infrequently performed for aphakic bullous keratopathy or Fuchs' corneal dystrophy.[42]

In the 1980s, pseudophakic bullous keratopathy became the leading indication for corneal transplant in the USA, peaking at approximately 29% in 1988.[43,44] Table 41.3 shows that through 2004, excluding non-specified causes, pseudophakic corneal edema remained the number one cause but was decreasing in frequency. There was an increase in the number of regrafts, both those related to rejection and those after graft failure for other causes. The rise in regrafting may reflect the larger pool of completed grafts, as the total number of transplants and the longevity of the population have increased. The rates of regrafting have increased particularly at tertiary-care centers.[45] The decline in aphakic and pseudophakic corneal edema is probably related to improvements in technique of lens extraction and in the design of intraocular lenses. In 2004, a new category dedicated to postrefractive surgery patients contained 46 patients, representing 0.1% of the total.

Although grouping of indications are not precise from study to study, European authors report increases in grafting for pseudophakic bullous keratopathy from the 1970s to the 1990s.[46–48] UK registries indicate, however, that keratoconus remains the number two reason for transplant at one center behind regrafting.[46,49] In a similar-sized series involving more than tertiary-care hospitals, keratoconus was the number one reason for grafting at 20%, with regrafts in 16% and pseudophakic bullous keratopathy in 15%.[46] In Denmark, pseudophakic bullous keratopathy was most frequent at 28%, followed by keratitis and endothelial dystrophy at 14% each and regraft at 11%. As in the USA, keratoconus was an infrequent indication for transplantation, perhaps reflecting the underlying populations. In Canada, the leading indications were regraft, keratoconus, and pseudophakic bullous keratopathy (Maeno et al).[49a] The Australian Graft Registry found that keratoconus was the most common indication at 31%, followed by bullous keratopathy at 25% and regrafts at 14%.[22] These indications affirm the similar genetic makeup of Australia and the UK. Despite improvements in the diagnosis and therapy of viral and other microbial keratitis, there has not been a substantial decline in the relative percentage of corneal transplants done for these indications.

In the developing world, the leading indications for corneal transplant remain corneal scar (due to infection, chemical injury, or trauma), acute infection, regrafting, and aphakic/pseudophakic bullous keratopathy.[50–53] Indications may vary within a country. For example, in Brazil, keratoconus is the main indication in San Paulo, whereas trachoma and scarring account for the majority of grafts in Amazonas.[54] In Israel and Saudi Arabia, ocular infections and scarring accounted for the majority of grafts in the 1970s and 1980s but have steadily declined. Since the 1990s, keratoconus has been the major indication for corneal transplant in each of these countries.[55,56]

CONTRAINDICATIONS

ABSOLUTE CONTRAINDICATIONS

Absolute contraindication to PKP would be the absence of any indication to do the procedure. Patients with high probability that they would not survive the operation should not be done. The patients' or their legal surrogates' decision not to have surgery should be respected. Situations such as no light perception vision with no hope for return of vision should not be attempted unless there is psychological contraindication to either enucleation or evisceration and there are no other suitable alternatives. Patients who are satisfied with current vision with their usual type of correction (glasses or contact lenses) or whose lifestyles are not compromised should not have surgery.

RELATIVE CONTRAINDICATIONS

Relative contraindications include the risk factors for failure of the PKP to remain clear or for the patient to obtain significant improve-

Table 41.2 Clinical indications for penetrating keratoplasty, 1996

1. Pseudophakic corneal edema	**7.** Viral/postviral keratitis	Thyroid eye disease
Pseudophakic bullous keratopathy	Herpes simplex virus	Rheumatoid disease
Anterior chamber lens implant	Varicella zoster virus	Rheumatoid arthritis
Iris-fixated lens implant	Epstein–Barr virus	Cocaine-induced keratopathy
Posterior chamber lens implant	Adenovirus	**11.** Corneal degenerations
2. Aphakic corneal edema	Epidemic keratoconjunctivitis	Terrien's marginal degeneration
Aphakic bullous keratopathy	**8.** Microbial/postmicrobial keratitis	Calcific band keratopathy
Vitreoendothelial touch syndrome	Bacterial	Polymorphic amyloid degeneration
3. Stromal corneal dystrophies	Infectious crystalline keratopathy	**12.** Chemical injuries
Granular and Avellino dystrophies	Spirochete	Alkaline
Lattice dystrophy	Luetic (syphilitic) interstitial keratitis	Acid
Macular dystrophy	Chlamydial	Petroleum
Central crystalline dystrophy of Schnyder	Trachoma	Tear gas
Central cloudy dystrophy of Francois	Fungal	**13.** Mechanical trauma, nonsurgical
Recurrent stromal dystrophy	Parasitic	Traumatic opacity
4. Primary corneal endotheliopathies	*Acanthamoeba*	Traumatic corneal edema
Fuchs' endothelial dystrophy	**9.** Optical/refractive	**14.** Regraft related to allograft rejection
Congenital hereditary endothelial dystrophy	Ammetropias	(Include triggers as a secondary indication)
Posterior polymorphous dystrophy	High and/or irregular astigmatism	**15.** Regraft unrelated to allograft rejection
Iridocorneal endothelial syndrome	Myopia	Primary tissue failure
Chandler's syndrome	Hyperopia	Vitreo-endothelial touch
5. Ectasias/thinnings	Previous refractive surgery	Glaucoma
Anterior keratoconus	epiK, RK, AK, ALK, PRK, LASIK, etc.	(Include indications listed elsewhere)
Pellucid marginal degeneration	**10.** Noninfectious ulcerative keratitis or perforation	**16.** Other causes of corneal opacification/distortion
Keratoglobus	Keratoconjunctivitis sicca	Uveitis
Posterior keratoconus	Sjogren's syndrome	Glaucoma
6. Congenital opacities	Neuroparalytic/neurotrophic keratopathy	Detached Descemet's membrane
Peter's anomaly	Exposure keratopathy	Thermal injury
Glaucoma/buphthalmos	Systemic vasculitides	Fundus laser keratopathy
Aniridia	Bullous oculocutaneous diseases	Intraocular silicone keratopathy
Sclerocornea	Mooren's ulcer	Epithelial downgrowth

epiK, epithelial keratoplasty; RK, radial keratotomy; AK, astigmatic keratotomy; ALK, automated lamellar keratoplasty; PRK, photorefractive keratoplasty and LASIK; laser in situ keratomileusis.

Data from Eye Banking Statistics for 1991 and 1995. Eye Bank Association of America.

ment in vision. Many of these risk factors have been based on clinical experience.[43,57] Several large, either single or multicenter trials have applied univariate and multivariate analyses to the more commonly considered causes of graft failure.[38,46,58–64] Not every study assessed the same risk factors and not all potential risk factors have been studied rigorously. Most studies found that, when adjusted for various factors, many of the commonly accepted risk factors were not significant. Table 41.4 outlines many of the risk factors found to be significant by authors of large trials.

In the largest study, from Australia, the factors that influenced survival in a univariate analysis were the transplant center (centers with more than 20 grafts per year showed increased survival);

Table 41.3 Corneal transplant recipient diagnoses

Recipient Diagnosis	1991 (%)	Relative Rank	1995 (%)	Relative Rank	2004 (%)	Relative Rank
Non-specified	18.9	2	21.5	1	21.9	1
Pseudophakic corneal edema	25.1	1	20.5	2	19.8	2
Ectasias/thinnings	11.4	3	12.3	3	15.1	3
Endothelial corneal dystrophies	11.1	4	11.9	4	13.9	4
Regraft unrelated to allograft rejection	2.41	11	5.6	5	5.3	6
Aphakic corneal edema	8.5	5	5.6	6	2.5	10
Regraft related to allograft rejection	4.7	6	4.8	7	5.9	5
Stromal corneal dystrophies	4.1	8	4.1	8	3.6	8
Noninfectious ulcerative keratitis	3.1	9	3.8	9	3.6	7
Corneal degenerations	4.2	7	3.4	10	1.9	11
Congenital opacities	0.6	14	1.5	11	1.1	14
Mechanical trauma	2.6	10	1.5	11	2.6	9
Viral/postviral keratitis	1.5	12	1.4	13	1.2	12
Syphilitic/postsyphilitic keratitis	0.4	16	1.0	14	N/A	
Microbial/postmicrobial keratitis	0.9	13	0.6	15	1.1	13
Chemical injuries	0.5	15	0.4	16	0.3	15
Optical (including postrefractive surgery)	0.2	16				

N/A, not available.

Source: Eye Banking Statistics for 1991, 1995, and 2004, Eye Bank Association of America.

indication for the graft (keratoconus shows the best survival); graft number in the ipsilateral eye; history of pregnancy or blood transfusion; inflammation before or at the time of the graft; corneal vascularization at the time of the graft; history of raised intraocular pressure; the source of the donor cornea (eye bank eyes showed a poorer survival than those obtained by individual surgeons); death to donor enucleation time (cutoff at 6 h); graft size less than 7 mm in diameter or greater than 8.5 mm in diameter or with more than 0.5 mm difference between host and recipient, and lens status (aphakic grafts have the shortest survival followed by pseudophakic and then phakic, and PC-IOL had the best survival followed by anterior chamber IOL, iris clip, or other style).[38] Evaluation of risk factors for failure in the postoperative period disclosed that increasing failure occurred with early removal of the graft sutures, neovascularization of the graft, herpetic recurrence in the graft, and rejection episode. Following adjustment for the various factors using Cox proportional hazards regression analysis, the Australian Corneal Graft Registry found the significant factors to be aphakia or the presence of an anterior chamber or iris clip lens, very small or very large grafts, prior history of transplant on the ipsilateral side, an indication for transplant other than keratoconus or corneal dystrophy, active inflammation at the time of the transplant, and a postoperative rise in intraocular pressure. They found specifically that there was no effect on outcome by donor age, donor cornea storage medium, or whether the transplant was performed simultaneously with cataract surgery or in a staged manner.

Yamagami et al found six preoperative risk factors that were associated with poor outcome using Cox multiple regression analysis. These were corneal endothelial damage, the presence of anterior synechiae, glaucoma, older donor, area of vascularization, and aphakia or pseudophakia.[62]

Price et al in a consecutive series of transplants from a single practice found immunologic allograft reaction as the most common cause of failure followed by problems with the external surface of the transplant.[60,63] They indicated that the risk of failure decreased with increasing postoperative time. The significant risk factors for secondary failure included previous failed graft, race, age, iris color, use of preoperative glaucoma medicines, deep stromal vascularization, and horizontal diameter of the host cornea.[63] Price further indicated that the risk factors for immunologic allograft rejection included horizontal corneal diameter of the patient, donor size, and the difference between the host cornea and the donor diameters and between the host diameter and recipient trephine size.

Williams et al, in one of the largest multivariate analyses based on the Australian Graft Registry, followed 10 952 PKPs up to 18 years.[64] Preoperative risk factors for graft failure identified by Cox regression analysis included donor age, preoperative diagnosis, previous ipsilateral grafts, lens status, corneal neovascularization, ocular inflammation, or raised intraocular pressure. Surgical factors influencing graft survival included requirement for anterior vitrectomy, graft size, and transplant center. Postoperative events including graft neovascularization, rise in intraocular pressure, rejection episodes, and surgical intervention for intraocular pressure were

Table 41.4 Risk factors for graft failure

Risk Factor	Australian Graft Registry[50]	Collaborative Corneal Transplant Study[43]	UK Transplant Study[46]	Indiana Study[45]	Japanese Study[47]
Number of transplants in study	3608	457	2242	1819	698
Number (percentage) failure/time of follow-up	28%/5 years	32%/3 years	9%/3–12 months	9%/5 years	
Characteristics of the host cornea					
Not keratoconus or other central corneal disease	Yes	Yes	Yes	Yes	Yes
Previous ipsilateral graft	Yes	Yes		Yes	
Vascularization before PKP	Yes	Yes		Yes	Yes
Anterior synechiae		Yes	No		Yes
Previous increase in IOP	Yes	Yes	No		Yes
Not phakic		Yes			Yes
Aphakic	Yes			Yes	
Pseudophakic	Yes			Yes	
Previous surgery, not PKP		Yes			
Inflammation at time of PKP	Yes		No		
Characteristics of the recipient					
Previous blood transfusion	Yes	No			
Previous pregnancy	Yes	No			
Smoker		Yes			
Younger than 40 years	Yes	Yes			
Characteristics of the donor or surgery					
Older donor age	No	No			Yes
Graft size	Yes (<7.0 or = 8.5 mm)	Yes (<8.0 mm)	Yes (trephine sum = 14.5 mm)		
Time to preservation					
= 6.0 h	No	No			
>6.0 h	Yes	Yes			
Method of donor storage	No				
Time to surgery (up to 96 h)	No	No			
Suture technique			0		
Interrupted		Yes	No		
Running		No	No		
Both		No	Yes		
Viscoelastic substance—not used		Yes			
Blood group ABO incompatibility		Yes			

Risk factors assessed by univariate analysis. Yes refers to statistically significant risk factor in the reference. No refers to tested risk factor that is not statistically significant in that study. Blank means risk factor not reported.

PKP, penetrating keratoplasty; IOL, intraocular lens.

associated with a higher rate of graft failure. They also found no improvement in graft survival over a 15-year time period.

In a study of high-risk transplant patients, Maguire et al, using multivariate survival analysis, found that many risk factors did not show a significant association in the very-high-risk recipient.[58] They found young recipient, number of prior transplants, history of prior anterior segment surgery, preoperative glaucoma, quantity of anterior synechiae, quantity of stromal vascularization, diagnosis of chemical burn, and blood group ABO incompatibility to be the strongest risk factors identified for graft failure. They found no association between donor and corneal preservation characteristics with outcome. Vail et al found the following risk factors after multifactorial analysis to be significant: surgeons with fewer than 50 transplants during the study period (1986–1992); recipients under 10 years of age; prior failed transplant; grafting for nonvisual indications; vascularization of the corneal bed; eccentric edema of the cornea as opposed to central edema; smaller trephine diameter, and differences between the donor and recipient of greater than 0.25 mm.[61]

HLA matching is discussed in another section of the book (Chapter 34). Other factors considered to be detrimental to good prognosis but not specifically assessed in these various analyses were corneal anesthesia, exposure keratitis, severe dry eye, systemic conditions of the patient, and patient compliance. Many of these conditions would fall under the sobriquet of inflammation at the time of the transplant and are associated with poor outcome. The mechanism by which many of the ocular surface conditions have interfered with long-term success of transplantation has been clarified with better understanding of the limbal stem cell.[40,65–68] Stem cells are lost from alkali and severe acid injuries and following Stevens–Johnson syndrome or other severe conjunctivitides and in specific ocular conditions such as aniridia and ectodermal dysplastic syndromes. To date no study has examined the absence of limbal stem cells as a separate risk factor for PKP failure in part due to the lack of a good clinical marker. Absence of the Palisades of Vogt and superficial conjunctival vessels crossing the limbus and presence of goblet cells on the corneal surface are non-specific markers for loss of stem cells and conjunctivalization of corneal epithelium. Holland and others have suggested improved outcome when the stem cells are replaced before PKP.[40]

Table 41.4 shows the relative risks of different characteristics in the long-term success of transplantation, as determined in five large studies using univariate analysis. Not all potential risk factors have been studied and these reports vary widely in definitions, length of follow-up, baseline characteristics, number of surgeons, and number of factors assessed. These risk characteristics are based on a much larger experience than the early pioneers who grouped corneal prognosis primarily by anatomic factors. However, there is much in common between Paton's and Buxton's groupings and these later studies. Some authors have reduced the confounding variables and biases of these uncontrolled studies using stepwise, multivariate analysis. Table 41.5 shows the quantification of the relative risks, confidence intervals, and per cent failed grafts, as determined in two studies related to the accepted prognostic groupings.

Table 41.6 outlines a modified prognostic chart generated from these large registries. Figures 41.5–41.8 show the morphologies and corresponding prognoses for a 1-year survival of corneal transplants. Prognosis can further be reduced by the presence of cofactors described in Table 41.7. Combining these estimates can provide a useful estimate of initial success for a clear transplant to a patient considering transplantation.

CONSENT

When explaining the risk and benefits of PKP to the patient and in assessing the risk factors for determining the best operation, the surgeon must keep in mind that risk is not the same as risk factors. The risks of corneal transplant surgery include nonimmunologic allograft failure, allograft rejection, expulsive choroidal hemorrhage, infection (both keratitis and endophthalmitis), loss of the eye, donor to host transmission of disease, glaucoma, retinal detachment and retinal cystoid macular edema, repeat transplant, fixed pupil, and astigmatism. In addition, there are major risks of anesthesia including stroke, myocardial infarction, and death, which have to be considered but rarely play a role in the patient's decision for surgery. Benefits represent the positive outcome and risk represents the negative outcome of transplantation or failure to transplant. In balancing these opposing forces, the surgeon makes a recommendation to the patient and when both are in agreement to proceed, a long-term relationship of careful attention and nurturing ensues.

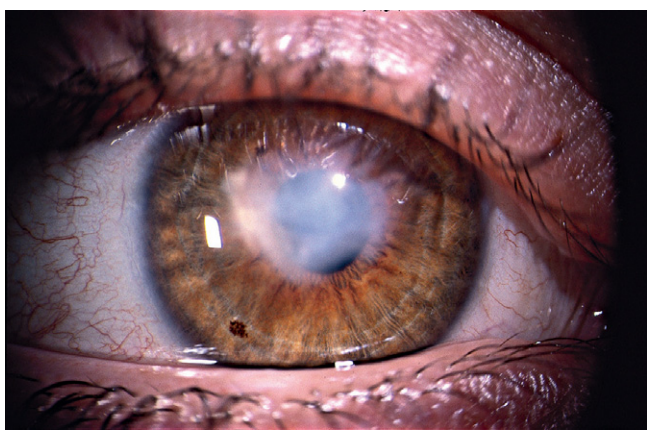


Figure 41.5. Prognostic Group I. Normal peripheral architecture with central corneal disease carries a 92–98% 1-year graft survival. (Photograph courtesy of F.S. Brightbill, MD, Madison, WI.)

Table 41.5 Relative risk of graft failure by specific factors

		Australian Graft Registry[50]		Collaborative Corneal Transplant Study[49]		Anatomic Basis for Risk (Paton[48] and Buxton[43])	
Risk Factor	**Value**	**Relative Risk (Confidence Interval)**	**% Clear at 1 Year/3 Years**	**Relative Risk (Confidence Interval)**	**% Clear at 1 Year/3 Years**	**Group**	**% Clear at 1 Year**
Indication	Number of transplants	936 transplants	91/79	457 transplants	89/68		
	Keratoconus/ corneal dystrophy	1.00	98/81			I	90
	Other condition	4.38 (2.04, 7.18)	83/68			II, III IV	0–85
Recipient age	= 40 years			1.00	95/77		
	<40 years			2.50 (1.75, 3.58)	81/47		
Previous failed PKP	None	1.00	92/83	1.00	93/77		
	= 1	1.43 (1.07, 1.91)	77/50	1.20 (1.09, 1.32)	88/64	II, III	75–85
Lens status	Not aphakic	1.00	93/83				
	Aphakic	1.98 (1.24, 3.18)	82/65			II	85
Inflammation	None at graft	1.00	97/94				
	Present at graft	2.05 (1.38, 3.03)	80/46				
Vascularization	None	1.00	95/85	1.00	93/77		
	After grafting	5.03 (3.33, 7.56)	83/70	1.14 (1.01, 1.28)	90/67	II, III	75–85
Anterior synechiae	None			1.00	Not available		
	Present			1.19 (1.07, 1.32)	Not available	IV	0–50
Glaucoma	None			1.00	92/77		
	Preoperative			1.58 (1.14, 2.21)	85/64	I–IV	Reduce by 10–50
Graft size	7.0–7.9 mm	1.00	95/85				
	Other	1.89 (1.28, 2.80)	86/65			II, IV	50–75
Intraocular lens (IOL)	No AC or iris-clip IOL	1.00	93/86				
	AC IOL	1.74 (1.03, 2.94)	89/57				
	Iris-clip IOL	3.59 (1.90, 6.79)	74/30				

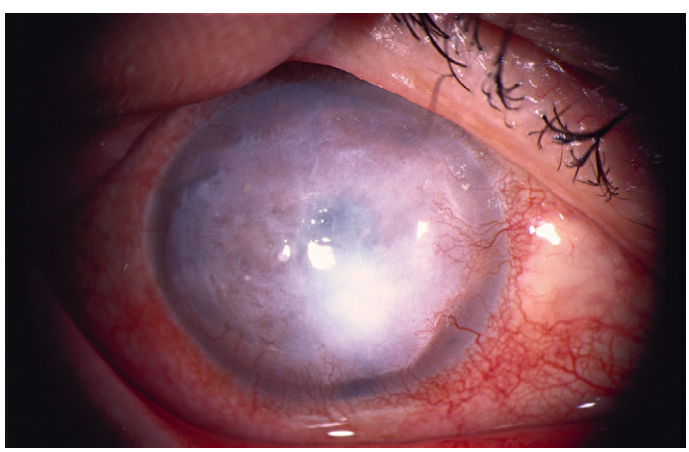
Percentages estimated from published graphs. Table is modified from references[43,48–50].

Table 41.6 Prognosis for graft clarity at 1 year

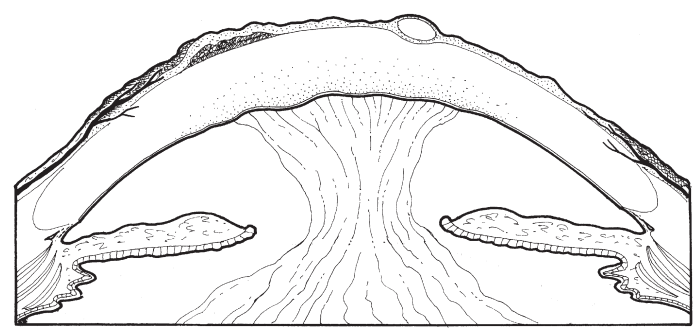
Group	Diagnosis	Morphology	Prognosis (%)
Group I	Keratoconus Early Fuchs' dystrophy Stromal dystrophy Other central opacity	Central corneal disease with normal peripheral architecture, limbal anatomy, and sensation, and healthy microenvironment of eyelids and tear film	92–98
Group II	Pseudophakic bullous keratopathy Aphakic bullous keratopathy Diffuse Fuchs' dystrophy Inactive peripheral scarring	Disease that crosses the graft–host junction with an intact surface, and minimal vascularization	85–90
Group III	Keratoglobus Pellucid degeneration Corneal perforation Pseudophakic bullous keratopathy with an iris-clip IOL	Extremes of peripheral corneal contour or thickness involving a large part of the recipient zone adjacent to limbus and Langerhans cells	70–85
Group IV	Ocular pemphigoid Aniridia Stevens–Johnson syndrome Anterior chamber cleavage syndrome Neuroparalytic or neurotrophic disease	Absence of normal limbal stem cells and normal maturation of corneal epithelium, loss of corneal sensation, and loss of anterior chamber	40–70

IOL, intraocular lens.

Modified from Payton and Jones[5] and J Buxton[6]. Prognoses are estimates only and must be modified by any significant cofactors such as the ones included in Table 41.7.



A



B

Figure 41.6. *A* and *B*. Prognostic Group II. Corneal edema that extends to the periphery; other lesion that involves the peripheral cornea, aphakia, or corneal neovascularization carries an 85–90% 1-year graft survival. (Photograph courtesy of F.S. Brightbill, MD, Madison, WI.)

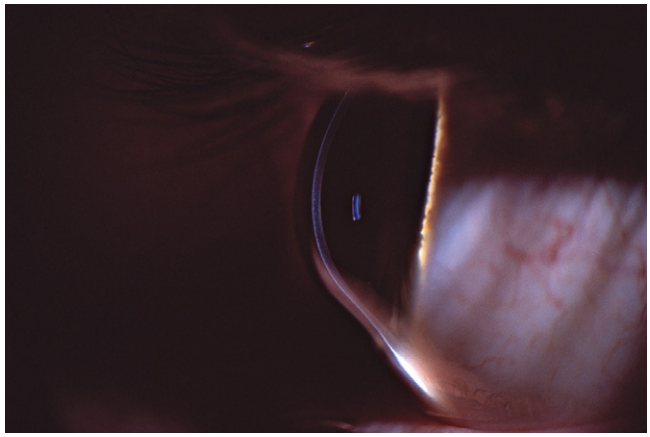
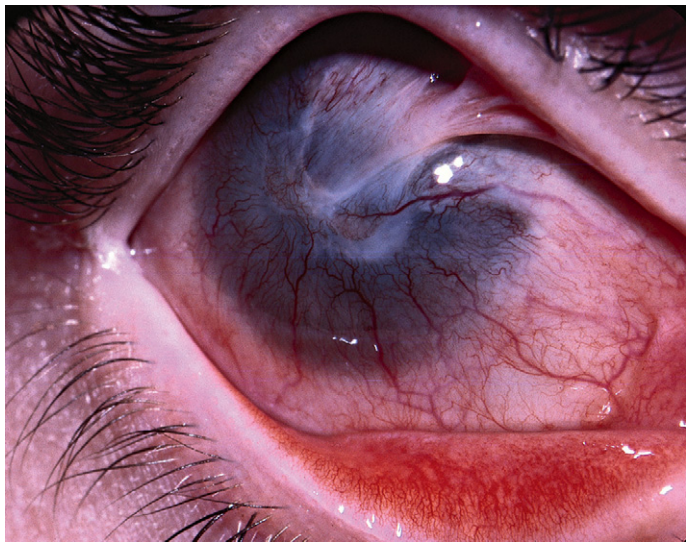
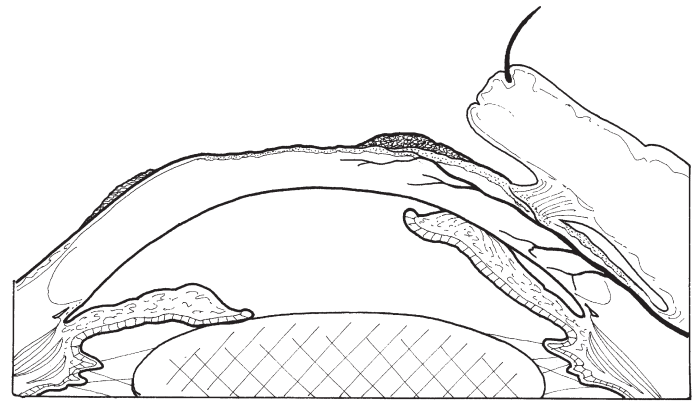


Figure 41.7. Prognostic Group III. Abnormal peripheral cornea with extreme thinning or variations in peripheral thickness carries a prognosis of a 70–85% 1-year survival. (Photograph courtesy of F.S. Brightbill, MD, Madison, WI.)



A



B

Figure 41.8. *A* and *B*. Prognostic Group IV. Ocular surface disease with diffuse loss of limbal stem cells, extensive peripheral anterior synechiae, and/or neurotrophic keratitis carries a prognosis of a 40–70% 1-year survival. (Photograph courtesy of F.S. Brightbill, MD, Madison, WI.)

Table 41.7 Ancillary factors modifying prognosis of 1-year graft survival

Factor	Reduction in Prognosis (%)
Vascularization	7 for each quadrant of vessels
Prior pregnancy or blood transfusion	2–5
Active inflammation in past	10
Active inflammation at time of transplant	20
Donor size <7.0 mm	25
Donor size >8.5 mm	20
Difference between donor and host trephines >0.5 mm	35
Increased intraocular pressure	10–25
Poor patient compliance	5–20

Prognosis reduction is estimate only. Factors are not intended to be algebraically additive.

Modified from Payton and Jones.[5]

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42 Phakic penetrating keratoplasty

Joel Sugar, Satya Reddy

TECHNIQUE

When performing penetrating keratoplasty in a phakic patient, the surgeon must account for a few differences from aphakic keratoplasty. The lens and lens capsule create a shallower anterior chamber. Contact with the anterior lens capsule can lead to a premature cataract. There is a greater risk of iris prolapse from the posterior pressure of the vitreous and/or lens complex. Also, phakic keratoplasties tend to be performed in younger individuals, which may add another set of considerations. We present a step-by-step approach of addressing these concerns. The frequency of phakic penetrating keratoplasty has decreased with the recently increased use of lamellar procedures.

ANESTHESIA WITH AKINESIA AND HYPOTONY

In patients with no planned lens procedure, the use of miotics is helpful in iris management, usually 2% pilocarpine, every 10 min for three doses starting 1 h preoperatively. This dosage serves to sufficiently constrict the pupil so that the risk of injury to the anterior lens capsule is minimized. Once in the operating room, local anesthesia is often chosen because of its greater convenience and because of the rapid postoperative patient mobilization that this technique allows. There is no evidence from a corneal standpoint that either approach, local or general anesthesia, is preferable. Adequate anesthesia and akinesia of both eyelids and the globe are essential and can readily be achieved with peribulbar or retrobulbar injection. However, these patients tend be younger and may need more intravenous sedation or be more comfortable under general anesthesia. An uncomfortable patient who is moving during the procedure or a patient whose eyelids squeeze or whose globe moves induces a greater risk of chamber shallowing and inexact suture placement. When local anesthetic is used, it is important to look for periocular hemorrhage. Retrobulbar hemorrhage or a pronounced preseptal hemorrhage causing increased pressure on the globe compromises the safety of the procedure. In those patients in whom general and peribulbar anesthesia are contraindicated, Price reported successful outcomes under topical anesthesia. Patient comfort and pain seem comparable to other forms of local anesthesia.[1,2] However, topical anesthesia carries a much higher risk of intraoperative complications secondary to patient-related and anatomic factors, and we believe it should only be used when other methods of anesthesia are contraindicated. Preoperative hypotony can be obtained through digital massage or the use of a mechanical balloon pressure maintainer preoperatively. This lack of posterior pressure appears to play a significant role in reducing endothelial and lens complications intraoperatively.[3,4]

EXPOSURE AND GLOBE FIXATION AND SUPPORT

Adequate exposure of the anterior segment of the eye and adequate fixation and support of the globe are exceedingly important and need to be established before proceeding with keratoplasty. In unusual circumstances, this approach may require lateral canthotomy, lysis of symblephara, and excision of fibrotic scar to provide such exposure. Although a closed-blade speculum and double adult or pediatric fixation ring may be used in phakic keratoplasty, a combined supporting ring and speculum, the McNeill–Goldman blepharostat,[5] also provides both globe support and exposure. These are fixated to the superficial sclera with four 5-0 Dacron or polyglactin 910 sutures. Adequate studies have to be carried out to demonstrate the most appropriate suturing technique. Many surgeons use more than four sutures, and many place sutures on both the anterior and the posterior rings of the device. The effect of such sutures is uncertain, but sutures that are too long or too tight distort the globe, presumably leading to distortions in wound shape and ultimate postoperative astigmatism.[6] One study found that sutures in the axis of the rectus muscles had a greater effect on postoperative astigmatism.[7] The presence of a supporting ring, however, appears to allow easier maintenance of the anterior chamber during both phakic and aphakic keratoplasties.

DONOR PREPARATION

Several questions arise in choosing a technique of donor preparation. Brightbill et al[4] have demonstrated that punching the donor

material from the endothelial side against a firm surface leads to less endothelial damage and cleaner cuts than corneal preparation from the epithelial surface. Various cutting blocks have been described for this purpose,[8,9] and they are discussed elsewhere in this text. Various punches have been developed for holding the trephine blade, and a handheld disposable trephine may also be used for cutting the donor. Great controversy has existed concerning the size of the donor material to be cut relative to the size of the recipient bed prepared. Troutman[10] and Olson[11] have demonstrated that a larger trephine is necessary to prepare tissue from the posterior surface than is needed to prepare the recipient bed. In aphakic eyes, a 0.5 mm larger donor led to less hyperopia in two of three studies.[12–14] In a study comparing a relatively small number of phakic eyes, Perl et al[14] showed more myopia in eyes using oversized donor material than same-sized donor material, but this difference was not statistically significant. Many surgeons use 0.25 mm larger trephines in preparing donor material in phakic eyes rather than 0.5 mm larger donor material in the hope of reducing myopia in these usually myopic persons. Others have used donor material of the same size or even smaller than that of recipient material to reduce myopia in keratoconus patients.[15–17] The effect of varying donor size on glaucoma does not appear to be an important issue in phakic keratoplasty. An additional issue is the question of retaining epithelium on the donor tissue. Although Tuberville et al[18] suggested that removing donor epithelium reduces the frequency of immune graft reactions, others have failed to confirm this finding,[19] and most surgeons maintain donor epithelium because of the greater ease of postoperative patient management.

Marking of the recipient and donor corneas to allow symmetric suture placement can be carried out using vacuum cutting blocks with marking holes or by marking directly on the anterior surface of the donor material using a radial keratotomy marker dyed with gentian violet.[20]

PREPARATION OF RECIPIENT BED

The recipient bed is prepared with a trephine that is large enough to surround the diseased tissue and escape the papillary axis while not being so large as to encroach upon the limbus. In eyes with keratoconus, the biomicroscopically abnormal cornea is surrounded with the trephine. Numerous trephines have been developed—both manual and automated—that have varying degrees of complexity.[21] An open-bladed, disposable trephine may be used for cutting the recipient bed. The advantages to this trephine include the ability to directly sight down the barrel of the trephine through the operating microscope to aid in accurate positioning and its lack of a central guard, which may distort tissue shape during trephination.[22] A forceps is used to grasp the fixation ring, and the trephine blade is held in the opposite hand and first pressed on the cornea and then gently rotated. Experience allows reasonable estimation of the depth of the cut being made. Automated trephines and suction trephines may be used as well. Various authors have compared automated trephines. Uniformity of cuts varies with the trephine type, and the ideal trephine that provides straight cuts without tissue distortion has yet to be found. van Rij and Waring[23] found a nondisposable suction trephine and a free disposable blade the most uniform. Other groups have compared various suction trephines and found graft curvature to be greater with suction trephines than with handheld trephines.[24] Visual recovery in one study was more rapid and complete using the Hanna vacuum trephine compared to the Hessberg–Barron system.[25] Ovoid cutting trephine systems have been suggested in the past for astigmatic corneas, but their usefulness has never been confirmed.[23]

Radial marks may be made on the recipient bed prior to trephination using a radial keratotomy marker and gentian violet, or marks may be made with a suction trephine, such as the Barron radial vacuum trephine, which leaves impressions in the cornea after the use of the suction trephine. This approach allows equal spacing of suture placement and matching of the donor and recipient markings.

CHAMBER ENTRY

The anterior chamber may be entered using the trephine while cutting the recipient bed. This technique is safe to do if the surgeon is aware of the need to immediately release pressure when the chamber is entered. It usually leads to a perpendicular cut and allows easier removal of the host cornea. Many surgeons prefer the more controlled entry that is allowed when they trephine approximately three-fourths of the way into the recipient bed and then use a sharp disposable blade to enter the anterior chamber. At this stage, many surgeons will inject viscoelastic material into the anterior chamber to both counteract posterior pressure and create space between the cornea and the iris–lens complex. Some surgeons have suggested the use of trypan blue staining in aiding depth of trephination and visualization of recipient endothelium in excison of the posterior lip.[26] A small portion of the posterior cornea may be left intact, creating a hinge to allow the recipient cornea to be reflected out of the way but leaving it available for restoring the chamber should a suprachoroidal hemorrhage take place prior to the time that the donor cornea is in place.[27]

HOST CUTTING AND REMOVAL

The host button is removed by cutting with curved, fine corneal scissors. The recipient cornea is grasped with a fine forceps during this maneuver, and the scissors are held perpendicularly or sloped to allow a posterior bevel of the tissue. This approach creates a slightly smaller posterior than anterior opening in the recipient bed, which may allow for easier wound apposition. The disadvantage of this technique is that an uneven posterior lip may lead to tilting of the graft and resultant astigmatism. When a posterior tag of stroma and Descemet's membrane is left in just one area, this area may be the site of graft displacement at the time of suture removal and subsequent induced astigmatism. For this reason, tags should be removed perpendicularly when they are present. Pulling too strongly on a tag while cutting it out may lead to actual undercutting of the recipient bed, which may also lead to astigmatism.

There is ongoing research into the use of excimer or femtosecond lasers to cut both the donor and the recipient corneas. Early studies suggest that the excimer laser induces less corneal neovascularization; however, the data are best considered preliminary.[28,29] The femtosecond laser may allow for a more precise, perpendicular edge and prevent damage to the iris–lens structures. However, this research is still in its early stages and further investigation is necessary.

IRIS MANAGEMENT

As mentioned earlier, constriction of the pupil in phakic keratoplasty protects the lens. For routine phakic keratoplasty, iridectomies do not appear to be necessary. In patients who have a history

of inflammation, it may be necessary to lyse posterior synechiae by gentle sweeping with viscoelastic or a cyclodialysis spatula through the pupil. In such patients, as well as in patients who are undergoing keratoplasty for herpes simplex keratitis or other disorders that may be associated with future anterior segment inflammation, a peripheral iridotomy may be appropriate. Extensive anterior synechiae may be lysed with a cyclodialysis spatula, but broadly adherent synechiae are often better managed when they are transected with a sharp scissors. Highly vascularized peripheral synechiae that do not extend to the region of the graft are often best left alone.

CONTROL OF POSTERIOR PRESSURE

As discussed earlier, preoperative hypotony can be obtained through digital massage or the placement of a mechanical balloon maintainer. Some surgeons also use either topical medications or intravenous mannitol preoperatively to further reduce intraocular pressure. In spite of these efforts, vitreous pressure may still be present, sometimes nearly prolapsing the lens out of corneal wound. In these cases, a vitreous tap or limited vitrectomy can be beneficial. The prior placement of external globe support is highly beneficial in these cases. A vitreous tap can be attempted using a 21 gauge sharp needle on a 1 cc syringe. A caliper is used to measure 3.5–4.0 mm posterior to the limbus. Then, a limited peritomy is performed, hemostasis as required is achieved, and the needle is inserted into the eye while aiming the needle at the center of the globe. Proper fixation of the globe is imperative during this step, otherwise the surgeon can cause an iatrogenic cataract through violation of the posterior lens capsule. Vitreous taps tend to be of limited utility in younger patients secondary to the consistency and adherence of the vitreous, therefore a limited dry vitrectomy usually provides a greater benefit. Similar to the vitreous tap, a limited peritomy and hemostasis are achieved. An 18 gauge MVR blade is inserted into the previously demarcated site, once again aimed at the center of the globe. Then, a vitrector handpiece (typically the one from a phacoemulsification unit can be used) without the irrigation sleeve is inserted into the wound. The machine should be set at a low vacuum with a high cut rate (>400 cpm). Typically, a very limited vitrectomy is all that is necessary. Upon resolution of the posterior pressure, the vitrector handpiece is removed and the wound checked for vitreous strands with a cellulose sponge. Once cleared of vitreous, the wound is closed with an absorbable suture. Caution is paramount so that the surgeon does not touch the posterior lens capsule or the peripheral retina. The fundus should be examined either at the conclusion of the case or the next day, with either direct visualization or ultrasonography.

GRAFT MANAGEMENT AND CHAMBER MAINTENANCE

The next step is to place the donor cornea onto the recipient bed for suturing in place. A viscoelastic substance is placed over the anterior lens capsule, and the anterior iris surface and then the donor cornea is placed over this layer. One comparison of viscoelastic materials demonstrated that a dispersive viscoelastic coupled with a cohesive viscoelastic in a 'soft-shell' technique resulted in less endothelial cell loss.[30] The combination of the preoperative massage, scleral fixation ring, and viscoelastic material appears to prevent forward movement of the iris–lens diaphragm and trauma to the donor corneal endothelium.[3] Saline solutions or air can be used for anterior chamber maintenance as well, but they are not so effective during the initial graft placement. Rotation of the graft for best alignment has been suggested in the past but has not been demonstrated to be effective. During subsequent portions of the procedure, much of the viscoelastic material may be lost from the chamber, but the chamber is still maintained. Many corneal surgeons prefer irrigating this material out after sufficient interrupted sutures have been placed because of the pronounced pressure elevations, which have been demonstrated with retention of viscoelastic materials in keratoplasty.[31] Removal can also be carried out through a paracentesis track following completion of graft placement. Some transplanting surgeons, concerned with potential endothelial damage from such maneuvers, discourage viscoelastic removal and treat anticipated ocular hypertension prophylactically.

SUTURING

Suturing is an area of perhaps the greatest inter-surgeon variability. Suturing techniques range from the use of multiple interrupted sutures to double running sutures and to combinations of running and interrupted sutures. With all techniques, it is first necessary to place four initial interrupted sutures so as to achieve fixation. The first suture is placed at the 12 o'clock position, followed by a suture at the 6 o'clock position. In placing the 6 o'clock suture, it is important to attempt to align the donor tissue so that there is equal distribution to both sides of the suture. Marking the donor and recipient corneas, as described earlier, aids in this effort. Additional sutures are then placed at the 3 and 9 o'clock positions. Subsequent suturing may consist of the placement of 12 additional interrupted sutures, four or eight additional interrupted sutures, a running suture, or a double running suture with removal of the interrupted sutures.[32] One option is to use 10-0 nylon for all interrupted sutures and 11-0 nylon when interrupted sutures are followed by a continuous suture. When all the interrupted sutures are to be removed before the end of the procedure, the first continuous suture may be of 10-0 nylon whereas the second may be of 10-0 or 11-0 nylon. It is appropriate to place the interrupted sutures as deep as possible without perforating Descemet's membrane. A continuous suture, when used in addition, is placed more superficial. Avoid through-and-through suturing because of the potential of endothelial damage.[33]

Suture tension is an important issue. With interrupted sutures, tight suturing may provide a more secure wound but leads to more epithelial difficulties postoperatively and greater difficulty in achieving optical correction while the sutures are in place. Sutures that are too loose may lead to wound displacement. All sutures are trimmed close to the knots, and all the knots are buried. The knots may be rotated into the host or the donor tissue. Knots buried in the host tissue may be more likely to stimulate vascularization when compared to knots buried in the donor tissue. This area requires further study.

FINAL CHECKS

The wound is checked for its integrity by deepening the chamber with balanced salt solution and checking the wound margins for fluid leaks using sponges and gentle pressure on the globe. When necessary, additional interrupted sutures are placed. If the iris is adherent to the wound, it is either swept free with a cyclodialysis spatula placed through the wound 90° from the adherent iris or forced posteriorly by the use of irrigation with either balanced salt solution or a small amount of viscoelastic material. At this point, some surgeons recommend the use of intraoperative keratometry to

ascertain anastigmatic positioning of the graft. Studies suggest earlier visual rehabilitation but no difference in the final visual outcome with intraoperative suture adjustment.[34,35]

MEDICATIONS

At the end of the procedure, antibiotics may be injected subconjunctivally. Evidence for the benefits of drug treatment and for optimal antibiotics to be used is lacking.[36] Subconjunctival soluble corticosteroids may be injected, but the ultimate benefit is also undetermined.

ALTERNATIVE APPROACHES

Lately, there has been renewed interest in lamellar procedures. Posterior lamellar procedures, such as Descemet's stripping endothelial keratoplasty (DSEK), are being increasingly used in situations of primary endothelial disease. These endothelial lamellar procedures need a substantial amount of space in the anterior chamber and are difficult to perform in phakic patients. Also, the use of air tamponade may cause premature cataracts in these patients.[37] Anterior lamellar procedures, such as deep anterior lamellar keratoplasty (DALK), are being used in situations with healthy endothelium, such as keratoconus and partial-thickness corneal scars. These procedures are discussed elsewhere in this text.

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43 Combined keratoplasty and lens removal: the triple procedure

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Combined penetrating keratoplasty, cataract extraction, and lens implantation has been the treatment of choice for patients with combined corneal and cataract disease. The combined procedure reduces surgical and visual morbidity by reducing the number of procedures necessary to rehabilitate the eye and may be more effective than performing surgery in two or more stages. Early and recent clinical results have been extremely encouraging, as reported by multiple authors over the past 25 years.[1–16] The long-term results continue to be encouraging, as reported by Hunkeler and Hyde[17] in 1983, Erb et al[18] in 1996, and Das et al[19] in 2005. Casey[13] reported the surgical techniques in the triple procedure, describing the implantation of the anterior chamber (AC) IOL, the iris-supported lens, or the posterior chamber (PC) IOL.

ADVANTAGES OF EXTRACAPSULAR TECHNIQUE AND POSTERIOR CHAMBER INTRAOCULAR LENSES

Acceptance of the triple procedure as the treatment of choice for patients with combined corneal and cataract disease has not been without controversy. The success of penetrating keratoplasty and long-term graft survival has improved dramatically along with the understanding of corneal function in relation to graft survival. Furthermore, the refinement of extracapsular surgical techniques combined with PC IOL implantation has served as a breakthrough to allow more surgeons to perform the triple procedure.

With the extracapsular technique, the posterior capsule functions as a protective barrier between the anterior and posterior compartments of the eye and as a platform of support for a PC IOL.[16] With the optic of the PC IOL behind a small pupil of a constricted iris, the endothelium is naturally protected during corneal suturing, an advantage that makes the operation much simpler. For this reason we prefer PC IOLs whenever possible. If there is inadequate capsular support, suture fixation to the iris is preferred. With AC IOLs more IOL material is exposed to the endothelial surface with the attendant risk of endothelial damage. With older flexible closed-loop AC IOLs, there is a greater risk of forward vaulting than with the less-flexible, solid, open-loop polymethylmethacrylate (PMMA) AC IOLs. Scleral sutured PC IOLs are a fourth option, although the long-term complication rate may be high with this technique.[20] Additionally, there have been reports of using the Artisan iris-fixated intraocular lens behind the iris. The long-term stability of this technique is unknown.[21]

VISCOELASTIC SUBSTANCES

The triple procedure was much more difficult to perform from a technical standpoint before the advent of viscoelastic substances. Viscoelastic substances allow us to expand the capsular bag and coat the endothelium, the implant, and the host rim to maintain tissue–plane separation throughout the surgical procedure. This approach is critical for preventing endothelial cell trauma during graft suturing and ensuring accurate placement of the PC IOL in the capsular bag. Prior to viscoelastic substances, mild-to-moderate pressure on the posterior lens capsule threatened to force the implant forward against the endothelium of the donor cornea. When this complication happened, the lens implant portion of the operation was abandoned, necessitating either spectacle or contact lens fitting postoperatively, or a later secondary IOL implantation.

INDICATIONS FOR SURGERY

The indications for the triple procedure are relatively straightforward. Patients with combined corneal and cataract disease who require improvement in vision within their own reasonable life expectancy are excellent candidates for the procedure. If the improvement in visual function can be achieved by either cataract and lens implant surgery or corneal surgery separately; the simpler procedure should be the procedure of choice. The assessment of the extent of corneal disease and lens opacity should be based on the preoperative evaluation; however, occasionally the surgeon may not determine the severity of the cataract until the cloudy cornea has been removed and the lens can be inspected intraoperatively. If the cataract appears to be sufficiently dense to decrease the vision to 20/40 or worse postoperatively, the lens should be removed at the time of keratoplasty. When the patient with a cataract is being assessed, if the surgeon believes the vision will be 20/50 or worse because of corneal opacification postoperatively, a triple procedure

Table 43.1 Published indications for triple procedures, 1976–2004

Corneal Disease	Range of Incidence (%)
Fuchs' endothelial dystrophy	31–80
Leukoma	19–35
Keratoconus	1–21
Herpes simplex keratitis	4.5–14
Interstitial keratitis	4–20

should be performed. Some patients with mild nonprogressive regular corneal scarring, as in eyes with inactive interstitial keratitis of luetic origin, may regain excellent visual activity after cataract surgery alone; in these cases, the opinion of a corneal specialist regarding single versus combined procedures is valuable. The corneal specialist will have to make a judgment call based on clinical appearance, potential acuity measurements, specular microscopy, and pachymetry.

In our center, most patients who undergo the triple procedure have Fuchs' corneal endothelial dystrophy combined with cataract. Evaluation of the patient with Fuchs' dystrophy and cataract requires careful evaluation to assess the need for combined corneal and cataract surgery. A critical evaluation of the endothelial function is necessary, as the presence of cornea guttata alone is not an indication for the triple procedure. Symptoms and manifestations of early-morning corneal edema certainly indicate endothelial decompensation, and epithelial edema in the contralateral eye should arouse suspicion of impending corneal decompensation. A documented increase in central corneal thickness, the presence of Descemet's folds, and central epithelial edema indicate possible impending corneal decompensation. We give weight to clinical signs when deciding if corneal transplantation will be necessary, but in the endothelial dystrophy patient with less than 1000/mm^2 healthy endothelial cells or a corneal thickness greater than 0.64 mm, there is a greater chance of corneal decompensation,[22] although patients who fall outside of these parameters have had cataract surgery alone with acceptable visual outcomes. When there is generalized epithelial edema, gross thickening of the cornea, extensive formation of bullae, and peripheral corneal vascularization, the diagnosis and suggested management are straightforward; more subtle cases require good clinical judgment.

Corneal scarring caused by prior injury or infection, keratoconus, and hereditary corneal dystrophy make up the bulk of the remaining indications. Brady and coworkers[23] reported on clinical indications for keratoplasty and found that 26% of all transplants at their center from 1983 to 1988 were triple procedures and that the incidence of triple procedures increased from 11% in 1983 to 26% in 1988. Published indications for triple procedures from 1976 to 2004 are outlined in Table 43.1.

COMBINED VERSUS SINGLE PROCEDURES

Several authors have examined the success of combined versus nonsimultaneous surgery and have found the results to be comparable.[24,25] There is controversy, with some surgeons preferring triple procedures while others favor sequential PKP followed by cataract extraction at a later date. The arguments for staged procedures center around a reduced need for open sky time and a greater accuracy in calculating IOL power. It is intuitive that IOL calculations should be better if these can be made after the corneal power has stabilized, but it has been difficult to show definitively that staged procedures produce superior refractive results compared to triple procedures in which surgeons have used IOL formulas with individualized constants and corneal powers. It is likely that measurement of true central corneal power and the prediction of IOL power in atypical eyes such as post-penetrating keratoplasty patients will continue to improve in the future with more advanced corneal imaging systems and IOL formulas that take into account a greater number of variables.

One concern in staged procedures is that there will be endothelial failure following cataract extraction. Modern case series have reported a low rate of graft failure following cataract surgery, similar to the control rate of failure in grafts not undergoing additional procedures.[26]

The eye is open longer in a traditional triple procedure compared to penetrating keratoplasty alone. The prolonged operating time increases the risk of posterior capsule rupture, vitreous loss, and the most devastating complication of corneal transplantation, expulsive choroidal hemorrhage. Although the complication can occur with corneal transplant or cataract surgery alone, it is more likely to occur in triple procedures. Most cases seem to occur in patients who move, cough, or squeeze the eyelids during the 'open sky' portion of the operation, and the importance of an adequate lid block cannot be overemphasized. The surgeon may consider staging the procedures or performing the cataract extraction in a more closed system for patients who are at risk of expulsive choroidal hemorrhage (advanced age and glaucoma) or who are likely to be restless during surgery.

In patients in whom adequate visualization of the lens is possible through the cornea, a small incision self-sealing phacoemulsification can be done followed immediately by keratoplasty. Authors have also described performing the capsulorrhexis only prior to removing the corneal button.[27] Menapace et al[28] described the use of a temporary keratoprosthesis as a modification of the triple procedure to perform the cataract portion with small incision surgery in a closed system. Farjo described a technique of non-coaxial illumination to aid visualization through cloudy corneas.[29] In our practice, if the cataract extraction or a significant portion of it can be performed under a closed system, we do so.

CONTRAINDICATIONS

Contraindications for triple procedures are identical to those for noncombined keratoplasties. For example, if a corneal transplant is contraindicated in an eye with uncontrolled ocular cicatricial pemphigoid or infiltrative keratitis with corneal melting, then a triple procedure should not be performed either. Patients with proliferative diabetic retinopathy, uncontrolled glaucoma, and uncontrolled recurrent episodes of moderately severe or severe uveitis are poor candidates for the triple procedure. Patients with a history of severe herpetic stromal keratitis or prior active keratouveitis may have complicated postoperative courses and will require pre- and postoperative oral antiviral prophylaxis and intensive follow-up.

INTRAOCULAR LENS POWER CALCULATIONS

After the decision has been made to proceed with the triple procedure, the lens-implant power calculation should be performed. Binder[9] and Crawford and coworkers[3] have evaluated the parameters

Table 43.2 Hoffer technique for intraoperative lens power calculation

Axial Length (mm)	Formula	Percentage Used
<22	Hoffer Q	8
22.0–24.5	Average of all three	72
24.5–26.0	Holladay 1	15
>26	Sanders–Retzlaff–Kraff/T	5

that assist in proper lens-implant power selection and have developed linear-regression formulas based on their clinical experience. Retzlaff[30] reported a linear-regression formula that has been used for cataract extraction with lens implantation.

$$\text{IOL power} = A(\text{constant}) - 2.5 \times \text{axial length} - 0.9 \times \text{average } K \text{ in diopters}$$

Several authors have reported that the choice of IOL power formula does not affect IOL power predictions in triple procedures, but others assert that IOL power calculation using theoretical formulas are most likely to be accurate with formulas chosen based on the axial length as recommended by Hoffer[31] (Table 43.2). The more important factor in postoperative refractive accuracy of triple procedures is the use of personalized constants within a given formula.[32,33] In the SRK formula this would be the *A* constant. Each IOL has a manufacturer-recommended *A* constant. Personalizing the *A* constant by analyzing postoperative outcomes will yield greater accuracy. When using the Holladay formula the surgeon factor (*S* factor) should be modified, and in the Hoffer Q formula it is the postoperative AC depth that should be personalized.[33]

Each corneal surgeon should also individualize IOL power calculations by noting the average keratometry readings for a series of patients after keratoplasty. The keratometry value selected is based on results of numerous triple procedures with the same trephine and suture techniques by the same surgeon. For example, using the same trephine and suture techniques an average value close to 44.5 D at 12 months postoperatively was found in a series of triple procedures. In order to attempt to further improve accuracy, one group analyzed the correlation between preoperative peripheral cornea power, as measured by computerized videokeratoscopic analysis (Corneal Analysis System, EyeSyS Laboratories, Houston, TX). In patients with flat peripheral corneas (40 D or less), a value of one was subtracted from the surgeon's average central corneal power in calculating the IOL power. This modification resulted in a statistically significant better postoperative refractive outcome.[34]

SURGICAL TECHNIQUE

SOFTENING THE GLOBE

On the day of surgery, pupillary dilatation is achieved with 1% cyclopentolate and 2.5% phenylephrine given 15, 30, 45, and 60 min preoperatively. A topical nonsteroidal anti-inflammatory drop can also be used to prophylax against premature intraoperative miosis. Some surgeons use preoperative antibiotics for 1–3 days preoperatively, although at this time there is not good evidence to support this. Either a local or a general anesthetic may be used. If general anesthesia is selected, endotracheal anesthesia is preferred. A lower rate of suprachoroidal hemorrhage is reported with penetrating keratoplasties done under general anathesia.[35] In our practice, most cases are done under local anesthesia with minimal preoperative sedation. Prior to retrobulbar injection the eye can be anesthetized with proparacaine. Some physicians prefer a combination of bupivacaine and lidocaine anesthetics. Equal parts of 0.75% bupivacaine and 4% lidocaine are mixed to give a solution that is 0.375% bupivacaine and 2% lidocaine. Hyaluronidase is also incorporated with the anesthetic to aid in tissue spread. This local anesthesia gives a rapid onset with the lidocaine, long staying power with the bupivacaine, and few adverse reactions. We always perform a lid block with retrobulbar anesthesia. Following injection, we use a Honan pressure cuff at 20–25 mmHg to soften the eye for 10 min. Some surgeons prefer to use the Honan device for 20–30 min preoperatively.

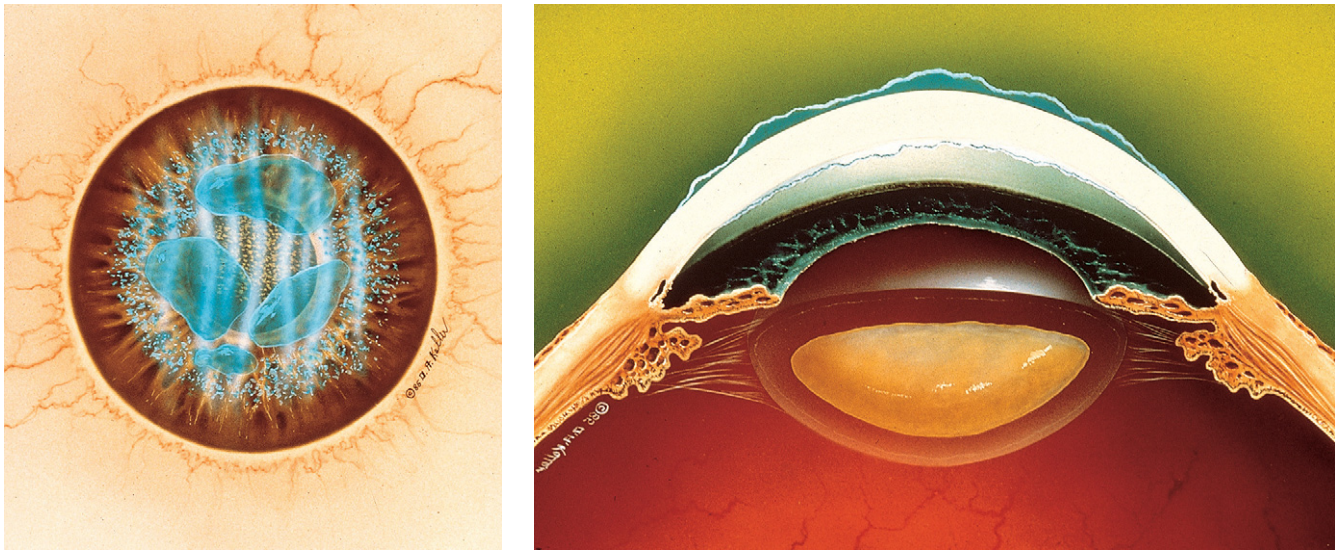
PREPARATION

The patient is positioned with the iris and facial features in a flat plane, the head in an apparently comfortable position, and the body relatively flat with some break at the knees for patient comfort. Some surgeons use a wrist rest system. The lids and lashes are prepped with betadine, including a drop of 5% solution in the eye. A paper drape is used to cover the head and the body, with a solid patch of adhesive plastic in the center. The lids are retracted by the scrub-nurse assistant, and the adhesive surface is applied directly to the retracted lids and exposed host cornea (the sticky adhesive will not adhere to the cornea but adheres nicely to the lids and lashes). A central cut is made in the drape adhesive plastic to allow the insertion of a wire lid speculum. The lashes remain everted and out of the surgical field.

It is important that the speculum system that is chosen does not apply pressure to the globe. We routinely use the McNeill–Goldman blepharostat ring, which is a combined speculum and scleral support ring. Some surgeons do not use a Flieringa ring routinely except in pediatric cases or when the eye has had or is scheduled to undergo vitrectomy. The ring is secured to the globe with four 5-0 silk or vicryl sutures. The tails of the suture can be left long to assist in maneuvering the globe during the operation. The speculum and ring should be inspected throughout the operation to ensure minimal pressure on the globe. Vitrectomy instrumentation should be available in case a vitrectomy becomes necessary.

REMOVAL OF EPITHELIUM

In cases in which no minimal peripheral epithelial edema exists, removal of healthy peripheral recipient epithelium is unnecessary. In eyes with Fuchs' corneal dystrophy (Fig. 43.1, *A* and *B*), several pathologic changes may have occurred by the time of surgery including epithelial edema, bullae, and striate keratopathy (resulting in significant corneal thickening); frank corneal decompensation; dense, nuclear cataract formation; and, occasionally, tremendous epithelial hypertrophy (associated with superficial vascularization). Edematous corneal epithelium with or without fibrovascular pannus can be removed with a #64 Beaver blade, decreasing the chance of trephine slippage and irregular cutting of Bowman's membrane and the anterior lamellae of the cornea. In addition, this step ensures that sutures will be passed securely into corneal stroma rather than into thickened fibrous tissue or epithelium. Occasionally, some cautery is required for prolific vessels, but bleeding normally ceases



A B

Figure 43.1 *A*, Cornea with advanced Fuchs' dystrophy showing microsystic and bullous epithelial edema, striate keratopathy, and circumciliary flush. *B*, Dense nuclear cataract in eye with advanced Fuchs' corneal dystrophy. Slit-lamp evaluation of lens changes may be difficult when significant corneal edema is present.

on its own. If phacoemulsification is to be performed prior to removing the corneal button, removal of edematous epithelium often improves visualization. Phacoemulsification can be performed at this stage and may be done via a scleral tunnel or clear cornea approach. The wound should be sutured at the conclusion of the case. Some surgeons prefer to perform a partial-thickness trephination prior to phacoemulsification.

DONOR TISSUE PREPARATION

Donor tissue should be prepared before trephination of the patient's cornea to ensure that adequate donor tissue is available immediately upon entry into the AC. There are a variety of techniques for the trephination of donor tissue. Most surgeons cut the donor tissue endothelial side up with an Iowa, Troutman, or Hanna corneal trephine punch. The disposable trephine selected should be 0.25 or 0.5 mm greater than the opening to be made in the recipient cornea. The slight oversize of the button allows for some tissue compression effect of the sutures without significant flattening of the central graft curvature.

When using the Iowa trephination system, the donor is placed epithelial side down and is centered on the cutting block. The trephine is then passed through the guide and is pushed straight down through the cornea, producing a crunching sound. Before withdrawing the trephine, the donor rim can be grasped, lifted, and turned to ensure complete separation. If the trephine does not cut full thickness for 360°, a blade or corneal scissors is used to complete the cut. The donor button is placed epithelial side down on a polytef punch block with a few drops of Optisol storage solution and covered before transplantation.

Some surgeons prefer to use a trephine such as the Hanna trephine with an artificial AC. The donor corneoscleral tissue is placed endothelial side down (epithelial side up) (see Fig. 43.2) over viscoelastic, and the artificial chamber is sealed by screwing the top down. Sterile balanced salt solution is then injected to fill the artificial chamber to an estimated intraocular pressure of approximately 50–60 mmHg. The donor center is marked by making an impression through the gunsight of the Hanna trephine with the tip of a cannula. Suture placement may be marked on the epithelial side of the donor with a 12-incision radial keratotomy marker. The Hanna trephine self centers and is then used to cut the donor tissue from the epithelial side in the same fashion as the patient's cornea is to be cut (see Fig. 43.3). The advantage of trephination from the epithelial side with an artificial AC is that the surgeon is cutting both the donor and the recipient corneas from the epithelial side. This approach eliminates the opposite beveled cut and tissue mismatch seen with traditional trephination and allows the surgeon to mark suture placement on both donor and recipient for more precise suture alignment.

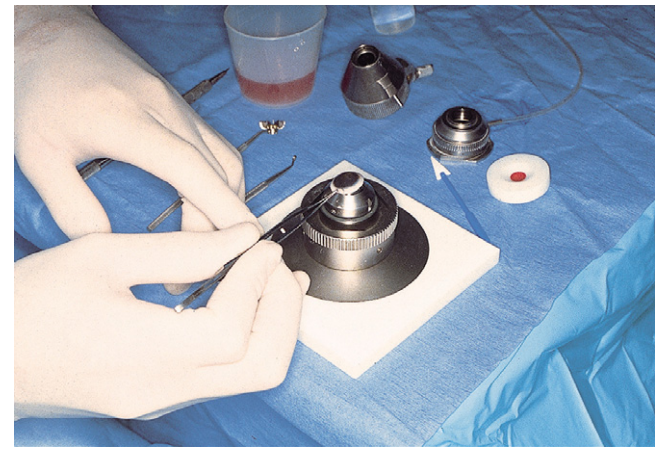


Figure 43.2. Donor corneal-scleral rim resting on Hanna artificial anterior chamber.

Another approach involves using an excimer laser to cut both the donor and the recipient tissue. Graft oversize need not be as high with this technique because of greater precision in cutting.[36] Enhanced precision should lead to better surgical results, especially

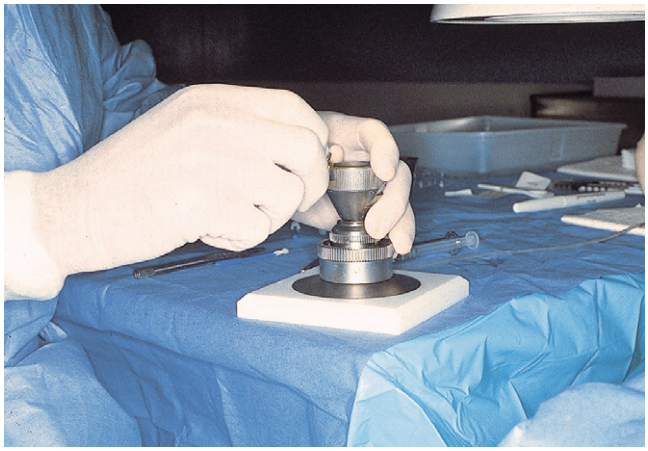


Figure 43.3. Hanna trephine on artificial anterior chamber cutting donor cornea.

Figure 43.5. View to patient's cloudy cornea through gunsight of Hanna trephine.

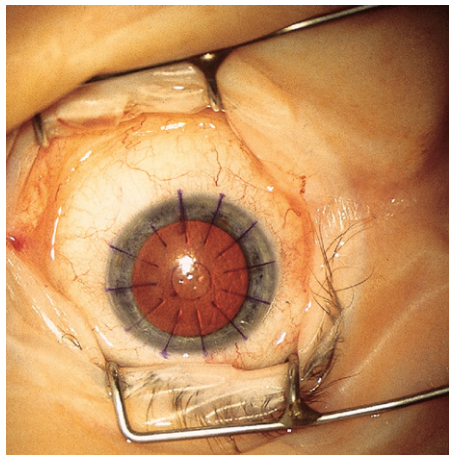


Figure 43.4. 3.0 mm optical zone mark and 12 radial marks of recipient cornea.

regarding postoperative astigmatism. Cost and availability may limit this technology in the near term, however.

RECIPIENT CORNEA TREPHINATION

The center of the patient's cornea is marked by measuring with 6 mm calipers from periphery to center at 3, 6, 9, and 12 o'clock positions. The cornea can be marked to assist in even spacing of sutures by marking the central optical zone with a 3 mm optical zone marker marked with gentian (Fig. 43.4). An inked 12-incision radial keratotomy marker is centered around the 3 mm and 12-radial marks to guide interrupted suture placement (Fig. 43.4). A limbal paracentesis incision is made between suture marks, and a moderate amount of viscoelastic is injected to protect the intraocular structures from the cutting action of the trephine blade. Both handheld and suction trephine systems are available. The most popular system is the Hessburg–Barron vacuum trephine to incise the recipient cornea. The blade is aligned with the edge of the trephine housing under operating microscope guidance (Fig. 43.5), and the blade is then retracted three quarter turns. The cross-hairs in the trephine are centered on the cornea with the syringe plunger held in. When the trephine is in the proper position, the plunger is released and the resultant vacuum suctions the trephine mechanism in place. The blade is then advanced 6.5 quarter turns, which corresponds to a corneal incision of approximately 0.30 mm, and is then removed. Alternatively the AC may be entered. The incision depth is checked with 0.12 mm tooth forceps, and dissection is carried deeper with a slight inward beveling by either a diamond knife or a disposable 15° blade. The AC is then entered, and the incision is extended 360° with right and left cutting corneal transplant microscissors. There is often an inner bevel to the incision.

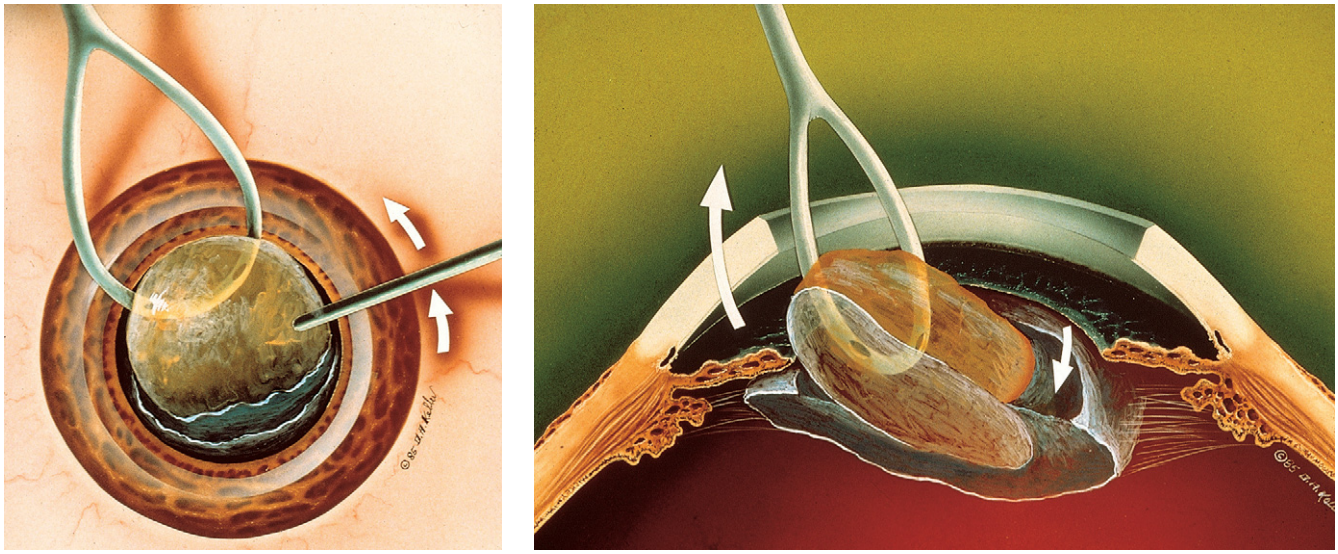
In the Hanna trephine system, suction is applied peripheral to the limbus and the central cornea is supported by a central obturator. This arrangement allows for trephination 100% through the cornea without significant bevel formation or chamber shallowing. In contrast, the Hessburg–Barron trephine suctions directly onto the cornea and lacks central support, which allows for beveled cuts and suction pressure to transmit to the AC once initial entry is achieved. The Hanna trephine also centers more precisely, as it contains a central gunsight target that rests directly on the cornea in contrast to the Hessburg–Barron's cross-hairs that are elevated off the corneal surface.

With either system, once the chamber is entered, it is imperative that suction pressure be removed to avoid rapid chamber shallowing and inadvertent cutting of the iris or lens capsule by the blade. We often use an 8 mm diameter blade. If the same marks are made on both donor and recipient corneas and the same Hanna trephine is used to cut both from the epithelial side, excellent alignment of tissue results in both the anterior–posterior and the circumferential aspects.

CAPSULOTOMY AND LENS REMOVAL

After excess viscoelastic and fluid are removed, a round capsulotomy is performed by capsulorrhexis. Staining the capsule can assist with visualization.[37] If there is any posterior vitreous pressure, the capsule edge often begins to tear radially. If this complication occurs, completion is best done with scissors. Some surgeons have suggested that depressing the center of the lens with a second instrument can assist in flattening the anterior capsule and completing a capsulotomy. It is wise to avoid contact with the iris to prevent premature miosis before removal of the nucleus. The central piece of anterior capsule is removed, leaving a round opening preferably around 6 mm in diameter.

One method of nucleus removal involves hydrodissection until one pole of the nucleus prolapses from the capsular bag and then



A B

Figure 43.6. Lens loop and irrigating cannula used to deliver nucleus after anterior capsulotomy.

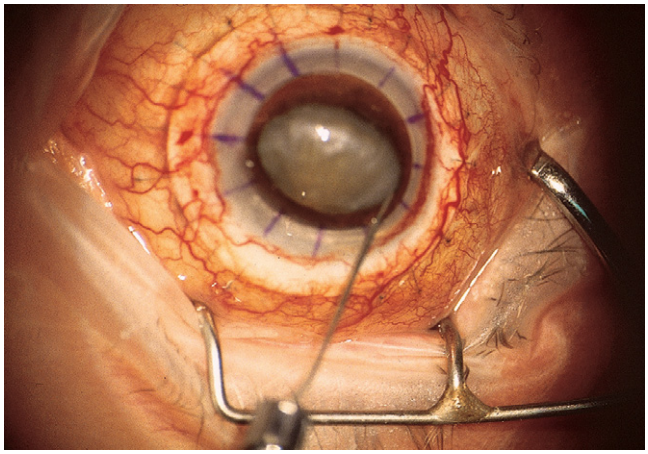


Figure 43.7. Open sky hydroexpression of cataractous lens nucleus.

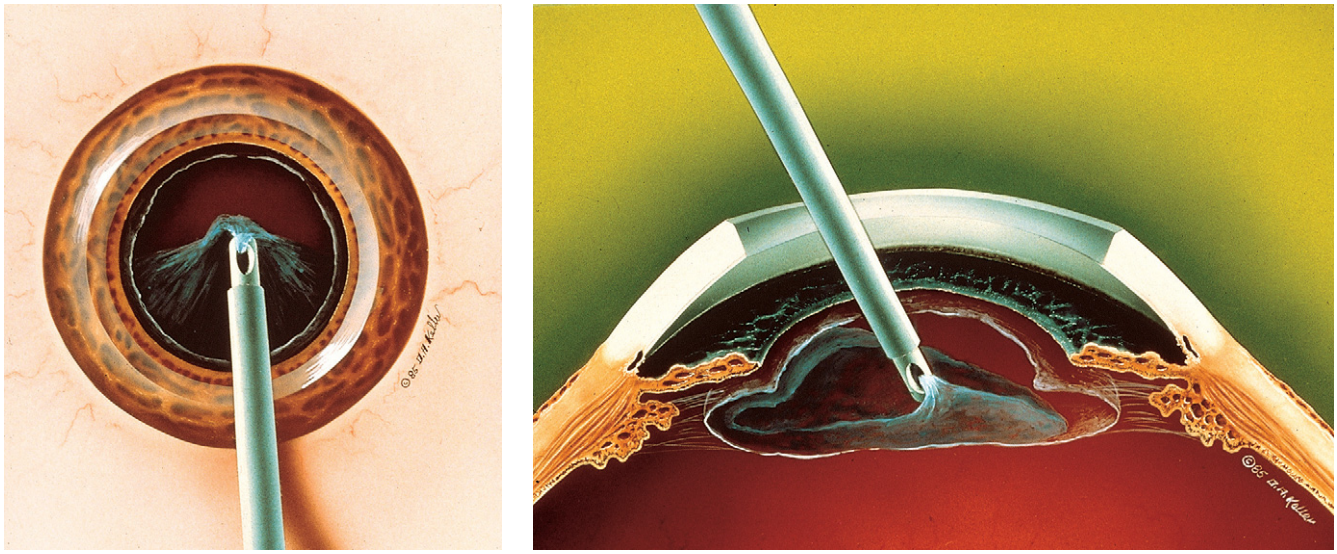
placing a lens loop under the inferior pole of the elevated nucleus (Fig. 43.6, *A* and *B*). The nucleus is raised superiorly and anteriorly with a 25-gauge irrigating cannula placed just above the inferior pole, then forced superiorly and anteriorly. The cleavage plane develops, allowing insertion of the lens loop with or without an irrigating component. Once this cleavage plane has been established, a counterclockwise rotary movement with a 25-gauge irrigating cannula spins the nucleus out of the capsule bag. If this approach fails, for whatever reason, the nucleus can be brought forward with posterior pressure on the peripheral cornea in the 5 o'clock meridian, which raises the intraocular pressure and brings the nucleus forward. At this point, the 25-gauge irrigating cannula can fix the nucleus, and the lens loop can be slipped underneath the nucleus before its removal. It is also possible to remove the nucleus by application of a cryoprobe to the dried central nucleus and to gently pull it up. The current preferred technique is more elegant and simply uses hydrodissection and hydroexpression to gently express the nucleus from the bag (see Fig. 43.7). A 27-gauge cannula is used to sweep the anterior capsule aside while injecting balanced salt solution posterior to the equator of the nucleus. This step usually results in the nucleus prolapsing anterior to the capsulorrhexis and standing on end. It is then gently rotated out of the eye by the cannula. If the lens cannot be prolapsed a phacoemulsification handpiece may be used to fragment the lens for removal.

IRRIGATION AND ASPIRATION

The remainder of the lens cortex can be removed with conventional cortical clean-up, irrigation, and aspiration systems (Fig. 43.8, *A* and *B*). Mechanical irrigation and aspiration and manual technique are equally effective. Excessive irrigation obscures the surgeon's view of the red reflex and creates multiple-mirrored images from the fluid surface, obscuring the view of the cortex and posterior lens capsule. The anterior cortical tissue is engaged with the aspirator and stripped toward the center (Fig. 43.9). Relatively high vacuum levels must be used for most irritation/aspiration systems to maintain purchase on the cortex in the open system. There is no special technique required for cortical stripping in the soft eye. Occasionally, with positive posterior pressure and a convex posterior lens capsule, aspiration in the fornix of the capsule bag is difficult but can be facilitated by applying gentle posterior pressure on the peripheral posterior lens capsule while the cortical material is stripped away. The gentle posterior pressure develops the cleavage plane, allowing engagement of the anterior cortex peripherally. Once most of the cortex has been removed, a Kratz sandblasted capsule polisher or silicone sleeve squeegee polisher is used to clean off the central posterior capsule.

POSTERIOR INTRAOCULAR LENS INSERTION

The 7-mm optic one-piece all-PMMA ultraviolet-absorbing PC IOL is our choice for placement within the capsular bag (Fig. 43.10, *A* and *B*). Viscoelastic is used to separate the anterior and posterior lens capsules to facilitate in-the-bag loop placement. Constant, gentle downward pressure should be maintained on the IOL during insertion as the vitreous pressure tends to push the IOL back out of the bag. If necessary, the lens position can be inspected with a hook,



A B

Figure 43.8. Aspiration of residual lens cortex after removal of nucleus. Stripping is best accomplished when the peripheral anterior cortex is engaged and gently pulled toward the center, with improved red reflex being noted.

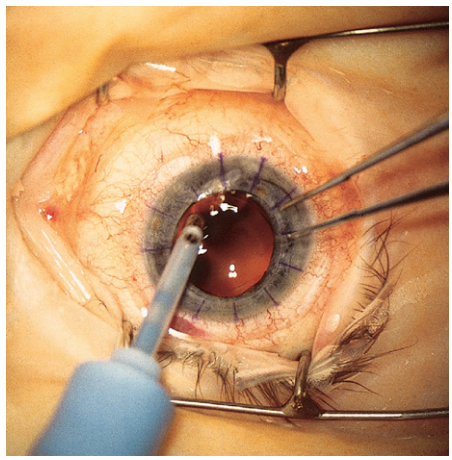


Figure 43.9. Automated irrigation/aspiration cortical clean-up.

and the lens implant rotated to achieve centration. A small peripheral iridotomy is optional, but it is not routinely done.

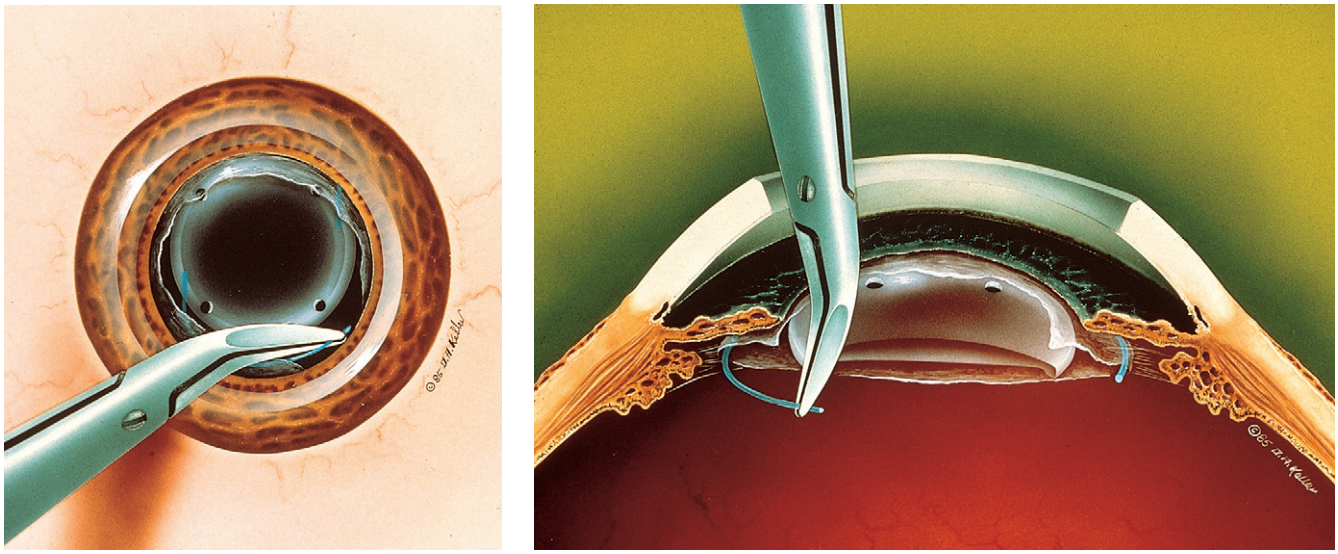
After the IOL is positioned, acetylcholine chloride is used for miosis and to ensure final placement of the lens behind the iris. Residual viscoelastic material is then evacuated out of the AC with irrigation and aspiration and the AC is left filled with balanced salt solution. Viscoelastic can be left in the AC to protect the donor endothelium during suturing. A cohesive agent is preferred at this point to aid in complete removal at the conclusion of the case, minimizing the potential for significant intraocular pressure rises. In all cases, a coating of viscoelastic should be placed along the rim of the recipient cornea to guard against endothelial damage from tissue sliding during placement of the four cardinal sutures.

INADVERTENT CAPSULAR RUPTURE

If the posterior lens capsule is inadvertently broken during the procedure with a small tear either centrally or peripherally in a small sector, a PC IOL may still be inserted. Provided that there is a stable capsular platform, the lens can be gently inserted within the capsular bag or in the ciliary sulcus. However, if significant capsular support is lost or extensive vitreous surgery is required, it is advisable to suture fixate a PC IOL to the iris, to insert a flexible AC IOL, or to suture fixate a PC IOL to the sclera. This can be accomplished through the keratoplasty opening, avoiding a second incision at the limbus. Iris fixation is preferable due to its rapidity, ease, dependability, and safety. Scleral fixation is used if there is inadequate iris to provide support and an AC IOL is contraindicated. In the past a PMMA AC IOL with four positioning holes in the optic was available for iris fixation, but lenses with positioning holes are no longer widely available. Alternatively a three-piece PC IOL can be fixated to the iris by passing a 10-0 prolene suture through the mid-peripheral iris, under the haptic of the IOL, and back through the iris. The exit points on the iris should be about 1 mm apart—less will allow for cheesewiring of the suture through the iris and more will 'bunch up' the iris and distort the pupil. A peripheral iridectomy is not routinely done, and postoperatively the pupil still dilates nicely. Complications such as iris chafing, pigment dispersion, pupillary block, and dislocation are rare with this technique. It is important to have alternative lenses available in an appropriate power should the need arise.

SUTURING THE GRAFT

A small amount of viscoelastic material (we currently use Provisc, Alcon) is placed in the AC and around the recipient rim to protect the donor endothelium. The donor cornea is removed from the polytef block with a corneal spatula and placed over the recipient hole (Fig. 43.11), where it is secured with four cardinal sutures placed sequentially at the 12, 6, 3, and 9 o'clock positions (Fig. 43.12). The chamber can be deepened with balanced saline solution at this point and if necessary supplemented with air or viscoelastic material. With a nice coat of viscoelastic material, it is possible to use air, which reduces the amount of viscoelastic material needed to give a firm eye for excellent suture placement. We have also used Viscoat (Alcon) in the past and have not experienced significant



A B

Figure 43.10. Following use of viscoelastic to separate anterior and posterior lens capsules, in-the-bag placement of posterior-chamber intraocular lens facilitates using needle-holder guidance of the superior loop.

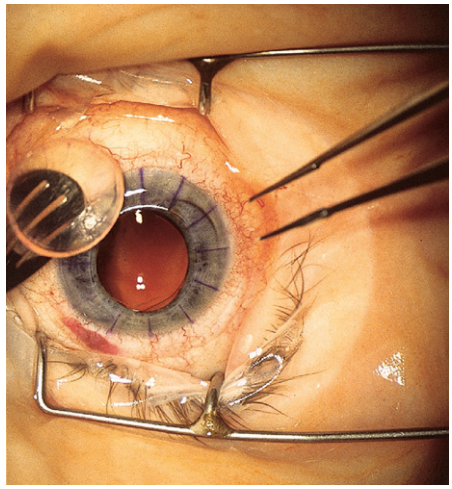


Figure 43.11. The donor button is brought onto the patient's eye with a spatula.

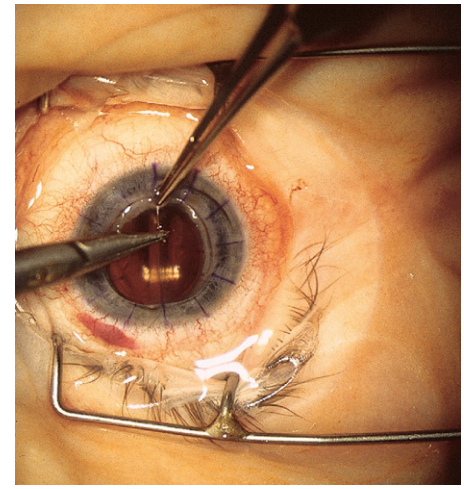
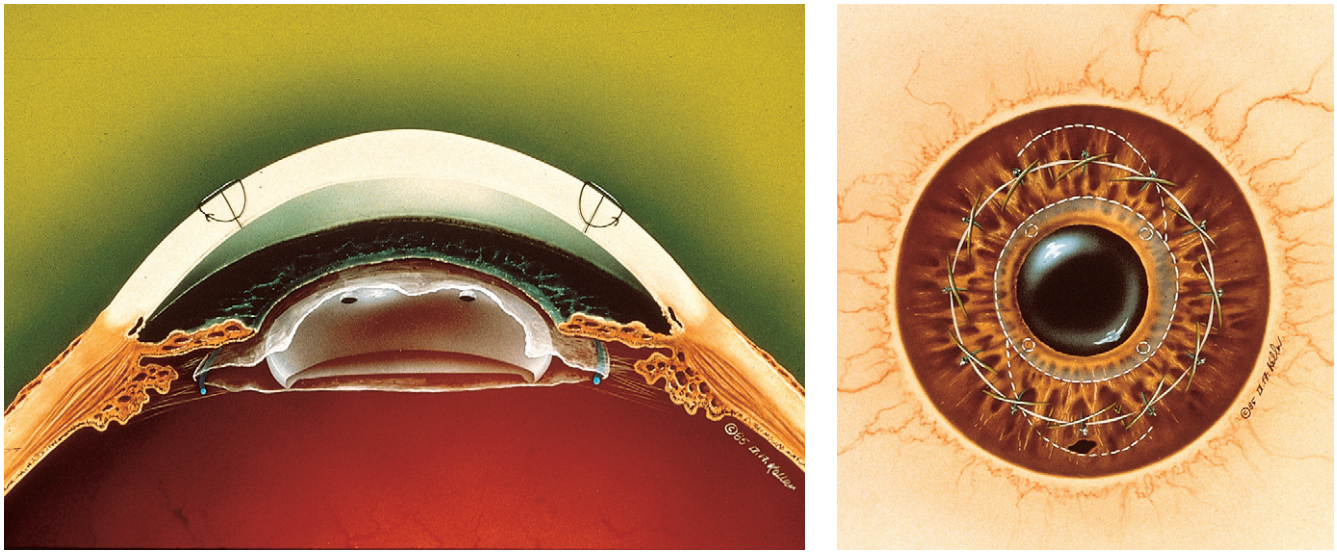


Figure 43.12. 11-0 Mersilene suture placement along previously placed radial marks.

postoperative intraocular pressure rises despite often leaving much of the material in the AC at the close of surgery.

The surgeon then completes suturing with interrupted sutures alone, combination of interrupted and running sutures, or single or double running sutures. Good results can be obtained with a variety of suturing techniques. In our current technique, eight additional interrupted sutures are placed equally spaced between the four cardinal sutures on each of the 12 radial keratotomy marks. All the knots are tied evenly and securely in a 3-1-1 fashion before being trimmed on the knot and buried in the peripheral host cornea (Fig. 43.13, *A*). Suture depth placement is at the 90% or greater level. Ideally, sutures are deep enough to directly approximate Descemet's membrane, but we avoid full-thickness sutures because of concern for postoperative endophthalmitis. Suture bites of approximately 0.75–1.0 mm are preferred to minimize tissue compression centrally, with a larger central optical zone being achieved. A 12-bite continuous running suture is then placed with bites between each of the 12 interrupted sutures in a slight antitorque direction (Fig. 43.13, *B*). Suture slack is taken up once around the circumference with nontoothed forceps while the AC is somewhat shallow and the eye moderately soft. The suture begins and ends in the incision so that the knot is already buried on the host side. Tying the continuous suture more gently than the interrupted sutures allows for effective reduction of graft astigmatism by selective removal of the interrupted sutures postoperatively. When the AC is filled at the end of the case, tension of the sutures tightens to the appropriate level.

Some physicians have reported using 11-0 polyester sutures for closure with the combined 12 interrupted and 12-bite running technique. The 11-0 polyester is a monofilament permanent suture material that can be left in place indefinitely. A theoretical benefit of this technique is enhanced long-term wound integrity provided by permanent sutures. Graft incisions heal very little, and wound dehiscence or trauma after suture removal is not uncommon even years postoperatively. In addition, at the time of regraft, most wounds can easily be separated using minimal blunt dissection with



A B

Figure 43.13. *A*, Corneal button held in place with interrupted nylon suture placed at three-fourths depth and knots buried on the recipient side. *B*, Closure with 12 interrupted nylon sutures with each continuous suture bite between each clock hour.

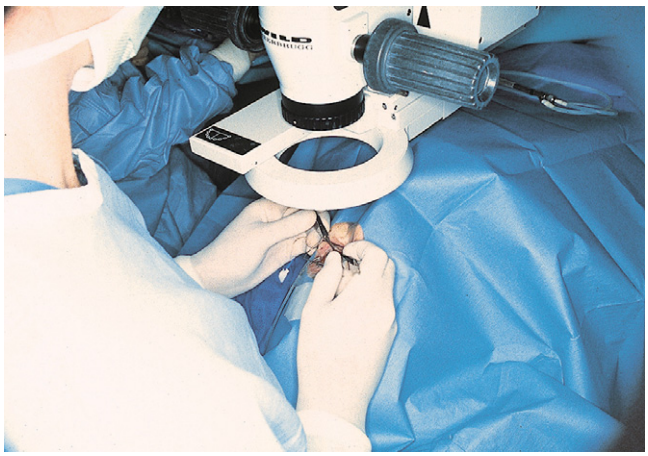


Figure 43.14. External view of Nidek surgical keratometer.

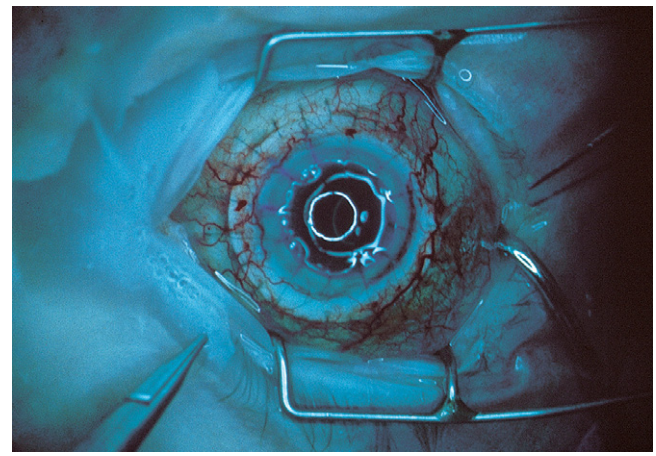


Figure 43.15. Round keratometry reflection on patient's cornea at the end of surgery.

jewelers' forceps. Unfortunately, one study showed that the short-term complications with polyester sutures were higher than with nylon.[38]

ADJUSTMENT OF SUTURE TENSION

Intraoperative adjustment of suture tension to minimize postkeratoplasty astigmatism is useful. Suture tension is adjusted twice during the operation: once after the interrupted sutures are in and again after the running suture is tied. A simple instrument such as the Hyde astigmatic ruler can be used to project a circular keratoscopic image onto the cornea.[39] The coaxial light of the operating microscope is directed toward the vertically aligned eye. A circular image is created as the coaxial light reflects off the inner circular ring of the astigmatic ruler, projecting such a ring onto the corneal surface, which can be monitored by the surgeon viewing through the oculars of the microscope system (Fig. 43.14). The round end of a sterile safety pin can be used in a similar fashion. More advanced instrumentation is also available. A Nidek qualitative and quantitative intraoperative surgical keratometer projects a continuous circle of light onto the corneal surface and can be brought in and out of the operative field mechanically using foot pedal control (Fig. 43.15). Examples of other surgical keratometers available include the Serdervaric Circle of Light, Terry keratometer, and Polack keratometer (Jed-Med). The interrupted or continuous suture can be relaxed in the steep meridian and tightened in the flat meridian. The oval mire can be converted to a circular configuration, which is the desired end point. Although this solution does not solve the long-term problems, it helps to minimize postkeratoplasty astigmatism until selective suture removal can be performed[40] and may obviate the need for such suture removal. This approach allows earlier visual rehabilitation for the patient with less cylindric correction in the short term and hopefully in the long term.

CONCLUSION OF PROCEDURE

Once the suture has been adjusted to minimize astigmatism, remaining viscoelastic has been irrigated from the eye, and eye inflated to

the appropriate pressure with balanced salt solution, the procedure is essentially complete. The Flieringa ring is removed, and subconjunctival injections of 0.3 mL betamethasone and 0.3 mL cefazolin (50 mg/mL) are given in the inferior temporal quadrant. To anticipate and prevent postoperative wound healing and re-epithelialization problems, preoperative basal tear secretion tests are performed on every patient and we have a low threshold for performing inferior punctal occlusion prior to or at the end of the procedure. In addition, the donor epithelium is inspected pre- and intraoperatively, and temporary tarsorrhaphies are done if the patient is at high risk of healing problems. This proactive approach has saved countless grafts from problems and is a quick adjunct to the surgical procedure. A patch and Fox shield is applied to the eye after instillation of an antibiotic–corticosteroid ointment. The procedure is typically performed on an outpatient basis, and the patient is then prepared for discharge. Rarely is a 1-day hospital stay necessary.

CLINICAL RESULTS

Many surgeons have reported clinical results of triple procedures with generally favorable outcomes.[1,2,4–8,11,12,14–18] Summaries of results compiled from the literature are outlined in Tables 43.3–43.5. Transplant studies have not usually evaluated uncorrected visual acuities but, as techniques improve, patients may be able to achieve excellent unaided vision. Triple procedures were reviewed by one author using his standard method (standardized suturing and suture removal techniques with the 12 interrupted and 12-bite running 11-0 polyester suture technique and intra- and postoperative suture adjustment, trephination diameters, the Hanna trephine and artificial AC, and an assumed keratometry value of 44.50 D). Data were gathered over a 1-year period on 49 consecutive patients with normal macular examinations who met the indications for triple procedure. Refractive data reflect selected sutures remaining given the assumed permanency of Dacron polyester suture. The results are detailed in Table 43.6. Both refractive and keratometric astigmatism values were excellent with refractive cylinder consistently under 2.25 D from 3 months onward and keratometric cylinder under 3.5 D after 3 months. Mean keratometric power was relatively consistent and shows gradual steepening from 43.06 D at 3 months to 44.21 D at 12 months, reflecting wound healing and suture removal events. This 12-month value is the basis for the 44.5 D keratometry value that we use in triple procedure IOL calculations. Finally, the mean spherical equivalent data show excellent targeting of IOL calculations in triple procedures using the standard technique, with an initial hyperopic overshoot of +1.56 D at 3 months but gradual steepening to +0.13 D at 12 months. Excellent refractive results were obtained in this series with the triple procedure, and visual rehabilitation may be very rapid with good refractive stabilization

Table 43.3 Published results of triple procedures from 1976 to 1991

Study	Eyes (n)	Mean Follow-up (mo)	Clear Grafts (%)	Visual Acuity 20/20 to 20/40 (%)
Taylor[41]	6	7.7	100	33.3
Aquavella et al[42]	5	15.0	80.0	N/A
Lee and Dohlman[14]	10	15.9	60.0	50.0
Alpar[8]	18	21.0	94.0	77.7
Taylor et al[43]	22	N/A	77.0	36.3
Gould[44]	11	N/A	72.0	54.5
Lindstrom et al[15]	18	21.0	89.0	55.5
Hunkeler and Hyde[17]	177	>6.0	89.0	88.7
Crawford et al[3]	56	15.8	90.0	65.2
Binder[9]	60	24.5	91.6	61.6
Bruner et al[45]	12	27.3	90	80
Polack[46]	60	6–48	98.3	35
Taylor et al[47]	66	24–120	95.4	54
Katz and Forster[48]	53	8.9	96	64
Gabel et al[49]	94	N/A	N/A	82
Binder[50]	78	24.5	97	71.8
Meyer and Musch[51]	166	17	98	83
Busin et al[2]	22	4	95	64
Skorpik et al[7]	21	22	100	71
Mattax and McCulley[52]	21	11.8	95.2	76

N/A, not applicable.

Table 43.4 Reported series on triple procedures involving posterior chamber lenses

Study	Posterior Chamber Intraoperative Lenses (%)	Mean Follow-Up (mo)	Clear Grafts (%)	Visual Acuity 20/20 to 20/40 (%)
Lindstrom et al[15]	100	21	89	55.5
Crawford et al[3]	91	15.8	>90	>77
Katz and Forster[48]	96	8.9	96	64
Binder[50]	100	6–72	97	75
Gabel et al[49]	100	N/A	100	82
Meyer and Musch[51]	100	17	98	83
Busin et al[2]	100	4	95	64
Skorpik et al[7]	100	22	100	71
Davis et al[53]	100	40	98	78
Sanford et al[54]	100	53	91	61 (20/50 or better)
Geerards et al[55]	100	12+	NR	37.5
Das et al[19]	100	N/R	97	NR

N/A, not applicable; N/R, not reported.

Table 43.5 Refractive results from the triple procedure

Study	IOL Type	IOL Formula	Mean Postoperative Spherical Equivalent (Range)	Astigmatism, (D) (Range)	2 D of Desired Power (%)
Taylor et al[47]	I, P	None used	–1.31 (–8.00/6.25)	3.6 (plano to 7.5)	60.9
Katz and Forster[48]	A, P	SRK	–0.61 (–6.88/7.89)	5.4	26
Gabel et al[49]	A, P	B	–0.77 (–14/4.5)	NR	57
Crawford et al[3]	A, I, P	NR	–0.33 (–5.5/6.62)	3.23 (plano to 8)	62
Binder[9]	A, I, P	B–SRK	–1.78 (–14.7/5.25)	3.1 (plano to 10)	58
Binder[56]	A, I, P	B–SRK	–1.57 (–14.7/5.25)	2.98 (plano to 11.4)	57.9
Meyer and Musch[51]	P	B–SRK	NR	4.39 (0.25–11.5)	57 B, 67 SRK
Mattax and McCulley[52]	A, P	B	NR	2.66 (0.78–4.54)	62.5
Davis et al[53]	P	SRK/Holladay	NR	NR	52
Sanford et al[54]	P	NR	–1.38	3.21	NR
Djalilian et al[57]	P/SS	SRK II	1.79 (–6.00/5.00)	NR	63
Geerards et al[55]	P	B	+0.68	2.27	76
Das et al[19]	P	Haigis	–1.1	3.0	58

IOL, intraoperative lens; A, anterior chamber; I, iris-fixated; P, posterior chamber; B, Binkhorst; NR, not reported; SRK, Sanders, Retzlaff, and Kraff.

by 12 months. Complication rates are quite acceptably low, as outlined in Table 43.7.

DESCEMET'S STRIPPING AUTOMATED ENDOTHELIAL KERATOPLASTY WITH CATARACT, THE NEW TRIPLE PROCEDURE

In an eye that is a good candidate for one of the many forms of posterior lamellar keratoplasty and also has a visually significant cataract, the surgeon should consider the alternative triple procedure of phacoemulsification followed by Descemet's stripping automated endothelial keratoplasty (DSAEK). In most cases of DSAEK the view into the AC is adequate to allow phacoemulsification. The cataract wound (scleral tunnel or limbal incision) can be made in a fashion to allow for DSAEK through the same wound. We try to have the internal aspect of our incision remain peripheral to the area of Descemet's stripping, but others prefer for the donor cornea to overlay the internal aspect of the incision. For the cataract

Table 43.6 Results of 49 triple procedures at Hunkeler eye center

Variable	3 Months	6 Months	9 Months	1 Year
Follow-up (%)	73	85	76	73
Mean visual acuity without correction	20/80	20/70	20/70	20/60
Mean visual acuity with correction	20/50	20/40	20/40	20/30
Refractive astigmatism (D)	2.18	2.06	2.25	2.10
Keratometric astigmatism (D)	2.57	3.00	3.49	3.08
Mean keratometric power (D)	43.06	44.07	45.12	44.21
Mean spherical equivalent (D)	1.56	0.61	–0.13	0.13

Table 43.7 Incidence of postoperative complications in reported series of triple procedures, 1976–2004[2,3,7–9,14,15,17,41–48,50–52,58]

Complication	Range of Incidence (%)
Graft rejection	0–14
Graft failure	6–31
Postoperative glaucoma	1.5–19
Posterior capsule opacification	7–10
Cystoid macula edema	0–6
Retinal detachment	0–4
Endophthalmitis	0–3
Traumatic wound dehiscence	6

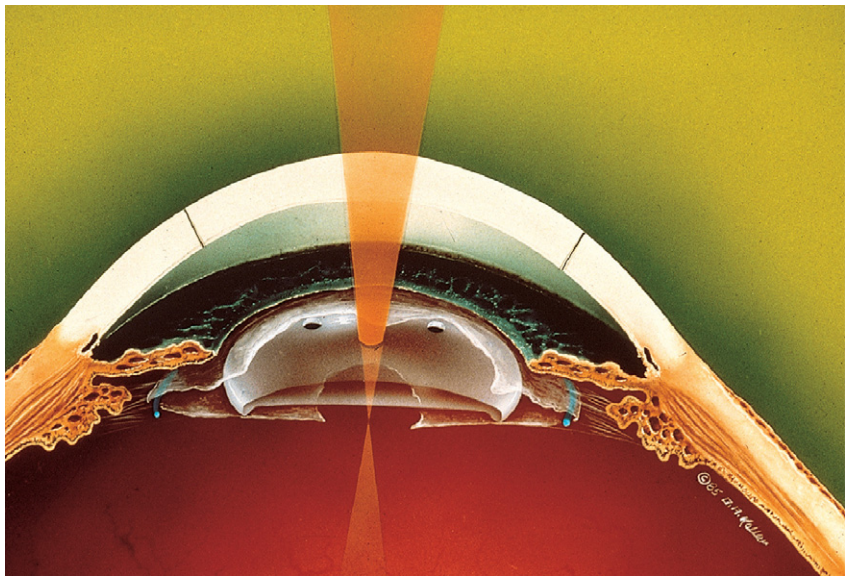


Figure 43.16. YAG laser capsulectomy through the graft. Any secondary iritis or glaucoma must be controlled to avoid graft failure and rejection.

portion of the procedure, a cohesive viscoelastic should be chosen, which can be completely removed from the eye such as Provisc or Healon. Capsular staining can aid greatly in the completion of the capsulorrhexis in this procedure. Phacoemulsification may then be carried out by the surgeon's usual technique, and an IOL can then be inserted into the capsular bag. The viscoelastic can then be completely removed from the eye prior to the stripping of Descemet's membrane. This minimizes the amount of viscoelastic left in the eye that can potentially interfere with donor adherence. Some surgeons prefer to leave the viscoelastic in the eye until after the stripping of Descemet's membrane. The donor button can then be inserted into the eye through the phacoemulsification incision, which may not even need to be enlarged.

CONCLUSIONS

Posterior capsular opacification occurs with about the same frequency in simple extracapsular cataract extraction and is treated by yttrium–aluminum–garnet laser capsulectomy (Fig. 43.16) with minimal threat to the graft. Certainly, variations on technique can give equally good results. Different suturing techniques with continuous or interrupted sutures alone (Fig. 43.17) or in combination using either 10-0 and 11-0 nylon or 11-0 polyester (Fig. 43.18) work very nicely. However, the combination of 12 interrupted sutures with a continuous 12-bite suture is our preferred method. The long-term results in the expanded series of triple procedures include 80% at 20/40 or better. The graft survival

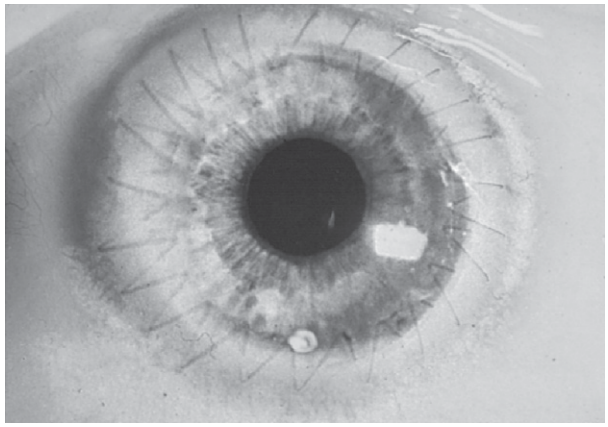


Figure 43.17. Eye 8 months after operation by triple procedure with continuous suture alone.

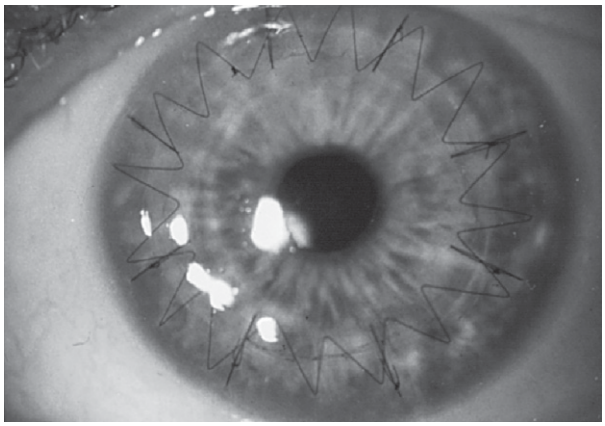


Figure 43.18. Eye 7 months after operation by triple procedure with interrupted 10-0 and continuous 11-0 nylon suture.

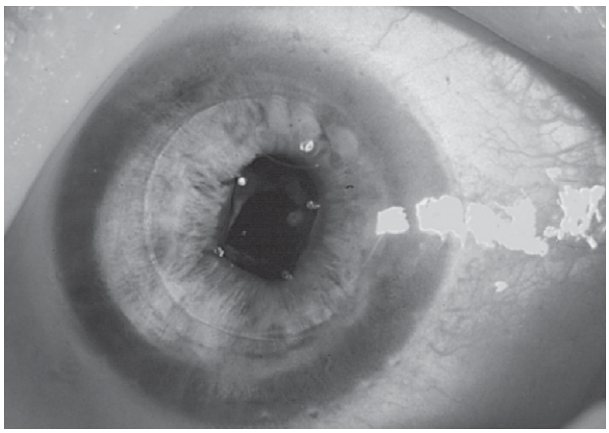


Figure 43.19. Eye 4 years after operation by triple procedure with medallion style of intraocular lens inserted into capsular bag for fixation.

rate is comparable to the results with keratoplasty in the absence of a lens implant (Fig. 43.19). The triple procedure continues to be the treatment of choice for most patients with combined corneal and cataract disease requiring surgery to restore functional vision.

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44 Pseudophakic and aphakic penetrating keratoplasty

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Pseudophakic corneal edema continues to remain the leading indication for penetrating keratoplasty (PKP) in the USA.[1–3] There are several reasons why this is the case: (1) there is an overall increase in cataract surgery and increasing patient age;[4–7] (2) despite newer cataract surgery techniques, intraocular lens (IOL) implants and viscoelastic materials, cataract surgery continues to cause significant endothelial cell loss[8] documented even 10 years after surgery;[9] (3) there are more donor tissues available[10] and surgeons trained to perform keratoplasty surgery; (4) the techniques and instrumentation for pseudophakic and aphakic penetrating keratoplasty have significantly improved, resulting in a more favorable prognosis for a clear graft and possibly improved vision.[6,11–14]

Aphakic corneal edema, on the other hand, is decreasing as an indication for PKP[1–3] due mainly to technological advances and widespread use of intraocular lenses.

In the last few years, transplantation of the posterior layers of the cornea for pseudophakic and aphakic corneal edema has been described[15–17] and is now being implemented in tertiary-care cornea practices with excellent results being reported.[18]

This chapter reviews the current surgical techniques and instruments used for pseudophakic and aphakic penetrating keratoplasty.

SURGICAL CONSIDERATIONS FOR PSEUDOPHAKIC AND APHAKIC KERATOPLASTY

Before keratoplasty is performed on a patient with pseudophakic or aphakic corneal edema, careful preoperative planning and attention must be given to the following potential problems:

1. Presence of irregular thinning or thickening and neovascularization of the host cornea
2. Presence of loose vitreous in the anterior chamber
3. Presence of anterior and posterior synechiae
4. Status of pupil and size and location of peripheral iridectomy
5. Increased incidence of elevated intraocular pressure (IOP)
6. Increased incidence of cystoid macular edema
7. Status of opposite eye (phakic, aphakic, or pseudophakic)

The surgical technique of pseudophakic or aphakic keratoplasty may vary depending on many of these findings. It is the obligation of the corneal surgeon to recognize these potential problems preoperatively so that the surgical approach can be appropriately tailored for best results. In addition, thorough familiarization with anterior vitrectomy techniques and instrumentation should be accomplished before this type of surgery is performed.

TECHNIQUES IN PSEUDOPHAKIC AND APHAKIC KERATOPLASTY

Surgery may be done under general endotracheal anesthesia or with retrobulbar or peribulbar and seventh-nerve regional anesthesia combined with intravenous analgesic and hypnotic medication administered by a standby anesthesiologist. If general anesthesia is used, a nonpolarizing muscle relaxant (e.g. pancuronium bromide) may be used to prevent any 'bucking' or possible movement of the patient during surgery. Before draping, attention should be given to the positioning of the patient on the operating table. Tilting the table in a slight reverse Trendelenburg position and avoiding significant hyperextension of the neck help to decrease positive vitreous pressure in the eye. Turning the patient's head slightly to the side opposite the eye to be operated on increases exposure and helps decrease any interference from the patient's nose during surgery (Fig. 44.1). Applying compression to the globe before surgery with either a mechanical device or a digital massage can lower the IOP, but excessive softening will hamper trephine cutting. In some cases, intravenous mannitol may be started 1 h before surgery to minimize vitreous bulging once the cornea has been trephined. The operating microscope is then positioned over the patient and adjusted to the surgeon's need for height and surgical field. A microsurgical vitrectomy instrument is brought into the operating room and prepared for possible use during the surgery. After routine preparation of the surgical field with 5% povidone-iodine and two drops of 5% povidone-iodine placed in the inferior fornix, sterile draping of the patient is performed and the operation is ready to begin.

A wire or solid blade lid speculum is inserted between the lids and carefully checked to ensure that there is no pressure on the globe. Either a single or a double Flieringa ring may be fixed to the

globe with sutures of 6-0 polyglactin 910 on a spatula type of needle. The 12 and 6 o'clock sutures are left long for stabilization of the globe by the assistant during the trephination. Extreme care must be taken in the placement of the scleral support ring because unequal placement of the fixation sutures can cause irregularity in the graft recipient bed and considerable graft astigmatism. Because of this problem, many corneal surgeons have discontinued using the Flieringa ring and simply place a bridle suture beneath the superior and inferior rectus muscles using 5-0 silk suture. These two sutures provide a means for stabilization of the globe during trephination (Fig. 44.2). If proper care has been taken in the preoperative positioning of the patient and placement of the lid speculum, there seems to be less need for the scleral support ring.

At this time, the eye is carefully inspected through the operating microscope. Attention is specifically directed to the status of the cornea and presence of neovascularization or anterior synechiae. The anterior chamber and iris are examined to confirm preoperative findings of vitreous involvement, secondary membranes, posterior synechiae, and the status of the pupil. Using a handheld trephine of suitable diameter (either disposable or reusable), a mark is made on the surface of the cornea to serve as a guide to help choose the appropriate graft size. This mark is best seen if the cornea is blotted dry. If the epithelium is edematous and loose, it should be removed to the periphery with a cellulose sponge or blade at this time. The graft size should be large enough to replace a significant portion of the edematous cornea, but not so large that peripheral anterior synechiae and secondary glaucoma become an increased postoperative risk. In addition, attention must be paid to other important findings (position of the pupil, presence of peripheral iridectomy, and location of deep corneal neovascularization) in the determination of the final size and position of the new corneal graft. Commonly used trephine diameters in pseudophakic and aphakic cases range from 7.5 to 8.5 mm.

At this point, a corneal protector is placed over the patient's eye, the microscope light is turned off, and attention is directed away from the recipient eye to a separate table where the donor cornea is prepared (Fig. 44.3). The donor cornea with scleral rim is trans-

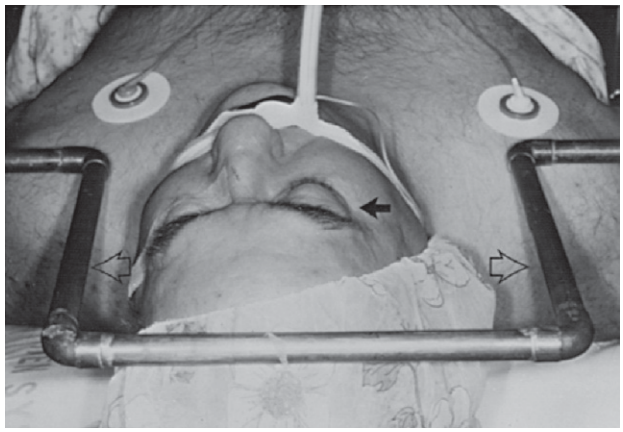

Figure 44.1. Slight rotation of patient's head to side opposite the eye to be operated (dark arrow) improves exposure. Light arrows are the surgeon's wrist rest.

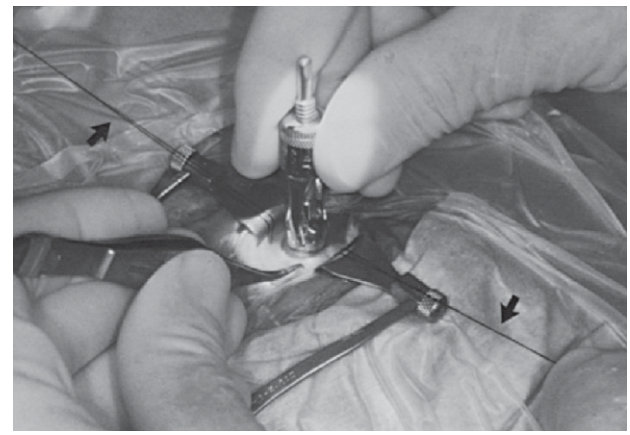

Figure 44.2. Bridle sutures (arrows) placed beneath superior and inferior rectus muscles help provide stabilization during trephination.

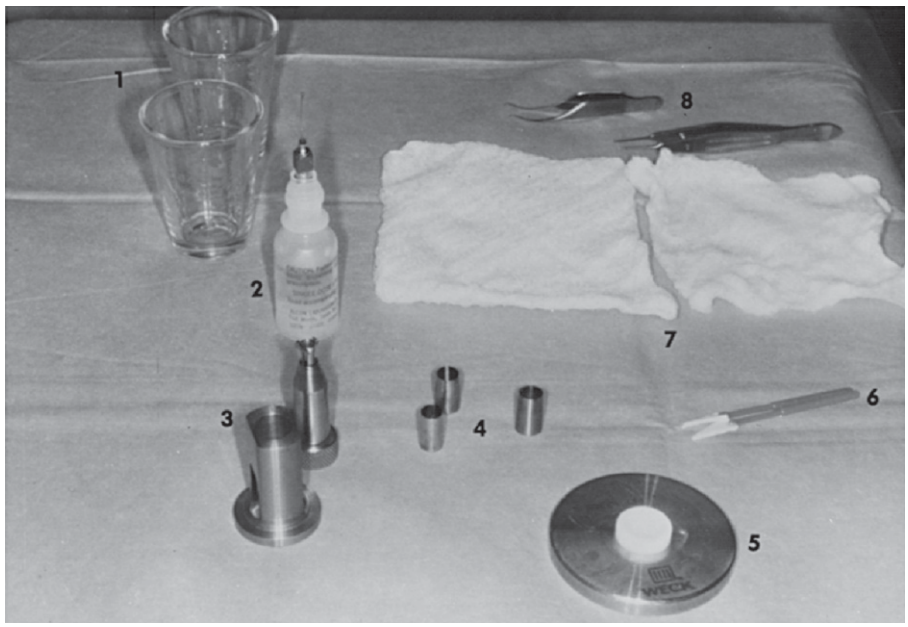

Figure 44.3. Donor preparation table includes the following: 1, two medicine glasses; 2, balanced salt solution; 3, corneal punch; 4, disposable trephine blades (different sizes); 5, polytef block and punch base; 6, cellulose sponges; 7, moistened gauze pads; and 8, 0.12- and 0.3-mm forceps.

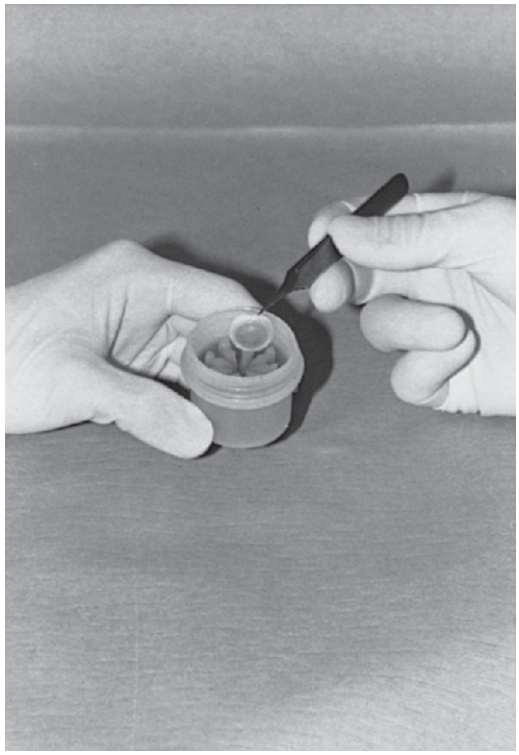

Figure 44.4. Donor corneal tissue is removed from its storage vial for transfer to the cutting block.

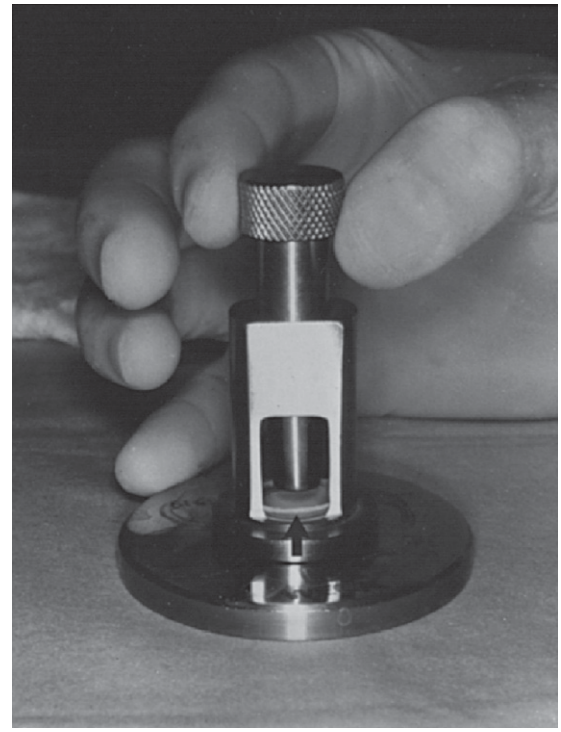

Figure 44.5. Donor corneal tissue (arrow) is centered on the polytef block before the button is cut.

ferred from a small vial containing Optisol GS (Bausch & Lomb, Irvine, CA) (Fig. 44.4) and placed on a polytef cutting block with the epithelial surface facing down. Extreme care is taken to minimize trauma to the endothelial cells. The donor cornea is carefully centered on the polytef block beneath the punch trephine to avoid cutting an oval button or creating a shelved edge (Fig. 44.5). A disposable trephine blade is used, usually 0.2–0.5 mm larger than the recipient graft bed. A slightly larger donor button is punched to avoid the disparity that is created by trephination of the recipient from the epithelial surface and donor from the endothelial surface with the same-size blade.[19,20] Firm, steady pressure is applied to the punch trephine to allow it to pass through the donor tissue into the polytef block (Fig. 44.6). When the trephine has passed through the donor corneal tissue and engages the cutting block, there is a sudden change in resistance and a distinct 'crunching' sound is heard. If a clean through-and-through cut has been made, the donor button should remain on the polytef block when the punch trephine is removed (Fig. 44.7). A drop of balanced salt solution, donor storage medium, or viscoelastic material is carefully placed on the endothelial surface to prevent drying. The donor button is placed into a moist chamber for temporary storage by covering the polytef block with a moistened medicine glass or transferring the donor tissue into a moistened petri dish (Fig. 44.8). The tissue is then brought back to the recipient table for later use.

Attention is now directed back to the patient in whom the corneal protector is removed from over the eye and the recipient cornea is once again carefully inspected. A handheld or a vacuum trephine can be used to trephine the recipient cornea. Although some studies have shown a slight increase in endothelial cell loss adjacent to the cut and slight beveling of the cut with vacuum trephines, many surgeons preferred them because they are easier to use and long-term results appear not to be different than with handheld trephines.[21,22] We prefer handheld trephines, and this is the technique

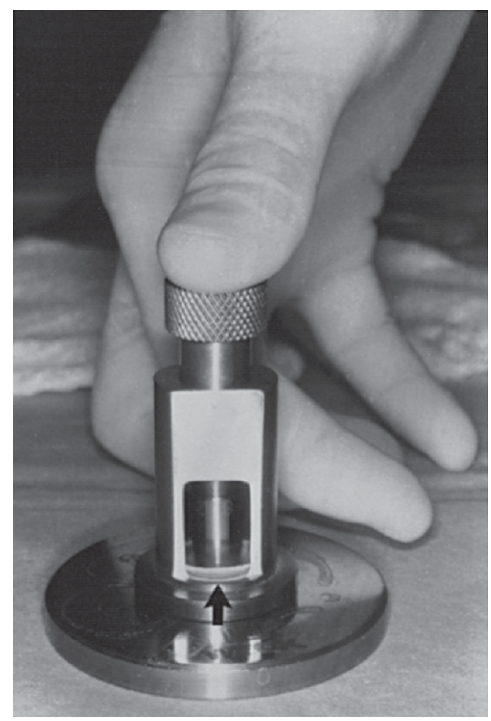

Figure 44.6. Firm pressure is applied downward on the punch trephine to allow it to pass through corneal tissue (arrow) and engage the polytef block.

described. If a guarded trephine is used, it should be set for cutting at 80% depth. The assistant holds the superior and inferior rectus sutures, and the surgeon grasps the horizontal limbal tissue at the 9 or 3 o'clock position with 0.12 or 0.13 mm tooth forceps to stabilize the globe (see Fig. 44.2). If a scleral fixation ring has been applied, it is grasped with large-toothed forceps during trephination.

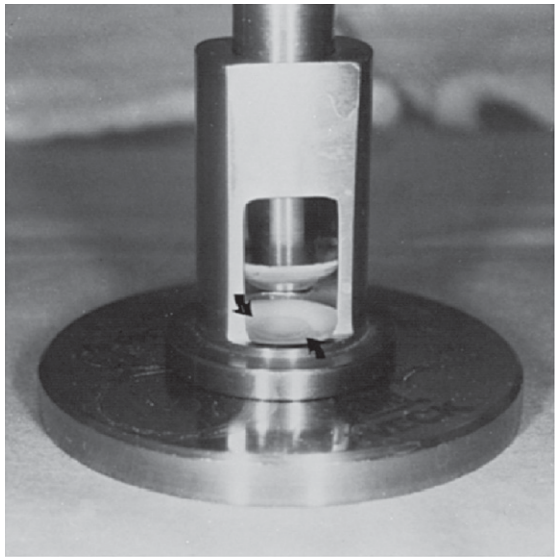

Figure 44.7. If a clean cut has been made, the donor button should remain on the polytef block (arrows) when punch trephine is withdrawn.

Figure 44.8. A medicine glass is moistened with balanced salt solution and placed over the corneal button and polytef block for temporary storage of donor tissue.

The trephine blade is then set within the previous mark on the corneal surface. After ensuring that there is not any undue pressure on the globe and the trephine is perpendicular to the corneal surface, the cutting of the corneal tissue is carefully begun. The surgeon gently rotates the trephine in a circular motion, attempting to apply equal pressure on all edges of the cutting surface so that uniform depth is obtained. While some surgeons will enter the anterior chamber with the trephine, our technique involves carefully avoiding uncontrolled entry into the anterior chamber at this time.

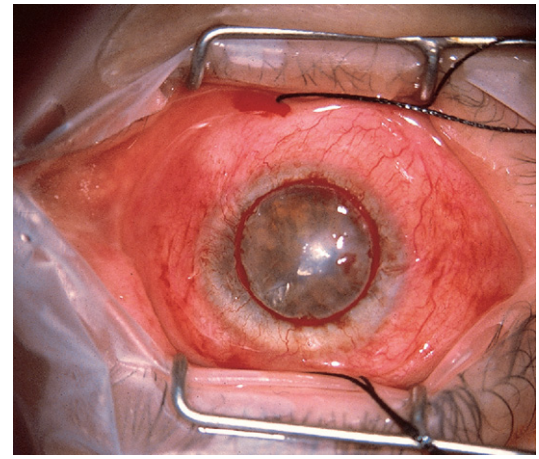

Figure 44.9. Initial partial-thickness trephination in vascularized corneas avoids hemorrhage into anterior chamber. Bleeding stops spontaneously within a few minutes.

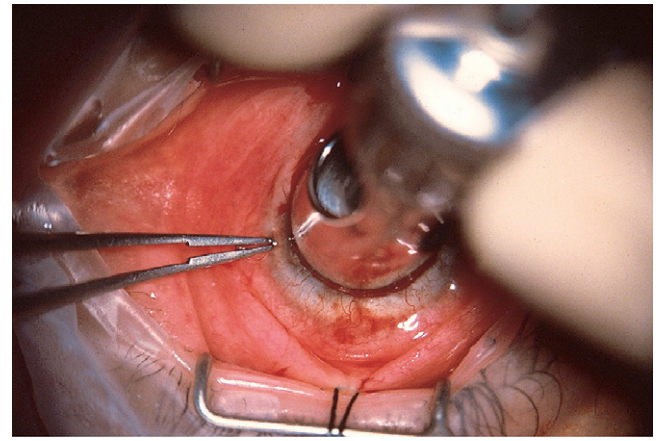

Figure 44.10. Handheld trephine may be placed within the previous cut to deepen the incision. Three-point fixation is used to stabilize the globe.

The trephine is removed, and the depth of the incision is checked with the microcyclodialysis spatula. In vascularized corneas, partial-thickness trephination allows bleeding and rapid spasm of the superficial and midstromal blood vessels, avoiding hemorrhage into the anterior chamber (Fig. 44.9). If the incision depth is found to be unequal, the trephine may be placed within the previous cut by 'skating' the trephine on the corneal surface and feeling the blade enter into the deeper portions of the incision (Fig. 44.10). Extreme care must be taken to avoid creating a 'double cut' in the corneal tissue. This step can be repeated as often as necessary until a deep cut is obtained in all areas. Beveling of the incision through the stroma should be avoided to allow precise fitting of the donor button within the recipient bed.

After trephination of a symmetrically deep wound, the anterior chamber is slowly entered with a microsharp blade within the incision close to the point of fixation. A 3–4 mm incision is made to allow easy entrance of the angulated curved microcorneal scissors. The blades of the scissors are kept perpendicular to the plane of the iris, leaving a narrow rim of endothelium and Descemet's membrane on the posterior margin of the recipient bed (Fig. 44.11). As the cutting of the cornea is completed, attention should be directed to

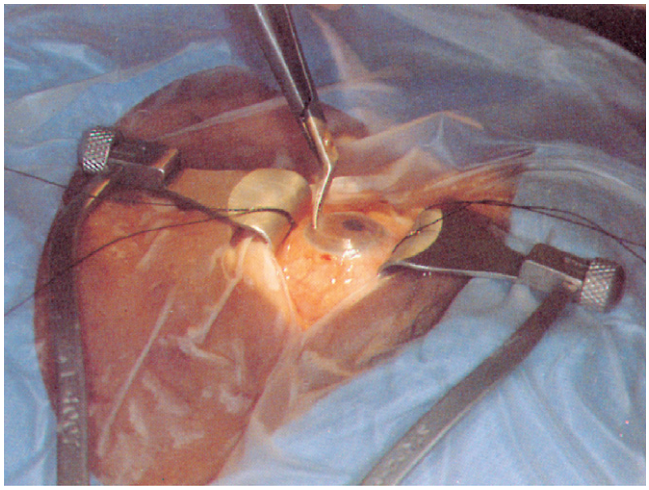

Figure 44.11. Blades of angulated curved microcorneal scissors are kept perpendicular to the plane of the iris to avoid creating a large posterior bevel in the wound.

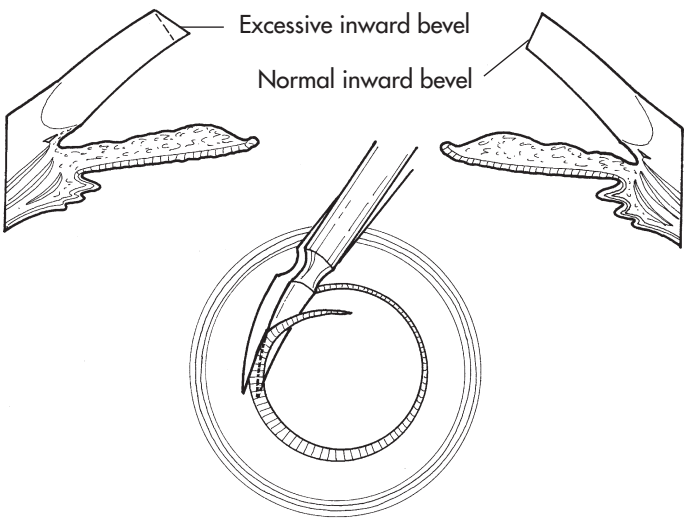

Figure 44.12. Excessive inward beveling from initial scissors cut is trimmed with a Vannas or Castroviejo scissors to achieve more gradual inward bevel.

its endothelial surface where vitreous attachments or iris adhesions may have to be cut before removal of the corneal tissue. In addition, any adventitious tissue should be removed from the wound with the Vannas scissors (Fig. 44.12). If the hyaloid face is intact and away from the cornea, the pupil may be constricted with acetylcholine chloride 1 : 100 (Miochol-E) to help maintain this state. Once the recipient cornea has been removed from the eye, several different approaches may be taken depending on the preoperative and intraoperative findings. These approaches may be divided into four separate groups and are discussed separately:

1. Pseudophakia with ruptured or absent posterior capsule
2. Pseudophakia with intact posterior capsule
3. Aphakia with loose vitreous in the anterior chamber
4. Aphakia with hyaloid face intact

PSEUDOPHAKIA WITH RUPTURED OR ABSENT POSTERIOR CAPSULE

The presence of an intraocular lens in a patient with corneal edema requires careful clinical examination and planning of the surgery before transport to the operating room. In most cases, plans should be made for removal of the pseudophakos combined with a partial anterior vitrectomy at the time of keratoplasty. The style of the implant and its position in the eye will help determine the surgical approach.

There are several important factors that must be considered when performing surgery on these patients. The following are the indications for removing the intraocular lens at the time of keratoplasty:

1. Patient history of pain and signs of recurrent hyphema, uncontrolled glaucoma, or persistent uveitis
2. Endothelial touch
3. Dislocated or subluxated haptics and unstable intraocular lens
4. Presence of chronic cystoid macular edema
5. Metal haptic materials
6. Iris sphincter erosion

Depending on the lens style and length of time that it has been in place, frequently there are strong adhesions to the angle, iris, vitreous, capsular bag, or ciliary sulcus. Removal of AC IOLs and iris-supported PC IOLs can be extremely difficult and traumatic to the eye and requires familiarity with the many styles of lenses (such as the Leiske, Azar 91Z, Stableflex, Sputnik, Copeland, etc.) that have been available for insertion over the years.[23,24] Various forms of iris clips and loops must be opened or cut before lysis of iris and vitreous adhesions that surround the implant. The use of blunt and sharp dissection in the removal of these lenses is required, and care must be taken to preserve as much iris tissue as possible. In some cases, supporting haptics must be cut from the lens optic and then carefully rotated free from dense fibrous tissue in the angle or ciliary sulcus. After removal of the implant, the anterior vitrectomy is performed (see description below in the section 'Aphakia with loose vitreous in anterior chamber'). Consideration for implantation of a different style of pseudophakos can be given.

The more recent use of posterior chamber lenses has decreased the incidence of uveitis, secondary glaucoma, and cornea-related problems, and frequently PC IOLs located in the capsular bag or ciliary sulcus cause no problems and can be left in place. Considerations for leaving the intraocular lens in place are summarized as follows:

1. Lens is in excellent position and appears stable
2. Eye is quiet
3. Pupil is mobile

PSEUDOPHAKIA WITH INTACT POSTERIOR CAPSULE

When the posterior capsule is intact or the hyaloid face is unbroken, the style of the implant and its effect on the eye primarily determine the surgical approach. The posterior capsule should be left intact, and preoperative yttrium–aluminum–garnet capsulotomy avoided if keratoplasty surgery is planned. In general, iris plane lenses should be removed; however, anterior chamber lenses that appear stable frequently can be left in place. Nonetheless, in cases where the posterior capsule is intact, many, if not all, of these eyes have a PC IOL implanted in the eye. Newer PC IOLs implanted into the capsular bag rarely cause any problems. Potential problems include decentration, inaccurate lens power, or glare problems. In these cases, repositioning or exchange of the IOL could be considered. An attempt to open the fibrosed capsular bag can be performed with

viscodissection[25] and a gentle surgical technique. Similarly, when the PC IOL is located in the ciliary sulcus, unless the implant is thought to be causing inflammation by rubbing on the iris or is associated with any of the problems listed above, it can be left in place.

If the pseudophakos can be retained, the operation is less complicated. Application of miotic drops such as pilocarpine prior to surgery or injection of acetylcholine chloride 1 : 100 (Miochol-E) into the anterior chamber during surgery will help maintain a PC IOL in place.

APHAKIA WITH HYALOID FACE INTACT

A decision to insert an intraocular lens into this eye is based on the following factors:

1. Phakic or intraocular lens in other eye
2. Aphakic and contact lens in other eye
3. Physical needs and activities of patient
4. Inability to wear a contact lens
5. Overall health of the involved eye to tolerate a secondary implant
6. Relative risk of insertion and possible vitreous involvement
7. Status of the capsular bag and or sulcus of the eye

If an intraocular lens is to be inserted into the eye, and there is adequate sulcus support or an intact capsular bag, a PC IOL should be implanted in the bag or the sulcus. If an intraocular lens is to be inserted into the eye, but there is no capsular or sulcus support, the options are to suture a PC IOL to the iris or sclera or insert a flexible open-loop AC IOL. We believe that if there are no contraindications for placement of an AC IOL (such as angle abnormalities), implantation of a flexible open-loop AC IOL is considerably less difficult and equal, if not better, results can be obtained compared to suturing a PC IOL to the iris or sclera.[11,12] To implant a flexible open-loop AC IOL, the pupil may be constricted with acetylcholine chloride and a small amount of viscoelastic material placed over the pupil and on the surface of the iris to help act as a 'cushion' for the underlying vitreous. Using a flexible open-loop anterior chamber-style lens with three-point or quadriflex fixation, insertion through a 7.5 mm or larger recipient bed opening can be accomplished without difficulty. Once the lens is in an adequate position, additional viscoelastic material and balanced salt solution are used to fill the remainder of the anterior chamber. The donor button is then transferred to the recipient bed and sutured in place.

APHAKIA WITH LOOSE VITREOUS IN ANTERIOR CHAMBER

During the preoperative evaluation of the patient, attempts should be made to determine the presence of loose vitreous in the anterior chamber. If vitreous is present or highly suspected, plans should be made before beginning the surgical procedure to prepare and have ready the use of a guillotine type of vitreous cutting and aspirating instrument. Use of a mechanical vitreous cutting instrument in these cases reduces vitreous traction and iris inflammation associated with the technique of removal by cellulose sponge absorption. Some surgeons have also advocated the evacuation of fluid vitreous through the pars plana[26] or the use of bimanual vitrectomy[27] before entry into the anterior chamber.

If formed vitreous is encountered in the anterior chamber at the time of removal of the corneal button, care must be taken to cut any adhesions from the posterior surface of the cornea. Once the cornea has been removed, an open-sky vitrectomy is performed with the mechanical vitreous instrument held within the center of the pupil or in the peripheral iridectomy using low suction (4–6 mmHg) and a rapid cutting rate (300–400 cuts/min) (Fig. 44.13). Balanced salt solution may be gently dripped into the anterior chamber as needed during vitrectomy. Recently, triamcinolone acetonide suspension (Kenalog 40 mg/mL) filtered and diluted 1 : 10 has been applied before performing the vitrectomy to better visualize the vitreous by staining it.[28] The vitrectomy is considered adequate when the iris has dropped posteriorly well back from the recipient bed and there is no formed vitreous left in the anterior chamber. A cellulose sponge is used to carefully touch the surface of the iris. Attempts should be made to free the pupil from vitreous adhesions and secondary membranes and to remove any strands of vitreous adherent to the peripheral cornea. After this step has been completed, the anterior chamber is filled with balanced salt solution before placement of the donor tissue within the recipient bed. If indicated, consideration for a secondary lens implant may be given before placement of the donor graft tissue.

A vitrectomy should not be performed if the vitreous face is unbroken and does not protrude anteriorly because there is an increased risk of cystoid macular edema and retinal detachment occurring after this procedure.

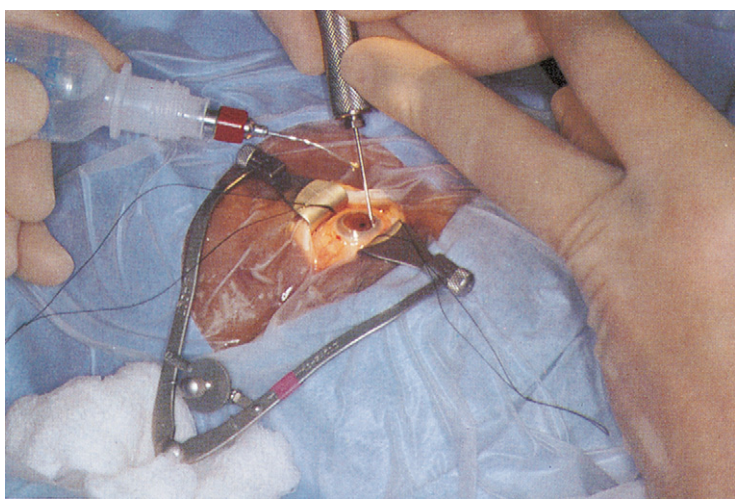

Figure 44.13. 'Open-sky' vitrectomy is performed with a mechanical vitreous cutting and aspirating instrument held within the pupil or in the peripheral iridectomy. Balanced salt solution may be dripped into the anterior chamber during vitrectomy.

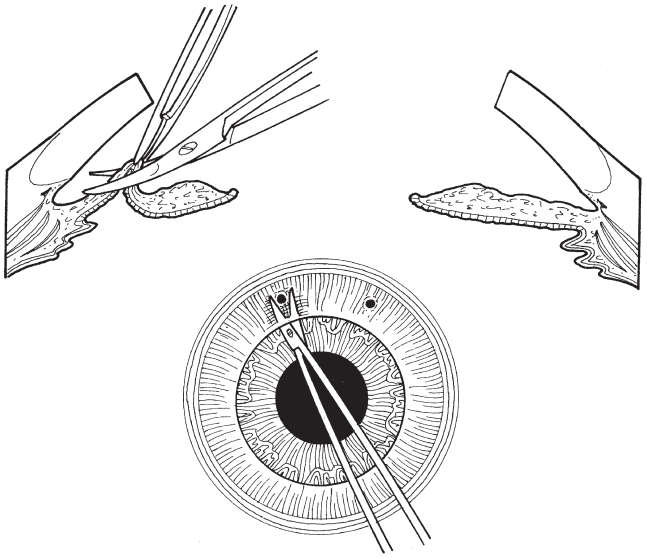

Figure 44.14. Creation of peripheral iridotomies with an open-sky approach using scissors to prevent focal pupil block and peripheral anterior synechiae.

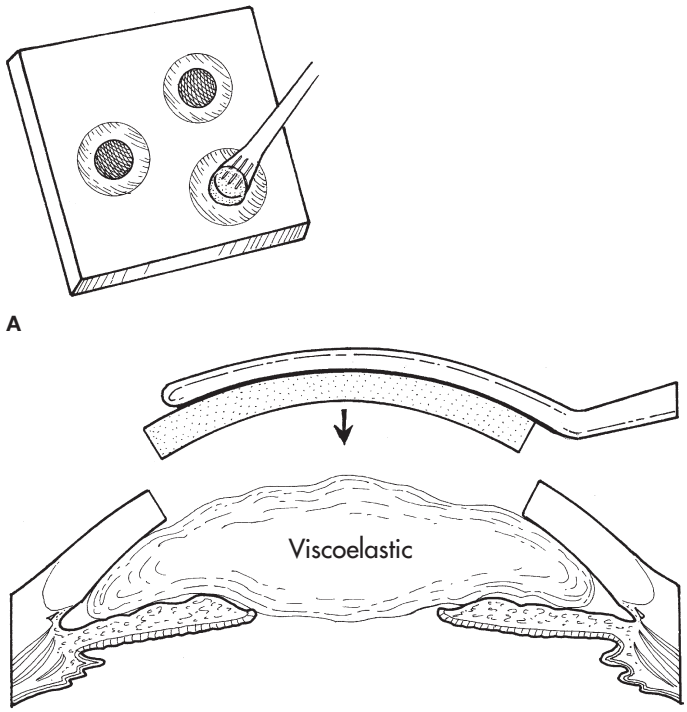

Figure 44.15. A Paton spatula is used to transfer the donor button from the polytef block to the recipient defect.

IRIDOTOMY

Aphakic and pseudophakic eyes with anterior chamber lenses should have one or two peripheral iridotomies performed to avoid later development of either focal or diffuse peripheral synechiae and a pupil block-like syndrome.

Technically, the iridotomies are more easily made in the mid-iris periphery between 4 and 8 o'clock positions using a Vannas, Fine stitch, or Castroviejo scissors and 0.10 or 0.12 mm forceps to partially 'tent up' the iris (Fig. 44.14). The iridotomies should be checked for patency to assure complete removal of posterior pigment. The use of viscoelastic to deepen the iridoendothelial distance will facilitate the iridotomy and contain hemorrhage.

SUTURING OF DONOR BUTTON

The donor graft, which has been temporarily stored in a moist chamber on the Mayo stand, is now transferred by the surgeon to the recipient bed. This transferal is accomplished either by grasping of the anterior edge of the button with a fine 0.12 mm forceps (Fig. 44.15) or by use of a corneal spatula to invert the graft onto the recipient bed. Depending on the condition of the anterior chamber, a large air bubble, balanced salt solution, or a viscoelastic substance will be present beneath the graft. If a pseudophakos is present, it is imperative that the endothelium not come into contact with it during the suturing of the graft. Care must be taken in the placement of the first corneal suture at the 12 o'clock position because the graft is freely mobile and can easily be displaced so that possible damage to the endothelium is caused. It is recommended therefore that this first suture be placed primarily to anchor the graft in position and can easily be removed and replaced with a deeper suture if necessary. All sutures should be placed deeply within donor and host tissue without too long a bite being taken.

The most important suture to be placed by the surgeon is the second cardinal suture at the 6 o'clock position. It is this suture that most affects the final position of the donor graft within the recipient bed, and careful attention should be paid to the alignment of this suture. It is recommended that the surgeon leave the needle in place after it has been passed through both the donor and the host tissue to check the graft edges at 3 and 9 o'clock positions for over-ride or gaping of the wound (Fig. 44.16). If this complication is detected, the needle can easily be backed out of the wound and repositioned; thus, the surgeon can correct the possible wound disparity (Fig. 44.17). The 3 and 9 o'clock sutures are then placed equidistant between the 12 and 6 o'clock sutures. The graft surface is dried to better observe the diamond crease that forms between the four cardinal sutures. If the sutures have been placed equidistant from each other, each side of the diamond will be equal and additional sutures may now be placed. Cardinal sutures may have to be repositioned, however, if the sides of the 'diamond' are not aligned, causing malposition of the donor graft

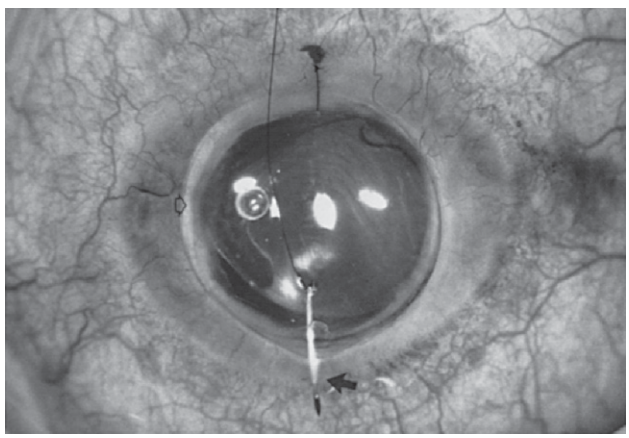

Figure 44.16. After 6 o'clock suture (solid arrow) is placed, graft edges are checked at the 3 and 9 o'clock positions for over-ride or gaping of wound. In this case, there is over-riding of graft at 9 o'clock (open arrow).

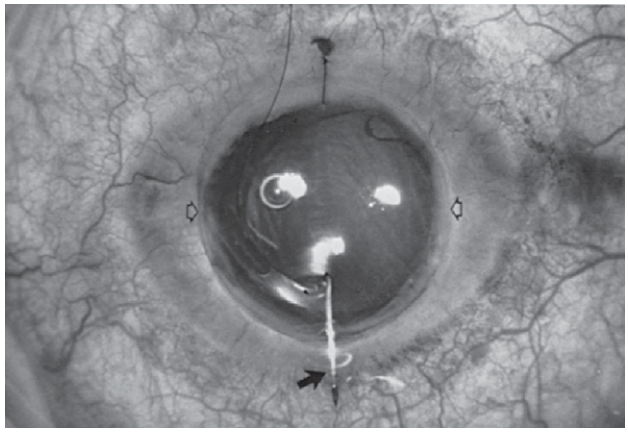

Figure 44.17. The 6 o'clock suture is removed and placed slightly to the right (solid arrow). New position of graft at the 3 and 9 o'clock positions (open arrow) is now better aligned.

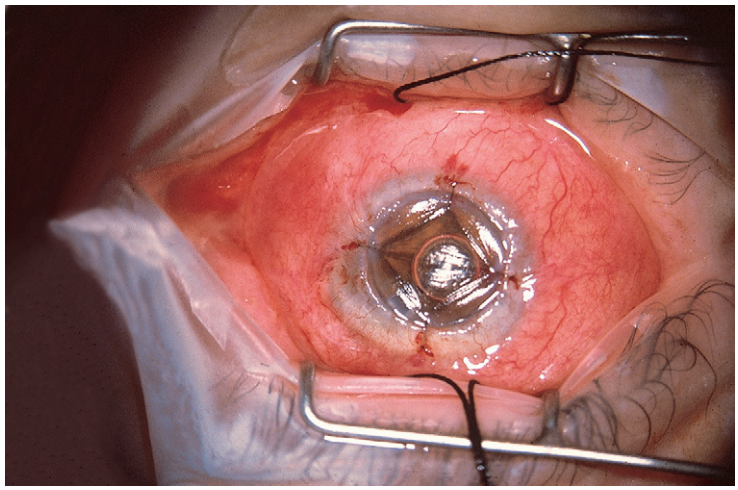

Figure 44.18. Once the four cardinal sutures have been placed, a diamond crease will be apparent on the graft surface. Wound alignment should be checked at this point before additional placement of sutures.

(Fig. 44.18). Once satisfactory placement of the initial four cardinal sutures has been completed, the anterior chamber should be redeepened with either balanced salt solution or viscoelastic material using a 2 mL syringe attached to a 30 gauge angulated cannula. Closure of the wound is now complete with either additional interrupted sutures of 10-0 nylon or a continuous suture of the same or finer nylon suture.

On completion of suturing, the anterior chamber is carefully examined to make sure that there are no synechiae present, the pseudophakos is in good position (if present), and large amounts of air or viscoelastic substance have been removed. The integrity of the wound is checked with topical fluorescein dye or by application of gentle pressure with a dry cellulose sponge between each suture on the host cornea. If any fluid escapes, a suture is either added or replaced to achieve satisfactory wound closure. The eye is left normotensive at the completion of the case. The bridle sutures are removed, and subconjunctival injections of antibiotic are given inferiorly. Subconjunctival injection of a corticosteroid is optional but encouraged when there has been a vitrectomy or significant manipulation of the iris at the time of surgery. Several drops of a topical steroid and a broad-spectrum antibiotic are given. Finally, the lids are closed and a monocular bandage and eye shield are applied.

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45 Anterior chamber-type intraocular lens replacement during penetrating keratoplasty for pseudophakic bullous keratopathy

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The choice of an intraocular lens (IOL) for IOL exchange in pseudophakic penetrating keratoplasty or secondary IOL implantation in aphakic penetrating keratoplasty remains debatable. The poor graft and poor endothelial survival observed with closed-loop anterior chamber (AC) IOLs in the early 1980s[1,2] led to a strong interest in the use of sutured posterior chamber (PC) IOLs, either iris- or scleral-fixated in these settings.[2–14] This interest was based on the assumed advantages of an IOL situated in a more physiologic position, posterior to the pupil and closer to the nodal point of the eye; improved visual results because of less cystoid macular edema from a possible barrier effect on the vitreous; less secondary glaucoma because of less trabecular meshwork damage; and, most importantly, reduced endothelial cell loss because of the posterior pupillary IOL location. There are disadvantages, however: the operating time is longer, vitrectomy is needed in all cases, iris or ciliary body suturing is required, and there may be increased potential for endophthalmitis, retinal detachment, and vitreous hemorrhage.

Experimental[15] and clinical evidence[1,2,5,7,8,16–22] indicate that a one-piece open-loop polymethylmethacrylate (PMMA) AC IOL, based on the Kelman design in the early 1990s, performs more favorably than the closed-loop IOL for AC insertion and is associated with improved long-term graft survival. The major advantages of this type of AC IOL technique over the sutured PC IOL technique are ease and speed of IOL insertion and fixation, lack of suturing for IOL fixation, and avoidance of vitrectomy in many cases. Although there is still some recent evidence[13] that insertion of an AC IOL is associated with higher incidence of secondary glaucoma, cystoid macular edema, and endothelial cell loss, these potential greater risks have not been supported in multiple studies comparing these techniques.[6,8,9,11,16]

TECHNIQUE

PSEUDOPHAKIC

The technique for pseudophakic penetrating keratoplasty with IOL exchange for a Kelman-style, open-loop PMMA AC IOL has been well described.[2,5,7,8,16–23] This chapter does not discuss IOL exchange during Descemet's stripping automated endothelial keratoplasty (DSAEK)[24,25] whose closed-chamber technique requires a limbal approach for the lens exchange. Preoperatively, a Honan pressure balloon is applied. The pupil is constricted with 1% pilocarpine hydrochloride applied three times, 5 min apart, 1 h before surgery. Surgery is performed under local anesthesia. The use of a single Flieringa ring is optional. If chosen for better anterior segment support, the ring is sutured to the episclera with six interrupted 6-0 polyglactin 910 sutures. The lid speculum is subsequently removed, and the polyglactin 910 sutures are anchored to the drape. Before trephination of the recipient bed, the size of the new AC IOL is determined by measurement of the horizontal limbal diameter and the addition of 1 mm. One method for determining power of the new AC IOL is to take the original AC IOL power and subtract 1 D, based on the assumption of an average of 1 D of corneal steepening postoperatively. Few remaining iris-plane-style IOLs are left in pseudophakic bullous keratopathy survivors, but if the original IOL is an iris-plane style, 2 D are subtracted. The graft is cut from the endothelial side, 0.25 mm larger than the recipient bed; we favor an 8.25 mm donor in an 8 mm recipient bed. The Barron system vacuum trephine (Katena Products Inc., Denville, NJ) is preferred, since it enables alignment of the donor with the recipient bed and a well-centered vertical cut on the donor. After partial trephination to two-thirds depth with the recipient trephine part of the Barron system, the AC is entered with a 67 Beaver blade and the host corneal button is excised with Castroviejo scissors, with a small shelf of Descemet's membrane being left. Lysis of any anterior or goniosynechiae is then performed in areas apart from the old AC IOL with a Barraquer cyclodialysis spatula.

Any closed-loop AC IOL, iris-plane IOL, as well as any lens that is unstable or associated with inflammation should be removed at the time of penetrating keratoplasty. Multiple techniques have been described for removal of closed-loop AC IOLs, most commonly the Stableflex lens.[1,17,21,23,26] Briefly, the optic is first removed by cutting each double closed-loop haptic two-thirds of the distance from the optic to the angle with Vannas scissors. The double-loop haptics are then slid out of the tunnel formed by peripheral anterior synechiae by pulling them with a curved hook placed in

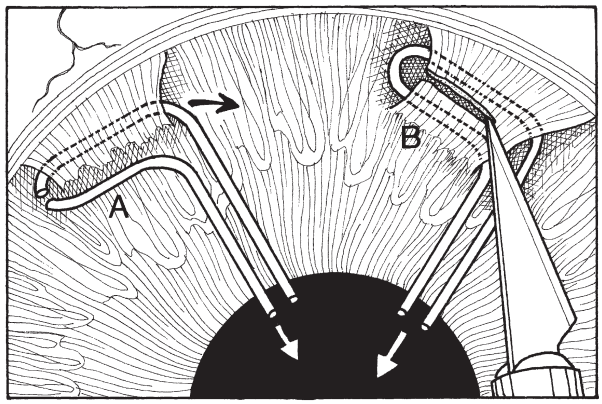

Figure 45.1. Removal of a double-loop intraocular lens (Stableflex) may involve A, cutting the loop in half and removing each arm separately, or B, cutting the iris adhesions then removing the loop in one piece.

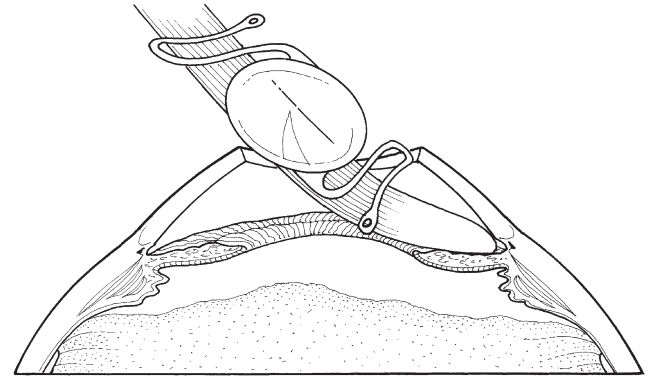

Figure 45.2. Insertion of a Kelman-style, one-piece, open-loop polymethylmethacrylate anterior chamber intraocular lens with a lens guide during pseudophakic penetrating keratoplasty.

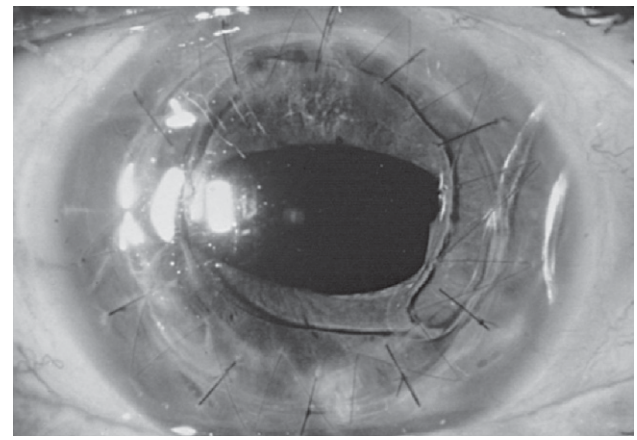

Figure 45.3. A horizontally placed open-loop anterior chamber intraocular lens 6 months after pseudophakic penetrating keratoplasty (Cilco Multiflex II, Alcon, Fort Worth, Tx).

the closed end of the loop, or they could be cut free (Fig. 45.1). Care should be taken not to leave a burr on the end of the loop that could tear the iris and produce bleeding or to allow excessive traction to result in dialysis of the iris root. Any bleeding is controlled by use of sodium hyaluronate viscoelastic in the angle or compression with a cellulose sponge soaked with epinephrine 1:1000. If excessive bleeding is encountered, any residual haptic material should be left within the angle, severing any exposed material at the iris root. After removal of the lens, the angle should be inspected by dental mirror gonioscopy or by inversion of the limbus using scleral depression.[26] Once the original AC IOL is removed, the eye is examined for any vitreous in the anterior segment. Using a vitrector with a fast cutting rate (400–500 cuts/min) and a low-medium aspiration pressure (150–200 mmHg) without irrigation, an anterior vitrectomy is performed to remove any vitreous strands from the AC, angle, iris, and ciliary body. A dry cellulose sponge is used to detect any residual vitreous, which should then be removed. The few survivors with pseudophakic bullous keratopathy associated with a rigid, PMMA AC IOL may either be left in place, if there is no history of cystoid macular edema, or be removed through a corneoscleral incision before corneal trephination. Iridoplasty is performed to repair pupillary deformities, if necessary, with a 10-0 polypropylene suture on a tapered needle. The pupil is then further constricted with intraocular acetylcholine, and the angle is deepened with sodium hyaluronate viscoelastic.

If an AC IOL is to be implanted, an all-PMMA, open-loop, four-point fixation AC IOL (our preference: S122UV Equiconvex, Bausch & Lomb, Rochester, NY) should be used. Previously it was argued that the positioning of the new AC IOL should be determined by the presence of residual peripheral anterior synechiae, but a comparative study[9] fails to support this hypothesis. Therefore, we recommend placing the new AC IOL in the orientation of the previous AC IOL. Once an adequate vitrectomy, if necessary, has been performed leaving the AC free of vitreous, sodium hyaluronate viscoelastic is injected into the AC to cover the pupil and deepen the angle. A lens guide is inserted in the direction of the original IOL haptic orientation and then the new IOL, held with fine tying forceps, is inserted with the leading haptic placed in the angle. The guide is then removed. The trailing haptic is placed under the corneal wound by retracting the corneal bed beneath the trailing haptic with 0.12 forceps and using a tying forceps to hold the optic and gently compress the leading haptic into the angle. This enables the trailing haptics to spring into the angle below the corneal wound. In the setting of a pre-existing sector iridectomy, the AC IOL should be positioned horizontally from the 3 o'clock to the 9 o'clock position within the angle with or without a lens guide (Figs 45.2 and 45.3). With proper placement, the pupil should remain round with no tenting of the iris. After implantation, the AC is filled sufficiently with sodium hyaluronate viscoelastic to protect the donor endothelium as the button is sewn into place. The viscoelastic may be left in the eye at the end of the case.

APHAKIC

The technique for aphakic keratoplasty with secondary AC IOL implantation is essentially the same as that described above, except that anterior vitrectomy is required in all cases and IOL power calculation differs. Power calculation can be determined based on the keratometry and axial length measurement of the fellow eye along with comparison of the previous spectacle correction of both eyes, or it may be based on the axial length measurement of the operative eye and an average keratometry reading (e.g. 43 D) determined from previous keratoplasty experience.

ANTERIOR CHAMBER INTRAOCULAR LENS VERSUS SUTURED POSTERIOR CHAMBER INTRAOCULAR LENS IN PSEUDOPHAKIC PENETRATING KERATOPLASTY

In the absence of capsular support during penetrating keratoplasty, the surgeon has three procedures that can be chosen: (1) implantation of a one-piece, open-loop, flexible AC IOL into the angle, (2) suture fixation of a PC IOL to the iris, and (3) trans-scleral fixation of a PC IOL. In recent years, trans-scleral fixation of a PC IOL has become the most commonly employed posterior change IOL fixation approach, if chosen. Iris fixation of an IOL has also been reconsidered in recent years using the Artisan-style IOL (Ophtec, Groningen, Netherlands), with one study showing comparable results to the former methods with an argument that the safety of these lenses and simplicity of the insertion may have an advantage.[27]

The numerous retrospective studies[28–37] that have directly and indirectly compared the three methods were recently compared in a comprehensive meta-analysis to determine the safety and efficacy of open-loop AC and scleral- and iris-sutured PC IOL in eyes with inadequate capsular support.[38] A subset of the analysis included eyes that underwent concurrent penetrating keratoplasty. Studies were evaluated and rated according to relevance and statistical power before being included in the meta-analysis. Table 45.1 summarizes portions of the pooled data from the seven, nine, and five studies that published data on the safety and efficacy of AC IOL and scleral- and iris-sutured PC IOLs, respectively. Graft survival rates were found to be between 82 and 100% for the AC IOL group, 90–100% for the iris-fixated group, and 87.5–100% for the scleral fixated group. Visual acuity better or equal to 20/40 was similar among the groups as well, with a slightly better result (47%) in the iris-fixated group, largely based on the disproportionately high success rate (60%) of a large study done at one site.[40] In addition, the percentage of patients with vision equal to 20/200 was also similar among the groups (~35%) with no increased incidence of graft failure regardless of lens type. Interestingly, these individual case series demonstrated that the incidence of glaucoma with secondary IOL insertion was much higher in the cases involving penetrating keratoplasty and PBK compared to secondary IOL insertion from complicated cataract surgery. The rates ranged up to 45% for AC IOL groups, 43% for the scleral-sutured PC IOL groups, and up to 62% for the iris-sutured PC IOL groups. Only one group has published long-term outcomes of penetrating keratoplasties and open-loop, flexible AC IOLs.[39] This retrospective study showed the probability of graft survival at 1, 2, 4, 6, and 8 years to be 93, 87, 78, 65, and 65%, respectively.

There have been, however, few studies performed at the same site comparing open-loop, flexible AC IOLs versus iris- or scleral-fixated PC IOLs. Our site studied 25 patients with an open-loop AC IOL and 24 patients with an iris-fixated PC IOL 1 year after penetrating keratoplasty.[8] Graft clarity, visual results, control of intraocular pressure, and endothelial survival were compared. The average best-corrected visual acuity was comparable between the two groups; 29% of the eyes were 20/40 or better in the AC IOL group and 25% in the iris-fixated PC IOL group. Comparable intraocular pressure control also was shown for the two IOL types, contrary to previous postulation.[6] In this study, average intraocular pressure did not differ for the two groups at 1 year (AC IOL 19 ± 6 mmHg versus PC IOL 20 ± 5 mmHg). In addition, no new cases of glaucoma occurred in the AC IOL group and only one new case (4%) in the iris-fixated group. Most importantly, the two IOL groups experienced the same average endothelial loss at 1 year (AC IOL 32 ± 26% versus PC IOL 27 ± 26%), disputing the assumed advantage of the posterior pupillary location of the PC IOL in protecting the endothelium, at least when the posterior capsule is absent.

Two other sites have also reported retrospective comparisons of open-loop, flexible AC IOLs versus either iris- or scleral-fixated PC IOLs.[6,10,11,16] Both sites showed no difference in clinical outcome when comparing graft clarity, visual acuity, and intraocular pressure. Furthermore, one site showed a significantly lower average endothelial cell loss at 1 year with the Kelman-style AC IOL (11.5%)[16] than that with an iris-fixated PC IOL (19.0%).[10,11] This site extended its observations to 2 years for 35% of its initial patient population and, surprisingly, found 38% cell loss in its iris-fixated PC IOL group[12] compared with 21% in its AC IOL group.[16] However, Brunette et al[4] advocate sutured PC IOLs over AC IOLs during penetrating keratoplasty. Comparing the AC IOL technique to both scleral and iris-fixated PC IOL techniques, they reported that the visual acuity during the first 12 months was similar between the two groups, but eyes receiving PC IOLs had significantly better visual acuity at periods greater than 1 year. They also argued that there is a greater increase in intraocular pressure (29.6%) with the AC IOLs versus PC IOLs (5%). Unfortunately, this study was retrospective and the numbers too small to accurately compare iris- versus scleral-fixation techniques.

To date, the study done by Schein et al[9] remains the only prospective randomized multicenter trial comparing the three techniques. In this study, 176 consecutive patients with pseudophakic corneal edema who underwent penetrating keratoplasty with IOL exchange were randomly assigned into one of three implantation techniques (AC IOL, $n = 60$; iris-fixated PC IOL, $n = 56$; scleral-fixated PC IOL, $n = 60$). There were no exclusions of patients or assignment to an IOL implantation technique on the basis of ocular history or anatomy, and all groups were similar in age, sex, and ocular morbidity. Evaluations were performed at baseline and at 6, 12, and 18 months postoperatively. Life-table methods were used to compare escalation of glaucoma therapy, loss of graft clarity, iridocorneal synechiae, adequacy of lens centration, and cystoid macular edema. At 12 months, the spectacle-corrected

Table 45.1 Results of penetrating keratoplasty in pseudophakic bullous keratopathy with intraocular lens exchange

Intraocular Lens (IOL) Type	Mean Follow-Up (mo)	Clear Grafts (%)	Visual Acuity (20/40 or better) (%)[a]
Anterior chamber (AC) IOL[4,8,16,18,22,23,39]	12–50	82–100	35.2
Iris-fixated posterior chamber (PC) IOL[3,5,36,37,40]	7.6–30	90–100	47.2
Scleral-fixated PC IOL[4,8,28,30–35]	12–26.8	87.5–100	40

[a] Average from pooled data.

visual acuity was 20/40 or better in 16.3% of the AC IOL group, 15.7% in the iris-fixated PC IOL group, and 20.0% in the scleral-fixated group. Survival analysis showed no significant difference in the escalation of glaucoma therapy and loss of graft clarity. The cumulative risk of iridocorneal synechiae ranged from 24.7% for the AC IOL group to 44.9% for the scleral-fixation group, although this finding was not statistically significant. Three scleral-fixated lenses required refixation because of either partial dislocation or visually significant tilt. There were no cases of dislocation in the iris-fixation group. The cumulative risk of cystoid macular edema was significantly less for the iris-fixated group than for either of the other two groups. According to their complication index, the chances of developing one of the major adverse outcomes was significantly higher in the scleral-fixated group compared to the iris-fixated IOL group. The AC IOL group complication index was intermediate and indistinguishable statistically. In this study, endothelial survival was not examined. However, a longitudinal cohort study done at a different site[6] did compare the endothelial attrition rates at 1 and 2 years of corneal grafts with secondary AC IOL and iris-sutured PC IOL implantation. For the AC IOL group ($n = 19$) the attrition rate was 16.5% and 28.4% at 1 and 2 years, respectively, with a 5.3% graft failure rate compared to the 19.0% and 38.2% attrition rate and 8.3% survival rate for the iris-sutured PC IOL group ($n = 60$).

CONCLUSIONS

Although the wave of pseudophakic and aphakic bullous keratopathy continues to decline with the advent of better surgical techniques and lens technology, one site[41] has recently demonstrated in a large, long-term, longitudinal review that in the setting of penetrating keratoplasty, insertion of a secondary IOL in aphakic eyes, as well as exchange of an IOL in eyes with PBK, led to a significantly higher graft survival rate in both cases when compared to eyes that were left aphakic or whose previous PC IOL was retained ($p = 0.0051$ and $p = 0.0031$, respectively). Therefore, understanding of secondary lens exchange in the setting of PK remains an important surgical issue. Careful consideration of the patients' ocular anatomy plays a large role in the choice of which IOL insertion technique to use. According to the largest meta-analysis comparing all the available literature to date,[38] all three IOL insertion techniques demonstrate comparable safety and efficacy in eyes with no anatomic contraindications. However, scleral-sutured IOL fixation involves a longer operating time and additional complications of lens tilt, suture erosion, and necrotizing scleritis.[42] Therefore, scleral-sutured PC IOL implants should only be considered for instances in which extensive peripheral anterior synechiae, iris atrophy, distortion, or absence, makes implantation of an open-loop, flexible AC IOL or iris-fixated IOL problematic. With the advent of deep lamellar endothelial keratoplasty (DLEK) and DSAEK increasingly replacing penetrating keratoplasty as the procedure of choice with endothelial failure in pseudophakic bullous keratopathy, implantation of AC IOLs in the setting of ABK and PBK may have a decreasing role. Amayem et al[43] described several successful cases in which DLEK was successfully combined with IOL exchange and secondary IOL placement in patients with ABK and PBK. At their site and ours, the technique of endothelial transplant involves the removal of all implanted AC IOLs and the implantation of secondary sutured PC IOLs in most cases to facilitate insertion of the endothelial graft and to prevent postoperative damage to the graft. There are currently no published reports comparing PK and DLEK associated with PBK or ABK and the management of the IOL. In any event, the need for additional long-term data and prospective analysis still remains if one technique is to emerge as superior in both safety and efficacy.

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46 Lens replacement in pseudophakic bullous keratopathy: iris-sutured posterior chamber lenses

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In 1985 Roger Hall and I presented the first series[1] of iris-sutured posterior chamber lenses at the time of keratoplasty for pseudophakic bullous keratopathy (PBK). At that time PBK was the leading indication for penetrating keratoplasty (PK).[2–5] We have seen patients as long as 21 years after this procedure with clear grafts, stable lenses, and stable vision, with no serious long-term effects. Others[6,7] have had similar results in large numbers of cases. For example, Akpek et al[6] reported, in 2003, on 264 eyes followed for an average of 5 years (up to 11). Eighty-one per cent of grafts were clear 5 years postoperatively. In 2004, Farjo[7] reviewed 366 eyes with similar iris-sutured lenses during a 9-year period with similar results. Vision improved, grafts remained clear, and complications were minimal, comparable for corneal transplantation in other types of PK.

There has been an ongoing controversy over the best surgical management of these patients. The choice was of whether to replace the lens explanted with another anterior chamber lens, or to suture the lens in the iris or with scleral fixation. One prospective randomized trial reported that the risk of complications was less for the iris fixation cohort than either the anterior chamber intraocular lens or the scleral fixation group.[8] Also, sulcus-fixated[8] and posterior chamber lenses fixated by posterior capsule or Soemerring's ring remnants have been reported, but with no long-term results (Gelender, personal communication).[9–10]

Recent reports have indicated a significant reduction in the number of cases of PBK; however, as recently as 2003, Thompson et al[11] reported a series of 3992 consecutive PKs from 1982 to 1996 with 32% PBK. Others reported, in 2004, only 13.5% of 8318 PKs from 1983 to 2002,[12] and in a group of 784 cases from 1990 to 1999, PBK represented only 7.6% of the total.[13] This reduction is obviously from improved technique, instrumentation, lenses, and, perhaps, better recognition of the importance of the appearance of the endothelium.

SURGICAL TECHNIQUE

Details of the procedure have been described elsewhere.[14] Most cases are done under local anesthesia. A Flieringa or McNeil–Goldman ring is used to stabilize the eye. Donor corneas are trephined with a Barron punch and made 0.25 to 0.5 mm larger than the recipient cornea, where sizes range from 7.5 to 8.0 mm. The posterior chamber lens used is an alcon model SKR21RU. This lens has four positioning holes. Two 10-0 polypropylene sutures (ethicon BV-100-4) are placed up through the holes on each side. The lens is placed aside, ready to suture in (Figs 46.1 and 46.2).

The cornea is trephined to a depth of about 90% and then entered and slowly decompressed. The pupil is contracted with miochol. The anterior chamber lens is removed, and goniolysis and repair of any large iridectomies that might cause glare in the optical axis. An anterior vitrectomy is usually needed. The lens is then placed behind the iris with the haptics placed in the ciliary sulcus. The optic is sutured to the iris, using a double throw square knot, with one extra loop to avoid pinching of the iris tissue. The sutures are placed at about the mid-iris. Additional miochol is instilled. A viscoelastic is utilized to coat the lens–iris diaphragm, and the corneal button sutured in place. Postoperative care is as usual for PK.

The manufacturer (ALCON Laboratories, Fort Worth, TX) no longer produces the lens we prefer to use in this procedure. Akpek et al[6] reported using three other lens types. My recommendation to surgeons who now wish to use our technique with currently produced lenses is to use lenses available from your suppliers.

DISCUSSION

Although the methods mentioned above have stood the test of time through many years and with many different surgeons, it appears that a new method of keratoplasty variously called, posterior lamellar keratoplasty,[15] deep lamellar endothelial keratoplasty (DLEK) championed by Terry et al,[16–18] or Descemet's stripping endothelial keratoplasty by Meles et al[19] and Price and Price,[20] will replace PK for most disorders of the corneal endothelium. Only Descemet's membrane and the endothelium are replaced. A donor containing posterior stroma, Descemet's, and endothelium are obtained with a Moria automated keratome and trephined to the size needed. The advantages of this procedure over PK are significant, including a much smaller, stronger wound; little if any change in the refractive error (avoiding the high and changing astigmatism); and more rapid recovery of vision. A 5 mm sutureless incision may be used and

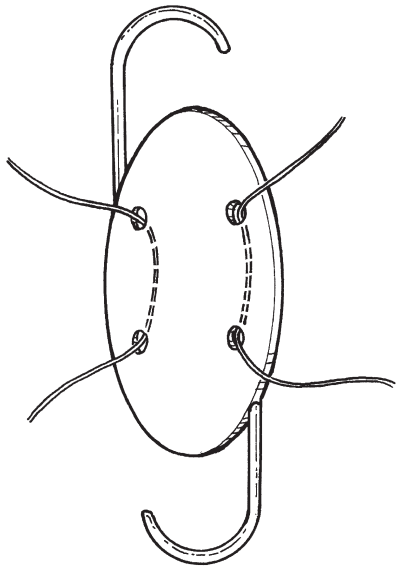

Figure 46.1. Before entering recipient eye, a four-hole posterior chamber lens is prepared on a tissue wipe with use of two 10-0 polypropylene sutures double-armed with tapered needles. Two needle ends of the first suture are passed upward through positioning holes on one side, and then a second suture is similarly placed through the opposite-side holes. Later, lenses with needles and sutures are transferred to the eye and viewed against the iris for best positioning.

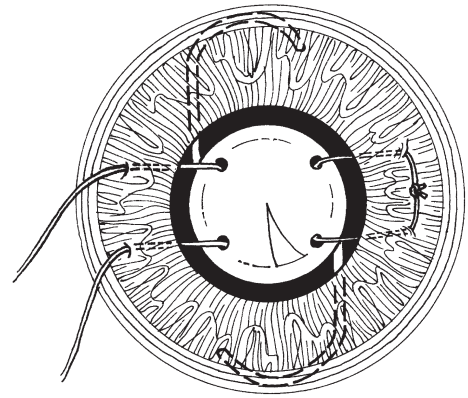

Figure 46.2. The first needle is placed up through the mid-peripheral iris in the lower quadrant and the other end through the mid-peripheral upper iris. Similar maneuvers are then carried out on opposite side. The inferior loop is then placed behind the iris, and the superior loop is last to be positioned behind the iris. The two ends of the right suture and the two ends of the left suture are tied together with knots in front of the iris.

has more recently been combined with lens explantation, vitrectomy, sulcus-sutured intraocular lenses, and cataract surgery.

Patients with vitreoretinal disease have had pars plana vitrectomy procedures within 4 months of DLEK.

Although it appears that these new procedures of endothelial transplantation are revolutionary and offer a safer, more predictable procedure (almost like intracapsular cataract surgery versus small incision phacoemulsification), the number of cases is relatively small and follow-up (especially in complicated cases) is relatively short. Therefore, as in all new procedures, these will have to stand the test of time and are certain to evolve into even better procedures.

SUMMARY

Iris-sutured intraocular lenses have been used in conjunction with PK since 1985.

Several reports have shown this procedure to be quite predictable, with clear grafts, improved visual acuity, and minimal long-term complications.

Recent developments in endothelial corneal transplantation may make these procedures obsolete.

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47 Intraocular lens replacement in pseudophakic bullous keratopathy: scleral-fixated type

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For the past several years, corneal edema following cataract surgery has been the most frequent indication for penetrating keratoplasty.[1,2] The management of the intraocular lens (IOL) during corneal transplantation, therefore, becomes a very important issue. At the time of penetrating keratoplasty, all iris-fixated IOLs and all small-diameter, round-loop, and closed-loop anterior chamber (AC) IOLs should be removed.[3–5] Flexible, open-loop, one-piece, all polymethylmethacrylate (PMMA) AC IOLs have had complication rates comparable to either iris- or scleral-fixated IOLs.[6,7] Some surgeons may elect, therefore, to retain this type of IOL at the time of corneal transplantation in eyes with less than 90° of peripheral anterior synechiae and controlled intraocular pressure.[8]

At the time of corneal transplantation for aphakic or pseudophakic corneal edema, a thorough anterior vitrectomy should be performed, taking particular care to remove the vitreous from the anterior and posterior surfaces of the iris as well as from the angle itself.[9] Retention of a previously placed AC IOL may make complete removal of the vitreous difficult. In any eye that has a history of persistent macular edema after cataract extraction and IOL insertion, the IOL should be removed, followed by a thorough anterior vitrectomy.

In the absence of capsular support, trans-scleral fixation of posterior chamber (PC) IOLs can be a safe and effective technique during penetrating keratoplasty with IOL insertion or exchange.[6–8,10] Perceived advantages of a trans-sclerally sutured PC IOL include reduced endothelial cell loss because contact with the corneal endothelium is avoided, less secondary glaucoma because contact with the trabecular meshwork is avoided, and decreased cystoid macular edema because contact with the iris is minimized. Trans-sclerally sutured PC IOLs have greater applicability in cases of distorted pupils, sector iridectomy, disrupted anterior segments, pre-existing anterior synechiae, or shallow ACs.[8,11]

Disadvantages of trans-sclerally sutured PC IOLs encountered during the development of this procedure included technical difficulty, increased operative time, the possibility for PC IOL dislocation, and the potential for endophthalmitis secondary to the erosion of the polypropylene suture through the conjunctiva.[10,11] These disadvantages have largely been obliterated by innovative designs in the IOL as well as by specialized needles and techniques[10,12–14] for trans-sclerally sutured PC IOLs that can now be safely, efficiently, and effectively performed in conjunction with penetrating keratoplasty.

INTRAOCULAR LENS REMOVAL

Removal of an IOL during corneal transplantation is considerably less difficult than through a limbal incision. However, the tendency for fibrosis to develop around the haptics[15] can make IOL removal difficult even from an 'open sky' approach.

Once the recipient button has been trephined and excised, the haptics of AC IOLs may be amputated with either Westcott scissors or a haptic amputator. When removing looped haptics, one arm of the loop should be amputated near the iris root to facilitate removal of the remainder of the haptic through the tunnel of fibrosis, which is frequently encountered. The haptics may be amputated individually, thereby freeing the optic, which is removed from the field. If vitreous is wrapped about the haptic or the optic, a limited anterior vitrectomy may be performed prior to amputation of the optic and haptics. Alternatively, as the optic portion is being removed, any attached vitreous may be amputated with a Westcott scissors. Bleeding from the iris root may be successfully managed by application of 1 : 1000 epinephrine or thrombin.

PC IOLs need not be removed unless there has been optic decentration or the lens power needs to be adjusted. PC IOLs that lack manipulating modifications of the haptic can generally be removed by clockwise rotation into the AC. IOLs that have manipulating modifications near the tip of the haptic may be removed by amputating the haptic near the lens optic followed by counterclockwise rotation, which generally frees the haptic.

TECHNIQUE FOR TRANS-SCLERAL FIXATION OF A POSTERIOR CHAMBER INTRAOCULAR LENS DURING PENETRATING KERATOPLASTY

Conjunctival peritomies measuring approximately 3 mm in length are created at the 2 and 8 o'clock positions or at the 4 and 10 o'clock positions of the limbus to avoid the ciliary blood vessels

and the long posterior ciliary nerve in the horizontal meridian. Bipolar cautery may be applied to the episcleral vessels to control any bleeding. In younger patients with prolific Tenon's fascia, the episclera may be scraped with a #64 or #69 Beaver blade to facilitate rotation of the knot at the conclusion of the procedure.

A Flieringa ring is attached to the episclera with 7-0 polyglactin 910 suture to provide scleral support, particularly during mechanical anterior vitrectomy and passage of the 10-0 polypropylene needle through the ciliary body. Placing sutures at each margin of the conjunctival peritomies securely stabilizes the sclera while burying the knot of the polypropylene suture fixating the sutured PC IOL (Fig. 47.1).

The recipient button is then trephined and excised. If necessary, previously placed IOLs are removed. A careful and thorough mechanical vitrectomy is completed, taking care to remove any vitreous from the anterior and posterior iris surfaces and from the ciliary sulcus.

The selection of an appropriate PC IOL is critical to the success of this technique and furthermore minimizes potential complications. The recommended PC IOLs include biconvex, large optic (6.5–7 mm), and one-piece, all-PMMA construction. Oversized eyelets are located 180° apart on the inside curve of both haptics. Eyelet-to-eyelet diameter is 12–12.5 mm, and the haptics are angled posteriorly to further minimize iris contact.

One needle of a double-armed 9-0 polypropylene suture is passed through the inferior eyelet of the PC IOL, taking care not to twist the newly created loop around itself (Fig. 47.1). A curved 9-0 polypropylene needle may be straightened using a second needle holder such that only a ski edge remains at the tip. The needle is passed through the pupil, underneath the iris, and through the ciliary sulcus, exiting perpendicular to the sclera approximately 0.75 mm posterior to the surgical limbus at the site of the previously prepared inferior conjunctival peritomy. The second needle of this suture is passed in a similar fashion a minimum of 2 mm adjacent to the first suture, but again 0.75 mm posterior to the surgical limbus. Ultimately, the two ends of the suture are tied together, allowing for the creation of a continuous trans-scleral loop whose knot may be buried beneath episclera. Another double-armed 9-0 polypropylene suture is placed through the second eyelet, and the needle is passed in an identical fashion 180° from the previously placed sutures, exiting sclera through the superior conjunctival peritomy (Fig. 47.2). Marking the recipient cornea with an eight-incision radial marker dipped in Gentian violet greatly facilitates placement of the second suture precisely 180° from the first.

While gentle traction is applied to the polypropylene sutures, the inferior lens haptic is inserted posterior to the iris and is directed into the ciliary sulcus. The superior lens haptic is then similarly positioned using a superior haptic compression technique. Lens centration, stability, and pupil contour are assessed (Fig. 47.3). Each end of the double-armed 9-0 polypropylene suture is then 'milked' to be sure that it slides freely and that the knot may be buried beneath episclera (Fig. 47.3, *inset*).

The ends of the double-armed 9-0 polypropylene sutures are tied together and cut short. The knot is then buried in a manner similar to limbal or corneal sutures (Fig. 47.4). Placement of a drop of viscoelastic on the suture just before burying the knot will facilitate rotation of the knot beneath the sclera. The knot is buried prior to securing the donor cornea; otherwise the time delay may allow for

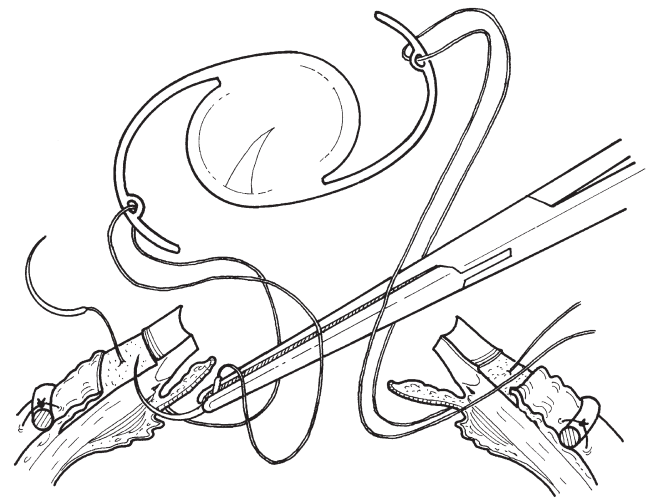


Figure 47.2. The needles are passed through the pupil, underneath the iris, and through the ciliary sulcus, exiting perpendicular to the sclera about 0.75 mm posterior to the surgical limbus at the site of the inferior conjunctival peritomies.

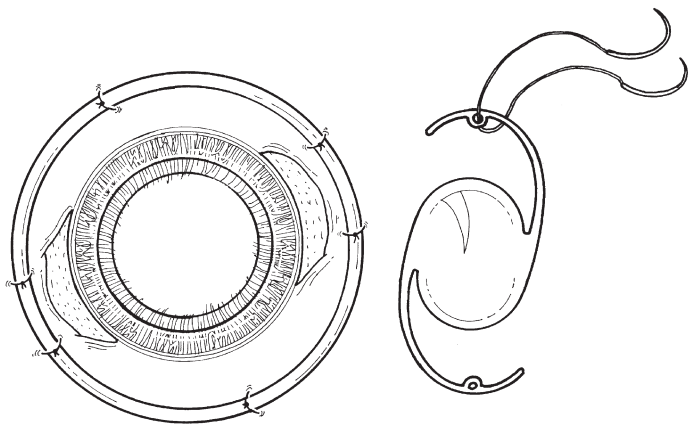


Figure 47.1. Securing the Flieringa ring at each margin of the conjunctival peritomies stabilizes the sclera for trans-scleral passage of the 9-0 polypropylene sutures and for burying the knot after the suture is tied to create a continuous loop. One needle of a double-armed polypropylene suture is passed through the inferior eyelet of the lens, taking care not to twist the newly created loop around itself.

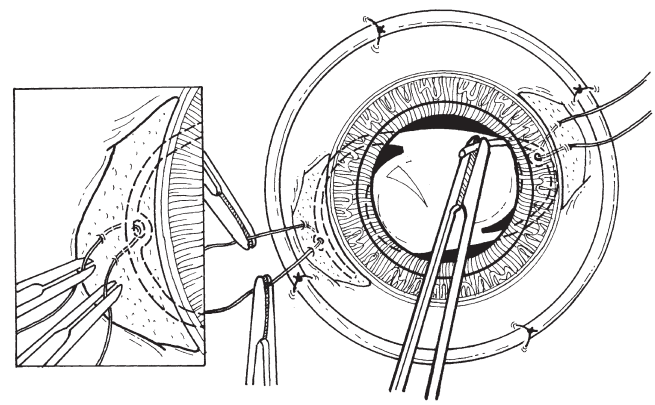


Figure 47.3. The inferior lens haptic is inserted behind the iris, and with gentle traction on the trans-scleral polypropylene sutures, it is directed into the ciliary sulcus. The superior lens haptic is positioned using a superior haptic compression technique. Each end of the double-armed suture is then 'milked' to be sure that it slides freely (*inset*).

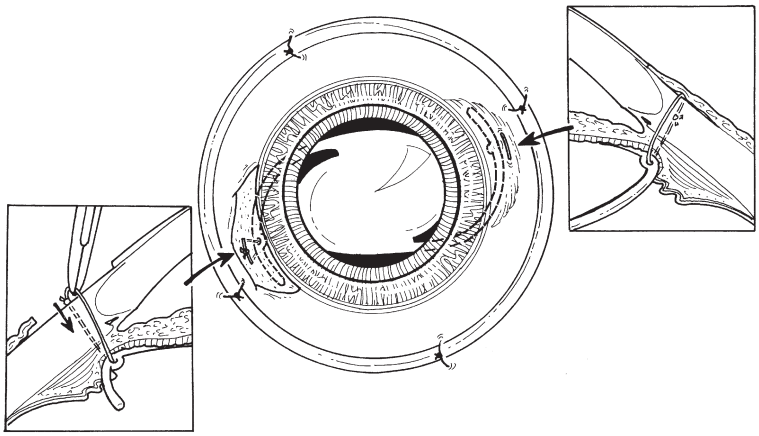


Figure 47.4. The ends of the double-armed sutures are tied together and cut short. The knot is then buried in a fashion similar to interrupted corneal or limbal sutures.

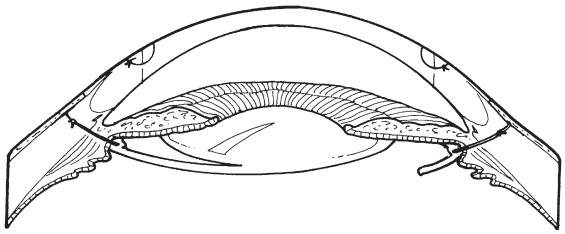


Figure 47.5. The donor cornea is then placed on a bed of viscoelastic and secured. Conjunctival flaps are closed over the trans-scleral sutures using 10-0 nylon or 8-0 polyglactin 910 sutures.

tissue swelling, which makes burying the knot considerably more difficult.

Viscoelastic is placed on the surface of the IOL optic. The donor cornea is then floated on this bed of viscoelastic and secured with 10-0 nylon suture. The conjunctival flaps are closed over the trans-scleral sutures using 10-0 nylon or 8-0 polyglactin 910 suture (Fig. 47.5).

AB EXTERNO SULCUS FIXATION

An alternative that has greater applicability for limbal insertion of a trans-scleral PC IOL is the ab externo technique.[16,17] During secondary lens insertion or IOL exchange in the absence of penetrating keratoplasty, this technique does not require the placement of a Flieringa ring.

A small conjunctival peritomy is performed at the 8 and 2 o'clock positions or the 4 and 10 o'clock positions as previously described. A straight transcorneal needle with 10-0 polypropylene suture penetrates the scleral bed parallel to the iris 1.5 mm posterior to the surgical limbus. The needle tip is passed through the ciliary sulcus posterior to the iris and is visualized in the pupillary space. A 28-gauge needle on a standard insulin syringe is passed through the sclera 180° from the straight transcorneal needle and is visualized in the pupillary space. The straight needle is threaded into the barrel of the 28-gauge needle and is maximally advanced (Fig. 47.6, *A* and *B*). The insulin syringe is then removed from the eye, carrying with it the straight needle and its attached suture. This approach creates a taut segment of 10-0 polypropylene suture extending from sulcus to sulcus. The straight transcorneal needle is then passed back across the sulcus in the opposite direction parallel to the initial pass but separated by a minimum of 2 mm on the scleral bed. A 28-gauge needle is passed through the sclera into the pupillary

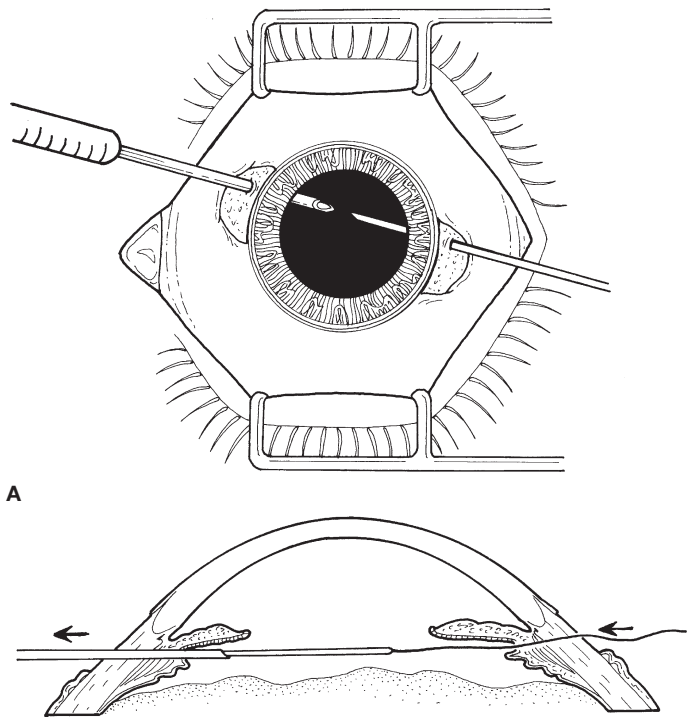


Figure 47.6. *A*, A straight transcorneal needle with 10-0 polypropylene suture penetrates the scleral bed parallel to the iris 1.5 mm posterior to the surgical limbus. The needle tip is passed through the ciliary sulcus posterior to the iris and is visualized in the pupillary space. *B*, A 28-gauge needle on a standard insulin syringe is passed through the sclera 180° from the straight transcorneal needle and is visualized in the pupillary space. The straight needle is threaded into the barrel of the 28-gauge needle and is maximally advanced.

space. Again the straight transcorneal needle is threaded into the 28-gauge needle and removed from the eye (Fig. 47.7).

The recipient button is then excised. A mechanical anterior vitrectomy is performed. The 10-0 polypropylene sutures are cut. One end from each pair is threaded through the eyelet of a specialized PC IOL. The sutures are secured to themselves (Fig. 47.8) and rotated out through the ciliary sulcus. The IOL is inserted within the ciliary sulcus while gentle traction is applied to the sutures. The sutures are tied to themselves creating a continuous loop (Fig. 47.9, *A*). The knot is rotated into the eye (Fig. 47.9, *B*). The overlying conjunctiva is then closed with 10-0 nylon or 8-0 polyglactin 910 suture.

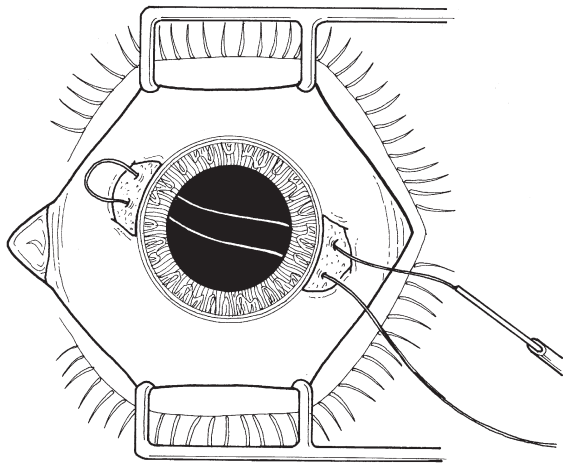


Figure 47.7. The straight transcorneal needle is passed back across the sulcus in the opposite direction parallel to the initial pass but separated by a minimum of 2 mm on the scleral bed. A 28-gauge needle is passed through the sclera into the pupillary space. Again, the straight transcorneal needle is threaded into the 28-gauge needle and removed from the eye.

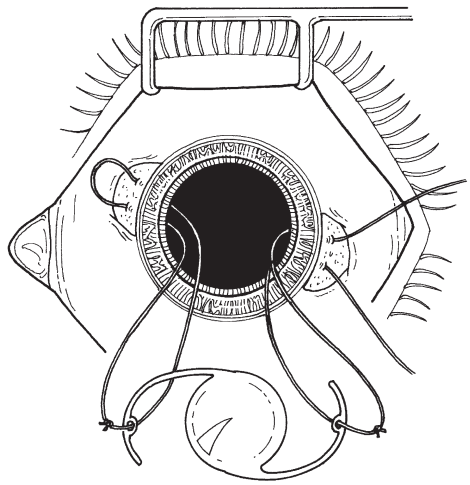
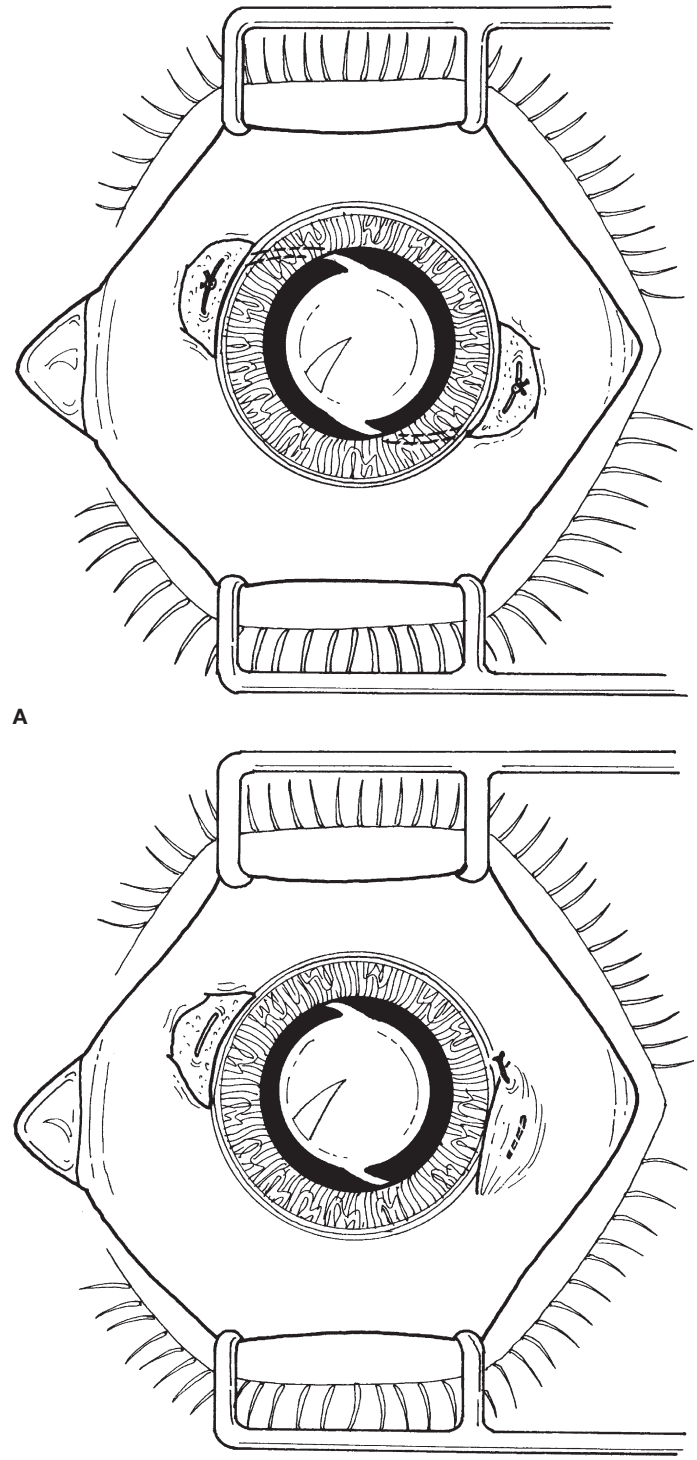


Figure 47.8. The 10-0 polypropylene sutures are cut. One end from each pair is threaded through the eyelet of a specialized posterior chamber intraoperative lens. The sutures are secured to themselves and rotated out through the ciliary sulcus.



A

B

Figure 47.9. *A*, The intraoperative lens is inserted within the ciliary sulcus while gentle traction is applied to the sutures. The sutures are tied to themselves creating a continuous loop. *B*, The knot is rotated into the eye.

COMPLICATIONS

EROSION OF THE POLYPROPYLENE SUTURE THROUGH THE CONJUNCTIVA

Prior to the availability of eyelets on the haptics of PC IOLs, erosion of the polypropylene suture knot through the conjunctiva created the potential for epithelial downgrowth or endophthalmitis. In two studies, erosion of the knot was noted in 20%[12] and 24%[18] of cases in which only a conjunctival covering was used. When the polypropylene knot was buried beneath a scleral flap, suture erosion developed in 15% of cases.[18] Suture erosion has not occurred when the knot has been covered by a portion of the donor cornea, which included Descemet's membrane.[19,20]

One case of epithelial downgrowth has been reported following trans-scleral fixation of a PC IOL; however, an interrupted nylon suture leak from the corneal transplant was implicated as the source rather than the polypropylene suture securing the IOL.[18]

Endophthalmitis has been reported following erosion of a 9-0 polypropylene knot through a conjunctival flap 5 months postoperatively[21] as well as following erosion of a 9-0 polypropylene knot through a partial-thickness scleral flap 6 years postoperatively.[22]

To minimize potential problems from suture-knot erosion, various techniques have been developed. When the polypropylene suture is tied to itself, the loop can be left intact, rather than cut, and the

free end may be passed beneath the sclera and cut flush with the surface such that no barb is left exposed. The knot itself, however, may erode through the conjunctiva in time. A similar technique can be used beneath a partial-thickness scleral flap, although the overlying sclera atrophies with time. This approach is supported by the finding that knots that were previously not visible in time become visible beneath partial-thickness scleral flaps. Half-thickness corneal autografts containing Descemet's membrane have been successfully used to cover polypropylene knots at the time of combined keratoplasty and trans-scleral fixation of a PC IOL.[19,20]

However, the availability of PMMA PC IOLs with islets on each haptic has allowed for fixation with a continuous polypropylene loop in which the knot may be buried beneath the episclera. This technique virtually eliminates the chance of knot erosion. Lewis[12] found no cases of suture erosion in 40 eyes using this technique. No conjunctival inflammation has been noted overlying the polypropylene suture lying on the episclera. The only drawback of this approach is that two needles must be passed through the pars plicata at each site of fixation to create a complete loop of polypropylene by tying a knot, which can then be buried. This technique virtually eliminates the potential for polypropylene knot erosion and the associated complications.

INACCURATE PLACEMENT OF HAPTICS WITHIN THE CILIARY SULCUS

In two eyes studied histopathologically after penetrating keratoplasty with trans-scleral IOL implantation, only one of four haptics were found to be within the ciliary sulcus.[23] When needles were passed perpendicular to the sclera, Duffey and coworkers[24] found that the relationship of the ciliary sulcus to the surgical limbus varied between the horizontal meridian and the vertical meridian. In the vertical meridian, the ciliary sulcus was found to be 0.83 mm posterior to the surgical limbus, whereas in the horizontal meridian the ciliary sulcus was 0.46 mm posterior to the surgical limbus. Oblique meridians are preferred for trans-scleral fixation, as this method minimizes the possibility of encountering the ciliary arteries or the long posterior ciliary nerves. When PC IOLs are trans-sclerally fixated in the oblique meridian, the 9-0 polypropylene suture should exit the sclera 0.75 mm from the surgical limbus. When trans-scleral needles are passed from an ab externo approach, the trajectory parallels the iris plane and requires a more posterior placement of the needles in the sclera to achieve sulcus penetration. It is recommended to initiate the ab externo pass 1.5 mm posterior to the surgical limbus in the oblique meridian.[12,16,25]

The mean diameter of the ciliary sulcus ranges from 11[26] to 11.25[27] mm. The haptic-to-haptic diameter of PC IOLs with eyelets on the inside haptic ranges from 12.0 to 12.5 mm. This diameter is more in keeping with the true anatomic diameter of the ciliary sulcus. When larger haptic-to-haptic diameters were used previously for trans-scleral fixation, there may have been an increased tendency for the haptics to slip out of the ciliary sulcus during insertion.

Knowledge of the precise localization of trans-scleral suture placement relative to the surgical limbus coupled with the improvement in PC IOL design for trans-scleral fixation should allow for consistent placement of haptics within the ciliary sulcus.

INTRAOCULAR LENS TILT

IOL tilt has been recognized as one of the most common postoperative complications of trans-scleral PC IOL implantation. In a randomized study comparing IOL fixation techniques during penetrating keratoplasty, Schein and coworkers[28] found IOL dislocation and tilt to be present in 7% of the trans-sclerally fixated group. This report did not include PC IOLs having eyelets on the haptic for trans-scleral fixation.

One-piece, all-PMMA technology gives the PC IOLs used in trans-scleral fixation marked stability in the anteroposterior dimension. Although the haptics are quite flexible when compressed, they resist tilting because of the one-piece technology uniting the haptic to the optic. The complications of IOL dislocation and tilt have been minimized by the improvements in PC IOL design, namely the presence of positioning eyelets and the stability incurred by one-piece, all-PMMA technology. Implanting foldable trans-sclerally sutured lenses[29] cannot provide the same stability of one-piece, all-PMMA PC IOLs.

Histopathologic evaluation of sutured PC IOLs has shown that the long-term position of the IOL is derived primarily from the trans-scleral suture and not from fibrous encapsulation of the haptic.[23] In one reported case, the trans-sclerally fixated PC IOL fell into the vitreous cavity after the external fixation suture was cut at the time of surgical removal.[18] However, gonioscopic evaluation of the haptic position in trans-sclerally sutured PC IOLs demonstrated a fibrotic membrane around the sutured haptic in 83% of lenses located within the ciliary sulcus, whereas no fibrosis was seen surrounding haptics outside the ciliary sulcus.[30] Although positioning the haptics within the ciliary sulcus may lead to fibrotic encapsulation, it is advisable to retain the polypropylene suture indefinitely.

DISLOCATION OF SUTURED PC IOLS

Dislocation of sutured PC IOLs has occurred years after trans-scleral fixation with 10-0 polypropylene suture.[31–33] Therefore, 9-0 polypropylene suture is now recommended to minimize suture dissolution and IOL dislocation.[33] Nevertheless, the possibility of PC IOL dislocation needs to be addressed in younger patients giving informed consent.

RESULTS

In a retrospective study of 122 eyes that underwent secondary IOL implantation at the time of penetrating keratoplasty, survival analysis showed the probability of a clear graft at 1 year to be 80% for eyes with an AC IOL and 90% for eyes with a PC IOL sutured to the iris or the ciliary sulcus.[34] Visual acuity was better than 20/200 in 48% of eyes with an AC IOL and 68% of eyes with a PC IOL.[34] Intraocular pressure rose by 5 mm Hg or more in 30% of eyes with an AC IOL and 5% of eyes with a PC IOL.[34]

In another study of 49 eyes that underwent secondary IOL implantation at the time of penetrating keratoplasty, the probability of a clear graft at 1 year was 88% for eyes with an AC IOL and 96% for eyes with a trans-sclerally sutured PC IOL.[35] At 1 year postoperatively, best-corrected visual acuity of 20/40 or better was noted in 25% of eyes with an AC IOL and 29% of eyes with a trans-sclerally sutured PC IOL.[35] No statistically significant difference in endothelial cell loss was noted between the two groups 1 year postoperatively.[35] Overall, in eyes that underwent secondary IOL implantation at the time of penetrating keratoplasty, eyes with a trans-sclerally sutured PC IOL had better results compared to eyes with an AC IOL.[34,35]

SUMMARY

Trans-scleral fixation of PC IOLs has applicability for IOL implantation in cases lacking capsular support. Improvements in lens design and modifications in technique have improved reproducibility of the procedure and greatly minimized potential complications. One-piece, all-PMMA PC IOLs with positioning eyelets on the haptics markedly reduce the likelihood of lens decentration and dislocation. The positioning eyelet also allows for the creation of a complete loop of polypropylene suture, which then allows the knot to be buried beneath the sclera, further minimizing any potential for knot erosion through the conjunctiva. Nevertheless, the long-term stability of trans-scleral fixation is derived from the polypropylene suture, which remains a limitation of this procedure. 9-0 polypropylene suture is now advised for trans-scleral fixation of PC IOLs to minimize degradation of the suture with possible lens dislocation years after insertion.

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48 Regrafting

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The patient with graft failure who is a candidate for repeat corneal transplant requires a thorough examination so that the cause of the graft failure can be determined, the post-regraft visual potential may be predicted, and a rational surgical approach can be devised to maximize graft survival. This chapter focuses on the causes and relative risks of failed keratoplasty, the indications and contraindications for repeat penetrating keratoplasty, and surgical techniques that can maximize survival of the corneal regraft. Additionally, we review endothelial keratoplasty as an alternative to a full-thickness regraft.

CAUSES OF CORNEAL GRAFT FAILURE

Corneal graft failure is the inability of the transplanted cornea to retain sufficient transparency for adequate vision. Functional graft loss usually can be attributed to one of two causes: mechanical graft failure that is caused by endothelial cell dysfunction or immunologic rejection by the recipient's immune system. Both mechanical and immunologic graft failure can occur at any time following transplantation.

PRIMARY DONOR FAILURE

Primary graft failure is defined as corneal edema that is present from the time of keratoplasty, does not clear, and is not associated with rejection or secondary causes of graft failure. The cause of primary graft failure is endothelial decompensation. In contrast to some other vertebrates, the human endothelium is not able to regenerate. Incorrect donor cornea removal, use of insufficient storage medium, intraoperative endothelial damage, and implantation of grafts of borderline quality all contribute to graft failure. To ensure that the donor material is of adequate quality, slit-lamp examination of the cornea, and especially of the endothelium, is essential before surgery.[1] Screening of donor endothelium using specular microscopy is performed by most eye banks today. Because of advances in surgical techniques and materials and improved donor tissue preservation, the relative risk of primary graft failure is low. Previously, Arentsen reported an incidence of 4% in a series of failed corneal grafts.[2] A more recent review of the literature reports more optimistic numbers; Price et al reported a 0.5% incidence of primary graft failure in a case review of 3640 initial grafts.[3] In the authors' experience, primary donor failure has occurred in less than 1% of cases. When it occurs, available options for restoring corneal clarity involve either regrafting with a full-thickness keratoplasty[4] or a posterior lamellar graft as is done in endothelial keratoplasty (see Section 4 of this text).

LATE DONOR FAILURE

Late graft failure seems to occur most often in corneal grafts in which a marginal endothelium proceeds to complete endothelial dysfunction. In the early postoperative period, the graft is clear, but it may become edematous months to years later without apparent predisposing causes. Accelerated endothelial cell attrition has been reported after keratoplasty.[5–8] One study found an overall 15-year risk of developing late endothelial failure of 12%.[9]

Nishimura et al observed that grafts with late endothelial failure had lower cell counts prior to transplantation and more loss of cells in the first 2 months postoperatively, but the subsequent cell loss was not accelerated compared to those in grafts that survived.[10] Thus, even after years, grafts seem to fail due to an initial endothelial cell count that is low, rather than from accelerated loss of endothelial cells at the time graft failure appears. In general, any grafted cornea has a higher basal rate of endothelial cell loss than the normal cornea. Bourne examined 500 corneas for changes in endothelial cells in the 20 years following penetrating keratoplasty and found that the rate of endothelial cell loss was 4.2% annually in grafts, whereas it is only 0.6% annually in normal corneas. If such cumulative cell loss is responsible for endothelial failure, it may be possible to prolong the life of a graft by setting criteria for higher donor endothelial cell counts.[8] Endothelial decompensation may also manifest following secondary events such as pseudophakic or vitreous touch, recurrent inflammation, glaucoma, or rejection. Even though there is slow, continuous cell loss over time, corneal grafts generally have a favorable prognosis for long-term clinical stability.[6,11]

Another rare but devastating mechanism for late donor failure is epithelial downgrowth, caused by a fistulous tract that allows

surface epithelium to migrate into and proliferate in the anterior chamber.[4] Clinical signs include a scalloped edge at the posterior graft surface that advances from the periphery toward the central cornea. Epithelial cells may be seen floating in the anterior chamber. Epithelial downgrowth can occur at any time postoperatively. Special caution should be taken with a suture track leak that persists for greater than 2 weeks. The suture should be removed as a fistulous track may be forming. Downgrowth may also appear many years after penetrating keratoplasty, often in the setting of graft dehiscence,[12] repeated surgery, or one involving iris manipulation.[13] Differentiation of epithelial downgrowth from the classical endothelial rejection line, which has been described by Khoudadoust, may be difficult[6,14]; therefore, any endothelial rejection that does not respond to steroid treatment should lead to suspicions of epithelial downgrowth and should be observed and documented closely using slit-lamp photography.[15] When the iris is involved, application of low-dose argon laser can be used to induce a diagnostic blanching effect on the ectopic epithelium.[16,17] Epithelial downgrowth has been treated by repeat keratoplasty,[18] or intraoperative peeling and excision of involved tissue,[12] but it is our experience that it is not easily corrected with either surgery. Cryotherapy has been used to limit further growth of the membrane but restoration of a clear cornea often requires regrafting.[13,17]

ALLOGRAFT REJECTION

Allograft rejection is the most common cause of corneal graft failure.[3,19–21] Early studies demonstrated that corneal graft failure can be caused by sensitization of the recipient to donor material.[22] Later, Khodadoust and Silverstein[23,24] showed that the epithelium, stroma, and endothelium each could exhibit an immune reaction. The clinical manifestation and frequency of the three types of corneal graft rejection have been described;[25–27] they may be characterized by epithelial and endothelial rejection lines (Fig. 48.1), subepithelial infiltrates, keratitic precipitates, and graft edema. Endothelial graft rejection is the most common, whereas isolated stromal rejection is rare.[28] In general, stromal involvement indicates a strong immune response; if it is not treated at an early stage, this can result in severe rejection episodes and graft loss caused by stromal necrosis.

Corneal graft rejection is an ophthalmic emergency that requires immediate attention because the time interval within which ongoing rejection may be reversed effectively is limited to a few days. Early symptoms include inflammatory signs such as conjunctival redness, ocular discomfort, photophobia, blurred vision, and tearing of the eye. Although these symptoms are not necessarily pathognomonic, in the grafted eye they must be considered as signs of rejection until proven otherwise. The Collaborative Corneal Transplantation Study (CCTS) demonstrated a significant correlation between patient-reported symptoms and apparent allograft reaction.[29] Patients who were diagnosed with reactions at scheduled visits during the first postoperative year were two and a half times more likely to report symptoms than were those without reactions; red eye and vision loss were reported most frequently.

HIGH-RISK PENETRATING KERATOPLASTY

Uncomplicated penetrating keratoplasty is a form of transplantation that enjoys a highly favorable prognosis,[30,31] currently with a 5-year survival rate of 90% and a 10-year survival rate of 82% in first-time grafts.[32] As Price et al point out, this is dependent on the preoperative diagnosis, with the most favorable graft survival rates in keratoconus (97.4%) and Fuchs' dystrophy (96.9%).[3] Any local (inflammation and neovascularization) or systemic (pre-sensitization) alteration of the recipient's responder status may affect this outcome, resulting in rejection rates as high as 50–70%. Regrafting in this situation therefore requires careful planning of the operation and thorough evaluation of the multiple risk factors involved.

IMMUNOLOGIC RISK FACTORS

Vascularization

Corneal vascularization potentiates allograft rejection because it creates a functional link between the antigenic material represented by the graft and the afferent and efferent arms of the immune system. Vascularization may be evident as preoperative recipient vascularization, as secondary graft neovascularization, or as both.

In vascularized recipient corneas (Fig. 48.2), rejection occurs at a significantly higher rate than in nonvascularized corneas.[2,3,19,21,33,34] Khodadoust[20] reported rejection rates up to 65% in densely vascularized corneas, with a significantly decreased time interval between the surgical procedure and allograft reaction compared with avascular conditions. Deep stromal neovascularization, especially, has been shown to increase rejection rates.[3,35] In the CCTS, stromal vascularization in four quadrants nearly doubled the risk for

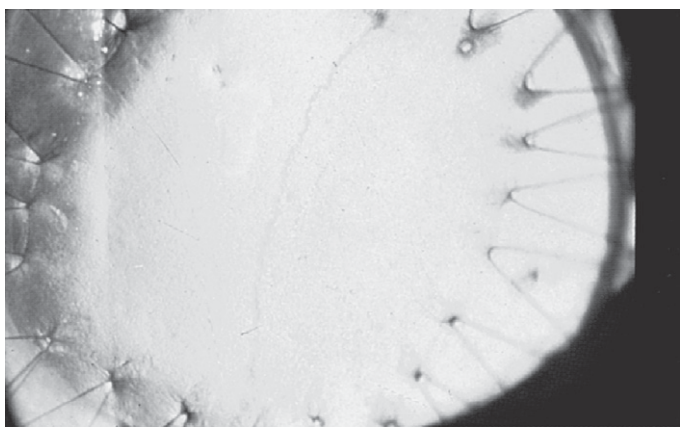

Figure 48.1. Retroillumination of endothelial rejection line.

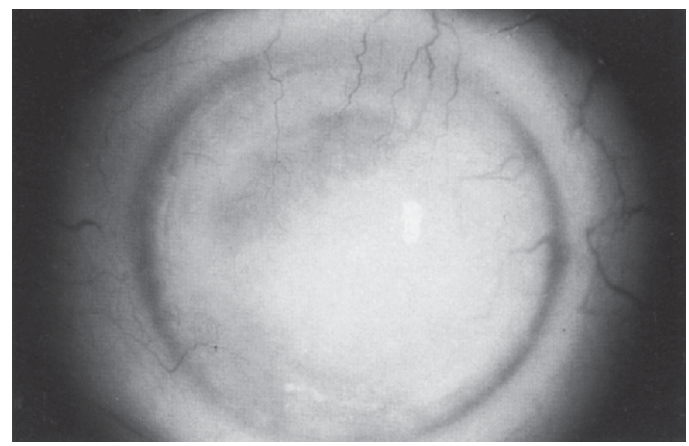

Figure 48.2. Corneal opacification with vascularization after herpes zoster keratitis.

allograft rejection,[36] which was confirmed by Hill,[37] and Price et al reported that deep stromal vascularization increased the risk of failure due to rejection by 2.7-fold.[3] Depth, extent, and density of graft neovascularization seem to be the critical factors for corneal allograft survival in prevascularized graft beds. Residual ghost vessels caused by old inflammatory disease did not appear to influence graft survival significantly.[37] Attempts to eliminate recipient vascularization preoperatively using argon laser or cryocoagulation show no lasting benefit.[38,39]

Postoperative graft vascularization can be induced by mechanical or inflammatory irritation of the corneal surface, such as suture abscesses, exposed knots, and contact lenses worn incorrectly.[2,34] Suture site neovascularization appears to be a trigger for corneal graft rejection. In the CCTS, the risk for rejection failure was doubled in eyes with interrupted sutures as compared with eyes with a running suture.[36] Additional suturing techniques that have been reported to increase risk of neovascularization include burying suture knots in the host stroma[40] (although the authors of this chapter do not find this to be the case in their practice), and a short limbus-to-suture distance. Lam et al performed serial photographs on transplants postoperatively, documenting the progressive development of neovascularization and allowing measurements of the distance between potentially angiogenic sutures and the limbus. They reported that 90% of postoperative corneal neovascularization occurred in grafts in which the distance between the sutures and the limbus was <406 μm. Graft to limbus distance of <1000 μm was another risk factor for neovascularization in this study.[41]

Inflammation

Corneal graft rejection represents an inflammatory event mediated by cellular and humoral immune mechanisms. The local pathology shares the classical features of a non-specific inflammatory response (i.e. vascular dilatation, edema, and cellular infiltration). Clinically, this correlates with conjunctival injection, chemosis, corneal edema, and the presence of circulating cells in the anterior chamber. Foulks notes that often circumcorneal vascular injection due to ciliary flush is the earliest sign of rejection, and it may occur before cellular infiltrates appear in either the cornea or the anterior chamber.[16]

Pre-existing inflammatory conditions such as herpetic keratouveitis[42–44] or bacterial suppuration resulting from a suture abscess (Fig. 48.3) may incite an allograft reaction. Inflammation at the time of transplantation is a risk factor for corneal graft rejection and failure.[45–47] From experience with the transplantation of solid organs, it is known that nonspecific inflammation can induce highly active cytokines that promote both endothelial adhesion and migration of immunocompetent lymphocytes, monocytes, and neutrophils, thus triggering specific graft rejection. A recent study showed that cytokines induce apoptosis in cultured endothelial cells, which may be the mechanism of damage to donor endothelium in graft failure.[48]

Previous graft loss

As with vascularized organ transplantation, previous graft loss is one of the leading predictors of corneal graft failure. Khodadoust[20] described a 50% loss rate following failed primary graft. The prognosis for repeat keratoplasty (Fig. 48.4) has improved, and success rates of 42–68% have been reported, with follow-up observations ranging from 1 to 12 years.[2,32,49–53] The CCTS[36] assigned a statistical risk of approximately 1.2 for each additional graft. Although Kirkness and coworkers[50] determined that allograft rejection appears to be the most common cause of graft failure in patients with repeat transplant, this is not necessarily related to the number of keratoplasties done in a given eye. In a single-surgeon series of 702 grafts, Hill found no significant difference in survival between repeat grafts into avascular corneas and first-time grafts into avascular corneas, suggesting that it is vascularization that triggers the rejection risk in repeat keratoplasty.[37]

The role of donor-specific allosensitization in corneal transplantation and its relative contribution to immunologic graft failure are still unclear. In the transplantation of vascularized organs, previous graft loss, preoperative blood transfusion, and pregnancy are known as potentially presensitizing factors.[54,55] In the case of corneal transplantation, while previous graft loss does remain a strong risk factor for immunologic graft failure,[46] blood transfusion and pregnancy do not.[36] Additionally, as discussed below, studies have failed to establish a clear benefit to histocompatibility matching.

Because corneal graft failure usually is accompanied by a certain degree of corneal neovascularization, it is likely that regrafted patients acquire an elevated level of donor-directed humoral immunity, which may account in part for the increased rejection rates that are reported for this patient collective.[36] Although Roy and coworkers found that corneal transplant recipients who developed post-transplant antibodies had a high risk of undergoing endothelial

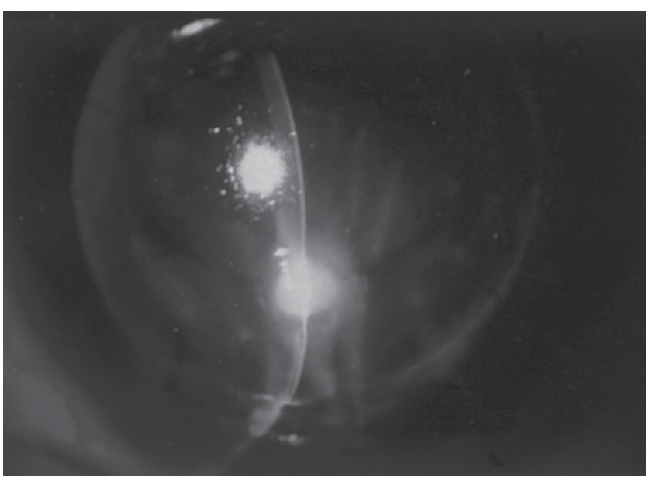

Figure 48.3. Allograft reaction 1 week after presentation with suture abscess caused by *Streptococcus pneumoniae*.

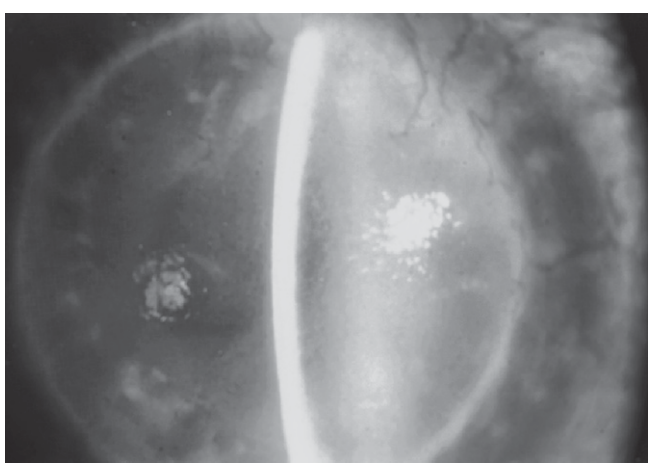

Figure 48.4. Recurrent lattice dystrophy 5 years after keratoplasty.

allograft rejection,[56] analysis of the CCTS and other data[36,57] does not establish a clear benefit to either histocompatibility or ABO matching. This finding was confirmed recently, with one exception: in the case of previous graft failures,[59] positive cross-matching significantly increased the risk of rejection. The lack of benefit of donor–recipient cross-matching in general is in clear contrast to the outcomes of solid organ transplantation[54,55] and indicates an as yet incomplete understanding of basic immunologic features regarding corneal graft rejection.

SURGICAL RISK FACTORS

Previous and subsequent anterior segment surgery

Corneal graft failure is associated with previous anterior segment surgery, including non-cornea-related operations such as lensectomy and vitrectomy.[36] A study of 2242 corneal transplants registered by the UK Transplant Service confirmed that surgical risk factors have a highly significant influence on the outcome of penetrating keratoplasty.[60] Previous implantation of a glaucoma drainage device is an independent risk factor for graft loss irrespective of control of intraocular pressure.[61] Postoperative clouding of clear corneal grafts following additional cataract surgery was reported in 16% of patients by Stark and Maumenee,[62] 20% by Lemp and coworkers,[63] and 25% by Binder.[64] As phacoemulsification has improved, cataract surgery after penetrating keratoplasty has become more successful; in a study of 29 postkeratoplasty patients undergoing cataract extraction, only one developed graft failure during an average follow-up of 44 months.[65]

Graft diameter

Increased graft size has been reported in some studies to be a significant risk factor for rejection.[45,66,67] Other studies, however, refute this and point to smaller grafts as more likely to be rejected.[36,60] Price et al found an increased risk of rejection and endothelial failure in small grafts (recipient size less than 7 mm) and an increased risk of rejection in large grafts (recipient size >8.5 mm).[3] These considerations do not include very large grafts (>9 mm), which usually are restricted to special indication such as severe infectious keratitis, corneal melting diseases,[68] and advanced keratoconus/keratoglobus[69,70]; these show a clear disadvantage compared with conventional graft sizes. The risk factor with regrafts may become critical if the surgeon increases the graft size successively so that opaque areas may be completely excised.[67]

Anterior synechiae

Iridocorneal synechiae are a significant risk factor for corneal graft failure.[2,3,36,71,72] Anterior synechiae may result from chronic inflammation or previous anterior segment surgery; they may predispose the patient to both immunologic graft failure through exposure of the endothelial layer to iris blood vessels and mechanical failure through direct traction on the graft endothelium.[71,73] In addition, anterior synechiae are often associated with elevated intraocular pressure.[73,74]

EPIDEMIOLOGIC RISK FACTORS

Recipient-related factors

The strongest risk factor for graft failure in the CCTS was the age of the recipient at the time of keratoplasty.[36] Recipients younger than 40 years of age had approximately twice as many graft failures from all causes and twice as many failures from immunologic rejection as did recipients older than 40 years. No difference in graft outcome was found within the three subdivisions of older patients up to 89 years of age. Similar findings have been reported by Musch and Meyer[75] and Boisjoly et al,[66] and others,[28,45,76] but Price et al did not find that age influenced graft failure rates.[3]

In the CCTS, male corneal graft recipients had a higher failure rate than female recipients, but they had similar rejection failure rates. No significant difference was found between black and white or other groupings of recipients,[36] but Price et al did report that African Americans were significantly more at risk than whites for endothelial failure and graft rejection and that sex did not influence graft failure.[3]

In the CCTS, current smokers had a substantially higher reaction rate than nonsmokers and a higher failure rate from all causes, whereas the rejection rate was similar.[36] Diabetes was a risk factor for endothelial failure, but not rejection in Price's series.[3]

Donor-related and other factors

The corneal donor study recently reinvestigated the effect of donor age on outcome of PK and found no difference in the 5-year graft survival rate with donors aged 66–75 years compared with donors aged 12–66 years.[76a] They did, however, find a slightly higher rate of endothelial cell loss in subjects receiving tissue from older donors. Patients that received a cornea from donors aged over 65 had a 5-year endothelial cell loss of 75% with a final endothelial cell count of 654 cells/mm^2. When the donor's age was 65 years or less, the endothelial cell loss at 5 years post-PK averaged only 69%, and the final endothelial cell density was 824 cells/mm^2.[76b]

Previously, the CCTS data revealed little systematic variation in outcome rates by donor age, donor race, or times either from donor death to corneal preservation or from donor death to surgery.[36] A waiting time of longer than 9 months until corneal transplantation increased the failure rate from 33 to 45%.[36] Evidence has been produced that bilateral grafts increase the risk for allograft rejection.[77]

SPECIAL CONSIDERATIONS

Chemical injuries

The prognosis for penetrating keratoplasty in eyes with chemical injuries, severe alkali burns in particular, is poor.[78,79] This most likely results from a combination of immunologic and nonimmunologic factors. The immunologic risk is attributed to the extensive vascularization that is seen in most cases of chemical burn. Nonimmunologic graft failure can be caused by tear deficiency, symblepharon, and trichiasis,[79] or by limbal stem cell loss that leads to persistent epithelial defects and chronic corneal ulceration.[80] Regrafting in this situation usually is contraindicated until these problems are controlled.

In the case of chronic surface disease, a conjuctival flap performed first may be used to quiet the inflamed eye. Penetrating keratoplasty can then be performed months or years later with an improved prognosis.[81]

In eyes with repeated graft failure due to severe ocular surface disease such as Stevens–Johnson syndrome, chemical burns, ocular cicatricial pemphigoid, or limbal stem cell deficiency, a keratoprosthesis may offer improved prognosis[82,83]; however, the long-term compliance of the patient is more critical, and the consequences of visual loss can be more severe.[83,84]

Limbal stem cell transplants, from stem cells cultivated on membranes[85] or from conjunctivolimbal allografts or autografts,[86] have

been performed prior to repeat keratoplasty to address surface disease from stem cell loss. The long-term outcomes of these are not yet clear and often require systemic immunosuppression.

Glaucoma

Elevated intraocular pressure has been called the single most serious complication that accompanies penetrating keratoplasty.[87,88] In two series,[2,89] uncontrolled glaucoma accounted for up to 20% of all failed penetrating keratoplasties. Postkeratoplasty glaucoma is clearly multifactorial in origin and varies with preoperative conditions and the indications for keratoplasty. The likelihood of developing glaucoma after penetrating keratoplasty is highest with aphakic and pseudophakic bullous keratopathy, up to 50%[89,90]; overall the cumulative 15-year risk of developing glaucoma is 20%,[9] and in repeat transplants, postoperative glaucoma occurred in 34–47% of cases.[50,52,91] Although elevated intraocular pressure may cause endothelial dysfunction,[92] the use of glaucoma drops has been identified as an independent risk factor for corneal graft failure,[3] possibly due to adverse effects on the ocular surface and stem cells.

The management of postkeratoplasty glaucoma is difficult and requires careful evaluation of the surgical and nonsurgical options that are available for pre- and postoperative pressure control. Failure of medical therapy indicates the need for surgical intervention.[93] For many years, cyclocryotherapy was the treatment of choice for medically intractable postkeratoplasty pressure control, with success rates ranging between 80 and 100%.[94,95] However, a significant percentage of eyes in these series developed phthisis and other serious complications, leading to final graft failure.[96]

A number of advanced techniques have been reported, which avoid the disadvantage of affecting structures adjacent to the ciliary body. The procedures are usually based on one of two principles: the implantation of aqueous shunts (as was described by Molteno,[96] Schocket et al,[98,99] and other authors[98–100]) or the elective application of contact or noncontact laser energy, such as trans-scleral neodymium : yttrium–aluminum garnet (Nd : YAG) cyclophotocoagulation.[101,102] Transvitreal endophotocoagulation of the ciliary processes[103] potentially provides similar success rates in achieving pressure control, but with fewer complications.

Trabeculectomy with antimetabolites performed at the time of penetrating keratoplasty can successfully control IOP.[93] Although glaucoma may be controlled with a glaucoma drainage device, the presence of a shunt predicts a poor long-term graft prognosis and is an independent risk factor of graft failure.[61]

Determining which technique to apply is an individualized decision. Surgical intervention of any kind following penetrating keratoplasty can be detrimental to graft survival. When intraocular pressure is controlled poorly with all types of therapy, regrafting may be contraindicated.[52]

Herpes simplex keratitis

Herpes simplex may cause primary graft failure even in the absence of prior known herpetic disease. One recent study found evidence of HSV DNA in 33% of cases of primary graft failure.[104] The source of this may be latent viral infection of either the host or the donor.

Recurrence of herpetic keratitis (Fig. 48.5) after keratoplasty ranges from 15 to 47%.[42–44,105–107] Although a history of preoperative inflammation does not appear to influence graft survival rate or the incidence of recurrent herpes keratitis in the graft,[42] grafts performed during active recrudescence may be complicated by defective wound healing, a flat anterior chamber, anterior synechiae, or glaucoma.[44,101,107–109] Ideally, keratoplasty should be postponed until the herpes keratitis has been quiescent for an extended period (6 months).[4]

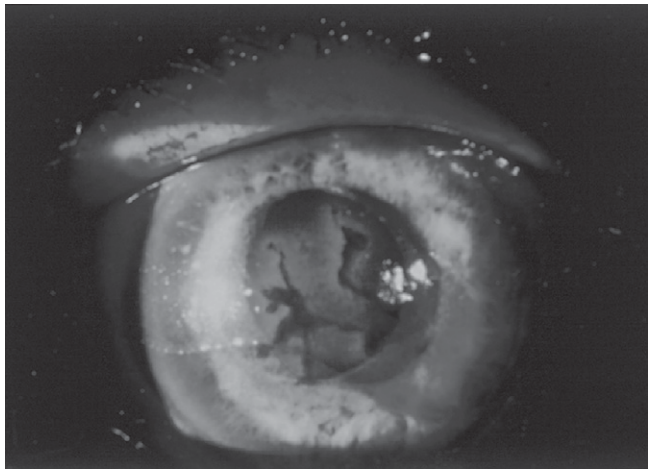

Figure 48.5. Recurrent herpetic dendrite 20 years after keratoplasty.

Allograft reaction may be difficult to distinguish from recurrent herpetic disease.[21] If the typical dendritic ulcers are not clinically apparent, it can be impossible to define the phenotype of corneal reaction, even with diagnostic methods such as rose bengal staining.[109] Fine and Cignetti[43] indicate that large keratitic precipitates in the presence of corneal edema with donor and recipient cornea involvement probably represent recurrent herpetic disease. Because these precipitates are not pathognomonic,[42] the authors recommend treatment with both topical steroids and topical antivirals. Ficker and coworkers[42] determined that rejection episodes complicated 23% of herpes recurrences, indicating that immunologic rejection can be induced by herpetic inflammation. Older studies[43,44] indicated that 50–60% of corneas with herpes recurrence develop graft failure.

Rejection rates are higher in grafts performed for herpetic disease, 29% at 1 year and 46% at 2 years in one recent study, but with reasonably optimistic graft survival rates of 84% at 1 year and 67% at 2 years.[106]

Topical steroids and antivirals have improved graft survival in herpetic keratoplasty. Ficker and coworkers[42,105] found long-term survival rates up to 70% over a follow-up period of 10 years, with herpes recurrence accounting for less than 20% and immunologic rejection representing the major cause of final graft failure. Similar tendencies are reported for repeat herpes simplex keratoplasties. Although subsequent regrafting usually decreases the overall survival rate,[42,105] one study reported decreasing regraft percentages of about 50% in the 1970s,[44] 22% in the 1980s,[51] and 6% in the 1990s.[110] This decline was ascribed to the improved medical treatment of herpes simplex keratitis.[111]

Prophylactic use of antiviral medications after keratoplasty for herpes simplex keratitis is common, and the literature reports support a beneficial effect of topical[111] and systemic[112,113] long-term treatment with trifluridine and acyclovir following penetrating keratoplasty.[111] Antiviral prophylaxis reduces the recurrence rate of herpes simplex, as well as the incidence of corneal graft failure. More recent studies have emphasized systemic prophylaxis over topical, and the authors use only systemic prophylaxis.

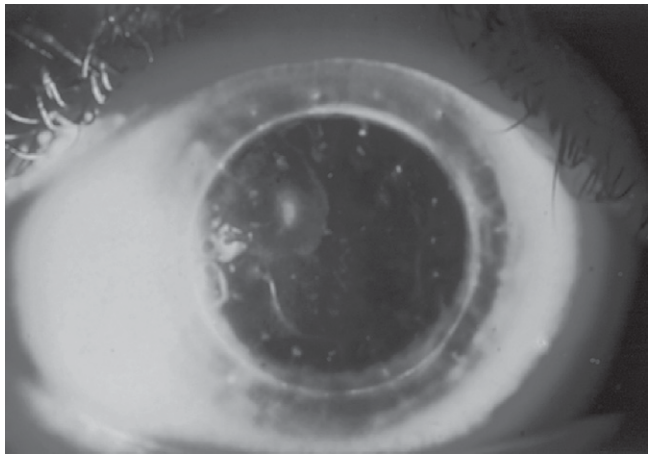

Figure 48.6. Recurrent hereditary stromal dystrophy after keratoplasty.

Recurrent corneal dystrophy

The recurrence of hereditary stromal dystrophy (Fig. 48.6) after keratoplasty has been reported in Reis-Bücklers',[114] granular,[115] lattice,[116,117] and macular dystrophies.[118,119] Recurrences occur most commonly in grafts for lattice dystrophy, with 25–48% of these grafts demonstrating recurrence within 25 years.[117,120] Regrafting may be necessary in 15% of patients in whom primary corneal transplantation has been performed.[117] Phototherapeutic keratectomy has been successfully employed on recurrent corneal dystrophies after penetrating keratoplasty.[121]

REGRAFT INDICATIONS, SURGICAL CONSIDERATIONS, AND VISUAL PROGNOSIS

INDICATIONS FOR REGRAFTING

Primary graft failure

Corneal grafts with gross stromal edema and large broad folds immediately after keratoplasty should be suspected of having endothelial decompensation. Intensive topical steroids may be of some benefit, but if no reversal is noticed within several days, irreversible graft failure is inevitable, and regrafting within 3 months is recommended. Stromal edema may also be caused by ocular hypotony, which may clear when ocular hypotensives are discontinued and intraocular pressure increases.

Graft rejection

Despite evidence that the risk of allograft rejection is increased with repeat keratoplasty, advances in corneal preservation techniques, operating methods, and medications have improved the prognosis for high-risk keratoplasty substantially. With advances in topical and systemic immunosuppression, even the small population with a history of multiple graft failure may enjoy useful vision because prolonged periods of graft survival can now be achieved.

Recurrence of host disease

Although many grafts with recurrent herpes keratitis remain clear, 23–30% require regrafting.[42,51] Recurrent corneal dystrophy, particularly lattice dystrophy, may reduce graft clarity.[117] A soft contact lens is usually of some benefit in reducing epithelial erosion symptoms; however, some patients require regraft.

CONTRAINDICATIONS FOR REGRAFTING

Uncontrolled glaucoma

An eye with increased intraocular pressure that is uncontrolled by medical or surgical therapy will likely have difficulties after a keratoplasty procedure. Before surgery, the pressure should be controlled through cyclocryotherapy, shunt, or filtering procedures, if necessary. In desperate situations, penetrating keratoplasty combined with a filtering procedure may be justified.

Inadequate tear function

Eyes with severe keratitis sicca or severe cicatrizing diseases should be considered for keratoplasty only rarely. The postoperative prognosis for these eyes is extremely poor.[36,78,79] If keratoplasty is attempted, tarsorrhaphy and punctal occlusion may be necessary to enhance the surface lubrication postoperatively.

Unsatisfactory lid margins

Trichiasis, ectropion, entropion,[122] extensive symblepharon, and scarred lid margins[80] are relative contraindications for keratoplasty. These conditions should be corrected before keratoplasty is undertaken.

SURGICAL CONSIDERATIONS

Principles

Fine states that two principles must be considered before regrafting is undertaken:[49]

1. The graft should be sized so that its margins lie in the most normal tissue, whether recipient or donor.
2. The graft margin should not be in proximity to the limbus.

The corneal surgeon should avoid successive increases of the donor size with each regraft. If the recipient bed includes a previous donor of excessive diameter and the tissue is of sufficient consistency, a penetrating keratoplasty may be performed within the boundaries of the original donor.

Suture technique

In the CCTS, the risk for rejection failure increased considerably for eyes with interrupted sutures as compared with eyes with a running suture,[36] but this could be because interrupted sutures are often used in grafts that have a poorer prognosis to begin with. Interrupted sutures are recommended in highly vascularized recipient beds that promote inflammatory responses during the early postoperative period, allowing selective suture removal when necessary.

VISUAL PROGNOSIS

Although it is difficult to compare visual acuity data across studies, the overall impression is that regrafts lead to improved visual outcomes.[123] Studies with prolonged follow up report clear regrafts at 2 years ranging between 64 and 85%, and for 5 years from 46 to 53%.[32,51,53,110,123,124] Rapuano and coworkers found a visual acuity of 20/20 to 20/40 in 32%, 20/50 to 20/100 in 40%, and 20/200 to 20/400 in 21% of regrafted patients.[110] Statistical analysis of this cohort revealed a relative accumulation of rejection failures within the first 18 months, whereas later onset of graft failure was decreased significantly.[51] It appears that regrafts that remain clear for a certain initial time period have excellent overall visual and survival prognoses. The long-term stability of corneal (re)grafts

confirms the idea that chronic rejection pathways do not contribute to functional graft declines, as was reported by researchers on solid organ transplantation. Specific investigations of this issue have not been reported.

REGRAFTING: DESCEMET'S STRIPPING ENDOTHELIAL KERATOPLASTY

Regrafting was the leading indication for PK in a recent study[125] accounting for 40.9% of all grafts performed. In the regraft subgroup of this study, endothelial failure was the most common indication. A new option has emerged for the management of regrafting due to endothelial failure: endothelial keratoplasty. DSEK surgery removes or strips the host's diseased Descemet's membrane and transplants donor Descemet's membrane with a small amount of posterior stroma.[126] When DSEK is performed for endothelial failure in a graft, the stripping of Descemet's membrane is omitted to prevent excess traction at the old graft–host junction. New posterior lamellar host tissue is positioned posterior to the old graft which is left in place unaltered.

Fig. 48.7 demonstrates a DSEK performed for graft failure. This patient was a 76-year-old male who was 3 years postop traditional keratoplasty for pseudophakic bullous keratopathy, now with endothelial failure. Preoperative best-corrected visual acuity (BCVA) was 20/400 and pachymetry was 0.938 mm. Ten weeks postoperatively, BCVA was improved to 20/60 despite history of a vein occlusion and glaucoma treated with a tube shunt.

The benefits of electing DSEK over full-thickness traditional keratoplasty for Fuchs' dystrophy or pseudophakic bullous keratopathy are superior tectonic strength, no induced astigmatism, and no corneal sutures. When DSEK is performed secondarily after a full-thickness graft has failed, it still offers the benefits of a sutureless graft that does not introduce astigmatism. Additionally, the immediate postop tectonic strength is more secure than if the full-thickness graft had been replaced. However, there is no reduced risk of rejection.

At this time it is not clear that regrafting by DSEK is preferable to full-thickness regrafting. DSEK can be considered as an alternative for regrafting, especially in candidates at risk of falls and trauma, as the smaller wound in a DESK may likely offer a lower risk of postoperative dehiscence.

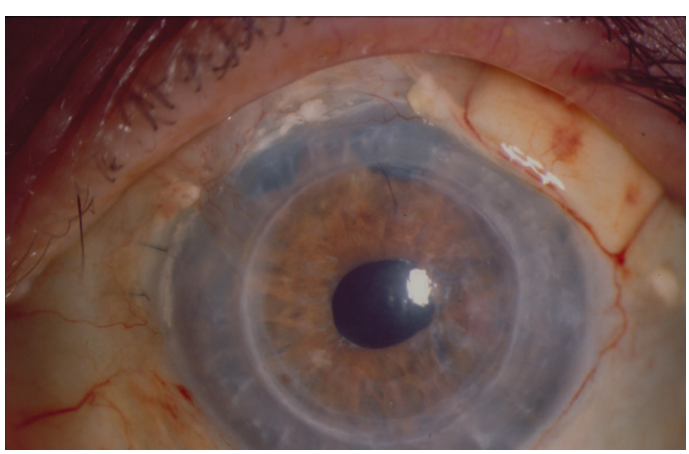

Figure 48.7. Regrafting with DSEK: photograph taken 10 weeks postoperatively.

APPROACHES FOR THE PREVENTION OF CORNEAL GRAFT REJECTION

Immunologic rejection remains the most common cause of corneal graft failure, particularly within the first 6 months following transplantation.[3,50,127] Although the primary corneal allograft enjoys a certain degree of immune privilege,[128] which is thought to be promoted by passive anatomic sequestration (avascularity) and active mechanisms that downregulate the number of attacking T lymphocytes by inducing apoptosis (Fas/FasL-System),[129,130] evidence has accumulated that the effector mechanisms responsible for corneal graft rejection are not principally different from those described for vascularized solid organ transplantation.[48,130,131]

The Cornea Donor Study, currently in progress, is again exploring the benefits of blood group compatibility in corneal transplantation. Until now, many studies have shown that in high-risk grafts, rejection is lower if there is ABO matching,[58,132] but the differences have often been statistically insignificant or simply not present in the case of low-risk grafts.

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49 Pediatric keratoplasty

Gerald W. Zaidman

Visual and surgical results in pediatric penetrating keratoplasty have seen significant improvement. At one time, corneal transplantation in children was considered to have a very high chance of failure and was contraindicated.[1,2] Advances in surgical technique and postoperative care now enable surgeons to frequently obtain a clear transplant in an infant or a child. Currently, prompt penetrating keratoplasty is the first step in averting irreversible loss of visual function due to amblyopia.

Corneal surgeons understand that many aspects of an infant's or a child's preoperative, intraoperative, and postoperative care differ from those of an adult undergoing a corneal transplantation. The difficulty in assessing the visual function of an infant or a young child, a child's inability to cooperate with the eye examination, and the great variability in outcome make the physician's decision regarding surgery more difficult than in an adult. It is for these reasons that these children are amongst the most challenging for corneal surgeons.

INDICATIONS

In North America the most common cause of a congenital corneal opacity is one of the anterior segment dysgeneses.[3–7] This is a group of disorders comprising Peters anomaly (Types I and II) (Figs 49.1 and 49.2), sclerocornea (Fig. 49.3), corneal dermoid (Figs 49.4–49.8), and congenital anterior staphyloma (Fig. 49.9). This group makes up nearly 60% of congenital corneal opacities in North America. The next most common cause is congenital glaucoma (Figs 49.10 and 49.11), comprising 10–15% of the patients. The third group, also consisting of approximately 15% of the patients, is the congenital corneal dystrophies (Figs 49.12 and 49.13). This includes congenital hereditary endothelial dystrophy, congenital heredity stromal dystrophy, and posterior polymorphous dystrophy. Finally trauma, infection, and metabolic and genetic disorders make up less than 10% of the patients.

Acquired pediatric corneal opacities (Figs 49.14–49.19) can be divided into two groups—acquired nontraumatic or acquired traumatic.[5,6] These two groups, separately, are less common than congenital corneal opacities. Although the etiologies in all three groups of children with corneal opacities are different, the difficulties in managing these children are similar.

DIFFERENTIAL DIAGNOSIS OF PEDIATRIC CORNEAL OPACITIES

Congenital

- Peters anomaly (Figs. 49.1 and 49.2)
- Sclerocornea (Fig. 49.3)
- Corneal dermoids (Figs. 49.4–49.8)
- Congenital anterior staphyloma (Fig. 49.9)
- Glaucoma with corneal edema (Figs. 49.10 and 49.11)
- Congenital corneal dystrophies (Figs. 49.12 and 49.13)
- Metabolic

Acquired, nontraumatic

- Herpes simplex keratitis (Fig. 49.14)
- Microbial keratitis (Fig. 49.15)
- Keratoconus
- Neurotrophic keratitis
- Interstitial keratitis
- Ophthalmia neonatorum

Acquired, traumatic

- Corneal or corneoscleral laceration
- Birth trauma (Figs. 49.16–49.19)
- Nonpenetrating injury with scar

SURGERY

PREOPERATIVE EVALUATION

The diagnosis and treatment plan are made after an office visit, family history, consultation with a pediatrician (to rule out systemic, genetic, and metabolic disorders) and pediatric ophthalmologist, and most importantly an examination under anesthesia (EUA). An EUA is done on all children with congenital corneal opacities and on many younger children with acquired opacities.[8] This is the most

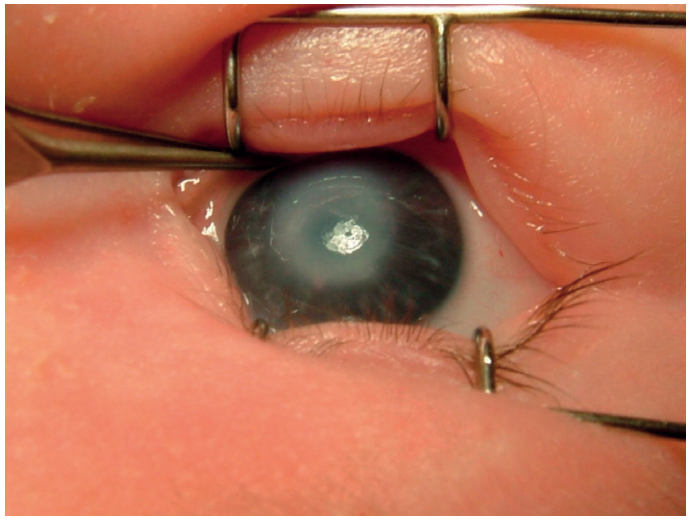

Figure 49.1. A 3-month old with Peters anomaly Type I.

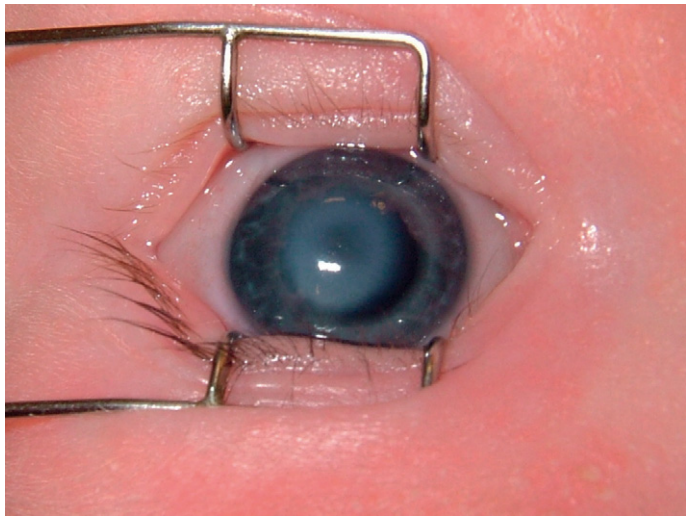

Figure 49.2. Infant with Peters anomaly Type I.

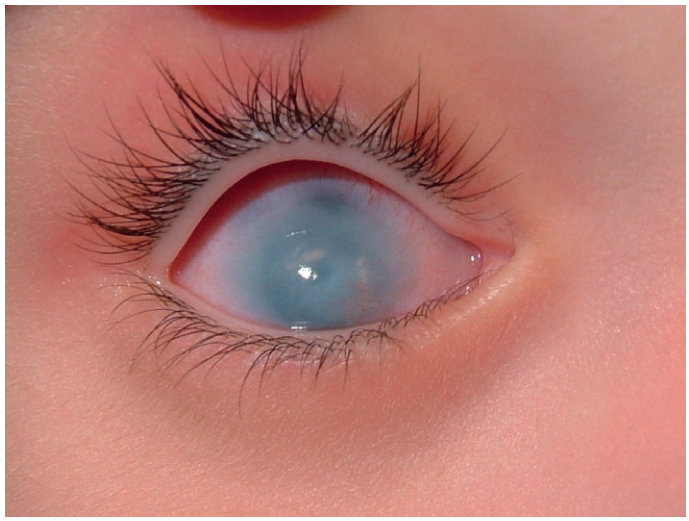

Figure 49.3. Infant with sclerocornea.

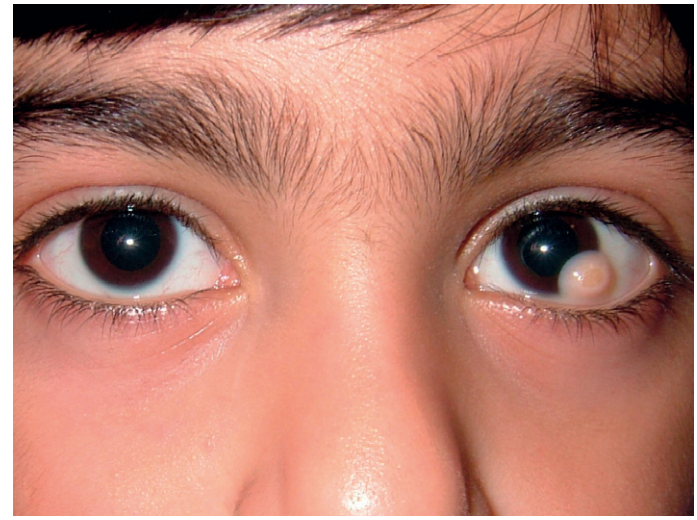

Figure 49.4. A 3-year-old boy with corneal dermoids.

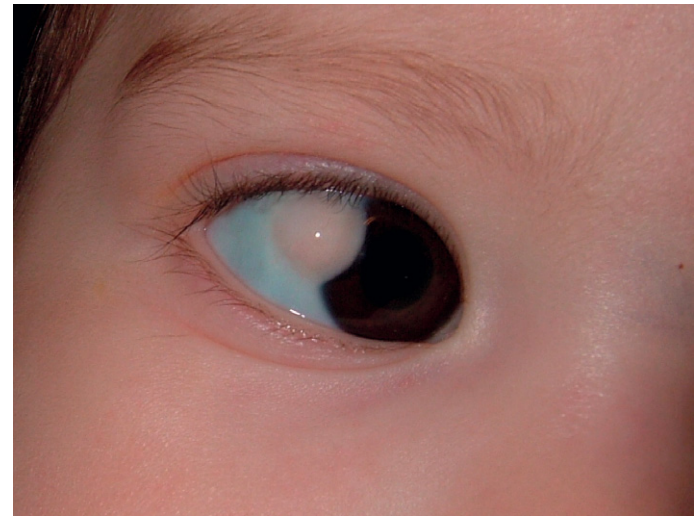

Figure 49.5. A 3-year-old boy with corneal dermoids.

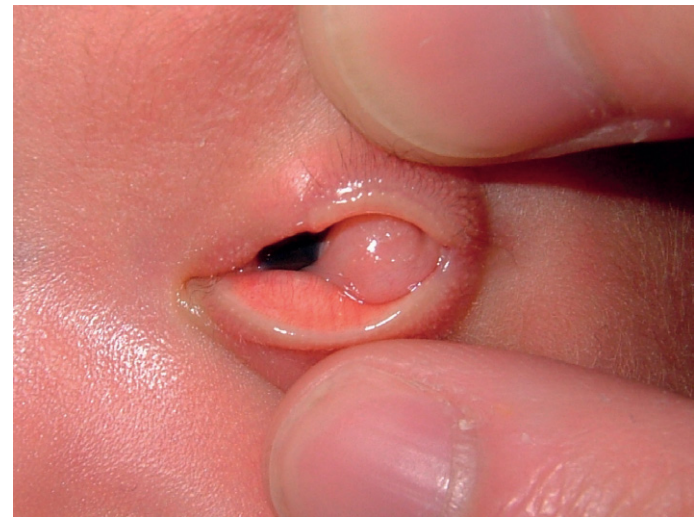

Figure 49.6. Infant with corneal dermoids.

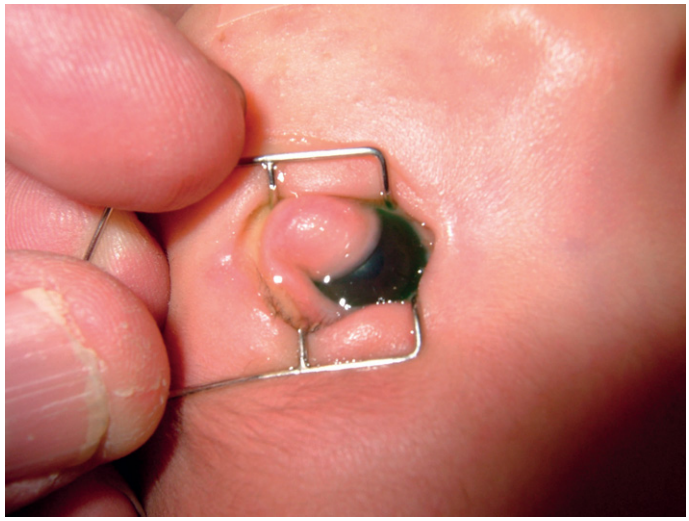

Figure 49.7. Corneal dermoid in an 8-month old.

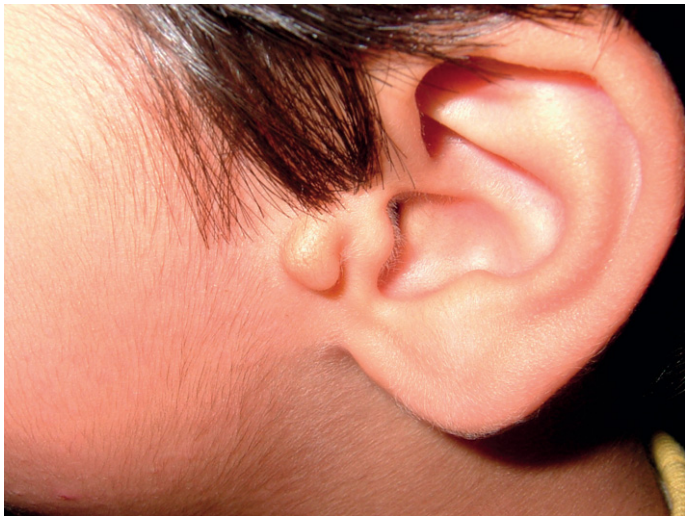

Figure 49.8. A 4-year old with Goldenhar's syndrome with a preauricular skin tag.

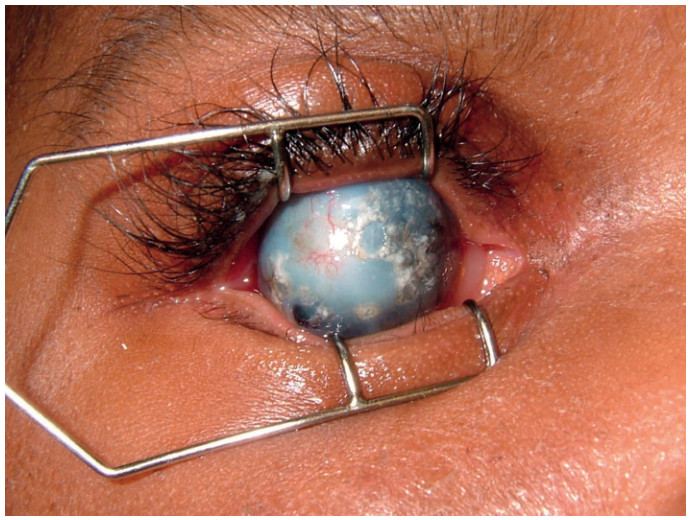

Figure 49.9. Infant with congenital anterior staphyloma.

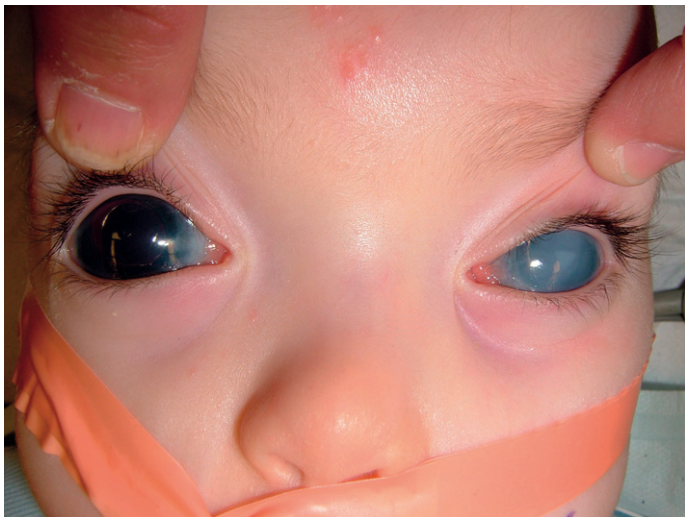

Figure 49.10. A 14-month old with congenital glaucoma and corneal edema OD.

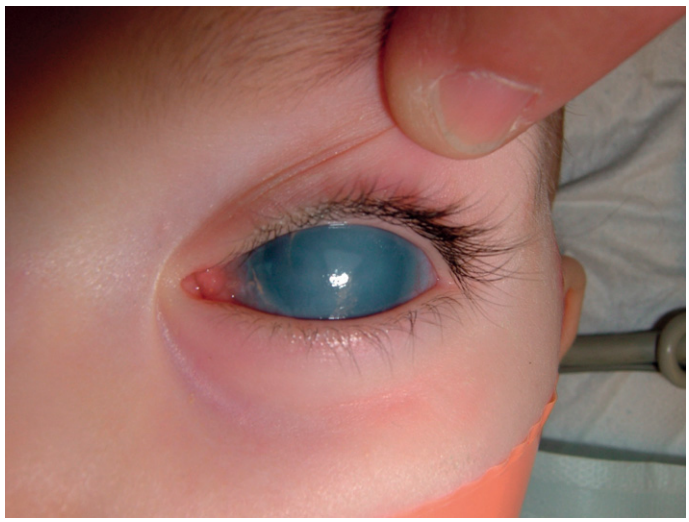

Figure 49.11. High-power photo of left eye of Figure 49.10 illustrating corneal edema insetting of congenital glaucoma.

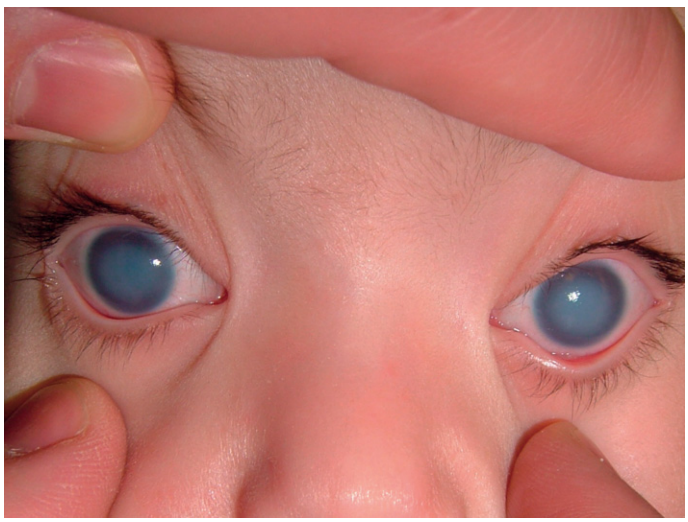

Figure 49.12. An 18-month old with congenital hereditary endothelial dystrophy (CHED).

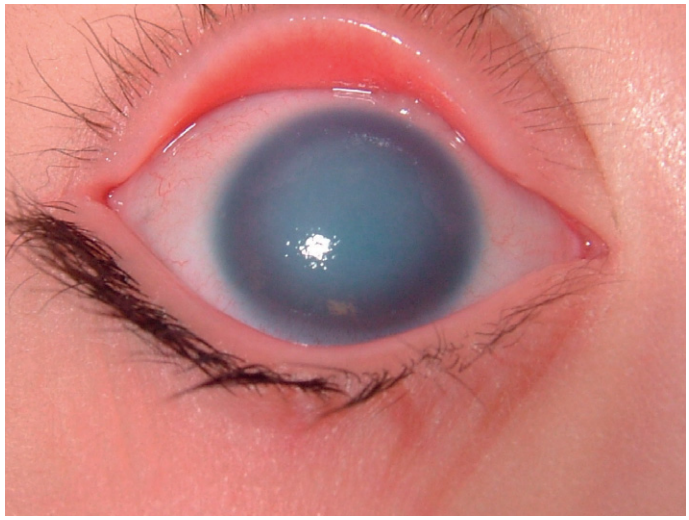

Figure 49.13. High-power photo of patient in Figure 49.12 with CHED.

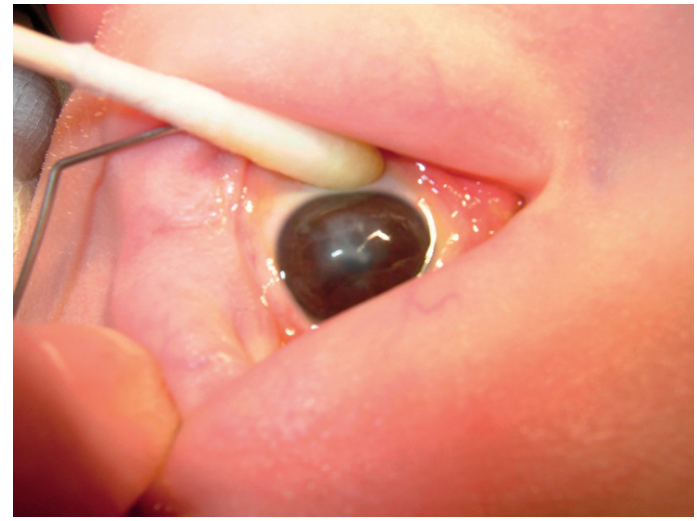

Figure 49.14. A 2-year old with corneal scarring after herpes keratitis.

Figure 49.15. A 2-year old with corneal scar due to bacterial keratitis.

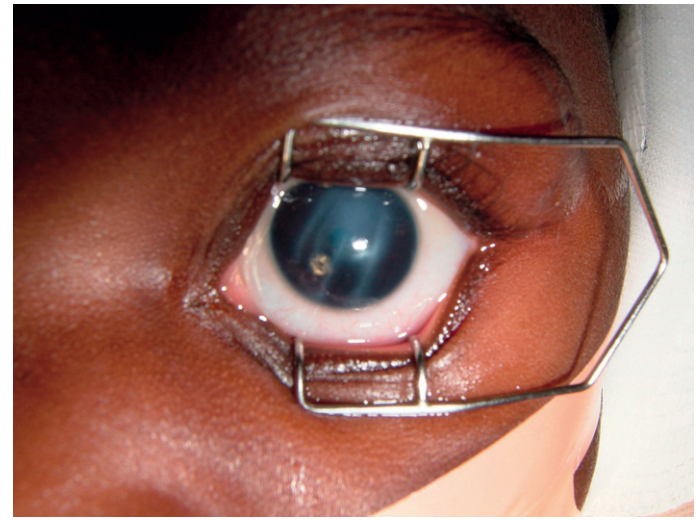

Figure 49.16. A 2-month old with a forceps injury.

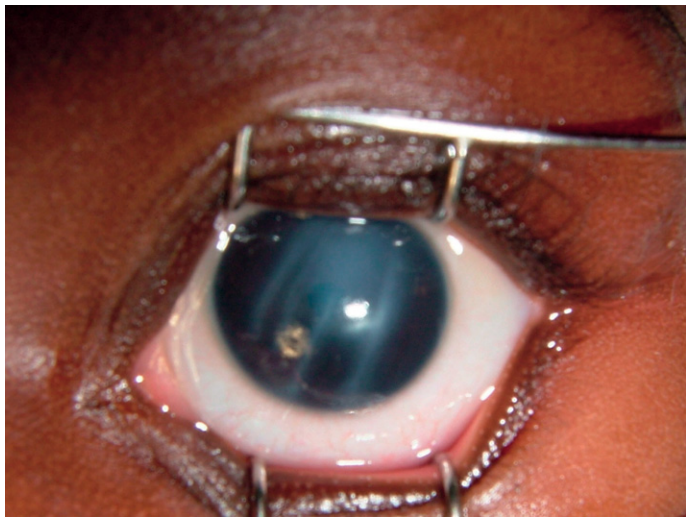

Figure 49.17. High-power view of forceps injury eye in Figure 49.16.

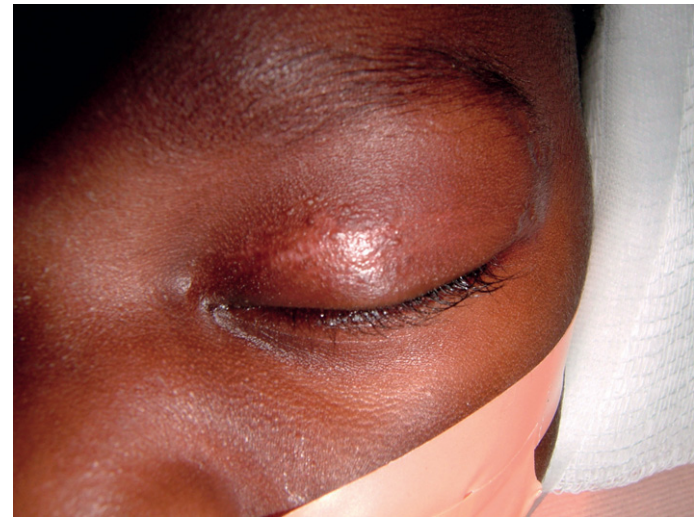

Figure 49.18. Scarring on eyelid of child with forceps injury.

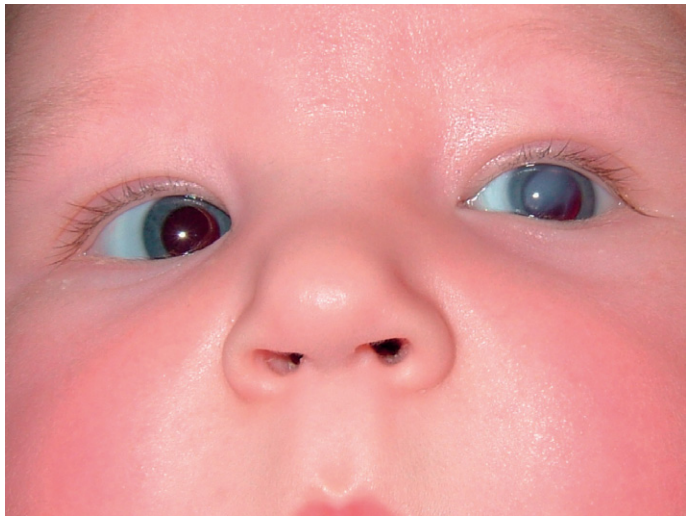

Figure 49.19. Corneal opacity in an 8-month-old with a forceps injury at birth.

accurate way to do a complete eye examination including slit-lamp examination and tonometry. During the EUA, the corneal diameter is measured and A-scan and B-scan ultrasonography are performed. At the same time refraction, VER, ERG, or ultrasound biomicroscopy can be done.[9,10]

After the EUA is performed and before surgery is scheduled, the parents are extensively counseled regarding the risks of surgery. They are taught the difference between surgical success (clear graft) and visual development. We teach the parents about amblyopia and its treatment. Finally, we tell the parents that the goal is functional and ambulatory vision and that they should not expect perfect vision.

Before surgery is scheduled one more factor is considered—the child's social situation. Supportive and motivated parents or caregivers are a necessity. In an unstable social environment surgery is doomed to fail and should not be undertaken.

Finally, intraocular pressure control is required before corneal transplant surgery. In my experience, except in patients with congenital glaucoma, if the untreated intraocular pressure is less than 30 mmHg it can usually be controlled medically. Patients are treated with prostaglandin inhibitors, beta blockers, or topical or systemic carbonic anhydrase inhibitors. Alphagan is not used because of reports of pulmonary side effects in infants. If medical control is unsuccessful glaucoma surgery is required prior to penetrating keratoplasty (PKP). Filtering surgery is generally preferable to tube shunts.[11]

TIMING

Because of the small size of the neonatal eye and the high risk of intraoperative complications, a PKP for a congenital corneal opacity is not done before the child is 2 months of age. In an ideal situation, the child is first seen in the office at 7–14 days of age. The EUA is scheduled for 3–6 weeks of age. In a unilateral congenital corneal opacity, the corneal transplant is then done at 8–12 weeks of age. With a bilateral opacity surgery, the first eye is done between 2 and 3 months of age. In bilateral cases, the more severe eye is not necessarily done first. Because of the risk of amblyopia and the need for the child to develop vision, the less severe eye is often done first. In bilateral cases, the second eye is usually done 6–8 weeks after the first. This allows at least 4 weeks of postoperative care to remove sutures, control glaucoma, avoid infection, and validate parental compliance. Once these have been accomplished, the second eye is done. For an acquired corneal opacity in an older child, surgery is performed once the eye has stabilized and all inflammation has resolved.

TECHNIQUE

Surgery is done under general anesthesia. A pediatric lid speculum is inserted, and a scleral support ring is sewn to the sclera with interrupted 7-0 silk suture. A weight-appropriate dose of intravenous mannitol (25%) is given before surgery commences, and all children are hyperventilated by the anesthesiologist.[12] Donor tissue is obtained from donors between 4 and 18 years of age. The recipient corneas are trephined between 5.0 and 7.0 mm, and the donor between 5.5 and 7.5 mm, thereby consistently creating a 0.5 mm difference between donor and recipient corneal buttons. The anterior chamber is entered with a 15° angled knife and reformed with a viscoelastic. Viscoelastic or a spatula is used to lyse any synechiae between the iris and the cornea. During these maneuvers, any bleeding can usually be controlled by sodium hyaluronate, topical epinephrine drops (in a concentration of 1/10000), gentle pressure, or microcautery to the bleeding vessels. Excision of the recipient corneal button is performed with pediatric corneal transplant scissors (STORZ E 3230 R, L). During excision of the patient's cornea, infants and children can develop significant amounts of positive pressure. The surgeon has to be experienced in handling this to avoid loss of the lens or vitreous loss. Grafts are sutured into position with 12–16 interrupted 10-0 sutures. All suture knots are buried. A subconjunctival injection of 0.5 mL of gentamicin (40 mg/mL) and 0.5 mL solumedrol (40 mg/mL) is given at the end of the procedure. At the end of surgery indirect ophthalmoscopy can be performed.

POSTOPERATIVE REGIMEN

Routine postoperative care includes a topical antibiotic four times a day, aggressive topical corticosteroids, and glaucoma therapy as needed. A topical corticosteroid (prednisolone acetate 1%) is used 10 times a day for the first month after surgery, 8 times a day for the second month, 7 times a day for the next month, and then tapered by one drop per month, every month (6 times/day for 1 month, 5 times/day for 1 month, etc). Therefore, patients are treated with topical corticosteroids for a minimum of 10 months after surgery.

For the first month after surgery patients are examined 2–3 times per week. In the second postoperative month, office examinations are done weekly (or more often if necessary). Office examinations are then slowly decreased from a frequency of once every 2 weeks to once every 6–8 weeks. Examinations under anesthesia are frequently performed, initially in the operating room and occasionally in an office setting (under chloral hydrate sedation) as needed. The first EUA is 2–3 weeks after surgery and then repeated in the operating room every 2–3 weeks until all sutures are removed. For infants all sutures are usually removed by 6–10 weeks postoperatively (see below). Office EUAs are usually done every 3 months using a portable slit lamp and a pneumotonometer or tonopen. Finally, parents are instructed as to how to examine the grafted eye (with a light and a magnifier) to note any signs of a loose suture or a graft rejection.

Both before and after all the sutures have been removed, patients are examined by a pediatric ophthalmologist, who dispenses a spectacle correction and a regimen for patching the unoperated eye. In patients with unilateral disease, patching is done for approximately 6 h/day. In bilateral cases, the second eye has surgery 2 months after the first eye and the same postoperative routine is followed.

Finally, the parents are warned that the graft is at risk whenever the child develops any severe febrile illness or is to be vaccinated. At these times, the corticosteroid drops are increased in frequency for a short time. For example, vaccinations are delayed until 1 year after surgery. When it is time to vaccinate the child the corticosteroid drops are increased to four times a day for 1 week before and 1 week after the vaccination.

SUTURE REMOVAL

For children who have their corneal transplant during their first year of life, sutures are removed by 5 weeks after surgery, in 1-year olds within 6–7 postoperative weeks, in 2- and 3-year olds by 3–4 postoperative months, in 4–6-year olds within 4–6 months, and in 7–10-year olds at 5–6 months postoperatively.[13,14] Patients 10–18 years of age are treated the same as adults.

CONCOMITANT SURGICAL PROCEDURES

If the lens is cataractous, adherent to the cornea, or abnormal in size or location, it is removed. If possible a standard extracapsular cataract extraction is done, the posterior capsule is kept intact, and a surgical capsulotomy is done at a future time. If the posterior capsule breaks (or if the lens is small or subluxed) then a generous anterior vitrectomy is performed. If cataract surgery is required, heparin, 2500 units in 500 cc, and epinephrine is added to the irrigating bottle.

A peripheral iridectomy is indicated if there are posterior synechiae to a clear lens. This is also performed when lensectomy and vitrectomy are undertaken.

Because of the high risk of intraoperative complications, it is not advisable to do a corneal transplant on a child's eye with uncontrollable glaucoma. The intraocular pressure should be controlled prior to transplant surgery. If medical control is not possible, a filtering procedure is done a few weeks prior to the transplant. Glaucoma tube shunts are not generally used because of the potential risk to the clarity of the lens or cornea.[11]

ALTERNATIVES TO PENETRATING KERATOPLASTY

Some children with corneal opacities can be treated without a PKP. These alternative operations consist of an optical iridectomy, rotating keratoplasty, or lamellar keratoplasty.[15–18]

The first two can be used when the child has a peripheral opacity that just impinges on the visual axis. Surgically enlarging the pupil (in an optical iridectomy) or moving the scar out of the way (rotating keratoplasty) can enable the child to see around the opacity.

In some children, especially those with corneal dermoids or scarring from corneal ulcers, the corneal opacity is not full thickness and the posterior cornea is relatively clear. In these cases, the opacity can be removed with a lamellar dissection. The lamellar dissection can be done manually or, as has been recently reported, using the microkeratome.[19]

The main problem with any of these three procedures is that they can result in unpredictable amounts of astigmatism. Also interface haze may be present after a lamellar graft, preventing the development of 20/20 vision. However, since a lamellar procedure is an extraocular procedure and not a full-thickness procedure, it lessens the chance of a wound dehiscence. It also eliminates the risk of an endothelial graft rejection.

OPTICAL CORRECTION AND AMBLYOPIA THERAPY

Without effective optical correction and amblyopia therapy, a pediatric PKP may be of limited benefit. Therefore, co-management with a pediatric ophthalmologist is mandatory in all children who have corneal transplants. Amblyopia can be reversed in younger patients if treated promptly and appropriately.

Correction of refractive error is a vital part of amblyopia therapy. At about the second postoperative week, the epithelium has generally healed and the graft has cleared sufficiently to perform cycloplegic retinoscopy. Retinoscopy may be difficult, and the refraction will change as the wound heals and sutures are removed, but the correction of a moderate and large refractive error can be prescribed at this time. The refraction should be repeated periodically until the sutures have been out for several months. Refraction of an aphakic eye can be confirmed if the axial length is known. The following formula is an approximation for an aphakic eye and assumes a keratometry measurement of 45 D and a vertex distance of 10 mm:

$$\text{distance spectacle power} = 63.7 - (2.28 \times \text{axial length in mm})$$

The results from this formula can be modified by keratometry measurements. For an aphakic eye, an infant is generally prescribed a near correction, which is +1.00 to +2.50 D sphere over the distance correction. The aphakic child should be put in a bifocal, with the top of the segment at the inferior border of the pupil. Contact lenses are also useful in visual rehabilitation of pediatric keratoplasty patients, especially in monocular aphakes. Silicone lenses offer the highest oxygen permeability of all lenses and are often well tolerated in aphakic patients with normal corneas.

If the contralateral eye is normal, occlusion therapy should be started as soon as the graft is partially cleared and correction of any refractive error is being worn. Ideally, this should not be later than 2 postoperative weeks. Occlusion during the first 6 months of life is usually limited to one-fourth to three-fourths of infant's waking hours. If the child is older than 6 months, full-time occlusion therapy can be started. The vision in both eyes is monitored carefully to check for improvement of the amblyopic eye or worsening of the normal eye.

RESULTS

For many years, ophthalmologists believed that the results of PKP in children were poor and surgery was doomed to failure. In earlier, now outdated, studies done between the 1970s and the early 1990s, a graft clarity rate of between 29 and 75% was reported after corneal transplant surgery for congenital corneal opacities. In these studies, the average graft survival was 49%.[5] Patients with grafts for acquired traumatic or acquired nontraumatic disorders generally did better with a graft clarity rate of between 64 and 81%.

Since then, with improved surgical techniques and better peri- and postoperative care, the success rate has improved. For example,

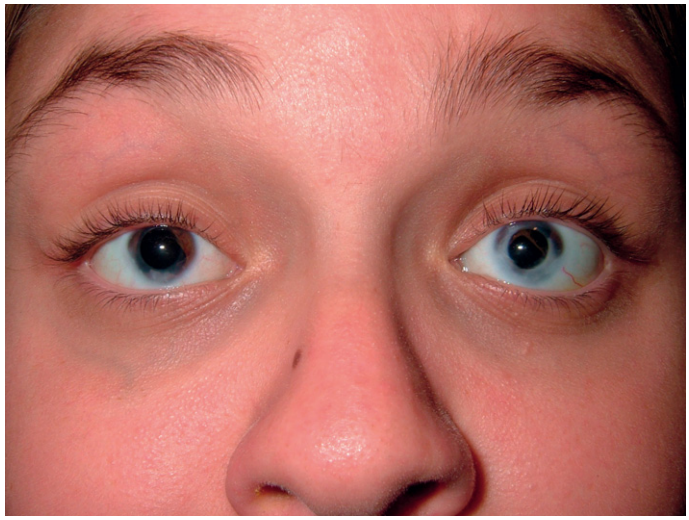

Figure 49.20. Postoperative photo of a teenager 15 years after bilateral PKP for Peters anomaly Type I.

Figure 49.21. Higher-power photo of Figure 49.20.

in our study of children with traumatic corneal lacerations, clear grafts were obtained in all of the patients and all had improved visual acuity.[20] Similar excellent results were obtained in other studies[21] with visual improvement in more than 80% of children. Frueh and Brown in 1997[22] determined that the probability of a clear graft is 75% in 1 year and 58% at 2 years in children with congenital corneal opacities. Dana et al in 1997[23] reported 61% graft clarity at 38 months after surgery in a diverse group of children. Yang et al in 1999[24] reported that about 50% of all grafts done in children with Peters anomaly were clear 1 year postoperatively. The authors of this paper also gave us a 'profile' of an eye with a clear graft. It had mild-to-moderate disease, a donor cornea less than 8 mm, a running suture and no intraoperative lensectomy, vitrectomy, or retinal detachment. Comer et al in 2001[25] reported a 61% rate of graft clarity in infants with a variety of disorders. Michaeli et al in 2005[4] reported clear grafts in 88% of their patients with Peters anomaly 1 year after surgery.

Our surgical techniques and our perioperative and postoperative care have been modified and designed using knowledge gained from these prior studies. Since 1988, the author has operated on 30 eyes with Peters anomaly Type I. These patients have been followed an average of 6.5 years; many of them are now more than 3 years of age and their vision has been tested (Figs 49.20 and 49.21).[26] A graft clarity rate (including regrafts) of 90% has been achieved in these patients. More than 50% of the patients have achieved vision of better than 20/100 and two-thirds were 20/400 or better. In this group of patients, the major risk factor for graft failure or poor vision was poorly controlled glaucoma (as has been shown by other authors).[27]

CONCLUSIONS

Although the prognosis still remains somewhat guarded, corneal transplant surgery can be successful in children with acquired or congenital corneal opacities. After surgery, useful vision can develop in these patients, especially in the absence of glaucoma or, if glaucoma is present, it is either transient or easily controllable with medical therapy.

Corneal surgeons can advise the parents of infants and children who require corneal transplant surgery that their children have a good chance of graft clarity if they are intensively managed (with frequent examinations, high-dose topical corticosteroids, and aggressive control of glaucoma) during their peri- and postoperative period. Furthermore, if the amblyopia is aggressively co-managed with a pediatric ophthalmologist, more than 50% of them can develop good or functional vision.

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50 Therapeutic penetrating keratoplasty

Prashant Garg, Gullapalli N. Rao

The term 'therapeutic keratoplasty' is used for a surgical procedure performed either for restoration of structural integrity of the eye or to resolve an infectious and inflammatory keratitis refractory to conventional medical therapy. The procedure can be a full-thickness penetrating keratoplasty (PKP) or a partial-thickness lamellar keratoplasty. The term 'tectonic keratoplasty' is used when the procedure is performed primarily to restore the structural integrity of the eye. The surgery is most often performed as an emergency procedure on an inflamed eye. Therefore, the surgical procedure, postoperative course, and chances of graft survival are different from optical keratoplasty. It is critical to understand various aspects of the surgery and postoperative care in order to maximize optimal outcome. It is also important to discuss these various aspects, including the expected outcome, with every patient before subjecting him or her to the surgery. In this chapter, we will discuss these aspects, including indications, preoperative evaluation, anesthesia, surgical procedure, and postoperative care.

INDICATIONS

MICROBIAL KERATITIS

Corneal blindness secondary to infectious keratitis is a major problem in developing countries.[1] Early diagnosis, better understanding of pathogenesis, and the availability of potent antimicrobial drugs have improved the chances for medical control of corneal infections, particularly those of bacterial origin. However, virulent and resistant forms of some bacteria,[2–5] fungi,[6–11] and *Acanthamoeba*[12–14] can progress inexorably, even with maximal medical therapy, and these may necessitate PKP. In addition, conditions such as infectious crystalline keratopathy and mycobacterial keratitis often require keratoplasty.[15–17] In general, the indications for PKP in infectious keratitis include the following circumstances (see Box 50.1 for details): (1) conditions that are refractory to maximal medical therapy; (2) advanced cases that carry the risk for scleral extension; and (3) instances of threatened or actual perforation.

Miedziak et al found that older age, delay in referral to a corneal specialist, topical steroid treatment, past ocular surgery, poor vision at presentation, large size, and central location of the ulcer are important risk factors in active microbial keratitis leading to PKP.[18]

The goal of therapeutic keratoplasty in these cases is to completely remove or reduce the infective inoculum to a level at which anti-infective therapy and host defense mechanisms can be effective.

HERPES SIMPLEX KERATITIS

Therapeutic keratoplasty for herpes simplex keratitis is indicated in patients with severe stromal keratitis refractory to medical therapy or progressing to perforation. In some cases, keratoplasty may be required to remove antigenic material responsible for recurrent inflammatory episodes.[19–21]

NONINFECTIOUS KERATITIS

In addition to infectious keratitis, keratoplasty may be required in cases with noninfectious keratitis resulting in progressive stromal loss. Such situations can occur in neurotropic keratitis, exposure keratitis, and severe dry eye of various etiologies.[22–25] In all these conditions, a nonresponding persistent epithelial defect progresses to stromal melt and perforation. Although the primary treatment in these conditions is directed toward the etiology, we need to provide local treatment that will promote epithelial healing, protect healing epithelium, and avoid further damage to epithelium. In cases with persistent epithelial defect, stromal loss can lead to perforation. Such cases require keratoplasty for tectonic support. Therapeutic keratoplasty performed for tectonic purpose in patients with either impending or actual perforation is also termed 'tectonic keratoplasty'. The goal of the surgery in these cases is to preserve or restore the structural integrity of the eye.

The decision about whether to perform keratoplasty in all these indications is fraught with great risk, however, and the risk-to-benefit ratio must be appraised carefully. A review of the literature clearly highlights the low rate of success that is associated with active cases of infectious keratitis.[26–29]

BOX 50.1 INDICATIONS FOR PENETRATING KERATOPLASTY IN THE TREATMENT OF INFECTIOUS KERATITIS

Bacterial keratitis

- Progressing despite maximal medical therapy
- Extensive corneal involvement
- Descemetocele or perforation
- Resistant to conventional medical therapy
  - Infectious crystalline keratopathy
  - *Mycobacterium* keratitis

Fungal keratitis

- Progressing despite maximal medical therapy
- Threat to the integrity of the globe
- Scleral involvement

***Acanthamoeba* keratitis**

- Failed medical therapy
- Threatened integrity of the globe
- Scleral involvement

However, advances in eye-banking methods and surgical techniques, and improved availability of effective pharmacologic agents for postoperative care have significantly improved the outlook for PKP in these cases. Proper donor corneal selection, the use of meticulous surgical techniques, and close postoperative follow-up are fundamental to the success of this procedure.

PREOPERATIVE EVALUATION

OCULAR EXAMINATION

Once the decision has been made to perform PKP, a detailed presurgical examination is mandatory for proper surgical planning. A detailed slit-lamp evaluation is required to determine the size of the infiltrate and its relation to the limbus. This evaluation facilitates planning of surgical details, such as the size of the trephine that can be used and its optimal placement in the recipient bed to ensure excision of the diseased cornea. A note should be made of the degree of thinning, including the presence of actual perforation. Extreme care is required in handling cases with gross thinning and perforation. You may want to apply tissue adhesive to ensure adequate pressure in eyes with actual perforation before trephination. The status of the anterior chamber should be assessed; cases with a flat anterior chamber or the presence of anterior synechiae must receive intravenous mannitol to control intraocular pressure and reduce vitreous volume. In such cases, entry into the anterior chamber needs to be guarded to prevent injury to the lens in phakic eyes. Retinal evaluation should be attempted, if at all possible. When an adequate view of the retina is not possible and the integrity of the globe is not compromised, an ultrasonography examination is mandatory. The status of the vitreous is very important owing to the potential for concomitant endophthalmitis, particularly in cases of fungal keratitis, cases with perforation, and in patients who have undergone cataract surgery. Intraocular pressure should be evaluated and controlled. All patients with high intraocular pressure must be given intravenous mannitol and must have a very careful entry into the anterior chamber to prevent sudden decompression and choroidal hemorrhage. Patients with a large perforation may require surgery under general anesthesia and therefore may require general medical evaluation. In all patients with gross thinning or perforation, the anesthetist must be informed about the ocular condition and the risk of perforation with expulsion of intraocular contents. This will help them to take appropriate precautions during both peribulbar and general anesthesia.

PREOPERATIVE TREATMENT

Patients with culture-proven keratitis must receive antimicrobial treatment directed against offending microorganisms. If an etiologic diagnosis has not been established, antibiotic coverage with combination therapy or with a broad-spectrum variety should be provided. We recommend therapy with both topical and systemic routes in cases with corneal perforation and fungal and *Acanthamoeba* keratitis and in patients with scleral extension. Use of antibiotic prophylaxis is controversial in sterile corneal melts and perforation; however, one must choose the least epithelial toxic antibiotic under such circumstances. Although Killingsworth et al[27] and O'Day et al[30] have recommended the use of topical and systemic steroids before therapeutic keratoplasty, even in cases of fungal keratitis, one must be aware of the potential for steroids to make the infectious process worse.

DONOR MATERIAL

Criteria for the selection of donor corneas are similar to optical PKP except in circumstances where waiting for cornea of good quality may further complicate the clinical situation. Corneal tissue of excellent grade offers the following advantages:

1. Healthy tissue with intact epithelium minimizes the risk of reinfection in the graft.
2. Compact and clear tissues permit monitoring of the anterior chamber reaction during the immediate postoperative period.
3. Because of the greater likelihood of extensive inflammation and elevated intraocular pressure that is associated with the treatment of large perforations, the use of healthy endothelium is critical for the survival of the graft.

Under emergent circumstances, corneas of poor quality or that have been in storage media longer than recommended can also be used; however, make sure that all appropriate medical standards are fulfilled.[31] Similarly, donor cornea qualities are not as important in patch grafts that are of small size and are off the visual axis.

SURGICAL TECHNIQUES

Although corneal transplantation for infectious keratitis follows the basic surgical technique of PKP, special attention must be given to certain details, which are highlighted here.

PREOPERATIVE PROCEDURES

The transplantation can be performed using local anesthesia, except in eyes with large perforations, which may require general anesthesia. It is important to obtain a good hypotony, akinesia, and anesthesia to avoid problems related to positive vitreous pressure, to facilitate relatively prolonged surgery, and to keep the patient comfortable all through the surgery. Peribulbar injection of a mixture of 1% lidocaine with epinephrine and 0.75% bupivacaine mixed with hyaluronidase and sodium bicarbonate produces a good aki-

nesia and long anesthesia. In patients with no risk of perforation, gentle digital massage or other measures to obtain a soft eye may be considered.

SURGICAL PROCEDURES

Penetrating keratoplasty

The various steps of the surgical procedure are shown in Figure 50.1, *A* to *E*.

Exposure

Lid sutures or self-retaining speculum can be used to obtain good exposure. It is important to avoid external pressure on the globe, especially in cases with corneal perforation. Whenever possible, a Flieringa ring should be used to provide scleral support. In eyes with very low intraocular pressure suturing of the ring may be difficult. In cases of large ulcers that reach up to the limbus, peritomy is required, and hemostasis is achieved by the use of wet-field cautery.

Preparation of the recipient bed

The goal of therapeutic keratoplasty is to excise all necrotic or infected tissue. Therefore, it is critical to choose a right size of trephine for recipient bed preparation. Measure the involved area using a caliper (Fig. 50.2, *A* and *B*). A trephine that is at least 1 mm larger than the size of the lesion will increase the chances of a stable and noninfected recipient bed (Fig. 50.3, *A* and *B*). Place the appropriate trephine over the cornea and create an indentation in the epithelium to further verify the appropriateness of trephine diameter. Trephination of the recipient bed can be technically difficult, especially in cases with corneal necrosis, gross thinning, and actual perforation. Applying pressure on the globe can lead to extrusion of intraocular contents and expulsive choroidal hemorrhage. It is, therefore, important to use an extremely sharp trephine and apply minimal pressure. Suction trephines can be advantageous under these situations. In eyes with a perforation, initial tectonic support can be obtained by applying cyanoacrylate glue during surgery.

A side-port entry with a sharp blade provides access for filling the anterior chamber with a viscoelastic before actual trephination; this will prevent a sudden decompression of the globe.

Occasionally, the lesion may be located near the limbus. An example of this situation would include infections of cataract wound, infection or perforations after pterygium surgery, and peripheral inflammatory disorders. In such cases, if the lesion is small a corneal trephine can be placed straddling the limbus. However, if the lesion is large, there is a large perforation, or the entire cornea is involved, freehand dissection of the recipient after marking with a trephine will be the option.

We recommend 80% depth trephination followed by a guarded entry into the anterior chamber with either a no. 11 surgical blade or any other sharp blade. Excision of diseased cornea can than be completed in the usual manner with right and left Castroviejo scissors. Leaving a relatively wider posterior ledge (nearly 1 mm), especially in large grafts, provides support and reduces the risk of postoperative wound leaks.

In all cases, the corneal specimen should be subjected to both microbiologic and histopathologic investigations. We divide the excised corneal button into two halves through the lesion; one half is sent for histopathology examination in 20% formaldehyde and the other half is sent in a sterile vial for microbiology evaluation.

Clearing the anterior chamber of exudate

Irrigation of the anterior chamber is done using a balanced salt solution. Elimination of all exudative material from the anterior chamber helps to prevent the recurrence of infection and reduces complications such as glaucoma. The membranes over the iris are dissected gently by the irrigating cannula and are removed with forceps (Fig. 50.4). Any membrane covering the iris surface should be removed very gently, and every effort should be made to arrest bleeding from the iris surface. Intracameral antibiotics or antifungals can be used whenever required.

Additional procedures

Performing two large peripheral iridectomies can prevent pupillary block. Careful examination of the iris may reveal septic foci that can be excised and sent for microbiology evaluation. Other intraocular procedures are best avoided. Removal of cataracts should be deferred because the lens forms an effective barrier that may prevent the spread of infection into the vitreous. However, removal of the crystalline or intraocular lens may be required in cases with concomitant endophthalmitis. When vitreous involvement is diagnosed, open sky vitrectomy is indicated and the vitreous sample is sent for microbiologic investigation, followed by intravitreal injection of appropriate antibiotics. The anterior chamber is reformed with a viscoelastic substance, and the margin of the recipient bed is trimmed.

Preparation of the donor cornea

Donor cornea preparation is similar to optical PKP. However, in therapeutic keratoplasty donor cornea trephination is performed only after excision of recipient cornea because necrosis of the wound edges may require additional trimming and may alter the size of the graft that is required. It is therefore important to measure the recipient opening with a caliper before trephining donor cornea.

In cases of total keratoplasty or sclerokeratoplasty, freehand dissection of the donor cornea is performed.

Suturing

In therapeutic keratoplasty wound closure should be accomplished using interrupted sutures. Sutures should pass through at least 75% corneal depth and not full thickness to prevent conduit of infectious organisms from the cornea to the anterior chamber. It is not uncommon to use a greater number of sutures and longer bite in recipient cornea than are used in optical keratoplasty in order to get proper wound closure (Fig. 50.5, *A* and *B*). In order to prevent cheesewiring of sutures it is important to maintain a moderate suture tension. At the end of the procedure, it is critical that the integrity of the wound is ensured to prevent the possibility of leakage from a necrotic recipient bed.

Modified surgical techniques under special circumstances are:

1. *Sclerokeratoplasty*: Sclerokeratoplasty with the use of a corneal scleral graft to replace a large area of excised diseased corneal and scleral tissue and restore structural integrity was first described by Castroviejo in 1951. However, these large grafts were associated with a high incidence of rejection and glaucoma. To ameliorate glaucoma Cobo et al proposed the use of sclerocorneal dissection avoiding internal angle structures, coupled with the use of angle-supported mattress sutures to maintain the angle and preserve trabecular meshwork function.[32] The technique as modified by Cobo et al consists of following steps:

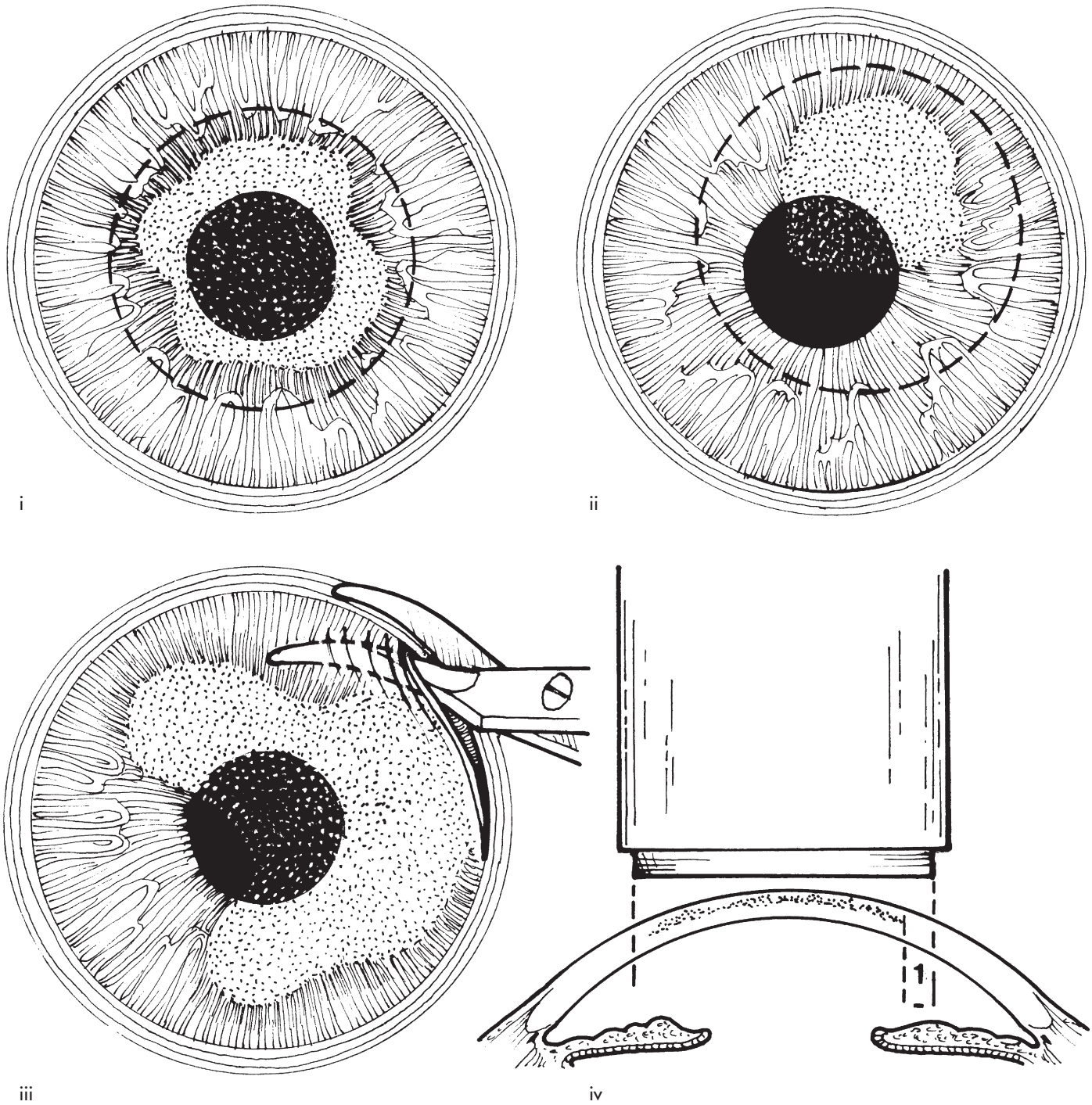
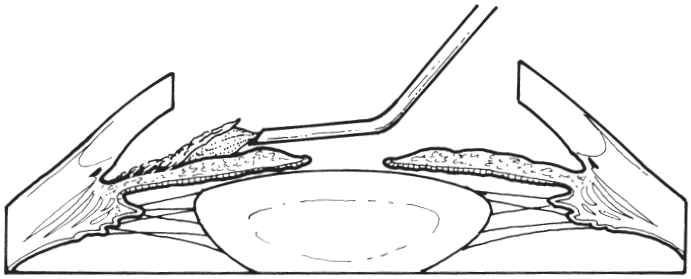


Figure 50.1. Surgical steps of therapeutic penetrating keratoplasty. *A*, Preparation of recipient bed, depending on the extent and location of the infiltrate. (i) Trephination concentric to limbus. (ii) Eccentric trephination. (iii) Freehand dissection. (iv) Note that the trephine chosen is at least 1 mm larger than the size of the lesion to ensure a stable and noninfected recipient bed. *B*, Procedure demonstrating removal of exudates using (i) irrigating cannula and (ii) forceps. *C*, Two peripheral iridectomies. *D*, Preparation of the donor button by (i) endothelial punch technique or (ii) freehand dissection (in larger grafts). *E*, (i) Suturing technique employing 16 interrupted 10-0 nylon suture. (ii) Note the suturing principles being the same as in optical penetrating keratoplasty.



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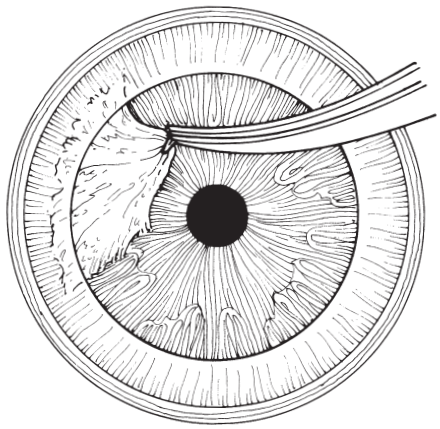

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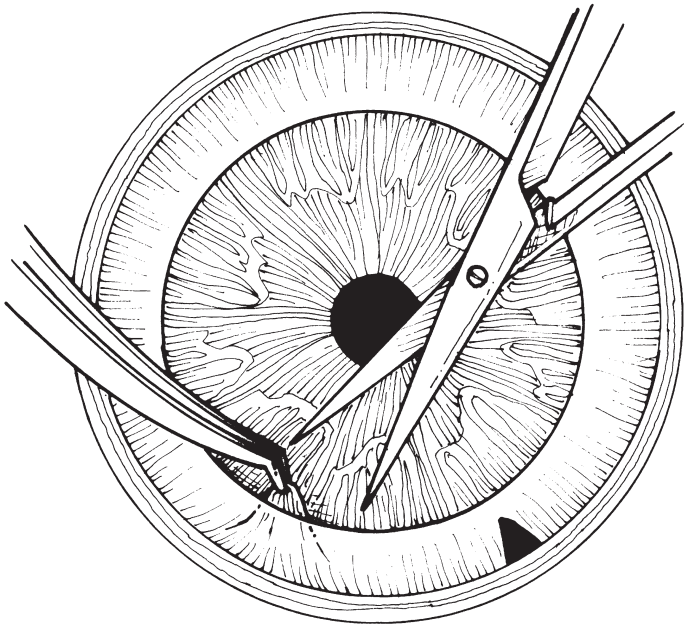

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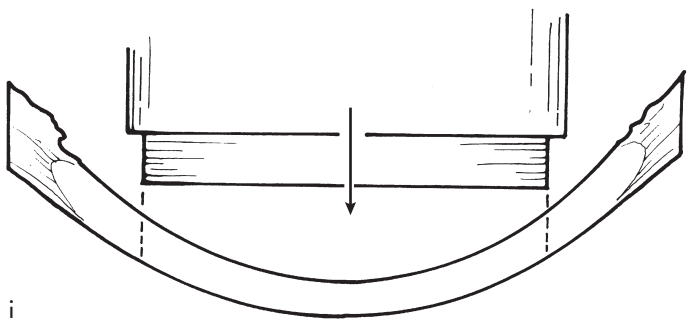

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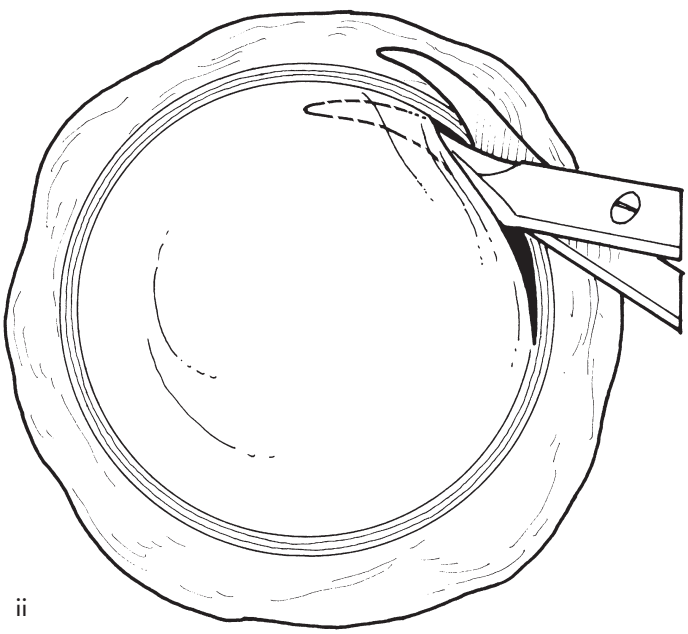

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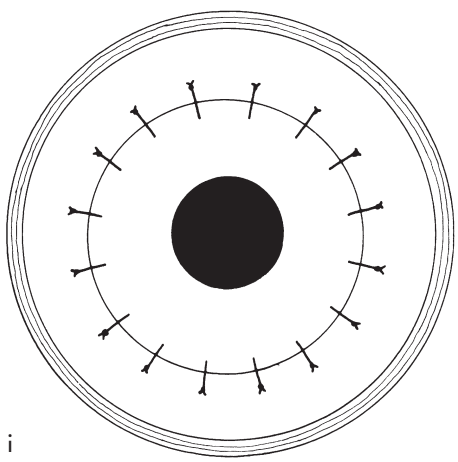

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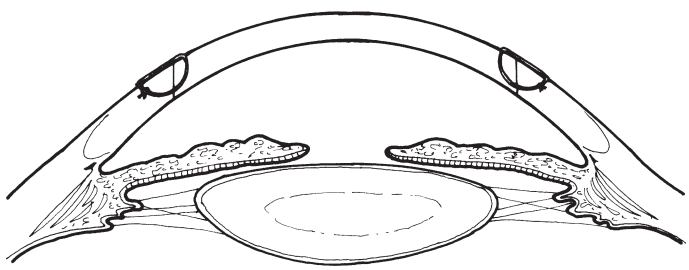
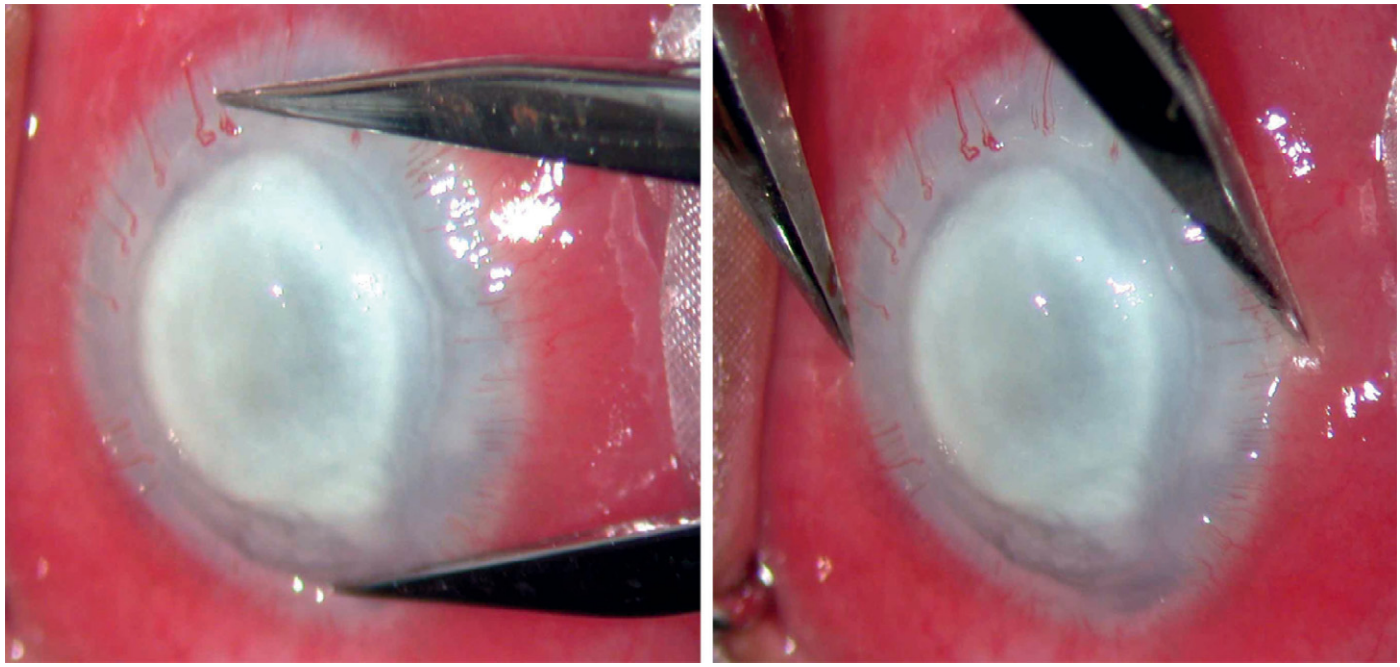


ii

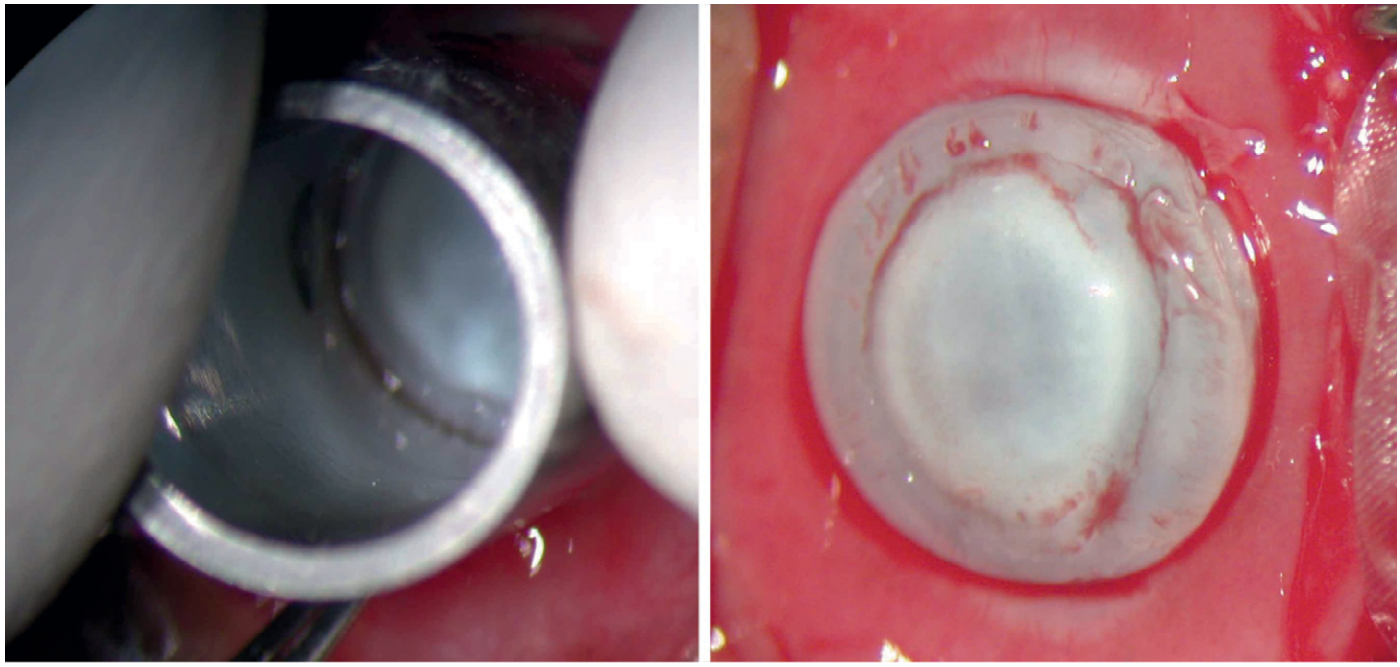
E

Figure 50.1. Continued



A B

Figure 50.2. Use of caliper to decide the trephine size for recipient cornea preparation. A, In horizontal meridian; B, in vertical meridian.



A B

Figure 50.3. Trephination of infiltrated cornea. *A*, Trephine in place; *B*, cornea after partial thickness groove made by trephine. Note that the size of trephine chosen is 1 mm larger than the infiltrate size.

- A 360° peritomy to reflect conjunctiva from limbus followed by cauterization of bleeding vessels.
- A 14 mm or larger trephine is used to outline diseased corneoscleral tissue.
- A 360°, 50% deep lamellar dissection of sclera is carried out up to limbus before entering into anterior chamber.
- Anterior chamber is entered anterior to the trabecular meshwork with a sharp knife, and Vannas scissors are used to complete the internal corneal incision. The diseased corneoscleral tissue is removed. A 1–2 mm lip or remnant of peripheral corneal tissue (posterior stroma and Descemet's membrane) is left for 360°.
- Donor tissue is prepared in a similar manner using either whole globe or a corneoscleral tissue over artificial chamber.
- Four equally spaced 10-0 prolene or nylon double-armed sutures are placed through the internal corneal lip in a mattress fashion, passed through the donor cornea, and tied. The

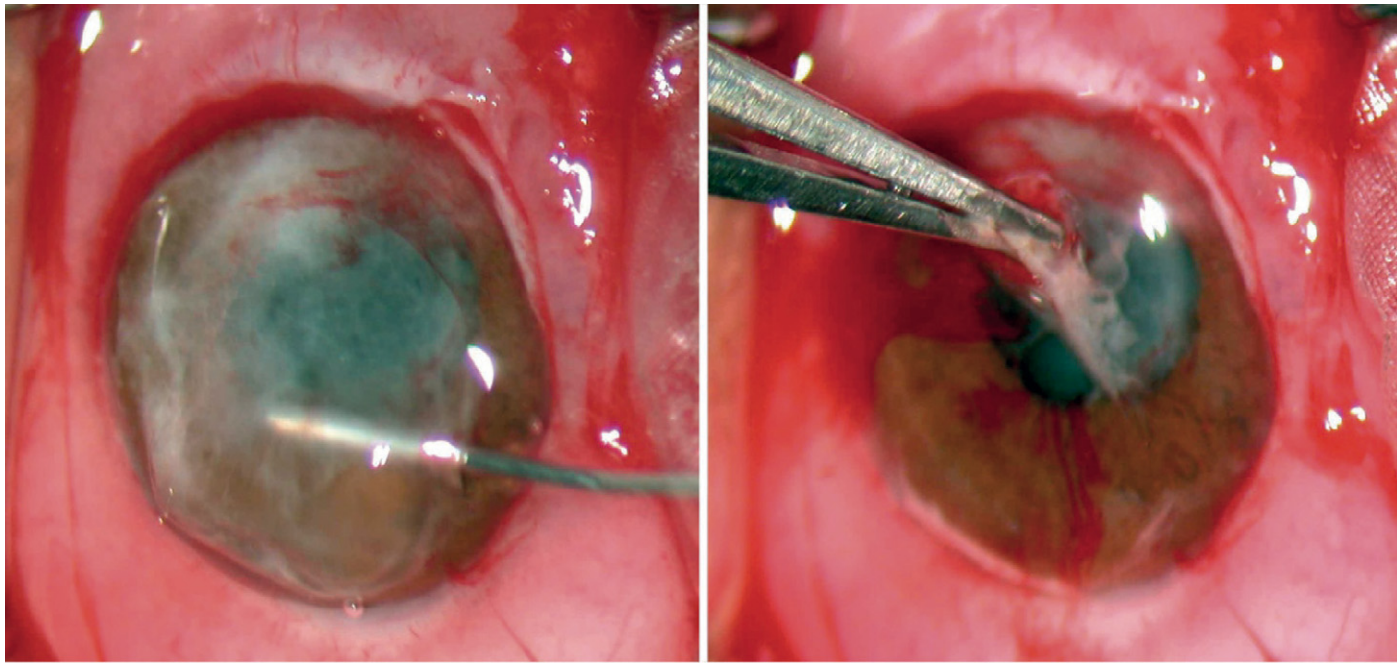


Figure 50.4. Clearing exudates over iris using gentle irrigation and forceps.

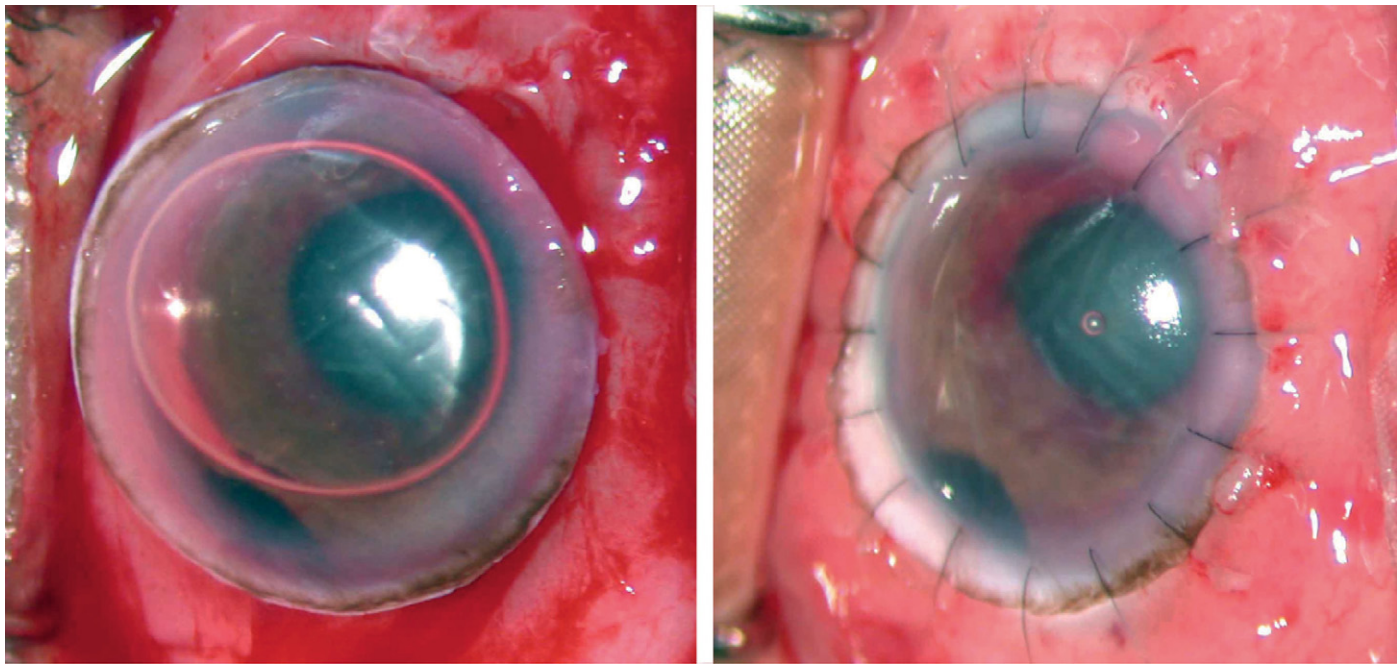


Figure 50.5. Suturing donor corneal button to recipient bed using 10-0 nylon suture. *A*, Donor cornea on recipient bed; *B*, cornea after completion of suturing.

scleral incision is closed using interrupted 10-0 nylon suture and covered with conjunctiva.

2. *Corneal debulking for corneal perforations*: This technique is described by Vajpayee et al.[33]
   - A vacuum trephine of size ranging from 7.5 to 9 mm is used to make the initial cut on the host cornea up to 75% depth.
   - Thereafter, lamellar dissection is performed at the level of posterior stroma using corneal lamellar dissectors such as crescent knife. The dissection is started peripherally and proceeds centripetally, with care taken to prevent perforation at the site of the iris incarceration. On completion of lamellar dissection, the superficial portion of corneal button, including the epithelium and the bulk of stroma, is removed.
   - The anterior chamber is then entered gently with a 26-gauge needle attached to a syringe containing viscoelastic, through the area in which iris is not incarcerated. The tip of the needle is directed tangentially between the deeper cornea lamella and the iris.

Figure 50.6. Surgical steps in therapeutic lamellar keratoplasty. *A*, Preparation of recipient bed. (i) Use a trephine that is at least 1 mm larger than the size of the infiltrate; (ii) make a partial thickness groove with the trephine. *B*, Perform a lamellar dissection so as to remove the infiltrated corneal stroma leaving behind a healthy bed. *C*, Preparation of donor button. (i) A blunt lamellar dissector is introduced through a small incision at limbus and a plane of cleavage is obtained. The dissection is completed by gently moving the spatula from side to side within the cleavage plane. (ii) When dissection is complete a trephine of suitable size is used to cut the graft. *D*, Lamellar donor cornea is sutured to recipient bed using (i) interrupted 10-0′ nylon suture. (ii) Suturing principles are the same as in optical keratoplasty.

- The deeper portion of the cornea and the overlying fibrous membrane are then gently dissected and peeled away from the iris tissue, taking care not to avulse the fragile iris. Viscodissection with 2% methylcellulose and a fine iris spatula release peripheral iris adhesions.

The principle of lamellar separation is based on the fact that the amount of force required to remove an adherent cornea from the underlying iris far exceeds the amount the iris can tolerate, resulting in iris tear and hemorrhage. This is because the total mass of the corneal tissue is greater than that of the adherent iris. With preliminary lamellar separation and excision of the superficial portion of the corneal button, the bulk of corneal tissue is significantly reduced. The integrity of iris tissue is essential to provide protection to the lens during surgery, formation of anterior chamber, facilitating implantation of intraocular lens, and preventing postsurgical photophobia and glare. However, one must keep in mind that the damaged iris is floppy and has a tendency to form adhesions with the graft, resulting in vascularization of the graft and subsequent rejection and failure. Moreover, the corneoiridic adhesions can result in the development of secondary glaucoma, which can further jeopardize the success of the corneal graft.

Lamellar keratoplasty for therapeutic indications

Paufique and Philips in 1950 first demonstrated the value of a tectonic lamellar keratoplasty in preserving the integrity of the globe.[34] Although there are reports of lamellar keratoplasty in active microbial keratitis,[35,36] it is preferable to avoid lamellar surgeries in active microbial keratitis as microorganisms may reside within the stroma well beyond the clinically involved cornea. This has been shown for fungal and *Acanthamoeba* infections of the cornea.[37] However, in cases of sterile or noninfective keratitis, lamellar surgery can be performed. Examples include ulceration occurring in Mooren's ulcer, Wegener's granulomatosis, polyarthritis nodosa, systemic sclerosis, and Stevens–Johnson syndrome.[38–40]

The surgical steps for lamellar keratoplasty are shown in Figure 50.6.

1. *Preparation of recipient cornea*: For lamellar keratoplasty the recipient cornea is dissected first. The extent and depth of dissection are designed to remove all affected corneal tissue while preserving as much healthy host tissue as possible. The limit of the area to be resected is first defined by either a circular trephine or a free hand using a sharp blade or diamond knife. This incision is then deepened to the required depth in one quadrant of the cornea or sclera to permit a lamellar dissector to be introduced parallel to the surface of the cornea (Fig. 50.6, A). Lamellar dissection is then carried out, undermining the edges at the margin of the resected tissue and approaching the thinnest or perforated area last. When the dissection is complete the lamellar flap is carefully grasped with forceps and peeled off (Fig. 50.6, *B*).
2. *Donor button preparation*: For donor button preparation a whole globe is preferred. If using a corneoscleral rim, we can use an artificial chamber to facilitate donor cornea preparation. A small incision of appropriate depth is made near the limbus. The graft material is cut so that thickness of donor material exceeds the depth of the recipient bed. A blunt lamellar dissector is introduced through this incision and a plane of cleavage is obtained. The dissection is completed by gently moving the spatula from side to side within the cleavage plane (Fig. 50.6, *C*). When the dissection is complete, a trephine of suitable size is used to cut the graft. In most circular grafts, a donor corneal button that is 0.5 mm larger than the recipient is used to avoid wound tension.
3. *Suturing*: The graft is then sutured into the lamellar bed with interrupted 10-0 nylon sutures (Fig. 50.6, *D*).

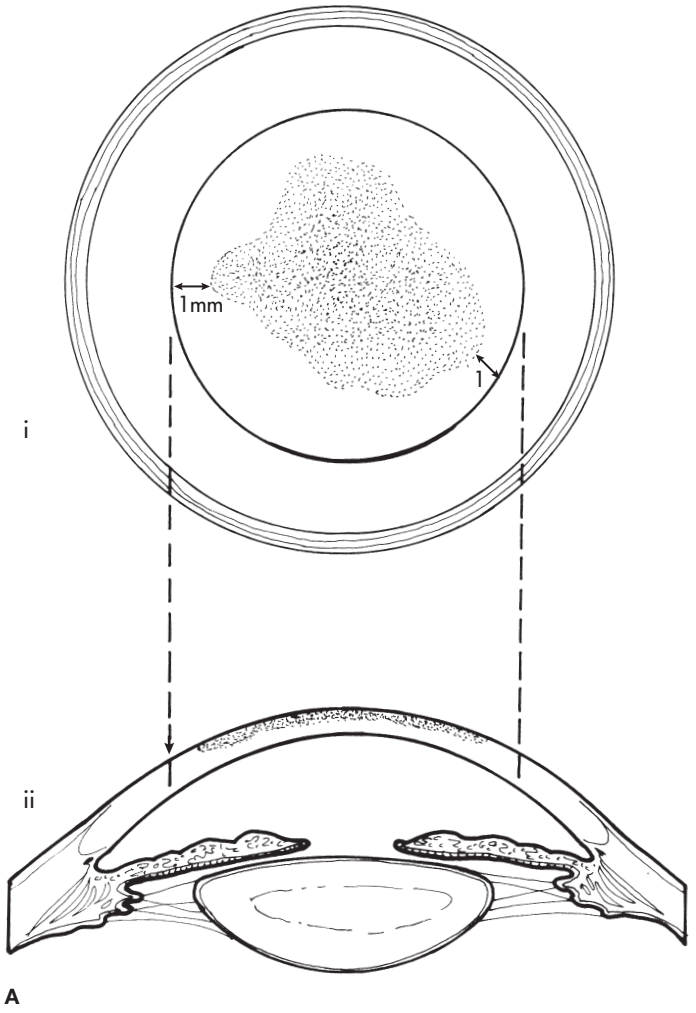
Lamellar keratoplasty offers several advantages over a PKP in eyes with active inflammation.

- A lamellar keratoplasty permits the preservation of the maximum amount of host tissue and adds to the thickness of the cornea. This may reduce the risk of recurrent perforation if the corneal melting process reactivates.
- As the endothelium is not transplanted, visually devastating endothelial immune rejections do not occur, and stromal rejections are rare.
- If perforation has not yet occurred, a lamellar graft is essentially an extraocular procedure, thus avoiding complications of intraocular procedures such as cataract and endophthalmitis.
- Because the quality of the donor endothelial cells is not an issue with lamellar keratoplasty, donor corneas deemed unsuitable for PKP may often be used.
- Lamellar keratoplasty serves as a stop-gap measure to stabilize the eye, giving it a chance to quiet down before a vision-restoring PKP is performed at a later time. Lamellar grafts are thus useful in the treatment of severe corneal melts, not only by providing structural support but also by buying precious time until systemic immunosuppressive medications have a chance to halt collagenolytic corneal breakdown. However, the procedure is technically more difficult because the inflamed stroma is soft and fragile and requires careful handling. Furthermore, the interface scarring will be a problem if the dissection plane is not uniform.

POSTOPERATIVE MANAGEMENT

The postoperative management of therapeutic keratoplasty is as challenging as the surgical procedure. One must pay attention to the following important issues:

1. *Prevent recurrence of infection*: Continue anti-infective therapy postoperatively in all cases where surgery has been performed for active infectious keratitis. Selection of the most appropriate antimicrobials and the duration of the therapy will depend on the pathogen. In cases where etiological diagnosis could not be made before PKP, histopathology and microbiology evaluation of the excised button can be helpful in guiding



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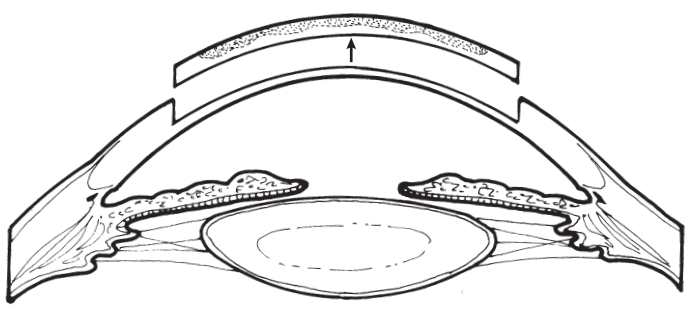

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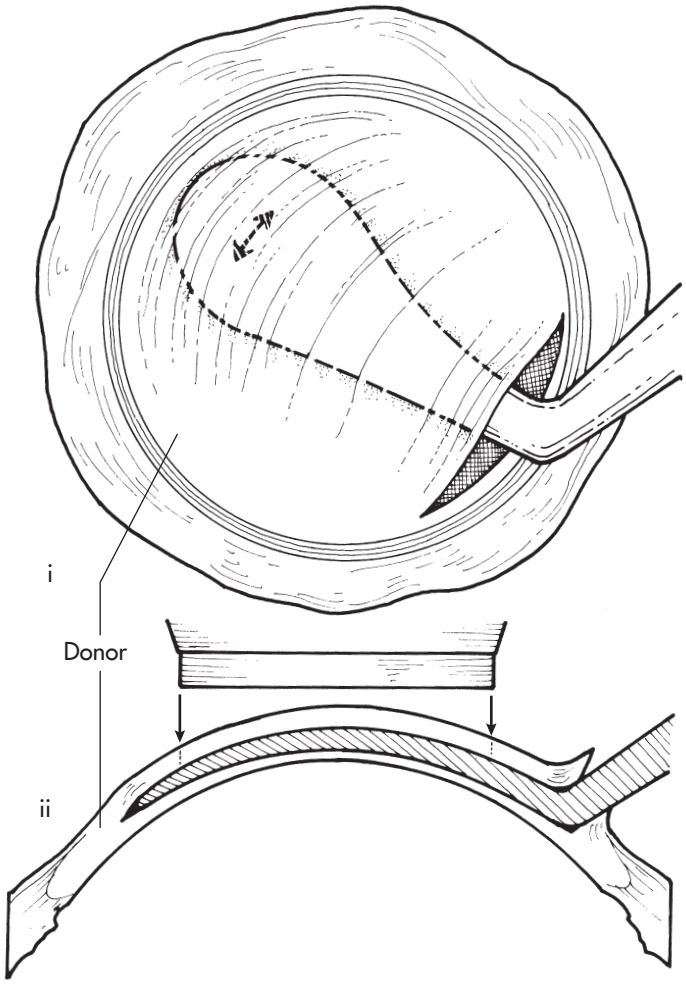

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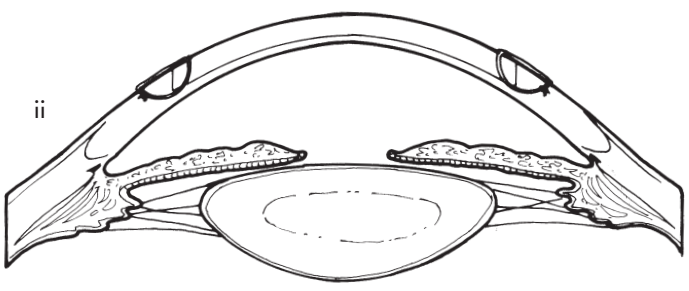

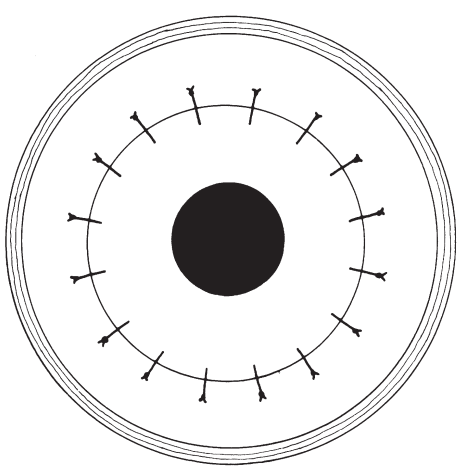

D

therapy. In general, cases with fungal and *Acanthamoeba* infection require more prolonged therapy to prevent recurrence of infection.

2. *Promote re-epithelization and protect corneal epithelium*: Epithelial integrity is very important for the success of corneal transplantation. This becomes critical in therapeutic keratoplasty because the surgery is performed in an inflamed eye. Unless absolutely essential, avoiding epithelial-toxic agents in the postoperative period is appropriate. Nonpreserved tear substitutes are used to treat epitheliopathy. Paramedian tarsorraphy and punctal plugs can be of great help in managing epitheliopathy in difficult situations.
3. *Control of inflammation*: The use of corticosteroids after therapeutic keratoplasty for infective keratitis is controversial. Since most antibacterial drugs are bactericidal, we believe corticosteroids can safely be used in keratoplasty for bacterial keratitis. In contrast, in fungal and *Acanthamoeba* keratitis corticosteroids must be used with extreme caution. One must start corticosteroids only after being sure of eradication of infection. In noninfective indications, both topical and systemic corticosteroids can be started safely immediately after the surgery; however, one needs to monitor epithelial healing.
4. *Intraocular pressure*: Since therapeutic keratoplasty is being done on an inflamed eye, we may often face aggravation of inflammation with consequent rise in intraocular pressure. Other factors such as large diameter graft and formation of peripheral anterior synechiae may further increase the risk of postoperative glaucoma. It is therefore very important to monitor and control intraocular pressure in the postoperative period.

The general guidelines for postoperative management of keratoplasty for infective keratitis are shown in Box 50.2.

BOX 50.2 GUIDELINES FOR POSTOPERATIVE MANAGEMENT OF CORNEAL TRANSPLANTATION

Bacterial keratitis

Antibiotic with most sensitivity given hourly and topically
Combination therapy or a broad-spectrum antibiotic sensitivity is unknown
Topical corticosteroids—every 1–2 h initially
Cycloplegics
Antiglaucoma medication, if intraocular pressure is elevated

Fungal keratitis

Topical antifungals—every hour initially
Systemic antifungals—oral ketoconazole 200 mg two times daily initially
Topical nonsteroidal anti-inflammatory drugs
Corticosteroids—only under extremely special conditions in which removal of the entire infected area is ensured
Cycloplegics

***Acanthamoeba* keratitis**

Topical amoebicidal drugs—every 1–2 h
Topical corticosteroids given judiciously
Cycloplegics

No organism in corneal scraping

Based on microbiologic and histopathologic report of half corneal button, an appropriate antimicrobial may be used

In conclusion, PKP has achieved a definitive place in the therapeutic armamentarium of infectious keratitis and other noninfective keratitis characterized by progressive thinning and perforation. Although the results are not encouraging in patients with active cases, judicious patient selection, careful planning of surgical technique and appropriate follow-up care can enhance the chances of a successful outcome.

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51 Intraoperative complications of penetrating keratoplasty

Jason S. Rothman, Juan Carlos Abad, Ernest W. Kornmehl

Most intraoperative complications of a penetrating keratoplasty (PKP) can be avoided if meticulous attention is given to each step of the procedure and the surgical plan is reviewed prior to surgery.

ANESTHESIA

In the majority of cases, regional anesthesia using either a retrobulbar block or a peribulbar with lid block can be performed safely under monitored anesthesia care.[1] Possible complications of retrobulbar anesthesia include globe perforation, orbital hemorrhage, and optic nerve trauma. In rare cases, inadvertent intradural injection can be associated with seizures, respiratory arrest, and brainstem anesthesia. Inadvertent intravenous injection may result in cardiac arrhythmias. Preoperative assessment identifying eyes with a posterior staphyloma is important, given their increased risk of scleral perforation.[2] The risk of an orbital apex injury is lower with peribulbar anesthesia, although the risk of scleral perforation persists.[3] General anesthesia is indicated for patients with a higher risk for a choroidal hemorrhage, those with a ruptured globe, or other circumstances such as young age or mental impairment.

FIXATION RING

The use of a fixation ring to stabilize the globe is common in pediatric patients (due to their elastic sclera), aphakic eyes, or in eyes rendered aphakic during the operation. The fixation ring helps prevent scleral collapse and facilitates intraocular manipulation and suturing of the donor cornea. The fixation ring may also induce unwanted astigmatism.[4]

Typically, an 18–20 mm Flieringa ring is fixated to the episclera overlying the pars plana with radial sutures passed from the periphery toward the limbus. Although rare, the sclera may be perforated creating a retinal hole. If a perforation is detected, cryotherapy should be applied and the patient observed carefully in the postoperative period. Bleeding in the angle may occur if the ciliary body is perforated, although this usually resolves within a few minutes.

DONOR CORNEA DAMAGE

The donor cornea needs to be handled with extreme care. While some surgeons wait to trephine the donor tissue until after preparing the recipient bed, in our opinion it is preferable to prepare the donor button prior to trephination of the host cornea. Then, if there is a complication during the preparation of the donor tissue, the surgery can be aborted and postponed until another donor cornea is available. The donor tissue should be centered with the endothelial side facing up and then cut in one pressing stroke with the trephine. Unnecessary manipulation increases the risk of endothelial cell loss. A sharp single-use trephine is preferred, as a dull trephine can detach Descemet's membrane (Fig. 51.1). The trephined graft should be kept on the Teflon block and covered with storage media and viscoelastic to help avoid desiccation. We recommend placing a plastic cover over the donor button for further protection while the surgeon is preparing the host corneal bed. The donor corneal button should be carefully brought to the surgical field on a Paton spatula, carried over the cupped hand of the surgeon.

Layering dispersive ophthalmic viscosurgical products over intraocular structures and the endothelial surface of the donor prior to suturing the donor button will help prevent endothelial damage.[5,6] The combination of Viscoat and Healon may be more protective against endothelial cell loss than Healon alone.[7]

COMPLICATIONS DURING TREPHINATION

For most PKP procedures, the donor button is oversized by 0.25 mm to improve coaptation and decrease the risk of glaucoma.[8,9] When the donor cornea is cut endothelial side up with a trephine, it measures approximately 0.25 mm smaller in diameter than a host cornea cut from the epithelial side with the same size trephine.[10] Albeit unusual, the trephines may be accidentally reversed and the smaller trephine used to cut the donor. If the recipient cornea has not been trephined or is partially trephined (without entrance into the anterior chamber), the host cornea can be trephined using a trephine

Figure 51.1. Localized area of corneal edema at the 11 o'clock position resulting from Descemet's membrane detachment.

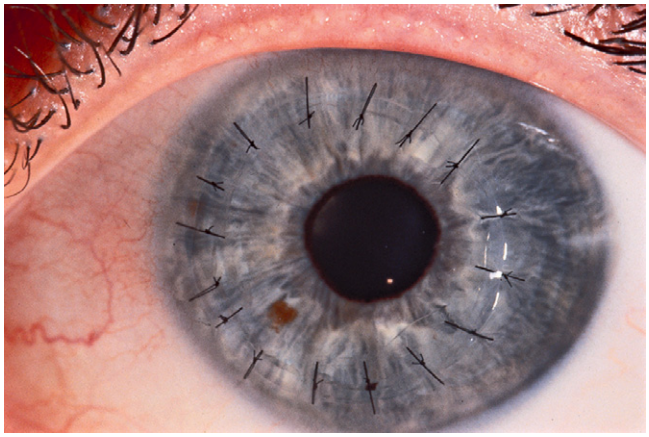

Figure 51.2. Nasally decentered graft in a patient undergoing penetrating keratoplasty for keratoconus.

0.25 mm smaller than the prepared donor button. If the host has already been trephined, the smaller button must be carefully sutured in place. The surgeon must ensure that there is no leak at the end of the procedure and that the hyperopic shift is taken into account by increasing the power of the intraocular lens by 2 or 3 D. The tighter sutures required to secure the smaller graft may deform the trabecular meshwork and increase the risk of postoperative glaucoma.[8] Should this complication occur, the graft can be replaced by an appropriate-sized graft at a later date.

Trephination of the host cornea should be centered on the geometric center of the cornea to ensure that the donor tissue is equidistant from the vascularized limbal tissue. A small adjustment can be made for eccentric pupils. When using a vacuum trephine, care must be taken to prevent the trephine from slipping, which may result in an eccentric graft (Fig. 51.2). If a handheld trephine is used, adequate counter-traction should be applied to the globe or ring to avoid eye rotation during trephination. Eccentric trephination of the host cornea may result in increased postoperative astigmatism.[11,12] If the surgeon recognizes the eccentric placement of the trephine prior to entering the anterior chamber, a larger trephine with proper centration may be used. If the host cornea is trephined with a larger-size trephine than originally planned, the size of the previously prepared donor button needs to be taken into account as previously described.

Occasionally, the anterior chamber is entered in a very asymmetric fashion during trephination, perforating the cornea in one quadrant and barely scratching the surface in the opposite quadrant. This is caused by failure to align the trephine perpendicular to the recipient corneal plane. The dissection must then be completed using scissors with no or minimal grooving of the host bed. This can lead to poor wound apposition and irregular astigmatism.

If the patient's cornea is highly vascularized, there may be bleeding during epithelial debridement or trephination. Measures to counteract this include partial trephination with delayed entry into the anterior chamber to allow time for clotting, using topical neosynepherine to induce vasoconstriction, and preoperative photothrombotic occlusion of the corneal vessels using corneal argon laser photocoagulation (CALT).[13,14] It is preferable to use the interrupted suture technique in vascularized corneas; this allows for selective postoperative suture removal from one region of the graft without altering wound integrity in other areas.

Descemet's membrane can easily be stripped from the overlying stroma of the host cornea during blade or scissors entry into the anterior chamber (Fig. 51.3, *A–C*) and inadvertently left behind.[15,16] This typically occurs if the anterior chamber is not entered with the trephine and the scissors remain above Descemet's membrane during excision of the corneal button. The iris should be thoroughly inspected with forceps or a cellulose sponge to ensure that Descemet's membrane was removed. This is more common with edematous corneas or corneas with a thickened Descemet's membrane. After transplantation, this may result in a pseudoanterior chamber, with aqueous between the retained Descemet's membrane and the donor cornea (Fig. 51.4). If there is apposition of the retained Descemet's membrane to the graft endothelium, the graft will likely fail. A retained Descemet's membrane may become opacified over time and require removal. A neodymium:YAG laser may be used to create a central opening in the membrane.[16]

IRIS DAMAGE

The iris may be damaged during trephination, during entry of the super-sharp blade into the anterior chamber, or during excision of the corneal button with scissors. This is more common in thin or perforated corneas. Some surgeons advocate making a paracentesis and injecting viscoelastic into the anterior chamber prior to trephination in order to protect the intraocular structures.[17,18] To reduce the risk of iris trauma in the setting of a ruptured globe, the anterior chamber should be reformed with viscoelastic and the corneal wound sealed with cyanoacrylate glue prior to trephination.[19,20] Some surgeons have had success using tissue adhesive to glue a custom polymethylmethacrylate hard contact lens over a corneal perforation to facilitate trephination.[21]

The authors prefer to perform a partial trephination, enter the anterior chamber focally with a blade, fill the chamber with viscoelastic, and remove the corneal button with scissors. When completing the dissection of the recipient cornea with scissors, it is preferable to maintain slight upward pressure to minimize the risk of iris and/or lens damage. Some surgeons prefer a slightly beveled cut, creating a posterior wound ledge, which helps to facilitate a watertight closure. Other surgeons cut the host cornea perpendicular to the corneal surface to minimize postoperative astigmatism.

Should inadvertent damage to the iris occur, this should be repaired with a 10-0 polypropylene or nylon suture. Iris bleeding can be controlled with viscoelastic, fine-tipped underwater diathermy, topical application of 1:10000 epinephrine or 1:100 thrombin on a soaked cellulose sponge.

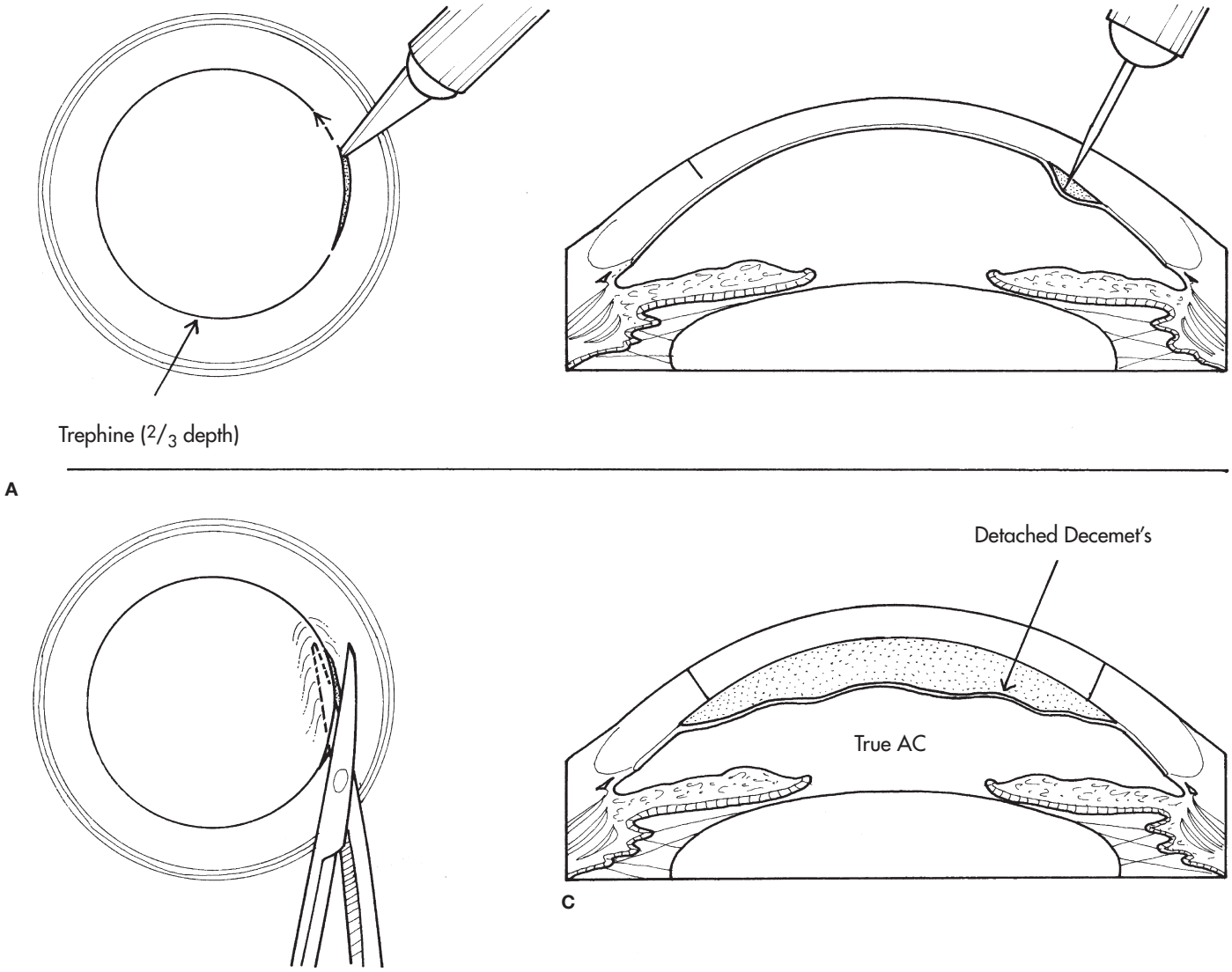

Figure 51.3. *A*, After trephination, a sharp blade incompletely enters the anterior chamber. *B*, A false anterior chamber is created. *C*, Scissors insertion further enlarges the chamber, resulting in retained Descemet's membrane.

LENS DAMAGE

Corneal trephination in a phakic eye is best performed with the pupil constricted prior to surgery with pilocarpine. If the anterior lens capsule is perforated during trephination, a cataract will develop, requiring an extracapsular cataract extraction. Inadvertent anterior capsular damage may also occur with the super-sharp blade or scissors. It may be prudent to take axial length measurements before a phakic PKP. If this complication occurs, the power of the intraocular lens can be estimated. Other alternatives include using a standard +21.00 D lens or to defer lens implantation to a later date. If the lens is not removed, the flocculent cortical material will likely result in chronic inflammation and elevated intraocular pressure.

INTRAOCULAR LENS EXPLANTATION

If a closed-loop anterior chamber intraocular lens (ACIOL) is present at the time of surgery, it should be removed and be replaced. If it is not removed, the graft will likely fail.[22,23] The IOL haptics should be cut from the optic and carefully threaded out from their adhesions in the angle to avoid bleeding or disinsertion of the iris.[24] If an iridodialysis occurs during removal of the haptics, it must be repaired. Haptics that are embedded in the angle and unable to be slid free from their attachments may be trimmed and left in place. Options for lens exchange include placement of a sulcus-fixated posterior chamber IOL, a scleral suture-fixed posterior chamber IOL, an iris-fixated posterior chamber IOL, a flexible open-loop anterior chamber IOL, or an iris-claw lens.[25–27] If an ACIOL is implanted, the haptics of the new IOL could induce further peripheral anterior synechiae (PAS), resulting in elevated intraocular pressure. If there is a shallow anterior chamber or insufficient iris tissue, a posterior chamber IOL would be the best choice.[28]

POSTITIVE VITREOUS PRESSURE

When the cornea is removed, the mechanical barrier to vitreous expansion is lost. If the vitreous swells, it may cause the anterior

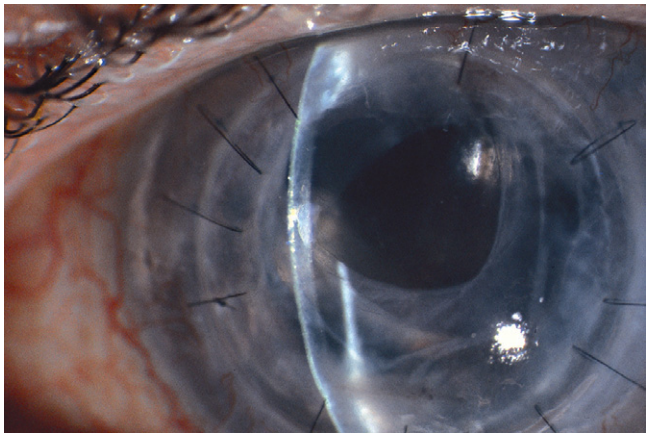

Figure 51.4. Retained ring of the host's Descemet's membrane at the graft periphery. The central cornea remains clear.

chamber to shallow with protrusion of the lens. Increased posterior pressure will significantly increase the risk of complications during a combined PKP and cataract surgery. The risk of positive vitreous pressure can be reduced by mechanical, medical, and surgical methods to decrease intraocular pressure.[29] Preoperative preparation to reduce intraocular pressure in these cases cannot be overemphasized.

Preoperative continuous pressure on the globe can mechanically reduce vitreous pressure. This may be carried out manually,[29,30] with a Honan balloon,[31] or with a super-pinky. An additional measure is to position the patient in reverse Trendelenburg, decreasing the orbital venous pressure. Medically, vitreous pressure can be reduced with a diuretic such as mannitol. Mannitol should be administered intravenously over 1–2 min while prepping the patient. Its greatest hyperosmotic effect will be about 10–15 min after administration, roughly the time when the eye will be open. Mannitol is dosed according to a patient's weight and medical status; caution needs to be exercised in patients with congestive heart failure. For a combined PKP and cataract extraction, we advocate using a Honan balloon for 20 min at 30 mmHg before starting surgery and intravenous mannitol administered just prior to draping the patient.

If positive vitreous pressure is encountered intraoperatively, without evidence of a suprachoroidal hemorrhage or effusion, it is commonly due to pressure transmitted from the lid speculum. This is very common with a wire lid speculum; a Schott lid speculum or Jaffe lid retractors do not exert as much pressure on the eye. Lifting or repositioning the speculum, or providing anterior traction on the globe with the fixating sutures of the scleral support ring should be performed first. If the vitreous face and posterior capsule are intact, some surgeons advocate performing a limited pars plana vitrectomy with an automated vitrector. Others recommend performing a pars plana vitreous aspiration with an 18-gauge needle attached to a 3 mL syringe to locate and tap a vitreous lake,[32] although with an open globe this is risky and may generate more posterior pressure.

CATARACT EXTRACTION

When a patient requires cataract surgery and a PKP, many surgeons prefer to perform these together as a triple procedure. If the cataract is removed using the open sky technique, reducing posterior pressure preoperatively is critical. During capsulorrhexis, positive vitreous pressure can make the advancing flap tear toward the lens equator. Pressing on the center of the crystalline lens with a cellulose sponge may facilitate the maneuver. The lack of a closed system and anterior bowing of the posterior capsule will hamper aspiration of cortical material. If the posterior capsule is torn and the vitreous face is violated, an anterior vitrectomy should be performed using an automated vitrectomy device. A guillotine-type cutter is preferred, as this will minimize vitreous traction. The surgeon should ensure that there is no vitreous in the anterior chamber or coming through the capsular tear.

As described above, when capsular support is inadequate for the placement of a posterior chamber IOL into the capsular bag or within the ciliary sulcus, an open-loop ACIOL, scleral suture-fixed posterior chamber IOL, or iris-sutured posterior chamber IOL are appropriate alternatives. There is debate in the literature about which alternative has the best outcome.[26,33–36]

SUPRACHOROIDAL HEMORRHAGE

A suprachoroidal hemorrhage has the potential to be the most visually devastating intraoperative complication during a PKP. The surgeon must always be aware of this possible complication and be ready to treat it immediately. Factors that predispose a patient to have a suprachoroidal hemorrhage include hypertension, atherosclerosis, inflammation with vascular congestion, intraoperative tachycardia, and long-standing glaucoma.[37] Valsalva maneuvers during surgery may also lead to an expulsive hemorrhage. Eyes undergoing a PKP are at an increased risk of an expulsive hemorrhage due to sudden globe decompression with an 'open sky' communication with the atmosphere (Fig. 51.5, *A–C*). During a suprachoroidal hemorrhage, the intraocular contents may extrude without resistance.[38]

If a suprachoroidal hemorrhage is recognized, the surgeon should be proactive and the open sky wound be tamponaded as quickly as possible with a finger or, if available, a Cobo temporary keratoprosthesis.[38–40] At the same time, a posterior sclerotomy into the suprachoroidal space (5–15 mm from the limbus) needs to be performed to drain the blood and decrease the forward pressure on the vitreous, retina, and lens. Several sclerotomies may be needed in four quadrants, usually beginning temporally, unless the clinical situation dictates otherwise. They need to be large enough for the expression of blood and clots, and should be left open to drain blood into the subconjunctival space. The prognosis depends on the status of the remaining intraocular contents. If anatomical reattachment is achieved, the potential visual acuity may be limited due to the disorganization of the blood supply of the outer retina. Immediate recognition and prompt treatment of a suprachoroidal hemorrhage are critical in managing this devastating complication.

SUTURING

When a running suture is used, the suture may break. Given this possibility, some surgeons advocate using a double-armed suture which, although technically more difficult, allows suturing in a direction opposite of the first when needed. Another option is to splice a new nylon suture to the broken suture and continue with the new needle. If the suture breaks near the needle, there may be adequate length allowing the spliced knot to be pulled

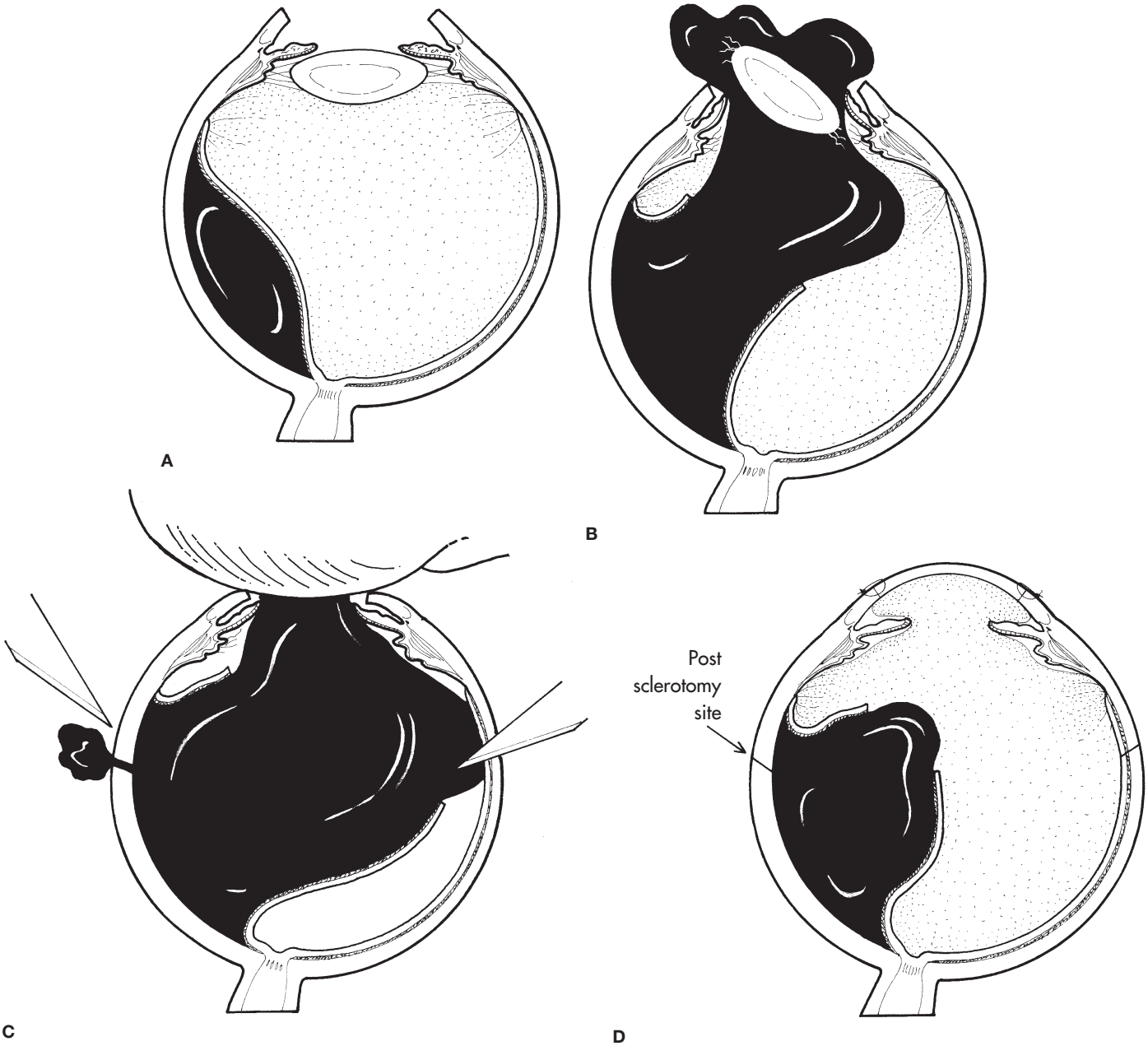

Figure 51.5. *A*, Choroidal detachments developing during keratoplasty often are seen through an operating microscope. *B*, Expulsive choroidal hemorrhage occurring after removal of diseased cornea. *C*, Closure of wound with fingertip and posterior sclerotomy for expulsive choroidal hemorrhage. *D*, Cornea sutured in place, normal anterior segment architecture restored, and posterior sclerotomy left open.

through, resulting in one rather than two knots. If two knots are required, the first spliced knot should be buried. The suture should then be tightened and adjusted in two sections.

The wound must be water tight and checked after reforming the anterior chamber with balanced salt solution. If a leak is noted (Fig. 51.6, *A–C*) because of a loose running suture, the knot should be exteriorized, slack taken out of the suture, and the suture cut and retied. Additional interrupted sutures may also be placed if necessary.

Most complications during keratoplasty can be prevented with meticulous attention to detail. If a technical error occurs, it can usually be corrected at the time of the initial procedure.

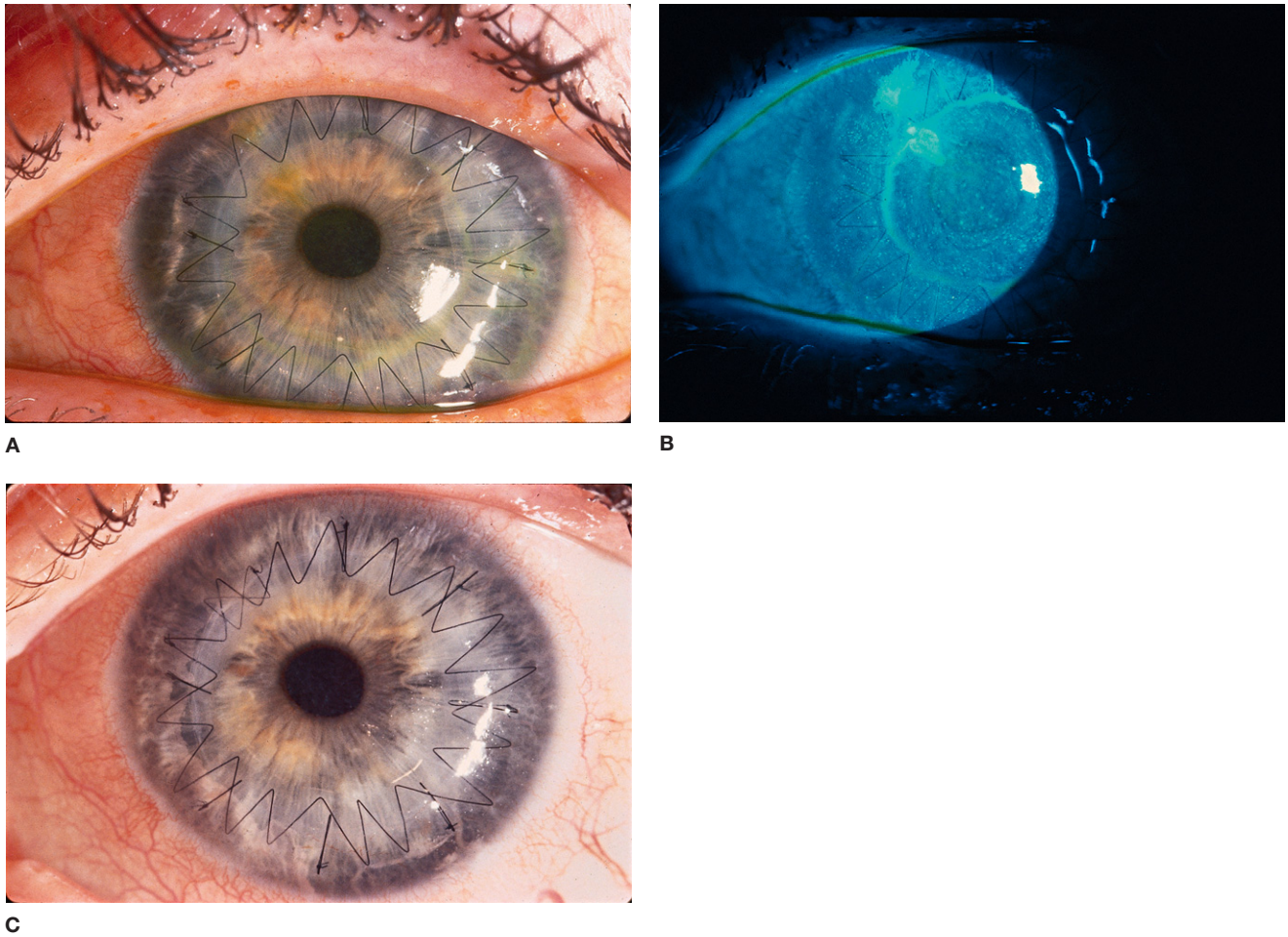

Figure 51.6. *A*, Wound leak after graft for corneal scar. *B*, Positive Seidel test under cobalt blue light. *C*, Wound leak requiring an additional suture to seal leak.

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52 Penetrating corneal transplantation: early postoperative management

Jeremy E. Levenson

While many surgeons are comfortable with the technical aspects of performing corneal transplants, it is the appropriateness of the care provided in the postoperative period that determines the outcome of corneal transplant surgery.[1] Identifying the minor and the major complications that can and often do occur in the postoperative period can make the difference between surgical success or failure.

POSTOPERATIVE CARE

There are probably as many postoperative care regimens as there are surgeons performing corneal transplants. Whatever the specific approach taken, the following factors must be monitored in the early postoperative period: signs of infection, evidence of a wound leak, thickness of the graft, status of the corneal epithelium, depth of the anterior chamber, intraocular pressure, degree of inflammation, presence of synechiae, and pupillary block.

SCHEDULE OF EXAMINATIONS

Patients are examined on the first postoperative day, an opportunity to discover any major surgical complications. During this examination, the patient should be questioned about the presence and degree of any pain experienced. The visual acuity should be determined, a careful slit-lamp examination undertaken, the intraocular pressure measured and, if possible, indirect fundoscopy performed. Based on the findings at this examination, the frequency of the visits for the next 1 or 2 weeks is decided. Even in an entirely uncomplicated case, the corneal epithelium will probably not be completely healed.[2] Because establishing complete corneal epithelialization is a major step in securing a clear corneal graft (as will be discussed in detail later), the patient should be seen frequently until this condition has been achieved. As soon as a stable state has been reached, a reasonable schedule of postoperative visits includes seeing the patient every 1 or 2 weeks for the first month and then every 2–4 weeks for the next 3 months. Because complications can develop between visits and their early treatment can be critical to successful surgery, patients are instructed to promptly report any change in the status of their operated eye, such as increased pain, redness, or decreased vision.

PATCHING

The surgical dressing is removed on the first postoperative visit. Many surgeons then continue full-time patching until the epithelial layer on the corneal transplant has completely healed. For most cases, this takes 1–3 days.[2] Although there is a trend toward not patching traumatic corneal abrasions, and at least one study found that patching does not speed healing,[1,3] the immediate postoperative transplant is anesthetic, and the protection of mild but effective pressure patching may be beneficial. The eye is protected in the longer term with eyewear during the day and a shield at night[4] for 2–3 months.

GRAFT THICKNESS

Most corneal grafts show some edema in the immediate postoperative period. This edema is manifested by increased corneal thickness with pachymetry readings exceeding 0.6 mm.[5] The amount of swelling is affected by the age of the donor, the death-to-preservation time, the amount of time preserved, the type of storage medium, the amount of surgical trauma, the nature of the condition requiring transplantation, the status of the endothelium and epithelium, and the intraocular pressure. The edema is caused by endothelial 'pump' dysfunction resulting from a combination of metabolic insult and actual endothelial cell loss. Epithelial edema may not be present because of the absence or thinning of the epithelial layer. Classically, corneal transplants in phakic eyes tend to have more endothelial cell loss than transplants in aphakic eyes, presumably because of the 'washboarding' effect of rubbing the donor button against the lens–iris diaphragm during surgery in the former.[5] The use of viscoelastic agents during surgery has removed this difference.[6] In the uncomplicated case, a gradual thinning of the graft should be anticipated, with most of the folds in Descemet's membrane gone by 2–3 weeks after surgery. Peripheral, circumferential folds may persist near the wound margin because of the compression of tissue by the corneal sutures and the use of an oversized donor. These folds tend to disappear with time or with removal of the corneal sutures. If there is normal endothelium on the patient's own cornea, longer-term thinning of a thicker than normal graft may occur

because of the gradual migration of endothelium from the recipient bed onto the donor graft.

MEDICATIONS

Routinely, corneal transplant patients receive topical steroid and antibiotic eye drops. On the evening of surgery and the following morning, if a significant amount of viscoelastic has been left in the eye or if there is a concern about the possibility of glaucoma, an oral carbonic anhydrase inhibitor can be administered, assuming no medical contraindications.[7] Starting on the first or second postoperative day, a topical steroid such as prednisolone acetate 1% or the equivalent can be prescribed four times per day and a topical antibiotic such as tobramycin 0.3% or fluoroquinolone two to four times per day. Combination steroid and antibiotic drops are popular but have the disadvantage of inflexibility because it is often necessary to use a steroid drop much more frequently than an antibiotic drop. In addition, many of these combination drops include neomycin, which can prove to be especially toxic to the unstable graft epithelium.[8] Some surgeons prefer to administer these drugs in ointment form. In the routine, uncomplicated case, the steroid drops are tapered after the postoperative inflammation is controlled, usually in 3–4 weeks. Typically in phakic grafts, by 2–3 months after surgery the steroid drops can be discontinued. In aphakic or pseudophakic eyes, where the complication of cataract formation is not a concern and intraocular pressure remains controlled, many surgeons continue a drop or two of topical steroid indefinitely in hopes of decreasing the long-term chance of graft rejection (Fig. 52.1). Use of steroids after surgery may vary greatly from case to case. In addition to the usual steroid side effects of cataract formation and secondary glaucoma, their effect on decreasing wound healing must be kept in mind.[9,10] Obtaining a wound of adequate tensile strength, especially in the elderly, is already a concern in corneal transplantation, and the intensive and prolonged use of steroids can exacerbate this problem. The steroidal effect on depressing local immunity can lead to opportunistic infection with bacteria and fungi, which are known to correlate with the development of crystalline keratopathy.[11] Still, until a good prospective study determines its relative value, low-dose, long-term steroid use in nonphakic patients is probably warranted. The use of topical antibiotics can be discontinued once the epithelial layer completely covers the cornea, typically in 3–4 weeks.

Many patients require frequent artificial tears to help stabilize and protect the delicate epithelium on the surface of the graft. If used more than four times per day, nonpreserved tears should be prescribed. If ointments are used, these too should be nonpreserved.

The use of topical cycloplegics is usually not routinely necessary. On occasion, a short-acting drug such as cyclogyl 1% or homatropine 5% can be used. Long-acting cycloplegics, such as scopalamine or atropine, limit the ability to manipulate the pupil pharmacologically, which can be necessary in the postoperative period to break synechiae. In addition, they have been implicated in the development of fixed, dilated pupils after surgery in eyes that have undergone corneal transplantation for keratoconus.[12] However, this cause has been seriously called into question by more recent studies,[13] and it seems more likely that the fixed, dilated pupil seen rarely after keratoplasty in keratoconus is the result of iris ischemia developing from posterior pressure.

Although not universally accepted,[14] the use of an antiviral is recommended for a patient with a history of herpes simplex keratitis (Fig. 52.2). Most surgeons use a drop of trifluorothymidine four or five times per day while steroids are being applied.[15] It must be kept in mind, however, that these agents are metabolic inhibitors and can only be effective if they are continuously present in adequate concentration. The studies that have been published concerning the prevention of recurrent herpes infections in patients using topical steroids used these agents in full dosage.[16] However, in full dosage these agents can be very toxic to the epithelium,[17,18] and, because they empirically seem to be effective in lower dosage, this trend will probably continue until studies to the contrary are presented. As soon as the steroid dosage has been decreased to one drop daily, the antiviral may be stopped. To avoid the toxicity of topical antivirals, oral acyclovir has been shown to be effective as prophylaxis against recurrent herpes simplex keratitis in patients receiving topical steroids after surgery.[19] Starting with an initial dose of 800–1000 mg in divided dosage, acyclovir can be gradually tapered over 12 months or more. Presumably, the newer oral antiviral agents, famcyclovir and valacyclovir, would be at least as effective.

ACTIVITY

Modern corneal transplant techniques have allowed early ambulation of the patient beginning on the day of surgery primarily by

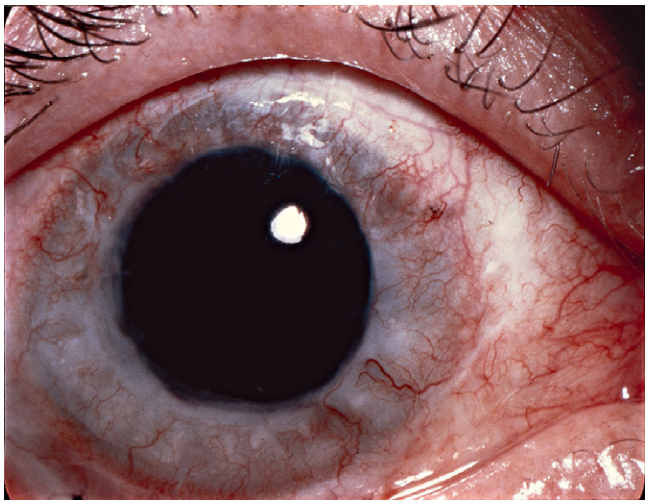

Figure 52.1. When a graft is placed in a vascularized bed, steroids must be continued indefinitely to prevent rejection.

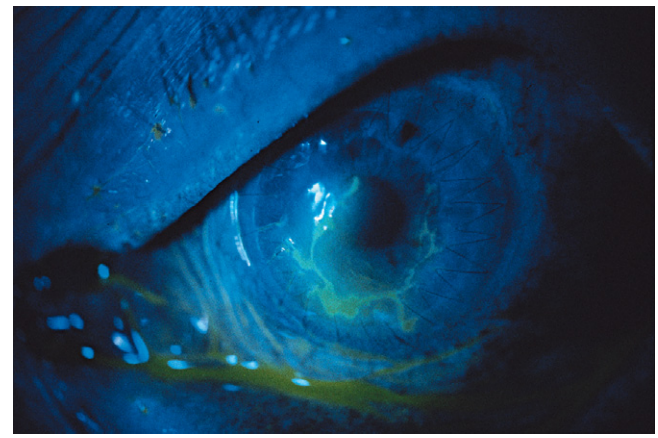

Figure 52.2. Recurrent herpes dendritic keratitis in a graft. This patient was given steroids without antiviral coverage.

producing wounds of sufficient integrity. Patients may resume taking care of their personal needs as soon as they have recovered from the effects of anesthesia. They should be reassured that the sutures holding their wound are sufficiently strong to permit them to return to the activities of normal living. Most wounds can withstand the stress of coughing, sneezing, and usually even vomiting. At the same time, patients must avoid a direct blow to the eye. Eye protection should be worn at all times, even when sitting at home. Protective eyewear usually consists of a sturdy pair of glasses during the day and a taped-on shield at night. This practice should be continued for the first 2–3 months after surgery. Patients should be instructed to avoid situations where there is a risk of trauma to the eye, such as large crowds, contact or racquet sports, skiing, and so forth. Heavy lifting or straining that could lead to increased intraocular pressure through the Valsalva maneuver or eyelid squeezing should be avoided for the first 2–3 months.

Patients should be made aware of the need to protect their eyes from potential sources of infection during the initial weeks after surgery. Wearing an eye patch until the epithelium is healed is part of this protection. Patients can have their hair washed, but this should be done with the head back so that the soapy water does not enter the eye. Bathing is permitted, but again dirty water should be kept out of the eye. As soon as the surface of the graft has fully epithelialized, usually by 2–3 weeks after surgery, these restrictions can be eased. During this same period, patients should be discouraged from working on their hands and knees in their garden and from swimming.

The amount of time a patient is away from work must be tailored to his or her individual situation and is determined in large part by the patient's type of work and the level of vision in the unoperated eye. In practice, most patients who are not engaged in heavy manual labor or do not work in a dusty, contaminated environment and who have adequate vision in their opposite eye can return to work as soon as their level of comfort permits, usually 1 week or less. For those who perform manual labor, 6–8 weeks of leave may be required. For those requiring the vision of the operative eye to be able to work, a number of months may be needed.

COMPLICATIONS IN THE EARLY POSTOPERATIVE PERIOD

Complications in the period after corneal transplantation can vary from the minor to the true ophthalmic disaster, resulting in the loss of the eye. The best chance for a successful outcome occurs with early intervention, so close and meticulous follow-up of the corneal transplant patient is essential. Recognition and treatment of the following complications, not necessarily in the order of frequency or potential severity, are discussed in this section: endophthalmitis and infectious keratitis, wound leak, epithelial defects, filamentary keratitis, synechia formation, hyphema, excessive iritis, pupillary block, glaucoma, vascularization, retained Descemet's membrane, and primary graft failure.

ENDOPHTHALMITIS AND INFECTIOUS KERATITIS

The risk of infection is inherent in the nature of corneal transplant surgery. Certain risk factors can, however, significantly increase the possibility of postoperative infection (Box 52.1).

Endophthalmitis can occur both immediately after and late in the course after corneal transplantation. The incidence, which has been reported to be between 0.1%[20] and 2%,[21] is low and similar to that of cataract surgery.[22] This is surprising because cultures taken from donor eyes before processing have been reported to be positive for contamination at a rate of between 12.4%[20] and 100%.[23] A wide variety of Gram-positive and Gram-negative bacteria and fungi have been isolated from cases of postkeratoplasty endophthalmitis.

Patients with endophthalmitis may report intense pain, lid swelling, marked conjunctival hyperemia, and hypopyon with even more corneal edema and clouding than typically found in the patient who has undergone cataract surgery.[22] At other times, the onset of endophthalmitis can be more insidious.[21]

Although no series has been reported to date in corneal transplantation, the laboratory diagnosis and treatment of endophthalmitis should probably follow the recommendations of the Endophthalmitis Vitrectomy Study Group,[24] with early vitreous aspiration followed by intravitreal antibiotics and possibly vitrectomy in nonresponding patients. Because the donor graft can be a potential source of infection,[25] all donor cornea-scleral rims should be cultured at the time of surgery. Information obtained from these cultures may provide a head start in choosing appropriate therapy should an infection develop after surgery. The prognosis for endophthalmitis after corneal transplantation has been very poor despite treatment.[21]

Given the high incidence of positive cultures from donor rims and the low incidence of actual postoperative infection, the surgeon not infrequently faces the situation 1 or 2 days after surgery of being informed that the rim culture is growing out a contaminant (most often *Staphylococcus epidermidis*, but occasionally a fungus). Having already seen the patient and believing that the postoperative course is uncomplicated, the surgeon is unsure how to proceed. Because most positive rim cultures do not translate into active infection,[22] in most cases, nothing more than continued observation is required.

BOX 52.1 RISK FACTORS FOR POSTOPERATIVE INFECTION PREOPERATIVE CONDITIONS

Keratitis sicca	Graft failure
Blepharitis	Previous herpetic keratitis
Acne rosacea	Ocular adnexa and lid abnormalities
Cicatricial conjunctival disease (ocular pemphigoid, alkali burns, and Stevens–Johnson syndrome)	Pre-existing corneal or external infection
	Systemic diseases (atopic disease, systemic immunosuppression, diabetes, rheumatoid disease)
Trichiasis	
Trachoma	
Intraoperative factors	
Contaminated instruments or solutions	Extensive tissue manipulation
Contaminated donor tissue or storage media	Aphakia
Postoperative factors	
Epithelial defects or severe punctate keratopathy	Wound dehiscence
Exposed or loose sutures	Corticosteroid use
Soft contact lens use	

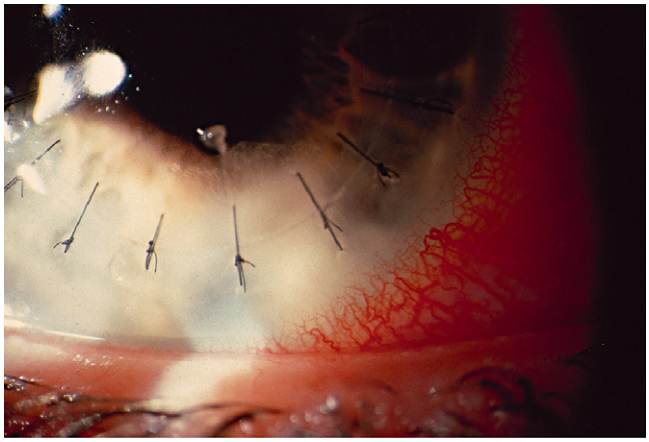

Figure 52.3. Fungal keratitis developing in the wound margin with a mass of hyphae extending into the anterior chamber.

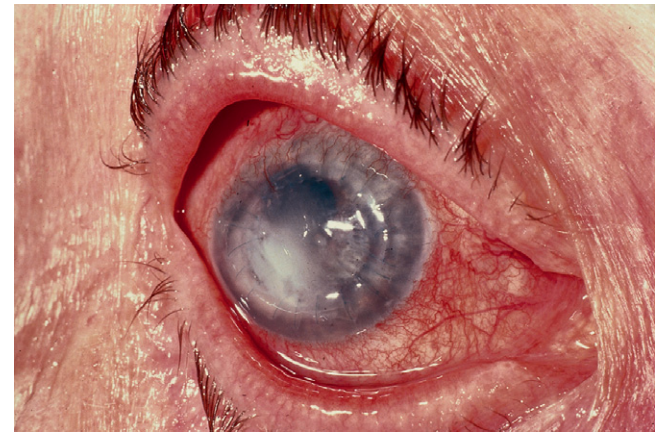

Figure 52.4. Neglected corneal ulcer that has led to perforation. Note the relatively mild inflammatory reaction resulting from the use of topical steroids.

BOX 52.2 ORGANISMS ISOLATED FROM POSTKERATOPLASTY ULCERS

Staphylococci coagulase-negative
Staphylococcus aureus
Streptococcus pneumoniae
β-Hemolytic streptococci
α-Hemolytic streptococci
Corynebacterium diphtheriae

Fungi

Candida species
Other fungi

Gram negative

Pseudomonas aeruginosa
Serratia marcescens
Klebsiella species
Proteus mirabilis
Haemophilus species
Moraxella species
Escherichia coli
Bacillus species

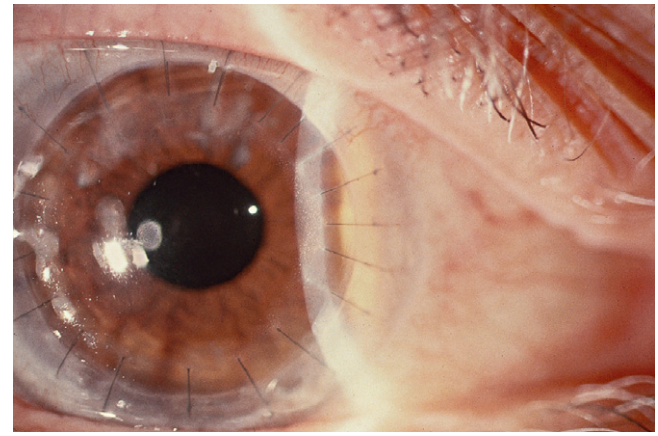

Figure 52.5. Minute white dots, sometimes referred to as Kaye dots, frequently develop in the epithelium in the base of the furrow near the wound margin. They are best seen here in the slit-beam light, between the 2 and 4 o'clock positions.

Infectious keratitis has been reported to develop after corneal transplantation with an incidence between 1.8%[26] and 4.9%[27] in the USA. Preoperative conditions that can lead to corneal infections are listed in Box 52.1.

Most agents that cause postkeratoplasty infectious keratitis are Gram-positive bacteria, but the full spectrum of agents associated with corneal ulceration (Fig. 52.3) are described in Box 52.2.[27–29] The prognosis for corneal graft infections that have progressed beyond a localized stitch abscess is very guarded.[27,30] Scarring or the associated irregular astigmatism even when the scarring is not directly in the visual axis can dramatically limit the final vision. Corneal perforation, wound dehiscence, and endophthalmitis occur more frequently than usually seen with corneal infections in otherwise normal corneas (Fig. 52.4).[28] Regrafting, either on an emergent or on an elective basis, is a common outcome.[31] Whether and how to modify steroid use in the setting of infection can be a quandary. Steroids may help prevent graft rejection and preserve graft clarity, or at least prevent or limit vascularization of the graft bed, allowing a better prognosis for a regraft. On the other hand, the immunosuppression may potentiate infection. Most treating physicians compromise by decreasing the steroid dosage but not stopping it, at least initially.

Other white lesions can develop in the graft after surgery, which are noninfectious in origin. The most common are the myriad of tiny, discrete, white, nonstaining dots that frequently appear in the epithelium in the furrow at the base of the ridge created by the corneal sutures (Fig. 52.5). These dots have been shown to be composed of degenerating epithelial cells.[32] These appear several weeks after surgery and usually persist until the sutures are removed or until the cornea assumes a more normal contour.

Of greater significance are the white to grey-white infiltrates that occasionally appear along the corneal sutures early in the postoperative course. They seem to be an immune response to the suture material or to a substance on its surface. Unlike the usual isolated stitch abscess, these infiltrates are minute foci of white cells located along many or all of the suture loops. Affected eyes tend to be moderately inflamed. The epithelium, unlike in the situation found with a stitch abscess, is usually intact over the sutures. Treatment consists of increasing the steroid dosage to a drop every 1–2 h until the inflammatory response is brought under control followed by a slow taper.

WOUND LEAK AND SUTURE PROBLEMS

Wound leaks and suture problems are uncommon with modern suturing techniques but often are related when they do occur. A patient with a broken running 10-0 nylon suture in the immediate postoperative period before there is significant wound healing will need to have the suture repaired. This should be completed quickly, even if there is no leak, because of the great risk of further unraveling of the suture with loss of the anterior chamber or the development of graft over-ride. The repair should be performed under the microscope in a sterile setting because of the danger of infection. A new segment of 10-0 nylon suture must be added, making several bites across the wound. It is then tied to both ends of the broken suture that have been withdrawn a loop or two on either side to provide enough suture for tying. This maneuver is made easier if the new suture is passed for several bites before the original suture is disturbed to lessen the chance of anterior chamber loss, if it is still formed. Before tying the final knot, tension on the sutures is adjusted appropriately. A broken running suture occurring a few months after surgery, as from mild trauma, does not necessarily need to be repaired. If it shows signs of loosening, the suture can be protected from the movement of the eyelids by a bandage soft contact lens. A broken interrupted suture can usually be removed without replacement unless there is evidence of wound gape.

A wound leak may be found on the first or second postoperative visit even with an intact suture or sutures, particularly when an attempt has been made to avoid an excessively tight suture. Checking for wound leaks is an important part of the postoperative examination and is carried out by placing a concentrated drop of fluorescein over the graft wound. A positive Seidel test occurs when a rivulet of fluorescing yellow-green dye is seen emanating from the wound under the cobalt blue light. This leak may be either from the wound itself or along a suture track. If the anterior chamber is of normal or near-normal depth, the patient can be treated with mild pressure patching or a bandage soft contact lens for a few days. Many small leaks will spontaneously close, particularly those around sutures, as the epithelial plug grows into the wound. If there is a running suture in place, a persistent leak can often be managed with a suture adjustment, as described above, tightening the suture in the area of the leak and distributing the released suture tension evenly about the wound. Occasionally, if the entire running suture seems too loose, the suture can be saved by tightening the suture all around and leaving one large loop of excess suture material. This loop is then attached to the peripheral cornea near the limbus with a single suture of 10-0 nylon whose knot is buried. A mattress suture of 10-0 nylon has been described that can be placed as a compression suture about a leaking suture tract but should rarely be necessary. A leaking interrupted suture tract can be resolved by removing the suture and replacing it if needed. Interrupted sutures can always be added to close the graft wound if needed. These can be placed under sterile conditions, taking great care that the side of the needle does not cut a running suture, if present.

If the anterior chamber is very shallow, the wound leak should be repaired promptly, depending on the level of inflammation, limiting formation of synechiae. A totally flat chamber requires an immediate wound repair.

EPITHELIAL DEFECTS

Obtaining an intact, stable epithelial surface covering the fresh transplant is the first step in obtaining a successful outcome of surgery. Unfortunately, a number of factors operate to interfere with this goal. First, the donor cornea may have had epithelial sloughing during the period from death to preservation, particularly if the eyes were not taped shut and cooled with eye bags while waiting for the corneas to be harvested. Second, depending on the storage media and the length of storage time, epithelial viability can be compromised.[33] Third, intraoperative trauma, either mechanical or through drying under the bright microscope light, can lead to further loss. For these and other reasons, many patients will not have an intact epithelial layer when seen for their first postoperative visit.[34]

Delayed or incomplete epithelialization of the corneal transplant can lead to potentially disastrous results (Fig. 52.6). After approximately 1 week, there can be damage to Bowman's membrane which, even if epithelialization occurs later, may leave the transplant with superficial haze and scarring. With a further delay, melting of the stroma begins to result in a graft with a depressed scar, which is even more optically disturbing. If the problem is still not corrected, continued melting will lead to perforation, necessitating additional surgery. In addition, epithelial defects are often the precursor of infection. Active and aggressive treatment of all epithelial defects, whether present initially or developing during the postoperative period, is mandatory.

Prevention of epithelial problems begins in the preoperative period. Lid problems, such as entropion, ectropion, trichiasis, lagophthalmos, or blepharitis, should be corrected. If tear production is deficient, punctal occlusion and topical cyclosporin should be considered. Certain conditions, such as ocular pemphigoid, Stevens–Johnson syndrome, and alkali, acid, and other chemical burns are notorious for resulting in postoperative epithelial problems. Unless such steps as limbal stem cell transplantation can be undertaken,[35] the prognosis in these conditions is very guarded. During surgery the epithelium should be left on the transplant, even though there are conflicting studies as to whether its removal lessens the long-term risk of graft rejection.[36,37] The epithelium can be protected from drying with a small amount of viscoelastic.[38] When epithelial problems are anticipated, as in patients with dry eye or rheumatoid disease, punctal occlusion or a tarsorrhaphy can be performed at the conclusion of the operation.

After surgery, treatment of epithelial defects can be approached in a stepwise fashion. Initially mild pressure patching can be attempted, even though one study found that small defects healed as fast without patching.[3] Care must be taken to ensure that the lids do not open under the patch, and this may be helped by directly

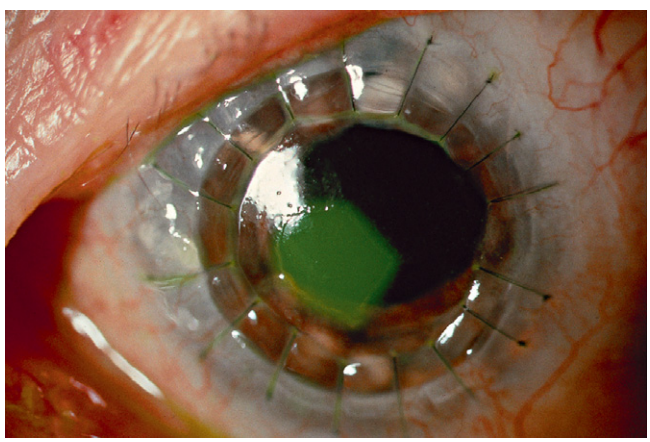

Figure 52.6. An epithelial defect, such as that shown above, requires prompt treatment to prevent secondary complications.

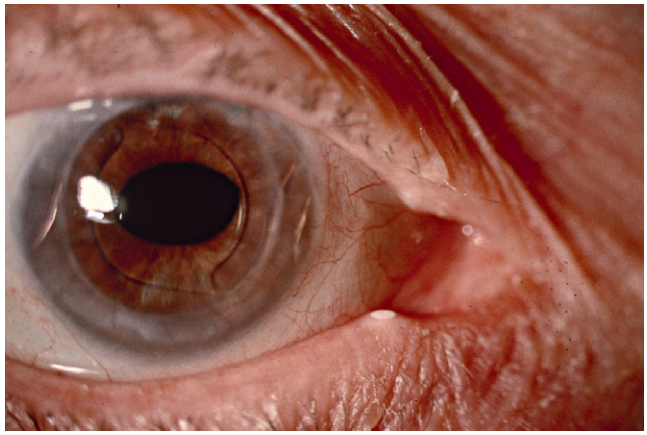

Figure 52.7. Punctal plug placed in a patient with dry eye to help protect the graft epithelium.

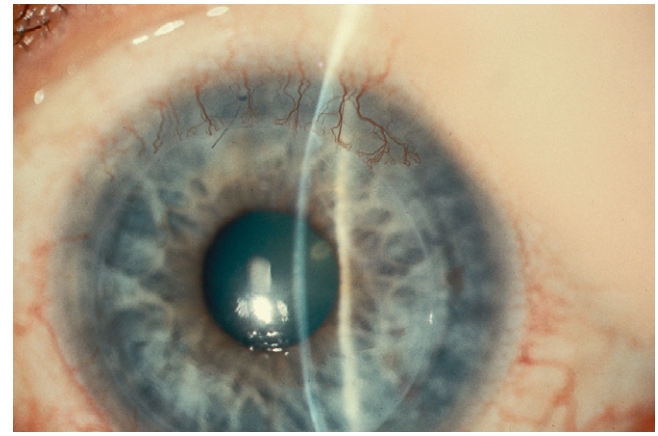

Figure 52.8. Superficial vascularization of the cornea after the placement of a bandage soft contact lens for chronic filamentary keratitis.

taping the lids together before applying the patch. The patch may be left in place for 24–48 h without being disturbed, if active infection is not a concern. Sutures with exposed ends should be removed or the exposed suture material amputated.[39] Aberrant lashes or lint trapped under a suture should be removed. Topical lubrication with frequent (every 30–60 min), nonpreserved artificial tears, nonpreserved bland ophthalmic ointment, or both can be used. If not already performed in the patient with dry eye, punctal occlusion either permanently with cautery or reversibly with punctal plugs should be attempted (Fig. 52.7). Because topical medications can contribute to poor epithelial healing, a re-evaluation of all eye drops the patient is receiving is in order. Any medication containing neomycin should be changed to a less epithelial toxic antibiotic.[40,41] Use of prophylactic topical antiviral agents should be considered carefully. Topical antiglaucomatous medications, in part because of their preservatives, can be toxic[42]; switching to a nonpreserved agent (unit-dose timolol) or using an oral antiglaucomatous agent should be attempted. Topical steroids might retard epithelial healing and their use minimized. In short, use the least number of drugs possible, in the least dosage.

If epithelial healing has not taken place after several days of conservative management, a more aggressive approach must be adopted. A soft contact bandage lens can be placed over the graft.[43] Obtaining a proper fit can be difficult because these corneas do not have a normal curvature, often being flat centrally. At times it is necessary to fit a large flat lens to obtain centration, despite a significant risk of infection. In addition to the usual factors causing corneal ulceration with extended soft contact lens, there is the increased risk of an already present epithelial defect and the immunosuppression induced by topical steroids.[44] These patients should be given a topical antibiotic such as moxifloxacin every 3–4 h and observed carefully. Once the defect has healed, an attempt should be made to remove the lens, because long-term use of soft lenses in corneal transplant patients has been associated with a high rate of infection and corneal vascularization (Fig. 52.8).[45]

In patients not responding to the above measures, a tarsorrhaphy should be performed. This can be carried out with a simple frost suture, by forming a temporary adhesion between the eyelashes of the upper and lower lids using cyanoacrylate glue,[46] or a permanent lateral tarsorrhaphy (Fig. 52.9). For those patients who have already had a lateral tarsorrhaphy, a medial intermarginal tarsorraphy can be added.

Figure 52.9. This lateral tarsorrhaphy was extended further medially because of continuing epithelial breakdown.

Once corneal melting has begun, the optical outcome for the transplant is compromised. At this point, if the condition of the donor tissue itself is believed to have contributed to the epithelial problem or if any contributing factors can be corrected, consideration should be given to replacing the graft. If it is believed that a further corneal transplant would produce the same result, a conjunctival flap can be pulled to save the eye from corneal perforation.

The possibility that a late-appearing or nonresponding epithelial defect actually represents a herpes simplex infection must be kept in mind. These ulcers tend to occur near the wound margin, often do not look like a typical dendrite, and may even occur in a patient without a known previous history of herpetic disease (Fig. 52.10).[47] When suspected, viral cultures and immunofluorescent staining for herpes is indicated. If herpes simplex virus is found, appropriate antiviral treatment can be started.

FILAMENTARY KERATITIS

Filamentary keratitis has been reported to occur in at least 25% of patients after keratoplasty.[48] This finding is not surprising because many of the conditions in which filaments occur (inflammation, increased mucus production, anesthetic cornea, patching, etc.) are present in the postkeratoplasty eye. Filaments consist of strings of

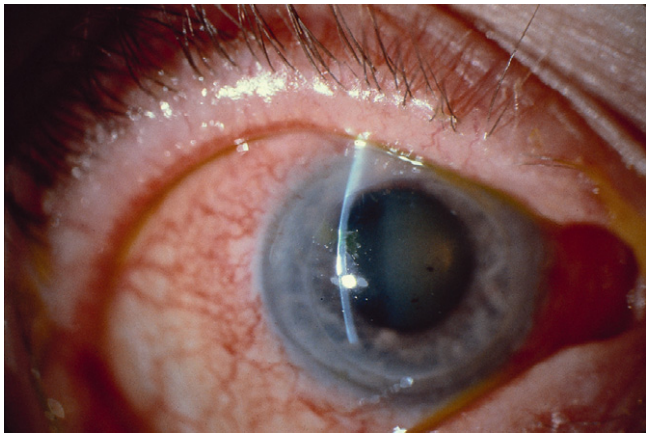

Figure 52.10. A late-appearing, irregularly shaped epithelial defect on an otherwise clear graft cultured positive for herpes simplex virus.

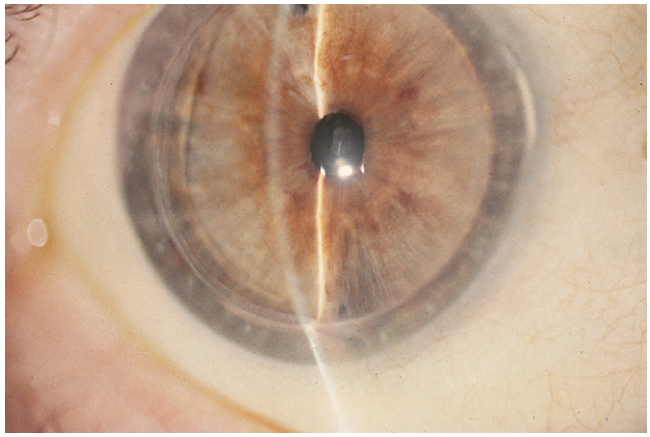

Figure 52.11. Limited anterior synechia to the graft wound that has been present for years without adversely effecting graft survival.

mucus with a few epithelial cells attached to receptor sites on the epithelial surface. They occur most frequently near the wound margin and may come and go over many months.

Patients experiencing filament formation may experience initial symptoms of irritation and foreign body sensation, particularly if the filaments occur near the edge of the graft. The eye tends to be slightly injected. The filaments stain poorly with fluorescein and brightly with rose bengal.

Treatment of filamentary keratitis proceeds in a stepwise fashion. For mild symptoms, the use of hypotonic artificial tears may give temporary relief. If used frequently, nonpreserved tears are indicated. For more pronounced symptoms, the filaments can be removed at the slit lamp under topical anesthesia, using fine jeweler's forceps. Care should be taken not to pull off surface epithelium with the filament. For recurrent problems, acetylcysteine diluted to a 10% solution in artificial tears can be attempted as a mucolytic agent. A bandage soft contact lens can also be applied. Fortunately, the frequency of filament formation decreases after suture removal.

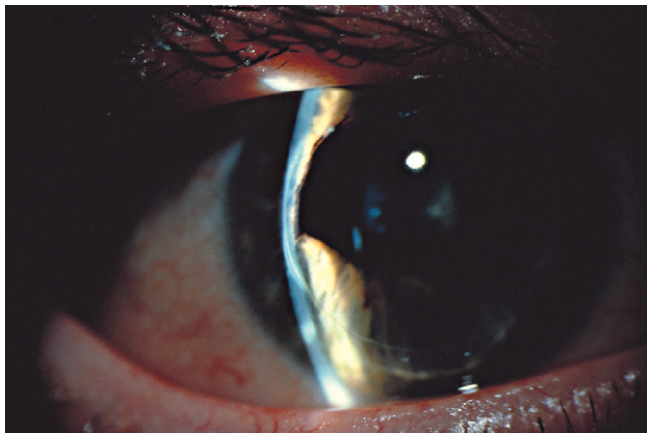

Figure 52.12. Iris incarceration (without prolapse) and loss of the anterior chamber from trauma in a patient with Down syndrome. It was elected not to repair the wound as the chamber reformed spontaneously. The graft has remained clear for years.

ANTERIOR SYNECHIAE

The significance of anterior synechiae depends on their location, their extent, and the time frame of their appearance. Anterior synechiae may develop at the peripheral cornea, in the corneal wound itself, or may extend from one to the other. The greatest problem with synechial formation occurs when operating on inflamed eyes with excessive fibrin in the anterior chamber. Synechiae to the wound found on the first postoperative visit were probably left in place at the time of surgery. It is much easier to deal with this problem on the operating table where the wound can be approached directly and any synechiae pushed back with a viscoelastic agent on a fine cannula. Anterior synechiae may form later as the result of a wound leak with a flat chamber, a persistent shallow chamber, or from trauma with partial or complete iris prolapse. The approach to treatment depends on the location and extent of the adhesions.

Limited synechiae extending directly to the graft wound, especially when the chamber angle is spared, have only a limited effect on graft survival, although on occasion they can be a source of vascularization and graft rejection (Fig. 52.11).[49,50] It may be possible to free these adhesions pharmacologically, especially if there is no significant tissue incarceration. On the third or fourth postoperative day, when the fibrin begins to break down, the pupil should be aggressively dilated with a phenylephrine hydrochloride-cyclopentolate series and, if this is not effective, constricted with pilocarpine. Long-acting cycloplegics, such as atropine or scopalamine, should not be used after surgery to preserve this pupillary capacity. If unsuccessful and the intraocular pressure remains under control, these synechiae are probably best left alone. When surgery is indicated, use of a viscoelastic agent to assist in sweeping iris adhesions from the back of the cornea helps to prevent irreversible damage to the graft endothelium.[51]

More extensive anterior synechiae, with broad contact between the iris and the back of the cornea threatening the filtration angle, usually develop in eyes that have been operated on in the inflamed state. Although the potential to develop severe glaucoma exists, surgical intervention includes risks of bleeding and increasing inflammation. The use of intensive topical steroids (prednisolone 1% every hour) and occasionally systemic steroids for a few days may control the inflammation and allow the iris to drop back. At this point, pharmacologic manipulation of the pupil may be helpful.

Iris prolapse usually occurs as a result of trauma and should be repaired immediately (Fig. 52.12). Depending on the extent of wound disruption, topical or general anesthesia can be used. If the iris tissue prolapse is limited in both extent and duration and if the

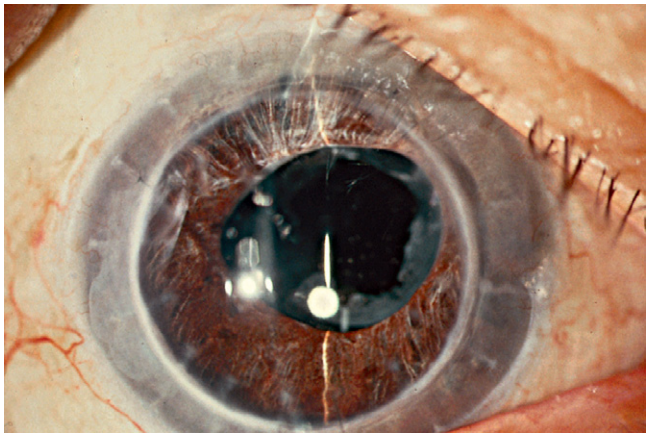

Figure 52.13. Total angle closure from progressive anterior synechiae formation developed in this patient with marked postoperative inflammation. The graft has remained clear, and the intraocular pressure has been controlled with medication.

tissue appears viable, it can be reposited directly. Exposed, nonviable iris tissue should be excised before repositing the portion of iris incarcerated in the wound. The wound usually requires repair with additional interrupted sutures until a watertight closure is obtained. These cases should be considered potentially contaminated, and appropriate antibiotic coverage should be administered.

Anterior synechiae can, on occasion, cause a progressive zippering of the chamber angle (Fig. 52.13). This situation most commonly develops in patients with active inflammation at the time of keratoplasty, particularly if there are pre-existing adhesions. These adhesions may have been lysed at surgery, such that the chamber initially seems of good depth. Then several weeks into the postoperative period, broad peripheral anterior synechiae begin to appear. At first these are localized, but gradually and relentlessly, the synechiae progress. Over a period of weeks the angle becomes 'zippered' up. Occasionally, the process stops at a large peripheral iridectomy, which has caused some surgeons to recommend performing an iridectomy in advance of the zippering process in hopes of halting it. Frequently, however, the process will 'jump' across the iridectomy until all or nearly all of the angle is closed. As may be expected, there is a gradual elevation of the intraocular pressure until a secondary glaucoma develops, which is very difficult to control medically. At times an anterior chamber lens holds the angle open, at least grossly, in the region of the foot plates so that the associated glaucoma may not be quite as difficult to control. There is no proven way to abort this process after it begins other than attempting to suppress the associated inflammation.[52] Surgical intervention is fraught with potential complications. Possible ways to control the glaucoma in these cases are discussed separately.

HYPHEMA

Blood in the anterior chamber after surgery is unusual. Even with very vascularized corneas, the vessels are tamponaded by the pressure created by the corneal sutures. When a hyphema does occur, it is usually the result of bleeding from the angle occurring when an anterior chamber lens foot process is being removed, from a vascularized synechia that is lysed during anterior chamber reconstruction, or from generalized oozing from the surface of a highly inflamed iris. Usually, these bleeding points can be managed at the time of surgery using a viscoelastic to tamponade them or a fine retinal cautery needle for direct cautery.[53] Alternatively, the use of thrombin 1 : 100 or epinephrine 1 : 1000 may be helpful. A small hyphema after surgery can be ignored and spontaneously absorbs in a few days if there is no further bleeding. A large hyphema that is causing uncontrollable glaucoma requires surgical evacuation.

EXCESSIVE IRITIS

All corneal transplant patients experience a variable degree of anterior chamber reaction immediately after surgery; its extent depends on factors such as the degree of iris manipulation and the condition of the eye before surgery. Excessive inflammation may be encountered after surgery and can include fibrin clot formation and a hypopyon in the anterior chamber. Clinical judgment must be exercised in deciding whether this is a sterile inflammatory reaction or whether an infection must be actively ruled out. The presence of excessive white blood cells in contact with the new endothelium can be damaging to the graft, as evidenced by the stromal edema and thickening that these grafts demonstrate.[54] If infection is believed to be unlikely, intensive steroid therapy is warranted. Prednisolone acetate 1% can be administered as often as one drop every hour. A short course of systemic steroids may be needed. A short-acting cycloplegic agent should be given to help prevent posterior synechiae and pupillary block.

If the fibrin clot does not respond to intensive steroid therapy and there is a risk of both pupillary block from a secluded or occluded pupil and damage to the graft endothelium, the use of tissue plasminogen activator can be considered. A 25 μg dose of tissue plasminogen activator given intracamerally has been described.[55] This drug causes complete resolution of the fibrin clot over several hours and appears to be nontoxic to the endothelium.[56] This drug can also result in intraocular bleeding, and therefore its use in any patient who has experienced intraoperative hemorrhage should be carefully considered. The possibility of infection must be considered in any eye that does not respond to treatment.

PUPILLARY BLOCK

With the development of pupillary block, aqueous is obstructed in its movement from the posterior to the anterior chamber, the anterior chamber shallows as the iris bulges anteriorly, and the angle is thus obstructed, with an elevation in intraocular pressure. The incidence of pupillary block is very low after surgery using modern corneal transplantation techniques. Air, which can be trapped behind the pupil at the time of surgery, has largely been replaced as a tissue separator by various viscoelastic agents.[38] Vitreous, which can adhere to and block the pupil, is either removed by an adequate anterior vitrectomy or held back by an intact posterior capsule or posterior chamber intraocular lens. Pupillary block can arise when an eye is left aphakic or a secondary anterior chamber or sewn-in posterior chamber lens is used. If no iridectomy has been performed or has been blocked with peripheral vitreous, pupillary block may ensue. In a phakic eye, marked inflammation can occlude the pupil with posterior synechiae. The elevated intraocular pressure usually will differentiate a shallow chamber because of pupillary block from a shallow chamber secondary to a wound leak. Vigorous dilation of the pupil with several drops of cyclocyl 1% alternating with neosynephrine 2.5% often relieves the situation. In situations where dilation is ineffectual or where the block recurs, a peripheral iridectomy is indicated. This can usually be done with a laser, but where the peripheral iris cannot be approached through the cornea,

perhaps because of a lack of clarity, a surgical iridectomy is warranted. This condition should be aggressively treated to avoid the formation of permanent peripheral anterior synechiae.

GLAUCOMA

Glaucoma after corneal transplantation can be difficult both to diagnose and to treat. It develops in approximately one-third of patients[57] and is unusual in uncomplicated phakic grafts but quite common in pseudophakic or aphakic grafts,[58] especially when there are associated anterior segment abnormalities. The most frequent association with postkeratoplasty glaucoma is the presence of preexisting glaucoma.[58] Because the inability to control intraocular pressure successfully after surgery is frequently associated with graft failure,[59] preoperative pressure control is mandatory. Diagnosing glaucoma before surgery can be difficult because of the problem of accurately measuring intraocular pressure in the presence of a scarred, irregular, or edematous cornea. Corneal opacification can also interfere with visualization of the chamber angle and optic nerve in addition to interfering with obtaining an accurate visual field. Patients whose pressures are controlled, but only on maximally tolerated medication, should be considered for possible glaucoma surgery before keratoplasty because pressure control will most likely be lost after corneal transplantation. Combining glaucoma surgery and keratoplasty has been reported.[60,61] This approach is risky because, if the glaucoma procedure fails, the surgeon must deal with the difficult problem of uncontrolled intraocular pressure in a patient with a fresh graft.

Measuring intraocular pressure after surgery presents a technical problem. The limited area of smooth surface contour of the cornea in the immediate postkeratoplasty period limits the ability to use applanation tonometry. Makay Marg electronic tonometry,[62] pneumatic tonometry,[63] and the newer Tono-Pen[64] give more accurate measurements under these circumstances, but even these instruments can, on occasion, be misleading. A very thin and clear corneal transplant on the first postoperative day raises the possibility of elevated intraocular pressure.[65] The high pressure compresses the stroma, but, because there is no epithelium or only a thin layer of epithelium present, the epithelial barrier is not functioning, and therefore epithelial edema is not seen. The presence of synechiae or the presence of blood, fibrin, or both in the anterior chamber should increase the suspicion of pressure problems. The knowledge of preoperative risk factors or intraoperative problems allows for the anticipation of postoperative glaucoma.

On the first postoperative day, elevated intraocular pressure is common.[66] An oral carbonic anhydrase inhibitor, such as acetazolamide 250 mg four times per day and topical agents such as timolol 0.5%, apraclonidine 0.5%,[67] and latanoprost may prove helpful.[68] Aggressive management of any associated pupillary block, synechiae, or excessive inflammation is appropriate. Elevated intraocular pressure from the presence of a retained viscoelastic agent usually clears spontaneously in 24–48 h.[6] In the rare instance where the pressure is so high that acute damage to the optic nerve is feared, a hyperosmotic agent can be given orally for 1 or 2 days. Such an approach can only be considered a temporizing measure until more definitive therapy is instituted.

On a more chronic basis, if elevated intraocular persists, it may be possible to change to a topical carbonic anhydrase inhibitor. A miotic, such as pilocarpine or carbachol, although initially contraindicated because of its effect on the blood aqueous barrier, can be added as soon as the postoperative inflammation is brought under control. Topical epinephrine or dipivefrin has only a limited use because of its known propensity to cause macular edema in the aphakic or pseudophakic patient. As pointed out previously, these agents and their preservatives may adversely affect the status of the corneal epithelium on the surface of the new graft, and this consideration must be taken into account in treating glaucoma.

The possibility that the use of a topical steroid is playing either a primary or a contributing role in the development of a patient's pressure elevation should be considered, particularly when this elevation develops 1 or 2 weeks after steroid administration is started. In addition to keeping the use of steroids to the minimal dosage necessary, switching to a steroid with less propensity to pressure elevation, such as fluoromethalone or loteprednol etabonate,[69] is warranted.

If patients fail to respond to medical therapy, the presence of a corneal transplant makes surgical intervention more risky because of the possibility of causing graft failure. The simplest and safest surgical approach is argon laser trabeculoplasty.[70] Most patients are not suitable for this procedure because they are either aphakic or pseudophakic, or because visualization of their angle is poor or much of their angle is closed. For many of the same reasons, a classic trabeculectomy has a low success rate.[71] Adding an antimetabolite, such as mitomycin C or 5-fluorouracil, may increase the risk of graft failure.[72] In the recent past, the best option available for most of these eyes was a cyclodestructive procedure. Originally, cyclocryotherapy was the procedure of choice for intractable glaucoma[73] and it still has a place in the therapeutic armamentarium when access to other treatment methods is unavailable.[52] Significant complications are associated with this treatment including iritis, hemorrhage, macular edema, graft failure, decreased vision, and especially late-term phthisis bulbi (Fig. 52.14).[74,75] For this reason a graded approach to treatment is indicated. Initially 180° of the ciliary body is treated using three applications in each quadrant for 60 s at 60–80°C. Depending on the response achieved, additional treatment applications can be added, one or two at a time, in the previously untreated quadrants of the globe. This approach is challenging because the difference in aqueous production between a high pressure and phthisis may be minimal in eyes with severely impaired outflow. Trans-scleral neodymium:yttrium aluminum garnet (Nd:YAG) photocoagulation, either contact[76] or noncontact,[77] has largely supplanted cryotherapy as a means of destroying the ciliary processes and decreasing aqueous production because

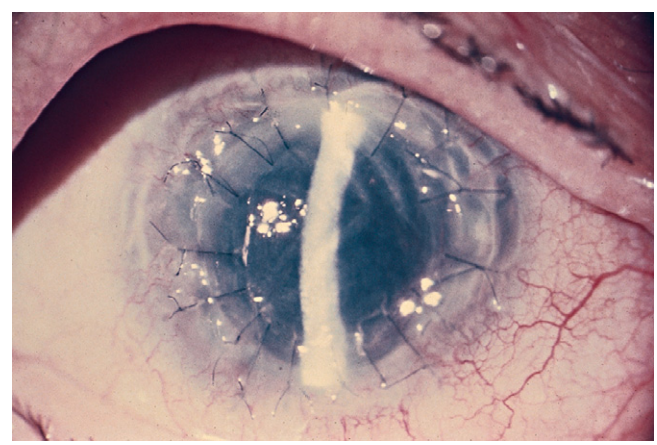

Figure 52.14. Graft failure after cyclocryotherapy.

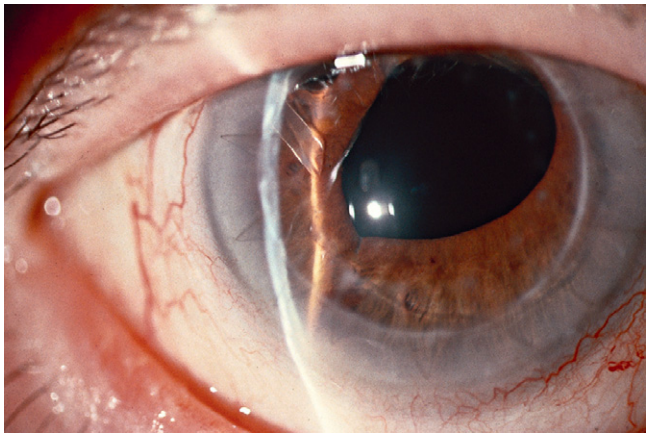

Figure 52.15. Note that the position of the tube from this valve is well away from the back of the graft.

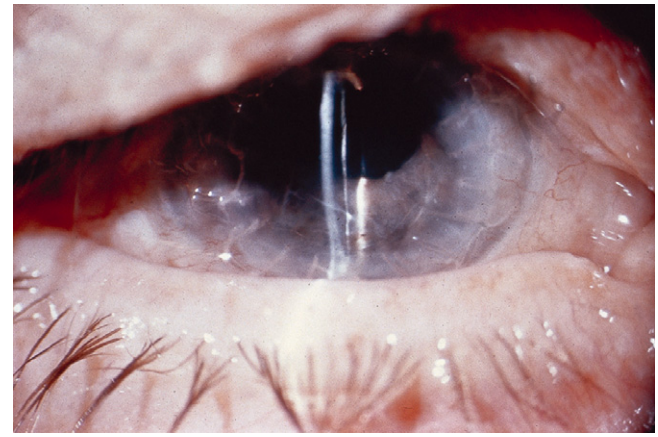

Figure 52.16. Retained Descemet's membrane as a thin, clear, wavy membrane separated by a false anterior chamber from a clear corneal transplant.

the associated complication rate appears to be less. A graded approach is used; the risk of graft failure increases with multiple treatment sessions. Whether other laser glaucoma procedures, such as transpupil[78] or endoscopic[79] argon laser cyclophotocoagulation, will have a place in the treatment of postkeratoplasty glaucoma remains to be seen.

Valves, such as the Ahmed,[80] Baerveldt,[81] or Molteno valve,[82] appear to give the best chance for long-term pressure control with little or no medication. The surgical approach is the same as in the nontransplanted patient. The drainage tube can be placed in the anterior chamber or, where none is present, in the posterior chamber after an adequate vitrectomy. With anterior chamber placement, particular care must be given to the length, position, and angle of the tube to avoid touching the back of the graft (Fig. 52.15). A significant incidence of graft failure and hypotony after surgery only underscores the difficulty of treating glaucoma in the postkeratoplasty patient.[83]

VASCULARIZATION

Vascularization of the graft bed greatly influences the incidence of graft rejection.[49] The most important sources of blood vessels extending up to and into a corneal transplant are pre-existing corneal vascularization, loose sutures and exposed corneal knots, corneal ulcers, and bandage soft contact lenses, especially when used on an extended-wear basis.

Unfortunately, there is usually no way to remove pre-existing vessels from the corneal bed. Rarely a single-feeder vessel, if it originates from the surface of the sclera, can be cauterized outside the limbus or is amenable to laser photocoagulation. A fibrovascular pannus can be stripped off the cornea at the time of surgery. Often removal of the diseased recipient button removes the impetus to vascular ingrowth, and the active vessels present before surgery regress after surgery.

Treatment of corneal vascularization involves the suppression of vessel growth by the appropriate use of topical steroids,[84] recipient-side focal subconjunctival triamcinolone injection (personal communication, Fred Brightbill, MD), removing loose sutures and exposed knots, aggressively treating corneal infections, and limiting the use of bandage lenses. Timing of suture removal plays a large role in preventing the complications of corneal vascularization. If the donor graft is healthy, pre-existing vessels or vessels approaching the host–graft junction tend to grow along the junction and not enter the graft. As soon as this has happened, the wound in this area has usually healed sufficiently to allow suture removal. If interrupted sutures have been used, the suture at this location should be removed. The flexibility of interrupted sutures in this situation is an indication for their use where pre-existing corneal vessels are present. If a running suture has been used, management is more difficult. If the rest of the wound has not sufficiently healed, suture removal can lead to wound dehiscence. The options then are to increase the dose of topical steroids, keeping in mind that this slows healing in the rest of the wound, or to remove a section of the running suture. After a section has been removed, the running suture tends to continue loosening, a loop at a time, because of the action of the eyelids. If this happens, the suture can be stabilized by the placement of a bandage soft contact lens, but the presence of the latter may cause further progression of the vascularization. Superficial vessels crossing the graft–host junction do not indicate wound healing but fortunately do not carry an increased risk of rejection. On occasion, however, superficial vessels, on reaching the junction, can dip down, enter the stroma of the graft, and thereby pose a risk of rejection.

RETAINED DESCEMET'S MEMBRANE

Finding a wavy, diaphanous membrane in the anterior chamber that creates a false chamber behind a graft on the first postoperative visit indicates that Descemet's membrane has been left behind at the time the recipient button was removed (Fig. 52.16). Retention of Descemet's membrane occurs most commonly in an edematous cornea where, after partial trephination, an opening is made into the anterior chamber and curved corneal scissors are introduced. By accident, the lower blade is not placed into the anterior chamber, but rather anterior to Descemet's membrane, stripping the latter from the corneal stroma. On completion of the excision of the recipient button, the button is lifted from the eye, leaving the central portion of Descemet's membrane behind. Descemet's membrane then settles down over the iris, where it is remarkably difficult to see.

A retained Descemet's membrane eventually leads to loss of graft clarity by clouding or by coming into contact with the graft endothelium. Several approaches to dealing with this problem are available. If the membrane has been mostly cut free at the time of surgery leaving only a small area of connection, its excision can be completed under a viscoelastic agent either through a limbal excision

or through the corneal wound. A technique using the Nd : YAG laser to make a central opening in the membrane has been described.[85] The long-term outcome of this procedure has not been reported. A long-term solution to this problem is to repeat the keratoplasty.

PRIMARY GRAFT FAILURE

Primary graft failure refers to the situation where the donor cornea is thick and edematous from the first postoperative day and never clears.[86,87] Technically, the term 'primary' would imply that the transplanted tissue itself was not healthy. This occurrence should be very rare if the tissue is harvested and used under current rigorous protocols. Usually, graft failure in this circumstance is secondary to intraoperative problems. Primary graft failure is best handled by graft replacement with a new donor before wound healing.[88] In this circumstance, the sutures can be cut and the failed graft removed without the need for trephining. Haste in making this decision is, however, not warranted because almost all grafts can be easily removed up to 1 month or more after surgery.

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53 Post keratoplasty infections

Namrata Sharma, Gaurav Prakash, Rasik B. Vajpayee

INTRODUCTION

Graft infection is a particularly devastating complication following corneal transplant surgery and may cause graft failure if not managed promptly and appropriately. The immunity of the ocular surface of a corneal graft is suboptimal due to altered tear film dynamics, loss of corneal sensations, and frequent instillation of topical corticosteroids in the early postoperative period, and a range of risk factors may predispose to infectious keratitis in a corneal graft. The important predisposing factors that may cause infectious keratitis in a corneal graft include donor tissue contamination, ocular surface diseases, and suture-related problems. In most instances, infection in a corneal graft is associated with poor visual outcome.

INCIDENCE

Graft infections are known to occur more commonly in developing countries, and the incidence has been reported to be as high as 11.9%.[1] In developed countries, the incidence of infectious keratitis after corneal transplantation surgery varies from 1.7 to 7.4%.[2–5] The incidence of infectious keratitis following lamellar keratoplasty has been reported to be 11.11%.[6] Most infections present in the first year of corneal transplantation surgery.[2–4] A higher occurrence of graft infection in developing countries is related to type of indications vis-à-vis primary corneal pathology, suboptimal quality of health-care services, and noncompliance of follow-up schedule due to socioeconomic reasons.

PREDISPOSING FACTORS

Various factors that can predispose to infection in corneal graft include type of corneal pathology of the recipient, donor tissue contamination, and ocular surface problems. In some instances, systemic diseases and socioeconomic status of the patient may be responsible for the occurrence of graft infection.

INDICATIONS FOR KERATOPLASTY

There are certain types of corneal pathologies that predispose to infections following penetrating keratoplasty. Corneal grafts performed for bullous keratopathy[7] and corneoiridic scars[8] carry a higher risk of infection as compared to corneal grafts done for cases like keratoconus, early Fuchs' endothelial dystrophy, and stromal corneal dystrophies.

CONTAMINATION OF DONOR TISSUE

Certain causes of donor death like malignancy, cardiac diseases, and septicemia are more frequently associated with graft infection.[9] Also, at times the preservation media for tissue storage may be a potential source of graft infection due to inadvertent contamination during the processing and storage of the donor tissue.[10]

PRE-EXISTING INFECTIONS

Pre-existing infections in the ocular adenexa like dacryocystitis, meibominitis, and blepharitis if not recognized and appropriately treated preoperatively, may predispose to infectious keratitis in an otherwise clear and healthy corneal graft.

RECURRENCE OF HOST INFECTION

Recurrence of infection is usually seen when there is an incomplete excision of infected tissue of the host cornea in cases of therapeutic grafts. While performing therapeutic keratoplasty, the surgeon should make sure that the host trephination encompasses the entire diseased tissue along with a 1.0 mm healthy rim. In cases where transplantation is performed for herpes simplex keratitis, recurrence is common and may occur in 23% cases of transplanted corneas.[4]

PERSISTENT EPITHELIAL DEFECT

A persistent epithelial defect compromises the mechanical barrier of corneal protection against entry of microbes and increases the

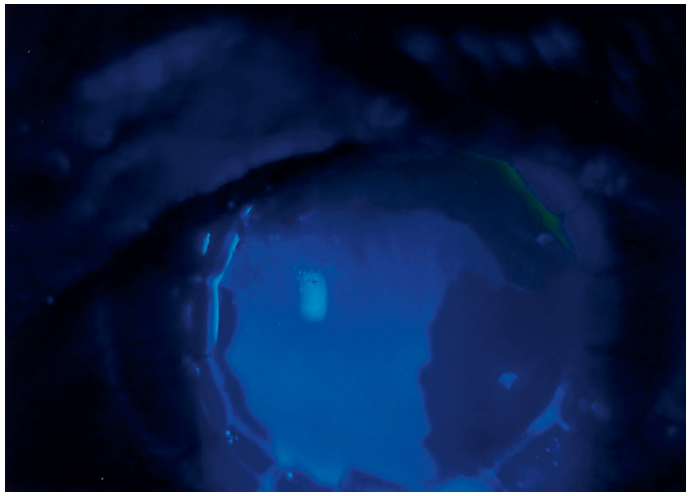

Figure 53.1. Persistent epithelial defect.

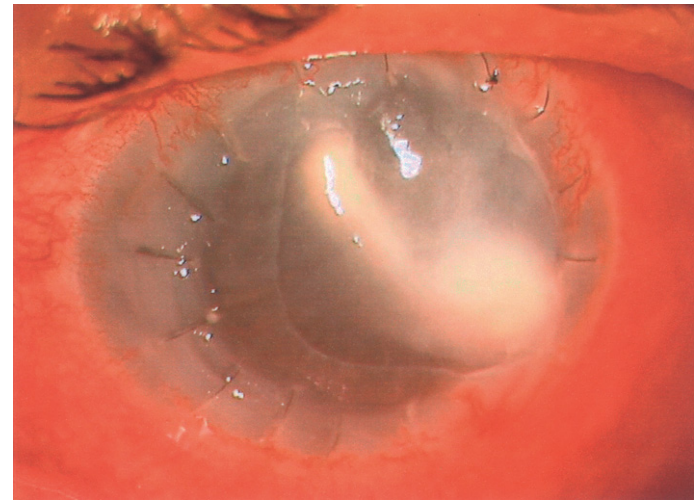

Figure 53.3. Loose suture with persistent epithelial defect leading to graft infection.

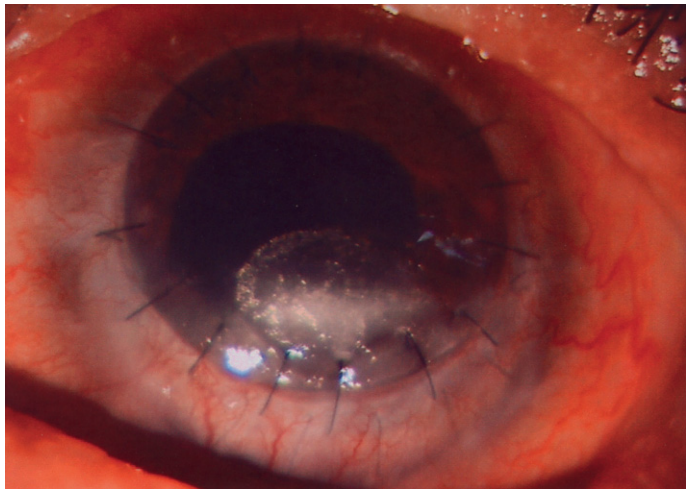

Figure 53.2. Tight suture with persistent epithelial defect with graft infection.

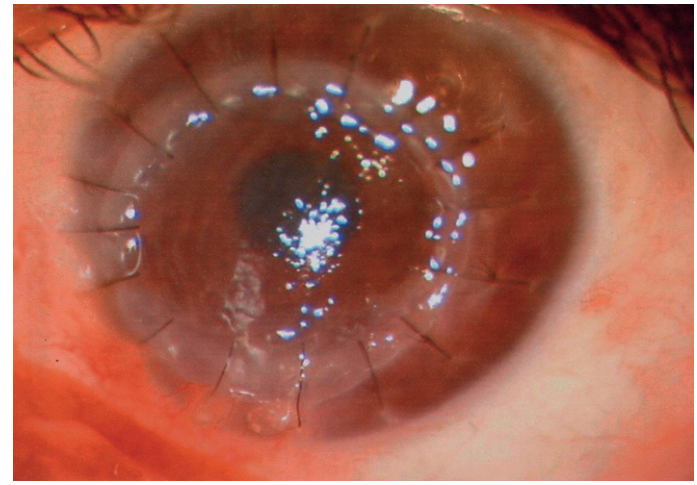

Figure 53.4. Loose suture with mucin deposits.

chances of occurrence of microbial keratitis in a graft (Fig. 53.1). Lid abnormalities like trichiasis, poor quality and inadvertent damage of the donor tissue, tight suturing (Fig. 53.2), loose suturing (Fig. 53.3), and toxicity of the preservative present in topical drops can delay the epithelialization of the corneal graft, leading to the occurrence of persistent epithelial defects. Epithelial defects as the inciting factors of infectious keratitis after corneal transplantation have been implicated in 14–74% cases in various series.[1,4,6,8]

CONTACT LENS

Bandage contact lenses are commonly used to manage persistent epithelial defects following corneal transplantation surgery. These lenses prevent microtrauma to the loose epithelium due to lid movement and thus promote healing of the epithelial defect. However, lenses also induce corneal hypoxia, reduce local immunity, and can cause increased microbial adherence and a subsequent keratitis.[7] In one study, lenses were implicated in 45% of cases of microbial keratitis after corneal transplantation.[11] It is unclear whether the contact lens itself or the persistent epithelial defect is responsible for causation of microbial keratitis in such cases.

DRY EYE AND OCULAR SURFACE PROBLEMS

Ocular surface disorders like dry eye and dellen result in altered tear-film dynamics and decreased tear-film coating. The tear film has antimicrobial substances like lysozymes, which act as the first line of defense. The tears also wash off the debris and microbes from the ocular surface. A compromised tear film increases the chances of adherence of the microbes to the transplanted corneas, thus causing microbial keratitis. A compromised ocular surface has been reported as a cause of postkeratoplasty infection in 33–66% of the cases.[1,4,6]

SUTURE-RELATED PROBLEMS

Suture-related problems are the most important predisposing factors for graft infection.[6,12–15] Loose, broken, and exposed sutures attract mucin (Fig. 53.4) and act as a nidus for microbial invasion and proliferation that can cause graft infection. A continuous suture (Fig. 53.5) has a higher chance of predisposing a graft to the occurrence of infection as compared to interrupted sutures. Unlike continuous sutures, interrupted sutures can be easily and selectively removed if there is a suture-related problem or at the first sign of a suture-related infection.[8]

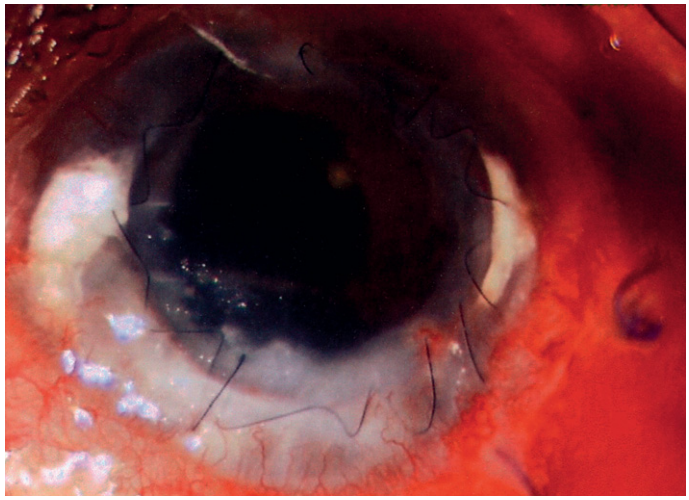

Figure 53.5. Loose continuous suture with graft infection.

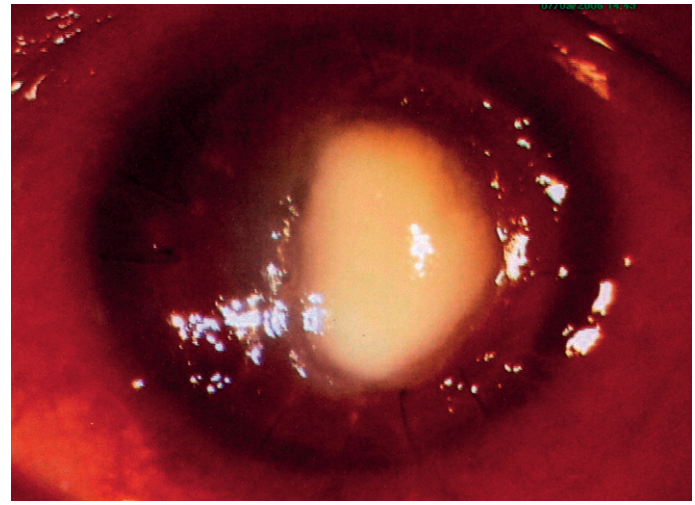

Figure 53.6. Fungal keratitis after keratoplasty.

A loose or broken suture or the recent removal of a suture may be associated with infectious keratitis in 14–60% cases.[3,4,6,8,15] Suture abscesses have been reported in 2–3.3% cases of penetrating keratoplasty.[14,15]

Systemic and other associations

Patients with diabetes mellitus reportedly have higher chances of developing graft infection.[7,8] In developing countries, graft infection is associated with low socioeconomic status of the patient.[8,16,17] In one study there was 2.5 times higher chances of infection in the lower socioeconomic group of patients compared to those in the higher strata; the difference was attributed to poor living conditions and inadequate hygiene.[16]

MICROBIOLOGY OF GRAFT INFECTION

The most common cause of graft infection is herpes simplex virus followed by bacterial organisms. More cases with Gram-positive cocci (coagulase-negative staphylococci, *Streptococcus pneumoniae*, and *Staphylococcus aureus*)[1,2,18] have been reported as compared to Gram-negative organisms (*Pseudomonas aeruginosa*, and *Serratia marcescens*). Mycotic keratitis after corneal transplantation has also been known to occur, and fungi of *Aspergillus* and *Mucoraceae* species[19] are most commonly isolated fungal organisms from these cases (Fig. 53.6).

CLINICAL FEATURES

A patient with graft infection usually presents with reduced vision and discharge from the eye. If the infection is related to a defective suture or if it is in the form of a localized dendritic keratitis, the vision may not be reduced much in early stages.

TIME OF PRESENTATION

Most cases of graft infections have been reported to occur within a year of the corneal transplantation surgery.[2–4,6] Infections caused by contaminated donor tissue and recurrence of the host infection usually occur during the early postoperative period. However, herpetic reinfections demonstrate a variable pattern and may occur years after the keratoplasty[20–22] (Fig. 53.7).

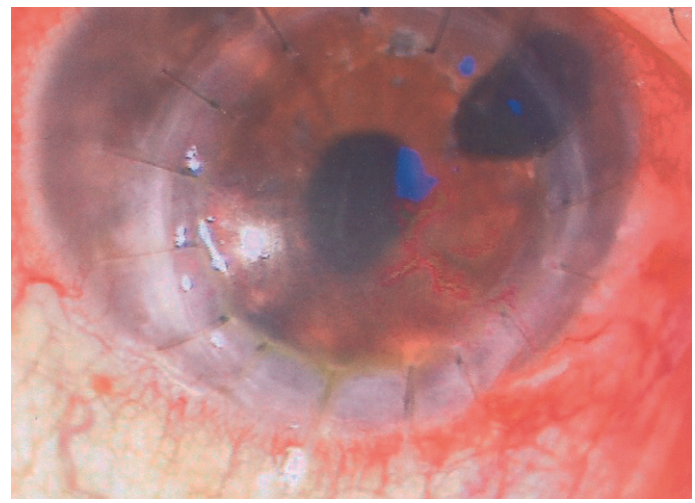

Figure 53.7. Herpetic infection in graft. Rose bengal staining shows dendritic pattern.

Symptoms and signs

Patients with graft infection in the early postoperative period commonly present with non-specific symptoms of redness, photophobia, foreign body sensation, and purulent discharge. There may be a sudden or gradual decrease in the visual acuity depending on the location of the lesion. Some patients with infection at the graft–host junction or with infection localized to the periphery of the graft may present with a normal visual acuity.

There may be a delay in diagnosis of infection in lamellar grafts, especially in the early stages, because an infiltrate may develop in the interface and may remain unnoticed.[6]

The ulcer should be examined with the biomicroscope and documented with a careful detailed drawing and photographs (if possible). The size of the epithelial defect, infiltrate, and hypopyon (if present) should be measured and documented at all visits (Fig. 53.8).

The ulcers in the grafted cornea may be either peripheral or central in location. Peripheral ulcers are usually associated with suture-related problems.[2] Centrally located ulcers suggest exposure and tear-film abnormalities. Advanced cases may present with frank graft dehiscence or melting.

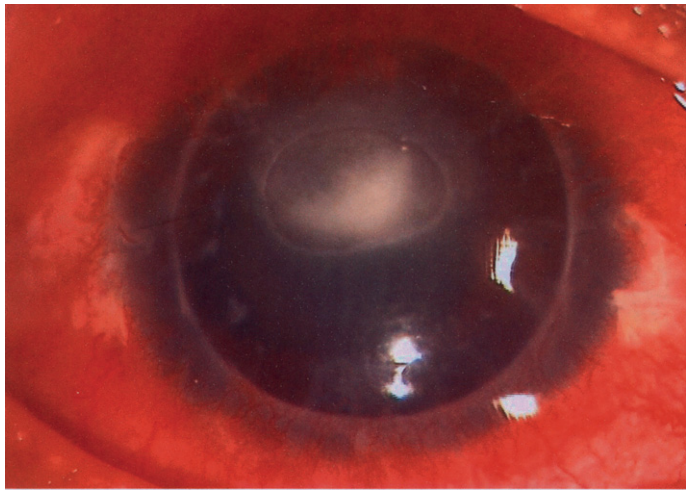

Figure 53.8. Bacterial keratitis after keratoplasty.

INVESTIGATIONS

Most corneal transplant surgeons prefer to culture swabs taken from the donor corneoscleral rim and the media. These may be of help in identifying the causative microbe, especially if the infection has occurred in the early postoperative period.

All cases of graft infection should be subjected to a detailed microbiological workup, which includes scraping of the ulcerated area, preparation of smears, and inoculation of the material obtained on appropriate culture media.

The corneal scraping should be done under topical anesthesia using a slit-lamp biomicroscope. Smears for Gram's stain and potassium hydroxide (KOH) wet mount should be prepared. In cases of suture-related problems, the offending suture should be removed and sent for bacterial and fungal culture examinations. If a contact lens is in place, it should be removed and placed on a separate culture plate. Initially the cultures should be done on blood agar, chocolate agar, and Sabouraud dextrose agar. Special culture media like Lowenstein–Jensen media, non-nutrient agar with *Escherichia coli*, and thyoglycolate broth should be used if there is clinical suspicion of infection by unusual pathogens.

If the infiltrate is deep within the graft and not accessible to superficial scraping, then a multifilamentous silk suture can be passed through the lesion and placed in culture media in an effort to recover the pathogen.

MANAGEMENT

Corneal graft infection requires a prompt and judicious management, which depends on a good clinical judgment and an early microbiological diagnosis of the ulcer.

MEDICAL MANAGEMENT

We prefer to hospitalize all cases with corneal graft infection. This helps us to optimize and monitor the therapeutic approaches applied, particularly in cases from poor socioeconomic backgrounds. In all cases of suppurative infectious keratitis of the corneal graft, topical corticosteroids should be stopped immediately (or rapidly tapered if there is the possibility of a *Pseudomonas* infection) and an intensive regimen of broad-spectrum combination therapy with fortified cefazolin 50 mg/mL and fortified tobramycin 14 mg/mL should be instituted every 30 min round the clock in the first 24 h. Alternatively, fortified cefazolin 50 mg/mL and gatifloxacin 3 mg/mL may be started in the same frequency. Monotherapy with fluoroquinolone antibiotic eye drops may also be instituted, although increasing instances of resistance of *S. aureus* and coagulase-negative *Staphylococcus* and *Streptococcus* to these agents have been reported.[22]

If there is microbiological evidence of fungus (on Gram's smear, KOH wet mount, or culture examination), 5% Natamycin eye drops every hour during the day and every 2 h at night are begun. Supportive topical medical therapy is given in the form of cycloplegics (preferably short acting such as tropicamide eye drops), lubricants, and antiglaucoma medications (if required). Topical corticosteroid therapy may be restarted in cases of bacterial infections only if the offending organism has been identified and there is a significant positive response to the antimicrobial therapy. Systemic antibiotics are indicated in cases with frank/impending scleral involvement, graft melting, perforation, or dehiscence.

The medical management is modified on the basis of clinical response and microbiological reports. The patient should be examined daily to monitor the clinical response of the ulcer. The signs of healing include a decrease in the size of the epithelial defect, infiltrate, anterior chamber reaction, and hypopyon, if present. The signs of worsening include increase in size of epithelial defect, stromal infiltrate, anterior chamber reaction, hypopyon, stromal thinning, and perforation. At every visit the graft–host junction should be carefully examined for wound dehiscence. Once the clinical improvement occurs, the topical medications should be tapered.

However, if the medical management fails, surgical options for the management of postkeratoplasty infections should be employed. If the cultures are negative and the keratitis worsens despite medical therapy, a diagnostic biopsy may be undertaken.

SURGICAL MANAGEMENT

Management of suture-related problems

If a loose suture is noted in the early postoperative period, it should be removed and replaced immediately, taking care that the exposed part of the suture does not traverse the corneal stroma. If a suture is the cause of infection during the late postoperative period, i.e. after 3 months, it should immediately be removed and sent for cultures. During the late postoperative period, removal of a single interrupted suture does not adversely affect the wound stability. However, if infection occurs due to a loose continuous suture, it should immediately be removed and replaced with interrupted sutures.

Emergency therapeutic keratoplasty or graft exchange

The indications for a graft exchange include nonresolving graft ulcers, deep-seated abscess nonresponsive to treatment, wound dehiscence, perforation, or graft melting. A graft exchange using the same-size graft as the one used in the prior surgery may be done in cases where the infection has not spread to the host cornea or a larger-sized graft may be used in cases where the infection spreads to the host cornea.

SPECIFIC ENTITIES

HERPETIC CORNEAL GRAFT KERATITIS

Herpes simplex virus keratitis may recur in cases of penetrating keratoplasty performed for herpetic scars or may develop following

keratoplasty without a clinical history of herpes keratitis in the host.[23] The incidence of recurrence of herpetic infection after penetrating keratoplasty varies from 10 to 25% during the first year of follow-up.[23,24] Most cases of herpetic keratitis are thought to represent reactivation from the virus putatively dormant in the neuronal ganglia. Herpetic keratitis of a corneal graft may have a variable presentation. It may present as a classic dendritic ulcer, persistent epithelial defect, graft rejection, or a herpetic stromal infiltration of the graft.[25] Distinguishing a geographical herpetic ulcer from a neurotrophic ulcer may be a challenge, but is achieved using slit-lamp biomicroscopy with rose bengal staining. The risk of recurrence of herpetic infection increases if corticosteroids are used without an antiviral agent after penetrating keratoplasty. A prophylactic dose of systemic acyclovir 800 mg per day is recommended for up to a year in cases of penetrating keratoplasty done for herpetic scars.[24–26]

INFECTIOUS CRYSTALLINE KERATOPATHY

Infectious crystalline keratopathy is an indolent corneal infection in which needle-like, branching crystalline opacities are seen underneath an intact epithelium within the corneal stroma, in the absence of appreciable corneal or anterior segment inflammation.[27,28] This has been reported to occur most frequently after penetrating keratoplasty and has been attributed to the chronic use of topical corticosteroids. Long-term use of topical corticosteroids, a routine therapy for cases of corneal transplantation, causes relative immunosuppression, allowing infection to develop with little or no inflammation in the cornea. The biofilm or the bacterial glycocalyx protects the organisms from penetration of antibiotics and interferes with phagocytosis of the organisms.[27] The most commonly reported organism includes *Streptococcus viridans*, but other organisms such as *S. pneumoniae*, coagulase-negative *Staphylococcus*, *P. aeruginosa*, and *Candida* species have also been implicated.[28] The lamellar architecture of the corneal stroma allows the organisms to spread laterally in a crystalline manner.

ASSOCIATED ENDOPHTHALMITIS

Endophthalmitis may occur early or late after penetrating keratoplasty, often with disastrous consequences. It may occur in 4–13% of the cases of graft infection.[2,3,8,13] The sources of infection are contaminated donor tissue or corneal storage media or irrigating solutions. Ulcerative keratitis at the graft–junction may progress to perforation and subsequent endophthalmitis. Anterior vitrectomy performed at the time of penetrating keratoplasty may increase the chance of endophthalmitis by 1.5 times.[29] In cases of corneal graft infection associated with endophthalmitis, intravitreal injection of vancomycin 1 mg in 0.1 mL and ceftazidime 2.25 mg in 0.1 mL should be given along with topical therapy for corneal ulcer.

GRAFT SURVIVAL AND VISUAL OUTCOME

Visual prognosis in eyes with postkeratoplasty graft infection is poor even after successful medical therapy due to corneal scarring after resolution of keratitis and a high rate of graft decompensation. A repeat keratoplasty is required in almost half of the cases.[2,8] Clear grafts following graft infection has been reported in 23–67% cases in various studies.[3,4,13,18] A best-corrected visual acuity (BCVA) of better than 6/60 on Snellen's acuity chart is seen in only 14–30% of the eyes, and only 6% of patients achieved a BCVA of ≥6/18 at the final follow-up in one study.[8] Infections after lamellar keratoplasty are associated with grave prognosis and may not be amenable to antimicrobial therapy.[6] This may necessitate the removal of the graft or a therapeutic penetrating keratoplasty.[6]

CONCLUSION

Microbial keratitis after corneal transplantation represents a serious vision-threatening complication and may lead to visual loss due to corneal scarring, graft failure, or endophthalmitis. It is difficult to restore useful vision with treatment and most of these cases require a regraft; hence, an early diagnosis and appropriate medical or surgical intervention are mandatory in such cases.

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54 Glaucoma

Catherine Newton, Linda L. Burk

One of the major causes of graft failure is inadequate control of elevated intraocular pressure (IOP). Although the endothelium may tolerate modest elevations of IOP, as seen in chronic open-angle glaucoma,[1] Bigar and Witmer[2] have shown that significant endothelial cell loss occurs as a result of acute and greatly elevated IOP. It is imperative to recognize and manage glaucoma after keratoplasty so that graft clarity is preserved.

DIAGNOSIS

Glaucoma is defined as elevated IOP sufficient to cause injury to the optic nerve, as evidenced by characteristic loss of the visual field or glaucomatous cupping of the optic nerve disc. Often it is not possible to assess adequately the optic nerve and visual field before surgery or in the immediate postoperative period because of preoperative media opacification and postoperative corneal distortion. The IOP, however, can and must be determined.

In a landmark article by Irvine and Kaufman,[3] attention was called to the association of elevated IOP associated with penetrating keratoplasty and the need for the accurate assessment of the post-keratoplasty IOP. The most accurate commercially available instrument for measurement of the IOP in the early postoperative period is the Tono-Pen.[4] The Tono-Pen reading must be correlated with corneal thicknesses.[5–7]

INCIDENCE

The incidence of moderately to greatly elevated IOP after penetrating keratoplasty is yet unknown. There are reported ranges of 12–27%.[8,9] Pre-existing glaucoma and anterior chamber dysgenesis are the highest risks for development of postkeratoplasty glaucoma.[10] Combined cataract with an artificial lens implant, anterior vitrectomy, and anterior segment reconstruction increase the overall incidence of postoperative glaucoma.[8–10]

PATHOGENESIS

In addition to pre-existing glaucoma, new onset of postoperative glaucoma may develop as a result of any number of mechanical problems, including sequelae of inflammatory conditions, wound closure technique, and paraoperative pharmacologic agents.

BOX 54.1 CAUSES OF ELEVATED IOP AFTER PENETRATING KERATOPLASTY

Inflammatory sequelae
- Fibrinous iritis
- Peripheral anterior synechiae
- Posterior synechiae

Suturing technique
- Compression of angle
- Trabecular meshwork collapse
- Wound leak with loss of anterior chamber volume
- Posterior wound gape with iridocorneal adhesions

Drug-induced elevation
- Corticosteroid
- Viscoelastic substances

Other
- Pupillary block secondary to intracameral air in endothelial keratoplasty
- Ghost-cell glaucoma
- Misdirected aqueous or ciliary block (malignant) glaucoma
- Preoperative angle recession
- Preoperative glaucoma

Bourne et al[11] corroborated the findings of Zimmerman and coworkers[12] by showing that using a 0.5 mm larger donor (punched from the endothelial side) resulted in significant decrease in the incidence of postoperative glaucoma in aphakic patients. The need for disparate-sized grafting is predicated on the use of tight wound closure with resultant tissue compression. Femtosecond laser preparation of the corneal donor button and the recipient bed increases the amount of lineal wound apposition and may accelerate the healing process as well as lessen the need for tight sutures leading to angle compression.[13] In a clinical study comparing the effects of Viscoat (3.8% sodium chondroitin sulfate and 3% sodium hyaluronate) and Healon (1% sodium hyaluronate), 4 of 24 eyes had pressures of 50 mmHg or more despite the surgeon's attempted removal

of the viscoelastic substance at the conclusion of the operation.[14] These pressures occurred at 24 h or less after surgery and there was no difference for either drug. Unacceptably high pressures may be sustained for several hours if no treatment is given.

MANAGEMENT

PREVENTIVE MEASURES

Thoft et al[15] as well as most corneal surgeons advocate the liberal use of topical corticosteroids in the early postoperative period to prevent the sequelae of severe ocular inflammation. François[16] and Goldmann[17] have demonstrated that long-term use of corticosteroids can cause glaucoma in susceptible patients. Therefore, consideration should be given to using fluorometholone-like drugs, including rimexolone (Vexol), loteprednol etabonate 0.5% (Lotemax), or 0.2% (Alrex) in patients at risk of steroid-responsive glaucoma.

MEDICAL TREATMENT

Depending on the cause of the elevated IOP after keratoplasty, medical management in the form of topical β-adrenergic blocking agents, α-adrenergic agonist agents, prostaglandin analogs, miotics, and carbonic anhydrase inhibitors may be useful. Shrader et al[18] found that 45% of the patients over 65 years of age treated with systemic acetazolamide experienced a malaise symptom complex consisting of fatigue, depression, anorexia, and weight loss. Hypokalemia and development of renal calculi are also known risks associated with systemic carbonic anhydrase inhibitors. Therefore, systemic carbonic anhydrase inhibitors must be used with great caution in the elderly keratoplasty patient population.

Topical β blockers are contraindicated in patients with congestive heart failure and obstructive pulmonary disease.

Apraclonidine hydrochloride (Iopidine) and brimonidine tartrate (Alphagan) are relatively selective, α_2-adrenergic agonists. They can be used in the paraoperative period. Suggested dosing would be 1 h before surgery and 12 h after surgery.[19] Although α_2-adrenergic agents have been shown to be effective over the short term, many patients sustain long-term benefits as well.[20] Ocular hypersensitivity to these drugs is a known problem, with the incidence of allergic reaction to apraclonidine being 48%[21] and that of brimonidine 25.7%[22]; however, in patients previously allergic to apraclonidine, only about 23% of those patients will develop an allergic reaction to brimonidine.[23]

The prostaglandin analogs, most notably latanoprost (Xalatan), bimatoprost (Lumigan), and travoprost (Travatan), have been shown to be effective in reducing IOPs by as much as 27–30%, with a single evening dose.[24] Caution, however, must be used in conjunction with corneal transplantation, as the mechanism of action of the prostaglandin analogs may be that of mediating inflammation. Indeed, conjunctival hyperemia is seen in approximately 30% of patients using these medications.[25]

Miotics are known to dilate the ocular blood vessels and break down the blood–aqueous barrier, and they may induce chronic iridocyclitis. Therefore, they are used with caution in eyes that are already inflamed.

Topical carbonic anhydrase inhibitors, dorzolamide (Trusopt) and brinzolamide (Azopt), can lower the IOPs in 17 and 25%, respectively.[26] There have been reports of irreversible corneal decompensation in patients who have had compromised endothelium.[27] Other studies have shown that the long-term effects on the corneal endothelium of dorzolamide are comparable to the β blockers.[28]

LASER TRABECULOPLASTY

Argon laser trabeculoplasty should be considered now that the transient increases in post-treatment IOP have greatly decreased in number with the introduction of apraclonidine (Iopidine).[19] The amount of trabecular meshwork available for treatment may be limited by peripheral anterior synechiae and anterior-chamber intraocular lens haptics. Studies have shown that argon laser trabeculoplasty and selective laser trabeculoplasty have similar 1 year results.[29] Long-term results show a diminishing effect with laser trabeculoplasty.[30]

MISDIRECTED AQUEOUS, CILIOVITREAL BLOCK, OR MALIGNANT GLAUCOMA

In cases of misdirected aqueous resulting in ciliovitreal block, or so-called *malignant glaucoma*, Epstein et al[31] have advocated neodymium: yttrium aluminum garnet (Nd:YAG) laser therapy to the intact hyaloid face. The theory is that the pathogenesis of ciliovitreal block is total obliteration of the posterior chamber by the vitreous body, which comes forward into apposition with the posterior surface of the iris and ciliary body because aqueous humor filters behind the vitreous body. In this situation, a peripheral iridectomy is of no help. They have reported successful therapy with rupture of the hyaloid face using the Nd:YAG laser. Indeed misdirected aqueous may occur even in the presence of a posterior chamber lens and intact posterior capsule. Tomey and coworkers[32] described the use of the Nd:YAG laser with 3–10 mW energy for a total of as much as 375 mJ.

PUPILLARY BLOCK

Pupillary block can occur with air in the anterior chamber following Descemet's automated endothelial keratoplasty procedures.[33] This problem can be addressed by relieving excess air by means of a paracentesis. In some cases, it may be necessary to perform an Nd:YAG laser peripheral iridotomy to relieve this condition.

CYCLODESTRUCTIVE PROCEDURES

Cohen et al[34] reported IOP control in 67% of patients at 1 year after Nd:YAG laser photocoagulation for postkeratoplasty glaucoma. Multiple treatments were required in 13 eyes (46%). Of the 14 eyes with clear pretreatment grafts, 6 (43%) became edematous during follow-up observation. All the failed grafts had multiple treatments. It is difficult to ascertain whether these grafts failed as a result of endothelial damage secondary to previously elevated IOP, inflammation caused by the cyclophotocoagulation, or endothelial rejection. No graft demonstrated classic signs of endothelial rejection.

Endoscopic cyclophotocoagulation has been performed in conjunction with phacoemulsification of a cataract with insertion of an intraocular lens, as well as in conjunction with penetrating keratoplasty via an open-sky approach.[35] Preliminary results are encouraging. The advantage of direct visualization of the ciliary process is touted by reports of successful endoscopic cyclophotocoagulation following previous attempts of trans-scleral diode laser treatments.[36]

SETON SURGERY

Modern seton devices have shown promise in the treatment of refractory glaucoma. While long-term results of keratoplasty in eyes

with glaucoma drainage devices have shown that the glaucoma is well controlled in 74% of eyes the first year and 63% of eyes the second year, the graft survival is not nearly as good. The grafts remaining clear after the drainage devices at 1 year were about 58% and at 2 years about 26%.[37] The main complication of these shunt devices is overfiltration in the early postoperative period, leading to prolonged hypotony, suprachoroidal hemorrhage, and choroidal effusion. Other complications include obstruction of the tube by vitreous or uveal tissue and implant exposure. Temporary tube ligation, anterior vitrectomy, and scleral patch graft have decreased the incidence of these complications.

A study by Arroyave et al concluded that the graft decompensation is significantly less a problem when the tube is placed in the posterior chamber following an extensive pars plana vitrectomy.[38] Increased inflammation may result from the presence of an implanted foreign body. Kirkness et al[39] suggested that inflammatory cells may transverse the altered blood–ocular barrier into the anterior chamber from the area surrounding the subconjunctival seton, causing increased rate of graft rejection and failure.

CONVENTIONAL SURGICAL INTERVENTION

Scarring of the conjunctiva from previous surgery may limit the successful formation of an avascular filtering bleb.[40] In a study of 35 eyes undergoing trabeculectomy for postkeratoplasty glaucoma, Gilvarry and coworkers[41] reported that 70% of eyes were controlled at 9 months and only 50% were controlled at 2 years, and 83% of the successful eyes required additional glaucoma medication to achieve IOP control. Combined penetrating keratoplasty and trabeculectomy with mitomycin-C have been studied in small numbers of patients with variable results. Wu Dunn et al found a relatively high risk of bleb failure within the first 3 months,[42] while Chowers and Ticho[43] found that 85% of eyes undergoing the combined procedure remained with pressures well controlled and clear corneal grafts at an average of 16.5 months follow-up. Adverse prognostic factors included multiple grafts and synechial closure of the angle.

Gilvarry and coworkers[41] considered trabeculectomy in eyes with little conjunctival scarring because there is a relatively low rate of complication. The use of adjunctive 5-fluorouracil with trabeculectomy has been widely investigated. It is known to produce large and persistent epithelial defects, which predispose the patient to microbial keratitis and stromal scarring and thinning.[44] It should be used with caution in the recently grafted eye. The occurrence of postoperative flat chamber has been decreased with the use of delayed argon laser suture lysis of the scleral flap.[45]

SUMMARY

Inadequate control of IOP after penetrating keratoplasty is one of the leading causes of graft failure. For avoidance of this complication it is mandatory that IOP be assessed accurately, early, and often. Careful paraoperative evaluation of the keratoplasty patient, keeping in mind risk factors such as inflammation, mechanical problems, and drug-induced side effects, will lead to better management. Glaucoma is a final outcome, but its pathogenesis is multifactorial. It is incumbent upon the keratoplasty surgeon to attempt to elucidate the pathogenesis of the postoperative glaucoma so that one or more appropriate therapies can be instituted to remedy the problem.

Surgical intervention is often necessary, although significant risks to the graft exist with any proposed procedure. Laser trabeculoplasty may be considered in eyes where a dramatic improvement in IOP is not necessary. Trabeculectomy with or without antimetabolites when the conjunctiva is mobile and not heavily scarred may be indicated. Seton devices are successful, but the rates of graft failure and complications are significant and placement location may be a factor. Endoscopic cyclophotocoagulation may be more precise than trans-scleral Nd:YAG laser cyclophotocoagulation. Ongoing study is needed to determine which of the available treatments will be the surgical procedure of choice in postkeratoplasty glaucoma.

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55 Suture removal

Frederick S. Brightbill, Edward L. Shaw

The decision to remove a corneal transplant suture is complex, yet it is critical to final visual outcome and is based primarily on sound clinical judgment.

CRITERIA FOR SUTURE REMOVAL

A crystal-clear corneal transplant with high astigmatism and poor vision does not constitute a successful case. Almost any well-prepared ophthalmologist can tie a nylon suture and close a wound, but the expertise comes in knowing when to remove the suture. Several criteria for considering suture removal appear in Box 55.1.

When the graft–host interface shows a visible, fine wound scar or there is obvious vascularization around a suture, removal is necessary. A loose suture that was not seen previously usually reflects scar formation with wound contracture and should be removed. Otherwise, mucus and debris may become trapped around the suture and provoke a foreign body reaction or act as a nidus of infection. This can also act as an immunologic stimulus leading to graft rejection. Numerous problems may be caused by loose sutures or exposed knots (Box 55.2).[1,2]

A loose suture may cause severe pain, photophobia, blepharospasm, and even blepharoptosis.[3,4] Upper tarsal conjunctival ulcers and giant papillary hypertrophy[5] may occur from loose or irritating sutures and, if conjunctival injection and corneal epithelial trauma continue, iritis may follow, leading to graft rejection and possible failure.

If a suture is too tight, severe corneal flattening occurs in the same meridian as the interrupted suture. Extreme flattening of the center of the cornea in a plateau configuration can be seen with a tight running suture. The impression of a tight suture may be easily confirmed by slit-lamp examination. One may see stress lines in the deep stroma and Descemet's membrane and a 'cheesewiring' effect as the suture cuts through the corneal tissue. The keratometer and corneal topography further confirm the astigmatic effect and irregular corneal surface.

If the knot of an interrupted suture has a long end causing significant foreign body symptoms but the suture cannot be removed because of inadequate wound healing, either cutting or cauterization of the suture end using a low-temperature disposable cautery is warranted. With slit-lamp observation, the tip of the cautery is brought to the immediate vicinity of the suture end and activated momentarily. After release of the 'on' button, the tip is touched to the suture end, melting it into a small, smooth ball. Care must be taken not to burn too closely to the epithelium because corneal ulceration or melting of the suture can occur.

Cutting the exposed suture end is also possible by using one hand to grasp the suture with a jeweler's forceps and the other hand to cut it, using a disposable knife blade. This can be accomplished under slit-lamp control using a lid speculum or with an assistant holding the eyelids open.

WOUND HEALING

Today most grafted corneas heal without obvious vascularization of the graft–host interface. The practice of burying suture knots either on the donor or on the recipient side of the wound has limited the growth of limbal vessels into the donor and resulted in white, quiet eyes with minimal irritation. Transplants with buried sutures require less corticosteroid than in earlier times when surface knots stimulated vascular ingrowth to the graft–host interface and threatened rejection. The object of corticosteroid treatment should be to use as low a dose as possible to limit iritis and vascularization but not interfere with wound healing. After the first few weeks of treatment, that may be as little as one or two drops daily of 1% prednisolone acetate.

Although corneal vascularization is usually a definitive sign of wound healing and an indication for suture removal, it may not be a foolproof sign. In fact, one may often be misled if vascularization alone is used as the sole measure of healing. One must be sure that, in cases of corneal scarring and edema, keratoconus with wound-thickness disparity, and chemical burns, adequate time has elapsed for full wound healing and maximal wound tensile strength.[6,7] This is especially true when one is administering antibiotics, topical and systemic steroids, antivirals, and bandage contact lenses, all of which may significantly alter wound healing while modifying the vascular response. It is well documented that some antibiotics prolong epithelial repair, which is known to be essential for proper

BOX 55.1 CRITERIA FOR SUTURE REMOVAL

A loose suture
A tight suture
Vascularization of the suture tract
Vascularization of the recipient or donor stroma
Pronounced inflammation or infiltration around a suture
Contraction of the graft–host wound
A thin, fibrous 'healed' graft–host wound scar

BOX 55.2 COMPLICATIONS OF LOOSE SUTURES OR EXPOSED KNOTS

Foreign body sensation and pain
Epithelial erosions and ulcers
Corneal vascularization
Dellen
Conjunctival injection
Tarsal ulcers
Giant papillary hypertrophy, conjunctivitis, or both
Blepharospasm, blepharoptosis, or both
Photophobia
Iritis
Infection
Graft failure

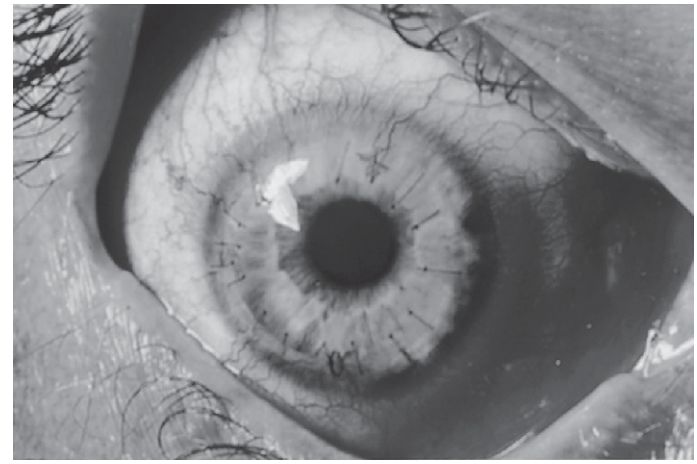


Figure 55.1. A 40-year-old woman with long history of herpes simplex keratitis with pronounced vascularization. Three months after surgery there is exuberant vessel growth over and through suture tracts. Note single 9-0 silk suture needed at time of surgery because of persistent leaking through needle tracts. Six sutures have already been removed.

wound healing. Idoxuridine, trifluorothymidine, and arabinoside monophosphate (the monophosphate ester of vidarabine) cause toxic changes in regenerating epithelium. Interestingly, only the last actually retards closure of corneal wounds while increasing stromal wound strength.[8–10] The first two antivirals reduce tensile wound strength by 50%.[10,11]

Corticosteroids have been implicated both clinically and experimentally in delayed corneal wound healing and in decreased tensile strength.[12–14] This effect is believed to be attributable to the direct reduction in fibroblastic activity at the wound edge. These fibroblasts are derived from the stromal keratocytes, which migrate from the limbal area.[15] The steroid effect, studied with DNA synthesis inhibition techniques, showed 73–82% reduction of cells incorporating isotopes and a 50% reduction in the area of healing.[16,17]

The use of a bandage soft contact lens after keratoplasty to treat an epithelial defect, ameliorate poor surface wetting, or alleviate suture irritation may lead to superficial vascularization, which may give the impression of deep wound edge vascularization. This effect would be very much like that seen when conjunctiva covers a poorly apposed cataract wound. If sutures are removed too soon, wound dehiscence may occur. However, a thick bandage lens or a lens fitting too tightly can cause deep vascularization and provoke graft rejections.[2]

The ultimate dilemma therefore occurs in the treatment of flagrant vascularization of the suture tract (Fig. 55.1). Graft rejection is of great concern and requires an increased dosage of corticosteroids. With more steroid use, wound healing is slowed. If the sutures seem to be provoking vascularization, one may need to remove them, keeping in mind the possibility of wound separation. If maintenance of the vascularized suture is imperative, injection of depot corticosteroid (such as triamcinolone 20 mg) subconjunctivally around the area of donor–recipient vascularization may solve both problems by causing regression of vessels and allowing suture retention. The intraocular pressure must be carefully monitored during this critical time.

The use of an argon laser specifically to close a particularly large vessel leading to an obvious area of the graft or to a suture has been advocated and may be helpful in preventing secondary lipid keratopathy or potential rejection. One of the authors (ELS) has had better success with conjunctival recession and cautery than with the laser. Using either method, the offending vessels have either remained inactive or slowly returned, but with far less aggressiveness.

NYLON SUTURES

Since its introduction in 1968, the 10-0 monofilament nylon (22 μm) suture has become the overwhelming choice of transplant surgeons. Some authorities advocate the use of 11-0 monofilament nylon (16–18 μm) suture combined with the 10-0 nylon,[14,15,18] and 8-0 white silk anchoring sutures are still used, but by only a few surgeons.

The development of this extremely fine, consistent, elastic, and minimally tissue-reactive suture has revolutionized corneal transplantation. The rate of corneal rejection has dropped because of diminished inflammation and vascularization of the wound. The negative side effect of controlled healing is that significantly more time is needed to achieve complete wound healing. Whereas silk sutures require only a few weeks to a few months for wound healing, nylon sutures take months and often a year to achieve the same effect. Wound over-ride and late wound dehiscence may still occur[19,20] but with diminished frequency, because most transplant surgeons now wait 7–12 months to remove the final nylon sutures. This contrasts with studies of wound dehiscence reported in the early and middle 1970s when experience was first being gained in their use.[4,18,19,21–23]

In an attempt to decrease postoperative astigmatism and achieve faster visual correction, the use of multiple interrupted, single, or double continuous sutures or a combination of these methods was developed. These suture closure styles have permitted variations on

the usual timing of suture removal. Development of selective interrupted suture removal and running suture adjustment techniques followed.[24–29]

These early suture removal or adjustment proponents all make the assumption that the manipulation of the wound and hence the corneal curvature in the first months after surgery will ultimately yield lower astigmatism and more stable faster vision. Although it is self-evident that removing a particularly tight suture tends to lower the astigmatism in the offending meridian, there is still no evidence that final vision or suture out astigmatism is affected.

The use of biomicroscopy, careful manifest refraction, keratometry, and topography all aid in the analysis of the offending tight suture. Recent studies have shown, however, that even with the most sophisticated topographic analysis, vector forces can still confound the appropriate axis of astigmatism. It has also been shown that if one were to decide to remove interrupted sutures early, one should remove only one suture at a time to control results better.[29] Consequently, surgeons are committed to conducting sequential additional postoperative visits for suture removal without real documentation of added success. Fortunately, there is only a small risk of complications such as wound gape, excessive meridian steepening and, rarely, wound leak.

Intraoperative adjustment of a single or double continuous suture has never been shown to be reliable because of the forces exerted by intraocular pressure, wound edema, a sutured scleral ring, or the lid speculum. Postoperative continuous suture slit-lamp adjustment should take place after epithelial healing and corneal thinning. The technique requires acquired skill and a gentle touch, usually using sterile tying forceps. The forceps are then used to break through the epithelium and Bowman's membrane, taking care to grasp gently but not pinch the suture. The continuous suture is then pulled, in a rotating fashion, loop by loop from the flatter meridian toward the steeper one. Great care is necessary to avoid twisting or torque to the suture during this maneuver. If the suture appears too tight or does not move easily, then the adjustment should be aborted. Obviously with the double continuous suture technique one usually adjusts the tighter, deeper suture, leaving the more superficial suture alone.

Both authors are still not convinced that the risk-to-reward ratio is acceptable in this problematic maneuver. There is no evidence that the risk of suture breakage and the need for urgent repair justifies the possible, but yet not proven, lowered postoperative astigmatism. Furthermore, it has been shown that the immediate positive results can be quite transient and can regress back to the original measurements.

Other complications related to suture removal[23,30,31] are summarized in Box 55.3.

THE TIMING OF SUTURE REMOVAL

Given the effect of factors such as recipient age, method of suturing, and medication on graft wound healing, an exact timetable for suture removal is of limited value, and only general guidelines follow:

1. In clear, nonvascularized grafts with buried, well-approximated sutures and good visual acuity, there is no need for suture removal.
2. In grafts sutured with both interrupted and running sutures, the usual sequence for removal of the cardinal (anchoring) 9-0 or 10-0 nylon sutures (if not removed at the end of surgery) begins around the fourth to sixth postoperative week.
3. When 16–20 10-0 nylon suture in interrupted fashion alone is used, suture removal is initiated at approximately 3 months and completed between 6 and 12 months.
4. For 10-0 nylon running suture alone, in most cases it is left in place for 7–12 months.
5. When 11-0 nylon suture is used (double running technique), the ophthalmologist has several choices: (1) The 10-0 running nylon suture may be removed between 2 and 4 months and the 11-0 suture left in place indefinitely.[13,32,33] (2) Both sutures may be left in place indefinitely if spectacle refraction provides good vision. (3) When scar formation is noted (6–12 months), either the 10-0 or the 11-0 suture is removed while retaining the other, and refraction is performed 4–6 weeks later.
6. Remove all broken or loose sutures protruding through or above the epithelium (except when no healing has occurred) to prevent induced infection, chronic irritation (which may lead to rejection), and frequent return visits for removal of suture remnants.

In infants and children, where wound healing may occur rapidly (weeks to just a few months), the timing of suture removal becomes extremely critical. Rapid new vessel formation, wound contraction, and loosening of suture[34] may lead to rejection at a much earlier time than in the adult eye. Parents should be encouraged to inspect the eye frequently for increased injection, discharge, or accumulation of mucus around loosened sutures. Often weekly visits are needed so that suture removal can be carried out and inflammation leading to rejection can be avoided.

TECHNIQUE

Many instruments and techniques can be used to remove sutures. Frequently used instruments are listed in Box 55.4.

BOX 55.3 COMPLICATIONS RELATED TO SUTURE REMOVAL

Wound gape
Wound over-ride
High astigmatism
Rapid graft edema
Graft rejection or failure
Endophthalmitis
Glaucoma
Hyphema with vitreous hemorrhage
Retinal detachment
Epithelial downgrowth

BOX 55.4 INSTRUMENTS USED FOR CORNEAL SUTURE REMOVAL

Vannas scissors
Westcott (sharp points) or fine stitch scissors
Razor blade knife (blade breaker)
Beaver blade no. 75
20-gauge needle
Argon or yttrium–aluminum–garnet (YAG) laser
Jeweler's forceps
Tying forceps

Topical anesthesia is used with either 0.5% proparacaine hydrochloride or 0.5% tetracaine hydrochloride given in both eyes. Suture removal may be carried out with the patient seated at the slit lamp, or a microscope may be used with the patient reclined in the office chair. In the former method, an assistant holds the upper eyelid against the supraorbital rim with a sterile cotton swab so that no pressure is exerted against the eye. A razor blade knife is used to cut the sutures in host tissue (when knots are buried in the donor cornea), and a jeweler's forceps removes the sutures by grasping the exposed suture end. The grasped suture is rotated so that the force is directed toward the periphery. This protects against the graft from being pulled away from the host. For recipient-buried suture knots, the opposite technique is performed.

The authors' preferred technique is to cut sutures at the bend or 'V' of the suture and then use the blade of the knife to tease the suture free of epithelium so that there is a long piece of suture to grasp with a jeweler's forceps. A 45° Alcon I-Knife or a no. 75 Beaver microsharp blade, originally used at surgery and then resterilized for one or two more uses, usually suffices.

With running 10-0 nylon sutures, every other loop in the host cornea is first cut, leaving an intact loop that is also grasped in the host tissue and pulled peripherally. Antibiotic prophylaxis, such as neomycin/bacitracin ointment, twice daily for 3 days after suture removal is recommended. Patients are instructed to contact the office if there is pain, excessive redness, decreased visual acuity, or photophobia. Significant change in vision is very common after suture removal, and patients must be forewarned of this possibility. Most patients are then examined 24–48 h after suture removal for epithelial defects, wound override, or dehiscence.

Children or patients with severe photophobia or blepharospasm may need general anesthesia, mask-assisted oxygen with deep intravenous sedation, or peribulbar blocks to facilitate wound inspection and suture removal.

COMPLICATIONS OF SUTURE REMOVAL

The four most commonly encountered problems after suture removal are (1) retained suture material, (2) infection, (3) wound dehiscence, and (4) induced astigmatism.

RETAINED SUTURE MATERIAL

Chronic low-grade inflammation, visual fluctuation caused by changes in astigmatism, and late suture erosion through the graft surface may occur with retained nylon sutures (Fig. 55.2). With running suture wound closure, this is usually not a problem except at the position of the buried knot (usually the 12 o'clock position). With multiple interrupted buried suture knots, however, suture breakage in attempted knot removal may occur, especially if the knot has not been placed close to the graft surface or if a significant amount of stromal fibrosis has occurred around the knot.

Bourne and Maguire[35] have suggested using an argon laser to cut the knot free of the suture in cases where the bulky knot and trailing suture cannot be removed with the usual technique. They use a laser setting of 300–500 mW, 50 μm spot size and a 0.2 s duration pulse. Although this technique seems like overkill, it may serve unique situations and should be considered.

INFECTION

Harris and coworkers[36] reported a large series of 108 bacterial and fungal ulcers in patients who underwent penetrating keratoplasties

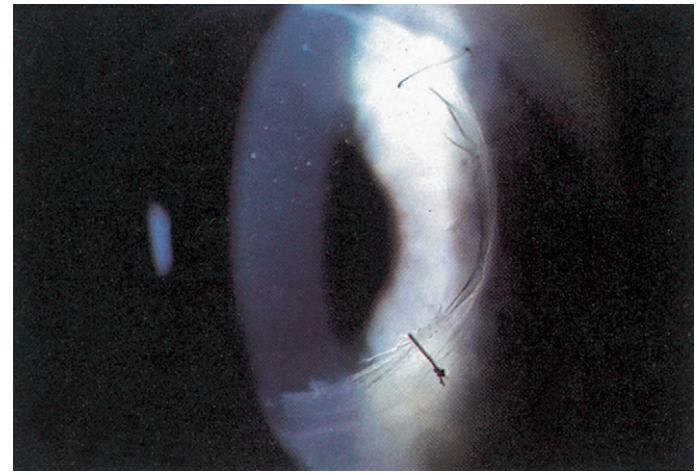


Figure 55.2. White, active keratitic precipitates (KP) in eye with retained, broken, buried 10-0 nylon sutures 8 months after penetrating keratoplasty for keratoconus.

1–72 months before 'an exposed suture having been noted and/or removed.' Thirty-three eyes (31% of total number of infections) had an infection within 10 days of suture removal. Most infections (89%) occurred in eyes receiving corticosteroids and maintenance antibiotics.

It is apparent clinically that the act of suture removal is a potentially dangerous time.[37,38] This is the case presumably because the epithelial surface is broken and mucoid debris and bacterial organisms are introduced into the graft as the nylon suture is rotated out of the stroma. The surgeon must show particular care when cutting and removing loose sutures so as to avoid introducing debris into the graft. Immediately after suture removal, an antibiotic ointment is placed in the eye, and topical antibiotics are instilled for several days thereafter.

WOUND DEHISCENCE

In the event of wound dehiscence, wound over-ride, or wound rupture (Fig. 55.3, *A* and *B*), the patient is scheduled for immediate surgical repair. Most adult patients treated by one of the authors (ELS) undergo repair under topical anesthesia to minimize the chance of further wound separation or even periorbital hemorrhage. The other author (FSB) prefers peribulbar injection before repair. A small percentage of patients (usually children) undergo intravenous sedation or anesthesia standby, or both. If there is only anterior wound dehiscence, interrupted 10-0 nylon sutures are placed in the center of the wound and past the obvious limits of poor wound healing to prevent further wound separation (Fig. 55.3, *B* and *C*). One should take care to pass the needle through the apparently intact wound without touching the wound edges, thereby lessening the chances of further dehiscence. As many sutures as needed are used. If there have been inordinate amounts of wound edema, instead of 10-0 nylon, one author (ELS) uses 9-0 polypropylene, or rarely 8-0 silk, for wound approximation. If there is a broken running suture, it is spliced to a new 10-0 nylon after the graft is aligned with interrupted 10-0 nylon sutures (see Figs 55.3, *B* and 55.4). In cases of complete wound dehiscence or rupture when there is a flat chamber, the anterior chamber is redeepened with air or sodium hyaluronate to separate the iris from the wound during suturing. Subconjunctival cephazolin sodium 100 mg and Celestone (Schering, Kenilworth, NJ) 6 mg are

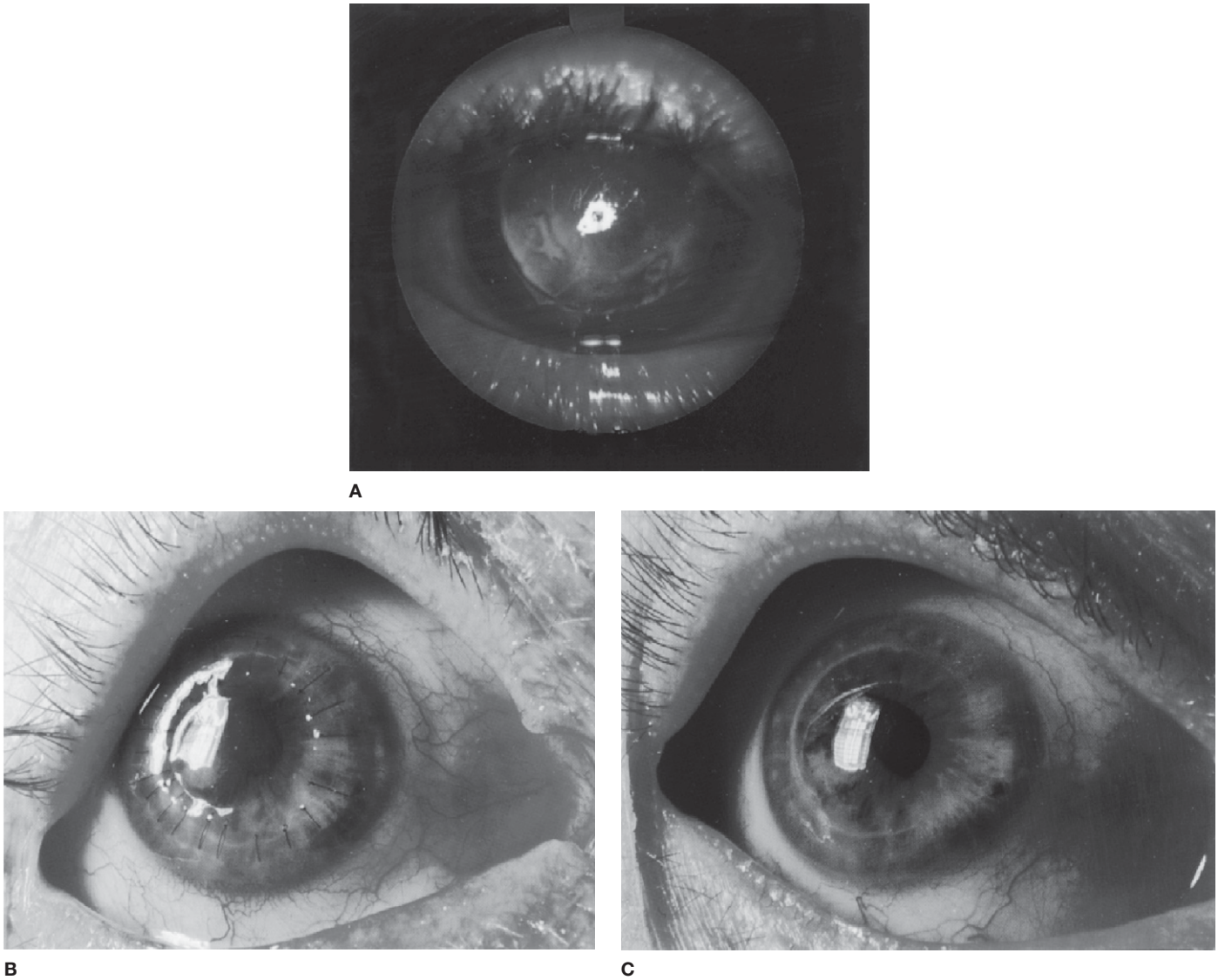


Figure 55.3. *A*, Wound dehiscence at the temporal half 4 days after running 10-0 nylon suture removal 9.5 months after surgery in a 72-year-old man. *B*, Appearance of the same patient 4 months after wound revision and placement of interrupted sutures. Note that nasal sutures are placed in an apparently healed wound as a precaution to further wound separation. *C*, The same patient 13 months after wound revision with vision corrected to 20/40 with a +8.50 +2.00 × 120 aphakic spectacle.

used by one author (FSB). The new sutures are considered as if they were initially placed, and wound healing is judged as previously described.

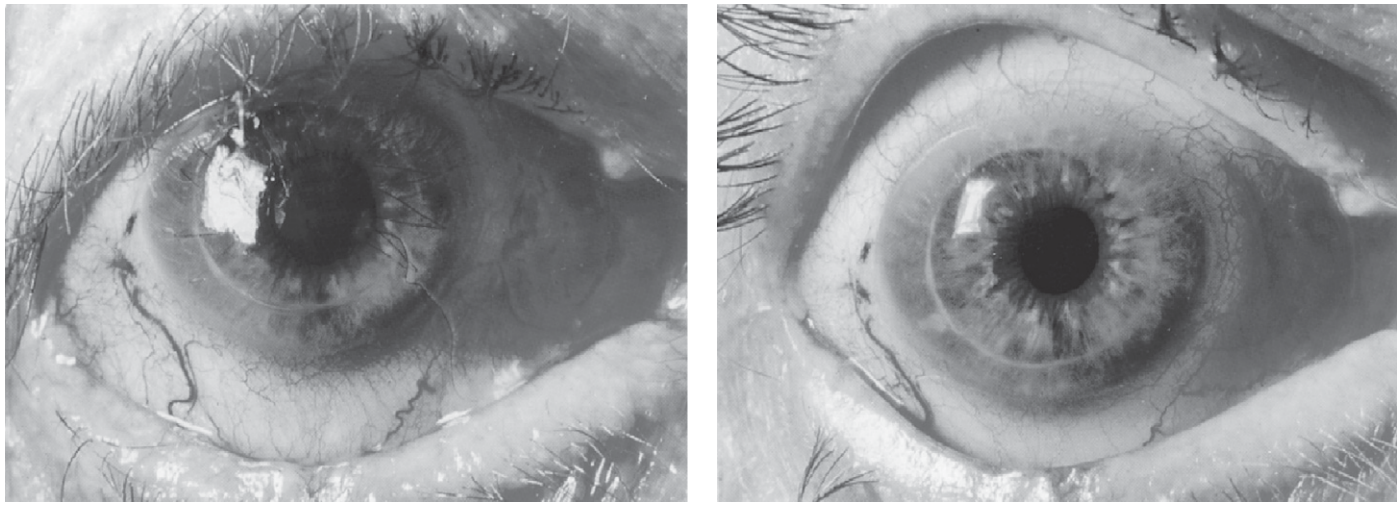
The overall incidence of wound dehiscence has been estimated at 2–9%.[16,20,21,32] Some cases in earlier reports occurred in the first months after surgery and were attributable to poor healing or necrotic recipient tissue and were not directly related to suture removal. Graft failure rates of 50% after wound dehiscence were reported in the older literature but have declined significantly in the authors' experience in recent years.

INDUCED ASTIGMATISM

Nylon sutures may induce wound compression when tightened because of their inherent elasticity and the need to achieve watertight wound closure at surgery. Many grafted eyes before suture removal have flatter K readings and become steeper (that is, more myopic) after suture removal. Significant changes in astigmatism (either greater or less) may also accompany suture removal.

A word of caution is advisable. Some corneal surgeons advocate observation rather than suture removal in quiet grafted eyes that are without progressive vascularization and have minimal postoperative astigmatism (less than 3.5 D). Many grafted eyes, particularly when the knots are buried, when individual sutures are selectively removed, or when the double running technique is used, have regular mires on keratometry and very acceptable distance and near visual acuity at the 20/30 level. Too many corneal surgeons have shared the unnerving experience of inducing large amounts of astigmatism and patient annoyance by removing compressive sutures in low astigmatic grafts. An evolving concept regarding suture removal in an otherwise quiet eye that is refractable using a spectacle or a contact lens to an acceptable level of vision is to allow the wound to heal as it is with the suture in place.

The trade-offs resulting in some eyes where suture retention is the decided course of action seem to be chronic changes in refractive error (that is, a mildly unstable wound) and very subtle inflammation, particularly surrounding the retained suture with subepithelial fibrosis, and, ultimately in many eyes, late suture breakage with accompanying inflammation (Fig. 55.5).



A B

Figure 55.4. *A*, Traumatic dehiscence between the 5 and 7 o'clock positions 3 months after surgery in a 79-year-old woman. Running suture was spliced onto new running 10-0 nylon suture for wound repair. *B*, The same patient 8.5 months with all sutures removed. Vision was 20/25 with a soft contact lens.

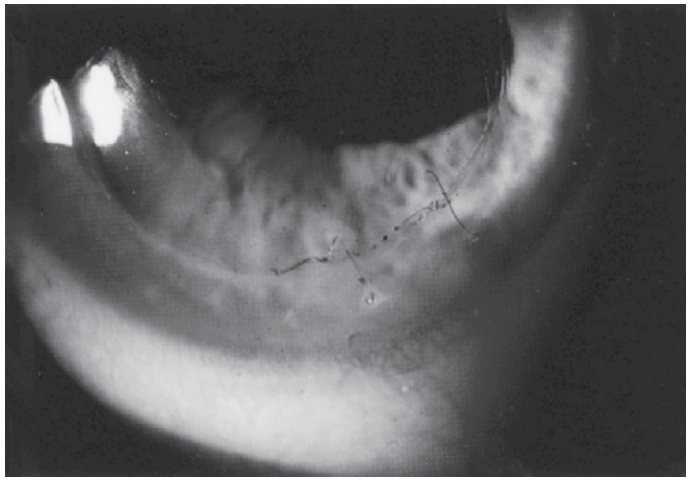


Figure 55.5. Late breakage of interrupted 10-0 nylon suture 3 years after penetrating keratoplasty for Fuchs' dystrophy in an 80-year-old man. Note whitish subepithelial reaction surrounding both protruding ends of 5:30 o'clock suture and secondary perilimbal inflammation.

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56 Astigmatism preoperative and operative factors

Sheraz M. Daya, Marcela Espinosa-Lagana

Since the goal of penetrating keratoplasty (PKP) in most cases is visual rehabilitation, maintenance of a clear graft in the long term is only one consideration. The other is to provide a good optical outcome by minimizing astigmatism and refractive error. Understandably there are a number of variables that influence astigmatism; however, standardization of technique and attention to several preoperative and operative factors can be very useful in reducing astigmatism in the long term.

DONOR CORNEA

Pre-existing donor astigmatism and orientation of the donor in relation to the host have been speculated to affect astigmatic outcome. The influence on astigmatism by orientation of the donor in a similar meridian to the host, as in suturing the 12 o'clock point of the donor to the 12 o'clock position in the host, as well as lateralizing for instance right donor eye to right host, was the subject of a multicentric investigation, the OWL (Orientation with Lateralization) study in the UK. The study was inconclusive and not published.[1] Another study, however, demonstrated that donor astigmatism could influence the axis and magnitude of astigmatism, and this could be influenced by orientation of the graft.[2]

HOST DISEASE

Host diagnosis as well as morphology can affect postoperative outcome. In keratoconus, removal of all visible diseased tissue encompassed by the Fleischer ring provides some reassurance that the rim will be thick enough for the donor and continued ectasia in the rim will be avoided. However, there have been reports of continued inferior ectasia and elevation 10–15 years postoperatively, with induced astigmatism successfully treated by wedge resection.[3,4] There are several possible mechanisms of this progressive astigmatism, including progressive corneal thinning of the host cornea, progressive misalignment of the graft–host interface over time, and recurrence of keratoconus in the graft. With newer imaging tools for the cornea, including corneal tomography and particularly ocular coherence tomography, it will be easier in the future to determine the true cause of progressive inferior steepening (Fig. 56.1).

Inflammatory disease such as *Herpes simplex* may result in a thin vascularized rim, which can affect outcome as well as the postoperative course. Sectoral vascularization can lead to differential healing, again making the astigmatic outcome unpredictable. Selective early suture removal in these instances may minimize the effect of wound healing and lends support to the use of interrupted sutures in these instances.

HOST TREPHINATION

This is felt by many to be one of the greatest influences in astigmatism, and the objective of predictably reproducing a similar cut from one case to the next has influenced the production of numerous devices and approaches. The goal of host trephination is to cut the cornea as vertically as possible.[5] Most trephination methods commonly used, including freehand and the Hessburg–Barron, result in cutting outward with a larger opening on the endothelial side compared with the epithelium. The pressure exerted on the cornea while trephining, the intraocular pressure, as well as the method of suction fixation (whether to the sclera or cornea) all influence the degree of outward sloping. Low intraocular pressure can be elevated by injection of viscoelastic through a limbal stab incision prior to trephination. Corneal fixation by the Hessburg–Barron trephine is felt to increase the overcut by drawing the peripheral cornea into the outer ring. The Barron trephine works on similar lines; however, it has 16 compartments to minimize the displacement of peripheral cornea. The more sophisticated Hanna- and Krumeich-guided trephine systems both attempt to minimize overcutting posteriorly and provide suction fixation onto the sclera. Both systems are excellent; however, they are complex and can be expensive.[6] An alternative system that appeared to be promising was the Asmatome.[7] This is a motorized system that uses vacuum fixation on the central portion of the cornea and draws the cornea (both host and donor) into a rotating motorized trephine. A comparative study did not demonstrate any convincing evidence of the benefit of this system over other similar trephination systems.[8]

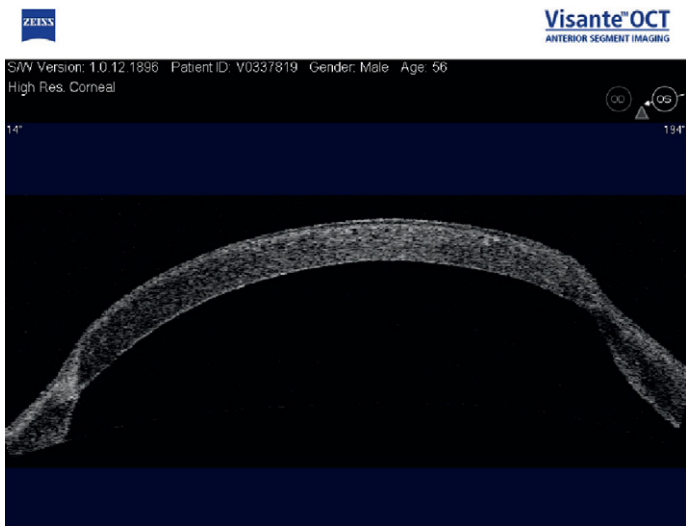

Figure 56.1. Visante (Courtesy of Zeiss-Meditec) ocular coherence tomography (OCT) image of the left eye of a patient who received a corneal graft 26 years earlier for keratoconus. The image demonstrates peripheral corneal thinning outside the corneal graft accounting for graft tilt and inferior steepening with high astigmatism.

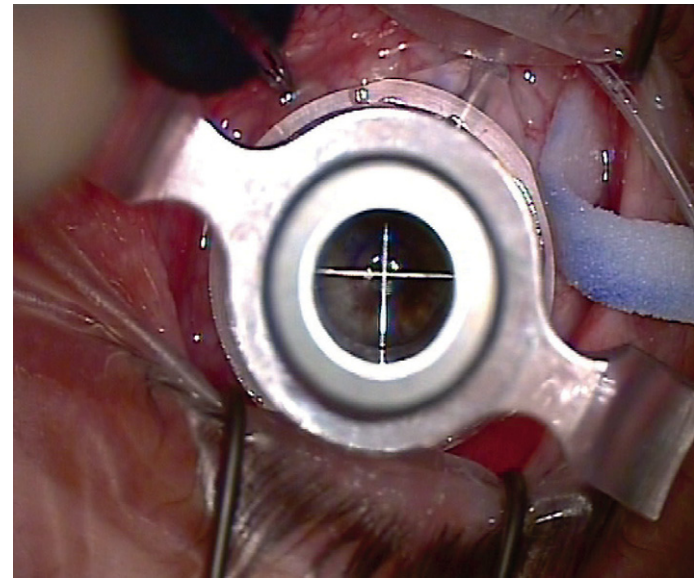

Figure 56.2. Daya Disposable Recipient Trephine System (Courtesy of Network Medical, UK), which uses scleral vacuum fixation to accurately guide an ultrasharp trephine.

Eccentric trephination on the host can induce astigmatism.[9] Centration is best ensured by carefully marking the center of the cornea. The correct location can be confirmed using calipers. Using a 3 mm optic zone marker around the central mark also provides a further point of reference during trephination.

TREPHINE QUALITY

Trephine quality in terms of sharpness can have considerable influence on cut quality. Newer developments in nanotechnology, including ion-forging of trephines, in combination with nanostructured carbon coatings can produce high-quality cutting edges, which are more stable with diamond-like properties.[10] With improvements in sharpness there is a reduction in the necessary force and consequent corneal deformation, resulting in a better cut with less posterior overcutting. However, sharp trephines are less forgiving and a guided mechanism is helpful in avoiding decentered and tilted cuts, and contributing to a more vertical cut (Fig. 56.2).

POSTERIOR LEDGE

The surgical technique of leaving a posterior ledge compensates for the overcutting and assists in producing a self-sealing incision. The ledge is created by trephination to over 90% of the cornea depth, preferably to Descemet's membrane, and then cutting the host button out with beveled corneal scissors. If performed correctly with a thin and narrow lip, the possibility of graft tilt is minimized and closure can be accomplished with loose sutures without the danger of a wound leak (Fig. 56.3). Excessive compressive forces of sutures to ensure closure are avoided, thereby minimizing astigmatism. On the other hand, a thick or irregular posterior lip can lead to graft over-ride and potentially increase astigmatism. The posterior lip is best examined after removal of the button to ensure that it is equally thin for 360°. If not, it is best removed entirely with curved corneal or Vannas scissors. Another technique to prevent graft over-ride is to make radial cuts in the ledge, decrease resistance from the ledge, and minimize over-ride, and still accomplishing the goal of wound security.

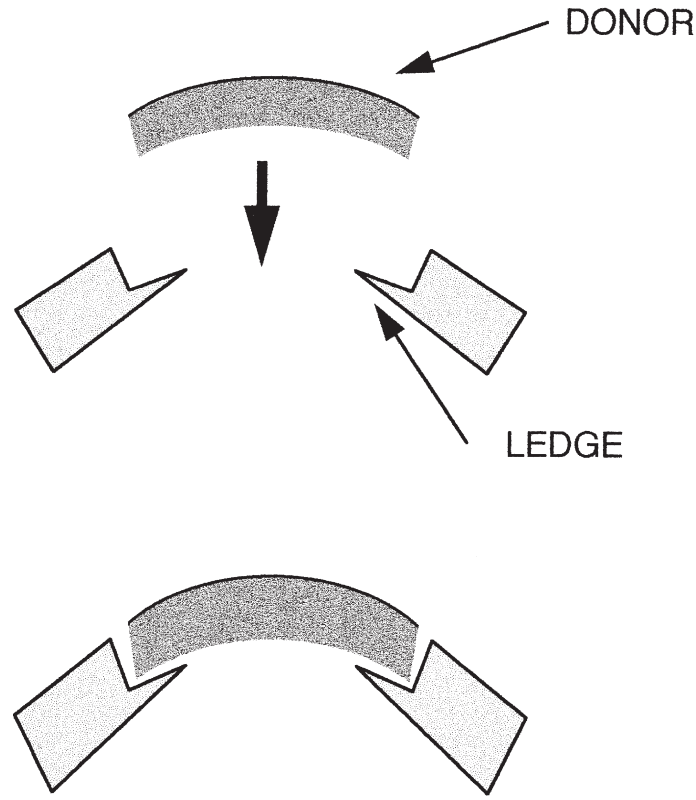

Figure 56.3. Schematic to demonstrate the benefit of a recipient ledge in preventing wound leaks and permitting loose suture closure. The posterior lip avoids tilt and acts as two-step incision, decreasing leakage and chamber flattening during surgery.

DONOR TREPHINATION

Most commonly, donor trephination is performed by cutting from the endothelial side to the epithelium. The rational basis for this is

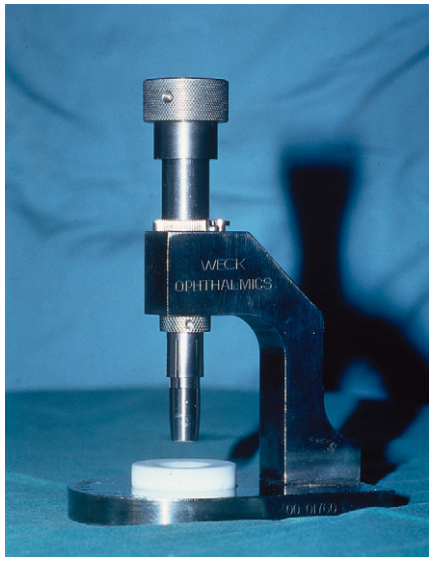

Figure 56.4. The Iowa Press (Courtesy of Bausch & Lomb Storz, Rochester, NY, USA), for donor creation cutting from the endothelial side to the epithelium.

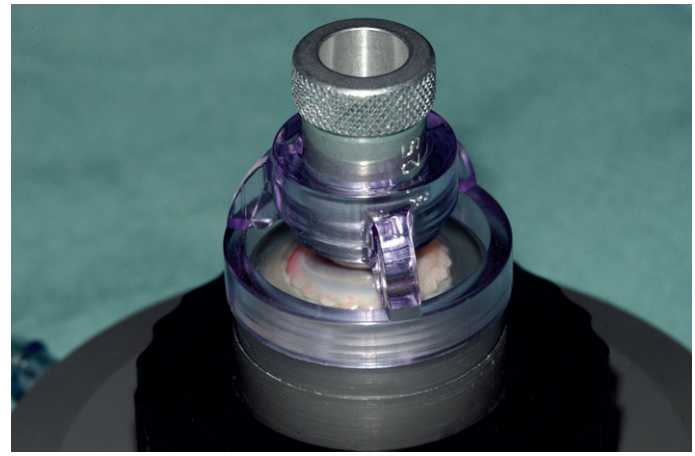

Figure 56.5. Donor preparation cutting from anterior to posterior using a disposable anterior chamber (Courtesy of Coronet Network Medical, UK).

to protect the endothelial surface and it is best accomplished by a vertical punch such as the Iowa Press (Fig. 56.4) or the Barron disposable donor punch. Centration as well as good apposition of the donor on the donor block helps to ensure a vertical and round cut. Compound curved donor Teflon wells with centration circles help to achieve these goals. Oversizing the donor by 0.25–0.5 mm compensates for the overcutting that generally occurs in host trephination. In high myopic cases such as keratoconus, the use of the same-size donor in effect undersizes the donor[11,12] in relation to the host, producing corneal flattening with reduction of myopia.[13]

Another approach that has become more popular has been to create an artificial anterior chamber and cut the cornea from the epithelial side in the same manner as the host using the same-size trephine. This is accomplished using nondisposable systems such as the Krumeich-guided trephine and Hanna systems. Disposable systems such as the Coronet (Network Medical, UK) are now available (Fig. 56.5). Theoretically the wound configuration in the host and donor will be identical if same-size trephines are used and the pressure of the artificial anterior chamber is similar to the recipient eye. Use of this approach has not been shown to minimize astigmatism.[14]

LASER TREPHINATION

Excimer laser trephination has been advocated by Naumann, who has suggested that high astigmatic change following suture removal can be decreased using this technique.[15] The technique, however, has not become popular partially because of limited access to this costly technology. Additionally, excimer laser trephination with existing lasers does take considerable time to accomplish complete trephination. Femtosecond laser technology has been used to perform trephination and is currently under investigation. This will be discussed briefly below under 'Future Directions.'

EXTERNAL COMPRESSION

An oval opening in the host will produce astigmatism. A speculum that places force on the fornices and globe can contribute to ovalization. The use of a three-dimensional speculum with rotatable blades like the Schott speculum (Katena Instruments, Denville, NJ) with rests placed on the forehead and cheek removes pressure from the globe. Decreasing the aperture size also reduces pressure on the globe but at the same time can reduce access to the eye.

The Flieringa ring is useful in maintaining scleral support and ensuring a circular opening when used in aphakic cases; however, when sutured in place improperly, it can produce an oval or distorted opening.

An oval opening sometimes cannot be avoided, for instance in keratoconus eyes, where the host rim has a tendency to retract, especially inferiorly. Compensation for an irregular opening can be made by careful placement of cardinal sutures and further interrupted sutures.

CARDINAL SUTURES

This is probably one of the most important operative factors in minimizing astigmatism. These sutures influence correct placement of the donor within the host and must be placed symmetrically. Placing 8- and 12-blade radial keratotomy markers on the host prior to trephination provides useful reference marks for symmetric suture placement. The second suture is considered the most important and is placed at the point where the donor cornea is bisected by toothed grasping forceps. A useful tip is to let go of the needle when it has been passed through the donor and into the host. The cornea is inspected to ensure that it is symmetrically placed without over-riding on either side (Fig. 56.6). If the needle is incorrectly placed, it can be withdrawn from the host and repositioned. A similar maneuver can be used for the 3 and 9 o'clock sutures.

SUTURING

There are many methods of suturing the cornea to minimize astigmatism, and each method has its own supporters. Whichever method is used, sutures should be passed as vertically as possible into the donor cornea to 90% depth and passed through just above Descemet's membrane. The needle should pass through the host at the same level and up vertically.[16] Depressing the posterior ledge and leveling the needle so that it appears that it is going 'downhill' is a good method to ensure maximal depth on the host. Because of the vector forces created, a shallow and sloped bite on the donor

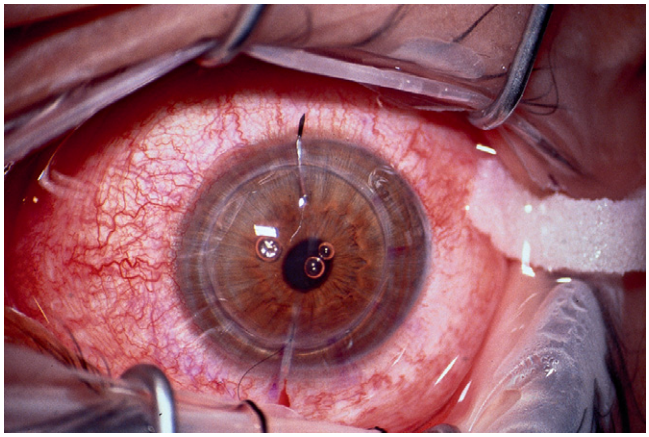

Figure 56.6. Graft alignment checked by releasing needle from the needle holder prior to complete passage.

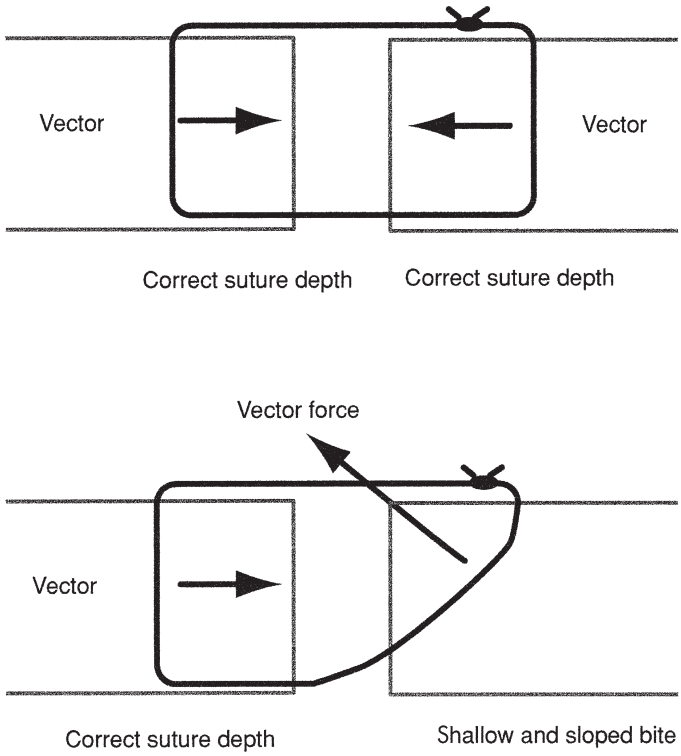

Figure 56.7. Schematic comparing the vector forces induced in a correctly placed suture compared with a sloped and shallow bite on the donor.

can lead to an over-ride, and a similar pass on the host can lead to an under-ride on the donor, both contributing to astigmatism (Fig. 56.7). Compound curved needles such as the CU8 needle (Alcon, Fort Worth, TX) help considerably in attaining short deep bites on the donor and host. Deep bites on both donor and host are easier to achieve using interrupted sutures.

Sixteen interrupted sutures provide excellent graft–host apposition; however, selective suture removal for early visual rehabilitation cannot be performed without risking graft dehiscence. More recently, because of improved graft stability derived from interrupted sutures, many corneal surgeons have been using 22 and 24 interrupted sutures and, although able to, find less need to selectively remove sutures during the early postoperative period. A 24-bite running suture is favored by many, as this suture can be adjusted operatively and postoperatively.[17,18] The Hoffmann double running suture is favored by many surgeons in some parts of Europe; however, it has not been demonstrated to be of any particular advantage in terms of astigmatism.[19] A combined 12 interrupted and 12-bite running suture combines the best of both worlds, but takes longer to perform.

On completion of suturing, qualitative measurements using reflective devices such as the Maloney ring can be used to adjust sutures to ensure that a circular mire is obtained. Surgical quantitative keratometers such as the Smirmaul or Varidot can be used, although a clear advantage has yet to be demonstrated.

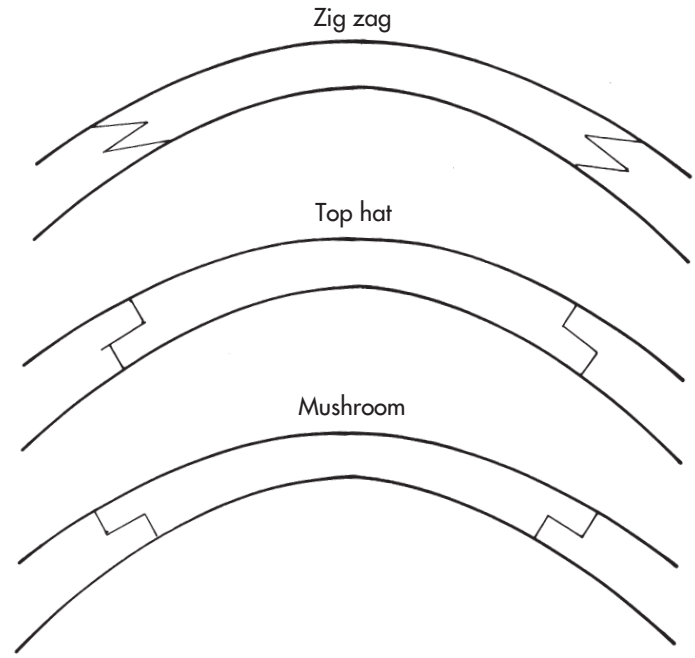

Figure 56.8. Schematic of the Steinert 'zig-zag' geometric configuration using the Intralase Femtosecond Laser (Courtesy of Intralase Inc., Irvine, CA).

FUTURE DIRECTIONS

FEMTOSECOND LASER TREPHINATION

The femtosecond laser approved for making cuts within the cornea has been popularized in refractive surgery and has become increasingly popular in flap creation. It has the advantage of being able to perform formed cuts in the cornea on both donor and recipient. A variety of geometric patterns including a top-hat, mushroom, and several 'tongue and groove' patterns have been developed, and preliminary evidence suggests that this results in better graft–host apposition with reduced astigmatism (Fig. 56.8). Experimental evidence has already demonstrated improved mechanical stability using the top-hat configuration.[20]

INTRACORNEAL RING (KRUMEICH)

A novel concept of incorporating an alloy ring (8 mm cobalt–molybdenum–titanium) in the graft–host wound has been pioneered by Krumeich and demonstrated to not only reduce astigmatism but also allow for postoperative manipulation to reduce astigmatism

further by intentional shape deformation. Recent evidence presented suggests that the ring not only arrests vascularization of the donor corneal button but also reduces the risk of graft rejection. The mechanism for this is unclear.[21]

SUMMARY

There are a number of pre- and postoperative factors that influence astigmatism. The more important aspects are preparation of both donor and host, as well as suture placement and proper wound apposition. Adherence to many of the concepts described above certainly minimizes astigmatism in both the long and the short terms. In spite of new technology, including improved trephination, basic principles and methods to minimize astigmatism are essentially unchanged.

Neither author has proprietary or financial interests in any of the products or materials described.

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57 Contact lens fitting after penetrating keratoplasty

Christine W. Sindt

Contact lenses fitted after penetrating keratoplasty (PKP) are usually provided either for therapeutic reasons, for example a soft lens used to treat a persistent epithelial defect or to correct residual refractive error, especially astigmatism.[1]

THERAPEUTIC FITTING

Hydrogel (soft) contact lenses have a long and well-accepted history of therapeutic applications. In PKP patients, these are primarily used for relief of pain, mechanical protection for a denuded or eroded corneal epithelium, maintenance of corneal hydration, barrier protection from the action of the lids or lashes, retention of medication in the eye during the few days after surgery, and the general promotion of ocular healing.

In the past, most practitioners have utilized conventional disposable HEMA-based (hydroxy-ethyl-methyl-methacrylate) hydrogels for these therapeutic purposes. HEMA lenses have widespread availability and low or negligible costs. HEMA lenses are commonly available in mid-to-high water content polymers. Ultrathin disposable hydrogel lenses should be avoided, as they may wrinkle and not provide adequate splinting function. While HEMA lenses may appear to move satisfactorily during the first few minutes of lens evaluation, their dehydration on the eye after 30 min or longer may make them behave in a much tighter fashion. As such, it is important to evaluate these lenses after at least 20–30 min on the eye, as well as in follow-up visits.

Penetrating keratoplasties often require regular use and overnight wear for several days to re-establish a barrier to infection and to prevent subepithelial scarring. Silicone hydrogel lenses are superior in this regard as they provide increased oxygen flux compared to conventional hydrogel lenses. Additionally, the risks of secondary microbial infection, while not entirely eliminated, are greatly reduced with the use of a silicone hydrogel (SiHy) lens.[1–4] SiHy lenses do have a stiffer modulus, which will translate into occasional lens awareness for some patients, although this settles quickly. The overall pain relief that it provides is far greater than any minor issues relating to modulus awareness, so this rarely is a problem.

Some disposable lenses are only available in one base curve and thus may potentially gape or move excessively and further aggravate a fragile or damaged epithelium (Fig. 57.1). Conversely, the lens may be too tight, preventing tear and cellular debris exchange (Fig. 57.2). The use of a steeper fitting lens with less movement may be more appropriate in cases involving pain relief or in splinting of the corneal surface. A lens that provides more visible movement is preferred, however, in cases of a corneal epithelium that is eroded, damaged, or absent.

FITTING METHOD

Centration with complete covering of the graft–host sutured junction, comfort, and slight movement on the blink are key signs to achieve satisfactory fitting. The patient is instructed to wear the contact lens until follow-up, which may be as soon as 1 day or as late as 1 week, depending on the physician's level of comfort and expectations of the problem being addressed. Treatment with an antibiotic, cycloplegic, and nonsuspension corticosteroid drop is given in the usual doses after keratoplasty.

When no underlying recipient cause exists for epithelial breakdown in the donor (such as exposure, dryness, or graft–host wound disparity), a therapeutic lens usually achieves healing in 1–2 weeks. Artificial tears such as 0.5 and 1% methylcellulose, guar-based agents like the Systane® (Alcon Laboratories, Fort Worth, TX) line of products, or thicker agents such as Refresh PM or Lacri-Lube (Allergan, Irvine, CA) should be used to maintain wetting of the corneal graft surface. Preservative-free products are preferred, when possible, to avoid a toxic keratopathy.

OPTICAL FITTING TO CORRECT REFRACTIVE ERROR

Among the most significant factors in the determination of final transplant astigmatism are the donor cornea, recipient disease, external compression factors and intraocular pressure (IOP) during trephination, graft centration, donor button to recipient bed size, tissue malapposition, suture placement, wound healing, and suture removal. Since no one surgical technique has eliminated the problem of astigmatism, the surgeon must be prepared to manage the frequent complications of both irregular and high corneal graft

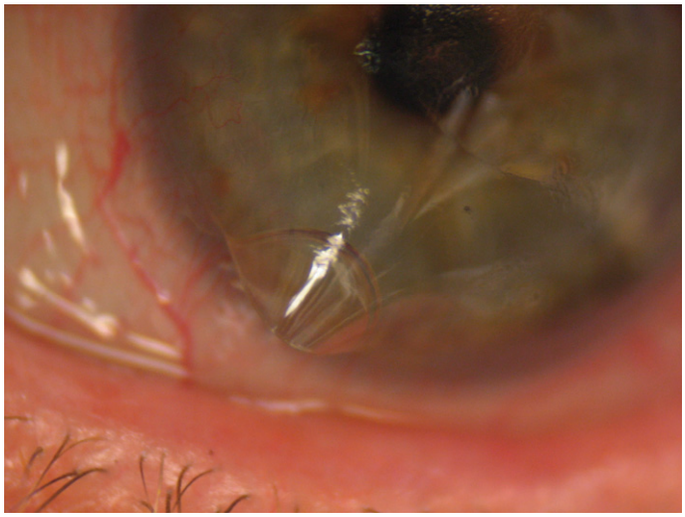


Figure 57.1. Highly irregular or steep corneas will prevent proper draping of soft contact lenses.

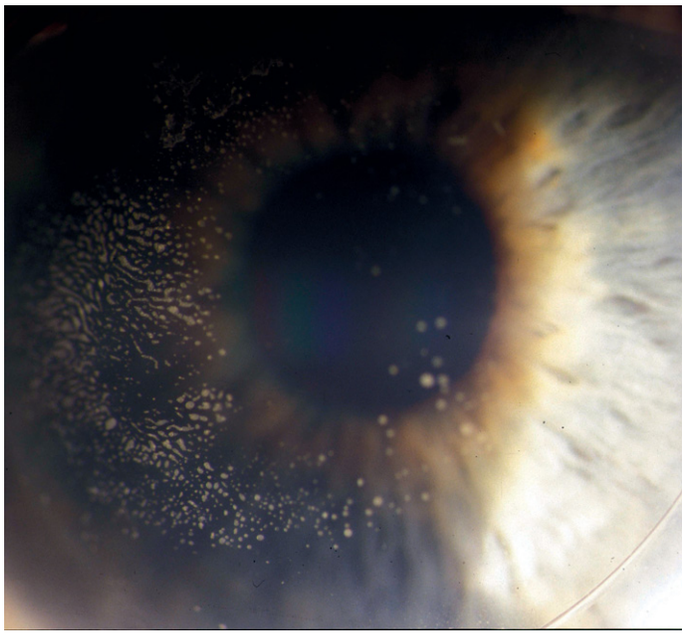


Figure 57.2. Mucus debris under a lens with poor tear exchange.

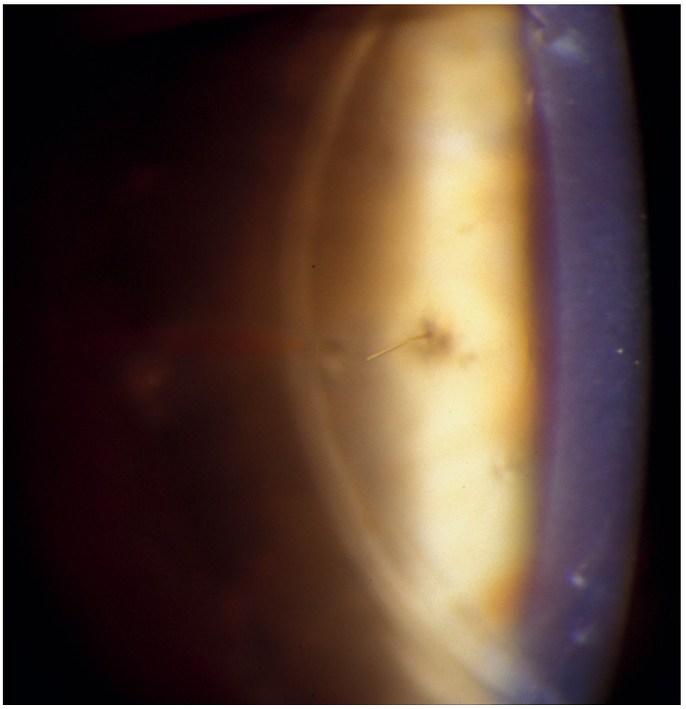


Figure 57.3. Loose or broken sutures must be removed to avoid discomfort and decrease risk of infection or inflammation.

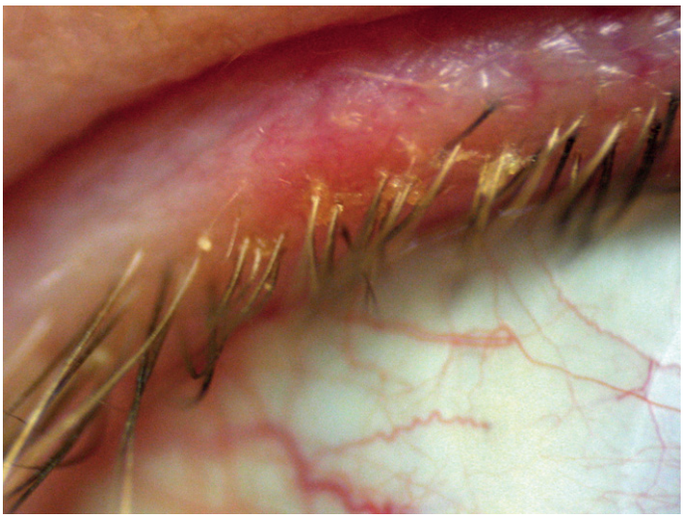


Figure 57.4. Post penetrating keratoplasty patients are wary of touching the eye area. Lack of lid hygiene may exacerbate lid disease, complicating contact lens fitting.

astigmatism.[3,4] Anisometropia is also common following PKP, especially if cataract surgery is concomitantly performed or if the patient had particularly high pre-existing refractive error. Contact lenses have been traditionally implemented to improve visual performance of optical errors after PKP.

The percentage of PKP eyes receiving contact lenses will vary, depending on the surgical technique, the surgeon's amicability toward contact lenses, and the relationship between the contact lens fitter and the referring physician.

TIME OF FITTING

A contact lens may be fitted anytime after the wound has healed and if there is intact epithelium over the corneal sutures. To avoid frequent and costly changes, it is best to wait until selective suture removal has been performed to the surgeon's satisfaction and the corneal topography is stable. Contraindications for optical contact lens fitting include persistent epithelial defects, inflammation, loose sutures, corneal infiltrates, and lid disease (Figs 57.3 and 57.4).

CONTACT LENS OPTIONS

Both soft and gas-permeable (GP) lenses have been used for post-PKP optical correction. Soft lenses have limited ability to correct irregular astigmatism; they also have a higher risk of infection and inflammation. In some cases, soft lenses may be useful to piggyback a GP lens; however, we will primarily limit our optical correction discussions to the use of GP lenses.

Hard versus soft lenses

The author's bias is toward GP lens fitting in grafts, for the following reasons:

1. The average refractive graft astigmatism requiring contact lens fitting is between 4 and 9 D. This precludes sharp visual acuity with most soft lenses.
2. Decreased corneal graft sensation allows for moderate comfort with GP wear compared with the cosmetically fit eye.
3. GP lenses are more durable, more easily verified, easier to clean, have high oxygen transmission, and are less likely to spoil.

GP LENS DESIGN

GP lenses can be classified into (1) corneal designs, (2) scleral designs, and (3) hybrid designs.

All GP lens designs are fitted using fluorescein to determine alignment. Areas of paracentral lens–graft touch and strange astigmatic patterns are invariably seen. The objectives of fitting are to limit this touch and to design a peripheral curve system that allows for adequate tear exchange. It is important to evaluate the fluorescein pattern before the lens is dispensed since small changes in lens design will have a large effect on the overall sagittal depth of the contact lens and will result in a significantly different-looking lens fit (Fig. 57.5, *A–D*). Peripheral curve and edge modification can be done in the office; however, with today's materials and computer-driven lathe technology, it is best to have the lens remade through the laboratory; this ensures repeatability on remakes and decreases future chair time.

As soon as the lens has been examined on the eye and found to be satisfactory, the lens can be dispensed. Dispensing includes practicing insertion and removal of the lens under technician observation and thorough instructions in the cleaning and care of the lens. Wearing schedules are comparable with those in cosmetically GP fit eyes, with all-day wear by 1 week (Table 57.1). The patient is instructed to return to the office immediately if redness, secretions, visual blurring, or pain (RSVP) should occur.

The patient is followed at 2 weeks after the initial dispensing, 1 month after that, and then at 6-month intervals. At each visit, the lens fit is evaluated, the lens is removed to check for graft complications, and the lens itself is verified to make sure that the parameters have not changed (and to make sure that the patient has the correct lenses in the correct eyes).

Corneal designs

Corneal designs include spherical, front toric, back toric, bitoric, larger or smaller diameters, and rotationally asymmetric and reverse geometry. In general, it is best to start with spherical lenses of varying diameters before trying to work with an alternative design.

A lens centered directly over the graft is in the ideal position. Perfect centration, however, rarely occurs in grafts with high or irregular astigmatism, a decentered button, or a peripheral wound irregularity. In difficult cases, even after many lens trials and modifications, the best lens fit may still have the patient apparently looking through the edge of the lens. If the patient sees well and has good comfort and the graft health is not compromised, a decentered fit is acceptable (Fig. 57.6).

Scleral designs

Scleral lenses primarily fit the sclera and vault the irregularity of the cornea (Fig. 57.7 *A* and *B*). These lenses offer superior comfort and handling compared to other lens types. New lens materials supply adequate oxygen transmission, however, in this author's experience, scleral lenses should not be fitted on eyes with endothelial cell counts of less than 1000 (Fig. 57.8) to avoid edema. Around 800 cells seem to be where problems arise, so 1000 leaves a margin of safety.

Scleral lenses are fitted based on sagittal depth as opposed to keratometric readings. While there are formulas to calculate the sagittal depth of the eye, a fitting set is the easiest way to determine necessary vault. The amount of sagittal depth of the eye is determined by the horizontal visible iris diameter, the corneal curvature, and the eccentricity value of the peripheral cornea.

The diameter of the scleral lens will determine the fitting technique, and the manufacturer should be consulted on the subtleties of a particular lens. In general, the lens should exhibit alignment with the sclera, without impingement of blood vessels (Fig. 57.9, *A* and *B*). There should be pooling in the limbal area and either complete vaulting or gracing touch over the central cornea. Notches can be cut in the periphery of scleral lenses to prevent impingement of pinguecula blood flow (Fig. 57.10).

Larger (18 mm or greater) lenses will create a suction on the eye. It is necessary to break the suction before removal. This is easily done by pressing on the eye and does not seem to be a deterrent to patient compliance or health of the graft (Fig. 57.11). Fenestration holes may be added in the limbal pooling area to relieve the suction effect and aid with removal of scleral lenses smaller than 18 mm. Larger lenses, however, cannot have fenestration holes due to pooling of air in the optical zone.

Hybrid designs

Hybrid lenses (rigid center and soft skirt) aid in the centration and comfort of the contact lens. The Synergeyes® (SynergEyes Inc, Carlsbad, CA) lens has a central GP lens with a Dk (oxygen transmission) of 100 and a 31% water low Dk skirt. These lenses are not intuitive to fit; they are fit much steeper than expected and, if the lens exhibits tightening, the lens fit must be made steeper yet. The lens should move vertically with the blink, like a standard soft contact lens.

The GP portion of the Synergeyes® lens is 8.2 mm, which is the average size of the donor button. One must watch the lens cornea junction to avoid corneal erosions. High cylinder corneas will induce flexure of the lens, and over-refractive cylinder will be demonstrated.

GP LENS MATERIALS

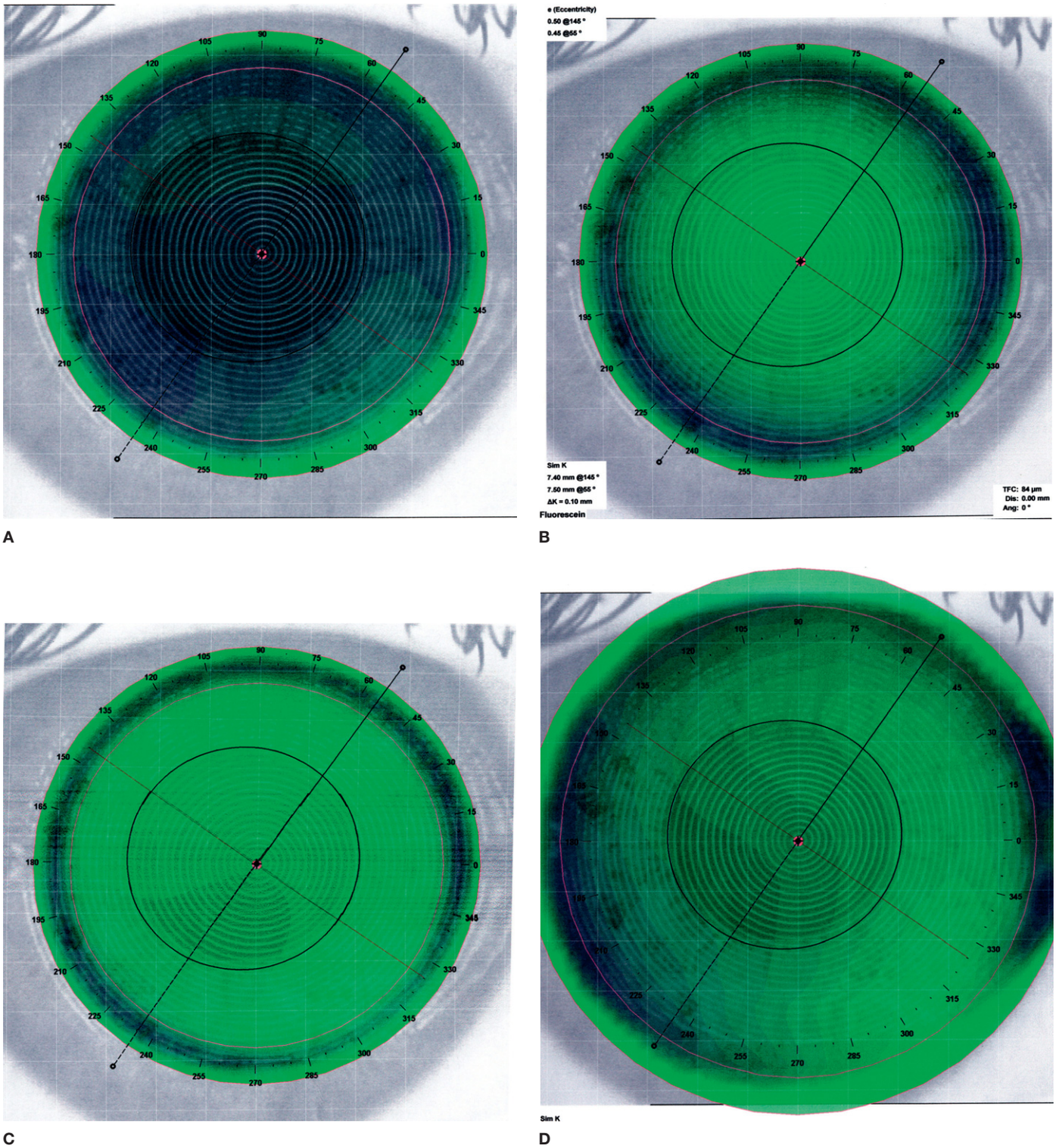
GP lenses are available in a variety of oxygen transmissibility, surface wettability, and button diameters. It is best to discuss the specific needs with the laboratory when selecting a material.

MEASURING THE CORNEAL CURVATURE

Topography is most helpful when analyzing a cornea for a contact lens fit. Elevation data are significantly more useful than axial images. Tangential maps, while having limited use in diagnosis, are of no value in contact lens fitting.

Axial maps describe rate of change. The axial map may be useful in selecting an initial base curve of the contact lens; however, it does not give information on how the lens will perform on the eye.

The elevation map, however, depicts the highs and lows of the cornea. This map is particularly useful in discerning where the lens



A B C D

Figure 57.5. The sagittal depth of a contact lens is affected by changes in base curve, peripheral curves, and diameter. Steepening the base curve and/or the peripheral curves or increasing diameter will tighten the fit. *A,* Alignment fit. *B,* Base curve 3 D steeper than alignment lens. *C,* Peripheral curves steeper than alignment lens. *D,* Diameter 2 mm larger than alignment lens.

Table 57.1 Recommended wearing schedules for penetrating keratoplasty contact lens wearers

Day 1: 2–4 h
Day 2: 4–6 h
Day 3: 6–8 h
Day 4: 8–10 h
Day 5: 10–12 h
Day 6: 12–14 h
Day 7: 14 h max

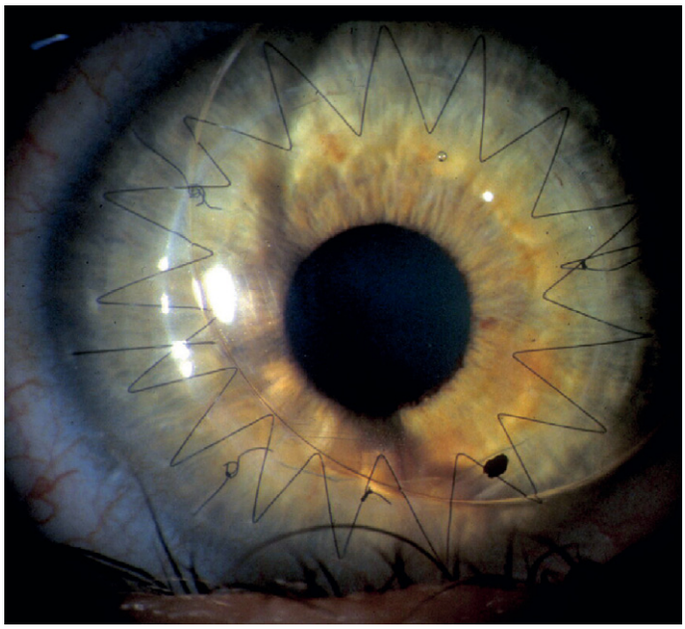


Figure 57.6. Graft fits are often poorly centered. Determination of a good fit should be made on comfort, physiological tolerance, and vision.

will ride (always over the highest elevation, unless the eyelid forces are particularly strong) and where problematic areas of erosions may occur.

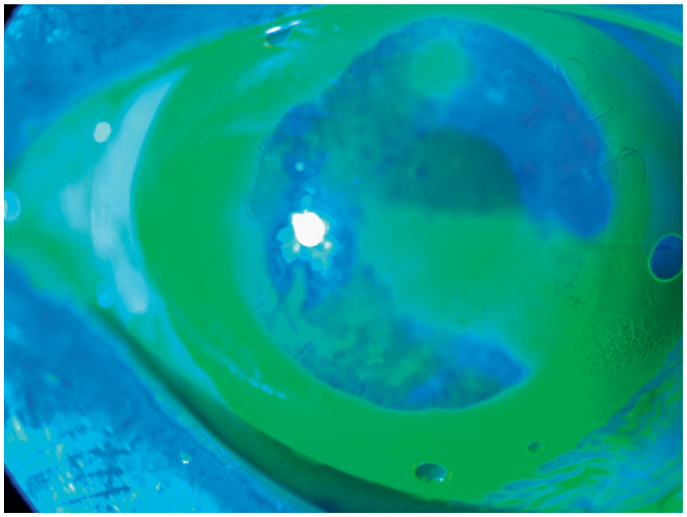
The fluorescein evaluation of a contact lens will correspond to the elevation map. Areas of touch correspond to the red or elevated areas on the elevation map, whereas on the axial map the red areas simply refer to the areas of greatest curvature, which could either represent an elevation or a dip in the cornea.

POST PENETRATING KERATOPLASTY TOPOGRAPHY AFFECTING THE CONTACT LENS FIT

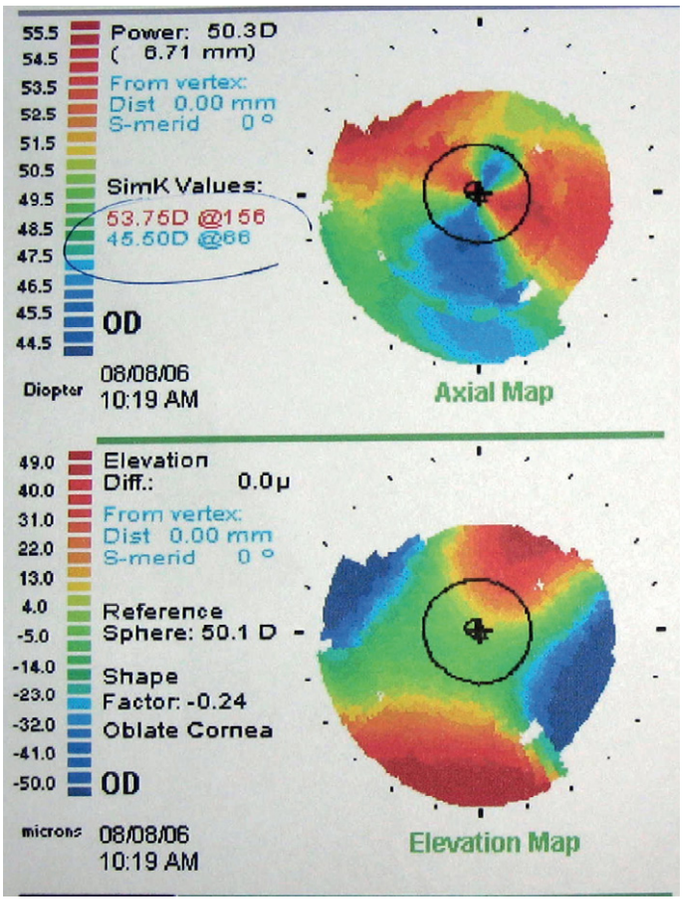
Lens design and selection is based on the topography of the eye.

The plateau graft

A plateau graft, also commonly called a drum head graft, has a relatively flat center and steeper periphery (Fig. 57.12). A plateau graft may result from several factors, including tight stitches, low IOP at the time of surgery, or a button that is less than 0.5 mm larger than the host. A relatively small button is frequently used in patients with keratoconus in order to reduce myopia. Therefore, a plateau graft is relatively common in this setting.



A

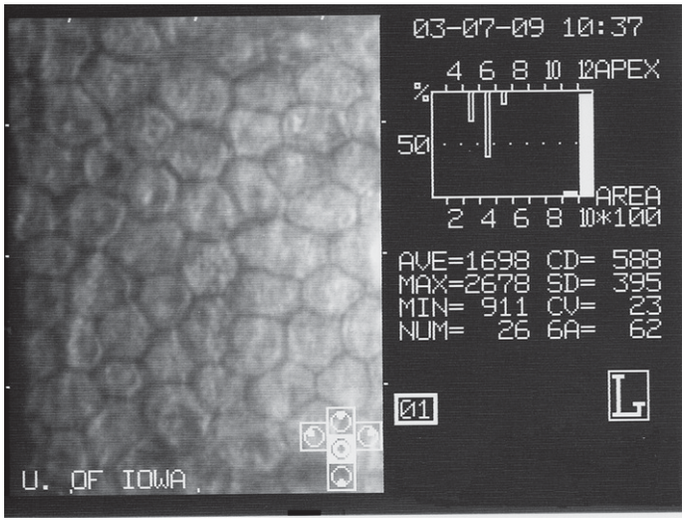


B

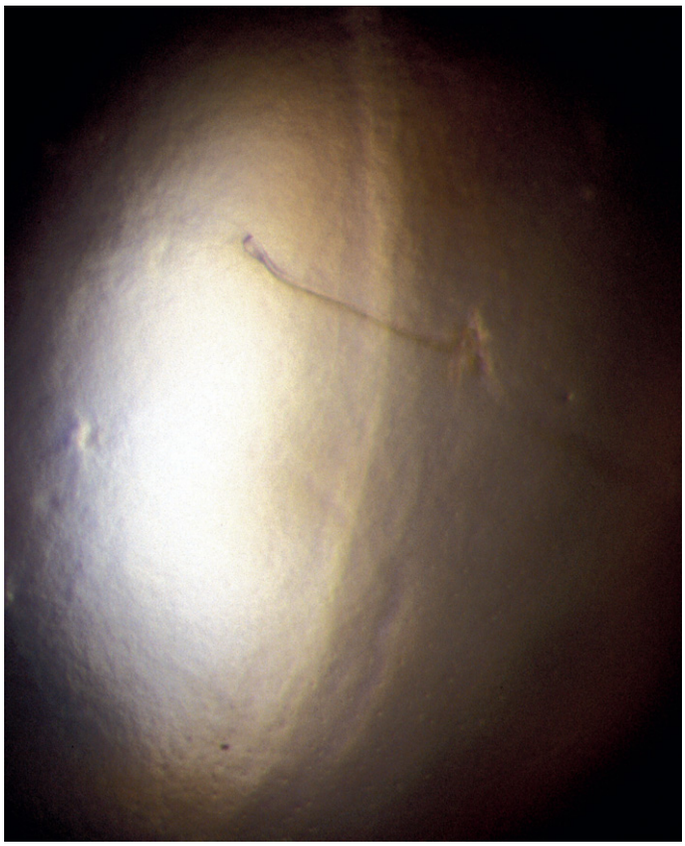
Figure 57.7. *A,* Scleral lenses align in the periphery and mask the irregularity of the cornea. *B,* The corneal toricity of the topographer corresponds to the fluorescein pattern of the contact lens.

This type of graft is arguably one of the most difficult to fit with a contact lens. It is also difficult to surgically correct and is best to avoid it at the time of surgery. Postsurgical correction includes resuturing or removal of the running suture.

A standard designed GP, such as typical 9.0 mm lens, is a very bad option for a plateau graft. The lens will decenter and align over the graft–host junction. Air bubbles will be trapped under the

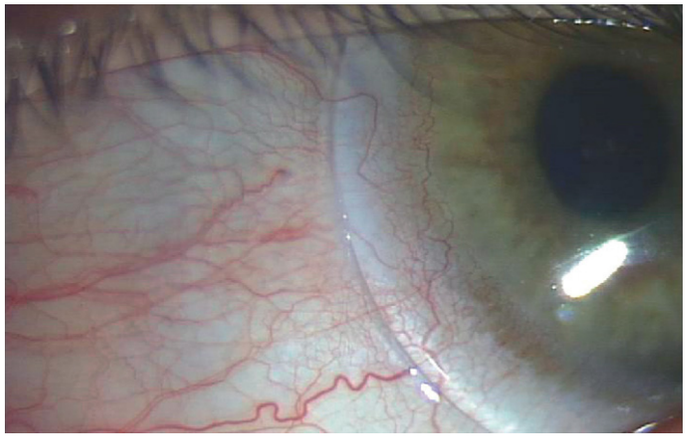


A

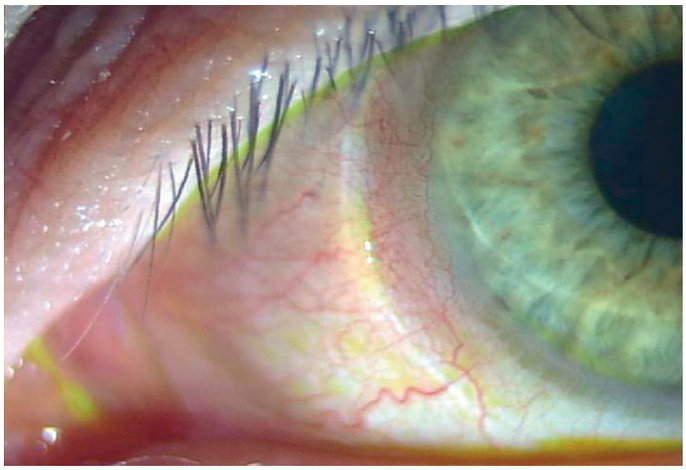


B

Figure 57.8. *A* and *B,* Stromal edema induced by contact lens wear on a graft with an endothelial count of 588.



A



B

Figure 57.9. *A,*Tight peripheral curves will indent the sclera and impinge blood flow. *B,* Removing the lens will cause rebound hyperemia and inflammation.

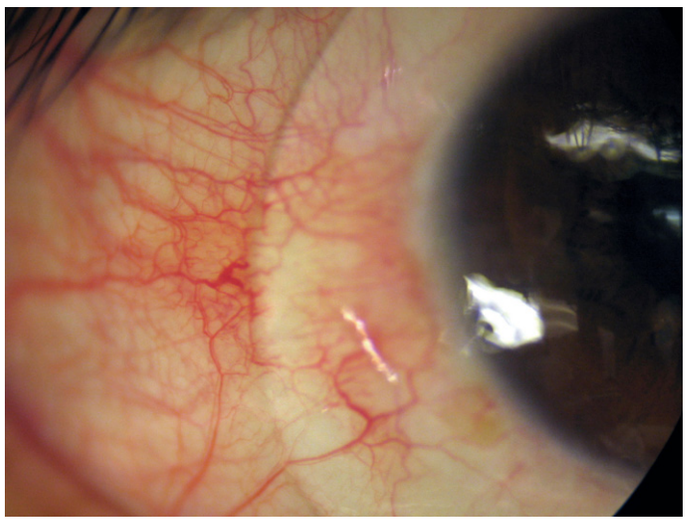


Figure 57.10. Local blood vessel impingement may occur over pinguecula causing inflamed pinguecula and subsequent lens intolerance. Notches can be cut out of the lens to relieve impingement.

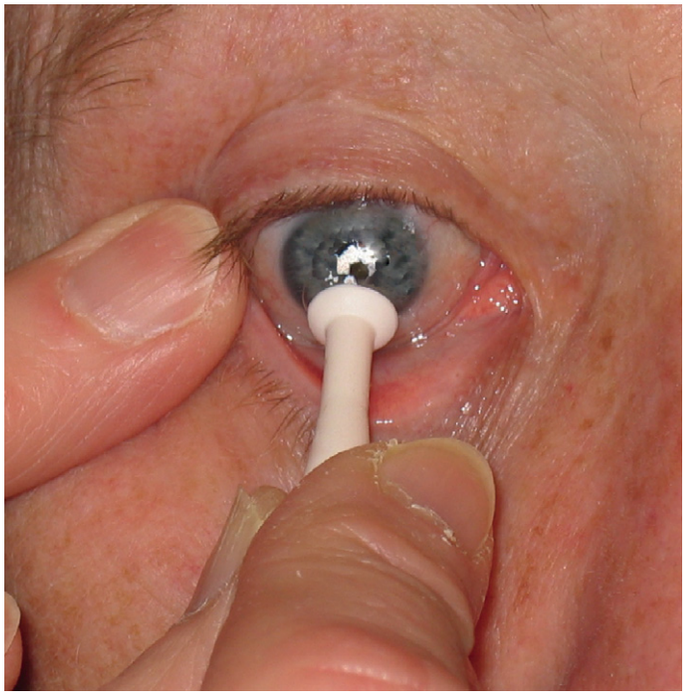


Figure 57.11. Suction must be released before removing lens. Place plunger in inferior one-third of lens. While lifting up on the plunger, push in on the globe to break the seal.

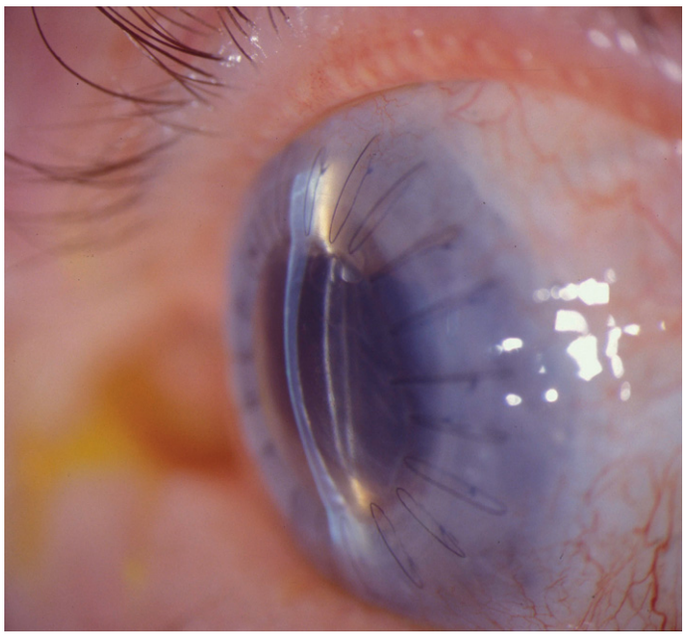


Figure 57.12. Centrally flat plateau grafts are often the most challenging to fit.

lens and/or there will be inferior edge lift off. Small, flat lenses, designed to align with the center graft, will ride very high (Fig. 57.13). A large-diameter reverse geometry or a scleral lens is the best option (Fig. 57.14). To fit a large-diameter lens to a plateau graft, select a lens that aligns in the periphery, and then select another lens that aligns centrally (usually with some coaxing of the lids to hold it in place). The laboratory will easily be able to take these two measurements and integrate them together in a reverse geometry design.

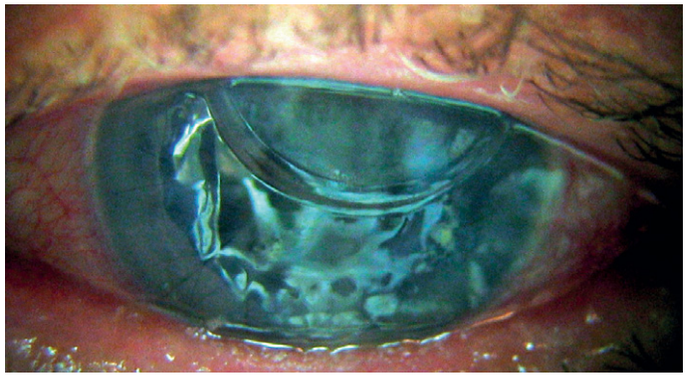


Figure 57.13. Contact lens fit in alignment to a 30.00 D graft rides high and does not cover the pupil.

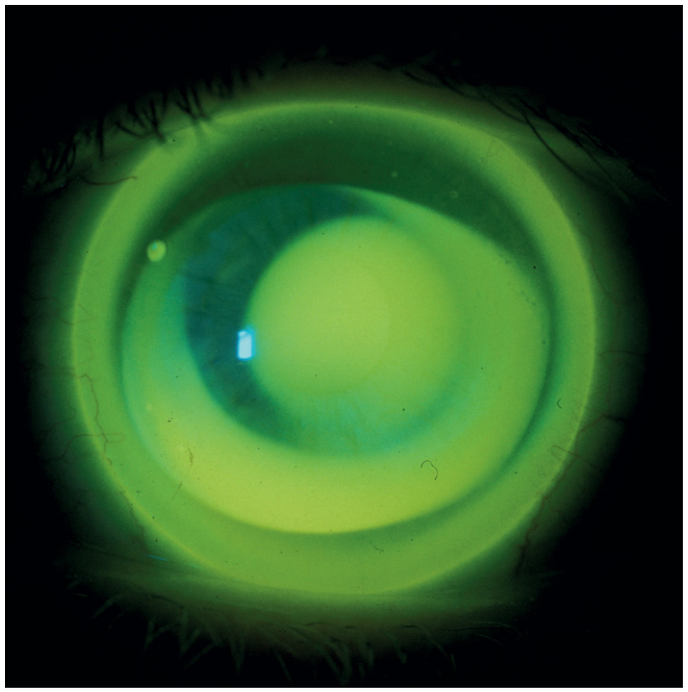


Figure 57.14. Large-diameter, reverse-geometry lenses are often the most effective lens on a plateau graft.

The proud graft

The proud graft has a steep center with significant flattening into the periphery (Fig. 57.15). In this case, the graft is evenly elevated above the host. The proud graft results from a small recipient bed or a large donor button. The result is a pseudo-cone effect. Surgical correction options for a proud graft include resuturing, repeat PKP, photorefractive keratectomy (PRK) for anisometropia (surface ablation recommended rather than LASIK due to concern about graft avulsion during flap creation), and epikeratophakia.

These grafts are fitted with the same principles as with keratoconus. The base curve radius needs to be steepened, while the peripheral curves need to be flattened. These corneas are more difficult to fit because, unlike the extreme prolate corneas of keratoconus, these corneas need a larger optical zone and there are few fitting sets that meet this requirement. If the optic zone is not steep enough or of sufficient diameter, the contact lens will rock on the apex of the cornea and exhibit inferior lift off as the upper lid holds the superior lens edge against the eye (Fig. 57.16).

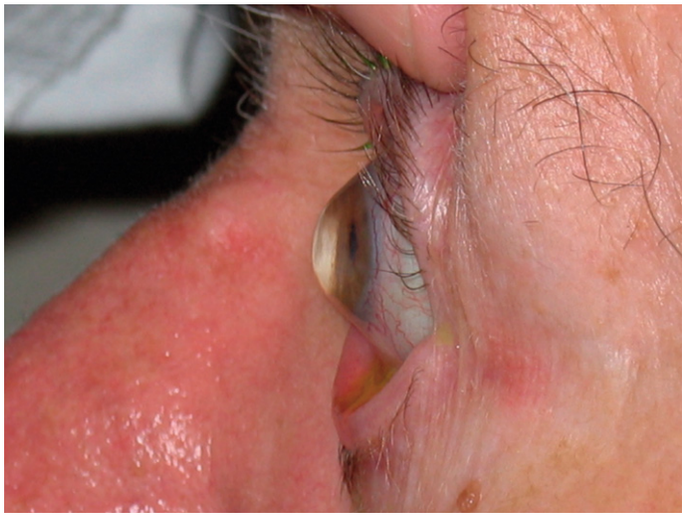


Figure 57.15. Pseudokeratoconus grafts require contact lenses with significant sagittal depth.

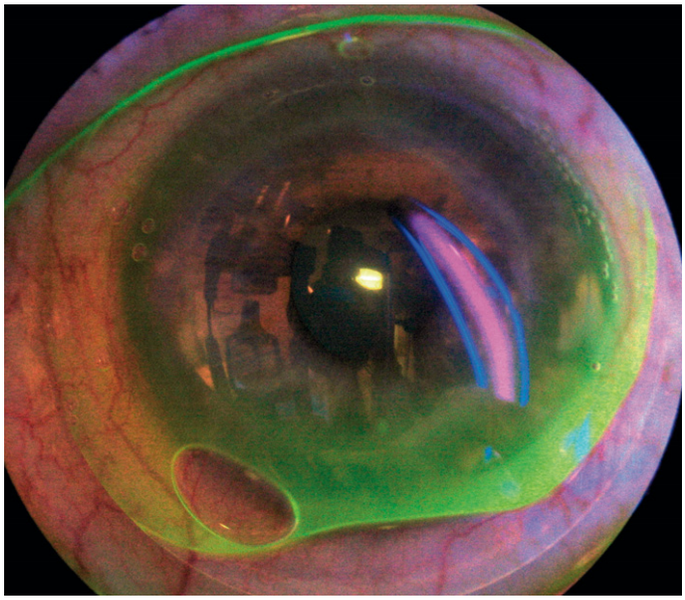


Figure 57.16. Inferior edge lift off on a proud graft caused by insufficient sagittal depth with resulting tipping of the lens.

The tilted graft

Graft tilt can happen anywhere on the graft but is usually seen inferiorly (Fig. 57.17). It is common in patients suffering from keratoconus or pellucid marginal degeneration when the entire ectatic area was not removed during surgery, often being called recurrence of keratoconus. Graft tilt is also trephine dependent and results from undercutting of the tissue. Wound dehiscence, tissue malapposition, improper suture placement, and unequal suture tension will also result in tilting of the graft. Surgical methods to correct graft tilt include selective suture removal, placing new sutures, wedge resections, and wound revision.

Lens fitting on a tilted graft takes a good bit of creativity. Lenses commonly used involve large-diameter corneal or scleral lenses, small lenses that are held up by the upper lid and avoid inferior lift off, keratoconus designs if there is an isolated point of elevation, or asymmetrical lenses that have different curves in different quadrants of the lens.

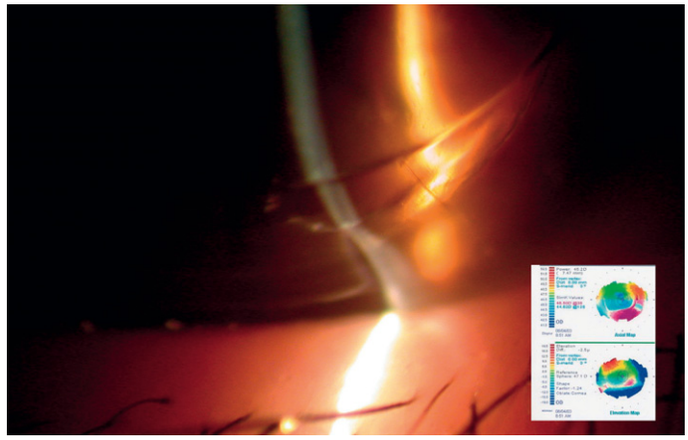


Figure 57.17. Graft tilt after a cornea transplant for pellucid marginal degeneration.

The high cylinder graft

A high cylinder graft results from an elliptical opening or improper cardinal suture placement or tension. While 5–6 D of astigmatism is common, fitting difficulties begin when there is an excess of this amount. Surgical correction of high cylinders includes selective suture removal, resuture, corneal relaxing incisions (with or without compression sutures), refractive procedures, wedge resection, repeat PKP, or refractive implants. Toric intraocular lenses are not advisable, in this author's opinion, because if a contact lens fit will be necessary anyway, all the lenticular (IOL) cylinder will show through the contact lens, equal and opposite in power to the original corneal cylinder.

Fitting high cylinder corneas with contact lenses is highly dependent on the extent and location of the cylinder. Contact lens options include spherical GP lenses, bitoric/back toric lenses, and large-diameter/scleral lenses.

On a graft, the cylinder can be located just on the graft (creating high refractive astigmatism), just on the host (creating difficulty with centration), or across the entire eye (Fig. 57.18.)

Always try a spherical lens first. On a graft where the majority of the astigmatism is centrally located, or if there is with-the-rule astigmatism, the lens will generally center nicely and the patient will have good visual acuity (often preferring the vision compared to better aligned by fluorescein evaluation) toric lenses (Fig. 57.19).

A cylinder wholly located on the host tissue will cause decentration of the contact lens, since the corneal contact lens will ride over the highest elevation on the cornea.

SUTURE REMOVAL

Contact lens fitting can take place approximately 2 weeks post suture removal. This time allows for healing of epithelial defects and stabilization of corneal topography. Topography of the graft immediately after suture removal, however, will show the approximate shape of the graft (Fig. 57.20). Approximate curvature readings can be reviewed immediately post suture removal to determine if special fitting requirements will be needed; however, it is preferable to wait 2 weeks to allow for smoothing and stabilization.

PIGGYBACKING

Using a silicone hydrogel lens to piggyback a GP lens will increase comfort and can protect the fragile epithelium of the graft. It can

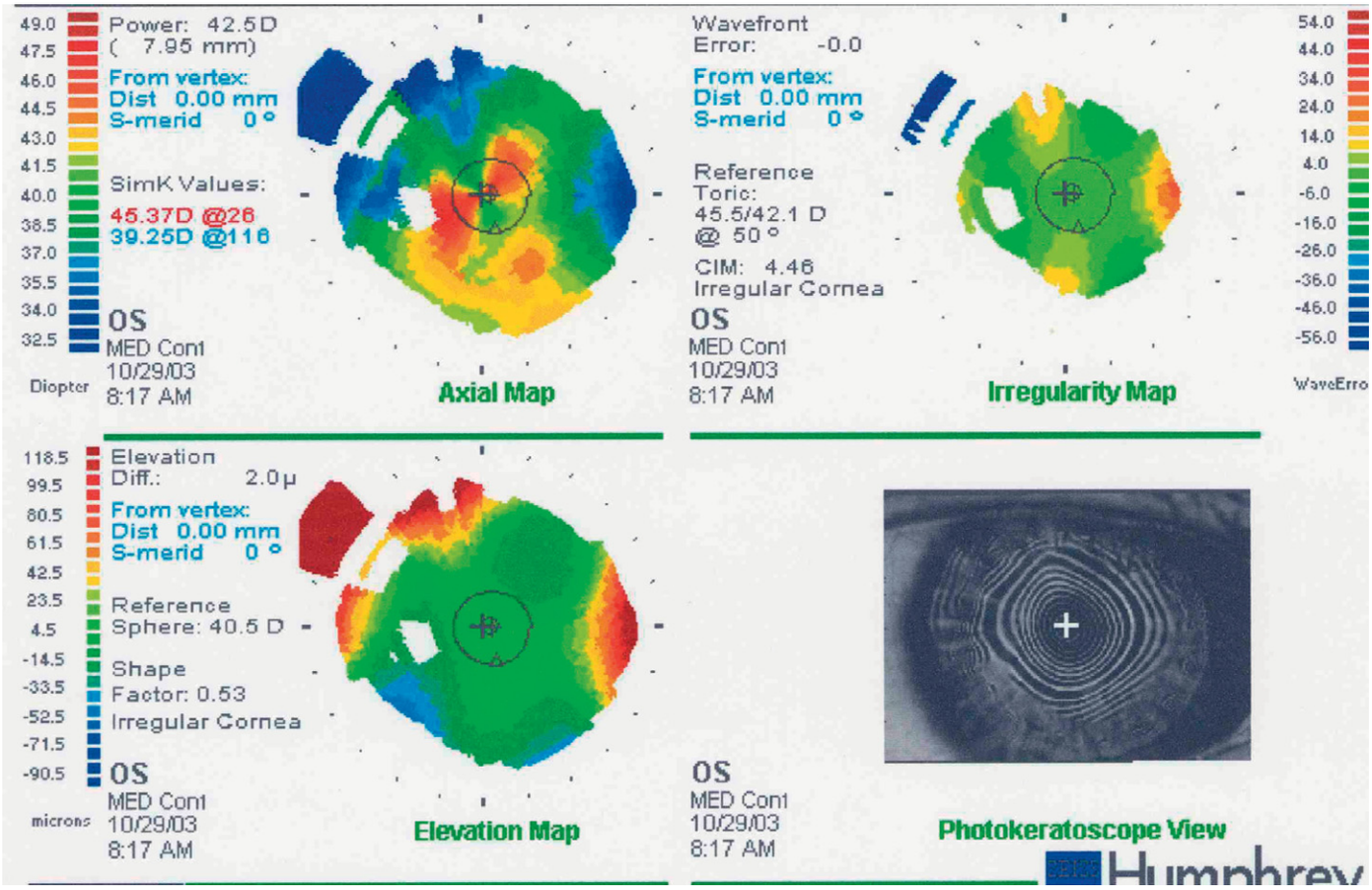


Figure 57.18. Cylinder located wholly on the graft tissue should be fitted with a spherical lens.

also reduce mucus buildup between the contact lens and the cornea. Cost and convenience are considerations, as some people have difficulty handling a two lens system or cannot afford additional lenses. Piggybacking does not reduce lid sensations and can increase risk of inflammation in people with chronic lid disease, so it should be used judiciously.

Selection of a piggyback lens not only includes material selection, but also power. In cases where a practitioner is using a Focus Night & Day® (CIBA Vision, Duluth, GA) lens as a bandage lens under a thick, complex-design GP lens, patient comfort may be less than one would expect. Using a lower modulus lens with better draping of the periphery, such as Acuvue Oasys (Vistakon, Jacksonville, FL) Air Optix (CIBA Vision) will increase comfort (Table 57.2).

The power of the piggyback lens, and subsequent lens configuration, can be used to alter the curvature of the eye. A plus lens can be used on a plateau (oblate) graft to create a more prolate surface. Corneal topography can be performed over the piggyback lens to determine the new surface shape. Similarly, minus lenses can be used on a proud graft (prolate) to create a more oblate shape, although this tends not to make quite as dramatic a difference.

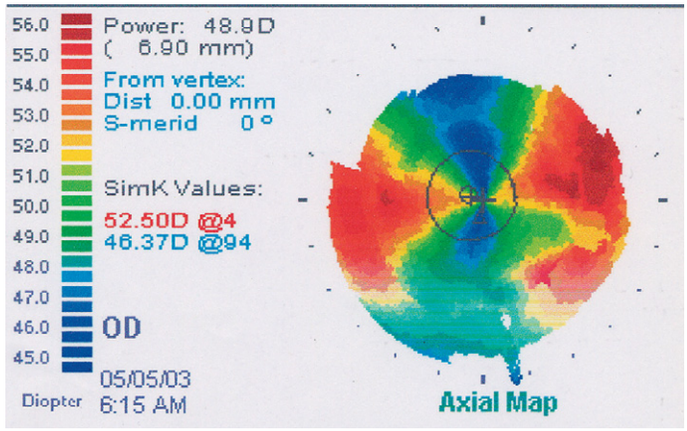
SUMMARY

Fitting a corneal graft with a contact lens is inherently challenging, but quite rewarding.

Skills in conventional rigid lens fitting are a necessary prerequisite, as is a good supply of trial lenses. Additionally, a willingness to be creative and innovative in lens selection, and persistence in lens modification, increases the chance of a successful fit.

The expectation of what is a good fit on a graft cannot be based solely on criteria used for conventional contact lens fitting. Good visual acuity, lens stability, and patient comfort without any sign of superficial punctate keratitis or neovascularization may be present in a lens that looks like it does not fit well.

Corneal surgeons continue to strive for the ideal keratoplasty result, but until the time when low astigmatism is as predictable as graft clarity is now, a need will exist for postoperative visual correction with a contact lens.



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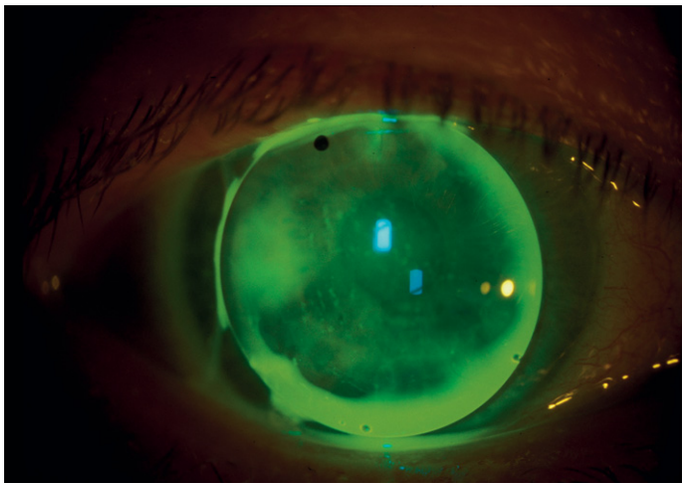

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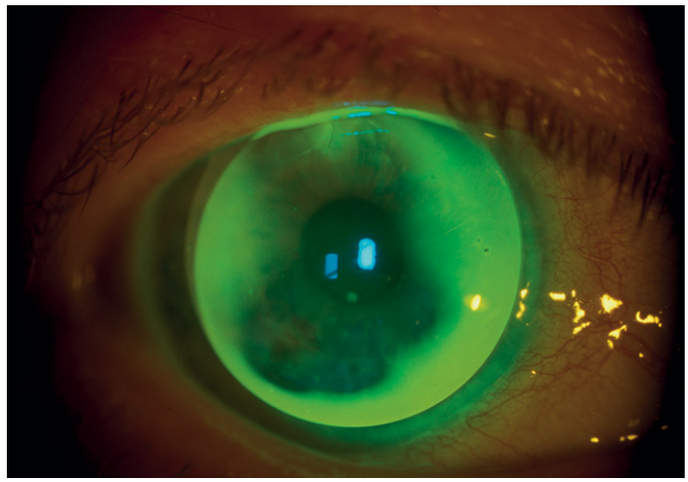
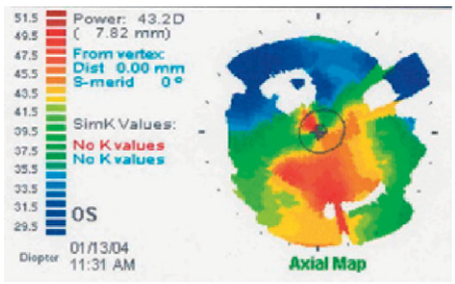
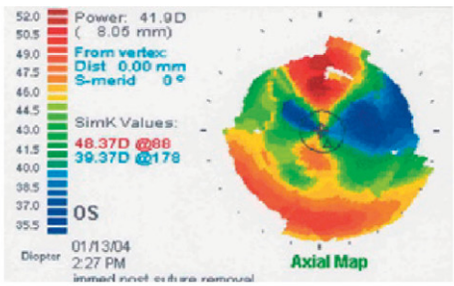
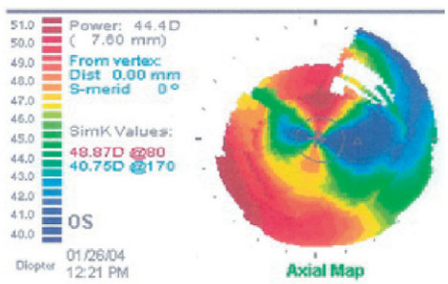


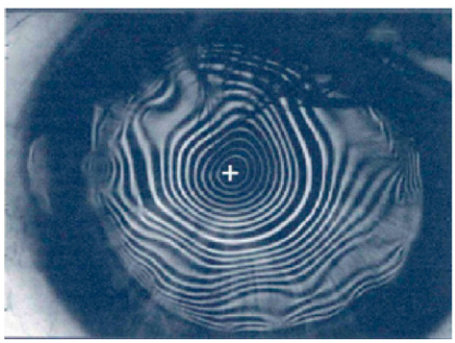
C

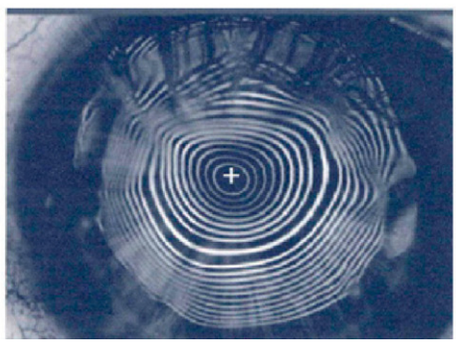
Figure 57.19. Regular cylinder located across the entire cornea may benefit from a bitoric lens, only if sufficient fit and comfort cannot be obtained with a spherical lens.











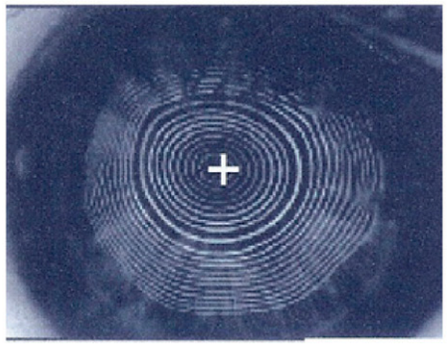


Figure 57.20. Pre, immediately post, and 2 weeks post removal of interrupted sutures.

Table 57.2 Silicone hydrogel properties

SILICONE HYDROGEL PROPERTIES						
	Focus Night and Day	**Biofinity**	**Acuvue Oasys**	**Air Optix**	**PureVision**	**Acuvue Advance**
Manufacturer	CIBA Vision	Cooper Vision	Vistakon	CIBA Vision	Bausch & Lomb	Vistakon
Material	Lotrafilcon A	Comfilcon A	Senofilcon A	Lotrafilcon B	Balafilcon A	Galyfilcon A
Dk	140	128	103	110	101	60
Dk/t @ –3.00	175	160	147	138	110	86
Water	24%	48%	38%	33%	36%	47%
BC	8.4, 8.6	8.6	8.4	8.6	8.6	8.3, 8.7
Power Range	+6.00 to –10.00	–0.25 to –6.00	+8.00 to –12.00	+6.00 to –10.00 Cyl –0.75 and –1.25 Sph Pl to –6.00	+6.00 to –12.00 Cyl –0.75, –1.25, –1.75 Sph –0.25 to –6.00 Multifocal low/high +6.00 to –10.00	+8.00 to –12.00 Cyl –0.75, –1.25, –1.75, –2.25 Sph +6.00 to –9.00
Surface	Surface Tx Plasma Tx	No surface treatment *'Natural Wettability'*	Internal *Hydraclear Plus*	Surface Tx Plasma Tx	Surface Tx Plasma Tx *Aergel w/Performa*	Internal *Hydraclear*
Replacement	1-month DW 1-month CW	Monthly	2-week DW 1-week EW	2-week DW 1-week EW	1-month DW 1-month CW	2-week DW
Therapeutic Approval	Yes 2003	No	Yes 2007	No	Yes 2005	No
UV			UV			UV
Group	1		1	1	3	1
Modulus	1.52	0.75	0.72	1.00	1.50	0.43

Dk = oxygen transmissibility.
Dk/t = oxygen transmissibility for a given thickness.
BC = base curve.
Cyl = cylinder.
Sph = sphere.
Pl = plano.
Tx = treatment.
DW = daily wear.
CW = continuous wear.
EW = extended wear.
UV = ultraviolet.

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58 Control of postkeratoplasty astigmatism

Woodford S. Van Meter

After penetrating keratoplasty (PKP), a clear graft is almost always expected with current eye banking techniques, microsurgical instrumentation, and knowledgeable postoperative care. However, even with a clear graft, ametropia, which includes spherical errors and astigmatism, is the leading cause of decreased visual acuity after surgery.[1–4] Astigmatism limits best-corrected acuity after surgery, impairs visual rehabilitation, and can make contact lens wear difficult. A highly myopic patient with a clear graft is significantly disadvantaged even without astigmatism. A patient loses 0.2 lines of vision with every diopter of refraction error from plano, so the closer a cornea is to emmetropia after surgery, the better the patient's potential visual acuity will be.[5] This chapter is devoted to the control of astigmatism after keratoplasty.

Postkeratoplasty astigmatism can be treated either with sutures in place or after they have been removed. Ultimately all sutures have to be removed, and so treatment with sutures in place may lose effectiveness once sutures are removed. Manipulating sutures to control astigmatism while the sutures are in place is determined by the specific suturing techniques used and suturing was discussed in a previous chapter. For example, removal of interrupted sutures can flatten the steep meridian but will not steepen a flat meridian. Adjustment of a continuous suture can flatten a steep meridian, steepen a flat meridian, or both, but will not address residual spherical refractive error. If astigmatism has been reduced to acceptable levels with sutures in place, a contact lens may be used over the cornea for visual rehabilitation and the sutures may be left in place indefinitely, excepting any suture complications.

After all sutures have been removed, visual rehabilitation should be attempted with glasses or contact lenses. Reduction of existing astigmatism requires surgical intervention to alter corneal topography to flatten the steep meridian, steepen the flat meridian, or both. Surgical techniques may include refractive surgery, such as laser-assisted in situ keratomileusis (LASIK), or photorefractive keratectomy (PRK) discussed elsewhere, or incisional surgery to alter the existing graft–host junction, discussed in the following pages. Relaxing incisions to flatten a steep meridian and compression sutures with or without a wedge resection to steepen a flat meridian are examples of incisional surgery. T-cuts and arcuate keratotomy serve the same function as relaxing incisions. Excimer laser procedures for astigmatism, including photorefractive keratectomy and laser in situ keratomileusis, are discussed in subsequent chapters.

The topography of the donor cornea is generally not stable until 2–6 weeks after surgery. Glycosaminoglycans in the corneal storage medium have higher osmolarity than the normal corneal stroma and cause an increase in thickness in the donor button immediately after surgery due to influx of aqueous fluid. Resolution of corneal edema is necessary to allow the postoperative suture tension to stabilize. The corneal epithelium should heal sufficiently to permit an accurate measurement of corneal shape, especially with reflection-based imaging systems. Corneal edema, epithelial irregularity, and subsequent fixation errors may all affect imaging and consequently intervention. Decisions concerning suture removal should be made only after reproducible topographic images have been achieved and, ideally, confirmed on consecutive visits.

The amount of residual astigmatism that can be tolerated depends on a number of factors, including the patient's age, occupation, fellow eye, binocularity, visual acuity, temperament, and expectations. A large amount of astigmatism may be tolerated in a patient with poor vision and minimal occupational visual requirements, whereas a low level of astigmatism may not be tolerated in a patient who is emmetropic in the other eye and must see fine print. The effort that a surgeon should put into astigmatism reduction depends on the experience of the surgeon and the patient's needs and expectations. Patient needs and surgical skill may be fixed and unalterable, but patient expectations can be tempered by frank discussion of corneal astigmatism before keratoplasty.

Visual rehabilitation following PKP has three stages: glasses, contact lenses, and surgical intervention. Surgical intervention should not be used until all sutures are cut. Rarely following a PKP does a patient achieve emmetropia. Glasses and/or contact lenses can be utilized for vision several months postoperatively, but frequently, some modification of the graft topography by the surgeon is necessary for the patients to achieve their best potential vision. Such intervention includes suture manipulation and surgical intervention.

BOX 58.1 CHRONOLOGIC EVENTS TO CONTROL ASTIGMATISM

1. Care in cutting donor and host, care in suturing
2. Suture adjustment
3. Removal of all sutures after wound is healed
4. Surgical intervention with relaxing incisions or wedge resection
5. Photoastigmatic refractive keratectomy with or without LASIK
6. Regrafting

The feasibility of glasses and contact lenses should be considered after each step.

CONTROL OF ASTIGMATISM

Postkeratoplasty astigmatism may be the result of a number of factors, including suturing techniques, wound morphologic characteristics, trephination of the donor or host tissue, or localized pathologic condition in the host (or donor) cornea. Specific suturing techniques are frequently dictated by the expertise of the surgeon and the presence or absence of localized structural abnormalities observed in the cornea, such as vascularization or scarring. The steps to control astigmatism are listed in Box 58.1.

All suturing techniques lend themselves to adjustment in one way or another even if the adjustment is only removal of the sutures. Suture manipulation can effectively reduce astigmatism if the astigmatism is caused by the suture. Suture adjustment does not completely overcome astigmatism resulting from other factors, such as uneven wound morphology, asymmetric or uneven graft–host fit, or wound abnormalities that result from irregularly placed cardinal sutures.

If suture adjustment achieves adequate control of astigmatism, then sutures should be left in place indefinitely. If suture manipulation does not adequately control astigmatism, then one must wait until all sutures can be removed safely. Sometimes removal of all sutures results in improvement in topography. If astigmatism is unacceptable after all sutures are out, surgical intervention using a relaxing incision or a wedge resection may be timed to make the cornea more spherical. Often minimal adjustments to a cornea with irregular astigmatism can drastically improve contact lens wear. If surgical intervention fails, then regrafting may be necessary to achieve an optically useful cornea.

ADJUSTMENT OF KERATOPLASTY SUTURES

Suture adjustment is an integral part of postoperative visual rehabilitation after keratoplasty. The adjustment may involve partial suture removal, removal of all sutures, or adjustment in the tension of existing (continuous) sutures. Sutures should remain in place once corneal astigmatism is satisfactory and until there is some indication for removal. Indications for removal are scarring or vascularization that increases the risk of graft rejection, suture breakage that may cause patient discomfort and serve as a nidus of infection or inflammation, infiltrate, stromal melting, or residual astigmatism that causes decreased vision.

Attention to several issues intraoperatively can be attempted to preserve the option of leaving sutures in place as long as possible. At the time of suture placement, surgeons should avoid excessive trauma to the nylon sutures when handling the suture. Bites should be placed at 90% depth to permit wound approximation without distortion. Minimal tissue trauma while handling wound edges, preserving the suture, and avoiding vascularization that may already be present improve the chances of postoperative suture adjustment, which effectively reduces astigmatism.

SINGLE INTERRUPTED SUTURES

The only adjustment possible with interrupted sutures is removal of one or more sutures. In the early days of corneal transplantation, silk sutures were used and of necessity had to be removed early to prevent inflammation and vascularization. Early removal reduced the effect of the suture on astigmatism; sutures were less likely to induce astigmatism after removal, but clear grafts were not as common with silk as with the less reactive sutures available today. There is a narrow therapeutic window of opportunity for effectively removing an interrupted nylon suture; early removal can cause wound dehiscence, but waiting too long can mean that no effect is realized from suture removal. Loose interrupted sutures provide no structural support and should be removed to avoid infection. With this idea in mind, the surgeon should not risk losing a 'good' result trying for a 'perfect' result. Tight interrupted sutures steepen the cornea, and removal of an excessively tight suture will flatten the steep meridian and may cause a little steepening of the flat meridian.[6] Little in general can be done to steepen a meridian that is already too flat except for resuturing the wound.

Qualitative adjustment of topography by removing interrupted sutures is problematic because there are only a finite number of sutures present and flattening is the primary outcome. As soon as an interrupted suture is removed, if too little or too much flattening is obtained, nothing else can be attempted in that axis using suture manipulation. Tight interrupted sutures can be removed earlier (for example, with 16 interrupted sutures, one suture could be removed as early as 2–3 months if it is too tight, although no two adjacent sutures should be removed before 6 months). Occasionally, earlier suture removal may be indicated at the discretion of the surgeon as long as it can be reliably determined that the wound is sufficiently healed to withstand suture removal without wound slippage or dehiscence.

As soon as the suture or sutures to be removed have been identified by topography, a drop of topical antibiotic and a drop of topical anesthetic should be placed in the eye. Cut the suture with a straight blade (Microsharp or Beaver no. 75 blade) and remove with tying forceps (Fig. 58.1). A sudden jerk to remove the suture, like tearing toilet paper with one hand, is more effective than slower, less forceful pressure. Buried knots are not a problem, but exposed loose ends can cause patient discomfort and infectious keratitis and should therefore be removed with moderate urgency. The eye should be patched for 18–24 h with a topical antibiotic ointment. Topical corticosteroid drops may be resumed on the following day or should be started if the patient was not taking drops before suture removal, because removal of sutures can incite inflammation that can potentiate a graft rejection. Re-evaluate the eye in 2–3 weeks and repeat the procedure until satisfactory corneal topography has been achieved or until there are no more sutures to remove in the steep axis.

Results

The effect of removing a single suture cannot be easily predicted. Photokeratoscopy or topography can be used to help determine

which interrupted sutures should be removed (Fig. 58.2, *A* and *B*) but do not precisely correlate with the amount of tension in the tight suture. Removal of a tight interrupted suture may result in anywhere from 0 to 10 D of change, depending on the tightness of the suture, the length of the suture, and specific details of the wound in the vicinity of the suture. When a single interrupted suture is removed, average anticipated astigmatic change is approximately 2–3 D. When no interrupted sutures remain in the steep axis, no additional sutures should be removed and the effect of suture removal is complete.

COMBINED CONTINUOUS AND INTERRUPTED SUTURES

The combined continuous and interrupted suture (CCIS) technique has both the advantages and the disadvantages of a continuous suture and interrupted sutures.[7] This technique is especially advantageous for surgeons learning the continuous suture technique. The continuous suture provides extra security when interrupted sutures are removed early for astigmatism control, and the interrupted sutures provide safety in the event of irregular bites or early breakage of the continuous suture.

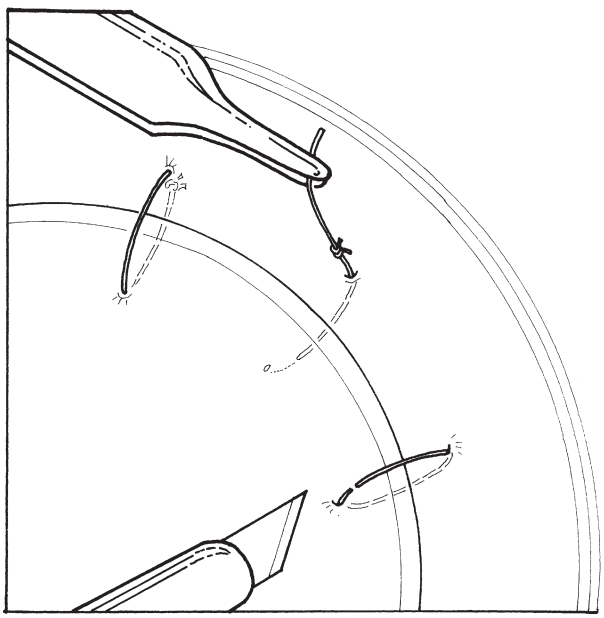


Figure 58.1. Interrupted suture with knot buried on recipient side of graft junction is cut on donor side. Loose suture segment is then pulled with a snap to remove knot from recipient, which puts less stress on wound than pulling knot from donor side.

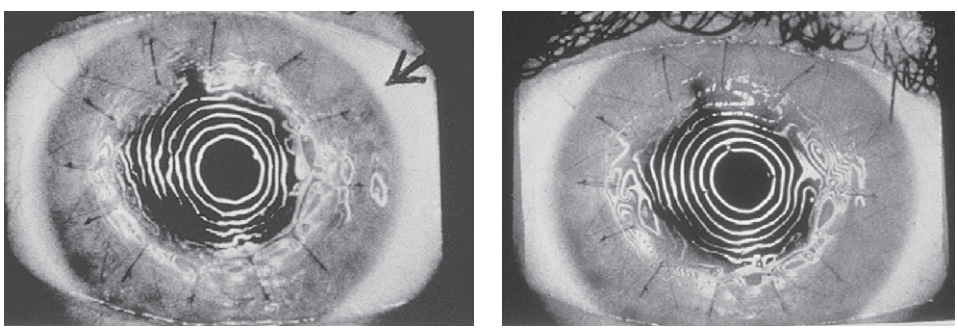
Technique

At approximately 3–4 weeks after keratoplasty surgery, corneal topography should be evaluated. A tight interrupted suture is identified with keratometry, photokeratoscopy (see Fig. 58.2), or videokeratography and then removed.[8] Two or three weeks later, corneal topography should be remeasured to assess changes in the patient's cornea resulting from removal of the suture and to assess whether additional suture removal is indicated. Subsequent sutures are removed as indicated until corneal astigmatism is reduced to an acceptable level, generally 3 D or less, or until there are no more interrupted sutures to remove in the tight meridian.[9–13]

One limitation of CCIS suture adjustment is that, like single interrupted sutures, only the tight suture can be removed and only the curvature in the steep axis can be reduced. A cornea that is excessively flat in one axis cannot be steepened by removing sutures. If removal of sutures in the tight meridian does not reduce corneal cylinder or there are no more sutures to remove, adjustment is not effective, and the patient and physician must then wait until all sutures can be removed before addressing corneal astigmatism or surgical methods. A second disadvantage of the CCIS technique is that interrupted sutures are very difficult to remove after several years. Sutures that are partially eroded, loose, or broken several years after surgery may be very difficult to remove because of fibrosis around buried, knotted segments. Loose suture segments over time can cause patient discomfort, infectious keratitis, or graft rejection.[14–17] Once acceptable corneal astigmatism is achieved, the suture should be left in place until there is an indication for removal.[18–20]

Results

Patients in whom the CCIS technique is used experience a reduction in corneal astigmatism from an average of 7.5 to 2.6 D at 1 year with sutures in place.[20] The ability to adjust astigmatism one suture at a time titrates the astigmatism reduction in small increments and is more controlled than the removal of all sutures. Average astigmatism when all sutures are out regresses to approximately 4 D in most series.[2,11]



A **B**

Figure 58.2. *A*, Photokeratoscopy (placido disc projection topography) is used to identify tight suture, causing steep meridian at 2 o'clock (black arrow). *B*, Same eye with suture out 2 months after surgery with 2.5 D of corneal astigmatism.

SINGLE CONTINUOUS SUTURE

The single continuous suture (SCS) technique is also effective for keratoplasty wound closure. The SCS technique requires less time than interrupted sutures but is technically more demanding and less forgiving than multiple interrupted sutures. Adjustment of an SCS can change corneal topography to reduce astigmatism with the suture still in place to support the wound,[21] and McNeill[22] and Wessels[23] described adjustment of an SCS to reduce postkeratoplasty astigmatism in 1988 and multiple surgeons have confirmed the effectiveness of this technique.[24–26]

The SCS can be adjusted using sterile tying forceps. The surgeons should first apply drops of topical antibiotic and anesthetic to the eye and carefully measure corneal topography. A keratometer is the most useful instrument to use for suture adjustment because reflection of central corneal topography in the mires permits measurement of both the quality and the quantity of astigmatism. Repeated glimpses of corneal topography are helpful during the adjustment procedure. One edge of the forceps can be used to carefully divide Bowman's layer with the tip of the forceps in the wound. The forceps are gently passed through Bowman's layer into the anterior corneal stroma, with care taken not to advance the tips beyond 50% of corneal depth or to traumatize the continuous suture. Division of Bowman's layer relaxes the wound to facilitate alterations in corneal topography with adjustment of suture tension and makes it easier to pick up the suture with the forceps. The suture can then be carefully advanced from the flat to the steep meridian, simultaneously flattening the steep meridian and steepening the flat meridian (Fig. 58.3). Laxity in the sutures advances loop by loop, with the goal of adjustment to distribute suture tension equally 360° around the wound. If the suture is tied too tightly, adjustment should not be pursued because attempts to move a very tight suture forcefully can result in suture breakage. If the suture is tied too tightly to move, adjustment should then be deferred, and attempts to resolve astigmatism should follow suture removal.

Suture adjustment in a theoretic cornea with K readings of $40.00 \times 180/50.00 \times 90$ is demonstrated in Figure 58.4. The suture in each quadrant is advanced from the flat meridian toward the steep meridian, resulting in a more spherical cornea as the flat meridian becomes steeper and the steep meridian becomes flatter. Regression of the measured astigmatism generally occurs, and a slight overcorrection in the adjustment end point for regression may be helpful.

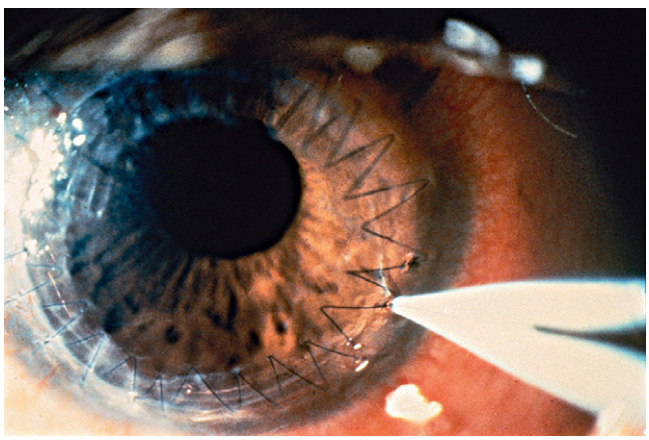


Figure 58.3. After Bowman's layer is broken, grasp the suture and advance from flat meridian toward steep meridian, taking care not to twist or cut the suture on the edge of the tying platform.

Corneal mires can be changed from an elliptic reflex on a toric cornea to a circular reflex on a spherical cornea, as shown in Figure 58.5, *A*. Figure 58.5, *B* shows adjustment from a D-shaped pattern, and Figure 58.5, *C* shows adjustment of a teardrop pattern.

Care must be taken to prevent suture breakage during the adjustment procedure because the wound itself is not stable enough to remain intact without suture support in the first weeks or months following keratoplasty. During the early postoperative period, when suture adjustment is most effective, suture breakage can result in wound dehiscence and requires immediate repair in the operating room. Consequently, adjustment of a continuous suture should not be attempted unless the surgeon has an oper-

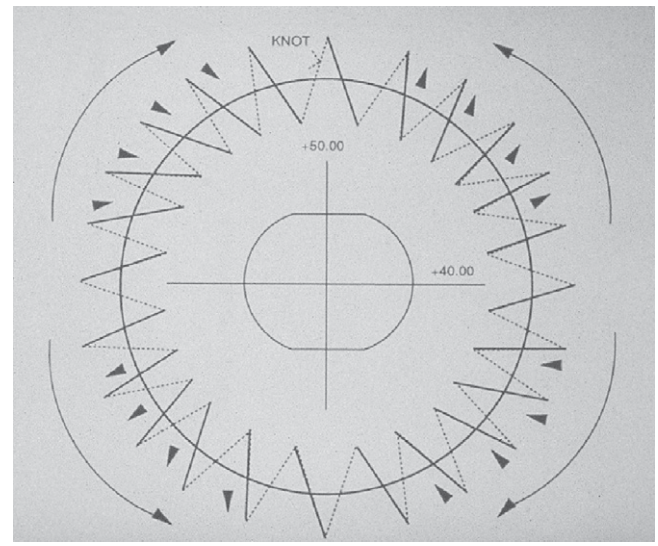


Figure 58.4. Suture is advanced from the flat meridian, steepening the flat meridian by increasing suture tension to the steep meridian, where a looser suture allows meridian to flatten.

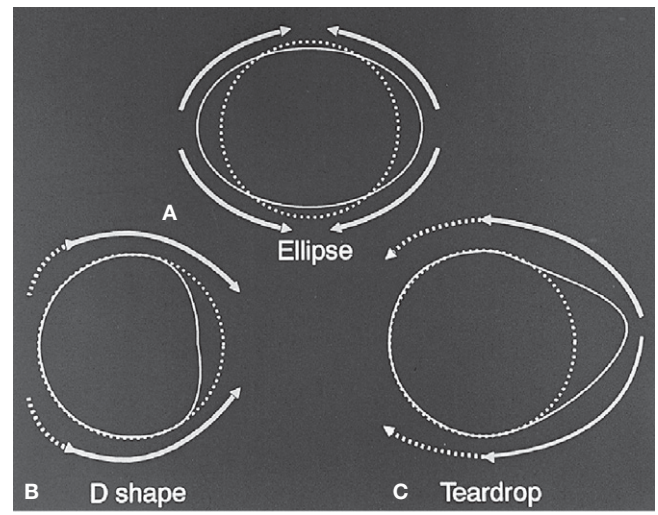


Figure 58.5. *A*, Adjustment of suture in astigmatic cornea with elliptical mires requires symmetric suture manipulation in four quadrants, advancing the suture from the flat to steep region. *B*, D-shaped pattern results from suture with excessive tension in one meridian. Suture tension is gathered from wound and used to loosen the wound at flat side of D and equalize the tension 360°. *C*, A teardrop pattern results from suture with less tension in one area. Adjustment of teardrop pattern is accomplished by taking up tension where suture is loose (at point of teardrop) and redistributing tension evenly around the wound to achieve spherical mires.

ating room available should more elaborate surgical intervention be necessary.

Regression after the second or third suture adjustment is a poor prognostic sign and rarely does repeat adjustment help when the first or second attempt does not change corneal astigmatism. Because residual postkeratoplasty astigmatism is multifactorial, other factors that cause astigmatism, such as wound morphologic characteristics, gross misplacement of sutures, or uneven wound trephination may prevent any suture adjustment from effectively reducing corneal astigmatism. If suture adjustment is not effective, the patient may be fitted with glasses or contact lenses when possible and await final suture removal as soon as the wound has stabilized. After suture removal, other invasive procedures, such as relaxing incision or wedge resection, may be indicated. These procedures are discussed later in this chapter.

Removal of a continuous suture is best accomplished by cutting the suture on the host side of the cornea in alternate loops and then loosening the center of the 'W' with a bent 30-gauge needle or the dull side of a no. 75 Beaver blade. The loosened loop can then be removed with tying forceps (Fig. 58.6). The eye should be patched overnight with a topical polymyxin and bacitracin ophthalmic ointment. Re-evaluation of topography to determine the effect of suture removal can be completed within 2–3 weeks.

Results

The results of an SCS in one study showed an average reduction from 6.5 to 1.5 D after adjustment, regression of 2.5 D when optically stable, and final average astigmatism of 3.5 D at 2 years with sutures still in place.[23] However, an SCS without adjustment had 2.5 of regression in a comparable population, suggesting that inherent wound stability may exist with a continuous suture closure. Sutures-out astigmatism in those patients with sufficient astigmatism to require adjustment was approximately 4 D, comparable to that with a CCIS technique.[20] However, astigmatism with sutures in was significantly less with SCS than with CCIS and was achieved in shorter postoperative time than CCIS, patients' satisfaction with the quality of vision being reported to be higher with CCIS than with SCS.[27]

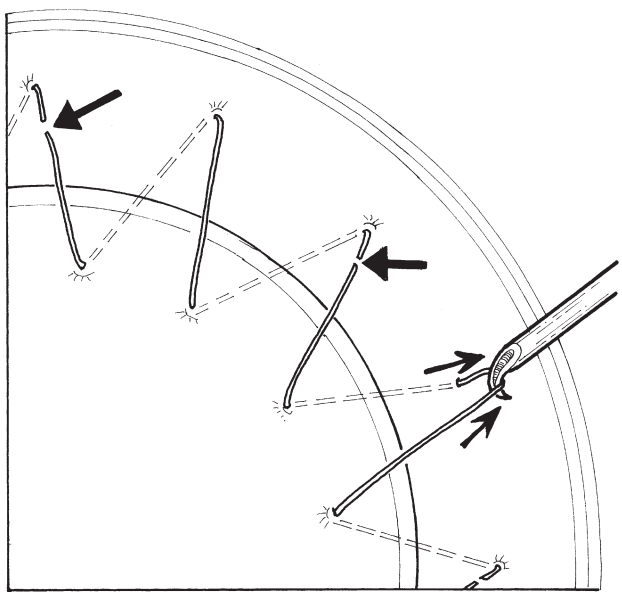


Figure 58.6. Continuous suture is removed by cutting alternate recipient side loops, then pulling from apex of the W to remove two-bite segment. Bent 30-gauge needle can pull suture bite to loosen.

DOUBLE CONTINUOUS SUTURE

Adjustment of the double continuous suture initially was reported using two 10-0 nylon sutures with early removal of one of the two sutures.[28] This technique was modified using a 10-0 and an 11-0 nylon suture with removal of the 10-0 nylon suture at 2 or 3 months, leaving the 11-0 suture in place for 12 months.[29] Removal of the deeper, tighter, 10-0 nylon suture reduced astigmatism, and the 11-0 nylon suture remained secured in place and the wound in place preventing wound dehiscence without placing untoward suture compression on the wound.

A double running suture with two 10-0 nylon sutures, which secure the wound with 12 bites each, has been shown effective, eliminating the technical intricacy of running an 11-0 nylon suture.[30] The deeper, tighter, 10-0 nylon suture is removed to reduce the suture effect on corneal topography, leaving the shallower suture in place as a safety net. Both sutures can be left in place after surgery if the patient is optically stable with acceptable visual acuity. If the patient requires suture adjustment, the deeper, tighter, 10-0 nylon suture can be adjusted in the same manner as an SCS to reduce corneal astigmatism. The second 10-0 nylon suture remains in place if the original suture is divided or if the deeper suture needs to be removed because of unacceptable astigmatism. After adjustment, both sutures remain in place until removal is indicated.

FINAL CONSIDERATIONS

Three important points should be impressed on keratoplasty surgeons regarding suture adjustment. First, corneal astigmatism is multifactorial and suture adjustment can only correct astigmatism that is the result of uneven suture tension in a reasonably well-approximated wound or if cardinal sutures are not evenly placed. If the wound is unevenly approximated, adjustment of suture tension may help to reduce astigmatism with sutures in place but will not reduce astigmatism after sutures are out. Wound astigmatism, at best, may be masked by an adjusted suture until such time as the suture is removed.

Second, as soon as the suture or sutures have been adjusted to achieve suitable topography, the suture should be left in place until such time as it has to be removed.[14–16] Patients may be well advised to 'take their sutures to the grave' if visual acuity is acceptable and there are no signs of suture intolerance. Some fibrosis can be expected around the suture tract, but fibrosis alone is usually not an indication for suture removal. The most common indication for removal of an SCS is suture breakage, which most frequently occurs around the 12 o'clock meridian because of the constant movement of the lids over the suture with blinking.

Third, after several years, continuous sutures are much easier to remove than interrupted sutures. The continuous suture causes less inflammation in the cornea than interrupted sutures, suture segments without knots are removed easier than buried knots, and there is less likelihood of residual buried suture remnants from broken segments attached to buried knots that cannot be removed.

CONTROL OF ASTIGMATISM WITH SUTURES OUT

If satisfactory corneal topography is not achieved by suture adjustment, then suture removal is indicated as soon as wound stability and safety factors permit. After all corneal sutures have been removed, careful measurement of corneal topography by qualitative

and quantitative methods should be repeated over a period of at least 2 weeks to establish stability. Videokeratography is most helpful, but important information can be obtained from combined use of keratometry and photokeratoscopy. The plan for astigmatism reduction is based on which areas of the cornea are steep and which are flat. Understandably, reduction in astigmatism with sutures out is more effective without wound interface abnormalities causing radial asymmetry.

Once astigmatism is quantified, visual rehabilitation can proceed. Visual correction means rehabilitation initially with spectacles. Contact lenses should be tried next if spectacles do not provide adequate vision and finally surgical intervention if contact lenses are not suitable (due to inadequate vision, inadequate comfort, inability to handle, or expense). Repeat keratoplasty may be the most reasonable option if surgical intervention does not provide adequate vision. Contact lenses and lamellar refractive procedures are discussed elsewhere in this volume.

Refraction should be performed postoperatively by someone experienced in low vision refraction techniques because patients with high astigmatism, irregular corneal astigmatism, or maculopathy may not appreciate 0.25 D steps in refraction, and 0.50 or 1.00 D increments may be necessary. Generally, the manifest refractive astigmatism is ⅔ to ¾ of the measured keratometric astigmatism.[30a]

Contact lens fitting is necessary in approximately half of PKP patients to achieve adequate useable vision. An experienced contact lens artisan, either on site or near by, dramatically improves results compared to distant contact lens services. Patients with keratoconus or high refractive error preoperatively who are used to wearing contact lenses will enjoy rapid visual rehabilitation because they are already used to wearing contact lenses. High DK (DK value is the oxygen permiability of a contact lens) rigid gas permeable (RGP) contact lenses are the lens of choice. Some patients who cannot tolerate RGP contact lens may be comfortable with a hybrid lens with RGP center and hydrogel carrier (Synergeyes, Carlsbad, CA).

Surgical techniques for astigmatism control, which include refractive surgical techniques to alter corneal astigmatism after suture removal, fall into two categories: relaxation (to flatten a steep meridian) and compression (to steepen a flat meridian). A steep meridian can be flattened with a relaxing incision (including arcuate incisions, transverse incisions, trapezoidal incisions, and incisions within the wound). A flat corneal meridian can be steepened with compression sutures, a wedge resection, or both. Both relaxing incisions and wedge resections affect the opposite meridian and the meridian of intent, but conceptually they are discussed as primary procedures that either flatten or steepen. Either or both of these techniques can be used to reduce postoperative astigmatism after all sutures have been removed.

RELAXING INCISIONS

Incisional keratotomy for astigmatism has been in use for over a century. Snellen[31] initially described relaxing incisions made in the cornea in 1869. Lans[32] confirmed the flattening effects of this technique, and Sato[33] used relaxing incisions in the posterior cornea in his well-publicized preradial incisional keratotomy.

Relaxing incisions with modern microsurgical techniques were described by Troutman and Swinger[34] as arcuate keratotomy in 1980. Relaxing incisions are placed in the steep meridian and act by directly flattening the central cornea in the meridian of the incision (Fig. 58.7, *A* and *B*). Up to 16 D of vector change in corneal astigmatism have been observed, although modifications in technique have made the procedure more titratable now.[35–37] The ratio of flattening in steep meridian to steepening in the flat meridian is approximately 0.975, so one expects the same amount of steepening in the perpendicular meridian as there is flattening in the meridian of the incision.[37] In the average patient, a relaxing incision is capable of correcting 4–5 D of astigmatism.

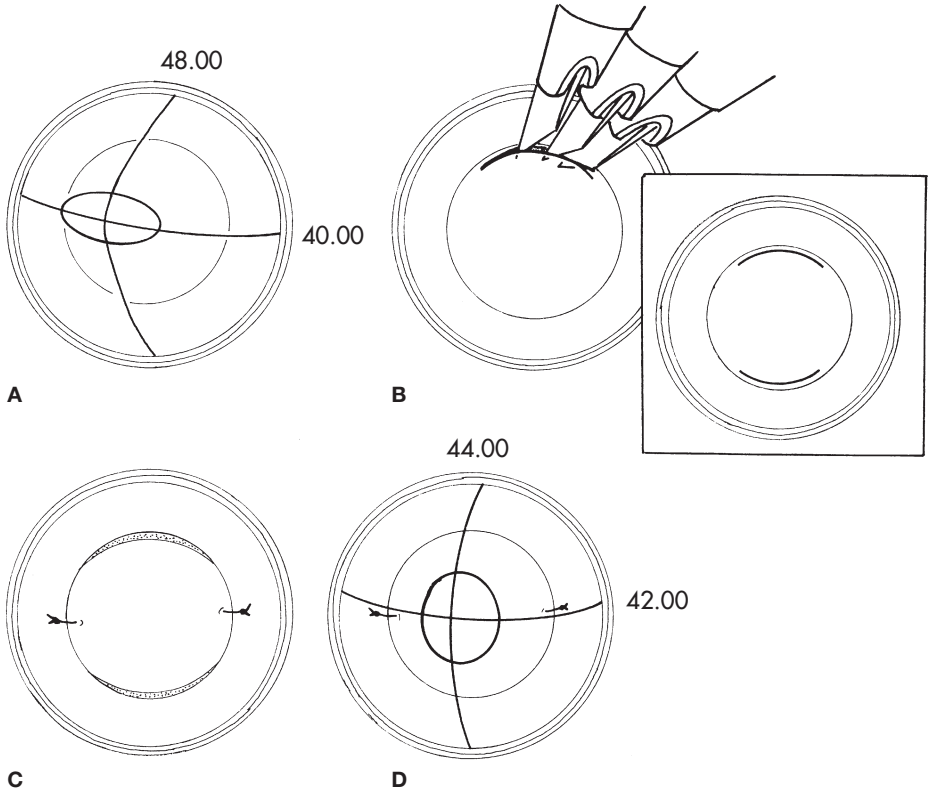


Figure 58.7. *A*, Eight diopters of with-the-rule astigmatism. *B*, Relaxing arcuate incision made at the graft–host junction in the scar with no. 75 blade at the slit lamp. *B* (inset), Alternative incision just inside the graft–host junction. *C*, Compression sutures alone or in combination with relaxing incisions. *D*, Effective reduction of astigmatism.

As the perpendicular meridian steepens, the total power of the spherical equivalent of the cornea does not significantly change after the procedure. The amount of correction obtained is influenced by the depth and length of the incisions and the proximity of the incisions to the optical axis.[35] Incisions are most effective when placed just inside the graft–host junction (Fig. 58.7, *B*). The keratoplasty wound generally makes significant astigmatism reduction refractory to incisions outside the corneal wound.

There are several advantages of relaxing incisions over wedge resections: there is generally a more rapid return of vision, sutures are not required, and the procedure can be performed under topical anesthetic at the slit lamp in the physician's office.

The technique for relaxing incision involves the placement of several drops of topical anesthetic and antibiotic in the eye. At the slit lamp under direct visualization, a no. 75 blade or a faceted (flat-edge) diamond blade is used to make an incision through Bowman's layer either at the graft–host scar or just inside the donor wound, in the steep meridian identified by topographical analysis. Slow and careful deepening of the incision is performed through the stroma, observing for and limiting wound gape. If perforation occurs with significant chamber loss, resuturing is necessary. The incisions may be made in one or both meridians and may be made in two irregular meridians (i.e. meridians not 180° apart).[38] Relaxing incisions are most effective if there are localized areas of wound compression, that is the host wound over-rides the donor (see Fig. 58.5, *B*, 'D' pattern) and if they are carried out within 3 months after suture removal. Relaxing incisions are less effective if there is smooth wound approximation, and the astigmatism is minimal and symmetrical, and if they are carried out more than 6 months after suture removal.

The Ruiz procedure, which makes multiple linear cuts in a trapezoidal shape, has been unpredictable in most reports from the USA. Transverse keratotomy, or T-cut, is a modification of the Ruiz procedure. These procedures do not show any advantage over arcuate keratotomy in or near the corneal wound.[39,40]

COMPRESSION SUTURES

Compression sutures using 9-0 or 10-0 nylon or 10-0 or 11-0 polypropylene or braided nylon (Mersilene, Ethicon, Somerville, NJ) may be placed across the graft–host junction to steepen the flat meridian.[41] Compression sutures alone may make only minimal changes in corneal topography, and the effect tends to regress over time. Placement of alternate 10-0 and 9-0 nylon sutures to achieve overcorrection, along with removing the 9-0 sutures to titrate the effect, and leaving the 10-0 nylon sutures, may provide some adjustability to the procedure. The sutures should be tied tight enough to achieve a slight overcorrection, and the compression sutures subsequently can be removed one by one several months later if overcorrection persists.

Compression sutures can also be helpful in the opposite meridian to accentuate the effect of relaxing incisions (Fig. 58.7, *C* and *D*).[42] Compression sutures may help open the tissue in the relaxing incision and may provide more steepening in the opposite meridian than relaxing incisions alone provide. In general, compression sutures are left in place permanently unless persistent overcorrection occurs, at which point selective removal may be beneficial.

WEDGE RESECTION

Corneal wedge resections were initially described by Poyales and Actas in 1953.[43] The corneal wedge resection with an operating microscope, microsurgical instruments was developed by Troutman in 1972.[44] A 95%-thickness wedge of tissue in a crescent shape is excised in the flat meridian of the wound (Fig. 58.8, *A–D*). The wedge can be removed from either the donor or the host cornea, with one of the two incisions made in the original wound and portions of the tissue resected from either the graft or the host side of the wound. Because wedge resections average 10 D of correction for each 1 mm in thickness of wedge tissue removed, these are usually reserved for eyes with more than 7–8 D of astigmatism, and

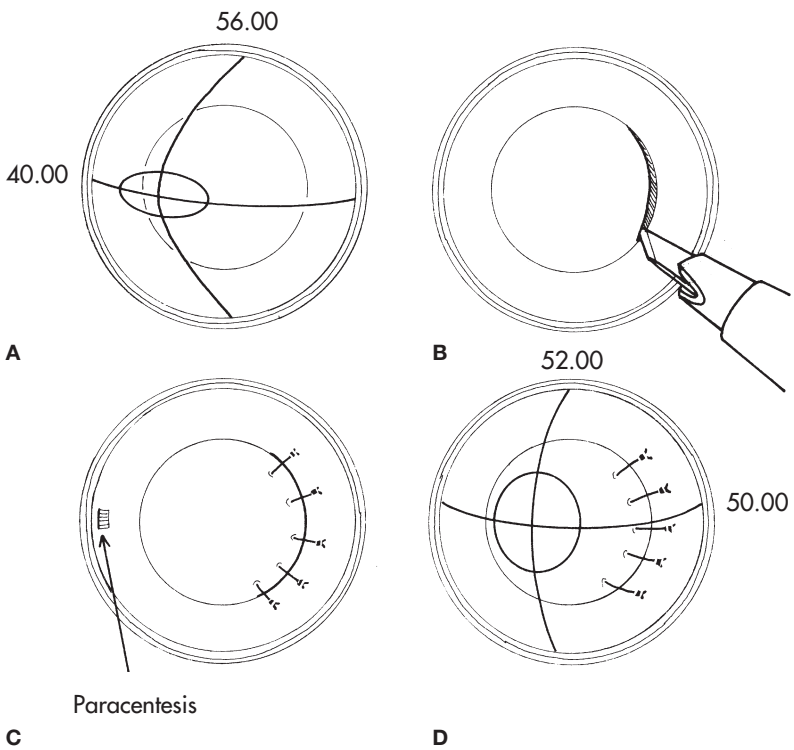


Figure 58.8. *A*, Sixteen diopters of with-the-rule astigmatism in sutures-out graft. *B*, Wedge resection performed in flattest meridian demonstrated on topography. *C*, Paracentesis may facilitate wound closure. *D*, Suture knots buried and astigmatic reduction achieved with cylinder modification in both axes.

therefore resections of 0.5–1.0 mm of tissue are performed. There is generally a flattening of the steep meridian in the perpendicular axis that is up to 50% of the steepening obtained in the flat meridian of the axis of the wedge resection. For example, to eliminate 9 D of astigmatism, one may try to achieve 6 D of steepening with the wedge resection in the flat meridian and expect 50% of the amount, or 3 D, of flattening in the steep meridian to make 9 D total correction.[45–47]

Wedge resections should be performed in the operating room because surgical instrumentation is required. There is risk of perforation, and the procedure can inadvertently lead to intraocular exposure. Occasionally, paracentesis of the anterior chamber is necessary to compress the wound fully with sutures placed in the wedge resection (Fig. 58.8, *C*). The postoperative course is more protracted than a simple relaxing incision because of slower wound healing, and the surgeon is cautioned against early suture removal, which may negate the procedure by the return of pre-wedge high astigmatism. Often wedge sutures are left in place indefinitely when astigmatic reduction is satisfactory.

FINAL CONSIDERATION

If surgical intervention with relaxing incision or wedge resection does not provide satisfactory reduction of astigmatism or if these procedures are outside the comfort zone of the operating surgeon, then regrafting may be indicated. The patient, after all, had a corneal transplant in the first place because of decreased vision. LASIK, LASEK (laser-assisted epithelial keratomileusis), and PRK have provided varying degrees of success in relieving postkeratoplasty astigmatism, but reports of improved astigmatism by cutting a microkeratome flap and then replacing the cap without laser suggest that cutting the flap alone can be helpful. All of these options will be discussed elsewhere in this volume.

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59 Refractive surgery following penetrating keratoplasty

Renée Solomon, Eric D. Donnenfeld

Over 45 000 penetrating keratoplasties (PKPs) are performed annually.[1,2] Although significant improvements in microsurgical techniques have resulted in PKP becoming more successful and more common, postoperative refractive errors are common following anatomically successful PKPs. Most patients will not tolerate more than 3 D of anisometropia, due to image size disparity or astigmatism of greater than 1½–3 D.[3,4] Refractive unpredictability following PKP is extremely common, due to the inherent imprecision of the operation, with most series documenting mean cylinders of 4–5 D and significant anisometropia.[5–11] The residual refractive error may be due to surgical technique, wound healing, and donor tissue variables and is often further complicated by implantation of an intraocular lens. Refractive anisometropia and high postoperative astigmatism can compromise the patient's return to normal binocular function. Anisometropia may result in headache, photophobia, burning, tearing, diplopia, and blurred vision.[3] Binder reported in a series of patients following corneal transplant and cataract extraction that only 21 out of 43 eyes achieved refractive errors within 2 D of emmetropia.[12] Davis et al evaluated patients having combined cataract extraction with PKP. Only 75% of patients fell between −4.00 and +2.00, when emmetropia was the goal.[13] Flowers et al evaluated intraocular lens power calculation in combined corneal transplant and cataract extraction and reported that only 39% of patients had a refractive error within 2 D of emmetropia. The range of ametropia was from −9.75 to +12.88 D, with 65% of the patients having myopic errors.[6]

Many of these patients who cannot be rehabilitated with spectacle correction can be aided by contact lenses. Contact lenses are vital to the rehabilitation of the postkeratoplasty patient. Ten to thirty per cent of patients who undergo PKP wear contact lenses for visual rehabilitation. The incidence of contact lens wear following PKP for keratoconus is 25–50%.[14,15] Both soft and gas-permeable contact lenses are extremely effective and remain the primary technique of visual rehabilitation following PKP for patients who cannot tolerate spectacles.[14–16] Their use is successful in 80–90% of cases.[14] For myopia with low degrees of astigmatism, soft contact lenses are highly effective. Fitting with a gas-permeable contact lens may be required for patients with greater levels of regular astigmatism and any level of irregular astigmatism.

Contact lens wear is not successful in many patients requiring visual correction following PKP. The topographic abnormalities created by the PKP wound can limit contact lens wear. In addition, contact lens intolerance may be caused by ocular, occupational, and systemic factors. Patients with dry eyes, blepharitis, lid abnormalities, and corneal neovascularization may not tolerate contact lenses. Occupational concerns include exposure to environmental factors such as wind, water, smoke, and poor sanitary conditions. Patients with poor manual dexterity, tremors, arthritis, or decreased visual acuity may be unable to manipulate a contact lens. Finally, unmotivated patients and patients unwilling or unable to practice good contact lens hygiene will be contact lens failures. In these patients, surgical alternatives may be the only option.

PHOTOREFRACTIVE KERATECTOMY FOLLOWING PENETRATING KERATOPLASTY

Given the success of the excimer laser in treating myopia and astigmatism,[17–19] photorefractive keratectomy (PRK) has been studied and used to treat post-PKP refractive errors.[20–32] However, the use of PRK in PKP patients is less predictable and less effective than for naturally occurring astigmatism and myopia.[20,21,33] A previously transplanted cornea may respond differently to PRK because corneal wound healing in a grafted cornea may differ from the normal wound-healing response of a patient's own cornea.[20] Post-PKP PRK is also associated with increased incidence of irregular astigmatism,[34,35] significant regression, and late-developing corneal haze, which limit the effectiveness of PRK after PKP.[20,23,24,31,36] Maloney et al, in a multicenter trial, reported a 29% rate of two lines or more visual acuity loss in patients treated with a PRK following prior ocular surgery.[27] Two case reports have documented allograft rejection following surface excimer laser photoablation.[37,38]

Recently, topography-modulated PRK after PKP has been investigated to treat irregular astigmatism.[39,40] The software program, corneal interactive programmed topographic ablation (LIGI, Taranto, Italy), has been shown to be extremely effective for the treatment of irregular astigmatism after PKP.[39] This software

program, by transferring programmed ablation from the corneal topography to a flying-spot excimer laser, is able to provide customized laser ablation to correct post-PKP astigmatism. There was improvement in uncorrected and best-corrected visual acuity in all 10 eyes studied. During the mean follow-up of 8.4 months, no haze or regression was observed. The authors attribute their good results to the nature of the localized abnormality seen with irregular astigmatism. Ablating this localized abnormality requires less tissue removal than that required to correct a similar amount of regular astigmatism. Alessio et al believe that this sparing of corneal tissue allows treatment of high levels of irregular astigmatism, achieving at the same time a regular and smooth surface.[39] Hjortdal and Ehlers have also studied astigmatism in postkeratoplasty eyes with customized laser ablation and have concluded that topography-guided PRK of highly astigmatic corneal grafts can improve best-corrected visual acuity and decrease corneal wavefront aberrations.[40]

While PRK is effective in reducing spherical equivalent to improve uncorrected and best-corrected visual acuity as well as refractive and keratometric astigmatism, there is frequently a decrease in best spectacle-corrected visual acuity (BSCVA) of at least one line. Visually significant haze, which develops from 3 to 12 months postoperatively, is the primary cause of the reduced BSCVA. More postoperative visually significant haze develops in PRK patients who have undergone prior keratoplasty, and a tendency for haze formation correlates positively with ablation depth.[20,23,34] In addition to reducing BSCVA, dense haze may also induce regression and irregular astigmatism and cause visual symptoms, including haloes, blurred vision, and glare. Many techniques have been tried that have had either little or no success in reducing postoperative haze or which produced severe side effects, including postoperative steroids,[41,42] corneal cooling and rehydration during PRK,[43] synthetic inhibitor of metalloproteinase and cyclosporin A,[44] and topical antitransforming growth factor-beta and topical interferon alpha 2b.[45,46] More recently, mitomycin C (MMC), an antibiotic with alkylating properties, has been shown to be effective in treating post-PRK haze by preventing the proliferation of keratocytes,[47–51] and MMC has been shown to decrease corneal light scattering after phototherapeutic keratectomy.[52] MMC inhibits DNA synthesis, preferentially affecting rapidly dividing cells, is fast acting, and demonstrates long-lasting suppression of keratocyte activity after only a single dose.[51] Typically only prolonged use of higher concentrations of MMC lead to significant complications.[53,54] Transient toxic side effects such as hyperemia, pain, and blepharospasm have been reported with 0.02% MMC but resolved with cessation of the drug.[47] Majmudar et al[49] used MMC in eight eyes of five patients who had undergone RK or PRK and demonstrated an improvement in corneal clarity and BSCVA in each eye. The technique described by Majmudar et al[49] and Raviv et al[55] is as follows. A no. 64 Beaver blade was used to remove the patient's corneal epithelium and as much fibrosis as possible. Then a 6 mm circular sponge soaked in MMC (0.02%) was applied to the central corneal surface for 2 min. After removal of the sponge, the ocular surface was irrigated with 30 mL of balanced salt solution. The eye was then covered with antibiotic-steroid ointment and covered with a contact lens or patch. In one of the eight eyes described by Majmudar et al[49] they used MMC to treat central haze in a PRK patient post-PKP. A 44-year-old patient, who underwent PRK post-PKP 18 years prior, developed corneal haze, which limited the BSCVA to 20/30. The described procedure resulted in a clear cornea and BSCVA of 20/20. Azar and Jain[56] emphasize that based on the data by Majmudar et al[50] it may be justified to use MMC to treat pre-existing corneal scarring; however, they caution against the use of MMC for the prevention of corneal scarring. Azar and Jain propose that, if MMC is used prophylactically, the use of annular application may be more beneficial than use of MMC-soaked discs.[56,57] They hypothesize that the beneficial effect of MMC may be due to the inhibition of keratocytes under the annular zone of application, thus decreasing the centripetal migration of activated keratocytes and subsequent collagen deposition. They also believe that the annular method may be beneficial in decreasing corneal toxicity and the contact of MMC with the central 3 mm of the cornea. We have applied 0.02% MMC for 30 s to nine patients undergoing PRK following PKP for keratoconus, with no loss of BSCVA, corneal haze, or adverse reactions to the corneal button. Solomon et al[58] presented a case of a 43-year-old male with a refraction of +7.00 -4.75×125 in the right eye who underwent PRK 10 months following PKP for keratoconus. A hyperopic ablation was performed ablating 72 µm of tissue in a 522-µm-thick cornea with a 6.0 mm optical zone and 9.0 mm ablation zone. After photoablation, 0.02% MMC was applied to the corneal stromal bed for 2 min with a sponge and then irrigated copiously with balanced salt solution. Six months postoperatively, the patient's uncorrected visual acuity (UCVA) was 20/30, and the BSCVA improved to 20/20 with a refraction of -0.25 -0.25×164. No corneal haze was reported postoperatively. Additional studies have been performed by the authors of this chapter to examine the effectiveness of PRK post PKP with MMC, and only one patient has experienced corneal haze, which was safely removed with a lamellar keratectomy.[48] When applied as described by Majumdar et al[49] MMC appears to be a safe and effective method for treating postoperative haze following PRK and may improve the efficacy of PRK following PKP.

Laser-assisted subepithelial keratectomy (LASEK) has also been evaluated in the management of ametropia and irregular astigmatism after keratoplasty. In a pilot study, 16 eyes of 15 patients who were intolerant of spectacle and contact lens correction due to astigmatic anisometropia after keratoplasty (15 penetrating and 1 lamellar) had topography-assisted customized excimer laser treatments. All eyes had LASEK using 15% alcohol with a 20–30 s application. Four eyes received an application of mitomycin-C (MMC) 0.2 mg/mL for 1 min after stromal ablation. The mean preoperative spherical equivalent (SE) was -3.50 ± 3.97 D (SD) (range +1.625 to −9.25 D). The preoperative cylindrical error was −7.2 D (range −2.75 to −13.5 D). The programmed laser correction was −3.14 D (range +1.62 to −9 D) with a maximum attempted cylindrical correction of −7 D. At the final follow-up visit of 18 months, the mean postoperative SE was -1.08 ± 1.85 D (range +3 to −4.78 D). Ten eyes (62.5%) were within ±1 D of the intended correction. The mean postoperative cylindrical error was −2.72 D (range −0.5 to −6.5 D). Analysis of higher-order aberrations using a 6.0 mm pupil size demonstrated a significant reduction of higher-order root mean square (RMS), trefoil, and fourth-order spherical aberration at 18 months compared with preoperative values. Uncorrected visual acuity improved in all eyes. Best spectacle-corrected visual acuity was unchanged or improved in 13 eyes (81%) and worse in 2 eyes by 1 line; 1 eye lost 3 lines due to an increase in preexisting cataract. In eyes that did not receive MMC, corneal haze (grades II–IV) was encountered in three eyes (27%). One eye

required phototherapeutic keratectomy with MMC application at 12 months. Of the four eyes treated with MMC, one had trace haze and three had no detectable haze. There were no other complications reported. A significant improvement of both lower- and higher-order aberrations was obtained with good refractive stability for over 18 months. Iatrogenic haze typically occurred but appeared to be minimized with adjunctive use of intraoperative MMC.[59]

LASIK FOLLOWING PENETRATING KERATOPLASTY

LASIK offers several advantages over PRK in the treatment of myopia and astigmatism. These advantages include, but are not limited to, rapid visual rehabilitation, decreased stromal scarring, less irregular astigmatism, minimal regression, and the ability to treat a greater range of refractive disorders.[17,60–63] The major disadvantage of laser in situ keratomileusis (LASIK) is the risk of complications related to the creation of the lamellar flap. There have been several reports demonstrating efficacy and safety of LASIK following PKP.[64–76]

PATIENT SELECTION AND PREOPERATIVE EVALUATION

LASIK following PKP is subject to the same constraints as conventional LASIK. Monocular patients or patients with limited visual potential in the fellow eye are not good candidates. In addition, patients with wound healing disorders, significant dry eye, and collagen vascular disease should be offered other options. Finally, patients should have realistic expectations for their rehabilitation following LASIK for PKP. The accuracy of the procedure is not as precise as conventional LASIK and patients should expect to require spectacles for residual refractive error. The goal of LASIK following PKP is the return of spectacle-corrected binocularity.

TIME INTERVAL BETWEEN PKP AND LASIK

The time frame between performing the PKP and the LASIK procedure has not been firmly established. However, all corneal sutures must be removed prior to the LASIK as they will induce astigmatism. The time frame for suture removal varies greatly depending on the variables of patient age, corneal vascularization, corticosteroid use, physical examination of the graft–wound interface, and surgeon preference. Following suture removal there are two variables, which dictate whether the eye is ready for LASIK: a stable refraction and a well-healed wound, which will withstand the increased intraocular pressure, created during the LASIK procedure. Conventional wisdom is that following gas-permeable contact lens wear, the lens should be removed for a month for every decade of contact lens wear. Following suture removal, the cornea should also be allowed to return to a stable configuration. Lam and colleagues[77] have recommended that the wound be examined for whitening and scarification, while the refraction and corneal topography should be stable on serial evaluation. Some authors recommend waiting for 2–3 years,[65,68] while others recommend for as little as 8 months[67] to perform LASIK following the PKP procedure. Of note, there have been no documented cases of wound dehiscence following LASIK for PKP refractive errors. We therefore recommend waiting a minimum of 3 months following suture removal and until serial topographies are stable to perform LASIK following PKP. We always perform monocular surgery.

PREOPERATIVE EVALUATION

The preoperative examination should be comprehensive and should include a thorough retinal evaluation. The ocular surface should be carefully evaluated, as patients following PKP will have decreased corneal sensation and may have accompanying tear-film abnormalities. The anticipated LASIK procedure will often cause a neurotrophic keratitis and worsen the dry eye condition.[78] Patients with preoperative lid disease should be treated with lid hygiene, antibiotic and/or steroid application to the lid margin as indicated, and oral tetracycline family antibiotics as indicated. Patients with aqueous deficiency dry eye should be treated with tear supplementation, ointments, and punctal occlusion when needed. The corneal graft should be carefully evaluated. Any sign of allograft rejection or intraocular inflammation is a contraindication to the procedure and should be treated. Areas of pannus should be noted, as they may cause significant bleeding during the LASIK procedure. In addition, the graft–host interface should be examined for adequate wound healing and particularly for signs of poor wound apposition. Patients with high astigmatism may have an unstable wound with over-ride of the wound, which would increase the risk of wound dehiscence. Typically, patients with wound over-ride will have marked hemimeridional flattening in the axis of the over-ride. These patients should have their wound reapproximated in the aberrant region and then resutured prior to considering LASIK. The corneal clarity and pachymetry should be evaluated and, when in doubt, specular microscopy should be performed. Patients with poor endothelial reserve may have an increased risk of flap slippage due to decreased endothelial pump function holding the flap in place. Patients with a history of keratoconus should have their topography examined carefully for signs of recurrent disease. When the topography is equivocal or additional information is needed, new technology, such as the Orbscan (Orbtek, Inc., Salt Lake City, UT) or high-frequency ultrasound may provide additional information regarding anterior corneal curvature, posterior corneal curvature, and corneal pachymetry. Patients with previous relaxing incisions should have the axis of the incisions carefully documented. The corneal hinge should be positioned away from the relaxing incision to decrease the incidence of free flaps. For example, a patient with a superior relaxing incision should have a nasal hinged flap.

The status of the lens should also be carefully evaluated. Following PKP there is an increased incidence of cataract formation. LASIK is contraindicated in these patients who would most benefit from cataract extraction and intraocular lens implantation to help correct spherical refractive errors. In patients with a history of previous cataract extraction and intraocular lens implantation the status of the implant should be evaluated. In general patients with posterior chamber lenses do very well with LASIK. On the other hand, LASIK is usually contraindicated in patients with an anterior-chamber intraocular lens, unless the anterior chamber is very deep. These patients are at risk of endothelial touch against the intraocular lens when the cornea is compressed during the microkeratome pass.

The most common indication in the USA for PKP is pseudophakic bullous keratopathy (PBK).[79–81] There is a high incidence of macular pathology following PKP for PBK. Patients whose final visual rehabilitation is limited by macular pathology are often less motivated to wear contact lenses. Chronic cystoid macular edema is seen in

42–50% of cases of PBK,[82,83] and there is a 6–24% incidence of involutional macular degeneration following PKP,[84,85] both of which can severely limit visual rehabilitation. These patients may have a best-corrected visual acuity ranging from 20/25 to count fingers, with the majority having visual acuities of 20/40 or less.[15] Price et al reported that only 50% of patients with grafts for PBK achieved a visual acuity of 20/40 or better,[15] while Zaidman and Goldman[86] reported 31% and Speaker et al[87] a 22% incidence of visual acuity of 20/40 or better following PKP for PBK.

Pseudophakic bullous keratopathy occurs overwhelmingly in an elderly population. Assuming that these patients have good visual acuity in their fellow eye, there may be little motivation for an elderly individual, with no possibility of visual rehabilitation to the level of the fellow eye, to wear a soft or gas-permeable contact lens. These patients have had previous cataract surgery, PKP, approximately 1 year of postoperative visits prior to suture removal and, often, a vitreoretinal consultation. When they are ready for their visual rehabilitation, they are told that they cannot be improved with spectacles due to significant anisometropia. Even though their central visual acuity may be diminished, these patients would benefit greatly from the expanded peripheral visual field. These patients are excellent candidates for post-PKP LASIK, which can offer permanent rehabilitation of their refractive error.

Recently Mann et al studied patients who have had bilateral PKP. They determined that patients who have undergone bilateral PKPs with good postoperative vision and low levels of myopia, astigmatism, and minimal wound over-ride are good candidates for bilateral nonsimultaneous LASIK.[88]

Surgical technique

There are several alterations of our normal LASIK technique when treating myopia and/or astigmatism following PKP. As in all LASIK, preservation of the epithelium is extremely important to reduce the risk of flap slippage, epithelial ingrowth, and flap melts. Following a PKP these concerns are even more important. The surgeon should optimize the ocular surface preoperatively as discussed earlier and at the time of surgery minimize the use of topical anesthetics with the first drop of topical anesthesia given immediately prior to the surgical procedure. The ocular surface should be irrigated immediately following surface marking with gentian violet to reduce toxicity but maintain the marking in the event of a free flap. Perioperatively, toxic medications such as the aminoglycoside antibiotics should be avoided, and, if a nonsteroidal anti-inflammatory is employed, we prefer nonpreserved ketorolac tromethamine (Acular LS, Allergan, Irvine, CA). Intraoperatively, following flap repositioning, we place a drop of carboxymethylcellulose 1% (Celluvisc, Allergan, Irvine, CA) directly on the center of the flap after approximately 30 s to lubricate and protect the ocular surface.[89] After repositioning of the corneal flap, we generally wait 2 min for the flap to adhere to the underlying stromal bed in conventional LASIK. In LASIK after PKP, we wait 5 min for flap adherence before removing the speculum. We carefully perform a striae test for flap adherence and, if the flap is not tightly apposed to the stromal bed or if there is an epithelial defect, we place a bandage contact lens. Immediately after exiting the surgical suite the patient is asked to gently keep their eyes closed for 30 min, and the flap is re-evaluated carefully by slit-lamp biomicroscopy. Any flap irregularity is dealt with, and we do not allow the patient to leave until we are fully satisfied that the flap is in good position. The patients are then asked to return home and keep their eyes closed for 2–3 h. The patient uses nonpreserved tears transiently or for a week and wears a shield for a week as well. We are also more liberal with our use of postoperative corticosteroids than in our normal LASIK patients. In LASIK following PKP, we use prednisolone acetate 1% four times daily for 1 week tapering to once daily for 2 weeks. We feel that the additional use of corticosteroids is indicated due to the potential risk of graft rejection following any surgical procedure on a PKP. For antibiotic prophylaxis we use gatifloxacin 0.3% (Zymar, Allergan, Irvine, CA) four times a day beginning the day prior to surgery and continuing 5 days postoperatively.

We also alter our perioperative management for specific indications. Patients with corneal neovascularization are given one drop of 1% epinephrine 30 s prior to the microkeratome pass to reduce intraoperative bleeding. Patients with a history of herpes simplex or herpes zoster should be evaluated carefully for corneal sensation. Patients with a history of herpes simplex are treated preoperatively with oral antiviral therapy, which is then continued for a minimum of 10 days postoperatively to reduce the risk of recurrent viral disease induced by surgical trauma.

The LASIK surgeon must maintain a high degree of concern for the possibility of flap instability and slippage in any postkeratoplasty eye, especially during the perioperative period. Solomon et al[90] presented three cases of flap slippage in postkeratoplasty LASIK eyes. The main risk for flap slippage was corneal edema. All three patients had PKB as the indication for PKP, and all had peripheral corneal edema at the time of flap slippage, which occurred at a mean of 7 days postoperatively (range, 3–10 days). The final results of treatment for flap slippage were mixed. One patient had a lift and smooth procedure with a one-line improvement in BSCVA to 20/40; one patient had a two-line loss of BSCVA and underwent removal of the surgical flap, with UCVA of 20/50 and no loss of BSCVA of 20/30. The third patient had a three-line loss of BSCVA following a lift and smooth procedure and underwent a repeat PKP for irregular astigmatism. This small case series highlights the importance of the endothelial pump function in maintaining the adherence of the LASIK flap. Any sign of corneal edema is an indication that the endothelial pump function has been overwhelmed and that the flap is at increased risk of slippage.

Corneal grafts are at higher risk of corneal edema because of their lower numbers of endothelial cells. The mean human endothelial cell density starts at around 4000 cells/mm^2 in the first decade of life, declining gradually to a plateau of around 2600 cells/mm^2 by the age of 40 years.[91] While the average cell density of donor corneas is around 2665 cells/mm^2,[92] grafts undergo a more rapid and continual decline in endothelial cell count than do normal corneas, with cell loss of 7.8% per year for the first 5 postoperative years, followed by a 4.7% annual decline for years 5–10, according to a Mayo clinic study.[93] This compares to a 0.5% per year decline in normal controls.[94]

Even if a graft is clear and nonedematous before LASIK, the surgeon must decide whether there is a possibility of endothelial compromise from LASIK itself. On the one hand, current studies have found no long-term endothelial effects of LASIK. Jones et al found no effect on the endothelium in 98 eyes that were followed up to 12 weeks postoperatively,[95] and Pérez-Santonja et al, who followed patients up to 6 months, found that endothelial parameters in contact lens wearers actually improved after LASIK because of the discontinuation of contact lens wear.[96] One study of four patients who underwent LASIK after PKP and were followed for 12 months found no change in the endothelium.[97] On the other hand, changes in endothelial cell morphology, probably related to transient corneal edema, were noted at 15 min postoperatively by Kim et al.[98]

Although these changes resolved by the first postoperative day, they could compromise endothelial pump function in postkeratoplasty eyes.

As part of the LASIK evaluation in postkeratoplasty eyes, we recommend a careful examination of the corneal graft for evidence of corneal edema. Pachymetry should be reviewed not only for adequate post-LASIK bed thickness but also for evidence of edema. Specular microscopy may be performed if there is clinical suspicion of low endothelial cell density.

In most cases of LASIK, especially in patients with a history of a dry eye, we recommend a nasal-hinged flap, which helps to retain corneal sensation. We maintain this recommendation in postkeratoplasty eyes because maintaining corneal sensation is vital to long-term success of a corneal graft. However, in the case of LASIK performed on a postkeratoplasty eye with Fuchs' dystrophy or PBK, or any postkeratoplasty eye in which the endothelial function may be marginal, we instead recommend an 8.5 mm-diameter superior hinge flap, particularly when the peripheral host bed has frank edema. If the peripheral cornea is edematous and the pump function of the endothelium is decreased, it is more likely that the peripheral flap will elevate and dislocate following a blink, compared to a superior-hinged flap. The smaller-diameter flap has less tissue overlying the edematous peripheral bed and is also less likely to elevate. We also recommend that patients with endothelial compromise who undergo LASIK wear protective shields for a longer than normal period and be followed closely to reduce the risk of flap slippage.

At the time of surgery we use our standard LASIK procedure altered only to avoid initiating the incision at the corneal transplant graft–host interface. The patient's donor corneas generally range in size from 7.75– 8.5 mm in diameter. The flap diameter created by most microkeratomes is approximately 8.5–9.5 mm. Therefore, the flap is almost exactly the same size as the donor cornea. We avoid initiating the flap temporally or inferiorly at the graft–host interface, while attempting to center the flap over the pupil. This allows the flap to drape over the wound. We believe that this creates better wound apposition of the flap to the recipient bed. The corneal scar tissue at the PKP wound tends to be less pliable than normal corneal tissue. In addition, initiating the LASIK incision away from the wound prevents applying additional pressure directly to the corneal transplant incision and may decrease the risk of wound dehiscence. We also avoid placing the hinge over corneal relaxing incisions.

ONE-STEP VERSUS TWO-STEP LASIK FOLLOWING PENETRATING KERATOPLASTY

When planning to perform LASIK on an eye with a previous corneal transplant, the surgeon must address the issue of whether to perform LASIK as a one- or a two-step procedure. In the two-step procedure, as described by Vajpayee and Dada,[99] the surgeon cuts and replaces the flap and then follows the corneal topography, keratometry, and refraction for a variable span of time (weeks to months). Once the measurements have stabilized, the flap is lifted and ablation is performed to correct any residual refractive error.

The main argument for performing a two-step procedure is that some corneal remodeling may occur following the creation of the microkeratome cut alone. This cut may change the biomechanics of the post-transplant cornea, which depends to a great extent on the dynamics at the host–graft interface. Changes in corneal shape following the creation of a flap, and prior to laser ablation, has been noted by Roberts.[100] Anecdotally, Vajpayee and Dada reported treating several of their patients successfully with the two-step procedure. Busin et al[101] sought to take advantage of the change in astigmatic power and/or axis that occurs following the creation of a lamellar cut. In a series of nine eyes, all of which were at least 22 months post-transplant, creation of lamellar flaps alone resulted in a mean reduction of 1.6 D of cylindrical error and 1.0 D mean reduction of myopia 3 months postoperatively, without laser ablation. Alio and colleagues[102] compared the correction of postkeratoplasty astigmatism using LASIK in a one-step (11 patients) versus a two-step (11 patients) procedure. The authors suggested that a two-step approach may lead to a more precise and better refractive outcome in PKP eyes. Mularoni and colleagues examined a two-step LASIK procedure using topography-guided ablation to correct astigmatism after PKP. In the first step, a flap was created using the Hansatome microkeratome. In the second step, topography-guided ablation using the LaserSight LSX was planned with interactive software (CIPTA) once topographical and refractive stabilization had been obtained. Uncorrected visual acuity improved in all 15 (100%) eyes. Mean postoperative astigmatism was −1.67 (range: −3.5 to 0; SD: 1.26). No patient lost Snellen lines of BSCVA.[103]

There are a few arguments for performing a one-step LASIK procedure in a postkeratoplasty eye. First, it is likely that most of the instability of the refractive error following flap formation (with or without stromal ablation) is due to a change in flap position rather than to changes in corneal biomechanics. Good flap position may be difficult to obtain even in normal corneas, and flap instability is especially problematic in postkeratoplasty eyes, in part because of the compromised pump function of the graft endothelium, and in part because of the irregularity of the bed and the graft–host junction. It is possible that the changes in refraction and topography, seen over the weeks to months following the creation of a corneal flap in a postkeratoplasty eye, are due to continued slippage of the flap. If this is the case, then performing a two-step procedure simply increases the uncertainty about the final flap position because the flap must be laid down twice. In addition, performing a two-step procedure gives rise to an additional episode of possible flap complications, including infection and allograft rejection. The adherence of the flap over some areas of the graft–host interface can be much more tenacious than is seen in normal corneas, making it more difficult for the surgeon to re-lift the flap without complications. Epithelial ingrowth becomes a higher likelihood with the irregular flap border that can occur in these situations.

Although the refraction in postkeratoplasty eyes seems to fluctuate more than in normal eyes, the results of the one-step procedure produce a considerable and immediate improvement in visual function that will be delayed with the two-step procedure and that is not achieved with the creation of a lamellar flap alone. Nirankari produced a 74% reduction in myopia with the one-step method, and Solomon et al achieved a 90% reduction in myopia in 22 patients (with an average improvement of 6.8 D at 3 months).[90] In contrast, Busin et al saw a reduction of myopia by 19% in eyes treated with a lamellar cut alone.[101] The cylindrical correction was also better with the one-step method (a 65% reduction in cylinder documented by Nirankari, and 59% by Solomon et al[90]) compared to the lamellar-flap-only method (32% reduction in cylinder).[101]

COMPLICATIONS OF LASIK AFTER PENETRATING KERATOPLASTY

Any complication reported following LASIK for visual rehabilitation of myopia, hyperopia, or astigmatism may occur following LASIK for postkeratoplasty refractive error. The complications cited in the

literature include intraoperative paracentral flap perforation,[68] flap dislocations requiring placement of a suture,[68,70] buttonhole flap,[71] hemorrhage in the stromal bed,[64] obstruction of the microkeratome path by graft sutures,[64] consecutive irregular astigmatism,[66] photoablation decentration,[94] corneal perforation concurrent with astigmatic keratotomy performed under the flap,[69] peripheral interface epithelial ingrowth not requiring treatment,[74] one case of severe epithelial ingrowth treated without success for 6 months at which time eye had irregular astigmatism and moderate stromal melt,[75] and three cases of diffuse lamellar keratitis, one of which caused a decrease in BSCVA.[76] We have additionally seen flap striae, epithelial ingrowth, and flap melts following LASIK in patients with previous PKPs (Figs 59.1–59.4).

In LASIK the intraocular pressure is elevated to over 65 mmHg, and there is a very small but very real risk of wound dehiscence. We recommend LASIK following PKP be performed by experienced LASIK surgeons who can minimize the suction time needed during surgery. A careful slit-lamp examination on the day of surgery is extremely important, as improper wound alignment may lead to wound dehiscence, epithelial ingrowth, poor flap adherence, and ectasia.[70]

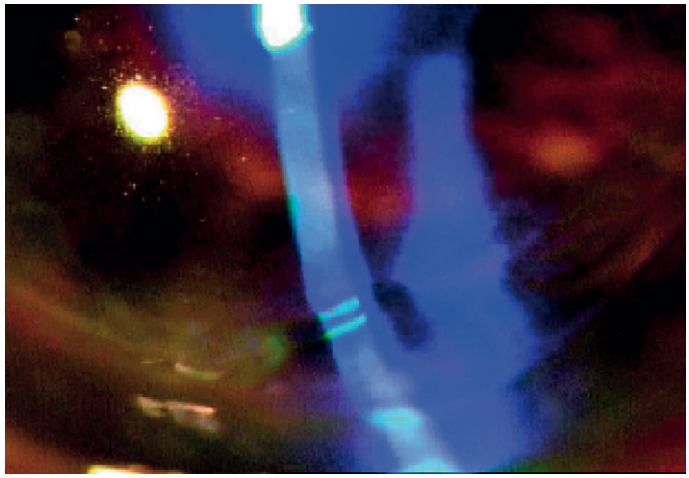

Figure 59.1. Epithelial ingrowth following LASIK in a patient with previous PKP.

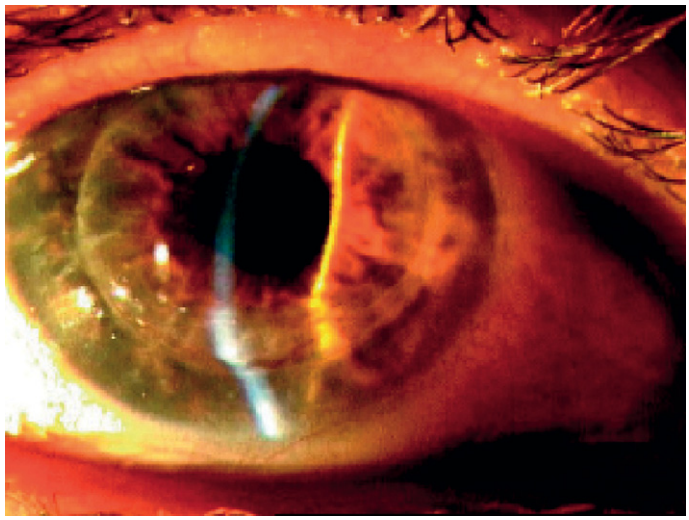

Figure 59.2. Flap melt in a patient with epithelial ingrowth following LASIK after PKP for residual refractive error.

If the placement of a flap on an eye post PKP needs to be adjusted, it is extremely important to carefully debride that epithelium, which rapidly grows over the exposed stromal bed. Flap stabilization with 10-0 nylon interrupted sutures should be considered if the flap does not properly adhere. It is important to bury the knots outside the flap to prevent epithelial defects on the flap and epithelial seeding at the stromal interface. Furthermore, burying the knots under the peripheral epithelium helps to prevent flap dislocation from suture tension caused by the resistance to sliding of the knot through the flap at the time of surgical removal.[70]

CLINICAL RESULTS

The first case reports by Arenas and Maglione,[64] Arenas and Garcia,[73] Zaldivar and associates,[65] as well as Parisi et al[67] in 1997 documented the efficacy of LASIK following PKP. In these case reports, all the patients were treated for residual myopia or myopic astigmatism following PKP for keratoconus.

The first large series of LASIK following PKP was presented by Donnenfeld and associates at the American Academy of Ophthalmology in 1998 and published in 1999 (Table 59.1).[66] The most common indication for the PKP was keratoconus (13 eyes), followed by PBK (5 eyes), Fuchs' endothelial dystrophy with combined cataract extraction (3 eyes), herpes simplex keratitis (1 eye), and herpes

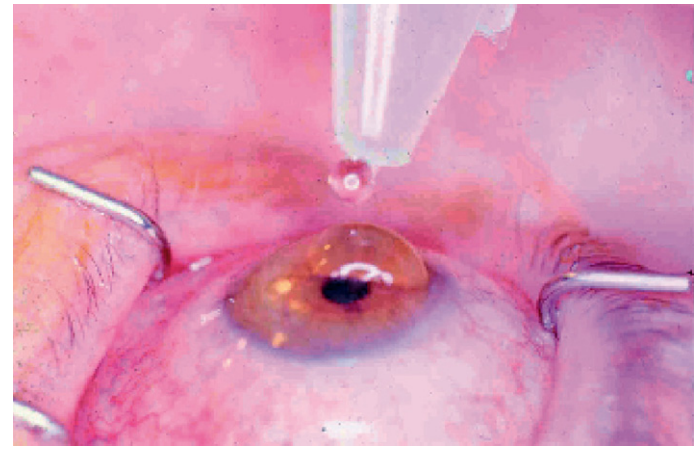

Figure 59.3. Protecting the flap with carboxymethylcellulose immediately following LASIK in a patient with a prior PKP.

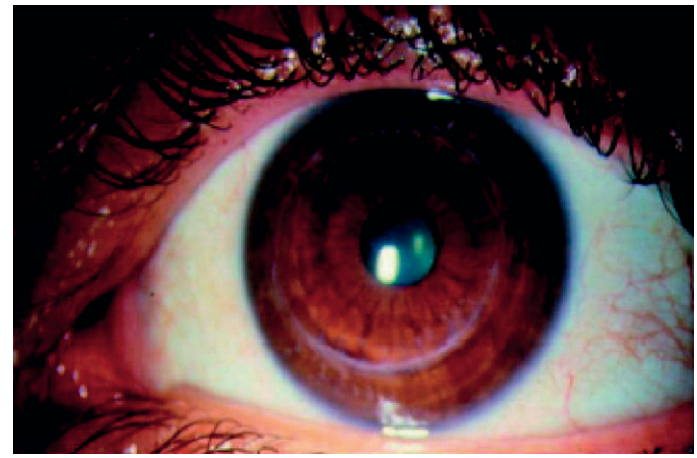

Figure 59.4. Relaxing incision post LASIK residual myopia and astigmatism following PKP.

Table 59.1 Summary of clinical results of LASIK after penetrating keratoplasty

Study	No. of Eyes	Change in Spherical Equivalent (%)	Change in Cylinder (%)	Patients with UCVA 20/40 after LASIK (%)
Donnenfeld et al	23	79.28–89.84	45.60–59.34	36
Preschel et al	25	79.79	65.07	31.81
Webber et al[a]	25	74.80	66.32	28
Forseto et al	22	85.27	57.78	54.5
Malecha et al	19	80.0	69.9	73.7
Buzard et al	26	92.9	60.9	86
Hardten et al	57	85.4	58.5	43

[a]Fourteen patients also received arcuate keratotomies in the stromal bed at the time of surgery.

LASIK, laser in situ keratomileusis; UCVA, uncorrected visual acuity.

zoster keratitis (1 eye). Fifteen eyes were phakic and eight eyes were pseudophakic. Three patients had undergone corneal relaxing incisions for high cylinder following PKP and antecedent to their LASIK surgery. Two patients underwent enhancements. Sixteen eyes were followed for 6 months, and seven eyes were followed for 12 months. The mean spherical equivalent preoperatively was −7.58 ± 4.42 D, which was reduced to −1.09 ± 2.01, −0.79 ± 1.84, −0.77 ± 1.25, and −1.57 ± 1.20 D, respectively, 1, 3, 6, and 12 months following LASIK. The mean cylinder preoperatively was 3.64 ± 1.72 D, which was reduced to 1.98 ± 1.15, 1.64 ± 1.14, 1.48 ± 0.92, and 1.29 ± 1.04 D, respectively, at 1, 3, 6, and 12 months following LASIK. Spherical equivalent anisometropia was reduced from a mean of 6.88 ± 4.4 to 1.42 ± 1.05 D at the final examination. Best-corrected visual acuity remained the same or improved in 21 of 23 eyes and decreased by one line in a patient who developed a nuclear sclerotic cataract and three lines in a patient who developed irregular astigmatism. Endothelial cell counts measured in nine patients preoperatively and at 3 months postoperatively demonstrated no statistically significant loss. There were no surgical flap or corneal transplant complications.

RESULTS AND VISUAL OUTCOME

There have been several other studies of comparably large series examining LASIK after PKP whose results are summarized in Table 59.1. Preschel and colleagues[70] examined 25 eyes treated with LASIK for astigmatism and myopia following PKP. Two eyes were enhanced with additional LASIK, but the authors did not include these postenhancement results in their analysis. Fifteen patients were followed for at least 6 months and five of those were followed for 1 year. The mean follow-up time was 5.52 months with a range of 1 day to 12 months. The mean preoperative spherical equivalent of −4.70 ± 2.98 D was decreased to −0.95 ± 1.45 D postoperatively. The mean cylinder preoperatively was −4.58 ± 2.12 D, which was reduced postoperatively to 1.60 ± 1.19 D. For this series, the UCVA was available in only 16 eyes at the last examination. Prior to LASIK, the UCVA was worse than 20/40 in all the eyes. After LASIK, 31.81% of the eyes demonstrated an UCVA of equal to or better than 20/40. Best spectacle-corrected visual acuity remained the same or improved in 16 of 23 eyes. Four eyes lost one line of BSCVA and three eyes lost two lines of BSCVA, one of which only had 1 day of post-LASIK follow-up. Another one of these eyes had a dislocated flap on the first postoperative day and had a BSCVA of 20/30 but gained four lines of UCVA. A third eye of this group had a postoperative BSCVA of 20/40 but gained eight lines of UCVA from 20/800 to 20/50. The complications in this series were two displaced flaps that were treated with 10-0 nylon interrupted sutures to stabilize the flaps after repositioning.

Guell and coworkers[74] performed LASIK in 87 eyes of which 20 had undergone prior PKP. The authors presented a pooled analysis of the results of LASIK after PKP and after other surgical procedures including RK, PRK, and cataract surgery. A distinct analysis of post-PKP results was not offered. They did note that the predictability in treating astigmatism in post-PKP eyes was comparable to that for eyes with no prior surgery. The authors reported that when examining stability of post-LASIK refraction for the entire group, a change of ±0.5 D was observed for 94.3% of patients. They point out that an important exception was one case of LASIK after a PKP, which regressed 2.00 D of cylinder. Guell et al also noted that for 45% of the eyes (9 out of 20 eyes) that were treated with LASIK post PKP, enhancements were necessary to treat undercorrections. Although not included in the studied series, Guell and coworkers mentioned that they perform relaxing incisions in post-PKP eyes with more than 6 D of cylinder and wait until the refraction is stable to treat the residual error with LASIK.

Webber and associates[69] studied 26 eyes and reported results of LASIK in 25 eyes with post-PKP ametropia. One eye was excluded from the analysis as it sustained a corneal perforation. The most common indication for PKP in the Webber et al study was keratoconus (23 eyes). The three other grafts were performed for PKB, childhood trauma, and *Acanthamoeba* keratitis. Four eyes had a history of ocular surgery after the PKP. One eye underwent a cataract extraction with intraocular lens implantation, one eye had a resuture of the graft–host junction, and two eyes had incisional refractive keratectomies. Fourteen eyes received arcuate cuts in the stromal bed at the time of surgery. Eighteen eyes were followed for 6 months or more and seven eyes were followed for 12 months. The mean preoperative spherical equivalent of −5.20 ± 2.31 D was reduced to −1.31 ± 1.63 D at the final follow-up. The mean cylinder preoperatively was −8.67 ± 3.22 D, which was decreased postoperatively to 2.92 ± 1.71 D. The patients who received arcuate cuts concurrent with the LASIK demonstrated greater target-induced

astigmatism, surgically induced astigmatism, and astigmatism correction index than those eyes, which did not. Three eyes showed a decreased BSCVA by one line and all eyes were unchanged or showed improvement in up to six lines of UCVA.

In their case series, Forseto and colleagues[68] studied the efficacy of LASIK in 22 eyes post keratoplasty. Eighteen eyes had a history of prior PKP, while four eyes underwent lamellar keratoplasty. The most common indication for PKP in the Forseto et al study was keratoconus (20 eyes). The two other grafts were performed for leukoma from herpes and irregular astigmatism after LASIK. The eyes were followed for an average of 10.09 months with 11 patients being followed for 1 year. Spherical equivalent demonstrated a mean reduction from –4.55 ± 3.66 D preoperatively to –0.67 ± 1.24 D postoperatively. Cylinder demonstrated a mean reduction from –4.24 ± 2.29 D preoperatively to –1.79 ± 1.12 D postoperatively. In 17 eyes the BSCVA was unchanged or improved. Of the five eyes not showing improvement, two lost two lines and three showed a decrease in one line of BSCVA. Stability of the refractive results was noticed between 1 and 6 months post-LASIK. At their final examination, 16 eyes (72.7%) demonstrated a refractive error within ±1.00 D of emmetropia. In 11 eyes it was determined that the mean endothelial cell count did not show any statistically significant loss. There were complications in two eyes, one eye had an intraoperative paracentral flap perforation and the other eye had a flap dislocation, which required stabilization with sutures.

In a series of 27 cases, Lima and colleagues[75] reported results of LASIK to correct ametropia after PKP for keratoconus for 26 of the eyes. One eye was excluded from the analysis because of an inability to obtain an exact postoperative refraction. The patient was treated for severe epithelial ingrowth for 6 months at which point the patient developed irregular astigmatism and moderate stromal melt. The average length of follow-up was 9.52 months for 23 myopic eyes and 5.75 months for 4 hyperopic eyes. Prior to LASIK, the mean refractive spherical equivalent in the myopic eyes was –5.27 ± 1.91 D and –0.45 ± 1.68 D at the final follow-up. Mean spherical equivalent for hyperopic eyes decreased from +5.18 ± 1.46 to +1.18 ± 0.94 D post-LASIK. In all of the hyperopic eyes and 18 (78%) myopic eyes, postoperative UCVA was 20/40 or better. Postoperative BSCVA was better than 20/25 in all of the hyperopic eyes and 22 (95.7%) of the myopic eyes. One eye lost one line of BSCVA. The significant complication was that one eye lost six lines secondary to refractory epithelial ingrowth, which resulted in irregular astigmatism and stromal melt.

Malecha and Holland[76] examined LASIK in 20 eyes following PKP. One eye was excluded from the analysis because of a severe traumatic injury post LASIK. In the majority of eyes (73.7%) keratoconus was the indication for PKP. Other causes included corneal scar secondary to injury (two eyes), corneal scar secondary to HSV keratitis (one eye), and corneal thinning (one eye). One eye received an accurate incision in the graft to reduce astigmatism. The average length of post-LASIK follow-up was 5 months (range 1–14 months). UCVA was 20/400 or worse in 73.7% of eyes before LASIK and improved to 20/40 or better post LASIK in 73.7% of eyes. The mean preoperative refractive spherical equivalent was reduced by 3.39 D (80.0%) from 4.24 ± 2.81 D preoperatively to 0.85 ± 0.84 D at the final follow-up. The mean cylinder was reduced by 2.83 D (69.9%) from 4.05 ± 1.71 to 1.22 ± 1.14 D. Seventeen of the nineteen eyes achieved a BSCVA of 30/40 or better. Myopic degeneration was responsible for the decreased BSCVA in one eye with BSCVA of 20/50 and DLK was noted in one eye with a BSCVA of 20/150. A total of three eyes developed DLK and were treated with steroids. Two of the cases resolved promptly with no decrease in BSCVA. In the third case, grade 2 DLK persisted, causing stromal haze and decreased BSCVA in a patient with a history of systemic lupus erythematosus.

Buzard and colleagues[104] evaluated 26 eyes that had LASIK at least 1 year after PKP. All eyes were followed for at least 6 months after LASIK; 22 eyes were followed for 12 months. Sutures were removed at a mean of 13 months post PKP. Before LASIK, the mean spherical equivalent (SE) was –4.94 ± 2.79 D and the mean astigmatism was 2.71 ± 2.33 D. At the last follow-up at 12 months, the mean postoperative UCVA was 20/30, the mean SE was –0.35 ± 0.65 D, and the mean residual astigmatism was 1.06 ± 0.67 D. Eighty-six percent of patients had an SE within ±1.00 D of emmetropia and a UCVA of 20/40 or better. Ten eyes (39%) had one or more enhancements, which were performed a mean of 6 months after the primary LASIK. The authors noted that significant complications such as wound dehiscence, epithelial ingrowth, and corneal decompensation did not occur. At the last follow-up, 18% of patients lost one line of best-corrected visual acuity and 27% gained one line.

Hardten and coworkers[105] performed a retrospective review of 57 eyes of 48 patients with anisometropia or high astigmatism who were unable to wear glasses or a contact lens after PK and who underwent LASIK for visual rehabilitation. UCVA, BCVA, and corneal transplant integrity were recorded before surgery as well as up to 60 months after LASIK. The mean follow-up after the LASIK was 21.4 ± 14.2 months (range 3–60 months). Mean preoperative SE was –4.19 ± 3.38 D. The mean preoperative astigmatism was 4.67 ± 2.18 D. Preoperative BCVA was 20/40 or better in 42 eyes (74%). At 2 years the mean SE was –0.61 ± 1.81 D, and mean astigmatism was 1.94 ± 1.35 D for the 28 eyes with follow-up. UCVA was 20/40 or better in 12 eyes (43%), and BCVA was 20/40 or better in 24 eyes (86%) at 2 years. A gain in BCVA of one line or more was seen in eight eyes (29%). Two eyes (7%) had loss of two or more lines of BCVA at 2 years. There were nine eyes (16%) that developed epithelial ingrowth and five eyes (9%) in this series had repeat corneal transplants.

SURGICAL ALTERNATIVES TO LASIK FOLLOWING PENETRATING KERATOPLASTY

The surgical alternatives for correction of postkeratoplasty astigmatism include corneal relaxing incisions and wedge resections.[106–108] Kirkness et al reported a series of 201 corneal transplants for keratoconus and found that 18% of patients required refractive surgery for the correction of astigmatism.[109] These procedures can significantly decrease corneal cylinder and are highly effective procedures. However, they have minimal effect on spherical equivalent. In addition, they can be unpredictable and may destabilize the graft–host wound.

Radial keratotomy can decrease low to intermediate levels of myopia. In a large clinical trial, radial keratotomy has been shown to be effective but is associated with glare, significant inaccuracy, refractive instability, increased risk of traumatic ruptured globe, and progressive hyperopia.[110] Most series document poor visual rehabilitation with radial keratotomy for postkeratoplasty myopia; therefore, radial keratotomy is not considered effective in its treatment.[111]

Pseudophakic patients with significant anisometropia can consider an intraocular lens exchange or a piggy-back intraocular lens.

Unfortunately, these patients have already often undergone a significant number of intraocular procedures. This alternative requires an additional intraocular procedure, which increases the risk of endothelial decompensation and glaucoma and may incite a graft rejection.[112]

CONCLUSION

The goal of therapeutic LASIK for visual rehabilitation following PKP is not necessarily the same as LASIK for the correction of myopia and/or astigmatism. The primary goal of LASIK following PKP is resolution of sufficient myopia and astigmatism to allow spectacle correction of the residual refractive error. Uncorrected visual acuity remains a secondary goal with LASIK following PKP, whereas UCVA is clearly the primary objective of cosmetic LASIK. For this reason, return to binocularity and optimized best-corrected visual acuity with spectacles is the true end-point for success with LASIK following PKP.

Unfortunately, irregular as well as regular astigmatism is a common finding after PKP. A potential advantage of LASIK is that there is evidence that the flap in LASIK creates a more regular ocular surface than occurs in PRK.[17] While irregular astigmatism can be a significant problem following LASIK for visual rehabilitation following PKP, we feel that there is less irregular astigmatism as compared to PRK.

Many patients following PKP will have irregular astigmatism, which, although not amenable to spectacle correction, can be rehabilitated with a gas-permeable contact lens. We discourage these patients, if they are at all contact lens tolerant, from having LASIK performed, as the excimer laser is currently not successful in treating irregular astigmatism. We anticipate that the development of customized corneal ablations guided by corneal topography or wavefront analysis will successfully treat some forms of irregular astigmatism in the next several years. This will allow even more accurate treatment of post-PKP refractive errors. While we only treated myopia and myopic astigmatism, LASIK may also be effective in the treatment of hyperopia and hyperopic astigmatism, although their larger peripheral ablations may impact directly on the corneal transplant wound.

In conclusion, LASIK is successful in treating postkeratoplasty myopia and astigmatism in most patients. Patients are overwhelmingly able to resolve their anisometropia and achieve binocular function. LASIK following PKP is more effective in treating residual myopia than astigmatism. We advocate a conservative approach to treating refractive errors following PKP with LASIK. Contact lenses remain the standard of care and are to be encouraged whenever feasible. When contact lens use is not possible, we suggest slightly undercorrecting the myopia, especially when the fellow eye is myopic. In addition, LASIK offers the advantage of allowing enhancements at a later date for residual refractive errors. LASIK offers the corneal surgeon an exciting new tool in the visual rehabilitation of the corneal transplant patient.

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60 LASIK and surface ablation

Eric D. Donnenfeld, Steven I. Rosenfeld, Renée Solomon

The era of modern refractive surgery began with the advent of excimer laser photoablation when the 193 nm argon–fluoride excimer laser was introduced. The field of refractive surgery was radically altered because this laser provided highly accurate ablations of the anterior corneal stroma to obtain a new range of curvature that facilitated innovative new surgical techniques.

In the early days of excimer laser refractive surgery, after first debriding the epithelium, surgeons performed photorefractive keratectomy (PRK) (Fig. 60.1) by ablating the cornea using the excimer laser. As the field progressed and laser in situ keratomileusis (LASIK) (Fig. 60.2) was introduced, the corneal stroma was ablated with the same excimer laser after creation of a lamellar flap made with a microkeratome.

Initially, IBM developed the excimer laser to photo-etch computer chips. The phrase excimer laser, contracted from *ex*cited d*imer*, reflects the events that occur in the excimer laser cavity, that is the argon and fluorine gas molecules are mixed. Usually, argon and fluorine are stable under normal physiologic conditions. However, that changes when the gas molecules are exposed to a transient high-voltage electrical charge. The result is molecular excitation to a higher energy state, and on return to the resting state the molecules emit the 193 nm excimer laser wavelength.

The excimer laser offers a number of benefits for ophthalmologic use. The instrument can precisely remove corneal tissue, and focal corneal edema develops in the tissue adjacent to the ablated area. This allows accurate shaping of the corneal tissue during refractive surgical techniques. This accuracy is possible because the cornea has an extremely high absorption coefficient at the 193-nm wavelength, where only one photon of excimer laser energy has the ability to break the carbon–carbon and carbon–nitrogen bonds that form the collagen molecules in the cornea. Discrete fragments of corneal tissue are released as the molecular bonds are broken, and the adjacent tissue remains undamaged. Specifically, the desired tissue is removed or excised, and this is accomplished with minimal damage.

The US Food and Drug Association (FDA) began studying PRK in the late 1980s and after completing the requisite studies in animals, Marguerite McDonald, MD,[1] performed the first procedure in a human eye in 1988. PRK was a successful and highly regarded technique; however, as with all surgeries, there were associated complications, the most important of which was delayed epithelial healing that spanned several days and was characterized by pain and photophobia. Other complications included corneal haze and scarring.

In 1990, Ioannis Pallikaris, MD, combined the techniques of lamellar corneal surgery (e.g. keratomileusis) and PRK, and performed the first LASIK procedure when he used the excimer laser to sculpt the corneal stroma beneath a corneal flap, fashioned with a microkeratome. The microkeratome was not new to ophthalmology; it had been designed and used by Jose Barraquer[2] for frozen tissue keratomileusis, and had undergone several subsequent modifications by other surgeons. The excimer laser produced better optical results than previous generations of lamellar corneal surgery because it ablated tissue with submicron accuracy and created larger optical zones.

With the introduction of LASIK, PRK lost a great deal of its acclaim. The advantages of LASIK over PRK are that following LASIK there is significantly less pain, the eye heals more rapidly, the vision returns more rapidly, and enhancement procedures to fine tune patient's vision can be performed sooner. Interestingly though, PRK has recently begun to regain its initial popularity, in part because of the recognition that the development of postoperative ectasia may be less likely to occur following PRK than LASIK.[3,4] In addition, surface ablation may allow for better fidelity with the customized wavefront patterns now utilized by the newer excimer lasers.

Surface ablation may be preferable to LASIK in patients with epithelial basement membrane disease and in those with thin corneas. PRK and the newer procedures of epi-LASIK and laser subepithelial keratomileusis (LASEK) avoid the increased higher order aberrations associated with creation of a LASIK flap. In addition, surface ablations remove the risk of flap complications such as incomplete flaps, buttonholes, and striae. These factors have resulted in increased use of surface ablation over the past few years.

Surface ablation consists of three main procedures, which are variations of one another: PRK, LASEK, and epi-LASIK. In the evolution of PRK, methods were developed to promote easier epithelial debridement, including the use of dilute topical alcohol. The

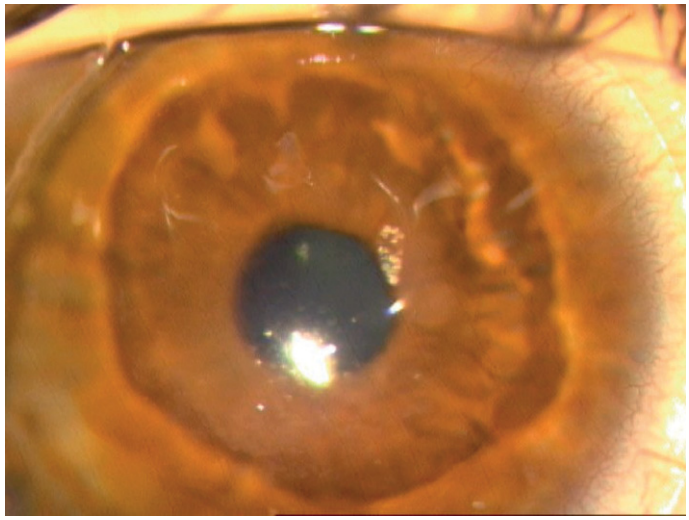


Figure 60.1. Central corneal epithelium has been removed in this eye undergoing photorefractive keratectomy.

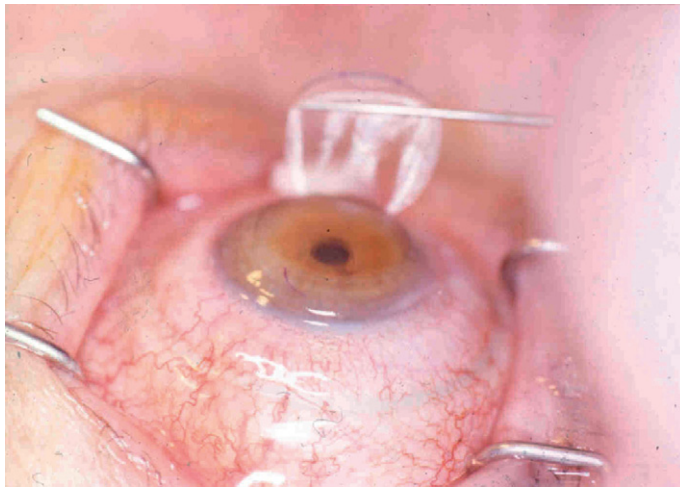


Figure 60.2. Image of elevated corneal flap during a LASIK procedure.

technique of LASEK developed when some surgeons thought that preservation of the epithelium would be beneficial. Alcohol was used to loosen the epithelium, which was then retracted manually. After photoablation was performed, the epithelium was replaced. In epi-LASIK, a microkeratome is used to mechanically create an epithelial flap using a modified dull blade and a thin applanation plate without using substances that are toxic to the epithelium, such as alcohol. The epithelial flap may be replaced over the ablation site or excised, depending on the surgeon's preference. Both epi-LASIK and LASEK are similar to PRK in that the epithelium is removed and the photoablation is performed directly on Bowman's membrane. The visual results seem comparable with all three procedures.

PATIENT SELECTION

The most important factor in determining appropriate candidates for PRK, the other surface ablation procedure, and LASIK is the capacity for healing. Patients who heal well tend to do well after corneal ablative refractive surgery and, conversely, patients with healing abnormalities should be considered carefully or denied surface ablation and LASIK. Generally, the major contraindication to surface ablation is a history of connective tissue disease, such as rheumatoid arthritis or systemic lupus erythematosus, thyroid disease, Sjögren's syndrome, or Wegener's granulomatosis, because these diseases are associated with less predictable wound healing and the potential for development of corneal melting and severe dry eye. However, patients whose diseases are well managed may achieve excellent outcomes after refractive surgery.[5]

Keloid formation initially was considered a contraindication to PRK; however, recent investigations have determined that that is no longer the case. Patients who have anesthetic or neurotrophic corneas, such as those with herpes simplex, herpes zoster, or trigeminal ganglion problems, are not candidates for LASIK because of problems with neurotrophic healing. Those with milder neurotrophic corneas, such as may be found in patients with diabetes, can be considered for refractive surgery; however, individuals with substantial diabetic maculopathy or corneal anesthesia are not candidates.

Another subgroup of patients who are not candidates for refractive surgery are monocular patients with significant loss of vision in their fellow eye. Refractive surgery is associated with a small, but real, risk of visually significant complications. If the patient were to lose vision in the good eye, and could not adequately function with the vision in their bad eye, they should not undergo refractive surgery.

A careful preoperative ocular examination is essential before any refractive procedure. Performing LASIK properly may be impeded by eyes that are deep set, by large brows, and by small interpalpebral fissures because these anatomic variations may reduce the ocular exposure needed for successful LASIK. A surface ablation procedure may be more suitable.

During the preoperative examination, the surgeon should closely examine the cornea for signs of pathology, including neovascularization, nodules, scarring, and corneal ectasia. The surgical plan may be altered or the hinge location changed in order to avoid areas of neovascularization or nodules. The best method to evaluate the cornea is with the red reflex through a dilated pupil. Although a thorough slit-lamp examination can reveal most corneal irregularities, corneal topography is a more sensitive method to look for subtle irregularities such as forme fruste keratoconus and pellucid marginal degeneration. Refractive surgery should generally be avoided in these latter two conditions because of the unpredictable outcomes and increased risks for postoperative ectasia.

Before refractive surgery, the size of the pupil under scotopic conditions should be determined. Even though it is controversial whether pupil size impacts night vision disturbances and visual outcomes after refractive surgery, patients with larger pupils preoperatively should be counseled that they may be at greater risk for postoperative night vision complaints. Recent studies by Schallhorn[6] revealed that preoperative pupil size had no significant effect on the incidence of glare, halos, and other night vision complaints. Rather, they found that the degree of preoperative myopia and ablation depth correlated more closely with these postoperative symptoms. The higher aberrations that were induced in the corneal periphery as a result of an interaction between the pupil size and the ablation zone were responsible for the resultant decreased visual acuity in the early days of excimer laser photoablation or sharp transition to unablated cornea) that was the cause of the complaints.

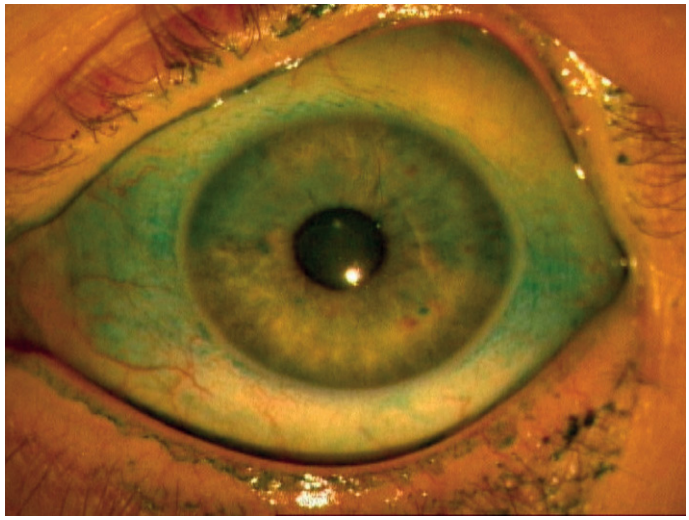


Figure 60.3. Conjunctival lissamine green staining in an eye with dry eye disease.

Another important part of the refractive evaluation is careful evaluation of the manifest and cycloplegic refractions. If the difference between the manifest and cycloplegic refractions exceeds 0.50 D, a post-cycloplegic refraction might be of benefit, attempting to 'push as much plus' as possible. Cyclopentolate 1% generally is used for younger patients and tropicamide 1% for older patients. The refraction must be stable prior to embarking on refractive surgery. Many surgeons require a 0.50 D change in refraction over the previous 6 months. If the interim change is greater, surgery should be postponed until stability is achieved.

Candidates for refractive surgery should also be evaluated for signs and symptoms of a dry eye syndrome, which may include assessment of the patient's history, the tear meniscus, Schirmer's testing, and supravital corneal and conjunctival staining with fluorescein, and lissamine green (Fig. 60.3) or rose bengal to identify early cases of dry eye. Dry eye can be a complication of LASIK more so than PRK, and the presence of dry eye preoperatively is a risk factor for dry eye postoperatively. If a dry eye is diagnosed, treatment should be instituted preoperatively with intensive lubrication including artificial tears and ointments, immunomodulating drugs (such as topical corticosteroids or cyclosporin), oral doxycycline, punctal occlusion, or all of these to limit postoperative keratopathy that can lead to flap irregularities, delayed healing, and even regression or under correction. Recently, patients have been reported to achieve better visual outcomes with less need for an enhancement procedure when the tear film and ocular surface are more stable.[7]

When evaluating the cornea before LASIK, it is of particular importance to look for signs of an anterior basement membrane dystrophy that could predispose the patient to epithelial defects with the microkeratome pass. These patients are usually best served by having PRK, depending on the refractive error.

Surgeons should use a preoperative stepwise checklist in which both the surgeon and the technician confirm the patient's name, the refraction, and the eye undergoing surgery. Some laser models require that the surgeon enter the size of the optical zone and whether or not a blend of the ablation zone (defined as an area of peripheral asphericity that reduces the possible undesirable effects of an abrupt transition from the optical zone to the untreated cornea) is to be performed. In the presence of sufficient corneal tissue, an ablation zone larger than the scotopic pupil size is usually selected.

SURGICAL PROCEDURES

Topical antibiotic prophylaxis is sometimes used preoperatively before the refractive procedure. Five to 10% povidone–iodine (Betadine) or alcohol wipes can be used to prep the skin before or after entering the laser suite, and 5% povidone–iodine drops can be applied to the ocular surface and then irrigated for further antisepsis. There is no consensus about the efficacy of these practices.

Before the actual laser treatment, the patient should be counseled about what to expect during the surgery, and the sounds and smell of the laser. Patients who are anxious can be given an oral sedative such as diazepam.

In patients with a high degree of astigmatism, some surgeons mark the horizontal or vertical corneal axis while the patient is sitting upright to ensure accurate alignment when the patient is positioned under the laser. The marks compensate for any cyclotorsion that commonly occurs when the patient moves from sitting to a supine or reclining position. A 15° offset in the treatment axis can decrease the effective cylinder power by 50% and result in a substantial axis shift.

A sterile drape can be placed over the skin and eyelashes based on surgeon preference after the patient is positioned under the laser. Topical tetracaine anesthetic drops, proparacaine anesthetic drops, or both, are applied to the eye. The drops should not be applied too early because they can cause a punctuate keratitis and substantial loosening of the epithelium. An eyelid speculum is placed in the eye to be treated, and an opaque patch is placed over the fellow eye to eliminate cross fixation. A gauze pad can be taped over the patient's temple between the operative eye and the ear to absorb the flow of excess eye drops and irrigating fluid. The patient is instructed to maintain fixation on the blinking red fixation light, while the surgeon focuses and centers the laser. For most patients, line-of-sight fixation during LASIK or surface ablation results in more accurate centration than globe immobilization.

Because corneal haze is a major complication associated with PRK, a soaked pledget of mitomycin (usually 0.02% or 0.2 mg/mL) can be placed on the ablated surface for anywhere from 12 s to 2 min at the end of the laser treatment. The length of time that the pledget is in place depends on surgeon preference. Recent studies seem to indicate that shorter application times are equally effective in primary surface ablations, hence the trend to 12-s applications. This treatment decreases the chances of the development of postoperative corneal haze after various procedures such as previous corneal surgery such as PRK, LASIK flap creation, penetrating keratoplasty, or radial keratotomy. Many surgeons also use mitomycin during PRK to treat moderate to high refractive errors. Irrigation of the corneal surface with copious amounts of chilled balanced salt solution (15–30 mL) to remove the excess mitomycin and minimize the toxicity is crucial. To avoid damaging limbal stem cells, the surgeon should avoid exposing the limbus or conjunctiva to the mitomycin. Human confocal microscopy studies have reported a reduced keratocyte population and less haze in eyes treated with mitomycin. However, the downside is that vision-threatening complications associated with the drug have been reported after glaucoma and pterygium surgeries, and they tend to occur many years later. There currently is no ideal topical wound-healing

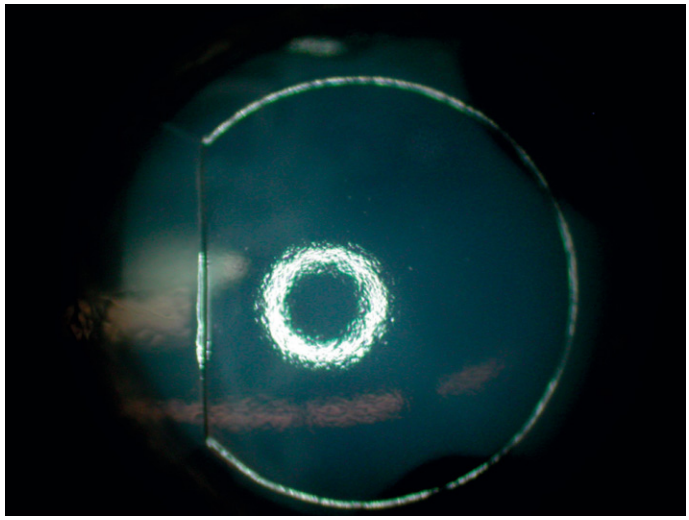


Figure 60.4. Stromal bed (in the center) and an elevated epithelial flap (on the left) during an epi-LASIK procedure.

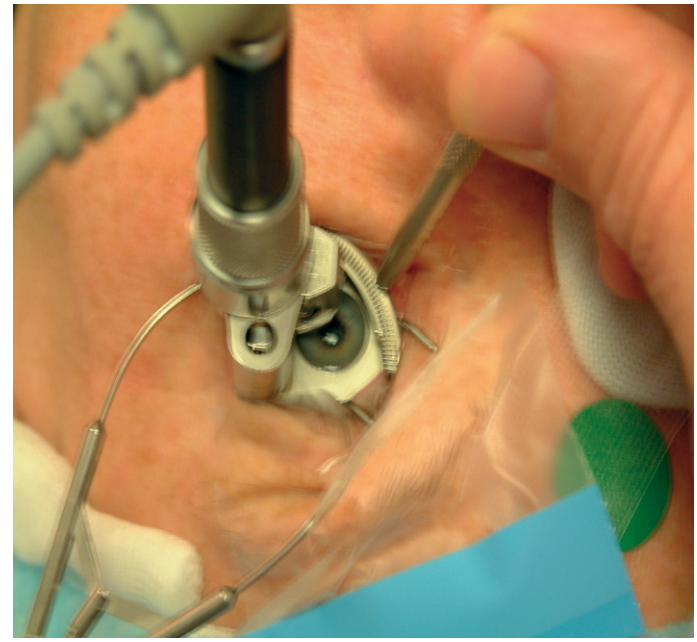


Figure 60.5. Microkeratome on the cornea being used to cut a corneal flap in a LASIK procedure.

modulator with high specificity for inhibiting collagen synthesis without toxic side-effects.

Epi-LASIK, which preserves the epithelium, has mostly replaced LASEK (Fig. 60.4). Epi-LASIK utilizes the special microkeratome to create an epithelial flap that preserves more viable epithelial cells which may improve epithelial flap adherence, reduce postoperative discomfort, and improve the visual outcomes compared to LASEK. Some surgeons perform epi-LASIK and deliberately excise the epithelial flap, claiming faster healing and visual recovery compared to preserving and replacing the flap. The primary disadvantages associated with these procedures are the degree of postoperative patient discomfort, the extended recovery time needed for visual rehabilitation, and the increased corneal haze in patients with higher refractive errors. There is also an increased risk of infectious keratitis with any surface ablation procedure compared to LASIK due to the extended healing time.

CONVENTIONAL AND WAVEFRONT-GUIDED ABLATIONS

Conventional excimer laser ablation can address lower order or spherocylindrical aberrations such as myopia, hyperopia, and astigmatism, which make up roughly 90% of all aberrations. Higher order aberrations, which make up the remainder, cannot be corrected with spectacles but may not adversely affect vision in small degrees. Their effects on the normal population recently have been reported. Higher order aberrations that develop after excimer laser ablation cause loss of contrast sensitivity and night-time halos and glare that result in lower quality of vision. Spherical aberration is most commonly associated with these visual complaints.

Wavefront-guided ablation creates customized ablation profiles for individuals to reduce both preexisting aberrations and reduce the induction of new aberrations. Wavefront-guided treatments can correct the spherical error and astigmatism and higher order aberrations, and thus can offer better visual quality. Wavefront-guided ablations seem to provide better contrast acuity and less induction of postoperative higher order aberrations compared with conventional ablations. However, most customized ablations do induce varying amounts of higher order aberrations. Advances in aberrometry and registration systems have resulted in improved outcomes with wavefront-guided ablations.

THE MICROKERATOME

Stopping the microkeratome pass just short of creating a free cap was an improvement that resulted in better outcomes. A hinge on the corneal tissue allows the flap to be lifted for the laser ablation and precisely returned to its original position. The flap adheres to the underlying stromal bed because of the corneal endothelial pump function. Flap repositioning eliminates suture-induced distortion and reduces irregular astigmatism.

The two basic components of the microkeratome are a suction ring and cutting head. The suction ring adheres to the globe to provide a stable platform for the microkeratome cutting head, and to raise the intraocular pressure (IOP) and stiffen the cornea to prevent movement away from the blade during flap creation. The dimensions of the suction ring determine the flap diameter and the size of the stabilizing hinge. The suction ring is connected to a vacuum pump, which typically is controlled by an on–off foot pedal.

The cutting head comprises a highly sharpened cutting blade, which is discarded after either each eye is treated or after a bilateral treatment, and the applanation head, or plate, which flattens the cornea as the cutting blade advances (Fig. 60.5). The length of the blade that extends beyond the applanation plate and the thickness of the applanation plate primarily determine the flap thickness. Another component of the cutting head is the electric or gas-driven turbine motor that oscillates the blade between 6000 and 15 000 cycles per minute. The same motor or a second motor mechanically advances the cutting head across the suction ring over the cornea. This is known as translation. In several models, the surgeon may manually advance the cutting head.

The actual flap thickness varies from the nominal flap thickness depending on the type of microkeratome, patient age, the preoperative corneal thickness, the preoperative keratometry, the preoperative astigmatism, the corneal diameter, and the speed of translation

of the microkeratome pass. In general, the faster the translation speed across the cornea, the thinner the flap that will be created. Maintaining a steady speed of translation avoids the creation of bumps in the stromal bed.

The flap diameter is determined based on the refractive error (hyperopic corrections and wavefront-guided treatments require a larger flap because of the larger ablation diameter), the corneal curvature and dimensions of the microkeratome suction ring (flatter corneas result in a smaller flap for the same size ring), patient's anatomy (peripheral corneal blood vessels and corneal diameter), and the surgeon's preference. Depending on the manufacturer, the suction ring is usually centered over the entrance pupil but if a suction ring creates a flap with a diameter under 9.5 mm, some surgeons prefer to skew it toward the hinge to ensure that the hinge will not be in the laser optical zone.

Thinner flaps leave more stromal bed thickness for the ablation and possible enhancements. However, thicker flaps have a lower risk of buttonholes and flap folds and may be more stable. Each type of microkeratome characteristically creates a flap with a range of thicknesses of which the surgeon must be aware and include them in the surgical plan to make sure there is an adequate residual stromal bed. The surgeon cannot predict the flap thickness based solely on the labeling of the microkeratome head.

Once the suction ring is properly positioned and the suction activated, the IOP should be measured, because low IOP can result in a poor-quality, thin, or incomplete flap. Excellent ocular exposure facilitates free movement of the microkeratome and proper suction ring fixation. Blockage of the suction ports from eyelashes under the suction ring or from redundant or scarred conjunctiva may result in inadequate suction. To avoid pseudosuction, the true suction can be ascertained by observing that the eye moves when the suction ring is gently moved, the pupil is mildly dilated, and the patient cannot see the fixation light. The IOP can be measured by using the Barraquer plastic applanator, a pneumotonometer, or palpating the eye. Novice surgeons should use an objective rather than a subjective method to measure the IOP.

Before making the lamellar cut, the cornea is moistened with proparacaine containing glycerin or with nonpreserved artificial tears. Balanced salt solution is not used because there is potential to create mineral deposits within the microkeratome that can interfere with its proper function. The microkeratome is placed on the suction ring, its path is checked for obstacles, and the microkeratome is activated and passed over the cornea until halted by the hinge-creating stopper, and then reversed off the cornea. Some surgeons believe that epithelial defects can be reduced by lowering the vacuum or discontinuing the suction during reversal; other models require the vacuum to remain at full pressure during reversal. Improvements in microkeratomes have decreased the incidence of epithelial defects. If an epithelial defect occurs in one eye during a microkeratome pass, an epithelial defect is highly likely to develop in the second eye, regardless of changes in the vacuum level, implying the presence of a subclinical epitheliopathy such as epithelial basement membrane disease that is made manifest by the microkeratome pass.

PEARLS TO PROTECT THE STROMAL BED THICKNESS AND FLAP

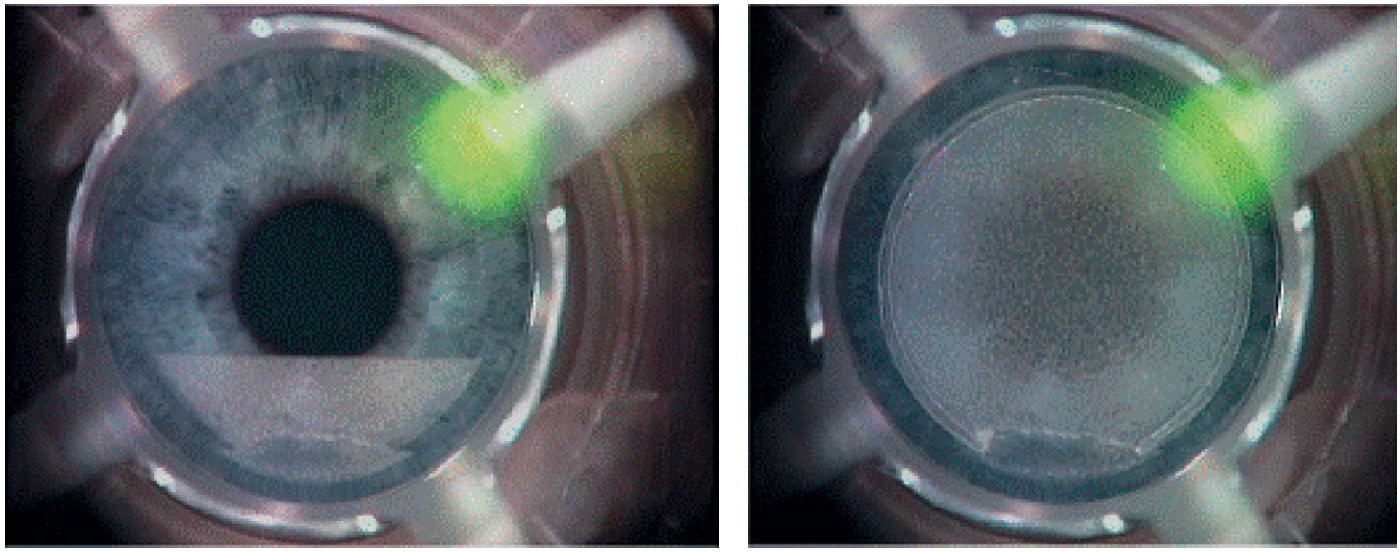
Most surgeons follow the guideline of 250 µm as the minimum residual corneal bed thickness. However, this thickness is anecdotal and not based on laboratory-based investigations or controlled prospective studies; 250 µm of tissue in the stromal bed after ablation does not guarantee that postoperative corneal ectasia will not develop. A retrospective study of 10 eyes of seven patients who developed corneal ectasia after LASIK showed that 30% had a residual stromal bed thickness of 250 µm or more. In that group of patients, 88% had previously undiagnosed forme fruste keratoconus. The actual LASIK flap created may be thinner or thicker than desired, despite the labeling of the microkeratome head. A thicker flap will leave a thinner stromal bed than anticipated after the ablation, which may result in a stromal bed thinner than 250 µm. Intraoperative pachymetry allows one to measure the flap thickness and stromal bed prior to the ablation. Subtracting the amount of tissue to be ablated from the pretreatment stromal bed measurement allows the surgeon to calculate the postoperative stromal bed thickness prior to the ablation. Intraoperative pachymetry is most helpful in patients with high myopia, thin corneas, and when doing enhancements.[8–10]

FEMTOSECOND LASER

In addition to a mechanical microkeratome, surgeons are increasingly using the femtosecond laser (IntraLase) to create flaps (Fig. 60.6, *A* and *B*, Fig. 60.7).[11,12] The laser also requires the use of a suction ring, with the accompanying elevation in IOP and potential for optic nerve damage, although the femtosecond laser requires a more prolonged period of suction and elevated IOP than does the conventional microkeratome. Proper centration of the suction ring is critical and as such is performed under a separate microscope. The suction ring is centered over the pupil, and suction is applied. The docking procedure is initiated under the femtosecond laser's microscope, with the patient's chin and forehead level and the suction ring parallel to the eye. The applanation lens is centered over the suction ring and lowered into place using a joystick; the suction ring then is unclipped to complete the attachment to the docking device.

Complete applanation of the cornea must be achieved or an incomplete flap or incomplete side cut may result. Once centration is confirmed by the laser's computer, the surgeon applies the femtosecond laser emission. In contrast to a mechanical keratectomy, the femtosecond laser creates an opaque bubble layer, which results from the cavitation bubbles produced by the interaction between the laser and the corneal tissue. The vacuum is released, the suction ring is removed, and the patient is repositioned under the excimer laser. One of several spatulas with a semi-sharp edge may be used to identify and score the flap edge near the hinge. The instrument is passed across the flap along the base of the superior hinge, and the flap is lifted by sweeping inferiorly and separating the flap interface, dissecting one-third of the flap at a time, which decreases the risk of tearing the flap. If bilateral LASIK surgery is planned, the flap in the second eye can be created before performing the excimer ablations.

The femtosecond laser works by causing photodisruption of the corneal collagen. When thousands of contiguous pulses are scanned across the cornea in a controlled pattern, the result is a lamellar flap. A computer controls the flap diameter and depth, and the hinge location and size. The advantages of the femtosecond laser are the potential for more reliable and reproducible flap thickness, lessening or avoiding complications such as buttonhole perforations, and precise control of flap dimensions and hinge location. In addition, some investigators have reported that using the femtosecond laser results in less induced astigmatism, and less epithelial



A B

Figure 60.6. Use of the femtosecond laser to cleave a corneal flap. *A*, Cavitation bubbles produced by the interaction between the laser and the corneal tissue can be seen at the bottom of the cleavage plane as the femtosecond layer is creating the flap. *B*, An opaque bubble layer covers the entire cleavage plane between the corneal flap and the stromal bed.

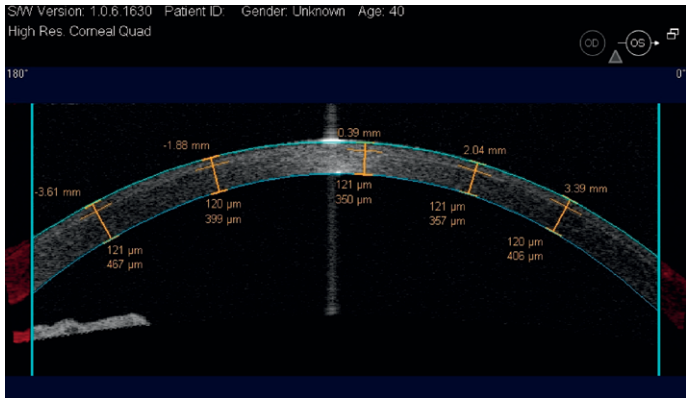


Figure 60.7. Planar flap is shown on ocular coherence tomography (OCT). The flap was created with the femtosecond laser (Courtesy of Eric Donnenfeld MD).

injury compared to mechanical microkeratomes. Other studies showed better uncorrected visual acuity and manifest refractive outcomes with the femtosecond laser.

The femtosecond laser has been gaining in popularity because it allows the surgeon to adjust for the variables involved in flap creation, including the thickness and diameter, hinge location and angle, bed energy, and spot separation. Hyperopic and wavefront-guided treatments usually require creation of a flap with a larger diameter. The femtosecond laser creates a planar flap while mechanical microkeratomes create a meniscus flap. The corneal morphology or curvature does not affect the flap thickness with the femtosecond laser.

Other postoperative complications, such as DLK, may be more likely to occur with the femtosecond laser and they have been reported to occur more commonly during the first cases performed by a surgeon, until the laser energy is reduced. Some surgeons use more intensive and prolonged topical steroid therapy with the femtosecond laser to reduce the risk of DLK.

COMPLICATIONS OF REFRACTIVE SURGERY

PROCEDURE LIMITATIONS

Despite the greater popularity of LASIK it has limitations. The procedure is generally not preferred for treating myopia exceeding −12.0 D or hyperopia exceeding +5.0 D because of poorer predictability and an increased potential for complications.

Interestingly, the visual outcomes after LASIK and PRK are similar. In one study of myopic patients with refractive errors ranging from −1.0 to −9.5 D, the refractive outcomes were equal. In another study of myopic patients with refractive errors between −6.0 and −15.0 D, the incidence of postoperative optical symptoms after LASIK was slightly decreased compared with PRK. In contrast, almost twice as many patients with refractive errors ranging from −2.5 to 8.0 D who underwent LASIK in one eye were highly satisfied with their results compared with the results in the fellow eye treated with PRK 1 year after treatment. The LASIK-treated eyes in these highly satisfied patients experienced less postoperative pain, more rapid visual recovery, were more likely to achieve an uncorrected visual acuity of 20/20 or better, and had a lower incidence of postoperative topographic irregularities.

The incidence of visually significant complications in LASIK is small and estimated to be less than 1%. As with most surgical procedures, the incidence of complications decreases with surgeon experience, and when complications do arise, rapid recognition and treatment can help to minimize their effect.

A brief list of LASIK complications includes button holes, incomplete flaps, free caps, epithelial erosions, macrostriae, microstriae, dislocated flaps, dry eye syndrome, DLK, infectious keratitis, epithelial ingrowth, interface debris, corneal ectasia, decentered ablations, and irregular astigmatism. The visual complications include night vision disturbances (glare and halos), reduced contrast sensitivity, loss of best corrected visual acuity, monocular or binocular diplopia, and, rarely, blindness.

Advances in technology continue to improve the visual outcomes. The planar flap and smooth stromal beds obtained with the femtosecond laser seem to improve the visual outcomes. Wavefront-guided laser ablation offers the potential for improved visual quality by reducing the incidence of laser induced higher order aberrations. PRK is increasing in popularity in conjunction with the wavefront-guided lasers because surface ablation avoids the higher order aberrations induced by the corneal flap in LASIK. The newer generation lasers provide smoother ablations, which when combined with immune modulating agents like mitomycin C seem to reduce the incidence of corneal haze following any surface ablation treatment. There is no substitute for randomized prospective studies to determine if any of these newer techniques or modalities are superior to their predecessors, despite what seem to be theoretical advantages. Interestingly, a recent review of the literature failed to demonstrate that wavefront-guided refractive surgery outperformed conventional LASIK with newer technologic refinements such as broad ablation zones, smoothing to the periphery, and eye-trackers. Currently, there is no treatment for irregular astigmatism, but the research into true custom ablation may eventually solve this condition.

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61 Rejection: clinical forms, diagnosis, and treatment

Matthew A. Dahlgren, Jay H. Krachmer

Allograft rejection is the most common cause of corneal graft failure after an initial period of graft clarity.[1] Surprisingly, the lifetime chance for a rejection episode is about 25%, but with timely diagnosis and treatment the majority of these rejection episodes can be reversed to prevent graft demise. Numerous prospective, retrospective, and case series have reported that rejection complicates 4–20% of routine low-risk penetrating keratoplasty surgeries.[2–10] The considerable range probably reflects different patient populations, host characteristics, postoperative management, and diagnostic criteria. Certain host factors increase the risk of allograft rejection episodes to about 50% in the first year and 65% in the first 3 years following surgery (Table 61.1).[10,11]

The first corneal transplant was performed by Edward Zirm in 1905,[12] but the rejection reaction was not described until 1948. Paufique, Sourdille, and Offret hypothesized that transplanted tissue contained unfamiliar proteins which could cause allograft clouding after initial clarity.[13] They coined the term *maladie du greffon* (graft sickness) to describe this pathology. Khodadoust and Silverstein first clinically illustrated in their 1969 paper that the allograft epithelium, stroma, and endothelium can all suffer a rejection reaction separately or together.[14] Early work on the pathophysiology of corneal rejection was done in rabbits by Maumenee in 1951[15] and in human subjects by Polack and Kanai in 1972,[16] in which they demonstrated sensitization of the host to the donor tissue as the primary cause of rejection.

With our current understanding of immunology, a rejection cannot occur unless three different principal elements transpire.[17] First, the antigens from the donor cornea must be carried by host antigen-presenting cells (APC) to a local lymph node or other nearby lymphatic tissue. While at the lymphatic site, the APCs must initiate and amplify an immune response causing host sensitization. Finally, helper T cells, cytotoxic T cells, B cells, and antibodies need to travel back to the allograft site. Here these and other effector components exert their inflammatory and destructive effect. Many of the known risk factors for rejection promote one or more of these principal elements.

The presence of ocular inflammation is perhaps the highest risk factor for a rejection reaction.[18] When preoperative inflammation is present, the host recipient bed will have a marked increase of APCs, escalating the chance of rejection.[19,20] Inflammation also increases endothelial growth factor, which promotes the growth of new vessels and stimulates lymphangiogenesis.[21] Major histocompatibility complex (MHC) antigens, both class I and II, are increased in an inflamed eye, enabling the immune response.[22] Finally, inflammation causes a breakdown in the blood–aqueous barrier, disrupting the immune privilege of the anterior chamber.[23,24] Suture abscess, recurrent herpes simplex virus infection, persistent epithelial defect, and uveitis are a few major causes of postoperative inflammatory incitement. If possible, corneal transplantation surgery should be delayed until inflammation is properly treated. Likewise, postoperative inflammation should be treated aggressively.

Preoperative deep stromal vascularization of the host cornea is a major risk factor for allograft rejection. Usually sequelae from inflammation, these blood vessels provide afferent outflow of APC and an efferent highway to the graft. Lymphatic channels are also coupled with the vascularization, which contributes to the afferent immune reflex arc. Intraoperatively, efforts should be made to free up anterior synechiae to minimize contact of the vascular iris with the endothelium.[9] Postoperative vessel ingrowth of the graft should be recognized early and treated to retain immune privilege.

Other known risk factors for a rejection reaction are repeat corneal transplantation, prior rejection episodes, larger grafts, and recipients under the age of 40. Up to 40% of patients exhibit an episode of rejection when there are two or more previous grafts.[25] Larger corneal grafts are closer to the limbus, predisposing patients to a higher risk of rejection. This is because the peripheral cornea and limbus are the natural habitat of Langerhans cells (LC). These cells are a type of APC that can trigger the immune cascade. Many retrospective studies have shown that younger patients exhibit a higher rate of rejection episodes.[26,27] The immune system in younger patients may be more prone to sensitization and capable of generating an aggressive response as compared to older donor recipients.

It is critically important that patients and their families be repeatedly educated in the postoperative period about corneal graft rejection. The three most common symptoms of redness, pain, and decreased vision should be reviewed with the patient at each office visit. If these symptoms persist more than 24 h, the patient should be instructed to call the clinic for evaluation. The four commonly

Table 61.1 Risk factors for allograft rejection

Ocular inflammation
Stromal vascularization
Repeat keratoplasty
Prior rejection reaction
Larger graft size
Young age
Iris synechiae

accepted forms of allograft rejection—epithelial, subepithelial, stromal, and endothelial—may all cause one or more of the three principal symptoms. Endothelial rejection is the most common type seen clinically, which causes permanent donor endothelial cell injury and can lead to subsequent graft failure.

EPITHELIAL REJECTION

The average onset of an epithelial rejection reaction is 3 months, and the cumulative risk is 10–14%.[9,10] It usually occurs after 1 month of surgery, but within the first year after transplantation.[10] It is more commonly seen in patients under 50 years of age. The true incidence may be underreported as the event is usually asymptomatic and discovered on routine postoperative examination.

Slit-lamp examination reveals an elevated thin rejection line in the epithelium that starts peripherally near the graft–host junction. The rejection line stains with fluorescein or rose bengal due to the destruction of the donor epithelial cells. Over the course of a few days, this line will migrate centrally across the entire donor tissue. The donor epithelium central to the line is irregular, but the host epithelium which follows the line is clear (Fig. 61.1). Minimal if any clinical inflammation is present.

During this episode, the host epithelium is thought to replace the donor epithelium. There is no correlation with vascularization of the graft. Graft failure from epithelial rejection is uncommon; however, epithelial rejection often forecasts or accompanies overt endothelial rejection.

SUBEPITHELIAL INFILTRATES

A subepithelial infiltrate (SEI) rejection reaction was initially described in 1978.[28] This phenomenon occurs in 10–15% of penetrating keratoplasty cases with an average onset of 10 months.[9,10] Similar to epithelial rejection, SEI rejection can be seen in isolation or concomitantly with other types of rejection. However, these patients are more likely to have ocular symptoms, notably redness and photosensitivity.

The subepithelial infiltrates are 0.2–0.5 mm hazy white lesions located in the anterior stroma (Fig. 61.2). They are most easily identified with a broad oblique beam or sclerotic scatter at the slit-lamp biomicroscope. SEIs are exclusively located in the allograft, characteristically in a central random distribution. Their appearance is identical to those of epidemic keratoconjunctivitis (EKC), but in EKC the infiltrates are located in both the donor and host tissue. The infiltrates represent areas of cellular infiltration, and topical corticosteroids will often make the SEIs quickly disappear. In isolation they will not cause any permanent graft harm or scarring, but their presence may portend an impending fulminant endothelial rejection.

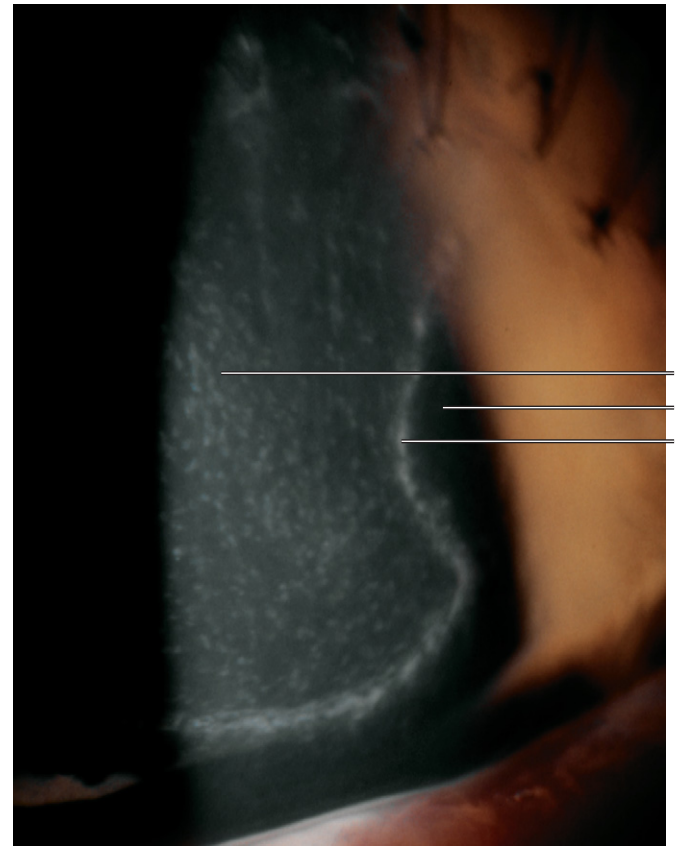

Figure 61.1. Epithelial rejection line. Irregular donor epithelium (1), clear host epithelium (2), and epithelial rejection line (3) are demonstrated. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

STROMAL REJECTION

Stromal rejection is very uncommon; however, its sequelae can cause permanent allograft opacity and failure. Typically, a mid to deep stromal infiltrate is seen in the graft associated with pain and intraocular inflammation (Fig. 61.3). Deep stromal vessels may invade the graft bringing additional inflammatory mediators and depositing lipid exudates. In rare instances, the graft stroma may become necrotic and perforation may ensue.

ENDOTHELIAL REJECTION

Endothelial rejection is by far the most common type of allograft rejection. This type of reaction is of utmost importance to recognize early in order to prevent graft failure. The average onset for endothelial rejection is 8 months.[10] It occurs after at least a 2-week period of graft clarity, but can happen as late as 20 years after penetrating keratoplasty.[10] Patients notice decrease in vision, redness, pain, and light sensitivity.

During this presentation, fine keratic precipitates are observed on the allograft endothelium in a random distribution or in an undulating line. This line, known as the Khodadoust line, begins in the periphery of the graft and processes centrally (Figs 61.4 and 61.5). Careful observation may reveal the rejection line originating near a focus of neovascularization. The graft behind the line often

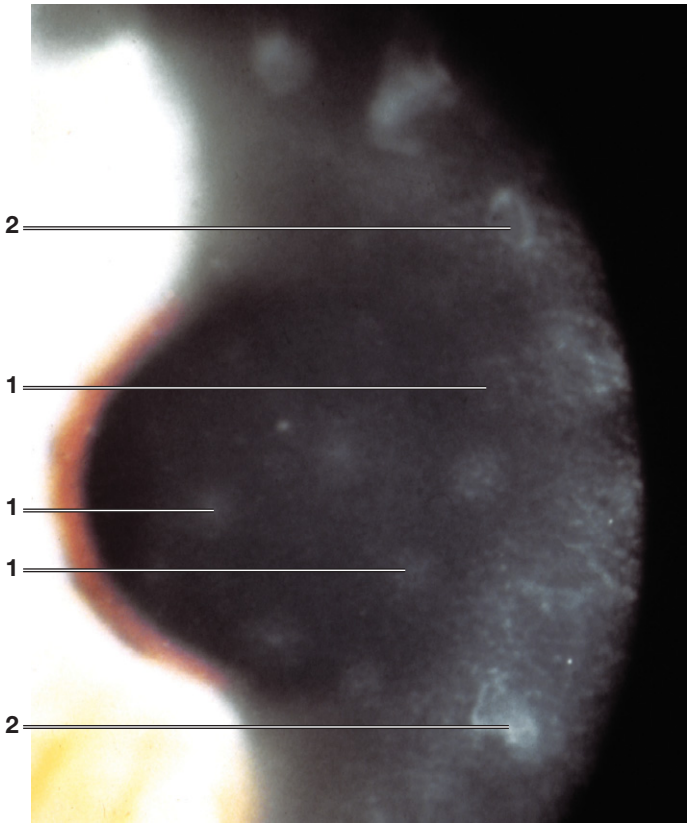

Figure 61.2. Subepithelial infiltrates. Hazy white subepithelial infiltrates (1) and corneal suture scars (2) are shown. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

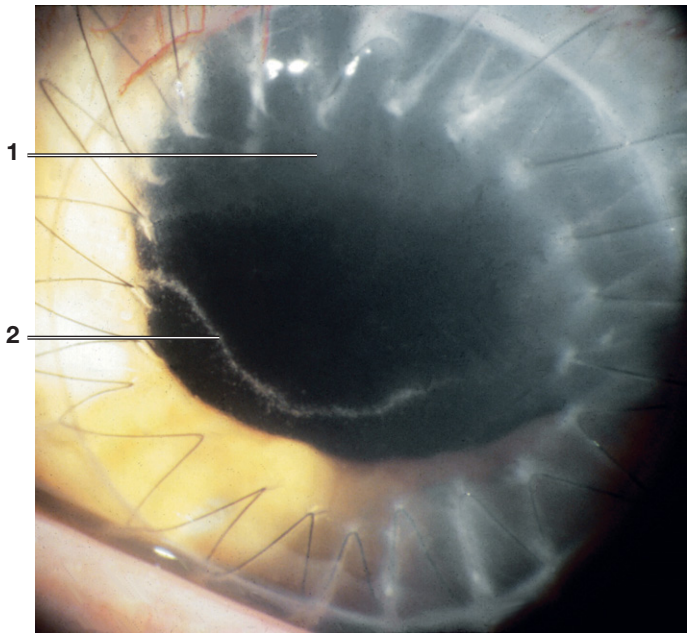

Figure 61.3. Stromal rejection. Superior mid-stromal infiltrate (1) with nearby stromal vascularization is present. An epithelial rejection line (2) is also seen. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

exhibits stromal and epithelial edema due to the stress on the local endothelial cells. If the keratic precipitates are randomly spread out over the endothelium, diffuse stromal edema with folds in Descemet's membrane will occur (Figs 61.6 and 61.7). Invariably, some element of conjunctival injection is present, especially around the limbus ('ciliary flush'). A mild to moderate anterior chamber cellular reaction with aqueous flare accompanies the rejection episode. The inflammation may also induce endothelial cell polymegathism.

DIFFERENTIAL DIAGNOSIS

It is often difficult to distinguish between endothelial rejection and inflammation caused by herpes simplex virus (HSV). Herpes simplex keratitis is a common indication for corneal transplantation, and the viral infection may recur anytime postoperatively. Patients may also acquire HSV in the postoperative period. HSV keratouveitis causes symptoms similar to graft rejection, and findings also include conjunctival hyperemia, anterior chamber reaction, and fine endothelial keratic precipitates. In this situation, the host endothelium should be carefully inspected for keratic precipitates. Host precipitates are more commonly seen in HSV, whereas precipitates from endothelial rejection are confined to the donor button. Stromal edema can make this task difficult, so often the two entities cannot be clinically distinguished. Oral acyclovir in a therapeutic dose should be co-administered if uncertainty is present.

Over time, cornea allografts may fail due to progressive endothelial cell decompensation unrelated to acute graft rejection. These grafts exhibit stromal thickening with Descemet's folds, microcystic epithelial edema, and occasionally frank bullous keratopathy. The picture may become obscured if old endothelial pigment is misinterpreted as being active keratic precipitates. However, late graft failure is not accompanied by inflammation. If doubt exists, treatment with corticosteroids should begin. If no improvement is observed in one week, then permanent endothelial dysfunction is present.

Epithelial ingrowth through the graft–host junction often advances across the endothelium in a chainlike pattern mimicking the Khodadoust rejection line. The line caused by epithelial ingrowth has more of a scalloped edge and, unlike rejection, it can also grow across the host endothelium, angle, and iris. Application of argon laser to an area of involved iris will produce a whitening effect. Angle involvement may produce a refractory glaucoma. The ingrowth usually can be traced back to a current or prior area of poor wound closure. Often large clumps of epithelial cells can be seen floating in the anterior chamber. These cells along with the epithelial line do not respond to corticosteroid treatment. Management can be extremely difficult.

Finally, low-virulent infectious endophthalmitis can cause signs similar to endothelial rejection. In these situations, the anterior chamber reaction may persist or worsen with corticosteroid treatment. Hypopyon and vitreous cell may be present, which are not seen in allograft rejection. If the patient is pseudophakic, the intraocular lens implant and capsule should be carefully examined for infiltrates caused by *Propionibacterium acnes* and *Staphylococcus epidermidis*. If suspected, aqueous and vitreous cultures should be obtained.

TREATMENT

Corticosteroids are the primary treatment for acute cornea allograft rejection reaction.[29] The initial treatment with these drugs should be prompt and aggressive, especially for endothelial rejection. In

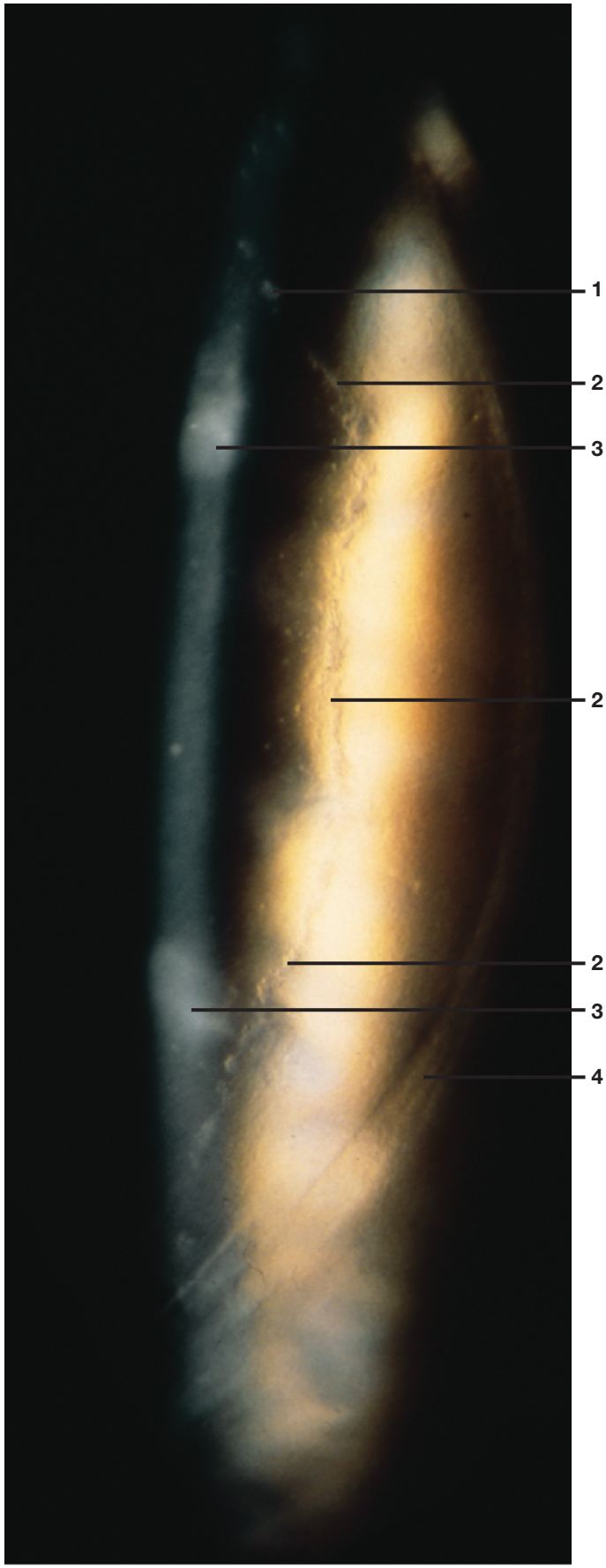

Figure 61.4. Endothelial rejection line. The undulating rejection line is white in direct light (1) but translucent in indirect light (2). Suture tract scars (3) and the graft host junction (4) are seen. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

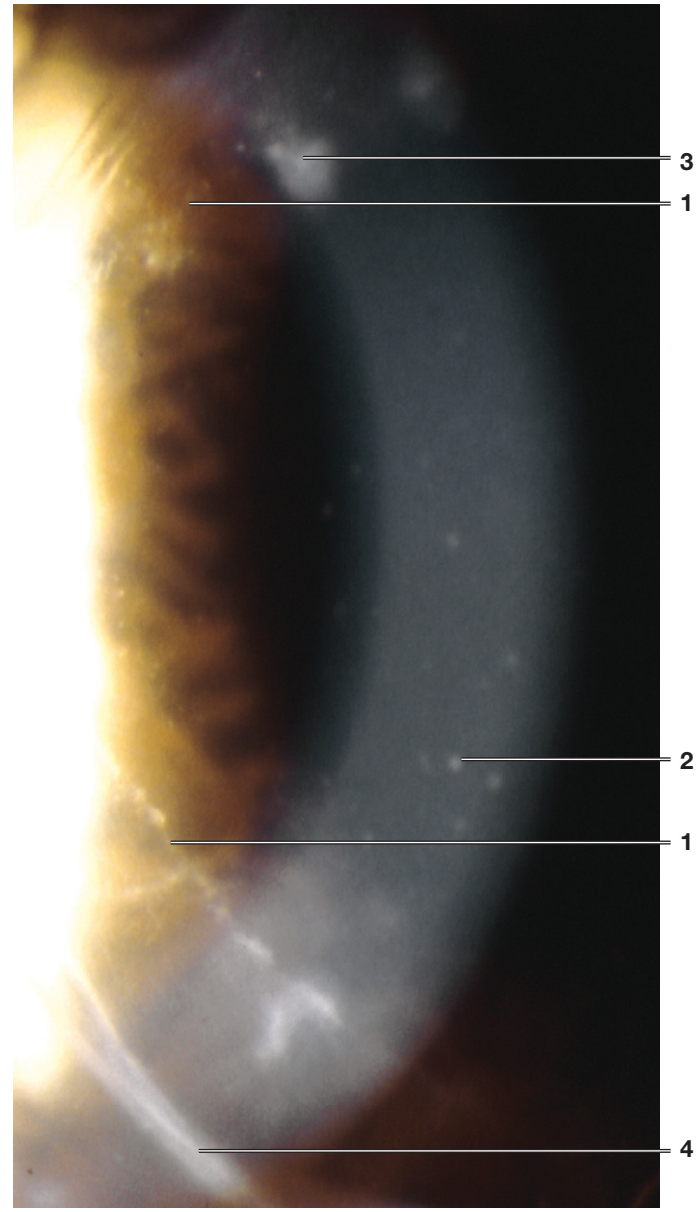

Figure 61.5. Endothelial rejection. The endothelial rejection line (1) and diffuse keratic precipitates (2) are shown. Suture tract scars (3) and the graft host junction (4) are seen. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

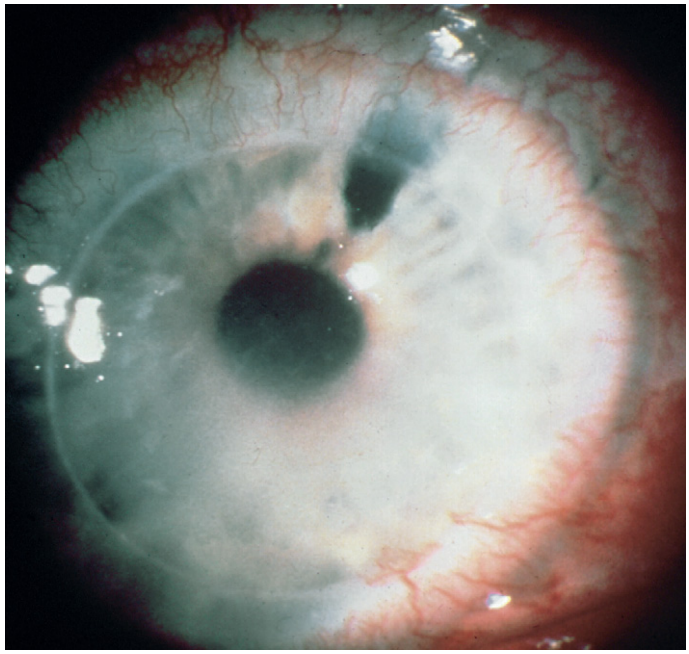

Figure 61.6. Endothelial rejection. There is diffuse inferior corneal edema from endothelial rejection. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

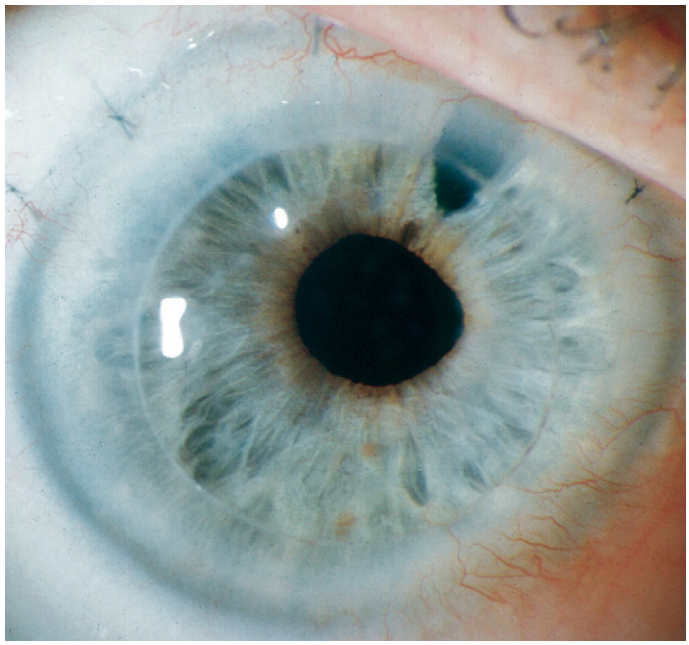

Figure 61.7. Same patient as Figure 61.6. Graft clarity is restored after aggressive treatment with topical and systemic corticosteroids. (Figure is taken from Krachmer JH, Palay DA. Cornea Atlas, 2nd edn. © Elsevier; 2006.)

the majority of cases, graft rejection can be reversed with swift and proper treatment. Patient response should be monitored frequently and carefully. Glaucoma and cataract are frequent ocular complications of steroid treatment, and may need to be managed concurrently to save the graft. Common side effects of short-term systemic steroid treatment include hyperglycemia, weight gain, hypertension, heartburn, insomnia, adrenal suppression, psychosis, and delirium. There are no large randomized controlled trials that show the definitive optimal route and dosage of steroids.

Epithelial and subepithelial rejection reactions usually can be handled with topical prednisolone 1% every 2–3 h while awake. The patient should be seen in follow-up in 5–7 days to ensure adequate response and to look for any signs of consequent endothelial rejection. If regression is seen, the topical medication can be slowly tapered down to a baseline level.

Endothelial rejection can be treated with topical, periocular, and/or systemic corticosteroids. In the event of a mild endothelial reaction, topical prednisolone acetate 1% should be used every hour while awake, and a steroid ointment should be placed at night. Cycloplegia with atropine or scopolamine should be considered. A 2006 survey showed that about 10% of respondent members of The Cornea Society also use topical cyclosporin for acute endothelial rejection.[29] The patient should return in 3–5 days, and the treatment may be slowly tapered if improvement is noted.

Severe endothelial rejection reactions, noncompliant individuals, and high-risk grafts should receive the same initial topical regimen with periocular and/or systemic steroids. Subconjunctival or sub-Tenon's injection of dexamethasone 12–24 mg (short acting) or triamcinolone 4–8 mg (long acting) can easily be done in the office under topical anesthesia. Periocular steroids are particularly advantageous in poorly controlled diabetics and elderly individuals to avoid systemic steroid-induced hyperglycemia and psychosis, respectively.

Intravenous methylprednisolone 3–5 mg/kg followed by oral prednisone 1 mg/kg/day or oral prednisone alone are also very rapid and successful methods to treat graft rejection. One small prospective randomized trial by Hill et al demonstrated that treatment with a single 500 mg IV dose of methylprednisolone combined with topical steroid was more effective and better tolerated than daily high dose oral prednisone with topical steroid, but the difference was not statistically significant.[30] Hill et al also showed in a later study that a second treatment with IV methylprednisolone in the following 24–48 h offered no additional advantage over a single dose.[31]

If oral steroids are administered and the patient has shown marked clinical improvement of the rejection episode within 5–7 days, they can be abruptly discontinued. Adequate topical therapy must continue. However, if the inflammation has only partially receded, oral steroid treatment should be prolonged until further resolution. A steroid taper regimen should be implemented if therapy is planned beyond 10 days. If no response in the first week is seen with high dose systemic steroids, it is doubtful that they will succeed in improving the reaction. They should be discontinued to prevent unwanted side effects.

PREVENTION

Grafts at high risk for rejection require judicious tapering of topical corticosteroids after transplant surgery. While low-risk patients may be able to discontinue topical steroids several months after surgery, high-risk individuals should continue use indefinitely. In 2004, additional prophylaxis with topical cyclosporin 2% in high-risk patients was routinely used by 50% of respondent members of The Cornea Society.[29] Retrospective evidence has established that topical cyclosporin 2% administered two to four times a day reduces the risk of allograft rejection.[32–34]

Systemic immunosuppression may be beneficial in grafts at high risk for rejection, but is not often used. No large randomized

controlled trials exist to demonstrate an advantage, and toxicity is worrisome. Favorable results of decreased allograft rejection for highly vascularized corneas and limbal grafts have been published regarding oral cyclosporin.[35–37] Other studies have shown no benefit.[38,39] The initial dose of cyclosporin is 2–5 mg/kg/day divided equally twice a day, and treatment is continued for about one year. Its mechanism of action includes selectively inhibiting T-helper and T-suppressor lymphocytes. Blood levels of the drug must be monitored because it is metabolized through the cytochrome P450 system, which can be altered by various medications. Toxicity can lead to nephrotoxicity and severe hypertension. Other important side effects include hepatotoxicity, gingival hyperplasia, and hirsutism.

Systemic tacrolimus (FK506) and mycophenolate mofetil also show promise in preventing allograft rejection in high-risk patients.[40,41] Tacrolimus also inhibits T-lymphocytes, but through a different mechanism than cyclosporin. Its side effects are similar to cyclosporin, but nephrotoxicity and hypertension occur less frequently. Mycophenolate disrupts de novo guanosine synthesis, which in turn selectively inhibits the production of T- and B-lymphocytes. Gastrointestinal symptoms are the most common side effects, but myelosuppression can also occur. Frequent monitoring of blood counts, electrolytes, kidney and liver function are required for both these medications.

The value of matching histocompatibility antigens between donor and recipient, especially in patients with risk factors for rejection, has long been debated. All nucleated cells express major histocompatibility class I (MHC-I) antigens. These HLA class I antigens, detected on corneal epithelial cells and keratocytes,[42] have been shown to elicit a host cytotoxic T cell immune response.[43] Class II antigens, found on donor epithelial APCs, can activate host helper T cells by causing a delayed hypersensitivity immune reaction.[44]

Outcomes in Canada and northern Europe have shown a benefit from HLA typing and matching.[44–46] However, the large multicenter prospective randomized double-blinded American Collaborative Corneal Transplant Study (CCTS) showed that there was no advantage in matching HLA class I and II antigen for high-risk corneal transplantation.[11] This same study did show that matching ABO antigens produced a significant decrease in rate of rejection and graft failure. HLA typing and matching on every patient would generate more initial cost, but it could save future expenditure if graft failure rates were less. A major drawback would be patients potentially spending months to years on waiting lists for a compatible donor, especially in heterogeneous populations like the USA.

Specific immunopharmacologic drugs may provide transplant surgeons future options for preventing and reversing allograft rejection reactions.[18] Local treatment with synthesized antibody fragments targeted at different arms of the immune casade may disrupt APCs, cytokines, immune effector cells, and other mediators. Gene therapy may also be used to modulate the immune response or restore function to the corneal endothelium.

SUMMARY

Acute cornea allograft rejection is the most common cause of postoperative graft failure. Patient education regarding symptoms is important to prevent delays in treatment. All types of rejection should be treated with topical corticosteroids, but severe rejection and high-risk patients should be administered a more aggressive regimen. Further prospective randomized clinical trials are necessary to determine if systemic immunosuppression should be employed in high-risk patients.

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62 Immunosuppression in high-risk keratoplasty

Ali R. Djalilian, Nariman Nassiri, Janet A. Lee, Edward J. Holland

The high success rate of corneal transplants can be attributed largely to the unique avascular structure of the cornea, absence of corneal lymphatics, low expression of major histocompatibility antigens, and expression of immune inhibitory factors such as CD95 (Fas) ligand, α-melanocyte stimulating hormone (α-MSH), and transforming growth factor (TGF)-β.[1,2] These features allow the graft to remain somewhat isolated from the immune system and effectively provide an immunologically privileged status. Nonetheless, immune-mediated rejection remains one of the leading causes of graft failure.[3,4] Up to 30% of penetrating keratoplasty patients will have at least one episode of rejection,[5] with 2.6–7% of all grafts eventually failing because of rejection.[4,6] The success rate of uncomplicated first grafts performed in nonvascularized 'low-risk' beds is as high as 90%. However, the success of corneal grafts placed in 'high-risk' beds is significantly lower with rejection rates of up to 50–70%.

Several host factors have been shown to increase the risk of immune-mediated rejection. The most important factor appears to be the degree of corneal neovascularization.[3,5] In vascularized corneas, the recipient's immune system can recognize and attack the donor tissue much more readily. Other factors that can increase the risk of immune-mediated rejection include repeat grafts, large grafts, bilateral grafts, past or present inflammatory eye disease, past or present elevated intraocular pressure, history of previous anterior segment surgery, younger age, ocular surface disease, and quadrants of anterior synechiae.[3,7,8] The term 'high risk' has been used to refer to those grafts that have a higher likelihood of rejection. Most authors consider patients to be high risk if they have two or more quadrants of neovascularization or have a history of graft failure resulting from rejection.

The management of high-risk keratoplasty continues to be a significant challenge, with the incidence of rejection reportedly between 50 and 90%, depending on the definition of high risk.[3,9–11] In general, two approaches can be taken to prevent immune-mediated rejection in high-risk corneal transplantation: (1) making the donor tissue less antigenic and (2) suppressing the host immune response. This chapter primarily addresses the latter approach.

MECHANISM OF REJECTION

The primary antigens that are recognized by the immune system as foreign include the major histocompatibility antigens (human lymphocyte antigens [HLA]) and ABO antigens, which are a subset of the minor histocompatibility antigens. Major antigens are further divided into class I and II antigens. Class I HLA antigens (HLA-A, -B, and -C) are expressed by all nucleated cells in the body and are found on the corneal epithelium, stromal keratocytes, and endothelial cells, whereas class II antigens (HLA-DR, -DQ, and -DP) are present mainly on antigen presenting cells (APCs) such as macrophages, dendritic cells, and Langerhans cells.[12] It has recently been demonstrated that Langerhans cells reside throughout the central and peripheral corneal epithelium,[13] and dendritic cells are present in the anterior stroma.[14,15] Under the influence of interferon-γ, both epithelial and endothelial cells have been shown to also express class II antigens. ABO antigens have been detected primarily on epithelial cells. However, some reports indicate that endothelial cells may also express these antigens.[16]

Corneal graft rejection involves an induction phase, called the afferent arm, and an expression phase called the efferent arm. During the afferent arm of the immune response, antigen recognition occurs by two pathways. In the direct pathway, donor APCs present donor MHC II antigens to T cells, thus directly sensitizing the host. The indirect pathway involves host APCs processing donor antigens, which are then presented to naïve T cells. The exact location of antigen presentation is under debate, but may occur in the cornea, uvea, conjunctiva-associated lymphoid tissue, or draining lymph nodes.[7]

The efferent arm of the allograft response is the destructive phase, incurring damage primarily via a cell-mediated process. CD4+ Th1 cells are the main mediators of the efferent phase. The secretion of IL-2 by CD4+ T cells activates other T and B cells, while IFN-γ activates macrophages and induces antigen expression in the donor tissue. The role of CD8+ cytotoxic T cells in the graft immune response remains controversial. Though they can contribute to tissue damage, graft rejection can occur in their absence.[17]

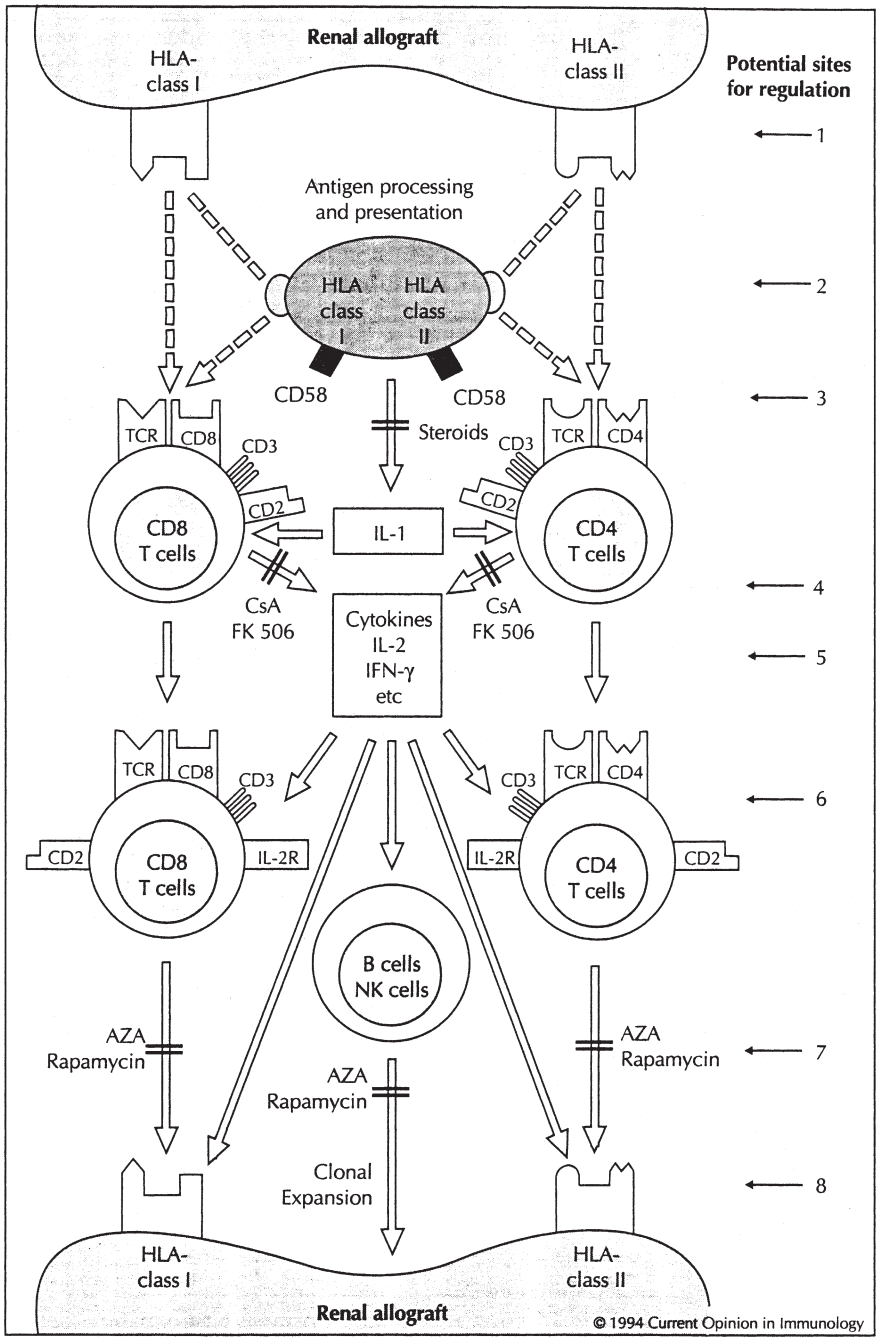

Figure 62.1. Schematic representation of the antiallograft response showing human lymphocyte antigen (HLA), which is the primary stimulus for the initiation of the antiallograft response, the cell surface proteins participating in antigenic recognition and signal transduction, the contribution of cytokines and cell types to the immune response, and the potential sites for the regulation of the antiallograft response. Potential sites for regulation are shown on the right. Site 1, histoincompatibility between the recipient and the donor can be minimized (e.g. HLA matching); site 2, monokine production by antigen presenting cells can be prevented (e.g. by corticosteroids); site 3, antigen recognition can be blocked (e.g. by OKT3 monoclonal antibodies); site 4, T-cell cytokine production can be inhibited (e.g. by cyclosporin A); site 5, cytokine activity can be inhibited (e.g. by anti-interleukin-2 antibody); site 6, cell cycle progression can be inhibited (e.g. by anti-interleukin-2 receptor antibody); site 7, clonal expansion can be inhibited (e.g. by azathioprine); site 8, allograft damage can be prevented by masking target antigen molecules (e.g. by antibodies directed at adhesion molecule sites). (Reproduced with permission from Sharma VK, Li B, Khanna A, et al. Which way for drug-mediated immunosuppression? Curr Opin Immunol 1994; 6: 784–790 © 1994 with permission from Elsevier.)

The anti-allograft response can be manipulated at a number of different levels. The potential sites for regulation of this process are shown in Figure 62.1 and are further discussed below.

REDUCING DONOR ANTIGENICITY

Several strategies have been used to reduce the antigenic load of the donor. Removal of the donor epithelium was also believed to decrease the risk of rejection because the epithelium is a source of class I and class II antigens. However, a prospective randomized study found no difference in rejection rate regardless of whether the donor epithelium was removed.[18] Donor tissue pretreatments have been successful in reducing its antigenicity in experimental conditions, such as exposure to ultraviolet light, hyperbaric oxygen, heterologous antibodies, and storage in organ culture.[19–22] However, none of these techniques has been shown to be clinically significant.

Tissue matching has been studied extensively as another strategy for reducing donor antigenicity in high-risk corneal transplantation. The American Collaborative Corneal Transplant Study (CCTS) reported no benefit from HLA class I and class II matching in high-risk corneal transplantation.[23] On the other hand, studies from other areas of the world have reported a benefit in HLA matching.[24–27] This discrepancy may be attributed to various factors, including errors in tissue matching, the heterogeneous patient population in the USA, differences in intensity of topical immunosuppression, and inclusion of patients with limbal stem cell deficiency in the CCTS. ABO compatibility was found to prolong graft survival in the CCTS, although this finding has also been met with controversy in comparison to other studies.[28,29] At this time, there is not enough

evidence to support routine HLA matching in high-risk keratoplasty. ABO matching is less expensive and has a higher likelihood of finding a match, making its use more practical in selected high-risk cases.

SUPPRESSING THE IMMUNE RESPONSE

Currently, pharmacologic suppression of the host immune response remains the mainstay of preventing corneal allograft rejection. Although corticosteroids continue to be the gold standard of ocular immunosuppressants, promising newer agents may provide a safe and effective adjunct for immunosuppressive therapy in high-risk corneal transplantation.

GLUCOCORTICOSTEROIDS

Corticosteroids are currently the most effective ocular immunosuppressants available. Their immunomodulatory actions are due to inhibition of the activity of transcription factors, such as activator protein-1 (AP-1) and nuclear factor kappa B (NF-kappa B), that are involved in activation of pro-inflammatory genes. They suppress the production and effects of cytokines involved in the inflammatory response, inhibit leukocyte adhesion and migration to the sites of inflammation, and interfere with the functions of endothelial cells, leukocytes, and fibroblasts. When given systemically, steroids also reduce the number of circulating T cells and inhibit their proliferation.

Corticosteroids are most commonly administered by topical application, which provides good ocular penetration and effective immunosuppression. In high-risk patients, topical steroids are started early in the perioperative period and applied frequently, followed by long-term indefinite use when no contraindications exist. A typical regimen involves 1% prednisolone acetate applied every 2 h for the first few weeks with a gradual decrease over the following several months. Because high-risk patients often require higher doses of topical steroids for prolonged periods, they are more prone to experiencing complications such as cataracts, glaucoma, and delayed wound healing.

Systemic steroids can be used as an adjunct to topical therapy, particularly in high-risk cases where topical steroids alone may be insufficient in preventing rejection. Patients may receive large systemic doses (methylprednisolone 125–250 mg intravenously) at the time of surgery followed by prednisone 1 mg/kg per day. The prednisone is then slowly tapered over 3–6 months. Unfortunately, systemic therapy with steroids has been associated with many adverse effects including osteoporosis, peptic ulcer disease, glucose intolerance, and weight gain.

Mild graft rejection is often reversible by reinstituting or increasing the dose of topical steroids. Severe rejections that involve the endothelium require more aggressive treatment. Initially, methylprednisolone 125–250 mg is given by intravenous bolus, followed by intensive topical therapy (every hour) and oral prednisone 1 mg/kg/day. A subconjunctival injection of steroids may also be given as an adjunct (triamcinolone 10–40 mg).

Although topical corticosteroids remain the mainstay of achieving corneal graft immunosuppression, rejections still occur in many high-risk patients receiving steroids. Except when indicated for severe post-op anterior segment inflammation (e.g. atopic patients), systemic steroids as a single agent are not likely to provide significant benefit over topical steroids in preventing rejection over the long term. Thus, newer immunosuppressive agents (as discussed below) are needed for long-term maintenance therapy in very high-risk cases.

CYCLOSPORIN A

Cyclosporin A (CsA) represents a newer generation of specific immunosuppressive agents that selectively interfere with immunocompetent cells without causing generalized cytotoxic effects. Structurally, CsA is a hydrophobic, cyclic undecapeptide derived from the fungus *Tolypocladium inflatumgans*. It works mainly on T cells by binding to an intracellular peptide known as cyclophilin. By inhibiting cyclophilin activity, CsA blocks the transcription and production of IL-2, thus limiting the activation of CD4+ and CD8+ T cells. In addition, CsA blocks the production of other lymphokines such as interferon-γ and inhibits the expression of high-affinity IL-2 receptors.

TOPICAL CYCLOSPORIN A

The topical absorption of CsA is hindered by its hydrophobic structure, which cannot penetrate the hydrophilic stroma. To enhance its ocular absorption, a number of lipid vehicles have been used. In this regard, an emulsion formulation of 0.05% was approved for the treatment of keratoconjunctivitis sicca.[30] Most studies have indicated very low penetration of CsA into the anterior chamber regardless of the vehicle or formulation, suggesting that the effects of topical CsA are mostly mediated through the ocular surface.

Several studies have demonstrated the efficacy of CsA as a topical immunosuppressant in high-risk keratoplasty. In a study of 11 high-risk keratoplasty patients treated with 2% CsA in olive oil, 10 corneas remained clear after a mean follow-up of 16 months.[31] Holland et al[32] reported the use of topical CsA to treat 43 patients with a variety of anterior segment inflammatory conditions, including 11 high-risk keratoplasty patients for whom topical corticosteroid therapy had failed. Zhao and Jin[33] used 0.5% CsA to treat 16 patients with refractory corneal graft rejection and achieved a complete cure in nine eyes and marked improvement in another six eyes. To prevent recurrence, they advocated continuing CsA for at least 12 months after graft rejection is reversed. Inoue et al retrospectively compared 86 high-risk penetrating keratoplasties treated with 2% CsA to 97 control eyes. The rejection-free graft survival rate was 70% in the CsA group and 45% in the control group. However, the long-term graft survival rate appeared to be similar in the two groups.[34]

Topical CsA when used alone appears to be effective for both treatment and prevention of corneal graft rejection. However, when used in conjunction with topical steroids, studies have shown mixed results. A large trial by Bouchard and Cavanagh[35] failed to demonstrate any improvement in graft survival when CsA 2% ointment was applied twice daily in high-risk patients receiving topical steroids four times a day. This study has been criticized for using patients who were not truly high risk, and for using a higher dose of topical steroid that may have masked the effect of CsA. In contrast, other studies have demonstrated an additive effect of topical CsA when used in conjunction with topical steroids.[36]

Topical CsA is well tolerated. Studies have demonstrated a self-limiting transient epithelial keratitis in some patients, even with frequent dosing. In the 43 patients reported by Holland et al,[32] only two experienced severe ocular discomfort. The remaining patients

tolerated the medication well, including several receiving hourly application. In the phase III safety evaluation of CsA 0.1% emulsion over 1–3 years, burning, stinging, and conjunctival hyperemia were the most common adverse events with twice daily dosing, but were severe in only 2 out of 412 patients for each.[37] The commercially available CsA 0.05% is considered to be at least as safe and well tolerated as the higher concentration, with side effects being mild to moderate and transient.

An investigation concerning the systemic absorption of topical CsA has demonstrated negligible systemic CsA levels.[30] Thus, monitoring of blood CsA levels does not seem necessary for patients using topical CsA.

SYSTEMIC CYCLOSPORIN A

Systemic CsA has played an important role in the success of many solid organ transplants, but its use in corneal transplantation has been limited primarily to monocular high-risk patients due to its significant side effects. Several studies have demonstrated that systemic CsA can be effective in preventing corneal graft rejection in high-risk keratoplasty.[38–40] Hill et al[38] demonstrated that high-risk patients receiving systemic CsA in conjunction with topical steroids had a significant improvement in graft survival compared to patients receiving topical steroids alone or in combination with systemic steroids. The maximum benefit was achieved in patients who had received CsA for 12 months, although a beneficial effect was noted in those treated for 4 and 6 months as well. More recent studies have demonstrated limited beneficial effect of CsA as a single agent in reducing graft rejection. Rumelt et al[39] studied oral CsA use for an average of 12 months in 28 repeated corneal grafts with four quadrants of vascularization. They found a rejection rate of 32% in treated versus 42% in controls. Poon et al[40] studied 49 patients with various high-risk keratoplasty characteristics who were treated with oral CsA for 1 year. Though a trend toward reduced rejection and failure in treated patients was observed compared to controls, this did not reach statistical significance. These groups have concluded that while systemic CsA has a limited beneficial effect, its role in high-risk keratoplasty needs further evaluation, given its significant cost and side effects.

Systemic CsA is associated with a number of side effects, including nephrotoxicity, hepatotoxicity, and hypertension. In the 43 patients treated by Hill et al,[38] 4 patients developed elevation of serum creatinine which reverted to normal with CsA dose reduction, and one became mildly hypertensive, requiring treatment.

To minimize the risk of adverse effects, the blood CsA level should be closely monitored and kept within the therapeutic range. A target trough level between 130 and 170 ng/mL has been suggested using the specific whole blood method (monoclonal antibody), though levels as high as 200 ng/mL may be necessary in some patients. A typical dosing regimen is 3 mg/kg per day. While there are no studies indicating the optimum duration of therapy, systemic CsA is considered a long-term strategy. Hill has demonstrated that 12 months of treatment is superior to 4 months, with maintenance of the benefit even after stopping treatment.[9,38] Short-term use is not likely to be as beneficial in preventing rejection. All patients require monthly monitoring of blood pressure, serum creatinine, liver enzymes, and blood counts while taking CsA. With appropriate screening and monitoring, systemic CsA can be a useful tool in restoring vision in many high-risk patients. Additionally, CsA may be considered especially for high-risk cases secondary to atopic dermatitis.[41]

TACROLIMUS

Tacrolimus (FK-506, Prograf) is a calcineurin inhibitor derived from the fungus *Streptomyces tsukubaensis*, with a mechanism of action very similar to CsA, but with 10–100 times more immunosuppressive potential in vitro. It binds to an immunophilin known as FK-506 binding protein, which then blocks the transcription of several lymphokines, including IL-2. This, in turn, inhibits T cell activation.

Tacrolimus has been shown to prolong corneal graft survival in animals following topical, subconjunctival, intraperitoneal, and systemic administration, including a high-risk keratoplasty model.[42,43] Additionally, tacrolimus-treated animals were found to have less corneal vascularization than controls.[44]

Topical tacrolimus, when used in combination with lamellar keratoplasty, was found to be effective in treating Mooren's ulcer.[45] A study by Wang et al[46] showed lower rates of rejection with topical tacrolimus 0.05% compared to topical CsA 0.1%. Out of 28 high-risk patients using tacrolimus, 64% experienced rejection compared to 95% in patients that were using CsA 0.1% topically.

In a study by Reinhard et al[47] on the use of topical tacrolimus in normal-risk keratoplasty patients, they observed local side effects including superficial punctate keratitis, burning, conjunctival injection, an erosion that persisted over 10 days, and development of a superficial opacity. These events all resolved with discontinuation of the medication and treatment with topical steroids. In the 20 patients on tacrolimus, there were no detectable levels of tacrolimus in whole blood samples.

Systemic tacrolimus has been used successfully in human kidney and liver transplantation. Sloper et al[48] treated 17 high-risk keratoplasty patients (23 grafts) with oral tacrolimus, including six patients who also required limbal transplantation, for a mean follow-up period of 24 months. Three cases of reversible rejection occurred, all of which were associated with low levels of tacrolimus, and no cases of failure occurred while on tacrolimus. This was significant in contrast to 12 out of 18 cases without tacrolimus that failed secondary to rejection. Four patients stopped treatment without any problems, but two patients experienced reversible rejection episodes shortly after cessation of at least a year of therapy, suggesting the need for long-term treatment in some cases.

Side effects of systemic tacrolimus are similar to CsA, including nephrotoxicity and hypertension. Sloper et al[48] reported onset of hypertension in 4 out of 17 patients, with two others experiencing an exacerbation of pre-existing hypertension requiring additional medication. Renal toxicity was seen in two patients, with three others showing small increases in serum creatinine. This elevation was reversible in three patients with a tacrolimus dose reduction, but remained slightly elevated in the remaining two. In a separate report, two patients experiencing renal toxicity due to tacrolimus eventually experienced graft failure after dose reduction.[49]

Tacrolimus has been used increasingly as an alternative to CsA in organ transplantation. Its efficacy and safety in high-risk human corneal transplantation compared to CsA remains to be studied. The recommended starting dose is 1 mg twice daily with incremental 1 mg increases up to 4 mg twice daily to maintain a trough level

of 5–8 ng/mL. Monthly monitoring of blood pressure, serum creatinine, tacrolimus trough levels, and electrolytes is necessary. Though optimal duration of therapy is not yet known, tacrolimus likely requires a long-term strategy for prevention of graft rejection and failure.

AZATHIOPRINE

Azathioprine is a cytotoxic agent that is converted to 6-mercaptopurine, which competitively inhibits purine synthesis. To effectively block DNA synthesis, the targeted cells must be actively dividing. Thus, azathioprine must be given early in the rejection process to effectively block T cell proliferation.

Clinical studies have demonstrated the efficacy of azathioprine in preventing and treating early corneal graft rejection.[50,51] However, its role in high-risk keratoplasty is limited to resistant or monocular cases, where systemic therapy is used in combination with a calcineurin inhibitor such as CsA or tacrolimus. It is no longer considered as a single agent in corneal transplantation.

Azathioprine is associated with a number of cytotoxic side effects, including bone marrow suppression, gastrointestinal toxicity, and alopecia. In a case reported by Sudhir et al,[52] aplastic anemia with associated bilateral pre-retinal macular hemorrhages and gastrointestinal bleeding occurred in a man treated with azathioprine 2 mg/kg after high-risk keratoplasty. Anemia and bone marrow suppression are usually dose related and reversible after dose reduction or cessation of treatment. Monitoring of blood and platelet counts as well as liver function is recommended weekly for the first month, bi-monthly for the next two months, and monthly thereafter.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) is an anti-metabolite that blocks the proliferation of T and B cells by inhibiting guanosine synthesis in T- and B-lymphocytes. It has been used extensively in organ transplantation as an alternative to azathioprine, often in combination with a calcineurin inhibitor.

MMF has demonstrated efficacy in reducing graft rejection in high-risk keratoplasty in humans. Reinhard et al[53] reported the preliminary results of a prospective, randomized control study comparing oral MMF to controls in high-risk keratoplasty. The MMF group received 1 g twice daily for 6 months, while all patients received oral and topical steroids postoperatively. A total of 89% of grafts in the MMF groups did not experience immune reactions, compared to 67% of controls, which was statistically significant. None of the MMF grafts experienced irreversible rejection, while three control grafts failed. They concluded that MMF considerably reduces the proportion of immune reactions in high-risk keratoplasty, but that long-term survival and optimal treatment duration remain uncertain.[53]

Compared to oral CsA, MMF appears to be equally efficacious in preventing rejection in high-risk keratoplasty. Reinhard et al[54] have reported the 3-year results of a randomized prospective trial comparing MMF to oral CsA in high-risk patients. MMF 1 g twice daily and oral CsA titrated to a trough of 120–150 ng/mL were given for 6 months. At 3 years, 74% of grafts in the MMF group remained clear, compared to 69% in the CsA group.

Overall, MMF appears to be a safe and effective immunosuppressant. Administration at a fixed dose of 500–1000 mg twice daily is the standard regimen. Monitoring blood levels of MMF is not required, which simplifies the management. The most commonly reported side effects of MMF include bone marrow suppression, gastrointestinal symptoms, and hepatotoxicity, all of which are reversible with cessation of treatment. The authors currently recommend MMF as an adjunct to CsA or tacrolimus in the management of high-risk patients, who are dependent on a clear graft for functional vision.

RAPAMYCIN

Rapamycin (sirolimus, Rapamune) is a bacterial macrolide with antifungal and immunosuppressant properties. It inhibits growth factor-stimulated cell proliferation, including inhibition of IL-2-stimulated T-lymphocyte proliferation. Rapamycin and its derivatives do not interfere with the calcineurin system, decreasing the potential for nephrotoxicity. This is in contrast to cyclosporin A and tacrolimus, which are both calcineurin inhibitors and are known for their nephrotoxic side effects.

A prospective pilot study in humans demonstrated similar efficacy between rapamycin and MMF in preventing immune reactions after high-risk keratoplasty.[55] Ten patients on oral rapamycin were compared to 24 patients on MMF, both treated for 6 months postoperatively with a 2 week taper. No immune reactions were observed in either group during the treatment period. Two reversible immune reactions occurred in the rapamycin group and five in the MMF group during a 2-year follow-up, showing no statistically significant difference between groups. No irreversible immune reactions occurred in either group.

All patients on rapamycin experienced side effects in this study, including dyslipidemia, furunculosis, exanthema, and gastrointestinal disturbance. Other reported side effects include thrombocytopenia, anemia, peripheral edema, urogenital tract infections, and arthralgia. One case of nephrotoxicity was reported associated with the combination of tacrolimus and rapamycin.[49] The use of rapamycin theoretically has a decreased potential for nephrotoxicity as monotherapy, which makes it an attractive alternative to cyclosporin A and tacrolimus, but its own side effect profile may be significant in certain patients.[56,57]

Dosing of rapamycin in renal transplantation is adjusted according to blood trough levels, with a target of 4–12 ng/mL in the early postoperative period when in combination with cyclosporin A. In the Birnbaum study, their target blood trough level was 4–10 ng/mL with a mean level of 5.5 + 2.0 ng/mL. Recently, a new intraocular drug delivery system using a glycolide-co-lactide-co-caprolactone copolymer (PGLC)-implant containing rapamycin was shown to prolong high-risk corneal allograft survival in rabbits.[58] More work is needed to determine appropriate methods of dosing and duration of treatment for rapamycin therapy in penetrating keratoplasty.

MONOCLONAL ANTIBODIES

Monoclonal antibodies directed against T cell antigens have been used extensively to reverse acute graft rejection in solid organ transplantation. However, topical therapy with antibodies has been generally ineffective due to poor absorption across the cornea. Ippoliti and Frontere first reported that intracameral injection of anti-CD3 or anti-CD6 monoclonal antibodies can reverse acute corneal allograft rejection.[59] Later on, a study in humans has shown

successful reversal of corneal graft rejection after treatment with topical anti-IFN-γ antibodies in 10 of 13 patients.[60]

Basiliximab is a new humanized monoclonal antibody with high binding specificity for the IL-2 receptor of activated T-cells. In a pilot study by Schmitz et al, use of basiliximab with cyclosporin A in seven patients undergoing high-risk keratoplasty demonstrated no immune reactions during a 14–25 month follow-up period.[61]

Campath-1H is a humanized anti-lymphocyte monoclonal antibody directed against the pan-lymphocyte antigen CD-52. It has been used for induction therapy after transplantation, followed by other immunosuppressive agents for long-term maintenance. Use of systemic Campath-1H has been reported in two cases of recurrent corneal graft rejection. One patient with rheumatoid arthritis and rejection of nine previous grafts was treated with Campath-1H and retained a clear graft for 24 months before developing proteus keratitis resulting in enucleation. A second patient with recurrent graft rejection had maintained a clear graft at 25 months after treatment with Campath-1H.[62,63]

Blockade of the CD40-CD154 co-stimulatory pathway has also been a recent target for therapy. T-cell activation requires interaction of the T-cell receptor with the MHC complex on antigen presenting cells (APC) as well as co-stimulatory signals from APCs. A major co-stimulatory signaling pathway is mediated by CD40 binding to CD40-ligand, also known as CD154. This interaction stimulates differentiation of CD4+ T helper 1 cells, which are the primary mediators in corneal allograft rejection.

Systemic administration of CTLA4-Ig and anti-CD154 monoclonal antibody has been shown to be beneficial in the survival of corneal transplantation,[64,65] but some reports of thromboembolic complications associated with systemic treatment in non-ocular transplantation may limit the clinical usefulness of this therapy in keratoplasty patients.[66] Qian et al have investigated subconjunctival anti-CD154 mAb in normal and high-risk murine keratoplasty.[67] Both normal and high-risk grafts had significantly increased rates of survival with treatment, though high-risk grafts required twice the dose and frequency of anti-CD154 mAb to achieve significance. Additionally, these benefits were largely lost after termination of treatment, suggesting that this mode of therapy would require combination with other agents, especially after cessation of anti-CD154.

Until now, the use of monoclonal antibodies in the treatment regimen of high-risk keratoplasty has remained limited, in part due to ineffective delivery methods and side effects of systemic therapy. However, with the evolution of safer humanized antibodies and more efficacious delivery systems, both systemic and local administration will gain more attention.

CONCLUSIONS

The management of high-risk keratoplasty continues to be a significant clinical challenge. The authors currently recommend indefinite use of topical steroids and topical CsA in all high-risk grafts. In patients with multiple graft failures who are dependent on graft clarity for functional vision a multi-drug regimen consisting of (1) oral steroids (on a tapering dose), (2) CsA or tacrolimus, and (3) azathioprine, MMF, or rapamycin may be considered. The patients will need careful monitoring for the potential side effects. With continuing advances in molecular biology and immunology, the development of safer and more specific immunosuppressive agents as well as strategies for the immunomodulation of the corneal graft before transplantation can be expected. Until then, early recognition and immunosuppression will continue to be the most important factors in preventing graft failure.

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63 Outcomes of penetrating keratoplasty

Douglas J. Coster, Keryn A. Williams

Corneal transplantation is usually performed to improve vision and to decrease visual disability, thereby improving quality of life. This being so, the most appropriate outcome measures are graft survival, the extent of postoperative visual disability, and the degree of patient satisfaction with the procedure.

CHOICE OF OUTCOME MEASURES

The relatively high rate of corneal graft failure, approximately 40% of all grafts at 10 years,[1] indicates that graft failure is a relevant measure of outcome. Furthermore graft function or failure is a simple call. The difference between a thin, transparent graft and a thick opaque graft is obvious, with little argument or disagreement amongst clinicians about the functional status of a graft, although there can be considerable contention about the cause of a graft failure. Invariably, those with failed grafts have poor vision. However, an analysis of corneal transplantation based solely on graft survival tells nothing about the relative success of the surviving grafts. Measuring the impact of a successful, functioning corneal graft is a complicated matter. Not all patients with a clear and functioning graft see well, and not all of those who see well are satisfied with the outcome.

Visual disability is the most common indication for corneal transplantation: the predominance of those having grafts do so to see better. The results of corneal transplantation should therefore be judged by the reduction in visual disability that is achieved. There are few studies employing this outcome measure. More often a surrogate measure is used, such as visual acuity in the grafted eye. While visual acuity may be a convenient measure, the link between visual acuity and visual disability can be tenuous. Inconsistencies between charts and lighting conditions, the impact of optical correction, and the influence of the other eye, all affect the integrity of the relationship.

There are few studies of the impact of corneal transplantation on patient well-being. In an early report, patient satisfaction was found to correlate with the acquisition and maintenance of a clear graft, of not needing a contact lens, and of achieving better vision in the operated eye than the contralateral eye.[2] Not surprisingly, patients with a nonfunctioning graft were dissatisfied.

ASSESSMENT OF LONG-TERM CORNEAL GRAFT OUTCOMES

The long-term outcome of corneal transplantation is relevant for at least two reasons. First, many graft recipients are young and have long-term expectations for their graft. Furthermore, successive grafts tend to have a decreasing prognosis for success. The aim must be to get a patient through life with as few corneal grafts as possible. Second, the impact of surgical variations and methods of processing corneal tissues for surgery may only show up after decades of observation. Data on corneal graft outcomes can be collected in various ways. Much of what is reported is in the form of retrospective case series, usually with short follow-up. There are a few randomized controlled clinical trials, and where they do exist the follow-up is short, usually no more than a year or two.

CORNEAL GRAFT REGISTRIES

Some of the most useful data are held in an increasing number of corneal graft registries.[1,3–5] These registries collect information on large numbers of patients receiving corneal transplants who have been followed for prolonged periods of time, in some cases decades. Such data are important in that they are collected from the real world of clinical practice, rather than the more contrived world of the academic medical center where most trials are conducted. A large number of surgeons contribute records, so that it is possible to consider the impact of a wide range of approaches. Appropriate statistical analysis can accommodate the inevitable losses to follow-up. As in other areas of clinical transplantation,[6] graft registries have proved to be a useful source of information about the long-term results of corneal transplantation.

The Australian Corneal Graft Registry was the first large-scale corneal graft registry.[3] It was established in 1985 to provide data on the long-term results of corneal transplantation and to identify factors influencing graft survival.[7] It now holds records of more than 20 000 grafts, some of which have been followed for over 20 years.[1] More than 200 surgeons contribute data to the registry and 400 other clinicians contribute to the follow-up. A number of

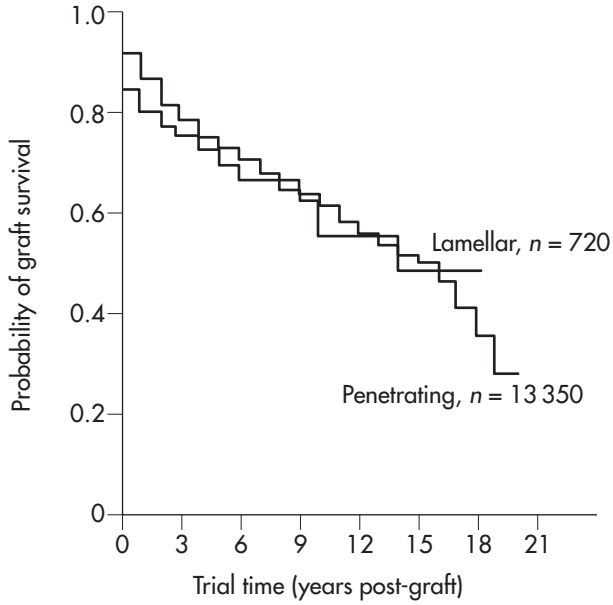

Figure 63.1. Kaplan–Meier survival of penetrating and lamellar corneal grafts. For each curve, *n* indicates the number of grafts initially at risk. Data reproduced with permission from the Australian Corneal Graft Registry, http://hdl.handle.net/2328/1002.

registries have been established elsewhere and work along similar lines, including the British register based in Bristol,[4] and a register in Sweden.[5] There is remarkable consistency in the results reported from the various registries.

Table 63.1 Factors influencing penetrating corneal graft survival in multivariate analysis (Cox proportional hazards regression analysis) to a significant extent

Variable	Range of Hazard Ratios
Surgeon identity	0.30–2.55
Donor age (each additional 10 years)	1.05
Indication for graft	1.00–2.60
Each additional ipsilateral graft	1.18
Lens status (phakic, pseudophakic, aphakic)	1.00–2.02
History of inflammation in grafted eye	1.00–3.14
Corneal vascularization at graft	0.83–1.67
History of raised intraocular pressure	0.64–3.87
Need for anterior vitrectomy at graft	1.00–1.29
Graft diameter	0.56–1.15
Early removal of graft sutures	0.38–1.00
Graft neovascularization	1.00–1.97
Postgraft raised intraocular pressure	1.00–2.24
Occurrence of graft rejection episode	1.00–3.41

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LONG-TERM CORNEAL GRAFT SURVIVAL

The 10 year survival of penetrating corneal transplants followed in the Australian Corneal Graft Register is 62% (Fig. 63.1). At 15 years, graft survival has reduced to 55%. This is similar to survival rates observed in other corneal graft registries. The extended rate of attrition is notable: there are few early graft failures but steady loss continues over many years. The survival curve fails to flatten out. The overall graft survival rate for corneal allografts is less than that of solid vascularized organs,[8] a result not widely appreciated.

In recent years there has been a renewed enthusiasm for lamellar transplantation. The premise has been to avoid transplanting corneal endothelium by performing lamellar surgery wherever possible, so as to avoid an allograft response directed at the irreplaceable corneal endothelium. Perhaps it is surprising that the survival of lamellar grafts is no better than for penetrating procedures, approximately 60% at 10 years (Fig. 63.1).

The collective results of all corneal transplants encompass a wide range of clinical factors related to graft outcomes. The procedure is carried out for an extensive range of conditions, under varying circumstances, by a large number of surgeons who employ a range of surgical approaches and diverse sources of corneal donors. The large number of patients followed in registries permits identification of some of the independent variables that affect graft survival (Table 63.1).

GRAFT SURVIVAL FOR MAJOR INDICATIONS

Keratoconus

Keratoconus is a common indication for corneal transplantation, accounting for 25–30% of cases in most developed countries. Patients with keratoconus have an excellent chance of achieving successful engraftment. The survival of penetrating corneal grafts performed for keratoconus is 97% at 1 year, 95% at 5 years, 90% at 10 years, and 82% at 15 years (Fig. 63.2, *A*). Survival is slightly reduced in patients with keratoconus who had hydrops at the time of surgery, and in those with intellectual disability.

Pseudophakic bullous keratopathy

Pseudophakic bullous keratopathy is another common indication for corneal transplantation, accounting for 25% of cases in a number of studies. The results of corneal transplantation are inferior to those observed in patients with keratoconus. Graft survival is 83% at 1 year, 60% at 5 years, 45% at 10 years, and 40% at 15 years (Fig. 63.2, B).

Previous failed corneal graft

Corneal transplantation is often performed to replace a previous graft that has failed. The survival of a first graft is 67% at 10 years and the estimated median survival is approximately 20 years (Fig. 63.2, *C*). Survival of successive ipsilateral grafts is reduced with every graft. For fifth and subsequent grafts analyzed together, survival is 1% at 10 years and the estimated median survival is 1 year.

Corneal dystrophy

Corneal dystrophies are also treated with penetrating keratoplasty. The most common indication for transplantation within this category is Fuchs' dystrophy, which is approximately five times more frequent than other dystrophies. Grafts for stromal dystrophies survive a little better than do grafts for Fuchs' dystrophy

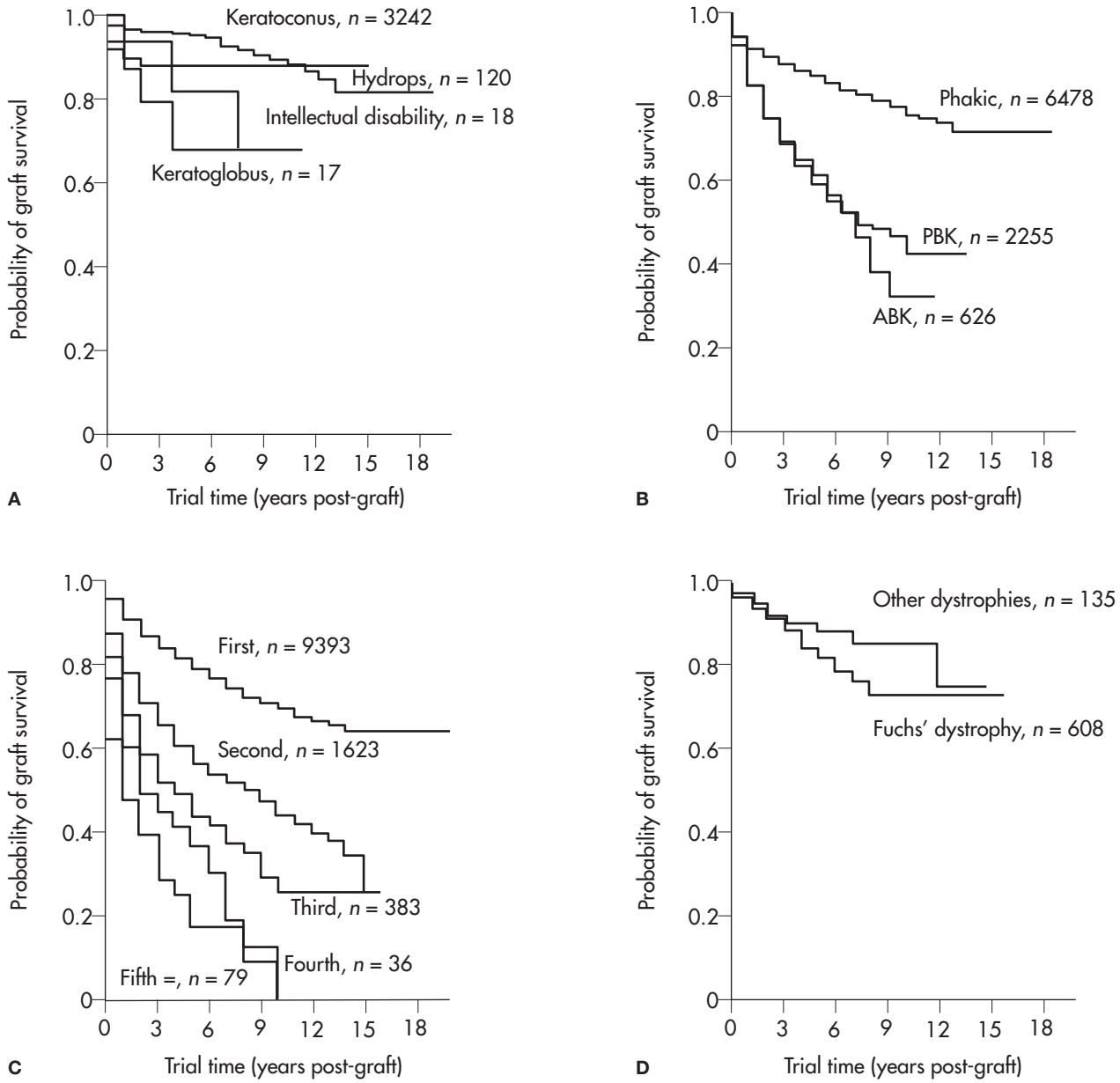

Figure 63.2. Kaplan–Meier survival of penetrating corneal grafts performed for common indications for graft. *A*, Survival of first ipsilateral grafts for keratoconus, keratoconus with hydrops, keratoconus in patients with an intellectual disability, and keratoglobus. *B*, Survival of first ipsilateral grafts in phakic eyes, in eyes with pseudophakic bullous keratopathy (PBK), and in eyes with aphakic bullous keratopathy (ABK). *C*, Survival of first, second, third, fourth, and subsequent ipsilateral corneal grafts. *D*, Survival of first ipsilateral grafts for Fuchs' dystrophy or for other corneal dystrophies. For each curve, *n* indicates the number of grafts initially at risk. Data reproduced with permission from the Australian Corneal Graft Registry, http://hdl.handle.net/2328/1002.

(Fig. 63.2, *D*). Graft survival for Fuchs' dystrophy is 95% at 1 year, 82% at 5 years, and 73% at 10 years. The corresponding figures for stromal dystrophies are 94%, 88%, and 85% at 1, 5, and 10 years, respectively.

Infective processes

At times corneal transplantation is required to control infective processes. Herpes simplex virus infections can cause sight-threatening corneal pathology. Chronic disease often results in scarring which can adversely affect vision; acute fulminating herpetic disease can threaten the survival of the cornea and lead to the loss of the eye. Where a corneal graft is performed for herpetic scarring, the 10 year graft survival is 68% (Fig. 63.3, *A*). In instances where the recipient cornea is inflamed due to active herpetic disease at the time of transplantation, the 10 year graft survival falls to 32%.

Corneal grafts for other infective conditions have a similarly poor prognosis. For example, the survival of grafts performed for nonherpetic perforations, the majority of which are likely to be due to microbial infection, is 59% at 1 year and 35% at 5 years, with an estimated median survival of 5 years. For those with a corneal abscess but not perforation the corresponding figures are 76% and 46%, with an estimated median survival of 6 years. For grafts performed for fungal keratitis the survival is poorer again: 52% at 1 year and 42% at 5 years, with a median survival of 2 years.

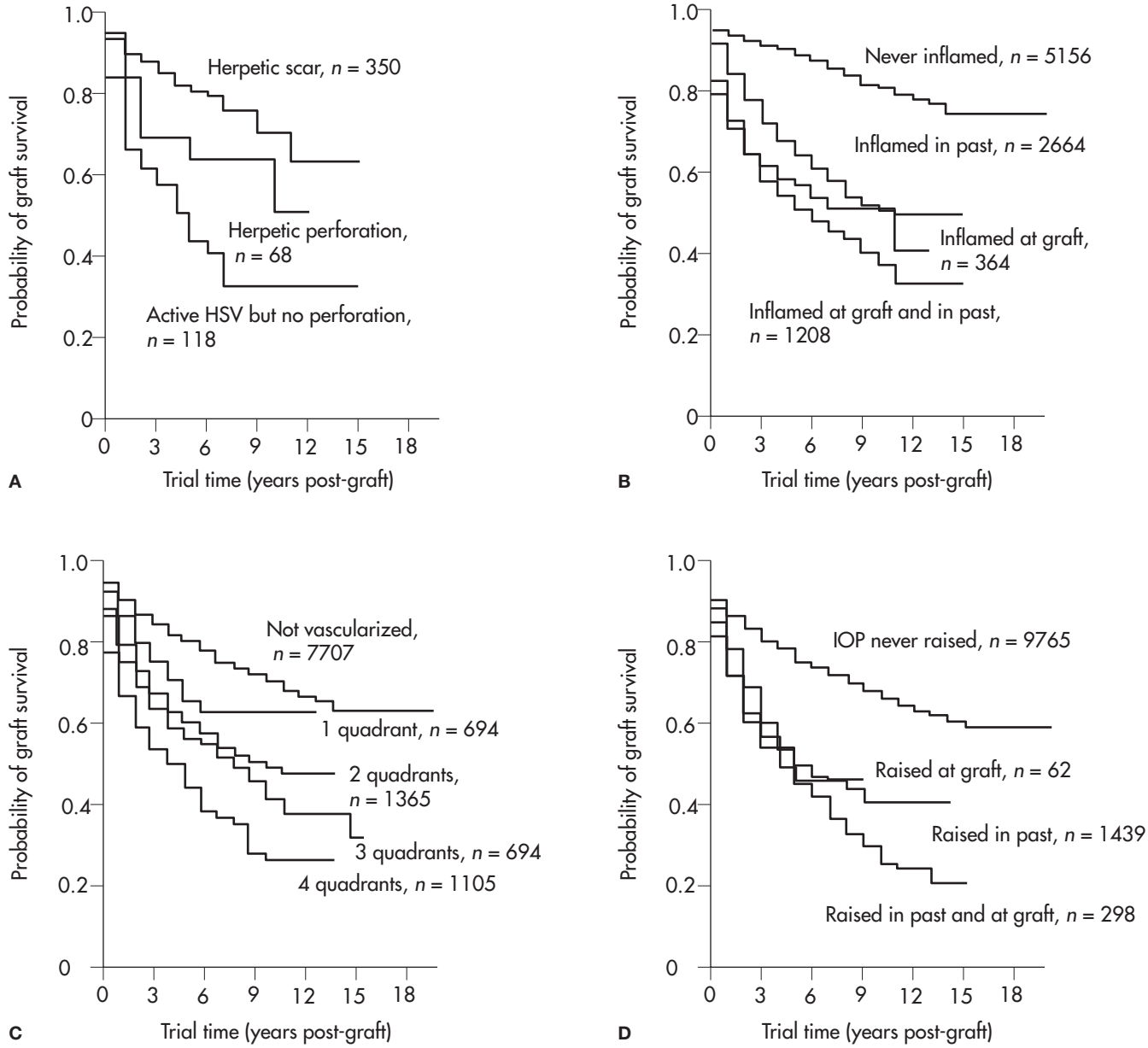

Figure 63.3. Kaplan–Meier survival of penetrating corneal grafts. *A*, Survival of first ipsilateral grafts for herpes simplex virus (HSV) infection. *B*, Influence of a history of ocular inflammation on subsequent graft survival. *C*, Influence of recipient corneal neovascularization, present at the time of corneal transplantation, on subsequent graft survival. *D*, Influence of a history of raised intraocular pressure (IOP) on subsequent graft survival. For each curve, *n* indicates the number of grafts initially at risk. Data reproduced with permission from the Australian Corneal Graft Registry, http://hdl.handle.net/2328/1002.

THE IMPACT OF INFLAMMATION ON CORNEAL ALLOGRAFT REJECTION

An obvious pattern emerges to explain the different survival rates for corneal grafts performed for different indications. Grafts for conditions where there is no history of corneal inflammation, such as keratoconus and stromal dystrophy, do better than those performed for acquired inflammatory conditions. If the etiological agent tends to persist after the graft, as is the case in herpetic keratitis and fungal keratitis, the outcomes are worse again. Those with active inflammation at the time of surgery have the poorest prognosis, but a history of inflammation prior to the graft, decades previously, is also associated with reduced survival rates (Fig. 63.3, *B*). The common path to graft failure in these cases is through allograft rejection.[9] Inflammation erodes graft privilege[10–12] and predisposes to corneal neovascularization, which has a well-established association with reduced graft survival (Fig. 63.3, *C*).

ELEVATED INTRAOCULAR PRESSURE

Elevated intraocular pressure at the time of the graft or at any time prior to the graft reduces graft survival (Fig. 63.3, *D*). Raised intraocular pressure in patients with corneal disease is almost always a

secondary phenomenon, rather than the result of primary glaucoma. Inflammation can reduce the functional reserve capacity of the aqueous drainage mechanisms and in this respect, elevated intraocular pressure may be a marker of previous or active inflammation.

SURGICAL FACTORS INFLUENCING CORNEAL GRAFT OUTCOME

The supposed improvement in the outcome of corneal transplantation over the last 100 years is often attributed to changes in surgical practice. The development of new surgical materials such as monofilament nylon, and the evolution of ocular microsurgery accompanying the widespread use of the operating microscope, have undoubtedly impacted strongly on corneal transplantation. However, it can only be assumed that these surgical developments improved surgical outcomes, because so little information on the outcomes of corneal transplantation prior to the 1950s is available.

In the past, personal opinion, case reports, personal series, uncontrolled studies and the like were used to justify the introduction of variations in surgical technique. With the emergence of the evidence-based medicine movement, there has been increasing interest in the quality of research evidence. As the evolution of surgical techniques continues, so too do the preferred methods of evaluating the impact of therapeutic advances. The gold standard is to compare the proposed advance with the existing therapy through a randomized, controlled clinical trial (RCT). Unfortunately, there are relatively few RCTs of surgical techniques in corneal transplantation, as is the case across most of surgery.

The evidence base for surgical techniques in corneal transplantation was recently reviewed.[13] Looking at the effectiveness of various surgical interventions, 26 trials were identified. Methodological problems were widespread—less than optimal outcome measures, small numbers and therefore low power, and short follow-up were common issues. None of the studies used patient-centered outcomes as the outcome measure, few used graft survival, most used refractive measurements (often keratometry), and a few used intraocular pressure.

Ocular refractive measures in response to intervention tend to be convenient but have limited meaning in terms of patient satisfaction and quality of life. The issue of astigmatism demonstrates this. It is convenient to measure keratometric astigmatism: small variations can be measured and almost any corneal surgery, however trivial, will alter the measurement. The usefulness of this approach in a clinical setting is limited because it only deals with the regular component of astigmatism, and the irregular component may have a profound effect on vision. In addition, keratometric astigmatism is not the same as the refractive astigmatism, which may be more important to the patient.

Despite the limitations of the reported studies, there is evidence of benefit being derived from some surgical approaches. Shrinking the apex of a cone prior to surgery reduces postoperative myopia.[14] There is some support for the use of an excimer laser to cut the donor and host cornea, compared with conventional trephination.[15,16] In addition, there is evidence that graft–host size disparity improves results. Oversizing has a beneficial effect on postoperative intraocular pressure in aphakic or combined cases.[17] Oversizing also increases keratometric readings, with corresponding changes in refraction.[18,19] The use of a viscoelastic agent has been shown to reduce endothelial cell loss to a statistically significant degree.[20] Whether this reduction is clinically significant is another issue, given that it does not improve the graft failure rate.[21,22] It was proposed a decade or two ago that removing the donor epithelium would improve graft survival by reducing allosensitization, and an early trial supported this notion.[23] A larger, more recent trial failed to identify any beneficial effect.[24] There has been much conjecture over the years about whether any particular suture pattern provides a better result by reducing postoperative astigmatism. There is no evidence from clinical trials that suture technique significantly influences the final 'sutures-out' astigmatism.

FACTORS RELATED TO THE DONOR CORNEA

The donor cornea is a key element in the corneal transplantation process. Eye banking has become a sophisticated enterprise and is rigorously regulated in most jurisdictions. Eye banking is aimed at eliminating, as far as is possible, the risk of transferring infectious diseases with the graft, and at providing a cornea with the maximal functional reserve capacity. Although it is not possible to eliminate completely the possibility of transfer of a communicable disease in a donor cornea, the measures that are currently employed ensure that this is a very rare event. So too is primary graft failure, although this does occur from time to time. Subtle variations in the functional reserve capacity of the donor cornea which might affect the long-term survival of the graft are difficult to identify, and evidence of diminished endothelial cell function might not emerge for decades, until the graft fails.

Donor age

Corneal surgeons commonly believe that younger donors provide better corneas. So widely held is the belief that donor age adversely affects graft survival, that surgeons often seek young donors for their young patients and accept old donors only for older recipients. Examination of long-term registry data shows that donor age does influence graft survival significantly in both univariate (Fig. 63.4)

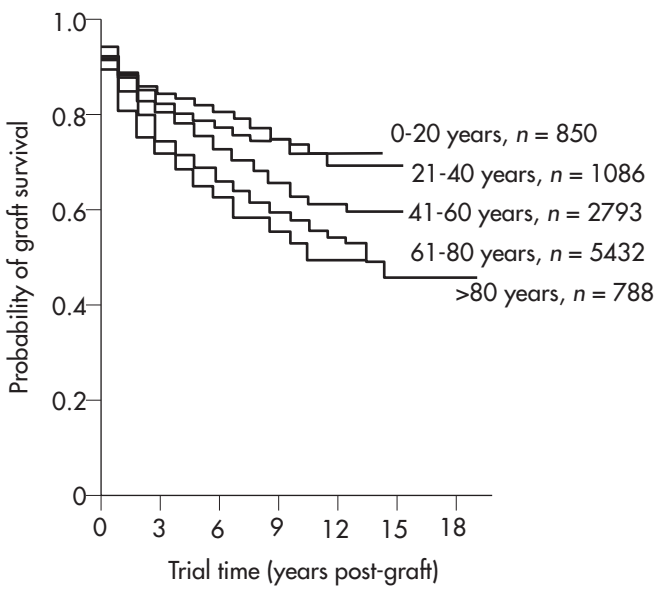

Figure 63.4. Kaplan–Meier survival of penetrating corneal grafts. Influence of donor age on graft survival. For each curve, *n* indicates the number of grafts initially at risk. Data reproduced with permission from the Australian Corneal Graft Registry, http://hdl.handle.net/2328/1002.

and multivariate analysis (Table 63.1), but that observations need to be maintained over decades to detect differences, and that the effect is extremely small. This is an important issue, because were the use of older donors to become more acceptable, the donor pool (a scarce resource in many parts of the world) could be expanded considerably.

HISTOCOMPATIBILITY MATCHING

With the prognosis for corneal transplantation in high-risk patients remaining poor, and the clinical context of corneal transplantation precluding the widespread use of approaches that have contributed to the striking improvements in survival of essential organ allografts, the impact of histocompatibility matching on corneal graft survival is of increasing interest. Better matching may be the only currently available method to improve the results of corneal transplantation, since systemic immunosuppression is not an option for most corneal recipients and there is no prospect of using living-related donors, two of the major approaches associated with the improvement of renal transplant survival over the past 25 years.

The results of the American Collaborative Corneal Transplantation Study (CCTS), a carefully conducted randomized clinical trial, indicated that HLA class I and class II histocompatibility matching had no influence on the survival of corneal transplants in patients at high risk of graft failure.[25] However, there are data from other sources (although not randomized controlled clinical trials) indicating that matching is helpful in prolonging corneal graft survival.[26–28] Histocompatibility matching has progressed to being more reliable and more reproducible with the development of modern molecular techniques for typing. A high error rate in the typing of patients in the CCTS trial was reported by the investigators soon after the study was completed,[29] and the impact of this error rate was subsequently assessed as being likely to have affected the reliability of the results.[30] Various groups, principally from Europe, have more recently reported substantial benefits of matching.[31] The most recent data and perhaps the most striking come from Berlin,[28] in which it was found that HLA matching improves the survival of corneal grafts by 40% at 3 years in high-risk patients. Perhaps it is time to reconsider the effect of matching on the results of corneal transplantation.

VISUAL OUTCOME AFTER CORNEAL TRANSPLANTATION

Graft survival tells the story of gross success or failure. It does not say anything about the degree of visual rehabilitation achieved by those with a clear graft. An assessment of visual performance is required to do this. Visual acuity is the conventional way of measuring vision in the clinical context. Snellen acuity, in the original form or modified to facilitate statistical analysis using logMAR charts, is the approach used in most countries and is the outcome measure most frequently employed in studies looking at the visual results of corneal transplantation.[5] However, there is significant variation in the way vision is measured from center to center.

The evaluation of visual acuity, often open to criticism in clinical assessment, is particularly problematic after corneal transplantation. A meaningful assessment cannot be made until after sutures are out and the final refraction is established. This is almost always at least a year after surgery and the very best acuity may not be achieved until into the third postoperative year. There is also the issue of the optical correction. Most patients will need to wear spectacles to achieve their best vision, and some will need a contact lens. Whatever the patient requires for best-corrected vision may not be tolerable or acceptable in every day life. It should be remembered that even patients very disabled by corneal disease can be expected to see the bottom line of an acuity chart with the aid of a pinhole and a chart lit by an atomic flash. Anisometropia may be a problem for some; others prefer to accept less than best-corrected vision rather than suffer the inconvenience of spectacles or a contact lens. For these reasons, it has been suggested that the acuity of patients with corneal grafts should be measured with their 'socially acceptable' correction.

Binocular acuity is related to visual acuity. How much a person can do with his or her vision depends on how well the better eye sees, not on how poor the worst eye is. Failure to recognize the importance of binocular acuity in corneal transplantation can result in patients having surgery which is complicated, resource-consuming, and hazardous to the patient if immunosuppression is used, without the prospect of reduced disability even if a functioning graft is achieved.

Within the Australian Corneal Graft Registry, Snellen acuity after corneal transplantation is found to be 6/12 or better in 40% of the patient cohort in whom the visual acuity has been measured (Fig. 63.5). The visual results for patients grafted for keratoconus are much better, with 71% achieving 6/12 or better and 89% recording at least one line of improvement on the Snellen chart following corneal transplantation. Several studies—all retrospective patient series–reveal remarkably consistent results, with 90% of patients achieving 6/12 or better.[32–34]

VISUAL DISABILITY AFTER CORNEAL TRANSPLANTATION

Patient-centered outcomes are seldom used in the evaluation of corneal transplantation. Although visual acuity and keratometric readings are convenient measures, they provide little information about the impact of the procedure on the patient. For example, there is a tendency to express the results of corneal transplantation in terms of corneal astigmatism. It is more convenient to measure the keratometric astigmatism rather the spectacle astigmatism. This approach is likely to provide solid numbers: keratometry is objective, and there is a subjective element to refractive astigmatism. However, the refractive astigmatism may relate more closely to the patient's visual performance. This general approach assumes that corneal astigmatism is a major factor limiting visual acuity, and that acuity in turn is the major factor influencing visual disability. In reality, not all individuals with good Snellen acuity consider themselves to see well: some patients with very high levels of acuity are quite frustrated by their vision. Visual acuity is only one domain of visual function, and other aspects of visual performance are also important. For example, good contrast sensitivity is necessary for everyday functioning. Subnormal contrast sensitivity has been reported after corneal transplantation for keratoconus.[35] There are also some studies which demonstrate increased wavefront aberrations in patients with corneal grafts.[36,37]

CONCLUSIONS

Paradoxically, corneal transplantation is both successful and unsuccessful. For patients with dystrophic conditions such as keratoconus or the corneal dystrophies, the results are excellent, at least when considered from the perspective of successful engraftment. Graft

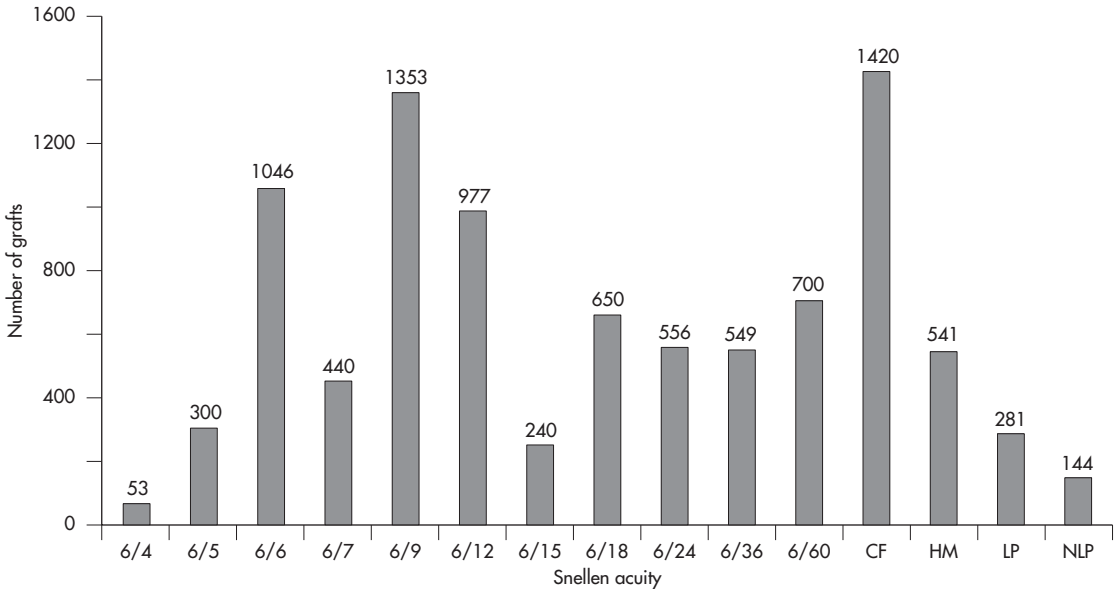

Figure 63.5. Snellen acuity recorded in the grafted eye at the time of most recent follow-up. CF, count fingers at 3 m; HM, hand movements; LP, perception of light; NLP, no perception of light. Data reproduced with permission from the Australian Corneal Graft Registry, http://hdl.handle.net/2328/1002.

survival in this group of patients is high. Unfortunately, acquired corneal diseases causing blindness are common around the world. For the group of patients with inflammation or corneal scarring, the results of corneal transplantation are less impressive, so unimpressive that many patients are not considered for surgery. The developments that have improved the outcomes of allotransplantation for vascularized organs are generally not applicable to corneal transplantation. To develop alternative management strategies to improve the outcome of corneal transplantation will require extensive research. For this research to be applicable to clinical corneal transplantation, more needs to be known about the long-term clinical course and the factors influencing outcomes, and there are surprising gaps in our knowledge. Examples include the relationship of corneal endothelial cell count to graft survival, the relationship of eye banking procedures to graft survival, and the incidence of transfer of slow virus and prion infections through corneal transplantation. One way to fill these gaps is through surveillance programs or registries. As regulation of transplantation programs increases, it may become obligatory to keep long-term data on the outcomes of transplantation. This has already been threatened in some jurisdictions, and it is difficult to envisage any other way of elucidating the long-term outcomes. Following patients over the long-term is necessary to answer important questions about corneal transplantation. There is also a need for more clinical trials. The only way to evaluate clinical interventions is with prospective, randomized clinical trials. Few have been performed in the area of clinical corneal transplantation and the approach deserves further encouragement.

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64 Surgical technique for DSAEK—Descemet's stripping automated endothelial keratoplasty

Mark S. Gorovoy

INTRODUCTION

The technique of Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) for endothelial failure is explained with clinical pearls to facilitate its use. DSAEK is a novel procedure that replaces penetrating keratoplasty (PKP) for endothelial disease.[1] The visual results of DSAEK exceed those of PKP.

HISTORICAL PERSPECTIVE

PKP has been the standard of care for corneal transplantation for over 50 years. Modern microsurgical techniques and improved eye banking have resulted in a very highly successful operation, especially if the measure of outcome is a clear cornea. PKP is a full-thickness procedure and applicable for a large range of disease including corneal decompensation from endothelial failure, stromal scars, and ectatic disease. However, visual results with PKP are highly variable, unpredictable, and visual recovery may be delayed. Unacceptable astigmatism, both regular and irregular, may limit spectacle correction. Full thickness trephinations and longterm sutures contribute to the refractive dilemmas and surface disease. The susceptibility to traumatic wound dehiscence and loss of vision remains permanent.

Clearly, a procedure that not only improves the anatomy (i.e. corneal clarity), but also consistently improves the function (i.e. visual acuity as measured by best corrected spectacle visual acuity—BCSVA) is highly desirable. DSAEK, by avoiding full thickness trephinations and long-term sutures, avoids the functional shortcomings of PKP and results in a rapid high-quality visual recovery. DSAEK is a focused surgery for endothelial diseases, such as Fuchs', pseudophakic, or aphakic bullous keratopathy (P/ABK), prior PKP endothelial graft failure or iridocorneal endothelial (ICE) syndrome. Is it not applicable for stromal scars or ectatic disease?

The origins of DSAEK stem from the work of Dr Gerritt Melles.[2–5] His original technique of posterior lamellar keratoplasty (PLK) involved a large limbal incision and deep manual lamellar corneal dissections with excision and transplantation of a similarly dissected donor disk. Next evolved a smaller (5 mm) clear cornea temporal incision and a taco-fold donor insertion. Dr Mark Terry renamed the procedure Deep Lamellar Endothelial Keratoplasty (DLEK) and has been instrumental in promoting the superior outcomes of DLEK.[6–9] PLK (DLEK) requires extensive surgeon skill to master the arduous lamellar dissections of both the patient and donor (performed on an artificial chamber).

The next evolution by Melles was the substitution of the patient dissection with Descemet's stripping.[10] This pivotal change gave birth to Descemet's Stripping Endo Keratoplasty (DSEK). Descemet's stripping eliminated the manual dissection of the patient and my adaptation of the Moria ALTK system eliminated the manual dissection of the donor and gave rise to DSAEK. The elimination of all manual lamellar dissections has resulted in a more consistent and reproducible surgical outcome. Visual recovery is hastened by the two smooth lamellar surfaces.

TECHNIQUE

DSAEK is this author's procedure of choice for all patients requiring corneal transplantation due to endothelial disease. DSAEK surgery is totally dissimilar to PKP surgery and because it is a relatively new procedure, the aim is to continue to modify technique to improve patient outcomes.

The Achilles heel of DSAEK is donor dislocation and most changes to the procedure are in an effort to reduce the risk of this complication. In the following sections the author's present surgical technique and postoperative maneuvers are described in detail.

PATIENT SELECTION

DSAEK is indicated for corneal endothelial disease. Fuchs' dystrophy comprises the largest cohort followed by P/ABK and prior graft endothelial failure. The technique is essentially the same for all diagnoses. All patients must be pseudophakic with a posterior chamber intraocular lens (IOL). It is preferred to do DSAEK as a stand-alone procedure, not combined with other procedures.

All phakic patients are rendered pseudophakic even if it requires a clear lensectomy. The only exception is a cornea too opaque for phaco. This approach deepens the anterior chamber for donor

unfolding and avoids future cataract surgery that is almost inevitable—thereby avoiding phaco-induced endothelial cell loss.

All anterior chamber IOLs are replaced with sutured scleral IOLs. Glaucoma must be well controlled and if necessary filtering or shunt surgery is performed pre-DSAEK. These staged procedures are completed approximately 4–6 weeks apart.

PREOPERATIVE TREATMENT

A fourth generation fluoroquinolone antibiotic is started q.i.d. the day prior to surgery. Topical anesthesia using 2% xylocaine jelly and i.v. sedation as needed are utilized. The pupil is left unaltered, i.e. no miosis or mydriasis.

In the operating room, 10% betadine solution preparation to the skin and lids is performed with direct instillation onto the globe. A nasal speculum is placed after the lid margin and lashes are draped with tegaderm. The author sits laterally with the microscope and marks the corneal surface with a 9 mm trephination marker inked with a marking pen. This allows the size of the donor tissue trephination to be judged. A 9 mm donor is used unless this marking approaches 2 mm to the limbus, indicating a smaller donor size is preferable such as 8.5 or 8.75 mm. It is important to avoid the donor lenticule from impinging too close to the angle. The patient's eye is left open with the speculum in situ and while attention is turned to the donor tissue preparation. This 'air drying' allows a swollen, edematous cornea to deturgesce and improves the operative visibility.

DONOR

Attention is then turned to the donor tissue. The donor cap is placed on the ALTK system and cut with a 300 keratome head as shown in Figure 64.1. Air is used to inflate the donor cap. A very firm corneal dome is verified with finger ballottment. The donor rim must be a consistent 16 mm rim size, without any divots. The local eye bank must be made aware that a large rim size is required. The anterior cap is removed from the keratome head and the remaining posterior lamellar donor tissue is removed from the ALTK 'hat' and placed on a cutting block and trephined endothelial side up. When lifting up the hat, simultaneous forced air pressure prevents the donor tissue from collapsing on the ALTK stage.

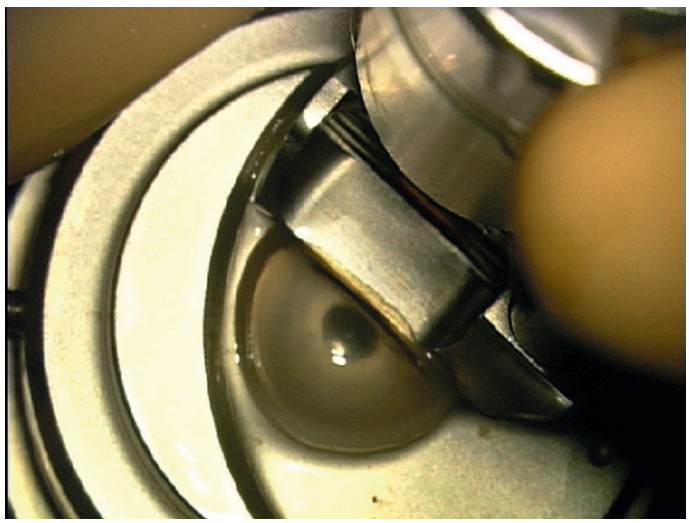

Figure 64.1. Tissue being cut on the Moria ALTK system.

Centration of the donor tissue on the cutting block is essential to avoid a decentered cut and a full thickness donor disk edge. If that occurs, recenter the tissue and recut it to remove the full thickness section. A perfectly round donor tissue is not required and causes no optical problems. A drop of transplant media is placed on the donor and attention is returned to the patient.

The 1 mm, diamond blade cut, vertical limbal paracentesis are made superiorly, inferiorly, and nasally. A clear cornea 2.75 mm keratome incision is made temporally. Through the right-handed paracentesis, the irrigating Descemet's stripper (Harvey Instruments) is introduced into the anterior chamber and Descemet's is scored along the surface trephination mark for close to 360° as shown in Figure 64.2. Descemet's membrane is then stripped 2–3 mm for several clock hours. The irrigation and aspiration 4 mm port hand piece (Bausch & Lomb millennium) is introduced through the keratome incision and the loose Descemet's edge is aspirated and dragged out of the wound (Fig. 64.3). This may take several passes to remove all of Descemet's membrane within the scored area. Three full thickness stabs using the same diamond paracentesis blade are made equidistant in the mid-periphery for future interface fluid drainage as previously described by Dr Frances Price. The temporal incision is enlarged to 5 mm.

DONOR INSERTION

The donor tissue in its cutting block is placed under the microscope and excessive fluid is removed with a sponge. Several drops of

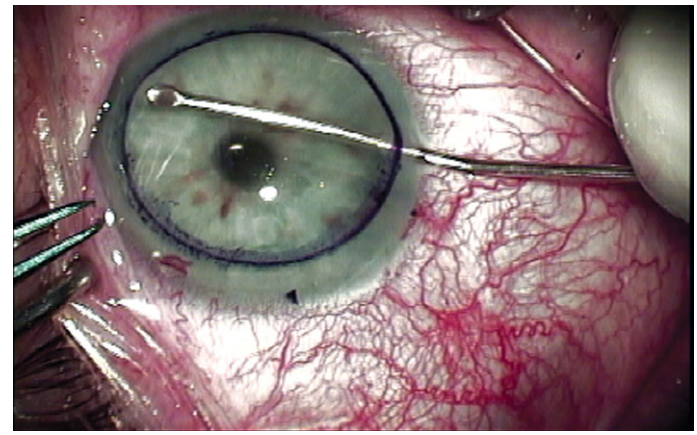

Figure 64.2. Stripper scoring Descemet's membrane.

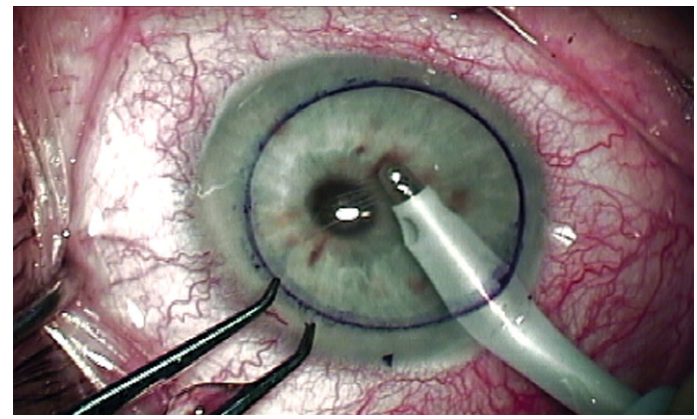

Figure 64.3. Irrigation and aspiration stripping of Descemet's membrane.

Healon (AMO) are placed on the donor tissue which is then folded over like a taco in a 60/40 fold. It is grabbed with Goosey inserter forceps (Moria) and inserted into the anterior chamber (Fig. 64.4). One 10-0 nylon is applied to partially close the incision and BSS solution is used to deepen the anterior chamber. The donor may unfold spontaneously. If not, the irrigation and aspiration hand piece is used to deepen the anterior chamber and grab the underside of the 'taco' and unfold it.

A final wound suture is placed and the tissue is centered to the limbus. This is accomplished by reforming the anterior chamber about 50% depth and balloting the limbus with any device, even your finger. The tissue will move away from the spot the limbus is 'smacked.' Once the tissue is centered a full air bubble fills the anterior chamber outlining the donor disk edge as demonstrated in Figure 64.5. If the donor decenters during this step the air is removed and the tissue is recentered. The mid-peripheral stab incisions are then probed with a spatula or cannula and interface fluid is visually expressed out. Dilating drops are applied and the patient is left supine for 1 h in the holding area. After 1 h, a slit lamp examination verifies the position of the donor and air is 'burped' out through the paracentesis or wound site until the lower air bubble meniscus is above the inferior pupil edge. This insures absolutely no chance for a pupillary block. A shield is applied. Drops of antibiotics q.i.d. and prednisone are started with office follow-up the next day.

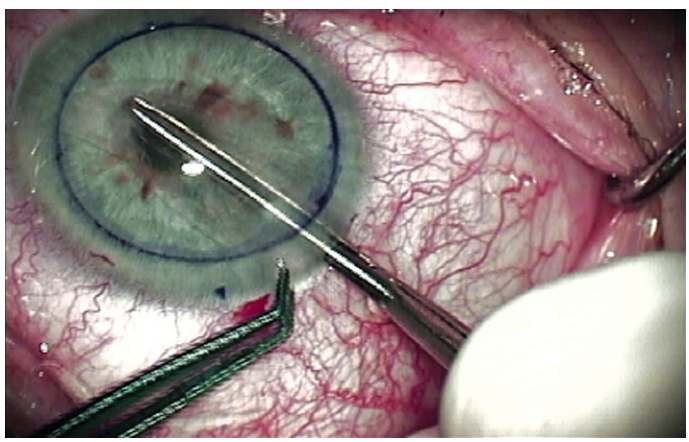

Figure 64.4. Folded donor inserted into the anterior chamber.

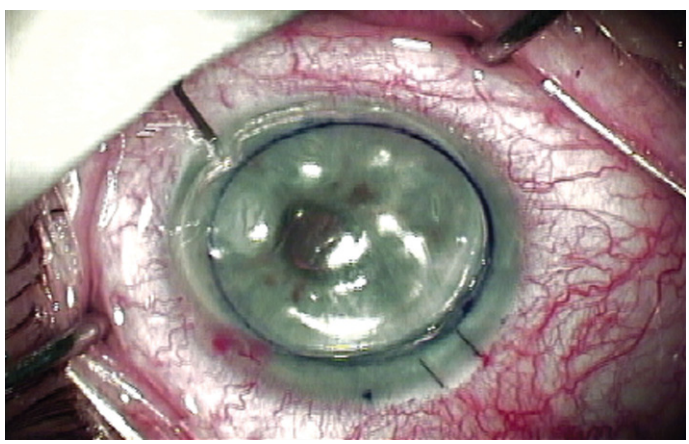

Figure 64.5. Full anterior chamber bubble.

POSTOPERATIVE DAY 1

Slit lamp examination confirms the appropriate position of the donor tissue. The two key questions at this stage are: is the cornea grossly edematous or has the donor disk slipped inferiorly? If the answer is yes to these two questions, donor dislocation if likely (Fig. 64.6). Careful slit-lamp examination can identify very tiny gaps in adhesion, even with +4 corneal edema. In these situations, repeat air bubbling is done in the minor operating room under the microscope and the supine positioning and air bubble burping is repeated just as in the original operating room procedure (Fig. 64.7).

In several DSAEK patients three bubbles have had to be placed. There is no harm to the 'loose' donor disk as the aqueous provides endothelial nourishment independent of stromal attachment. Interestingly, one patient had delayed donor adhesion for 7 weeks and yet has a perfect result with an excellent endothelial cell count. The surgical goal is to achieve a donor dislocation of less than 5%.

The postoperative drop regime is 1 week of antibiotic drops and prednisone drops q.i.d. for 3 months then tapered to once a day by month 6. Steroid responders may need accelerated tapering and even a switch to Lotemax (Bausch & Lomb BID) or topical

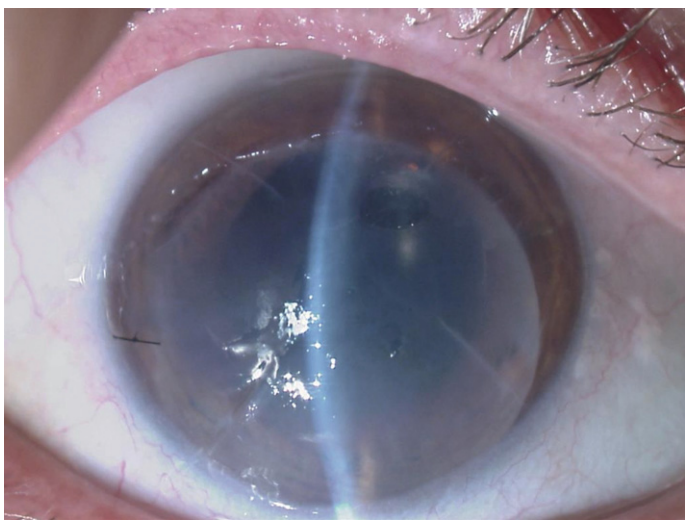

Figure 64.6. Dislocated donor tissue.

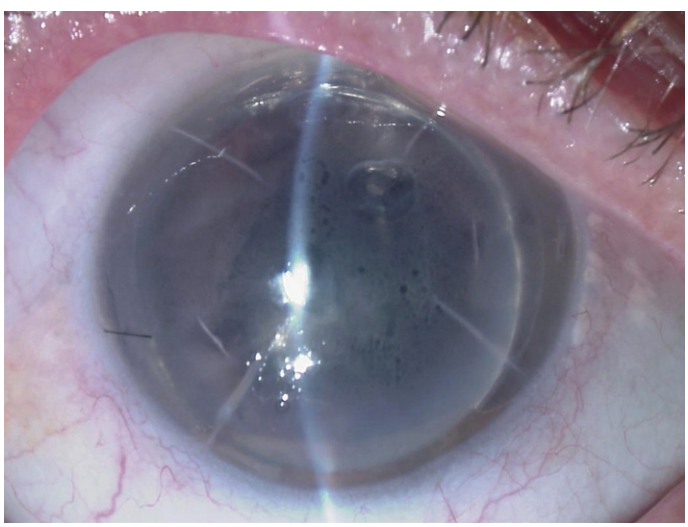

Figure 64.7. Dislocated donor re-bubbled and re-centered.

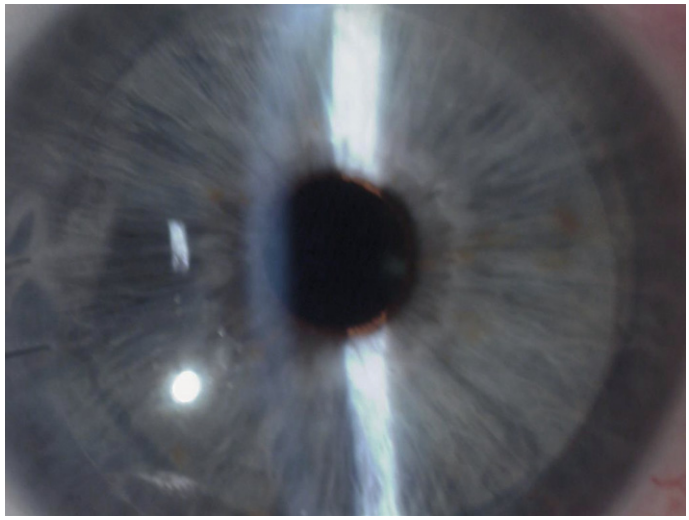

Figure 64.8. Clear DSAEK at 6 weeks postsurgery—BSCVA 20/40.

cyclosporin , plus glaucoma agents. Best spectacle corrected visual acuity (BSCVA) is obtained between 6 and 12 weeks at which time a new spectacle script can be provided. Figure 64.8 shows a clear DSAEK at 6 weeks postsurgery. Limbal sutures can be removed after 6 weeks for astigmatism control.

DISCUSSION

DSAEK has revolutionized the way this author approaches and treats endothelial corneal failure. This paradigm shift has given the confidence to be appropriately aggressive when counseling patients about the risks and options of corneal transplant surgery without concomitant retinal disease. A BSCVA of 20/40 by 6 weeks in over 80% of patients is generally expected. This improves to 20/40 in over 90% of eyes by week 12 and BSCVA of 20/20 is reached in 16% by 6–12 months. Typically, there are no significant refractive surprises. Price has published a large series of DSAEK outcomes, confirming the excellent postoperative visual results.[11]

Patients with bilateral disease are requesting second eye surgery by 3 months. However, appropriate patient counseling must never ignore the risks of any corneal transplant surgery: infection, primary failure, rejection, and glaucoma.

This author's enthusiasm for DSAEK has resulted in offering monthly courses for corneal surgeons. Their positive feedback is infectious. I no longer recommend DSAEK as an alternative to PKP. It has replaced PKP as my standard of care for endothelial disease and I anticipate it will be the universal standard of care in the very near future.

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65 Posterior lamellar keratoplasty and deep lamellar endothelial keratoplasty

Neda Shamie, Edwin S. Chen, Mark A. Terry

BACKGROUND AND HISTORY

Corneal endothelial dysfunction accounts for most of the nearly 40 000 penetrating keratoplasties (PKP) performed in the USA annually.[1] This is despite the clear understanding of the pathophysiology of endothelial keratopathies such as Fuchs' endothelial keratopathy as well as pseudophakic bullous keratopathy in which the stromal and the epithelial layers are at least initially healthy and that primarily the endothelial layer and the posterior corneal layers are diseased.[2–4] With that understanding, many scientists and corneal surgeons have been intensely studying a more selective approach to the surgical treatment of corneal endothelial dysfunction for many years. As a result of their efforts, selective endothelial keratoplasty (EK) has now reached mainstream practice with increasing number of corneal surgeons performing EK for their patients with corneal endothelial dysfunction. This is thought to be due to the many improvements and simplifications of the surgical techniques and clearly proven excellent clinical results.[5–20]

Drs Polack, Barraquer and others initially introduced endothelial keratoplasty ca. 1965, with a technique that involved creating a hinged corneal flap which would then be retracted for trephination and transplantation of the posterior stroma and endothelium.[21,22] This required suturing of the hinged flap at the very least. The technique was clearly more selective than penetrating keratoplasty in treating endothelial dysfunction as it replaced only the posterior stromal and endothelial layers. Despite its selective approach, it did not address the many problems associated with surface sutures and penetrating corneal wounds such as irregular astigmatism, delayed visual recovery, and a potentially unstable globe. To address these problems, in 1993 Ko et al presented results from laboratory experiments on rabbits in which they performed endothelial keratoplasty through a scleral limbal approach.[23] This led to a resurgence of interest in the subject and intense examination of EK as a valuable surgical option.

Gerrit Melles of the Netherlands performed the first human scleral limbal approach to EK in 1998 through a 9.0 mm incision.[24] He named the procedure posterior lamellar keratoplasty (PLK), the same name used by many surgeons performing endothelial keratoplasty under a hinged flap.[18–20,25,26] The Melles' PLK technique utilized air for both resection of the recipient tissue and stabilization of the donor tissue after insertion. This technique obviated the need for the use of any corneal sutures. Melles' PLK procedure proved to be extremely technically difficult but his contribution to the field indeed led to the accelerated movement toward further improvements in EK techniques.[20]

In 1999, Mark Terry of Portland, Oregon, began intensive laboratory experimentation in pursuit of simplifying the technique's approach while maintaining or improving its results. He utilized the cohesive viscoelastic agent Healon (Pfizer, New York, NY) in the laboratory and through prospective clinical studies has shown that Healon can be safely used in stabilizing the anterior chamber and thus simplifying the procedure. The cohesive nature of Healon allows it to be easily removed in its entirety without residual coating of tissue and without hindering donor graft adhesion.[27,28] Terry renamed the procedure deep lamellar endothelial keratoplasty (DLEK) to differentiate it from the hinged procedure originally named PLK and to emphasize the endothelial transplantation involved in this procedure.[6,26] A prospective randomized study of EK under the approval of Institutional Review Board (IRB) was begun and Terry performed the first human case of DLEK in the USA in March 2000.[27] Since then, surgeons have performed the procedure in the appropriate patients and have heralded its many benefits over PKP for their patients with corneal endothelial dysfunction.[12]

The many benefits of this procedure compared to penetrating keratoplasty stem from its preservation of the normal corneal surface as it does not require penetrating corneal wounds and thus avoids the need for surface sutures. The tensile strength of the scleral tunnel wound of EK is also much greater than the PKP wound and allows for more rapid wound healing. The lack of surface sutures inherently lowers the risk of suture-related complications such as irregular astigmatism, unpredictable corneal curvature, suture-related graft rejection, and infections. Also, there is no need for rigorous and prolonged postoperative follow-up with the need for selective suture removal.

Despite proven benefits over PKP, DLEK/PLK poses a number of challenges to the corneal surgeon. First and foremost, the difficulty

in performing the surgery limits its utility on a large scale as many surgeons may avoid adding these procedures to their surgical armamentarium. Another concern stems from the creation of the deep lamellar dissection in the recipient as well as the donor cornea; it is postulated that this deep stroma to stroma interface limits the final visual potential in the DLEK/PLK eyes.[9,12,29,30]

Descemet's stripping endothelial keratoplasty (DSEK) and Descemet's stripping automated endothelial keratoplasty (DSAEK) are modifications of Melles' PLK which circumvent the need for a manual lamellar stromal dissection of the recipient cornea by selectively removing the endothelial layer through a Descemetorhexis, a technique originally described by Melles.[31,32] Since their introduction, DSEK and DSAEK have quickly replaced DLEK/PLK in popularity given the simplified surgical steps and better visual outcomes.[13,15,17] However, the skills and the techniques involved in performing DLEK such as the deep manual lamellar dissection of the recipient cornea should be maintained as there still remain indications for performing DLEK or PLK in patients at high risk for the complications unique to Descemet's stripping surgery.

The Descemetorhexis step in DSEK and DSAEK leaves the recipient corneal bed extremely smooth as demonstrated on electron microscopy.[33] This is thought to explain the higher rates of graft dislocation in DSEK/DSAEK as compared to DLEK in which the recipient stromal bed's roughened properties are thought to create better adherence.[13,16] Many steps have been proposed to lower this rate of graft dislocation in the DSEK/DSAEK cases with the use of prolonged intraocular air in the anterior chamber for continued stabilization of the graft the most commonly advocated.[16,33] Therefore, any condition in which retention of this air bubble in the anterior chamber is in question would preclude DSEK/DSAEK and lead to DLEK as the procedure of choice in that patient. Examples of these include a stable anterior chamber intraocular lens (IOL) that is deemed unnecessary to be explanted or exchanged, aphakia in a patient who is to be left aphakic (i.e. a very high axial myopia) and significant irreparable iris defects. In these and similar cases, there is no hindrance to the movement of the anterior chamber air bubble to the posterior pole. With the posterior migration of the air bubble, the risk of graft dislocation can potentially increase as the benefits of the air bubble acting to hold the donor graft in place is lost. The posterior migration of the air bubble can also result in pupillary block or secondary angle closure with increased postoperative intraocular pressures. Although the current indications for DLEK may seem limited, it continues to be an excellent option for the appropriate candidate and thus the lamellar corneal surgeon must continue to know the skills involved in performing this form of EK.

PREOPERATIVE CONSIDERATIONS

SURGICAL PLANNING

In the preoperative evaluation when the decision is made to proceed with EK, attention needs to be paid to several other factors to help in planning the surgical approach as well as to offer the patient the most realistic expectations. These could include the status of the lens (crystalline or previously implanted IOL), any evidence of vitreous prolapse, presence of anterior segment abnormalities (e.g. iris synechiae), and evidence of retinal or macular pathology. One can then better plan the surgical approach in case, for example, a scleral fixated IOL, anterior vitrectomy, or anterior segment reconstruction may be needed.

INFORMED CONSENT

An informed consent is obtained with a clear representation of outcomes expected. The patient should be informed of the risk of graft failure as well as dislocations requiring further surgery. There is the high risk for developing cataract in the cases in which the patient is to be left phakic. If, with further discussion, the patient and the surgeon do in fact decide to proceed with crystalline lens extraction to avoid secondary cataract extraction, the patient needs to understand the expected loss of accommodation. There is also the possible limitation of visual potential secondary to the surgical interface.[7] Additionally, the patient should be made aware of other risks associated with intraocular surgery per se such as developing glaucoma, retinal detachment, endophthalmitis, etc.

INTRAOCULAR LENS POWER CALCULATIONS

One great benefit of EK over PKP is the preservation of surface corneal curvature.[5,7,8] This simplifies the calculation of the power of the IOL to be implanted as one can simply use the preoperative average keratometry readings of the virgin (original) cornea in the calculations. This of course is very different from the scenario in PKP patients in whom the average keratometry readings change drastically due to the vertical wounds and the surface sutures of PKP.[34–37] If epithelial edema of the surgical eye prohibits accurate keratometry readings, then keratometry readings from the fellow eye can be used. If both corneas are edematous and prohibit accurate keratometry readings, then the EK can be performed first and the cataract extraction with IOL implantation performed 3 months later when more accurate measurements can be performed. If combined EK surgery with cataract extraction and IOL implantation is to be done the target postoperative refraction should be approximately −1.0 diopters using standard IOL calculation. This is to compensate for the myopic shape of the microkeratome prepared donor lenticule which results in a 0.5–1.0 diopters of hyperopic shift.[38].

PREOPERATIVE MEDICATIONS

In the case of patients requiring cataract extraction with IOL implantation or exchange of an IOL with possible scleral fixated IOL in conjunction with endothelial keratoplasty, the usual preoperative dilating drops are used as per surgeon's protocol. Preoperative antibiotic eye drops are also used per the surgeon's preference. Apraclonidine 0.5% drops are also instilled in the operative eye to lower the intraocular pressure and to minimize conjunctival injection. The eye is prepped and draped in the usual sterile ophthalmic manner with the use of povidone-iodine solution.

In the case where the patient undergoing EK is to be left phakic or has stable implanted IOL, the pupil is constricted using G. pilocarpine.

ANESTHESIA

DLEK surgery is usually done under retrobulbar block anesthesia with a seventh nerve (orbicularis) block to obtain, not only sufficient anesthesia, but also akinesia of the lids. General anesthesia (either endotracheal or laryngeal mask airway technique) may be considered in patients who may not be cooperative or in whom posterior pressure needs to be minimized (e.g. an eye with a shallow chamber). It is even possible to perform DLEK surgery on selected

high-risk patients under topical anesthesia, but this is not recommended for the initial cases of the novice surgeon as lack of akinesia can potentially increase intraoperative complications.

TECHNIQUES AND INTRAOPERATIVE CONSIDERATIONS FOR DLEK SURGERY

MANAGEMENT OF THE PHAKIC, APHAKIC, OR PSEUDOPHAKIC PATIENT

When cataract extraction is to be performed, the procedure is done prior to the DLEK and possibly after epithelial scraping to improve visualization if significant surface haze is present. Dispersive viscoelastic agents such as Viscoat (Alcon, Fort Worth, TX) should be avoided during any and all portions of the surgery as they can adhere to the stromal interface and prevent donor disk adherence to the bare recipient stromal bed. It is also recommended to perform the cataract surgery through a separate scleral limbal incision. This small cataract wound is sutured tightly prior to creation of the stromal pocket of DLEK.

An anterior chamber intraocular lens (ACIOL) need not be exchanged for a posterior chamber lens in all cases. The decision should depend on the stability of the anterior chamber lens and the type of lens. If the ACIOL is of the more modern flexible open looped type and seems to be nicely sized and positioned in the angle, it can be left in place. Otherwise, it may be prudent to replace the ACIOL with a posterior chamber lens (i.e. a sulcus or a scleral-fixated PCIOL) to decrease chance of endothelial damage.

In the case of the aphakic patient, if the posterior capsule is intact, a PCIOL can be safely placed in the capsular bag or the sulcus. Otherwise, the decision must be made to scleral fixate a PCIOL or leave the patient aphakic (i.e. in the high axial myopic patient or the rare patient with no visual potential undergoing surgery only for symptom relief).

PREPARATION OF THE RECIPIENT CORNEA

Surgery is usually performed from the temporal side for ease of access. An 8.0-, 8.5-, or 9.0-mm diameter circular corneal marker (depending on the size of recipient cornea) is used to imprint a circular mark onto the corneal surface. When the centration of the mark meets the surgeon's approval, the circular indentation is then accentuated with dotted marks using a sterile marker. This mark will act as the template to performing the posterior lamellar resection later in the procedure.

Prior to creating the scleral incisions, two clear corneal limbal stab incisions (about 1 mm diameter) are placed about 5 clock hours apart, to be used as access points to the anterior chamber later in the operation. A 1 mm diamond knife can create a better paracentesis wound with greater ease of anterior chamber entry as compared to a metal blade. For ease of identification and reentry, these ports can also be marked with a sterile marker. Additionally, great attention must be paid to creating the paracentesis ports in an angle that does not interfere with the edge of the 8.0-, 8.5-, or 9.0-mm lamellar graft (i.e. entry should be at a sharper angle than one is accustomed to in ports created for cataract extraction). Through one of the stab incisions, the cohesive viscoelastic Healon is placed into the anterior chamber to replace the aqueous fully and to maintain normal pressure.

Conjunctival peritomy is performed to allow for the 5.0-mm temporal scleral tunnel. Hemostasis is obtained using cautery. A 5.0-mm length incision at 350 μm depth is created parallel to, and 1 mm posterior to, the limbus temporally using a trifaceted, guarded diamond knife. Using a crescent blade, a deep lamellar pocket is dissected at about 80% depth into approximately 1 mm of clear cornea. Straight and curved stromal dissectors (e.g. Devers Dissectors, Bausch & Lomb, St Louis, MO or Melles Dissectors, DORC, Netherlands) are used to extend the lamellar pocket through and beyond the pupillary axis, from limbus to limbus. The most difficult aspect of creating the lamellar dissection is finding the right plane and making sure not to perforate anteriorly or posteriorly. The Devers dissectors used in creating this lamellar interface have semi-sharp tips with blunted sides which if advanced without significant force should maintain a plane and not perforate through the cornea. Melles has proposed performing this step of the surgery with air in the anterior chamber to create an 'air-to-endothelium interface' and thus an optical surface to help delineate the depth of dissection.[39] After the stromal pocket has been created limbus-to-limbus, additional Healon should be used to fill the chamber in preparation for resection of the recipient tissue.

After a satisfactory deep stromal pocket is created, a 2.8-mm keratome is used to enter the anterior chamber through the scleral tunnel at the proximal mark of the corneal circular template mark. Intracorneal, low profile, highly curved microscissors of surgeon's choice (i.e. Cindy scissors, Bausch & Lomb, St Louis, MO) are used to excise a posterior disk of the recipient cornea using the circular mark made on the corneal surface as a guide. The wound is extended to the full 5.0 mm. Utrata forceps are then used to remove the lamellar disk that is subsequently inspected for thickness and diameter. After the posterior disk has been removed, 10-0 nylon, interrupted, sutures are placed in the corneal wound to help maintain the anterior chamber while allowing a 3.0-mm opening. Using an irrigation/aspiration handpiece inserted through this opening, meticulous aspiration of all of the Healon viscoelastic is completed. Thereafter, the chamber is deepened and maintained using balanced saline solution (BSS) (Alcon laboratories, Dallax, TX.) and attention is turned to preparing the donor tissue.

It is also worth noting that nowhere in the procedure should Viscoat or other dispersive viscoelastic materials be used. The real concern is that complete removal of dispersive viscoelastic agents is very difficult and that any remaining viscoelastic in the anterior chamber, prior to inserting the donor disk, can adhere to the interface between the donor and the recipient cornea and result in non-adherence and subsequent dislocation of the graft. Healon or cohesive viscoelastics on the other hand are easily removed from the anterior chamber with careful and thorough irrigation and aspiration and have not contributed to any dislocations in the largest prospective study of DLEK.[11,12] The use of cohesive viscoelastic has in fact simplified many of the steps in all forms of EK surgery.[11,12,30,31]

PREPARATION OF THE DONOR CORNEA

We currently use donor tissue that has been precut with an automated microkeratome by a technician at the Lions Eye Bank of Oregon (Portland, OR). We have found that results have been comparable with surgeon-prepared tissue.[39] If a surgeon cuts the donor tissue himself, an artificial anterior chamber system such as the Moria ALTK artificial anterior chamber equipped with a microkeratome (Moria/Microtech Inc., Doylestown, PA) can be used to prepare the donor lamellar graft. The chamber is initially primed by injecting Optisol-GS (Chiron Vision, Irvine, CA) until a meniscus is

formed on the post. The standard corneal-scleral cap tissue received from an eye bank is coated with Healon on the endothelial side and placed onto the post of the artificial anterior chamber endothelial side down. Others have suggested placing the donor cornea epithelial side down onto the artificial anterior chamber to avoid compromising the endothelial cells;[41] this is not common practice in the large centers performing endothelial keratoplasty. The donor tissue is capped into place and more Optisol-GS injected into the artificial anterior chamber until a desired pressure is obtained. Using the sterile marker, a mark is made centrally onto the cornea as well as peripherally at the horizontal meridian.

In the case that manual lamellar dissection is to be performed, random and scattered marks can be made on the surface to be used as reference points to help in visualizing the depth of dissection. A Barron suction recipient trephine (Katena Products, Denville, NJ) of 0.5 mm larger diameter than the desired donor graft size is placed over the donor tissue, suction applied and trephination is carried out at approximately 60% depth. For example, if the original circular surface mark on the recipient cornea was 8.0 mm with the posterior disk of the same size resected, an 8.5-mm trephine should be used for this step. After the trephine is removed, the depth of the cut should be inspected. The crescent blade and stromal dissectors described above are then used to dissect a lamellar pocket at approximately 80% depth through the donor tissue. The lamellar dissection can also be initiated by using the trifaceted diamond knife set at 350 μm in the same fashion as described in preparing the recipient cornea.

In the case that an automated microkeratome (i.e. Moria, CBm, 300 μm) is to be used, the artificial anterior chamber should be pressurized by injecting Optisol. The pressure is verified to be at least 65 mmHg using a Barraquer tonometer (Ocular Instruments, Bellevue, WA). The epithelium is then removed using a Merocel surgical sponge (Medtronics Ophthalmics, Jacksonville, FL). The microkeratome is inserted onto its gear tract without the stopper in order to create a free cap. The corneal surface is then painted with a Merocel sponge soaked in Optisol, and the microkeratome cut made smoothly across the cornea.

After the lamellar cut is made with a microkeratome, the cut cap is inspected for the completion of the cut as well as for thickness. Its diameter is also measured to ensure that it is at least 1.0 mm larger than the planned graft size and thus allow for a 0.5-mm margin for error in centration of the punch (i.e. for an 8.0-mm graft, the cap should ideally be at least 9.0 mm in diameter). If the cap is not adequate in size, the surgeon can manually extend the lamellar dissection beyond the outer edge of the cut stroma using stromal dissectors. The circular outer edge of the exposed stromal bed of the donor cornea is accentuated with small dotted marks; this allows for better centration of the trephine in a later step. The stromal bed is dried using Merocel sponges, and the free cap replaced in the correct orientation using the horizontal mark as a guide. In the case where manual dissection of the donor graft is performed, the dissection should extend as far as the metal cap of the artificial anterior chamber that once more ensures a large enough margin of error for unplanned decentration.

The pedestal of the anterior chamber is slowly lowered while paying close attention to the contour of the cornea; to avoid trauma to the endothelial cells, the natural contour of the cornea must be maintained during this step of the surgery by gently injecting Optisol into the artificial anterior chamber as the pedestal is being lowered and the chamber depressurized. Once there is adequate separation between the pedestal and the metal cap, the edges of the tissue need to be freed from the artificial anterior chamber's metal cap with gentle nudging using the tip of closed forceps. Freeing of the cornea from the artificial anterior chamber is verified by ensuring no movement of the corneal-scleral tissue while the metal cap is rotated and then removed. The tissue is then gently and slowly removed from the pedestal allowing the cohesive Healon to fall away in one mass. Any residual Healon on the endothelial side of the donor cornea is carefully and gently washed off using Optisol. If Eyebank "precut" tissue is used, the donor cornea is placed endothelial-side down onto a sterile, lint-free surface vaulted on its scleral rim. The peripheral gutter of the microkeratome prepared cap is then accentuated using a sterile marking pen to aid in centering the trephination. The tissue is then placed endothelial side up onto a standard punch trephine block and a same size donor button is punched making sure to center the trephination using the earlier marks made on the donor cornea as a reference. A small linear ribbon of Healon is then injected onto the horizontal meridian of the donor tissue. Thereafter the tissue is folded, with the endothelial surface on the inside, into an asymmetric 'taco' shape being vigilant not to damage the endothelium—the fold should be asymmetric with the anterior lip of the folded donor button 40% of the full diameter and the posterior lip 60%.

DONOR GRAFT INSERTION AND ATTACHMENT

Any sutures previously placed in the 5.0-mm tunneled wound should be removed. The folded donor tissue is grasped using specialized forceps (i.e. Charlie insertion forceps) that are non-coopting to avoid crushing the tissue centrally. The tissue is then inserted into the anterior chamber with the 60% side of the 'taco' facing up. The insertion is accomplished in one swift move, placing the distal tip of the Charlie forceps all the way across the anterior chamber and with unremitting surveillance of the unfolding of the graft. It is not unusual for the anterior chamber to partially collapse as the forceps exit the wound. If this occurs, BSS should be injected through the paracentesis ports to deepen the chamber. In order to normalize the chamber depth, the scleral wound may need to be closed using interrupted 10-0 nylon sutures. At this juncture, the tissue typically opens partially with the 60% stromal side of the 'taco' already adhering to the recipient bed and the remaining 40% unfolding perpendicular to the iris plane. An air bubble can then be injected into the anterior chamber, between the two sides of the unfolding 'taco,' to aid in the opening and the self-adhesion of the donor button. Final positioning of the donor disk is done with a reverse Sinskey hook or equivalent instrument if necessary. The reverse Sinskey hook is inserted into the anterior chamber through one of the side-ports furthest away from the direction toward which the graft needs to be shifted. The hook is passed across the midline and engaged in the periphery of the graft while gently pushing the graft into position trying to avoid causing striae. This is more easily done if the anterior chamber is only partially filled with air as a complete air bubble hinders mobility of the graft. When the graft is positioned in the desired location, the anterior chamber is completely filled with a large air bubble and any interface fluid is swept out using a Cindy sweeper (Bausch & Lomb, St Louis, MO) or similar instrument of surgeon's choice to indent the surface cornea and sweep from centrally to peripherally in all quadrants. Using the reverse Sinskey hook or a similar instrument, the edges of the donor graft

are tucked under the peripheral flap of the recipient's uncut outer posterior corneal edge. This is done by gently pushing back the recipient posterior corneal lip and allowing the donor graft edge to fall into the gap created by the lamellar plane of the recipient cornea which extends beyond the cut circular diameter.

CONCLUSION OF THE PROCEDURE

After the wound is fully closed, knots buried, and conjunctiva is closed, the air bubble is fully removed and replaced with BSS. It is believed that when the air bubble is replaced by BSS, the natural endothelial pump function of the donor disk allows for adherence to the stromal bed. A collagen shield soaked in cefazolin, moxifloxacin, and dexamethasone is placed over the eye. Detailed description of the procedure can be found in original papers by Terry et al.[9,11,27]

SUMMARY

Over the last decade, the techniques used in endothelial keratoplasty have improved and evolved with many modifications simplifying and advancing EK surgery to be more widely accepted and utilized. This evolution has led to DSEK/DSAEK in which the easier approach to preparing the recipient cornea has helped catapult this technique to the forefront of EK surgery. However, DLEK/PLK remain excellent options for the patients who are at high risk for complications of DSEK/DSAEK surgery. With this in mind, it is important for the corneal surgeon treating patients with endothelial keratopathy to know and maintain the skills needed in performing DLEK/PLK and more importantly recognize the circumstances in which it is the preferred procedure in treating endothelial keratopathy.

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66 Descemet's stripping with endothelial keratoplasty (DSEK)

Marianne O. Price, Francis W. Price

INTRODUCTION

Descemet's stripping with endothelial keratoplasty (DSEK) has been one of the most important breakthroughs in transplant surgery in the last 30 years. Earlier iterations of endothelial keratoplasty, including Melles original posterior lamellar keratoplasty (PLK) technique and the closely related deep lamellar endothelial keratoplasty (DLEK) technique, simply did not provide as rapid visual recovery and were so technically difficult that few corneal surgeons were willing to perform them.[1] DSEK provides so many advantages compared with penetrating keratoplasty (PK) that the authors believe that all corneal surgeons should be performing it and patients are even demanding it.[1,2]

The most challenging aspects of the earlier PLK/DLEK technique were the manual recipient lamellar dissection and the excision of the posterior recipient stromal button using small curved scissors and trephine.[3] Melles greatly simplified his earlier procedure by describing a Descemetorhexis technique that merely involved stripping Descemet's membrane and dysfunctional endothelium from the host cornea.[4] The basic DSEK procedure can be further facilitated by employing a microkeratome to perform the donor lamellar dissection, a variation known as Descemet's stripping with automated endothelial keratoplasty (DSAEK).[2,5,6] Several eye banks now provide microkeratome pre-dissected donor tissue for DSEK.

SURGICAL TECHNIQUE

Surgical instruments to facilitate DSEK are available from multiple sources, including DORC International (Zuidland, the Netherlands), Moria (France), and Bausch & Lomb Surgical (St Louis, MO). Beginning the case with preparation of the donor tissue allows the surgeon to make sure the donor tissue is suitable for transplantation before opening the patient's eye.

DONOR TISSUE PREPARATION

Lamellar dissection of the donor tissue can be performed manually or with a microkeratome, or the donor tissue can be pre-dissected by the eye bank. In the USA it is difficult to obtain donor tissue less than 48 h from death to use because of required testing, so whole globes can seldom be used. Corneal/scleral rims should have a diameter of 16–17 mm to ensure firm and air-tight fixation on an artificial anterior chamber during dissection. Artificial anterior chambers are available from Bausch & Lomb, Moria, and Katena.

The donor tissue should be examined carefully to ensure there are no divots or cuts through the peripheral cornea to the limbus that might allow the tissue to slip or depressurize during the dissection. After mounting the donor tissue on an artificial anterior chamber, the center of the cornea should be marked with gentian violet to facilitate centering the tissue on the trephine block after the dissection.

Estimating the dissection depth can be a challenge with manual dissections. Melles found that filling the anterior chamber with air creates a reflection that helps the surgeon gauge the dissection depth.[7] Some surgeons utilize this technique, while others prefer to use tissue storage solution, balanced salt solution, or viscoelastic in the artificial anterior chamber to help protect the corneal endothelium.[8] However, use of anything other than air makes it harder to judge the dissection depth, because the depth can only be estimated by direct visualization of the anterior tissue, without direct feedback on the amount of residual tissue under the dissecting blade. If viscoelastic is used, it should be thoroughly removed prior to autoclaving the artificial anterior chamber, because byproducts can form that could be transferred to the next donor cornea and cause toxic anterior segment syndrome in subsequent cases.

Manual dissections can be performed in several ways. A small one-third depth incision can be made in the peripheral cornea and a series of curved dissecting blades of increasing length can be used to extend the dissection plane across the cornea (Fig. 66.1).

Some surgeons place a Barron suction recipient trephine over the donor tissue for trephination to approximately 60% depth and then extend a dissection plane across the tissue. With either method the surgeon should aim for approximately 80% dissection depth. If the posterior donor button is too thin it will be difficult to manipulate and more prone to develop wrinkles that can be difficult to remove when applanated against the recipient cornea. Also, extremely deep donor dissections are more likely to damage the endothelium.

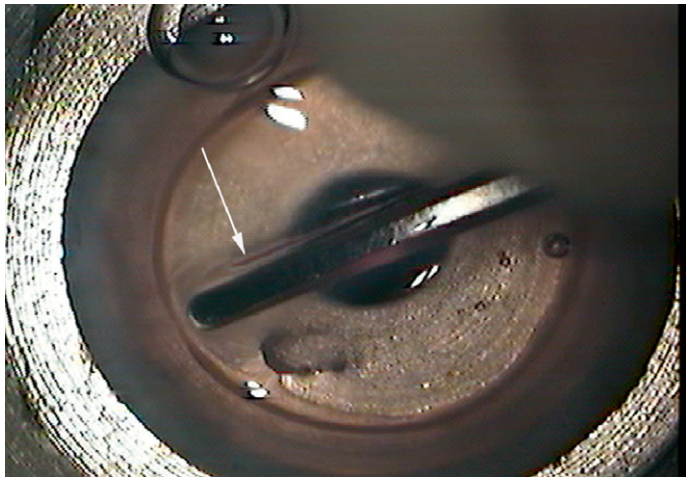


Figure 66.1. Manual lamellar dissection of a donor corneal/scleral rim mounted on an artificial anterior chamber. A series of three curved blades of increasing length are used to extend the dissection plane across the donor cornea. Air in the anterior chamber creates a reflection (arrow) that helps indicate the depth of the dissection.

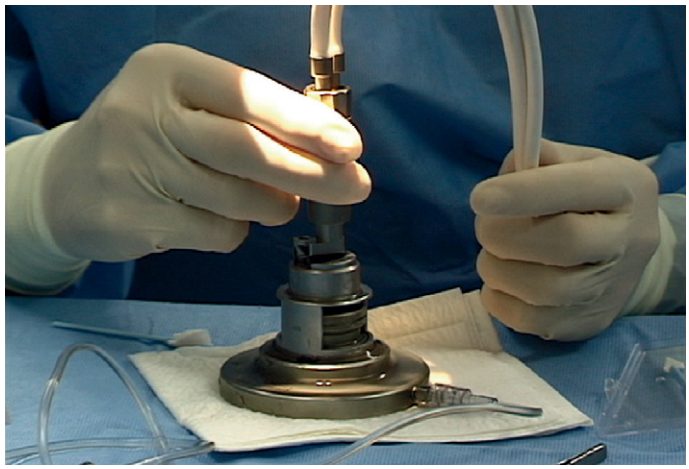


Figure 66.2. Microkeratome dissection of a donor corneal/scleral rim mounted on an artificial anterior chamber.

With microkeratome dissection (Fig. 66.2), the surgeon should aim for posterior donor button thickness of 0.10–0.18 mm. Depth plates (head sizes) are available that provide nominal dissection depths of 250, 300, 350, and 400 µm. To guide selection of an appropriate dissection depth, the donor thickness can be measured using ultrasonic pachymetry if the artificial anterior chamber is pressurized with viscoelastic, balanced salt solution, or tissue storage solution. Donor tissue thicknesses vary substantially, but typically range from 0.45 to 0.70 mm after epithelial removal for donor corneas stored in tissue storage solution, as provided by USA eye banks. Posterior thicknesses of less than 0.10 mm after dissection should be avoided because vital staining indicates that the endothelium can be damaged by extremely deep dissections (Craig Fowler, personal communication).

After dissection, the donor tissue is carefully removed from the artificial anterior chamber and placed endothelial side up on a standard punch trephine block, where it is punched to a diameter that has been selected based on the width of the recipient's cornea. The donor tissue can be covered with tissue storage solution while the recipient's eye is being prepared.

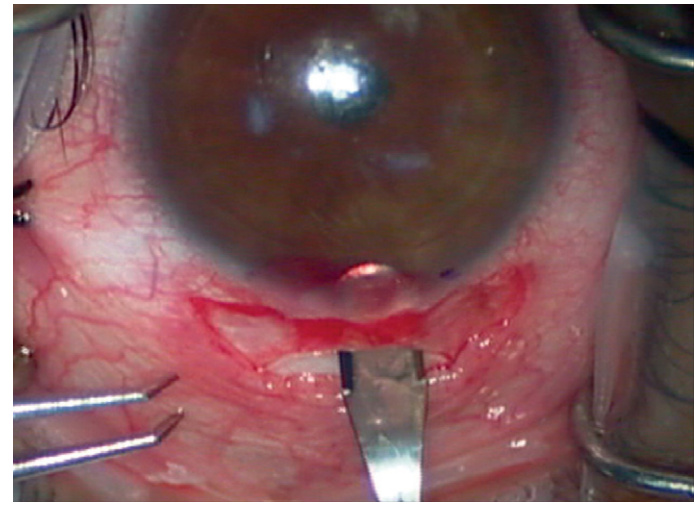


Figure 66.3. Temporal scleral tunnel incision in the recipient eye.

RECIPIENT PREPARATION

DSEK is often performed with topical anesthesia and monitored intravenous sedation. Topical anesthesia may consist of proparacaine hydrochloride eye drops and application of pledgets soaked in 2% xylocaine to the conjunctiva at the site where the incision will be made. However, local anesthesia (retrobulbar or peribulbar block) is generally preferable for the surgeon's first several cases. With local anesthesia it is important to apply a pressure device, such as a Honan balloon (the Lebanon Corporation, Lebanon, IN), to soften the eye prior to surgery, because back pressure from periorbital swelling can lead to forceful shallowing of the anterior chamber while the donor tissue is being inserted. In some cases backpressure can even push the donor tissue back out of the eye.

With the patient in a supine position, the horizontal corneal diameter of the recipient eye is measured with calipers to guide the selection of an appropriate donor tissue diameter. Placement of traction sutures can help stabilize the eye during surgery.

A 5-mm temporal clear corneal or scleral tunnel incision is made in the recipient eye (Fig. 66.3). A properly constructed scleral tunnel incision can form a watertight seal, allowing the surgery to be performed without the use of any sutures, and it provides an extra margin of safety because it can be closed quickly if the patient coughs or develops a suprachoroidal hemorrhage during the procedure. Temporal placement of the incision facilitates donor tissue insertion because the corneal diameter is longest in the horizontal direction. In addition, temporal placement preserves the superior conjunctiva for future glaucoma surgery, should that ever become necessary.

If the recipient epithelium is hazy or scarred it can be removed, and this will usually improve the view into the eye. The trephine used to punch the donor button can also be used to lightly mark the surface of the recipient cornea to delineate the area for Descemet's membrane removal. Descemet's membrane is then scored in a circular pattern along the perimeter of the area to be removed, using a modified Sinskey hook (Fig. 66.4). The recipient endothelium should only be stripped from the area that will be covered by donor tissue, because any stripped areas not covered with donor tissue will become edematous. To prevent this from happening, some surgeons score an area somewhat smaller than the planned donor diameter. Trypan blue can be introduced into the anterior

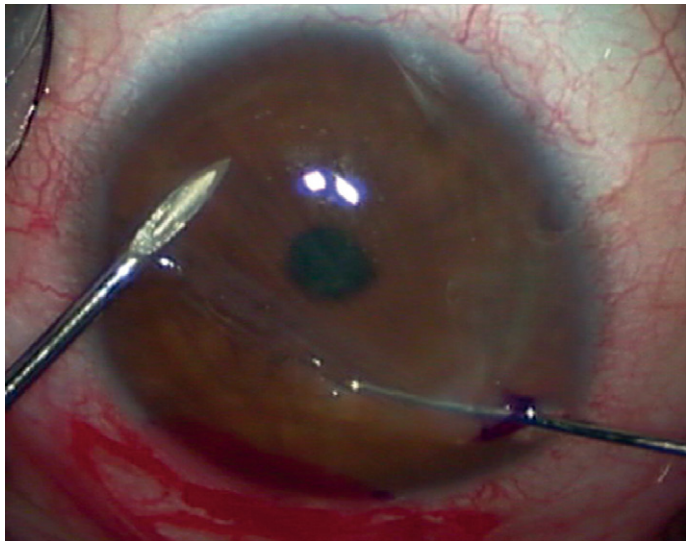
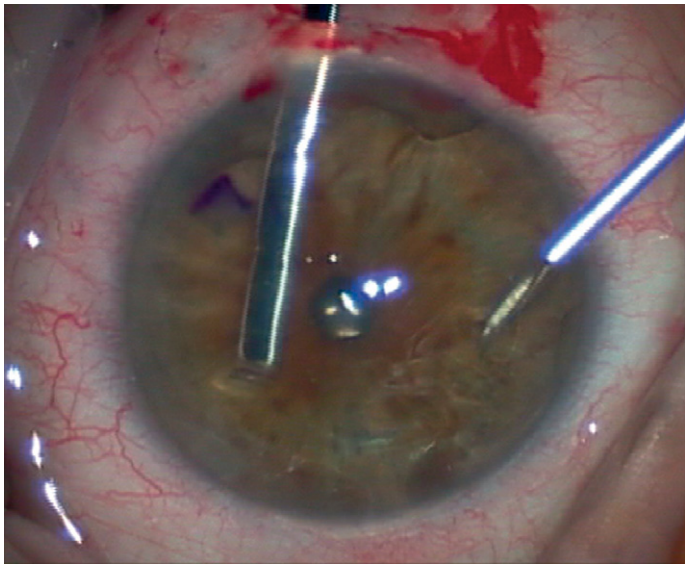
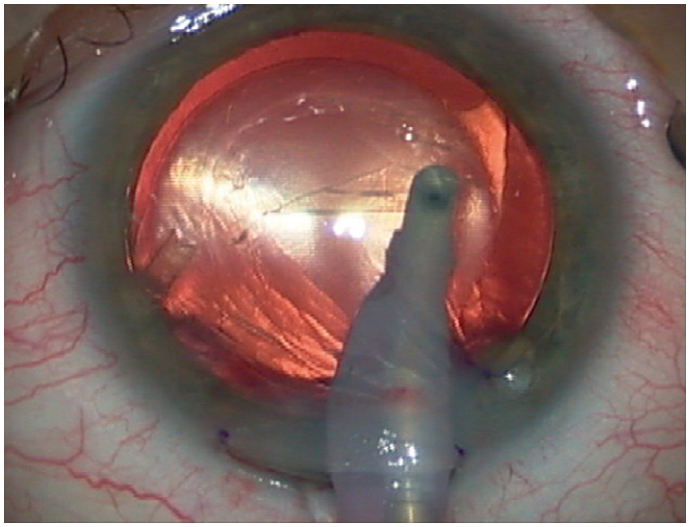


Figure 66.4. Scoring of Descemet's membrane, with continuous infusion of balanced salt solution to maintain the anterior chamber.



A



B

Figure 66.5. *A,* Stripping of Descemet's membrane with a stripping instrument; *B*, Stripping of Descemet's membrane with an infusion and aspiration device.

chamber to improve membrane visualization during the stripping procedure. It preferentially stains exposed membrane.

The far edge of Descemet's membrane is grasped with a stripping instrument (Fig. 66.5, *A*) or infusion/aspiration tip (Fig. 66.5, *B*) and carefully peeled off and removed from the eye. The membrane can be spread on the eye to determine whether removal was complete. Sometimes the membrane fragments must be removed in pieces. During the scoring and stripping steps, the anterior chamber can remain formed by injecting viscoelastic or by intermittent or continuous infusion of balanced salt solution or air. If viscoelastic is used, it must all be completely removed before inserting the donor button because residual viscoelastic will impair donor adherence.

DONOR IMPLANTATION

A small drop of cohesive viscoelastic is placed in the center of the donor button on the endothelial side, and the posterior tissue is gently lifted away from the anterior tissue. The posterior button can be folded over on itself like a taco, with the endothelial side inward (Fig. 66.6). Most surgeons overfold the tissue with approximately 60% on the anterior side and 40% posterior. Although this exposes some peripheral endothelium to potential damage during insertion, it makes it easier for the posterior side to sweep across and unfold in the correct orientation after placement in the eye. This is particularly important when the anterior chamber is relatively shallow. The folded donor taco is gently grasped with forceps and inserted into the recipient eye (Fig. 66.7). Several companies make forceps that only compress the tissue at the tip, which should help minimize endothelial damage.

Another way to insert the donor tissue is to pull the folded tissue into the eye from an incision 180° away using a suture.[9] The tissue can also be laid endothelial side upward on a funnel glide which curls the tissue into a cylindrical shape as it is pulled into the eye with a small forceps.[10] An advantage of the latter two methods is that the tissue automatically unfolds stromal side up as it enters the anterior chamber. After the donor tissue is inserted, the anterior chamber is inflated by injecting air or balanced salt solution, which allows the posterior portion of the donor taco to unfold (Fig. 66.8). The anterior chamber is then completely filled with air to firmly press the donor tissue up against the recipient cornea.

While the anterior chamber is filled with air, the surface of the recipient cornea is massaged to help center the donor button and move any entrapped fluid out of the donor–recipient interface (Fig. 66.9). A variety of instruments have been utilized for this maneuver, but use of a Lindstrom LASIK roller is recommended to help minimize damage to the recipient epithelium.[6] Four small incisions can be made in the recipient cornea down to the graft interface to help drain any residual fluid trapped between the donor and recipient (Fig. 66.10).[6] Most surgeons remove some of the air after 8–10 min to prevent pupillary block,[6] although some leave the anterior chamber completely filled for 1–2 h.[5] A residual air bubble approximately the same diameter as the donor button can then be left in the eye. At the end of surgery, antibiotics, steroids, and nonsteroidal anti-inflammatory (NSAID) medications are applied to the treated eye. Some surgeons have the patient lie face-up in the recovery area for 30–60 min after the procedure and/or instruct them to lie

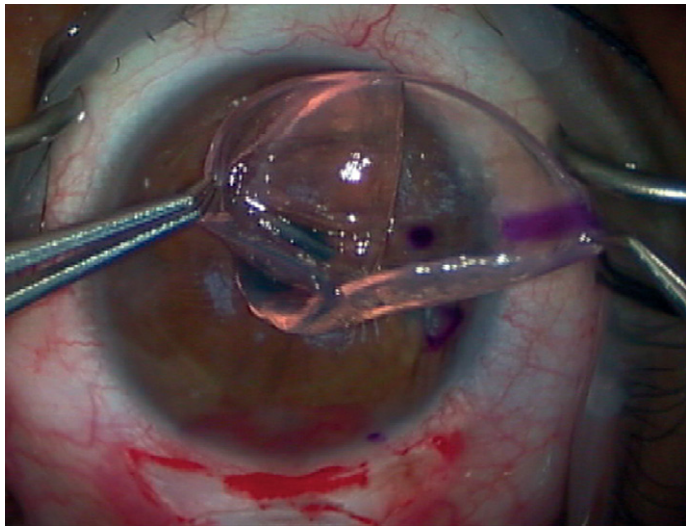


Figure 66.6. Separation of the posterior donor tissue from the anterior tissue, and folding it over a drop of viscoelastic into a taco configuration.

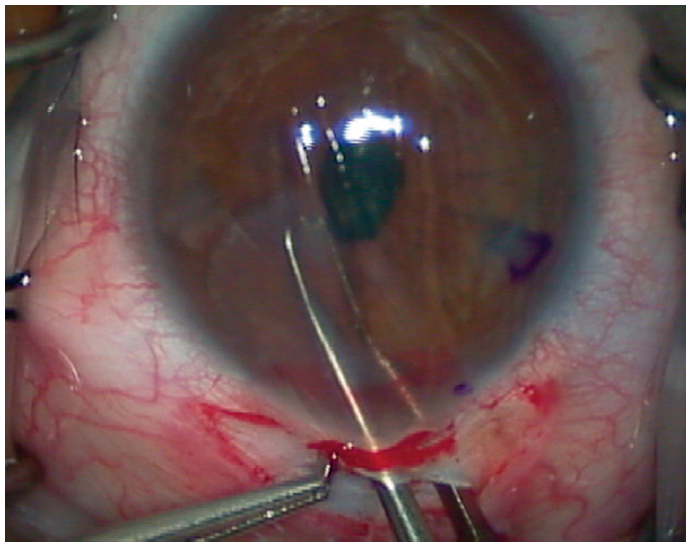


Figure 66.7. Insertion of the folded donor tissue into the recipient eye using forceps that only compress the tissue at the tip.

face-up as much as possible for the first postoperative day so that the residual air bubble can continue to press the donor tissue against the recipient cornea.

MODIFIED TECHNIQUE FOR ANIRIDIC APHAKIC EYES

Eyes lacking lens and iris tissue pose a special challenge because there is no barrier to prevent donor or recipient tissue from falling back onto the retina. If no guttata are present, the recipient Descemet's membrane and endothelium can simply be left in place, rather than run the risk of dropping any pieces back into the posterior segment.[11] Also, the donor tissue should be secured at all times. During donor insertion, the trailing end of the donor taco can be held in the scleral tunnel incision while an anchor suture is placed in the anterior portion of the donor taco, to secure it to the recipient cornea (Fig. 66.11).[11] The anchor suture can be removed after the eye is totally filled with air. There is no need to remove

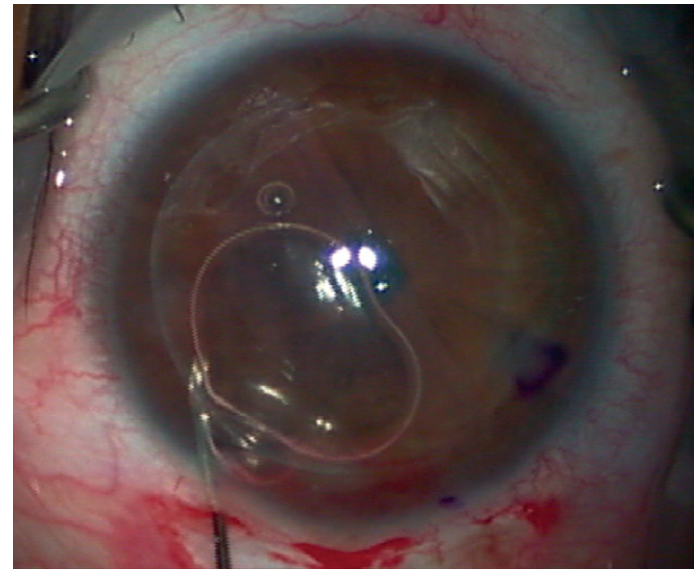


Figure 66.8. Injecting air into the anterior chamber to unfold the donor taco and press it firmly against the recipient cornea.

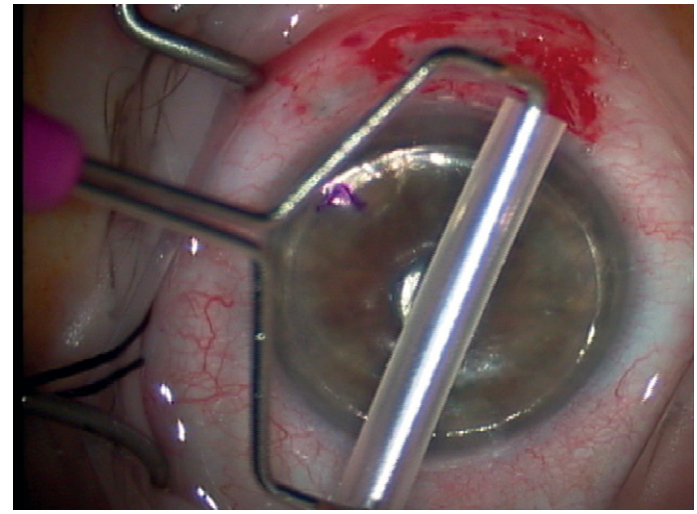


Figure 66.9. Massaging the surface of the recipient cornea with a Lindstrom roller to help center the donor tissue and remove fluid from the donor–recipient interface, with the anterior chamber completely filled with air.

some of the air to prevent pupillary block in eyes with congenital or traumatic aniridia.

MODIFIED TECHNIQUE TO RESTORE CLARITY TO FAILED PENETRATING GRAFTS

DSEK can restore clarity to a penetrating graft that has failed from endothelial decompensation and it will usually provide an easier postoperative course for the patient compared with a PK regraft.[12] In a healed PK wound, the principal areas of strength are the scarring that occurs at Bowman's and at Descemet's membrane. To preserve as much of the wound strength as possible, Descemet's stripping can be omitted, if the surgeon is sure there are no guttata or other abnormalities present that might impair postoperative visual acuity. Otherwise, the procedure is similar to performing DSEK on a virgin eye.

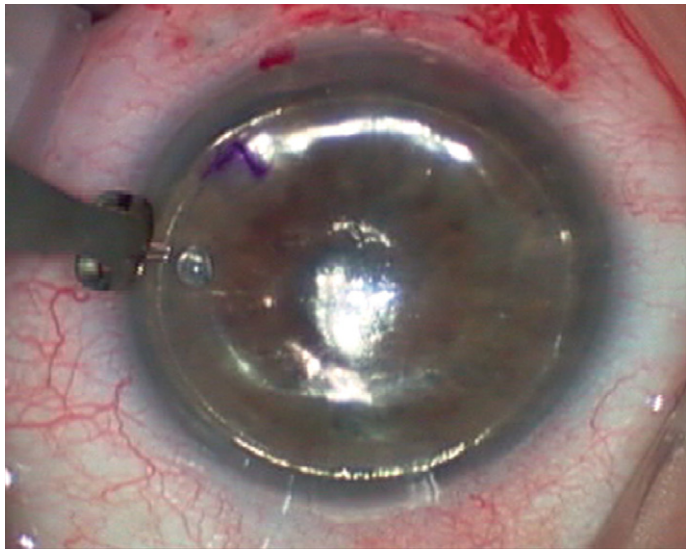


Figure 66.10. Making small peripheral corneal incisions to release any residual fluid entrapped at the graft–recipient interface, while the anterior chamber is completely filled with air.

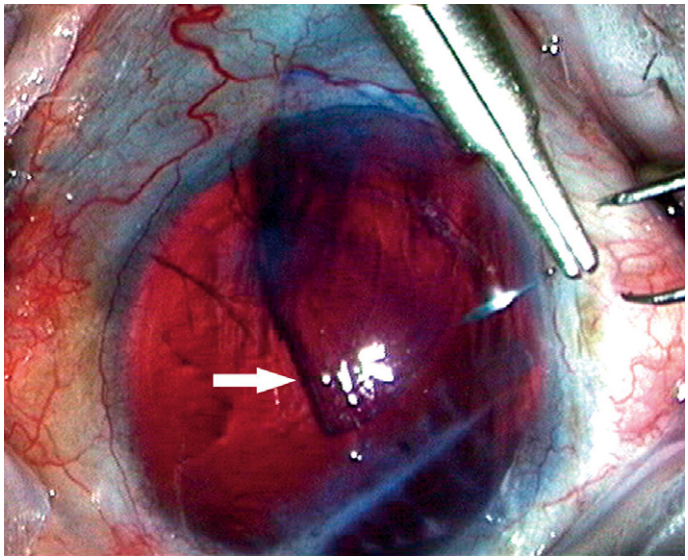


Figure 66.11. Securing the peripheral anterior edge of the folded donor tissue to the recipient cornea with a temporary anchor suture in an eye that was aniridic and aphakic following traumatic injury.

COMBINED PROCEDURES

Other intraocular surgeries, such as phacoemulsification, intraocular lens (IOL) implantation, IOL exchange, secondary IOL implantation, pars plana vitrectomy, or anterior vitrectomy can be combined with DSEK.[6] However, it is often preferable to perform these other procedures beforehand as a separate procedure. In particular, performing cataract extraction and IOL implantation prior to DSEK helps deepen the anterior chamber and facilitates unfolding the donor taco. With standard PK, the opposite sequence is usually preferable—cataract extraction and IOL implantation are typically delayed until after the final refractive outcome has been determined because refractive outcomes are so unpredictable after PK. DSEK has the advantage of being more refractive-neutral.[1]

WHAT TO EXPECT AFTER DSEK/DSAEK?

Patients typically instill topical antibiotics for a week and topical corticosteroids four times daily for several months. Although corticosteroids delay wound healing, this is of minimal concern with the small DSEK incision, so many surgeons maintain pseudophakic DSEK eyes on once or twice daily dosing with topical corticosteroids indefinitely to prevent graft rejection, unless the patient is a steroid-responder.

The most frequent postoperative complication with DSEK/DSAEK is that sometimes the donor tissue detaches in the early postoperative period (usually 1 day to 1 week after surgery). If this happens, air can be injected into the anterior chamber to again firmly press the donor tissue against the recipient cornea.[6] A complete air fill is often maintained for 1–2 h when the donor tissue needs to be reattached.

DSEK/DSAEK requires much less manipulation of the recipient cornea and anterior chamber, compared with the earlier PLK/DLEK procedure, and this helps minimize intraoperative and postoperative complications. For example, we found that PLK/DLEK could cause cataracts when performed in phakic eyes.[2,13] Also, the two hand-dissections required in PLK/DLEK provide more opportunity for graft–recipient interface haze or other problems to interfere with visual recovery.[14–16] Wrinkles in the graft can also be a problem and are potentially more likely with PLK/DLEK, because the graft tissue can become compressed if the hand-cut recipient bed is somewhat undersized or the graft is not well-centered in the bed.[17] Finally, perforation of the recipient cornea sometimes occurs during the PLK/DLEK lamellar dissection, requiring intraoperative conversion to PK.[8] This is not an issue with DSEK/DSAEK because the recipient cornea is not dissected.

A major advantage of the DSEK/DSAEK technique is that it does not significantly alter corneal topography and is essentially a refractive neutral transplant procedure. For example, in a series of 100 consecutive DSEK cases and a similar series of 100 consecutive DSAEK procedures, mean refractive cylinder was 1.5 D both before and 6 months after surgery.[2] Mean spherical equivalent refraction also changed less than 0.5 D after DSEK/DSAEK.[2] In contrast, mean refractive cylinder of 4 D is common after PK,[18,19] and 10–15% of PK patients usually require hard contact lenses for best vision. Unfortunately, hard lenses can be difficult to manage, especially for older patients.[20] Subsequent surgical interventions, such as relaxing incisions to correct astigmatic errors, are frequently performed after PK,[21,22] but rarely needed after DSEK or DSAEK.

Visual recovery is relatively rapid and predictable after EK compared with PK, and seems to be faster with DSAEK compared with DLEK or DSEK, probably because it produces the smoothest donor and recipient interfaces. For example, one month after surgery, mean visual acuity was approximately 1 line better in a series of 100 DSAEK eyes compared with a series of 100 consecutive DSEK eyes.[2] By 3 months after surgery, mean visual acuity was equivalent for the DSEK and DSAEK procedures.[2] By 6 months after surgery, 69–77% of DSAEK eyes achieved 20/40 vision in two case series.[2,5] By comparison, visual recovery after DLEK is somewhat slower, taking 12–18 months.[23] In a series of 100 consecutive DLEK cases, 49% of the eyes achieved 20/40 vision within 6 months of surgery.[8]

The average patient age is around 70 years in most DSAEK, DSEK, and DLEK series, so retinal problems limit some patients' visual

potential.[2,5,8] When eyes with documented preoperative retinal or amblyopia problems were excluded from the analysis, 80% of DSAEK eyes achieved 20/40 visual acuity within 6 months of surgery and none had vision worse than 20/80.[2] In contrast, after PK, anisometropia can prevent 10–20% of the treated eyes from achieving functional vision.[21] Younger DSEK/DSAEK recipients were significantly more likely to achieve better postoperative visual acuity than older recipients even after eyes with documented retinal problems were excluded ($p = 0.001$).[2] Interestingly, although DSEK/DSAEK increases central corneal thickness because some donor stroma is implanted without removal of any recipient stroma, corneal thickness does not have a statistically significant correlation with postoperative Snellen acuity as measured using a Snellen chart in a darkened room.[2]

DSEK and DSAEK provide significant advantages for the patient compared with PK. Perhaps the most significant advantage of an EK procedure is that it reduces the risk of losing the eye. Whereas the eye is completely open for part of the PK procedure, EK can be performed through a small scleral tunnel incision, which can be easily closed should the patient cough or develop a suprachoroidal hemorrhage. Also, a healed PK eye never fully regains the strength of a virgin eye and remains at increased risk of loss from traumatic injury for the remainder of the patient's life.[24,25] In contrast, EK maintains most of the structural integrity of the eye.

EK should also minimize if not eliminate the risk that ocular surface complications will interfere with recovery. In a series of over 1800 PK surgeries, ocular surface complications were responsible for 25% of the graft failures in the first 5 years after surgery.[26] PK severs the corneal nerves leaving the central cornea neurotrophic and susceptible to dryness, epithelial defects, and infection. PK also requires prolonged presence of corneal sutures, which can provide a path for infection as they loosen. In contrast, EK preserves most central corneal innervation and does not require any sutures.[6] These features make EK particularly well suited for regions of the world where sanitation challenges increase the risk of infection and where transportation challenges make it difficult for patients to return quickly if they develop a loose suture.

The risk of graft rejection also seems to be lower with EK procedures compared with PK and this may be related to the fact that EK patients are often maintained indefinitely on low dose topical steroids.[27] Whereas PK patients are often taken off topical steroids to help accelerate wound healing and prevent cataract formation, rapid wound healing is less of a concern with EK because the incision is relatively small. Also, most EK patients are pseudophakic, so that eliminates the concern that long-term topical steroids can induce cataract formation.

DSEK/DSAEK has improved the risk/benefit ratio of corneal transplants so substantially that increasing numbers of potential candidates are now choosing to have a transplant. When PK was the only option, some patients who had experienced the lengthy PK recovery period in one eye never wanted to have it done in their second eye. Also, many patients preferred to postpone a PK until after retirement because the lengthy recovery would severely impair their ability to work. In contrast, in the authors' experience, many DSAEK patients request to have their second eye treated within a month of having DSAEK performed on the first eye, and many Fuchs' patients are choosing to have DSAEK performed before the glare and visual impairment become so disabling. In fact, many Fuchs' patients are choosing to have DSAEK one or even two decades sooner than they would have had PK, and this is increasing the demand for donor corneas.

HOW CAN THE TECHNIQUE BE IMPROVED?

Endothelial keratoplasty techniques continue to evolve, with efforts being directed toward achieving a smaller host incision, smoother donor interface, and ex vivo generation of corneal endothelium.

Various methods of inserting the donor tissue through a smaller incision are being evaluated. The effect of incisions smaller than 5 mm on long-term endothelial cell survival remains to be determined.

Regardless of the method used to perform the donor lamellar dissection, the donor interface is not as smooth as the recipient stromal surface exposed after stripping Descemet's membrane. Work is underway to optimize femtosecond laser parameters to produce smoother posterior lamellar dissections.[28,29] The precision and flexibility of the femtosecond laser should potentially allow more accurate control of donor thickness and provide the ability to match the contour of the donor dissection to the posterior corneal curvature of the recipient. An alternative approach to achieve a smoother donor interface is to remove donor Descemet's membrane with attached endothelium for implantation into the recipient eye.[30] The principal challenge is that the membrane and single cell layer are fragile and can be easily torn or damaged. Also, the thin membrane can develop intractable wrinkles when pressed against the recipient cornea. Innovative techniques and insertion instruments are being developed to address these challenges.[31–33]

Ex vivo generation of corneal endothelium could bypass the need for better donor dissection techniques and allow more patients to benefit from a transplant despite the chronic worldwide shortage of donor corneas.[34,35] Cultured endothelium has been successfully derived from endothelial cells harvested from donor corneas. Eventually, it may be possible to generate autologous corneal endothelium from recipient adult stem cells. Autologous endothelium would eliminate graft rejection concerns and the need for prolonged corticosteroid therapy to prevent rejection.

CONCLUSION

DSEK/DSAEK has significantly increased the benefits and reduced the risks of transplantation for patients with endothelial dysfunction. The relatively rapid and predictable visual recovery and minimal postoperative restrictions are increasing the demand for corneal transplants.[36] Our next challenge is to find ways to increase the supply of high-quality donor tissue and accelerate development of ex vivo derived sources to meet this need.

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67 Microkeratome-assisted posterior lamellar keratoplasty

Suy Anne R. Martins, Guillermo E. Noguera, Ashley Behrens

Corneal endothelial cell failure is one of the leading causes of corneal visual loss in the USA and other industrialized countries of the world.[1–3] This fact may be of importance in the selection of the procedure to be performed, in developed and developing countries, to correct the endothelial cell failure.

Since the 1930s, penetrating keratoplasty (PK) has been the procedure of choice to manage corneal disorders. Despite the advantages of a lamellar procedure—i.e. less risk of intraocular complications and allograft rejection—penetrating keratoplasty has proved to be a technique preferred by most surgeons around the world, and for many years has been the only treatment for visual impairment resulting from corneal endothelial cell decompensation. Endothelial cell loss, pleomorphism, and polymegethism may progress following PK and result in late graft corneal failure.[4] Lamellar keratoplasty (LK) may avoid many of these problems, but it is limited by delayed epithelialization, persistent epithelial defects, difficult surgical technique, and graft–host interface haze and vascularization.[5] However, in the 1960s, Malbran described the 'peeling-off' technique, in which the recipient cornea of patients with keratoconus was removed by applying traction to the partially dissected cornea overlying the cone.[6–8] Other authors describe a surgical technique for LK that consists of a partial trephination of the anterior corneal stroma, and a single plane dissection of the recipient stroma. It is often demanding to meticulously dissect the recipient stroma and by performing a PK, one is able to avoid the challenges of a lamellar dissection.[9]

The concept of deep LK is not new. Previous published reports have confirmed the advantages and limitations of LK.[5,10–16] and it has been the focus of intense study over the past decade, with an acceleration of technique modifications over the past 4 years. Since at least 1998, there have been two separate approaches to deep LK. Several surgeons resurrected a technique described long ago by Polack and others,[17] whereby an anterior flap was created either manually or with a microkeratome, the flap was retracted, and the posterior recipient stroma was trephined out. The tissue was replaced with a donor posterior lamellar button and the overlying flap was sutured into place.[18–21] This approach is attractive to the corneal surgeon because it required only familiar surgical skills and promised a smooth stromal interface by means of a microkeratome cut.

PENETRATING KERATOPLASTY

Penetrating keratoplasty (PK) is the most common and successful tissue transplantation worldwide. For over 100 years, it has been the standard of care for certain corneal diseases that cause visual impairment.[22,23] The total number of cases of corneal transplants with reported recipient diagnoses in the USA in the year 2000 was 31 532. Likewise, the leading indications for PK have changed over the years. Before the mid-1970s, keratoconus and regrafts were the primary indications for corneal transplants,[24,25] whereas bullous keratopathy has become the leading cause for PK, with the advent of cataract extraction and placement of intraocular lenses (IOLs).[26–31] Fuchs' dystrophy, keratoconus, corneal scarring, failed graft, and aphakic bullous keratopathy followed pseudophakic bullous keratopathy as the other major indications for PK.[31] Remarkable progress has been achieved in corneal surgery during the last century that include surgical techniques, tissue storage, and immunosuppression.[1,32]

PK has become a safe and effective procedure but it is sometimes complicated by high and/or irregular astigmatism,[1,33,34] insufficient wound healing,[34,35] prolonged recovery time, and tissue rejection.[36,37] Ing et al[4] showed a decline in endothelial cell count after PK in a large-scale study, from mean cell counts of 2467 cells/mm^2 at 2 months, to 1958 cells/mm^2 at 1 year and 960 cells/mm^2 at 10 years. This endothelial cell data is comparable to that found in other studies.[1,4,38–41] Furthermore, risk of suture-related problems,[42] and other interface complications[43] are associated with PK.

The major clinical complication between 10 and 15 years after keratoplasty is graft failure, predominantly caused by late endothelial failure.[44] Graft failure after PK can be defined as an irreversible loss of graft clarity due to endothelial cell failure.[45] By 2000–2001, Kang et al reported that failed grafts were the leading indication for PK.[31] This trend has also been observed in other centers and Sugar reported that failed grafts surpassed other indications for PK

at both of their institutions for the last 100 cases that they each performed in the 1990s.[46]

Each year, the Eye Bank Association of America (EBAA) reports statistics on corneal transplant activity in the USA. Statistics from the past decade indicate that there were fewer corneal transplants performed in the USA in 2000 (33 260) than in 1990 (36 037).[47] The decrease in the number of corneal transplants performed in the USA today, compared with 10 years ago, invites the question of what factors are affecting the demand. Has the need (or clinical indications) for corneal transplantation decreased, e.g. less traumatic techniques of phacoemulsification with a resulting decline in the prevalence of pseudophakic corneal edema or a transition to posterior lamellar keratoplasty techniques?

CLASSIFICATION OF CORNEAL TRANSPLANTATION ACCORDING TO THE REPLACED STRUCTURE

The popularity of lamellar procedures has been increasing in recent years as highlighted in the preceding chapters. One of the factors is the development of better instrumentation for the surgery: easier to use and safer microkeratomes, and the introduction of femtosecond lasers for lamellar dissection. In parallel to these advances, new variants of corneal transplantation have been proposed, several lamellar keratoplasty surgical techniques have been developed, modified or improved, including microkeratome-assisted anterior and posterior lamellar keratoplasty,[20,21,48,49] anterior lamellar keratoplasty using air-dissection or visco-dissection,[14,16] sutureless posterior lamellar keratoplasty,[48,50,51] LASIK for post-keratoplasty astigmatism,[52] and excimer laser-assisted keratophakia for keratoconus or to manage complications after LASIK.[53]

We summarize below some popular types of lamellar corneal transplantation according to the replaced structure:

1. Anterior lamellar keratoplasty (ALK): In this procedure the superficial corneal layers are removed leaving intermediate and posterior stroma intact.[12,49–53]
2. Deep lamellar keratoplasty (DLK): Resection of the corneal stroma, leaving either minimal or no residual posterior stroma—only Descemet's membrane.[10,11,14–16]
3. Posterior lamellar keratoplasty (PLK): Consists of removing posterior stroma, Descemet's membrane, and the damaged endothelial cell layer leaving superficial corneal layers including anterior stroma intact.

In PLK a graft comprising posterior stroma, Descemet's membrane and a healthy endothelial cell layer of suitable dimensions is placed in the recipient bed of the cornea. Several approaches have been reported to achieve this form of transplantation. Deep lamellar endothelial keratoplasty (DLEK), and a variation of this technique called Descemet's stripping endothelial keratoplasty (DSEK) are currently the most popular techniques.[9,13,48,50]

POSTERIOR LAMELLAR KERATOPLASTY (PLK)

The PLK technique for endothelial keratoplasty (EK) was first introduced by Tillet several decades ago.[54] However, starting from this concept, two separate PLK techniques evolved: one which comprises his original open-sky, hinged flap approach and another which changed the approach such that the recipient's anterior chamber is entered from a smaller curvilinear incision. The former is commonly named microkeratome-assisted PLK (MAPLK, also called endokeratoplasty or endothelial lamellar keratoplasty) while the latter is designated deep lamellar endothelial keratoplasty (DLEK).

Recently, PLK has undergone some modifications, and published reports on several small series suggest advantages over standard PK.[55–58] In this surgical procedure there is a selective corneal endothelial cell layer replacement that reduces or eliminates surface incisions or sutures.[55,56] In addition, rejection episodes may be lower.

Lamellar keratoplasty approaches have been successful in the treatment of anterior corneal pathology for over 100 years.[59–61] However, only relatively recently have these lamellar techniques been applied to the replacement of the posterior stroma and the endothelium and gained renewed widespread interest.[4,10,11,13–16,48,50,55–58]

The concept of a scleral-limbal approach to endothelial keratoplasty was first described by Ko et al[57] in 1993. Melles et al brought selective endothelial keratoplasty to fruition with the first human limbal approach in 1998.[62] Melles had the insight to solve the problems associated with corneal sutures in transplantation by substituting intraocular air to support the tissue.[12] This critical breakthrough began the transformation of modern endothelial surgery. The procedure was named posterior lamellar keratoplasty (PLK), and this was a name that was also being used by many surgeons using the 'flap' technique of endothelial replacement surgery.[63]

SCLERAL-POCKET INCISION APPROACH

As outlined in earlier chapters, the initial technique of Melles et al[55] involved a 9-mm superior incision and use of an air bubble for recipient tissue dissections and resections, as well as donor placement and attachment. However, in the absence of viscoelastic use, the PLK procedure was technically difficult to the extreme.[12,62,64–66]

Terry and Ousley established a USA prospective study of endothelial keratoplasty to broaden its scientific validity with a large prospective database.[56] They performed the first USA endothelial keratoplasty in March 2000, using a highly cohesive viscoelastic to stabilize the anterior segment and make the surgery easier. They renamed this procedure as deep lamellar endothelial keratoplasty (DLEK). The essential surgical steps in this procedure have been fully outlined in a preceding chapter.

In 2002, Melles and associates further developed a modified approach for a small-incision PLK technique.[50] They were able to reduce the incision size to 5 mm by folding the tissue before insertion. Their single case report showed proof of concept for a folded graft to clear the cornea, but the resultant endothelial cell count was considerably less than his prior large-incision series. A 5.0-mm scleral tunnel incision was made, and a stromal pocket was dissected across the cornea, just above Descemet's membrane, at a visually controlled depth.[65] Then, trypan blue 0.06% (VisionBlue, DORC International, Zuidland, The Netherlands) was diluted 1:6 with balanced salt solution and injected into the stromal pocket to stain the stromal interface. With an 8.5-mm punch trephine, an indentation was made in the corneal surface epithelium to outline the size of the posterior lamellar disk that was to be excised. Custom-made curved microscissors were used to excise an 8.5-mm diameter recipient posterior lamellar disk. In a whole donor globe, obtained less than 48 h after death, a deep corneal pocket was dissected at 80% of stromal depth.[65] The corneoscleral rim was excised from the globe, and an 8.5-mm diameter posterior lamellar

disk was trephined (endothelium to epithelium). After covering the donor endothelial surface with a viscoelastic material, the posterior lamellar disk was folded with the endothelium at the inside, using a custom-made inserter. After removing all air from the eye, the donor posterior disk was positioned into the recipient anterior chamber. After unfolding the posterior lamellar disk, it was positioned in the recipient posterior opening without suture fixation. The anterior chamber was then completely filled with air, and after 5 min all air was exchanged by balanced salt solution. The disk was found to keep its position by the adherence of the stromal tissue at the donor-to-host interface, and/or the negative stromal pressure created by the donor endothelial pump. Because no sutures are used and the tissue is transplanted through a scleral tunnel incision, the surgically induced astigmatism may be minimized, suture-related complications eliminated, and the risk of wound dehiscence reduced.

However, due to the high level of skills to perform these surgeries, DLEK has been the subject of several investigations and modifications over the past 6 years. Several corneal surgeons have performed large numbers of DLEK procedures and sufficient data is available. On average, best corrected visual acuity (BCVA) is 20/48 at maximum 2-year follow-up.[55,67–69] Melles et al reported that all patients operated on with the initial PLK procedure who did not have concomitant ocular disease had a BCVA of 20/30 or better; and several had 20/20 (Netherlands Institute for Innovative Ocular Surgery, unpublished data). Similarly, these same studies also showed that DLEK yields minimal postoperative astigmatism, on average, of 1.46 D. One study showed an average postoperative spherical equivalent of –0.369 D at 1 year.[55] Postoperative endothelial cell density averages 1790.5 cells/mm^2 at 36 months at a maximum of 3 years postoperatively.[55,67–69] Clearly, DLEK specifically has potential benefits, mostly due to its lack of corneal incisions and suture use.

However, some possible pitfalls are also incurred specifically with DLEK, which largely lie in its steep surgical learning curve. The accuracy (and thus success) of this technique is strongly dependent on the surgeon's abilities, making the procedure complex to reproduce.

More recently, Seitz et al have demonstrated in a laboratory model the feasibility of using the femtosecond laser for DLEK to create both the opening incision as well as the stromal dissection, which may allow a more straightforward surgical procedure.[70] Other authors have also corroborated this with further experimental studies.[71–73] This technique may become popular in the near future with the expansion of the femtosecond laser market for corneal surgery.

MICROKERATOME-ASSISTED PLK (MAPLK)

The advent of new microkeratomes (both manual and automated) has allowed therapeutic lamellar keratoplasty to be readily performed in a reproducible manner. These instruments are predominantly adopted from those available for laser in-situ keratomileusis (LASIK). In addition, artificial anterior chambers have been developed for use with corneoscleral buttons when whole eyes are not available. Therapeutic automated lamellar keratoplasty can be used both for anterior stromal pathology and endothelial dysfunction, but here we will only describe the MAPLK surgical approach.

In MAPLK, a hinged anterior stromal flap of approximately 350 μm (200–450 μm) in thickness is first cut in the host cornea, and the diseased posterior cornea is trephined (the trephine size used depends on the diameter of the flap and hinge width obtained). The donor cornea is prepared using the same microkeratome parameters to cut the anterior corneal disk. The residual posterior stroma and endothelium are trephined to the same size. The donor is transplanted and may be sutured on the recipient bed, although most surgeons (including the authors) do not find it necessary to suture the posterior lamellar button.[48] Finally, the anterior flap is repositioned and sutured.

The creation of a flap by means of a microkeratome to perform a PLK is easier and faster than the manually dissected sclerocorneal approach, and the risk of damaging the endothelial cells may be lower. In short follow-up series, 50% of patients had a BCVA of 20/60 or better (range: 20/30–20/200) at a maximum of 1 year of follow up.[19,74] One study reported a 1 month average spherical equivalent of –1.25 D.[19] At 12 months, Ehlers et al[74] found that the endothelial cell density was in the range of 1200–2300 cells/mm^2. None of these studies reported episodes of graft rejection or wound dehiscence.

However, in the corneal flap technique, a minimal number of sutures are still required to secure the corneal flap and the transplanted corneal disk, which remains a potential drawback. Corneal sutures have been associated with several problems, particularly following PK, indeed, a 5-year retrospective study of 361 grafts (1993–94) reported erosions over the nylon sutures in 10.8% of cases, infiltrates at suture entrance site in 9.4%, and infectious keratitis in 3.3%.[41] Similarly, the use of sutures may induce some astigmatism, although in MAPLK significantly lower and for a shorter period than in classic PK.[75]

In 2002, we described an experimental laboratory model for posterior lamellar keratoplasty using an artificial anterior chamber.[21] Thirty-six human eye bank corneas (18 donors and 18 recipients) were mounted on an artificial anterior chamber, and a manual microkeratome was used to create a hinged anterior lamellar keratectomy. A 7.0-mm diameter posterior lamellar disk (posterior stroma, Descemet's membrane, and endothelium) was then trephined from the recipient cornea. Three different sizes (7.0, 7.25, and 7.5 mm) of donor buttons were compared. They were sutured into the recipient bed with a running 10-0 nylon suture and covered by the host corneal flap. The flap was replaced without sutures. The resulting corneal surface was analyzed by computerized videokeratography and graft stability studied by resistance to high intraocular pressures. Regular and minimal postoperative astigmatism was present in all cases. There was an average change in astigmatism of 1.47 D (SD 1.49) postoperatively. The grafts and flaps maintained watertight seals with average bursting pressures of 66.9 mmHg (SD 46.4). Although donor buttons oversized by 0.5 mm had the least change in average keratometry, those oversized by 0.25 mm had the best stability at higher pressures. With this model, it was possible to evaluate the effects of many variables such as flap thickness, flap diameter, donor button diameter, and number of sutures and technique of suturing. This comparison was also performed with a running suture and a sutureless hinged anterior lamellar corneal flap.

To compare postoperative astigmatic change and graft stability, we used two different donor button diameters in endothelial lamellar keratoplasty to treat corneal endothelial failure. They showed that average intraocular pressures of up to 88 mmHg could be resisted in laboratory human eyes when a 200-μm flap is used for the MAPLK procedure. This laboratory model system should be useful in evaluating different mechanical factors that contribute to graft success.

An important principle of lamellar refractive and LASIK surgery is that in order to preserve the tectonic integrity of the cornea, a minimum of half or more of residual corneal tissue must remain after the creation of a flap to prevent refractive instability. However, in our clinical series, the thickness of the transplanted posterior stroma appears to have a somewhat different contribution to corneal stability compared to that in LASIK patients. Even when the transplanted disks are thinner than half of the cornea, these corneas appear to remain stable over time avoiding ectasia. Wound healing after this type of approach may be different as compared to LASIK, and the circumferential cut perpendicular to the orientation of collagen fibers may increase the strength of the wound and the posterior cornea.

One of the possible advantages of the microkeratome approach, compared to manual dissection, is related to the optical properties of corneal flaps with smoother cut surfaces. Interface scarring is almost absent after microkeratome dissection in LASIK. When compared with manual dissection, microkeratomes create a smoother donor–recipient interface and a more consistent depth than manual dissection. However, similar to other lamellar approaches including hand-dissection, there seems to be a limit of improvement in visual acuity close to 20/30–20/40 in regards to the maximum best average Snellen visual acuity achieved in the clinical series of MAPLK.

Based on information collected from clinical observations of keratorefractive surgery and various types of keratoplasty, we have postulated a hypothesis that may provide some explanation to the limited optical results observed in MAPLK. These are the facts:

1. LASIK has demonstrated that corneal dissection performed by means of a microkeratome can easily achieve an optical quality compatible with 20/20 or better vision. However, when a corneal free-cap is accidentally obtained, it is necessary to be replaced in exactly the same orientation it had before the cut to avoid visual problems after the surgery. Mismatch may create reduction in best-corrected visual acuity.
2. Anterior lamellar keratoplasty and former classic keratomileusis procedures with donor tissue have traditionally provided a limited best corrected visual acuity.
3. Deep anterior lamellar keratoplasty down to Descemet's membrane provides potential best-corrected visual acuities of 20/20 or better.

From these three facts, we believe that the different orientation of collagen fibers in the interface between two corneas may create optical distortions not currently measurable by available methods and with potential to affect the resulting visual acuity. Even in cases of using the same cornea (LASIK), this orientation of structural fibers is very particular for each individual (resembling a fingerprint), and a simple rotational mismatch induces optical distortions. Therefore, a perfect match is essentially impossible when two different corneas are used and a stroma–stroma interface exists, which is perhaps the major limitation of any procedure involving stroma–stroma interface.

Some other possible pitfalls of MAPLK have also been observed. This procedure induces a shift in postoperative average corneal power and astigmatism similar to a stromal flattening of the corneal surface in LASIK. In MAPLK there is a donut effect of donor–recipient interface due to sutures, which is transmitted to the surface flap. Surface sutures may also contribute to this astigmatism and high absolute power. As with LASIK, flap complications may also occur; epithelial ingrowth in the flap–graft interface can decrease the BCVA and it has been reported in clinical cases of MAPLK.[76] Similarly, it is suspected that corneal melting and micro/macrostriae are also possible adverse outcomes of MAPLK.

MODIFIED MICROKERATOME-ASSISTED POSTERIOR LAMELLAR KERATECTOMY (MMAPLK)

The modified microkeratome-assisted posterior lamellar keratoplasty (MMAPLK) is essentially similar to previously microkeratome-assisted techniques.[19,21,48,54] However, Pirouzmanesh et al, in an attempt to reproduce a more stable postoperative cornea and reduce the dependence on sutures, proposed a wider flap hinge in the recipient cornea as a result of a partial flap cut up to the pupillary margin.[77] A 300-µm-thick partial flap keratectomy was performed in human donor corneoscleral rims using an artificial anterior chamber and a manual microkeratome (Fig. 67.1).

The flap was stopped at the left central opening border, providing a wide hinge to add stability. Differing from previously published techniques, this approach attempts to obtain a wide flap hinge with relatively less likelihood of flap slippage, to provide more stability to the corneal flap and reduce the overall corneal opening to preserve corneal integrity.[20,21,48] After flap reflection, undermining the cornea at the level of the hinge allows for the trephine to be expanded underneath the hinge (Fig. 67.2). A 6.25-mm trephination was performed to obtain a disk of posterior stroma, Descemet's membrane, and endothelium (Figs 67.3 and 67.4). The disk was subsequently positioned in a sutureless fashion, and the flap secured with either five interrupted sutures or a chondroitin-sulfate-aldehyde-based adhesive (Fig. 67.5). Increasing intrachamber pressures were created to detect graft stability. Videokeratographic data were recorded to evaluate astigmatic change. The mean (SD) astigmatic change was 3.08 (0.84) D in the sutured group and 1.13 (0.55) D in the corneal adhesive group ($p = 0.008$). Mean (SD) resisted pressures were 95.68 (27.38) mmHg and 82.45 (18.40) mmHg in the sutured and glued groups, respectively ($p = 0.97$), which is significantly higher than the numbers observed with standard MAPLK using the same setting.

Sutures remain the gold standard for corneal incisions and wound repair because of the efficiency and strength of the closure. However, sutures may not be the ideal method for wound closure, especially in the cornea: many corneal surgeons recognize that sutures can be

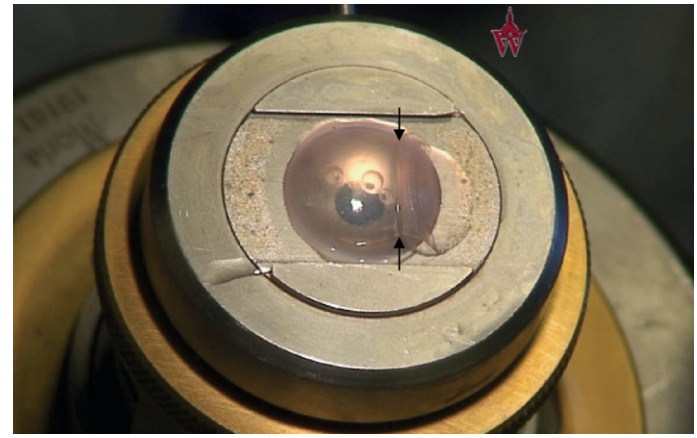

Figure 67.1. Simulation, in an artificial anterior chamber, of a partial flap in the recipient. Flap with a large hinge (arrows) at the pupillary margin. This allows more stability of the flap and the cornea as a whole.

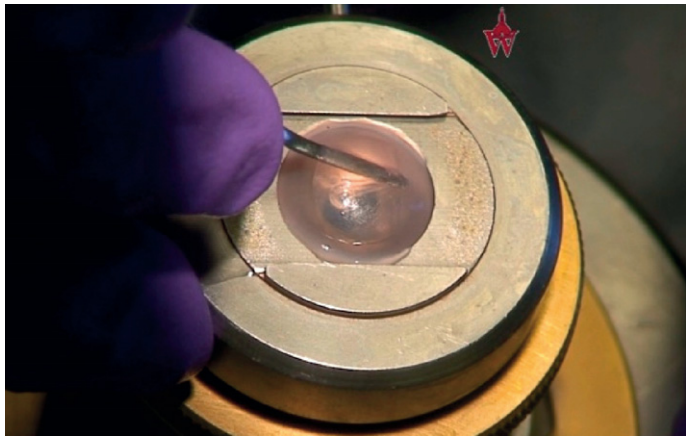

Figure 67.2. Flap hinge dissection. The spatula is inserted underneath the flap hinge and a pocket is created to allow the trephine blade to create an opening in the stromal bed.

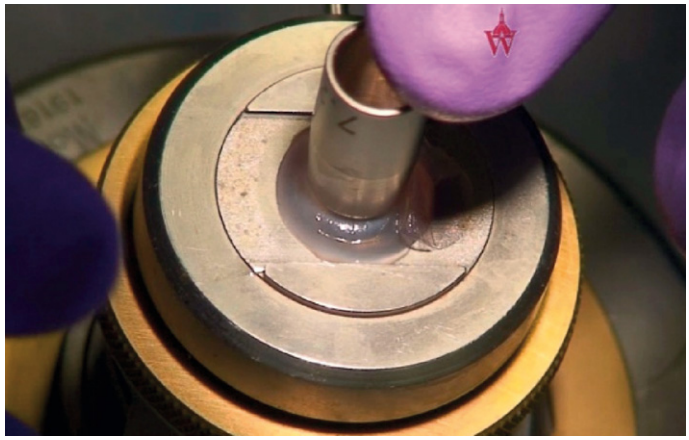

Figure 67.3. After flap reflection, a freehand trephine is centered on the stromal bed surface, avoiding the cut of the flap hinge.

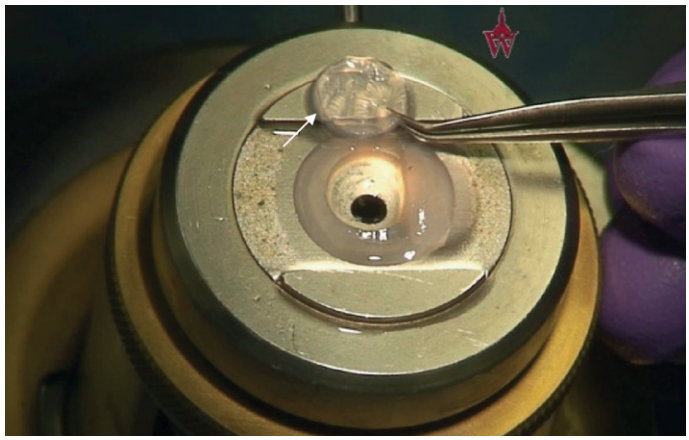

Figure 67.4. A disk is obtained with diseased endothelium (arrow), which is to be replaced with a disk obtained in similar fashion from a donor.

a source of potential problems. The use of tissue adhesive in this study produced less astigmatism than other reports of MAPLK.[20,21,48] Furthermore, the absence of sutures made the technique more simple and considerably less time-consuming.

DONOR TISSUE PREPARATION

Donor corneal tissue can be obtained from a fresh globe or a preserved corneoscleral button. When a button is used, an artificial anterior chamber is required to perform the microkeratome cut.[78]

For both the MAPLK and DLEK methods, donor tissue is prepared a few different ways using an artificial anterior chamber. In one method, the donor corneoscleral button is mounted on the artificial chamber endothelial side down and a lamellar pocket is dissected similar to the DLEK recipient procedure. Then the button is turned epithelial side down on a punch and trephined at a diameter that is dependent on the measured diameter of the recipient posterior lamellar disk. The donor posterior disk is then separated from its anterior corneal layers and used as indicated in the respective procedures. Another method may use a microkeratome for the lamellar dissection. In 2002, Behrens et al[79] evaluated the safety and accuracy of a manual microkeratome and an artificial anterior chamber to harvest corneal lenticules for lamellar keratoplasty. They found that the system was reproducible for harvesting corneal lenticules for lamellar keratoplasty. Its ease of use and high accuracy under controlled conditions may warrant its use for the lamellar dissection part of the donor preparation, following the trephination of the posterior stromal lenticule as previously described.

Another technique for harvesting donor tissue for posterior lamellar keratoplasty was described by Suwan-apichon and associates,[80] in which a corneoscleral button is mounted onto an artificial anterior chamber endothelial side up and the stromal dissection is accomplished with a simple blunt spatula. The planarity and endothelial cell loss associated with the harvest appear comparable to previously described techniques.[81] This modified method is advantageous in that a standard reusable blunt corneal dissector is employed without the added complexity and cost associated with sharp, disposable three knife sets. Furthermore, the orientation of the endothelium up on the anterior chamber allows greater surgeon control during the harvest.

The concerns with donor preparation techniques lie in ensuring endothelial cell survival and technical ease. All procedures have shown comparable endothelial cell survival and no particular method is favored over the other (Figs. 67.6–67.9).

DESCEMET'S STRIPPING WITH ENDOTHELIAL KERATOPLASTY (DSEK)

As highlighted in the preceding chapters, a revolutionary refinement of the DLEK procedure was performed when Melles et al[82] proposed the stripping of Descemet's membrane from the recipient's stromal bed so as to create a smooth recipient surface, without the incision or dissection of the corneal stroma. The technique enables the surgeon to consistently excise Descemet's membrane, to significantly reduce the surgical time required to perform the entire transplantation, i.e. the preparation of the recipient bed and the implantation of the donor posterior lamellar button, and to use a 'closed system' by performing the transplantation through a small tunnel incision. However, other surgeons working on pure Descemet's membrane replacement have found that Descemet's membrane is quite fragile and manipulations of donor tissue, which are reasonably well tolerated in the current endothelial keratoplasty techniques, result in wrinkles, folds, tears, and unacceptable endothelial cell loss. Various modifications of carriers have been used in an attempt to overcome these challenges.[83,84]

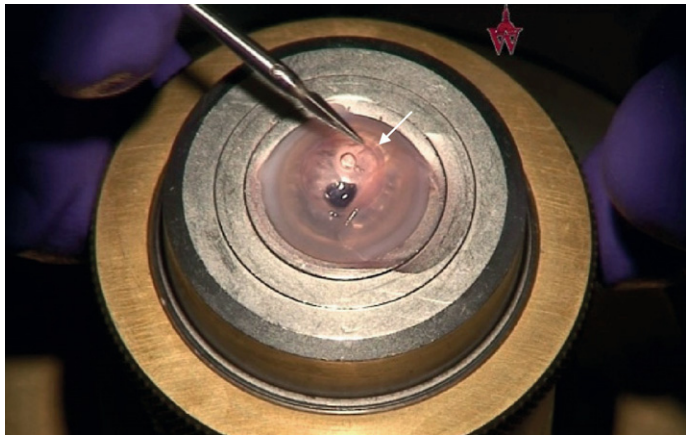

Figure 67.5. Donor disk is in place (arrow) and ready to suture the flap only.

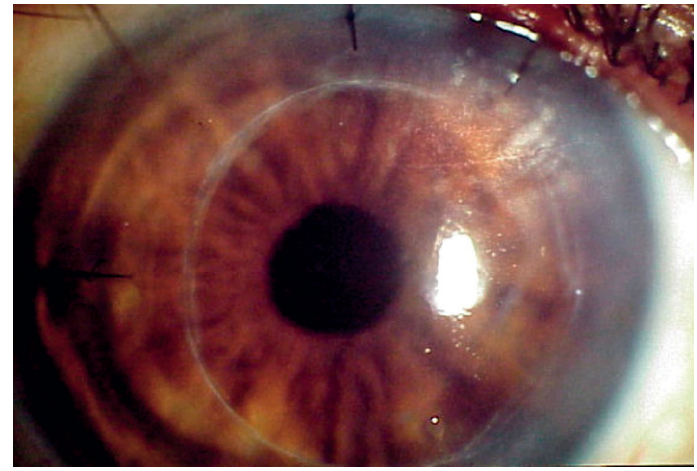

Figure 67.7. MAPLK, 1 month postoperatively. Flap secured with four sutures only. (Photograph courtesy of Angel Pineda, MD.)

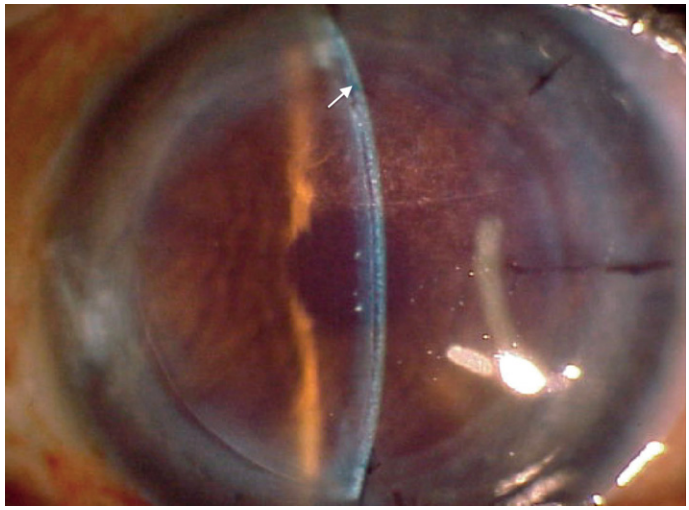

Figure 67.6. Results in a patient at 24-h postoperative period. Only four sutures are securing the flap. There is a space between donor and recipient (arrow), which spontaneously resolves within the first week postoperatively. (Photograph courtesy of Angel Pineda, MD.)

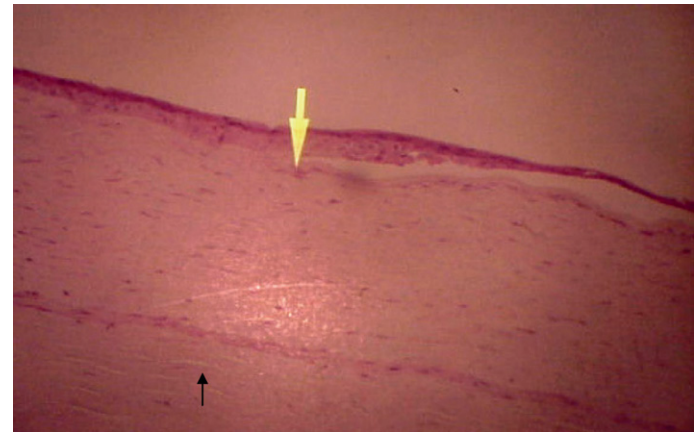

Figure 67.8. Histology of a MAPLK from a failed graft. Bullae (yellow arrow) are observed in the epithelium. A cellular reaction is observed in the interface in this case (black arrow). (Photograph courtesy of Angel Pineda, MD.)

FUTURE DIRECTIONS OF PLK

In summary, four techniques for PLK may be distinguished, although various modifications may exist: (1) PLK through a 9.0-mm scleral incision using a spoon-shaped glide for insertion of a 7.5-mm donor,[13,55] made popular in the USA as DLEK;[58] (2) PLK through a 5.0-mm self-sealing scleral incision using a 9.0-mm folded donor,[50] made popular as small-incision DLEK;[85] (3) MAPLK and MMAPLK, which attempt to achieve a smoother surface that may lead to a better surgical outcome with a clearer interface;[20,21,77] and (4) PLK by stripping Descemet's membrane and the insertion of a 9.0-mm folded donor, now referred to as DSEK,[86] or Descemet-stripping automated endothelial keratoplasty (DSAEK), when a microkeratome is used for preparation of the donor tissue. Compared with a penetrating keratoplasty, all these techniques may produce minimal change in refractive power of the transplanted cornea, minimal induced astigmatism, elimination of long-term suture-induced complications, elimination of late wound dehiscence, faster visual rehabilitation, and a lesser demand of postoperative care.[51]

Further development in endothelial keratoplasty will be directed at eliminating the stroma–stroma interface to achieve cases with 20/20 vision. However, neither microkeratomes nor femtosecond lasers are currently capable of deep stromal dissections that are as smooth as the Descemet's-stripped recipient interface side.[87,88]

Melles et al presented the first published report of a successful pure Descemet's membrane transplantation through a small 3.5-mm corneal incision, and have extended the endothelial keratoplasty lexicon to 'Descemet's membrane endothelial keratoplasty' (DMEK).[86] While the visual recovery in this one case was rapid and complete due to the exquisitely smooth surface now on both sides of the interface, what was most astonishing in this single case report was the early donor endothelial cell survival measured at 2350 cells/mm^2 and 1 week postoperative best corrected visual acuity of 20/20.

The current work with in situ human corneal endothelial cell regeneration is exciting and complementary to the evolution of the surgical techniques of endothelial transplantation. Azar's group in Boston (ARVO, 2006) has recently shown success in amplification of human endothelium in the laboratory with good hexagonal morphology. This technique has the potential of taking the recipient's peripheral endothelial cells, increasing the cell density in the laboratory and re-transplanting them back to the recipient central cornea, thus circumventing any issues of immune-mediated graft rejection.[89] If we can extrapolate these laboratory models to the

clinical realm, endothelial keratoplasty as we know may be completely transformed. Ultimately, it may be possible in the future to prevent the need for endothelial transplant by directly stimulating the patient's remaining endothelial cells to regenerate, using viral vectors to transfer genetic material that induces and controls endothelial mitosis.[90]

For all of these newer procedures, long-term follow-up data is needed to determine whether these techniques will become safe and effective alternatives to penetrating keratoplasty in years to come.

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68 Descemet's stripping automated endothelial keratoplasty: avoiding complications

James Rowsey, Jason A. Evangelista, John Williams, Bradley D. Fouraker

Corneal transplantation is fraught with numerous surgical and postoperative complications,[1–5] which may be avoided by the newer techniques of endothelial replacement alone. Melles, Culbertson, Terry, and Price have developed a coterie of techniques to allow replacement of either the posterior stroma and adjacent endothelium or Descemet's membrane with attached endothelium to avoid many of these complications.[6–15] These newer techniques, however, are associated with their own unique complications that can confound the visual recovery with these modalities. Terry has reviewed the early deep lamellar endothelial keratoplasty (DLEK) complications including:[15]

1. Intraoperative conversion to penetrating keratoplasty (PK)
2. Uneven recipient or donor bed thickness
3. Excessive posterior pressure from the vitreous or lid speculum
4. Iris prolapse
5. Bleeding from the scleral wound into the interface
6. Dislocation or decentration of the donor disk
7. Early postoperative disk dislocation
8. Graft rejection
9. Late endothelial graft failure
10. Cataract formation requiring cataract removal
11. Steroid or surgical induced glaucoma
12. Persistent epithelial or surface irregularities requiring debridement.

We review the current Descemet's stripping automated endothelial keratoplasty (DSAEK) technique with the attendant complications from this procedure modification and the methods to minimize these and additional complications by approaching the surgical procedure in a stepwise fashion. Each surgical maneuver may induce new or cumulative complications (Table 68.1) that can cause graft failure or poor postoperative visual acuity recovery.

PREOPERATIVE DECISION MAKING

We initially avoided patients with anterior chamber intraocular lenses as the narrow chamber angle makes unfolding the donor material in the anterior chamber more difficult causing endothelial cell loss (Table 68.1). In addition, an anterior chamber intraocular lens may be a harbinger of previous surgical frustration. Vitreous strands may remain in the anterior segment precluding good coadaptation or positioning of the donor material. We also prefer eyes with no prior sector iridectomy as the air injection performed at the conclusion of the case may not be held in the anterior chamber when the patient is upright. If the air proceeds to the posterior chamber it causes anterior displacement of the iris, peripheral corneal touch, and donor dislocation centrally as the iris is repositioned upon air removal. Furthermore, the need for repeated repositioning of the donor material appears to be associated with increasing endothelial cell loss.

AVOIDING OPERATIVE COMPLICATIONS

Two drops of 100% glycerin are placed on the recipient cornea prior to prepping the patient to allow for maximum deturgescence of the corneal stromal preoperatively. This allows better visualization of the anterior segment and a thinner stroma, which is vital when phacoemulsification is anticipated. Deturgescing the corneal stroma also increases the osmotic pressure of the stroma, decreasing the propensity for donor dislocation. The diameter of the recipient cornea is measured with calipers. A cornea of 10 mm or less makes it exceedingly difficult to unfold the standard 8 mm donor in the anterior chamber. We use a smaller donor if the anterior chamber is shallow, in the presence of an anterior chamber intraocular lens, or with a smaller cornea.

DONOR PREPARATION

Inspect the donor to insure that it is of adequate size with the scleral rim to fit the artificial anterior chamber. If the donor is too small in one quadrant, inadequate adhesion in the anterior chamber will occur. Leakage of the anterior chamber at the time of the pass causes an uneven cut. Remove iris from the posterior surface of the donor material and excess conjunctiva. Excess conjunctiva may prolapse onto the surface of the cornea and produce an irregular cut or cause the anterior chamber to collapse with inadequate pressure during the microkeratome pass. Pay careful attention to placing the donor material over viscoelastic on the base of the artificial anterior

Table 68.1 Successful Descemet's stripping automated endothelial keratoplasty (DSAEK) surgery

Avoid Surgical Problems Process Steps	**Postop Complications Observed**	→												
↓	Endothelial cell loss	Donor dislocation/ Decentered donor	Difficulty unfolding donor	Uneven cut artificial AC collapse	Epithelial ingrowth	Hyperopia excessive donor edge	Loss of best vision	Decentered cut with donor trephine	Slow re-epithelialization	Scarring recipient bed	Edema recipient postop edema/ pain	Pupillary block	Endophthalmitis	Cystoid macular edema
AC IOL	X		X											X
Vitreous in AC	X	X	X											
Excessive recipient edema		X							X	X	X			
Microcornea			X											
Small sclera on donor				X										
Slipping donor on AC	X													
Epithelium on donor				X	X									
Uneven cut						X	X							
Donor inverted	X													
Thick donor edge						X								
Loss chamber pressure	X													

Table 68.1 continued

Avoid Surgical Problems Process Steps	Postop Complications Observed	→												
↓	Endothelial cell loss	Donor dislocation/ Decentered donor	Difficulty unfolding donor	Uneven cut artificial AC collapse	Epithelial ingrowth	Hyperopia excessive donor edge	Loss of best vision	Decentered cut with donor trephine	Slow re-epithelialization	Scarring recipient bed	Edema recipient postop edema/ pain	Pupillary block	Endophthalmitis	Cystoid macular edema
Storage donor touch endothelium	X													
Poor visibility of donor edge in AC/ on block		X	X					X						
Irregular epithelium							X							
Loss of recipient epithelium		X							X					
Excessive stromal manipulation							X			X				
Bleeding in interface			X				X							
Healon in interface	X													
Donor touches infusion port	X													
Inadequate Descemet's removal		X												

Table 68.1 continued

Avoid Surgical Problems Process Steps	Postop Complications Observed	→												
↓	Endothelial cell loss	Donor dislocation/ Decentered donor	Difficulty unfolding donor	Uneven cut artificial AC collapse	Epithelial ingrowth	Hyperopia excessive donor edge	Loss of best vision	Decentered cut with donor trephine	Slow re-epithelialization	Scarring recipient bed	Edema recipient postop edema/ pain	Pupillary block	Endophthalmitis	Cystoid macular edema
Excessive Descemet's removal										X	X			
Donor/iris prolapse	X													
Large RK incision						X								
Repeated air injections	X	X	X								X			
Repositioning of donor	X	X					X		X					
Air in AC removal		X												
Tight patch		X												
Resuture donor							X							
Graft rejection	X													
Additional surgical procedures	X													

AC = anterior chamber.

ACIOL = anterior chamber intraocular lens.

RK = radial keratotomy.

chamber to avoid slippage of the cornea with the endothelium touching the adjacent steel producing endothelial cell loss.

After the cornea donor is secured on the artificial chamber, remove the donor epithelium with a #15 blade and Weckcell sponges until a clear Bowman's membrane is observed. This avoids the potential smearing of epithelium under the cap during the microkeratome pass and production of epithelial ingrowth. Maintenance of the artificial anterior chamber pressure by an assistant is useful at this time. Cut the microkeratome pass smoothly with no skittering, which produces an uneven cut. Be certain that the microkeratome head is well seated before the pass is attempted or an unduly thick donor material will be provided, with loss of best potential vision.

Mark the center of the cut stromal bed with a gentian violet 'S' after drying. This avoids initially placing the donor material in the anterior chamber upside down which requires further manipulation and possible endothelial cells loss. While still on the artificial anterior chamber, undermine the edge of the donor material with a 2.2 mm sharp point crescent blade from the edge of the microkeratome cut to the limbus for 360°. The undermining of the donor corneal incision to 12 mm prevents excessive donor thickness on one side when the cornea is subsequently punched. This avoids uneven donor thickness and subsequent astigmatism or a hyperopic shift from a thickened cornea in the periphery. Mark the stromal side of the donor at the cut edge in four quadrants with gentian violet to assist in producing a centered cut with the trephine when the donor material is inverted on the cutting block.

Increase the fluid flow in the artificial anterior chamber during removal of the donor material to avoid anterior chamber collapse and loss of the endothelium. Irrigate all remaining viscoelastic from the endothelial surface to avoid excess in the anterior chamber during donor insertion, since this could result in poor co-aptation and donor dislocation.

Dry the stromal side of the donor and place it on a dry, cooled cutting block. The hole in the center of a wet cutting block may act as a piston during the cutting procedure jettisoning the donor material forward with excessive trauma to the donor and producing endothelial cell loss. Observe the donor through the 8-mm trephine during the cutting for adequate centration to avoid a decentered cut (Fig. 68.1).

Gently dry the stromal edges of the donor with a Weckcell sponge to avoid excessive Optisol hydration of the donor. A thinner donor decreases the chances of subsequent donor dislocation. Protect the donor under Optisol on the back table while addressing the recipient bed. Cover the donor material on the back table but preclude touching the donor endothelium with any covering that is utilized, to prevent endothelial cell loss.

RECIPIENT PREPARATION

Examine the recipient bed for any surface scars or secondary Cogan's map-dot-fingerprint dystrophy from recurrent corneal edema. A decision must be made to either debride the recipient epithelium with a Weckcell because of the common preoperative subepithelial fibrosis in Fuchs' dystrophy patients or to wait for this debridement in the postoperative period. The advantages of removing the epithelium at the time of surgery are better visualization of the cornea and anterior chamber and a second surgical encounter is avoided. The disadvantages of removing the epithelium at the time of the initial surgical procedure is that epithelial removal leads to keratocyte apoptosis which itself leads to a slower re-epithelialization. In addition, the slower re-epithelialization allows for excess stromal hydration from the tear film decreasing the inhibition pressure of the stroma, leading to potential donor dislocation.

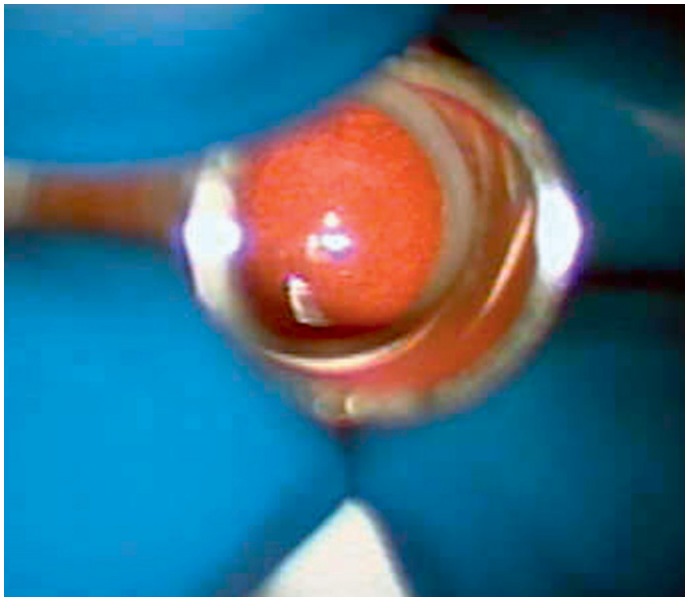

Figure 68.1. Cutting the donor with a hand-held trephine.

Mark the center of the host cornea with a Sinskey hook and the edge of the proposed endothelial resection site with an 8-mm trephine. Avoid excessive pressure or scarring of the recipient bed with the trephine.

Provide a limbal incision 500 μm deep, two clock hours in length (6 mm) in the temporal cornea. Place 1-mm limbal stab incisions at the 12 o'clock, 6 o'clock and 11 o'clock positions for infusion port placement and subsequent unfolding of the donor, as required. Advance the temporal incision 2 mm as a corneal tunnel, avoiding bleeding into the interface. If bleeding occurs, cauterize the bed to insure that the bed will be dry and bleeding will not occur either in the interface between the donor and the stroma or into the anterior chamber. Bleeding in the subsequent interface produces loss of best vision. Place an infusion port in one of the limbal incisions where unfolding of the donor material is anticipated. The infusion port itself can be used quite judiciously to assist in unfolding the donor material even without an air bubble.

Enter the anterior chamber by a 1-mm incision through the original temporal stromal dissection plane (Fig. 68.2). Utilizing the Asico–Price Sinskey hook, scribe the outline of the proposed Descemet's dissection area (Fig. 68.3). This scribing should be slightly smaller than the 8-mm overlying epithelial mark of the trephine. Making the recipient bed slightly smaller than the donor avoids recipient peripheral stromal edema and subsequent postoperative discomfort from bullae over denuded stroma. Bullae formation is exacerbated if all of Descemet's is removed or a significantly larger area of Descemet's is removed than the donor material can clear adequately, giving a foreign body sensation until the cornea deturgesces. At the completion of the scribing technique, the infusion line is turned off and the anterior chamber is filled with Trypan blue. The edges of the bed are now stained allowing for better visualization of the Descemet's lifting off the stroma. The Trypan blue is then irrigated out of the anterior chamber and from behind the iris when infusion is resumed. The Asico–Price Sinskey hook is utilized to gently peel Descemet's membrane from the posterior

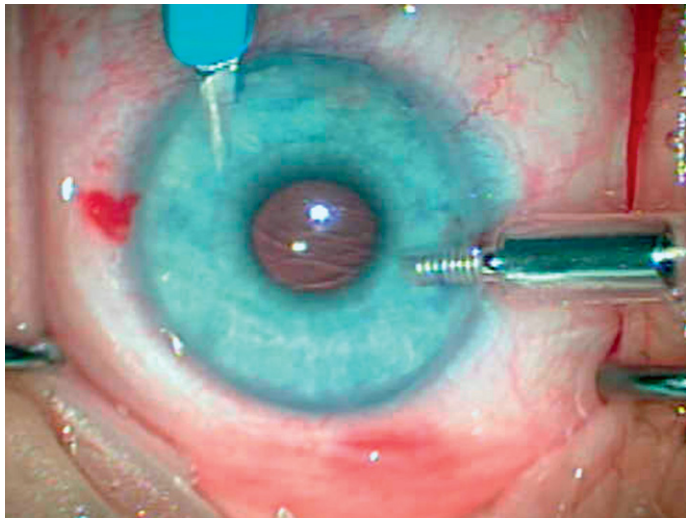

Figure 68.2. Entering the anterior chamber through a 1-mm portion of the temporal corneal tunnel.

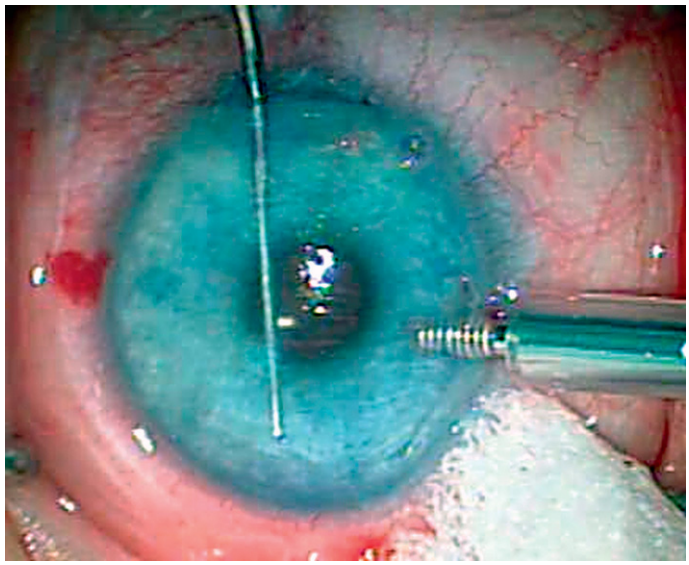

Figure 68.3. Reverse Sinskey scoring Descemet's membrane and endothelium.

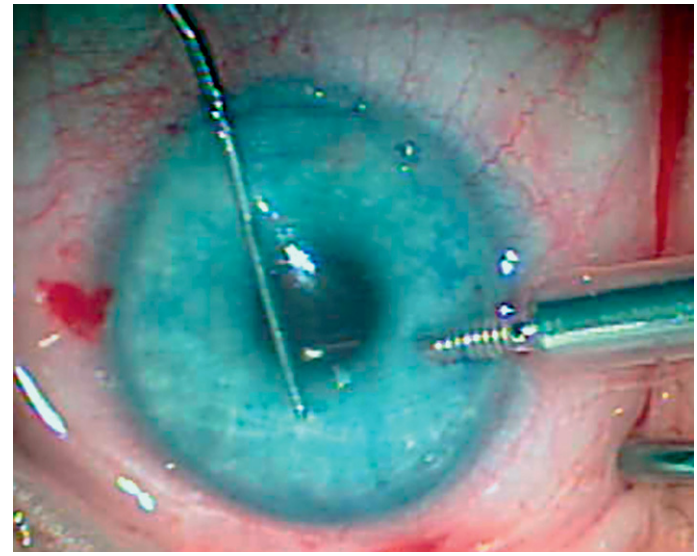

Figure 68.4. Reverse Sinskey pulling Descemet's membrane from overlying stroma.

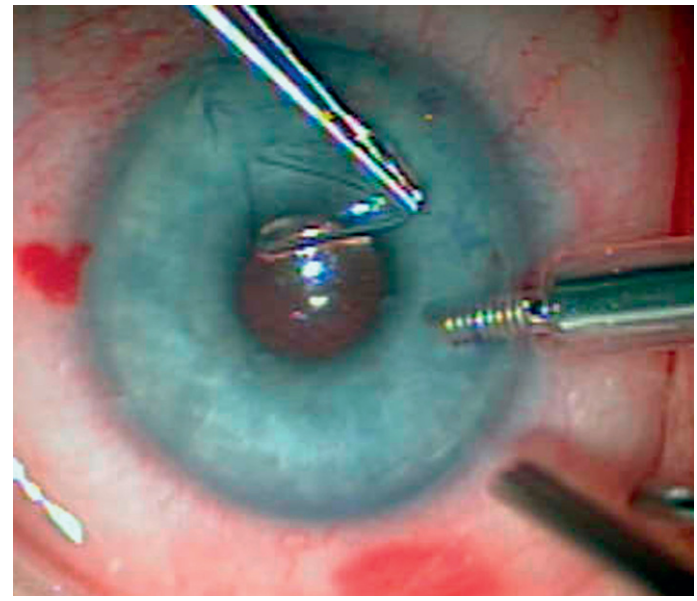

Figure 68.5. Removed Descemet's membrane and endothelium.

stroma (Fig. 68.4). This procedure requires an exceedingly gentle touch. Excessive pressure causes perforation and dehiscence of the delicate posterior stromal fibers with a subsequent scar in the stroma. We have found that utilizing a light pipe with the microscope light turned off during the Descemet's stripping technique is helpful with scleral scatter from the limbus to see the relucency of the dislocated Descemet's membrane. Both Trypan blue and the light pipe are advantageous with very edematous corneas to determine the Descemet's has been stripped to avoid any residual Descemet's pieces at the edge of the recipient bed. It is possible to either pull Descemet's off the stroma or push it off with the Sinskey hook. The infusion port will normally assist in lifting the edge adjacent to the infusion port but will blow Descemet's back onto the stroma 180° away. Others routinely utilize the irrigation–aspiration (I/A) tip to assist in Descemet's stripping and we have found this technique advantageous during a triple phacoemulsification-intraocular lens implantation-DSAEK when the I/A tip is already prepared.

Enlarge the internal opening of the limbal incision to the full 2 clock hours, watching for any bleeding. Remove the freed Descemet's with forceps (Fig. 68.5). Drape the Descemet's sheet over the host cornea to ensure the removal was complete. Utilize the Terry scraper to remove any remaining Descemet's membrane and provide a roughened surface for 360° just inside the 8-mm optical zone for subsequent adherence of the donor material. Do not scrape in the visual axis as this could cause stromal scarring and loss of best corrected vision. Do not enlarge the Descemet's stripping outside of the proposed donor coverage for this will cause an edematous recipient rim.

Under the operating microscope fold the donor in a 60/40% taco configuration with a viscoelastic bead in the fold (Fig. 68.6). Utilize enough Optisol on the block that the folded donor endothelium does not touch the block during this step (Fig. 68.7), producing loss of the endothelium.

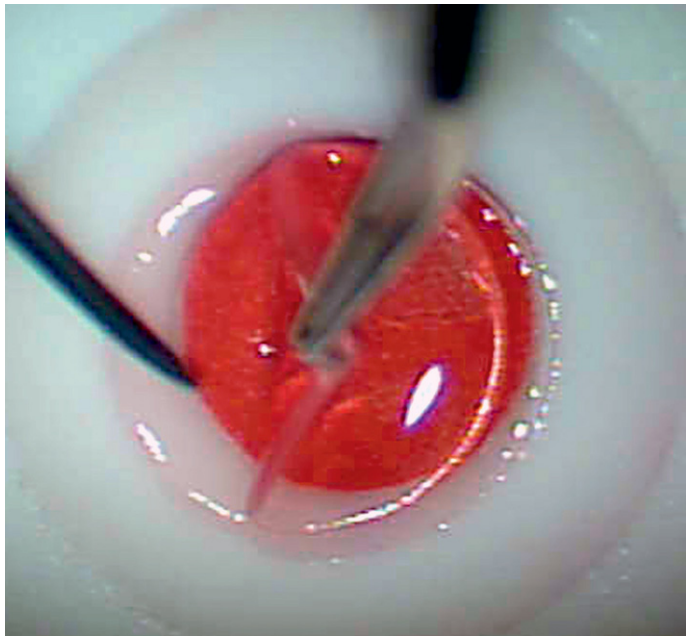

Figure 68.6. Folding of posterior donor cornea.

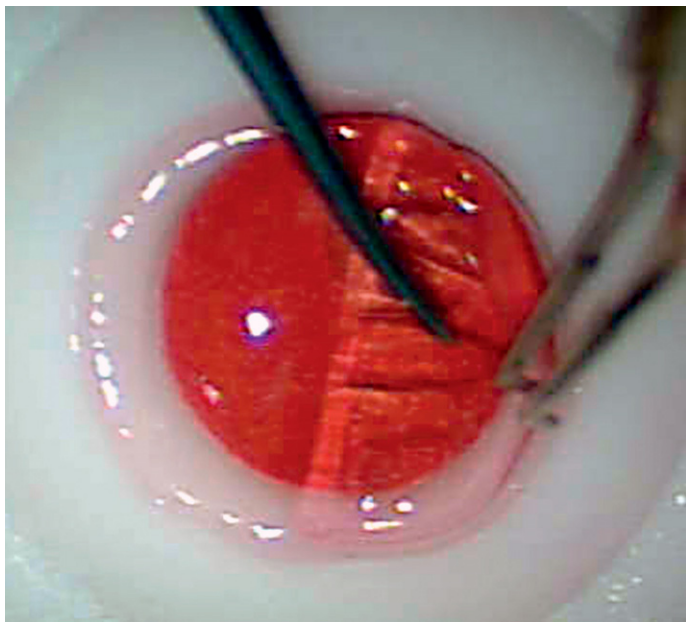

Figure 68.7. Folded donor cornea.

DONOR INSERTION

Grasp the donor 1 mm from the fold with the Charlie forceps (Fig. 68.8), and insert the donor quickly into the anterior chamber to the opposite limbus (Fig. 68.9). Gently release the donor material near the infusion port. The infusion port assists in the unfolding procedure. Do not touch the infusion port as this can cause endothelial cell loss. Be careful that the pressure of the infusion port is not excessive, which will prolapse the iris or donor back out of the anterior chamber onto the surgical drape causing endothelial cell loss. Place a single 10-0 nylon suture through the incision to maintain the anterior chamber.

Unfolding may occur spontaneously when the anterior chamber is filled. If the unfolding is inadequate there are two options. Grasping the edge of the donor material at the limbus through the limbal ports with a Sinskey hook can manipulate the edges in place (Fig. 68.10). Use the infusion line or air to assist the unfolding. It may be necessary to place an additional suture in the limbus to maintain the anterior chamber since collapse produces endothelial cell loss. Another alternative is filling the anterior chamber with air. Place a second suture in the limbus, and use a 30-gauge needle on a tuberculin syringe placed obliquely through a new limbus site and inject air between the donor edges. Avoid air in front of the donor material as this can prolapse the donor onto the iris or intraocular lens producing endothelial cell loss. It is convenient to place the 30-gauge needle through a new insertion site that can preclude air evacuation spontaneously through a previously used limbal incision. Longer scleral tunnels with the original DLEK procedure avoided this air extrusion. However, the larger tunnels require more attention to avoid bleeding. Limbal incisions allow more frequent prolapse of air especially during a manipulation procedure.

When the donor is in place, close the main wound with sutures and completely fill the anterior chamber with air to an intraocular pressure of 50 for 8 min. This procedure avoids donor dehiscence. Place four full-thickness 1-mm radial keratotomy incisions at the

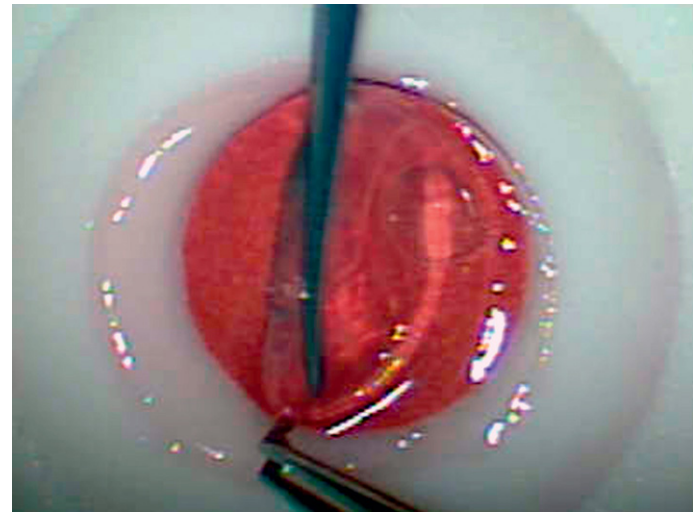

Figure 68.8. Grasping folded edge with Charlie forceps.

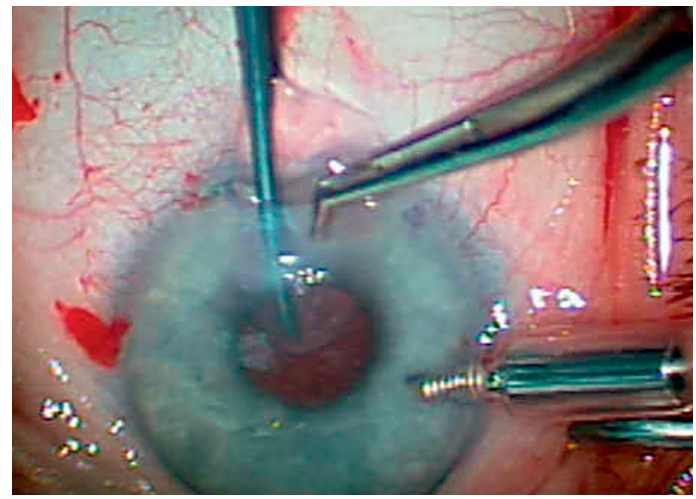

Figure 68.9. Charlie forceps inserting donor cornea through temporal wound.

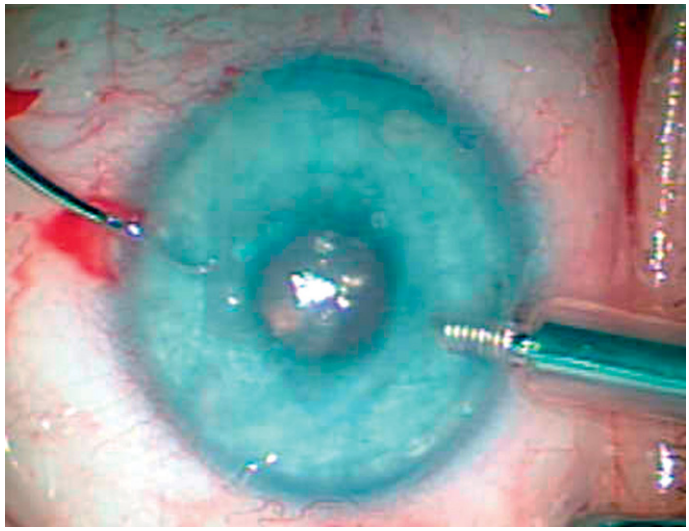

Figure 68.10. Unfolding donor edge.

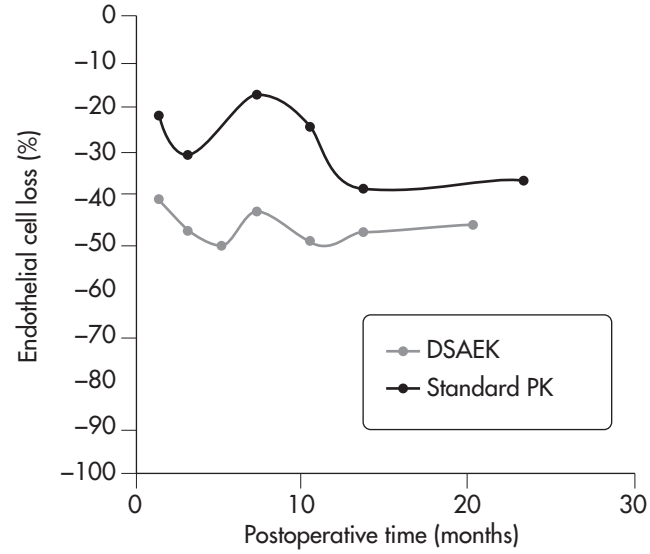

Figure 68.11. Percentage of postoperative endothelial cell loss of Descemet's stripping automated endothelial keratoplasty (DSAEK) versus standard penetrating keratoplasty (PK).

6-mm optical zone with a diamond blade to allow for fluid egress from the donor recipient interface. This is done over air and it is easy to observe when excess fluid is removed. If longer incisions are placed, excessive flattening of the cornea can occur with subsequent hyperopia.

Roll the recipient's epithelium with an iris spatula to move the donor material to a final position, avoiding decentration. This roll is accomplished with approximately 50 strokes of the iris spatula from the center of the cornea to the periphery with fluid or viscoelastic on the surface to avoid damaging the epithelium. Remove half of the air leaving an air bubble the size of the donor material. This procedure avoids donor dehiscence.

Apply two drops of 1% atropine solution and topical glycerine at the end of the procedure. The atropine allows for the pupil dilation and avoids subsequent pupillary block with air. Pupillary block causes the iris to adhere to the donor material with subsequent donor dislocation during the postoperative care. Lightly patch the eye over dexamethasone/tobramycin (0.1%/0.3%) ophthalmic ointment. A tight or indenting patch can produce donor dehiscence. On the first postoperative day prescribe the above ointment six times a day and inspect for donor adherence. In one week, ointment is changed to prednisolone acetate ophthalmic 1% suspension six times a day for 1 month to avoid graft rejection. The limbal sutures are removed at 1 month to decrease corneal astigmatism.

POSTOPERATIVE COMPLICATIONS

At 1 h postoperatively verify that the air in the anterior chamber has been adequate to provide good adherence of the donor material to the stroma. Glycerin is re-applied at the examination to allow for further stromal drying and better donor adherence avoiding donor dislocation. Additional air is placed in the anterior chamber if any donor dislocation is noted. A Povidone iodine re-prep is required as inadequate sterilization may produce endophthalmitis. Any fluid in the interface is removed through one of the previous radial incisions with a Sinskey hook and a 31-gauge needle is also useful to aspirate this fluid if it persists in the interface. Further manipulation can produce endothelial cell loss. Vitreous in the anterior chamber with entanglement of the donor material may produce corneal donor dehiscence.

A primary donor failure may be observed. This donor failure is normally seen in approximately 1 in 400 cases; however, it is unlikely without excessive surgeon manipulation. The donor material can be replaced through the same or an additional limbal incision. At 1 week, if the donor is dislocated we add air to the anterior chamber. This may produce further endothelial cell loss. At 2 weeks, if the donor remains off, we add air to the anterior chamber and suture the donor in four quadrants with a mattress suture from the recipient into the anterior chamber. This can also be associated with endothelial cell loss. If the donor is off at 2 months we replace it through the same limbal incision. Additional surgical procedures may be associated with cystoid macular edema.

We have found long-term endothelial cell loss to be greater when compared to standard PK (unpublished data). We compared preoperative endothelial cell counts obtained from the reference eye bank and the postoperative specular microscope data (Fig. 68.11). These differences were statistically significant until the 15-month postoperative period. Long-term differences are still being analyzed. In the 143 eyes with prolonged follow-up, we have observed nine cases (6.3%) of primary graft failure and, of those that survived, nine cases (6.7%) of late graft failure.

Graft rejection has been observed in two patients, one who discontinued their steroids, and one who was transferred off Pred Forte to generic prednisone acetate 1%. Although these drugs are 'pharmaceutically' equivalent they do not appear to be physiologically equivalent when rejection is the defining criteria.

In summary, the newer techniques of the Descemet's stripping endothelial keratoplasty provide excellent opportunities to avoid surface sutures, incisions, and irregular astigmatism and especially fragile wounds that may rupture. The complications for these new procedures are being demonstrated with prolonged follow-up. However, the rapid visual recovery, reduced astigmatism, wounds resistant to traumatic rupture, and negligible suture-related strife make this new advance advantageous to both the patient and surgeon.

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69 The future of keratoplasty

Omar Ahmad, Shahzad Mian, Alan Sugar

INTRODUCTION

In the 100 years since Eduard Zirm performed the first successful penetrating keratoplasty, corneal transplantation has progressed through the application of innovative technology and surgical technique to become arguably the most successful type of tissue transplantation.[1,2] Despite the advances that have been made in keratoplasty outcomes, graft survival remains a major concern, particularly in patients with repeat keratoplasty and inflammatory conditions.[3] The primary goal of successful keratoplasty is preservation of a clear graft and optimal rehabilitation of visual function, assessed by factors such as postoperative visual acuity, astigmatism, and time to recovery. This chapter focuses on new trephination techniques, sutureless adhesion technology, and alternatives to human cadaveric cornea transplantation, including keratoprostheses and bioengineered corneas. These are areas of development which we feel will dramatically improve the art and science of keratoplasty over the next decade.

TREPHINATION TECHNIQUES

Trephines that are currently used to incise the donor graft button and remove the recipient diseased cornea include handheld, suction, and automated devices. Skilled trephination technique is needed to avoid irregular and decentered cuts, which can lead to astigmatism and refractive error postoperatively.[4] Optimal outcome with both handheld and automated trephination systems is dependent on a centered perpendicular cut, use of a sharp blade edge, and a well-matched donor button and recipient bed.[5] Advances in manual trephination and the development of laser trephination devices can lead to improvement intraoperatively and postoperatively.

MANUAL TREPHINES

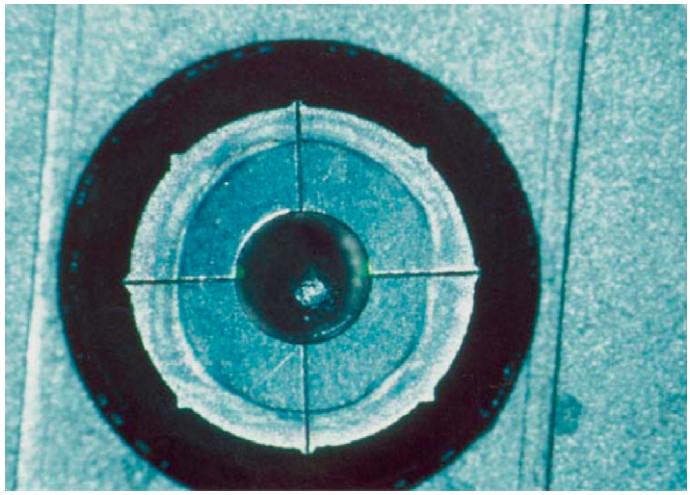
Manual trephination remains the most common incision technique because of ease of use, availability, and prohibitive aspects of laser trephination such as increased operative time and surgical cost. The development of suction and automated systems has improved reliability and reproducibility of corneal cuts. Sharp blade edges can reduce tangential and axial contact forces when cutting corneal tissue.[6] Nanotechnology, such as carbon coating of conventional trephine blades, can confer diamond-like cutting properties. While this is an improvement on current manual trephines, laser trephination can provide superior performance.[6]

LASER TREPHINATION

The use of lasers for trephination in keratoplasty was proposed over 15 years ago.[7] The theoretical advantages of nonmechanical trephination include elimination of axial and tangential contact forces, reduction of cut edge disparity with subsequent topographic distortions, and minimal trauma to intraocular tissue. The first laser trephination system to be used in penetrating keratoplasty was the excimer laser, which can create noncircular (i.e. elliptical) cuts through the application of variably shaped hardware masks.[8] Techniques such as positional spikes and orientation teeth can be used for the precise placement of the donor button in the recipient bed and as a visual aid for the placement of cardinal and secondary sutures (Fig. 69.1, *A–C*).[9] In a prospective, randomized, single center study, Seitz et al demonstrated an improvement in postoperative astigmatism, corneal topography, and best corrected visual acuity using excimer laser trephination compared to mechanical trephination in penetrating keratoplasty.[10,11] Astigmatism in the excimer trephination group was 3.0 D ± 2.1 D compared to the control group astigmatism of 6.1 D ± 2.7 D. While the control group astigmatism was significantly higher than most other previously published results using manual trephination, the laser trephination still produced slightly less astigmatism than most previously published studies. The results of the excimer laser series are important because they represent the largest and best-studied series of laser trephination keratoplasty.

FEMTOSECOND LASER KERATOPLASTY

The limitations of excimer laser keratoplasty include increased surgical time and cost associated with need for bulky machinery. To address some of these concerns, lower cost mid-infrared lasers such



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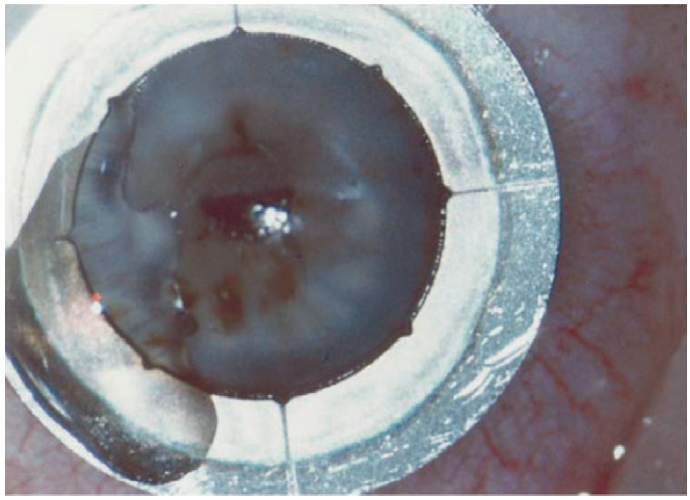

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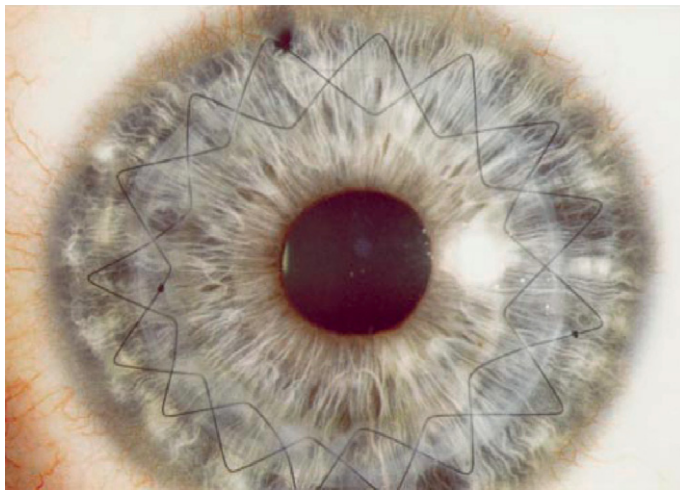

C

Figure 69.1. Excimer laser trephination: *A*, metal donor mask with eight orientation teeth on corneoscleral donor button fixed in an artificial anterior chamber; *B*, metal recipient mask with eight orientation notches on patient's cornea after focal perforation with exit of aqueous humor; *C*, 34-year-old male patient with keratoconus 6 months after nonmechanical penetrating keratoplasty with double-running suture in place. (Reprinted with permission from Seitz B, Langenbucher A, Nguyen NX, et al. Results of the first 1000 consecutive elective nonmechanical keratoplasties using the excimer laser. A prospective study over more than 12 years. Ophthalmologe 2004; 101(5): 478–488. With kind permission of Springer Science & Business Media).

as the hydrogen fluoride laser and erbium:YAG laser are being evaluated.[12,13] Most recently, the femtosecond laser is being investigated for lamellar and penetrating keratoplasty.[14–17]

The femtosecond laser is currently used in the USA for making anterior corneal flaps in LASIK surgery. It is a focusable infrared laser, similar to the more familiar neodymium-YAG laser, but utilizes instead ultrafast pulses in the hundred femtosecond (100×10–15 s) duration range. With the energy and firing pattern controlled by a computer, the femtosecond laser is capable of cutting tissue at various depths and patterns, producing very minimal inflammation and collateral tissue damage.[15–19] Thermal damage to adjacent tissue in the cornea has been measured to be in the order of 1 μm.[20] The laser essentially vaporizes small volumes of tissue by photodisruption, producing a plasma, shock wave, cavitation, and gas (CO_2 and H_2O) bubble generation. Unlike lasers employing visible wavelengths, the ability of the femtosecond laser to cut cornea is less hampered by optical haze, making it more useful in treating edematous corneas. The laser-control software may be programmed to produce intrastromal lamellar, axial, or pocket cuts at any depth or diameter. The laser spots may be fired in a spiral pattern or a zigzag (raster) pattern to achieve lamellar cuts. During treatment, the cornea is flattened with a suction-applanating lens to help immobilize the eye and to allow treatment of a geometrically simpler planar cornea. The femtosecond laser uses low energy coupled with higher power pulses to achieve a more rapid trephination. The laser-control software is also customizable to achieve different graft geometric configurations, potentially allowing for sutureless, self-adhesive keratoplasty, which will be discussed in greater detail later.[18,19]

FEMTOSECOND LASER-ASSISTED POSTERIOR LAMELLAR KERATOPLASTY

Femtosecond laser-assisted posterior lamellar keratoplasty has been performed with the laser control parameters, including energy, depth, and treatment diameter, programmed on the clinical femtosecond laser (FS-Laser, Intralase Corp., Irvine, CA) in both human eye bank eyes and an in vivo rabbit model (Fig. 69.2). Short applanating interface lenses (100–150 μm shorter in axial length than the standard LASIK lenses) are employed to allow the deep corneal treatment. The posterior trephination energy is higher (6.0–8.8 μJ) with trephination diameters of 6.0–7.0 mm diameter to assure complete detachment of the peripheral edges in deep stroma. The laser firing sequence for the trephination begins in the anterior chamber and moves progressively forward through endothelium, Descemet's membrane, and posterior stroma. Following completion of posterior trephination, the laser parameters are reset to cut the lamellar interface at a depth of 150–200 μm anterior to the endothelial surface with the energy set at 6.0–8.7 μJ. The diameter of the lamellar cut is oversized 1–2 mm larger than the trephination diameter in order to assure that the two cuts intersect. A limbal corneal paracentesis is made. The femtosecond laser or a blade may be used to create a 4-mm tunnel incision in the peripheral cornea in order to enter the lamellar interface plane. The interface is swept with a Barraquer iris sweep to release the posterior corneal disk, which is then removed from the eye through the incision with Utrata capsulotomy forceps.

The donor tissue is prepared by mounting the corneoscleral buttons in an artificial anterior chamber device. The laser treatment is rendered through the applanating lens in the same manner as with the globes and the corneoscleral button is removed from the artificial anterior chamber and placed on a Teflon block endothelial-

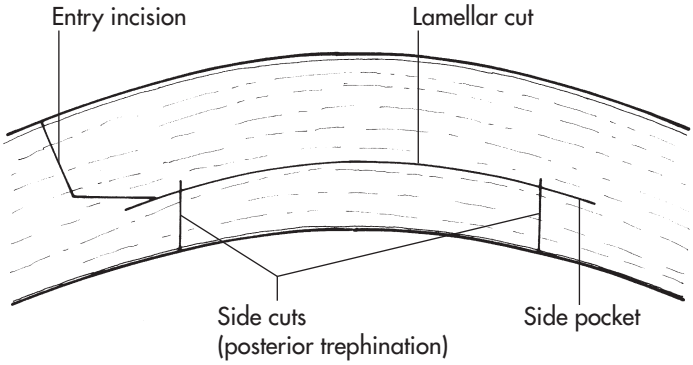

Figure 69.2. Femtosecond laser posterior lamellar keratoplasty: schematic cross-sectional view of lamellar and trephination cuts. Lamellar bed is oversized peripherally to assure intersection of cuts and to create side pocket to secure donor disk edge. Laser spot firing sequence begins in anterior chamber, just posterior to endothelium, and progresses in anterior direction into stroma. Peripheral corneal incision is made manually from anterior corneal surface with crescent blade and connects to lamellar interface. (Reprinted with permission from Soong HK, Mian S, Abbasi O, Juhasz T. Femtosecond laser-assisted posterior lamellar keratoplasty: initial studies of surgical technique in eye bank eyes. Ophthalmology 2005; 112(1): 44–49, © Elsevier 2005.)

side up. Grasping an edge of the posterior corneal disk with Utrata forceps and an edge of the parent corneoscleral button with Harms forceps, the disk is gently peeled apart from the button. The posterior corneal disk is then folded taco-style, with the endothelial surface inside, protected by a thin coat of viscoelastic material. The folded disk is held with Utrata forceps and inserted into the posterior stromal bed through the incision.

SUTURELESS CORNEAL ADHESION

Sutures are currently the gold standard for the adhesion of the corneal graft to the recipient bed. Sutures play a particularly vital role in penetrating keratoplasty, where they may remain for over a year to allow full support during tissue healing. However, astigmatism is the major flaw of sutures as a fastening agent.[20] Numerous suture techniques have been developed in attempts to reduce astigmatism.[21–23] Significant interest remains in sutureless techniques that could theoretically reduce this undesirable surgical outcome. Sutureless adhesion techniques can possibly reduce surgical time and epithelial growth beneath flaps/grafts, decrease postoperative follow-up, and eliminate a possible source of irritation, inflammation, graft rejection, and infection.

GLUE

Glues have been used previously in ophthalmology, particularly for treating corneal perforations. Glues commonly used in ophthalmology can be subdivided into synthetic adhesives (e.g. cyanoacrylate derivatives) and bioadhesives (e.g. fibrin glues). Cyanoacrylates are not suitable for use as a tissue adhesive in penetrating keratoplasty because they behave as a foreign body that is impermeable to fluids and metabolites. Bioadhesives, on the other hand, disappear over time but still provide the necessary tensile strength for successful closure of the adhesive surface.

The use of glues as a corneal surgical aid is still being explored. Kang et al described the successful use of two novel biodendrimer tissue adhesives in the closure of laser in situ keratomileusis (LASIK) flaps in human eye bank eyes.[24] The authors postulated that the use of these adhesives in surgeries that involve stromal flap creation, such as lamellar keratoplasty, can reduce the incidence of epithelial ingrowth. Pirouzmanesh et al developed an experimental model for microkeratome-assisted posterior lamellar keratoplasty comparing the tensile strength provided by a chondroitin-sulfate-aldehyde adhesive versus five interrupted sutures. They found that the mean pressure at which leakage occurred were slightly lower for the bioadhesive but not by a statistically significant amount (95.68 for sutures vs 82.45 for the adhesive). In addition to this, there was a significant decrease in the amount of astigmatism as recorded by videokeratoscopy (3.08 D for sutures vs 1.13 D for adhesive).[25] Kaufman et al successfully used fibrin glue in a small series of sutureless lamellar keratoplasties.[26] While these surgeries were successful, the authors concluded that further improvements would need to be made before the fibrin glue could gain widespread use.

LASER TISSUE WELDING

Tissue welding has been extensively studied in vascular surgery using low energy laser beams. Laser tissue welding is defined here as the attempt to produce full-thickness, continuous adhesion of ocular tissue without the aid of photosensitizing dyes or chromophores. Several animal models have studied the application of lasers such as hydrogen fluoride and CO_2 for corneal tissue welding.[27,28] A porcine model of keratoplasty using a near infrared (NIR) laser has been used to form full length welds of corneal tissue with high tensile strength.[29] Initial results from this study suggest that laser tissue welding may be used as an adjunct for sutureless closure in corneal surgeries since the welding creates minimal tissue disruption, resulting in minimal corneal opacification or change in surface contour. Ultimately, the mean tensile strength of the laser-welded tissue was only one-tenth of sutured tissue, likely limiting its use as an independent corneal tissue adhesive.

KERATODESMOS

Photochemical keratodesmos (PKD) is a method of producing sutureless adhesions by applying a photosensitizer to wound surfaces followed by low energy laser irradiation. The laser promotes cross-linkage between collagen molecules on opposing surfaces to produce a tight seal without inducing thermal damage to the adjacent tissue. A specific PKD model which utilizes rose bengal dye activated by low-energy laser irradiation with argon ion laser at wavelength of 514 nm has been studied in rabbit models in the setting of lamellar incisions, corneal incisions, and PKP models.[30–32] An initial ex vivo model using enucleated rabbit eyes demonstrated that the intraocular pressure needed to produce leakage from a lamellar wound sealed with PKD was similar to that seen with radial 10-0 nylon sutures. An in vivo study looking at the closure produced by PKD for a 3.5-mm non-self sealing corneal wound 2 mm anterior to the limbus in New Zealand white rabbits demonstrated strong closure up to 14 days after surgery. This same PKD system was ultimately tested for penetrating keratoplasty in New Zealand white rabbits (Fig. 69.3). One eye received both 16 interrupted sutures and rose bengal PKD with 2 min of irradiation at 532 nm. The other eye, with only 16 interrupted sutures, served as the control group. The wound leakage began at 250 mmHg of intraocular pressure in the control group and 410 mmHg in the treated eye group ($p < 0.05$, paired t-test). The authors concluded that photochemical keratodesmos may be a useful adjunct to sutures in the immediate postoperative period.

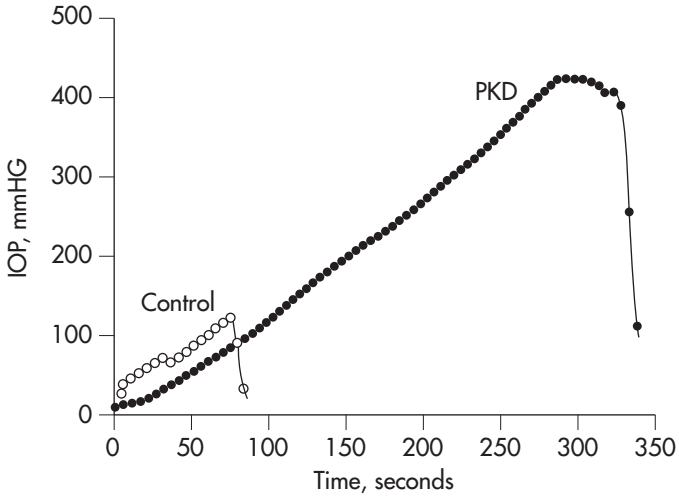

Figure 69.3. Photochemical keratodesmos (PKD) with penetrating keratoplasty: The intraocular pressure (IOP) in the PKD-treated eye (•) is significantly higher when compared to the control eye (◦) of the same rabbit. (From Proano CE, Azar DT, Mocan MC, Redmond RW, Kochevar LE.[30] © 2004 with permission from Elsevier.)

Clinical confirmation that PKD can be used was demonstrated by Pini et al, who successfully utilized diode laser radiation (805 nm) at low power in conjunction with the chromophore indocyanine cardio-green (ICG).[33] This system was used for the successful closure of three penetrating keratoplasties in conjunction with placement of eight sutures.

CUT AND PASTE KERATOPLASTY

Traditional penetrating keratoplasty relies on preparation of a circular donor button to fit into a matched recipient bed. The wound in routine penetrating keratoplasty utilizes vertical, edge-to-edge wound healing where fairly tight sutures are needed to secure the donor button. A fundamental change in shape of the donor button and recipient bed in order to produce an inherently stable corneal graft may reduce the need for sutures or allow for sutureless adhesion.

SURGICAL CUT AND PASTE

Busin has described a 'nut and bolt' or inverse mushroom configuration surgical technique for penetrating keratoplasty.[34] The technique as described by Busin attempts to create a corneal donor button that closely matches the recipient bed. Shaped keratoplasty is a two-level keratoplasty characterized by a different size of the anterior and posterior layers of the cornea. The donor button is prepared using a 7.0-mm Barron suction trephine to make a circular, 0.3-mm incision in the corneal bed from the epithelial side. Next, a bevel up stromal lamellar dissection is performed with a knife out to the limbus. Finally, the cornea is placed endothelial-side up in a Barron suction punch and a 9.0-mm donor button is punched out. Similarly, the recipient bed is prepared using a 7.0-mm Barron suction trephine to make a 0.3-mm deep incision. A bevel up knife dissection is done 1.0 mm peripherally in the lamellar stroma. Finally, corneal scissors are used to complete the excision of the corneal button from the peripheral end of the posterior lamellar stroma. The corneal graft is then placed in the recipient bed and secured with a loose running 10-0 nylon suture. The sutures are removed as early as 3 months, thus, significantly reducing the dependency on sutures to hold the edges firmly together. The ability to remove all sutures as early as 3 months in Busin's series implies that there may be improved stability of this graft configuration.

LASER CUT AND PASTE KERATOPLASTY

Laser techniques are well suited for carrying out the steps of cut and paste keratoplasty. Both the excimer laser and Er:YAG lasers are able to create divergent cut angles that produce conical incisions with wider endothelium diameter than epithelial diameter.[35,36] The advantages of this configuration include use of intraocular pressure to push the corneal graft into the recipient bed, increase in wound surface, and increase in number of endothelial cells transplanted, especially important in disorders with endothelial cell dysfunction (e.g. Fuchs' dystrophy).

Ex vivo animal cornea studies looking at the femtosecond laser and the use of alternative incisions such as 'inverse mushroom' and conical incisions have yielded interesting results. Animal models have shown the feasibility of using the femtosecond laser to create conical corneal incisions that range from 0 to 60° from the sagittal axis, as well as the addition of positional orientation spikes.[19] Taking this one step further, a femtosecond laser was used to create 'top hat' configurations out of both polymethylmethacrylate (PMMA) and porcine corneas.[18] A laboratory model showed that the 'top hat' configuration created by the femtosecond laser was slightly more mechanically stable than that of traditional penetrating keratoplasty.[37]

ALTERNATIVES TO HUMAN TISSUE KERATOPLASTY

There has been great interest in the development of alternatives to human tissue keratoplasty due to risk of graft failure and rejection, limited supply of human tissue, and risk of transmission of infections. Graft failure remains a significant concern, especially in high-risk groups like herpes simplex keratitis, repeat keratoplasty, and Stevens–Johnson syndrome. In addition, rates of graft survival vary greatly amongst different clinical series, with geographic region being one major variable. The rate of graft rejection in these high-risk groups can range from 30 to 50%.[38] When viewing blindness secondary to corneal pathology in a worldwide perspective, there is even more motivation to develop alternatives to cadaveric corneas. For example, while there is currently no waiting list for corneal transplantation in the USA, in developed countries such as Japan there is much less cadaveric tissue available. This shortage will likely only continue to increase as factors such as refractive surgery continue to reduce the potential tissue supply. On a global level, there are currently over 10 million cases of blindness secondary to corneal opacification, with infectious and ocular surface disease causing scarring being quite common in underdeveloped countries.[39] The potential advantages of artificial corneas include eliminating the risk of graft rejection and reducing the need for long-term follow-up. We will examine three possible alternatives to human donor tissue keratoplasty: new corneal replacements, which can be subdivided into keratoprosthesis and tissue-engineered corneal equivalents; stem cell and endothelial cell transplantation.

KERATOPROSTHESIS

Numerous keratoprosthetic devices are already available such as the Boston (Dohlman-Doane) (Chapters 78, 79), osteo-odonto, Alpha-

Cor, and BIOKOP prostheses. However, all of these prostheses have features that can be improved upon such as biocompatibility of materials and long-term complications including inflammation, infection, and glaucoma. An ideal synthetic keratoprosthesis must perform all of the basic functions of a native cornea. These include but are not limited to (1) transparency, (2) barrier functions, (3) permeability to oxygen and nutrients, (4) avoid toxic, immune, and inflammatory responses, (5) biocompatibility and integration into the surrounding tissue.[40] Current research aims to improve keratoprosthetic materials and growth of a corneal epithelial cell layer over the anterior surface of the keratoprosthesis.

Both PMMA (polymethylmethacrylate) and pHEMA (poly-2-hydroxyethyl methacrylate) are being evaluated to optimize keratoprosthesis function as assessed by all five native cornea functions. While the use of pHEMA in the AlphaCor prosthesis has improved biointegration, there continues to be a lack of epithelialization of the anterior surface and inferior mechanical strength. Tensile strength is an important characteristic for the skirt portion of the core-and-skirt model because it anchors the prosthesis to the eye. Research is being carried out to strengthen pHEMA by copolymerization and altering the cross-linking agents.[41] PDMS (polydimethylsiloxane), PDMS-poly (*N*-isopropyl acrylamide), and perfluoropolyether-based products are being developed in hopes of creating even better keratoprosthetic materials. For example, PDMS-poly (*N*-isopropyl acrylamide) shows improved glucose permeability levels over previous materials.[42]

The ability to maintain an epithelial surface is important as it provides a barrier of protection from the tear film, proteinases, and inflammatory cells. Properties of the implant surface such as hydrophilicity, porosity, topography, adhesiveness, and permeability to nutrients are vital to an implant's epithelialization ability. For example, pore sizes of less than 1 μm promote epithelial cell proliferation.[43] In an attempt to liken the implant surface to that of the epithelial basement membrane, extracellular matrix proteins (collagen, laminin, etc.) and fibronectin have been coated over implant surfaces and have been shown in in vitro studies to increase epithelial cell adhesion and proliferation. Growth factors are another promising way of both promoting epithelialization on the anterior surface of implants and avoiding retroprosthetic membrane formation. Epidermal growth factor (EGF) is being studied as a promoter of epithelium on the anterior surface of PDMS, while coating TGF-beta on surfaces results in a downregulation of cell adherence.[44,45]

ARTIFICIAL CORNEAS

Tissue engineered corneal equivalents have the same basic goal as keratoprostheses; however, they are made of the same central collagen layer and cell types (epithelial cells, keratocytes, endothelial cells) that are found in the cornea. These corneal alternatives aim to improve integration into the eye while retaining important functions of the cornea such as wound healing and sensitivity (if nerve innervation can be achieved).

There are several artificial cornea models that have been proposed including the French LOEX model, the University of Minnesota collagen sponge model, and the University of Ottawa composite model. The University of Ottawa composite model developed by Griffith et al may represent the closest of these models to a system that would be practical for human use. This artificial cornea model has been shown to resemble the human cornea optically while at the same time being mechanically strong enough to be successfully sutured onto human corneal limbal rings and rabbit eyes.[46,47]

Preliminary results demonstrate that tissue-engineered corneas can reproduce some of the desirable features of the cornea. For example, in an in vitro study using collagen scaffold cross-linked with *N*-isopropyl-acrylamide, acrylic acid, and acryloxysuccinamide, neurite ingrowth was demonstrated in the collagen hydrogel with the application of nerve growth factor (NGF) and Tyr-Ile-Gly-Ser-Arg (YIGSR) peptide.[48,49] These reconstructed corneas regained some touch sensitivity 7–14 days after surgery and demonstrated epithelial growth with nerve ingrowth.

There still remain significant issues to be addressed before tissue-engineered corneas can be considered for human use. The corneal scaffolds developed to date lack the requisite strength to be considered for long-term use in humans. The strength of these collagen hydrogels has been improved by increasing collagen concentrations as well as cross-linking the collagen with different agents.[50] Further in vivo studies will be needed to determine how close artificial tissue-engineered corneas are to becoming a feasible alternative in humans.

EPITHELIAL CELL TRANSPLANTATION

The corneal epithelium is replenished by a population of stem cells located in the basal epithelium at the corneoscleral limbus. This population of cells is particularly important in keratoplasty as conditions lacking epithelial stem cells, such as aniridia and severe chemical burns, are much more difficult to successfully treat with PKP. It has been shown that the renewal of this stem cell population by either autologous or homologous transplantation of limbal stem cells can help to maintain a healthy ocular surface in these conditions.[51,52]

While the successful transplantation of corneal epithelial stem cells has already been achieved, two exciting areas of future improvement are the better identification of the stem cells using cellular markers and the application of cultured epithelial stem cells. The identification of stem cell cellular markers is an area of keen interest as better identification of these cells could allow for more effective cell transplantation. Determining which markers most effectively distinguish true epithelial limbal stem cells from their early progeny has proven difficult because there are conflicting data on several of the most promising markers, including the p63 transcription family, ATP binding cassette transporter G2, and different cytoskeletal proteins.[53–55] Another interesting application of better identification of stem cells is that stem cells from tissue other than the corneoscleral limbus may be a potential source of cells, such as the conjunctiva.[56]

ENDOTHELIAL CELL TRANSPLANTATION

Endothelial dysfunction (Fuchs' dystrophy, post-cataract surgery endothelial cell loss, etc.) is a major indication for keratoplasty currently, particularly in developed countries. Optimal treatment involves endothelial cell transplantation alone, with the transfer of either primary or transfected human corneal endothelial cells (HCEC) into a patient's eye. Research into this promising field currently focuses on two major areas: the preparation of appropriate cultured HCEC that can be functional after transplantation and the development of an appropriate carrier for the cells.

The challenge in establishing a functional pool of cultured HCEC is to ensure that the cells have enough proliferative capability to maintain a sufficient cell density in the transplanted cornea but at

the same time to control the proliferation so that the proliferation stops after the establishment of a close monolayer. An immortalized line of HCEC that has been transfected with the large and small antigen of the SV-40 virus shows the necessary regenerative capacity, however they continue to divide after establishing a monolayer.[57] For transfected cell lines like these to be effective, the vector system that exerts its proliferative influence would have to shut down after the successful establishment of a monolayer with sufficient cells.[58] Alternatively, manipulation of external influences on the endothelial cells such as growth factors can be used. Different cell transport systems include gelatin membranes, coated hydrogels, and amniotic membrane with all of these systems showing potential for facilitating cell transportation.[59–61]

SUMMARY

In summary, techniques for keratoplasty are continuing to evolve with technological advances such as the femtosecond laser. Laser trephination may help improve visual outcomes with improved wound apposition and reduced astigmatism. Sutureless or near sutureless keratoplasty may also further improve visual outcomes and reduce rates of neovascularization, rejection, and infection secondary to sutures. Finally, alternatives to human tissue keratoplasty may not only allow for optimal visual outcomes and reduced complications but reduce dependency on donor tissue availability.

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70 Chemical injuries of the eye

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Concentrated chemicals splashed into the eye produce severe and prolonged ocular complications. The result can be devastating, with major medical, surgical, personal, social, and economic ramifications. When the injury is bilateral, the patient's world collapses, forcing family, and ultimately society, to bear the brunt of personal and financial needs. Although these events are fortunately not very frequent, the magnitude of the problem and the benefits of reestablishing vision have forced a major effort to uncover the best management protocol for control of complications and to determine optimal treatments to regain vision. To this end, a generation of research has significantly improved the prognosis and made visual rehabilitation a realizable goal.

EPIDEMIOLOGY

Chemical injuries are sustained in the workplace, in home environments, or as a method of assault. Only in large industrial workplaces can safety engineers control the incidence of injury through education and minimizing risk from dangerous equipment or areas. Despite such programs, the storage and use of powerful alkalis, sometimes under extreme pressure and high temperature, continue to pose serious threats even to the properly attired worker wearing protective clothing and goggles. Unprepared farmers using liquid ammonia as fertilizer and homeowners using powerful cleansing agents often do so without eye protection.

The most common cause of a severe alkali injury of the eye in USA has been an assault. Data gathered from a large urban hospital show that young black men are at greatest risk, usually in a domestic setting, where there is low income, high-density housing, and a record of alcoholism and prior assaults.[1] In the industrial sector, approximately 10% of 52 142 cases of ocular trauma reported from 16 states were chemical injuries (1.6% acid, 0.6% alkali).

Of 221 chemical injuries reported in 180 patients at the Croyden Eye Unit, UK, almost half were caused by alkali in males (75.6%) between the ages of 16 and 25.[2] Accidental injuries accounted for 89.4%; the remainder assaults. Work-related accidents numbered 63%, 33% occurred at home and 3% at school.

Two large series of chemical injuries were reported by Kuckelkorn and colleagues in Aachen, Germany in 1990–1991.[3,4] In the first report, 236 injuries occurred in 171 patients of whom 70% were males. Industrial accidents numbered 61%, 37% were household and 2% unknown. Most injuries were classified as mild (88%). In their second series, they evaluated 42 patients sustaining severe alkali injuries occurring over a 7-year period. The industrial sector contributed 73.8% while the rest were sustained at home.

Certain types of automobile airbags, upon deployment, can release sodium hydroxide as part of the chemically driven rapid inflation process, causing corneal abrasions and mild alkali injuries. Although these cases make up 21.6% of eye injury cases caused by airbags, in most cases they heal readily.[5]

The type of chemical injury can be acidic, alkaline, or toxic. Strong acid injuries include sulfuric, hydrochloric, muriatic, etc. Alkalis causing eye injury include ammonium hydroxide, sodium hydroxide, potassium hydroxide, magnesium hydroxide, and calcium hydroxide. Toxic agents include a huge variety of chemicals which are destructive to biological tissues, but which are not particularly acidic or alkaline. Table 70.1 summarizes the possible source and relevant comments pertaining to the commonest types of acid and alkali injury. Wagoner presents a comprehensive review of chemical injuries.[6]

MAJOR CHEMICAL DIFFERENCES BETWEEN ALKALI, ACID, AND TOXIC INJURIES OF THE EYE

ALKALINE

The pain, lacrimation, and blepharospasm following an ocular alkali injury result from direct injury of free nerve endings located in the epithelium of the cornea, conjunctiva, and eyelids. Ammonium ions penetrate the eye almost instantaneously but a delay of 3 to 5 min occurs after sodium hydroxide.[7] Depending on the severity of the injury, a wave of hydroxyl ions rapidly advance through ocular tissues, causing saponification of cellular membranes with massive cell death and extensive hydrolysis of the corneal matrix consisting of glycosaminoglycans and collagen. Lye injuries (i.e. sodium hydroxide (NaOH), caustic soda, sodium hydrate) occur most often when it is used as a drain cleaner. Potassium hydroxide

Table 70.1 Common causes of chemical injury

Class	Compound	Common Sources and Uses	Comments
Alkali	Ammonia [NH_3]	1. Fertilizers 2. Refrigerants 3. Cleaning agents (7% solution)	1. Combines with water to form NH_4OH fumes 2. Very rapid penetration
	Lye [NaOH]	Drain cleaners	Penetrates almost as rapidly as ammonia
	Potassium hydroxide [KOH]	Caustic potash	Severity similar to that of lye
	Magnesium hydroxide [$Mg(OH)_2$]	Sparklers	Produces combined thermal and alkali injury
	Lime [$Ca(OH)_2$]	1. Plaster 2. Mortar 3. Cement 4. Whitewash	1. Most common cause of chemical injury in workplace 2. Poor penetration 3. Toxicity increased by retained particulate matter
Acid	Sulfuric acid [H_2SO_4]	1. Industrial cleaner 2. Battery acid	1. Combines with water to produce corneal thermal injury 2. May have associated foreign body or laceration from battery acid
	Sulfurous acid [H_2SO_3]	1. Formed from sulfur dioxide (SO_2) by combination with corneal water 2. Fruit and vegetable preservative 3. Bleach 4. Refrigerant	Penetrates more easily than other acids
	Hydrofluoric acid [HF]	1. Glass polishing 2. Glass frosting 3. Mineral refining 4. Gasoline alkylation 5. Silicone production	1. Penetrates easily 2. Produces severe injury
	Acetic acid [CH_3COOH]	1. Vinegar—4–10% 2. Essence of vinegar—80% 3. Glacial acetic acid—90%	1. Mild injury with less than 10% concentration 2. Severe injury with higher concentration
	Chromic acid [Cr_2O_3]	Used in the chrome plating industry	Chronic exposure produces chronic conjunctivitis with brown discoloration
	Hydrochloric acid [HCl]	Used as a 32–38% solution	Severe injury only with high concentration and prolonged exposure

Adapted from McCulley JP. Chemical injuries. In: Smolin G, Thoft RA, eds. The Cornea: Scientific Foundations and Clinical Practice. 2nd edn. Boston: Little Brown; 1987.

(KOH, caustic potash) and magnesium hydroxide ($Mg(OH)_2$) are encountered infrequently as causes of chemical injuries of the eye. Magnesium hydroxide is found in sparklers and flares; the combination of thermal and chemical injury accounts for more severe injury.

Lime ($Ca(OH)_2$), fresh lime, quicklime ($CaO + H_2O = Ca(OH)_2$), calcium hydrate, slaked lime, hydrated lime, plaster, mortar, cement, and whitewash are some of the more commonly encountered substances producing ocular burns.

ACIDIC

Weak acidic compounds on contact with the outer eye precipitate proteins within the corneal and conjunctival epithelium, thus acting as a partial barrier to further ingress of the chemical. In its wake is left a grayish white epithelium, which often obscures all tissues, posterior to it. Stripping off this opacified epithelial layer often reveals an underlying clear corneal stroma. As long as the corneal stem cells ringing the cornea are not damaged

then epithelial recovery is likely with relatively little or no stromal cloudiness.

Very strong acids, however, overcome this precipitated proteineous obstacle handily and progress through tissue much as alkali. The end result of a very severe acidic injury is often indistinguishable from that of an alkaline injury. For that reason this chapter will deal with alkaline and acid injuries as one, unless otherwise specified.

TOXIC

Hydrofluoric acid, used for centuries in industry, has found a new use in the semiconductor industry where it is essential technology in the manufacture of silicon chips for computers and other devices controlled by digital technology. It is so highly toxic that as little as 7 mL, or 2.5% burn of the body is sufficient to cause death from uncontrolled hypocalcemia.[8]

For the subgroup comprising mustard gas injuries occurring during military campaigns, the reader is referred to a comprehensive review.[9]

NATURAL CLINICAL HISTORY

The immediate pain, lacrimation, and blepharospasm following an ocular alkali injury result from direct stimulation and destruction of pain receptor nerve endings located in the epithelium of the cornea, conjunctiva, and eyelids. Pain is also associated with severe burns of cornea and sclera where there is a sudden, spiking rise in the intraocular pressure, lasting about 10 min, caused primarily by shrinkage of the collagenous envelope of the eye. A more prolonged rise in pressure quickly follows, secondary to prostaglandin release.[10] Strong alkali rapidly penetrates into the eye and remains unneutralized, overcoming the poor buffering capacity of the aqueous humor and anterior segment tissues. In much less than 1 min the aqueous humor pH rises to greater than 12, causing saponification of plasma membranes with lysis of corneal cells as well as those lining and adjacent to the anterior chamber. The blood–aqueous barrier is destroyed, removing the physiologic cellular pumping mechanisms and releasing necrotic cellular debris into the aqueous humor. A severe fibrinous inflammatory reaction supervenes in the entire anterior segment of the eye.

Glaucoma may ensue from necrotic and inflammatory debris accumulating in the aqueous humor and chamber angle obstructing outflow, later promoting anterior synechial closure, especially inferiorly. The trabeculum and ciliary body might be injured directly by the penetration of alkali through the sclera or by contact with alkalotic aqueous humor percolating through the meshwork. Ocular hypertension, hypotension, or both may occur at different time periods, depending on the predominance of one or more factors. Chemical injury to iris, crystalline lens, and ciliary body may produce mydriasis, cataract, and even phthisis bulbi, respectively. Externally, this inflammatory reaction may be so profound as to lead to extensive symblephara and even ankyloblepharon from the apposition of raw conjunctival surfaces.

WOUND HEALING

Repair of the chemically damaged eye is a complex process unique to each tissue and involving each cellular and extracellular tissue layer, including the eyelids, corneal and conjunctival epithelium, fibroblasts and collagen, endothelium, and all other tissues contiguous to the anterior chamber.

Epithelium

Destruction of the corneal epithelium alone in a mild injury might lead to nebular superficial scarring or to recurrent corneal erosions, resulting from injury to basal lamina and anterior corneal stroma. When the injury to cornea is more intense, but limited to the cornea and leaving the epithelial stem cell population intact, then epithelial healing is likely to proceed unimpeded. On the other hand, a very severe experimental alkali injury of 12 mm in rabbits, which does not destroy the limbal stem cells, showed substantial epithelial adhesion problems leading to persistent epithelial defects.[11,12] In this animal model, epithelial movement initially proceeds at a rate similar to that occurring after an abrasion, but stops at 84 h at the time when the leading epithelial edge loses its adherence to the stroma and then subsequently peels back as a sheet at 96 h. Thereafter a persistent epithelial defect is maintained. It has been suggested that this loss of epithelial adhesion might result from accelerated degradation of the fibronectin surface coating by plasminogen activator, a substance probably secreted in excessive amounts by the basal epithelial cells in the alkali-injured eye.[13] Therefore, in the chemically injured cornea, the presence of a normal corneal stem cell population does not necessarily imply that epithelial healing is assured. In fact, some of these persistent epithelial defects might issue from the consequences of a severely degraded stromal matrix. Clearly, epithelial–stromal interaction plays an important role in the adhesion of epithelium to stroma.

When a portion of the limbal stem cells is destroyed, the remaining stem cell population heals by centrifugal propagation of pluripotential epithelial stem cells around the corneal periphery combined with centripetal ingrowth of transient amplifying and terminally differentiated cells on to the denuded cornea. If the injury destroys the entire limbal palisades of Vogt containing stem cells, then the phenotypic source of corneal epithelium is lost and the cornea remains denuded for months, finally resurfaced by the spread of viable conjunctival epithelial cells over a blanket of vascularized scar tissue (pannus).

Stroma

Healing of the corneal stroma in a timely manner is the key to avoidance of ulceration and perforation of the globe. Two events proceed simultaneously in the repair process: (1) degradation and removal of necrotic debris, and (2) replacement of portions of the fixed cells, collagenous matrix, and glycosaminoglycans. Concentrated alkali strips the cornea of its vital cells and glycosaminoglycans, leaving behind much of the skeletal framework of the collagen in a denatured form. Alkali degradation of cellular and extracellular proteins yields inflammatory mediators, which are chemotactic to neutrophils.[14] At high concentrations, these simple tripeptides, consisting of acetylated or methylated proline–glycine–proline tripeptides, constitute powerful attractive agents, appearing to initiate and promote neutrophilic invasion of the cornea. This might represent one of the signals from the wound inducing the secretion of adhesion molecules from the vascular endothelium (*E*-selectin) and the intravascular leukocytes (L-selection) to incite leukocyte rolling leading to adhesion to the vascular endothelium.

Once neutrophils accumulate, their release of leukotrienes, and in the presence of interleukin-1 alpha and 6, serves to recruit successive waves of inflammatory cells resulting in a downward spiraling cascade of tissue destructive events. These inflammatory

components serve to perpetuate surface inflammation, with continued release of a variety of degradative enzymes including *N*-acetylglucosaminidase and Cathepsin-D into the tissues and tear film. The positive side of neutrophil presence is the finding that they seem to stimulate epithelial proliferation when examined by its proliferative cellular nuclear expression.[15] In this study, neutrophils appear to act as the initiating messenger promoting the process of corneal vascularization.

Alkali injury of collagen also releases a second inflammatory mediator which metabolically stimulates the local neutrophils to undergo a respiratory burst. Prodigious oxygen use by the stimulated neutrophils results in the by-product superoxide radicals, an unstable form of oxygen that is highly destructive of tissues. When the mediator is present in excess there is also extreme stimulation, causing polymorphonuclear leukocyte (PMN) lysis with the release of granules containing a wide variety of enzymes. The release and activation of degrader enzymes from the specific and azurophilic granules of PMNs act to destroy tissue by cleaving proteins and other molecular species. These responses serve to promote dissolution of the remaining degraded corneal stroma, tipping the scales toward corneal ulceration and perforation.

Fibroblasts invading the cornea after severe alkali injuries are immature, with their polysomal systems in disarray. Collagen produced from these cells is underhydroxylated, preventing it from winding into the triple helical structure of normal collagen. These individual strands of amino acids are highly vulnerable to enzymatic lysis. These tissue characteristics are the sine qua non of localized tissue scorbutus.[16] As a result of this ascorbate deficiency, the repair process is faulty, with the destruction–repair equation shifted in the direction of tissue disappearance and hence corneal ulceration. In very severe injuries, fibroblasts invade the cornea slowly or not at all, resulting in rapid conversion of stroma to a necrotic sequestrum.

Endothelium

In mild injuries, penetration of alkali is minimal and the endothelium is undamaged. Moderate injuries probably cause some endothelial cell death but mostly interfere with the pump mechanism, leading to a variable degree of reversible corneal edema. Severe injuries will destroy endothelium, leading to severe corneal thickening. Alternately, the simultaneous loss of glycosaminoglycans, which bind water in the cornea, might result in less significant net gain or loss of thickness during the early stages; only an opaque cornea.

CLASSIFICATION OF ALKALI INJURIES

Understanding and documenting the salient findings in an alkali injury of the eye permit proper classification so that appropriate immediate treatment can be initiated and accurate prognostication adduced. Documentation of the following physical data is recommended in the form of a labeled drawing:

1. Epithelial defect: Instill fluorescein and measure the size and draw the shape of the defect. Include any conjunctival epithelial defects, especially as they relate to the perilimbal conjunctiva (stem cells).
2. Stromal opacity: Gradations are made on the basis of a penlight examination. Grade 0 represents clear cornea; grade 1, mild corneal haze; grade 2, mild to moderate opacity; grade 3, moderate opacity; grade 4, moderate to severe opacity, in which details of iris trabeculae cannot be seen but the pupil is visible; grade 5, severe corneal opacity, in which the pupil is not visible with a penlight.
3. Perilimbal ischemia: Document the clock hours at which the conjunctiva is whitened. In these areas, the conjunctiva and episclera are devoid of blood vessels. This whitening is not to be confused with less severe injury in which there is chemosis and thrombosed blood vessels but the conjunctiva is still pink.
4. Adnexa: The blinking pattern, exposure, or lagophthalmos should be measured and documented.

These measurements and findings can then be applied to the classification of alkali injuries as described by Hughes[17] and modified by Pfister and Koski[18] (Figs 70.1–70.5). This classification, with accompanying drawings, represents the span of damage encountered after alkali injury. The accuracy of early assessment becomes very important in subsequent evaluation and treatment plans.

Regarding terminology, the literature is replete with allusions to alkali burns, potentially confusing the alkali injury terminology with a thermal component that might or might not exist. This

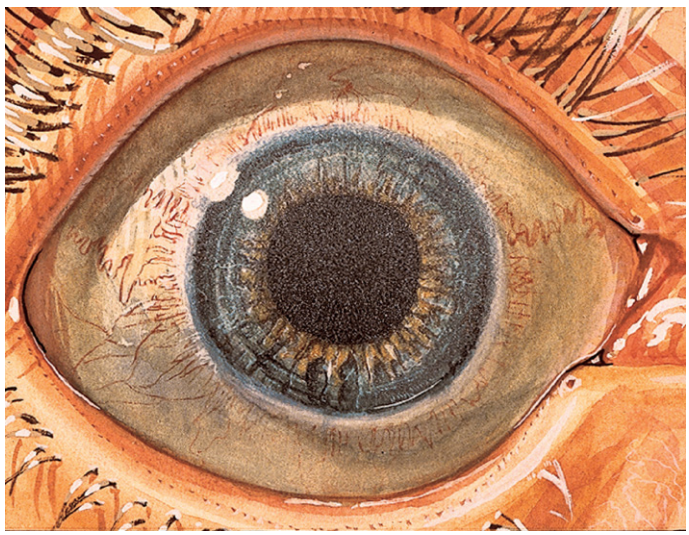

Figure 70.1. Classification of alkali-burned eyes—mild (1-a): Corneal epithelial erosion, faint anterior stromal haziness, no ischemic necrosis of perilimbal conjunctiva and sclera. Prognosis: healing with little or no corneal scarring; visual loss usually no greater than one or two lines.

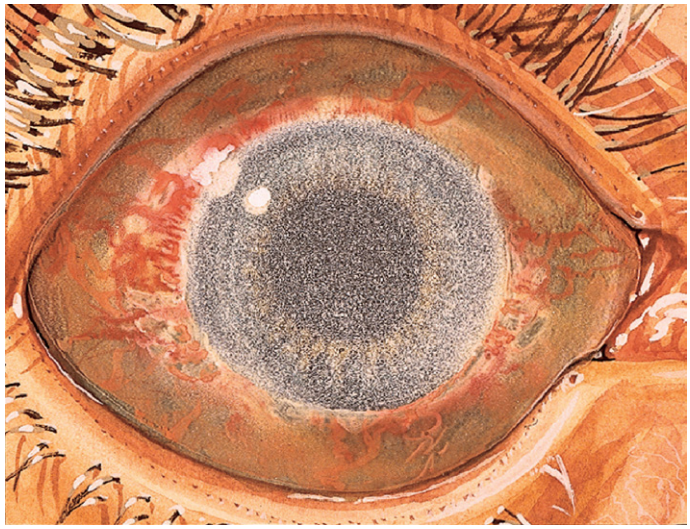

Figure 70.2. Classification of alkali-burned eyes—moderate (1-b): Moderate corneal opacity, little or no significant ischemic necrosis of perilimbal conjunctiva. Prognosis: slow healing of epithelium with moderate scarring, peripheral corneal vascularization, and visual loss of two to seven lines.

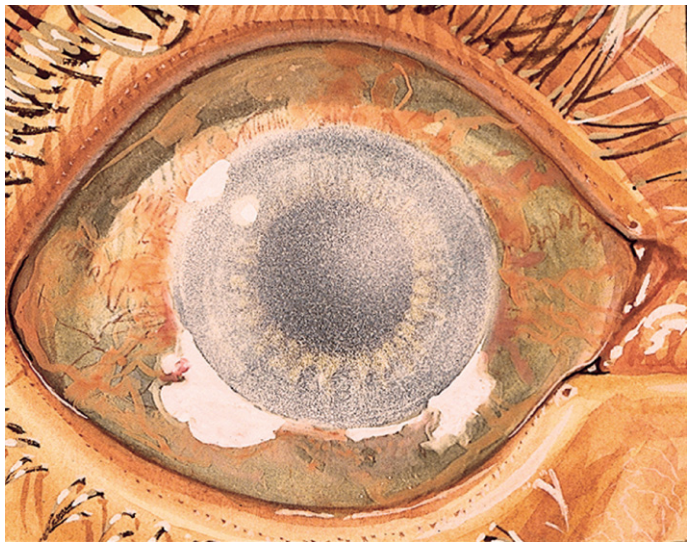

Figure 70.3. Classification of alkali-burned eyes—moderate to severe (1-c): Corneal opacity blurring iris details, ischemic necrosis of conjunctiva limited to less than one-third of perilimbal conjunctiva. Prognosis: prolonged corneal healing with significant corneal vascularization and scarring; vision usually limited to 20/200 or less.

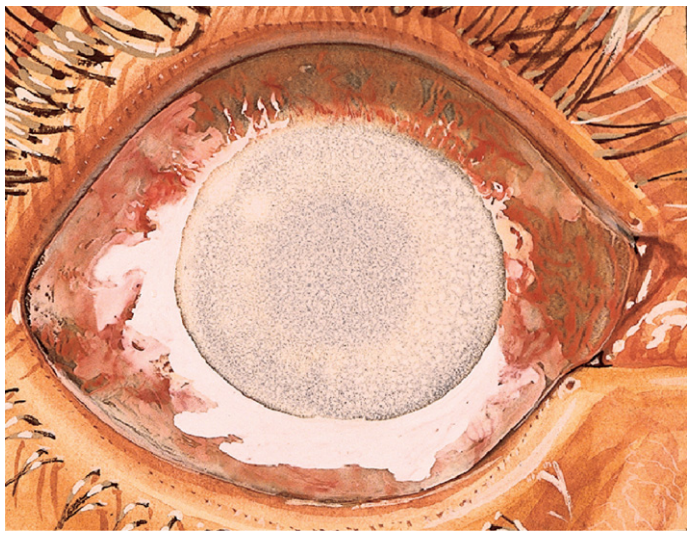

Figure 70.4. Classification of alkali-burned eyes—severe (1-d): Blurring of papillary outline, ischemia of approximately one-third to two-thirds of perilimbal conjunctiva, cornea often marbleized. Prognosis: very prolonged corneal healing with inflammation and high incidence of corneal ulceration and perforation. In the best cases, severe corneal vascularization and scarring with counting-fingers vision.

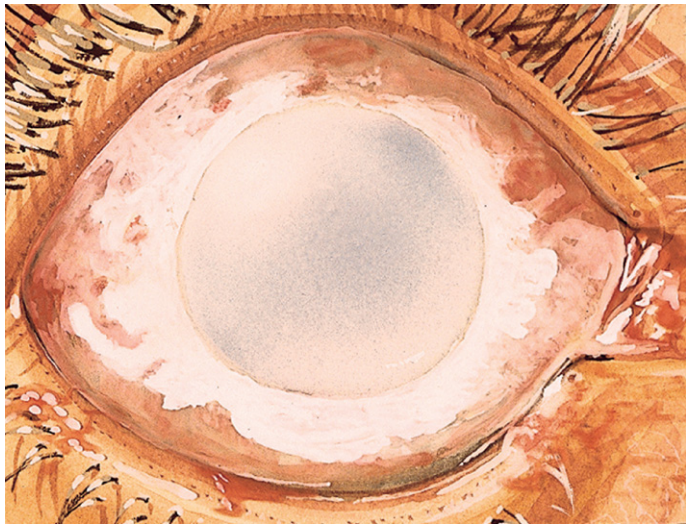

Figure 70.5. Classification of alkali-burned eyes—very severe (1-e): Pupil not visible; more than two-thirds ischemia of perilimbal conjunctiva, cornea often marbleized. Prognosis: very prolonged corneal healing with inflammation and high incidence of corneal ulceration and perforation. In the best cases, severe corneal vascularization and scarring with counting-fingers vision. (Courtesy Pfister R, Koski J. The pathophysiology and treatment of the alkali burned eye. South Med J 1982; 75: 417–422.)

chapter designates alkali injury or acid injury of the eye to distinguish chemical from true thermal burns. When both injuries occur simultaneously, then alkali–thermal injury or thermal–alkali injury might be used, with what is thought to be the most prominent injurious agent stated first. Acid injuries should be referred to in a similar way.

EMERGENCY TREATMENT

The harm caused by alkali injury is predicated on the concentration of the cation, the duration of exposure, and the pH of the solution. To remove the source of the caustic agent from the external eye, immediate irrigation of the eye at the scene of the accident and for 1–2 h thereafter is mandatory. Using this technique alone to reduce the alkali concentration in the corneal stroma and aqueous humor after a severe alkali injury is open to question. Studies on the effect of 90 min of external irrigation on intraocular pH in an animal model of a severe alkali injury has shown only a 1.5 pH unit reduction of the elevated pH.[19] It is necessary to lavage the external eye, but relatively little progress can be made to end the intraocular cauterization by alkali using this technique alone. However, in a noncontrolled clinical study copious irrigation of 49 eyes with milder alkali injuries resulted in grade 1 injury, while no irrigation of 17 eyes resulted in grade 2 injury.[20] Removal of the aqueous by paracentesis lowers the pH by 1.5 pH units. Reformation of the aqueous humor with buffered phosphate solution lowers the pH by an additional 1.5 pH units. It is premature to suggest that all severe alkali injuries should undergo paracentesis. However, in the absence of strict scientific information, it is reasonable to suggest that, in severe injuries occurring 1–2 h previously, paracentesis and removal of an aliquot of aqueous humor be performed when facilities permit. This approach can be accomplished at the slit lamp or in the minor operating room suite. Under topical anesthesia, a razor blade fragment or commercially available super-sharp blade can create a partial-thickness, self-sealing tunnel at the limbus down which a 25-gauge needle is inserted, finally penetrating into the anterior chamber. If available, it is preferable to replace the aqueous humor with a buffered phosphate solution or balanced salt solution to reduce the intraocular pH to near normal levels.

Several chemical injuries require special treatment. For example, the pultaceous character of lime used in cement compounds clings to the conjunctiva. The bulk of material can be removed with a cotton-tipped applicator, but the sticky paste in contact with the conjunctiva can be released from the tissue with greater ease by irrigation with a solution of ethylenediamine tetraacetic acid (EDTA) 0.01 mg/mL. Removal of this alkaline paste or powder from the cul-de-sacs is mandatory.

The intraocular pressure rise after alkali injury can usually be treated by topical α- or β-blockers topically and/or systemically administered carbonic anhydrase inhibitors. If the pressure is extremely high and/or fails to respond, temporary control can be achieved by paracentesis at the limbus, under topical anesthesia, followed by periodic release of aqueous humor through a beveled incision made at the slit lamp or in the minor surgical suite. This approach also releases debris from the eye and buys time in the initial phases until the pressure dissipates spontaneously or glaucoma medications gain control of the intraocular pressure.

The presence of necrotic tissue in the external eye gives rise to inflammatory mediators, attracting PMN into the damaged cornea and stimulating release of the full range of PMN enzyme and metabolic products destructive to even the remaining normal tissues. To avert some of these devastating consequences, careful excision of necrotic tissues might be carried out early to reduce the mediator load encouraging this process.

Eyelid function must be assessed after alkali injury since it is critical to the healing process in the cornea. The greater the failure of lid function the more likely corneal healing will be incomplete. Chronic ocular exposure and/or trichiasis will usually worsen the ocular prognosis by encouraging the development of persistent epithelial defects. The consequence of these defects can be ulceration and perforation of the globe. Attention to lid malfunction might be as minimal as the use of ointment or more aggressively with a plastic bubble or wrap to minimize air exposure.

Alkali destruction of conjunctival epithelium, in combination with the inflammatory response, causes fibrinous adhesions which must be opened periodically under topical anesthesia. When extensive damage of conjunctiva has occurred, fibrous proliferation in the subconjunctival tissues shrinks the linear surface of conjunctiva and promotes the formation of symblephara, particularly by contact between the raw surfaces of naturally apposed conjunctiva. In the most severe cases, the eyelids become scarred to the globe (ankyloblepharon), either permanently closing the eye or causing the exposed cornea to dry, with resulting epithelial defects, leading to further PMN infiltration, ulceration, and eventually perforation.

Prophylactic approaches to maintain eyelid mobility and limit conjunctival and fornical contracture might be helpful but are of unproven value. These approaches consist of lining the palpebral conjunctiva with a thin plastic wrap, which is secured by sutures passing through the upper and lower fornices. When lid mobility has already been compromised by scarring, surgical incisions to recreate tissue planes can seldom be covered by rearrangement of existing conjunctiva. Coverage of these raw areas with mucus membrane obtained from the mouth might have a better chance of remaining open. Amniotic membrane has been found to have powerful anti-inflammatory properties and a suitable substrate for epithelial expansion on to the conjunctival surface and improving eyelid function. When total ankyloblepharon is present, any known effort to reconstitute a semblance of the natural conjunctival environment, for the purpose of preparation for corneal transplantation, is very likely to be unsuccessful.

Pain management during this stage of the disease is not complicated. The pain at the time of injury can be excruciating, but usually short-lived. Pain receptors are destroyed by the alkali; hence, they do not continue to transmit a pain response. When necessary, pain control might be required for several days; rarely greater than 1 week. Photophobia can, however, be extreme, creating a painful environment that can be improved only with UV protective dark wraparound sunglasses, or occasionally complete exclusion of ambient light.

TRANSITIONAL STAGE TREATMENT

The transitional stage treatment of the alkali-injured eye begins as early as 1 to 2 weeks in milder injuries and as late as 1 to 2 months in more severe cases. Problems such as epithelial defects, inflammation and ulceration, glaucoma, symblephara, and eyelid dysfunction might appear or continue from the acute stage through the subacute to the chronic stage imperceptibly and without interruption.

Epithelium

The healing of a corneal epithelial defect after alkali injury is largely predicated upon the severity of the injury and the extent of perilimbal injury. Part of the significance of perilimbal injury is the finding that the stem cell phenotype for corneal epithelial cells resides deep within a narrow band of cells located on, and partially straddling, the limbus. Loss of some portion of the stem cells requires that corneal epithelium be repopulated from the geographically distant remaining stem cells. If all corneal stem cells have been destroyed, then corneal re-epithelialization proceeds from the viable edge of the conjunctival epithelium with cells phenotypic for conjunctiva. If the conjunctival stem cells, located in the fornices, are also destroyed, then extensive symblephara are likely, including ankyloblepharon. At this time, there are no data regarding conjunctival stem cell replacement.

The formulation and frequency of applied medications used during this period can be toxic to fresh epithelium covering the alkali-injured cornea. Preservatives such a benzylalkonium chloride and ointments, especially those containing lanolin, can perpetuate or create epithelial defects. It is wise to avoid topical treatment with multiple medications in the hope of preventing corneal ulceration when there is no clear-cut indication to do so. At most, initial treatment with an antibiotic four times a day and a mydriatic and cycloplegic twice a day is indicated.

Inflammation and corneal ulceration

Alkali injury of the cornea has been shown to trigger the release of inflammatory mediators, which are believed to be responsible for chemoattraction and subsequent activation of PMNs within the corneal stroma. The density of the PMN infiltrate appears to be directly related to the severity of the injury and to the likelihood of subsequent ulceration. Although all cells of the cornea have been shown to be capable of releasing a broad spectrum of enzymes destructive of collagen and glycosaminoglycans, the presence of enormous numbers of PMNs and absence of any other cells in significant numbers point to PMNs and their products as the major cellular elements causally related to ulceration.

Historically, treatment of ulcers resulting from alkali injuries has been directed at inhibition of collagenase production by PMNs and corneal cells. Although controversy still exists, acetylcysteine, L-cysteine, and EDTA all have been reported to inhibit mammalian collagenase in vitro and significantly reduce the incidence of ulceration in animal corneas after alkali injuries. In contrast, one study in extreme alkali-injured animal eyes showed no favorable effect of acetylcysteine when compared to control eyes (81% versus 75%).[21] In an open clinical study, L-cysteine (0.2 mg solution) was begun on the seventh day after a 'total' alkali injury in 33 human eyes and only one perforated eye.[22] An alkali injury study including 28 human eyes substantiated the favorable effect of L-cysteine in the acute stage, in the presence of an ulcer, and before or after corneal transplantation. In 35 patients with corneal ulceration (diseases unspecified) treated with 0.2 mg EDTA, 86% healed or remained unchanged compared to 46% of the 26 control eyes.[23] Cysteine and acetylcysteine are both effective inhibitors of collagenase, but the latter has the advantage of greater stability and ready availability in the marketplace. Although it is suspected that acetylcysteine has a favorable effect in some human alkali-injured corneas, this effect has not been proven by clinical trial. If desired, acetylcysteine or L-cysteine drops should commence as soon as possible after the injury.

The use of topical corticosteroids after chemical injury is very controversial. If used for the first 7 days after injury, it may decrease the inflammatory reaction of the entire anterior segment, possibly reducing some of the late side effects, such as glaucoma. If used for longer than 7 days, topical corticosteroids interfere with the repair process and may result in corneal ulceration and perforation. It seems most reasonable to avoid topical corticosteroids if possible, but especially later than 7 to 10 days after the injury.

A surgical emergency arises when a leaking descemetocele or frank perforation supervene. If the perforation is smaller than

1.0 mm in diameter (the ulcer itself is usually much larger) and relatively free of blood vessels, then adhesive closure with isobutylcyanoacrylate is the least invasive and the most effective way of reestablishing the integrity of the eye.[24] A soft contact lens diminishes the discomfort of the adhesive. The adhesive remains in place for 2 to 10 weeks after which it falls off, or is loosened enough to be picked off with jewelers' forceps. Larger corneal ulcerations and perforations require a fresh corneal patch graft to replace tissue lost from ulceration. The ulcer bed and edges are cleaned of epithelium and inflammatory debris. Necrotic tissue is excised from the edges and base to create a viable bed of stroma into which the transplanted tissue is positioned. The donor patch graft is trephined about 0.5 mm larger than the greatest diameter of the recipient bed, trimmed during the suturing procedure to fit the contours of the ulcer bed, and fastened to the edges of the ulcer with interrupted sutures of 10-0 nylon with their knots buried into the stroma.[25]

Glaucoma

Any caustic agent might damage the trabecular meshwork directly, or necrotic and inflammatory debris can clog the outflow channels. Organization of this inflammatory sediment results in fibroproliferation, collagen retraction, and the formation of extensive anterior synechiae, further impeding outflow facility.

Treatment of this type of glaucoma consists mainly of diminishing aqueous production. Oral and topical carbonic anhydrase inhibitors and topical α and β-blockers are the major agents of intraocular pressure control. Prostaglandin-derived drugs are likely to be beneficial but an awareness of a possible stimulation of inflammation must be kept in mind. Severe scarring of the perilimbal conjunctiva and bulbar conjunctiva, combined with foreshortening of the fornices, makes filtration surgery much less successful. Cautious use of wound modifying agents such as mitomycin-C can improve success significantly. If one or more filtration surgeries fail, the use of translimbal intraocular setons, linked to equatorial filtration plates, offers an effective way to syphon aqueous from a severely glaucomatous eye.

VISUAL REHABILITATION

The application of new methods issuing from research has changed the formerly dismal outlook for the chemically injured eye. A substantial degree of success has been achieved by diligent attention to creating an intraocular and extraocular milieu favorable to corneal transplantation. Success in any type of restorative surgery will be governed by (1) lid globe congruity with normal blinking and the absence of corneal exposure; (2) sufficient resurfacing tear film layer to which a transplanted cornea can adapt; (3) the presence of epithelial stem cells phenotypic for cornea; (4) the absence of any inflammation, current ulceration or uncontrolled glaucoma; (5) flawless surgical technique; (6) fresh corneal transplant tissue; and (7) mental stability and cooperation of the patient to withstand occasional setbacks.

Preparatory procedures to lyse symblephara, expand cul-de-sacs, and eliminate lagophthalmos are often required to reestablish normal lid physiology and anatomy. Secondary glaucoma must also be controlled with medications, cyclocryothermy, or filtration surgery. Laser of large feeder vessels at the limbus may be done to control bleeding at the time of surgery.

Alkali-injured eyes and anterior segment necrosis share a similar fate of vascular insufficiency. To improve vascular support of the anterior segment in alkali-injured eyes, Reim and coworkers have popularized excision of necrotic conjunctiva and advancement of viable tenons capsule, the latter obtained by careful dissection to preserve the posterior vascular supply.[26] The procedure, referred to as tenon-plasty, prevented or arrested corneal ulceration in 24 eyes of 21 patients sustaining severe alkali injury.

Amniotic membrane sutured over the injured cornea and conjunctiva has proven to be of immense value in suppressing inflammation and providing a new substrate over which epithelium readily grows. Although amniotic membrane alone is insufficient to maintain an intact epithlelial layer on the cornea devoid of a stem cell source, it is of exceptional value when combined with corneal stem cell transplantation. Its fate after transplantation is unclear, but it is of inestimable value as an immediate prelude to corneal stem cell transplantation. The technique of amniotic membrane transplantation is covered in another chapter.

Replacement of the corneal stem cells lost from disease or injury is a new and exciting surgical procedure.[27,28] If the injury is monocular, then autotransplantation of corneal limbal stem cells from the uninjured eye offers an opportunity to replenish the stem cell supply autogenously. When the injury is bilateral, research by Pfister indicated that allografted limbal tissue was capable of restoring the stem cell population from an unrelated donor. Replacement of the entire cornea and adjacent stem cells by penetrating keratoplasty has been performed successfully and reported in two different series.[29,30] Kukelkorn replaced the entire cornea in sterile ulcerating, alkali-injured eyes, preserving an intact epithelium and absence of ulceration over a 1-year period. Redbrake reported nine eyes operated this way, preserving the epithelium but only maintaining clarity in two. Nevertheless, under the circumstances, these results should be considered a successful outcome. One potential danger might be that such large transplants might interfere with the trabecular outflow channels and hence increase the likelihood of glaucoma. The use of a 12 or 13 mm lamellar corneal transplant, including the limbal epithelial stem cell population, managed to restore the epithelial integrity, without complications, in an average of 5.2 days.[31] The latter approach, performed an average of 29.5 months after injury, might gain all the advantages of replacement of the cornea and associated stem cells but reduce the chance of consequent glaucoma. An alternative approach in the case of deep corneal ulceration, descemetocele or frank corneal perforation would be to suture a piece of cornea into the ulcerated bed to reestablish integrity of the globe.

The optimal medical and surgical conditions necessary to promote allografted corneal stem cell growth and to protect them from the immune process are currently in discovery. It is clear, however, that immunosuppression, of some type, is required to sustain the vitality of these allografted tissues. As an adjunct, amniotic membrane stretched over the alkali-injured cornea has proved to be useful when transplanting corneal stem cells by replacing the abnormal surface of the cornea with a new surface tending to quiet the inflammatory process.[32,33] Amniotic membrane alone does not substitute for corneal stem cells in a severe alkali injury where there is a stem cell deficiency or loss. The advent of in vitro techniques to culture and expand corneal stem cells might soon provide a new and immunologically more suitable source of corneal stem cells.[34]

If corneal surgery is delayed 18 months to 2 years after a chemical burn, it increases the chances of success, especially in the absence of preexisting ulceration, perforation, or glaucoma.[35] Corneal surgery is indicated for the worst eye in bilateral burns

when serviceable vision is not available. If the injury is monocular, restorative corneal surgery is still an option, given that the overall status is favorable as noted above.

There are some patients with severe monocular injuries in whom a definite need for binocularity does not exist and in whom all presurgical conditions are not met. Corneal transplantation might not be advised in these patients because transplantation in chemically burned eyes is fraught with numerous potential complications.

If it is elected to perform corneal transplantation, it is important to pay meticulous attention to the rigorous protocol of this difficult surgery. A few points of importance will be mentioned. Trephination with a vacuum cutter and a vertical section of the remaining attachments with scissors improves the quality of the wound architecture. If suction cannot be achieved because of surface irregularity, layering a ring of viscoelastic on the cornea usually assists vacuum adherence. Unless bleeding is severe, it is wisest to avoid cautery of wound vessels. Most bleeding can be controlled by absorbing fresh blood from the wound edges with sponges and simple pinching of bleeding vessels with forceps before the wound is fully opened.

When cataract is present, it is usually wisest to remove the cataract at the time of corneal surgery. Cataract surgery should follow modern techniques with special emphasis on the approach to the open eye. If preoperative pressure devices reduce the vitreous volume such that the crystalline lens has no tendency to prolapse forward, then a capsulorrhexis can be performed. Efforts to create a capsulorrhexis in the presence of positive vitreous pressure can result in a radial tear, zonular dehiscence, and possibly vitreous loss. If positive vitreous pressure is noted, a 'can opener' technique should be used. In either case, hydrodissection of the lens usually prolapses the lens nucleus for easy removal. Cortical clean-up with irrigation and aspiration and intracapsular placement of an intraocular lens can then be accomplished. Choice of the intraocular lens should be dictated by haptic design, namely torsional strength, easy collapsibility, and null antero-posterior movement on linear contraction of the haptics. These requirements are met with the Bausch & Lomb model #122 dualens.

The donor cornea should be fresh, with intact epithelium, and cut 0.50 to 0.75 mm larger than the recipient bed. Retraction of the recipient tissue opening requires a larger donor diameter to avoid tension on the wound. Donor tissue is age matched but human leukocyte antigen or blood typing is not usually done for the first transplant. A continuous 10-0 nylon suture may be used if the recipient corneal tissue is sufficiently firm and of near normal thickness. It is occasionally necessary to use interrupted sutures, especially for more extensively vascularized or thin corneas. The knots must be buried to avoid epithelial defects and as a portal for infection. For the same reasons it is critical to remove loose or broken sutures as soon as possible.

If epithelial defects are noted, an assessment of the reasons behind the problem is necessary. Eyelid congruity, exposure keratitis, tear abnormalities, corneal stem cell population, corneal matrix deficiency, and topical drug preservatives can be responsible for initiating and perpetuating persistent epithelial defects of the cornea. In addition to correcting these abnormalities an old but effective concept of using the patients' own serum, applied as topical drops every 3 h, has been revived. Occasionally, a soft contact lens might be fitted for continuous wear on a temporary basis.

In the most severe cases, implantation of a keratoprosthesis might afford the only means by which vision can be restored. Corneas exhibiting exuberant vascularity, repeated failures of freshly transplanted corneal tissue, and the inability to restore normal lid anatomy are potential indications for this procedure. The operation is only advisable in those with severe bilateral injuries in whom serviceable vision is not present in either eye. All currently available devices are investigational and are difficult to implant. A surprising degree of success has been achieved, but this success must be balanced against the sometimes serious and untreatable complications that can occur.[36]

NEW RESEARCH DIRECTIONS

Pathophysiologic understanding of chemical injuries of the eye has been refined by basic biochemical, physiologic, and anatomic studies. This refinement has been driven by the evolution of the disciplines of molecular biology and biochemistry as applied to ocular disease. As a result, ophthalmologists are now able to use orthomolecular approaches to supplement traditional treatment.

EXPERIMENTAL TREATMENT MODALITIES

The ascorbic acid level is depressed to one-third of normal in an animal model of severe alkali injury to the eye. Topical or subcutaneously administered ascorbate (10%) significantly decreases the incidence of corneal ulcerations and perforations if the aqueous humor ascorbate level can be elevated to 15 mg/dL. Light and electron microscopy and radioactive tracer experiments show that the mechanism of action is replenishment of ascorbic acid to the scorbutic fibroblasts of the cornea. Ascorbic acid is a powerful reducing agent required by fibroblasts to synthesize collagen, thereby promoting healing of damaged corneal tissues.

Neutrophils (PMNs) play a central role in corneal ulceration developing as a consequence of alkali injury. Topically applied citrate has been shown to be extremely effective in decreasing the incidence of corneal ulceration after alkali injury of the animal eye.[37] Citrate is a chelator of extracellular calcium; necessary for all activities of the PMNs by acting as an important intracellular second messenger within the cell. Inhibition of the PMNs through calcium depletion may be caused by interference with calcium–calmodulin microfilament or microtubule interfaces in the plasma membrane. Hence, topical treatment with citrate can entirely halt PMN activities. Citrate also inhibits the efferent leg of the inflammatory response by interfering with the adherence of PMNs to vascular endothelium. This effect decreases the migration of PMNs into the damaged cornea, thus diminishing the discharge of hydrolytic enzymes into the corneal stroma.

Ascorbate and citrate reduce the incidence of corneal ulceration in alkali-injured eyes by different mechanisms, accounting for the substantial further reduction in corneal ulceration in alkali-injured animals when these foodstuffs are used together. Corneal ulcers decreased from an untreated incidence of 80% to a transitory 4.6% when citrate and ascorbate eye drops were alternated concurrently throughout the day.[38]

Using the Roper–Hall modification of Hughes classification of alkali injuries, Brodovsky showed that grade III injuries treated with a combination of ascorbate, citrate, and FML attained vision of 20/40 or better in the treated group including 27 of 29 eyes, (93%) compared to 3 of 6 eyes (50%) in the control group.[39] There was also a trend toward shorter hospital stays in the treatment group. Specific topical treatment consisted of 10% ascorbate, 10% citrate and fluoromethalone every 2 h, day and night, and 1% atropine t.

i.d. and chloramphenicol q.i.d. To this was added 500 mg ascorbate q.i.d. and 4 g of a proprietary urinary alkalinizer containing 720 mg of citric acid anhydrous and 620 mg of sodium citrate anhydrous t.i.d. In none of the other groups is there any statistical differences between the treated and control groups.

Other putative treatments to prevent corneal ulceration in severe alkali injury, such as oral tetracycline, subconjunctival progesterone, intramuscular nortestosterone, and thiol dipeptides, have all shown favorable effects in animal models of alkali injuries. However, a clinical trial will be needed before any of these approaches can be considered for routine human use.

OTHER POSSIBLE CHEMICAL THERAPIES

Fibronectin has been implicated as a key element in wound healing for its involvement in cell-to-cell and cell-to-matrix adhesion and cell spreading. Eye trauma causes exudation of large proteins such as fibrinogen from conjunctival blood vessels, reaching the bare basement membrane where polymerization and deposition take place. Epithelial defects occurring in herpetic keratitis, in trophic corneal ulcers, and after cataract surgery have responded to fibronectin drops when used in an open-labeled study. However, albumin eye drops were as effective as fibronectin in the treatment of persistent epithelial defects after alkali injuries in rabbits.[40] This finding suggests a nonspecific response. The determination of the value of fibronectin in persistent epithelial defects again can only be gleaned from a prospective, randomized clinical trial.

Epidermal growth factor enhances the rate of healing and induces hyperplasia in corneal epithelium.[41,42] Epidermal growth factor stimulated complete epithelial healing after alkali injury in two studies, but in each instance recurrent erosions re-established the defect.[43,44] This epithelial proliferation is clearly stimulated by epidermal growth factor, but its usefulness in corneal diseases is unknown.

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71 Corneal and scleral ruptures and lacerations*

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The overall goals of treating the patient with a corneal or scleral rupture or lacerations include: (1) preventing further injury to the eye before surgery; (2) triaging and treating associated injuries; (3) expediting preoperative evaluation and anesthesia clearance, if needed; (4) obtaining infection-control cultures and providing systemic antibiotics, if indicated, as well as tetanus prophylaxis; (5) documenting medical records meticulously; and (6) engaging in comprehensive and honest discussion with the patient and family members.

When a patient with ocular trauma presents, a quick global assessment of the patient's overall condition should be done before a complete ocular examination is performed. Life-threatening trauma must be treated before all else. Additionally, severe pain or nausea should be treated as soon as possible to minimize lid squeezing and Valsalva effects, which could lead to the loss of intraocular contents. If at all possible, surgical consent should be obtained prior to the patient receiving narcotics or other drugs that could affect the sensorium. If it is obvious that the patient has an open or unstable globe, a rigid eyeshield should be secured in place until definitive eye care can be administered. The use of a plastic rather than a metal shield allows it to remain in place during most radiographic imaging studies. Computerized tomography (CT) scanning may be necessary for foreign body assessment; requesting 1 mm cuts through the orbits will increase the sensitivity of the imaging. Gentle, non-contact ultrasound may be useful to verify the integrity of the posterior segment if there is suspicion of posterior globe laceration.

HISTORY AND PHYSICAL EXAMINATION

The mechanism of injury should be determined to assess the likelihood of a retained intraocular or orbital foreign body and to identify its likely composition. For medico-legal reasons, the time of the injury, use of protective eyewear, alcohol and/or drug involvement (especially in the setting of transportation-related injuries), any history of previous eye disease, injury or surgery, and any history of treatment for the present injury should be recorded.[1] Although gross disruption of the globe is obvious, one should always be suspicious of occult injury. Searching for a hidden ocular perforation is essential in the treatment of high-risk injuries involving sharp, slender objects (e.g. darts, ice picks, wire, knives, glass shards, and Taser dart electrodes[2]) or high-speed projectiles produced by machinery or metal-on-metal contact, which can leave small, self-sealing ocular wounds. Air guns are another significant source of injury and account for approximately 1200 ocular injuries per year, predominantly in young males.[3] Lacerations to the eyelids or brow should raise the suspicion of an associated occult perforating eye injury. Relevant history and salient aspects of the examination are summarized in Box 71.1.

RUPTURE IN EYES WITH PREVIOUS OCULAR SURGERY

Any ocular surgery involving a penetrating wound or focal thinning of the corneoscleral shell could increase the risk of rupture or dehiscence at the site of the wound. When a history of the previous surgery is obtained or is suggested by the examination, the ophthalmologist should maintain a high index of suspicion for tissue disruption at the pertinent wound locations. The structural integrity of the globe with prior surgery is affected by the length, location, and shape of the wound, with the longest incisions having the greatest adverse effect, and a 3-mm scleral pocket yielding less disruption of globe structure.[4] Therefore, large limbal wounds associated with extracapsular cataract surgery are a more significant risk factor for traumatic wound dehiscence than the beveled wounds of a small scleral tunnel or small clear corneal incision. In the same setting, shearing forces can lead to pseudophacodonesis, iridodonesis, and corneal edema from endothelial injury.[5]

In the setting of blunt trauma, a rapid increase in intraocular pressure leads to a transient increase in stress throughout the

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BOX 71.1 HISTORY AND PHYSICAL SUMMARY OF THE OCULAR TRAUMA PATIENT

I. History

A. Events of current injury

1. Mechanism of injury
2. Activity at time of injury
3. Time elapsed since injury
4. Use of protective equipment/eyewear
5. Previous treatment
6. Time since last food ingestion

B. Ocular history: routine, plus—

1. Previous trauma and surgery
2. Level of visual acuity in involved eye before injury

C. Medical history: routine, plus—

1. Use of anticoagulant medications—especially over-the-counter medications, which often contain aspirin
2. Status of tetanus prophylaxis
3. Any difficulties with previous anesthesia or surgery
4. Recent alcohol or drug use to assess need for delirium tremens prophylaxis

II. Physical examination

A. Visual acuity

1. Best corrected (ideal)
2. Pinhole

B. External assessment

1. Associated life-threatening injuries—consult appropriate personnel
2. Associated orbital and facial injuries—oculoplastic, ear, nose, and throat, neurosurgical or oral-maxillofacial surgeons
3. Gross inspection of involved eye (exerting minimal pressure)
4. Evidence of visible foreign body on adenexa, skin

C. Motility—omit if globe is, or may be, lacerated

D. Confrontational visual fields

E. Pupils—use as dim a light as possible to minimize patient squeezing

1. Relative afferent pupillary defect (RAPD)—if efferent abnormality is present in injured eye, RAPD assessed by observing the unaffected eye's consensual response during illumination of the injured eye
2. Distortion/peaking toward limbus?

F. Slit-lamp examination: routine, plus—

1. Presence of conjunctival laceration/hemorrhage—risk of underlying scleral laceration or foreign body
2. Scleral laceration
3. Corneal laceration or foreign body
4. Presence of extruded intraocular contents
5. Seidel test, if indicated
6. Gonioscopy to look for anterior chamber foreign body and angle damage ONLY if globe is intact
7. Note iris irregularities
8. Iridodenesis, phacodonesis or pseudophacodonesis
9. Intraocular pressure ONLY if globe is intact

G. Dilated fundus examination: routine, plus—

1. Rule out vitreous hemorrhage, intraocular foreign body
2. Retinal dialysis, tears, detachments, commotion
3. Choroidal or scleral rupture
4. Optic nerve head edema, avulsion
5. Depressed examination ONLY if globe is intact and no hyphema

H. Additional testing

1. Ultrasound—noncontact or GENTLE pressure
2. Imaging study—computed tomography is safest in the acute setting
3. Preoperative testing as indicated

corneoscleral shell. Wherever stress is more highly concentrated, a marked increase in risk of mechanical failure exists. Wound strength is only partially restored by the wound healing process and a focal deficit in wound integrity presents a lifetime risk for future dehiscence.[6]

For the same reasons, the wound of a full-thickness penetrating keratoplasty presents a considerable risk of dehiscence with blunt trauma.[7] In one case series, wound dehiscence occurred with inanimate objects, a fist, eyeglasses, fingers, eye rubbing, accidental fall, an eye-drop bottle, and unknown causes.[7] This risk is likely compounded by inhomogeneous healing of the graft–host junction, which leads to the development of focal areas of weakness prone to dehiscence at lower pressure loads than other regions.[8]

Ocular rupture due to blunt trauma after refractive surgery has been reported, but the risk relative to nonoperated eyes has not been well characterized in vivo. In eyes with a history of prior incisional refractive surgery, rupture most frequently occurs at an incisional site.[9,10] Ex vivo studies of excimer laser photorefractive keratectomy (PRK) and phototherapeutic keratectomy (PTK) suggest that myopic PRK, up to 10 D, does not significantly affect ocular integrity.[10] However, a lower bursting strength with rupture occurring at the edge of the ablation zone was observed with PTK ablations greater than 40% of central corneal thickness.[10]

PATIENT COUNSELING AND PROGNOSIS

Frank counseling of the patient and family before surgical repair regarding the extent of the injuries and the prognosis for visual recovery is time well spent. Ensuring that all involved have realistic goals and expectations eases future discussions about visual potential, the need for additional surgeries, and the possibility of enucleation. From a medico-legal perspective, this is critical. The clinician should approach these discussions with honesty and 'guarded optimism', if appropriate, but must stress that the full extent of the injury often cannot be discerned until the time of surgery, and that the primary goal is to save the eye. Restoring vision is an important but secondary goal. By taking time to answer questions, the clinician can assess the patient's level of understanding of these essential issues and can clarify areas of misunderstanding as time allows.

The National Eye Trauma System Registry recorded data from 48 centers in 28 states from 2939 patients over 6 years (1985–1991) and found the majority of injuries occurred in the home (28%) and involved males (83%) under the age of 40 (78%). Projectiles accounted for 40% of penetrating injuries overall, with 24% arising from sharp objects (most commonly metal, glass, and plastic) and 19% from blunt objects. Alcohol use was identified as a significant risk factor for injury, and non-polycarbonate lenses were found to add to the injury in some cases. The majority of cases involved the anterior segment with or without posterior segment involvement, and 21% of patients ended up with 'no light perception' vision.[1] A realistic picture should be painted regarding the guarded prospect of good visual outcome.

Advances in microsurgical techniques have improved the overall visual prognosis in penetrating ocular trauma, but in many cases the guarded prognosis for useful vision and/or saving the eye persists. On presentation, factors that are associated with a 'better' prognosis include visual acuity of count fingers or better, isolated corneal lacerations (less than 8 mm), absence of vitreous or uveal prolapse, and absence of vitreous hemorrhage.[11,12] Vitreous hemorrhage in children may resolve quickly without surgical intervention.[13] Therefore, it may be prudent to observe vitreous hemorrhage in children for a time before proceeding to surgery. There is a slightly better prognosis with penetrating injury caused by a sharp object than with disruption of the globe resulting from blunt injury.[12]

NONSURGICAL MANAGEMENT

Corneal injuries should be examined carefully at the slit lamp for evidence of ocular penetration. Under high magnification, one should scrutinize the integrity of Descemet's membrane and look for evidence of microtrauma to the lens capsule and iris. A Seidel test should be performed by painting the injured surface with fluorescein-impregnated strips to look for any leak of aqueous fluid. If no obvious leak is seen, gentle pressure should be applied through the upper or lower eyelid to reveal any self-sealing injury or 'slow' leaks. The treatment principles for self-sealing or partial-thickness wounds are (1) to stabilize the wound to promote healing and (2) to prevent infection.

A simple partial-thickness corneal wound that maintains good tissue approximation may be managed medically with a broad-spectrum antibiotic ointment or drop. Cycloplegic drops may provide comfort. A self-sealing puncture wound or short laceration may be treated by applying a bandage soft contact lens. With a small corneal laceration (2 or 3 mm) that maintains good tissue approximation and a formed anterior chamber, a bandage contact lens (in conjunction with a topical antibiotic) may be effective in splinting the wound, thus obviating the need for sutures. A slightly thicker soft contact lens provides more corneal support. The patient must be followed closely to monitor for infection and ensure that the anterior chamber remains formed.

For small lacerations, puncture wounds, wounds with minimal tissue loss, or wounds with slow but persistent aqueous leakage, cyanoacrylate tissue adhesive may be useful. The tissue bed must be dry and free of epithelial cells at the time of adhesive application. A thin film of adhesive is applied using a small-gauge disposable needle, a microcapillary applicator, or the broken wooden end of a sterile cotton-tipped applicator. Alternatively, a drop of adhesive can be placed in the center of a cut-out piece of sterile plastic surgical drape that is placed on the wound as a 'patch'. Following the application, adhesive should be given several minutes to dry before any further manipulation is performed. A bandage contact lens is fitted to keep the adhesive from prematurely dislodging and to minimize irritation to the tarsal conjunctiva. The adhesive dislodges on its own as re-epithelialization occurs. While the contact lens remains in place, prophylactic antibiotic drops and a cycloplegic agent are recommended; a topical nonsteroidal anti-inflammatory drop may prove helpful for increasing patient comfort for the short term. Prolonged use of topical nonsteroidal anti-inflammatory drops should be avoided due to their propensity for a corneal melt. In poorly cooperative patients (e.g. children, demented, or intellectually impaired) or in those with questionable compliance, a definitive surgical closure may be more appropriate.

If there is evidence of ocular penetration, even in the presence of a self-sealing wound, the patient is at increased risk for developing endophthalmitis. Such patients require close observation; treatment with intravenous antibiotics may be considered, although the efficacy of this approach remains unproved. Children should be followed closely for the development of amblyopia.

SURGICAL MANAGEMENT

FORMATION OF A SURGICAL THERAPEUTIC STRATEGY

The ophthalmologist must integrate information gathered in the history and physical examination and prepare a rational approach to repair of the traumatized ocular tissue. The goals of ocular trauma repair are to (1) restore the integrity of the globe, (2) restore normal anatomic relationships, and (3) minimize the risk of complications either at the time of initial surgery or during subsequent surgical procedures. These goals are oriented toward preserving the eye and restoring useful vision. To this end, the ophthalmologist must reform a watertight globe, remove any disrupted lens fragments and/or vitreous, reposition viable uvea, excise necrotic uvea, and remove any intraocular foreign body.

General anesthesia is preferred for a patient with a ruptured globe because any peribulbar or retrobulbar injections would increase orbital pressure, which could lead to further loss of intraocular contents. A nondepolarizing muscle relaxant such as vecuronium prevents the associated increase in intraocular pressure that is caused by contraction of the extraocular muscles, thereby decreasing the risk of expulsion of intraocular contents. In a patient with extensive facial trauma and a difficult airway, succinylcholine may be appropriate.[14] The eye then is prepped carefully—with as little pressure on the globe as possible. Direct topical exposure of betadine solution to an obviously open wound is to be avoided. Exposure can be obtained by carefully inserting a lid speculum that exerts minimal pressure on the globe, by passing 4-0 silk traction sutures through the tarsus of the upper and lower lids, or by using Steri-Strips to retract the lids to the cheek and to the brow. All movements and manipulations of the globe should be performed in such a way so as to avoid undue pressure on the globe, at least until a watertight closure is achieved, thus reducing the risk of additional prolapse of intraocular contents.

SIMPLE CORNEAL LACERATIONS

The traditional teaching regarding wound closure is to align first the limbus and any angled aspects of the laceration. Any pigmented lesions or scars also can be used to aid in alignment. The remaining wound(s) then are bisected continually using successive suture bites. This method assures that the lateral aspects of the wound return to their original relationship, thus providing a straightforward approach to the restoration of normal anatomic relationships and ensuring a watertight closure.

Some basic keratorefractive principles can be applied in the initial repair to minimize distortion of corneal topography. The cornea tends to flatten over any laceration or sutured wound (Fig. 71.1), and lacerations that are longer or closer to the visual axis induce greater flattening.[15,16] To counteract these effects, large compressive sutures are used to close the peripheral aspects of the corneal laceration, which flattens the peripheral cornea and steepens the central cornea (Fig. 71.2). The central aspect of the laceration then is closed using smaller and looser suture bites to approximate wound edges without causing excessive distortion. To aid accurate wound closure, a temporary suture may be placed that bisects the length of the wound to minimize lateral displacement of wound edges during closure. Sutures across the visual axis may be required to achieve adequate closure—the surgeon's first priority—but are avoided if possible due to the risk of visually significant fibrosis.

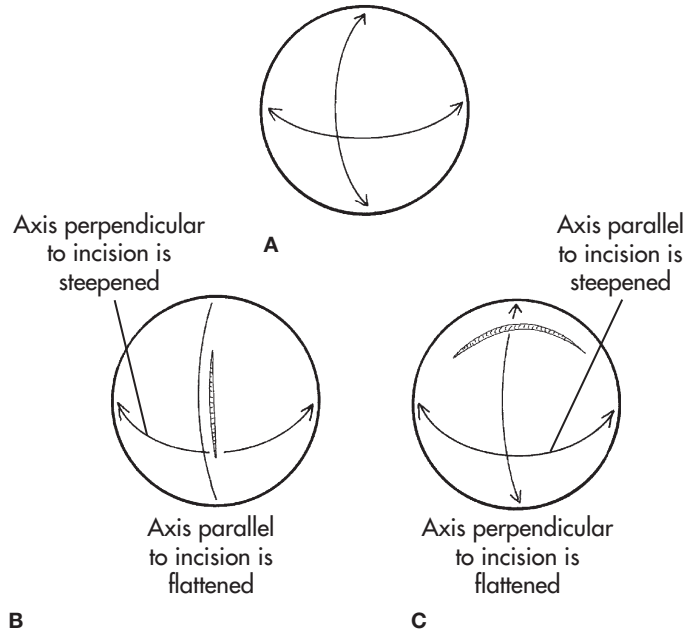

Figure 71.1. *A*, Normal symmetric (astigmatic) cornea radii of curvature. *B*, Effect of a radial incision on axes perpendicular and parallel to the incision. *C*, Effect of a circumferential incision on axes parallel and perpendicular to the incision.

Certain high-risk, full-thickness, self-sealing wounds that involve longer lacerations (>3 or 4 mm) and wounds occurring in uncooperative patients are managed best by primary surgical closure. In cases of a self-sealing wound that maintains a formed anterior chamber, the wound may be closed directly with minimal manipulation to avoid distortion of the wound. Gentle fixation of the sclera at the limbus is attempted using a toothed forceps (Fig. 71.3). A one-handed technique then is used to pass the corneal sutures. The needle is directed into the cornea at a 90° angle and is passed through the stroma following the curve of the needle. This technique avoids manipulation of the wound edge, thereby minimizing leakage of aqueous fluid and keeping the anterior chamber formed. This minimal touch technique also is advantageous when suturing is done near the visual axis as it minimizes iatrogenic tissue trauma from fixation forceps.

In general, monofilament suture (nylon or polypropylene) should be selected: 10-0 suture for clear cornea and 9-0 suture near the limbus. One should consider using 11-0 suture near or in the visual axis to help minimize scarring. A spatulated needle is preferred because it facilitates the maintenance of suture passes at partial stromal thickness. Suture passes should be approximately 1.5 to 2.0 mm total in length. Slightly longer passes may be needed if the wound margin is edematous or macerated, to ensure the incorporation of healthy tissue by the suture. The suture should be approximately 85 to 95% of stromal thickness, incorporating an equal depth of tissue on each side of the wound. Sutures that are too shallow allow the internal aspect of the wound to gape, and sutures that are too deep (full thickness) may act as a conduit, enabling microorganisms or epithelial cells to enter the eye and aqueous to leak out. Suture bites should be oriented perpendicularly to the path of the wound. Obliquely placed sutures exert a shearing force along the length of the wound that can lead to lateral displacement of the wound margins.

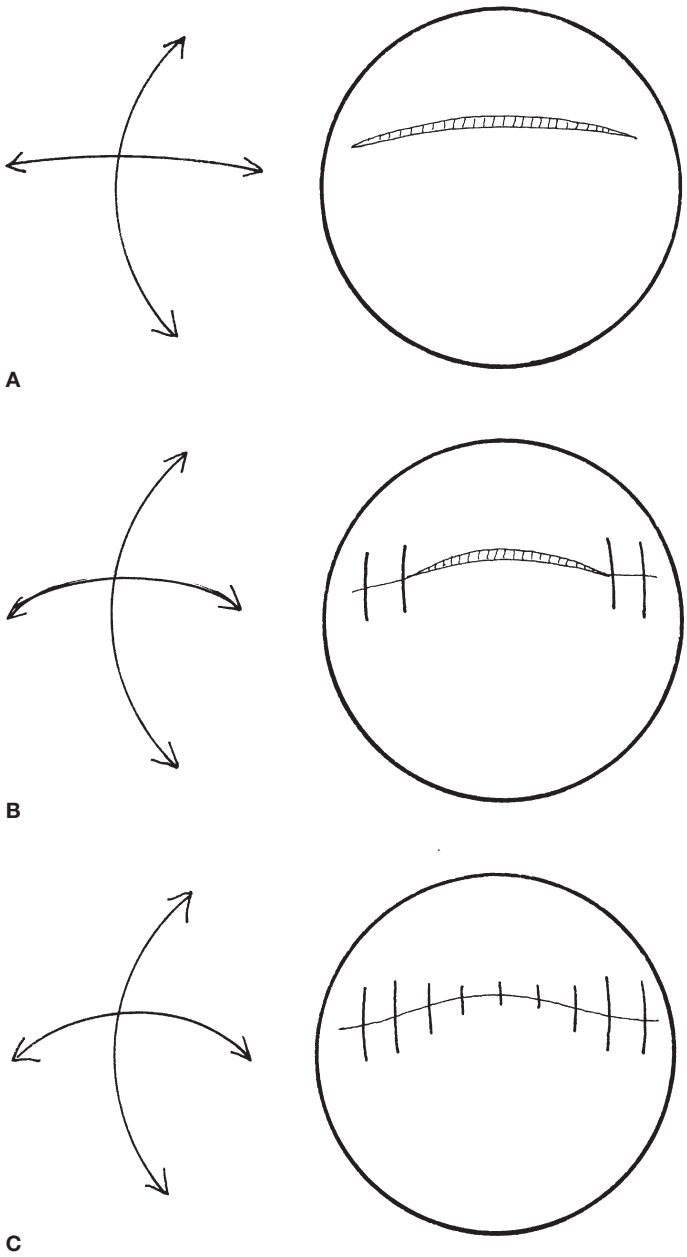

Figure 71.2. *A*, Cornea flattened in axis perpendicular to the laceration. *B*, Longer peripheral compression sutures act to steepen the central curvature. *C*, Shorter central sutures reappose the cornea while limiting flattening.

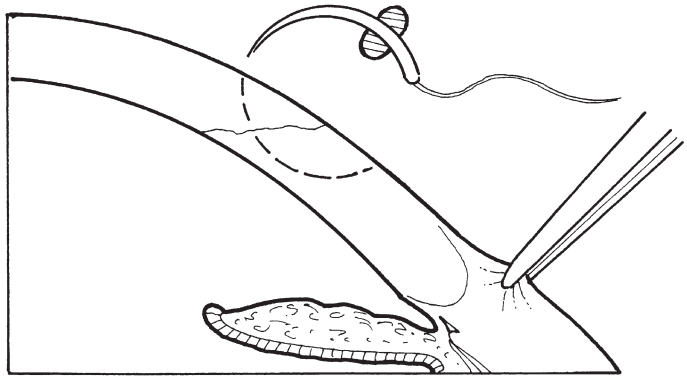

Figure 71.3. Demonstrates minimal touch of the needle and suture to avoid disruption of self-sealing corneal wound.

A running suture may allow for normalization of suture tension across a wound, which may decrease induced astigmatism; however, unless the wound is perfectly straight, it can cause lateral displacement of the wound margins, leading to irregular closure and wound gape. Closure with a running stitch places the integrity of the entire wound on a single suture and knot, which may pose a safety risk. The use of simple interrupted sutures facilitates a more anatomic repair and simplifies both postoperative management of loose sutures and selective suture removal.

A simple suture exerts a zone of tissue compression along the axis of the wound that is approximately the same length as the suture. These compression zones must just overlap for a watertight repair to be constructed. Longer suture bites allow a greater distance between sutures, and smaller bites require more closely spaced sutures. Excessive overlap of compression zones can lead to excessive scarring and tissue flattening.

Suture knots should be tied with either slipknots or square knots (3-1-1 or 2-1-1 throws), and the loose ends cut short with suture scissors or a sharp blade. The knots then should be buried away from the visual axis, and the cut suture ends should be directed away from the corneal surface to facilitate future suture removal.

The architecture of a beveled corneal laceration or incision provides it with a self-sealing mechanism (the basis for shelved cataract incisions, Fig. 71.4). A full-thickness, perpendicularly oriented laceration or incision is prone to leak because any pressure (interior or exterior) serves to displace the wound edges. Therefore, all perpendicular aspects of the laceration should be repaired first to allow a more rapid watertight closure, thus facilitating reformation of the anterior chamber. Passage of temporary sutures may be needed to form a watertight closure, which allows the anterior chamber to be reformed and better-placed 'permanent' sutures.

It is often difficult to obtain a watertight closure with stellate corneal lacerations, especially when they involve tissue avulsion. When there is no tissue loss and the apices are well formed, simple suture closure with the aid of bridging sutures may be helpful. With tissue loss, or apices that approximate poorly, the purse-string technique proposed by Eisner[17] may provide closure (Fig. 71.5). A diamond blade set at half stromal thickness is used to make a small incision in the normal cornea between the base and the apex of each pedicle. A continuous 10-0 nylon suture is passed from incision to incision in a purse-string fashion and is tied. The knot is buried. If there is persistent leakage from the wound, tissue adhesive and a bandage soft contact lens may be used. A conjunctival flap does not stop a persistent corneal wound leak, and it obscures the view of the anterior chamber, making follow-up more difficult. Additionally, conjunctival flaps are visually and cosmetically inferior to direct surgical repair.

If an avulsed piece of corneal tissue is present, it should be sutured back into place. The apices of the avulsed tissue should be secured first, and then additional sutures should be added as needed to reapproximate the wound.

A flat or shallow anterior chamber must be reformed with balanced salt solution, an air bubble, or a viscoelastic. Balanced salt solution or air should be tried first because, if it adequately maintains the chamber, viscoelastics can be avoided. Viscoelastics can complicate matters by mimicking vitreous, thus making tissue and suture manipulation more difficult, and they require removal from the eye to prevent intraocular pressure spikes. The chamber may be

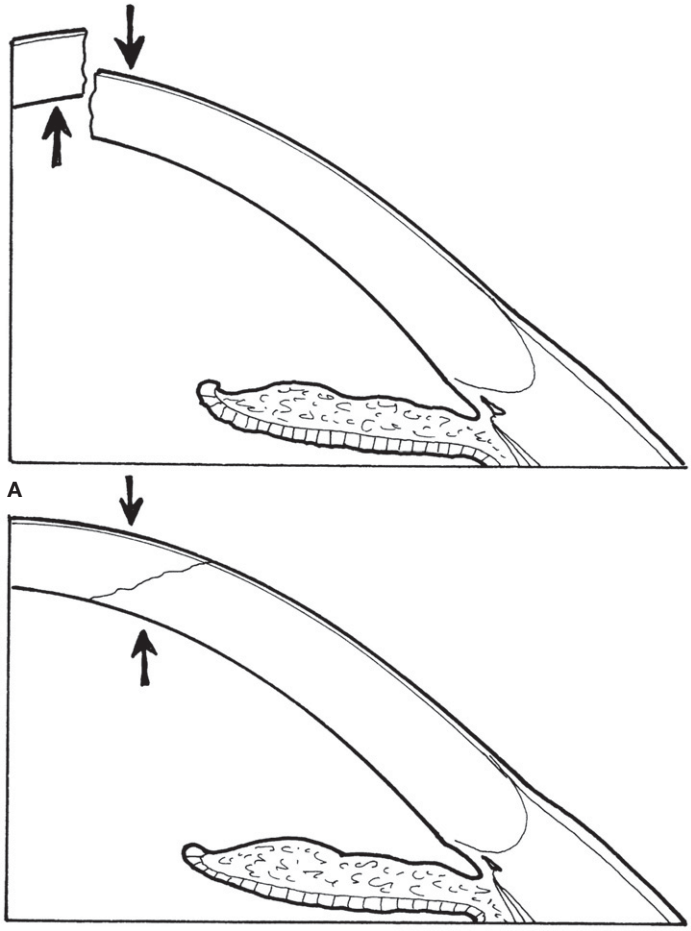

Figure 71.4. *A*, Perpendicular corneal wounds subjected to compressive forces tend to disrupt more easily than *B*, beveled wounds.

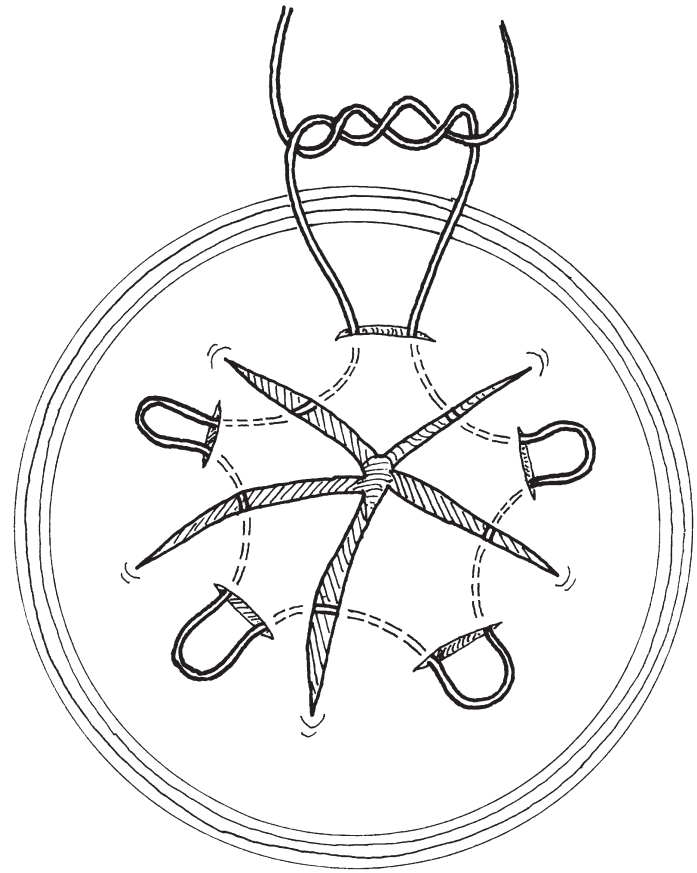

Figure 71.5. Eisner's method of wound closure for a stellate laceration.

reformed either through the original wound or through a separate limbus-based paracentesis positioned away from the wound. A separate paracentesis, although difficult to perform in a hypotonous eye, is advantageous because it is self-sealing and avoids further manipulation of the wound margin. A diamond rather than a metal blade may better facilitate formation of the paracentesis. All wounds should be checked for watertight closure using a dry cellulose sponge.

TREATMENT OF IRIS PROLAPSE

Patients with larger and more peripheral corneal lacerations or flattening of the anterior chamber are prone to iris incarceration in the wound or iris prolapse. To minimize postoperative complications such as refractive problems secondary to excess light scatter, peripheral anterior synechiae formation, and undesirable cosmetic appearance caused by the missing iris, prolapsed tissue should be repositioned and the repaired wound freed of incarcerated tissue. In general, tissue that is exposed for less than 24 to 36 h is probably safe to reposition if it appears healthy. However, prolapsed iris tissue that is obviously necrotic, macerated, or contaminated should be excised to avoid the increased risk of infection and inflammation that is associated with repositioning the tissue. If any sign of surface epithelialization exists, it is better to excise the tissue so that epithelial cells are not introduced into the anterior chamber. To excise prolapsed tissue, one must grasp gently the edge of the exposed iris with smooth forceps, exerting minimal traction; then the tissue can be cut flush with the cornea using Vannas or Castroviejo scissors. The surgeon must preserve as much viable-appearing iris tissue as possible to facilitate reconstruction of the iris diaphragm.

Pharmacologic manipulation may suffice for repositioning the iris in patients with minimal incarceration and a formed anterior chamber. A dilating agent (intraocular epinephrine 1:10000) may free iris that is entrapped in the central aspect of a corneal laceration. Conversely, a miotic agent (acetylcholine or carbachol) may free iris that is entrapped in the peripheral aspect of a corneal laceration.

If the anterior chamber is at least partially formed, further deepening the chamber with intraocular saline or viscoelastic may relieve iris incarceration. A viscoelastic that is injected between the iris and the peripheral cornea can be used to push or 'steamroll' the iris out of the wound. An instrument such as a cyclodialysis or iris spatula, or a blunt irrigating cannula, may be used to sweep the iris from the wound. While avoiding the corneal endothelium and the lens, the surgeon must try to 'tease' the iris from the wound. Working from the center toward the periphery minimizes tension on the iris root, thereby reducing the risk of creating an iridodialysis cleft or tearing the iris root, which can cause additional bleeding.[18]

With a flat anterior chamber, the corneal wound must be closed. It may be necessary to place shallow temporary suture bites to avoid impaling iris tissue while allowing a watertight closure so that the anterior chamber can be reformed (Fig. 71.6). Through a paracentesis site, injected viscoelastic or a mechanical iris sweep separates

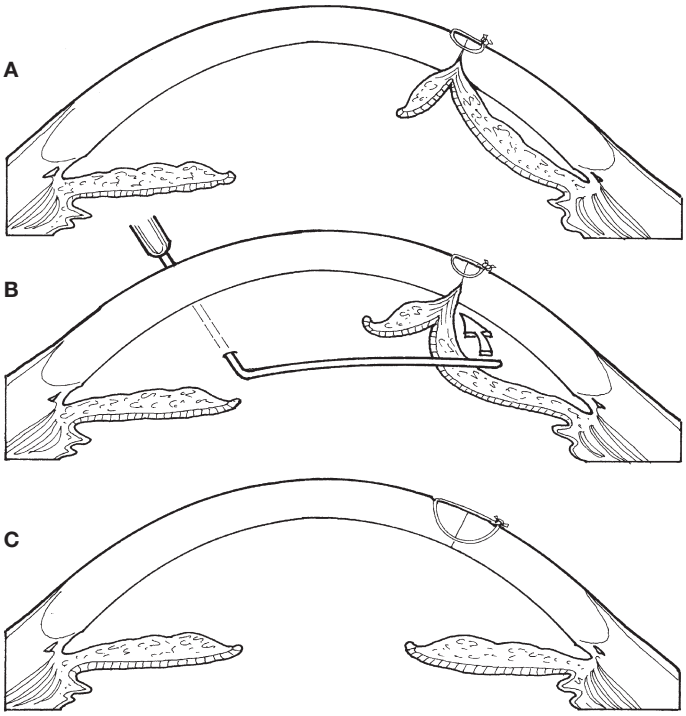

Figure 71.6. *A*, Corneal laceration with a flat anterior chamber. Initial shallow suture bites are passed to reform the chamber and avoid capturing the iris. Viscoelastic through the wound may be used initially to move the prolapsed iris posteriorly. *B*, Once the anterior chamber is reformed, a cyclodialysis spatula and/or viscoelastic is used through the paracentesis site to pull the iris free from the posterior aspect of the wound. *C*, Deeper sutures (pre-Descemet's level) are passed and shallow temporary sutures are removed.

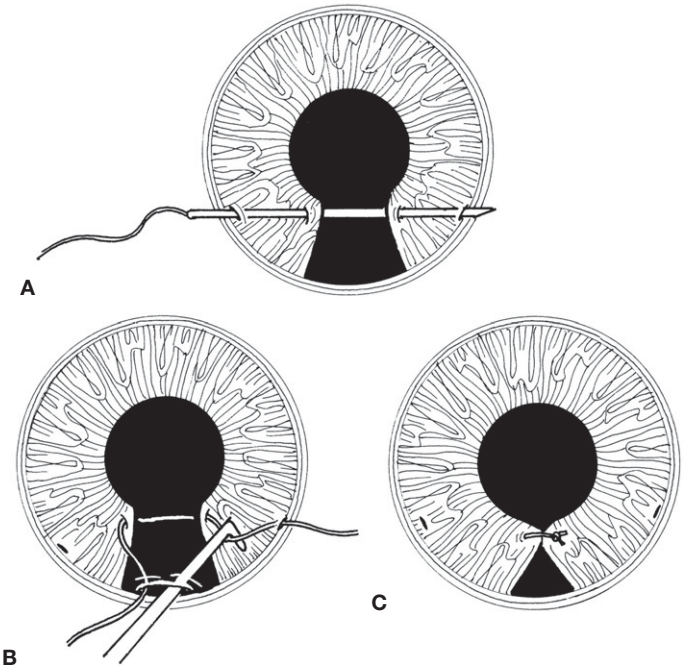

Figure 71.7. *A*, McCannel suture technique for the repair of iris trauma. A straight needle is passed through each side of the iris. *B*, The needle is removed and a Sinskey hook is used to retract the suture end through a third incision. *C*, The suture is tied and cut short, and the iris is reposited in the anterior chamber.

the incarcerated iris from the posterior aspect of the wound. The temporary sutures then can be replaced with deeper, more appropriate sutures.

Before the prolapsed peripheral iris is excised, or when one is treating lacerations near the limbus, the involved uveal tissue must be inspected carefully to ensure that the ciliary body is not involved; any unnecessary manipulation can cause bleeding. If significant iris bleeding is encountered during surgical repair, viscoelastic can be used as a tamponade. If the globe is watertight, gentle pressure may be applied to the globe, or infusion pressure may be increased if an infusion line is in use. Additionally, intraocular epinephrine 1 : 10 000 can be injected for its vasoconstrictive effect. A surgical peripheral iridectomy should be performed in an area in which peripheral iris incarceration was relieved to minimize the risk of peripheral anterior synechiae formation.

ASSOCIATED IRIS TRAUMA

An iris laceration is repaired to maintain a tight iris diaphragm, which decreases the risk of peripheral anterior synechiae and iris–corneal adhesions. Restoring pupil shape is important for refractive and cosmetic reasons. Repair of the iris defect can be accomplished either primarily or secondarily. At the primary surgery, a 10-0 Prolene suture on a vascular needle can be used to close the iris defect. The cut suture ends must be kept short to avoid contact with nearby tissues. Alternatively, iris laceration may be repaired using the McCannel suture technique (Fig. 71.7). A similar technique can be used to repair an area of iridodialysis.

ANTERIOR SEGMENT TRAUMA WITH ASSOCIATED LENS DAMAGE

Once a projectile or foreign body breeches the cornea, there is little to prevent it from disrupting the crystalline lens as well. A thorough preoperative and intraoperative evaluation of the lens is often difficult owing to poor visibility from corneal edema and anterior chamber blood and/or fibrin. Depending on the type and extent of the corneal wound, a meticulous evaluation may be accomplished most accurately before wound closure. In patients with poor pupillary dilation, it may be necessary to use a Graether collar-button or cyclodialysis spatula to push or retract the iris, thereby enabling the lens to be inspected thoroughly. A fibrinous anterior chamber reaction, which deposits across an intact anterior lens capsule, may obscure the lens or appear as a dense cataract. After the anterior chamber is restored, adequate visibility of the lens may not be achieved secondary to corneal edema; in these instances, it is better to wait and let the eye settle, reevaluate, and possibly do a secondary cataract extraction, if indicated. Further, a small breech of the lens capsule (such as occurs after a penetrating injury from a wire or a small in-and-out projectile) may seal spontaneously and cause only a localized opacity of the lens that is not visually significant and that may be observed.

In patients with a dense cataract and an adequate view after complete repair of the corneal laceration a primary lensectomy may be carried out.[19] This allows for a more accurate examination of the fundus, prevents additional phacogenic inflammation, and may obviate the need for additional ocular surgery. The use of flexible iris hooks that are inserted through multiple paracentesis incisions may aid in expanding the pupil. When there appears to be minimal capsular disruption, good zonular support, and an intact posterior capsule, a standard extracapsular or phacoemulsification technique

may be used. A limbus or temporally based incision is constructed, and surgery is carried out according to standard technique. The surgeon should be vigilant for significant amounts of zonular dehiscence and must be prepared to use capsular tension rings or to convert the surgical technique for lens delivery, if necessary. In cases with extensive zonular dehiscence, an intracapsular cataract extraction technique can be employed if the lens is accessible from a limbal incision.

If the lens is severely subluxated, disrupted, or dislocated with vitreous prolapse into the anterior chamber, then vitrectomy instrumentation should be used to perform a lensectomy and vitrectomy. Every attempt should be made to preserve as much capsule as possible so that a posterior chamber intraocular lens (PC-IOL) may be placed either in the bag or in the sulcus, primarily or secondarily. The vitrectomy-cutting instrument and irrigation are introduced through the limbus or the pars plana, depending on the surgeon's preference and the type of injury, to remove vitreous and liberated lens material from the anterior chamber. An anterior capsular rent can be trimmed and if possible converted to a capsulotomy or possibly a continuous capsulorrhexis. The remaining lens material may be removed using aspiration and cutting. Very hard nuclear material may be removed by nuclear expression or phacofragmentation. If necessary, a thorough anterior vitrectomy is performed. The anterior chamber is evaluated carefully to ensure that there is no vitreous remaining that could become incarcerated in the wound and lead to postoperative vitreous traction, inflammation, or retinal traction. Also, such incarcerated vitreous could act as a 'vitreous wick', causing wound leakage and increasing the risk of infection.

The insertion of an IOL at the time of primary surgery remains controversial. A primary IOL implant could save the patient from additional surgery, yet the selection of proper IOL power, the correct anatomic placement, and the risks associated with implanting a prosthetic device in the face of potential intraocular infection are of concern. A secondary IOL implantation has the advantage of using more reliable IOL power calculations based on actual keratometry readings. In eyes with an adequate view through the cornea after repair and with no gross wound contamination or evidence of infection, a primary IOL implantation may be a reasonable choice.[20–22] In eyes that have adequate anterior or posterior capsular support a PC-IOL should be considered. If the capsular bag is intact, an IOL may be implanted in the bag; if not, a sulcus-fixation PC-IOL may be appropriate. Without capsular support, a PC-IOL may be sutured trans-sclerally or an anterior chamber lens inserted if the iris and angle structure are preserved.

Lens power determination can be sufficiently accurate when keratometry and axial length measurements of the fellow healthy eye are used.[20,21] Even if this calculation is inaccurate, it could be reasoned that it would be better to be a 4 or 5 D ametrope than an aphake. Children in the amblyogenic age range may experience rapid visual rehabilitation, and therefore may avoid the difficulties of an arduous contact lens fit atop corneal scarring or sutures. Patients may need to wear a rigid contact lens to neutralize irregular astigmatism after corneal laceration.

CORNEOSCLERAL LACERATIONS WITHOUT LOSS OF TISSUE

A localized peritomy is made to improve visibility of the wound that is being repaired. Excessive manipulation of the globe and extensive exploration should be avoided until all visible wounds are closed. If the wound edges are separated significantly, regrasping the needle after passage through the first wound edge facilitates closure. Well-delineated corneoscleral lacerations or small, isolated, scleral lacerations from sharp penetrating injury may be repaired primarily and may not require extensive exploration. Extremely posterior lacerations and those associated with severe blunt trauma require exploration of all quadrants of the globe to look for scleral disruption. Smaller scleral lacerations may be repaired using non-absorbable 8-0 nylon suture or absorbable 7-0 polyglactin (Vicryl). For larger corneoscleral lacerations, it is best to start by approximating the limbus using non-absorbable 8-0 or 9-0 nylon suture. One must proceed posteriorly with the repair using simple interrupted sutures and closing the wound as it is exposed ('zippered' closure).[18] In lacerations that extend far posteriorly, the use of a half-round needle makes suture passes easier when work is being done in a deep 'hole'. If exposure of the posterior aspect of the wound is difficult owing to orbital tissue prolapse, a small malleable retractor or a pediatric nasal speculum can be used to improve visibility, with care taken not to exert pressure on the globe.

Prolapsed vitreous should be engaged with a dry cellulose sponge and cut flush with the wound using Wescott scissors; alternatively, a vitreous cutting device may be used. Care should be taken to minimize unnecessary traction on the vitreous. Prolapsed uveal tissue should be repositioned before wound closure is completed. Ideally, there should be no vitreous or uveal tissue incarcerated in the wound. Every attempt must be made to preserve prolapsed uveal tissue. Repositioning of prolapsed uveal tissue may be facilitated if an assistant gently pushes the prolapsed tissue back into the wound using a smooth flat spatula as the surgeon passes the sutures. The wound edges also may be raised gently with a forceps while passing suture bites to keep uveal tissue from being impaled by the suture needle. Uveal tissue is handled with extra care because it can bleed easily and profusely. If it is necessary for uveal tissue to be removed, pre-cauterizing helps to control bleeding. Wounds with extensive uveal prolapse have a worse visual prognosis.[11] Viscoelastics should not be injected into the subretinal space to reposition uveal tissue because they are absorbed poorly and may cause excessive inflammation and increase the risk of retinal detachment.

Once all visible wounds are closed, a 360° peritomy is made, and all four quadrants are opened through Tenon's capsule and explored. Placement of one or more bridle sutures of 4-0 silk under an extraocular muscle or tendon, or through the limbus, may be useful for rotating the globe to aid in exploration. Particular attention is directed to the anatomically thinnest area of the sclera, which is posterior to the insertions of the extraocular muscles, to inspect for occult scleral rupture.[23] If lacerations extend through, or under, extraocular muscles, an assistant can retract the muscle gently using a muscle hook to aid in exposure. If more exposure is needed, the muscle tendon can be secured using a double-armed polyglactin (Vicryl) suture with a spatulated needle; then it can be severed from its insertion and reattached after the laceration is repaired.

It may not be possible to close a scleral wound surgically that extends far posteriorly, near the optic nerve. Prolapsed vitreous and uveal tissues are also more difficult to manage in far posterior lacerations. In these cases, it is better to leave the posterior aspect of the wound open than to cause additional damage and further tissue prolapse with extreme manipulations.

An isolated posterior scleral laceration or rupture from blunt trauma, a projectile injury, or a perforating wound of the globe may occur without associated corneal injury. This should be suspected when the history is appropriate and the examination demonstrates decreased visual acuity, focal subconjunctival hemorrhage and che-

mosis, conjunctival laceration, uveal 'show' under the conjunctiva, decreased intraocular pressure, hyphema, vitreous hemorrhage, pupillary irregularity, or a shallow or excessively deep anterior chamber.[18] These injuries are repaired, as are anterior scleral lacerations, by using a 360° peritomy with exploration of all four quadrants and wound closure as the wound(s) are uncovered. An isolated posterior scleral wound near the optic nerve can be seen in penetrating trauma of the globe and may be managed best without primary surgical closure for the same reasons cited above. In these cases, the orbital tissue serves to tamponade the wound as it heals.

CORNEOSCLERAL LACERATIONS WITH ASSOCIATED TISSUE LOSS

Every attempt should be made to find and reposition any avulsed corneal or scleral tissue. Injuries involving loss of a small tissue area may be closed using tight sutures, although this can lead to significant amounts of tissue distortion and wound tension, which may impede healing and complicate visual rehabilitation. Tissue adhesive may aid in closure. Avulsion of larger tissue areas requires replacement with either fresh or preserved donor corneal and/or scleral tissue. It is best to remove frankly necrotic or infected-appearing tissue before a graft is placed. Devitalized or irregular margins then are trimmed using scissors or a sharp blade to form a smooth circular recipient bed. Care should be taken to avoid further injury to underlying uveal tissue. Alternatively, a partial-thickness trephination may be performed and the remaining tissue removed with scissors or a sharp blade, as in penetrating keratoplasty. Trephination of an open, hypotonous globe is technically more difficult to perform. A suction trephine may accomplish incision in these cases. Alternatively, the trephine blade may be inked and used as a marker to define a distinct border that can be excised with a free-hand technique using blades and/or scissors. This makes it easier to fit a watertight patch. Depending on the wound architecture, either partial-thickness (lamellar) or full-thickness grafts may be used.

A full-thickness or penetrating graft requires a recipient bed with a well-defined rim of healthy tissue to suture to. The patch is cut approximately 0.25 to 0.5 mm larger than the recipient bed and is secured into place using simple, interrupted, 10-0 nylon sutures for a corneal patch and 8-0 nylon for a scleral patch. First, four cardinal sutures should be placed at the 3, 6, 9, and 12 o'clock positions to secure and align the graft and make watertight closure easier. The anterior chamber then can be reformed and the wound integrity checked.

A lamellar graft is indicated for areas of tissue loss that have irregular, macerated, or thin stromal margins. Partial-thickness corneal lacerations may be managed with therapeutic deep anterior lamellar keratoplasty,[24] and residual superficial scars may be amenable to PTK.[25]

Lamellar grafting is begun by creating a partial-thickness incision around the wound using a trephine or a sharp blade. A partial-thickness recipient bed then is formed. The lamellar graft is fashioned to be slightly larger than and similar in thickness to the recipient bed. If the recipient bed is trephined, the patch may be trephined 0.25 to 0.5 mm larger; if the recipient bed is irregular, the patch can be hand-fashioned. The patch is laid into place and secured using 10-0 nylon sutures. The sutures should exit from the donor material at approximately 90 to 95% thickness and enter the deepest portion of the recipient shelf. The knots are trimmed and buried.

Penetrating keratoplasty is rarely performed for repair of acute trauma. Graft survival is guarded owing to the added inflammation associated with acute trauma.[26–28] For short-term repair, a patch graft may be used until full-thickness keratoplasty can be performed secondarily. In the setting of extensive tissue loss, a penetrating keratoplasty may be appropriate.

The peri-operative medication regimen for corneoscleral lacerations with associated tissue loss may include systemic antibiotics as well as postoperative topical antimicrobials and steroids. In cases of extensive inflammation, systemic steroids may also be warranted.

IRREPARABLE TISSUE INJURY

With extensive tissue loss or severe disruption of the globe with loss of intraocular contents, primary surgical repair may be impractical. Every attempt should be made to restore the integrity of the globe to allow time for patient and family acceptance of imminent enucleation. If primary repair is not possible, and primary enucleation has been discussed and consent has been obtained preoperatively, enucleation can be performed at the initial surgery. This saves the patient the time and risk of a second surgery under general anesthesia, and it reduces the risk of sympathetic ophthalmia.

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72 Epithelial downgrowth, pearl tumors, and fibrous ingrowth

Albert S. Jun, Elizabeth C. L. Vito, Julia A. Haller, Walter J. Stark

INTRODUCTION

Ophthalmologists have long recognized the ability of ectopic ocular surface cells to proliferate in the anterior segment of the eye as epithelial downgrowth and fibrous ingrowth. MacKenzie first described an epithelial cyst in 1832.[1] Collins and Cross[2] were the first to describe the clinical and histologic features of epithelialization of the anterior chamber. Though rare, these disorders can be devastating sequelae of trauma or anterior segment surgery and must be considered in the differential diagnosis of postoperative complications. Despite increased awareness among ophthalmologists and improvements in anterior segment surgical techniques, these entities remain a diagnostic and therapeutic challenge.

TYPES OF EPITHELIAL PROLIFERATION

In 1937, Perera[3] divided epithelial proliferation into three separate categories based on prognosis and treatment: (1) 'pearl' tumors of the iris, (2) epithelial cysts, or (3) epithelial ingrowth or downgrowth. Most authors still follow Perera's classification scheme. In recent years, however, the term 'epithelial ingrowth' has been used to describe complications resulting from lamellar refractive laser surgery to the cornea, while 'epithelial downgrowth' denotes complications arising from intraocular surgery or penetrating trauma.

EPITHELIAL CYSTS AND SHEET-LIKE EPITHELIAL DOWNGROWTH

CLINICAL/DIAGNOSTIC FEATURES

Risk factors and incidence

The conditions leading to epithelial cysts and sheet-like epithelial downgrowth are the same. Both disorders are preceded by intraocular surgery or penetrating trauma, especially if the healing process was prolonged or complicated. The time from surgery or trauma to presentation can be days to years,[4] with the longest such reported interval being 52 years.[5] It should be noted that the incidence of epithelial downgrowth in its various forms has never been clear. Large studies of this entity are usually histopathologic in nature.[6,7] Clinical studies of epithelial downgrowth usually encompass many decades over which knowledge and surgical techniques have changed substantially.

Chen and Pineda's 2002 literature review ranked the relative risk of epithelial downgrowth in descending order as cataract extraction, penetrating injury, and penetrating keratoplasty.[8] However, it requires mention that none of the case series they cite are limited to modern surgical techniques. Although rigorous studies are lacking, it is generally assumed that the risk of epithelial cysts and downgrowth has decreased in recent decades with the advent of improved microsurgical instruments and techniques. In 1993, Holliday and coworkers[9] reported the first case of epithelial downgrowth after a sutureless cataract operation using phacoemulsification. Since then, two additional cases have been reported by Vargas et al.[10]

Presenting signs and diagnostic features

A patient with an epithelial cyst may present with pupillary distortion, iridocyclitis, glaucoma, or occlusion of the visual axis (Fig. 72.1). The clinician will see a translucent or gray cyst that commonly connects with the surgical or traumatic wound. Epithelial cysts discontinuous with the wound are thought to arise from surface cells implanted by intraocular instruments.[11–13] In Weiner et al's 30-year review of 124 cases, the most common presenting signs of epithelial downgrowth included a retrocorneal membrane (45%), glaucoma (43%), a positive Seidel test (23%), and corneal edema (21%).[7] According to Solomon et al, hypotony is also present in approximately one-third of cases.[13]

Early detection and treatment of epithelial downgrowth are important for a favorable outcome. Unfortunately, epithelial downgrowth is rare and may be mistaken for more common conditions such as keratoplasty rejection, corticosteroid-induced glaucoma, or iritis.[14] In a review of 207 histopathologically proven cases of epithelial downgrowth at a major referral center, it was found that 36% of the cases were clinically misdiagnosed.[6] In addition, 50% of cases were not clinically suspected until the pathology report

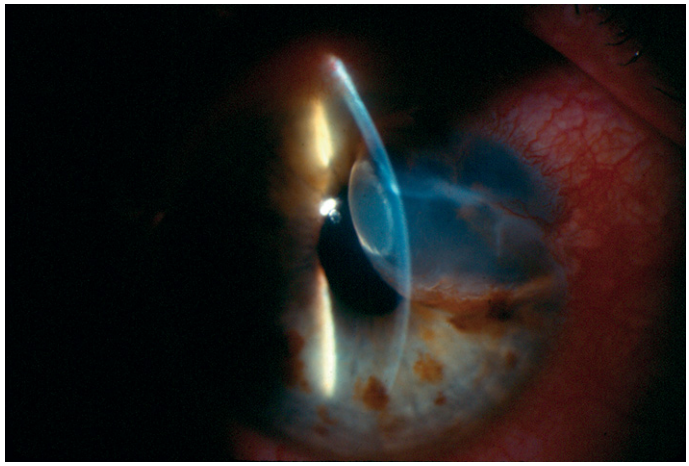


Figure 72.1. Slit-lamp biomicroscopy of an anterior chamber epithelial cyst extending into the visual axis. Note the healed, traumatic corneal laceration overlying the cyst and extending to the limbus.

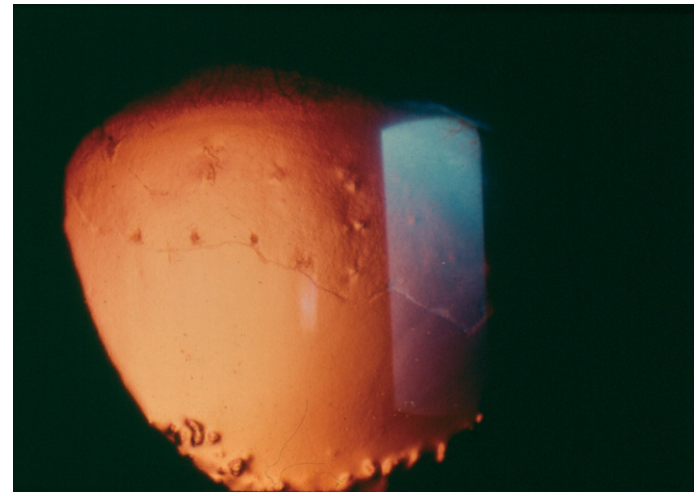


Figure 72.2. Retroillumination of a translucent retrocorneal membrane extending across the superior half of the cornea. Note the typical scalloped profile of the membrane's central border. Reproduced with permission from Stark WJ, Michels RG, Maumenee AE, et al. Surgical management of epithelial ingrowth. Am J Ophthalmol 1978; 85: 772–780.

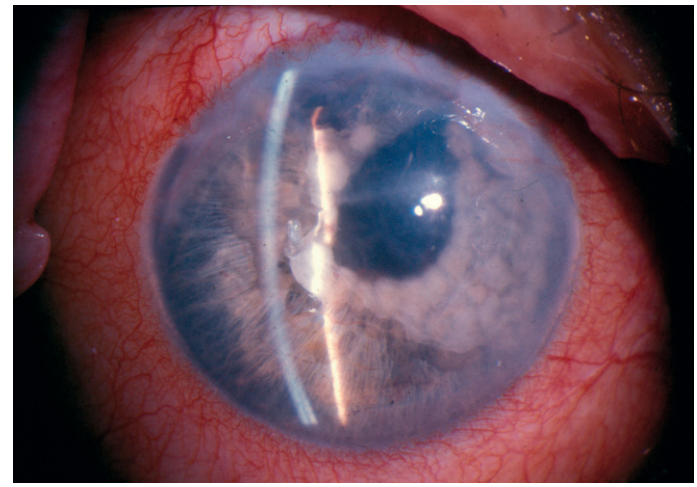


Figure 72.3. Epithelial downgrowth appearing as a whitish membrane on the iris surface extending to the right of the slit beam. Note the peaked pupil indicating incarceration of iris tissue into the superior limbal wound. Reproduced with permission from Stark WJ, Michels RG, Maumenee AE, et al. Surgical management of epithelial ingrowth. Am J Ophthalmol 1978; 85: 772–780.

became available. Therefore, the clinician should have a high index of suspicion for epithelial downgrowth and consider the following diagnostic features/maneuvers:

(1) Retrocorneal membrane as clearly visualized in retroillumination (Fig. 72.2). A scalloped leading edge is typical in most cases of sheet-like epithelial downgrowth.
(2) Epithelialization of the angle on gonioscopy. Glycerin 50% can be used to clear the edematous cornea before gonioscopic examination.
(3) Wound-incarcerated tissue such as iris, lens cortex or capsule, or vitreous (Fig. 72.3).[13]
(4) Abnormal eye pressure (high or low). Although estimates of prevalence vary widely, sheet-like epithelial downgrowth can cause glaucoma via obstruction of the trabecular meshwork. Furthermore, fistulous tracts can produce hypotony in these patients.
(5) Misshapen pupil.
(6) Corneal or iris neovascularization. These vessels are proposed to nourish the ingrowth, and are found in approximately 50% of cases.[13]
(7) Seidel test positive fistula or bleb.
(8) Confocal or specular microscopy. Studies may disclose cells with epithelial morphology on the posterior corneal surface.
(9) Vitreous biopsy. Cytopathology of vitreous specimens may disclose epithelial cells.[15]
(10) Argon laser photocoagulation of the iris. Blanching of epithelial cells on the iris after photocoagulation can be used to diagnose downgrowth or delineate treatment areas (Fig. 72.4).

MANAGEMENT

Epithelial cysts

The treatment of epithelial cysts varies according to the presenting findings and progression. When cysts remain small and stable, periodic observation is sufficient. If the cyst enlarges, medications or eventually surgery may be required to prevent or treat complications such as loss of vision, pupillary distortion, secondary glaucoma, iridocyclitis, corneal edema, and pain.[16]

As reviewed by Solomon et al,[13] epithelial cysts have been treated in prior decades with diathermy, electrolysis, repeated aspiration, aspiration then diathermy, and irrigation of the cyst with radioactive, corrosive, and desiccating agents. While apparently successful in isolated cases with limited follow-up, they have all since been abandoned as unreliable or unsafe.

Photocoagulation has gained popularity as a method to puncture and shrink epithelial cysts. Although minimally invasive, this approach has been reported to require multiple applications to achieve lasting clinical success.[13] Furthermore, photocoagulation may show limited benefit in situations where the cyst shows minimal pigmentation, is firmly adherent to cornea or vitreous, or is present in the posterior chamber. In addition, puncturing the cyst without removing it may lead to conversion into sheet-like epithelial downgrowth.

A variety of techniques have been proposed for surgical excision of epithelial cystic downgrowth. The overarching caveat is to avoid

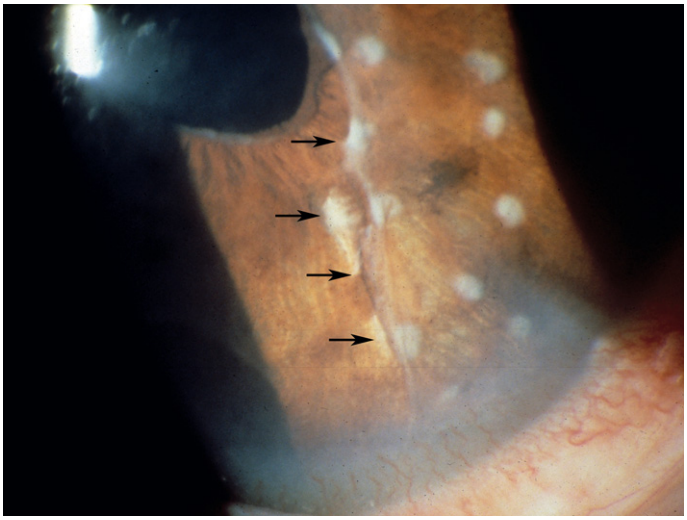


Figure 72.4. Argon laser photocoagulation of sheet-like epithelial downgrowth on the iris; 500 μm spot size is used. Epithelial cells turn white in response to laser energy compared with iris tissue, which turns brown. This method is used to delineate the border between affected and unaffected iris tissue (arrows).

turning the more manageable epithelial cyst into the much more invasive sheet-like epithelial downgrowth via intervention.

Haller et al[16] advocate a conservative approach which begins with viscodissection of the cyst away from adjacent intraocular structures (Fig. 72.5). A 30-gauge needle is used to puncture the apex of the cyst and aspirate its contents. An endolaser probe is then used to collapse and destroy the cyst wall with photocoagulation (Fig. 72.5). Haller et al report the successful use of this technique in four eyes with postoperative visual acuity ranging from 20/20 to 20/40.[16] Such a conservative approach with sparing of the iris, lens, and other ocular structures has obvious benefit and may be particularly helpful in children where amblyopia management can be an issue.

A second, more aggressive approach for treating epithelial cysts includes surgical excision and devitalization of the epithelial tissues, including vitrectomy, lensectomy, fluid-air exchange, and cryoablation of residual cells in the affected area.[17] Corneal edema may occur after cyst excision and freezing; penetrating keratoplasty has been performed to improve visual acuity in some of these cases.[17] One potential drawback to this method, however, includes conversion of the cyst into the more difficult to manage sheet-like epithelial downgrowth.[16] In addition, removal of the lens and iris may contribute to amblyopia in children.[16]

Some contemporary authors promote an even more radical en bloc resectioning procedure[18,19] consisting of simultaneous removal of epithelial downgrowth together with adjacent iris, pars plicata of the ciliary body, and cornea and sclera in full-thickness. This method is promoted as a way to avoid turning epithelial cysts into epithelial downgrowth. Corneal endothelial decompensation and vitreous hemorrhage occurred in more than 20% of cases in a single, large series of 51 patients, and median visual acuity showed a decrease from 20/60 to 20/100.[18]

Mitomycin C (MMC) is a more recent treatment adjunct for epithelial cysts. Two case reports[20,21] have been published in which an epithelial cyst was first aspirated, then injected with MMC, and finally rinsed with balanced salt solution. Neither recurrence nor complications were reported at follow-up of 18 months and 1 year, respectively. Although promising, this approach should be undertaken with caution as MMC is toxic to the corneal endothelium and could potentially cause corneal endothelial failure.

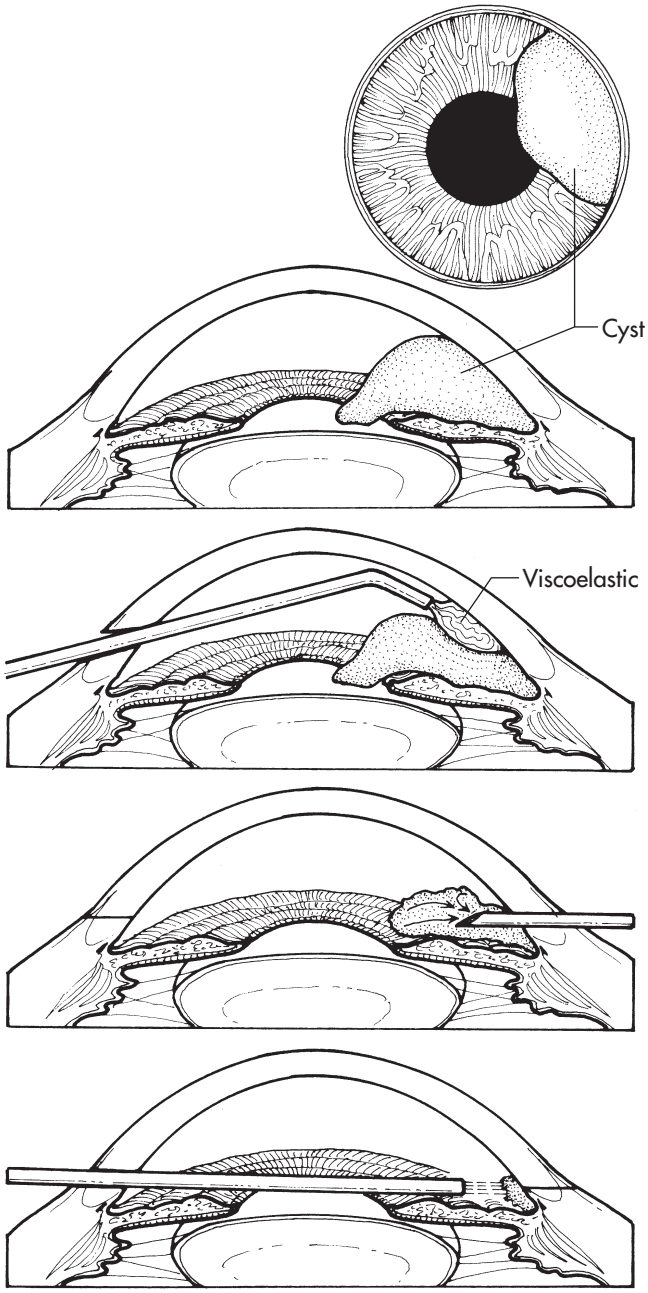


Figure 72.5. Conservative surgical management of epithelial cysts including viscodissection, aspiration, and endolaser photocoagulation. Reproduced with permission from Haller JA, Stark WJ, Azab A, et al. Surgical management of anterior chamber epithelial cysts. Am J Ophthalmol 2003; 135(3): 309–313.

One important caveat to surgical excision of epithelial cysts is potential conversion to the more difficult to treat sheet-like epithelial downgrowth. Furthermore, in light of the unpredictable natural history of epithelial cysts, larger series of cases with longer follow-up would be beneficial for determining optimal approaches to therapy including observation, photocoagulation, excision, or pharmacologic agents.

Sheet-like epithelial downgrowth

Over the years, ophthalmologists have vigorously attempted to eradicate sheet-like epithelial downgrowth in a variety of ways,

knowing that if left untreated, this condition frequently leads to severe loss of vision and enucleation due to intractable glaucoma, pain, and other complications. Previous management techniques for treating epithelial downgrowth included X-rays, freezing, and photocoagulation.[13] These approaches have since been discontinued in favor of Stark's and Michels' modification of Maumenee's original surgical technique.[17,22]

Preoperatively, argon laser photocoagulation is applied to the iris surface in order to outline the extent of epithelial growth (Fig. 72.4). Photocoagulation spots are applied along the advancing edge of the epithelial sheet in such a way that one half of each spot turns white, corresponding to the presence of epithelial cells, and the other half turns brown, corresponding to uninvolved iris tissue.

The procedure begins with the placement of traction sutures under each rectus muscle. A conjunctival peritomy is constructed to expose the superior corneoscleral limbus. If a fistula is present, a partial thickness scleral flap is reflected over the opening and sutured to the peripheral cornea as described by Maumenee.[22]

A sclerotomy is performed 4 mm posterior and parallel to the corneoscleral limbus in the superotemporal quadrant. A vitrectomy instrument, equipped with an overlying fiberoptic sleeve, is inserted into the pupillary space. Areas of involved iris and vitreous are excised. Hemostasis is achieved by increasing the intraocular pressure or by applying bipolar diathermy.[23]

After excising the involved iris and vitreous tissue, any vitreous gel remaining in the anterior half of the vitreous cavity is removed. The vitrectomy instrument is then withdrawn and the sclerotomy site closed with sutures. The fundus is examined with indirect ophthalmoscopy with scleral depression. Any retinal tears are treated with cryotherapy and their position marked on the sclera. A scleral buckle can be placed beneath any retinal breaks.

The anterior half of the eye is filled with sterile air by fluid–gas exchange. Cryotherapy is applied in a transcorneal and transscleral fashion to devitalize remaining epithelium on the posterior surface of the cornea, the anterior chamber angle, and the ciliary body (Fig. 72.6). The air bubble in the anterior chamber allows advancement of the full-thickness freeze from the corneoscleral limbus onto the cornea with considerable precision. Cryotherapy is extended onto the cornea to just beyond the edge of the epithelial sheet as visualized pre-operatively or intraoperatively (Fig. 72.7). If no retinal breaks are present, the air bubble is replaced by balanced salt solution at the conclusion of surgery. If retinal breaks are present, positioning of the patient can be used to achieve gas tamponade. Topical corticosteroids are used postoperatively with frequency and duration determined by the extent of postoperative inflammation. Remaining intraocular epithelium in the treated area typically sloughs during the first few postoperative days.

Using this approach, Stark et al reported visual improvement in eight of ten consecutive cases, and better than 20/50 vision in four eyes.[17] Penetrating keratoplasty for endothelial decompensation after transcorneal cryotherapy can be performed with good results.[24]

Some surgeons advocate en bloc excision of the cornea, sclera, iris, ciliary body, and vitreous.[18,19,25] Using this method for sheet-like epithelial downgrowth, a recurrence rate of 0% was reported in a total of 69 cases. However, this approach is associated with transient intraocular pressure rise and uveitis, decrease in median visual acuity, and postoperative astigmatism.[18,19,25] Lai and Haller described the use of 5-fluorouracil (5-FU) as an adjunctive therapy for sheet-like epithelial downgrowth.[26] Two injections of 500 μg of 5-FU were placed into the anterior chamber of a monocular patient with extensive involvement of epithelial downgrowth. Eight months after the second 5-FU injection, the treated eye showed complete resolution of the epithelial downgrowth. Although limited to a single case report to date, this approach is promising and deserves further evaluation for safety and efficacy. It may have particular value in cases of extensive involvement in which more conservative initial therapy is warranted.[26]

HISTOPATHOLOGY

Epithelial cysts and downgrowth disclose identical histopathologic features including one or more layers of nonkeratinized, stratified squamous cells (Fig. 72.8, *A* and *B*).[27] When goblet cells are present, the source of the downgrowth or cyst is believed to be conjunctival; when goblet cells are absent (the more common scenario), the source of the downgrowth or cyst is believed to be corneal.[28] Immunohis-

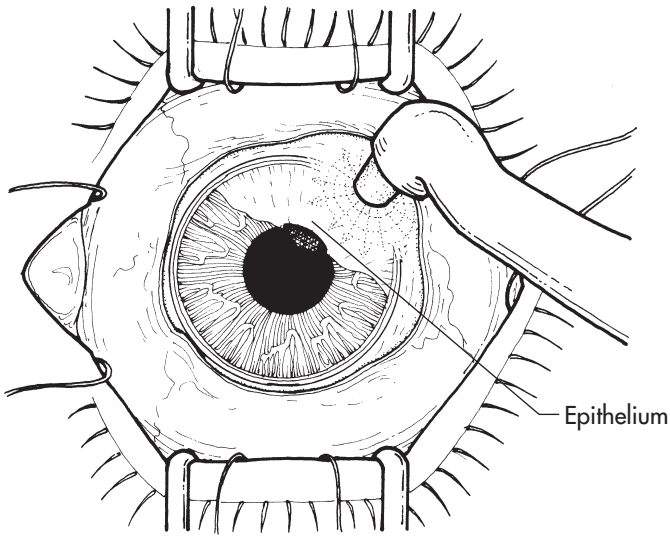


Figure 72.6. Application of cryotherapy to the peripheral cornea and anterior chamber angle affected by sheet-like epithelial downgrowth. Cryotherapy is performed after the anterior chamber is filled with air to enable precise application of freezing.

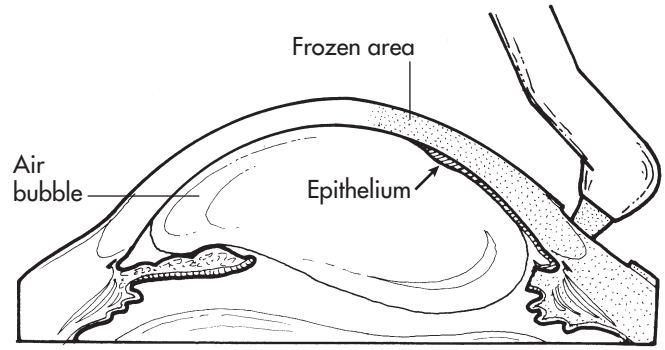
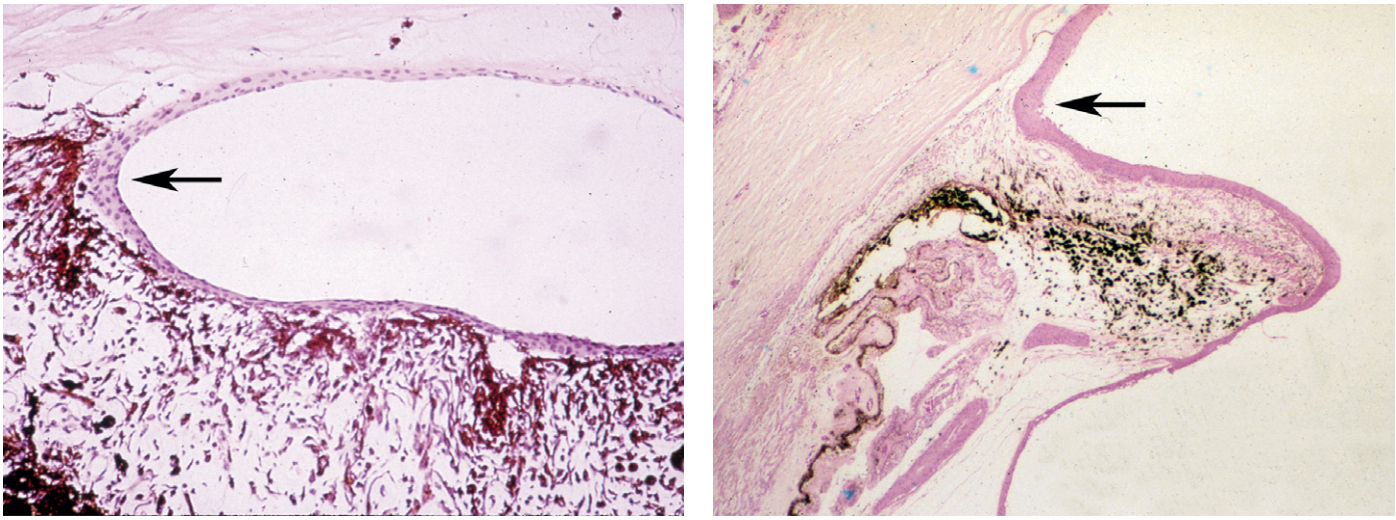


Figure 72.7. Full thickness cryotherapy for sheet-like epithelial downgrowth is applied to a point just beyond the borders of the involved area on the posterior cornea. The anterior chamber remains filled with air during cryotherapy and is replaced with balanced salt solution at the end of the procedure. The de-vitalized epithelial tissue sloughs into the anterior chamber during the first 24–48 h after treatment.



A B

Figure 72.8. Hematoxylin and eosin staining of cystic (*A*) and sheet-like (*B*) epithelial downgrowth (original magnification = 200X). *A*, Note the cyst wall consisting of a nonkeratinized, stratified, squamous epithelium (arrow). *B*, In the sheet-like epithelial downgrowth, a histologically similar epithelium is seen extending continuously from the posterior cornea, over the anterior chamber angle (arrow), and around the iris margin into the posterior chamber.

tochemical staining using monoclonal antibodies to keratin (e.g. in the microvillus processes and hemidesmosomes) can also be used to determine the conjunctival or corneal origin of growths in the eye.[29]

Surface epithelium can be seen extending deep into the surgical wound, and careful sectioning may reveal its continuity with epithelium lining the anterior chamber.[6] The intraocular tissue such as iris, lens capsule, or vitreous may be incarcerated in the wound.[6] Several authors have noted that the corneal endothelium is missing[30] or has undergone epithelial metaplasia[31] in areas of posterior corneal epithelialization.

EXPERIMENTAL STUDIES

Despite our understanding of risk factors (difficult surgery, slowly healing wounds, postoperative hypotony, etc.) the underlying mechanisms leading to epithelial downgrowth remain poorly understood. A limited number of experimental attempts to reproduce the clinical spectrum of epithelial downgrowth have met with modest success. In the 1930s, investigators succeeded in producing epithelial downgrowth when they implanted epithelium continuous with its surface origin in hypotonous, inflamed eyes.[13] The most successful of these experiments placed the conjunctival or corneal epithelium in contact with the iris (thought to play a nutritive role), and maintained the eye in hypotony by placing vitreous, lens capsule, or celluloid in the wound.[13]

Theoretically, the breakdown of the blood–aqueous barrier in hypotonous, inflamed eyes provides serum-borne growth factors needed by proliferating epithelium.[32] These factors are not normally present in uninflamed aqueous humor which though sufficient to maintain viable epithelium,[13,33,34] is insufficient to induce proliferation. Clinical and experimental studies suggest that healthy endothelial cells inhibit the advance of ectopic epithelium[35,36] and, conversely, that damaged or missing endothelium poses an increased risk of epithelialization.[13]

In the mid-1980s, Burris et al reported the development of a cat model of epithelial downgrowth which exhibited strong morphologic and ultrastructural similarities to the human disease.[31] Such a model could be used to test the safety and efficacy of potential antiproliferative agents for the treatment of epithelial downgrowth such as the antitransferrin receptor immunotoxin,[37] 5-FU, or MMC.

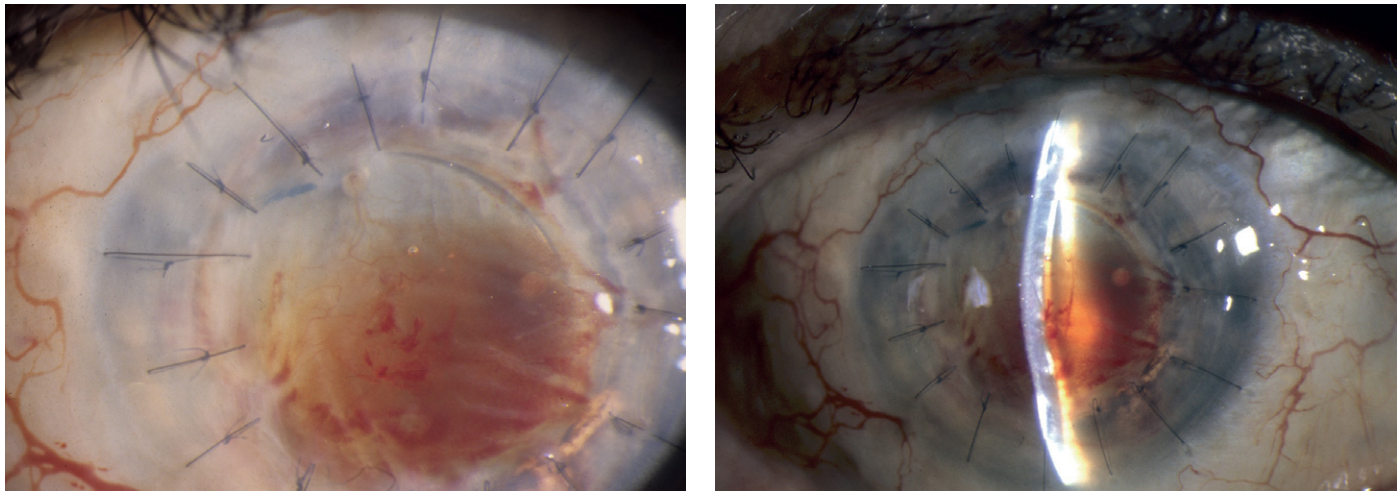
Pearl tumors

These lesions are extremely rare and appear as solid pearly tumors or opaque cysts implanted on the iris surface. Unlike epithelial cysts, which generally appear more translucent, pearl tumors do not show a connection with the entrance wound as they result from traumatic implantation of skin or hair follicles. Pearl tumors are usually small and may not enlarge substantially. Growth occurs slowly, and in extremely rare cases these lesions will reach a clinically significant size or extend posteriorly behind the iris.[38] Mild iridocyclitis may be present. Histopathologically, these tumors disclose encapsulated stratified or cuboidal epithelium surrounding keratinized cells or necrotic debris. Cholesterol, fat, hair follicles, or foreign bodies may be present within the core. If the tumor is small, does not affect vision, and is not growing, it may simply be monitored. If the tumor enlarges or recalcitrant iridocyclitis develops, total excision is indicated, generally with good results.

FIBROUS INGROWTH

CLINICAL/DIAGNOSTIC FEATURES

Ernst Fuchs first described fibrous ingrowth in 1901.[13,39] This entity appears as projections or sheets of fibrous, collagenous tissue interposed between Descemet's membrane and the corneal endothelium (Fig. 72.9, *A* and *B*).[40] Vascularization is sometimes present. In advanced cases, the cornea will appear cloudy and edematous.[41] Fibrous ingrowth often occurs in the setting of elevated intraocular pressure and has been reported to be present in 38 to 55% of epithelial downgrowth cases.[7] The risk factors for fibrous ingrowth-penetrating trauma and surgery are the same as those of epithelial downgrowth.



A B

Figure 72.9. Slit-lamp biomicroscopy of fibrous ingrowth. *A*, Note the opaque, fibrovascular membrane extending across the corneal graft. *B*, A slit-beam indicates the location of the membrane on the posterior corneal surface.

PATHOPHYSIOLOGY AND HISTOPATHOLOGY

Fibrous ingrowth is essentially a healing process—fibroplasia—gone awry. Factors that potentially contribute to this process include prolonged inflammation, poor wound apposition, or a damaged corneal endothelium.[40] The source of the aberrant fibroblasts is unclear. Competing hypotheses postulate that the fibroblastic cells arise from a stromal scarring process; metaplastic corneal endothelium; subepithelial connective tissue; or blood mononuclear cells.[40,41] The theory that retrocorneal fibrous membranes originate from metaplastic corneal endothelial cells was supported by experiments done in 1972 in which rabbit endothelial cells were repeatedly damaged via freezing, but Descemet's membrane was left intact as a barrier for corneal stromal cells.[41] However, these experiments do not rule out the possibility that under different circumstances fibrous ingrowth can arise from other sources such as keratocytes or subconjunctival fibroblasts. Histopathologic analysis discloses the presence of spindle-shaped, fibroblastic cells within a fibrous membrane.[42,43] These cells can be seen within vitreous strands (if present),[43] and the fibrous membrane may contain blood vessels.[42] Ultrastructural analysis discloses fibroblastic cells containing 20 nm fibrils indicating new collagen synthesis.[43]

MANAGEMENT

Unlike epithelial downgrowth, fibrous downgrowth is more amenable to conservative management due to the generally slow growth rate of the aberrant fibrous tissue. Initial treatment approaches can focus on the clinical complications that may be apparent at the time of presentation, in particular glaucoma and corneal decompensation. The former can be treated with varying success using intraocular pressure lowering medications or filtering/drainage device surgery. A more aggressive approach includes membranectomy using a combination of sharp and blunt dissection depending on the degree of tissue thickness and adherence to anterior segment structures.[42] Penetrating keratoplasty can be performed if corneal decompensation is already present or develops subsequently. Such a procedure would be considered at high risk for premature graft rejection or failure. However, results can be quite satisfactory as Bloomfield et al report 20/30 visual acuity with 1-year followup after penetrating keratoplasty for fibrous ingrowth in a single eye.[42]

CONCLUSIONS

Epithelial downgrowth, pearl tumors, and fibrous ingrowth are rare complications of anterior segment surgery or penetrating trauma. Although the incidence of these entities is difficult to estimate, they have become less common with the advent of modern microsurgical techniques. Epithelial cysts, pearl tumors, and fibrous ingrowth can be relatively indolent and may not require intervention. Sheet-like epithelial downgrowth in particular can grow extensively, leading to severe sequelae. Thus, some authors recommend aggressive treatment with cryotherapy or en bloc excision. A relatively small number of reports suggest the value of more conservative treatments such as laser photocoagulation or intraocular agents such as 5-FU or MMC. Despite increased awareness among ophthalmologists, these disorders remain diagnostic and therapeutic challenges. As early diagnosis and initiation of therapy may be beneficial for final outcome, these entities should be considered with vigilance in the settings of postoperative complications and penetrating trauma.

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73 Traumatic cataract, vitreous prolapse, and loose zonules

Michael L. Nordlund, Robert Cionni

INTRODUCTION

Cataract surgery is a common, safe, and highly efficacious procedure with which most ophthalmologists develop proficiency and comfort. In eyes with zonular instability, however, the procedure becomes significantly more challenging and complex. This chapter discusses these challenges and describes methods for managing these difficult surgeries. The procedures detailed in this chapter relate to cataract extraction through a small incision approach. Triple procedures involving corneal transplantation in combination with cataract extraction and intraocular lens (IOL) placement are detailed in chapter 43.

The human lens is an anatomical marvel. It is composed primarily of crystalline proteins encapsulated in a membrane primarily composed of collagen and suspended from the ciliary body by the radial zonules of Zinn[1,2] (Fig. 73.1). Lens zonules are composed primarily of fibrillins. Fibrillins are large proteins that form extracellular microfibril suprastructures ubiquitously found in elastic and non-elastic tissues.[3] Microfibrils appear to have dual roles. Mechanically they confer stability and limited elasticity to tissues and physiologically they modulate the activity of growth factors of the transforming growth factor beta (TGF-β) superfamily. Studies of human lens zonules confirm the remarkable elasticity conferred by their microfibril composition. In fact, human zonules can stretch four times their resting length.[2] In contrast, the importance of TGF-β regulation in zonular function or development has not yet been determined. Despite the remarkable elasticity of lens zonules, these structures provide impressive stability to the crystalline lens. This dual character of stability and elasticity contributes to the accommodative function of the lens and facilitates the surgeon's ability to perform cataract surgery.

The function of the lens zonules can be compromised by trauma or disease. Blunt force, perforating trauma, and iatrogenic events can result in zonular disruption. Most commonly, these etiologies cause localized or segmental breaks in the zonular apparatus.[4,5] Alternatively, disease states such as Marfan's syndrome, homocysteinuria, and pseudoexfoliation can cause diffuse weakening of the entire zonular apparatus.[6–8] While these patients will often present with spontaneous lens dislocation resulting from localized breaks in the zonules, the stability of all the zonules is often compromised.

Compromised zonular function greatly complicates cataract extraction and IOL placement. Firstly, zonular weakness or loss can allow for marked posterior displacement of the crystalline lens when the patient is placed supine and the anterior chamber is inflated with viscoelastics or balanced salt solutions. In cases of traumatic zonular loss, disruption of the anterior hyaloid and vitreous prolapse into the anterior chamber may be present. Secondly, zonular instability can significantly reduce the resistance of the lens to the radial forces applied during creation of the capsulorrhexis, phacoemulsification of the nucleus, or stripping of cortical material from the capsular bag. Postoperative centration of the IOL can also be compromised in the presence of zonular instability. Finally, zonular instability resulting from systemic conditions is commonly accompanied by other co-morbid conditions such as axial myopia, reduced scleral rigidity, vascular fragility, and iris and corneal abnormalities which can significantly increase the unpredictability of the surgery. As a result, the surgeon must be prepared to handle the expected unique challenges of zonular instability as well as the unexpected challenges that may occur during the procedure.

EVALUATING THE PATIENT WITH ZONULAR INSTABILITY

As with all patients being considered for cataract surgery, patients with zonular instability need a complete eye exam to determine the nature of the cataract and assess its impact on visual function. Additionally, the visual potential of the eye needs to be assessed in order for surgeons to provide patients with realistic expectations of their visual recovery. In addition to the standard evaluation, however, patients with zonular instability need to be assessed for additional specific characteristics. First and foremost, the extent and type of zonular instability needs to be assessed. Obtaining a thorough patient history is the first step in this analysis. Soliciting information such as a history of Marfan's syndrome, homocysteinuria, or other systemic disease that may affect zonule integrity suggests the presence of diffuse and more severe zonular disease. In patients with a history of trauma, the nature and severity of trauma can be useful in predicting the extent and location of

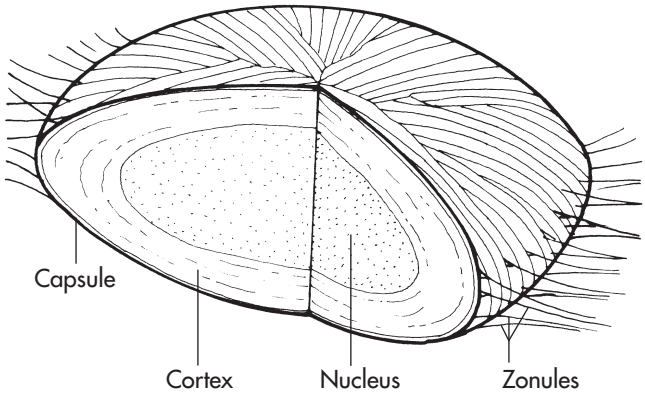


Figure 73.1. Zonule anatomy: The schematic demonstrates the extensive network of zonules that support the lens. While individual zonules are quite elastic and capable of stretching four times their resting length, the arrangement and large number of zonules provides robust support for the lens in the normal eye. Disease and trauma can dramatically impact the integrity of the zonular complex.

zonular loss. For example, severe blunt trauma will often have more widespread effects on the zonules than a perforating injury created by sharp objects. Reviewing the nature of the patient's visual symptoms can also be informative. Complaints of a 'wiggle' or 'shimmer' quality to their vision suggest moderate to severe phacodonosis. Similarly a complaint of the vision changing significantly with head position is consistent with severe phacodonosis. In patients with previous ocular surgery, the type and timing of the surgery should be evaluated and operative reports can be reviewed for evidence of zonular laxity or loss.

Examination of patients with zonular instability begins with gross external examination of the globe and orbit. The orbit should be assessed for its depth and size in order to gauge accessibility of the globe and plan incision placement. Evaluation of the globe for evidence of trauma can often reveal the location of previous trauma and alert the surgeon to potential areas of zonular weakness or loss. Gross analysis of the shape, size, and function of the pupil can further help isolate potential areas of zonular damage.

On slit-lamp examination, the clarity of the cornea and presence of scars should be assessed to determine if there will be limitations in visualization. Scar locations can also help predict areas of zonular weakness. The presence of vitreous in the anterior chamber indicates likely zonular loss. Pigment deposits on the anterior capsule and corneal endothelium are suggestive of significant trauma and pseudoexfoliative material on the anterior capsule indicates potential zonular instability associated with pseudoexfoliation syndrome. In patients with a history of trauma, gonioscopy can help localize areas of potential angle recession that may correspond to areas of zonular trauma. The iris should be evaluated for iridodenesis, iridodialysis, and transillumination defects that provide clues to the nature and location of areas of potential zonular abnormalities. Segmental dysfunction of the pupillary sphincter can help localize areas of potential zonular trauma. Poor dilation is common in eyes with trauma and pseudoexfoliation and may further complicate visualization of the lens during surgery. Finally, the integrity of the lens capsule and lens zonules must be evaluated. Phacodonosis or decentration of the crystalline lens is indicative of more severe zonular loss. Phacodonosis is more evident prior to dilation as the dilated pupil and ciliary body tends to tamponade a loose lens. After dilation, the position of the lens with the patient supine and face up can be assessed with a direct ophthalmoscope or portable slit lamp. Posterior dislocation of the lens during this maneuver suggests severe zonular loss.

Typically, obtaining axial length and keratometric measurements is not difficult in these patients unless there is significant scarring in the cornea. Predicting postoperative anterior chamber depth in these patients can be difficult, however. In general, patients with significant zonular weakness or loss will have deeper anterior chambers than predicted postoperatively. Thus, when choosing a lens power, we aim for a little more myopia than usual. This hedge minimizes the chance for a postoperative hyperopic result.

PLANNING THE SURGERY

Unpredictability is a cardinal feature of cataract surgery in patients with zonular instability. Thus, the surgeries are often more involved and longer than expected preoperatively. Therefore, it is prudent to use long-acting anesthetics such as peribulbar or retrobulbar anesthesia. In young or particularly anxious patients, general anesthesia is sometimes required to ensure patient cooperation. Patients with pseudoexfoliation syndrome and no other abnormality on exam are an exception to this rule and can safely undergo cataract surgery using topical anesthesia. However, if there is any concern that vitrectomy or suturing of a capsular tension ring or lens may be required, regional anesthesia will greatly facilitate the surgery and provide additional comfort to the patient.

Preoperative preparation of the eye with zonular instability is not different from routine cataract surgery. The eye is dilated with 2.5% phenylephrine and either 1% tropicamide or 1% cyclopentolate. A topical nonsteroidal anti-inflammatory is helpful in preserving mydriasis and may minimize cystoid macular edema. Topical fluoroquinolones and 5% betadine may be instilled into the cul-de-sac preoperatively to reduce levels of microbial flora.

In planning surgery for patients with zonular instability, we find it useful to preoperatively stage patients into one of three categories.

Type I zonular stability is characterized by mild generalized zonular weakness or with localized zonular loss. Examples of patients in this group are those with pseudoexfoliation syndrome or localized trauma. On examination, the pseudoexfoliation patient will typically have pseudoexfoliative deposits on the anterior chamber, small pupils even with dilation, and iris transillumination defects. In the eye with a small area of localized trauma, there is often vitreous prolapse and iris trauma in the area of zonular loss. However, no phacodonosis or lens decentration is present preoperatively. These patients represent the mildest form of zonular instability.

Type II zonular instability is characterized by those eyes with marked regional zonular loss but with apparent retained zonular integrity in at least one quadrant. These patients typically have had significant trauma or systemic conditions such as Marfan's syndrome, homocysteinuria, congenital ectopia lentis, and Weil–Marchesani syndrome. On examination there is usually obvious evidence of zonular compromise. There may be associated iris abnormalities such as an iridodialysis. Vitreous prolapse into the anterior chamber is common. Posterior or anterior displacement of the lens in the area of zonular loss is common and there may be phacodonosis with eye movements. The lens is typically decentered and may tilt posteriorly when the patient is supine. Despite these findings, the eye appears to have at least one quadrant where the lens zonules appear intact.

Type III zonular instability includes those patients with diffuse and severe zonular weakness or with near total or total zonular loss. Patients in this group can include patients with advanced systemic conditions or severe trauma.

TYPE I INSTABILITY

The expectation for patients with minimal zonular instability is that the cataract can be removed with little deviation from the standard cataract surgery. The defining feature of these patients is that the lens is well stabilized and can tolerate the stresses of a gentle cataract surgery. The zonular deficiencies in these patients, however, can result in decentration of the posterior chamber IOL. Thus, the primary surgical deviation in most of these cases consists of placement of a standard capsular tension ring (CTR) to stabilize the capsular bag. The patient with segmental zonular loss may also require vitrectomy.

Capsular tension rings were first described in rabbits by Hara and Yamada in 1991,[9] in patients by Legler and Witshcel (1993), and in human cadaver eyes by Nagamoto and Bissen-Miyajima in 1994. The current standard CTR is a flexible, circular, open ring segment composed of polymethylmethacrylate with eyelets at each end (Fig. 73.2, *A*). When inserted into the capsular bag, CTRs are compressed to the size of the capsule and provide centripetal force to the equator of the capsular bag. This distention helps maintain the normal shape of the capsular bag allowing for centration of the IOL within the capsular bag. Additionally, the tension created by the CTR provides rigidity to the capsule. Thus, stability provided by areas of strong zonule integrity is transferred via the inherent rigidity of the compressed CTR to areas with less stability. Capsular tension rings work best in eyes with less than approximately 120° of consecutive zonular loss.

In eyes with more than 120° of consecutive zonular loss, there is often insufficient support in the axis of loss to prevent decentration of the capsule and thus a sutured or modified CTR or capsular tension segment (CTS) may be required. Modified CTRs were developed by Cionni and are similar to standard CTRs with the exception that they have suture eyelets that extend anteriorly around the anterior capsule and allow suturing of the CTR to the sclera without having to pierce the capsule with a needle (Fig. 73.2, *B–D*). The CTS is a similar device developed by Ahmed in that it contains an anteriorly displaced eyelet for suturing of the device to the sclera, but differs in that it extends only 120°[10] (Fig. 73.2, *E*). These devices are discussed in more detail in the discussion of type II stability.

Standard capsular tension rings are currently produced by two manufacturers: Morcher GmbH (Stuttgart, Germany) and Ophtec (Groningen, The Netherlands). CTRs are available in different sizes and are packaged according to the diameter of the CTR in its uncompressed state. When selecting a standard CTR, it is preferred that the length and diameter of the CTR be greater than the circumference and diameter of the capsular bag to ensure enough expansile force to expand and stabilize the capsular bag. Axial length and white to white measurements can be used to approximate the capsular bag diameter, and thus may be helpful in selecting the appropriate size CTR.[10,11] However, with the exception of very small eyes, it is difficult for the CTR to be too long. Thus, we typically use the longest CTR, which is 14.5 mm in diameter in the uncompressed state. Other authors also prefer routinely using larger-sized CTRs.[10] The only downside to using the largest CTR in each case is the largest CTR is also the stiffest and one needs to be more careful during insertion to avoid damaging zonules further.

Incision placement is an important consideration in planning surgery in these patients and can greatly facilitate or hinder the surgery. In patients with pseudoexfoliation and no other abnormalities on examination, we use a standard temporal clear corneal incision. In those eyes with segmental zonular loss, we find it helpful to place the clear corneal incision 90–180° from the area of loss. The advantage of this incision placement is that it facilitates suturing of a capsular tension ring in the area of loss if it becomes necessary to do so. Suturing a ring adjacent to or below the incision can be difficult. However, it is also important to pay attention to the anatomy of the patient's orbit. Deep and small orbits can interfere with access to the incision. Thus, in these patients it is helpful to keep the incision in the temporal cornea.

In type I zonular instability, the creation of the capsulorrhexis, phacoemulsification, and cortical removal can typically be performed using standard cataract surgery techniques. There are a few potential modifications that may simplify the surgery, however. First, in eyes with zonular loss, vitreous tends to follow the flow of fluid. We recommend placing a generous amount of a dispersive viscoelastic agent over the area of zonular loss to help prevent vitreous prolapse. Additionally, it is important to avoid collapse of the anterior chamber in these cases. When pressure in the anterior chamber decreases, a posterior to anterior pressure gradient develops which can promote anterior displacement of vitreous. This situation occurs most commonly with withdrawal of large instruments from the main incision. Thus, simultaneous introduction of viscoelastic or balanced salt solution through a paracentesis each time instruments are removed from the main incision will help maintain a formed anterior chamber and minimize the chance of vitreous advancing forward. Slow motion phacoemulsification using lower bottle heights and aspiration and vacuum settings can also be useful in preventing sudden pressure changes that contribute to chamber collapse and instability.[12] The management of vitreous in the anterior chamber is discussed below. Careful but thorough hydrodissection to separate the lens from the capsule will minimize stress during manipulation of the nucleus and cortical stripping.[13,14] In dense nuclear cataracts, higher ultrasound power can increase the cutting power of the phacoemulsification tip, and therefore reduce lateral force on the lens and zonules. Finally, careful cortical stripping in the area of zonular dehiscence is required to prevent additional disruption of the intact zonules adjacent to the area of loss. The surgeon should consider cortical viscodissection to decrease the zonular stress during cortex removal (Fig. 73.3). In cases where the zonular loss is sufficient to interfere with gentle cortical stripping, a CTR can be placed to help stabilize the bag for cortical removal. While the ring may trap some cortical material, viscodissection prior to CTR placement will limit entrapped cortex. This maneuver is not commonly required in eyes with type I zonular instability, but is often necessary in more severe cases.

In eyes with zonular loss, vitreous may prolapse into the anterior chamber. If vitreous is not present at the beginning of the case, the use of dispersive viscoelastics to tamponade the area of loss can prevent vitreous prolapse. The tamponade may need to be reapplied during the case if some of the viscoelastic is accidentally removed during phacoemulsification or cortical removal. If the tamponade fails or if vitreous is present at the beginning of the case, a vitrectomy must be performed. Vitrectomy is best performed using a bimanual technique through either an anterior chamber approach or through a pars plana approach. It is commonly recognized that bimanual vitrectomy with an irrigating cannula placed through a paracentesis and a vitrector inserted through a pars plana

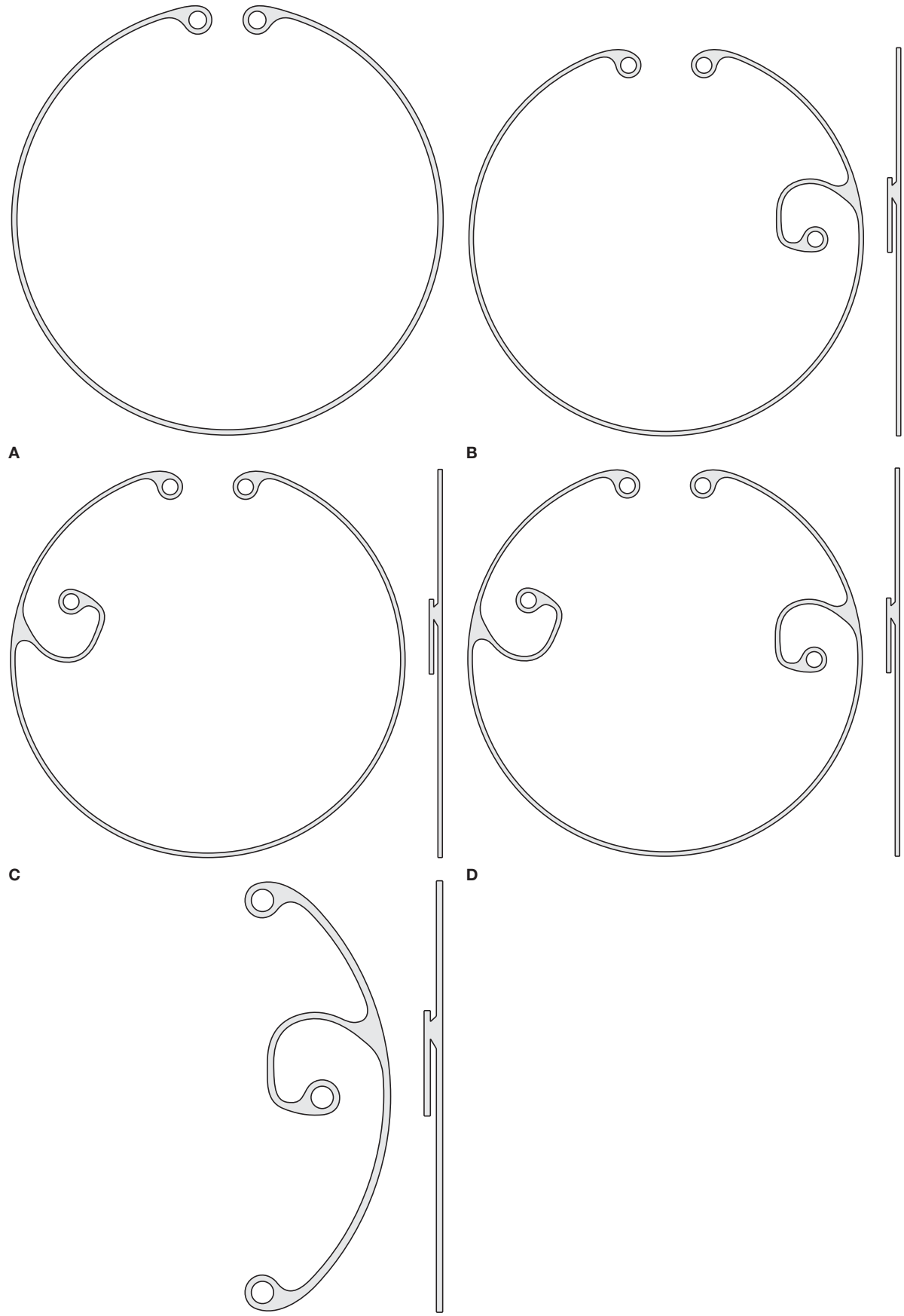


Figure 73.2. Capsular support devices. *A*, The appearance of the standard capsular tension ring (CTR). *B*, *C*, and *D*, Modified capsular tension rings (MCTRs). These devices possess an anteriorly displaced suture fixation eyelet to allow for suturing of the device to the scleral wall without having to compromise the integrity of the capsule. The MCTR in *D* has two fixation eyelets for eyes with little or no zonular support. *E*, The capsular tension segment.

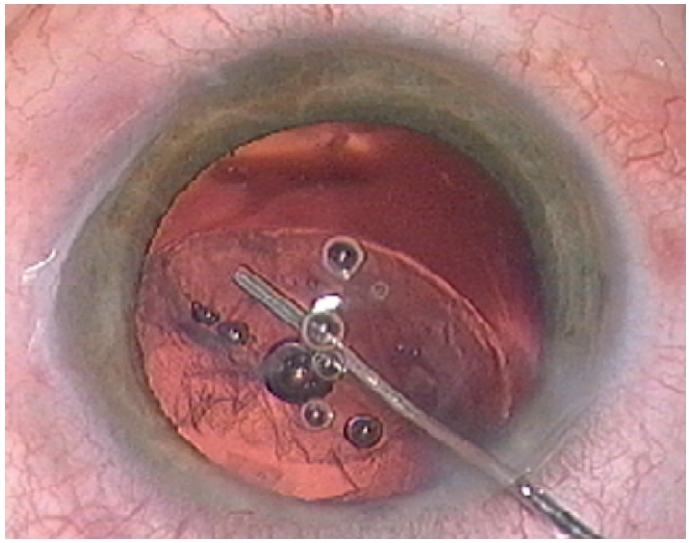


Figure 73.3. Viscodissection of lenticular cortex is achieved by gentle injection of a dispersive viscoelastic between the capsule and the lens cortex. This procedure greatly reduces adhesion of the cortex to the capsule and thus facilitates subsequent cortical removal. Viscodissection is particularly useful when a CTR must be placed prior to cortical removal. In these cases viscodissection is performed prior to placing the CTR and can significantly reduce the chance of equatorial cortical material being entrapped between the CTR and capsule.

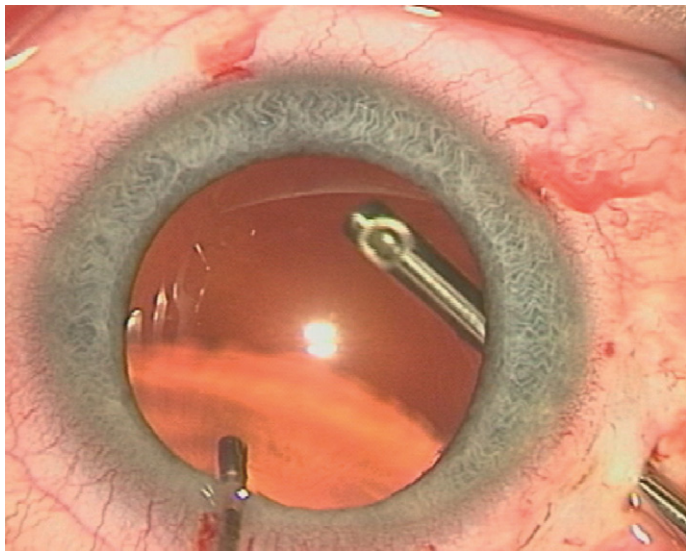


Figure 73.4. The photograph demonstrates bimanual vitrectomy in a patient with lens subluxation and vitreous prolapse into the anterior chamber. An irrigating cannula is inserted through a paracentesis. The vitrector is then inserted through a pars plana sclerotomy and can be visualized posterior to the lens. The bimanual approach greatly facilitates vitreous removal.

sclerotomy is generally the most efficient approach.[15,16] The advantage of this approach is that the flow of fluid is from the anterior chamber to the posterior chamber, and thus, vitreous is swept out of the anterior chamber. We typically use a 20 gauge vitrector and make a sclerotomy 3.0–3.5 mm posterior to the limbus directly below the main corneal incision (Fig. 73.4). With the main incision 90–180° from the area of zonular loss, this location facilitates placement of the end of the vitrector in the affected area while maintaining visualization of the instrument through the pupil. Often, only

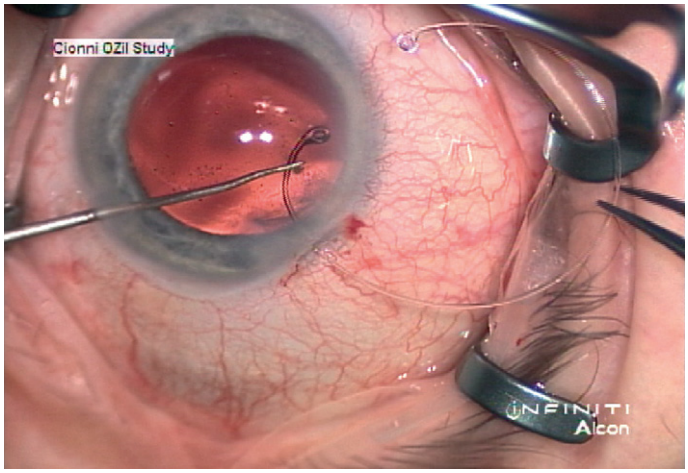


Figure 73.5. Placement of a standard CTR is achieved with the inserter or with a bimanual technique using standard instrumentation. In this photograph, the CTR is being inserted with a forceps. Once the leading edge is in the capsule, it is advanced by gently pushing the trailing end using the forceps. A second instrument, such as a y-hook, can be inserted through a paracentesis and used as a guide if necessary. The trailing end can be dialed into the capsule using either the forceps or y-hook.

a small, localized vitrectomy is required to clear the anterior chamber using this technique. Another significant advance in the management of vitreous prolapse into the anterior chamber is the use of purified intracameral triamcinolone acetonide to stain the vitreous.[17] Identification of the vitreous in this manner greatly facilitates vitreous removal by allowing the surgeon to properly direct the vitrector and visualize when the normally transparent vitreous is gone. Upon completion of the case, the sclerotomy and the conjunctiva are closed with a suture of choice. Newer 25 or 23 gauge vitrectomy probes can be used in conjunction with transconjunctivally placed trocars and typically do not require scleral and conjunctiva closure.[18] Specifics regarding the settings for the various vitrectomy methods differ depending on the equipment used and are beyond the scope of this chapter. Details are best obtained from surgeons or company representatives familiar with the specific equipment in question.

Following cortical removal we typically place a standard CTR in eyes with type I zonular instability. An important prerequisite, however, is that the posterior capsule and the capsulorrhexis be intact. CTRs exert radial tension on the equator of the capsular bag, which can promote extension of tears and can result in migration of the CTR into the posterior chamber.[19–21] If the capsule is torn, a posterior chamber IOL will likely need to be sutured in order to achieve stability and centration or an anterior chamber lens must be placed. Methods for suturing of IOLs are discussed in the section of type III zonular instability. With an intact capsule, a CTR can be placed using specially designed inserters or using standard instrumentation. To place the ring, the capsular bag and anterior chamber are inflated with viscoelastic and one end of the ring is inserted through the main incision and into the bag (Fig. 73.5). The ring is slowly advanced with the inserter or a forceps with one hand and gently guided in the proper direction with a second instrument through a paracentesis. The second instrument helps minimize tension on the edge of the capsulorrhexis and lateral displacement of the capsular bag. When the trailing end approaches the main incision, a y-hook or the inserter engaged in the trailing eye hook

is used to advance the ring until the trailing end is under the edge of the capsulorrhexis and the eyelet is released. If one encounters difficulty 'feeding' the CTR along the capsular bag equator, a 10.0 nylon suture can be looped through the leading eyelet, left trailing out the incision and gently tugged during ring insertion to help guide the leading eyelet circumferentially. If it is unclear whether a suture will be required to maintain centration of the IOL, a modified CTR can be placed instead of a standard CTR. If it is subsequently determined that a suture is not required, the fixation hook of the MCTR can be placed posterior to the capsulorrhexis edge, inside the capsular bag and the MCTR will perform as a standard CTR. It is important in these situations, however, that the suture loop be placed into the capsular bag to avoid the risk of postoperative iris capture in the loop.

After placement of the CTR, the IOL is inserted into the bag. Viscoelastic can then be removed with automated irrigation and aspiration. If vitrectomy has been performed or if there is an area of zonular loss, reduced aspiration and vacuum settings may help prevent forward displacement of vitreous into the anterior chamber. It is also advisable to leave some dispersive viscoelastic in the area of the dehiscence to prevent late intraoperative vitreous prolapse. Postoperative elevations of intraocular pressure are typically transient and can be managed with topical or oral medications if necessary.

The safety and effectiveness of CTRs in patients with type I zonular instability has been well documented. Gimbel et al published a retrospective review of 14 cases in which the CTR was used for mild zonular laxity or loss.[22] He concluded that the use of CTRs in these patients helped prevent capsular bag collapse and vitreous loss and maintain centration of the IOL. Byraktar et al published a prospective randomized trial of 78 eyes with pseudoexfoliation. In the study, half of the patients received a CTR and half did not. In the eyes without a CTR, five developed zonular loss and three had a posterior capsule rupture. In contrast, no eyes in the CTR group had zonular loss and only two eyes suffered a posterior capsule rupture. Additionally, IOL centration was better in the group that received the CTR.[23] Finally, Price et al published interim results of a multicenter trial using the Ophtec CTR.[24] In this paper, 255 eyes with weakened or broken zonules comprising one-third or less of the circumference of the lens capsule received a CTR. At 1 year following surgery, only 4 of 172 eyes had decentration of the IOL. Complications during surgery were rare and included posterior capsular rupture in 3 eyes and vitreous loss in 6 eyes. The authors concluded that the use of the CTR in these patients was safe and provided capsular support during and after cataract surgery.

TYPE II INSTABILITY

Eyes with type II instability present additional challenges. These eyes are characterized by significant zonular loss and nearly all phases of the surgery become more difficult. In these patients, the surgical objective is to remove the cataract while maintaining an intact capsule and provide long term, in-the-bag, support for a posterior chamber IOL (PCIOL) by securing the capsule with a sutured capsular tension ring or segment. Since suturing is likely to be required, selection of incision site is particularly important. Again, our preference is to have the incision 90–180° from the location, the suture will likely be required, in deep obstructed orbits, somewhere in the temporal aspect of the eye. Some of these cases may have vitreous prolapse in the anterior chamber and thus require vitrectomy early in the case. Vitreous provides significant support to the lens, however. Thus, if the vitreous does not interfere with access to the lens, it is typically easier to perform the capsulorrhexis and stabilize the capsule with hooks or a CTS prior to the vitrectomy (Fig. 73.6) Our approach to vitrectomy in these patients is described in the previous section on type I instability. The use of triamcinolone acetonide resuspended in balanced salt solution (BSS) to label the vitreous is particularly helpful in these cases since it allows the surgeon to visualize the removal of vitreous, and therefore remove as little vitreous as required.

The capsulorrhexis in eyes with marked zonular loss can be very challenging. First, the lens may have a tendency to drift posterior while trying to grasp or penetrate the anterior capsule. For this reason, it is best to begin the capsulorrhexis in an area of maximum fixation and tear away from this area. If there is too little support to begin the capsulorrhexis, it is often helpful to support the lens with a blunt second instrument passed through a pars plana sclerotomy. A capsulorrhexis forceps may perform better than a cystotome in these patients since the forceps can grasp the capsule and pull tangentially without any downward force on the lens. In fact, gentle anterior elevation can be applied with the forceps during the creation of the capsulorrhexis to further help stabilize the lens. Care must be taken not to pull too anteriorly, however, or it is likely the advancing tear of the capsulorrhexis will extend radially. The second difficulty in performing the capsulorrhexis in these eyes is that during the tearing of the capsulorrhexis the lens will tend to decenter as the tear is directed away from the area of zonular loss. One method of addressing this problem is to use a second instrument to stabilize the capsule while completing the capsulorrhexis. Iris hooks or a CTS can be used to secure the edge of the anterior capsule in an area where the capsulorrhexis has been performed[10,25–27] (Fig. 73.6). This additional fixation will provide the necessary counter traction to stabilize the capsule while tearing away from this area. Additional hooks or a second CTS can be

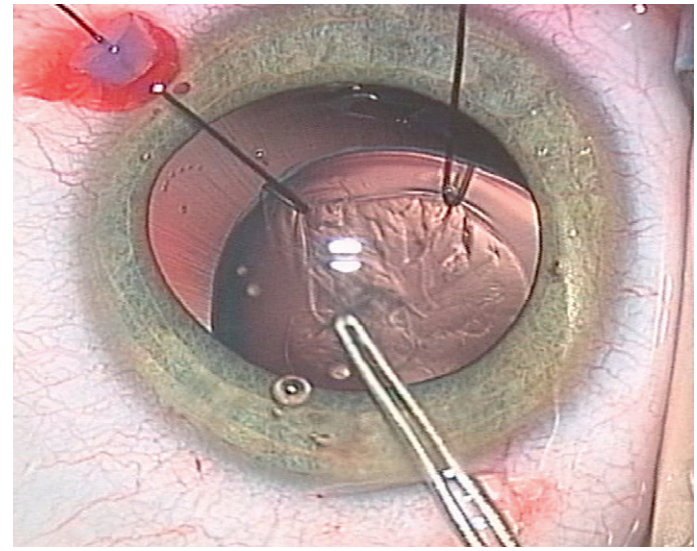


Figure 73.6. Nylon iris hooks are utilized to stabilize the capsular bag during creation of the capsulorrhexis. The capsulorrhexis is started in an area of zonular integrity and the tear is directed away from this area. As the tear advances into areas of less integrity, there may be insufficient counter traction to control the advancing tear. In these situations iris hooks can be used to secure the edge of the capsulorrhexis. The hooks provide the needed capsular stability to resist the forces of the advancing tear during completion of the capsulorrhexis.

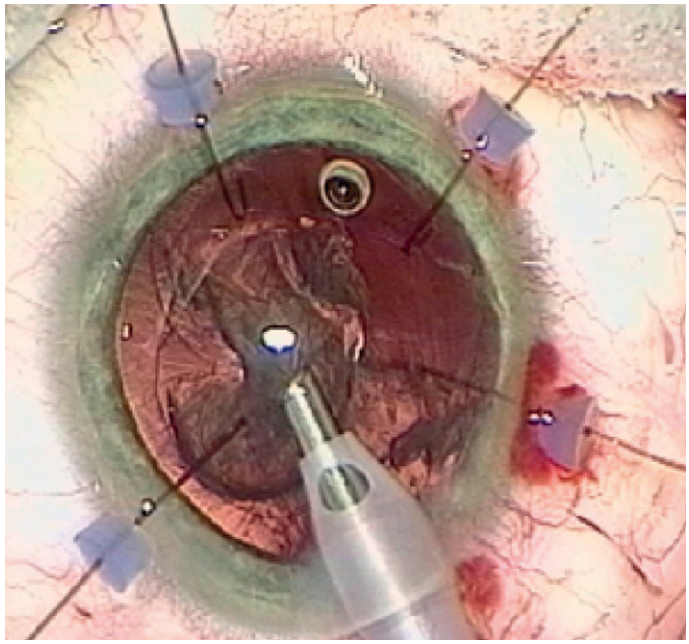


Figure 73.7. Four iris hooks have been used to secure the edge of the capsulorrhexis. The hooks provide marked capsular support which prevents posterior and lateral displacement of the capsule during phacoemulsification and cortical removal.

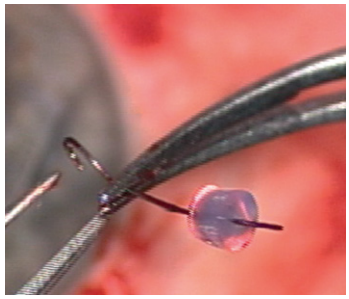


Figure 73.8. When placing iris hooks to secure the capsule, the ideal positioning is to have the bend in the hook engage the capsulorrhexis edge and apply a primarily lateral force. In eyes with deep anterior chambers, iris hooks inserted at the limbus must course posteriorly to reach the capsule which can result in the ends of the hooks exerting more anterior force on the capsule. This positioning increases the risk of capsular tears. To prevent this from happening, the shaft of the iris hook can be bent to change the orientation of the hook relative to the shaft. In this photograph, two forceps are used to bend the shaft to the desired position where it is held for 10–15 s.

placed if needed as the capsulorrhexis is created. It is not always possible to achieve a centered capsulorrhexis of ideal size (5–6 mm) in these eyes. It is better to have a decentered intact capsulorrhexis than a radial tear. If the capsulorrhexis edge is in the visual axis and symptomatic, it can be enlarged with the YAG laser, but no sooner than 2 months post-op.

In some eyes an intact capsulorrhexis may not be possible. The CTS can often be used to provide intraoperative and long-term stability in these cases. Unlike the modified CTR, the CTS has a short intracapsular segment that does not exert radial tension on the equator of the capsule. Rather it slips under capsule edge to provide localized stability of the anterior capsule. Like the modified ring, it has an anteriorly located fixation eyelet to facilitate suturing of the device to the sclera for permanent fixation. These unique features allow the CTS to be used in cases with radial tears of the anterior capsule or posterior capsular rupture.[10]

Once the capsulorrhexis is completed, it is helpful to stabilize and center the capsule in preparation for cataract removal. Iris hooks or the CTS are ideal for this purpose[10,25–27] (Fig. 73.7). The hooks are inserted through limbal stab incisions and the edge of the capsulorrhexis engaged in the areas of zonular loss. Bending a disposable nylon iris retractor back on itself and holding it in that bent position for 10–15 s will allow it to maintain a more usable configuration throughout the procedure (Fig. 73.8). Depending on the amount of instability, one to four hooks can be placed. As mentioned earlier, multiple capsular tension segments can also be placed if necessary to stabilize the capsule.[10] While it is prudent to use caution, an intact capsulorrhexis can typically withstand significant tangential pressure. Stabilization and centration of the capsule greatly facilitates subsequent phacoemulsification of the nucleus and cortical removal. Prior to cataract removal, however, all vitreous should be removed from the anterior chamber. The anterior chamber can be inspected for additional vitreous with triamcinolone acetonide suspended in balanced salt solution as previously described. Once the anterior chamber is clear of vitreous, tamponade of the area with zonular loss should be performed with a copious amount of dispersive viscoelastic. Typically, phacoemulsification can then be performed as previously described for type I instability. Cortical removal can then be attempted. The loss of zonular support across large areas of the lens, however, often results in inadequate stability of the equatorial capsule. Thus, as cortex is stripped centrally, the equatorial capsule migrates centrally with the cortical material and further stress and damage may occur to adjacent intact zonules. When this occurs, cortical stripping can be greatly facilitated by placing a modified CTR prior to cortical removal. As mentioned above, viscodissection will also help immensely. In patients where the surgeon has placed a CTS to stabilize the capsule, it is important to realize that the CTS does not provide equatorial stability to the capsule. If the capsule is intact, a standard CTR can be placed in these patients to assist with cortical stripping and IOL centration.[10]

Patients with type II instability require suture fixation to maintain centration of the IOL. To achieve centration and maintain an intact capsule, a modified CTR or a CTS is required. The modified CTRs come in left- and right-handed versions which differ in the axial orientation of the suture loops relative to the curvature of the leading edge of the ring. When placing the modified CTR, it is important that the suture loop project anteriorly to capture the edge of the anterior capsule. Thus, left-handed rings are passed in clockwise and right-handed loops are inserted counterclockwise.

When suturing the modified ring with two fixation hooks (Model 2-L), suture the eyelets at whatever axes achieve centration. This may not necessarily be 180° apart and depends on the diameter of the capsular bag. Prior to placing the ring, one end of a double armed 9-0 prolene suture or 8.0 gortex suture with long needles such as CIF-4 or CTC-6 needles, is passed through the suture fixation eyelet (Fig. 73.9). Other suture types can be used and are discussed below. An inserter can be used for Model 2-C or standard instruments can be used to place any of the MCTRs which are inserted as described previously. Once the ring is in the capsule, it must be rotated to orient the fixation hook in the area of zonular loss.

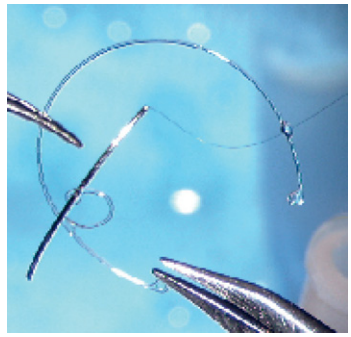
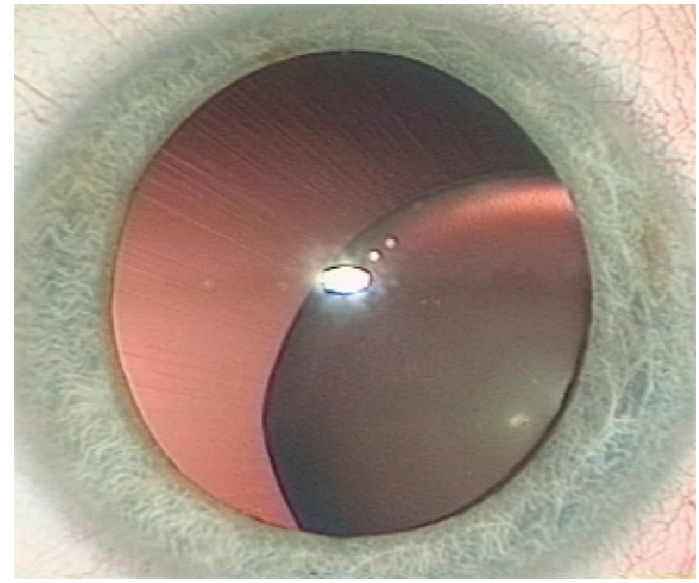
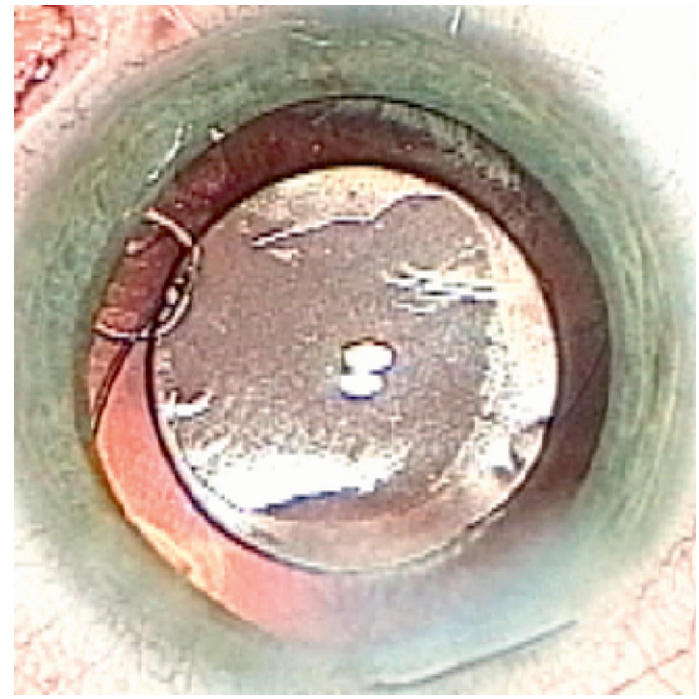


Figure 73.9. This photograph demonstrates placement of the MCTR. A 9-0 prolene suture is passed through the fixation eyelet. The MCTR is then placed in the capsule as described. Specially designed inserters allow for one-handed insertion. Alternatively, bimanual insertion can be performed using standard instrumentation such as forceps and y-hook.

Once the desired positioning is achieved, the sutures are placed. We typically perform an ab interno suturing technique. A conjunctival peritomy approximately 2–3 clock hours in length and a small conjunctival relaxing incision are performed in the area the sutures are to be placed. Hemostasis can be maintained by light cautery. Prior to passing the sutures, we typically make a partial thickness scleral flap. The role of the flap is to cover the suture and reduce the risk of erosion of the suture through the conjunctiva, which is a risk factor for late postoperative endophthalmitis. Scleral flaps are not needed if the suture knot is rotated and buried in the sclera. In fact, rotation of the knot intraocularly has been demonstrated to be superior to covering the knot with a sclera flap in preventing suture erosions.[28] It is our intention to rotate and bury the suture knots in these cases, but it can be difficult to rotate 9-0 prolene or 8-0 gortex knots. Thus, we may typically prepare a scleral flap in case the knot cannot be buried. The sleral flaps can be hinged at the limbus or posteriorly. Posteriorly hinged flaps provide the best visualization of the flap bed, however. Additional viscoelastic is placed between the iris and anterior capsule to maximize space for passing the needle. One needle of the double-armed suture is passed through the main incision, between the iris and anterior capsule, then through the sclera 1.0 mm posterior to the limbus and out through the flap bed.[29] While the needle is in the scleral wall, the needle track can be slightly enlarged by scoring the sclera at the needle exit site with a pointed 15° blade. This procedure increases the likelihood that the suture knot will rotate through the sclera later in the case. The second needle is passed in a similar fashion at least 1 mm away from the first. Care must be taken to avoid tangling the suture ends. The needles are removed and the suture tension adjusted to achieve desired centration. Alternatively, an ab externo suturing technique can be used to secure the modified CTR.[30] If iris hooks have been used to stabilize the capsule, they can be removed once the sutures are passed. The suture is then temporarily secured with a slipknot. An IOL of choice is then inserted into the capsular bag and viscoelastic removed from the capsular bag and anterior chamber. If automated irrigation and aspiration are used, lowered bottle height, aspiration, and vacuum setting can help prevent reintroduction of vitreous into the anterior chamber. With the anterior chamber inflated with balanced salt solution and a normal intraocular pressure established, the centration of the capsule is re-evaluated and the suture tension adjusted to achieve the desired result. The suture is then secured, trimmed, and rotated to bury the knot. The scleral flap is then repositioned and the conjunctiva redraped to the limbus and secured. While no sutures are typically required to close the scleral flap directly, it can be sutured with a 10-0 nylon or fine absorbable suture if desired. Figure 73.10, *A* and *B* demonstrates the preoperative appearance of a patient with marked subluxation of a lens and the immediate postoperative appearance of the secured MCTR. Typically, miotics are used in these patients to constrict the pupil in order to ensure no vitreous is within the anterior chamber. It is essential that the wound be watertight to prevent anterior



A



B

Figure 73.10. *A*, The preoperative appearance of a patient with lens subluxation secondary to Marfan's syndrome. *B*, The same but immediately after cataract surgery, placement, and suturing of a modified CTR, and placement of a posterior chamber IOL.

migration of vitreous seen with anterior chamber collapse. If necessary, the wound should be stabilized with interrupted 10-0 nylon sutures.

Several alternative sutures are available for securing IOLs and capsular tension rings. A thorough discussion of these options is beyond the scope of this chapter. We have used 10-0 prolene and 8-0 gortex suture in addition to the 9-0 prolene. Although the 10-0 prolene is easier to work with than 9-0 prolene, in our experience it is prone to breakage a year or more after surgery.[31] Gortex suture appears to be robust and the material is easier to tie than prolene. However, Gortex suture is only available on thick tapered needles, which can be difficult to pass through the sclera. It is less likely to erode overlying conjunctiva or sclera when it is not buried, however, and is a good alternative to 9-0 prolene.

The safety and efficacy of modified CTRs have been demonstrated by several authors. Moreno-Montanes et al published a series of seven eyes with subluxated lenses from Marfan's syndrome, trauma, megalocornea and unknown etiology that received a modified CTR at the time of cataract surgery.[31] The primary complication was posterior capsule opacification in five eyes. YAG capsulotomy can be performed normally on these eyes as long as the patient is at least 2 months post-op. All eyes maintained excellent IOL centration at 1 year. Similarly, Cionni et al described 90 eyes with congenital loss of zonular support resulting from Weill–Marchesani syndrome, Marfan's syndrome and idiopathic ectopia lentis that received a modified CTR at the time of cataract surgery.[32] The authors demonstrated marked increase in lens stabilization and centration. Postoperative complications were uncommon and included increased intraocular pressure (2%), persistent iritis (3%), broken fixation suture (10%), retinal detachment (1%), and posterior capsule opacification (20%).

TYPE III INSTABILITY

Patients with type III zonular loss have little or no zonular support and require multiple suture fixation points to stabilize the lens. The absence of any significant support makes manipulation of the lens difficult without the lens migrating posteriorly. Often these eyes are best approached with the help of a retina specialist to perform a lensectomy and vitrectomy. An IOL can then be sutured to the iris or sclera. Not infrequently, patients with apparent type II instability can progress to type III pathology intraoperatively. Thus, in questionable cases of type II instability, it may be worth having a retina specialist on call if possible. Invariably, however, surgeons working on this patient population will encounter cases in which the lens wants to drop posteriorly. In these situations, a couple of options are available. First, posterior-assisted levitation of the lens can be attempted with a second instrument or viscoelastic introduced through a pars plana sclerotomy. Posterior-assisted levitation was first described by Kelman[33] as a procedure to stabilize a sinking nucleus. Others have used the technique to stabilize fragments or IOLs.[34–37] The goal of this procedure is to reposition and stabilize the lens into the anterior chamber or at the iris plane, where it can be removed with phacoemulsification or with the vitrector. Frequently, the end result of cataract removal in patients with type III instability is complete loss of the capsule. However, occasionally, a capsule can be maintained.

In eyes with minimal zonular support and an intact capsule, capsular fixation can be managed using a modified CTR as described for type II instability. However, an MCTR with two suture loops opposing each other is used (Fig. 73.2*D*). An IOL can then be inserted into the capsular bag. In eyes with no capsule, the IOL must be sutured to the iris or sclera or an anterior chamber lens used.

The decision of whether to fix the IOL to the iris or sclera or use an anterior chamber lens is made based on several factors. Surgeon preference, patient age, and other ocular pathology are the most important determinants. Anterior chamber lens design has dramatically improved since its initial development and several publications document their safety.[38–40] However, concerns regarding angle trauma, peripheral anterior synechia formation, pigment dispersion, secondary glaucoma, and cornea endothelial trauma still exist.[41–43] Thus, these lenses are probably best utilized in patients with a normal iris anatomy, angle function, and corneal endothelium. We also refrain from using these lenses in young patients with a long expected lifespan. The decision to use iris or scleral fixation is also controversial. Potential risks of iris fixation include chronic inflammation, pigment dispersion, and iris atrophy[44,45] and the use of scleral sutures can result in suture erosion and endophthalmitis.[46,47] Again, patient age is an important factor. Elderly patients with a limited expected lifespan are good candidates for either procedure. Younger more active patients will likely benefit from the more stable fixation of scleral sutures. Obviously, a normal or nearly normal iris is required for iris fixation. Below we describe both suture fixation techniques.

There are several methods and numerous variations for scleral fixation of an IOL through a small incision. In this chapter, we discuss the general principles and demonstrate our preferred approach. Alternative approaches are described in an excellent review by Por and Lavin.[48] We prefer fixation of scleral sutured IOLs in the ciliary sulcus and typically use an ab interno approach as previously described for scleral fixation of the modified CTR. One important difference, however, is that foldable IOLs that fit through small incisions do not have suture eyelets. Thus, the haptics must be snared or secured with the suture. Two general approaches can be used to secure the haptics. The first option is to tie one end of a single-armed suture to each haptic.[48–50] Each needle is then passed through the corneal incision, behind the iris to exit the sclera approximately 1.0 mm posterior to the limbus at the desired points of fixation. The IOL is inserted and gentle tension applied to center the IOL. A second bite is taken adjacent to the initial needle exit site and the needle removed. The suture is then tied to itself. An alternative option is to use a double-armed suture and lasso the haptic[51] (Fig. 73.11). Both needles of each suture are then passed as described for the MCTR to exit the sclera adjacent to each other and the suture ends tied to each other (Fig. 73.12). With both of these techniques, the suture will not rotate and thus a scleral flap is recommended to prevent late postoperative erosion of the knot. Preparation of the incision site and selection of the suture material is the same as described for suturing of CTRs above. Reforming the anterior chamber and reforming the globe prior to securing the IOL sutures will minimize the risk of overtightening the sutures and inducing corneal astigmatism.

IOL selection for scleral fixation is important. Choosing an IOL with a large optic will minimize the risk of edge glare with mild decentration. Additionally, three-piece IOLs with polymethylmethacrylate (PMMA) haptics are preferred since the inherent rigidity of the haptics help stabilize the IOL. Our preference is the Alcon MA50BM lens (Alcon Labs Inc, Fort Worth, TX) with a 6.5 mm optic and PMMA haptics. Several lenses are specifically designed for suturing to the sclera and possess suture eyelets on their haptics; however, these lenses are rigid and require enlargement of the wound to accommodate the diameter of the optic. The lenses can

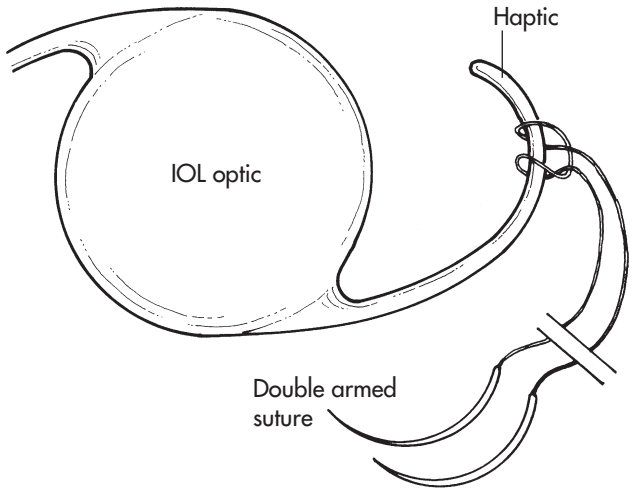


Figure 73.11. One method of securing the haptic of a standard posterior chamber intraocular lens for scleral fixation with a double-armed suture is a girth hitch.

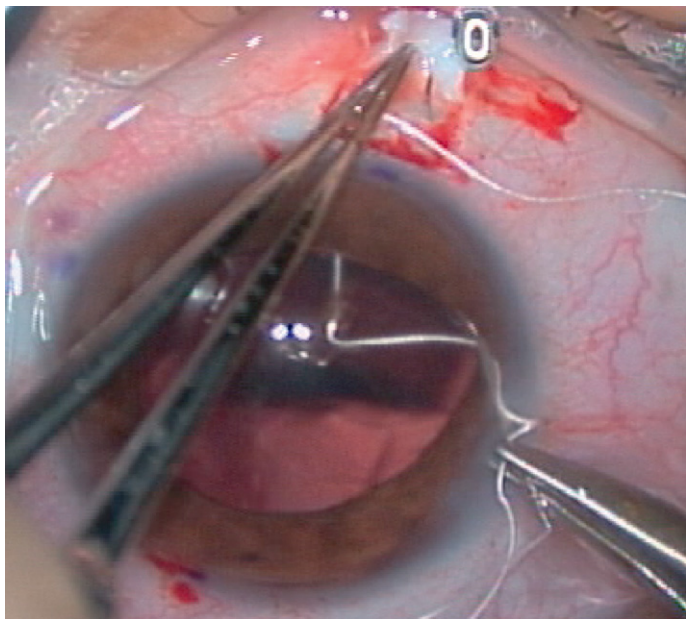


Figure 73.12. Scleral fixation of a standard PCIOL involves suturing the haptic to the sclera. In this patient one needle of a double-armed 8-0 Gortex needle has been passed. Here the pass of second needle can be seen through the main incision, behind the iris and out the sclera 1.0 mm posterior to the limbus in a previously created scleral flap. Once both needles are passed, the needles are removed and the suture secured. The sclera and conjunctiva are then closed with a suture of choice.

be secured by either suturing one end of a single-armed suture to the eyelet or passing one end of a double-armed suture through each eyelet. The advantage of the latter procedure is that the suture knot can be rotated. When passing the double-armed suture through the suture eyelet, care must be taken to ensure that the sutures are passed in similar directions through both eyelets to avoid torquing and tilting of the lens.[52] The IOL is inserted, the incision is sutured closed and the sutures secured as described above.

Iris fixation of IOLs can be achieved with iris claw lenses or suturing of standard foldable IOLs. Currently, the only iris claw lens

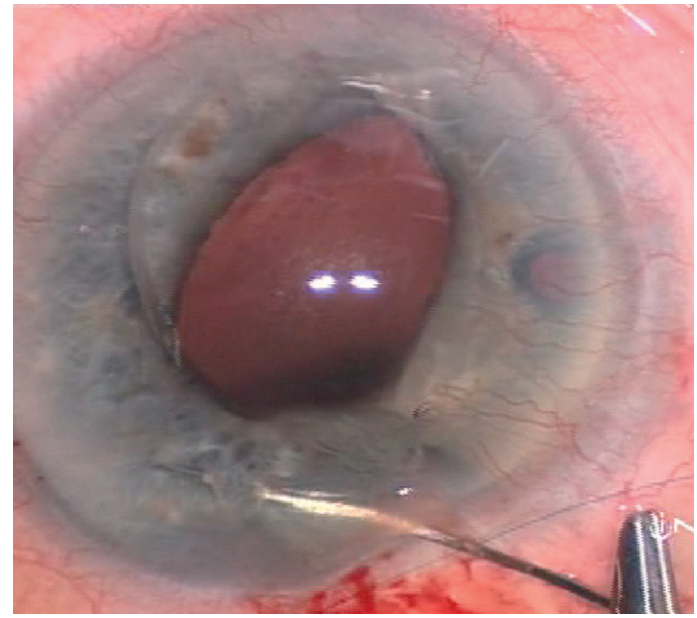


Figure 73.13. Iris fixation of a standard three piece foldable PCIOL is achieved by placing the lens in the eye with the haptics posterior to the iris and the optic captured anterior to the iris. The intraoperative photograph demonstrates passage of a CIF 4 needle on a 10-0 prolene suture through the main incision, through the iris, around the haptic and back through the iris. The needle is then passed out the cornea near the limbus. The needles are removed and the suture ends are retrieved through the main incision and secured using a Siepser knot.

available is the Verisyse (AMO, Santa Ana, CA). It has successfully been used as an alternative to sutured IOLs in eyes without capsular support and can be fixated to the anterior or posterior aspect of the iris.[53] Cost and the lack of a foldable version of this lens in the USA have limited its use for nonrefractive applications. However, further investigation of this approach is warranted.

Most iris fixated lenses are sutured. Again, several variants have been described. Our preferred approach is based on the method first described by McCannel.[54] In this procedure a standard foldable three piece IOL with PMMA haptics is introduced into the anterior chamber with the haptics behind the iris and the optic captured by the pupil anterior to the iris. Miotics are often required to achieve the capture. Folding the IOL transverse to the axis of the haptics will facilitate introduction of the haptics behind the pupil. If properly positioned, the location of the haptics will be apparent as they tent up the iris. A single-armed 10-0 prolene suture on a CIF-4 needle can then be passed through the main incision, through the iris adjacent to the haptic approximately one-third the distance from the iris insertion to the pupil margin (Fig. 73.13). The needle is then passed around the haptic, back through the iris out the cornea near the limbus on the opposite side. Often slight elevation of the optic with a second instrument is useful to stabilize the IOL and visualize the position of the haptic under the iris while passing the suture. Once the suture is passed, the needle can be removed and the suture ends retrieved through the main incision with a forceps or hooked instrument. The suture can then be tied intraocularly using a Siepser slip knot.[55] The second haptic is secured in a similar fashion and temporarily secured. The IOL is then positioned into the posterior chamber and the pupil further constricted with

miotics. Once the chamber is formed and the desired lens position obtained, the sutures can be permanently secured and trimmed. Viscoelastic is removed from the anterior chamber and the wound sutured if necessary.

CONCLUSIONS

Zonular instability greatly increases the difficulty of cataract removal and risk for postoperative IOL decentration. Technological advances such as capsular tension rings, IOL designs, and modern phacoemulsification systems have greatly improved the ophthalmologist's ability to manage these difficult patients. Detailed preoperative evaluation and staging of these eyes aids the surgeon to more accurately predict intraoperative findings and prepare for the surgery. Unfortunately, cataract surgery in patients with zonular loss remains unpredictable and the surgeon must try to prepare for all circumstances.

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74 Iris biopsies and iridocyclectomy

Samir G. Farah

Iris masses can be benign or malignant. They can be primary or metastatic from extraocular neoplasms. Malignant melanoma is the most feared and most frequent primary malignancy in the anterior segment. Compared to ciliary body melanomas, iris melanomas tend to be smaller and visible, thus they are detected earlier. In contrast, ciliary body melanomas are considered more aggressive. Hidden behind the iris, ciliary body melanomas are usually detected after they have become relatively large.

In this chapter we review the current diagnostic trends of iris masses with emphasis on the different techniques of iris mass sampling and the new introduction of anterior segment optical coherence tomography (OCT) that have increased the diagnostic yield, and improved the management planning, and follow-up of anterior segment tumors. The iridocyclectomy procedure is also discussed.

IN THE CLINIC[1–8]

The diagnosis of anterior segment tumors is mostly done in the clinic. The clinical approach involves a complete ophthalmic examination, with past medical history, best corrected visual acuity, tonometry, slit-lamp biomicroscopy, gonioscopy, ophthalmoscopy with scleral depression, and transillumination of the tumor and the sclera. High-resolution photographs of the tumor should be taken to document its visible characteristics and for later comparison. Additional examinations may include water-bath ultrasonography, high-resolution ultrasound biomicroscopy (UBM), OCT, and fine-needle aspiration biopsy (FNAB). Computerized tomography and magnetic resonance imaging are done in special cases.

Usually the past medical history and the ophthalmic examination provide enough information to determine the diagnosis. A history of non-ocular cancers must be investigated: primary tumor organ location, type, treatment, and history of metastasis (Table 74.1). A past ocular history of ocular trauma, surgery, and inflammation is important.

Slit-lamp biomicroscopy and gonioscopy are essential. Inspection of the conjunctiva, the anterior chamber angle, and the iris are performed. After pupillary dilation, an examination of the ciliary body and lens is completed. Direct, indirect, and contact lens ophthalmoscopy help determine the posterior extension of an anterior segment tumor. When a suspected lesion is found, its morphology (plateau, dome, mushroom), surface (smooth, rough), color, size and width, anatomic location (e.g. iris, ciliary body), quadrant or clock hours affected, antero-posterior location (pupillary margin, mid-iris, or iris root) as well as involvement of surrounding structures (episcleral sentinel vessels, invasion of the angle, or iris root) are described. Secondary uveitis, sector cataracts, dislocated lens, scleral invasion, and posterior extension to the choroids are also noted.

Transillumination of the globe should be performed for tumors affecting the ciliary body and anterior choroid. Slit-lamp and gonioscopic photography can be extremely useful for documenting the tumor's clinical characteristics, allowing for accurate determinations of subsequent changes.

DIFFERENTIAL DIAGNOSIS OF IRIS TUMORS

The differential diagnosis of iris tumors is broad (Table 74.2). As a general guideline, the clinical differences between benign and malignant anterior segment lesions are as follows. Benign lesions tend to be flat or slightly elevated; they do not distort the iris stroma and they do not grow. Multiple or bilateral lesions are more commonly benign. Malignant melanomas generally present as solitary nodular lesions located in the lower half of the iris. They tend to be unilateral and they can be associated with abnormal vascularization, ectropion uvea, pupillary distortion, sector cataract, pigment dispersion, and glaucoma (Table 74.3). Pigment dispersion and tumor infiltration can be visualized on the corneal endothelium, the lens surface, the iris stroma, the trabecular meshwork, and ciliary processes. Secondary glaucoma is typically either melanomalytic (due to pigment dispersion) or due to a tumor growing within the aqueous outflow system. Malignant iris neoplasms also cause heterochromia, spontaneous hyphema, and chronic uveitis. Because the iris hides ciliary body tumors, the clinical differentiation between benign and malignant tumors is more difficult. Ciliary body tumors are more likely to be malignant if they induce a sector cataract, lenticular astigmatism, extrascleral extension, or a visual field defect. They can be darkly pigmented or amelanotic with evidence of vascularization. Documented growth and pigment dispersion are strong predictors of malignancy. These

Table 74.1 Primaries that may metastasize to the iris

Breast
Lung
Bronchial carcinoid
Melanoma
Colon
Oesophagus
Larynx
Prostate
Kidney
Uterus
Cervix

Table 74.2 Differential diagnosis of iris tumors

Primary iris cyst
Iris nevus
Essential iris atrophy
Iris foreign body
Peripheral anterior synechiae
Metastasis to the iris
Leiomyoma
Melanocytoma
Adenoma of iris epithelium
Iris lymphoma
Iris nevus syndrome

tumors can also cause anterior displacement and/or infiltration of the iris (Fig. 74.1, *A* and *B*).

An early sign of an occult ciliary body melanoma is a sentinel vessel, which is one or more dilated episcleral blood vessels feeding the metabolically active tumor and is visible through the conjunctiva overlying it. Another early physical sign of an occult ciliary body melanoma is unexplained unilateral low intraocular pressure, as compared to the normal fellow eye. A difference of 5 mmHg or more may be the only initially detectable external sign of a tumor affecting the ciliary body.

COMPLEMENTARY DIAGNOSTIC TESTS

Although there have been recent advances in the diagnosis of iris tumors, it is still based on clinical and historical findings. The diagnosis of anterior segment tumors has been greatly enhanced by FNAB, UBM, and OCT. Clearly; these tests help the surgeon plan for appropriate treatments. The aim of these tests is to detect malignancy and tumor extent as early as possible, so that eye preserving surgical procedures may be done.

Table 74.3 Clinical characteristics differentiating between benign and malignant anterior segment tumors

Feature	Benign	Malignant
Elevation	Flat or slight elevated	Nodular
Number	One or more lesions	Solitary
Laterality	Unilateral or bilateral	Unilateral
Size	<3 mm	>3 mm
Growth	No	Yes
Prominent vascularization	No	Yes
Ectropion uveae	No	Yes
Iris infiltration	No	Yes
Pupillary distortion	No	Yes
Cataract	No	Yes
Sentinel vessels	No	Yes
Elevated IOP	No	Yes
Tumor seeding	No	Yes
Hyphema	No	Yes
Pigment dispersion	No	Yes

IOP = intraocular pressure.

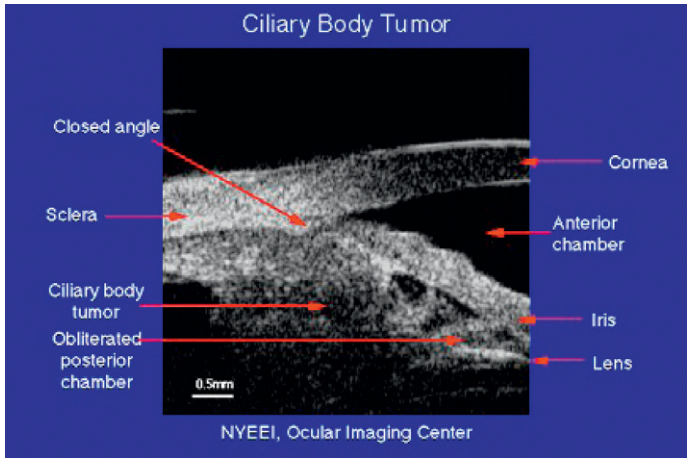
1. CYTOLOGIC CONFIRMATION: FINE-NEEDLE ASPIRATION BIOPSY (FNAB)[9–14]

The most common indications for FNAB are:

1. when noninvasive methods cannot establish the diagnosis;
2. for a presumed metastatic tumor with an undetectable primary site;
3. when the patient requests histopathology or cytology verification prior to treatment;
4. to assist in therapeutic recommendations;
5. an iris tumor in which a malignancy is suspected but cytopathologic verification is necessary before proceeding with definitive therapy of enucleation or radiotherapy;
7. an iris tumor with glaucoma, in which a surgical glaucoma procedure is contemplated after confirmation of the lack of malignancy;
8. to differentiate between primary iris tumor and secondary metastatic neoplasms to the iris thus offering guidance for therapy where primary iris tumors are managed by resection, plaque radiotherapy, or enucleation, and metastatic neoplasms are managed with systemic evaluation and treatment.[12]

Representative material can be obtained in about 88–99% of cases. FNAB 180° away from the main tumor should be done to rule out a ring melanoma.

The most commonly reported complication is intraocular hemorrhage with secondary glaucoma. No case of clinically apparent tumor proliferation or tumor seed growth in the needle tract has been noted. It seems that transcorneal sampling minimizes the risk of extraocular seeding. When FNAB is inconclusive, a surgical iridectomy may be indicated.



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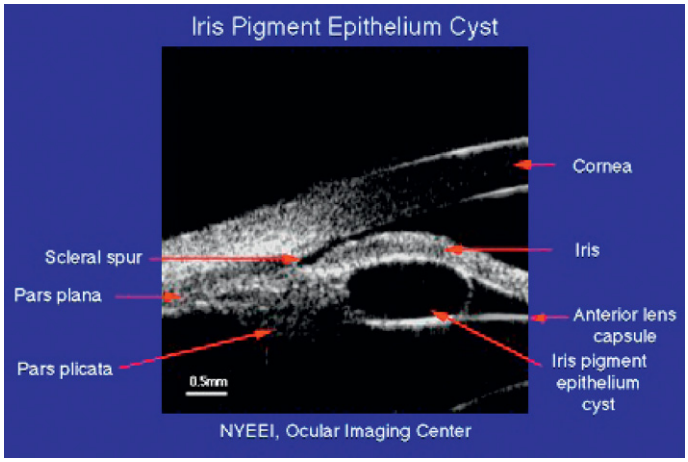


B

Figure 74.1. Ultrasound biomicroscopy (UBM) of iris masses. *A*, Ciliary body melanoma. *B*, Iris pigment epithelium cyst.

Several methods of FNAB have been described. Each technique involves proper instrumentation, planning of tumor approach, handling of harvested cells, and preparation of cytologic specimen.

Method 1: vacuum cleaner technique[14]

Patient sitting at the slit-lamp after a peribulbar block is obtained. A sterile 26- to 30-gauge needle connected to a 1 mL tuberculin syringe is introduced into the anterior chamber at a 45° to 90° angle to the lesion. The bevel is facing down and the needle opening is swept over the surface of the lesion in a 'vacuum cleaner' fashion while gentle aspiration is applied until approximately 0.5 mL of fluid is obtained. No entry into the tumor is made. The needle is withdrawn from the anterior chamber and the aspirate immediately diluted with an equal amount of 95% ethyl alcohol.

The most important limitations of this technique are an inconclusive cytopathologic diagnosis caused by inadequate sampling and risk of intraoperative bleed or laceration of the intraocular structures with the sharp needle tip.

Method 2: internal biopsy technique[9]

Instrumentation includes a 25-gauge needle attached to straight tubing, 50 cm long, attached to a 10 mL syringe. The connector tubing is essential because it prevents transmission of the movements of the surgeon's hand and syringe during aspiration to the needle tip so that the needle can remain stable within the tumor without abrupt dislodgement or shifting. The connector tubing should have proper volume (2.5–5 mL) and length (30–50 cm) thus providing adequate suction and lower resistance. The FNAB is done under the operating microscope and under local anesthesia. The entry site is temporal or nasal, approximately 90° from the meridian of the tumor. The needle, bevel side up, is passed into the tumor. The tumor aspiration point should be in a relatively avascular site and at the thickest portion. After secured entry into the tumor, a gentle back and forth sliding motion of the needle along its trajectory within the mass is performed three or four times to shave and loosen cells for aspiration. Then the full 10 mL aspiration is maintained for a few seconds with the needle in the tumor and also as the needle is withdrawn from the eye. During removal of the needle, some aqueous enters the tip and occasionally a partially or completely flat anterior chamber is found. Refilling the anterior chamber is done with balanced salt solution (BSS). The aspirated cells which are predominantly located in the needle tip are flushed into the syringe using BSS, but first air is expelled from the syringe by unscrewing the syringe from the connector tubing and slowly pushing the air completely out of the syringe and then reattaching the syringe to the connector tubing. Immediately after collection, 30 mL Shandon cytospin collection fluid is added to the BSS.

Method 3: iridectomy technique[11]

Two 0.9 mm limbal incisions are performed at distant sites to the iris tumors. A 21-gauge anterior chamber infusion cannula is inserted into the anterior chamber and intraocular pressure (IOP) elevated to 70 mmHg. A 20-gauge vitreous cutter is inserted through the second limbal incision and placed on the tumor surface in such a way that its opening is occluded by tumor tissue. With a high aspiration setting (400 mmHg) and low cutting frequency (80/min), one bite is obtained from the tumor surface. In case of hemorrhage, the infusion-controlled IOP is raised even further for a few minutes. The fluid that is contained within the cutter tube is aspirated with a 20 mL syringe.

Method 4: finger iridectomy technique (FIT)[15]

Under microscope and local anesthesia a paracentesis is created with a microvitreo-retinal (MVR) blade. Miochol is injected to constrict the pupil and then sodium hyaluronate is injected to maintain the chamber and position the iris for biopsy away from the crystalline lens. A 25-gauge vitrectomy probe is introduced and the aspiration opening rotated as to be occluded by the tumor. Aspiration/cutting is started on suction of 300 mmHg and cutting rate of 60 cuts per minute. These settings are adjusted as to maximize the efficiency of the process under direct visualization while trying to keep the cut rate as low as possible. Two to three biopsies are usually performed and each time the cutter is removed from the eye, it is placed in solution and the aspirate flushed from the effluent tube into an empty 3 mL syringe with 0.5 mL BSS. Specimens are immediately sent to the pathologist for cytological evaluation. The biopsy procedure can be repeated until the pathologist reports that the specimen is adequate for diagnosis. Then the sodium hyaluronate is irrigated out of the eye.

Intraocular biopsy by a vitreous cutter may allow the histopathologic examination of formalin-fixed paraffin-embedded tumor tissue. This increases the diagnostic accuracy of sampling. The cytospin technique is used to optimize the biopsy yield.

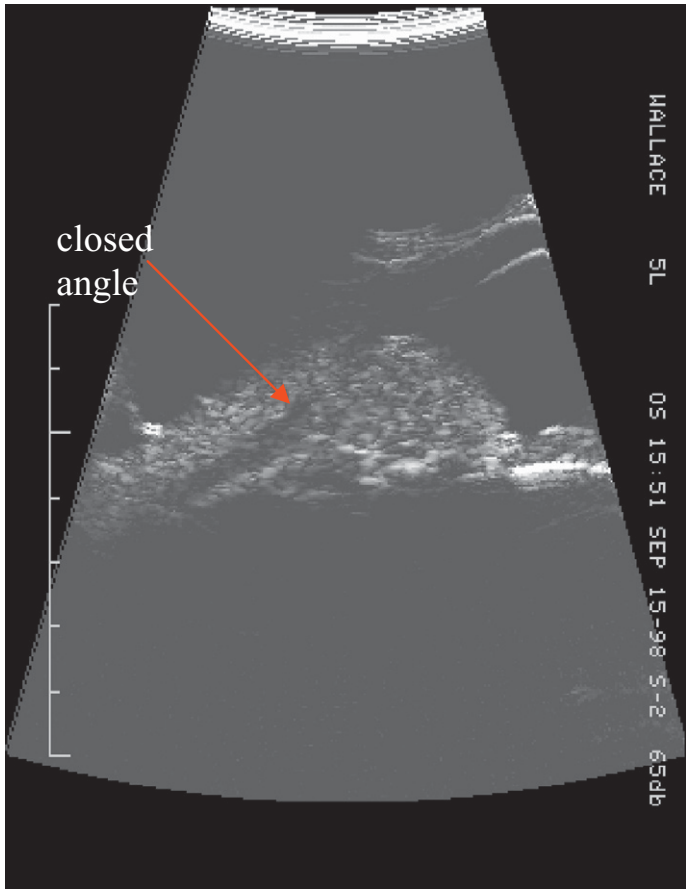


Figure 74.2. Low-frequency ultrasound with immersion technique showing iris mass with angle involvement.

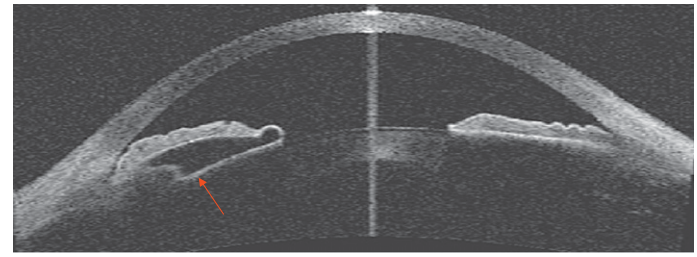


Figure 74.3. Ocular coherence tomography of iris mass. Iris cyst with narrowing of the angle.

2. VISUALIZATION PROCEDURES: ULTRASONOGRAPHY AND OPTICAL COHERENCE TOMOGRAPHY[16–19]

The diagnosis and treatment recommendations of iris and ciliary body masses are influenced by the tumor location, size, and local extension. This information is given by the ultrasound and OCT.

Ultrasound

Currently used ophthalmic ultrasounds employ 10 MHz transducers. These low-frequency transducers penetrate up to 40 mm and offer a relatively low (200–300 µm) resolution image. To optimize imaging of the anterior segment tumors, with low-frequency transducers the immersion technique is used (Fig. 74.2).

Higher frequency systems (50 MHz) offer better resolution of the anterior segment tumors. The UBM employs a 50 MHz transducer that provides high-resolution (50 µm) images up to a typical distance of 3 mm. This technique provides us with high-resolution ultrasound images of iris tumors, deep margins, and internal reflectivity (Fig. 74.1). UBM has allowed for quantitative follow-up tumor dimensions, more precise determinations of tumor borders, and a better evaluation of the involvement of the surrounding structures. UBM is an essential tool for the diagnosis, measurement, and follow-up of anterior segment tumors.

Iris melanomas (as imaged by UBM) are typically low to medium reflective and nodular arising from the iris surface or a medium to highly reflective thickening of the iris stroma. Displacement of iris surfaces results in a bowed profile, which indicates infiltration of the iris stroma. This is a common finding in that the stroma is typically involved. Tumor infiltration of the iris pigment epithelium can be seen by ultrasonography and suggests malignancy. The presence of acoustically empty (acoustic hollowing) or cystic spaces in the iris stroma has been found to be blood vessels. Small projections attached to the main tumor may be seen extending to the angle and ciliary body. Excavation of underlying uveal tissue and shadowing of subjacent soft tissues are also distinctive.

Ocular coherence tomography (OCT)

OCT is just beginning to become available for anterior segment tumors (Fig. 74.3). Light beams are directed into tissue and reflections coming from different layers are received by a detector and then processed to generate a 2 D image. It is similar to B-scan ultrasound but uses light instead of sound. It is a noncontact test with higher resolution. The light wavelength of 1310 nm allows for optimal anterior segment imaging. The axial resolution is 18 µm and the transverse resolution is 60 µm. OCT is very precise in (1) determining tumor borders, size, and location; (2) presence of satellite lesions; (3) involvement of the surrounding structures; (4) reflectivity; and (5) presence of cystic component. The absence or presence of tumor growth can be established by serial examinations.

UBM and OCT are essential in the evaluation of ciliary body abnormalities, including melanomas. They can differentiate tumors of the ciliary body from those of choroidal origin and help define the anterior border and invasion of the angle.

In conclusion, efficacy of tumor treatment, tumor infiltration, or invasion of adjacent structures, and observation for recurrence of the tumor are possible through serial UBM or OCT examinations.

3. TREATMENT[20–22]

Treatment indications for anterior segment melanomas are based on size, location, and extension of the tumor. The various methods of treatment employed follow on the type of tumor and condition of the eye. The preoperative assessment is critical for the planning of management.

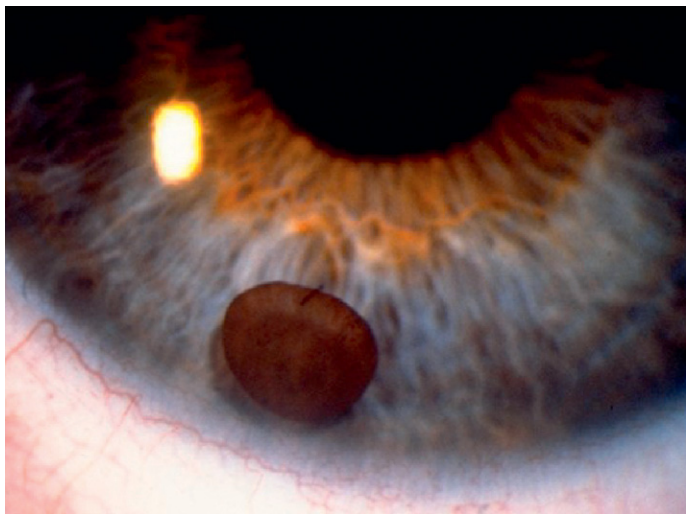
The treatment options include observation, local resection, and radiation therapy (brachytherapy or proton beam irradiation). Enucleation is typically reserved for large tumors or eyes with untreatable glaucoma. As new modalities of therapy offer lower morbidity as compared to enucleation, more physicians and patients are opting for eye and vision-sparing treatments (Table 74.4).

Observation

Lesions with benign clinical characteristics present little immediate threat for ocular morbidity and can be observed for growth. Most

Table 74.4 Treatment options

Observation
Surgery
Iridectomy
Iridocyclectomy
• Tumor involving pars plicata or trabecular meshwork
• Tumor less than 4 clock hours
Plaque radiotherapy
Irradiation
Enucleation



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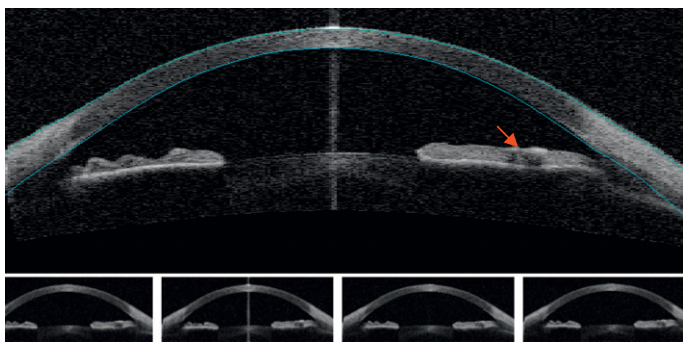


B

Figure 74.4. *A*, Iris melanoma confined to iris. *B*, Ocular coherence tomography precisely showing size and limits.

iris tumors and small melanocytic lesions of the ciliary body fall in this category. Lesions selected for observation must be well documented to allow objective follow-up evaluations. High-quality photographs are used to document the surface characteristics of the tumor. Tumor size, boundaries, and thickness with distance from surrounding structures should be determined by UBM or OCT (Fig. 74.4, *A* and *B*). Treatment should be considered if an anterior segment tumor demonstrates growth on serial exams or is the cause of secondary glaucoma. In case of stability of the tumor, the follow-up should be done every 6–12 months.

Local resection

The indications for excision are:

- If the lesion is impinging on the pupillary margin, interfering with vision or if impinging on the trabecular meshwork with secondary glaucoma.
- If the lesion grows rapidly.
- If the fine-needle biopsy specimen shows malignant histology.

Excision must be complete with either a sector basal iridectomy or an iridocyclectomy if the lesion affects the ciliary body.

SECTOR BASAL IRIDECTOMY[23–29]

This procedure involves removing a tumor confined to the iris with a margin of normal appearing tissue. The approach may be limbal or scleral. A scleral approach is preferred to minimize postoperative astigmatism. The incision is done 3 mm from the limbus in face of the lesion; a scleral tunnel is dissected to 1 mm in cornea. Viscoelastic is injected in the anterior chamber and the tumor resection performed by sector basal iridectomy with macroscopic free margins of 1 mm from the tumor edges.

It is important to make a large incision to allow for tumor removal without brushing the tumor cells on the adjacent tissues. At least 1–2 mm of tumor free margins and 'no touch' technique (without handling the tumor tissue directly) are planned for all surgical resections.

In case the iris mass has invaded the anterior part of the ciliary body to a minimal extent, or to avoid tractional iridodialysis in confined iris masses, a cryosurgical iridocyclectomy may be done. After a bilateral radial iridotomy around the tumor is made, the iris flap is lifted as high off the crystalline lens as possible and a cataract cryoprobe is placed on the undersurface of the iris. Following freezing for approximately 30 s, the iris is stretched to create traction on the ciliary body. The ciliary body comes forward with no sign of iridodialysis. The iris flap together with the anterior ciliary body is then excised.

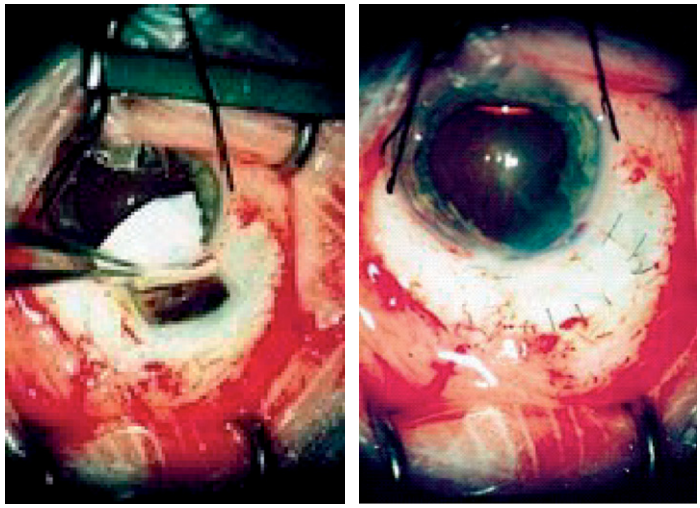
The main complications of sector iridectomy are glare, hyphema, cataract, infection, and IOP fluctuations.

IRIDOCYCLECTOMY[30–43]

When the tumor is located near the iris root, ciliary body extension must be considered. Gonioscopy, transillumination, and ultrasound examination should be performed. If the ciliary body is affected, iridocyclectomy is performed (Fig. 74.5 *A* and *B*).

The indications of iridocyclectomy are (1) monocular patients, (2) elderly or chronically ill patients whose life span is presumed to be short, (3) patient refusing enucleation, (4) tumor covering less than 4 clock hours of the ciliary body.

Transscleral excision of the ciliary body is carried out after diathermy. A 90% thickness, anteriorly hinged, scleral flap is created, generally allowing 2–3 mm on each side of the tumor circumference —determined by 180° transillumination supplemented with direct tumor visualization. A triple row of penetrating diathermy is placed around the sides and posterior edges of the resection bed. The deep scleral lamella is incised down to the ciliary body and the tumor is lifted with the sclera and dissected anteriorly with a combined iridectomy. The anterior incision is made through the limbus for predominantly iris or iris–ciliary body tumors. This incision is placed anteriorly so the angle structures can be removed in en bloc resection. In cases in which there is suspicion of a possible ring mela-



A B

Figure 74.5 *A* and *B*. Iridocyclectomy through a lamellar scleral approach.

noma, an intraoperative FNAB is performed 180° away from the mass. After the tumor is removed, if there is no vitreous loss, the incision is closed with 8-0 Vicryl sutures to the sclera and 10-0 nylon to the cornea. If vitreous loss occurred through the incision, a vitrectomy through that site is performed. In tumors that involve less than 3 clock hours of iris, the iris defect is closed with an 11-0 proline suture.

In cases with localized extrascleral extension, no scleral flap is made. The sclera and uveal tissue are incised and removed en bloc and the defect closed with a scleral graft.

The main contraindications of iridocyclectomy are: involvement of more than one third of the ciliary body or anterior chamber angle, significant extraocular extension, and contraindication for hypotensive anesthesia such as previous cerebral thrombosis or carotid artery occlusion.

The main complications observed involve vitreous and expulsive hemorrhage, retinal detachment, cataracts, residual tumor, hyphema, induced astigmatism, photophobia, phthisis, and tumor seeding being the most dreaded complications. To reduce the incidence of hemorrhage, extensive preoperative photocoagulation is applied as to encircle the tumor. Then intraoperative hypotensive anesthesia is employed.

The premanagement evaluation of ciliary body melanomas should include a thorough physical examination, with particular attention to the hepatic abdominal region and the skin and subcutaneous tissues, which are frequent sites of metastatic spread. Always obtain a chest X-ray in patients with ciliary body melanomas for the possibility of lung metastasis.

Although undetected metastatic spread at the time of diagnosis and treatment of ciliary body melanoma is a major concern in every patient, adjuvant systemic treatment currently is not advocated.

Irrespective of the treatment modality chosen, patients with ciliary body melanomas need to be followed carefully for many years. Close observation and measurement of the tumors' dimensions with any of the diagnostic tools mentioned earlier is critical. Follow-up care in treated patients includes thorough physical examinations, liver function tests, and imaging of lungs, repeated about every 6–12 months. Early detection of distant metastases may affect management and survival.

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75 Iris reconstructive and restorative procedures

Andrea C. Kara-Jose, Marian S. Macsai

The inherent fragility of iris tissue and its close proximity to the corneal endothelium and anterior lens capsule create a challenge in the surgical management. The iris lies in front of the anterior lens capsule and the ciliary body, separating the anterior chamber from the posterior chamber. The iris consists of two layers: the stroma, located anteriorly and originating from the mesoderm, and the pigmented epithelium, located posteriorly and originating from the neural ectoderm. The function of the iris is dependent on both the sphincter pupillae muscle, located in the pupillary zone of the posterior stroma, and the dilator muscle, located between the stroma and the posterior layer of the pigmented epithelium. The dilator muscle extends from the iris root at the ciliary body to the sphincter pupillae muscle. The blood supply of the iris is provided by radial vessels in the stromal layer that extend from the major arterial circle of the iris in the ciliary body to form an incomplete minor arterial circle of the iris at the pupil. The endothelial cells lining the blood vessels of the iris have tight junctions that prevent passage of large molecules. These junctions, together with the tight junctions of the pigment epithelium of the ciliary body processes, create the blood–aqueous barrier. Healthy iris tissue tends to return spontaneously to its original shape when it is displaced, owing to its elastic resiliency and the action of the pupillary muscles.

IRIS DISPLACEMENT AND REPOSITION

As a result of its high mobility, the iris can be exteriorized by means of traction (with forceps) or pressure (resulting from expression or trauma). Grasping the iris with a fixation forceps produces force in two directions. One tractional force moves toward the iris root, and the other extends to the pupil margin. Awareness of the tension created toward the iris root is critical to prevent tearing of the major arterial circle of the iris and resultant bleeding. Pathologic tissue changes radically alter iris tissue mobility, resulting in inelastic, immobile tissue that may tear with traction. Excessive traction may result in an iridodialysis or significant bleeding.

An incarcerated but nonprolapsed iris should rarely be sacrificed. The most atraumatic method of repositioning an incarcerated iris is with viscoelastic material that is injected either directly through the wound or obliquely to draw the iris away from the area of incarceration. If this technique fails, a fine cyclodialysis spatula may be passed through a peripheral paracentesis to sweep the iris gently out of the wound.

Iris that is prolapsed through a wound must be evaluated thoroughly to determine if repositioning or excision is indicated (Fig. 75.1). Repositioning diseased tissue may result in intraocular inflammation and potential endophthalmitis. Exposed iris that is severely macerated or exposed for longer than 24 h should be excised and sent for culture. If a decision has been made to reposit the prolapsed iris, the tissue should be cleaned carefully with balanced salt solution soaked cellulose microsurgical sponges to remove any particulate debris and sent for culture.[1]

SYNECHIOLYSIS

Separation of posterior synechiae may be achieved with either a solid spatula (metal) or a soft spatula (viscoelastic material). A spatula utilizes blunt dissection to increase tissue tension, and applied at right angles to the adhesions. If numerous central posterior synechiae exist, a metal cannula may be placed through a peripheral iridectomy to insert viscoelastic material to protect the anterior lens capsule and lyse the synechiae with either viscodissection or blunt dissection with the cannula. A tear may occur in the lens capsule, or an unintended zonulolysis or iridodialysis may result if the adhesion is too strong. If the attachment of the synechiae is stronger than the anatomic attachment of the iris root, sharp dissection may be indicated. Iris adhesions with cortical remnants or corneal stroma frequently require excision with sharp dissection using intraocular scissors. Angulated intraocular scissors can be inserted through the peripheral iridectomy and used to cut the attachment after viscodissection is attempted. Careful dissection of the synechiae may open the ciliary sulcus, allowing for placement of a posterior chamber intraocular lens.

ENLARGEMENT OF THE PUPIL

Pupil enlargement can be performed medically or surgically. The use of mydriatics to dilate the pupil pharmacologically is useful when there are no pathologic structural changes and the tissue is

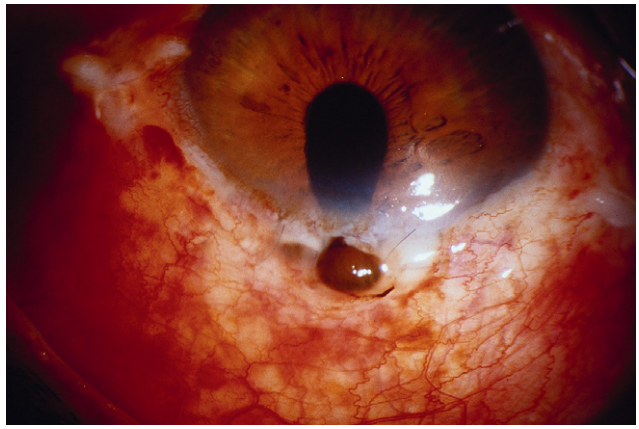


Figure 75.1. Iris prolapse through a limbal wound due to blunt trauma from a pencil in the left eye of a 9-year-old boy.

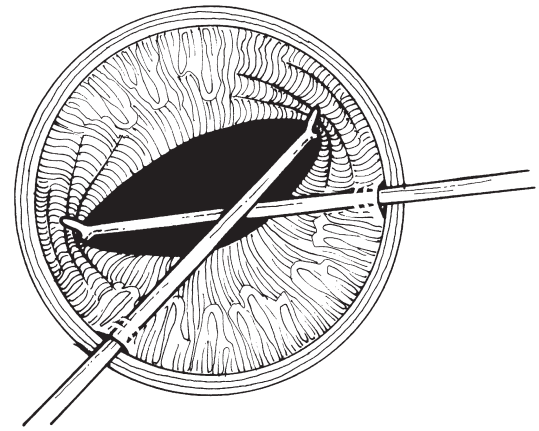


Figure 75.2. Intraoperative bimanual stretching of a pupil.

normal. If medical enlargement of the pupil is not successful, surgical enlargement of the iris may be necessary in some patients with eccentric or secluded pupils, or it may be used intraoperatively to aid in cataract extraction or vitreoretinal surgery.

ADEQUATE IRIS TISSUE

The dilation of a small pupil for cataract or vitreoretinal surgery in the presence of elastic and mobile iris tissue can be achieved with surgical methods such as pupil stretching techniques, iris hooks, or pupil expanders.

The stretching of the pupil can be performed with a push–pull technique using bimanual stretching or the Beehler pupil dilator (Moria) (Figs 75.2 and 75.3).[2,3] Both methods provide good yet temporary pupil enlargement.[4] These time-saving techniques may cause microsphincterotomies that are usually functionally insignificant.[4] Iris hooks, the Morcher polymethylmethacrylate (PMMA) pupil-dilator ring, and Graether 2000 pupil expander are other useful instruments for mechanical pupil enlargement, especially when pupil stretching is insufficient or when a more stable and larger pupil size is required (Figs 75.4–75.6).[3–5] The Morcher ring and Graether pupil expander are placed at the pupillary margin to expand and hold a formerly small pupil to around 7.5 mm during surgery.[4,6,7]

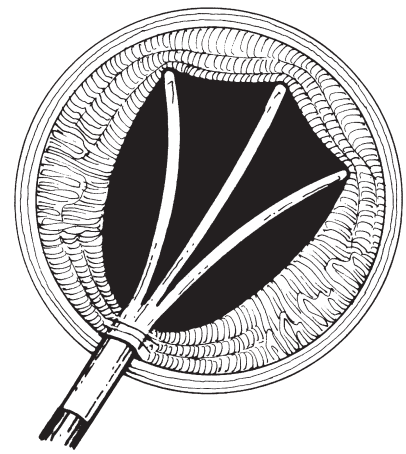


Figure 75.3. Intraoperative use of the Beehler pupil dilator.

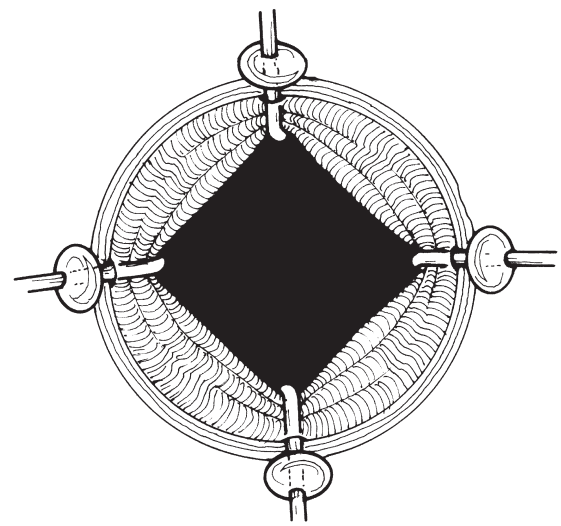


Figure 75.4. Intraoperative use of iris-retractor hooks.

INADEQUATE IRIS TISSUE

In cases of pathologic iris tissue that is inelastic and immobile, the pupil must be enlarged by surgical incision. When pathologic changes are confined to the iris sphincter, a sphincterotomy may be performed after injection of a viscoelastic into the pupillary space (viscomydriasis), which enables the insertion of angulated microscissors. It is important not to cut completely through the sphincter to the iris stroma. The sphincterotomies need not be precisely radial, but they must interrupt the continuity of the sphincter edge. After completion of the sphincterotomies, the chamber is deepened with viscoelastic, resulting in further dilation of the pupil.[8] Leaving a portion of the pupillary muscle intact preserves pupillary function while enabling mydriasis and miosis postoperatively. A larger sphincterotomy abolishes pupillary function, but this may be indicated if pathologic changes are extensive.

In some cases of extensive pathologic changes, an iridectomy may be required to center the pupil on the visual axis. A superior iridotomy is preferred as the upper eyelid position may obscure any residual abnormalities. Laser surgery with the neodymium: yttrium–aluminum–garnet (Nd:YAG) laser also may achieve adequate sphincterotomy in aphakic or pseudophakic patients (Fig. 75.7, *A* and *B*). In phakic patients, the argon laser may be used to create a sphinc-

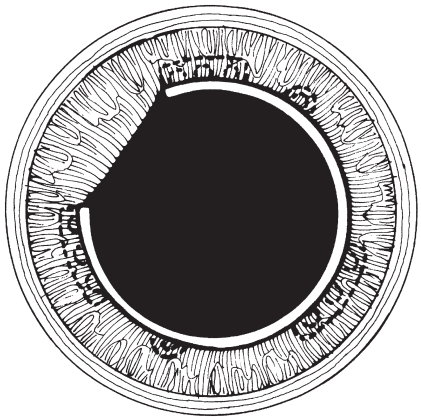


Figure 75.5. Intraoperative use of Morcher polymethylmethacrylate pupil-dilator ring.

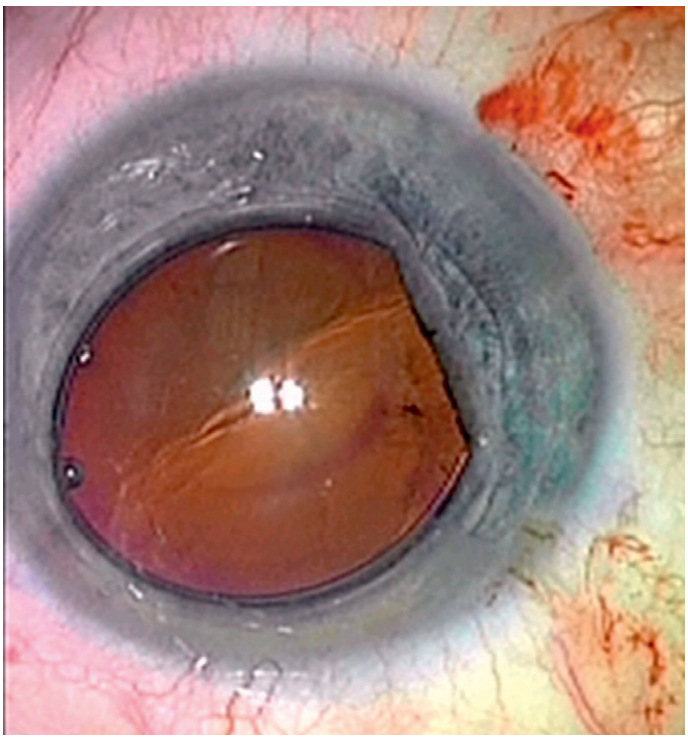


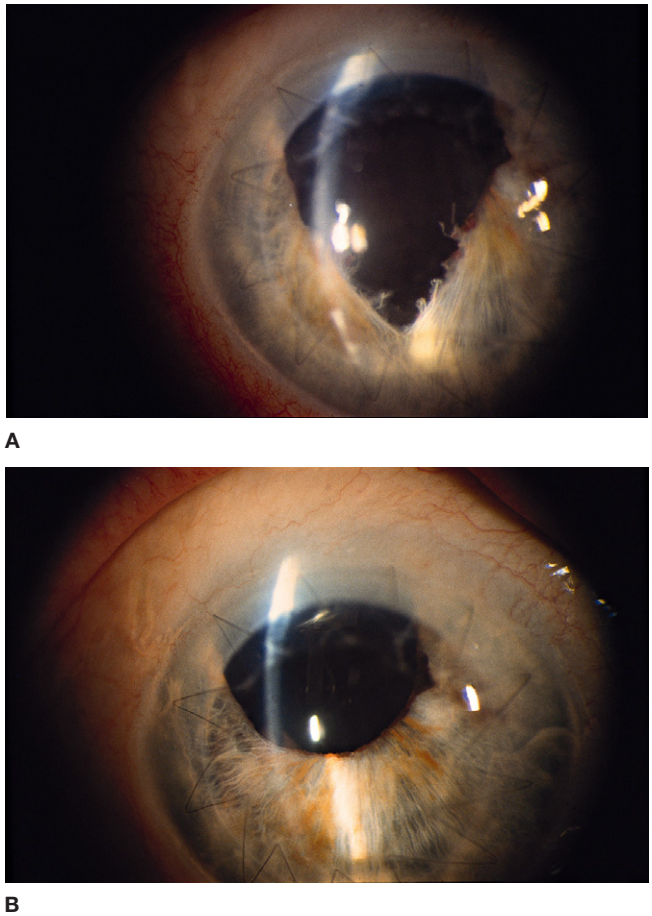
Figure 75.6. Intraoperative use of Graether 2000 pupil expander.

terotomy with linear photocoagulation. The argon laser decreases the risk of lens capsule rupture as compared to the Nd:YAG laser.

IRIS RECONSTRUCTION

SUTURING THE IRIS

Iris sutures are used for three basic purposes: (1) to attach iris to iris (closure of iris defects); (2) to attach iris to ciliary body (repair of iridodialysis); and (3) to attach iris to foreign material (fixation of implants). Different approaches, including transcorneal, intracameral, or transscleral methods, may be used to suture the iris. In a transcorneal or transscleral approach, the needle piercing the cornea or sclera must be very sharp and strong enough to overcome the resistance of the cornea or scleral tissue. In the transcorneal approach, multiple paracentesis incisions may simplify suture placement. Needles used for transscleral or transcorneal suturing are classified in Table 75.1.



A

B

Figure 75.7. *A*, An eccentric pupil after extracapsular cataract extraction. The eccentric placement of the pupillary margin resulted in significant visual distortion for this patient. *B*, Immediately post Nd: YAG laser sphincterotomy, the pupil is now centered more inferiorly, allowing the patient's optic axis to pass through the center of the intraocular lens.

When iris tissue is sutured with an open sky or intracameral approach, the use of a noncutting taper point microsurgery needle is recommended. Blood vessel (BV) needles have a round cross section with an atraumatic taper point, which helps to minimize trauma and tearing of the iris tissue. In iris surgery, 10-0 polypropylene (Prolene) is used when permanent or long-term support is needed as it is less prone to hydrolysis and biodegradation.

Before suture placement, sufficient space must be provided both anterior and posterior to the iris. Viscoelastic material can expand this space and protect the lens capsule and corneal endothelium at the same time. The main technical difficulty in suturing the iris involves the extreme mobility and fragility of the tissue. In a transcorneal suture, the site of needle insertion through the cornea can be defined precisely by the surgeon, as can the site of insertion of the needle into the proximal iris. Stabilizing the iris with viscoelastic or small intraocular forceps allows passage of a needle through the iris. A preplaced paracentesis tract will simplify emergence of the needle through the cornea, or a large bore needle (25-gauge) can be inserted through the intended cornea exit site and the iris suture can be placed through the hollow needle and pulled through the cornea as the needle is withdrawn.

IRIS DEFECTS REPAIR

Closure of iris defects is indicated for cosmetic reasons or to restore the normal optical axis at the eye. In addition, disruption of the iris

Table 75.1 Microsurgical needle characteristics

Model	Needle Type	Length (mm)	Curvature	Wire Diameter (mm)
CIF-4	Taper cutting point	13.34	1/4	0.20
CTC-6	Spatula cutting point	11.99	1/4	0.15
STC-6	Spatula cutting point	16.00	Straight	0.15
PC-7	Taper cutting point	13.34	1/4	0.23
BV 100-4	Taper cutting point	5.11	3/8	0.10

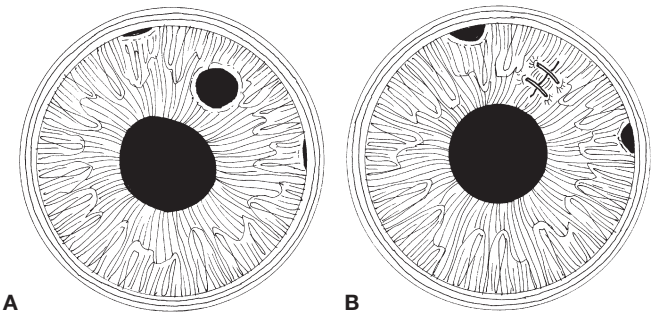


Figure 75.8. Two small limbal peripheral iridotomies are created to increase mobilization of the iris and allow closure of a stromal defect.

diaphragm may increase iris mobility and result in the formation of anterior synechiae. Restoring normal tension to the diaphragm of the iris may prevent anterior synechiae formation.

Normal iris tissue may be repaired by approximating the margins of the defect with simple interrupted sutures.[9] However, if the tissue is immobile or rigid, relaxing incisions may be required to mobilize the iris tissue.[10] These may be made at the pupil margin or in the iris stroma. Placement of peripheral iridotomies may be required to mobilize the iris tissue. The peripheral iridotomies should be placed where the imaginary transverse axis through the defect intersects with the iris root (Fig. 75.8). The edges of the stromal defect are reflected with viscoelastic. Transcorneal sutures are placed through peripheral limbal paracenteses and passed through the everted edges of the iris stromal defect to close the iris defect. Compensatory iridotomies at the iris root cause no optical disturbances when they are placed in the far periphery.

SECTOR IRIDECTOMY REPAIR

ADEQUATE IRIS TISSUE

In the presence of adequate and mobile iris tissue, several suturing techniques can be adapted to repair a sector iridectomy. Both an open-chamber and a closed-chamber approach may be successful.

Open-chamber approach

An intracameral suture can be used to repair a sector iridectomy in an open-system approach. The anterior chamber is maintained with viscoelastic and the free edges of the sector iridectomy are everted. A microneedle (BV) is introduced into the anterior chamber with a fine microneedle holder through a limbal incision and passed through both edges of the sector iridectomy. The suture is grasped, and the needle is pulled backward out of the anterior chamber through the limbal incision. The suture is tied and cut short. Excessive traction on the suture may disinsert the iris root; alternative techniques such as the Siepser knot[11]may eliminate this traction. Two or three interrupted intracameral sutures may be required for closure of the iridectomy.

Closed-chamber approach

Single-armed, peripheral approach

The repair of sector iridectomy in a closed-chamber is based on the concepts first described by McCannel.[12] The McCannel technique is a transcorneal peripheral approach that uses a longer needle such as the Ethicon CIF-4 and a single-armed suture. The surgery may be performed in a phakic or aphakic eye. In the McCannel technique, a limbal paracentesis wound facilitates transcorneal passage of the suture. However, the iris is distorted as it is pulled toward this limbal paracentesis tract when the polypropylene suture is cut. A modification of this technique, utilizing transcorneal 10-0 polypropylene suture and a paracentesis in the same meridian as the sphincter tear, is demonstrated in Figure 75.9.

An alternative iridectomy repair is the Shin modified McCannel's technique.[13] A 1.6-cm 25-gauge needle tip pierces the proximal iris wound margin from anterior to posterior and then pierces the distal wound edge from posterior to anterior and subsequently exits through the opposite limbus. A 10-0 polypropylene suture is threaded into the lumen of the 25-gauge needle until it reaches the other end. The needle is removed, leaving the suture in place.

An improvement on the McCannel technique is the Siepser slip knot.[11,14] This method is useful to tie sutures in the anterior chamber while minimizing iris distortion and is elaborated in Figure 75.10. With the development of bimanual surgical instrumentation for cataract surgery, iris surgery has become easier for the surgeon who has mastered bimanual techniques. MST technologies have developed intraocular microforceps that allow the surgeon to stabilize iris tissue for suturing, and aid in suture manipulation. When space allows, these forceps can be used for internal fixation and cutting of the suture without moving in and out of the eye several times.

INADEQUATE IRIS TISSUE

In the presence of an inadequate or insufficient iris tissue, closure of sector iridectomy can present a significant surgical challenge, as simple closure with interrupted sutures results in distortion of the pupil and may result in optical aberrations. To maintain a central pupil, relaxing incisions must be made to lengthen the iris tissue without increasing tension on the pupil. A large sector iridectomy can be converted into a peripheral iridectomy that is visually insignificant. This may be accomplished by placing numerous small

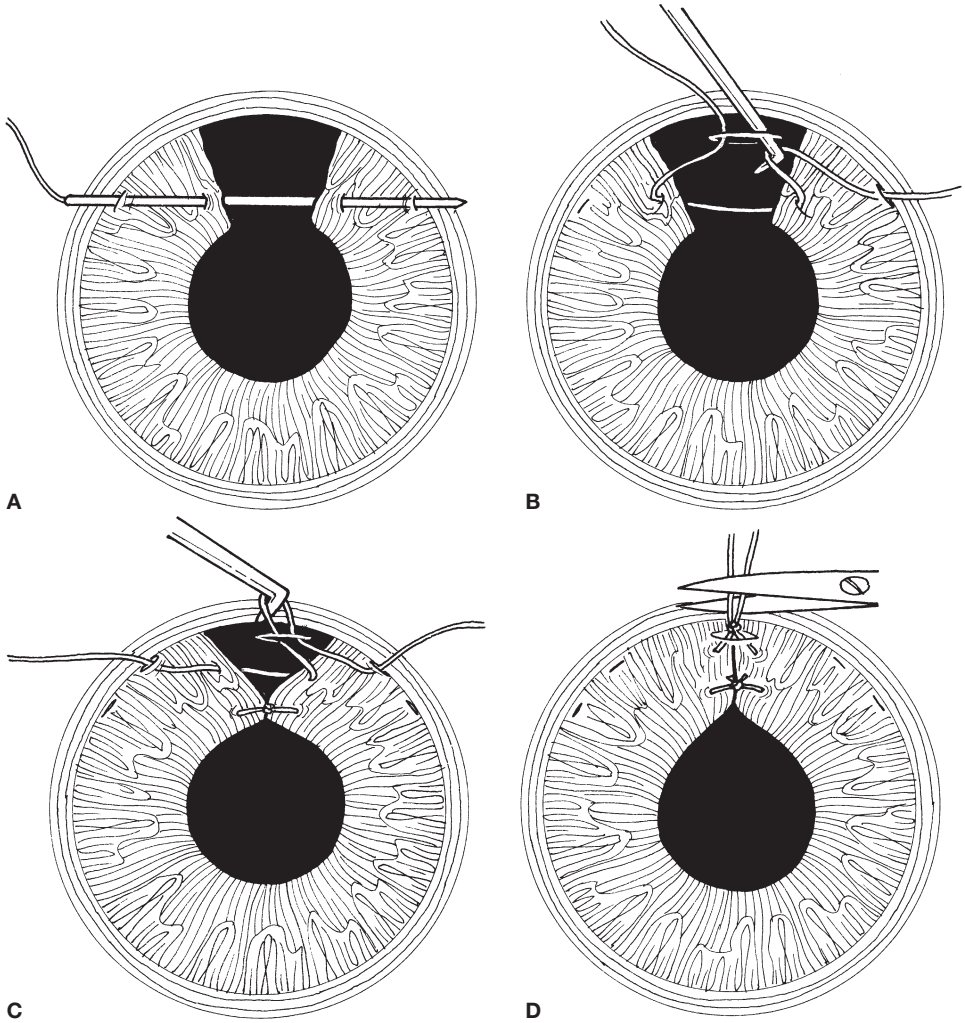


Figure 75.9. *A*, After placement of a self-sealing paracentesis in the meridian of the iris tear, viscoelastic is used to maintain the anterior chamber. The transcorneal suture is passed perpendicular to the edge of the iris laceration as the needle is passed through each edge of the iris and then is driven out through the peripheral cornea. *B*, After the needle is pulled through the cornea, a Sinskey hook is introduced through the paracentesis tract and around the suture. The hook draws the free end of the polypropylene suture back through the cornea as it exits the paracentesis tract. *C*, A second suture is passed in the same manner. The suture then is tied securely with three or four square knots. *D*, The ends are cut short by drawing the knot up to the wound. In the case of large lacerations, two or more sutures may be needed to close the laceration.

peripheral sphincterotomies at the pupillary margin and numerous microincisions along the edge of the sector iridectomy. The microincisions at the edge of the sector iridectomy are cut into the iris stroma to increase the mobility of the scarred tissue. The necessary degree of relaxation is determined by drawing the iris into the desired position using a small hook or microforceps, until the tissue may be advanced sufficiently to close the sector iridectomy with numerous interrupted sutures through the iris stroma (Fig. 75.11). If the pupil is to retain a mydriatic response postoperatively, sutures should be placed only in the stroma, not in the iris sphincter. Thus, the sector iridectomy is converted into an optically insignificant peripheral iridectomy.

In the aniridic patient or a patient who has had traumatic loss of iris tissue, iris replacements may be placed during cataract extraction.[15–21] Complete or partial replacement of the iris can be achieved with intracapsular iris segments or complete interdigitating iris replacement capsular tension rings. While readily available in the international market, these iris replacement systems remain investigational in the USA as of the publication of this chapter.

BLOWN PUPIL REPAIR

A closed-system suture technique was described by Behndig to correct postoperative atonic pupil or traumatic mydriasis using a lasso suture through three small entries, with minimal surgical trauma and induced astigmatism (Fig. 75.12).[22] The pupil suture tension can be regulated for the desired pupil size prior to tying the final knot, which will constrict the pupil.[22]

DISINSERTED IRIS REINSERTION (IRIDODIALYSIS REPAIR)

A traumatic iridodialysis should be repaired when it is large enough to cause visual aberrations, multiplopia, or glare. Once the resultant hyphema is resolved, repair of the iridodialysis should be performed before the development of significant scar tissue, which will decrease the mobility of the iris. Resuspension of the peripheral iris stroma to the sclera is the goal of these procedures.

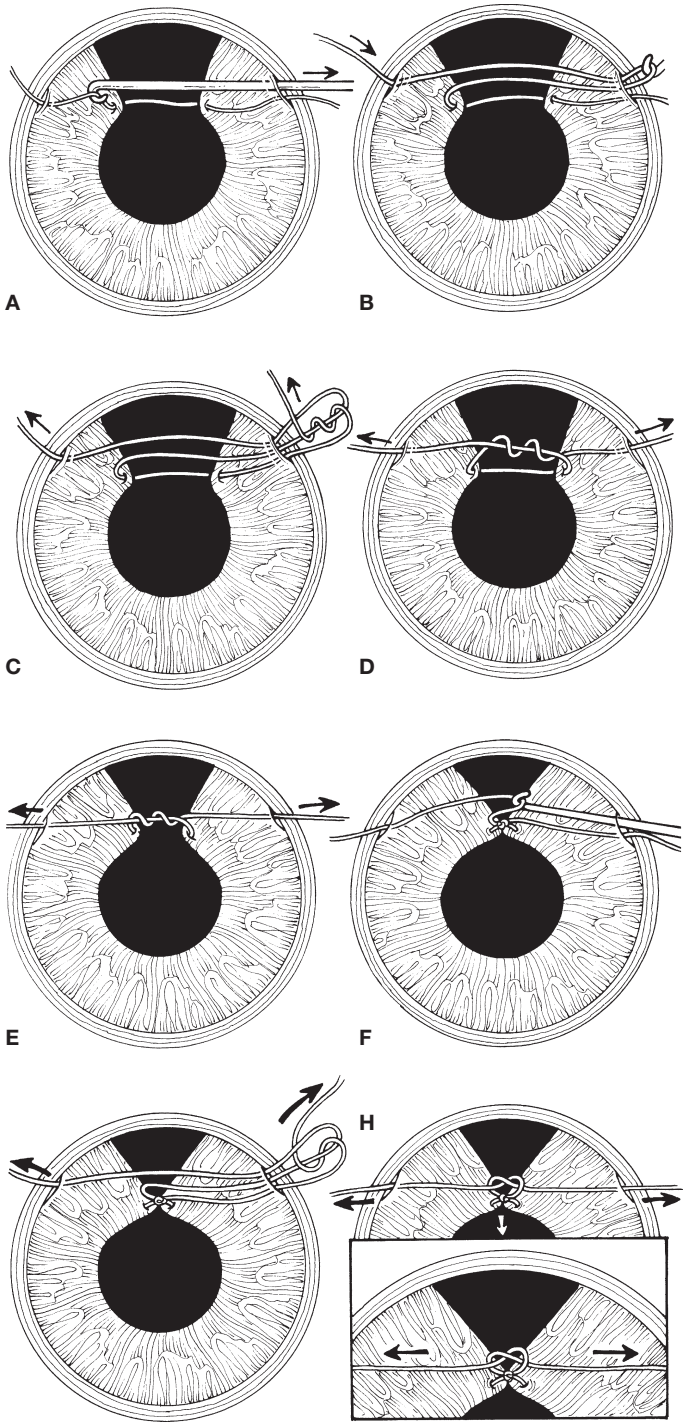


Figure 75.10. *A*, Two limbal paracenteses are created in line with the planned suture tract. The 10-0 polypropylene suture is passed through the entry paracentesis, through the opposite edge of the laceration and out through the other paracentesis. *B*, A microhook is used to manipulate the distal suture within the anterior chamber and create a large loop, which is pulled out through the entry paracentesis. *C*, The suture end is tied to the loop with a simple double-throw slip knot. *D–E*, Both suture ends are pulled outwards and the knot slips down apposing the iris defect edges. *F*, The hook is introduced and the distal suture is pulled out through the entry site. *G*, The suture end is tied to the loop with a single throw. *H–I,* The slip knot is drawn down over the first tie to lock the square knot in place.

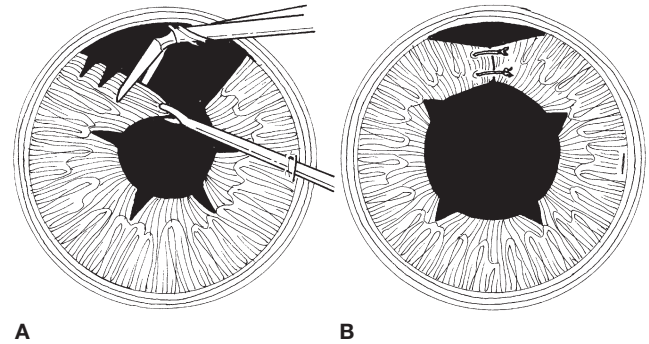


Figure 75.11. Microincisions are made at the edge of the sector iridectomy to increase mobility of the scar tissue after numerous small peripheral sphincterotomies have been performed at the pupillary margin. Mobilized tissue is closed with interrupted 10-0 polypropylene sutures. The most peripheral aspect of the sphincter iridectomy is not fully closed, thereby converting the sphincter iridectomy into an optically insignificant peripheral iridectomy.

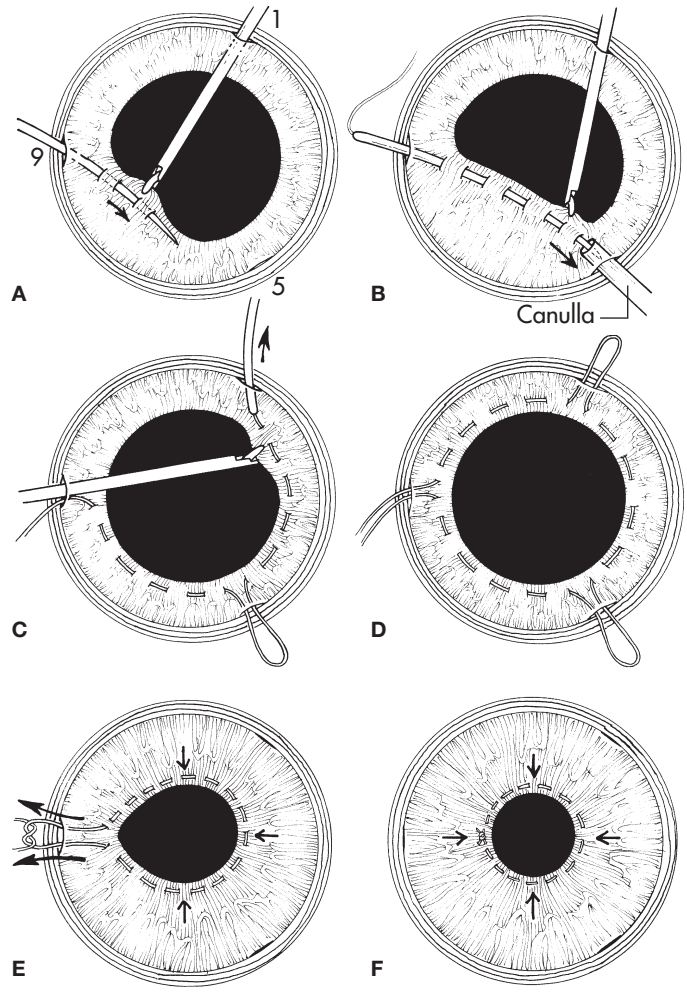


Figure 75.12. *A*, The needle with a 10-0 polypropylene suture is inserted through 9. A suture is made outside the pupil margin assisted by a forceps. *B*, This step is repeated, resulting in a continuous row of suture bites in the iris toward 5. Then with the help of a cannula, the needle is removed through 5. *C–D*, The suturing steps are repeated to place a continuous loop around the pupil margin. *E*, The suture ends are tied. *F*, The pupil size is regulated by the loop tension.

OPEN-CHAMBER APPROACH

It is easier to repair an iridodialysis with an open-system technique, but this requires a large wound (usually around 90–180°) that is associated with increased astigmatism and potential wound instability. A full-thickness scleral incision is placed in the iridodialysis quadrant. The iris edge is grasped with a forceps or iris hook, drawn to the wound edge, and then sutured to the sclera.[7]

CLOSED-CHAMBER APPROACH

Single-armed, peripheral approach

McCannel was one of the first to describe a closed-chamber technique for iridodialysis repair[12] using a 10-0 nylon suture on a curved needle, and it was further modified by the development of the 17-mm straight McCannel needle with 10-0 polypropylene.[23] A 10-0 nylon suture on a curved needle is passed through the limbus, under a small conjunctival flap in the quadrant of the iridodialysis, and then passed under the peripheral, torn iris root (Fig. 75.13, *A*) and out through the cornea. A small limbal stab incision is made beside the suture entry site and a small iris hook is used to pull the 10-0 suture out of the eye (Fig. 75.13, *B–D*). The two suture ends are tied, pulling the torn edge of the iris into the iris root cleft (Fig. 75.13, *F*). Other sutures can be placed in a similar manner to properly reposition the iris.[12]

Chang and Coll developed a variation of this technique[24] using a 30-gauge straight needle with a 10-0 polypropylene suture to enter the eye through a prefashioned grooved paralimbal scleral incision to catch the peripheral iris edge (Fig. 75.14). Alternatively, using a scleral flap, transcorneal sutures are passed through the disinserted iris peripherally, across the chamber angle to give an essentially normal anteroposterior iris position. The sutures exit below the scleral flap about 1 mm posterior to the limbus. The end of the sutures is brought through the scleral tunnel with a Sinskey hook and tied beneath the scleral flap. Numerous interrupted sutures can be used to resuspend the iris root.

Single-armed, cross-pupil approach

Nunziata reported a cross-pupil approach using a 17-mm single-armed straight needle on 10-0 polypropylene suture.[25] The needle is inserted through a limbal paracentesis 180° opposite the iridodialysis.

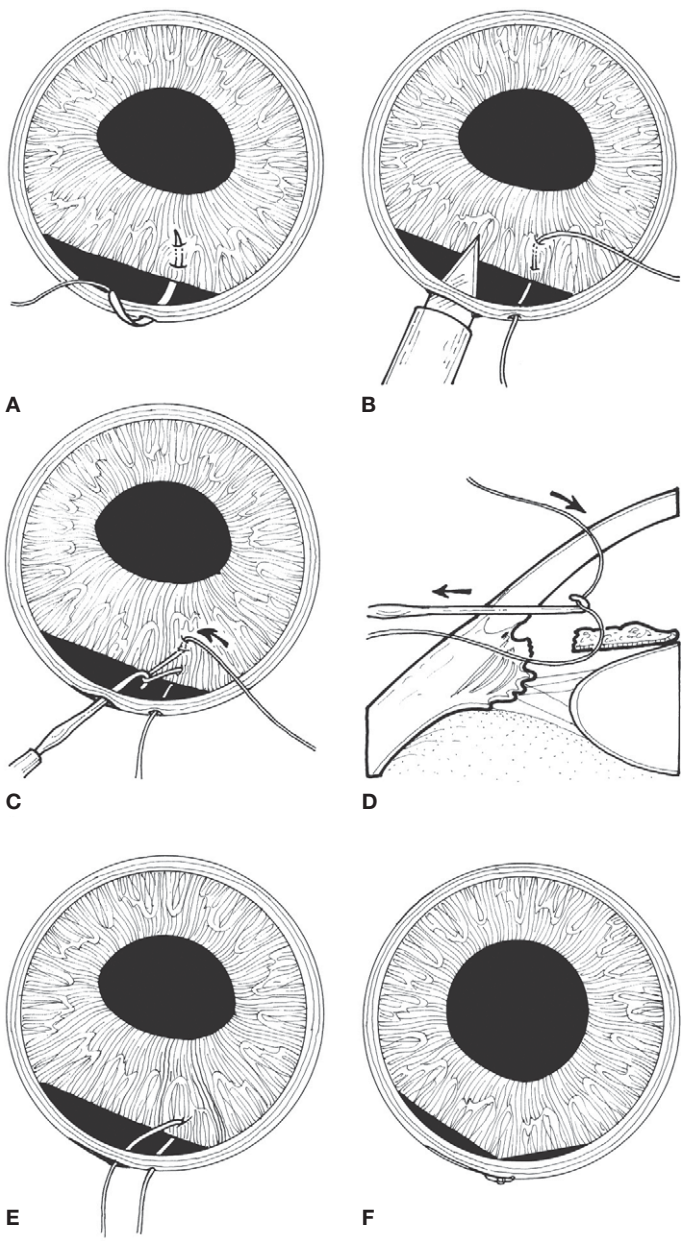


Figure 75.13. *A*, The suture is passed through the limbus, under the torn iris edge and out through the cornea. *B–D*, A limbal stab incision is made beside the entry site and an iris hook is introduced into the anterior chamber to engage the vertical suture and pull it out in a loop. *E*, The corneal suture is cut flush at its exit and its loop is drawn out in a single strand. *F*, The suture is tied pulling the torn edge of the iris into the iris root cleft.

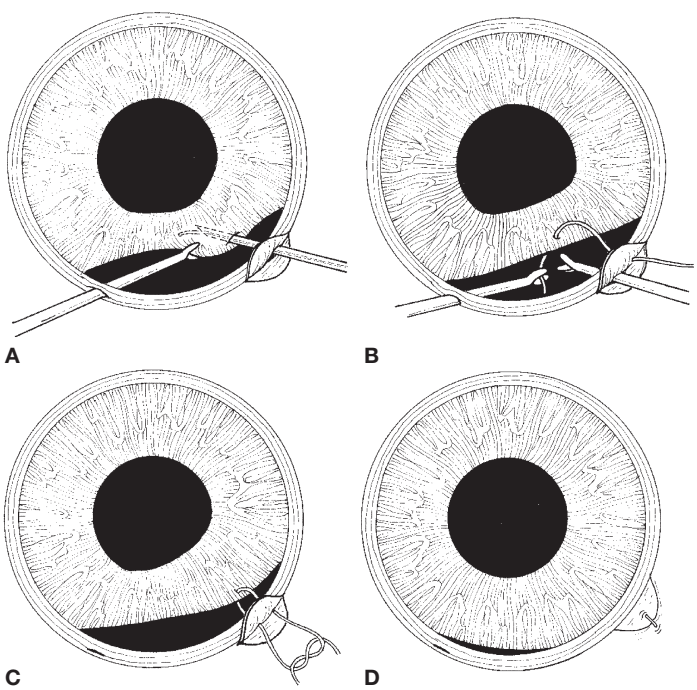


Figure 75.14. *A*, A 30-gauge needle with a 10-0 polypropylene suture enters the eye through a grooved paralimbal scleral incision and passes through the peripheral iris edge. A 25-gauge forceps, inserted through a more lateral paracentesis, unrolls the peripheral iris and assists the needle as it passes through the iris. The forceps then grasp the end of the suture as the needle is withdrawn. *B*, Another 25-gauge forceps, inserted adjacent to the initial 30-gauge entry site, removes the suture from the eye. *C*, The suture is tied. *D*, The knot is buried by closing the scleral incisions.

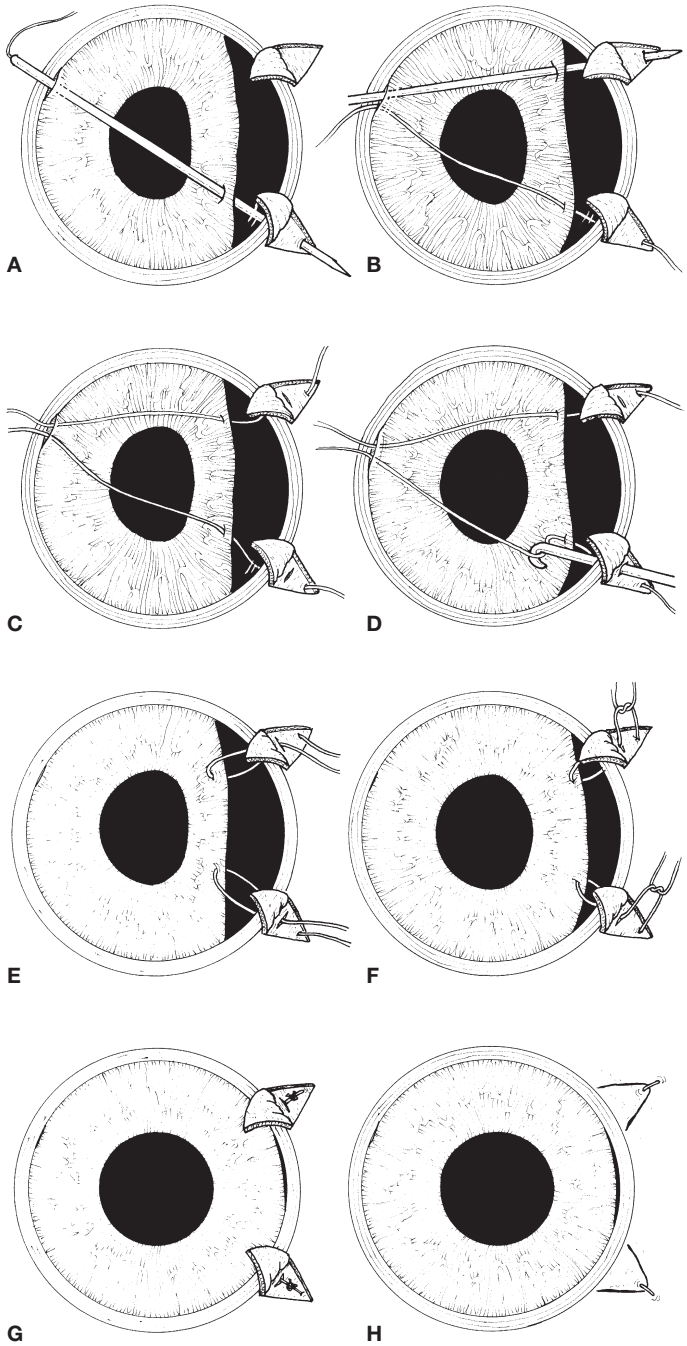


Figure 75.15. *A*, Two scleral flaps are made. A 17-mm needle passes through a limbal paracentesis, through the tear iris edge, and into the scleral bed. *B*, A second needle is introduced in a similar manner. *C*, Paracentesis are placed through the scleral bed nearby to the sutures. *D*, Iris hook is used to pull out a suture loop. *E*, The sutures are drawn out. *F–G*, The sutures are tied, bringing iridodialysis edge into the angle. *H*, The scleral flap is closed.

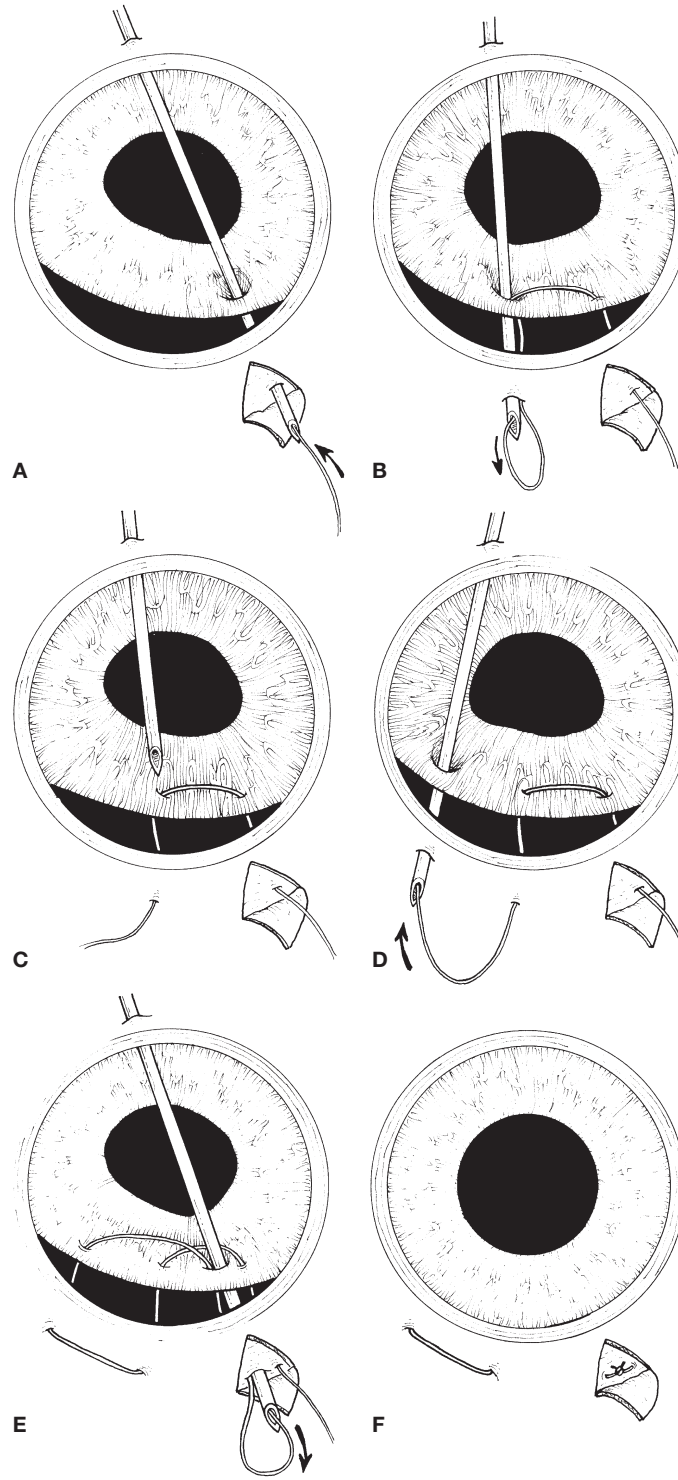


Figure 75.16. *A*, The 25-gauge needle is inserted in the anterior chamber, pierces the peripheral torn iris edge and emerges under the scleral flap. A 10-0 polypropylene suture is threaded into the needle lumen. *B*, The needle is reinserted back through the iris edge and exits 2–3 mm from the scleral flap. The suture is removed from the needle. *C*, The needle is retracted back into the anterior chamber. *D*, A third pass pierces the torn iris edge and emerges 2–3 mm from the last exit site. The suture is threaded into the needle lumen. *E*, The needle is retracted back into the anterior chamber, passed through the torn iris edge and exits under the scleral flap. *F*, The suture is removed from the lumen and tied to its other end, beneath the scleral flap.

dialysis, through the iris at the edge of the tear and out the sclera at the point of normal iris insertion under a triangular scleral flap (Fig. 75.15, *A* and *B*). A paracentesis site is made beneath the scleral flap just above the suture exit site to retrieve the other end of the suture with a microhook (Fig. 75.15, *C* and *D*). The suture is tied, repositioning the iridodialysis (Fig. 75.15, *E–G*). In a large iridodialysis, multiple fixation points are required. Another method was developed by Bardak et al as a modification of the previously mentioned technique.[26] It uses a 22-mm, plastic handled, 26-gauge hypodermic straight needle with a hole at the distal end to thread a 9-0 or 10-0 suture. Zeiter et al reported a technique in which a 3.8-cm long 25-gauge hypodermic needle is used to place a 10-0 polypropylene suture in a sewing-machine fashion (Fig. 75.16, *A–F*).[27]

Double-armed, cross-pupil approach

Wachler et al described a cross-pupil technique that uses a 10-0 polypropylene suture double-armed on 17-mm straight needles.[23] Through a limbal paracentesis placed 180° away, one needle enters the anterior chamber, passes through the peripheral dialyzed iris root, and exits through the sclera.[23] The other needle of the double-armed suture enters via the same entry site, engages the iris 1.0 to 1.5 mm adjacent to the first suture, and exits the eye in the same plane as that first suture but 1.5 to 2.0 mm laterally. The suture is tied repositioning the iris base, and the knots are rotated into the needle tract. The procedure can be repeated if necessary to adequately reposition the iris.[23]

It is important to note that nonabsorbable suture and unburied knots may erode through the conjunctiva, leading to suture-related discomfort, focal inflammation, giant papillary conjunctivitis, endophthalmitis, or inadvertent cutting of the suture by an ophthalmologist unaware of its function.[28,29] The creation of a scleral flap to cover the external portion of the sutures is imperative to prevent these problems.[29]

In conclusion, iris reconstruction and reparative procedures offer unique surgical challenges. Advances in viscoelastics, needle design and suture material have expanded our ability to face these challenges. Improved design of microsurgical instrumentation and development of artificial iris segments have vastly changed our approach to these patients. Restoration of a normal pupil, iris diaphragm, and iris root improves the visual function and cosmetic appearance of the eye. Iris defects repair can eliminate diplopia and glare, and improve the quality of vision for patients. The numerous techniques in this chapter expand the surgical armamentarium needed to successfully repair these patients and improve their visual function.

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76 Conjunctival and corneal tumors

Amol D. Kulkarni, Heather A.D. Potter, Thomas J. Liesegang, and Daniel M. Albert

MICROSCOPIC FEATURES OF THE CONJUNCTIVA AND CORNEA PERTAINING TO NEOPLASIA

Stratified columnar epithelium with goblet cells covers most of the conjunctiva and transitions at the limbus, the palpebral margins, and the caruncle into stratified squamous epithelium. There is polarity or a normal sequence of maturation from the basal layers to the more superficial layers. Melanocytes are present in the basal layer of the conjunctival epithelium, and melanin granules may be transferred to adjacent basal epithelial cells.

The substantia propria is composed of fibrovascular connective tissue of varying density and thickness. It is thin in the palpebral region, creating a firm connection between the epithelium and the tarsus. In the fornices and over the globe, it is thick and loose, but at the limbus it is thin and compact as it attaches to the episclera. Fibroblasts and inflammatory cells are usually found in the conjunctival stroma. Aggregations of lymphocytes within subepithelial tissues in the fornices forming follicle-like structures, some of which contain germinal centers, are present in most 'normal' patients.

Certain regions of the conjunctiva, such as the plica semilunaris and the caruncle, have a distinct anatomy. The plica semilunaris is a structure consisting of redundant bulbar conjunctiva and is a remnant of the nictitating membrane found in some species. The caruncle is lined by a nonkeratinized stratified squamous epithelium and the underlying stroma contains structures found both in the conjunctiva and skin.

CLASSIFICATION OF CONJUNCTIVAL AND CORNEAL TUMORS

Tumors of the conjunctiva can be classified as tumors of the surface conjunctival epithelium, tumors of melanocytic origin, tumors of the adnexal structures, tumors of lymphocytic or hematopoietic origin, and tumors of soft-tissue origin (Box 76.1).[1] Tumors arise in a similar yet less frequent manner in the corneal epithelium, but tumors of the stroma or endothelium are exceedingly rare.

BENIGN LESIONS OF THE SURFACE EPITHELIUM

SQUAMOUS CELL PAPILLOMA

Squamous cell papillomas are benign tumors of the conjunctiva in which acanthotic squamous epithelium covers fibrovascular cores (Fig. 76.1). They are associated with conjunctival infection with the human papilloma virus subtypes 6, 11, 16, and 18.[2–4] In children, they are typically pedunculated, multiple, and located inferiorly in the fornix. In adults, they tend to be sessile and occur on the bulbar conjunctiva. In some cases, they have been found to grow quite large, covering the surface of the cornea and simulating a squamous cell carcinoma. Clinically, papillomas appear as pink, fleshy masses, often having an irregular, cauliflower-like surface (Fig. 76.2).

Most squamous papillomas are asymptomatic without associated conjunctivitis and can easily be observed. Large tumors may cause foreign body sensation, irritation, bleeding, or be cosmetically unacceptable. In these circumstances, the most effective treatment of papillomas is excision of the lesion without direct manipulation, with subsequent cryotherapy to the base and the resection margins. The lesions should be submitted for histopathological examination. They may recur or become multifocal after excision, and in these instances, topical interferon and mitomycin C have been employed.[5,6]

PSEUDOCARCINOMATOUS HYPERPLASIA (PSEUDOEPITHELIOMATOUS HYPERPLASIA)

The conjunctival epithelium may respond to irritation by becoming acanthotic, parakeratotic, or hyperkeratotic. Histologically, the acanthotic epithelium forms irregular nests of epithelial cells containing keratin pearls and simulating a squamous cell carcinoma. This is termed pseudocarcinomatous hyperplasia or pseudoepitheliomatous hyperplasia (PEH). The distinguishing features of PEH are that it (1) develops rapidly over weeks or months, (2) lacks nuclear

BOX 76.1 CONJUNCTIVAL AND CORNEAL TUMORS

Tumors of surface epithelium

Benign
- Squamous cell papilloma
- Leukoplakic plaques
- Pseudocarcinomatous hyperplasia
- Benign hereditary intraepithelial dyskeratosis

Intraepithelial neoplasia
- Actinic keratosis
- Conjunctival or corneal intraepithelial neoplasia (CIN)

Malignant
- Squamous cell carcinoma
- Mucoepidermoid carcinoma

Tumors of melanocytic origin

Benign
- Nevus
- Congenital epithelial melanosis
- Primary acquired melanosis

Malignant
- Melanoma

Tumors of adnexal sructures

Benign
- Oncocytoma
- Pleomorphic adenoma
- Apocrine adenoma
- Sebaceous adenoma

Malignant
- Sebaceous carcinoma

Tumors of lymphocytic or hematopoietic origin

Benign
- Reactive lymphoid hyperplasia
- Atypical lymphoid hyperplasia

Malignant
- Lymphoma
- Leukemia
- Plasmacytoma

Tumors of soft-tissue origin

Benign
- Lipoma
- Neurofibroma
- Fibrous histiocytoma
- Myxoma
- Hemangioma
- Lymphangioma

Malignant
- Fibrous histiocytoma
- Rhabdomyosarcoma
- Kaposi's sarcoma

Choristomatous tumors
- Dermoid
- Dermolipoma
- Complex choristoma

atypia, and (3) contains intraepithelial microabscesses. Because this lesion is not premalignant, simple excision is usually curative.

LEUKOPLAKIC PLAQUES

Leukoplakic lesions on the bulbar or limbal conjunctiva show epithelial thickening with hyperkeratosis. In contrast to leukoplakic plaques on other mucosal surfaces, these have little to no malignant potential and show no cytologic atypia. When associated with vitamin A deficiency, these are referred to as Bitot's spots.

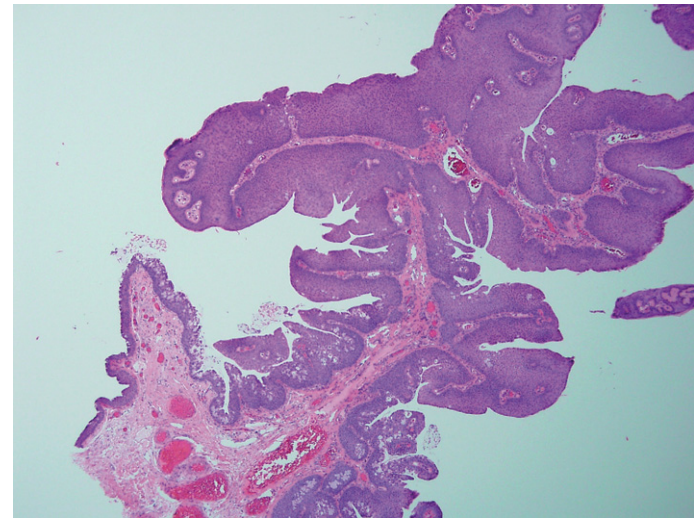


Figure 76.1. Conjunctiva papilloma with finger-like projections extending from the lesion base is seen. The surface consists of acanthotic nonkeratinized squamous epithelium lined by a core of fibrovascular tissue. The substantia propria shows a mild lymphocytic infiltration with congested vessels (Hematoxylin and eosin, ×40).

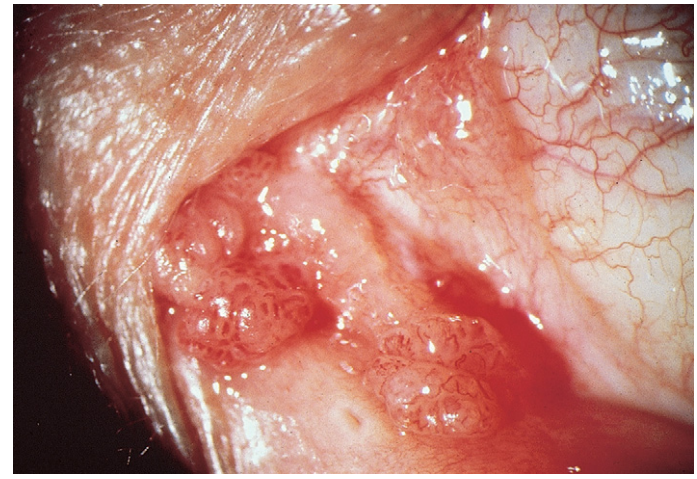


Figure 76.2. Multiple pedunculated squamous cell papillomas involving the fornix and caruncle area in a middle aged individual. When seen in young patients, they are usually of viral origin; when seen in adults, there is concern about conjunctival intraepithelial neoplasia (CIN). Treatment is with surgical excision and cryotherapy; recurrences are frequent.

BENIGN HEREDITARY INTRAEPITHELIAL DYSKERATOSIS

Benign acanthosis of the conjunctiva and oral mucous membranes, with dyskeratosis of epithelial cells, occurs in Haliwa Indians. The disorder is inherited as an autosomal dominant trait with a high degree of penetrance in descendants who lived in northeastern North Carolina. Patients develop bilateral elevated plaques on the interpalpebral areas of the limbal conjunctiva, along with dilated vessels that cause the eyes to appear red. In most cases, the lesions are asymptomatic, but extensive lesions can involve most of the bulbar conjunctiva and the cornea, resulting in corneal opacifica-

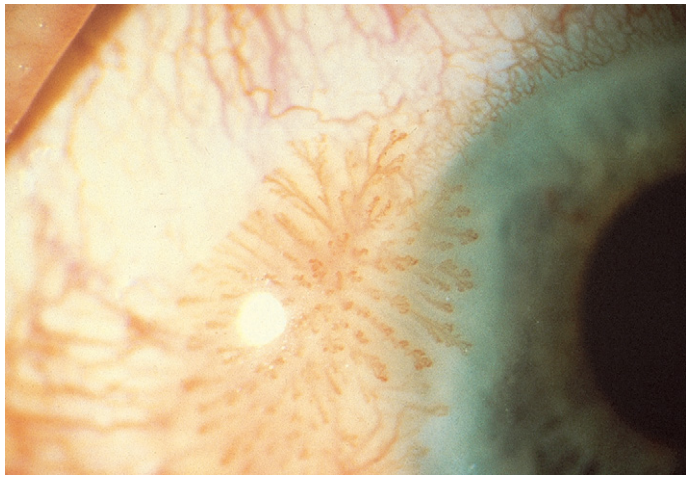


Figure 76.3. Conjunctival intraepithelial neoplasia (CIN) at the limbal area with a typical opalescent papillary appearance. Such tumors usually grow slowly, and removal is recommended at this stage to determine the histopathology.

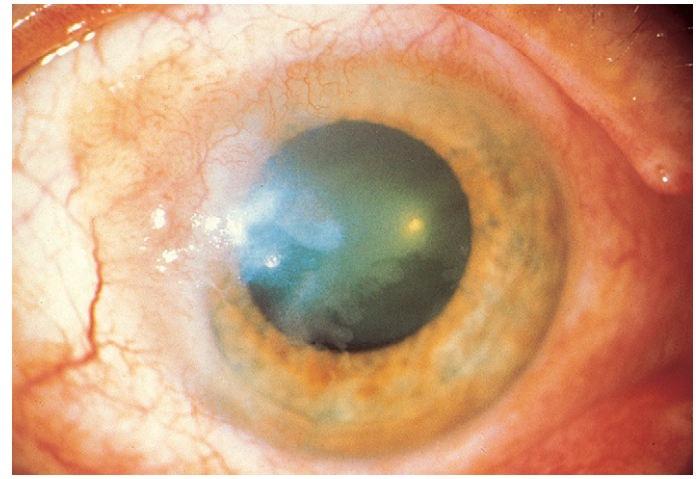


Figure 76.4. CIN involving the limbus and spreading over cornea in an elderly Caucasian male. Excision of the limbal lesion with cryotherapy is recommended. The corneal lesion can be removed with scraping since the basement membrane remains uninvolved.

tion and vascularization with marked loss of vision.[7] Plaques also develop on the oral mucosa. Complete excision is the treatment of choice, although recurrences are likely because of the inherited nature of these lesions.

INTRAEPITHELIAL NEOPLASIA OF THE SURFACE EPITHELIUM

ACTINIC KERATOSIS

Actinic keratosis, or solar keratosis, develops slowly within the interpalpebral epithelium after prolonged exposure to ultraviolet light. The epithelial change often overlies a pre-existing pinguecula or pterygium. Actinic keratosis appears as a sharply circumscribed leukoplakic plaque with atypia in the epithelium. As a result, it is considered a precancerous lesion, but its opacity and elevation distinguish it from a flatter and translucent intraepithelial neoplasia.

CONJUNCTIVAL AND CORNEAL INTRAEPITHELIAL NEOPLASIA

Conjunctival or corneal intraepithelial neoplasia (CIN) is now the preferred nomenclature generally replacing the terms dysplasia and carcinoma in situ. CIN is graded depending on the degree of cellular atypia and disorganization of epithelial cell maturation. Mild CIN consists of abnormal epithelial cells occupying a partial thickness of the epithelium. Severe CIN occurs when the atypical cells are seen in the full thickness of the epithelium. In both forms of CIN, the atypical cells are confined to the epithelium and there is a loss of polarity with suprabasalar mitoses. Also, there is minimal hyperkeratosis and parakeratosis, giving the lesion an opalescent, gelatinous surface (Figs 76.3–76.5), and an abrupt transition from normal conjunctiva corresponding to its sharply demarcated clinical appearance (Fig. 76.6).

Human papillomaviruses (HPV) 16 and 18 have been implicated in the pathogenesis of some of these lesions.[8] Human immunodeficiency virus (HIV) infection should be ruled out in persons younger than 50 years presenting with these lesions, as is the case with other severe viral dermatologic conditions.

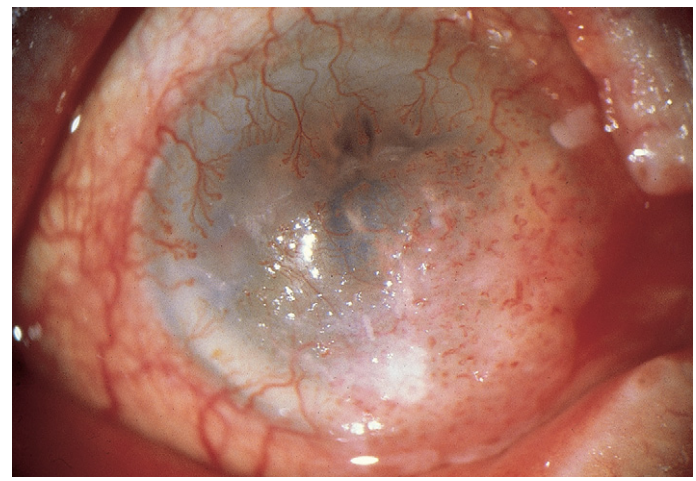


Figure 76.5. A more extensive CIN involving the limbus and central cornea. Despite its appearance, the tumor did not invade Bowman's membrane and can be removed with excision, cryotherapy to the limbal area, and superficial scraping of the cornea.

Mild and severe conjunctival intraepithelial neoplasias are precursors of squamous cell carcinoma, and excisional biopsy with careful clinical follow-up is recommended. These lesions, however, may undergo spontaneous regression.[9]

MALIGNANT TUMORS OF THE SURFACE EPITHELIUM

SQUAMOUS CELL CARCINOMA

Squamous cell carcinomas are characterized by invasion of the abnormal epithelial cells into the underlying stroma. In the USA, most squamous cell carcinomas are only superficially invasive and have a relatively benign clinical course, with intraocular and orbital invasion being uncommon.[10] Squamous cell carcinomas that arise from CIN are more likely to be poorly differentiated and display downward spread into the cornea or sclera (Figs 76.7 and 76.8).[11]

Most squamous cell carcinomas arise in the interpalpebral limbal conjunctiva and grow slowly in an elevated or papillary

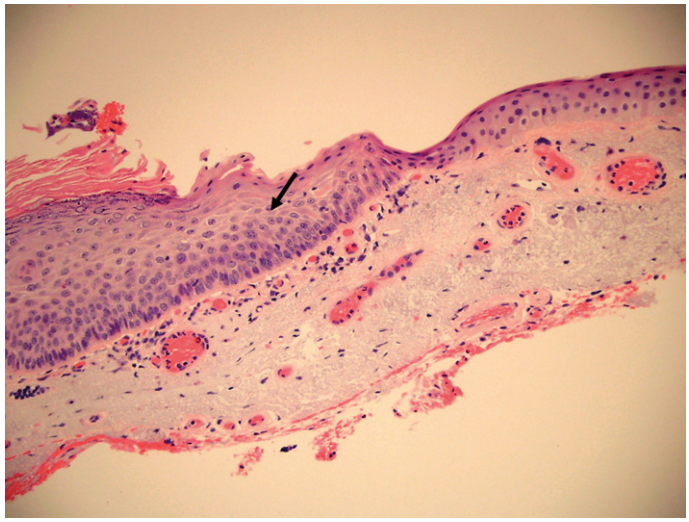
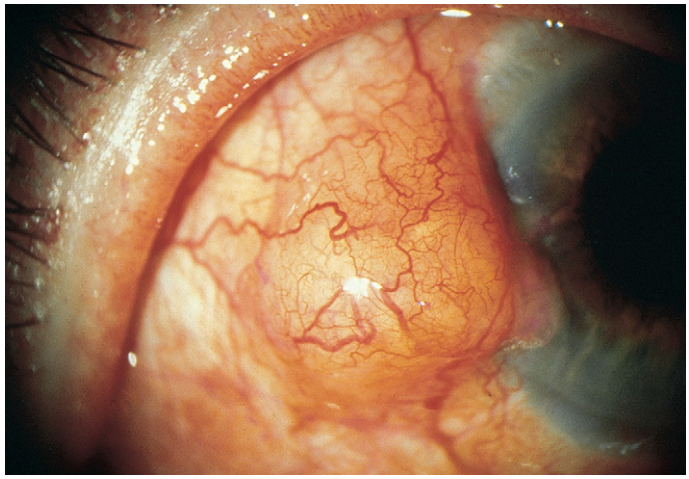


Figure 76.6. Conjunctival epithelium with normal maturation and polarity one side, and an area of abrupt change beginning in the center and extending to the other end showing epithelial thickening and nuclear atypia (arrow) is seen. This appearance is consistent with conjunctival intraepithelial neoplasia. The substantia propia also shows actinic change and mild lymphocytic infiltrate (Hematoxylin and eosin, ×200).



Figures 76.7. A squamous cell carcinoma adjacent to the limbus and fixed to the scleral tissue. Surgical exploration revealed scleral involvement which was resected with frozen section control until the deep and peripheral margins of the clear were free to the base and surrounding tissue.

fashion.[12] They are usually well differentiated and have a leukoplakic appearance but vary in vascularity and amount of associated inflammation.

Although these tumors are more common in the elderly, they are also seen with some frequency in young adults. As is the case with CIN, squamous cell carcinoma in a young individual should alert the physician to the possibility of HIV infection.[13,14]

Histopathologically, most are well differentiated, with exophytic growth of atypical epithelial cells. In more advanced tumors, the substantia propria is usually inflamed and contains invading masses of atypical epithelial cells that vary greatly in size, configuration, and degree of differentiation.[15,16] Squamous cell carcinoma may exhibit mucoepidermoid differentiation; mucin production may occur in only a portion of the tumor. These features may be more common in a recurrent lesion.[17] The mucoepidermoid variant of

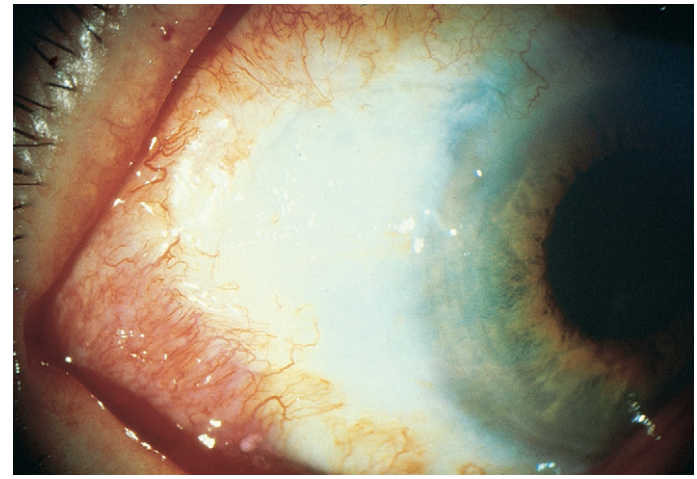


Figure 76.8. Same patient after cryotherapy was applied.

squamous cell carcinoma is more aggressive in its local behavior and may invade the eye and orbit if incompletely excised.

DIAGNOSIS OF EPITHELIAL TUMORS

Exfoliative cytology,[15,18] impression cytology,[19,20] and fine needle aspiration biopsy have been used to diagnose conjunctival epithelial neoplasia lesions. None of the aforementioned methods can help determine the depth of invasion and, hence, conjunctival biopsies are indicated when a specific tissue diagnosis is required. The biopsies may be excisional or incisional depending on the size and predicted depth of invasion. Conjunctival biopsies are discussed elsewhere in this text. Frozen sections are generally not practical for determining during surgery whether surgical margins of conjunctival and corneal epithelial tumors are clear.

MANAGEMENT TECHNIQUES FOR EPITHELIAL TUMORS

SURGICAL THERAPY

Excision of the lesion is the most accepted method of treatment for squamous neoplasia of the ocular surface. Dissection of all abnormal tissue with a wide surgical margin of 2–3 mm ensures removal of most lesions. Rose bengal staining may aid the delineation of the extent of abnormal tissue (Fig. 76.9).[21] Deep corneal invasion may require deep lamellar keratoplasty and scleroplasty (see Figs 76.5 and 76.8).[22,23] A technique analogous to Mohs' micrographic technique for cutaneous tumors has been described for corneal and conjunctival squamous lesions.[24] Extensive corneal limbal resection might necessitate limbal grafting from the opposite eye.[25,26] Excision of intraocular invasive tumors may occasionally be successful; a modified iridocyclochoroidectomy with adjunctive cryotherapy has had limited success.[22,27] Inadequate excision margins has been identified as a major risk factor for recurrence.[28] Partially excised tumors tend to recur with increased aggressiveness.[28] Excised lesions with free surgical margins have had a recurrence rate of 5%, as opposed to a 53% recurrence rate in lesions that were incompletely excised.[28] Gonioscopy is recommended to confirm that the tumor has not invaded the angle or anterior chamber. Enucleation or, more rarely, exenteration may be required in instances of intraocular or intraorbital extension.[29]

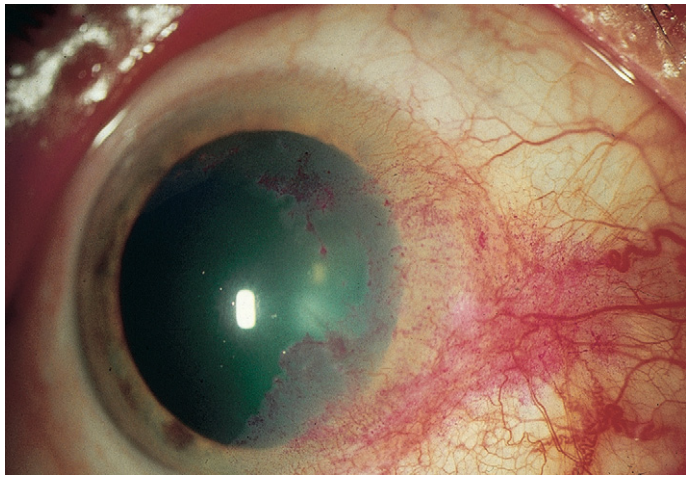


Figure 76.9. Rose bengal staining aiding determination of the extent of corneal and conjunctival involvement from a CIN. This can guide surgical therapy.

The use of a 193 nm argon–fluoride excimer laser for the removal of recurrent corneal intraepithelial neoplasia has been reported.[30] Despite its simplicity, no histologic examination can be performed as an assessment of the ablated tissue, and no evaluation of margins is possible.

RADIOTHERAPY

Generally, radiation alone is not recommended as a definitive therapy; however, it may be used for diffuse or spreading lesions, for which initial excision would be too extensive. The two most common types of radiation sources are strontium-90 and radium. Strontium 90 is a β source that delivers 100% of its dose to the most superficial layers of the tumor location.[31] A cup-shaped applicator is used to apply the therapy directly to the ocular surface. β-radiation has been used for recurrent corneal intraepithelial neoplasia.[32] γ-radiation has also been studied using radium as a source.[33] Recurrence rates range from 2 to 47%, with an average of 18%.[15] Complications include moderate to severe conjunctivitis, dry eye, cataract, telangiectasia, scarring, scleral ulceration, symblepharon, and corneal rupture.[15]

CRYOTHERAPY

Cryotherapy is effective because of its immediate thermal effect and subsequent obliteration of the microcirculation, resulting in ischemic infarction of normal and tumor tissues. Cryotherapy may also act by means of an immunologic response to liberated tumor antigens, which may play a late role in ongoing policing of residual or recurrent tumor cells at a cellular level.[15] Repeated freeze–thaw cycles are recommended to get adequate cellular destruction. Early side effects include iritis, altered intraocular pressure (high or low), thermic inflammatory edema and late corneal scarring, sector iris atrophy, ablation of the peripheral retina, ectropion, and uncommonly, corneal hemorrhage and superficial corneal vascularization.[15]

CHEMOTHERAPY AND IMMUNOTHERAPY

Topical mitomycin-C 0.02% applied four times daily for 10–22 days has been used to treat corneal intraepithelial neoplasia,[34] but only short-term follow-up has been reported. Adverse reactions included hyperemia, ocular pain, and blepharospasm; however, these symptoms disappeared quickly. Fluorouracil has also been used to treat epithelial neoplasia.[35] Other chemotherapeutic agents, including thiotepa[28] and urea,[36] have been used to treat in a limited number of patients with these lesions.

Immunotherapy with dinitrochlorobenzene requires systemic sensitization before tumor treatment by applying 2000 μg of the agent to the skin of the forearm.[37] After delayed hypersensitivity has been demonstrated, minute amounts of concentrated solution in acetone are applied to the surface of the tumor for several weeks. This form of treatment is labor intensive and requires continuous clinical monitoring and frequent application of the drug.

The recent therapeutic recommendations for squamous cell cancer include excision of the tumor and 2 mm of surrounding conjunctiva or superficial sclerotomy in adjacent areas.[38,39] A nitrous oxide cryoprobe is used to form an iceball extending 2 mm for the conjunctiva, 1 mm for the episclera tissues and limbus, and 0.5 mm for the cornea; the process is repeated twice. Recurrence rates average 12%.[15]

TUMORS OF THE MELANOCYTIC SYSTEM

Melanocytes are melanin producing cells which give rise to nevi, melanosis, and melanoma. African Americans and other heavily pigmented individuals may develop significant degrees of melanotic pigmentation of epithelial lesions (e.g. papilloma, actinic keratosis, carcinoma) that are, by definition, not of melanocytic origin. Conversely, melanocytic lesions may contain no clinically discernable pigment, or the pigmentation may be easily apparent. Melanosis oculi and nevus of Ota both involve episcleral and scleral pigmentation that can be mistaken for conjunctival pigmentation.

NEVI

Conjunctival nevi are composed of multiple nests of nevus cells and are classified based on the location of these nests. If the nests are at the junction of the epithelium and substantia propria, the nevus is termed junctional. If they are only in the substantia propria, the nevus is subepithelial. If both elements are seen, then the nevus is classified as compound. Most conjunctival nevi are compound or subepithelial. Junctional nevi are uncommon and occur primarily in young individuals.[40] The spindle-epithelioid cell, blue nevus, and cellular blue nevi are rare in the conjunctiva, but these can occur in combination with typical nevi.[41]

Nevi are almost always seen in the interpalpebral bulbar conjunctiva near the limbus.[40,42] Subepithelial and compound nevi typically elevate the conjunctival surface, and this may be attributable to the epithelial inclusion cysts commonly seen in these lesions (Figs 76.10 and 76.11). Junctional nevi, however, characteristically do not thicken the conjunctiva.[43] Over time, junctional conjunctival nevi frequently transform into compound and subepithelial nevi. The appearance of these lesions can change drastically because of an increase in the size of the nevoid nests, downward migration of these nests, and formation of epithelial inclusions. The appearance of a nevus might also change as a result of irritation. This can result in increased pigmentation, an inflammatory cell infiltrate, and increased vascularity. The same changes can be seen in malignant transformation to melanoma, so these lesions must be photographed and/or closely observed, and may require an excisional biopsy.

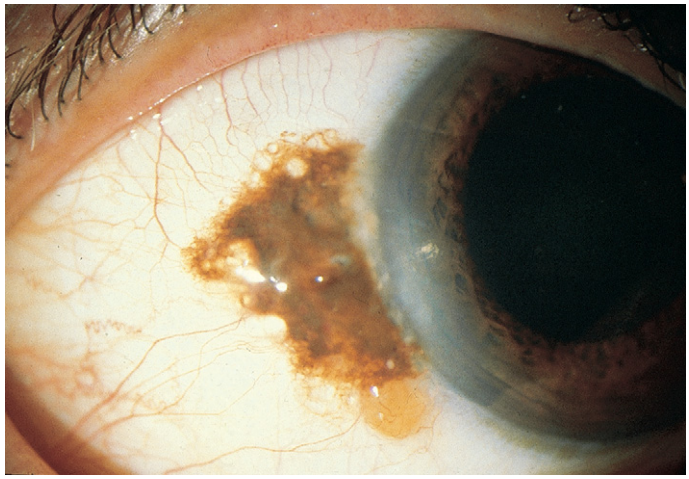


Figure 76.10. A compound conjunctival nevus in a young adult demonstrating typical pigmentary changes and cystic epithelial inclusions.

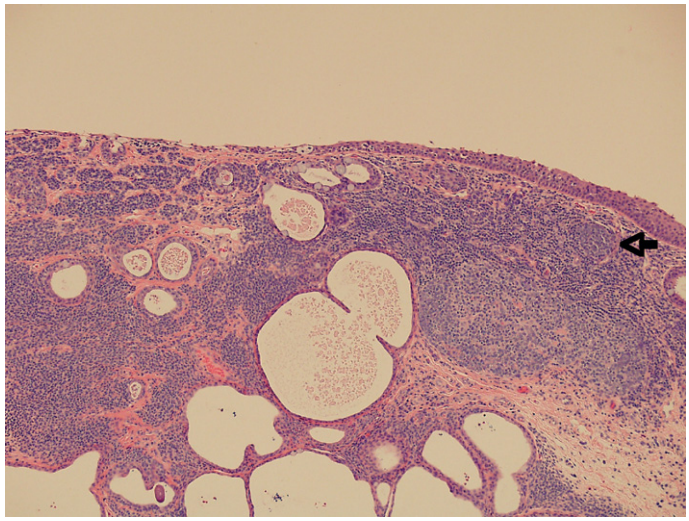


Figure 76.11. Conjunctival tissue with nests of nevus cells (arrow) in the substantia propria is seen. Some nevus cells contain pigment. The nevus cells are intermixed with cystic structures, lined by uniform epithelium including goblet cells. The substantia propria also shows scattered lymphocytic infiltrate (Hematoxylin and eosin, ×100).

Conjunctival nevi can be amelanotic and these may clinically resemble epithelial lesions or angiomas.

MELANOSIS

Melanosis is excess melanotic pigmentation and can be classified based on whether it is congenital or acquired, epithelial or subepithelial, and primary or secondary. All the congenital melanoses are primary, and they are divided into epithelial or subepithelial types. The acquired melanoses are epithelial, and they are divided into primary and secondary types (Box 76.2).

Congenital epithelial melanosis

Congenital epithelial melanosis (freckle) is a discrete stationary lesion that is present from early childhood in the basal layers of the conjunctival epithelium. The melanocytes are not atypical, and this lesion is not a precursor of melanoma.

BOX 76.2 MELANOSIS

Congenital (all are primary)
- Epithelial
- Subepithelial

Acquired (all are epithelial)
- Primary
- Secondary

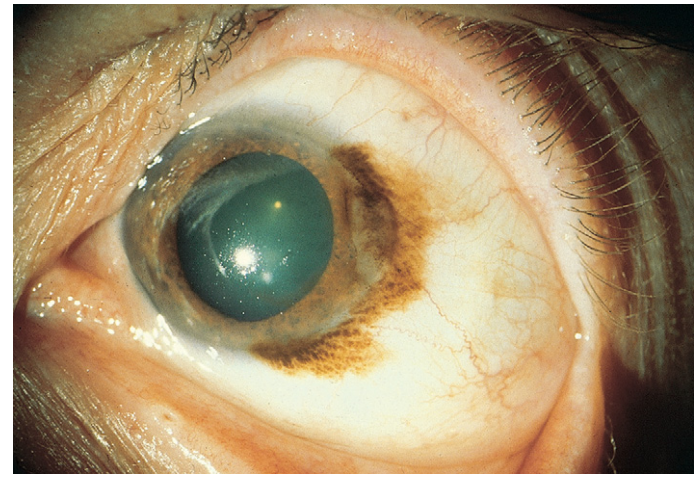


Figure 76.12. Primary acquired melanosis in a middle-aged Caucasian male. The pigmentation has increased gradually over the past 2 years. Biopsy is recommended to stage the lesion; further therapy depends on the histopathology.

Congenital subepithelial melanosis

Congenital subepithelial melanosis is actually abnormal melanocytes in the sclera and episclera deep to the substantia propria. It is seen in the conditions of melanosis oculi and nevus of Ota. They are both unilateral conditions with increased number, size, and pigmentation of melanocytes in the sclera and episclera as well as the entire uvea. The nevus of Ota additionally has increased pigmentation of the deep dermal tissues of the lids, periocular facial skin, or both. The affected tissues are a characteristic slate blue-grey, in contrast with the golden brown to brown-black of intraepithelial forms of melanosis. These conditions are occasionally associated with malignant change; most melanomas in these two conditions arise in the uveal tract or orbit, not the conjunctiva. They are more frequent in African American and Asian patients, but malignant change in these individuals is rare.

Primary acquired melanosis

Primary acquired melanosis (PAM) is a unilateral neoplastic melanocytic proliferation within the conjunctival epithelium. PAM is observed almost exclusively in Caucasian patients, especially those of European ancestry, with a prevalence of up to 36% (Fig. 76.12).[44] PAM typically begins insidiously in middle or older age as a subtle, golden brown stippling within the epithelium. It is analogous to lentigo maligna of the skin. PAM can arise in any part of the conjunctiva, although it is more common on the bulbar portion. The lesion is usually flat which helps to distinguish it from nevi. When elevated areas develop in PAM, they are often a sign of malignant melanoma. Approximately one-third of the conjunctival melanomas arise from PAM. PAM has an unpredictable course and may wax, wane, or spontaneously disappear, although its changes usually are

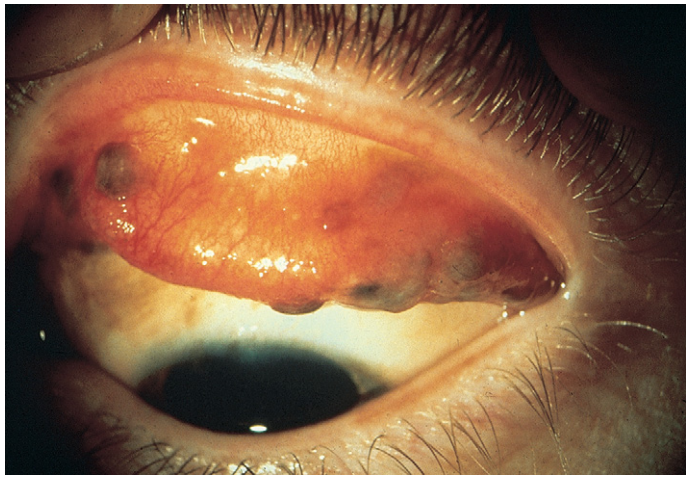


Figure 76.13. Primary acquired melanosis with multiple elevated nodules on the palpebral conjunctiva of the upper lid usually indicative of melanoma.

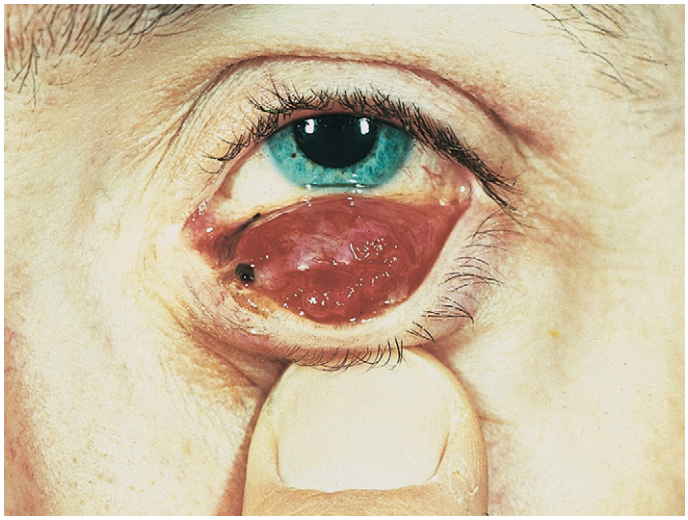


Figure 76.14. Minimally pigmented melanoma apparently arising de novo in the inferior cul de sac. Biopsy confirmed the diagnosis in this 40-year-old Caucasian. Despite exenteration, he died 16 months later with extensive metastases.

gradual. Use of the Woods lamp may indicate a larger lesion than is otherwise evident.

Histologic examination provides significant prognostic information; hence biopsy of PAM lesions is often essential for clinical management. Biopsies are classified as either PAM without atypia, which carries almost no risk of melanoma; or PAM with atypia, which carries a 50% risk of melanoma.[1,45,46] When atypical melanocytes invade the epithelium in a pagetoid fashion or replace the epithelium, the risk of melanoma is 90%; when they are confined to the basal layer of the epithelium, the risk of melanoma is 20%. Of tumors that contain epithelioid cells, 75% progress to melanoma. Lesions in which no or only minimal atypia can be detected do not progress to melanoma.[45–47] All lesions with high risk should be considered for resection, if feasible. Subtotal excision combined with cryotherapy provides effective therapy for extensive lesions that cannot be completely resected.[48]

MELANOMA

Conjunctival melanomas are rare tumors that occur predominantly in fair-skinned adults, although they have been reported in more heavily pigmented individuals. They may arise from PAM with atypia, from pre-existing nevi, or from normal conjunctiva (de novo) (Fig. 76.13). Therefore, any change in a pigmented lesion of the conjunctiva, particularly growth with increasing elevation and prominent feeder vessels, should be suspected of being a malignant melanoma (Fig. 76.14). Melanoma can be suspected clinically based on the history of the lesion and the slit-lamp biomicroscopic findings, but a histopathological examination is essential to confirm the diagnosis.

Histopathologically, conjunctival melanoma is characterized by the presence in the conjunctival stroma of atypical melanocytes exhibiting prominent nucleoli and altered nuclear : cytoplasm ratio. There may be an associated PAM lesion or nevus. Occasionally, melanoma cells are amelanotic. In these instances, certain silver stains (Fontana's and Warthin–Starry methods) may be helpful in making fine melanin granules visible by light microscopy. Also, positive immunoperoxidase staining for HMB-45, S-100 and anti-melan-A and negative staining for cytokeratin provide a reliable method for distinguishing melanocytes from epithelial cells.[49]

Conjunctival melanomas tend to be invasive, involving nerves and extending posteriorly into the orbit. The behavior of conjunctival melanomas, however, remains unpredictable in individual cases.[50] Poor prognostic factors include tumor arising from PAM, tumor thickness, involvement of the nonbulbar conjunctiva (especially invasion of the skin margin), invasion of the sclera or orbit, pagetoid spread, recurrence, and increased mitotic activity.[51–53] A better prognosis is associated with bulbar location or with an inflammatory infiltrate around the invasive tumor.

Conjunctival melanomas share with cutaneous melanomas the ability to invade lymphatics and spread initially to the regional lymph nodes, especially the preauricular and intraparotid nodes. Although lymph node involvement indicates a poor prognosis, it does not always herald widespread dissemination.

DIAGNOSTIC TECHNIQUES FOR PIGMENTED LESIONS OF THE CONJUNCTIVA

CYTOLOGY

Atypical melanocytes ascend to the surface of the conjunctival epithelium with malignant transformation; however, there are a lack of superficial melanocytes in benign nevi, primary acquired melanosis without atypia, and early primary acquired melanosis with atypia. This makes impression and exfoliative cytology less desirable as a method of diagnosing a pigmented lesion.

BIOPSY

Pigmented lesions should be documented photographically or with drawings. Significant increase in size, deepening of color, or change in appearance warrants excision. Small lesions should be removed in toto with generous margins and double freeze–thaw cryotherapy to the surgical margin. Larger lesions, such as primary acquired melanosis, require incisional biopsies taken from the thickest and most pigmented areas. A map of the biopsy sites should accompany the specimens to the laboratory. To prevent curling of the specimen,

tissue can be placed on filter paper and then immersed in fixative. A suture or dye can be used to help the pathologist orient the specimen. Many biopsy sites need no closure, but occasionally a conjunctival autograft from the opposite eye is needed. In addition to the histologic evaluation, investigational tests are being performed in some laboratories, including nucleolar organizer region evaluations and monoclonal antibody studies to HMB-45, S-100, and anti-melan-A.[49]

MANAGEMENT TECHNIQUES FOR PIGMENTED LESIONS OF THE CONJUNCTIVA

EXCISION AND CRYOTHERAPY

As stated above, a complete excision with wide margins is indicated for small suspicious pigmented lesions. Lesions of primary acquired melanosis with atypia should be completely removed if possible because of the risk of progression to melanoma. Conjunctival tissue may be fragile and should be handled carefully to provide a good diagnostic specimen and avoid dissemination of tumor cells. Although thorough microscopic excision of tumor is the preferred treatment, recurrence can still develop in up to 65% of patients with melanoma arising from PAM at 15 years follow-up.[54]

Adjunctive cryotherapy increases the success rate to 80–90% in patients with primary lesions of unifocal melanoma and is recommended at the time of the initial surgery (Figs 76.15 and 76.16). Tumor cells are more sensitive to destruction by the double freeze–thaw method of cryotherapy, with tissue temperatures between −15 and −20°C,[55] and those that are not destroyed become depigmented. Complications of cryotherapy include conjunctival symblepharon, lash loss, ptosis, pseudopterygium, corneal ulceration, iris atrophy, cataract, macular edema, anterior segment necrosis, scleral melting, and phthisis bulbi.

The value of additional removal of scleral tissue has not been determined. Peripheral corneal pigmentation can be scraped and absolute alcohol used to devitalize any remaining cells. If regional metastasis is present, regional lymph node removal along with parotidectomy should be considered if there is no sign of distal seeding; however, the prognosis in this situation remains poor. Evaluation for metastases should always be performed before undertaking these major surgical approaches.

RADIOTHERAPY AND CHEMOTHERAPY

β-radiation and radioactive plaques have been used following local excision but not in a controlled fashion. Hematoporphyrin photoradiation has been tried in only a few patients. Topical mitomycin-C has been used with limited success for treating primary acquired melanosis and melanoma. The deeper cells may remain unaffected by the drug; however, it may be useful in preventing symblepharon after extensive cryotherapy. Dacarbazine, a cytotoxic purine analog, has been used systemically to treat malignant melanoma; its effectiveness with local application is under investigation.

CARBON DIOXIDE LASER

The carbon dioxide laser has been used to destroy the conjunctival epithelium without damaging the underlying sclera. It may be useful for treating diffuse bulbar conjunctival lesions, in which the risks of treatment with cryotherapy may be excessive. It is not recommended for treating the fornices and palpebral conjunctiva or the cornea. This technique needs further evaluation before being accepted as a recommended therapy.

EXENTERATION

In patients with extensive infiltration of the conjunctiva by melanoma, there are limits to the amount of conjunctiva that can be removed.[56] An orbital exenteration may be necessary, although most patients with orbital involvement ultimately develop distant metastases.[54] The alternative is to excise all invasive nodules and treat the remaining flat areas of intraepithelial disease with cryotherapy.

OTHER PRIMARY CONJUNCTIVAL TUMORS

CARUNCLE LESIONS—ONCOCYTOMA

As mentioned earlier, the caruncle is a complex anatomic location containing elements of both the conjunctiva and skin. This com-

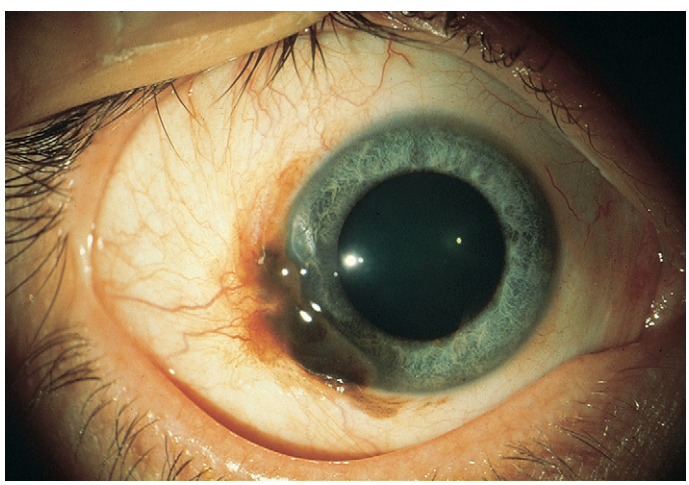


Figure 76.15. Deeply pigmented melanoma arising at the limbal area, apparently de novo, although histopathology showed elements to suggest prior nevus.

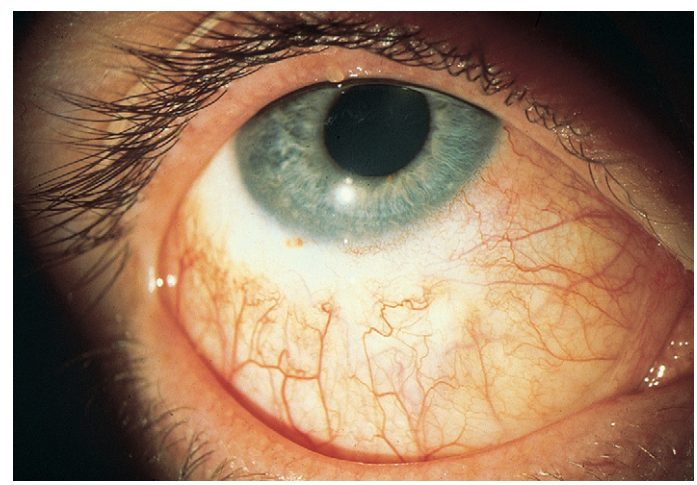


Figure 76.16. The postoperative appearance of the eye in Figure 76.15, 2 months after excision of the melanoma with a 3-mm margin and cryotherapy to the base and surrounding tissue.

plexity can result in a myriad of different lesions, the most common being papilloma, nevus, and pyogenic granuloma.[57] The caruncle also contains adnexal structures: accessory lacrimal glands, sweat glands, sebaceous glands, and hair follicles. Oncocytoma (oncocytic adenoma) is a tumor that arises from the accessory lacrimal glands.[58] Oncocytomas are usually asymptomatic, slowly enlarging, bluish cystic lesions of the caruncle in older individuals. There is a predilection for these tumors in women.[59] Observation may be the preferred approach if one is sure of the clinical diagnosis and the lesion is stable to these and many other caruncular lesions. Excision should be considered if the lesion is symptomatic or if there is a question regarding the clinical diagnosis.

SEBACEOUS GLAND TUMORS

Sebaceous carcinoma arises almost exclusively in the skin of the eyelid and is extremely rare in the skin elsewhere. In the periocular area, it most commonly arises in the Meibomian (tarsal) glands, and less commonly in the sebaceous glands of the lashes, the caruncle, or the skin of the eyebrows. Sebaceous carcinoma is usually seen in elderly patients, with a female preponderance in incidence. It may present as a firm nodule resembling a chalazion, with a diffuse, plaque-like thickening of the tarsus, or a generalized erythema of the lids, with conjunctival injection simulating a chronic blepharitis or conjunctivitis. This clinical picture is referred to as the masquerade syndrome[60] (Fig. 76.17).

Diagnosis of this tumor requires biopsy. The involved epithelium is very friable, and if the biopsy specimen is not carefully handled, the abnormal cells may be lost. It is often necessary to obtain multiple biopsy specimens from the lid margin as well as the palpebral and bulbar conjunctiva to determine the extent of intraepithelial involvement. The tissue may either be submitted fresh or in 10% neutral-buffered formalin. In either instance, prior to tissue processing, a frozen tissue section and subsequent staining with Oil Red O can be useful diagnostically.

Histopathologically, sebaceous carcinoma usually appears as finger-like projections and lobules of large, cohesive cells with foamy cytoplasm, increased nuclear to cytoplasm ratio, and prominent nucleoli. Mitoses are usually prominent. In certain lesions, central necrosis of the tumor lobules is seen; this is termed a comedo pattern. Intraepithelial spread to the conjunctiva, cornea, or skin of the eyelids may be observed in sebaceous gland carcinomas. There are two patterns of intraepithelial spread: pagetoid (so called because of analogy to Paget's disease of the breast) and carcinoma in situ-like. The neoplastic cells in pagetoid spread invade the overlying epithelium as single cells or as small nests of cells that typically do not form intercellular bridges with the surrounding normal squamous epithelial cells. The spread also can be a diffuse process, with full-thickness replacement of surface epithelium by neoplastic cells, resembling squamous cell carcinoma in situ. Many times, the intraepithelial spread will elicit a chronic inflammatory response, thus producing the clinical picture of chronic blepharitis or conjunctivitis. Rarely, there may be intraepithelial sebaceous neoplasia of the conjunctiva and cornea without an underlying invasive carcinoma.[61] The epithelium of the conjunctiva, cornea, or epidermis of the lids often displays multifocal involvement, with skip areas of unaffected epithelium. In cases that pose a diagnostic dilemma, immunohistochemical staining can be employed. Positive staining for epithelial membrane antigen (EMA) and BRST-1 in sebaceous carcinoma distinguishes this from basal cell carcinoma, and positive staining for Cam 5.2 can rule out squamous cell carcinoma.[62]

A worse prognosis is indicated if the origin of the tumor is in the upper eyelid, if the size is 10 mm or more, if the origin is from Meibomian glands, when duration of symptoms is more than 6 months, with infiltrative growth pattern, with moderate to poor sebaceous differentiation, and when invasion of lymphatic channels is present. The treatment is primarily surgical, with wide local excision of the lesion until the surgical margins are histologically clear of tumor. Adjunctive cryotherapy is effective. Because of pagetoid invasion, the Mohs' surgical technique has been less successful in the management of sebaceous carcinoma than in basal cell or squamous carcinoma.[63] Many patients with diffuse pagetoid invasion or carcinoma in situ-like changes involving the skin of the lid, the conjunctiva, and the cornea require orbital exenteration. Sebaceous carcinomas are relatively radioresistant, and radiotherapy is unlikely to control the disease.[64] Removal of involved regional lymph nodes has resulted in long-term survival of some patients.[65]

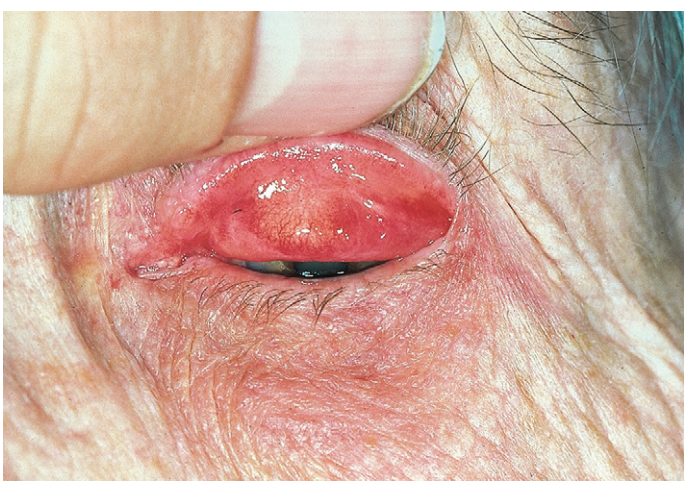


Figure 76.17. The 'masquerade syndrome' of sebaceous cell carcinoma in an elderly woman with prolonged unilateral ocular irritation and conjunctival injection.

KAPOSI'S SARCOMA

Kaposi's sarcoma of the conjunctiva was previously a rare disease, primarily occurring in older individuals with similar lesions on the skin.[66] It is now encountered almost exclusively in the palpebral or forniceal conjunctiva of younger individuals with acquired immune deficiency syndrome (AIDS).[67] It can be one of the earliest clinical manifestations of AIDS. Histopathologically, the tumor shows capillary clusters in a malignant spindle cell stroma. A characteristic finding in Kaposi's sarcoma is the presence of multiple, small, PAS-positive intracellular hyaline globules that are believed to be degenerated erythrocytes.[68] Often there is a lymphocytic infiltrate that has led to the term 'malignant granulation tissue.' The lesions are classified in AIDS patients into three types: Type I and type II tumors are patchy and flat and of less than 4 months' duration. They are different in that type II has plump endothelial cells and foci of immature spindle cells. Type III tumors are nodular and elevated with a duration of more than 4 months.

This aggressive tumor presents as a chronic reddish dermal mass in the skin or as a reddish conjunctival lesion (Fig. 76.18). Human herpes virus 8 has been detected in the vascular endothelial cells

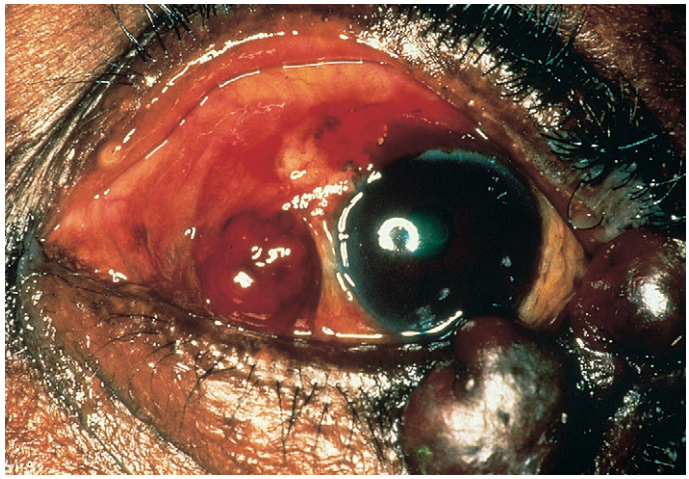


Figure 76.18. Multiple lesions of Kaposi sarcoma of the eyelid and conjunctiva in a patient with AIDS.

lining vascular spaces and perivascular spindle cells in Kaposi's sarcoma lesions.[69] In addition to its prevalence in AIDS, Kaposi's sarcoma is also associated with malignant lymphoma, leukemia, or a distant primary carcinoma.

Therapy for Kaposi's sarcoma associated with AIDS is based on cryotherapy and surgical excision.[70] An alternative therapeutic approach is radiation, as these tumors are highly responsive. Additionally, chemotherapy and immunotherapy have been described.[71–73]

VASCULAR LESIONS

The various vascular lesions that can be present on the conjunctiva include capillary hemangiomas in children, cavernous hemangiomas in young adults, and racemose hemangiomas as a part of Wyburn–Mason syndrome. Lymphangiomas that are commonly regarded as orbital lesions may have a more superficial conjunctival component.

LYMPHOID TUMORS

Lymphoma can occur as an isolated conjunctival lesion (Mucosa Associated Lymphoid Tumors—MALToma) or can be a component of systemic lymphoma. The classical clinical appearance is that of a 'salmon patch,' consisting of pink diffuse elevated forniceal mass in the substantia propria or deep to the Tenon' capsule. A biopsy is essential to make a definitive diagnosis and classify the lesion into the cell of origin. Most lesions are B cell lymphoma; however, T cell lymphoma can rarely occur. Histopathologically these lesions consist of sheets of pleomorphic and atypical lymphocytes many times displaying a nuclear cleft. A monotonous uniform lymphoid cell population is suggestive of MALToma (Fig. 76.19). Immunohistochemical staining is useful in identifying the cell type. The commonly used markers include CD20 for B cell lymphoma, CD3 for T cell lymphoma, CD10 for follicular cell lymphoma, and cyclin D1 for mantle cell lymphoma. A thorough clinical workup is essential in all patients to rule out systemic lymphoma. External beam radiation is useful for localized conjunctival involvement; however, adjuvant chemotherapy is necessary in cases of systemic lymphoma. The other treatment modalities that have been used include excisional biopsy, cryotherapy, and local interferon injections.

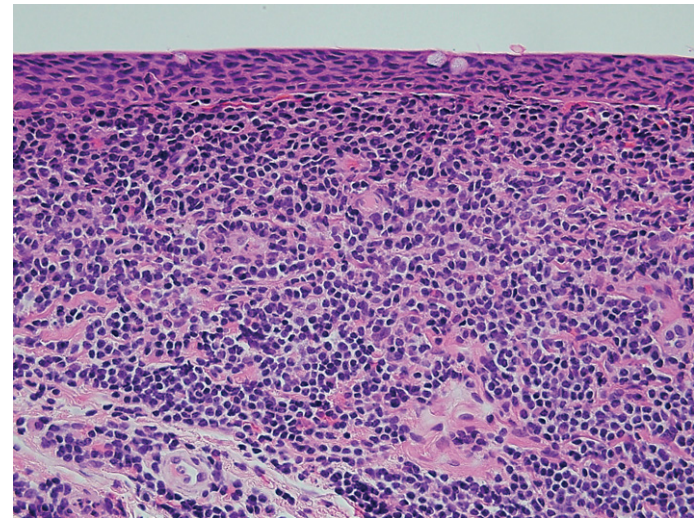


Figure 76.19. Conjunctival tissue with lymphoid infiltration in the substantia propria is seen. The infiltrate consists of monotonous uniform lymphoid cell population consistent with MALToma (Hematoxylin and eosin, ×400).

SOFT TISSUE, HEMATOPOIETIC, NEURAL AND HISTIOCYTIC TUMORS

Although most of these tumors arise in the eyelids and orbit, rarely conjunctival involvement can be seen. The various tumors include fibroma, fibrous histiocytoma, lipoma, myxoma, leukemia, neurofibroma, neurilemoma, xanthoma, juvenile xanthogranuloma, and metastatic tumors.

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77 Temporary keratoprosthesis

Elmer Y. Tu, Joel Sugar

INTRODUCTION

Performing keratoplasty for a visually significant corneal opacity is usually most successful after optimizing the condition of the eye. If visualization is adequate, other medical and surgical interventions are performed prior to keratoplasty to minimize trauma to the new graft and to improve the likelihood of graft survival. In these cases, the amount of time to achieve optical clarity is usually not critical and is indeed often unpredictable, taking days to weeks in many cases. In situations where there is a more urgent need for visualization, as in the case of retinal detachment or other acute surgical disease, a number of surgical options are available. These include combining the procedure with concurrent penetrating keratoplasty, utilizing endoscopic vitrectomy, or placement of a temporary keratoprosthesis (TKP).

Combined surgery with visualization through a new graft presents many challenges.[1] The transplant tissue may not be optically clear secondary to irregular or edematous epithelium, stromal haze, and/or stromal folds. Even with epithelial debridement, the clarity of the graft at the time of the surgery is highly unpredictable. The new graft, sutured to withstand high intraocular pressures often utilized in complex retinal surgery, may present significant peripheral aberrations, restricting the field of view. Finally, extensive intraocular manipulation and irrigation may reduce the viability of the transplanted endothelium. Lamellar procedures may offer more rapid rehabilitation, but, at present, it is unclear whether they will reliably allow contemporaneous retinal surgery.[2,3] Endoscopic vitrectomy circumvents media opacities entirely, but the equipment is expensive, the surgery more technically challenging, and the therapeutic options more limited for the retina surgeon.[4]

TKPs have transformed the performance of combined corneal and retinal surgery. They can provide excellent, wide field visualization of the posterior segment, withstand elevations in intraocular pressure and extensive manipulation, as well as avoid trauma to the new corneal graft. Since their introduction, they have undergone a number of modifications to improve their ease of implantation and increase their utility in posterior segment surgery.

DESIGN

The requirements for a functional TKP are significantly different from those of a permanent keratoprosthesis. There is no need for integration or biocompatibility, but the TKP should leave the host corneal rim structurally intact to accommodate the new cornea. A TKP should allow an excellent view of not only the posterior pole, but clear peripheral retinal visualization as well. The TKP also needs to withstand manipulation and high intraocular pressures characteristic of some retinal procedures while keeping a tight seal at the prosthetic–corneal junction. Secondarily, the prosthesis should be simple and quick to apply, should not interfere with retinal instrumentation and should minimize the number of special lenses and equipment needed.

There is some variation in design of currently available TKPs, but some design elements are shared (Table 77.1). To ensure a tight seal and stability, TKPs either consist of a screw type mechanism to create areas of tight pressure apposition of the host corneal rim to the ridges of the TKP or a wide anterior flange to increase the surface area in contact with the cornea (Fig. 77.1, *A* and *B*). These allow the TKP to remain closely applied when the host cornea is deformed during scleral depression or during periods of high intraocular pressure. Current TKPs are fixed with two to six sutures facilitating rapid placement and do not require scleral fixation. The optical elements have been widened and the cylinders shortened to expand the viewable field and allow use in pseudophakia and, in some cases, phakia. Some prostheses include an integrated infusion port to allow anterior pressurization of the eye and, in selected cases, obviate the need for pars plana infusion. Finally, the curvature and index of refraction approximate those of the normal cornea to allow the use of standard vitrectomy lenses.

INSTRUMENTATION

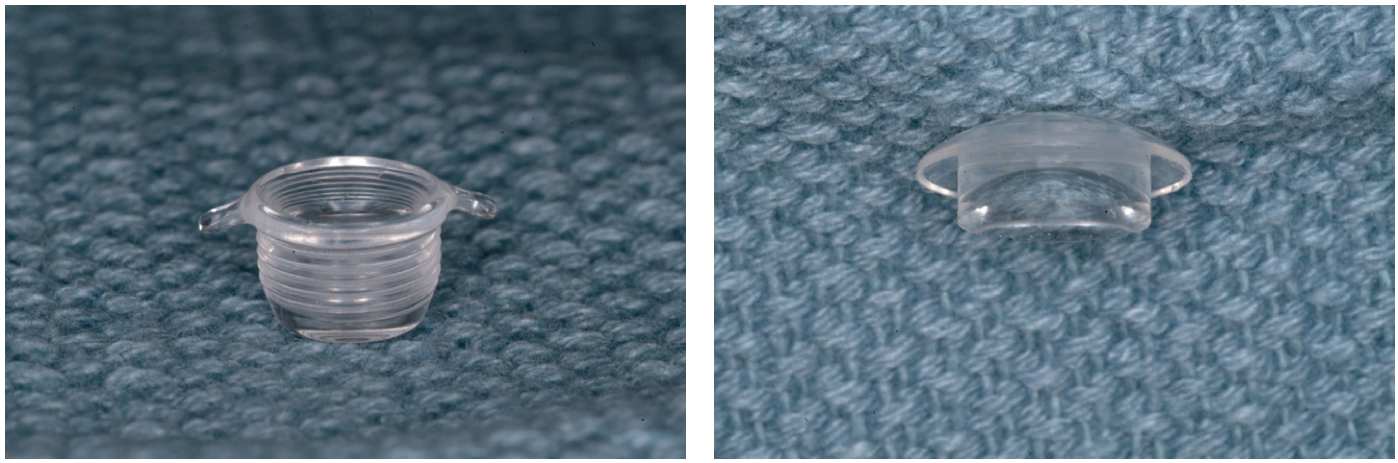
LANDERS-TYPE KERATOPROSTHESES

The introduction of the three Landers-type keratoprostheses in 1981 revolutionized the performance of combined corneal–retinal

Table 77.1 Characteristics of available temporary keratoprostheses

	Landers Type 2	Landers Wide Field	Eckardt	Aachen	Cobo
Material	PMMA	PMMA	Silicone	Silicone rubber	Quartz/stainless steel sides
Cylinder width	5.0 mm	6.2, 7.2, and 8.2 mm	7.0 and 8.0 mm	7.0 mm	6.5–8.5 mm
Cylinder length	6.2 mm	1 mm	1.6–2.8 mm	0.5 mm	5.0 mm
Refractive power	–135.6 D Air –85.4 D Aphakia		–35 D Air		Plano
Anterior curvature	7.8 mm	15.5 mm	7.8 mm	7.9 mm	Plano
Overall diameter	10 mm	14 mm	10 mm	14 mm	9.5 mm

PMMA = polymethylmethacrylate



A B

Figure 77.1. *A*, Landers type 2 temporary keratoprosthesis (TKP), note the 'screw' type scoring of the cylinder creating lines of tight apposition to the host cornea and the two struts for additional suture support. *B*, Eckardt TKP, note the wide flange and short optic to accommodate pseudophakos.

surgery.[1] All three types were re-usable and made entirely of polymethylmethacrylate, consisting of central cylinders with a 5.0-mm wide optic and a 6.2-mm cylinder. Type 1 was a simple threaded optical cylinder with a small anterior flange while type 2 (Fig. 77.1, *A*) is of similar design but with two posteriorly angled, radial struts allowing suture fixation to paracentral cornea. Type 3 was a smooth cylinder with a circular wheel-type flange, which allowed broad suture fixation. With proper fixation, the prostheses remained stable at intraocular pressures of up to 70 mmHg.[1]

A third generation wide-field design (Fig. 77.2) was introduced in 1993 with a central cylinder shortened to 1 mm with an overall diameter of 14 mm, six integrated suture holes, and is available in optical cylinder widths of 6.2, 7.2, and 8.2 mm.[5] The addition of an infusion port in 1996 added the further capability of anterior infusion with or without pars plana infusion.[6]

Operative technique

A Flieringa ring is recommended to support the peripheral corneal rim and provide counterpressure for insertion of the TKP. The ring is also helpful in supporting the vitrectomized eye, which has a tendency to collapse once the TKP is removed, especially when an air–fluid exchange has been performed. The center of the trephination is marked and a 6.0-mm corneal trephination performed. The TKP is then twisted back and forth and advanced into the eye until the anterior flange is in contact with the corneal surface. Two 6-0 silk sutures or 8-0 nylon sutures are placed over the horizontal

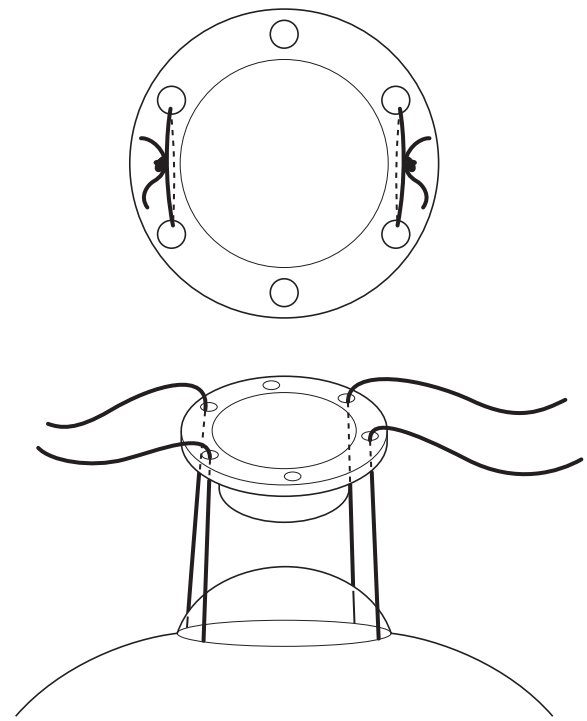


Figure 77.2. Wide field Landers with alternative method of suture fixation. Note the six holes for radial sutures can also be used as entrance and exit suture access with the suture tied over the flange.

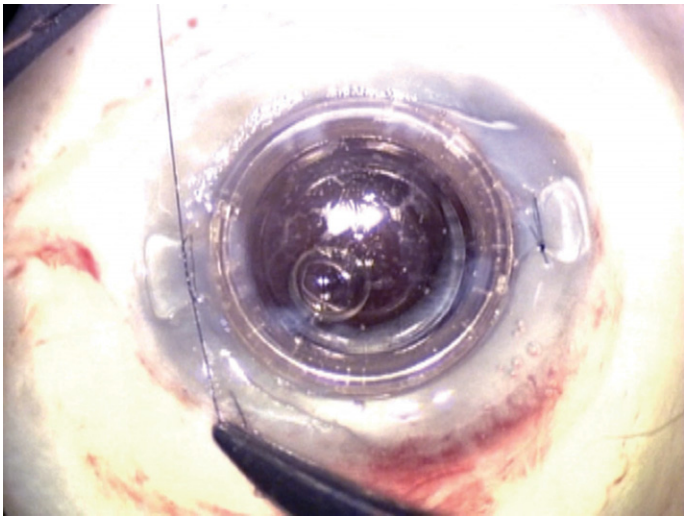


Figure 77.3. Landers type 2 TKP with sutures in place providing additional support to prevent intraoperative extrusion.

struts to secure the type 2 keratoprosthesis (Fig. 77.3). At the end of the case, the donor cornea is punched with a 6.5-mm trephine and the cornea secured with 10-0 nylon.

The Landers wide-field keratoprosthesis is also placed with a Flieringa ring, but utilizes a recipient bed 0.2 mm smaller than the optical cylinder and is secured with six interrupted 5-0 Mersilene sutures passed through the six peripheral suture holes in the anterior flange through limbal tissue.[6] The sides of the cylinder are smooth and short, making insertion less difficult. Alternatively, two 6-0 silk sutures may be passed, one from 2 to 4 o'clock and the other 8 to 10 o'clock.[7] The two ends of the suture are then passed through the corresponding suture holes loosely. The keratoprosthesis is pushed aside and the 7.0-mm trephination performed. The four suture ends are then pulled taut and tied over the anterior flange tightly, securing the TKP (Fig. 77.2). At the end of the case, the donor cornea is punched with a 7.5-mm trephine (0.3 mm larger than the optical cylinder) and secured with 10-0 nylon.

ECKARDT KERATOPROSTHESIS

The Eckardt keratoprosthesis (Fig.77. 1, *B*) was introduced in 1987 and is made entirely of silicone with a 7.0-mm wide and 2.8-mm long central cylinder.[8] An 8.0-mm diameter cylinder is also available. It has a wide silicone flange, which conforms to the anterior corneal surface, maintaining a tight seal even with deformation of the corneoscleral rim. The wide optic and short cylinder allows excellent peripheral visualization as well as compatibility with pseudophakos. Since securing sutures are placed through the silicone material there is considerable flexibility in suture placement, especially in traumatized eyes to avoid areas of unstable cornea. The TKP can be reused until repeated suture holes reduce its ability to create a watertight seal.

Operative technique

A Flieringa ring is recommended to support the corneoscleral rim since insertion requires significant support.[8] The collapse of the globe on removal of the TKP can be avoided by filling the eye with perfluoro-octane.[9] The original recommended corneal bed trephination was 6.5 mm, but a 6.7-mm trephination has been found to allow easier insertion and a continued watertight closure. One edge of the cylinder is placed against the corneal rim and the keratoprosthesis pushed down into the opening, creating a seal. If the pars plana infusion is pre-placed and open, the occlusion of the trephination should cause the pressure in the globe to rise, expanding the corneal rim opening enough to 'pop' the keratoprosthesis into position. While pressing down in the center of the Eckardt to prevent extrusion, four or six 8-0 or 9-0 nylon sutures are evenly spaced circumferentially and passed from the limbus centrifugally, continuing intrastromally and exiting at the junction between the flange and central cylinder (Fig. 77.4, *A* and *B*). If the infusion cannot be pre-placed or opened because of poor visualization, placement of the first suture and lifting, and stretching at the limbus 180° away should allow the implant to be pushed into position. Inclusion of some of the optical cylinder in the suture does not reduce the surgeon's view or stability of the TKP (Fig. 77.5). Because the opening is stretched to the size of the optical cylinder for an extended period of time, the corneal donor is later punched with a 7.25-mm trephine to fit properly and secured using 10-0 nylon. A method has been described to allow larger donor grafts by partial thickness trephination of the larger graft prior to the smaller central trephination.[10] Performing the central trephination after the destabilizing outer trephination may be made easier by pressurizing the eye (Fig. 77.4, *C*). The secondary rim is then removed with scissors after removal of TKP resulting in a larger pre-cut recipient bed.

AACHEN KERATOPROSTHESIS

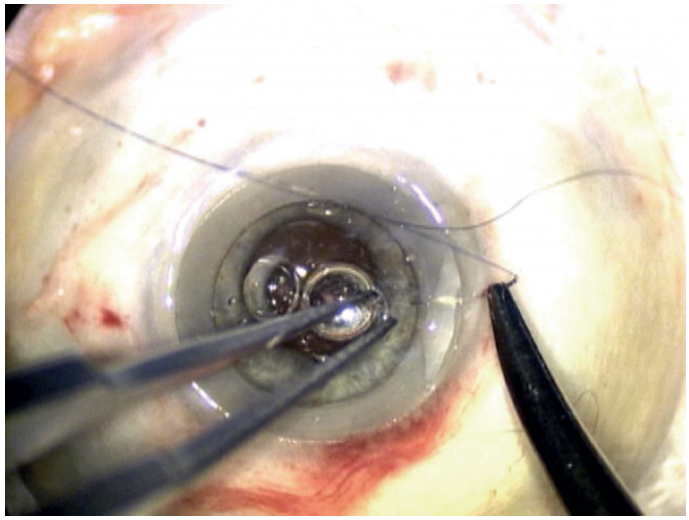
The Aachen keratoprosthesis is made of soft silicone rubber with a 7.0-mm wide and 0.5-mm long central optic.[11] It is designed as a permanent keratoprosthesis, but may be used as a TKP.[12] The design features a wide anterior flange, which overrides the sclera and provides optics similar to the Eckardt and wide-field Landers keratoprostheses. The material withstands suturing well and is well-tolerated. Its short optical cylinder lends itself to use in pseudophakic and possibly phakic eyes.[12]

Operative technique

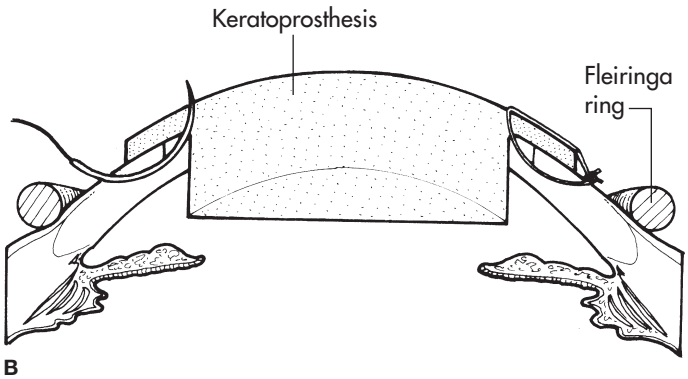
It is recommended that a pars plana infusion port be pre-placed prior to dissection. Its 7.0-mm optic is designed to fit into a 6.8-mm corneal trephination. The optical cylinder is placed and with downward pressure screwed into place. Like the Eckardt keratoprosthesis, the TKP is not self-retaining and downward pressure needs to be maintained to prevent extrusion prior to suturing. Reducing the infusion flow may aid in keeping the TKP in place during fixation. The haptic is then sutured to host sclera with 4 7-0 nylon sutures with subsequent fixation of the circumferential ring to the more peripheral sclera. A 7.0-mm donor graft is recommended.

COBO KERATOPROSTHESIS

The Cobo keratoprosthesis (Fig. 77.6) is made of quartz and constitutes an inverted, truncated cone when in proper orientation. It is 6.5 mm at its internal base, expanding to 8.5 mm at the top. It has an integrated 40-mm infusion handle for injection of fluid or air to tamponade choroidal hemorrhage (Fig. 77.7). It is meant primarily for emergency use during open-sky procedures when expulsion of intraocular contents is imminent and because of its design can quickly fit various trephination sizes without custom sizing. It may also be used to restore intraocular pressure if delay in securing the graft is anticipated. The plano curvature allows a clear view of the anterior segment while in place.



A



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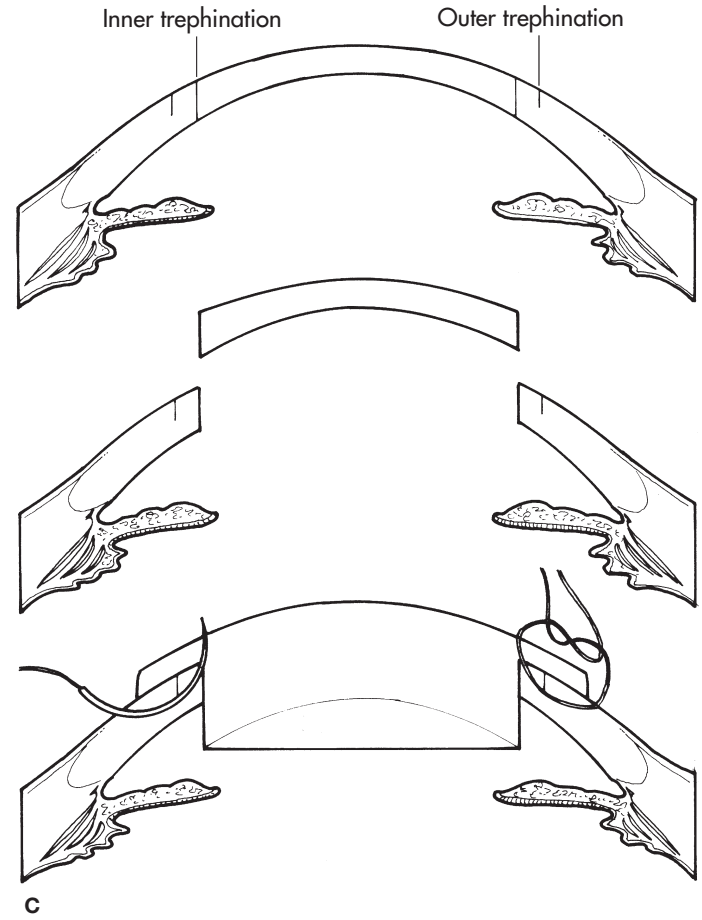

C

Figure 77.4. *A*, Eckardt temporary keratoprosthesis (TKP). Sutures are passed from the limbus deep, angling upwards targeting the optic–flange junction. *B*, Centripetal deep sutures secure the Eckardt TKP. *C*, A partial thickness outer trephination can be placed prior to the full thickness central trephination to accommodate a larger diameter corneal transplantation after removal of the Eckardt TKP.

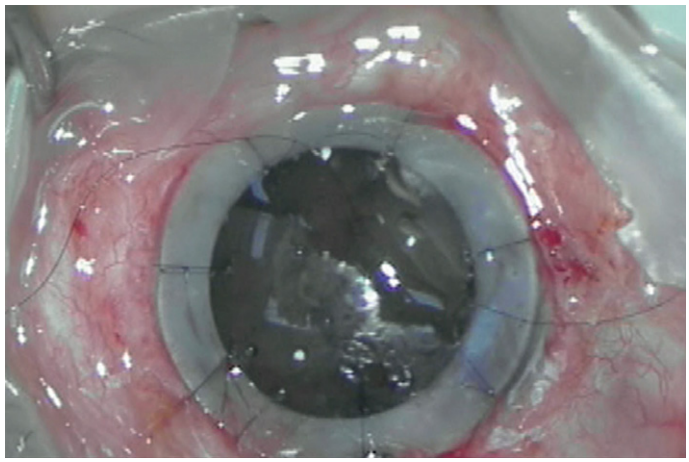

Figure 77.5. Eckardt temporary keratoprosthesis (TKP) in place with six sutures securing its position.

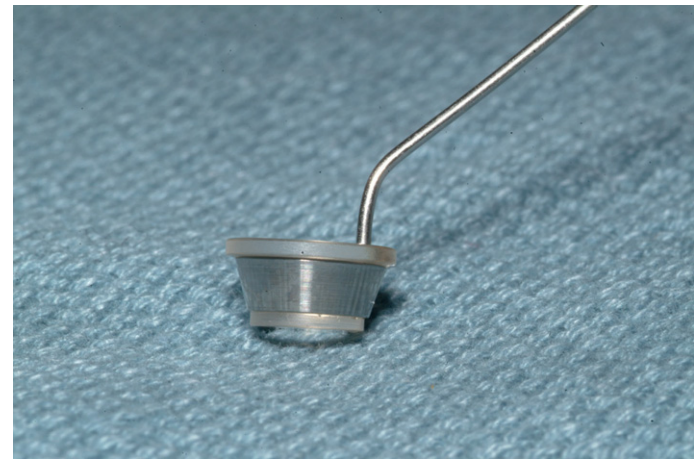

Figure 77.6. Side view of the Cobo temporary keratoprosthesis (TKP). Note the truncated cone profile allowing it to tamponade corneal openings from 6.5 to 8.0 mm.

Operative technique

In order to be effective, the Cobo keratoprosthesis should be assembled with flexible tubing and primed with balanced salt solution prior to every case and available for immediate use, especially for high-risk cases. Once the need for the keratoprosthesis is recognized, the inverted cone is placed into the wound deep enough to achieve occlusion. The instrument will fit trephinations from 6.5 to 8.0 mm obviating the need for sizing preoperatively. Once in place, an infusion of balanced salt solution or gas is started to raise the intraocular pressure and tamponade the hemorrhage. This may be held in place, or sutured with two horizontal overlay mattress sutures 90° apart. The suture can be tucked into a superficial circumferential groove at the top of the keratoprosthesis for more stability. After control of intraocular structures is achieved, the preplanned corneal donor button can then be sutured in place.

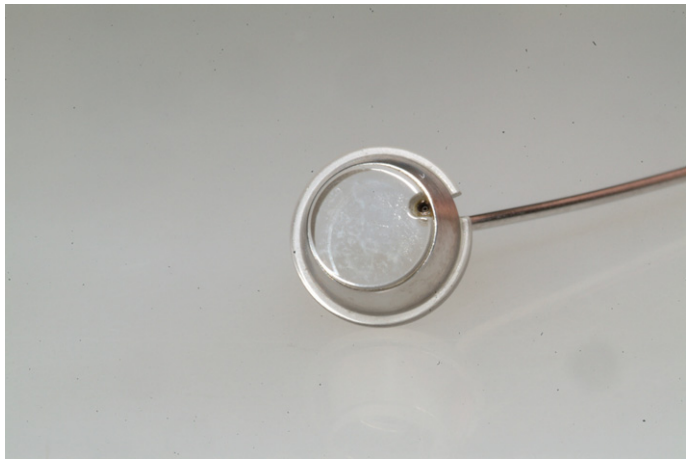

Figure 77.7. Cobo temporary keratoprosthesis (TKP), bottom view. Note opening for infusion suitable for air or fluid to raise intraocular pressure.

USES

Cases suffering from both anterior and posterior segment disease, especially of an acute nature, tend to have more severe disease and a poorer prognosis. The indications are predominantly trauma, but may also consist of nontraumatic conditions including silicone keratopathy, bullous keratopathy, blood staining, endophthalmitis, cataract and retinal surgical complications, and uveitis.[12–15] While the use is primarily to allow visualization during pars plana vitrectomy, the Eckardt keratoprosthesis has also been reported as an aid to allow small incision cataract surgery during combined penetrating keratoplasty (PKP) and cataract extraction surgery[16,17]. The Aachen keratoprosthesis has been reported to be used as a 'bridge' prosthesis, sutured in place for 8 weeks before definitive PKP.[18] We have used the Eckardt in the same manner for several days prior to eventual PKP without complication or extrusion. The Cobo keratoprosthesis is unique in that it is designed to be an emergency instrument for use during routine PKP to prevent anterior migration of intraocular contents through an open-sky approach. Because of its versatility of sizing and integrated infusion port, we have utilized it during vitrectomy cases to clear dense anterior vitreous membranes when the pars plana infusion port was not visible. Vitrectomy lenses can be utilized over the surface of the Cobo keratoprosthesis.

OUTCOMES

As stated previously, the cases requiring combined surgery involve acute 'multisystem' diseases, carry a very poor prognosis and can represent an extraordinary intervention to salvage the eye. A number of studies have examined the outcomes of combined TKP/pars plana vitrectomy. Most studies show an early postoperative increase in visual acuity in a little less than 50% of cases, but this number decreases to 16–21% on longer term follow-up.[15,19] The vast majority of cases with measurable vision cite visual acuities of count fingers or worse. Still 50–70% of patients had either improved or stable vision on last exams.[13,15] Graft survival is difficult to assess in these patients in comparison to normal grafts because of the severe co-morbidities in these patients. A very high rate of phthisis bulbi and hypotony (37–52%) is noted and is the most common cause of graft failure. Gallemore et al[10] reported that 70% of their grafts remained clear, but it should be noted that their series included a lower percentage of trauma patients and a lower preoperative retinal detachment rate, two risk factors for graft, and surgical failure. Other studies had graft clarity rates of 42% at 3 months and another of 65% at 1 year.[14,15] Silicone oil was also a significant risk for graft failure.[13] As expected, smaller grafts utilized in cases of TKP led to more irregularity, steeper corneas, and higher astigmatism postoperatively[10]. The above-described modification to allow larger grafts reduces these complications.

SUMMARY

The instrumentation is simple, and TKPs provide an excellent view of the posterior segment for pars plana vitrectomy. In these severely diseased eyes, graft clarity rates are acceptable and allow earlier surgical intervention. Despite the often poor visual and anatomic outcomes in cases necessitating combined TKP/pars plana vitrectomy, this technique allows surgical intervention in eyes otherwise destined for phthisis.

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78 Permanent keratoprostheses

Kaevalin Lekhanont, Vasudha Panday, Esen Karamursel Akpek

Diseases of the cornea are a major global cause of blindness, ranking second only to cataract, with an estimated 10–15 million affected people worldwide. Corneal transplantation, whether penetrating or lamellar, has become the main visual rehabilitation surgery for such disorders. Penetrating keratoplasty is the most frequently performed and most successful solid tissue transplantation, with a success rate greater than 90% for low-risk cases, such as patients with keratoconus, traumatic corneal scars, and corneal dystrophies and degenerations.[1] However, the success rate of penetrating keratoplasty is exceedingly low for patients with ocular surface disorders such as Stevens–Johnson syndrome (SJS), ocular cicatricial pemphigoid (OCP), chemical burns, severe keratoconjunctivitis sicca, stem cell deficiencies, and severe vascularization resulting from other causes.[2] Pediatric keratoplasty is also a high-risk procedure with very limited success. In addition, there is another, larger group of patients who have repeated graft failures, for whom a subsequent graft carries a poor prognosis.[2]

Keratoprosthesis surgery, the transplantation of an artificial cornea, is a potential alternative for restoring vision in these patients with complicated corneal blindness. Some indications for keratoprostheses and limbal stem cell transplantation overlap. In these cases, one has to consider the advantages and disadvantages of both techniques. Limbal stem cell transplantation seems to be less destructive to the anterior segment, and in successful cases the patients may have a larger visual field. However, the lifelong need for systemic immunosuppression and the high risk of rejection in the short term are distinct disadvantages.

There are two types of keratoprostheses: temporary and permanent. A temporary keratoprosthesis is used to help visualize the posterior segment of patients with corneal diseases intraoperatively and is removed after surgery (see preceding chapter). A permanent keratoprosthesis is a device implanted in the eye, similar to the human donor cornea used in penetrating keratoplasty. In this chapter, the term keratoprosthesis is used to mean a permanent keratoprosthesis, unless otherwise indicated.

Keratoprostheses have been in use for more than two centuries, but substantial improvements in device designs, techniques, and clinical management have been achieved only over the past few decades, with variable, but growing, success. The history of keratoprosthesis development dates back to Guillaume Pellier de Quengsy, a French ophthalmologist who in 1789 suggested replacing an opaque cornea with a silver-rimmed glass window.[3] In 1853, Nussbaum placed a quartz crystal implant in a rabbit eye, and later performed the first such surgical procedure in a human.[4,5] Initial attempts to develop other types of keratoprostheses were continued by many pioneers over the following 50 years, but all failed.[6] In the early 20th century, interest in keratoprostheses abated with the introduction and increasing success of penetrating keratoplasty, until it became apparent that penetrating keratoplasty was not the answer for all cases. As new, inert plastic materials such as polymethylmethacrylate (PMMA) were introduced, keratoprosthesis research again drew attention, particularly in the early 1950s. Unfortunately, despite promising results in the early postoperative period, the procedures were catastrophic failures due to extrusions of the keratoprosthesis, endophthalmitis, or other adverse outcomes. In the 1990s, several new-generation keratoprostheses made of biomaterials were introduced, with the assumption that porous materials would improve biointegration by host tissue, preventing extrusion. Comparisons between the various devices and techniques can be difficult because of differences across studies in sample size, type of patients recruited, data profiles, and duration of follow-up.

Keratoprosthesis designs can be categorized into three main groups. The first type uses a transparent, rigid central optic attached to a peripheral skirt/haptic. It is usually implanted and secured to the corneal stroma, and occasionally is covered with autologous mucous membrane and/or eyelid skin. The haptic can be made of several kinds of materials that supposedly allow for biological incorporation by host tissue; these include: Dacron, Proplast, polytetrafluoroethylene (PTFE), polyurethane, other copolymers, and dental bone. The optic portion is made of medical-grade PMMA. The osteo-odontokeratoprosthesis (OOKP) is an example of this design.

The second type of keratoprosthesis consists of a flexible-plate optic with a porous peripheral skirt that supports tissue ingrowth and stability of the device. This type is designed to be implanted in an intra-stromal pocket. AlphaCor is a classic model of this version. BIOKOP II is another example.

The third type is a 'collar button' shaped device, consisting of two plates made of PMMA and joined by a central stem. This device is implanted with the plates sandwiching the corneal donor ring between them, then sutured in place in the same way as standard penetrating keratoplasty. A representative of this group is the Boston keratoprosthesis. Only the Boston and AlphaCor devices have been approved by the US Food and Drug Administration (FDA) and are available for clinical use.

BOSTON KERATOPROSTHESIS

The Boston KPro has been under development since the 1960s. The FDA approved it in 1992. Unlike most other designs, it is a nonintegrated keratoprosthesis. The Boston KPro is made entirely of medical-grade PMMA and comes in two main types. Type I, the single 'collar button' design, is the most commonly used in the USA. It consists of two plastic parts: an anterior plate, 5.0–7.0 mm in diameter, attached to a 3.35-mm diameter central stem with screw threads, and a removable back plate, 7.0–8.5 mm in diameter, with eight holes of 1.3-mm diameter (Fig. 78.1). A new threadless design has 16 holes, 1.2 mm each. The device requires donor corneal tissue to be sandwiched between the two plates, and the entire device is then sutured into the eye (Fig. 78.2). The holes in the back plate are postulated to enhance nutrition and hydration of the clamped corneal stroma adjacent to the stem and to help prevent necrosis of the surrounding tissue and extrusion of the device. The interplate distance is 0.50–0.60 mm. The titanium locking ring is a recent addition, used to secure the unit after assembly and to prevent unscrewing of the back plate in situ.[7] Type 1 Boston KPro allows a maximal 60° field of vision. This type of device is suitable for eyes with sufficient tear secretion and normal blinking.

The type II device is similar to type I, except for an additional 2-mm long anterior nub for through-the-lid implantation. The front plate is usually 6 mm in diameter and the back plate is 8.5 mm. The back plate also has eight holes of 1.5-mm diameter. Use of the Boston KPro II is reserved for extreme dry eye conditions and end-stage ocular surface diseases such as OCP and SJS, in which there is a lack of fornices to support a good tear film. The type II device allows a maximal visual field of 40°. Both types of Boston KPro have a range of dioptric powers to match the axial length of the patient's eye and are suitable for pseudophakia or aphakia.

The Boston KPro is generally considered suitable for patients with bilateral corneal blindness who have potentially usable vision but little or no chance of success with standard penetrating keratoplasty, such as patients with end-stage SJS or OCP, or after severe chemical burns or repeated graft failure with poor prognosis for further grafting. Generally, visual acuity in the affected eye should be less than 20/400 and the fellow eye should have suboptimal vision.[8] Patients must have no end-stage glaucoma or retinal detachment.

In cases of corneal blindness with clear remaining ocular media and functioning retina and optic nerve, keratoprosthesis surgery can give immediate, excellent, vision. However, the prognosis for long-term success with Boston KPro surgery varies with preoperative diagnosis and with the degree of ocular surface inflammation.[7,8] Clearly, the most favorable group for receiving the Boston KPro is patients with multiple graft failures in noninflammatory conditions such as bullous keratopathy, trauma, and other corneal dystrophies. Patients with graft failures after infectious keratitis (viral, bacterial, or fungal) are also likely to have a good prognosis. The prognosis for patients with a previous history of recurrent herpes simplex (HSV) is especially favorable, with no increased rate of melting or extrusion.[7] On the other hand, patients with an underlying autoimmune or inflammatory ocular surface disease, such as OCP and SJS, have the worst prognosis.[7,8] Patients who have sustained chemical burns have an intermediate, fair prognosis. The differences in prognosis seem to correlate with the degree and chronicity of preoperative inflammation. In patients with SJS, the smoldering inflammation around the implanted keratoprosthesis makes the tissue vulnerable to de-epithelialization and hence necrosis, melting, leakage, and secondary infection. The clinical findings that suggest a smoldering active immunologic process in these cases are consistent with the results of histopathologic studies, which show marked acute and chronic inflammatory reactions in the area of the keratoprosthesis–cornea junction and at the periphery of the originally healthy corneal graft.[9] Additionally, patients with SJS are often younger and thus a conservative approach is recommended for this group.

An ongoing multicenter Boston keratoprosthesis study[10] is gathering data on Boston KPro I implant procedures since January 2003. The preliminary results from 101 eyes (106 procedures) at 16 centers show a retention rate of 95.3%. There has recently been a report of Boston KPro surgery in carefully selected children with complex

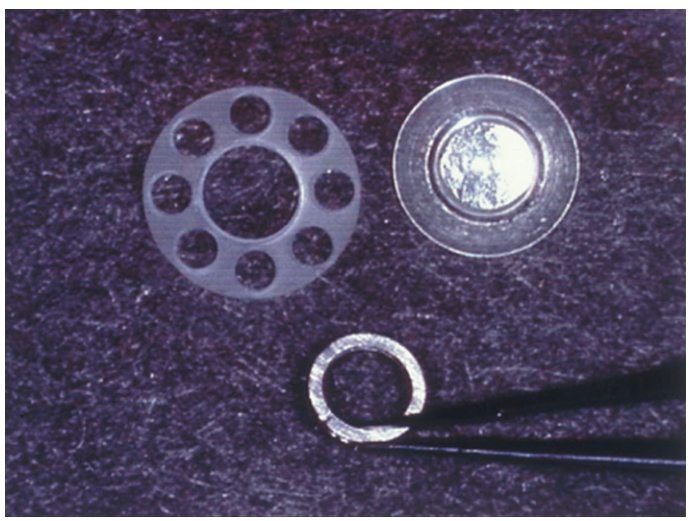

Figure 78.1. Type I Boston keratoprosthesis, consisting of a front and back plate made of PMMA and a titanium locking ring on top of the back plate to prevent unscrewing in situ.

Figure 78.2. The fully assembled graft-device combination for the type I Boston keratoprosthesis, ready to be transplanted.

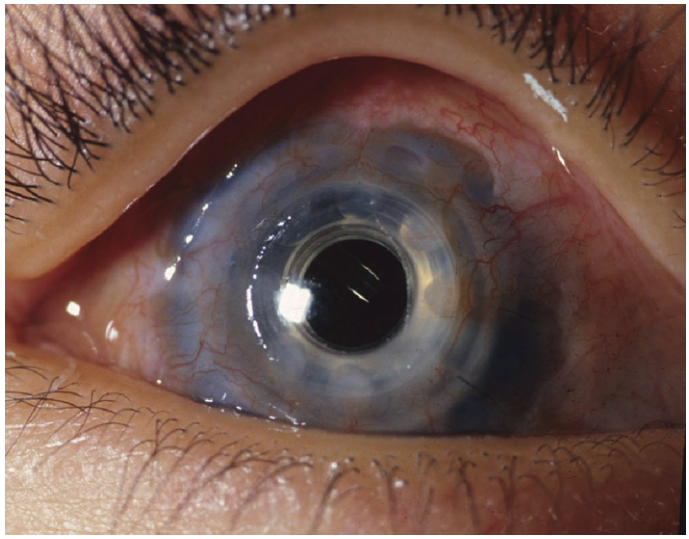

Figure 78.3. Type I Boston keratoprosthesis in situ in a 22-month-old girl with a history of Peters anomaly, 6 months after surgery with no complications.

ocular diseases who are at high risk for graft failure, with promising results[11] (Fig. 78.3). The excellent optical properties of PMMA and the lack of induced postsurgical astigmatism may accelerate visual recovery, reducing the risk of amblyopia. The Boston KPro may thus have a future role in the management of pediatric corneal blindness. Nevertheless, one should recognize that a failure of keratoprosthesis surgery can be associated with much more serious complications than repeated graft failures.

Although uncommon in properly selected cases, necrosis of tissue around the keratoprosthesis, with subsequent melting, can lead to aqueous leakage, infection, or extrusion of the device. The continuous use of a large-diameter soft contact lens with high water content in the postoperative period has significant protective value.[12] Postoperative use of medroxyprogesterone 1% suspension is also helpful in preventing/treating melting.

Patients requiring keratoprosthesis have usually had multiple previous eye surgeries, episodes of inflammation, or autoimmune diseases such as OCP, SJS, or rheumatoid arthritis. Therefore, postkeratoprosthesis inflammation can be a significant issue in these patients. Chronic or profound postoperative inflammation can cause retro-prosthetic membrane, glaucoma, epiretinal membrane, and vitreous opacities.

Approximately 30% of eyes receiving a keratoprosthesis eventually develop retro-prosthetic membranes.[13] Postoperative uveitis, vitreous hemorrhage, multiple ocular procedures, vitrectomy, and diabetes mellitus are known risk factors. Some investigators suggest using steroid injections at the first sign of membrane formation.[6] Most retro-prosthetic membranes are amenable to Nd:YAG laser treatment, but energy higher than 2.0 mJ should be avoided because the device can crack or become pockmarked. If the membrane is thick or vascularized, it is more safely managed by surgical excision.[13] In refractory cases, repeat keratoprosthesis surgery might be preferable.

In the past, the rate of endophthalmitis following keratoprosthesis surgery was higher than for other intraocular procedures. However, bacterial endophthalmitis has now been almost eliminated by a postoperative prophylactic antibiotics regimen. It is crucial to emphasize to patients the critical role of lifelong prophylactic use of topical antibiotics. Most cases of bacterial endophthalmitis are caused by gram-positive organisms, and patients with SJS or OCP are at the highest risk.[14] The current postoperative antibiotic regimen typically includes fourth-generation fluoroquinolone and vancomycin (14 mg/mL) eye drops. To date, no vancomycin resistance has emerged.[15]

Sterile endophthalmitis, or a peculiar phenomenon of sudden reversible, massive vitritis with reduced vision, is seen in a small percentage of patients.[16] The clinical pictures of sterile and infectious endophthalmitis can be varying and perplexing, but, in general, the sterile type has a more insidious onset, with hardly any external signs of inflammation such as conjunctival injection and without ocular pain. This condition is thought to result from some sort of immune reaction.

Nevertheless, in all patients suspected of having endophthalmitis, vitreous tapping as well as intravitreal and intravenous antibiotics should be vigilantly administered. The initial intravitreal antibiotics of choice are 1.0 mg vancomycin and 0.4 mg amikacin, though these doses are tailored once the culture results become available.[15] The most common organisms are endogenous flora, including *Streptococcus* species, *Staphylococcus* species, *Propionibacterium* acnes, *Candida* species, *Cryptococcus* species, and *Moraxella* species.[13] Vitrectomy may eventually be necessary.

With the dramatic decrease in incidence of postoperative endophthalmitis, glaucoma is now the primary vision-threatening complication following Boston KPro surgery. In addition to postoperative worsening of pre-existing glaucoma, new glaucoma can develop after surgery, particularly in patients with chemical burns or autoimmune diseases. Current reports show that glaucoma is present in about two-thirds of patients receiving Boston KPro.[17] Gradual closure of the anterior chamber angle is the most likely mechanism.[6] The problem is more difficult to detect and manage in patients with Boston KPro because of the inability to measure intraocular pressure (IOP) directly. Standard tonometry can give erroneous readings, and digital palpation seems to yield the most reliable measurement. Visual fields and serial optic nerve pictures should be obtained during follow-up of these patients. Although topical and systemic glaucoma medications are usually effective, most patients will require a glaucoma tube shunt surgery or a cilioablative procedure at the same time as or soon after the KPro surgery.

Boston KPro has several advantages, including the simplicity of the surgical technique, minimal postoperative discomfort, immediate visual recovery, the ability to view the posterior pole from the first postoperative day, the short time frame to achieve maximal visual rehabilitation, and good cosmetic appearance. However, the long-term prognosis for patients with underlying inflammatory ocular surface diseases needs to be improved.

ALPHACOR KERATOPROSTHESIS

AlphaCor, originally known as the Chirila Kpro, was developed in an attempt to create an alternative to human donor cornea for high-risk cases of corneal blindness that are unlikely to be successfully treated with a donor corneal graft. In other words, the device provides another option for treatment that lies somewhere between a low-risk graft and traditional keratoprostheses such as the OOKP that is indicated for bilaterally blind patients with end-stage dry eyes.[18] The AlphaCor keratoprosthesis has recently been approved by the FDA and is now commercially available in the USA.

AlphaCor artificial cornea is a hydrophilic, soft, flexible, biocompatible one-piece device made entirely of poly (2-hydroxyethylmethacrylate) (PHEMA) (Fig. 78.4). PHEMA was selected for this

Figure 78.4. The one-piece, flexible AlphaCor device, consisting of a transparent optic and a biointegrating skirt made of PHEMA.

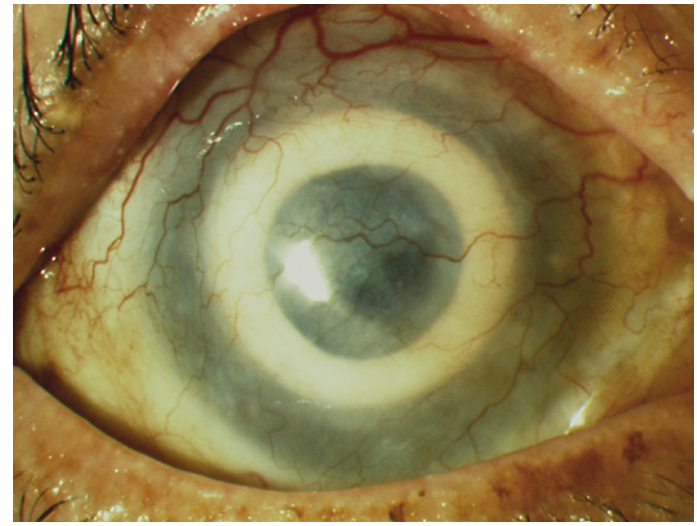

Figure 78.5. AlphaCor keratoprosthesis implantation, after stage 1. The device is covered by the conjunctival flap.

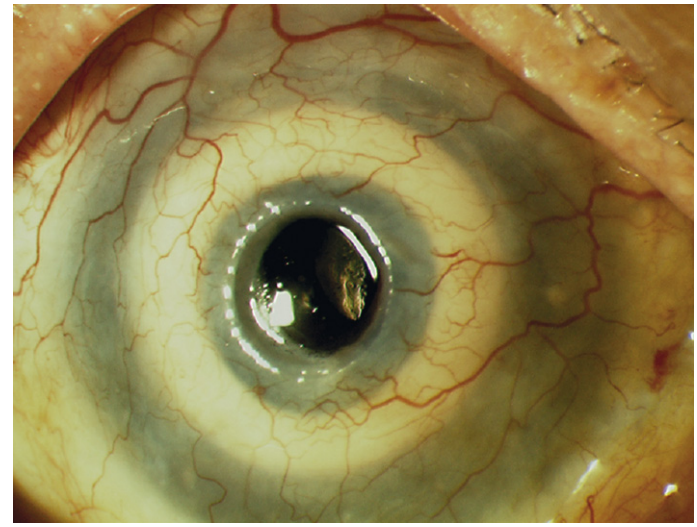

Figure 78.6. AlphaCor keratoprosthesis after stage 2 of implantation.

device because of its hydrophilic properties, flexibility, and ability to take on different physical characteristics with changes in its water content. The device consists of a central optic region surrounded by a peripheral skirt that is chemically identical except for its water content.[19] The outer skirt is macroporous, has a high water content, and promotes bio-integration via cellular ingrowth and collagen deposition.[20] The transparent optic has a relatively low water content, is microporous, and provides the refractive power and the optical clarity. These two concentric regions are joined by a zone known as the interpenetrating polymer network (IPN), a permanent junction that prevents dehiscence, leakage, or downgrowth at the interface. The AlphaCor device has a radius of 7.0 mm and a thickness of 0.5 mm. The refractive index of hydrated PHEMA gel is 1.43. There are two versions of the device designed to deliver the appropriate power in the human eye. AlphaCor-P has a lower power (approximately +42 D) for either phakic or pseudophakic eyes, and AlphaCor-A has a refractive power of about +58 D, suitable for aphakic eyes.[18]

AlphaCor is implanted in a two-stage surgical procedure.[21] Briefly, stage 1 begins with a 360° conjunctival peritomy and corneal epithelial debridement. A superior half-thickness incision extending about 180° is made at the sclera, 1–1.5 mm posterior to the limbus, and extended into the cornea at 50% depth with a lamellar dissecting blade. The dissection continues to form an intralamellar pocket about 7.5 mm in diameter. The superior flap is retracted inferiorly, allowing the posterior lamella to be visualized. A central opening is then created with a 3-mm disposable trephine in the posterior corneal lamella. The AlphaCor device is positioned within the pocket, carefully centering the optic over the posterior opening. The superior flap is replaced and sutured at the limbus with interrupted 10-0 nylon sutures. A Gunderson flap is pulled to cover the entire corneal surface (Fig. 78.5). The conjunctival flap is not always needed but is recommended with this device.[21] After 8–12 weeks, stage 2 of the procedure is performed to expose the optic by removing the conjunctiva and anterior corneal lamella, using a 3-mm disposable trephine and scissors. Topical anesthesia is usually applied (Fig. 78.6).

Multicenter clinical trials of this device have been in progress for more than 5 years, with promising outcomes.[18] The probability of AlphaCor retention at the end of 1 year is 82%, and postoperative best-corrected visual acuity ranges from light perception to 20/30. No cases of serious complications such as endophthalmitis or device-related rhegmatogenous retinal detachment have been reported. Cosmetic outcomes are acceptable. In contrast to the Boston KPro, AlphaCor does not seem to lead to glaucoma in a significant proportion of patients.

Anatomical failure is related to loss of corneal stromal tissue adjacent to the device skirt. Stromal melting is the most common complication, observed in 41.5% of cases and strongly associated with a history of ocular HSV infection.[21] A history of ocular HSV is therefore considered a contraindication for AlphaCor implantation. There is an association, although not statistically significant, between concurrent or subsequent cataract surgery in patients with an AlphaCor implant and melting-related complications.[19,22] Likewise, a possible association between a history of chemical injury and postoperative melting has been recorded.[23] It is thought that reactivation of HSV or retained lens material after cataract surgery may stimulate chronic inflammation, which can upregulate inflammatory cytokines, reduce bio-integration, and facilitate melting of corneal stroma anterior to the device.

Medroxyprogesterone is a progestational steroid with mild anti-inflammatory effects and has anticollagenase activity with less inhibition of collagen production than corticosteroids. Earlier

reports suggest a potential utility for medroxyprogesterone as eyedrops following AlphaCor implantation to prevent the onset or suppress the severity of stromal melting, particularly in high-risk cases.[24] When melting occurs, initial management is first aimed at improving the quantity and quality of the tear film with artificial tear supplements, punctal occlusion, bandage contact lens, or lateral tarsorrhaphy. In non-responsive cases, reconstructive surgery may be needed. Removal of the device and donor cornea replacement is reserved for refractory cases to maintain ocular integrity and prevent any serious complications.

Optic problems occur in about 11% of cases, and are related to surface spoliation or deposition of substances in the hydrogel, reducing its transparency.[25] Diffuse white deposition, confirmed by histological study to be calcium phosphate, is associated with prior co-administration of topical steroids and beta-blockers. A brown discoloration is associated with patient-related or environmental conditions, particularly cigarette smoking and some ophthalmic prescription medications (e.g. levobunolol). Optic complications have not been observed in PMMA devices.

Retro-prosthetic membranes occur in about 9% of patients during the first year after surgery.[26] Systemic risk factors are higher in African Americans and in patients with hypertension or diabetes. Perioperative manipulation is likely to contribute to the incidence of retro-prosthetic membranes. To minimize this complication, peri- and postoperative preventive measures such as subconjunctival steroid injections and topical steroids may be used, particularly for patients at high risk. If an early retro-prosthetic membrane forms, management by Nd:YAG laser has proved successful. However, thick and vascularized membranes are difficult to remove by laser. Recurrences are common.[17] Surgical treatments via a limbal approach, vitreoretinal techniques, or removal of the device and donor graft replacement may be required. Adjunctive heparin or recombinant tissue plasminogen activator (rTPA) may be beneficial in some cases.

In summary, despite the challenges of maintaining clarity and retention, clinical experience with AlphaCor is encouraging. The AlphaCor device should not be used in eyes with severe ocular surface disease, significant dry eye, or active/smoldering inflammation.[18,19] It is important to control IOP before surgery. Any topical therapy after implantation should be carefully considered to prevent optical spoliation. Results from longer-term studies are needed to allow comparisons between this device and the Boston KPro.

OSTEO-ODONTOKERATOPROSTHESIS (OOKP)

The OOKP was first described by Strampelli in the early 1960s[27] and was modified over the years by Falcinelli and co-workers.[28] It was originally designed to improve the biointegration of the device with host corneal tissue by encircling the optical cylinder with an autologous tissue such as tooth, bone, or cartilage. The OOKP has a reputation for the best long-term retention and low rate of infection.

The OOKP has an optical cylinder made of PMMA glued to a biological haptic made of the autologous osteodental lamina. It was the first keratoprosthesis to use biological material as a supporting carrier or haptic. The haptic is prepared from the root of a tooth with its surrounding alveolar bone, ligament, and periosteum.[28] All cases of bilateral corneal blindness resulting from severe ocular surface diseases such as severe dry eye, limbal stem cell insufficiency, or densely vascularized corneas—for which there is virtually no reasonable expectation of medium or long-term success with other well-established methods such as penetrating keratoplasty, lamellar grafts, or limbal stem cell transplantation—are good candidates for the OOKP.[6]

The surgical procedure is complex and consists of two steps separated by a period of 2–4 months; it requires cross-specialty expertise.[29,30] Step 1 includes preparation of the anterior bulbar surface and the osteodental acrylic (ODA) complex. After a 360° conjunctival peritomy, a lamellar keratectomy is performed to remove any degenerative pannus or scar tissues. The anterior bulbar surface, including the cornea and sclera up to the muscle insertions, is covered by a buccal mucosal membrane graft to create a new ocular surface. The buccal mucosa is harvested from the patient's cheek at the time of surgery and trimmed to approximately 2 mm in thickness, large enough to avoid any retraction once in place. If the mucous membrane is inadequate, the patient's lid skin, after removal of the tarsal plate, can be used in a 'transpalpebral approach.' A scleral shield is applied in some cases to avoid shrinkage of the fornices for a few weeks after step 1 surgery.

The patient's own monoradicular tooth is harvested to prepare an osteodental lamina. When the available osteodental lamina has too small a surface to fit an optical cylinder (due to dental or periodontal diseases), two teeth are extracted to prepare two laminae, which are then glued together to create a single lamina with a larger surface. Generally, the superior canine is the most suitable tooth because it has the longest and largest root with the greatest quantity of alveolar bone. For patients who have no suitable tooth for implantation, a tooth from an HLA-matched, first-degree relative can be used. The osteodental tissue is suitably shaped to a rectangular lamina, approximately 9–10 mm by 14.5–16 mm and 2.5–3.25 mm thick. The periosteum is preserved and used to circumscribe the alveolar tissue. The lamina is drilled through the dentine and alveolar bone to generate a central hole about 3.7 mm in diameter. The PMMA optic is inserted into the hole and cemented in place. The resulting ODA complex is then temporarily buried into a subcutaneous pocket, often just below the lower orbital rim of the fellow eye, and allowed to vascularize for 2–4 months.[6,30]

In step 2, the ODA complex is retrieved from the pocket, and the surrounding excess soft tissue is trimmed. The buccal mucosal graft in the eye is partially detached and reflected to expose cornea. A full-thickness, central corneal trephination is performed, followed by complete iridectomy, lens extraction (either natural lens or intraocular lens) plus posterior capsulotomy and anterior vitrectomy. The ODA complex is then implanted into the central trephination, and the borders of the lamina are sutured to the cornea and sclera. The buccal mucosa is repositioned on top of the ODA complex and secured in place, after making a hole through the mucosal graft in the region corresponding to the PMMA optic cylinder.

Topical steroids and antibiotics are given postoperatively. Topical antibiotics should be continued once daily indefinitely. Additional systemic corticosteroids are recommended to prevent excessive intraocular inflammation, and systemic anti-glaucoma medications should be given if the IOP remains elevated, as is frequently the case. A cosmetic scleral shield with a central opening for the anterior optical cylinder is usually applied 1 month after surgery, to improve cosmetic appearance and protect against dehydration.[29]

Although the OOKP technique is a complex and invasive surgical approach, it provides tight bio-integration and a better long-term retention rate with satisfactory functional visual outcome than is currently attainable with other types of keratoprosthesis.[29,30] Long-term outcomes in 181 cases of OOKP procedures showed an 85% probability of retention 18 years after surgery.[30]

The other advantages of OOKP, related mostly to its unique biological properties, include low rates of cylinder extrusion, aqueous leakage, endophthalmitis, epithelial downgrowth and retro-prosthetic membranes.[6,30]

However, some patients experience partial bone resorption of the osteodental lamina, causing decentration of the optic cylinder. The exact mechanism remains unclear, but epithelial downgrowth and localized inflammation seem to play an important role. Preservation of the alveolar-dental ligament is essential for maintaining the integrity of the device.[17] An evaluation of the status of the OOKP lamina with appropriate imaging studies is thus mandatory so that prophylactic measures can be taken to prevent subsequent complications. Glaucoma is the most vision-threatening complication in OOKP cases, occurring in 7–75% of patients, depending on the report.[29] Other limitations of OOKP are a limited visual field, the inability to measure IOP, and the extensive interventions required in the anterior segment, which can predispose to several complications. This demanding and time-consuming surgery may place a great burden on patients, family members, and surgeons alike.[29]

A tibial keratoprosthesis (TKPro) is a variant of the OOKP.[31] A cortical chip of tibial bone serves as an alternative material for a biological haptic in cases where no suitable tooth is available. The implantation procedure is the same as for a general OOKP. However, resorption of tibial bone might be faster because of the considerably higher turnover of bone than of dentine, resulting in reduced long-term stability.

SEOUL-TYPE KERATOPROSTHESIS

The Seoul-type keratoprosthesis (S-KPro) consists of three parts: a central PMMA optic 4 mm in diameter surrounded by a mushroom-shaped anterior flange, a porous polymer skirt made of polyurethane or polypropylene, and U-shaped polypropylene haptics.[32] The anterior flange is dark brown in color to mimic the iris color of Asian patients. Fibrovascular ingrowth and biointegration occur at the skirt portion. The main difference between previous keratoprostheses and the S-KPro is the manner of fixation to the eyeball. S-KPro has a double-fixed design, which includes external corneal fixation of the skirt and internal scleral fixation of the haptics. Another characteristic of the S-KPro is the polyethylene glycol-grafting polymerization of the optics to improve tear stability and reduce cell adhesion, in the expectation that this will decrease the incidence of retroprosthetic membrane after surgery.

The surgical technique is complex.[32,33] After pupil dilation, the patient's cornea is trephined halfway through, with a 6-mm diameter. A 360° intralamellar dissection is then performed with a disposable crescent blade, toward the limbus to make an intrastromal pocket 2 mm in length. After excision of the trephinated cornea, capsulorrhexis of the lens capsule is performed and a nucleus is removed. The residual cortex and part of the anterior vitreous are also removed with a vitreous cutter. A sector iridectomy is then performed. The S-KPro is placed into the eyeball and the haptics are fixed to each side of the sclera with 10-0 polypropylene suture, from the inside out (ab interno technique). The skirt is inserted into the previously prepared corneal pocket, and secured with 10-0 nylon interrupted sutures to the anterior lamellar part of the cornea. Amniotic membrane transplantation is performed to protect the surface of the S-KPro.

The preliminary results with this device suggest the important role of scleral fixation of the haptics in providing adequate stability to prevent extrusion, even in the case of in situ loosening or absence of corneal support. Anatomical success without extrusion was achieved in 6 of 7 eyes during an average follow-up of 25.6 months. Partial extrusion was found in one patient with advanced glaucoma. One patient experienced retinal detachment after exchange of S-KPro. Enterococcal endophthalmitis developed in one patient with OCP. Retro-prosthetic membrane occurred in one case and was treated with Nd:YAG laser membranotomy.[33] Inability to use an adjunct glaucoma drainage shunt is the primary drawback of the S-KPro.[33] Also, the IOP cannot be directly measured as well as with the more conventional keratoprostheses.

BIOCOLONIZABLE MICROPOROUS FLUOROCARBON HAPTIC (BIOKOP) KERATOPROSTHESIS

The BIOKOP keratoprosthesis was developed to improve the integration of the keratoprosthesis and surrounding host tissue, in accordance with the concept of biocompatibility that underlies AlphaCor. The BIOKOP has two models. BIOKOP I consists of a skirt, 9 mm in diameter, made of microporous fluorocarbon, and a PMMA optic, 4 mm in diameter and 2.67 mm long, providing a visual field of 110–130°. BIOKOP II has the same haptic design, but its 7-mm diameter soft optic is made of medical-grade polydimethylsiloxane (PDMS) coated with polyvinylpyrrolidone.[34] The surgical procedure is described by Legeais and Renard.[34] The outcomes for patients with severe ocular diseases, after 5 years of follow-up, were disappointing.[35] Nearly half of the patients had blindness caused by retinal detachment, endophthalmitis, or phthisis bulbi.

SUPRA-DESCEMETIC KERATOPROSTHESIS

A novel, nonpenetrating, lamellar supra-Descemetic synthetic cornea (sDSC) implantation has recently been developed to avoid the necessity of entering the anterior chamber, leaving the Descemet membrane and the endothelium intact. In theory, this technique minimizes the risk of complications attributed to the penetrating nature of the other keratoprostheses, such as epithelial downgrowth, endophthalmitis, and retinal detachment.[36] The pre-Descemetic implant is a one-piece device with an overall diameter of 7 mm. A central optic zone, 4.5 mm in diameter and 450 µm in thickness, is surrounded by a 100-µm thick outer flange. The flange has 24 holes, 350 µm in diameter, allowing for nutrient transfer and tissue ingrowth. To date, the procedure has been performed only in rabbit models.[37] Three different materials were tested to evaluate the biocompatibility of the device: hydrophobic PMMA, hydrophilic hydroxyethylmethacrylate-methylmethacrylate (HEMA-MMA), and hydroxyethylmethacrylate-*N*-vinylpyrrolidone (HEMA-NVP). HEMA-MMA showed the most promising results, with a clear Descemet membrane and no vascularization or scarring.[37] However, opacification of the remaining stromal tissue may compromise the potential visual benefit in the long run. Ingrowth of fibrous tissue beneath the optic can also occur, reducing visual outcome. Further studies are needed to develop this device.

TISSUE-ENGINEERED CORNEAS

Tissue engineering is a novel area of research with widespread applications. In recent years, in vitro reconstruction of skin cells and blood vessels has been accomplished.[38] Similar attempts have been made in the area of bioengineered corneal tissue, with some

degree of success.[39] To ensure the viability of tissue-engineered corneas, several requirements must first be met. First, the tissue must have the same optical clarity as the native cornea. Second, it must have enough tensile strength to withstand intraoperative manipulation and suturing. Third, the tissue must be compatible with the ocular surface into which it is being implanted. Lastly, some form of surface re-innervation is essential to maintain hydration and decrease the risk of infection.[40]

At least three of the five layers of the cornea need to be effectively engineered to create a successful corneal substitute: epithelium, stroma, and endothelium. Each component can now be regenerated successfully. Corneal epithelium can be cultured using limbal stem cells with different tissue types as a scaffold for cell growth. Human amniotic membrane and cross-linked human fibrin gel have been used to successfully grow corneal epithelial cells.[41,42] The stromal component can be reconstructed by mixing corneal keratocytes with either bovine type I collagen[38] or with human types I and III collagen.[43] Both have been shown to replicate human corneal stroma, without Descemet or Bowman membrane.[38] Human corneal endothelial cells have been regenerated on type IV collagen-coated dishes.[44]

Several research groups have attempted to bioengineer complete corneal equivalents, with all three layers cultured simultaneously. Fibrillar collagen sponge or gel was used to culture all three requisite cell types.[45] Co-cultures of epithelial/endothelial and epithelial/keratocyte pairs were also investigated. Epithelial and endothelial cells formed a monolayer on the surface of the sponge; an epithelial/endothelial co-culture displayed epithelial migration, with the cells forming three to four cell layers on the sponge surface. Keratocytes migrated and proliferated, repopulating the matrix of the sponge. This collagen sponge model demonstrated excellent transparency and could potentially be used to modulate the wound-healing response. However, extensive contraction of the matrix occurred, which could limit transparency and wound-healing abilities.

Another bioengineered corneal equivalent used bovine or human collagen thermogel as the scaffold, with human corneal epithelial cells and stromal cells.[42,46] Human fibroblasts were induced to produce collagen in sheets, which were then stacked together and seeded with epithelial cells. Endothelial cells were not initially included, but subsequent research has focused on including these cells.[47] This method was unique in its approach, but the tissue produced did not have the structural integrity to withstand implantation. However, important elements of the wound-healing response were evident.

Recently, scaffolds of type I collagen were cross-linked with a copolymer based on *N*-isopropylacrylamide, acrylic acid, and acryloxysuccinimide.[48,49] This yielded a gel with superior optical clarity and better tensile strength that could withstand manipulation and suturing. An additional important characteristic unique to this model is the ability of the host tissue to generate neural ingrowth into the gel. Implantation of this model into Yucatan pig corneas successfully demonstrated in vivo regeneration of the host corneal epithelium, stroma, and nerves at 3 weeks post-implantation. The presence of the nerves also seemed to improve epithelial growth and provide protection to the epithelium from external injury.

The main requirements for bioengineered corneas—namely optical clarity, tensile strength, and innervation—continue to be challenging. Each of the above three bioengineered corneal substitutes described above fulfills some of these requirements. As progress continues in engineering the requisite cell types, alone and in combination, viable implantable corneal constructs may well become available in the not too distant future.

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79 The Boston keratoprosthesis

Stephen G. Waller, Claes H. Dohlman

As we pass the centennial of the first successful human corneal transplant, there is much to celebrate.[1] Sight has been restored to hundreds of thousands of patients worldwide. The majority are successful by any reasonable standards, and excellent vision persists for years or decades for many recipients. However, a portion of these allografts fail, often due to underlying disease, occasionally due to repeated rejection episodes. The rate of transplant performed for failed graft is increasing, being 12% in a recent large USA study.[2] Undoubtedly, there is an additional percentage of patients with high risk for failure who are never suitable candidates for this surgery. Patients with Stevens–Johnson syndrome, severe chemical burn, ocular cicatricial pemphigoid, and a history of multiple graft failures all carry a dismal rate of success with standard keratoplasty.[3–5] Fortunately, some of these patients are candidates for keratoprosthesis as a means of visual rehabilitation.

Keratoprosthesis surgery is experiencing a dramatic increase in its clinical application. While the authors believe that fewer than 15 keratoprostheses were implanted in the USA in 1992, the Boston keratoprosthesis and the implantation procedure we describe in this chapter have now been utilized in over 1000 cases (2006). We expect as many as 400 may be placed in the year 2007 alone. The Kaplan–Meier survival analysis of 173 type I keratoprosthesis patients, excluding those with end-stage autoimmune disease or severe chemical burn, showed only two (both with likely autoimmune disease) requiring surgical revision in 36 months of follow-up (Aquavella, Sippel, Dohlman, April 2006, unpublished data). About a dozen centers worldwide are seriously involved in keratoprosthesis programs, and scientific conferences and peer-reviewed publications are increasingly common. While our cases are performed in Boston, other centers are reporting considerable success with the Boston keratoprosthesis.[6,7]

The authors believe that the prognosis for keratoprosthesis has improved in recent years, and that technical and scientific advances have led to expanding indications for this procedure (Table 79.1). Since we have no experience with other keratoprosthesis devices and surgery, we will focus on the Boston keratoprosthesis exclusively in our discussion.

HISTORY

The concept of an artificial cornea for the treatment of blindness was first suggested in writing in 1789 by the noted French surgeon, Pellier de Quengsy.[8] He recommended the implantation of a glass lens held by a silver ring, and described the surgical procedure and necessary instruments. Nussbaum published the results of the implantation of a quartz crystal in human corneas in 1853.[9] The German literature includes at least four additional 19th century reports of innovative design and insertion techniques.[10–13]

With the first successful human allograft in December of 1905, attention was diverted away from keratoprosthesis development. After the initial excitement of this innovation was tempered by graft limitations and failures, Verhoeff inserted a quartz button into a human cornea, achieving brief success.[14] Filatov reported a full-thickness glass device implanted into the opacified cornea of a patient in 1935.[15] The glass was surgically covered with a double conjunctival flap, and the patient briefly recovered 1/200 ambulatory vision.

The World War II discovery that the transparent windscreen material used in aircraft canopies, polymethylmethacrylate (PMMA), was well tolerated by the eye, led to its adaptation for intraocular lens use. It also stimulated experimentation by several investigators to show that discs of this plastic could be retained in the cornea of rabbits.[16–18] Another period of human use ensued, but the severe complications encountered in the postoperative period once more slowed the rate of keratoprosthesis progress.

Among the most active work on keratoprosthesis in the past 40 years has come from Strampelli and colleagues.[19–22] His osteo-odontokeratoprosthesis technique uses osteodental lamina from a tooth as the skirt for a PMMA optical cylinder. The tooth is harvested in a first surgery from the keratoprosthesis recipient, and then the device is implanted into the cornea in a second surgery and covered by lid skin or a buccal mucosal graft. The procedure has a reputation for stability and low rate of infection.

Other investigators have replaced the autologous tooth skirt with porous plastic materials that are considered 'biocolonizable'.[23–25] Russian surgeons, using devices of different design and a PMMA

Table 79.1 Factors improving Boston keratoprosthesis outcomes

Identification of prognostic categories of patients
Design of device
Use of fresh graft tissue as carrier for keratoprosthesis
Placing posterior plate (haptic) totally behind graft
Posterior plate holes to facilitate nutrition and hydration of graft
Tissue coverage (conjunctiva, tarsorraphy, soft contact lens)
Minimize evaporative forces on surface
Glaucoma shunt implant
Aggressive steroid regimens
Prophylactic topical antibiotics for life
Nd:YAG laser membranectomy
Repair techniques
Meticulous, frequent clinical follow-up

optical core, have implanted a large number of patients, many suffering from chemical burn sequellae and its dismal prognosis.[26–27] A core-and-skirt device, utilizing a hydrogel sheet with porous edges as an artificial cornea, has also shown promise.[28] Now known as the AlphaCor keratoprosthesis, it is implanted intrastromally and covered primarily with a conjunctival flap. The center of the device is surgically exposed later. The ingenious Seoul-type keratoprosthesis has also had reported success.[29] These devices are discussed in Chapter 79.

GENERAL CONSIDERATIONS

The combined experience of surgeons pre-eminent in the development of keratoprosthesis surgery worldwide may have amounted to merely 5000 cases during the past half-century, a trivial number compared to the number of corneal blind. The published results of keratoprosthesis outcomes are often difficult to interpret, as follow-up and device survival times are sometimes not cited. Considerable literature focus on device design and materials has overshadowed attention to postoperative biological complications, particularly glaucoma, retroprosthetic membranes, tissue melting, and retinal detachment. Despite these limitations, a considerable body of knowledge in this complex field has accumulated.

In this chapter, we report our experience and outcomes after implantation of the Boston keratoprosthesis at the Cornea Service of the Massachusetts Eye and Ear Infirmary. For a number of years, we have used this medical-grade PMMA keratoprosthesis of collar-button design, the general configuration being suggested by Dorzee, Barraquer, and earlier work at our center.[30–32] The device consists of a front and back plate, joined by an optical stem, and locked in place by a titanium c-ring.[33] The optical portion is manufactured with a range of dioptric powers to fit the axial length of the patient's eye and the aphakic or pseudophakic situation.

The keratoprosthesis comes in two main designs (Fig. 79.1). The simple collar-button, or type I, is the device of choice for patients with a reasonable blink and tear production, the more common situation for our keratoprosthesis cases. It is implanted into a fresh donor corneal graft, which is then sutured into the patient's cornea

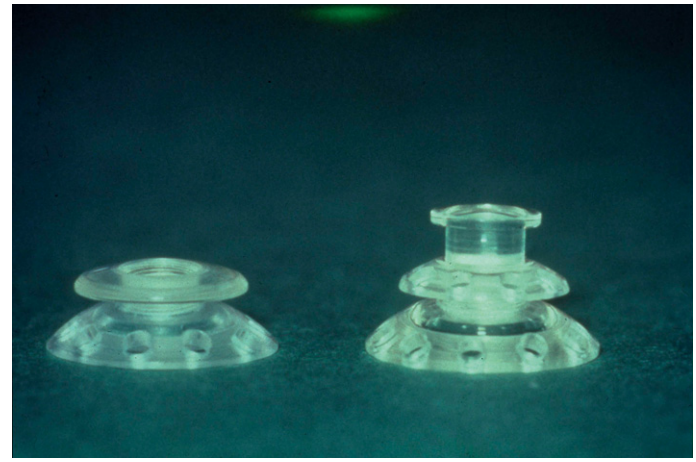

Figure 79.1. Boston keratoprosthesis, type I and type II.

Table 79.2 Keratoprosthesis design

	Type I	Type II
Front plate diameter	5.0–6.0 mm	7.0 mm
Back plate diameter	7.0–8.5 mm	8.5 mm
Stem diameter	3.35 mm	3.35 mm
Inter-plate distance	0.6 mm	0.6 mm
Hole diameter	1.3 mm	1.5 mm
Anterior–posterior length	3.7 mm	4.7 mm
Visual field	60°	40°

in the standard manner. The wide plates prevent the device from tilting off axis. The optical stem is short, giving the patient a generous visual field, and providing the surgeon a good view with the slit lamp, helpful for Nd:YAG laser membranectomy and for viewing the posterior eye structures. The design of the type I device includes a low profile, to minimize the tendency for adjacent graft dellen and to allow a soft contact lens to fit comfortably over it. Holes in the back plate permit better nutrition and hydration into the donor allograft from the aqueous side in an effort to reduce the tendency for graft necrosis and subsequent extrusion of the device.

Cases with end-stage dry eye conditions are suitable candidates for the type II Boston keratoprosthesis, designed for through-the-lid applications. Tarsorraphy is believed to reduce tissue dehydration and melting in these cases and the type II device has a 2 mm long anterior nub to penetrate the skin or pass between the lids. It is otherwise similar to the type I device (Table 79.2). The keratoprosthesis can be purchased from The Massachusetts Eye and Ear Infirmary, Boston, Massachusetts.

PREOPERATIVE ASSESSMENT

Bilateral corneal blindness with light perception or hand motion vision can be an indication for keratoprosthesis surgery. If one eye has relatively good vision, the keratoprosthesis approach is less often indicated. Severe retinal or optic nerve damage, including end-stage glaucoma, or dense amblyopia are contra-indications for the procedure. Assessment of the posterior segment often will require B-scan ultrasound in these cases, and the final decision for

or against surgery can be a difficult one. Neither visual evoked response nor electroretinography testing has been particularly helpful in our experience. Monocular status, young age, or poor general health must also be considered. In patients with no other hope of recovery from bilateral corneal blindness, keratoprosthesis may be the best option.

Our experience has shown that the underlying disease process can often be the key issue in providing guidance to both surgeon and patient.[34] The etiologies with markedly worst prognosis are Stevens–Johnson syndrome and ocular cicatricial pemphigoid. The former are often young and have ongoing ocular inflammation that increases their risk of postoperative complications. Their desperate need is often exceeded by the requirement to be free of sight-threatening complications for many years. Ocular cicatricial pemphigoid patients, on the other hand, are usually older, and eventual keratoprosthesis failure might be less tragic than in a younger patient.[35] Both groups are prone to postoperative skin retraction, with tissue melting and device extrusion, and to blinding glaucoma. Close, long-term follow-up is mandatory if the patient is to have any hope of prolonged vision.

In our hands, chemical burn patients have an intermediate prognosis for success with the Boston keratoprosthesis.[34] Inflammation can eventually subside, and glaucoma is the most important long-term complication.[36] We often recommend a simultaneous glaucoma shunt procedure before or after the keratoprosthesis surgery. These patients have a tendency for retinal detachment, presumably from the chemical damage. Again, frequent and careful clinical follow-up is critical to success.

Patients with repeated graft failure, non-inflammatory edema, and trauma, tend to fare best by a wide margin.[37] Patients with the etiology of corneal infection, including those with herpetic etiology, fall within this group, with only a slightly increased risk of long-term keratoprosthesis failure. This group of patients has the least likelihood of unmanageable glaucoma, postoperative uveitis, or tendency to tissue necrosis and keratoprosthesis extrusion. Blink mechanism and tear production are often normal. Good vision is often restored rapidly with keratoprosthesis, more rapidly than with a successful re-graft.

SURGICAL TECHNIQUE—TYPE I DEVICE

Efforts in recent years to simplify the procedure of Boston keratoprosthesis implantation have led to improvements in technique.[37] The present one-step surgical procedure does not require autologous tissue from other body sites (e.g. teeth, fascia lata). We prefer general anesthesia when safe, as the keratoprosthesis surgery usually takes longer than a standard keratoplasty. We recommend an intravenous antibiotic (cefazolin 1.0 g if no allergy or other contraindication) dose be given at the beginning of surgery. The list of preoperative materials is shown in Table 79.3.

The fresh donor cornea is brought to a side table and the central 8.5 mm is excised with a trephine. The patient's own cornea can be used in situations where the cost of donor corneas is prohibitive. Using a 3.0-mm punch (Acu-Punch, Acuderm Inc., Ft Lauderdale, FL), a central hole is made in the donor material. It is important that the opening be centered well and not be eccentric. The front plate is placed with its anterior surface down and the stem up on an adhesive tape (included in the set), and viscoelastic is applied to the screw threads of the stem. The graft is gently pushed over the stem until its front surface is fully up against the anterior plate. The posterior haptic plate is screwed into place and locked with the titanium snap ring (see Fig. 79.2). The graft–prosthesis combination is placed back into the storage solution while attention is turned to the patient.

On those occasions when a glaucoma shunt is indicated, insertion of the tube into the anterior chamber should occur before the cornea is trephined. Using a trephine with a 0.5 mm smaller diameter (usually 8 mm) than the prepared graft, the patient's cornea is cut

Table 79.3 Materials to prepare before surgery

Boston keratoprosthesis type I or II, with suitable dioptric power (Massachusetts Eye and Ear Infirmary, Boston). Package includes adhesive patch and spanner wrench to facilitate keratoprosthesis assembly (JG Machine, Woburn, MA)
Donor cornea (patient's own cornea can be used if necessary)
Troutman punch device (Pilling Weck Surgical, Ft. Washington, PA)
Trephine blades, 8.0 and 8.5 mm (Storz # E3095)
Skin punch, 3.0 mm (Acuderm, Ft. Lauderdale, FL)
Hessberg–Barron vacuum trephine (Barron Precision, Grand Blanc, MI)
Universal trephine handle
Standard keratoplasty instrument set
Irrigation/aspiration unit, vitrectomy unit, and light pipe
Fine bipolar cautery
Plano soft contact lens (Kontur Lens, Richmond, CA). We recommend 16.0 mm diameter and 9.8 mm base curve.
Video recording capability (optional but useful)
If needed, glaucoma valve shunt and Tutoplast (Ahmed S-2, New World Medical, Rancho Cucamonga, CA)

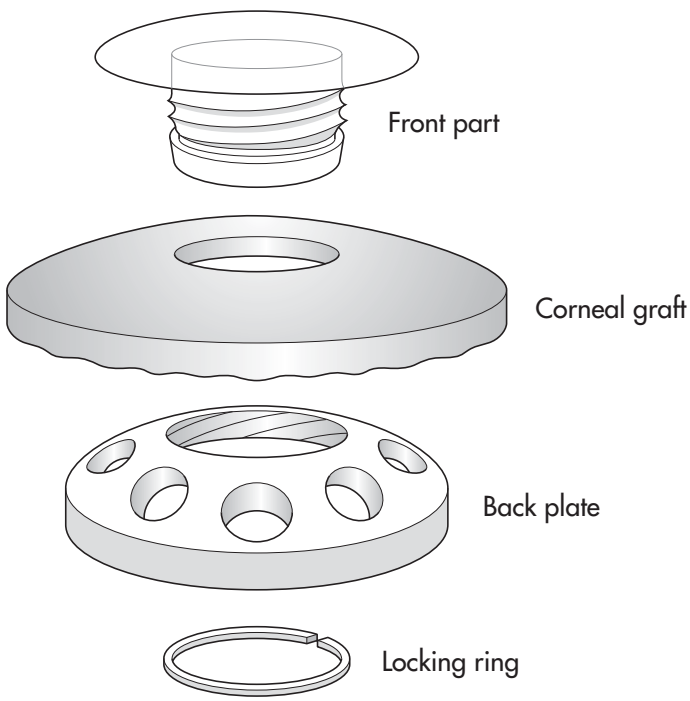

Figure 79.2. Principle of assembly of a type I device.

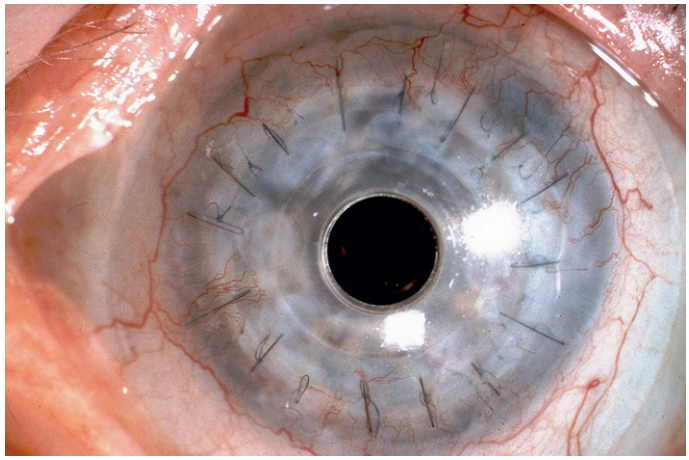

Figure 79.3. Postoperative example of a type I device in place.

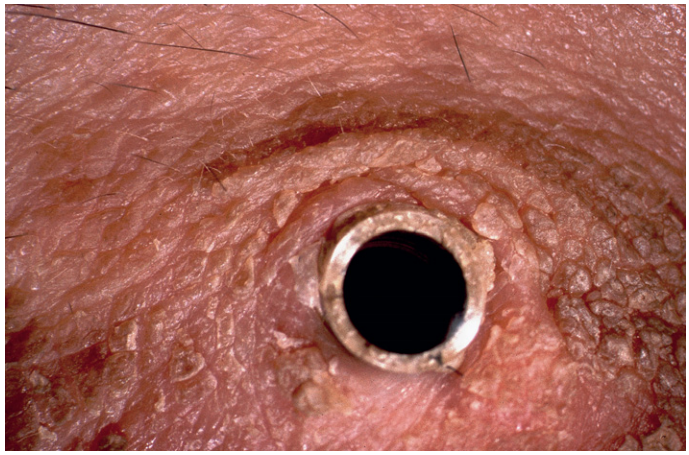

Figure 79.4. Postoperative example of a type II device in place.

to partial depth. Bleeding vessels are cauterized and the trephination is completed. One or two iridotomies are made and the native lens is excised by extracapsular technique. If the patient is pseudophakic, the intraocular lens should remain in place and a device with corresponding optical power can be chosen. If vitreous is evident, a deep core vitrectomy is necessary and all efforts should be made to prevent any bleeding into the posterior chamber.

The graft–prosthesis unit is now placed into the trephined opening in the cornea, and sutured in place with 12 9-0 nylon sutures. The knots are buried. A bandage contact lens is applied and antibiotic drops are administered to complete the surgery (Fig. 79.3). If a bandage contact lens is not available, we recommend performing a total conjunctival flap with central opening. This is easiest done prior to the trephination. In more extreme cases of exposure, partial lateral and medial permanent tarsorraphies may be required, allowing only the plastic optic to be exposed.

SURGICAL TECHNIQUE—TYPE II DEVICE (Fig. 79.4)

The surgical principles for the type II device are similar to those described for type I, although the surgery is more complicated and time-consuming. A glaucoma shunt is often necessary in these cases.[36] The fornices must be cleaved to allow for implantation of the graft–prosthesis combination. The keratoprosthesis is placed so that the optical nub protrudes through the closed lids, as originally described by Cardona and DeVoe.[38] An alternative technique is to perform a tight permanent tarsorraphy on both sides of the protruding optic nub.

OUTCOMES

Meticulous and frequent clinical follow-up are key to successful, long-term keratoprosthesis survival. In most cases, the severe complications are seen within the first postoperative year. However, the risk of potential complications continues for the life of the keratoprosthesis, and close monitoring with early diagnosis offers the best chance of successful treatment. We see postoperative cases that are doing well at 1 day, 1 week, 3 weeks, and then monthly intervals after surgery. The anterior surface of the type II device can be cleaned as necessary with baby shampoo and a cellulose sponge during examinations.

Sharing the postoperative responsibility with a glaucoma colleague is wise. With the drastic reduction in endophthalmitis,[39] glaucoma is probably the most serious complication of keratoprosthesis surgery. Its pathogenesis is multifactorial, but gradual closure of the anterior chamber angle is the most likely cause of marked aggravation of intraocular pressure. Tonometers are not useful in this clinical situation, so glaucoma evaluation should include finger palpation of the globe for intraocular pressure assessment, as well as visual field examination and visualization of the optic nerve head. Topical glaucoma medications have some effect in type I keratoprosthesis patients, although their effect seems somewhat diminished compared to more routine glaucoma eyes. Oral carbonic anhydrase inhibitors, as expected, have the usual effect, and are the only choice in the type II case. They should be used with great caution in patients with Stevens–Johnson syndrome and avoided in patients with sulfa allergy. Ahmed valve placement at the time of keratoprosthesis surgery has been a significant advance in the treatment of this condition.

We use postoperative prophylactic antibiotics indefinitely. An oral antibiotic, such as cephalexin 500 mg twice or three times daily is used for 10 days following surgery. A topical fourth-generation fluoroquinolone is used initially four times daily, then tapered to once per day (twice daily for type II keratoprosthesis patients). In autoimmune cases (Stevens–Johnson syndrome, ocular cicatricial pemphigoid, etc.), we also recommend vancomycin 14 mg/mL with benzalkonium preservative once daily, and our patients use both topical medications as long as the keratoprosthesis is in place. In cases of recurrent herpes simplex, a systemic antiviral (acyclovir 400 mg twice daily) is recommended on a permanent basis. The rare endophthalmitis is usually from gram-positive organisms in our experience, and vision can be lost in hours. Should endophthalmitis occur, immediate 'tap and inject' are crucial. An aqueous tap via the limbus for smear and culture and an injection of 1.0 mg vancomycin, 0.4 mg amikacin, and 0.4 mg dexamethasone are performed. The patient should be hospitalized for topical and intravenous antibiotics, and a vitrectomy performed later as necessary. We have not had any postoperative endophthalmitis cases since the institution of this prophylactic antibiotic regimen.[40,41] Patients with autoimmune disease or severe chemical burns may require a more aggressive antibiotic regimen than in the majority, non-autoimmune, cases. It is particularly important to impress upon the patient that compliance for life is mandatory.

Both devices, particularly the type II, are susceptible to adjacent tissue necrosis, and close observation for this complication is indicated. Necrosis with the type I device is now very rare. However,

early evidence of a surface melt near the edge of the type I anterior plate, that threatens to become a substantial gap between the stem and adjacent tissue, should be treated aggressively. Total replacement with a fresh graft–prosthesis combination is recommended.

In the type II keratoprosthesis, the adjacent skin can retract away from the nub due to evaporative damage to the skin edge. Topical methylprogesterone 1% suspension twice daily reduces necrosis around the incision, presumably due to suppression of collagenase synthesis.[42] Topical tetracycline 1% suspension, a direct collagenase inhibitor, has been less helpful in our hands. Skin revision is advisable when the skin retracts to the edge of the front plate. A horizontal lid skin incision with undermining and freshening of the edges, followed by 6-0 nylon suture looped around the nub, will usually restore the interface integrity.[37] If a frank leak and hypotony occurs with either type of keratoprosthesis, the entire keratoprosthesis–graft system should be replaced.

Addition of a continuous-wear bandage plano soft contact lens after type I keratoprosthesis surgery has created a remarkable improvement in the stability of the postoperative course.[43] Before its use, evaporation and irregular drying of the corneal graft tissue around the device led to dellen formation, epithelial defects, and stromal thinning. The lens seems to diffuse evaporative forces and allow better hydration of the eye surface. Inadvertent lens loss and replacement can increase the cost of care.

After type I surgery, a postoperative topical corticosteroid is tapered from four applications per day to a lower dose during the first postoperative months, depending on clinical circumstances. The type II patients may require occasional sub-Tenon triamcinolone injections during the first postoperative months to reduce the prolonged intraocular inflammation common in these patients. Injection of 40 mg triamcinolone a few days after surgery, then every 2–3 weeks for several more months, will often keep exuberant, self-destructive inflammation at bay.

We have seen sudden, massive vitritis in a few patients with reduction of vision to hand motion. There is no accompanying pain, tenderness, or redness, but the vitritis otherwise appears as an infectious endophthalmitis, and should be so treated. Within a few weeks or months, the vitreous clears and vision returns to baseline, leading to our opinion that this is an immune event.[44]

Another immune event is the formation of a retroprosthetic membrane after prolonged, severe inflammation in autoimmune eyes. Vision is dramatically worsened, and triamcinolone injections are indicated at the first sign of membrane formation. Once formed, the Nd:YAG laser should be used to open the membrane before it becomes too thick or vascularized.[45] Laser pulses with energy above 3.0 mJ can crack or mark the optical portion of the device. If the laser cannot cut the membrane, a closed vitrectomy and membranectomy under high infusion pressure are necessary to restore vision.[46]

Retinal detachment is not common following keratoprosthesis placement, but it does occur. It can be rhegmatogenous or tractional in nature, and prognosis is ominous. Diagnosis is by direct visualization or B-scan ultrasonography. Multiport vitrectomy should be performed and long-acting tamponade used.[46]

In conclusion, keratoprosthesis offers a visual rehabilitative option to patients whose prognosis for standard keratoplasty is poor. The outcome of the type I device compares favorably with keratoplasty for multiple graft failures in nonimmune disease.[47] It is perfectly reasonable for any ophthalmologist with experience in corneal surgery to perform this type of operation. It should be re-emphasized, however, that keratoprosthesis in the autoimmune diseases fares much worse and we recommend that these cases be referred to surgeons with considerable experience.

Several clinical groups around the world have contributed substantially to progress on preventing and treating the complications of keratoprosthesis implantation during the last few decades. The rapid rehabilitation and improving long-term outcomes of keratoprosthesis will undoubtedly increase the use of this device in the worldwide ophthalmic community.

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80 Classification and terminology of refractive surgery

George O. Waring

Most specialized fields develop their own technical terminology and jargon. Refractive surgery is no exception. The penchant for professional shorthand has produced jargon such as 'keratorefractive' surgery, a Greek–Latin hybrid that flows easily from the tongue and pen of those enamored by neologisms. Some surgeons have become 'keratomists,' and their patients are 'keratotomized.' Words have been invented, such as 'lenticle,' instead of the correct term, 'lenticule'—the piece of tissue or synthetic material used to change corneal shape. Commercial trademarked terms have appeared. Eponyms abound. Common use of some colloquial terms has fixed them in our vocabulary. For example, some say 'myopic LASIK' (is the LASIK myopic?), instead of the more precise designation: LASIK for myopia. Thus far we have been spared 'myopic intracorneal rings'.

To clarify the language we use in this rapidly changing area of ophthalmology, I propose a classification of refractive surgery, which I hope is broad enough to include all procedures that have a major refractive component, systematic enough to organize our present knowledge, clear enough to distinguish techniques in current use from those of historical interest, flexible enough to accommodate new developments, and precise enough to decrease the proliferation of jingly keratospeak.

REFRACTIVE SURGERY

Refractive surgery is any operation intended to alter the refractive state of the eye.[1] Thus, laser in situ keratomileusis (LASIK), cataract extraction with implantation of an intraocular lens (IOL), and Descemet's stripping endothelial keratoplasty (DSEK) are all forms of refractive surgery. Refractive corneal surgery refers to corneal operations that are intended to alter the refractive state of the eye. This type of surgery is popularly referred to as both *refractive keratoplasty*, an appropriate term because keratoplasty means 'molding the cornea', and keratorefractive surgery.

All IOL implantations—both aphakic and phakic—qualify as refractive surgery; indeed, the phrase 'refractive cataract surgery' has become popular as more meticulous attempts to correct the total refractive state of the eye at the time of cataract surgery have evolved: correcting the spherical error with an IOL, correcting the astigmatism with transverse keratotomy (either in the cornea or as part of the limbal incision) or with a cylindrical IOL, and correcting presbyopia with a multifocal or accommodating IOL.

CLASSIFICATION OF REFRACTIVE SURGERY

The classification I propose (Table 80.1) is based on surgical technique. It describes basic techniques that can be applied to many refractive errors, such a keratomileusis for both myopia and hyperopia. It accommodates new techniques that are modifications of previously used ones, such as LASIK as a modification of keratomileusis. It requires only one description of a technical procedure that is used in different refractive operations, such as the use of a microkeratome in keratomileusis.[2]

The classification specifies first three broad categories of refractive surgery: refractive keratoplasty, IOLs, and scleral surgery. The classification then specifies basic surgical techniques such as keratomileusis and refractive keratotomy, presenting variation in each technique. The classification also divides all techniques into two basic groups: those in active use in 2007 and those used less frequently or of historical interest only.

LAMELLAR REFRACTIVE KERATOPLASTY

Lamellar refractive keratoplasty involves altering the central curvature of the cornea to change its refractive power. Changing the refractive index with a corneal inlay or the optics with a small aperture inlay is refractive corneal surgery as well. There are three basic lamellar refractive keratoplasty techniques:

1. *Keratomileusis* ('to curve the cornea') is the creation of an anterior disc or flap of corneal tissue. The stromal surface of the bed (or, in the past, the disc) is then reshaped to effect a refractive change by changing the radius of curvature of the cornea most commonly with an excimer laser. The disc or flap is then replaced and allowed to adhere on the cornea.
2. *Intracorneal inlay or lens* ('keratophakia, lens in the cornea'). Placing an intracorneal lens in the power beneath the lamellar flap changes the anterior curvature of the cornea. Placing a

Table 80.1 Classification of refractive surgery, 2007

Category of Surgery	Basic Surgical Technique	SPECIFIC SURGICAL TECHNIQUES Variation of Surgical Techniques or Material	Techniques in Active Use in 2007	Techniques Used Less Frequently or Abandoned
I. Refractive keratoplasty				
A. Lamellar				
	1. Keratomileusis (KM): Cutting planoanterior Corneal flap	a. Anterior corneal layer	i. Hinged flap	ii. Complete disc
		b. Methods of cutting flap or disc	i. Mechanical microkeratome	
			a) Automated advance	b) Manual advance
			a) Mechanical or manual advance	
			c) Oscillating blade	d) Rotating blade
			ii. Femtosecond laser (raster or circular beam path)	iii. Water jet
				iv. YAG laser
		c. Attachment of flap or disc	i. No sutures: tissue adhesion and endothelial pump	ii. Sutures
		d. Source of tissue for flap, disc	i. Patient (autoplastic)	ii. Donor (homoplastic or allograft
				a) Lenticule placed on patient corneal surface
				i. Epikeratoplasty with refractive power (H,A)
				ii. Plano lamellar onlay (KC)
				b) Donor—lenticule under disc or flap (homoplastic)
				i. Keratophakia—donor disc with power (H,A)

				i. Additive keratoplasty for keratoconus—plano donor disc (KC)
		e. Location and method of refractive cut	i. Stromal bed—excimer laser, 193 nm (laser in situ keratomileusis-LASIK) (M,H,A,P)	iii. Stromal bed—microkeratome —
				a) Automated lamellar keratoplasty (ALK) (excise plano disc) (M)
				b) Keratokyphosis (refractive mold in microkeratome) (M,H)
				ii. Stromal side of disc
				a) Cryolathe (M,H)
				b) Non-freeze (microkeratome cut made on suction mold)
				c) Excimer laser
			a) Beam delivery method	
			i) Flying or scanning spot—random pattern	
			ii) Translating slit	
			b) Spherical ablation pattern	
				iii) Single-zone diameter
				i) Multiple-zone diameter (e.g. optical + transition)
				ii) Blended ablation zones
			c) Cylindrical ablation pattern	
			i) Flatten steep meridian	
			ii) Steepen flat meridian	
			d) Timing of treatments	
			i) Single treatment	
			ii) Multiple sequential treatments (enhancements, retreatments)	
			iii) Treatment after IOL implantation (bioptics)	

Refractive error treated: M, myopia; H, hyperopia; A, astigmatism; P, presbyopia; KC, keratoconus (all grades)

Table 80.1 continued

Category of Surgery	Basic Surgical Technique	Variation of Surgical Techniques or Material	SPECIFIC SURGICAL TECHNIQUES Techniques in Active Use in 2007	Techniques Used Less Frequently or Abandoned
			iv) Treatment after previous corneal surgery (transplantation, RK, and PRK)	
	2. Intracorneal inlay	a. Annular lamellar dissection	i. Intrastromal corneal ring segments (ICRS), (M)	
				ii. Complete ring (ICR) (M)
				iii. Gel injection adjustable keratoplasty (GIAK) (M)
		b. Inlay with power under lamellar flap or disc flap (keratophakia)		
			i. Permeable lenticule (e.g. hydrogel) (H,P)	
				iii. Nonpermeable material (e.g. glass and plastic)
			ii. Small aperture inlay (P)	iv. Human donor lenticule (A)
		c. Pocket lamellar dissection		i. High-index refraction lenticule (e.g. fenestrated polysulfone) (H,A)
				ii. Small-diameter lenticule (P)
				iii. Fresnel or diffractive optics
		d. Autokeratophakia		i. Folded corneal flap (A)
	3. Lamellar keratoplasty (corneal transplantation human donor) (remove host, place donor)			
	4. Lamellar keratotomy	a. Lamellar dissection		
			i. Manual	
			ii. Microkeratome	
		b. Anterior central		

		c. Posterior central		i. Descemet's stripping endothelial keratoplasty (DSEK)
				ii. Deep lamellar endothelial keratoplasty
		d. Onlay lenticule on corneal surface (epikeratoplasty) (H,A)		a. Donor lenticule without power (KC)
				b. Donor lenticule with refractive power (H,M,A)
				c. Synthetic lenticule (laboratory development)
B. Corneal surface refractive profiling (keratotomy)				
	1. Excimer laser, 193 nm, ablation	a. Epithelial removal (photorefractive keratectomy, PRK); advanced SURFACE ablation, ASA) (M,H,A,P)		
			i. Microkeratome with epithelial separator	
			ii. Alcohol loosening	
			iii. Rotating brush	
				iv. Manual scrape
				v. Transepithelial ablation
		b. Epithelial flap retention	i. Alcohol loosening (laser assisted subepithelial keratomileusis—LASEK)	
			ii. Microkeratome with epithelial separator (epi-LASIK)	
		c. (See IA1ei-LASIK??)		
C. Keratotomy				
	1. Radial (M)			a) Single nomogram

Refractive error treated: M, myopia; H, hyperopia; A, astigmatism; P, presbyopia; KC, keratoconus (all grades)

Table 80.1 continued

Category of Surgery	Basic Surgical Technique	Variation of Surgical Techniques or Material	SPECIFIC SURGICAL TECHNIQUES Techniques in Active Use in 2007	Techniques Used Less Frequently or Abandoned
				b) Sequential procedures, enhancements, more, longer or deeper incisions
	2. Transverse (T cut) (partial-thickness incision made transverse to steep corneal meridian, axis of plus refractive cylinder)		a. Corneal incision Arcuate—T (Arc-T)	
			b. Limbal incision	
			i. Cataract surgery	
			a) Limbal relaxing incision (LRI)	
			b) Astigmatism—neutral small (<3.0 mm) incision	
			c) 5–7 mm full-thickness limbal incision	
			c. Penetrating keratoplasty (relaxing incision)	
			i. In wound	
			ii. In donor	
			d. Straight—T	
			e. Combined with radial	
	3. Circular		a. Hexagonal keratotomy (Hex) (A)	
			b. Partial-thickness trephination with sutures (A)	
D. Suture adjustment				

			1. Removal or cutting of interrupted suture in steep meridian (A)
			2. Distribution of tension on running suture (A)
			3. Placement of compression sutures in flat meridian (A)
E. Mechanical keratectomy			
		1. Crescentic keratectomy or lamellar corneal tuck (Terrien's or pellucid marginal degeneration)	
			a) Wedge resection after PK (A)
			b) Wound repair during or after cataract extraction (A)
F. Thermal keratoplasty (H,P)			
	1. Radiofrequency current (350 kHz) (Conductive keratoplasty—CK)	a. Paracentral burns along 7 and 8 mm-diameter circles (H)	
	2. Holmium: YAG laser (2.06 μm) (multiple paracentral spots)	a. Slit-lamp delivery	
		b. Contact probe delivery	
	3. Deep stromal hot needle thermocoagulation		
	4. Flat probe, central (KC)		
G. Penetrating keratoplasty (refractive aspects)			
		1. Donor–host disparity	a. Donor oversized (H)
			b. Donor same or undersized (M)

Refractive error treated: M, myopia; H, hyperopia; A, astigmatism; P, presbyopia; KC, keratoconus (all grades)

Table 80.1 continued

Category of Surgery	Basic Surgical Technique	Variation of Surgical Techniques or Material	SPECIFIC SURGICAL TECHNIQUES Techniques in Active Use in 2007	Techniques Used Less Frequently or Abandoned
		2. Suture adjustment during or after surgery (A) (see I.D.)		
II. Intraocular lenses (IOLs)				
	A. Phakic IOL (M,H,A)			
		1. Lens fixation		
			1. Anterior chamber angle, multiflex	
			2. Iris-fixated claw	
			3. Posterior chamber, plate	
	B. Aphakic IOL (M,H,A.P)			
		1. Purpose of lens removal		
		a. Cataract		
		b. Refractive lens exchange		
		2. Lens structure		
		a. Foldable		
		b. Rigid		
		3. Lens optic		
		a. Monofocal		
		b. Multifocal		
		c. Accommodative		
			i) Single optic	
			ii) Dual optic	

	2. Lens fixation site and haptic		
		a. Anterior chamber angle, multiflex	
		b. Iris, claw	
		c. Posterior chamber open loop or plate	
		i) Lens capsule support	
			a) Within capsular bag
			b) Ciliary sulcus
		ii) No capsule support	
			a) Iris sutured
			b) Trans-scleral
III. Scleral surgery			
	A. Posterior scleral support (M)		
			1. Strips of sclera, fascia lata, synthetics
	B. Equatorial implants (M)		
			1. Plaques of sclera, subtenons, in four oblique quadrants
	C. Anterior radial sclerotomy (P)		
			1. Radial incisions with or without separators
			2. Laser radial sclerectomy (nm)
	D. Anterior scleral expansion bands (P)		
			1. Synthetic inlays in lamellar tunnel

Refractive error treated: M, myopia; H, hyperopia; A, astigmatism; P, presbyopia; KC, keratoconus (all grades)

small aperture inlay beneath the corneal flap increases the depth of field for presbyopia correction. Placing a ring segment paracentrally in a tunnel flattens the central cornea to treat myopia.

3. *Lamellar keratoplasty* is a form of corneal transplantation in which donor lamellar tissue (without induced changes in corneal power) replaces diseased anterior corneal tissue to preserve more normal corneal endothelium or to replace diseased posterior corneal tissue when the anterior cornea is not diseased. An onlay plano donor may be placed to flatten the cornea and help treat keratoconus (epikeratoplasty).

KERATOTOMY

Keratotomy ('*cutting the cornea*') involves making a partial-thickness incision into the cornea to change its radius of curvature and refractive power. The term 'refractive keratotomy' designates all such incisions. A description of the pattern of the incisions usually modifies the term,[6] such as radial for myopia or transverse across the steep corneal meridian (arc-T) for astigmatism. Radial keratotomy for myopia is not in current clinical use; however, transverse keratotomy for astigmatism is used—in three basic arcuate patterns: (1) arcuate keratotomy in the cornea or in a penetrating keratoplasty wound, (2) 'limbal relaxing incision' approximately 1 mm inside the limbus, and (3) as part of an IOL implant procedure. The transverse incision is placed perpendicular to the steep meridian (the plus refractive cylinder) for the purpose of flattening that meridian and reducing astigmatism—although it can certainly induce astigmatism as well.

KERATECTOMY

Keratectomy ('*excision of a piece of cornea*') is used to change the refraction of a cornea. There are three basic types of keratectomy: (1) keratectomy with an excimer laser, (2) wedge-shaped keratectomy (wedge resection) to decrease astigmatism after penetrating keratoplasty[9] or cataract surgery, and (3) a lamellar crescentic keratectomy for Terrien's marginal degeneration or pellucid degeneration.[10] Revising and resuturing a slipped or separated corneal or limbal wound acts like a keratectomy because it steepens the cornea in the meridian of surgery.[11,12]

LASER REFRACTIVE CORNEAL SURGERY

Because the field of laser refractive corneal surgery[13] is expanding rapidly, I present here more detail concerning the classification and terminology used in laser corneal surgery (Fig. 80.1).

Fundamental to all designations is the fact that the pulsed excimer (193 mm) laser light removes tissue from the cornea. The mechanism on the tissues is a photochemical one: the laser photons

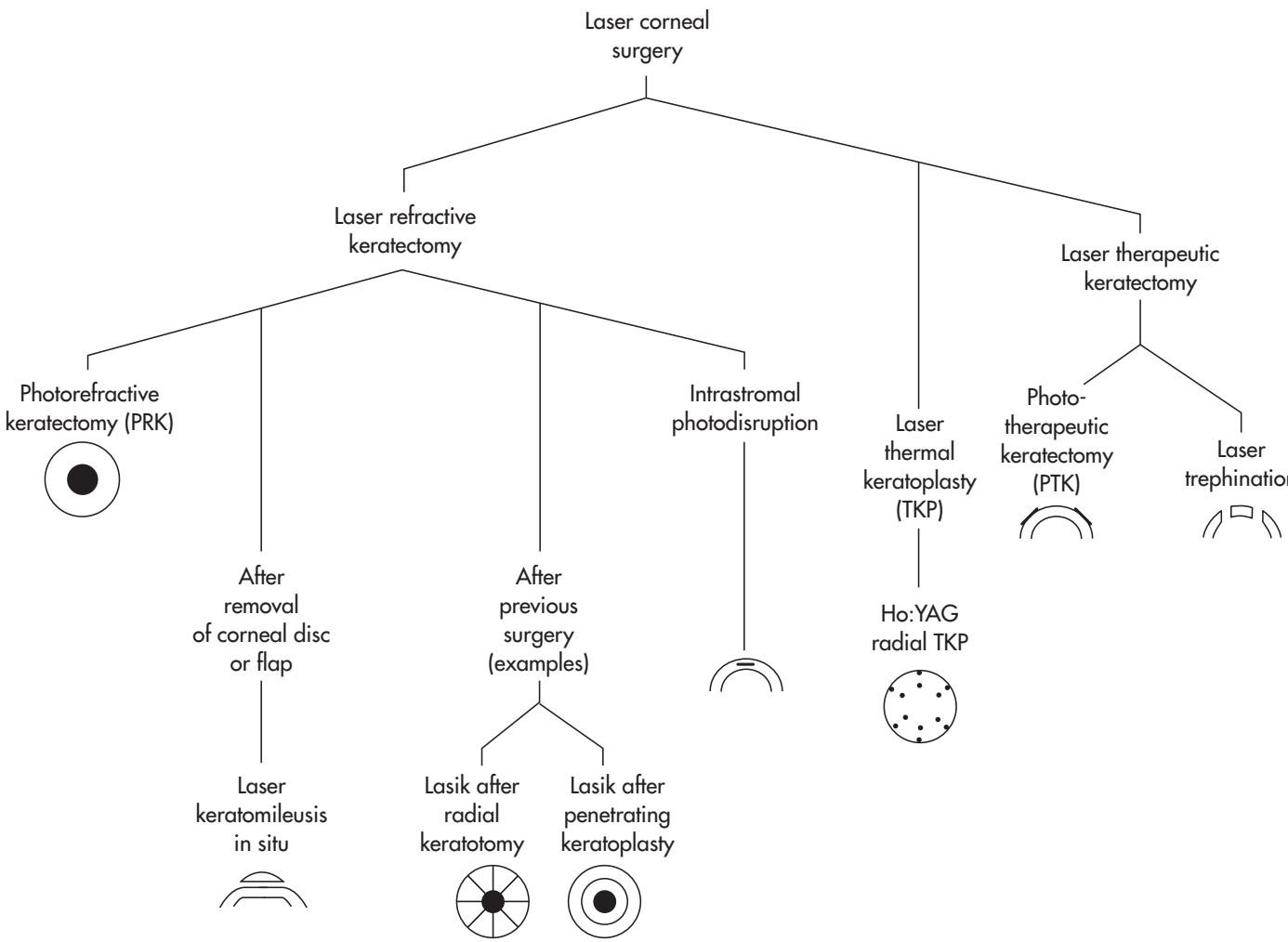

Figure 80.1. Classification and preferred terminology for laser corneal surgery. (Modified from Waring GO. Refract Corneal Surg 1990; 6: 318.)

breaking molecular bonds, with fragments flying from the surface at supersonic speeds. This process has been designated *photoablative decomposition*—photoablation for short. This process contrasts with the more familiar photocoagulation of an argon laser and photodisruption of an Nd:YAG laser emitting at 1064 nm.

The use of other types of lasers in corneal surgery complicates the terminology. For example, femtosecond laser (1053 nm) produces photodisruption by shock waves, not photoablation. So, intrastromal surgery performed with this type of laser is called intrastromal photodisruption, not intrastromal ablation.

The generic term 'laser corneal surgery' can easily be modified to the terms 'laser refractive corneal surgery' or 'laser therapeutic corneal surgery', to designate the two major categories. Because lasers remove tissue, the term 'keratectomy' is used in the proposed terminology.

There are three types of laser refractive surgery keratectomy: (1) removal of a graded amount of tissue from the anterior central cornea, (2) removal of a graded amount of stroma after a microkeratome flap resection (laser keratomileusis), and (3) intrastromal photodisruption 0 used today to create cuts in the cornea.

The term 'photorefractive keratectomy' has come to mean the central removal of a specific profile of Bowman's layer and anterior stroma to change the anterior curvature of the cornea. This is a good example of how the usage of language determines its meaning because, strictly speaking, the term 'photorefractive keratectomy' refers to all types of excimer laser refractive corneal surgery. Nevertheless, photorefractive keratectomy, in both its original and its present meanings, designates the refractive reshaping of the anterior corneal surface after removal of the epithelium. In this sense, it is a type of anterior surface ablation. Two other types of surface ablation involve specific techniques of removal and then replacement of the epithelium: laser epithelial keratomileusis (LASEK) folds back a corneal flap that is loosened with alcohol and replaces it after the excimer laser ablation and epiLASIK aims to create an epithelial flap with a microkeratome, using a dull blade to separate the epithelium from the underlying tissue with subsequent replacement of that epithelial flap.

Removing stromal tissue without disrupting the surface of the cornea requires a nonultraviolet laser that is not absorbed by the cornea but that can focus energy within the stroma, such as an Nd:YLF laser. This creates an intrastromal cavity by photodisruption, but this technique is not used clinically.

Another surgical use of the laser is to refine the result of a previous refractive surgical procedure, such as LASIK after radial keratotomy.

Laser therapeutic keratectomy comes in two varieties. The first involves the removal of a superficial corneal opacity or irregularity. Some have termed this 'superficial keratectomy', which is accurate but inadequate because the term also includes photorefractive keratectomy, which is a type of superficial keratectomy. Again, usage dictates meaning, and the term 'phototherapeutic keratectomy' generally means the removal of anterior diseased layers of the cornea—presently with an excimer laser.

There is a second type of laser therapeutic keratectomy, laser trephination: using a femtosecond laser to make circular or other shaped incisions for penetrating or lamellar keratoplasty.

During cataract surgery

The implantation of IOLs at the time of cataract extraction is standard practice for correcting the aphakic hypermetropia that would result from leaving the eye without its crystalline lens. Lens styles and implementation techniques continue to evolve and improve, with most lenses now being placed within the lens capsule (capsular bag), the anterior portion of which has been removed with a continuous circular capsulorrhexis. These lenses correct the spherical refractive error, based on preoperative IOL power calculations. Lenses with a cylindrical correction must be aligned with the known astigmatic axis of the cornea, and lenses with multifocal or accommodative capability can be used in selected patients to obviate the need for near spectacle correction that would otherwise be needed because of the absence of accommodation.

Refractive lens exchange

Patients who are ametropic and presbyopic after approximately the age of 45 years, and who wish both refractive disorders to be treated, may elect to have their clear crystalline lens removed and replaced by a multifocal or accommodating IOL—the technique known as refractive lens exchange. As of 2007, this is an appropriate option because there is no generally accepted excimer laser pattern that can create a multifocal cornea for presbyopia—and certainly not an accommodating cornea!

Phakic intraocular lenses

Phakic IOLs are implanted in an eye with retention of the normal crystalline lens (therefore remaining phakic). There are three major indications for this type of lens: (1) high myopia and high hyperopia outside the range reasonably treatable with an excimer laser, (2) corneas that are thin or somewhat irregular (e.g. keratoconus suspects) but that allow good spectacle-corrected visual acuity, and (3) patient preference.

PENETRATING KERATOPLASTY

The major reason for performing a penetrating keratoplasty is to replace the central portion of a scarred or distorted cornea by clear regular donor tissue. Between 1940 and 1980, the major clinical challenge was to maintain a clear graft. However, now that grafts remain clear in approximately 85% of cases,[14,15] control of the refractive effect of the donor has become increasingly important, especially when an IOL is used, as in a combined penetrating keratoplasty, cataract extraction, and IOL implantation (triple procedure). The surgeon not only must control factors that affect the spherical power of the graft (such as wound configuration, suture pattern, and donor size) but also must select an IOL power that approximately matches the final refractive power of the graft and the axial length of the globe.[16]

Control of astigmatism during and after penetrating keratoplasty is an important refractive component. Creating a uniform wound configuration by using a mechanical or femtosecond laser trephine and ensuring regular suture placement and tension will help diminish astigmatism. Adjustment of sutures after surgery can do the same, either by selective removal of interrupted sutures in the steep semimeridian or by adjustment of the tension on a running suture to distribute it more evenly and create a more spherical cornea.[9,17,18]

LAMELLAR KERATOPLASTY

Although lamellar keratoplasty using manual dissection techniques was used with varying frequency in the past, it was abandoned in most cases in the 1980s and 1990s because the quality of vision was not as good as that achieved with contemporary penetrating

keratoplasty. However, two new techniques of lamellar keratoplasty are being used with increasing frequency, and increasingly improved refractive outcomes.

The first is deep lamellar keratoplasty, using either a microkeratome or an air dissection technique that allows removal of almost all of the corneal stroma down to Descemet's membrane, leaving a minimal interface between the lamellar donors with less disruption of the quality of vision after surgery. This technique is indicated when the corneal endothelium is healthy, but the stroma is not, as in keratoconus, stromal corneal dystrophies, and anterior stromal scarring.

The second technique is endothelium keratoplasty, in which the diseased endothelium and Descemet's membrane are removed, retaining the more healthy anterior corneal layers, as in Fuchs' endothelial dystrophy. The variants of this technique include a deep lamellar resection in which some of the posterior cornea is also removed and the Descemet's stripping technique in which only Descemet's membrane and the endothelium are removed. The donor cornea is folded and inserted through a limbal incision. From the refractive point of view, this technique has great promise, since it preserves the basic anterior corneal curvature and general preoperative refractive state of the eye.

THERMAL KERATOPLASTY

Techniques of thermal keratoplasty are over 100 years old. A large variety of techniques have been abandoned, including the use of a temperature-controlled flap probe to flatten the cornea and keratoconus, using a hot tip probe penetrating deeply into the stroma and shrinking the collagen paracentrally to steepen the center and treat hyperopia, holmium:YAG laser thermal keratoplasty to create focal spots of intrastromal thermal coagulation paracentrally to steepen the central cornea, and others.

Currently, the only technique of thermal keratoplasty in clinical use is radio-frequency current (350 kHz), known as conductive keratoplasty (CK), with applications of approximately eight burns around a 7 mm- and/or an 8 mm-diameter circle, which shrink the stroma, steepening the central cornea and rendering the eye more myopic. Currently, the technique is used primarily to treat emmetropic presbyopes by creating monovision for near vision in one eye.

SYNTHETIC PROCEDURE VERSUS TISSUE ALTERATION

Another way to classify techniques of refractive surgery is to distinguish two broad categories: synthetic materials such as intracorneal ring segments and IOLs, as opposed to techniques that alter tissue by cutting or removal, such as refractive keratotomy and keratomileusis. The major distinction between the two is that surgery that uses synthetic materials is reversible, that is the material can be removed and the eye returns to its preoperative condition in most cases. This has a great appeal to patients. Both types of procedures are adjustable: synthetic procedures are replaceable, and tissue alteration procedures are modifiable with repeated (enhancement) surgery.

Of course, combinations of synthetic and tissue-altering techniques can be used, most commonly with the implantation of an IOL followed by a LASIK or PRK to adjust the refractive result, a technique known as bioptics (one optic in the eye and the second optical change in the cornea).

One can conceive of future procedures that might also combine these two elements. An example is laser-adjustable synthetic epikeratoplasty (LASE), in which the corneal epithelium is removed and an onlay of synthetic material with a specific refractive correction is bonded to Bowman's layer and allowed to re-epithelialize. If the refractive outcome is inaccurate, the epithelium can be removed and an excimer laser photorefractive keratectomy performed on the acellular synthetic material without concern for wound healing, allowing the epithelium to resurface the synthetic lenticule. If the procedure is ineffective or complicated, the synthetic lenticule can be removed, allowing the cornea to re-epithelialize and return to its original condition.

OTHER CLASSIFICATION SYSTEMS

There are other approaches to the classification of refractive corneal surgery. One is to use the ametropia being treated[22]—myopia, hyperopia, aphakia, or astigmatism—as the basis, but this requires repeated description of similar surgical techniques for each refractive error, such as keratomileusis for myopia and for hyperopia. A more abstract classification is based on the type of alteration of the cornea: resection of tissue (e.g. keratomileusis and wedge resection), relaxation of the tissue (e.g. transverse keratotomy and suture removal), addition of material (e.g. corneal inlay and epikeratoplasty), substitution of tissue (e.g. penetrating keratoplasty), retraction of tissue (e.g. thermal keratoplasty), and compression of tissue (e.g. tight sutures and epikeratoplasty for keratoconus). One may also classify refractive corneal surgery in bioengineering terms: changes in corneal volume, thickness, surface area,[23] and, in the future, even stress–strain forces. Meanwhile, a classification based on surgical technique (see Table 80.1) will enhance communication and understanding among those interested in refractive surgery.

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81 Principles of biomechanics in refractive surgery

William J. Dupps, Jr.

Few biological systems are as functionally sensitive to changes in tissue geometry as the eye. Even with elegant ocular registration, high-speed tracking systems, and the submicron surgical precision afforded by the excimer laser, discrepancies between intended and realized optical outcomes in photoablative refractive surgery still occur and are often visually significant. Accordingly, corneal refractive surgery is evolving into a field whose precision is limited primarily by the innate biological and biophysical responses of the patient. This chapter surveys corneal biomechanical behavior and highlights its increasingly important role in improving the safety and predictability of refractive surgery.

THE GEOMETRIC–EMPIRICAL MODEL OF PHOTOABLATIVE KERATOREFRACTIVE SURGERY

The ablation algorithm is the fulcrum of surgical control in photoablative refractive surgery. As such, it can be modified, either at the proprietary level or with surgeon-adjustable spherical offsets, in an attempt to reduce unexpected visual outcomes through the process summarized in Figure 81.1. This process begins with the surgical candidate's preoperative measurements. While our conceptualization of the patient is based on an extensive history and physical examination, the surgical recipe is ultimately determined from a reduced data set based largely, if not solely, upon the phoropter refraction (in conventional laser vision correction), the wavefront aberration map (in custom or wavefront-guided procedures), or the corneal topography map (in topography-guided ablation).

From any of these numerical representations of the patient, a treatment algorithm is derived (depicted as a 'black box' in Fig. 81.1) that is optimized for producing the desired corneal power change in a typical patient. Although the details of platform-specific ablation algorithms are protected for proprietary reasons, all ablation routines appeal at some level to the shape-subtraction[1] model of refractive keratectomy that was specified in geometric terms by Munnerlyn et al in 1988.[2] In the familiar reduced form of the model for myopia, t_o represents the central stromal ablation depth in microns, S the diameter of the ablation in millimeters, and D the dioptric correction attempted. According to this model, photoablative subtraction of the specified thickness profile from the corneal surface should produce the intended refractive shift.

In practice, however, early investigators noted systematic discrepancies between intended and measured outcomes that prompted empirical modifications of the algorithm. What are some sources of this predictive error? In every step of the surgical process depicted in Figure 81.1, a certain degree of imprecision exists, even if clinically insignificant when considered alone. But these small uncertainties propagate through the surgical process and manifest as outcome variability that is no less than the sum of the errors from every stage of the process. For example, imprecision or inaccuracy in the refraction used to generate the ablation algorithm preoperatively and to assess its effectiveness postoperatively contribute error that limits the precision of the next surgical plan. Objective assessments of refractive status such as wavefront aberrometry afford certain advantages over subjective refraction[3] but errors in reproducibility, although low in many cases,[4] are still nonzero. Furthermore, the laser–tissue interaction itself is complex, and ablative efficiency is affected by corneal hydration, ambient humidity, ablation plume interference, laser beam incidence angle, laser energy nonuniformities, and multiple surgical variables that exert their influence through similar mechanisms. For treatments that are neither wavefront-guided nor aspheric (where the latter have been called 'Wavefront-Optimized®' on the Allegretto Wave platform), the ablation pattern incorporates simplifying assumptions such as paraxial optics and spherical corneal surfaces that contribute additional error at the intraoperative stage.[5]

While imprecision due to measurement error, algorithm simplifications, and laser-tissue interaction nonidealities is important to address, the individual patient's response to surgery is the most important and most challenging source of outcome variability in refractive surgery. The shape-subtraction paradigm of refractive keratectomy assumes that the cornea is biologically and biomechanically inert.[6] Our experience with incisional refractive surgeries such as radial keratotomy has taught us that the cornea is anything but mechanically inert. Biomechanics figure prominently in any surgery in which corneal tissue is removed or incised, including routine LASIK, and the effect is more profound when we operate on corneas altered by previous refractive surgery or penetrating

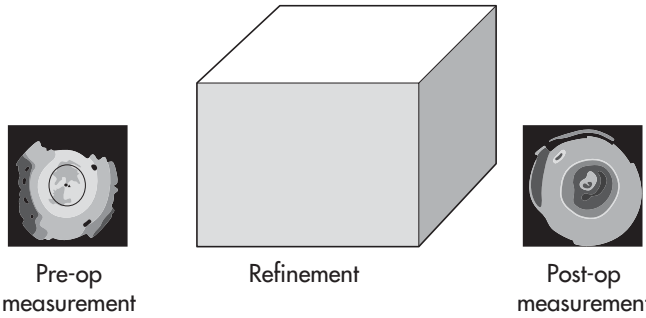

Figure 81.1. Surgical outcomes are leveraged through the ablation algorithm. Algorithms are specific to each laser vision correction platform and generally provide for surgeon-specific spherical modifications based on personal nomograms. Preoperative measurements are used to generate the ablation recipe, surgery is performed, and then postoperative measurements are obtained. Results may be compared to attempted corrections to evaluate the performance of the algorithm and nomogram and to make modifications. The refractive effects of the biomechanical and wound healing responses are not accounted for explicitly in laser algorithms, although empirical adjustments have been partially successful in reducing the systematic error associated with these effects. Further refinement and improved predictability in individual patients will depend on novel preoperative measurements capable of better-predicting patient-specific biophysical and biological responses.

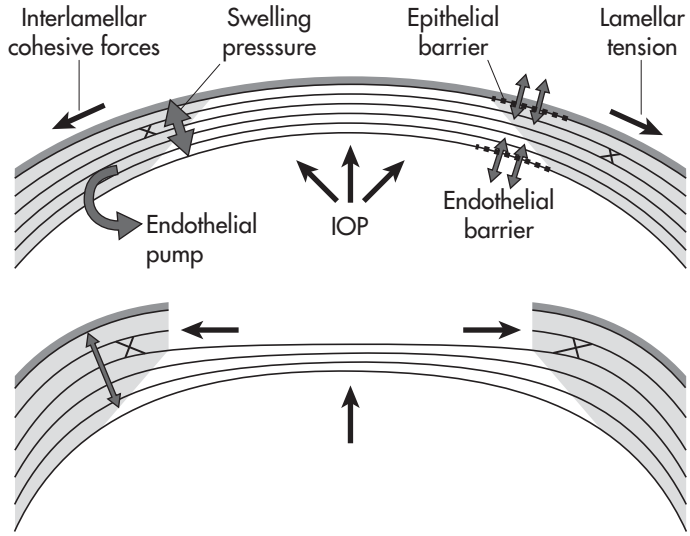

Figure 81.2. Biomechanical forces in the cornea and a model of biomechanical central flattening associated with disruption of central lamellar segments. A reduction in lamellar tension in the peripheral stroma reduces resistance to swelling, and an acute expansion of peripheral stromal volume results.[10] Interlamellar cohesive forces[11] and collagen interweaving,[12] indicated by grey shading, are greater in the anterior and peripheral stroma and provide a means of transmitting centripetal forces to underlying lamellae. Because the central portions of these lamellae constitute the residual stromal bed (RSB), flattening of the optical surface occurs, resulting in hyperopic shift. The degree of flattening is associated with the amount of peripheral thickening.[10] This phenomenon is exemplified clinically by PTK-induced hyperopic shift but is important in any central keratectomy, including PRK and LASIK. Offsetting elastic weakening and steepening of the RSB may occur,[13] and the threshold for inducing irreversible (plastic) or progressive (viscoelastic) steepening (or ectasia) is a matter of ongoing clinical concern.

keratoplasty. And while the iterative loop in Figure 81.1 is valuable for retrospective adjustment of systematic errors in large patient series, it is of little value in preventing the idiosyncratic or random errors attributable to biological and biomechanical variation, particularly if we have not identified critical preoperative predictors of response or have no capabilities to measure them.

The corneal biomechanical response manifests clinically as (1) intraoperative corneal shape changes affecting the immediate postoperative refractive state; (2) ongoing postoperative shape changes that contribute to refractive regression, irregular astigmatism, and ectasia; and (3) an increased propensity toward shape change when challenged by altered hydration, hypoxia, or subsequent surgery. The importance of these biomechanical responses is greater than ever in an era of wavefront-guided treatments for correction of higher-order optical aberrations.[7–9] Continued empirical refinement and major advances in laser delivery platforms[3] have markedly improved the predictability of outcomes, and most often the remaining imprecision leads to minor refractive errors that fall within a well-tolerated range. In some cases though, a predisposition to mechanical instability or abnormal healing can lead to gross over- or undercorrection or sight-threatening complications such as keratectasia.

STRUCTURAL FOUNDATIONS OF THE BIOMECHANICAL RESPONSE

The cornea is a complex biomechanical composite whose behavior depends on its structural subcomponents and their organizational motifs (Fig. 81.2). Bowman's layer and the stroma are the only collagenous layers of the cornea and thus provide the majority of the cornea's tensile strength. The epithelium is attributed a minimal role in this tensile strength, and its removal causes little or no change in the anterior corneal curvature.[14] The extensibility and low stiffness of Descemet's membrane ensure its laxity over a broad range of intraocular pressures (IOPs)[15] and may serve as a high-compliance buffer to protect the endothelium from the effects of high stromal stresses. The role of Bowman's layer, an 8–12 μm-thick acellular condensation of stroma with more randomly oriented collagen fibrils,[16] has been a subject of controversy.[17,18] Although some have proposed a structural role distinct from that of the stroma, extensiometry studies in normal corneas suggest that removal of Bowman's layer does not measurably alter the bulk mechanical properties of the cornea.[18] The biomechanical importance of Bowman's layer in abnormally thin or ectatic corneas is suggested by the fragmentation of Bowman's layer observed during histological examination of keratoconic tissue.

The mechanical response of the cornea to injury is dominated by the stroma. On a weight basis, the stroma is approximately 78% water, 15% collagen, and 7% noncollagenous proteins, proteoglycans, and salts.[19] A total of 300–500 lamellae run from limbus to limbus and are stacked with angular offsets; this orientation becomes increasingly random in the anterior stroma where significantly more oblique branching and interweaving are noted.[16] Interlamellar branching is also more extensive in the corneal periphery than in its center (Fig. 81.2).[20,21] Interweaving of collagen bundles between neighboring lamellae provides an important structural mechanism for shear (sliding) resistance[22] and sharing of tensile loads between lamellae.[6,10] In addition, X-ray diffraction studies provide evidence of a predominantly circumferential fibril orientation in the corneal periphery[23] that may favor conservation of limbal circumferential dimensions even in ectatic disease.[24] Proteoglycans play a critical

role in collagen fibril assembly and spacing,[25] and their mechanical importance may be greater than currently recognized.

CORNEAL MATERIAL PROPERTIES

The mechanical properties of the cornea and its constituent materials link the cornea's morphology to its mechanical behavior under the stresses of surgery or disease. In the terminology of material science, the cornea is a complex anisotropic composite with nonlinear elastic and viscoelastic properties. It is a *composite* because its properties are determined by the interaction of disparate materials like collagen and a polyanionic ground substance and *anisotropic* because its properties are not directionally uniform. The cornea is also highly heterogeneous in the central to peripheral, anterior to posterior, and rotational dimensions. A generalized solution of the three-dimensional equations describing such a complex system is untenable, and reduction of the problem to the linear, isotropic case is used to arrive at the more familiar definitions of Young's modulus and other properties described below.

Friedenwald defined the *ocular rigidity coefficient* and performed some of the earliest characterizations of ocular biomechanical properties.[26] A pressure–volume curve is recorded during a volumetric distention experiment and provides a measure of whole-globe stiffness. This relationship is characterized by the slope of the pressure–volume curve (mmHg/μL). It is nonlinearly dependent on IOP and has been shown to increase with age.[27] Its utility in refractive surgery remains to be demonstrated and may be limited to the extent that corneal contributions to rigidity are inseparable from scleral and uveal components.

The *elastic (or Young's) modulus* may be one of the most critical material properties in understanding the corneal response to refractive surgery[13] and provides an indicator of stiffness. An *elastic* material regains its original geometry when an imposed stress is removed and does so in a reversible manner along the same stress–strain pathway. The elastic modulus is traditionally measured in excised tissue with an extensiometer that measures force generation during steady axial elongations of the sample. The slope of *stress* (force per unit area, N/m^2) over *strain* (a dimensionless quantity defined by the current length divided by the starting length) is calculated for a representative portion of the curve. A high modulus indicates a stiff or low-compliance material. While most biological soft tissues approximate linear elastic behavior when a small range of stresses is considered, their overall elastic behavior is highly *nonlinear*. A linear approximation can be obtained from the instantaneous slope of the stress–strain curve (*tangent modulus*) or as a chord between two points on the curve (*secant modulus*).[28]

In Figure 81.3, *A*, an example of nonlinear elastic behavior in a donor cornea specimen is presented. Nonlinearity arises from an initially slow uptake of load as the collagen takes up slack, followed by stiffening as maximal fibril recruitment is approached. *Plastic* responses such as *yield* and *failure* occur when a permanent strain is incurred and the material does not recover its original configuration upon unloading.

The range of reported values for the elastic modulus of the human cornea spans orders of magnitude.[29] Although some biological variability is expected, this variability also reflects the challenges of obtaining representative data with a range of tissue hydrations, loading conditions, and experimental techniques in ex vivo tissue. It should also be clear from the above discussion that a nonlinear function does not allow definition of a single modulus value but, instead, requires its definition as a function of load or as a mean value over a specified loading interval. Membrane inflation experiments in normohydrated donor globes provide a more physiological alternative to extensiometry[30] but do not abrogate the ultimate need for in vivo measurement techniques.

Poisson's ratio is a conversion for relating strain in one direction to secondary strain in the transverse direction. A stromal lamella under tensile stress will thin or narrow to some degree in its other dimensions. An out-of-plane/in-plane strain ratio of 0.49 is typically assumed because it approximates the cornea's fluid-filled, near-incompressible status. In reality, Poisson's ratio is a true physical property of the tissue and not a constant; as such, its role as a variable in elastic, plastic, and viscoelastic thinning of the residual stromal bed (RSB) after LASIK could be important.

Viscoelastic properties arise from the time-dependent nature of biomechanical responses and are a feature of all biological soft tissues. These properties are represented by the phenomena of *hysteresis*, *stress relaxation*, and *creep*. As opposed to the symmetric loading and unloading behavior of purely elastic materials, viscoelastic materials return to their pre-stress configuration via different stress–strain pathways that depend on loading rates. This discordance between loading and unloading behavior can be partially characterized by *hysteresis*. Viscoelastic *creep* is a time-dependent elongation that occurs under a sustained stress (such as IOP) and may be an important contributor to the mechanics of ectasia.[31] Finally, Figure 81.3, *B* illustrates a viscoelastic *stress relaxation* experiment in which strain is increased then held constant while a slow time-dependent relaxation of the load is observed.

Shear strength describes stromal resistance to sublayer sliding. The shear resistance provided by collagen interweaving and other matrix forces may be related to metrics such as the interlamellar cohesive strength.[11,21] Corneal shear strength is low relative to its tensile strength[32] but provides a mechanism for load transfer between lamellae that may contribute to hyperopic shift after photoablation according to the model presented in Figure 81.2 and discussed below.[10] Abnormalities of bending strength and lamellar sliding also have potential relevance in the pathogenesis of ectasia.[24,33,34]

COMPUTATIONAL MODELING IN REFRACTIVE SURGERY

The ultimate goal of any corneal modeling effort in this setting is development of an accurate simulation vehicle for optimizing the accuracy and safety of refractive surgery procedures. Models of corneal refractive surgery range from conceptual models to complex computational simulations that integrate structural, biomechanical, and optical representations of the corneal response. Complex structures like the cornea can be divided into a mesh of representative geometries ('finite elements') with their own material properties; the physical solutions during a surgical or disease simulation can then be obtained iteratively from element to element until the solution for the entire structure is obtained. Geometric data sets can be used as a scaffold for superimposing substructural features. The predictive value of any model depends on valid input, and recent progress in anterior segment imaging has improved our ability to accurately measure corneal geometry.

Finite element analysis has been used in attempts to simulate surgical results in radial keratotomy,[35–38] astigmatic keratotomy,[39–41] phototherapeutic keratectomy,[42,43] PRK,[44,45] and LASIK.[45–47] Even with the most elegant models, however, assignment of appropriate material properties is a great challenge and has a profound impact

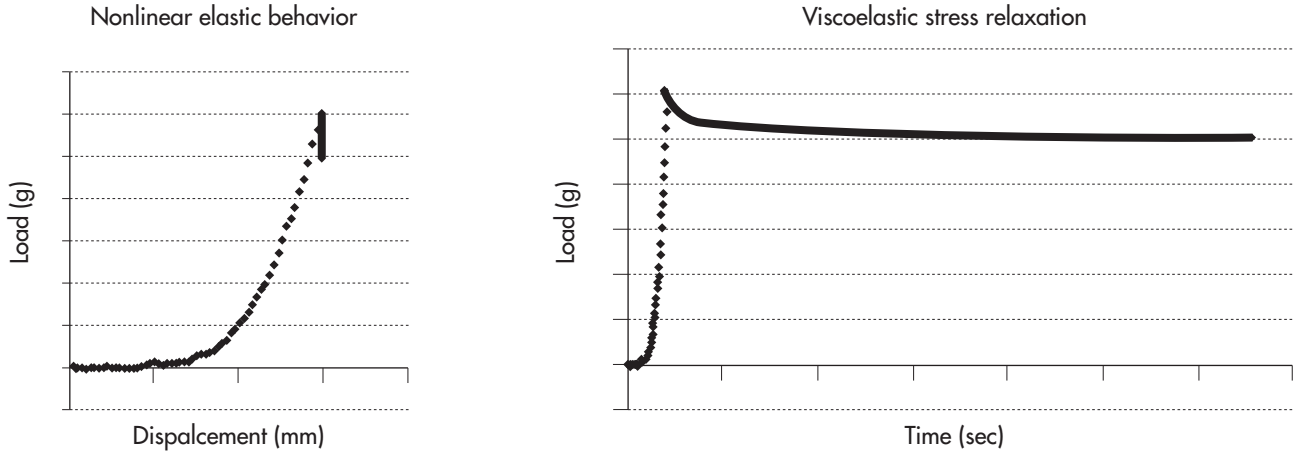

Figure 81.3. Experiments illustrating elastic (*A*) and viscoelastic (*B*) behavior in a 7-mm, full-thickness horizontal corneal strip from a 63-year-old donor. *A*, Progressive stretching of the sample and measurement of the induced load allow calculation of the elastic modulus from the slope of the stress–strain relationship. The relationship is nonlinear. *B*, A second experiment in which a constant displacement is imposed in the same sample demonstrates time-dependent stress relaxation, a viscoelastic property of biological soft tissues.

on the accuracy of surgical simulation and optimization. For example, if heterogeneity of the elastic modulus and the stromal swelling pressure are neglected, then an elastic thin-shell model of the cornea fails to predict hyperopic shift in PTK as discussed below.[42] Models that incorporate these properties and their heterogeneous distribution[37,43] are better capable of representing clinical results but are still exquisitely sensitive to errors in specified material properties, particularly the elastic modulus.[13,31] To the extent that material property values from ex vivo experiments reflect in vivo properties of the typical surgical candidate, models based on such measurements have the potential to reduce systematic error at the populational level. The utility of computational simulations will be further increased when clinical techniques for measuring key properties in individual patients are refined and then integrated into the modeling process.

CLINICAL MEASUREMENT OF CORNEAL BIOMECHANICAL PROPERTIES

Traditional extensiometry, despite its limitations, has revealed deficits in elastic tensile strength in keratoconus[48] and suggests a diagnostic role for elastic modulus determination in the clinical setting. The obvious lack of suitability for in vivo testing, however, has led to accelerated efforts to develop nondestructive, noninvasive tools for clinical biomechanical property measurement.

Ultrasonic shear wave propagation velocity has been investigated as a method for measuring the elastic modulus without need for tissue destruction.[49,50] Recent experiments with a prototype handheld device (Sonic Eye, PriaVision, Inc., Menlo Park, CA) have demonstrated the ability to measure directional and regional stiffness differences in porcine[50] and human donor globes,[51] corneal stiffness changes with keratotomy, and marked increases in stiffness with stromal collagen crosslinking, which also produce artifactual increases in applanation pressures.[50] Young's modulus is related to the product of corneal density and the square of the wave velocity measured between the two transducer tips, which are positioned along the anterior corneal arc. Stiffness is measured *in the plane of the lamellae*, similar to traditional extensiometry, and thus may be more comparable to published elastic modulus values than properties elicited from out-of-plane perturbations. Signal attenuation in the presence of the precorneal tear film is the primary challenge to clinical implementation, and developmental efforts are ongoing.

The commercially available Ocular Response Analyzer (ORA, Reichert, Inc., Depew, NY) utilizes a high-speed air-puff to quantify the dynamics of corneal deformation and recovery as an indicator of corneal hysteresis (CH).[52] Figure 81.4 illustrates a typical response waveform. In- and outgoing applanation events are indicated by the two peak intensities of reflected infrared light (in red), and the air pressures (in green) intersecting these two applanation events are recorded as P_1 (ingoing) and P_2 (outgoing). Corneal hysteresis is simply the difference between the in- and outgoing applanation pressures ($P_1 - P_2$), where a higher CH indicates a greater capacity for absorption of kinetic energy (a *viscoelastic* property). Eyes with more viscoelastic 'momentum' produce a higher CH due in part to a delay in deformation (and therefore applanation) relative to the onset and decay of the pressure stimulus. As illustrated in Figure 81.4, this viscous delay shifts the applanation peaks to the right, resulting in a rise in P_1, a decrease in P_2, and an increased CH. The corneal resistance factor (CRF) is derived from the same dual-applanation signal and is proposed to be a measure of the *elastic* resistance of the cornea. The formula for the CRF is similar to CH but incorporates an empirical adjustment (k_{CRF}) to P_2 ($CRF = P_1 - k_{CRF}P_2$) designed to reflect a greater dependence on central corneal thickness (CCT) and IOP. The ORA also reports two IOP values: the Goldmann-correlated IOP (IOP_G) derived from the mean of P_1 and P_2 and the cornea-compensated IOP (IOP_{CC}). The IOP_{CC} was designed to be less sensitive to corneal properties than traditional applanation tonometry and was calibrated empirically to be relatively unaffected by LASIK.

The ORA is being investigated in glaucoma, keratoconus, and refractive surgery patients. Both CH and CRF are lower after LASIK[52,53] and in eyes affected by keratoconus.[52] Lower CH has also been associated with a higher risk of visual field progression in a cross-sectional study of glaucoma patients.[54] The role of these measurements in screening refractive surgery candidates for ectasia risk or evaluating the risk of optic neuropathy in glaucoma suspects is an important area of investigation, and the ORA clearly provides novel information about biomechanical risk for which CCT is an incomplete proxy. Both CH and CRF measure the *bending resistance* to a high-speed insult without regional or directional discrimina-

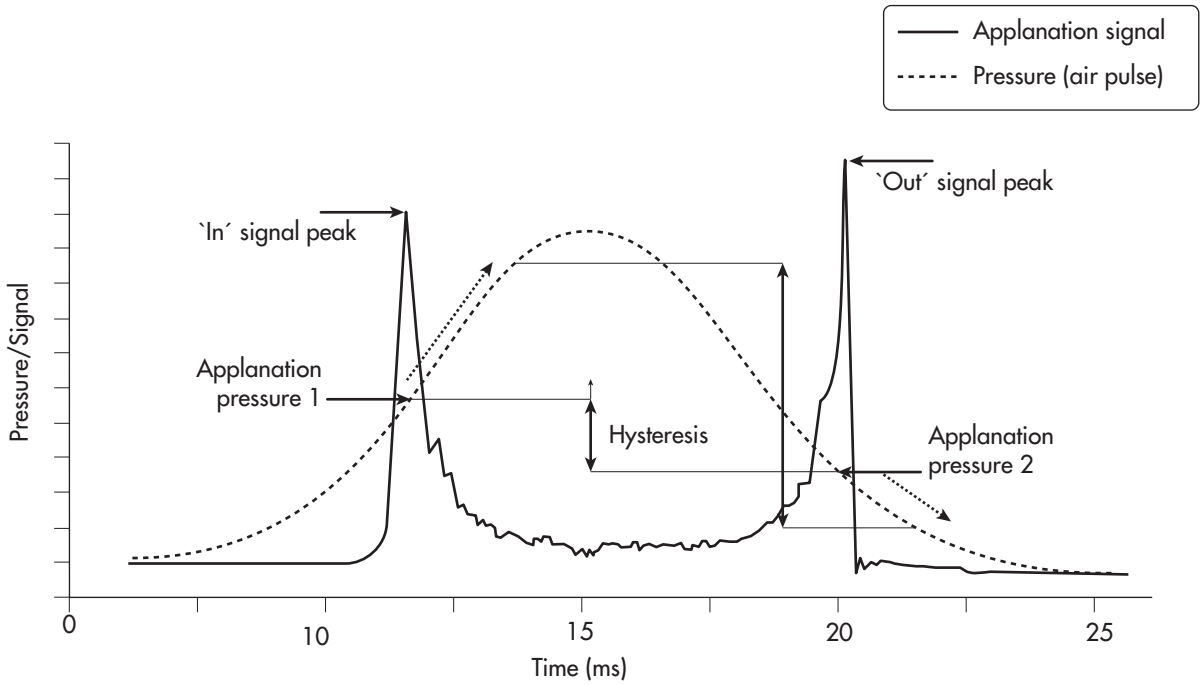

Figure 81.4. A typical response waveform for the Reichert Ocular Response Analyzer. In- and outgoing applanation events are indicated by the two peak intensities of reflected infrared light (in red). The air pressures (in green) intersecting these two applanation events are recorded as P_1 and P_2. Corneal hysteresis (CH) is the difference between the in- and outgoing applanation pressures ($P_1 - P_2$). A higher CH indicates a greater viscoelastic capacity for absorption and thus damping of kinetic energy. Eyes with more viscoelastic damping capacity result in greater dissipation of perturbation energy and thus a delay in applanation relative to air pressure. This viscous delay shifts the applanation peaks to the right, resulting in a higher P_1, a lower P_2, and an increase in CH. (Figure adapted from Luce[52] and modified.)

tion, and the values are not directly comparable to measurements of the corneal elastic modulus by techniques described above. The morphology of the infrared signal contains additional information that is not represented by CH or CRF, and further analysis of these signal features is underway.

Other emerging techniques include measurements of bending resistance to stepwise indentations during Placido-ring topographic imaging,[55] interferometric determinations of apical displacement during IOP changes,[56] and two- and three-dimensional corneal optical coherence elastography.[57] Because different combinations of perturbations and imaging modalities interrogate entirely different aspects of the ocular biomechanical state, investigators will need to determine which measures are best suited for answering a particular clinical question.

THE BIOMECHANICAL RESPONSE TO KERATECTOMY

Several forces contribute to the preoperative steady state and undergo complex disruptions during corneal refractive surgery (Fig. 81.2). The hydrophilia of stromal glycosaminoglycans contributes to a negative intrastromal fluid pressure under which the entire stroma is heavily compressed.[58] The IOP manifests both as a centripetal force and as a lamellar tension[19] to counteract this stromal swelling pressure, which is also balanced by tear film evaporation, the epithelial and endothelial barriers, and active endothelial transport.[59] Cohesive forces between lamellae provide further resistance to expansion of the interfibrillary space during swelling, and their greater relative strength in the peripheral and superior cornea may have implications for the inferocentral predilection of keratoconus[11] and in induced astigmatism after ablation and flap creation.

During LASIK, PRK, or any other procedure involving central ablation, an immediate circumferential severing of corneal lamellae is produced. In simple elastic shell models, this results in a forward herniation that, if considered alone, would result in corneal steepening.[42] However, central ablation also relaxes lamellar tension in residual peripheral lamellar segments, which decreases local resistance to swelling and results in peripheral stromal thickening.[10] Expansion of the peripheral stroma's dimensions and any limbal displacement owing to lamellar disruption may generate centripetal stress in underlying lamellae through the dense interlamellar connections at the margin of the ablation zone. Because the central portions of these lamellae comprise the new anterior surface, there is resulting central flattening (Fig. 81.2). This flattening response appears to dominate any central steepening tendency when ablation is limited to the anterior stroma, but progressively deeper insults result in a net shift toward corneal steepening[14,60] and can ultimately result in ectasia. The elastic modulus of the residual stroma bed and the shear (sliding) resistance in the bordering peripheral stroma may influence the rate of ablation-dependent flattening and the depth at which flattening effects lose ground to pre-ectatic elastic steepening.

This model provides a rationale for hyperopic shifts that occur even before the onset of epithelial healing and in the absence of a concave ablation profile. This response is most clearly demonstrated by unintended hyperopic shift during PTK, in which an ablation depth-dependent flattening can be observed in donor and clinical studies despite attempts at a uniform (and thus plano) ablation profile.[10,61] In a multivariate paired-control donor analysis of PTK-

induced hyperopia, biomechanical peripheral thickening was more strongly associated with the degree of flattening than the measured ablation pattern itself.[10] While the relative influence of ablation profile is presumably greater in ametropic treatments than in PTK, this analysis demonstrated in a controlled fashion that changes in central curvature are not solely a product of ablative shape subtraction.

In clinical practice, an intrinsic flattening response augments the effects of a myopic procedure and impedes efforts to correct hyperopia. This is supported by the fact that large overcorrections must be attempted to effectively treat high levels of primary hyperopia.[62] If an identical algorithm is used to treat secondary hyperopia of the same magnitude (i.e. after previous myopic LASIK), significant overcorrection results. This difference in effectiveness can be attributed to fundamental differences between the biomechanical status of a virgin cornea and that of a surgically altered cornea that has adapted to an entirely different load-bearing milieu. Larger treatment zones may reduce the tendency toward biomechanical central flattening[63] by distancing the central cornea from the effects of peripheral stromal poroelastic forces.

A COMPARISON OF SURFACE ABLATION AND LASIK

During any procedure involving central ablation, an immediate circumferential severing of corneal lamellae occurs and triggers the cascade of biophysical changes presented in the previous section. LASIK clearly represents a more complex biomechanical insult than surface ablation (PRK, LASEK, or epi-LASIK), and its effects are additive to those described above. First, the total depth of the lamellar disruption is greater for a given refractive correction and will alter the balance between hyperopic effects and steepening effects from weakening of the corneal cap. Depth-dependent differences in corneal properties will affect this balance and likely vary from eye to eye and patient to patient.[64] Creation of the LASIK flap even without subsequent photoablation induces hyperopia, astigmatism, and higher-order aberrations that depend on hinge position and microkeratome type.[65,66] The meniscus-shaped flap produced by some mechanical microkeratomes interrupts more lamellae in the mid-peripheral bed than in its center, possibly potentiating the biomechanical response[67] and confounding nomogram adjustments based on central flap thickness estimates. The optical effects of flap creation may not be limited only to changes in the residual stromal surface but may also extend to shape changes *within the flap* related to the circumferential keratotomy of flap creation.[64]

To account for the separate effects of flap creation and photoablation, some have investigated a staged procedure incorporating a remeasurement delay after flap creation.[68,69] This approach is more strongly advocated for correction of ametropia and astigmatism after penetrating keratoplasty, where the biomechanical and wound healing responses to flap creation are far less predictable.[70,71] Sub-Bowman's keratomileusis (SBK) involves creation of a stromal-epithelial flap 90 μm in depth or thinner, often facilitated with a femtosecond laser, and could provide modest advantages over traditional LASIK by reducing variability associated with the depth-dependent biomechanical response. Femtosecond lasers may also allow more precise specification of flap morphology, thus reducing the astigmatic effects of flap creation and improving nomogram quality by reducing variability between patients. But even absolutely repeatable flap geometry cannot eliminate the differences in residual stromal and flap responses due solely to the specific biomechanical makeup of the patient's cornea. Biomechanically 'neutral' flap patterns could be explored to minimize unintended refractive effects that affect the aggregate of patients, but predictors of individual responses will be necessary to prevent undesired outcomes in patients not represented by the mean.

By circumventing the immediate and long-term biomechanical effects of flap creation on the cornea, surface ablation significantly reduces the number of variables and range of effects that can adversely affect the optical predictability of laser vision correction. But many of these advantages are offset by the greater impact of wound healing on the predictability of surface ablation procedures,[64] which is a subject beyond the scope of this chapter.

ECTASIA

Debate continues about whether postrefractive surgery ectasia is an iatrogenic condition or a subclinical keratoconus that manifests after laser vision correction. Clinical risk factors for post-LASIK ectasia include high myopia, forme fruste keratoconus, and low RSB thickness.[72] While a lower limit of 250–300 μm has been recommended for the RSB thickness,[73] its actual value cannot be wholly determined preoperatively because it is affected by microkeratome predictability and a stromal ablation rate that varies with hydration and from patient to patient. Most importantly, even the most accurate estimates of RSB thickness will not fully account for elastic and viscoelastic risk factors, just as presence of a presumably normal CCT does not rule out keratoconus.[74] Because focal weaknesses produce marked increases in local stress, spatial inhomogeneities in material strength may be more important than bulk properties in some cases. Conversely, evenly distributed material strength may allow for long-term stability of some corneas with an RSB thickness less than 250 μm.[75]

Previous sections have commented on possible biomechanical abnormalities in keratoconus and post-LASIK ectasia. Elastic steepening with progressive central thinning is inversely related to the elastic modulus of the residual central corneal bed.[13] However, an elastic forward protuberance of the cornea must be distinguished from ectasia. Although the former can be a precursor of ectasia,[13] ectasia requires a progressive deformation, by definition, and is therefore a viscoelastic phenomenon.[31] Furthermore, immediate postoperative increases in central posterior corneal elevation often noted on scanning slit topography do not necessarily represent a pre-ectatic anterior vaulting. Instead, posterior corneal steepening may reflect a relative *posterior* movement of the peripheral stroma in response to the differential swelling described previously.[10,76] Artifactual posterior steepening can also result from minification of the central posterior radius of curvature after myopic photokeratectomy.[77] LASIK may introduce a greater risk of viscoelastic failure than surface ablation procedures because of deeper forays into the posterior stroma. Lower keratocyte density, less collagen interweaving, and more hydrophilic proteoglycans may all contribute to a region more prone to viscoelastic failure and abnormal repair. Intrastromal ring segments and ultraviolet light/riboflavin-mediated collagen crosslinking are two biomechanical approaches under investigation for modifying structural stability in affected patients.

IOP MEASUREMENT AFTER REFRACTIVE SURGERY

Friedenwald acknowledged the importance of corneal resistance in applanation tonometry in 1937.[26] Many studies have demonstrated a decrease in applanation pressures after myopic PRK and LASIK

that was initially attributed to decreases in CCT.[61] Other studies demonstrating decreases in central applanation pressures after hyperopic LASIK—without a decrease in CCT[78]—suggest that a decrease in corneal resistance to applanation does occur and can affect IOP measurement independently of the CCT. A sensitivity analysis of the various factors influencing applanation pressure suggests that the elastic modulus may be considerably more influential than corneal thickness or curvature.[79] Using pneumotonometry to compare responses between PRK and LASIK over 36 months, LASIK exhibited a greater long-term drop in apparent IOP than PRK in two populations with carefully matched refractive corrections, providing support to the possibility of procedure-specific reduction in corneal resistance.[80] This issue and the important role of CCT in risk of progression from ocular hypertension to glaucoma[80] have spawned efforts to distinguish corneal biomechanical properties from true IOP using devices such as the Ocular Response Analyzer[33] and the Dynamic Contour Tonometer (DCT).[68,81] The DCT provides a measure of IOP without applanation of the cornea, thus reducing the influence of corneal properties and corneal thickness on the measurement.

BIOMECHANICS AND WOUND HEALING

The cornea undergoes significant biomechanical alterations during and after refractive surgery. Wound healing is also a major factor in refractive overcorrection, undercorrection, regression, and induction of irregular astigmatism.[82] Wound healing plays a key role in ongoing maintenance and modification of the biomechanical steady state, and investigation at the interface of these fields promises to bring new insights to the field of refractive surgery. For example, a histopathological study in LASIK flaps of organ donors found a relationship between wound maturity and resistance to flap distraction (lifting) forces.[83] Flap cohesive strength was maximal at the flap margins, was associated with hypercellular fibrotic scars, and increased as a function of postoperative time. Flap-edge cohesion was only 28% that of normal specimens, however, and was adversely affected by the presence of epithelial ingrowth. The central interface was characterized by primitive scar and presented far less cohesive strength. The contribution of flap cohesion to the overall biomechanical stability of the cornea is not known but it may be a factor in late flap dislocation and ectasia.

Given that one evolutionary goal of healing is restoration of mechanical integrity,[71] mechanisms must exist by which keratocytes or their derivatives 'sense' local changes in stress or strain and then respond with an appropriate (or inappropriate) series of actions for remodeling such areas to decrease the mechanical stimulus. The matrix-deforming interactions of corneal fibroblasts and collagen gels have been characterized in culture under direct visualization.[72] As our understanding of these processes improves, so will our ability to offer rational interventions for improving the predictability of refractive surgery and minimizing its complications.

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82 Preoperative evaluation of the refractive surgical patient

Marjan Farid, Roger F. Steinert

INTRODUCTION

A thorough preoperative assessment of a refractive surgery patient and education of the patient based on the result of the evaluation are of paramount importance for achieving successful postoperative outcomes. Determining whether the patient is a good candidate for surgery is the primary question during the evaluation. The preoperative assessments of patients undergoing refractive surgery consist of four elements: (1) a complete medical and ocular history, (2) a comprehensive examination of the entire visual system, (3) ancillary testing of the refractive status and anatomy of the optical system, and (4) information transfer from the patient to the surgeon about the patient's visual needs and expectations and information transfer from the surgeon and staff to the patient about the goals, risks, and outcomes of the treatment options. These key steps drive both technical refractive success and patient satisfaction.

COMPREHENSIVE HISTORY

PAST MEDICAL HISTORY

Medical and surgical history as well as current and prior medications should be well documented during the preoperative assessment. Connective tissue diseases such as systemic lupus erythematosis, rheumatoid arthritis, and polyarteritis nodosa may affect corneal wound healing after surgery. Postoperative corneal melting and perforation have been reported in patients with active or uncontrolled connective tissue diseases.

Patients with diabetes should be considered with caution, as they may also have problems with corneal epithelial healing, with persistent epithelial defects that could take several months to resolve. The judicious use of preoperative and intraoperative artificial tears helps minimize corneal toxicity and decrease the incidence of erosions. Besides the increased risk of retinal disease, uncontrolled diabetes mellitus is notorious for altering the lenticular hydration status with fluctuations in refraction. Multiple refractions may be needed to ensure stability of the refractive error to be corrected prior to surgery. Patients with diabetes also tend to have a hastened progression of cataract formation. This may influence decisions about the type of refractive surgery (e.g. lens extraction and intraocular lens (IOL) implant vs laser in situ keratomileusis (LASIK).

Several medications can also potentially result in poor corneal healing including isoretinoin (Accutane, Hoffman-La Roche, Inc, Nutley, NJ), amiodarone (Cordarone, Wyeth, Collegeville, PA), and sumatriptan (Imitrex, GlaxoSmithKline, Research Triangle Park, NC). Furthermore, medications that worsen dry eye symptoms, including anticholinergics, hormone replacement therapy, and antihistamines, will affect overall corneal epithelial regeneration and healing. Corticosteroids hasten the progression of cataracts. Use of systemic corticosteroids or chemotherapeutic agents will also increase risk of infection and affect healing by affecting immune status, as will HIV and some malignancies.

Unstable refraction and altered corneal hydration states may also be seen in pregnancy and breastfeeding. It is generally recommended to wait at least 3 months after delivery and until breastfeeding has been stopped before considering refractive surgery. Caution should be taken in patients with cardiac pacemakers or defibrillators, as the effects of excimer laser and femtosecond laser electromagnetic emissions are unknown.

OCULAR HISTORY

The pertinent ocular history includes history of dry eye symptoms, blepharitis, recurrent erosions, cataract surgery, glaucoma, and retinal disease or retinal lasers/surgery. A list of ocular medications may clue the physician to current ocular problems. Caution should be taken in patients with a prior history of herpes simplex keratitis. In such patients, prophylactic systemic antivirals for several months before and after surgery are warranted. Precautions and risk awareness need be addressed in patients with glaucoma, as intraocular pressures will be elevated for a brief period of time during the creation of the flap in LASIK and applanation pressure measurements will be artifactually lower postoperatively. A history of retinal surgery or laser treatment for diabetic macular edema or proliferative disease is a relative contraindication to refractive surgery as the visual potential in those patients tends to be suboptimal.

In cases of high amblyopia in the fellow eye, patients should be discouraged from refractive surgery as they should be wearing polycarbonate glasses for protection of their one good eye.

Verification of refractive stability is very important. If the glasses or contact lens prescription has been changing significantly over the past few years (usually defined as greater than 0.5 D in sphere or cylinder), then the patient may not yet be a good candidate for refractive surgery. A history of contact lens wear needs to be obtained. This includes type of contact lens (soft vs. rigid), wearing schedule, length of use, and age of current lenses. The use of contact lenses should be discontinued several weeks prior to refractive surgery. Corneal warpage, or change in the shape of the cornea, can occur with long-term use of contact lenses. As rigid contact lenses have a greater influence on corneal shape, most refractive surgeons recommend that patients discontinue use at least 3 weeks prior to surgery. Soft contact lenses should be discontinued for at least 1–2 weeks prior. Repeat refractions and corneal topography measurements every few weeks may need to be obtained in patients with unstable corneas until stability has been established.

COMPREHENSIVE EXAMINATION

A comprehensive ophthalmic examination starts with measurements of uncorrected visual acuity at distance and near. The power of the current glasses should also be noted and visual acuity with current prescription also obtained. At this point, a manifest refraction should be done with defogging to minimize overminusing the patient. This best-corrected visual acuity should be documented. After dilation, a cycloplegic refraction is performed. If there is a significant (>0.75 D) discrepancy between the cycloplegic and manifest refractions, the patient should be brought back for a repeat manifest refraction. An overminused manifest refraction in the myope or latent hyperopia in the hyperope is usually the culprit.

A pupillary examination should be done prior to dilation. The pupillary examination should show appropriate reaction to light and no pathologic anisocoria or relative afferent pupillary defect before proceeding with refractive surgery. Furthermore, a measurement of the pupil size under mesopic conditions needs to be performed to determine the treatment zone for the laser if conventional treatment is being performed. This can be done with the patient fixating at distance in dim illumination (closely reflecting light during nighttime activities) while using a near card with pupil sizes, or, preferably, with a light amplification or infrared pupillometer. In conventional, nonwavefront-guided ablations, the effect of spherical aberration can be reduced when the optical zone is larger than the mesopic pupil size. Pupil size alone, however, does not seem to be an accurate predictor for who will experience postoperative halos and glare.

Ocular motility and presence of any tropias or phorias should also be evaluated at this time. Altering best-corrected visual acuity may cause phorias to become tropias. Patients need to be made aware of this risk and appropriate preoperative orthoptic evaluation done. Confrontation visual fields and general orbital anatomy assessments should also be done on all patients. High brows with deeply set globes or narrow palpebral fissures will present a difficulty in flap creation with the microkeratome, prompting the use of a femtosecond laser to create the flap or a shift to surface ablation instead of LASIK. Placing of the suction ring for the femtosecond laser can also be challenging in patients with extremely narrow palpebral fissures.

A complete slit-lamp examination starting with an external examination to a full dilated fundus examination should be performed routinely as part of the initial preoperative assessment. External disease such as blepharitis or ocular rosacea should be noted and treated prior to embarking on any type of ocular surgery. Particular attention should be given to the corneal surface to assess for aqueous tear deficiency, including a diminished tear meniscus, short tear film breakup time, and presence of punctate staining of the corneal or conjunctival surface. Refractive surgery will tend to worsen dry eye issues, especially during the first few postoperative months. Patients should be made aware of this risk and optimized with judicious use of artificial tears preoperatively and possible placement of punctal plugs before or during surgery. Careful examination of the cornea should be done to rule out any undiagnosed corneal dystrophy. Endothelial dysfunctions such as Fuchs' dystrophy and corneal thickening or frank edema are contraindications for refractive surgery. Basement membrane dystrophies can increase the risk of flap complications, and, in that situation, surface ablation treatment (e.g. photorefractive keratectomy (PRK)) would be preferable to LASIK, as PRK may be therapeutic. Signs of corneal ectasia such as keratoconus or pellucid marginal degeneration are absolute contraindications to refractive surgery, as postoperative corneal instability and ongoing ectasia are likely in these patients.

The dilated examination should note the presence of cataract or any lenticular changes that may alter the decision to do corneal laser treatment. Even visually insignificant changes in the lens, especially in patients over the age of 50 years, should prompt discussion with the patient of the future need for cataract surgery and the alternatives of postponing refractive correction until the time of cataract/IOL surgery or undergoing refractive lens exchange in lieu of corneal laser ablation. If the patient chooses to proceed with corneal laser treatment, the preoperative refractions and keratometry measurements as well as amount of laser ablation performed should be given to the patient to aid the future cataract surgeon in the IOL calculations. Shallow anterior chambers should be noted as it is a contraindication for certain phakic IOLs. An anterior-segment optical coherent tomography (OCT) scan (Visante OCT, Carl Zeiss Meditec, Dublin, CA) can be helpful in making this assessment. Finally, the fundus examination should rule out macular or optic nerve pathology that may affect best-corrected visual acuity. Histories of laser treatment for diabetic retinal disease or macular degeneration are contraindications for refractive surgery. Optic nerve disease, such as advanced glaucoma or optic nerve pallor, is also a general contraindication for refractive surgery. Lastly, patients with high myopia or history of retinal tears/detachments should be advised that laser vision correction will not lower their risk of further retinal disease. Strict retinal monitoring and retinal detachment precautions would still need to be observed.

Intraocular pressure measurements should be done on all patients after corneal topography and refraction. There are multiple risks in refractive surgery for patients with glaucoma. Flap creation, whether it is done with a microkeratome or the femtosecond laser, will significantly elevate the intraocular pressure for a short period of time intraoperatively and may snuff out the nerve in advanced glaucoma. Furthermore, patients need to be on corticosteroids, often for several months after surgery and will risk having steroid response

elevations in their pressures. Lastly, the thinning of the cornea after refractive surgery will affect accurate IOP measurements in the future.

ANCILLARY TESTING

There are several additional tests including corneal topography, pachymetry, and wavefront analysis that need to be obtained during the preoperative assessment, which will guide treatment options. Corneal topography is obtained to determine the overall shape of the cornea and to detect any irregular astigmatism that may indicate subclinical corneal ectasia. Computerized videokeratography has largely taken the place of manual keratometry for determining corneal curvature in the setting of keratorefractive surgery preoperative assessment. Placido disk, scanning slit beam, rotating Scheimpflug photography, and high-frequency ultrasound systems are some of the different techniques employed to gather data on corneal shape. By imaging the cornea, these systems of topography provide color maps that represent the overall curvature and power of the cornea. When using a microkeratome for creating the LASIK flap, flat corneas (<40 D) may be at increased risk for small flaps or free caps whereas steep corneas (>48 D) increase the risk of buttonhole flaps. With the advent of the femtosecond laser for flap formation, this problem has mostly been nullified. Spherical corneal shape or regular astigmatism indicates a generally healthy cornea for keratorefractive surgery, whereas a significant finding of irregular astigmatism may indicate keratoconus, pellucid marginal degeneration, or corneal warpage from contact lens wear. If contact lens-induced warpage is suspected, serial topography and refraction measurements should be obtained to ensure that the cornea has returned to a stable shape and refraction prior to keratorefractive surgery. Preoperative topographic analysis can also disclose any disparity between the refractive astigmatism and the corneal cylinder, possibly accounted for by lenticular astigmatism, significant posterior corneal curvature, or inaccurate refraction. In the case of lenticular astigmatism, because the refractive astigmatism is treated with the laser, the patient needs to be aware that there may be a return of astigmatism in the future following cataract surgery. After surgery, the preoperative topographic analysis provides the baseline against which postoperative results are measured.

In evaluating patient risk factors for postoperative ectasia, certain clinical signs should raise suspicion and videokeratography plays an important role in confirming the diagnosis. A group of refractive surgeons identified possible risk factors for the development of ectasia after refractive surgery.[1] In addition to the typical clinical signs of keratoconus, high myopia, thin corneas, a low calculated residual stromal bed thickness, and asymmetrical corneal steepening on topography raise suspicion for risk of ectasia. There is no single distinguishing feature or clinical test that can definitively predict which normal-appearing corneas will develop ectasia after LASIK. The report concluded that videokeratography should be performed on all patients preoperatively and that any asymmetric inferior corneal steepening or asymmetric bowtie patterns with skewed steep axes, which are suggestive of forme fruste keratoconus, are unsuitable for LASIK. Similarly, 'crab-claw' patterns with central flattening are high risk for pellucid marginal degeneration and should be avoided for LASIK. In the case of irregular inferior steepening on topography, most physicians will use adjunctive pachymetry measurements showing inferior or inferocentral corneal thinning correlating with the topography before making a final diagnosis of subclinical ectasia. The decision to perform LASIK should be based on multiple factors and not necessarily rely on topography alone. Some of these cases of apparent subclinical keratoconus may be artifacts of the topography system. In Placido image systems, deviations of the corneal apex from the visual axis are generally depicted as patterns resembling keratoconus. Patients who do not fixate precisely may also give this type of pattern. Finally, development of ectasia can occur even in the absence of any risk factors, suggesting that in some cases ectasia may not necessarily mean that LASIK was the causative factor.

BOX 82.1 RISK FACTORS FOR POSTOPERATIVE ECTASIA*

1. Keratoconus
2. Subtle signs of keratoconus on keratometry (non-superimposed mires, irregular mires)
3. High myopia
4. Thin corneas
5. Low calculated residual bed thickness
6. Abnormal video keratography such as:
   a. asymmetric inferior corneal steepening
   b. asymmetric bowtie patterns with skewed steep axes
   c. 'crab claw' patterns with central flattening
   d. interior corneal thinning

*Source: Binder PS, Lindstrom RL, Stulting RD, et al. Keratoconus and corneal ectasia after LASIK. J Cataract Refract Surg 2005; 31(11): 2035–2038.

There are a paucity of data in regard to surface ablation and ectasia. It is not yet known whether risk factors for postoperative ectasia after LASIK also predict ectasia after surface ablation.

To determine adequate corneal thickness prior to surgery, corneal pachymetry measurement is performed. Corneal pachymetry can help diagnose subclinical keratoconus when measurements are unusually thin (especially in the inferocentral area) or pending endothelial decompensation when readings are unusually thick. In both of these situations, keratorefractive surgery would be contraindicated. In the case of a Fuchs' suspicion, specular microscopy may be a helpful adjunct. Besides ultrasound pachymetry, pachymetry maps are now available on several topography systems such as anterior-segment OCT and are helpful in localizing areas of thinning at various locations.

Calculation of residual stromal bed thickness is vitally important for optimizing results and lowering the risk of postoperative ectasia. The strength and integrity of the postoperative cornea depend on the amount of residual stromal bed thickness. The residual stromal bed thickness is calculated by subtracting the flap thickness and the amount of laser ablation depth from the preoperative central pachymetry measurement. There are no conclusive data on exactly how much residual stromal bed thickness will cause instability and ectasia. Many surgeons currently utilize a guideline of a minimum of 250 µm and some surgeons add a further limit of 50% of the preoperative corneal thickness, whichever is greater. A specific minimum acceptable preoperative pachymetry limit is not yet established, but some surgeons view any cornea thinner

than 470–480 μm as a contraindication to LASIK, even with entirely normal-appearing topography.

The actual flap thickness obtained with the microkeratome is variable. Intraoperative pachymetry to determine flap thickness should be considered if there is a risk of inadequate residual stromal bed thickness. If the calculated residual stromal bed would measure below the acceptable minimum, then the flap should be replaced and a surface ablation such as PRK should be considered as a later procedure after the flap has healed.

A wavefront optical analysis has become commonplace in preoperative assessments for keratorefractive surgery. A detailed evaluation of higher-order aberrations of the visual system is obtained. This information can then be directly fed into the excimer laser computer, which then performs a wavefront-guided or 'custom' ablation. This system therefore not only treats lower-order aberrations (myopia, hyperopia, and regular astigmatism) but also addresses the higher-order aberrations such as spherical aberration and coma that may cause significant visual disturbances despite good high-contrast visual acuity. The wavefront analysis has the potential for being particularly valuable in retreatments and in the evaluation of persistent postoperative visual disturbances. Although the treatment is based on the wavefront analysis, the surgeon should carefully compare the data to the manifest refraction to prevent input errors.

PATIENT EXPECTATIONS

An understanding of the patient's expectations and motives for desiring refractive surgery is the most important part of the preoperative assessment. The refractive and emotional goals of the patient should be discussed. Individuals who have unrealistic expectations such as a guarantee of 20/20 vision and 'perfect' results or believe that refractive surgery will 'change their lives' should be discouraged from having refractive surgery. Candidates should be motivated by a desire to reduce their dependence on glasses or contact lenses. The occupational and recreational activities of the patient should also be discussed. The refractive goals of the patient may vary based on their social and occupational needs. Furthermore, the physician will need to know if the patient's activities place him or her at a higher risk for ocular trauma. In the case of a wrestler or basketball player, for example, the physician may opt to perform a surface ablation where a risk of flap trauma would not be an issue.

A discussion of the patient's age and the issue of presbyopia should be done at this time. Patients need to understand that after the age of 40 years, accommodation for near work will become compromised. Myopic patients, who could read well by simply taking off their glasses, need to understand that once they are corrected to emmetropia, they will not be able to read without glasses. A discussion regarding monovision should take place with these patients. In monovision, the dominant eye is usually treated for distance, and the nondominant eye is left slightly myopic for near vision. The degree of monovision for the near-corrected eye is determined based on patient's desires and amount of anisometropia tolerated. The side effects of monovision including loss of depth perception and anisometropia should be discussed with the patient. Before committing to monovision, a trial frame simulation and, in many cases, a contact lens trial can be given to determine if the patient will be happy with the refractive goal.

PATIENT EDUCATION AND INFORMED CONSENT

The final element in the preoperative evaluation, therefore, is the determination that refractive surgery in general and one or more specific procedures in particular are appropriate for the individual patient. For the physician, this assessment is a combination of an analysis of the objective outcome data and of the patient's understanding of the procedure and expectations. For the patient, a fully informed decision requires the transfer of large amounts of information about refractive errors, the treatment method, the risks and benefits of the proposed treatment, and the alternatives. A discussion of the expected uncorrected visual acuity, possible need for reading glasses after surgery, the chance of needing an enhancement, and whether or not maximal surgery is being performed initially needs to take place. Common side effects including halos/glare, an overall change in quality of vision, and worsening dry eye symptoms need to be addressed. Furthermore, the patient also needs to be aware of the risks of severe complications, including loss of best corrected visual acuity and severe visual loss, as well as flap complications and the possible need for revision due to displacement, striae, or epithelial ingrowth. The alternatives to refractive surgery including glasses or contact lenses should be offered.

The informed consent should be read and reviewed by the patient prior to surgery and before dilation or sedation. Patient education and informed consent is a complex process that is never perfect. Aids to effective communication of technical material include brochures, booklets, videotapes, and the consent form itself. These do not replace, but only supplement, a personal discussion with a professional and the opportunity for the patient to ask questions.

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83 Interpreting corneal topography, tomography, and wavefront analysis

Carole A. Cooke, Charles N. J. McGhee

As a result of the emergence, development, and refinement of excimer lasers over the last quarter century as well as the exponential public interest in the permanent surgical correction of refractive errors, refractive photoablative surgery is now widely accepted by ophthalmologists and the general public. Driven by the increased interest in refractive surgery and key technical developments such as the personal computer and video frame grabbers, there also have been dramatic developments in videokeratoscopy and corneal analysis in the same time period. In the era of photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), incisional refractive surgery, and clear lens extraction, a thorough understanding of corneal topography, tomography, and wavefront analysis is essential for any ophthalmologist who performs corneal or cataract and refractive surgery or who manages patients who have previously had refractive procedures.

In the refractive surgery setting, corneal topography, tomography, and wavefront analysis are utilized in three main areas: (1) accurate assessment preoperatively, (2) determining and monitoring change after surgery, and (3) planning enhancement procedures. These issues, although inter-related, will be discussed separately in this chapter.

ASSESSING THE REFRACTIVE SURGERY PATIENT PREOPERATIVELY

Before refractive surgery it is imperative that patients are carefully screened for potential corneal abnormalities. The surgeon should always personally examine the topography/tomography map for each case preoperatively.[1] In order to become competent in detecting the abnormal, a thorough knowledge of topography of the normal cornea is obviously vital.

THE NORMAL CORNEA—TOPOGRAPHY AND TOMOGRAPHY

Placido-based corneal topography is discussed in greater detail in Chapter 9 by Klyce and Oshika, and the essentials of corneal tomography are covered in Chapter 10 by Wheeldon and McGhee; therefore, only a concise review of the relevant interpretation of these investigations with respect to refractive surgery will be provided in this chapter.

The normal cornea is a prolate shape that flattens peripherally, especially in the nasal region.[1] Although the exact topographic features of each cornea are unique,[2] generally the central cornea has an average radius of curvature of 7.8 mm, which equates to an average central power of 43.5 D.[3] However, the range of power found in the normal human cornea is 39.0–48.0 D, and a very small percentage of emmetropic patients with normal corneas can have a central power as high as 50.0 D or more.[4] Interestingly an individual's corneas are often nonsuperimposable mirror images of each other, i.e. they exhibit enantiomorphism[2] (Fig. 83.1), and knowledge of this concept is useful in that comparison of corneal topography with the contralateral eye may help in deciding whether a cornea is 'normal' or not.

Bogan and coworkers[5] initially described a now widely recognized classification of computerized corneal topography illustrating the variation in a normal population. They described five subgroups based on patterns seen on color-coded topographic maps: round, oval, symmetric bow tie, asymmetric bow tie, and irregular. Some workers include oval with round in a combined category because neither is associated with significant corneal astigmatism. Analysis of corneal topographic maps with too sensitive a scale, i.e. small dioptric steps, can be confusing by highlighting minor features that are not clinically relevant.[1] Smolek and coworkers, building on their earlier work, have proposed a Universal Standard Scale (USS) based on both scientific principles and clinical usefulness where the contour interval is set to 1.5 D.[6] Most corneas are toroidal aspheres and, as the prevalence of astigmatism increases with increasing ametropia,[7] it is unsurprising that the most common patterns identified are symmetric and asymmetric bow ties.[5] Whilst placido-based corneal topography will only measure corneal surface aberrations, wavefront analysis includes aberrations from the eye as a whole.

The Orbscan (Orbtek, Inc.) is discussed fully in Chapter 10. Currently, Orbscan is perhaps the most widely used topography instrument for corneal surgeons;[8] therefore, normal values have been included in this chapter. Curvature maps are comparable to other instruments, but anterior and posterior elevation maps can also be created using a best-fit sphere to the surface measured. This allows

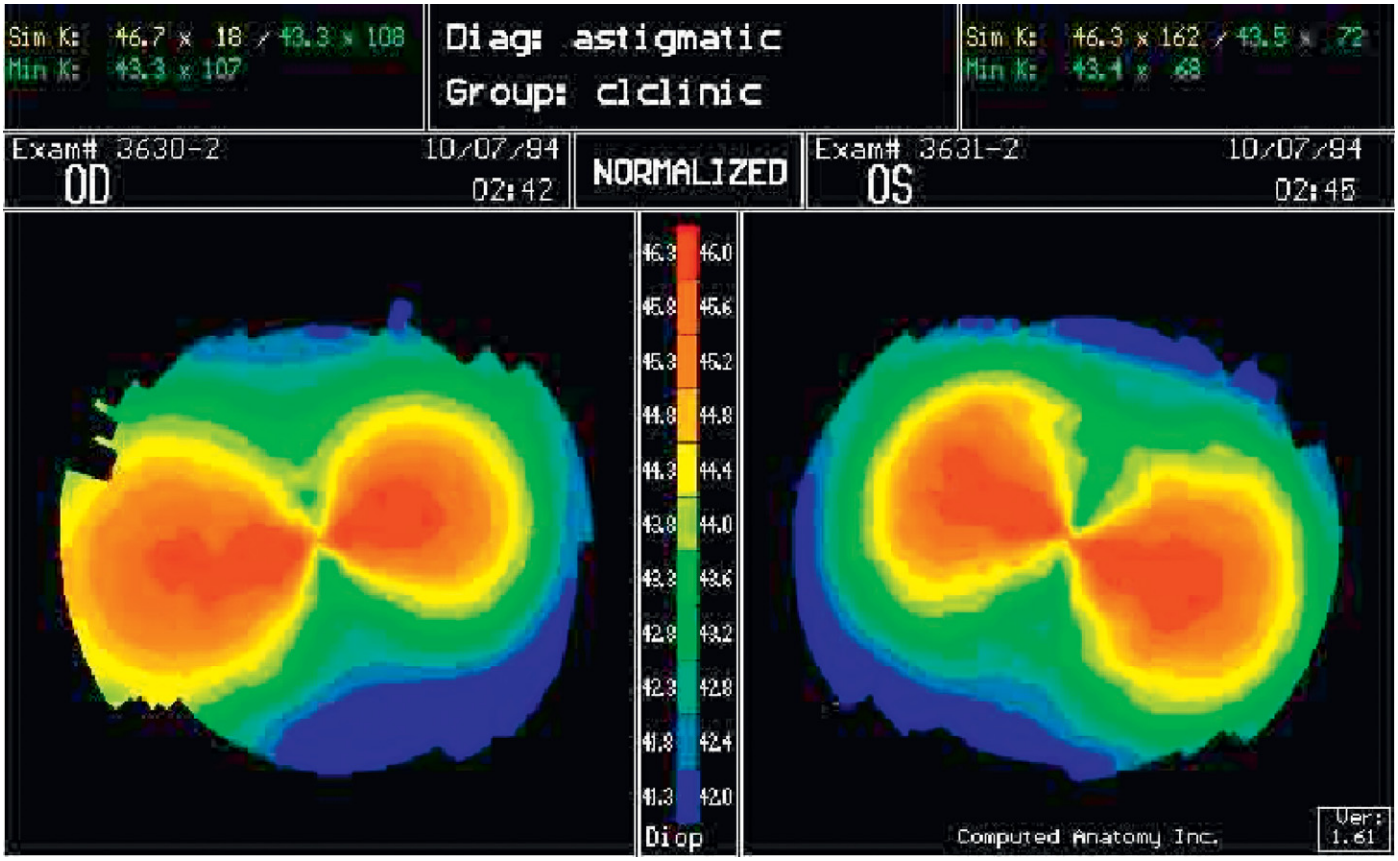


Figure 83.1. Axial power map of enantiomorphism—an individual's corneas are often non-superimposable mirror images of each other.

microdeviations in the surface shape to be noted.[8] The normal anterior elevation value is taken to be less than 16.5 μm,[9] whereas the normal maximum value of the posterior elevation map is generally less than 40 μm.[8,9] When compared to ultrasound pachymetry, the Orbscan overestimates corneal thickness in normal corneas but underestimates post-LASIK pachymetry.[8]

THE NORMAL CORNEA—WAVEFRONT ANALYSIS

Topography measures corneal power in diopters or millimeters of radius of curvature, whereas wavefront aberration describes departure from perfection in the total optical system. In the human eye, once the sphere and cylinder are corrected for, any residual deviations are termed higher-order aberrations.[10] Wavefront analysis is a measuring system that accounts for all these elements of the optical system,[11] and wavefront-guided laser treatment can theoretically correct higher-order aberrations.[10] Before the application of wavefront analysis, only corrections of the spherical and cylindrical errors were widely considered in refractive surgery. However, wavefront systems can describe refractive error to within 0.05 μm—theoretically up to 50 times more accurate than standard topography-based systems. In addition, various errors previously described under the umbrella term 'irregular astigmatism' can now be further defined with wavefront as other higher-order aberrations.[11] In order to understand the concept of wavefront analysis, a few relevant terms and concepts will first be explained.

Point spread function

The point spread function (PSF) is a measure of what subjects would observe if they looked at a distant point of light like a star. The emmetropic image would be a circle of finite size instead of a point, due to diffraction at the pupillary margin; however, other aberrations in the eye can further alter the PSF (Fig. 83.2).[11]

Wavefront aberrometers

Wavefront sensors are technically aberrometers. They measure light wave distortion as it travels through the eye's optical system. They do not measure diffraction or chromatic aberrations.[12] If an optical system has aberrations, reflected or refracted rays do not converge to one image point. The wavefront aberration is the optical path situated between the true wavefront and the ideal reference wavefront measured in the exit pupil as a function of position within the pupil (Fig. 83.3).[13] Pupil size during the examination is important and should be documented, because as the pupil size increases, so do higher-order aberrations.[12] It is always important to recall that factors such as the condition of the tear film, head tilt, or ability to fixate can all influence corneal topography or wavefront sensing.[14] Various wavefront sensing devices based on different principles of wavefront analysis are available commercially.[12]

These include

1. *Shack–Hartmann aberrometry*: Shack–Hartmann devices evaluate the light bounced back from the eye (outgoing reflection). Numerous lenses (lenslets) focus the reflected wavefront.[12] If there are no optical aberrations in the system, a uniform pattern

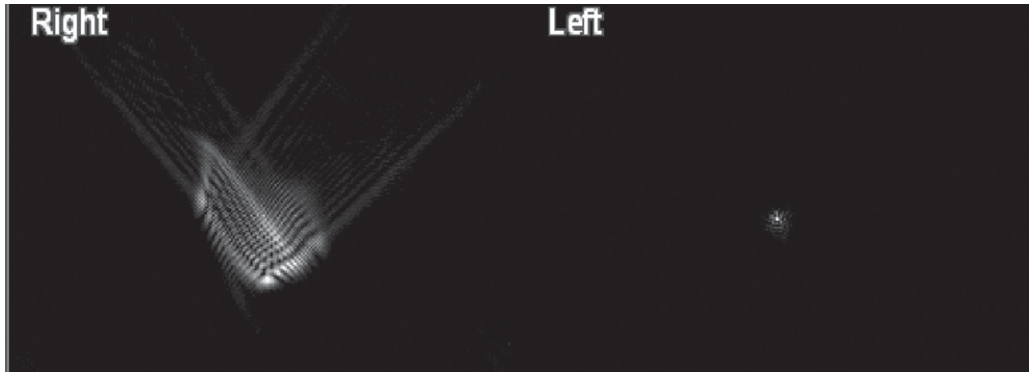


Figure 83.2. Point spread function images from the Nidek OPD-Scan. The left eye sees the image as a circle of finite size instead of a point. Significant aberrations in the right eye significantly alter the PSF.

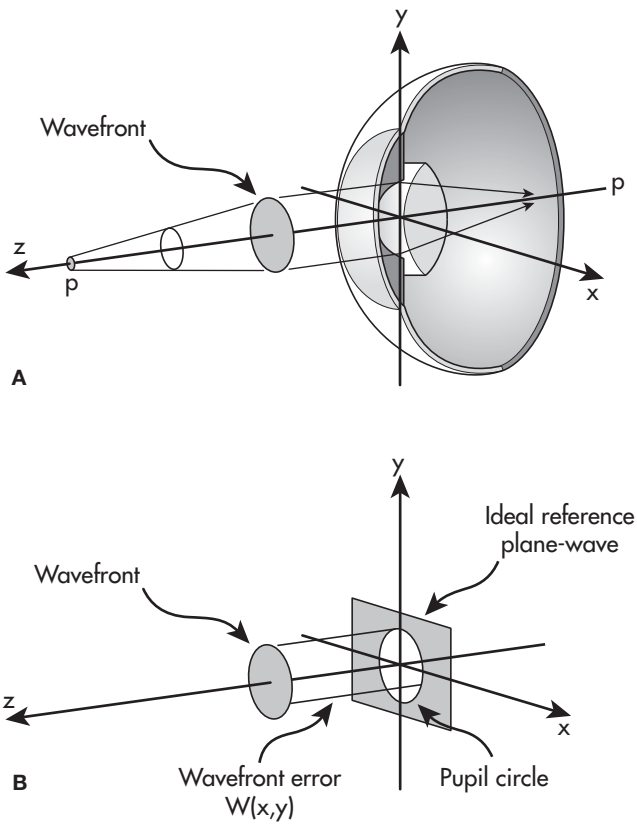


Figure 83.3. Wavefront diagram. The wavefront aberration is the optical path situated between the true wavefront and the ideal reference wavefront measured in the exit pupil as a function of position within the pupil. (Diagram redrawn and reproduced courtesy of Nisha Sachdev, MD, PhD.)

of perfectly spaced dots will be seen. In eyes with significant aberrations, the image will be distorted. Examples of devices using this principle include the LADARWave (Alcon Surgical, Fort Worth, TX)[12] and the Zywave Aberrometer/Wavefront Analyser (Technolas GmbH of Munich, Germany) in the Bausch & Lomb Orbscan combined aberrometry/topography device (B&L Surgical, Claremont, CA).[11] Other devices include the WASCA (Meditech, Jena, Germany) and WaveScan (VISX, Santa Clara, CA).[12]

2. *Tscherning and ray tracing aberrometry*: The retinal image formed is imaged (retinal imaging aberrometry) and then evaluated by charge-couple device sensors that determine the deviation of the spots from the ideal.[12] Examples of devices using this technology include the WaveLight (WaveLight Technologies, Erlangen, Germany) and the Schwind aberrometers (Schwind, Kleinosterm, Germany).[12]
3. *Slit skiascopy*: This is double-pass aberrometry and is available as the Nidek OPD-Scan (ARK 10000 Optical Path Differences Scanning System, Gamagori, Japan). An infrared slit beam scans the retina, and the reflected light is measured to create a wavefront pattern.[12] The OPD-Scan can also measure corneal topography, autorefraction, and keratometry.[15] It has been found to be useful in detecting differences in ocular aberrations between normal, keratoconic, and postkeratoplasty eyes. Root-mean-square (RMS) values are generally higher in the latter two groups; therefore, this technique is reported to have uses beyond refractive surgery.[15]

Wavefront analysis and polynomials

There are several methods used to mathematically describe wavefront data. A set of measured wavefront slopes over the complete pupil are given, and reconstruction algorithms fit the data to a set of polynomials with a least-square technique. Usually these are Zernike or Taylor polynomials, which reduce the absolute error between the slopes measured and the reconstructed wavefront.[14] Zernike polynomials are now the most widely understood mathematical functions used to describe wavefront analysis, and the aberrations are classified in a pyramid of increasing complexity (Fig. 83.4). Each polynomial represents a specific element of distortion of the wavefront. Zero order refers to the *piston* of the lens system (the mean of the *wavefront* profile across the pupil of an optical system that has no effect on image quality),[13] first-order aberrations are *tilt* or *tip*, and second order aberrations are simply *defocus* (sphere and cylinder). Third order aberrations are *coma* and *trefoil*, whilst *spherical aberration* is a fourth-order aberration.[11] Once defocus errors are corrected for, spherical aberration is probably the most important of the higher-order aberrations.[10] One can continue classifying further orders of increasingly less significant higher-order aberrations, but clinically more than 99% of wavefront error is contained in the first four orders of a Zernike expansion.

In one study of wavefront aberration of 108 healthy eyes from a young university student population (measured with a 5 mm pupil), of the total aberrations second order accounted for 90.8%, third order 6.4%, fourth order 2.6%, and fifth order merely 0.2% (Fig. 83.5).[16] Higher-order aberrations will also increase with pupil size, and Zernike coefficients are only relevant for the specific pupil

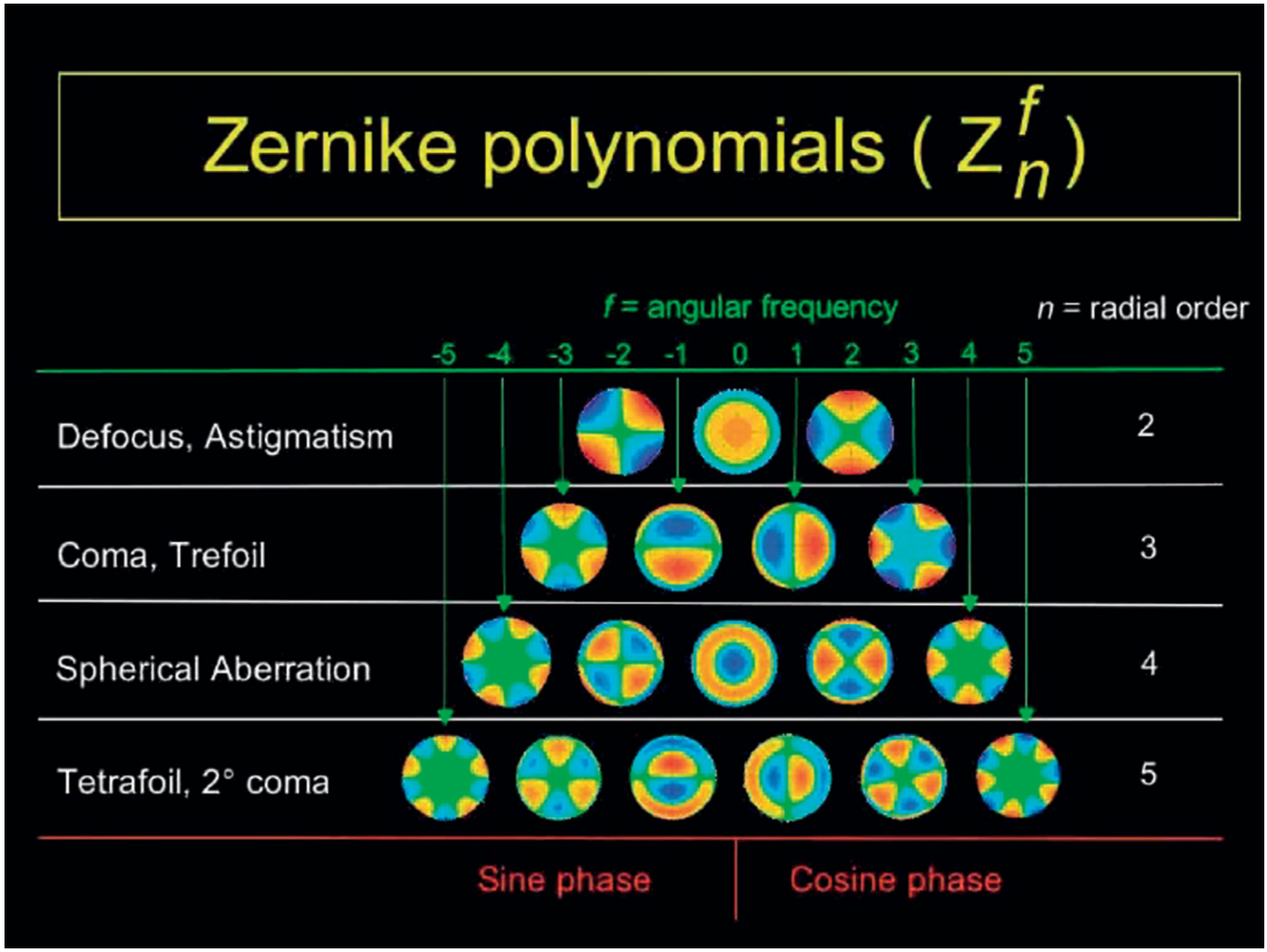


Figure 83.4. Zernike polynomials pyramid, second to fifth orders. (Diagram redrawn and reproduced with courtesy of Nisha Sachdev, MD, PhD.)

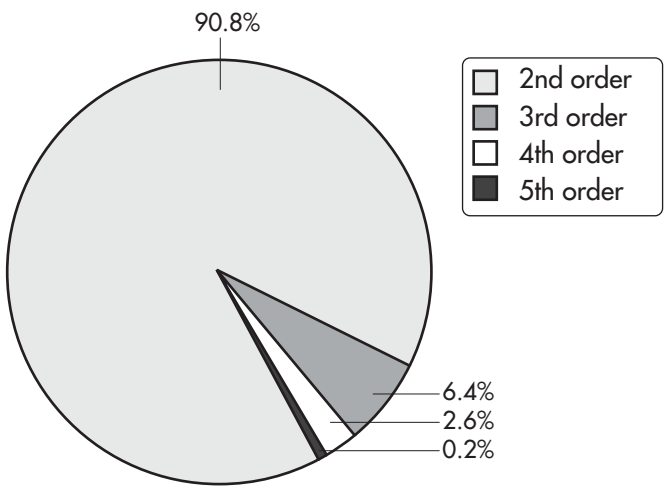


Figure 83.5. Impact of each Zernike polynomial order on the total RMS value for a 5-mm pupil. (Data taken from Castejon-Mochon JF, Lopez-Gil N, Benito A, Artal P. Ocular wave-front aberration statistics in a normal young population. Vision Res 2002; 42(13): 1611–1617.)

diameter at which they were measured (Fig. 83.4). As we move down the Zernike polynomial pyramid, the wavefront maps get increasingly complicated,[13] and wavefront error concentrated near the center of the pyramid adversely affects visual acuity more than modes near the edge of the pyramid.[17]

As Zernike polynomials use only a limited number of Hartmann–Shack lenslets to generate the wavefront, they therefore cannot represent all known aberrations particularly in significantly aberrated eyes.[18] Fourier mathematical analysis of corneal topography power data has been reported to be a powerful method of extracting clinically meaningful descriptors.[19] Indeed, in wavefront analysis, Fourier algorithms use approximately 240 Hartmann–Shack spots (for a 7-mm pupil) and therefore more data are available to create the wavefront.[18] Theoretically, the Fourier approach can therefore fit corneal and wavefront error surfaces in eyes with greater aberrations.[20]

Root-mean-square error

The RMS error is the spot-size error of the overall wavefront error and is a term that describes the error magnitude without describing its nature or where the main components are. It is calculated by taking all the errors above and below the reference plane and squar-

ing them. The mean value is then taken to be the RMS error. Its value indicates the quality of the retinal image. HOMS represents the higher-order aberrations RMS error.[11] In Castejon–Mochon's university student study population cited above, the 5-mm pupil total RMS mean value was 1.49 μm.[16]

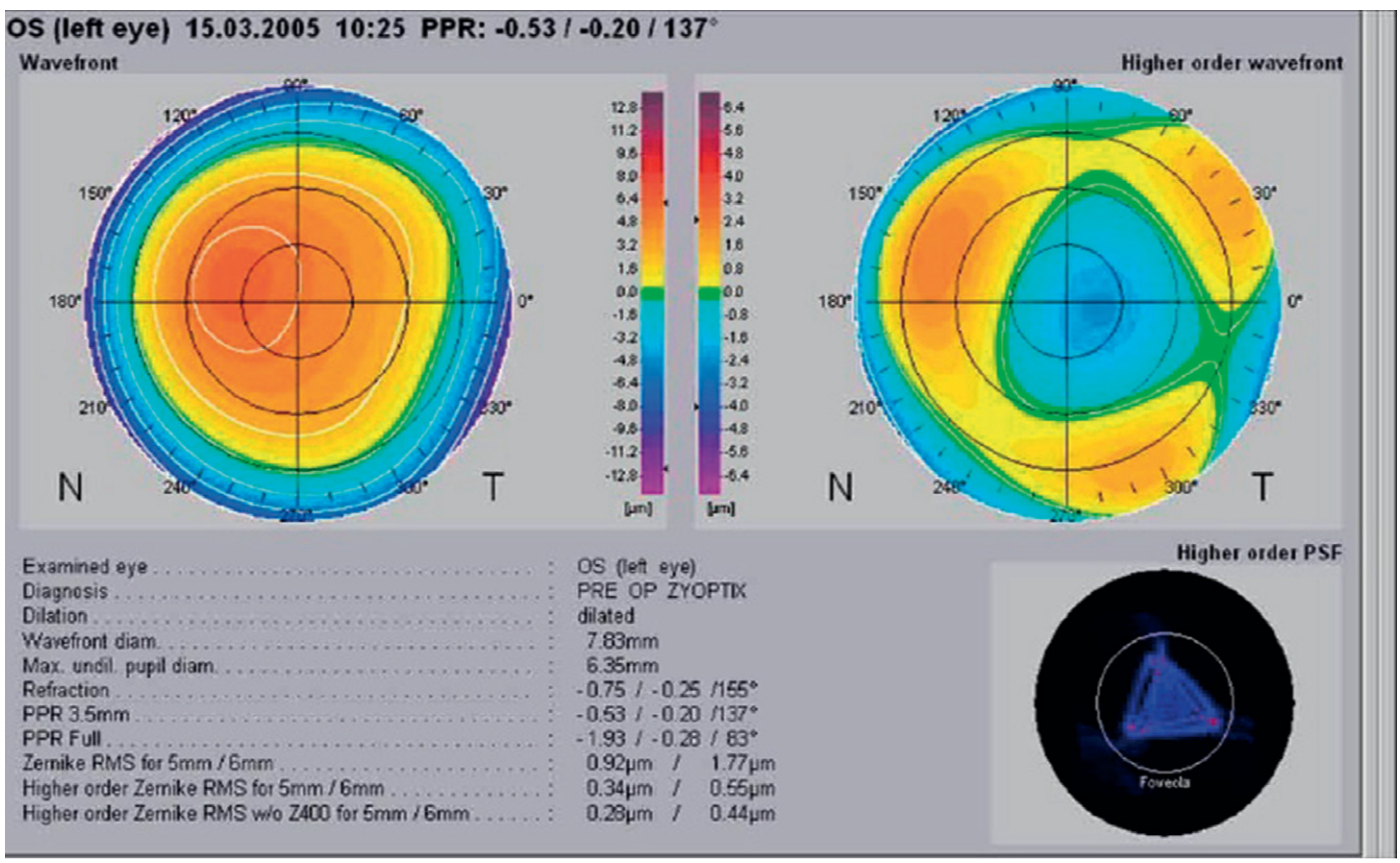
To deliver wavefront-guided treatment, a small scanning spot laser, with a fast, accurate eye tracker, is required.[12] A 1-mm beam has been found to be small enough to correct up to the fifth-order higher aberrations, although some lasers use a 0.50-mm laser spot.[21] Eye-tracking systems can follow and compensate for small eye movements, but all procedures require patient cooperation. Error may also arise due to inaccurate calibration between the video camera and the scanning mirrors. Verification of machine calibration should be performed before each customized treatment.[14]

TOPOGRAPHY AND WAVEFRONT ANALYSIS—THE ABNORMAL CORNEA

Computerized videokeratography (CVK) is an invaluable tool when screening potential candidates for refractive surgery. As already discussed, there is wide variation in corneal power and shape across the normal population. It is important to exclude changes due to artefact from factors such as poor tear film or poor alignment before diagnosing an abnormality. Analysis may need to be repeated and the videokeratoscopic ring visualized before making a final decision. Particularly for LASIK ablations, good preoperative screening with topography to exclude ectatic corneal degenerations is imperative to avoid disastrous consequences.[1] Contemporary devices, such as the Nidek OPD-Scan, may now include both wavefront and topographic analyses that can produce useful data even on highly distorted corneas, e.g. following penetrating keratoplasty (Fig. 83.7).

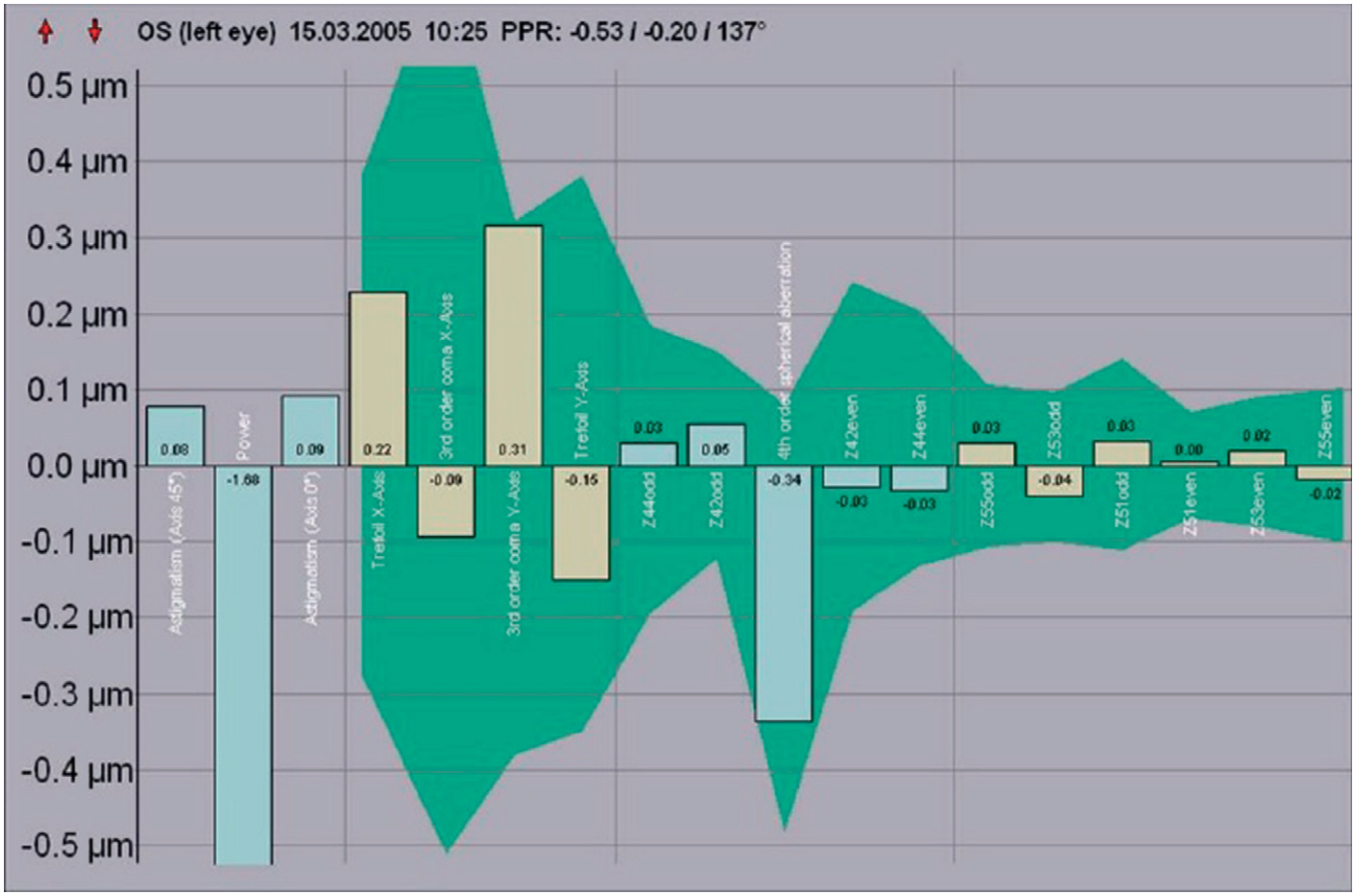
Undiagnosed keratoconus

The presence of visual symptoms or clinical signs can vary widely in this condition. The prevalence of clinically significant keratoconus is 0.03–0.05% but, in fact, may be as high as 6–12% in patients requesting refractive surgery.[7] This higher prevalence is probably due to the fact that keratoconic patients self select toward seeking a refractive procedure due to increasing blur. Highly sensitive detection programs for screening and diagnosis of subclinical and



A

Figure 83.6. Zywave aberrometer/wavefront analyzer (Bausch & Lomb) of a healthy eye with a modest refractive error (–0.75 D/–0.25 D × 155°) and modest wavefront aberration. Image A demonstrates the whole wavefront on the upper left and the higher-order wavefront on the right as color-coded maps. The statistics below the maps highlight a total Zernike RMS of 0.92 μm and HOA RMS of 0.34 μm (both for a 5.0-mm pupil) and a higher-order PSF image.



B

Figure 83.6. continued *B*, Image B provides a graphic breakdown of the contribution of the individual Zernike polynomials.

clinical keratoconus have proven valuable. Subclinical topographic changes have been identified by Maguire and Bourne[22] and Rabinowitz and McDonnell,[23] who found central corneal power, difference in central corneal power between fellow eyes, and steepening of the inferior cornea compared with the superior cornea to be significantly different in patients with keratoconus compared with control patients. Maeda et al developed an automated system using computer-assisted videokeratoscopy to differentiate keratoconus patterns from other conditions including the Keratoconus Predictability Index (KPI) and the Keratoconus Index (KCI).[24] These and other such guidelines are now incorporated into software programs on corneal topographers to help surgeons assess the risk of forme fruste keratoconus in suspicious cases. Further details regarding interpretation of placido-based corneal topography can be found in Chapter 9.

Pellucid marginal degeneration

This condition is probably part of the spectrum of keratoconus, but some authors believe that it has a distinct topographic appearance: characterized by against-the-rule astigmatism and arcuate claw-shaped inferior corneal steepening. Some of the software programs that screen for keratoconus will not detect changes associated with pellucid marginal degeneration. The surgeon must be alert to this fact as these eyes are potentially at high risk of ectasia if LASIK is performed.[1]

Displaced apex syndrome

A subgroup of corneas may demonstrate *displaced apex syndrome* with the zone of greatest corneal power displaced inferiorly with an elevated inferior–superior cornea value, but no clinical signs of keratoconus and a history of stable refraction for a number of years. Wide-field slit-scanning pachymetry (see Chapter 10) may be useful in discriminating between the topographic variant of displaced apex and early keratoconus. Two studies have demonstrated that PRK or PARK in eyes with nonkeratoconus, atypical inferior steepening is associated with outcomes that are not statistically different from those with similar refractive errors and 'normal' topography.[25,26] However, LASIK is perhaps best avoided in these patients.

Contact lens-related corneal warpage

This condition has been defined as contact lens-induced change in corneal topography not associated with corneal edema. Warpage is most commonly linked with rigid polymethylmethacrylate lenses, is less common with rigid gas-permeable lenses, and infrequent in soft contact lens wearers.[27] Initial topography demonstrates flattening of the corneal contour underlying the resting position of the decentered contact lens. Superior-riding lenses cause topographic changes similar to keratoconus.[27] Topographic screening to establish stable topography before refractive procedures is mandatory. There is no gold standard for the period of discontinuation of contact lens wear required before surgery. Many surgeons stop all contact lens wear

Figure 83.7. Nidek OPD-Scan (ARK 10000 Optical Path Differences Scanning System, Gamagori, Japan) of a cornea postpenetrating keratoplasty. Clockwise from top left, an axial topographic power map highlights significant oblique astigmatism (–7.05 D @ 139°), the Zernike OPD bar chart records a highly aberrated wavefront with a total RMS of 3.046, the classifier statistics include, amongst others, SimK, potential visual acuity, surface regularity index, and surface asymmetry index, and the final classifier graph (erroneously in this case) classifies this corneal topography with a 99.0% association with pellucid marginal degeneration.

for 2 weeks prior to surgery, but for RGP wearers some experts suggest 1 week of discontinued lens wear for every year of use. Tsai et al studied 55 eyes of rigid gas-permeable contact lens wearers seeking refractive surgery and reported that 43.6% of these eyes took longer than 3 weeks of discontinued contact lens wear to reach topographic stability. The main factor that correlated with the time to refractive stability after discontinuation was the total length of time of contact lens use. As a result, they suggest that RGP wearers should be advised to cease lens use for 6 weeks before assessment and specifically advised that multiple visits may be required before stability is evident.[28]

The physiologically thin cornea

Orbscan and Oculus Pentacam topographic maps include wide-field pachymetry, and thus abnormal corneal thickness can be readily identified. For particular patients, the degree of laser ablation necessary to treat the refractive error must be considered in the context of their residual corneal thickness. Candidates with particularly thin corneas should be excluded from LASIK treatment if the residual bed thickness is too low to avoid the risk of post-LASIK ectasia. As previously noted, it should be remembered that the Orbscan overestimates corneal thickness in normal corneas.[8]

DETERMINING AND MONITORING TOPOGRAPHIC AND WAVEFRONT CHANGES POSTOPERATIVELY

Topographical analysis of eyes following refractive surgery is necessary in many situations. Firstly, it can be difficult to determine the exact cause of patient dissatisfaction after photoablative laser surgery particularly when the patient has good unaided Snellen vision.[29] Topography and wavefront analysis can be invaluable tools in these patients to gain important information such as ablation centration. Secondly, it is useful to monitor patient progress, and in particular the posterior elevation map may show subtle signs of post-LASIK ectasia in cases of unexpected regression. Finally, it is paramount that surgeons continue to monitor and improve the quality of their practice, and topography is vital when auditing results or conducting research. High-quality, reproducible topographic images should be obtainable from all eyes no later than 1 month after PRK or LASIK.

Ablation pattern classification

Corneal topography in early PRK studies established that ablation zone patterns were variable and may change for up to 1 year postoperatively.[30] Numerous topographic patterns after PRK have been described and two large series highlight most of these.[31,32] Lin[31] classified 502 consecutive eyes 1 month after PRK into one of four ablation zone patterns: uniform, 44%; keyhole, 12%; semicircular, 18%; and central island, 26%. The central island group constituted most eyes that lost lines of best-corrected spectacle visual acuity (BSCVA), although, with gradual resolution, only 2% demonstrated central islands 12 months postoperatively. Hersh and Schwartz-Goldstein,[32] reporting data on 181 eyes, described seven topography patterns: homogenous, 58.6%; keyhole or semicircular, 2.8%; toric with axis, 17.7%; toric against axis, 2.8%; irregularly irregular, 13.8%; and 4.4% showed focal topographic variants. In this study, using a Summit excimer laser (Summit Technologies, Watertown, MA), no central islands were identified. At 1 year, a significant improvement in topographic appearance was noted, with 54.3% demonstrating an evolution to a topographically better group, 17.4% remaining in an equivalent category, and 28.2% changing to a poorer category.[32]

Hersh[33] suggested a standardized eight-category classification of ablation zone topography after photoablative surgery. This system is based on the use of subtraction maps and creates the following categories: homogeneous, toric with axis, toric against axis, semicircular, keyhole, central island, irregularly irregular, and focal topographic variant.[33] Clinically important topographic changes after LASIK or PRK include irregular astigmatism, smaller than predicted optical zones, decentration, and of course central islands or peninsulas.[29]

Steep central islands

A steep central island is an area of steepening in the central cornea that leads to multifocality. It can occur after both PRK and LASIK.[34] There are several definitions of a central island, including central area of as little as 1 D increased power and 1 mm diameter relative to the surrounding ablation zone.[33] A 'steep central island' may be better defined as a well-circumscribed, usually central, circular, or oval area of relatively greater corneal topographic power (>3 D) within the region of reduced corneal topographic power created by excimer laser PRK or PARK (Fig. 83.8).[35,36] A central island in effect is an area of insufficient tissue removal by the excimer laser[37] and may contribute significantly to delayed visual rehabilitation and visual symptoms such as monocular diplopia and decreased best-corrected visual acuity.[31]

Central steep islands were relatively common and previously reported mainly after surgery with broad-beam lasers; however, they are rarely encountered with modern algorithms and flying-spot and scanning-slit laser treatments.[38] Theories regarding the origin of central islands are varied, including localized 'cold spots'[36] or differences in laser beam profile and diameter, laser energy absorption by the rising plume of photoablative products, regional differences in hydration of the cornea during photoablation,[39] and an increased stimulus to epithelial healing/hypertrophy (in PRK) over the central, more deeply ablated treatment zone. However, central islands have been demonstrated before re-epithelialization, suggesting a stromal rather than epithelial origin.[40]

Most transient central islands after LASIK are as a result of flap or bed hydration or stromal swelling.[37] Transient early postoperative visual problems induced by central topographic islands were problematic, with up to 32% of eyes with central islands losing two lines of BSCVA at 2 months after PRK compared with 8.7% loss of two lines in eyes not demonstrating islands at the same time point.[35] Although the natural history of such islands is typically that of spontaneous resolution, usually within 6 months,[31,35] accompanied by recovery of lost lines of BSCVA, modifications that have largely eliminated islands have been incorporated to excimer laser treatment algorithms to reduce their occurrence and speed visual rehabilitation. However, following LASIK, if a central island has not improved over the first 4 months and the patient is symptomatic, then customized laser treatment may be necessary.[29] As most steep central islands are not symmetrical, Hafezi et al proposed that customized ablation algorithms are necessary.[34]

Post-LASIK ectasia

LASIK reduces the cornea's tensile strength.[41] Post-LASIK ectasia is characterized by increasing corneal protrusion or steepening, often inferiorly. The incidence of corneal ectasia after LASIK has been reported to range from 0.04 to 0.6%. It is particularly a risk in eyes that have had higher corrections and have a thin residual bed (typically less than 250 μm).[41] It will usually become manifest within a year of LASIK surgery but can present much later (Fig. 83.9). To minimize the risk of post-LASIK ectasia, careful preoperative topographic analysis should be performed and LASIK avoided in those with asymmetric, inferior steepening that may signify conditions such as forme fruste keratoconus.[41] In addition, surgeons should beware of the patient with an unstable refraction preoperatively and central pachymetry of less than 490 μm. Intraoperative pachymetry of the residual bed is useful should an enhancement be required at a later stage.

Centration issues

Decentration of ablation zone occurs when the centre of the ablation zone does not correspond to the intended optical center, e.g. center of the virtual pupil.[42] This was particularly problematic with early excimer laser systems using small ablation zones and noncoaxial microscopes. The commonest cause of decentration is believed to be due to poor patient fixation and the latter can particularly be a problem during LASIK surgery, as it is difficult for the patient to

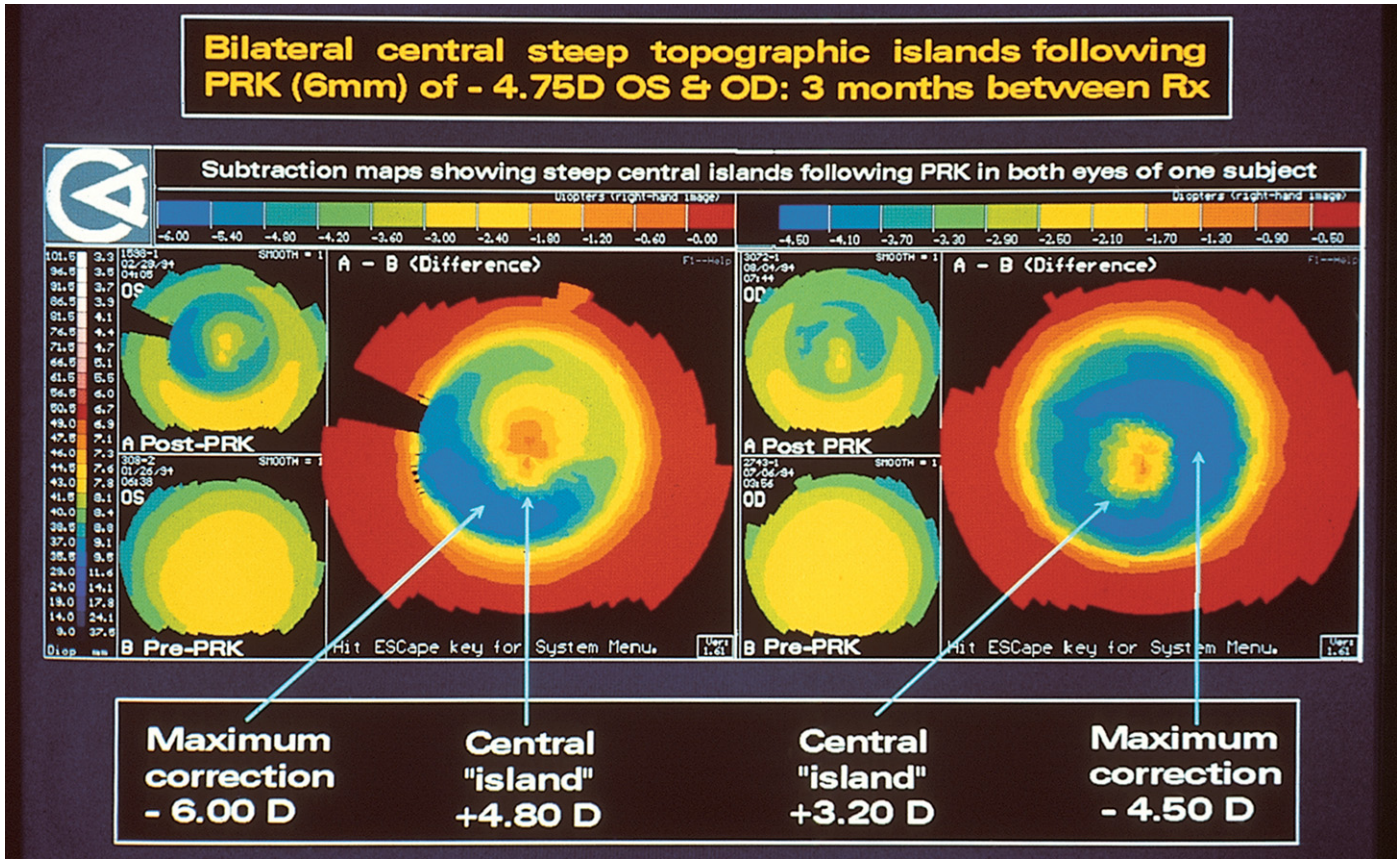


Figure 83.8. Preoperative, postoperative, and differential power maps for bilateral (–4.75 D OS and OD) PRK using a 6.0 mm treatment zone in the same patient (treatments 3 months apart). The subtraction maps clearly show steep central corneal islands, with greater than 3 D central power. Difference scales using 0.6 D increments OS and 0.4 D increments OD.

see the fixation beam once the flap has been elevated.[37] A positive angle kappa can also cause difficulties.

Centration is especially important in hyperopic eyes, and excellent centration is possible even in eyes with positive angle kappa when the ablation is centered over the coaxially sighted corneal light reflex.[43] Most surgeons recommend that pharmacological pupil dilatation should be avoided on the day of surgery to aid in centration,[37] but occasionally an excimer laser device such as LADARVision system (Alcon Laboratories) requires pupil dilation preoperatively.

Decentration causes multifocality of the optical zone[42] and a decentration of more than 1 mm may be associated with troublesome night-time symptoms of glare and haloes in younger patients with large pupils, particularly if true optical zones (as opposed to diameter of ablation including blends) of 5-mm diameter or less have been used. In a study of 38 eyes treated with a 5-mm ablation zone, multivariate analysis demonstrated that ablation zone decentrations of less than 0.89 mm from the pupil center were not associated with untoward visual symptoms.[44] Nonetheless, greater decentrations can be associated with persistent glare, halo, and induced astigmatism of up to 6.4 D.[45] Accurate centration of the ablation is particularly important when treating astigmatism with an elliptical ablation zone, or in the correction of hypermetropia with small optical zones (Fig. 83.10).

Eye-tracking systems in the current generation excimer laser systems have reduced decentration problems significantly.[42] In a cohort of patients who had PRK with a small beam tracking excimer laser by Coorpender et al, the mean decentration in 49 eyes was 0.42 mm and only 6% of corneas had a decentration of more than 1 mm.[46] Management options for decentered ablations after LASIK include topographically supported customized ablation (TOSCA). This has been reported to allow correction of the eccentric ablation and reduction in higher-order aberrations, without causing overcorrection. This may be a useful technique for patients with decentrations and a very high amount of higher-order aberrations, as wavefront aberrometers may not have the ability to measure the latter.[42] Failure to document the difference between true decentration and differential regression (healing) of the ablation zone can be difficult, and therefore early rather than late topographical analysis is advisable.

Regression and healing

Regression is the gradual loss of initial refractive correction. It occurs much more frequently after PRK than after LASIK. This may be because with larger epithelial defects there is a greater stimulus for epithelial regeneration and stromal cellular change.[47] Corneal topography is vital in documenting the postoperative course of refractive surgery. Despite limited opportunity for intervention in the healing process, early topography is important if the practitioner is to avoid such common pitfalls as asymmetric healing being mistaken for decentration[29] or preferential healing of a cylindrical correction being presumed to be a primary undertreatment. Such topographic information is vital in the planning of excimer laser retreatment (Fig. 83.11).

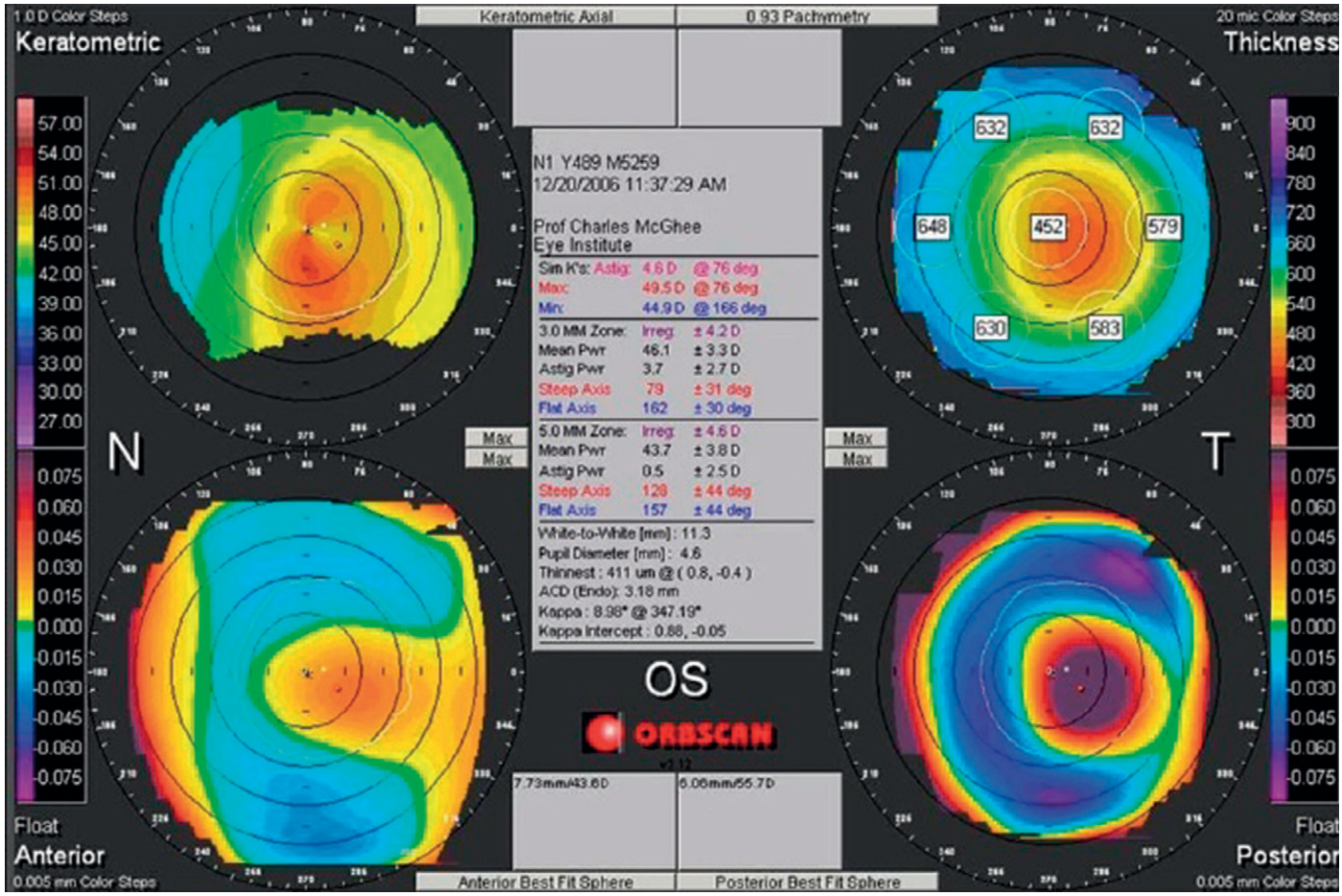


Figure 83.9. Orbscan II quad map showing keratectasia 3 years after a myopic correction of approximately –3.00 D. Clockwise from top left: the keratometric map highlights a very steep bowtie/central cone appearance with SimK values of 49.5 and 44.9 D @ 166°, the thickness map shows central corneal thinning with the thinnest measurement of 411 μm slightly inferotemporal to center, the posterior elevation map reveals confirmatory paracentral forward vaulting of more than 75 μm, and the anterior float map exhibits a paracentral elevation of approximately 40 μm (both posterior and anterior elevation maps are relative to best-fit spheres).

Epithelial ingrowth after LASIK can also cause pseudodecentration, because the epithelium elevates the flap peripherally and appears to decenter the ablation zone. Removal of this epithelial tissue after lifting the flap should correct this problem, although epithelial ingrowth is difficult to fully eradicate.[29] More recently, anterior segment OCT has been used to measure the thickness of the corneal layers and therefore may help determine in an individual patient whether regression is due to epithelial hyperplasia or stromal healing. This knowledge is important as the former may resolve very slowly and change the refraction, so any enhancement procedure should be delayed.[47]

Wavefront-specific changes

LASIK and PRK introduce higher-order aberrations whilst treating lower-order errors.[12] Indeed, some higher-order aberrations in myopes may increase after wavefront-guided LASIK. There is simultaneous induction and reduction of these aberrations contributing to the overall change.[48] Flattening the cornea by myopic laser treatment reduces its natural prolate shape and hence increases spherical aberration.[11] A strong correlation has been reported between post-LASIK patients' visual symptoms and higher-order aberrations analyzed at scotopic pupil size with the LADARWave wavefront device.[49]

PLANNING ENHANCEMENT PROCEDURES

Most topography devices can create pre/postoperative differential or subtraction maps, which show the changing effect of the initial laser treatment.[50] It must be remembered, however, that when analyzing a subtraction map, there may actually be a slight over- or underestimate of the refractive change compared to subjective refraction. Therefore, although the topographic map may be considered as a template for retreatment planning, it must be guided and modified by the manifest refractive error. It is imperative that stability is reached before retreatment is considered and generally this is achieved at 3 months, or later, following laser ablation.[50] Topography maps should be analyzed carefully for signs of post-LASIK ectasia where retreatment is obviously contraindicated and the Orbscan posterior elevation map is useful in this situation.[50]

Residual stromal bed measurement

Due to the risk of post-LASIK ectasia, knowledge of the residual stromal bed thickness is crucial before enhancement is to be considered. The standard of 250 μm as the residual stromal bed after LASIK has been rather arbitrarily adopted. Significant variability in predicted flap thickness and actual thickness exists when flaps are

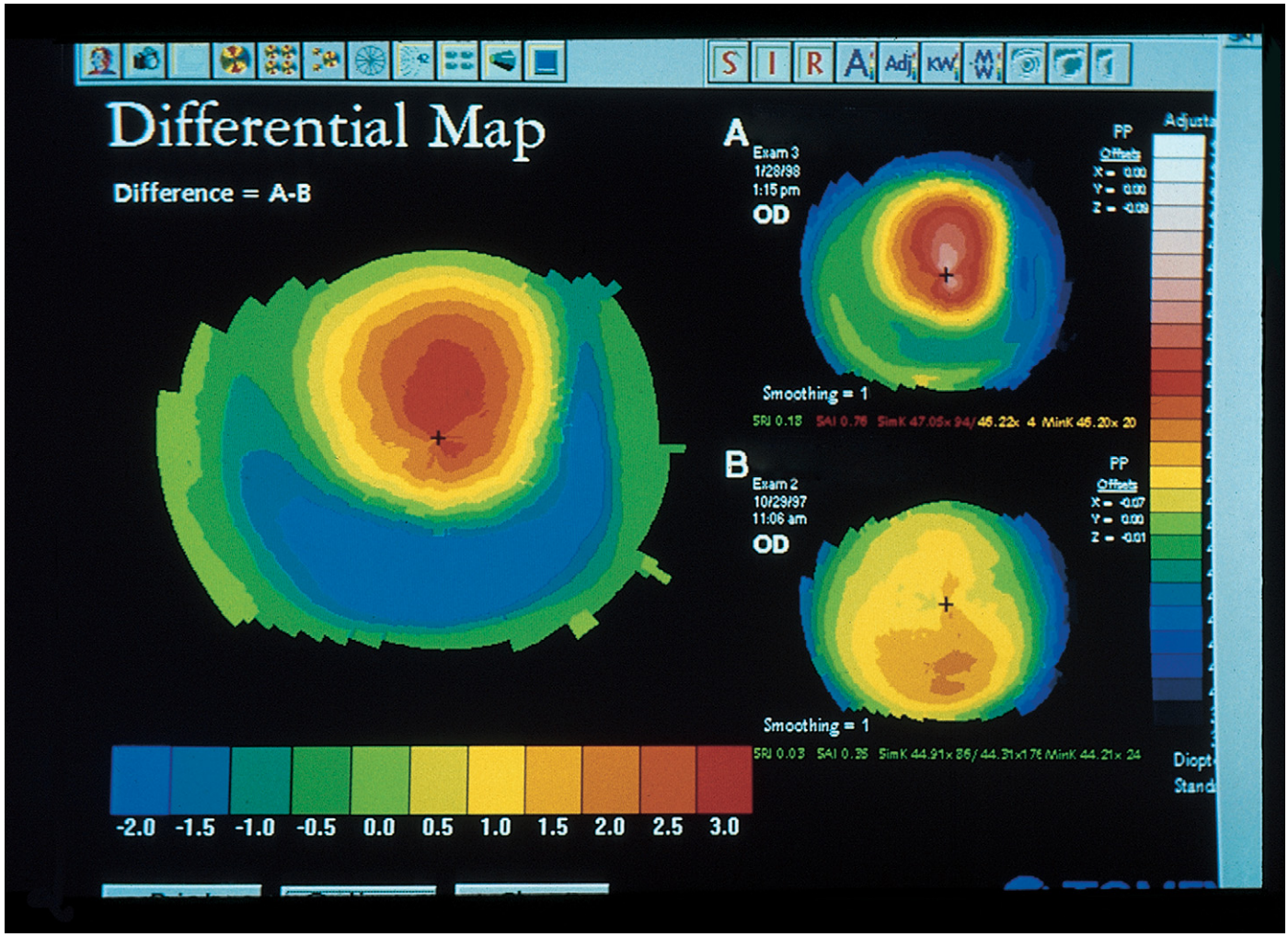


Figure 83.10. Not to be confused with a central topographic island, this difference map shows a slightly superiorly decentred hypermetropic treatment zone with an area of increased power located superior to the corneal vertex, circumscribed by an annulus of decreased corneal power (difference map power scale –2.00 to 3.00 in 0.5 D steps).

created with a microkeratome. If intraoperative pachymetry has been performed at the initial LASIK treatment then this can be accurately calculated. Other options include in vivo confocal microscopy, which can determine the actual residual stromal bed thickness before considering enhancement.[41] Anterior-segment OCT can be used to measure the flap and stromal bed thickness but has been found to be of use only within the first few weeks of surgery. Beyond this, the interface is more difficult to accurately detect due to healing. This noncontact technique has the advantage over intraoperative ultrasound pachymetry in that the latter requires direct contact with the corneal stroma, which theoretically may increase the risk of keratitis and may affect the ablation profile due to irregular corneal hydration.[51] Interestingly, OCT has been reported to successfully detect the interface from previous LASIK treatment in donor corneas up to 15 months postmortem.[52]

Irregular astigmatism

In addition to the retreatment of simple undercorrection or regression in cases of well-centered, regular ablations, the refractive surgeon frequently encounters cases of irregular astigmatism. Ablation-related problems that lead to irregular corneas include small or decentered optical zones and irregular ablations.[53] Irregular astigmatism is associated with higher-order aberrations such as coma, trefoil, and secondary astigmatism, which can all be detected with wavefront analysis.[54] With wavefront-guided surgery, in theory the final anterior corneal surface can be remodeled to compensate for internal aberrations to make the sum of all aberrations equal to zero. However, in practice this is hindered by various factors including limited ablation precision, flap induced new aberrations, and changes in aberrations with age.[53] When dealing with irregular astigmatism, anterior corneal aberrations predominate; therefore, some surgeons argue that treatment should be directed at correcting the abnormal corneal contour, rather than considering aberrations that come from intraocular structures. Topography-guided treatment uses only corneal front surface data, and internal structures of the eye are not considered. It is therefore useful when treating irregular astigmatism, as, in theory, it is possible to re-create the normal aspheric corneal shape. Media opacities do not pose a problem as surface reflections are the only necessary consideration and very irregular corneas can be measured, which may be beyond the capability of wavefront systems.[53]

OTHER CONSIDERATIONS

Overnight orthokeratology has undergone a resurgence in interest in the last few years. This term refers to the overnight wear of

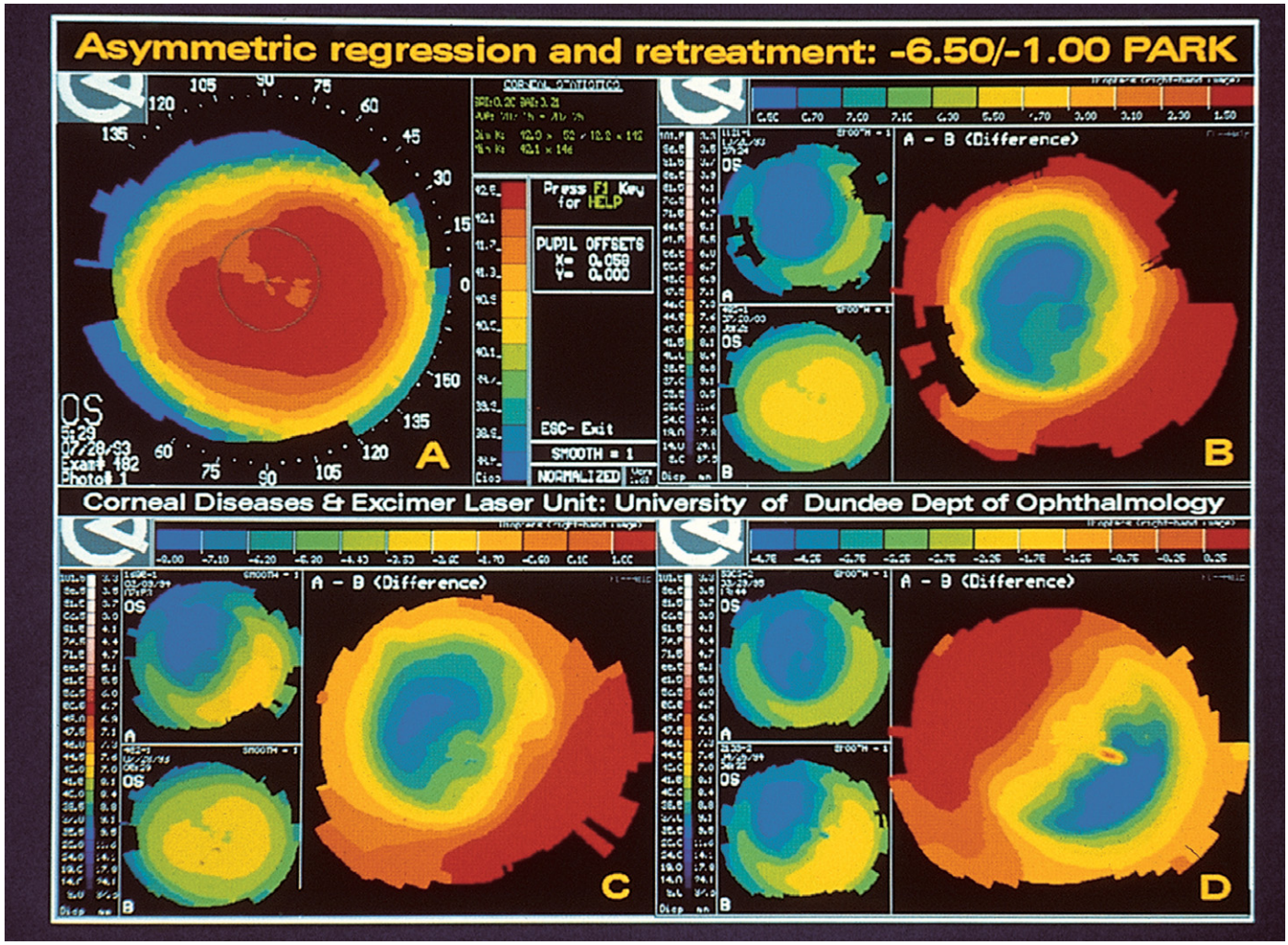


Figure 83.11. Preferential healing and myopic regression of a –6.50/–1.00 D PARK ablation can lead to a CVK map appearance suggestive of ablation zone decentration. *A*, The preoperative power map shows an aspheric cornea (normalized scale in 0.4 D steps). *B*, The difference map, comparing preoperative and 1-month postoperative data, shows a reasonably well-centered, vertically oval ablation (difference scale in 0.8 D steps). *C*, The difference map comparing preoperative and 7 months postoperative data reveals what could be mistaken for a simple superonasal decentration; however, comparison of the two difference maps reveals that the change in ablation zone appearance is due to asymmetric healing—as indicated by increasing power in the inferotemporal quadrant of the ablation site (difference scale 0.8 D increments). *D*, Following retreatment, pre-retreatment subtracted from post-retreatment provides a difference map showing that focal retreatment can be successfully guided by the difference map and manifest refraction to correct the area of asymmetric healing identified in *C* (difference scale using 0.5 D steps).

specially designed rigid gas-permeable contact lenses, which flatten the anterior corneal curvature and subsequently the subject experiences improved unaided vision the following day after lens removal. Corneal topography in these patients is similar to that after LASIK surgery in that there is central flattening and a steeper ring in the mid-periphery.[55] The changes are temporary, but it is a procedure that is considered a useful alternative to corneal surgery in certain situations. These include patients who are too young for LASIK and residual myopia after LASIK unsuitable for an enhancement procedure.[55]

CONCLUSIONS

In summary, our knowledge of the pre- and postoperative assessment of the surgical correction of refractive errors has advanced rapidly in part because of the significant improvements in corneal topography and tomography systems. With the development of real-time eye tracking, flying-spot laser beams, and wavefront analysis it is theoretically possible to custom ablate corneas with asymmetric or irregular topographies. In such cases, the ability of the corneal or cataract and refractive surgeon to fully understand the full potential of corneal topography/tomography and wavefront assessment takes on even greater importance. Indeed, as the relationship between corneal topography and visual performance is further elucidated, the central question may finally be answerable, what shape should the cornea be?

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84 Lessons from radial keratotomy

Mitul R. Vakharia

Radial keratotomy (RK) was the primary refractive surgery in the USA in the 1980s and into the 1990s, with several hundred thousand being performed.[1] With the advent of excimer laser refractive surgery and the long-term complications of RK identified in the mid-1990s, RK has become an 'RKhaic' corneal refractive surgery,[2] alongside keratomileusis,[3] automated lamellar keratoplasty,[4] epikeratophakia,[5] laser thermal keratoplasty,[6] and hexagonal keratotomy[7] (Fig. 84.1, *A–E*). Nevertheless, as the prototype of modern refractive surgery and the forerunner of incisional corneal surgery, there are many lessons to be learned from RK for today's corneal surgeon.

HISTORY OF INCISIONAL KERATOTOMY

The surgical correction of astigmatism was first proposed in 1869 by Dutch ophthalmologist Herman Snellen, who suggested that incisions within the steep corneal meridian might affect astigmatic magnitude.[8] In 1885, Norwegian ophthalmologist Hjalmar Schiotz confirmed Snellen's hypothesis by reporting significant corneal flattening with the placement of a corneal incision tangential to the steep meridian after cataract surgery.[9] American ophthalmologist William Bates in 1894 observed that, in patients with corneal scars, there was flattening of the corneal surface along the meridian of tangential scars.[10]

The scientific groundwork for modern incisional keratotomy was laid in 1898 by Dutch ophthalmologist Jan Lans, who conducted extensive studies in rabbits and demonstrated that anterior tangential corneal incisions resulted in corneal flattening in the meridian of the incisions.[11] Lans further demonstrated that deeper and longer incisions were associated with greater flattening, and there was associated steepening in the meridian 90° away from the tangential incision.

The work of these early ophthalmic pioneers was largely ignored until the late 1930s, when Japanese ophthalmologist Tsutomu Sato noted that patients with keratoconus who experienced breaks in Descemet's membrane developed significant corneal flattening and reduction of myopia.[12] Not yet recognizing the role of the corneal endothelium, Sato reported surgical corneal flattening by posterior radial incisions of the corneal endothelial surface, later combined with anterior radial incisions for an enhanced effect.[13] Unfortunately, long-term follow-up of this procedure demonstrated bullous keratopathy in up to 70% of patients.[14,15]

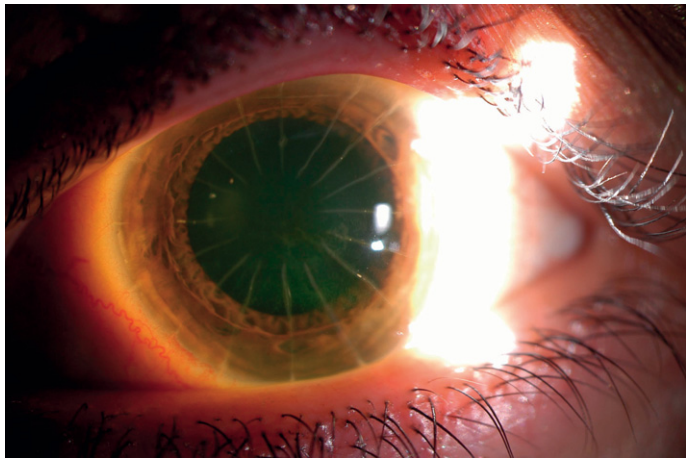
In the 1970s, Russian ophthalmologists Beliaev, Ilyina, Durnev, Fyodorov, and Yenaliev modified and perfected modern techniques of anterior corneal RK.[16–20] Their work defined a central clear optical zone and surgical variations that could titrate the effect of the procedure. Beginning in 1978, Bores et al performed the first RK procedures in the USA and published their optimistic results.[21]

PROSPECTIVE EVALUATION OF RADIAL KERATOTOMY STUDY

The National Eye Institute funded the Prospective Evaluation of Radial Keratotomy (PERK) study in 1980 to evaluate the safety and efficacy of a standardized surgical technique for RK and measure its predictability and stability.[22] The Vision Program Ad Hoc Committee and the National Advisory Eye Council approved funding of the PERK study on human subjects despite the lack of previous vigorous animal testing, as RK was already being performed on humans and they wanted to evaluate its safety and efficacy before it gained widespread application.[2]

The PERK data were collected from 12 investigative ophthalmic surgeons at nine clinical research centers, on 793 eyes of 435 patients with 2–8 D of myopia and 1.5 D or less of astigmatism. These patients were treated with eight RK incisions extending from a central clear optical zone to the limbus. The radial incisions were directed centrifugally, which is known as the American method of incision, starting at the central clear optical zone and extending toward the limbus. These were in contrast to centripetal incisions, known as the Russian method of incision, which showed more efficacy due to deeper incisions but were deemed less safe due to the potential for overshoot into the central clear optical zone. The differences in depth were due to differences in force vectors, as illustrated in Figure 84.2, *A* and *B*.

The incisions were made with a guarded diamond blade, with two footplates to stabilize the incision, and a 45° cutting angle. The footplates were set at a depth equal to 100% of the thinnest paracentral corneal thickness by ultrasound pachymetry. Preoperatively



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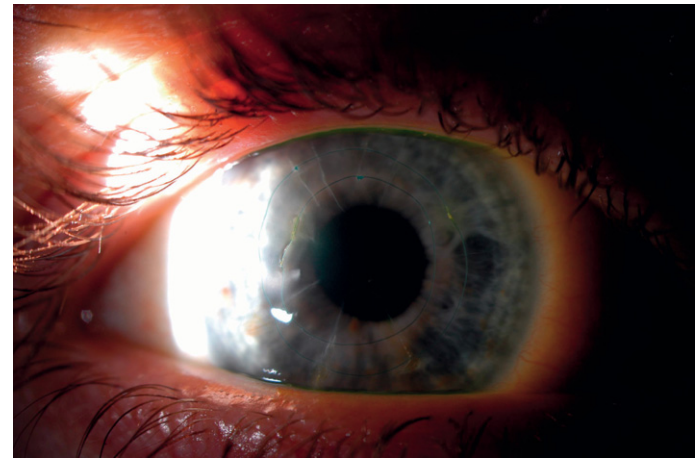

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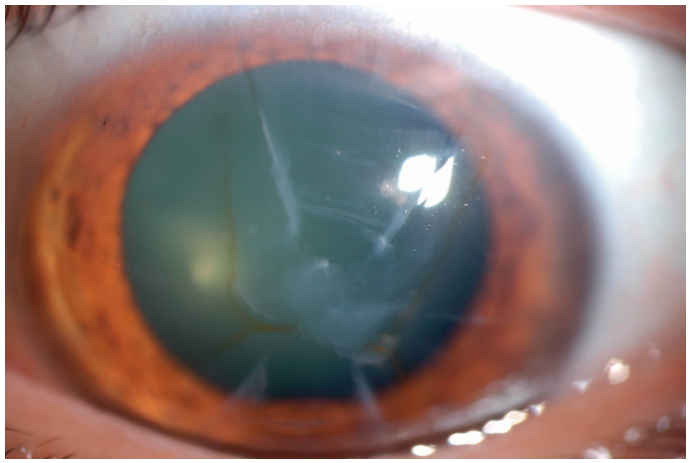

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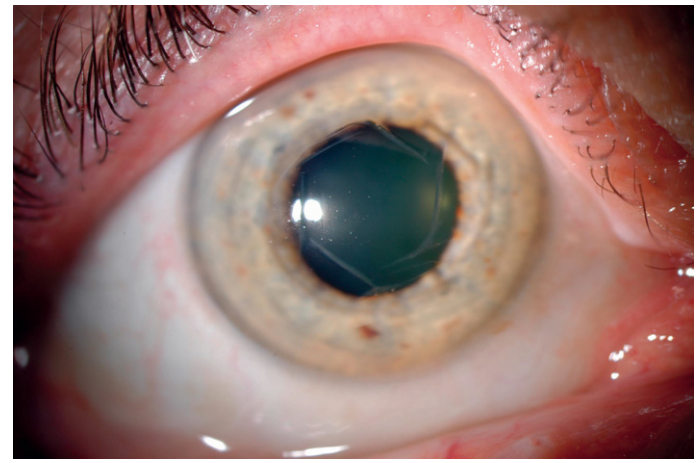

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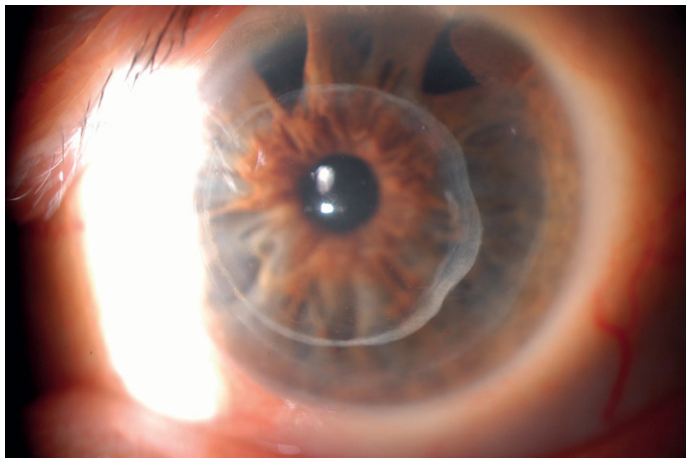
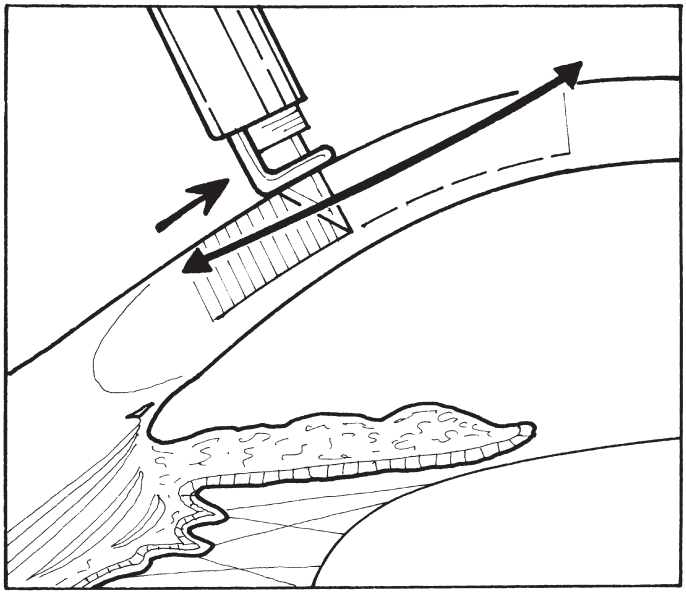
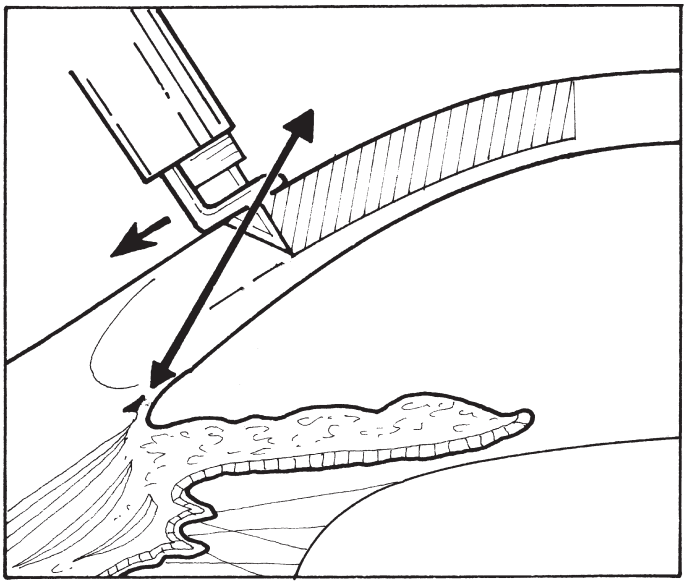


E

Figure 84.1. *A*, Early RK with 16 incisions extending to the limbus. Note the superior tangential incision for astigmatic correction. *B*, Double purse-string compression sutures after RK to reduce postoperative hyperopia, a technique used before hyperopic excimer laser algorithms. *C*, Central subepithelial fibrosis after RK. This patient was successfully treated with superficial keratectomy. *D*, Hexagonal keratotomy, an incisional procedure for hyperopia. Thirteen years after surgery, refraction in this eye was −15.50 +4.50 × 0.50. *E*, Epikeratophakia, a treatment for aphakia after cataract extraction. A donor cornea is lathed to the required power to create a lenticule, which is sutured to the corneal surface after removal of the epithelium or secured under a microkeratome flap. This patient subsequently had LASIK for hyperopic regression. Courtesy of Mark Mannis MD, University of California Davis Department of Ophthalmology.



A



B

Figure 84.2. Different vector forces generated by the two incision methods result in significant differences in incision depth. *A*, In a centripetal (uphill) incision, the vertical knife edge performs the incision with a force vector relatively parallel to the corneal tissue, enabling a uniformly deep incision. *B*, In a centrifugal (downhill) incision, the angled knife edge performs the incision at an oblique angle relative to the tissue plane, displacing the blade tip upward, resulting in more variable incision depth.

designated central clear optical zones measured 3.0, 3.5, or 4.0 mm in diameter, corresponding to subjects classified as having high, middle, or low myopia levels, respectively.

The PERK research teams achieved an 88% patient follow-up rate 10 years after surgery, and these data were published in 1994.[23] Ten-year follow-up data demonstrated an uncorrected visual acuity of 20/20 or better in 53% of eyes and 20/40 or better in 85% of eyes. Among a subgroup of 310 patients at 10-year follow-up who had bilateral RK, 70% reported not wearing spectacles or contact lenses for distance vision. These data for efficacy were encouraging, although not on par with modern refractive surgery outcomes.

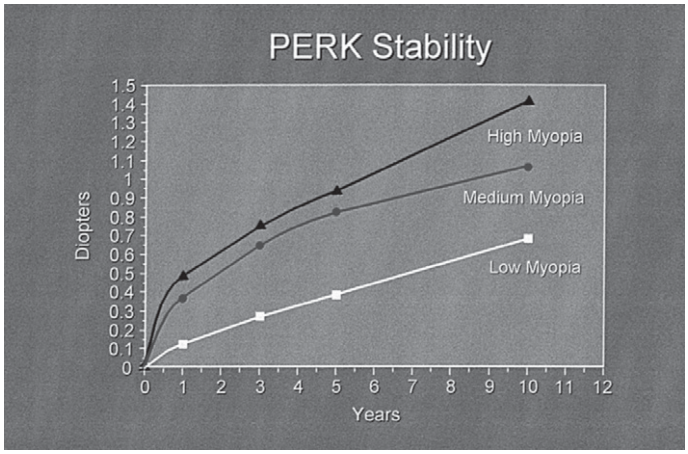


Figure 84.3. For all three groups of eyes in the PERK study based on preoperative myopia, the average spherical equivalent cycloplegic refraction showed a progressive hyperopic shift over time. Even at 10 years after surgery there was no trend toward stabilization of refractive error.

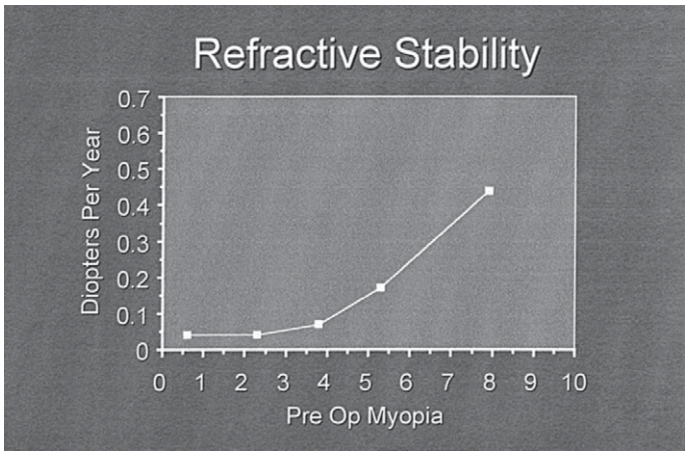


Figure 84.4. One- to three-year follow-up data from another study[25] showed the rate of progressive hyperopic shift after RK was greater for higher amounts of preoperative myopia.

However, the data for predictability and stability were not encouraging and ultimately led to the disuse of the procedure. Four-year follow-up data for refractive outcome following surgery showed a 90% prediction interval that was 4.42 D wide, indicating a lack of predictability.[24] Ten-year follow-up data showed a significant progressive hyperopic shift, with an average change of +0.21 D per year from 6 months to 2 years after surgery and an average change of +0.06 D per year from 2 to 10 years after surgery. A consistent rate of hyperopic shift 10 years after surgery was particularly worrisome as it showed no sign of stabilization, and another study showed the rate was higher for higher amounts of preoperative myopia (Figs 84.3 and 84.4).[23,25]

Additionally, an analysis of a subset of patients 11 years after surgery showed persistent diurnal fluctuation in refraction, with a mean change in spherical equivalent of 0.31 ± 0.58 D of increased myopia from morning to evening, with 13% of patients experiencing a decrease in uncorrected visual acuity of two to seven Snellen lines over the course of the day.[26] Ten-year follow-up data showed a loss of best spectacle-corrected visual acuity of two or more Snellen lines in 3% of patients, an unacceptable safety profile by today's standards.[23] Furthermore, 6-year follow-up data of the PERK

study showed that only 60% of patients were 'highly satisfied' with the results of surgery, and this correlated with having a visual acuity of 20/20 or better in at least one eye.[27] These data showed that a 20/20 outcome should be the goal of refractive surgery, and RK could not consistently provide such results.

SURGICAL PROTOCOL FOR RADIAL KERATOTOMY

What follows is a general surgical protocol for the safe and effective delivery of RK. This section is partly for historical interest and partly for surgeons who may still be performing RK in parts of the world where excimer lasers are prohibitively expensive. This section also contains details that would be of interest to any surgeon performing any form of incisional corneal surgery.

The screening preoperative assessment for RK includes a stable cycloplegic refraction and a series of measurements of paracentral corneal pachymetry. This is done with an ultrasound pachymeter at eight points circumferentially, 1.5 mm from the optical center, which is identified by the patient focusing on a point light source. The thinnest paracentral pachymetry is used to determine the depth setting of the guarded diamond blade, which is set at 100% of this value. This allows the deepest possible incisions for greatest efficacy, while minimizing the risk of perforation.

The advent of computerized corneal topography has allowed the identification of subclinical keratoconus in the preoperative screening examination, which is a contraindication to RK. Corneal topography also determines the precise axis and amount of astigmatism, which was concurrently treated with later incisional nomograms. Corneal topography is also essential in the identification of postoperative-induced irregular astigmatism and surgical planning for incisional enhancement procedures, which later became more conventional.

Routine preoperative topical medications include 1% pilocarpine to constrict the pupil, as this gives the surgeon a better estimation of the visual axis around which to center the treatment. Topical anesthetic is also given, with a potential regimen being two drops of 0.5% tetracaine given 5 min apart, followed by two drops of 4% lidocaine given 5 min apart. Although there is no convincing clinical evidence that prophylactic topical antibiotics decrease the incidence of bacterial keratitis, a broad-spectrum topical antibiotic is used due to its low cost and ease of administration. A sedative such as 10 mg of oral diazepam could also be given 20 min before the procedure as an anxiolytic and an eyelid muscle relaxant.

The patient is positioned on the operating table with the nonsurgical eye patched to facilitate fixation on the operating microscope light. A folded towel may be placed beneath the patient's shoulders to help maintain the chin-up position and provide improved exposure during placement of the superior incisions. The surgical eye is prepared with periocular povidone-iodine (Betadine) solution and an eye drape over the patient's face after excess Betadine has been dried with sterile 4 × 4 gauze. The patient is then instructed to blink frequently to prevent epithelial desiccation, which may lead to excessive friction during incision. The surgeon then instills an additional drop of anesthetic into the fornix before placing the eyelid speculum.

To determine the visual axis, the PERK study group recommended the patient fixate on the microscope light while the surgeon looks through one eyepiece and marks the epithelial surface at the light reflex, at the opposite lower border. For example, if the surgeon views through the right eyepiece, then the mark is placed on the left lower border of the light reflex. The cornea must be well centered within the operative field to avoid parallax-associated decentration. Alternatively, the center of the pupil can be marked to estimate the visual axis.

Marking is done by placing a drop of fluid to enhance the corneal light reflex, gently indenting the epithelium with a Sinskey hook and then using a spear sponge to make the indentation more apparent. A central clear optical zone marker of predetermined diameter is centered over this indentation by aligning the cross-hairs with the indentation. The surgeon may apply a quarter-revolution turn to the central clear optical zone marker to enhance the marking and again gently dry with a spear sponge. A radial marker is then centered with respect to the central clear optical zone mark, and moderate pressure is applied on the epithelium for several seconds.

The paracentral corneal thickness at the thinnest paracentral site (determined at the screening examination) is confirmed with ultrasound pachymetry. The diamond blade is then set to 100% of this depth, which can be confirmed using a calibrating microscope. The surgeon then incises the thinnest quadrant first and the thickest quadrant last. This incision sequence can reduce microperforation because the cornea slightly thins further throughout the procedure due to desiccation.

RADIAL KERATOTOMY TECHNIQUE

As alluded to earlier, the Russian-method (uphill) centripetally directed incisions provide consistently deeper incisions than the American-method (downhill) centrifugal incisions that were used in the surgical protocol of the PERK study (Fig. 84.2).[22] These deeper incisions were found to be more effective in reducing myopia but were less safe due to the potential for overshoot into the central clear optical zone.

An incisional technique, which combined the safety of the centrifugal method with the efficacy of the centripetal method, became a popular RK procedure, known as the *combined technique*.[28] The incision is begun at the central clear optical zone, extends out toward the limbus, and then reverses direction back toward the central clear optical zone without invading that zone (Fig. 84.5, *A–C*). In a study conducted on human cadaveric eyes, eight incision RK with a 3-mm central clear optical zone was performed comparing the three incision methods, and the combined technique achieved more corneal flattening (9.3 ± 1.7 D) than the centrifugal (4.2 ± 1.5 D) or the centripetal method (7.7 ± 2.8 D).[28]

The surgeon incises along the radial marks entering at the central clear optical zone margin, with sufficient pressure to indent the cornea slightly. After a 2 s pause, gentle pressure is applied toward the central clear optical zone, undermining it (Fig. 84.5, *A*). The centrifugal (downhill) radial incision then is initiated while the diamond blade is reoriented perpendicular to the tissue plane with slight indentation pressure, extending to 1 mm from the limbus. Without removing the diamond blade from the incision groove, the surgeon reverses the incision direction returning back to the central clear optical zone margin (Fig. 84.5, *B*), with slightly less indentation pressure during this uphill pass. The diamond blade should then be removed from the incision groove without any pressure being exerted against the central clear optical zone, resulting in a deep, effective, and safe incision (Fig. 84.5, *C*). Postoperatively, a topical NSAID is used immediately for analgesia along with a broad-spectrum antibiotic, and the antibiotic with or without the NSAID is continued four times daily for 5 days.

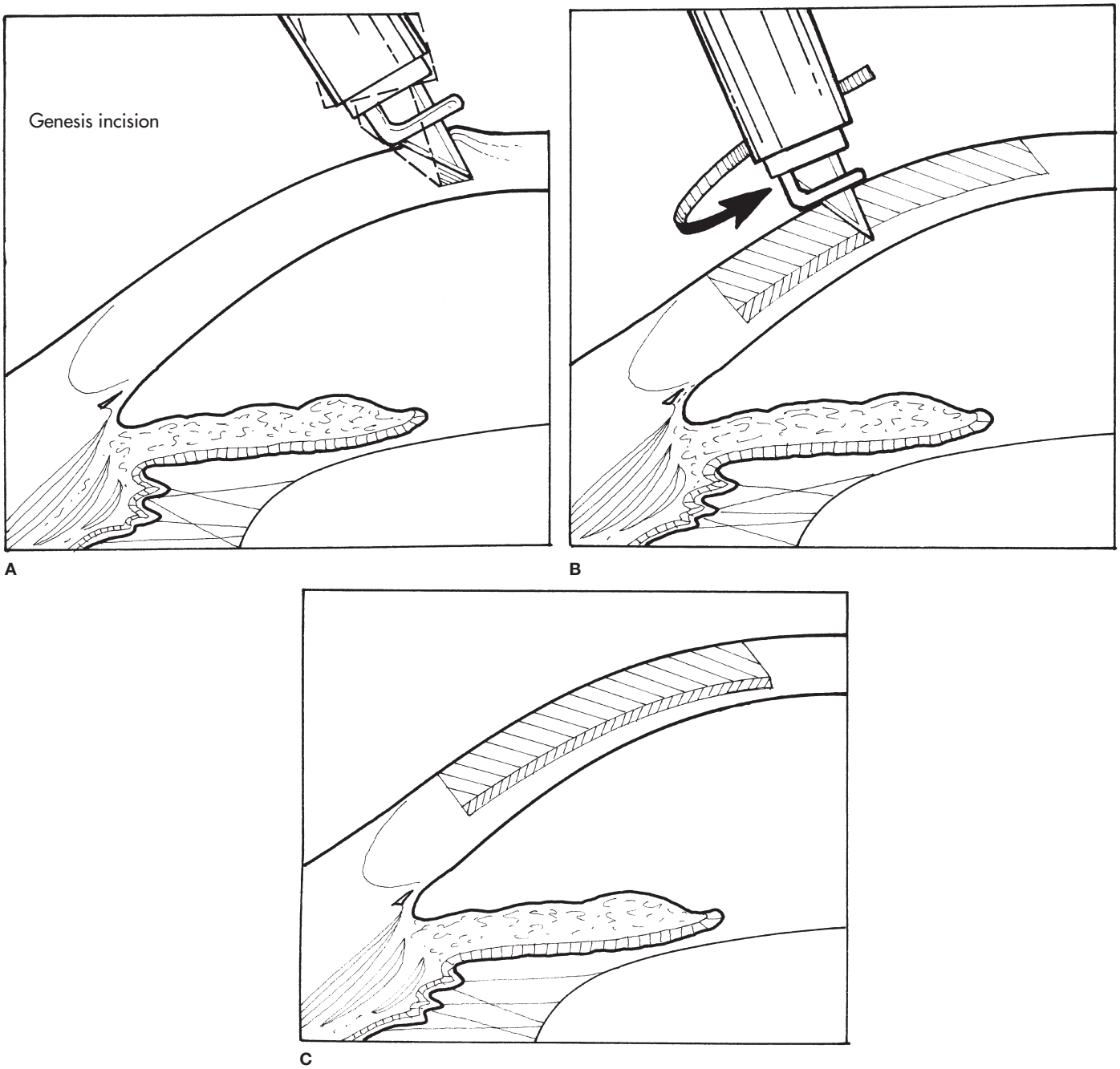


Figure 84.5. *A*, Initial corneal entry is with the diamond blade tip at a slightly oblique angle. After a 2 s pause, the optical zone margin is slightly undermined before perpendicularly orienting the diamond blade to perform the centrifugal (downhill) incision. *B*, The completed centrifugal incision is followed by a reversal in incision direction without removing the diamond blade. This centripetal (uphill) incision is deeper and guided within the initial incision. *C*, The completed *combined technique* incision has the advantages of each incision method, resulting in a uniformly deep and safe incision, with slight undermining of the optical zone margin for maximal efficacy.

The ideal RK incision should terminate 1 mm from the limbus to prevent neovascularization. The incision should remain at least 80% of corneal stromal depth throughout its length. At its central extent, the incision should undermine slightly at the margin of the central clear optical zone (Fig. 84.5, *A*), which enhances its efficacy.

The guarded diamond blade used in *combined technique* RK has a 45°-angled edge (the 'front' surface), which is the centrifugal cutting component in the combined technique, and is sharpened along its entire length. The vertical edge (the 'back' surface) has a cutting edge for only 250 µm from the blade tip (Fig. 84.6). The blunt upper part of the blade's vertical edge prevents unwanted invasion of the central clear optical zone margin during the final centripetal return in the combined technique.

Thinner diamond blades, although more susceptible to damage, were found to offer less resistance during incision, thereby providing a more consistent depth of incision. The 45° cutting angle of the diamond blade was also determined after experience with more acute angles, which meandered due to insufficient resistance, and broader angles, which offered too much resistance on initial insertion. The two footplates of the guarded diamond blade allow for precision of incision depth as well as forgiveness of nonperpendicular pressure by the surgeon, as shown in Figures 84.7, *A* and *B*

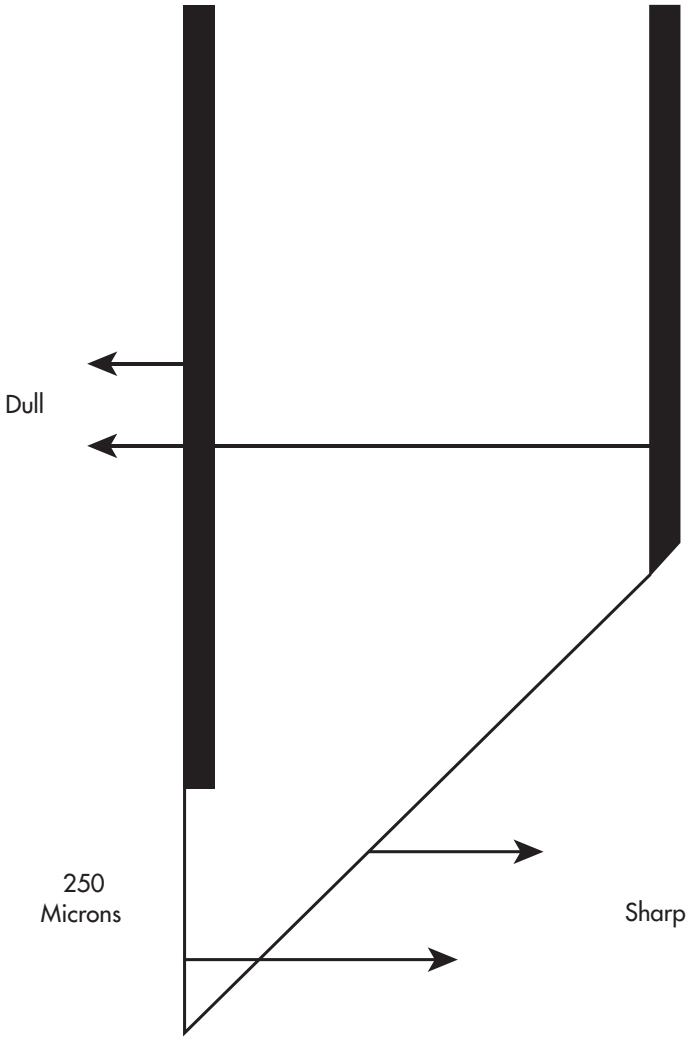


Figure 84.6. The diamond blade design for the *combined technique* incision has a 45°-angled edge, which is sharpened along its entire length, and a vertical edge, which is sharpened only 250 μm from the blade tip. The sharp part of the vertical edge provides additional depth of incision during the reverse centripetal pass, while the dull part of the vertical edge allows the blade to remain guided within the initial incision during this reverse pass.

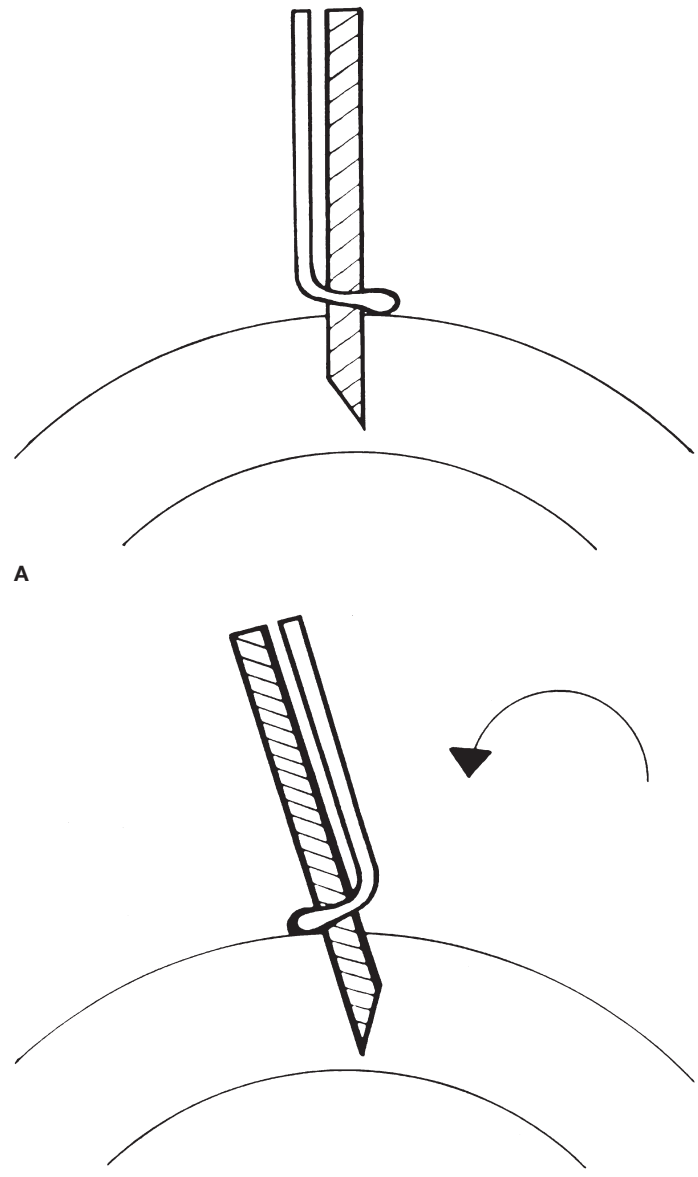
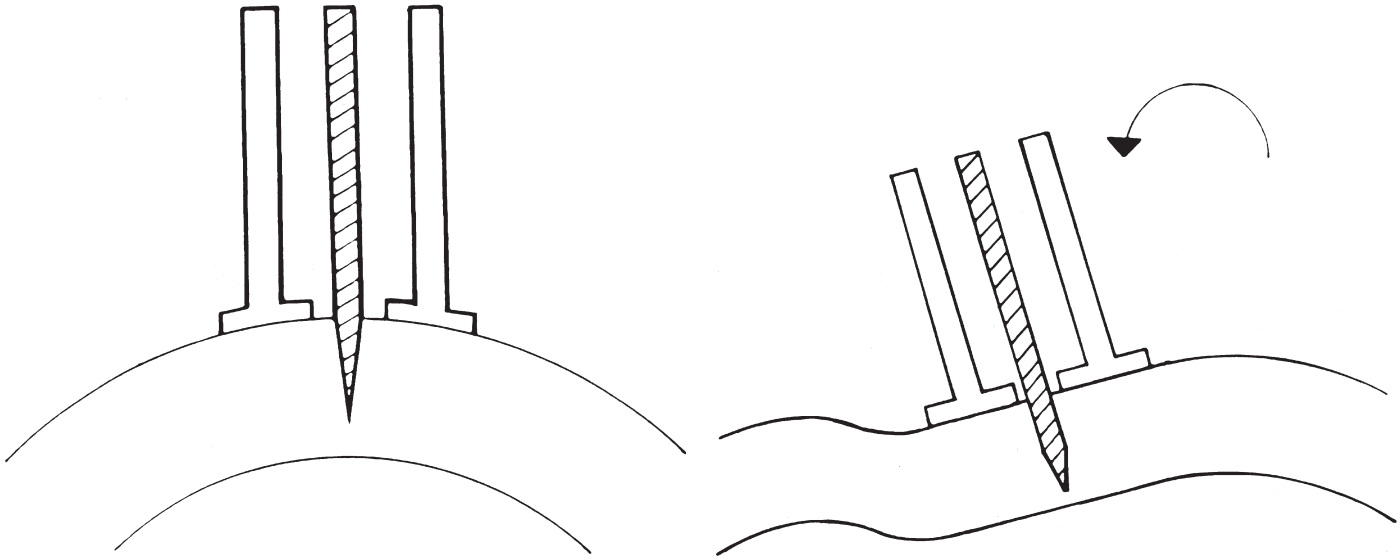


Figure 84.7. *A*, The footplates allow the guarded diamond blade to achieve a consistent depth of incision regardless of indentation pressure. *B*, The depth of incision remains consistent even when asymmetric pressure by the surgeon rocks the blade toward the vertical edge as shown. When the blade is rocked toward the angled edge, the blade tip can be displaced upward, resulting in some variability of incision depth.

and 84.8, *A* and *B*. The spacing between footplates was found to affect incision depth by allowing more or less bowing of the cornea between the footplates and contact with the diamond blade, and this spacing was also made uniform.

Numerous incisional nomograms were developed by experienced RK surgeons, attempting to offer greater predictability of results and guiding the titration of enhancement procedures. Nomograms were also developed for the incisional treatment of astigmatism. Later nomograms took patient age into account, as it became apparent that age accounted for almost 1 D of greater refractive effect per decade of subject age.[29] Surgeons generally would aim for 0.50–1 D of residual myopia to allow for hyperopic shift, adjustment for presbyopia, and possible enhancement procedures, as there was no effective surgical treatment at the time for hyperopia from overcorrection.

Nomograms would vary the incisional factors that cause central corneal flattening, which include (1) the number of incisions, (2) the depth of the incisions, and (3) the length of incisions either centrally or peripherally. Regarding the number of incisions, it was found that approximately 90% of the effect of a 16-incision RK was present after the first eight incisions, and 70% occurred after the first four.[30] This 'law of diminishing returns' led to the development of nomograms using eight incisions or less. The depth of incisions is affected by incision technique as discussed earlier, and at least 80% corneal stromal depth is required for efficacy.[30] Shallow incisions were a common cause of undercorrection. With regard to incision length, the original Russian technique of peripheral extension to the limbus was found to have little refractive effect and carry a risk of neovascularization and increased pain.[30–32] Central incision length, namely the size of the clear central optical zone, was found to be the primary parameter in all RK nomograms, with smaller optical zones leading to more



A B

Figure 84.8. *A*, The broad area of contact between the footplates and the epithelium provides a consistent incision depth. *B*, This broad footplate base allows the depth of incision to remain consistent despite lateral asymmetric pressure by the surgeon as shown.

corneal flattening. However, attempts to correct greater degrees of myopia with smaller optical zones led to complications including disabling glare, irregular astigmatism, and loss of best-corrected visual acuity.[33] Ultimately it was thought that 6 D or less of myopia could be treated safely, with a central clear optical zone no smaller than 3 mm.[1,33,34]

COMPLICATIONS

Many of the long-term complications of RK were discovered by follow-up of the PERK study patients as discussed earlier, namely poor predictability, progressive hyperopic shift, diurnal fluctuation, and loss of best-corrected visual acuity. There were also intraoperative complications such as self-sealing microperforation in 4–10% of patients and frank perforation, which required nylon suture closure in 0.2% of patients in later studies.[32,35] Other long-term complications, which would be unacceptable by today's standards, include relatively high rates of irregular astigmatism, significant glare, loss of contrast sensitivity, neovascularization, epithelial inclusion cysts, subepithelial fibrosis, endothelial cell loss, bacterial keratitis, and even endophthalmitis.[32,36–39] Traumatic globe rupture along RK incisions have been reported as late as 18 years after surgery,[40] as the force required to rupture a porcine model globe after standard RK is only around a third of the force required to rupture an unoperated eye.[41] Case reports of RK incision dehiscence during phacoemulsification surgery suggest that a scleral tunnel incision can minimize corneal manipulation and reduce this complication.[42]

LASIK FOLLOWING RADIAL KERATOTOMY

The advent of excimer laser refractive surgery has not only supplanted RK as the primary refractive procedure but also provided a modality to treat the significant number of under- and overcorrected RK patients. PRK after RK showed a high risk of postoperative haze,[43] but LASIK after RK has consistently shown a reduction in refractive error with relatively few complications, as presented in a recent review of multiple studies.[44] The largest of these studies, of 80 and 69 eyes, showed similar results with preoperative mean spherical equivalent of $+2.36 \pm 1.17$ and $+3.40 \pm 1.60$ D, and postoperative mean spherical equivalent of $+0.62 \pm 0.61$ and -0.32 ± 1.2 D, respectively.[45,46]

The most common complication in both of these studies was a 5–6% rate of epithelial ingrowth, sometimes accompanied by loss of best-corrected visual acuity. Patients having LASIK after RK should, therefore, be monitored closely for any signs of epithelial ingrowth and treated with an early flap lift and scraping with any signs of progression. There was also a 12% rate of RK incision opening within the LASIK flap in one of these studies, but careful flap repositioning after ablation followed by 1 day of bandage contact lens wear resulted in no loss of best-corrected visual acuity in any of these patients.[46] A recent study of 11 RK eyes using the femtosecond laser for LASIK flap creation showed a 100% rate of RK incision opening within the LASIK flap due to disruption by the microcavitation bubbles and the greater resistance required to lift a femtosecond laser flap.[47] This study also showed an 18% rate of loss of best-corrected visual acuity, higher than in studies using a microkeratome, likely due to greater postoperative inflammation from femtosecond laser treatment.

LEGACY OF RADIAL KERATOTOMY

As a recent survey of refractive surgery in the USA shows RK to be nearly extinct less than 25 years after the PERK study began,[48] it is easy to become cynical about new procedures that are introduced today with equal enthusiasm. However, the important lessons learned from RK continue to have significance in modern refractive surgery. Radial keratotomy introduced the concept of an optical zone and provided our first understanding of the critical relationship between the optical zone and the pupil size with regard to symptoms of glare and contrast sensitivity.[36] The intricacies of the guarded diamond blade, which was refined for RK, are very relevant to modern incisional corneal surgery, and the corneal tissue response to astigmatic keratotomy, limbal relaxing incisions, and even clear

corneal cataract incision architecture are based on the knowledge gained from the various studies of RK.

But perhaps the lasting legacy of RK is the field of refractive surgery, which began its emergence with RK in the early 1980s. The idea that a patient's refractive error could be corrected surgically to reduce dependence on spectacles and contact lenses has created a demand that we still strive to meet today with new investigations and new procedures. Radial keratotomy introduced our approach to a patient presenting for elective refractive surgery, which today is among the most common ophthalmic surgeries performed in the USA.[49] As a recent European study of RK for the treatment of early keratoconus indicates,[50] perhaps the concepts and techniques of RK will be revisited in the future.

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85 Astigmatic keratotomy and peripheral corneal relaxing incisions

David R. Hardten, Daniel H. Chang

INTRODUCTION

Correcting astigmatic refractive errors utilizing incisional techniques was among the first refractive corneal procedures performed. Astigmatism in the naturally occurring state is common, and up to 95% of eyes have some clinically detectable astigmatism, with up to 75% of the general population having clinically significant astigmatism.[1,2] This chapter provides an overview of astigmatic keratotomy and peripheral corneal relaxing incisions for the correction of astigmatism.

HISTORY

It appears that astigmatic keratotomy may have been the first corneal refractive surgical procedure performed by ophthalmologists. In 1885, Schiötz,[3] a Norwegian ophthalmologist, reported the case history of a patient who developed 19.50 D of astigmatism after cataract surgery. Four months postoperatively, he used a von Graefe knife to make a 3.5-mm penetrating incision at the limbus in the steep meridian, which reduced the astigmatism to 7.00 D. Lucciola of Terrin, Italy, was the first surgeon to report using nonperforating corneal incisions to correct astigmatism.[4] In 1894, Bates,[5] of New York City, described six patients who developed flattening of the cornea in the meridian that intersected a surgical or traumatic scar. He postulated that incisions of the cornea, made at right angles to the steeper meridian, might be used to correct astigmatism.

A Dutch ophthalmologist, Lans,[6] performed one of the first systematic studies of refractive surgery while at the University of Leiden in 1896. His doctoral thesis titled 'Experimental Studies of the Treatment of Astigmatism with Non-perforating Corneal Incisions' described carefully planned experimentation in rabbits to evaluate patterns of keratotomy, keratectomy, and thermokeratoplasty. These studies also defined some basic principles of astigmatic keratotomy. Lans showed that flattening in the meridian perpendicular to a transverse incision was associated with steepening in the opposite meridian and that deeper and longer incisions had a greater effect.

Even though radial keratotomy is rarely used today, its history is intertwined with that of astigmatic keratotomy. In 1939, Sato et al[7–13] of Tokyo observed that spontaneous breaks in Descemet's membrane in patients with keratoconus could flatten the cornea and reduce their myopia. Sato discussed the concept of coupling, in which transverse incisions might be expected to flatten the steep meridian while simultaneously steepening the flatter meridian.

In the early 1970s, Fyodorov and associates[14–16] varied Sato's technique and introduced the concept of radial incisions performed only in the anterior peripheral cornea and sclera. These investigators varied the diameter of the central clear zone according to the degree of correction desired. Fyodorov and Durnev[17] also devised a multifactorial formula using patient and surgical variables in an attempt to improve predictability of the procedure. Fyodorov and Durnev[18] discussed using several nonperforating anterior keratotomy patterns to correct myopic astigmatism.

The first RK procedure in the USA was performed by Bores and coworkers in 1978.[19] Subsequently, there has been substantial laboratory and clinical research, including technological advances in ultrasonic pachymeters and diamond micrometer knives that have made incisional procedures more predictable. In 1980, the National Eye Institute funded the Prospective Evaluation of Radial Keratotomy (PERK), which helped to define the safety and efficacy of RK.[20] Predictability, refractive instability, and visual quality are limitations of these procedures.[21–24] These problems, which could not be overcome by improved techniques and refined nomograms—as well as advances in the excimer laser—led to the rapid increase in excimer-based techniques with the concurrent decrease of incision-based techniques for the primary correction of refractive error in the mid- and late 1990s.[25] Nevertheless, the adjunctive use of incisional techniques such as astigmatic keratotomy and peripheral corneal relaxing incisions concurrently with other surgical procedures remains an excellent modality for the correction of astigmatism.

PRINCIPLES OF INCISIONAL KERATOTOMY

The cadaver eye model has played a major role in predicting qualitative and quantitative results achieved with incisional refractive surgery.[26–32] Corneal incisions increase the radius of curvature in a direction perpendicular to the incision, as if tissue were being added.

Arcuate or transverse incisions therefore flatten the cornea in the meridian perpendicular to their location (with compensatory steepening of the orthogonal meridian).

ASTIGMATIC KERATOTOMY

Several basic incisional patterns have been investigated, including nonperforating, straight transverse, and arcuate keratotomy incisions, for the reduction of astigmatism (Figs 85.1–85.3). The following principles of astigmatic keratotomy[33] apply to all types of astigmatism:

1. Astigmatic keratotomy incisions are placed in the steep corneal meridian. This is the meridian that is parallel to the plus-cylinder refraction axis and has the greatest power on central keratometry (Fig. 85.4).
2. Coupling refers to the ratio of corneal flattening along the incised meridian relative to the steepening along the unincised orthogonal meridian 90° away. Most arcuate incisions near the limbus are considered to have a coupling ratio of 1, and there is no change in the spherical equivalent. The exact coupling ratio depends on the length, location, and depth of the incision. Relatively short transverse incisions measuring 1–1.5 mm or arcuate incisions approximating 20° tend to flatten the incised meridian more than they steepen the unincised meridian 90° away, thereby creating a hyperopic shift in the spherical equivalent (coupling ratio >1). Transverse incisions measuring 2–5 mm in length or arcuate incisions of 30–90° create a coupling ratio that approximates 1. Longer transverse incisions measuring 5–6 mm or arcuate incisions of 90–120° tend to induce more steepening in the orthogonal meridian than flattening in the incised meridian, thereby creating a myopic shift in the spherical equivalent (coupling ratio <1).
3. The astigmatic change per unit length of arcuate keratotomy incision varies inversely with the optical zone size. Therefore, transverse incisions at a 5 mm optical zone produce greater astigmatic correction than incisions placed near the limbus (limbal relaxing incisions). However, since the amount of

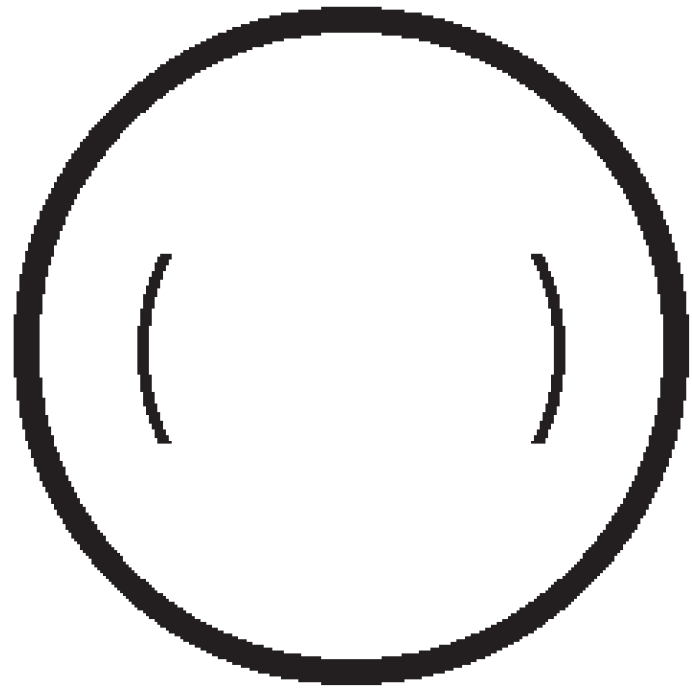

Figure 85.2. Arcuate incisions follow the same curvature as the limbus. These are most commonly used as they induce the least amount of irregular astigmatism compared to the other patterns. (Courtesy of VISX, Santa Clara, CA.)

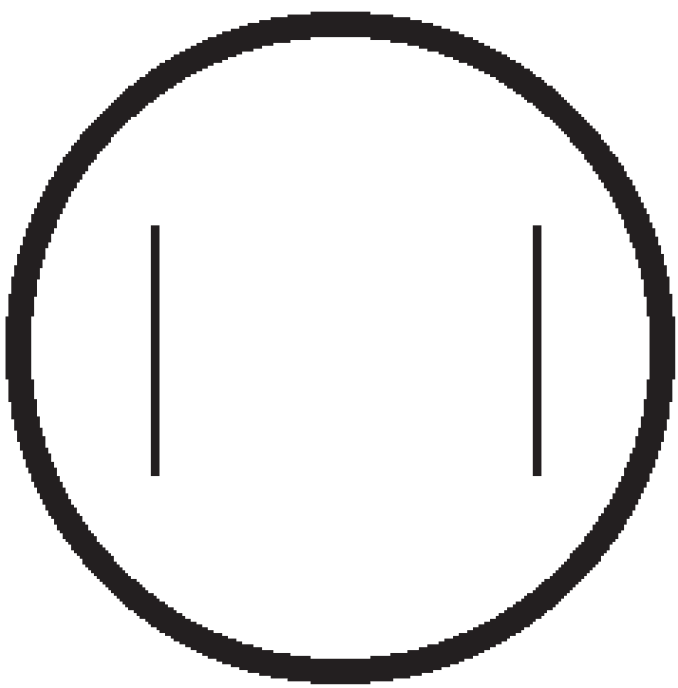

Figure 85.1. Multiple patterns of incisions can be used to reduce astigmatism. A transverse incision is a straight incision that is perpendicular to a radial incision. If these incisions are made very long, significant irregular astigmatism can occur, so are not used for significant degrees of astigmatism. (Courtesy of Meditec, Jena, Germany.)

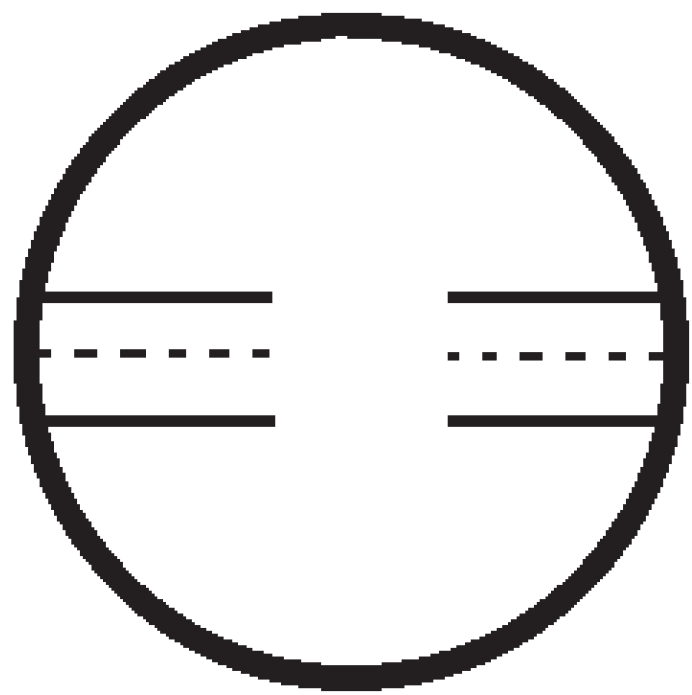

Figure 85.3. Semiradial incisions are parallel to a radial incision, yet set apart from the radial incision. In this figure, the dashed lines represent radial incisions and the solid lines, semiradial incisions. These incisions are not commonly used, as they also lead to greater irregular astigmatism than arcuate incisions. (Courtesy of VISX, Santa Clara, CA.)

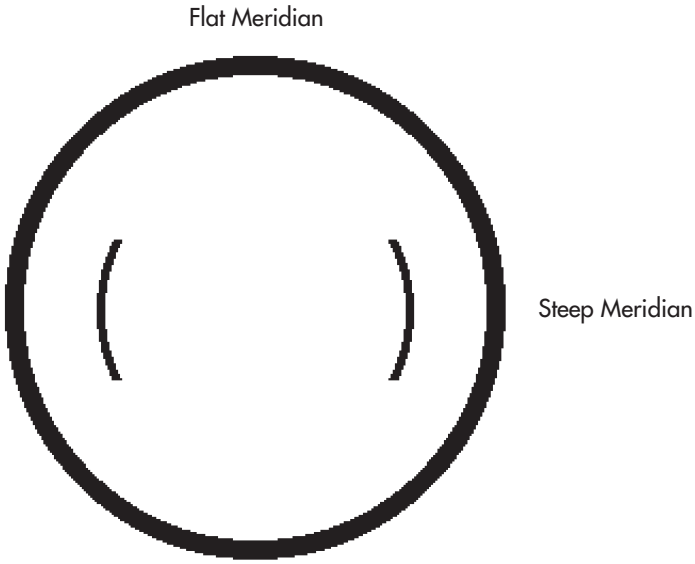

Figure 85.4. To reduce astigmatism, incisions are placed in the meridian that has the steepest corneal curvature, thus creating a more spherical cornea. (Courtesy of Alcon, Fort Worth, TX.)

induced irregular astigmatism and glare also varies inversely with the optical zone size, incisions at an optical zone less than 7 mm are rarely used.

4. Most of the effect of arcuate incisions is achieved with the first symmetric pair of keratotomy incisions; this accounts for about two-thirds of the effect. Placement of an additional pair of incisions will increase efficacy 25–33%, but this is now rarely used because of an increase in irregular astigmatism.
5. Transverse or arcuate incisions should not cross radial or semiradial incisions. Previous clinical studies have shown that when two incisions intersect, the point of intersection undergoes poor wound healing, which often leads to epithelial inclusion cysts, exaggerated scar formation,[34,35] and early and late wound dehiscence.

RADIAL KERATOTOMY (See Chapter 84 also)

Although no longer routinely performed in the USA,[36] basic principles are described for conceptual purposes of understanding corneal biomechanical properties. There are four surgical variables that can be adjusted to achieve the desired result.[37–41]

1. A smaller-diameter central clear zone has a greater net effect such that RK incisions with an optical zone of 6 mm or greater have virtually no effect on the refractive error.[42]
2. The degree of central corneal flattening varies directly (but nonlinearly) with the number of incisions. Four radial incisions achieve greater than 70% of the effect of eight incisions.
3. The degree of central corneal flattening varies with the depth of the incisions such that a double-pass technique offers a deeper incision centrally with less risk of inadvertently entering the clear optical zone.[43–45]
4. Incisions do not need to be carried to the limbus to achieve a near-maximal effect.[42,46]

The degree of correction and the patient's age affect the outcome of incisional keratotomy.[39–41,47] Patients older than 30 years have an increased effect of 1.5–2% per year over the age of 30 years, and patients younger than 30 years have a lesser effect of 1.5–2% per year under the age of 30 years. Other variables that affect the outcome and are hard to predict or control include corneal curvature, preoperative intraocular pressure, gender, corneal thickness, corneal diameter, axial length of the globe, and ocular rigidity. Most studies show that male patients, high intraocular pressure, larger corneal diameter, a thicker cornea, a flatter cornea, and a higher ocular rigidity tend to result in a greater effect.

PATIENT SELECTION

Because of its inherent unpredictability, instability, and poor visual quality, radial keratotomy has largely been abandoned for more modern techniques.[36,48] Astigmatic keratotomy is less commonly performed as a primary procedure for the correction of refractive error but remains a useful adjunct at the time of cataract surgery.[49–51]

Astigmatism greater than 0.5 D is seen in 44% of the population; 8% of the total population has astigmatism of 1.5 D or greater.[1] Generally, about 10% of the population can be expected to have astigmatism greater than 1 D. At this level, the quality of uncorrected visual acuity might be considered unsatisfactory. An astigmatic refractive error in the range of 1–2 D might be expected to reduce uncorrected visual acuity to the 20/30 to 20/50 range, and 2–3 D likely reduces uncorrected visual acuity to the 20/70 to 20/100 range.[52]

Visually significant astigmatism is also quite common after surgery. After extracapsular cataract extraction, astigmatism greater than 1 D is extremely common,[53] with astigmatism greater than 3 D being present in as many as 20% of cases. High astigmatism after penetrating keratoplasty is even more common, with astigmatism being greater than 1 D the norm.[54] Troutman and Swinger[55] estimated that nearly 10% of all penetrating keratoplasties are complicated by high postoperative astigmatism. The use of intraincisional relaxing incisions to correct this common postoperative problem is less predictable than correction of naturally occurring astigmatism.[55–61]

Patients considering astigmatic keratotomy and peripheral corneal relaxing incisions should have stable refractions for best results. Corneal topography can help ascertain which patients might be poor surgical candidates because of preclinical keratoconus, irregular astigmatism, or some other corneal abnormality. Topography maps are helpful in preoperative assessment, surgical planning, and postoperative monitoring of patients undergoing incisional keratotomy.

Nomograms for astigmatic keratotomy are based on averages for large numbers of procedures, so the outcome of surgery cannot be predicted for an individual eye. Additional refractive keratotomy or excimer laser vision correction may be needed to achieve the desired result, and spectacles or contact lenses may still be required for best visual acuity, even after surgery.

TECHNIQUE

Manifest refraction is performed preoperatively. In most cases, the keratometric, topographic, and refractive cylinder power and axis will be compatible. In cases of significant disparity, remeasurement is warranted; but lenticular or posterior corneal astigmatism may account for a difference in refractive and anterior corneal cylinder. Primary astigmatic keratotomy for naturally occurring astigmatism is based on the refractive cylinder and axis. At the time of cataract surgery and for postkeratoplasty astigmatism, keratometric values

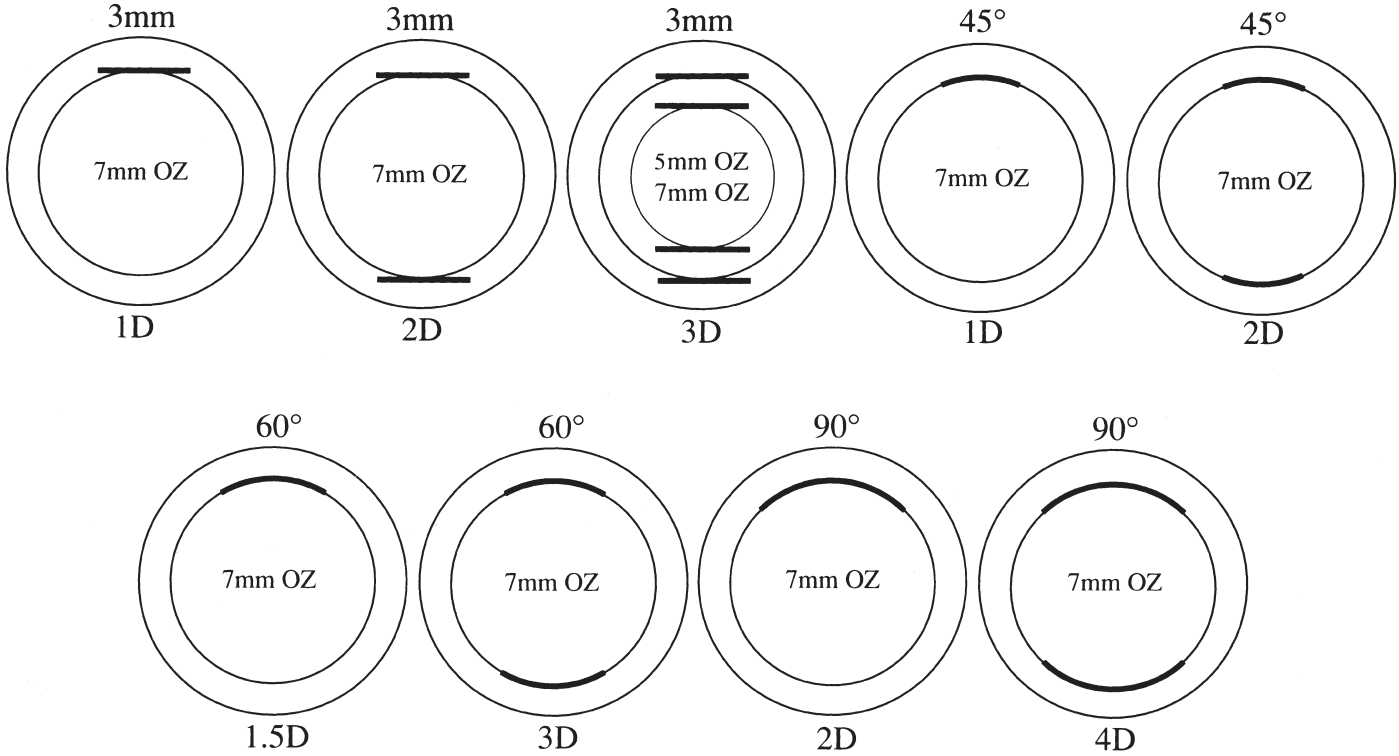

Figure 85.5. Lindstrom nomogram for astigmatic keratotomy. (Courtesy of Aesculap-Meditec, Jena, Germany.)

and topographic maps are generally used in conjunction with the refractive cylinder and axis.

Arcuate keratotomies are placed coincident with an optical zone, typically 7 mm or larger. Transverse incisions are easier to make, yet may induce more irregular astigmatism than arcuate keratotomies. Incisions placed closer to the center of the visual axis induce more glare secondary to irregular astigmatism and carry a greater risk of inadvertently violating the visual axis. Arcuate keratotomy corrections are shown in Figure 85.5 and Table 85.1.

When using these nomograms, it is assumed that the transverse incisions flatten the steeper meridian the same amount as they steepen the flatter meridian (a coupling ratio of 1); so the net effect is no change in the spherical equivalent. This applies to paired arcuate incisions between 30° and 90°, similar to 3 mm-long paired transverse incisions. Arcuate incisions less than 20° have a coupling ratio greater than 1, and arcuate incisions greater than 100° have a coupling ratio less than 1. Arcuate incisions greater than 90° are not recommended because the coupling ratio diverges from 1, and late wound dehiscence is more common. In general, limiting the initial procedure to arcs of less than 60° is preferred.

Younger patients tend to achieve a lesser effect than older patients, therefore the nomogram is adjusted according to the patient's age. The expected result should be decreased by 2% per year for patients younger than the age of 30 years and increased by 2% per year for patients older than the age of 30 years.

Equipment needed includes an operating microscope, arcuate keratotomy markers, a diamond knife, and an ultrasonic pachymeter. The patient is centered under the operating microscope, and the eye is positioned perpendicular to the microscope. The eye is anesthetized with 0.5% proparacaine. The patient fixates on the operating microscope light, which is turned to a low level, or a red fixation light mounted on the microscope. The optical zone is then marked with an appropriate optical zone marker, depending on the amount of astigmatism to be corrected. Special arcuate keratotomy markers are available that imprint both the desired optical zone and a graduated scale (Figs 85.6 and 85.7). The marker blades can be coated with ink for better visualization.

The steeper meridian is marked with a skin-marking pen using preoperative landmarks and an axis marker. Use of photokeratoscopic guidance from a corneal topographer can be beneficial in identifying the axis of astigmatism. By superimposing a printout of the eye image over a printout of the computed axial map, surgical planning and location of incisions can be diagramed. Intraoperatively, correlation of iris landmarks from the eye image printout to the actual eye can be used to help determine the proper rotational alignment independent of cyclorotation.

The corneal thickness coincident with the intended optical zone in the steepest meridian is measured on both sides of the cornea intraoperatively with ultrasonic pachymetry. A diamond knife blade is set at 50 μm deeper than the thinnest paracentral pachymetry measurement or at 100% of the thinnest pachymetry reading at the desired optical zone. For 9 or 10 mm optical zone incisions, many surgeons set the blade at a fixed 600 μm setting.

The patient is asked to fixate on the operating microscope light or the fixation light. The knife is placed into the cornea and allowed to seat for a second. This is followed by a slow, steady guidance of the knife through the incisions (Fig. 85.8). A front-cutting knife allows the surgeon good visibility while pushing through the length of the keratotomy incision, thus improving accuracy. A square blade may provide better tracking. When combining the surgery with cataract surgery, performing the astigmatism incisions first allows for a firmer globe that facilitates the placement of the astigmatic incisions.

The patient is generally seen 1 day and 1 month postoperatively. Topical antibiotics are continued until the corneal epithelium is

Table 85.1 ARC–T 8–9 mm nomogram

How to use this nomogram

- Identify the patient's age and the diopters of refractive cylinder that you wish to correct.
- Find the patient's age in the first column on the left.
- Move to right until you reach the surgery results closest to the refractive cylinder of the patient. In order to avoid overcorrection, typically you would select a surgical goal somewhat less than the actual refractive cylinder. The column heading then tells you which surgery is typical to achieve closest to this result.

Example

- A 45-year-old patient with a refractive cylinder of 2.25.
- Moving to the right on the Age 45 line, you see that 2.25 falls between 1.95 and 2.60. Looking at the column headings, you see that a Paired 60° ARC-T will correct 1.95 D of cylinder. A Paired 90° ARC-T will correct 2.60 D of cylinder.
- In this case you would typically perform a Paired 60° ARC-T procedure.
- Expected surgical results were calculated using Lindstrom's formula:

$\Delta D = [100 + (\text{Age} - 30) \times 2] \times [\Delta D \text{ at age } 30] \times 0.01$

	SURGICAL OPTION					
Age	1 × 30°	2 × 30° / 1 × 45°	1 × 60°	2 × 45° / 1 × 90°	2 × 60°	2 × 90°
20	0.20	0.40	0.60	0.80	1.20	1.60
21	0.21	0.41	0.62	0.82	1.23	1.64
22	0.21	0.42	0.63	0.84	1.26	1.68
23	0.22	0.43	0.65	0.86	1.29	1.72
24	0.22	0.44	0.66	0.88	1.32	1.76
25	0.23	0.45	0.68	0.90	1.35	1.80
26	0.23	0.46	0.69	0.92	1.38	1.84
27	0.24	0.47	0.71	0.94	1.41	1.88
28	0.24	0.48	0.72	0.96	1.44	1.92
29	0.25	0.49	0.74	0.98	1.47	1.96
30	0.25	0.50	0.75	1.00	1.50	2.00
31	0.26	0.51	0.77	1.02	1.53	2.04
32	0.26	0.52	0.78	1.04	1.56	2.08
33	0.27	0.53	0.80	1.06	1.59	2.12
34	0.27	0.54	0.81	1.08	1.62	2.16
35	0.28	0.55	0.83	1.10	1.65	2.20
36	0.28	0.56	0.84	1.12	1.68	2.24
37	0.29	0.57	0.86	1.14	1.71	2.28
38	0.29	0.58	0.87	1.16	1.74	2.32
39	0.30	0.59	0.89	1.18	1.77	2.36
40	0.30	0.60	0.90	1.20	1.80	2.40
41	0.31	0.61	0.92	1.22	1.83	2.44
42	0.31	0.62	0.93	1.24	1.86	2.48
43	0.32	0.63	0.95	1.26	1.89	2.52
44	0.32	0.64	0.96	1.28	1.92	2.56
45	0.33	0.65	0.98	1.30	1.95	2.60
46	0.33	0.66	0.99	1.32	1.98	2.64
47	0.34	0.67	1.01	1.34	2.01	2.68

Table 85.1 continued

	SURGICAL OPTION					
Age	1 × 30°	1 × 45° 2 × 30°	1 × 60°	1 × 90° 2 × 45°	2 × 60°	2 × 90°
48	0.34	0.68	1.02	1.36	2.04	2.72
49	0.35	0.69	1.04	1.38	2.07	2.76
50	0.35	0.70	1.05	1.40	2.10	2.80
51	0.36	0.71	1.07	1.42	2.13	2.84
52	0.36	0.72	1.08	1.44	2.16	2.88
53	0.37	0.73	1.10	1.46	2.19	2.92
54	0.37	0.74	1.11	1.48	2.22	2.96
55	0.38	0.75	1.13	1.50	2.25	3.00
56	0.38	0.76	1.14	1.52	2.28	3.04
57	0.39	0.77	1.16	1.54	2.31	3.08
58	0.39	0.78	1.17	1.56	2.34	3.12
59	0.40	0.79	1.19	1.58	2.37	3.16
60	0.40	0.80	1.20	1.60	2.40	3.20
61	0.41	0.81	1.22	1.62	2.43	3.24
62	0.41	0.82	1.23	1.64	2.46	3.28
63	0.42	0.83	1.25	1.66	2.49	3.32
64	0.42	0.84	1.26	1.68	2.52	3.36
65	0.43	0.85	1.28	1.70	2.55	3.40
66	0.43	0.86	1.29	1.72	2.58	3.44
67	0.44	0.87	1.31	1.74	2.61	3.48
68	0.44	0.88	1.32	1.76	2.64	3.52
69	0.45	0.89	1.34	1.78	2.67	3.56
70	0.45	0.90	1.35	1.80	2.70	3.60
71	0.46	0.91	1.37	1.82	2.73	3.64
72	0.46	0.92	1.38	1.84	2.76	3.68
73	0.47	0.93	1.40	1.86	2.79	3.72
74	0.47	0.94	1.41	1.88	2.82	3.76
75	0.48	0.95	1.43	1.90	2.85	3.80

Find patient age, then move right to find result closest to refractive cylinder without going over.

re-epithelialized. The 1-month result correlates well statistically with the 1-year result, but additional astigmatic enhancement should not be considered until the refraction and keratometry measurements are stable.

INCISIONS WITH CONCURRENT CATARACT SURGERY

The principles of astigmatic keratotomy and peripheral corneal relaxing incisions can be a useful adjunct in refining refractive outcomes at the time of small-incision cataract surgery.[49–51] The cataract wound itself is an incision that can alter the astigmatism of the eye. Variation of the incision parameters such as length, width, and location can be useful but requires rotation around the operating table and adjustments of the hand position and technique. Additionally, with increasing awareness of wound placement and construction for the prevention of bacterial endophthalmitis after cataract surgery,[62] altering wound anatomy for astigmatism control may compromise the self-sealing quality of the incision. Some authors have suggested the creation of an opposite clear corneal incision during cataract surgery to augment the astigmatic effect of the cataract wound.[63] While this approach may be advantageous without requiring the acquisition of additional skills or equipment, creation of a second full-thickness incision may increase the risk of postoperative infectious complications.[64]

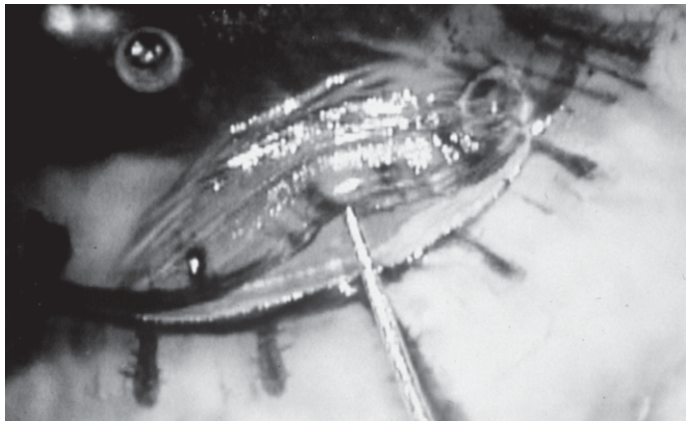

Figure 85.6. An arcuate keratotomy marker can be used to mark the orientation and length of incisions. The marker is aligned in the proper orientation of the steep axis of astigmatism, and the incision then is created along the line of the marker. (Courtesy of Bausch & Lomb, Rochester, NY.)

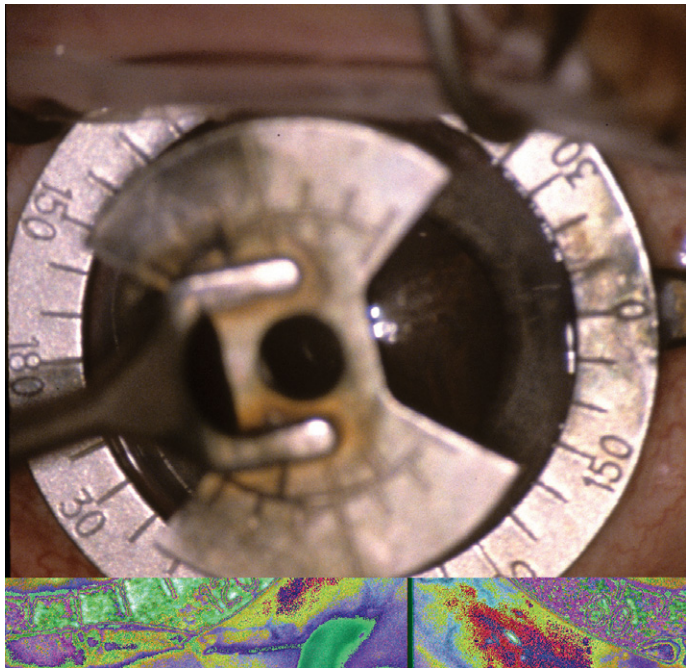

Figure 85.7. Using an AK marker to make an imprint with or without ink on the cornea can be helpful in aligning the AK incisions on the correct axis. Marks on the conjunctiva can be used to align the reticule to the proper orientation. A marker that marks at a 9-mm optical zone can be used, although using a 7-mm marker and following the outer tips of the marks also allow an incision at the 9-mm optical zone. A reticule is used to align with marks at the 3 and 9 o'clock positions to verify the axis of the incision. (Courtesy of Nidek, Fremont, CA.)

Since most surgeons prefer a single approach to the majority of their cases,[48] the use of peripheral corneal relaxing incisions in conjunction with a small-incision cataract wound surgery is an effective method of astigmatism control.[51] Although most surgeons prefer a clear corneal temporal wound, peripheral corneal relaxing incisions can be used with any wound, provided that the surgeons accounts for the astigmatic effect of the wound. The peripheral corneal relaxing incisions can be placed before or after the cataract surgeon, although large incisions at the phaco wound may case excess gaping and fluid egress.

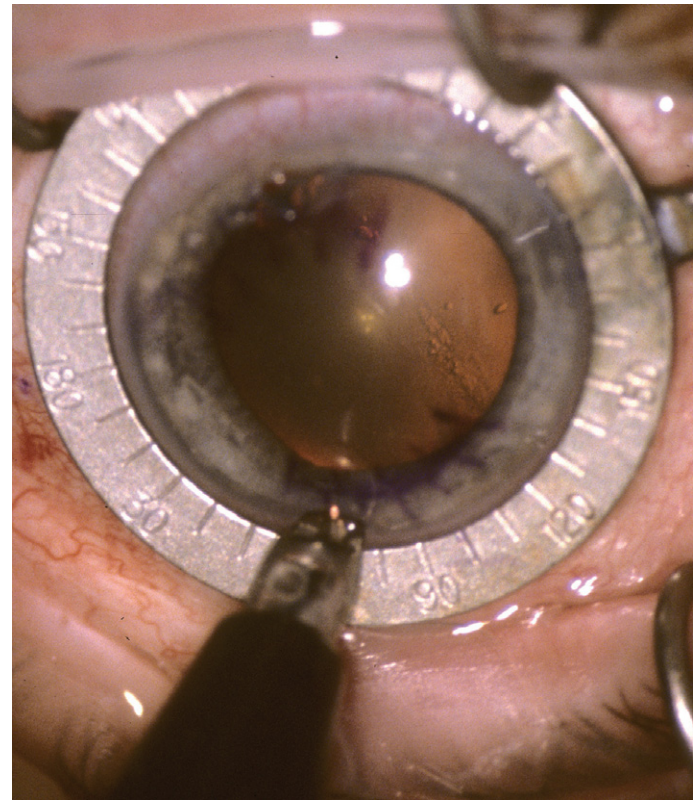

Figure 85.8. A slow, steady movement of the knife in the tissue is used to follow the marks for the incision. A reticule is used to align with marks at the 3 and 9 o'clock positions to verify the axis of the incision. (Courtesy of Nidek, Fremont, CA.)

INCISIONS FOR POSTKERATOPLASTY ASTIGMATISM

High corneal astigmatism is a common complication after penetrating keratoplasty. While there are now many modalities for reducing postkeratoplasty refractive error, incisional techniques such as relaxing incisions, compression sutures, and wedge resections remain useful in the correction of large degrees of astigmatism.[65]

In eye-bank eyes, a marked disparity in the magnitude of change after symmetric 60–90° incisions indicated a narrow surgical 'safe' zone. Clinically, marked under- and overcorrections have been achieved in postkeratoplasty astigmatism with the use of relaxing incisions, making the determination of a suitable endpoint somewhat difficult.

The operative procedure involves careful dissection of the graft–host interface in a graded fashion. A gradual and careful deepening of the incision in the graft–host interface with use of a metal knife appears to be more controlled than with use of a diamond knife. In some cases, blunt dissection with the noncutting edge of the knife may actually be helpful. The use of a surgical keratometer is helpful for assessing the endpoint. Alternatively, the patient's keratometric values can be obtained intermittently with use of a conventional keratometer until the desired endpoint is obtained. The preferred endpoint is a spherical cornea or slight (up to 33%) overcorrection in most cases. Longer incisions, however, tend to progressively gape as they heal; and in 75–90° incisions, it may be desirable to leave a small amount of undercorrection. An appro-

priate incision length should never exceed 90° of the circumference of the graft.

A major disadvantage of incisions in the graft–host interface is the possibility of wound dehiscence. To avoid this complication, incisions can be placed in the donor graft. Standard 600 µm deep paired 60° incisions placed 6 mm apart resulted in a decrease of postkeratoplasty astigmatism from 10.99 to 3.33 D.[66] Interestingly, the amount of astigmatic correction was linearly proportional to the amount of preoperative corneal astigmatism, suggesting that nomograms for correcting naturally occurring astigmatism may not apply to postkeratoplasty corneas.

COMPRESSION SUTURES

The addition of compression sutures to either relaxing incisions or arcuate keratotomy incisions can markedly increase the net effect of astigmatic correction. Compression sutures can be placed on each side of the graft–host interface 90° away from the astigmatic incisions. Suture depth should be about 75%. The sutures are tied with a slipknot and adjusted under keratometric or intraoperative computerized topographic control until the eye is spherical or an overcorrection of 33% is achieved. The knots are cut short and then buried. The use of 11–0 polyester suture can be advantageous over 10–0 nylon because, if perfect surgical correction of astigmatism is achieved, it may be desirable to leave the sutures in place for extended periods of time. Nylon will hydrolyze in 2–5 years, whereas polyester suture will last longer than 7–10 years. Compression of the corneal tissue with conductive keratoplasty in the meridian opposite of the relaxing incisions can also be considered.

WEDGE RESECTION

The wedge resection technique is reserved for correction of large degrees of postkeratoplasty astigmatism. In general, resection of 0.1 mm of tissue results in about 2 D of astigmatic correction. This operation is reserved for patients with greater than 10 D of astigmatism; it is capable of correcting up to 20 D of astigmatism. Wedge resection, however, requires prolonged postoperative rehabilitation because of the placement of multiple sutures, which induce a significant amount of irregular astigmatism. Nevertheless, the alternative to wedge resection is repeating penetrating keratoplasty. Therefore, an attempt at wedge resection may be preferable to immediate repeat keratoplasty.

The overall effect of wedge resection is to steepen the flatter meridian about twice as much as it flattens the steeper meridian. The net effect is an increase in myopia or a decrease in hyperopia. For example, if the preoperative refraction was $-6.00 + 12.00 \times 90°$ and keratometry was $40.00/52.00 \times 90°$, a perfect result should give postoperative keratometry measuring 48.00/48.00 with a refraction of –2 D. This would result in a 2 D myopic shift.

COMPLICATIONS

OPERATIVE COMPLICATIONS

Corneal perforations may be identified as a microperforation (in which a loss of one or two drops of aqueous humor) or as a macroperforation (in which there is shallowing of the anterior chamber). Macroperforation usually requires termination of the procedure and possible closure of the perforation with suture. The PERK study reported a 2.3% microperforation rate, with no cases requiring suturing or termination of the surgery.[67] Most microperforations occur in the inferior and temporal cornea, where the cornea is relatively thinner, although they may appear in any location.[68–70] Macroperforations occur with a frequency of 0–0.45%[70–73] and can result in scar formation at the level of Descemet's membrane, damage to the corneal endothelium, iridocorneal adhesions, and laceration of the anterior lens capsule.[74]

POSTOPERATIVE COMPLICATIONS

Complications such as epithelial iron lines,[75] anterior corneal epithelial basement membrane changes,[76] epithelial inclusion cysts,[24,77] and epithelial ingrowth[78]—as seen after RK—are occasionally noted after astigmatic keratotomy and peripheral corneal relaxing incisions. Incisions that cross the limbus may cause bleeding into the wound, stimulating a vascularized limbal scar, and enhancing growth of neovascular vessels into the wound.[79] Intersecting incisions produce severe wound gape and significant degrees of scarring.[34,80] Intersecting radial and transverse incisions creates a wound gape at the area of intersection that fills with stromal scarring and is frequently accompanied by extensive subepithelial opacification spreading out from the wound (Fig. 85.9).[81] Such scars induce irregular astigmatism but also substantially increase light scattering and glare.

Bacterial or fungal keratitis, with the infiltrates contiguous to the keratotomy scars, can occur in the immediate postoperative period or can be delayed several years after incisional keratotomy.[71,82–86] The persistent epithelial plug in the keratotomy wound is implicated in delayed bacterial and fungal keratitis.[87] Bacterial endophthalmitis may occur due to corneal perforation and introduction of microorganisms into the eye, either during or shortly after the surgical procedure.[88–91]

Any corneal incision results in a scar that does not have the same tensile strength as the original cornea. This is true not only after incisional keratotomy but also after corneal transplantation or acci-

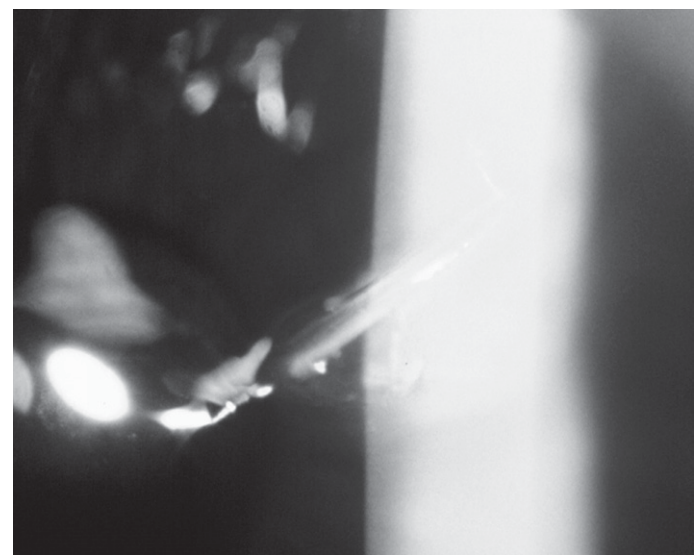

Figure 85.9. Crossing radial or astigmatic incisions can cause areas of poor wound healing with ectasia of the tissue or scar formation and epithelial inclusion cyst formation. (Courtesy of WaveLight, Erlangen, Germany.)

dental trauma.[92] There are several reports of traumatic rupture of keratotomy scars after blunt trauma.[93–95]

Blepharoptosis is a reported complication of incisional keratotomy.[96,97] Because retrobulbar injections and superior rectus bridle sutures were not used in the cases reported, the most likely cause of blepharoptosis was damage to the levator aponeurosis by the eyelid speculum. It has been suggested that a gentle wire speculum might be less likely to induce ptosis than a solid, rigid eyelid speculum.[97]

REFRACTIVE COMPLICATIONS

The most frequently reported complication of astigmatic keratotomy and peripheral corneal relaxing incisions is an inaccurate outcome—overcorrection, undercorrection, and induction of irregular astigmatism. Diurnal fluctuation of vision and progressive shifts in refraction, as seen with RK, are rare.[98–100]

Refractive over- and undercorrection after incisional keratotomy can be managed by spectacles or contact lenses. Contact lenses are advantageous if anisometropia is present, but contact lens fitting after incisional keratotomy has its own unique problems. Neovascularization of perilimbal incisional scars has limited the fitting of patients with soft contact lenses.[101,102]

For the surgical management of overcorrections after astigmatic keratotomy, one can reopen previously placed keratotomy incisions and then close with interrupted sutures instead of placing additional astigmatic incisions.[103] Suture pattern can be varied based on the number and location of incisions.[104,105] Previously placed incisions can be bluntly opened with a Sinskey hook and then copiously irrigated with balanced salt solution to the depth of the incision. The incisions can then be closed with two or three 10–0 nylon or 11–0 polyester sutures. Intraoperative control of suture tension with a surgical keratometer or intraoperative computerized topography and the use of slipknots are helpful. The sutures are used to obtain a spherical result or a slight overcorrection of up to one-half of the preoperative cylinder in the appropriate direction. The overcorrection is important because much of the effect will decay with time.[106] Selective suture removal can begin 8 weeks after suture placement as needed.

Although potentially beneficial in the short term, suture techniques can be meticulous, challenging, and yield unpredictable refractive results. With the advent of the excimer laser, PRK[107] and LASIK[108–110] have been used to correct induced refractive errors after incisional keratotomy. Although early studies of PRK after RK without the use of mitomycin C resulted in significant anterior stromal scarring and haze, the addition of mitomycin C has reduced this unwanted complication.[111] Wavefront-guided technologies offer exciting new possibilities for treating postoperative refractive complications after incisional keratotomy with both LASIK and PRK.

CONCLUSION

Although once a mainstay of refractive surgery, incisional keratotomy is now reserved for specific applications where safety and efficacy are still comparable to modern techniques. Although technologic advances have introduced newer methods for correcting refractive error, it appears that modern incisional surgery will continue to have a role in the future of refractive surgery as a reliable method of correcting low degrees of astigmatism, particularly at the time of small incision cataract surgery. Therefore, a thorough understanding of the corneal biomechanical response to incisional keratotomy will continue to be important to corneal and refractive surgeons.

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86 Conductive keratoplasty

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INTRODUCTION

Conductive keratoplasty (CK) is a laserless, nonablative, radiofrequency-based collagen shrinking treatment that has been shown to change corneal curvature effectively and safely in numerous clinical trials. Conductive keratoplasty was first used to treat spherical hyperopia,[1–4] and was approved by the USA Food and Drug Administration (FDA) for the treatment range of +0.75 to +3.25 D in patients aged 45 years or older in April 2002. Clinical experience with this refractive group revealed that patients frequently gained near vision without losing as much distance vision as could be expected. This observation led to the exploration of a new CK application—the treatment of presbyopes in the nondominant eye to improve near visual acuity without marked loss of binocular distance vision.

In March 2004, CK was approved by the FDA for treating symptoms of presbyopia in emmetropes or mild hyperopes (+1.00 to +2.25 D), 40 years of age or older, through induction of 1.00–2.00 D of myopia in the nondominant eye. Other potential uses of the CK technique under investigation include treatment of over- or undercorrections following LASIK or other excimer laser procedures, enhancing outcomes of cataract surgery, and treating astigmatism.[5–9] This chapter will explain the mechanism of action of CK, how to perform the procedure, and its application for treating hyperopia, presbyopia, and other conditions.

HISTORY OF CORNEAL STEEPENING PROCEDURES

While hyperopia and presbyopia share little but the inability of patients to see well at near, both conditions have been treated through corneal steepening procedures. Early attempts to steepen parts of the cornea involved direct, local application of heat, which became known as thermokeratoplasty. In the late 19th century, Dutch ophthalmologist L. J. Lans induced collagen shrinkage with resultant corneal curvature changes by heating rabbit corneas.[10] Since then, various attempts have been made to shrink corneal collagen in humans. The Russian surgeon, Svyatoslav Fyodorov, was the first to use thermokeratoplasty to change corneal refraction in 1981. Using a probe tip heated to 600°C, he and other investigators applied controlled thermal burns to a reported depth of 95% to treat spherical hyperopia and hyperopic astigmatism.[11–13] Although high hyperopic corrections were achieved, later studies showed lack of predictability and marked regression.[14–16]

Also in the early 1980s, Rowsey and Doss developed the Los Alamos thermokeratoplasty probe.[17] This instrument heated stromal collagen by means of radiofrequency waves instead of by direct thermal conduction from a heated instrument.

However, the topographical effect with this probe was short lived, and testing was terminated.

Subsequently, several types of lasers were used in attempts to change corneal curvature with varying results. Of these, the only commercially successful system for steepening the central cornea to treat hyperopia was the noncontact method of holmium:YAG laser treatment by Sunrise Technologies of Fremont, California. This system came to be known as laser thermal keratoplasty (LTK). Early histology studies in animal eyes showed a cone-shaped zone of collagen shrinkage in the stroma after LTK treatment.[18] A later histology study in rabbit and human corneas showed a broad spectrum of histological changes in the epithelium and stroma, and a brisk wound healing response.[19] Among the questions that remained after study completion was the extent of postoperative regression induced by new collagen formation during stromal wound healing following LTK.

For treatment of hyperopia, LTK was applied to the surface of the cornea in one or two rings (at the 6- and 7-mm optical zones) of eight focal spots in each ring, while the patients sat with their chin in chin rests. A foot switch activated the simultaneous release (to all spots at once) of Ho:YAG infrared laser energy. Clinical studies with 2-year follow-up of LTK treatment of hyperopes were published.[20–22] The FDA approved the Hyperion LTK device in June 2000 for treatment of patients 40 years of age or older with a stable refraction of +0.75 to +2.50 D and less than 0.75 D of astigmatism. Approval was based on results from a study cohort of 612 eyes, with 80% available for analysis at 12 months and only 12% at 24 months postoperatively.[23] Longer-term data of Sunrise LTK showed disappointing efficacy,

predictability, and stability, and the device is no longer manufactured by Sunrise Technologies.

In the 1990s, Antonio Mendez, MD, studied radiofrequency as an alternative to procedures that applied heat directly to the corneal surface.[24] His success in denaturing collagen and steepening of the cornea led to the development of the Conductive Keratoplasty® procedure (CK), performed with the ViewPoint CK System (Refractec Inc., Irvine, CA). Conductive keratoplasty was approved by the FDA in April 2002 for the treatment of mild to moderate (0.75–3.00 D) previously untreated, spherical hyperopia in persons aged 40 years or older. This was followed by the approval in March 2004 of CK to reduce the symptoms of presbyopia in presbyopic hyperopes (+1.00 to +2.25 D) or emmetropes through induction of a mild myopia in the nondominant eye. Other potential uses of the CK technique under investigation include treatment of over- or undercorrections following LASIK or other excimer laser procedures, enhancing outcomes of cataract surgery and treating astigmatism.

THE PRESBYOPIC CONDITION AND TREATMENT OPTIONS

PRESBYOPIA PREVALENCE

Although CK was shown to be an excellent treatment for hyperopia, its most popular use is in the treatment of presbyopia. This is due to the large and growing number of presbyopes worldwide and their desire for improved functional near vision without spectacles. Eighty-six million Americans (baby-boomer generation) and 73 million Eastern and Western Europeans are currently 41–59 years old and are or will soon become presbyopic. Although the myope may have delayed onset of presbyopia, the condition spares no one as it is universal and correlated with aging. Beginning with the age of 40 years, the nearest point that can be focused recedes gradually, leading eventually to the need for spectacles for near tasks, such as reading, and perhaps even for focus at an intermediate distance.

Studies indicate that many presbyopes, especially emmetropic presbyopes who did not need an optical correction in their younger years, dislike wearing spectacles to perform common, everyday tasks and are interested in a treatment that can extend the period of spectacle-free near vision. However, unlike young myopes seeking refractive correction, patients seeking surgical correction for presbyopia are greatly concerned about procedure safety and are decidedly more averse to risk. Many presbyopes would rather stay with their spectacles than undergo a procedure they perceive as risky. In addition, many older patients have subclinical dry eye that can become problematic following LASIK. Thus, the CK procedure, which does not require the creation of a flap or ablation with a laser can be especially appealing to the older presbyopic patient. Furthermore, the safety of CK has been demonstrated in clinical trials and in the vast majority of patients treated by numerous surgeons after the trials. Other available procedures for improving near vision in presbyopes, on the other hand, such as monovision LASIK or PRK, are associated with compromised stereopsis for central vision, small reductions in binocular acuity, and reduced contrast sensitivity.[25]

TREATMENT OPTIONS FOR PRESBYOPIA

Treatments for presbyopia can be grouped into those for phakic eyes and those for aphakic eyes. Dan Durrie, MD, has developed a model grouping presbyopic patients into stages and his recommended treatment is that those who are risk averse, have good distance vision, less than 1+ to 2+ nuclear sclerosis, and need only spectacles for near are treated with NearVision CK, while those with 1+ to 2+ lens changes or a family history of lens changes are treated with cataract surgery and intraocular lens (IOL) implantation (D. Durrie, personal communication). In this way, the aging patients receive a continuum of care from their ophthalmologists.

For phakic presbyopes, excimer laser procedures, including monovision PRK and monovision LASIK, have been successfully applied, with patients showing a fairly high degree of satisfaction regarding visual outcome and postoperative function.[26–32] However, compromises in binocular vision; reduced contrast sensitivity, especially at higher spatial frequencies; and reduced stereoacuity are sequelae of these procedures, and careful patient education and selection are essential for postoperative patient satisfaction. In addition, LASIK surgery itself is associated with certain safety issues, such as the risks of flap creation and management, severing of corneal nerves that causes dry eye, healing problems, and possibility of diffuse lamellar keratitis.[33–36] As mentioned above, safety issues are a major concern with older patients and can be the deciding factor in a patient's decision to undergo a procedure.

THE CK SYSTEM

The CK procedure is performed with the ViewPoint® CK System (Fig. 86.1, *A* and *B*) and is based on the delivery of radiofrequency energy through a fine tip (Keratoplast® tip) inserted into the peripheral corneal stroma. Energy delivery at the treatment spots causes collagen in the area surrounding the tip to shrink and form a uniformly cylindrical thermal lesion in the stroma. A full circle of CK spots, applied to the peripheral cornea, produces a 'cinching' effect that increases the curvature of the central cornea. The peripheral cornea flattens and the central cornea steepens. This produces a myopic shift (Figs. 86.2 and 86.3). Figure 86.4 shows a Pentacam image of the optical changes in the cornea and in the entire optical system of the eye following NearVision CK. This analysis may explain why CK improves patients' near vision without the patients losing functional distance vision.

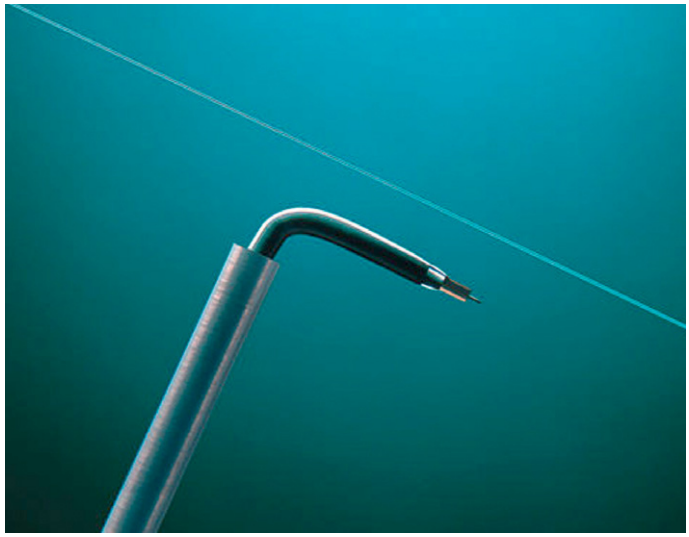
The Keratoplast tip only delivers radiofrequency energy and acts as a heat sink, rather than as a heat source. The increase in tissue temperature progresses from bottom (deep in the stroma) to top (corneal surface), and corneal tissue is exposed to the same temperature at the bottom of the probe as at the top of the probe. This is in contrast to treatment with the Sunrise LTK system, which had a significant axial gradient and produced the highest temperatures at the corneal surface because of the high absorption of light energy in water. The Ho:YAG beam is attenuated as it passes through the cornea so that the heat energy diffuses radially and axially into the tissue. The result is a cone-shaped collagen shrinkage zone,[37] with corneal denaturation decreasing from top to bottom. The footprint after CK treatment is cylindrical and extends deep into the stroma to approximately 80% depth (Fig. 86.5). This is in contrast to the conical stromal footprint that was reported with the LTK technique.[18]

PERFORMING THE CK PROCEDURE FOR THE TREATMENT OF PRESBYOPIA

PATIENT SELECTION

For the improvement of near vision in presbyopic emmetropes and hyperopes with the CK procedure, the goal is to overcorrect the

A



B

Figure 86.1. *A*, ViewPoint® CK system. The ViewPoint CK system from Refractec, Inc. consists of a portable console, a corneal marker, choice of lid specula, a handpiece that holds the Keratoplast® tip, and a foot pedal. An insulated stop at the base of the probe controls the depth of penetration of the Keratoplast tip. Energy is delivered into the cornea by activation of the foot pedal, *B,* The Keratoplast tip (shown next to a 7–0 suture). The tip is 450 μm long and 90 μm wide and is used to deliver radiofrequency energy into the corneal stroma at selected treatment points. A cuff on the probe assures correct depth of penetration.

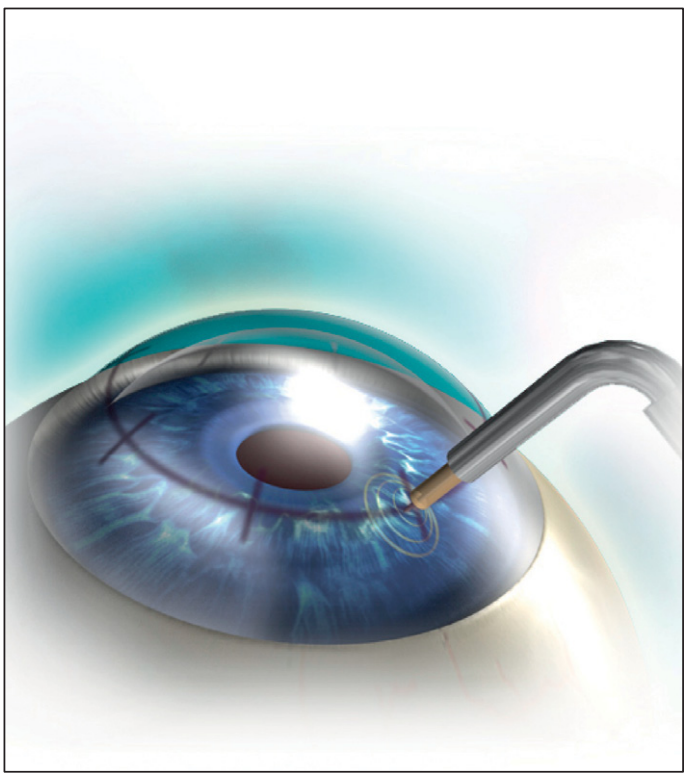


Figure 86.2. Application of treatment spot in the peripheral cornea.

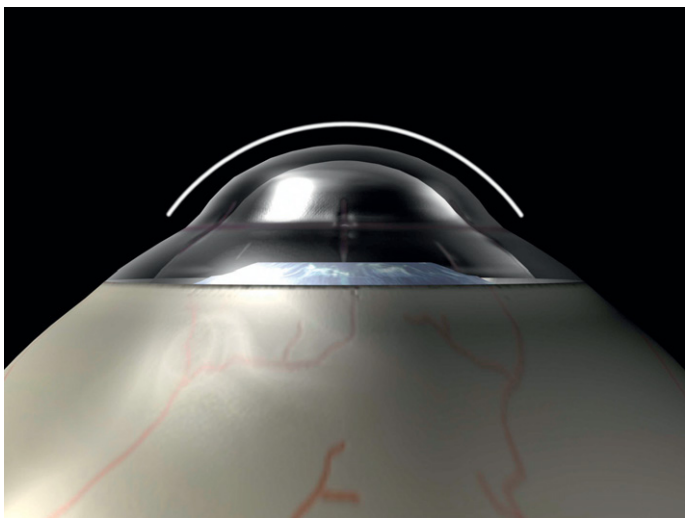


Figure 86.3. After a full circle of treatment, the peripheral cornea flattens and the central cornea steepens.

nondominant eye by inducing slight to moderate myopia, −1.0 to −2.0 D, for near vision tasks. Patients should be carefully selected for the CK treatment for presbyopia. Emmetropic and low hyperopic (+1.00 to +2.25 D) patients are the best candidates. Suitable patients should be 40 years of age or older, should have visual acuity correctable to at least 20/40 in both eyes, and should have corneal pachymetry readings of 560 μm or more at the 6-mm optical zone. Contact lens wearers should have a stable refraction. Hard lens wearers should discontinue lens use 3 weeks and soft contact lens wearers 2 weeks before the procedure. Preoperative testing includes slit-lamp examination, keratometry, pachymetry, corneal topography, eye dominance determination, near and distance vision assessment, and monovision tolerance assessment. Performing topographic corneal analysis and Orbscan anterior and posterior elevation determination will reveal eyes that should not undergo CK treatment. These include corneas with keratoconus, pellucid marginal degeneration, and those with a decentered apex or peripheral, asymmetric, or nonorthogonal astigmatism that are potential sources of induced cylinder. Eyes with significant dryness, tear-function compromise, high target anisometropia, or strong ocular dominance should also be avoided.

Setting realistic patient expectations is highly important as part of the patient selection process. Patients must understand that vision for 'daily life' is the goal of the NearVision CK procedure

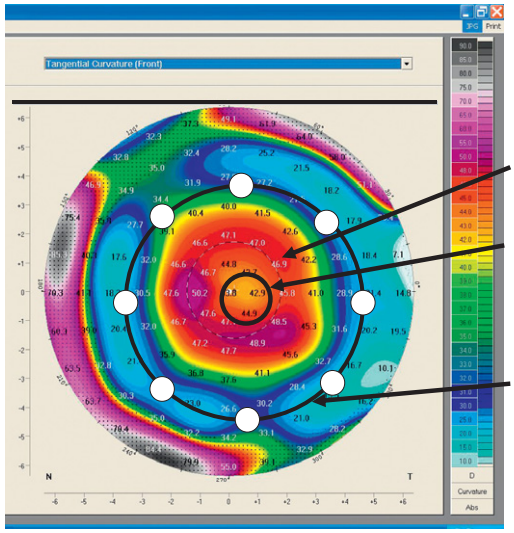


Figure 86.4. The anterior topographic surface map of a cornea treated with one ring of eight CK treatment spots applied at the 7-mm optical zone. The map shows a change to a more prolate shape, an increase of central corneal power, and slightly less increase in power in the exact central 1 mm. A modified multifocal prolate surface is created. A flattened area can be seen at the application spots (in white). The flattening increases and extends farther peripherally than it does centrally. Closer to the center of the cornea, the paracentral zone steepens, exaggerating the prolate shape of the cornea in the 3.0–4.5-mm optical zone. However, the flatter area in the central cornea is preserved. (Courtesy of Jack Holladay, MD, MSEE.)

and that, after the procedure, they will most likely need reading glasses for prolonged detailed work. The surgeon must inquire about the patient's occupation and hobbies and the possible need for the patient to wear spectacles for these activities after the surgery. If the patient finds any spectacle use unacceptable, it is best not to proceed with the surgery, for an unhappy patient will be the likely result. Because the CK procedure targets only one eye for near vision, it may not be suitable for patients who operate potentially dangerous machinery, drive frequently at night (may require a spectacle overcorrection), or engage in visually demanding work at close distances. Patients must also be aware of the naturally progressive nature of hyperopia and presbyopia and that this progression may diminish the surgical effect with time and increase their need for reading glasses. In most cases, they will retain some of the visual benefit they gained from the NearVision CK procedure even as their presbyopia advances.

PERFORMING THE CK PROCEDURE

Following screening and a discussion of expectations, the surgeon can develop a treatment plan for each patient that considers patient age, accommodative amplitude, occupation, and hobbies. For the improvement of near vision in presbyopic emmetropes and low hyperopes, the goal is to overcorrect the nondominant eye by inducing slight to moderate myopia, −1.0 to −2.0 D (myopic endpoint) through the application of 8–24 CK treatment spots. Most well-selected patients treated for presbyopia will initially need only 8–16 spots in one eye.

The CK procedure is performed with topical anesthesia. The patient lies under a 6.5× magnification microscope with his or her head aligned so that the cornea is centered in the field. The iris is parallel to floor, and the fixation light is equally spaced between

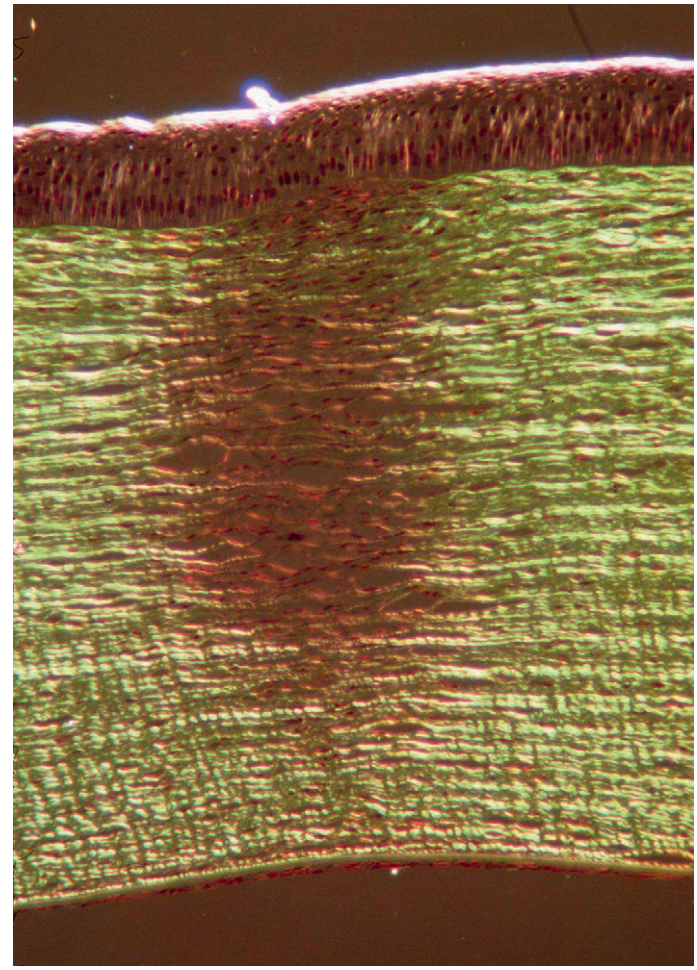


Figure 86.5. CK footprint. A polarized light micrograph of a histological section from a pig cornea, 7 days after CK treatment. The footprint (dark region) is cylindrical and approximately 80% of corneal depth. Deep treatment penetration contributes to permanence of effect.

oculars in the patient's view. A lid speculum is placed in the eye to obtain maximal exposure and provide the electrical return path. While the patient fixates on the microscope's light, the surgeon gently makes an indentation mark in the center with a Sinskey hook over the center of the entrance pupil. Precise centration, using the pupillary center, and not the corneal light reflex or the line of sight, as the centration reference is highly important in avoiding surgically induced astigmatism. After drying the cul-de-sac, the cornea is then marked with a gentian-violet-dampened CK marker, aligning the marker cross-hairs with the Sinskey mark and the 6- and 12-o'clock points on the cornea (Fig. 86.6). The motion for marking is straight down with the marker onto the corneal surface; hold and then straight up.

After proper marking, the Keratoplast tip is inserted into the stroma at the marked spots in a ring pattern around the peripheral cornea according to the supplied nomogram. Figure 86.7 shows the conventional CK nomogram for the treatment of presbyopia and the sequence of spot application. The number (8–24) and location (6-, 7-, or 8-mm optical zone or a combination) of spots determines the amount of refractive change, with an increasing number of spots and rings used for higher amounts of correction. Each radiofrequency treatment spot should be symmetrically placed to avoid surgically induced astigmatism. Tip alignment should follow three-

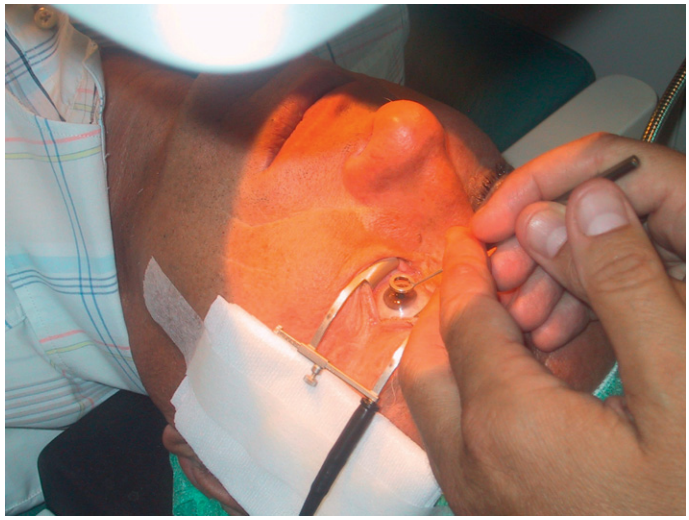


Figure 86.6. Marking a patient's eye with a corneal marker before CK.

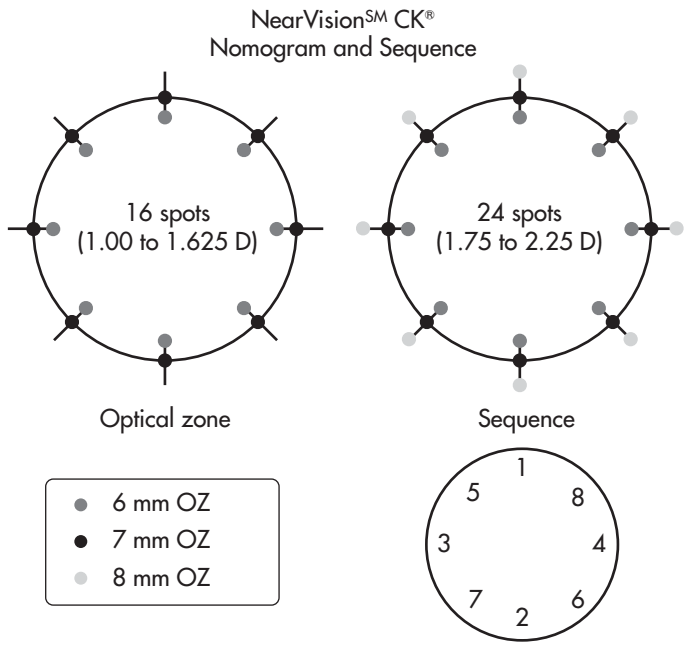


Figure 86.7. Conventional CK nomogram for the treatment of presbyopia. Sixteen spots are applied at the 6 and 7-mm optical zones (OZ) for correction of 1.00–1.625 D of correction and 24 spots are applied at the 6-, 7-, and 8-mm optical zones for 1.75–2.25 D.

dimensional principles (alignment of *x*-, *y*-, and *z*-axis). Alignment in the *x*- and *y*-axis is controlled by hitting the target mark, while alignment of the *z*-axis is controlled by the angle of approach. If the treatment takes place with an incorrectly aligned tip, the treatment effect will be less predictable. In a primary CK treatment, any induced astigmatism can be observed intraoperatively through an operating microscope that incorporates a ring light attachment.

Radiofrequency energy is applied to each treatment spot by depressing the foot pedal. A tone sounds as the energy is applied. The default setting for treatment is 350 kHz, 60% power (0.6 W) for 0.6 s. At each treatment spot, the tip is kept in place until the preprogrammed treatment time has been completed (the tone stops). The procedure is repeated until the full series of spots has been made, according to the treatment plan. After each treatment spot, the tip is cleaned with a fiber-free sponge to remove any tissue debris. Following a full circle of treatment spots, the peripheral cornea flattens and the central cornea steepens. Postoperative care includes instillation of a topical antibiotic solution, a topical nonsteroidal anti-inflammatory agent, and artificial tears, as needed.

The conventional CK nomogram was used in the trial for FDA approval of CK for the treatment of presbyopia. Following approval and wider use of the conventional CK technique and nomogram, it became apparent that refractive results varied among surgeons; some surgeons had on-target results while others had undercorrections at a greater than desired frequency. Rick Milne, MD, was the first to observe that a varied degree of corneal compression during treatment spot application accounted for the variability of surgeons' results, while poor alignment of the Keratoplast tip in the placement of an individual treatment spot and the asymmetrical placement of spots in the ring were responsible for any induced astigmatism (Milne HL, LightTouch technique for CK. Presented at ASCRS, Washington, DC, April 2005). In the conventional CK treatment, the cornea is compressed (creating a 5–7-mm dimple on the cornea) with the Keratoplast tip from the time the tip is inserted into the cornea to the time of radiofrequency energy is delivered. However, it appears that greater pressure or compression of the cornea decreases the amount of refractive change obtained with CK treatment.

In contrast to the 5–7-mm dimple created on the corneal epithelium by compressing the cornea with the Keratoplast tip in the conventional NearVision CK technique, the cornea is only minimally depressed with the tip to create a 2-mm dimple in the NearVision CK with LightTouch technique (Fig. 86.8). The desired pattern is to penetrate the cornea with the tip, hesitate about 2 s, apply energy by depressing the foot pedal, hesitate, and remove the tip. Compared with the conventional CK technique, the LightTouch technique has produced a more robust effect, more predictable results, and less or no induction of cylinder. Because of the more robust effect, fewer spots can be applied for a given refractive change, and treatment is applied to fewer optical zones.

The LightTouch nomogram shown in Figure 86.9 and Table 86.1 was developed by Rick Milne, MD, using his own technique. As seen in the table, the myopic shift is greater with LightTouch. Individual surgeon's results may vary, and it is strongly recommended that the physicians develop their own CK nomogram based on personal practice results. At this time, results after NearVision CK with LightTouch appear to be stable at 6 months, but stability in a large population of patients is yet to be determined.

PRESBYOPIA CLINICAL RESULTS WITH CONVENTIONAL NOMOGRAM

A multicenter, FDA-approval study was conducted to determine the safety and efficacy of CK for the treatment of presbyopic symptoms in emmetropic and mildly hyperopic eyes. Eligible patients were treated to correct up to 2.0 D of presbyopia. To be eligible for the study, patients had to have a preoperative spherical equivalent (SE) of plano (considered as +0.5 to –0.5 D) to +2.0 D and less than or equal to 0.75 D of refractive astigmatism, as determined by cycloplegic refraction. Screening for eligibility included a history of monovision contact lens wear or success with a contact lens trial of monovision, and preoperative assessment with the 'Loose Lens' test. In this test, handheld lenses of three dioptric powers were used: (1) a +0.75 D lens for one ring of CK treatment at 7 mm, (2) a +1.25 D lens for two rings of treatment, one each at 7 and 8 mm,

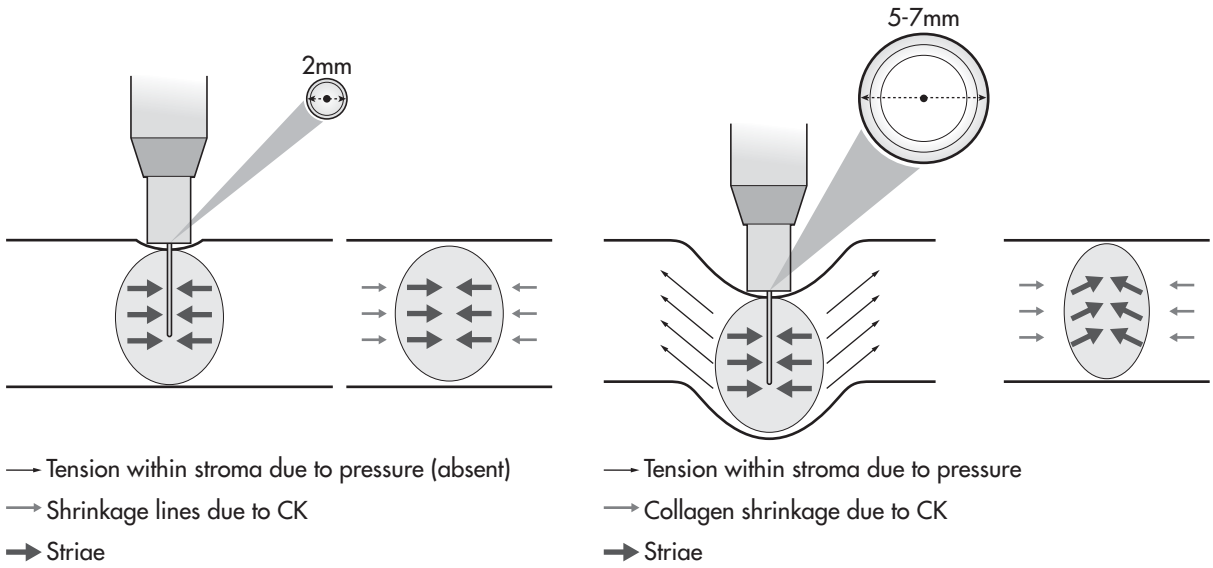


Figure 86.8. Illustration of theory behind conventional and LightTouch CK treatment. In conventional CK (left), the cornea is indented with the tip to make a 5–7-mm diameter indentation on the corneal surface. With the LightTouch technique (right), a dimple of only 2.0 mm is created. This does not create tension within the stroma and consequently the effect is greater.

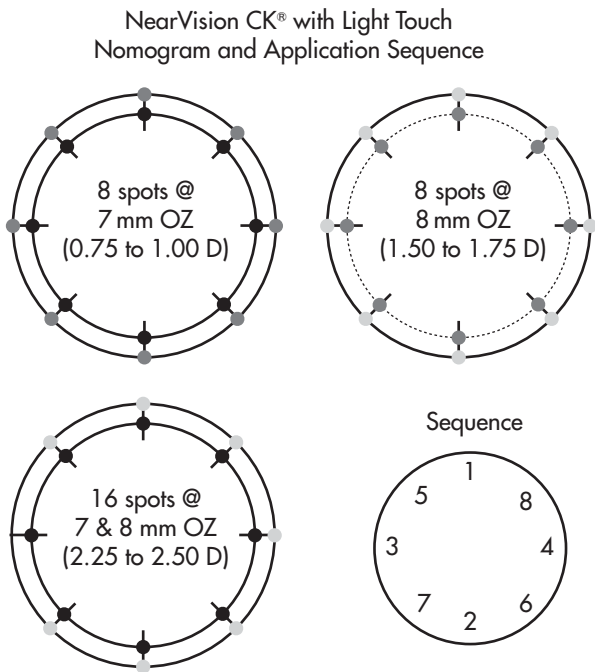


Figure 86.9. NearVision CK with LightTouch: nomogram and application sequence.

Table 86.1 NearVision CK with LightTouch: Milne Nomogram

Spot Pattern (Number of Spots and Optical Zone)	Effect with Conventional CK Nomogram	Effect with Milne's CK with LightTouch Nomogram (D)[a]
8 spots @ 8 mm	—	1.50–1.75
8 spots @ 7 mm	0.75 D	0.75–1.00
16 spots @ 7 and 8 mm	—	2.25–2.50

[a] Individual surgeons' results may differ; personal nomograms must be developed.

and (3) a +1.75 D lens for three rings of CK treatment, one each at 6, 7, and 8 mm. The 'Loose Lens' test can assess near and distance visual acuity, monovision tolerance, clarify patients' expectations, and help to determine the final surgical plan.

The target refraction was up to −2.0 D (myopic endpoint) in the nondominant eye. Emmetropic patients were treated unilaterally in the nondominant eye with an intended correction of up to 2.0 D (target of −1.0 to −2.25 D) to attain near vision in that eye. Hyperopic patients were treated bilaterally: the nondominant eye was treated up to 3.0 D (target of −1.0 to −2.0 D) to provide near vision, and the dominant eye was treated with a correction of up to 2.0 D (target of plano) to improve distance vision.

A total of 188 eyes (150 patients) at five centers in the USA who met eligibility requirements were enrolled consecutively into the study and signed informed consent forms. Of these, 150 eyes were emmetropic or hyperopic presbyopes and were treated to improve near vision. The patients' mean age was 53 ± 4.7 years, and the intended refraction was 2.03 ± 0.625. None of the eyes was retreated.

At 12 months postop, 89% of the eyes treated for near with the full correction (1.00–2.25 D) had binocular uncorrected near visual acuity (UCVA-Near) of J3 or better (newspaper-size print) (Fig. 86.10). This was a marked improvement from preoperative vision. A total of 97% had UCVA-Distance of 20/20 or better and 100% had 20/40 or better. For binocular combined UCVA-Distance and -Near, only 15% of eyes had 20/32 or better distance together with J3 or better near preoperatively. At 12 months, however, 77% had 20/25 or better distance together with J2 or better near, 89% had 20/32 or better distance together with J3 or better near, and 89% had 20/40 or better distance together with J3 or better near (Fig. 86.11). Figure 86.12 shows the percentages with the combination of 20/20 UCVA-Distance and J1, J2, and J3 UCVA-Near at 1 year. According to the patient questionnaire, 86% of eyes treated for near could read newspaper print and also had good distance

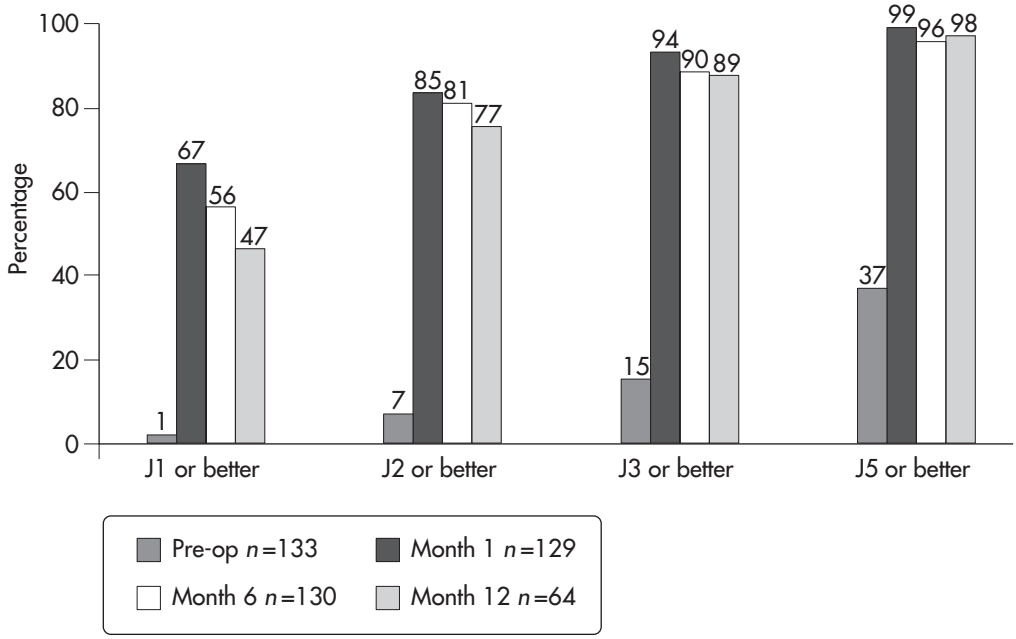


Figure 86.10. Binocular UCVA-Near 1 year after CK presbyopia treatment. Marked improvement from preoperative vision is apparent.

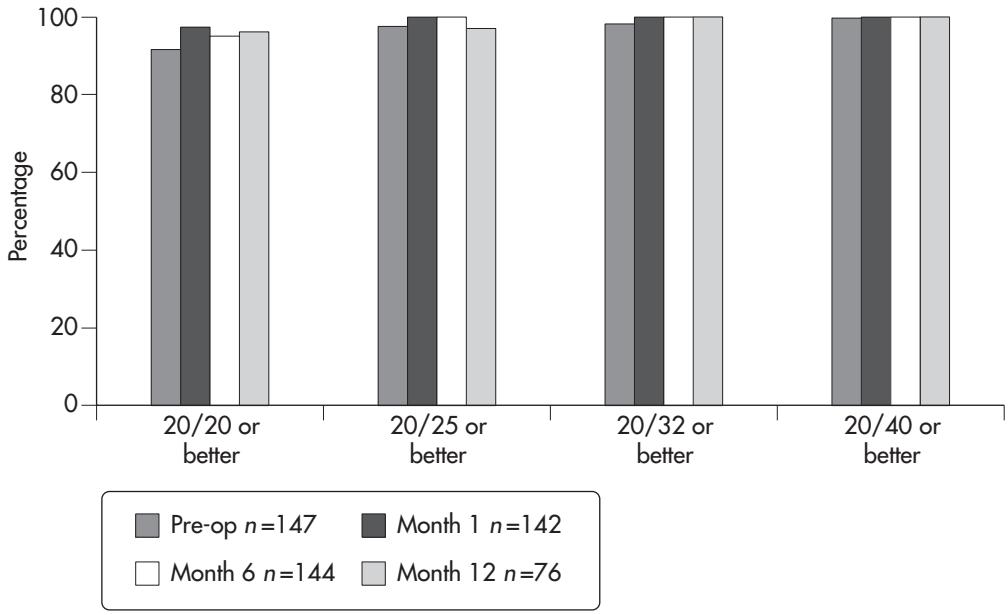


Figure 86.11. Binocular combined UCVA-Distance and Near 1 year after CK presbyopia treatment maintenance of binocular vision can be seen.

vision, as indicated by the 100% who could see a street sign (Fig. 86.13).

Safety at 12 months was exceptional. A transient loss of more than two lines of BCVA-Distance was seen in two eyes at 1 month, but this resolved in both eyes by 3 months. No eye had BCVA-Distance worse than 20/40, had an increase of >2.00 D cylinder, or had BCVA-Distance of 20/20 or better preop that became 20/25 or worse postop (Table 86.2). Mesopic contrast sensitivity with and without glare was unchanged from preop through month 12. No device-related serious adverse events occurred. Extreme/marked/moderate improvement in quality of vision was noted by 89–95% of the patients over the course of the study. A range of 79–86% reported being satisfied or very satisfied with the results. Patient satisfaction with the procedure is similar to that with monovision LASIK. Quality of depth perception was rated excellent, very good, or good in 91–93% over the study course.

CONDUCTIVE KERATOPLASTY FOLLOWING LASIK AND OTHER EXCIMER LASER PROCEDURES

Patients previously treated with LASIK who are now presbyopic can be treated safely with CK to achieve functional near vision. With CK there is no need to lift or recut the flap. Treatment involves inducing a mild myopia (refraction of −1.0 to −2.0 D) in the non-dominant eye, as described above for eyes without previous refractive surgery.

A prospective, multicenter clinical trial of CK is being conducted to evaluate the ViewPoint CK system for performing CK in emmetropic presbyopes who have previously had LASIK or PRK (Data on file, Refractec Inc.). A total of 55 patients (55 eyes) with a mean pre-LASIK MRSE of −3.33 D, a mean age of 53 years, mean pre-CK MRSE of +0.50 D, and less than 0.75 D of cylinder have undergone

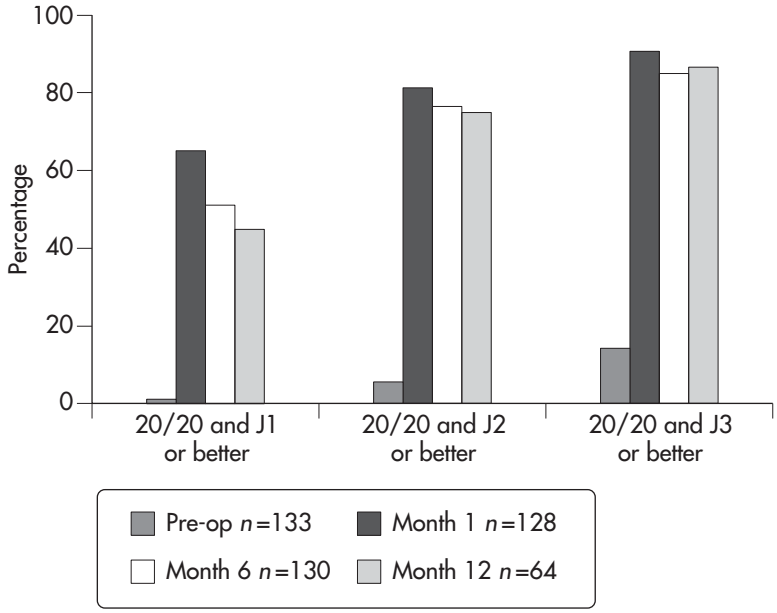


Figure 86.12. Binocular combined UCVA 20/20 Distance and J1, J2, or J3 UCVA-Near 1 year after CK.

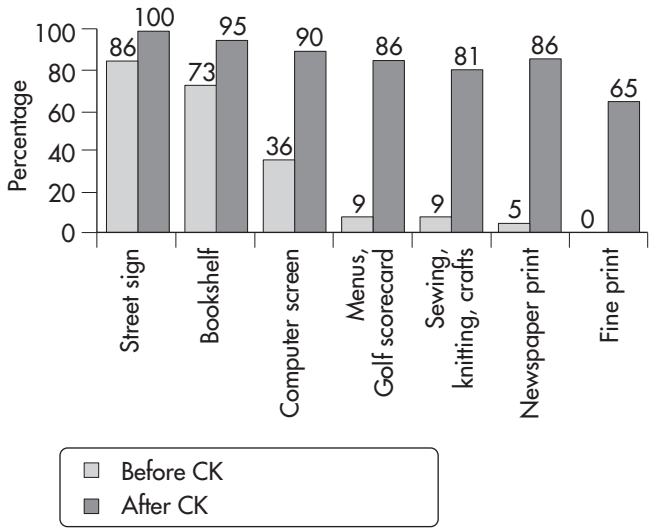


Figure 86.13. Patient subjective responses to the question: What can you see without glasses?

the procedure. All patients had residual central pachymetry greater than 400 μm and peripheral pachymetry greater than 560 μm before undergoing CK. All patients received a very conservative CK treatment in their nondominant eyes: eight CK spots at the 8.0 mm optical zone for a 1.25 D addition.

At 1 month postoperatively, the mean postoperative effect was 1.39 ± 0.394 D. Near UCVA and refractive accuracy results at 1 month are shown in Table 86.3. All results surpassed the FDA-desired target values. At 1 month, 94% of patients had J2 or better binocular near UCVA, and 98% had J3 or better. Furthermore, patients' subjective responses demonstrated very little loss of distance vision: pre-CK 98% were able to see a street sign without spectacles, while after CK the percentage was 94%. Near vision without spectacles improved markedly: 24% could see newspaper pre-CK, while after CK the percentage increased to 88%. Fine print could be read by 8% pre-CK and 76% after CK.

Safety results were similarly excellent. No eyes lost more than two lines of BCVA-Distance, and 88% showed no change from preop in induced cylinder. Of the 12% (six eyes) with induced cylinder, all had J1 or J1+ near acuity. There were no adverse events or complication with the corneal flap that had been created during the previous LASIK procedure. At 1 month, 43/50 (86%) of patients were satisfied or very satisfied with their CK procedure.

While the number of patients who have reached a 1-month postoperative follow-up in this study is small, outcomes have been very good. However, evaluation of the safety and effectiveness of treating post-excimer laser patients with CK is still ongoing in the above-described FDA-approval study. It is important to note that a greater refractive effect from CK treatment has been observed in post-excimer laser eyes compared with eyes that have not undergone excimer laser surgery, and the nomogram must be adjusted in view of this. All use of CK following previous excimer laser treatment is empirical and off-label at this time. It is best to treat these patients very conservatively, informing them that they may need additional treatments later if they are over- or undercorrected.

CONCLUSION

The large number of persons born in the USA during the 'baby-boom' following World War II are now at least 42 years of age and have undergone or will soon undergo the decrease in accommodative ability characteristic of older individuals. Many who were effectively emmetropic in their youth are now distressed by the need for near-vision spectacles, but they would not consider a surgical procedure that would free them from spectacles if they perceive the procedure as risky. CK appears to have the ideal characteristics for these presbyopic persons.

Conductive keratoplasty has a remarkable record of safety. Studies have shown a low rate of postoperative loss of best-corrected distance vision, no loss of high-frequency contrast sensitivity, and the maintenance of stereopsis. In fact, CK treatment has improved near visual acuity without an accompanying loss of binocular intermediate or binocular distance vision. Safety findings with CK stand in contrast to findings seen after monovision LASIK procedures. Furthermore, the CK procedure is not susceptible to surgical flap complications or postoperative dry eye seen after excimer laser procedures.

Table 86.2 Incidence of safety variables following CK presbyopia treatment (FDA study)

	Month 1 ($n = 90$) (%)	Month 6 ($n = 93$) (%)	Month 12 ($n = 63$) (%)
Loss of >2 lines BCVA-Distance	2	0	0
BCVA-Distance worse than 20/40	0	0	0
Increase >2.00 D cylinder	0	0	0
Patients preop ≤20/20 who had ≥20/25 postop	0	0	0
BCVA-Near worse than J3	0	0	0

Table 86.3 One-month results of CK used to treat presbyopic patients who have had previous excimer laser surgery for myopia ($n = 50$)

	% of Patients	FDA Target (%)
UCVA < J1	90	—
UCVA < J2	94	—
UCVA < J3	98	75
+0.50 D within target	74	50
+1.00 D within target	96	75

UCVA, uncorrected visual acuity.

The LightTouch technique proved effective in addressing some of the concerns associated with the conventional CK treatment of presbyopia, namely the variability of results among different surgeons and the occurrence of undercorrections. This modification of the conventional CK nomogram is pending FDA approval, but off-label use by a number of surgeons has demonstrated the same efficacy with even greater safety. Compared with conventional CK, LightTouch appears to produce a greater clinical effect with fewer treatment spots applied at a larger optical zone. Fewer treatment spots make the CK treatment more comfortable for the patient and allow a faster visual recovery. The refractive effect is more predictable, and less cylinder is induced, possibly because treatment spots are applied more uniformly and at a larger optical zone. Long-term stability is to be determined. Results differ slightly for different surgeons, and surgeons need to develop a personal nomogram.

Treatment of over- or undercorrections following LASIK or other excimer laser procedures, treatment of presbyopes who previously had LASIK, and enhancing outcomes of cataract surgery are other potential off-label applications for CK. Procedures that can correct or refine such conditions appeal to surgeons and patients alike, as they can improve vision without involving a laser procedure. The number of patients who had LASIK in their youth and are now presbyopic is large and growing. These patients, accustomed to good spectacle-free vision, are now dissatisfied with reading spectacles and are seeking other solutions. Also growing in numbers are the pseudophakes who are increasingly well read and informed about vision-enhancing procedures and also desire improved functional near vision without spectacles.

Because of its unique safety and efficacy, the CK procedure is likely to grow in popularity among surgeons and patients who do not yet have a cataract. The downsides of monovision LASIK are not likely to change, and presbyopic LASIK will not be a viable option for at least 5 years. If the CK correction regresses, an enhancement can be performed. When the patient develops a cataract, the surgeon can perform cataract extraction with implantation of one of the new-technology IOLs. If the IOL does not provide the required near vision, the surgeon can then perform CK to increase near vision. Thus CK can be a patient's entry point for a lifetime of functional near vision without spectacles.

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87 The intrastromal corneal ring

Steven M. Verity, David J. Schanzlin

The alteration of the corneal stroma as a means of producing a change in the refractive status of the eye has been studied for more than half of a century. These techniques were characterized by stromal inclusions of plastic lenses and alloplastic lenticules.[1–6] A greater understanding of refractive change associated with corneal stromal addition and subtraction can be directly attributed to the work of Barraquer[7] and his law of thicknesses as applied to the cryolathe techniques. The problems of lack of tissue biocompatibility, extrusion of implants, poor predictability, and other wound healing-related issues prevented the advancement of these keratorefractive techniques. In April 1999, the USA Food and Drug Administration (FDA) granted approval of Intacs intrastromal corneal ring segments (Addition Technology, Des Plaines, IL) for the correction of low spherical myopia.

BACKGROUND

The idea of a ring-shaped device placed within the corneal stroma was initially conceived by Reynolds.[8] The device was initially developed as a 360° open-ended plastic ring manufactured from optically transparent polymethylmethacrylate. In the original conception of the device, the plastic ring had an adjustable diameter so that expansion or constriction of the ring could be titrated to correct myopic or hyperopic refractive errors, respectively.[9] The problems with this model included poor predictability and difficulty in adjustability of the keratorefractive effect. Further studies with fixed-diameter intrastromal rings placed within cadaver eyes demonstrated that a significant flattening of the corneal curvature could be achieved with the degree of flattening directly related to ring thickness. Further studies and refinement of the device allowed further characterization of the means by which the desired keratorefractive effect is achieved.[10] A nearly linear relationship between corneal flattening and ring thickness has been predicted by finite element modeling and confirmed by cadaver eye testing.[11]

Initial feasibility studies were performed in 1991 with a 0.30 mm-thick intracorneal ring in a series of patients with one nonfunctional eye. These studies, performed both in Brazil and in the USA, demonstrated that the intracorneal ring was safely tolerated within the corneal stroma, with no evidence of migration or extrusion of the device.[12,13] The study further demonstrated that elective removal of the device, after successfully tolerating its presence for over 1 year, could be safely performed with a return to baseline corneal curvatures.[14] The first sighted eye trials were initiated in Brazil in 1991 and in the USA in 1993 with five ring thicknesses, ranging from 0.25 to 0.45 mm in 0.05 mm increments. Results from these trials further demonstrated biocompatibility of the device within the corneal stroma and demonstrated that a stable myopic correction could be achieved.

Concerns regarding wound healing at the incision site prompted alterations in the design of the device. A segment design (intrastromal corneal ring segments [ICRS]) minimized the incision healing problems and greatly simplified the surgical technique because a continuous stromal channel was no longer required (Fig. 87.1).

There are several aspects of the ICRS procedure that make it unique compared to other keratorefractive techniques. Reduction of myopia occurs with the placement of the device within the midperipheral cornea. The attendant corneal flattening occurs without the removal of any tissue. The degree of myopic correction is titrated by the thickness of the implanted segments.

An additional benefit of this approach is the potential for exchange of the device, allowing adjustability of the achieved correction depending on the visual needs of the patient. This feature also allows potential reversibility of the refractive effect, as has been shown in the early clinical trials. Patients who have had the rings removed have returned to their baseline status, as determined by both refractive and topographic criteria, within 3 months after segment removal.[14]

The Intacs procedure does not involve any surgical incursion of the central cornea. Another unique feature of this procedure is the maintenance of a normal physiologic prolate corneal profile with concomitant reduction of the central corneal curvature. It is believed that maintenance of the physiologic corneal asphericity may reduce the incidence of postoperative contrast sensitivity reduction or spherical aberration errors and may be associated with better optical performance of the treated cornea.[15,16]

The surgical procedure is typically performed using topical anesthesia and is performed with the aid of a set of proprietary instruments (Addition Technology, Des Plaines, IL) designed to accomplish

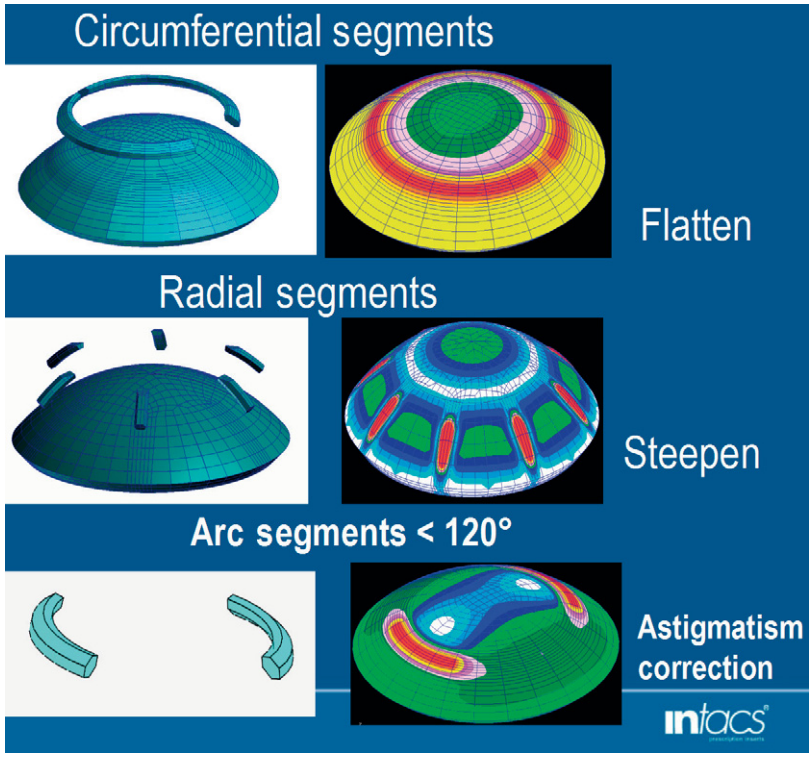

Figure 87.1. Intrastromal ring designs developed to produce various desired corneal-shape changes and refractive effects. The segment design is composed of two 150° arcuate elements. (Courtesy of Addition Technology, Inc.)

placement of the device at a stromal depth of two-thirds of the peripheral corneal thickness. The corneal center is identified and marked. An incision and placement marker is applanated on the corneal surface using the geometric center of the cornea as a landmark. A 1.2-mm radial incision is then made at the 12-o'clock position to a depth of 68% of the measured peripheral corneal thickness. A vacuum centering guide is then applied to the ocular surface and suction fixation is initiated. Blunt stromal dissection of a lamellar tunnel is performed in a clockwise and counterclockwise fashion in the paracentral cornea using stromal dissectors. The Intacs segments are then carefully threaded into the intrastromal channel and positioned so that no part of the device is situated directly beneath the incision site (Fig. 87.2). The incision is typically closed with one to two interrupted sutures to approximate the corneal wound edges. Topical antibiotics and steroids are applied for approximately 1 week.

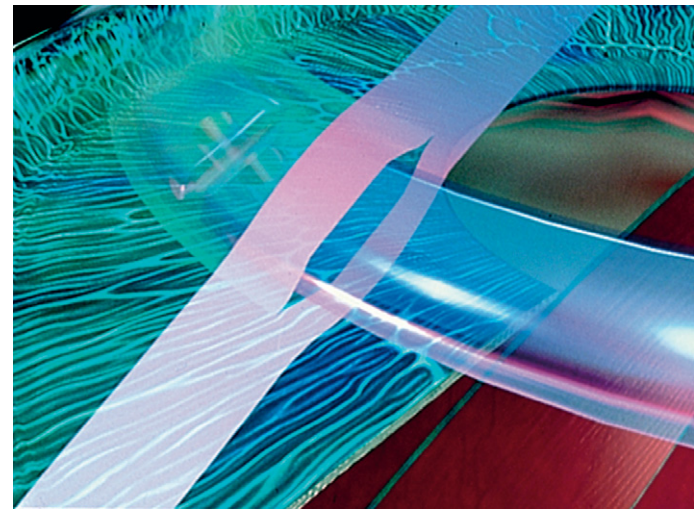

Figure 87.2. Diagrammatic representation of the Intacs device insertion within the lamellae of the corneal stroma. (Courtesy of Addition Technology, Inc.)

CLINICAL TRIALS WITH INTACS

On May 3 1995, the USA phase II clinical trial of the Intacs product was initiated. A total of six investigational sites were scheduled to implant a total of 150 sighted eye patients requiring myopic correction between −1.00 and −6.00 D. Segment thicknesses to be implanted ranged from 0.25 to 0.45 mm in 0.05 mm increments for a total of five patients per thickness per site. All patients had a preoperative best spectacle-corrected visual acuity of 20/20 or better. To evaluate the safety and efficacy of the procedure, follow-up data collection included uncorrected and best spectacle-corrected visual acuity (BSCVA), cycloplegic and manifest refraction, corneal topography, keratometry, and slit-lamp biomicroscopy. A preliminary analysis was performed on available data for patients who completed 3 months of postoperative follow-up.[17] Of 99 patients, 95 (96%) had an uncorrected visual acuity of 20/40 or better. More than half of the study patients (53 of 99, 54%) saw 20/20 or better without correction. The predictability of correction appeared good, with 77% of patients within 1 D of their intended correction. At the 3-month time gate, 99% of patients were within two lines of their preoperative best spectacle-corrected visual acuity.[17] These data also revealed a slightly higher standard deviation of refractive outcomes with thicker devices, as observed in higher myopic corrections attempted with other keratorefractive procedures. Accordingly, the lower ring sizes (0.25, 0.30, and 0.35 mm) were selected for further evaluation in phase III clinical trials.

The phase III trials began in December 1996 with enrollment of 361 patients at 10 investigational sites. Enrollment criteria were restricted to patients with myopic refractive errors ranging from −1.00 to −3.50 D with less than 1.00 D of refractive astigmatism.

A 2-year follow-up analysis of 449 eyes of both phase II and phase III trial cohorts evaluating only the 0.25, 0.30, and 0.35 mm segments demonstrated that 97% of eyes achieved an UCVA 20/40 or better and 76% was 20/20 or better.[18] This did not differ significantly from the 3-month postoperative data in which 97% of eyes were 20/40 or better and 71% of eyes were 20/20 or better. Fifty-five per cent of eyes saw 20/15 or better uncorrected acuity at 2 years. Predictability of correction appeared good as 93% of eyes were within ±1.00 D of predicted correction and 73% were within ±0.50 D of attempted correction. Two eyes (1%) experienced greater than two line reduction of BSCVA; however, both eyes maintained a BSCVA of 20/20 or better. Intraoperative complications included posterior corneal perforation (one eye) and anterior corneal perforation (three eyes). Segments were not placed in five eyes due to intraoperative adverse events. All patients maintained their preoperative levels of BSCVA. Postoperative adverse events included one case of infectious keratitis and one case of shallow segment placement. These eyes were treated appropriately and a BSCVA of 20/20 was maintained. Intacs segments were removed in 37 (8%) eyes due to dissatisfaction with visual outcome, bothersome visual symptoms, or healing-related issues. Among patients who underwent elective removal due to dissatisfaction, 97% returned to within ±1.0 D of their baseline refractive error within 3 months.

POSTOPERATIVE OBSERVATIONS AND SIDE EFFECTS

Essentially all patients develop a mild stromal haze in the area of the tunnel dissection as a result of separation of the stromal fibers. This haze is generally mild in degree and visually insignificant and resolves over time. Another slit-lamp finding characteristic of the Intacs procedure is the development of small deposits within the intrastromal channel and product-positioning holes. These deposits, usually noted by the third postoperative month, are noninflammatory and are clinically insignificant. They are believed to consist of collagen and wound-healing proteoglycans.[19] Similar lamellar deposits have been reported in association with other intrastromal refractive procedures.[20–23] Deposits were seen in 68% of patients at 1 year in the phase III clinical trial.

Other clinical observations associated with the intrastromal ring procedure include corneal iron lines[24] and a temporary reduction of central corneal sensation. All of the clinical trial adverse events associated with the Intacs procedures were easily managed with or without removal of the device.

Visual side effects were noted in the phase II and phase III clinical trial patients.[18] These included difficulties with night vision (5.1%), blurred vision (2.9%), glare (1.3%), and halos (1.3%). Patients with a preoperative mesopic pupil size of 7.0 mm or greater were more likely to develop postoperative visual side effects. Patients in the earlier phases of the clinical trials were more likely to request removal of the implant due to dissatisfaction. This was due to a learning curve as to refractive outcome with the initial nomogram (a large incidence of thicker devices removed because of undercorrection in the phase II studies prompted revision of the nomogram) and inclusion of patients with large mesopic pupil sizes.

A separate analysis of the refractive effect after removal of the Intacs inserts was performed.[25] A total of 46 eyes underwent removal of the Intacs inserts after being followed in the FDA clinical trials. The primary reasons for removal were visual side effect (51%) and unresolved refractive error (48%). Removal procedures were performed with topical anesthesia and were generally brief procedures. These procedures were successful in all cases, and there were no operative or postoperative complications or sequelae. At 3 months post removal, 73% of eyes returned to within ±0.50 D and 97% were within ±1.0 D of their baseline spherical equivalent manifest refraction. Additionally, all eyes were within ±1.0 D of their original manifest refractive astigmatism. All eyes achieved a BSCVA of 20/20 or better. There were no significant safety issues as a result of Intacs removal. This study demonstrated that the refractive effects of Intacs are rapidly and completely reversed upon removal.

A smaller number of patients have undergone exchange procedures for either under- or overcorrection. These procedures, performed with topical anesthesia, consisted of dissection to the previous lamellar channel, retrieval and removal of the ring by securing its positioning hole, and, finally, replacement with a thicker or thinner device.

THERAPEUTIC INDICATIONS

KERATOCONUS

Probably the most exciting development in Intacs technology is the application of the device for treatment in therapeutic indications. Shortly after FDA approval of Intacs in the USA the first reports of applying this technology for the treatment of keratoconus became available.[26,27] The ring segments were placed in a horizontal configuration through a single temporal incision. The goal of reducing irregular astigmatism was sought by placing a thicker segment inferiorly to elevate the cone along with a thinner segment superiorly to flatten the keratoconic cornea. These procedures resulted in a significant reduction in astigmatism and an improvement in topographic regularity (Fig. 87.3). In this initial series of 10 patients, uncorrected visual acuities improved from a mean of 20/200 to 20/50 at 12 months.[27] One patient underwent removal of the device due to superficial placement but returned to preimplant status by 1 month after removal.

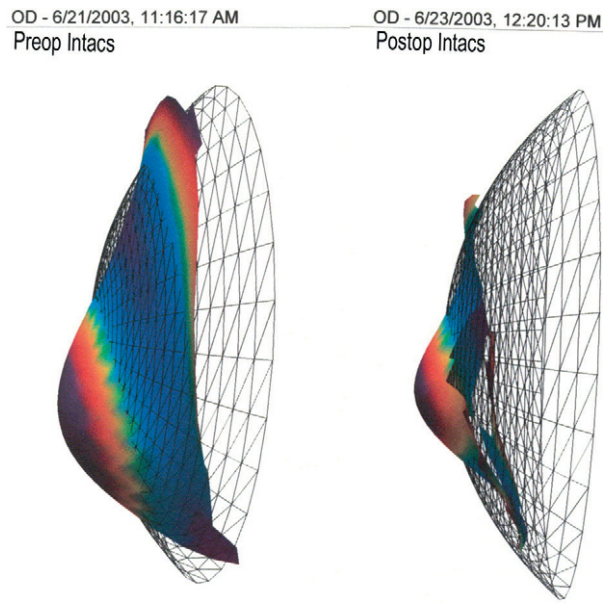

Figure 87.3. Topographic contour representation demonstrating the effects of Intacs placement in a keratoconic cornea. (Courtesy of Addition Technology, Inc.)

Siganos et al reported a prospective nonrandomized trial of 33 eyes of keratoconus patients with clear central corneas that were contact lens intolerant.[28] Segments of similar thickness (0.45 mm) were inserted based on the topographic image in an attempt to maximize corneal flattening. After an average follow-up of 11.3 months (range, 1–24 months), there was a mean improvement in UCVA of 2.5 lines (range, loss of 1 line to gain of 10 lines). Similarly, a mean improvement in BCVA of 1.7 lines (range, loss of two lines to gain of six lines) was noted. In two eyes, Intacs segments were removed due to superficial placement and patient dissatisfaction, respectively. The authors noted that the Intacs procedures had less effect in more advanced keratoconus while more encouraging results were observed in early stages of the disease. Stability of refractive effect was noted to occur after the first 9 months.

Alio et al reported reversibility data among five eyes of four patients who underwent Intacs placement in centrally clear keratoconic corneas.[29] Segments were removed between 3 and 6 months after implantation due to migration or extrusion. The authors noted that the patients' refractive and topographic statuses were returned to near baseline levels by 3 months after segment removal. Interestingly, a subset of two patients underwent reimplantation of Intacs segments at a deeper level and achieved a marked improvement in UCVA and refraction.

Colin reported the results of the first large-scale prospective clinical trial of Intacs for keratoconus among multiple sites and surgeons.[30] A total of 59 eyes were enrolled in this study. Six-month data were available for 34 eyes. Sixty-two per cent of eyes experienced a gain of two to eight lines of BCVA while 32% had no change in BCVA. Thirty-two per cent of these eyes achieved 20/50 or better UCVA, while only 4% of the patients saw this level preoperatively. While no complications were noted among eyes successfully implanted with the device, seven eyes (12%) underwent explantation of the inserts due to dissatisfaction with visual symptoms.

A number of methods to implant Intacs segments have been devised. These include inserting segments vertically through a superior incision, horizontally via a temporal incision, incision location in the steep refractive meridian, similar or dissimilar segment sizes (typically 0.25 mm ring superior and 0.45 mm ring inferior), and single or paired segment placement. Because all of these methods can result in some level of efficacy it is clear that we do not fully understand the mechanism of correction in corneal ectasia.

Alio et al reported the results of 26 eyes with keratoconus who underwent implantation of single or paired Intacs segments based on the preoperative corneal topographic appearance.[31] The devices were placed horizontally with a temporal incision. With 1 year of follow-up, both groups experienced significant improvements in both UCVA and BCVA. The mean UCVA improved from 20/100 to 20/50 in single-segment eyes and from 20/400 to 20/63 in paired-segment eyes. The level of BCVA improved in both groups from a mean of 20/50 to 20/32, postoperatively. Four eyes underwent removal of the inferior segment due to partial extrusion of the device.

Several insights as to why some keratoconus eyes respond well to Intacs while others do not were offered in a subsequent study.[32] A retrospective analysis separating good and poor responders was reported in this study. A much better response was observed among patients with low spherical equivalent refractive errors and average *K*-readings of less than 53 D. Poor responders had greater spherical equivalent refractive errors and mean *K*-readings of greater than 55 D. The authors explain that the Intacs' ability to flatten the corneal curvature is limited by the degree of the keratoconic protrusion, and this factor may be valuable in predicting patient response.

Pokroy and Levinger reported a subset of patients who underwent a secondary adjustment procedure consisting of removal, exchange, or realignment of an Intacs segment.[33] Of a series of 58 eyes, 7 eyes had additional intervention. In five of those eyes a 0.45 mm superior segment was removed, thus leaving the patient with a single 0.45 mm segment inferiorly. Only two of the eyes experienced no improvement after the secondary procedure while an average gain of almost four lines UCVA was achieved among the remainder. These data demonstrate the adjustability of effect of the Intacs insert in the keratoconus patient, a feature shared in the myopia application.

Long-term follow-up of Intacs for keratoconus has revealed stability of refraction, BCVA, and topographic parameters.[34] However, a statistically significant increase in mean *K*-value of 1.67 D over a 36-month follow-up period was noted in one group of patients.

Complications associated with intrastromal ring implantation for keratoconus has included migration of ring segments, thinning of the cornea over superficially placed segments, extrusion of segment implants, and infectious keratitis in the early and late periods after segment implantation.[35,36] Contact lens wear has been identified as a possible risk factor for infectious keratitis after intracorneal rings for keratoconus, although it is not possible to state that the placement of rings places a contact lens wearer at a higher risk of infection.

PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration (PMD), like keratoconus, is a progressive, noninflammatory corneal ectatic disorder. In PMD the area of thinning is typically located in the inferior cornea. A characteristic crab claw appearance is noted on topography maps and is associated with against-the-rule astigmatism.

In the first case report of Intacs for the correction of PMD, the devices were implanted with a temporal incision, as in previous keratoconus applications.[37] While the patient's uncorrected visual acuity did not improve after the procedure, a hybrid contact lens (Softperm, CibaVision) allowed a corrected acuity of 20/25.

Mularoni et al reported a series of eight patients with contact lens-intolerant PMD who underwent Intacs implantation using a temporal incision and dissimilar segment sizes.[38] The patients were followed from 12 to 42 months. All patients experienced an improvement in UCVA, and six eyes (75%) had a BCVA of 20/25 or better. The mean UCVA improved from 20/325 (range, 20/1000 to 20/200) to 20/63 (range, 20/200 to 20/32) while the mean BCVA improved from 20/45 (range, 20/63 to 20/25) to 20/25 (range, 20/32 to 20/20). Refractive stability was noted to occur by 3 months postoperative. Similar results treating PMD with the Ferrara intrastromal corneal ring have been reported.[39]

INTACS AFTER LASER-ASSISTED IN SITU KERATOMILEUSIS

Intacs have been used after LASIK in a number of different circumstances. The concept of applying Intacs to correct residual myopia after maximal LASIK surgery is credited to Michiel Kritzinger, MD. In an initial series of patients, he noted an improved uncorrected visual acuity and a more prolate topographic profile after Intacs implantation.

Fleming and Lovisolo published a case report of Intacs for the treatment of myopic regression after LASIK for high myopia.[40] Ten months after LASIK the patient had a residual refractive error of −3.37 D (spherical equivalent) and underwent implantation of a 0.40 mm Intacs ring. Four months after this procedure the patient saw 20/20 without correction.

Several subsequent reports have confirmed the efficacy of Intacs for targeting residual refractive error after LASIK or photorefractive keratectomy (PRK).[41,42] Guell et al reported a series of 13 patients who underwent Intacs after LASIK for residual myopia (seven eyes), secondary ectasia (three eyes), and decentered ablations (three eyes).[41] The authors applied the standard myopia nomogram and inserted the segments in the standard fashion through a 12 o'clock incision site. Secondary procedures were performed 14 months to 6 years after the LASIK procedure. All eyes experienced an improvement in UCVA with no loss of BSCVA. Eyes with larger degrees of residual refractive error tended to remain slightly undercorrected after Intacs implantation. The authors noted that Intacs can significantly enlarge the effective optical zone of treatment and can help to correct moderately decentered ablations. One segment required explantation 7 months after surgery due to corneal thinning over a superficially placed segment.

Regression of refractive effect associated with the development of astigmatism in the postoperative LASIK patient generally suggests iatrogenic ectasia. Topography reveals a steep central or paracentral cornea, and elevation topography is associated with an elevated posterior float pattern. Symptoms may be correlated with a loss of best-corrected visual acuity.[43]

Several reports have demonstrated the efficacy of Intacs for the treatment of iatrogenic keratectasia after LASIK.[44–46] Siganos et al reported the results of Intacs implantation in three eyes of two patients.[44] Both patients had undergone LASIK a year earlier for high myopia. The Intacs were inserted using standard techniques for myopia and the standard nomogram for ring size selection. All eyes had an improvement in UCVA ranging from 20/20 to 20/25 at 9 months after the secondary procedure.

Lovisolo and Fleming applied the keratoconus surgical approach to iatrogenic ectasia cases in four patients.[45] A temporal incision was used to place dissimilar segment sizes in a horizontal configuration with a thicker segment in the inferior channel and thinner segment in the superior channel. All eyes experienced an improvement in UCVA and BSCVA, obviating the need for rigid gas-permeable contact lens correction or penetrating keratoplasty.

Longer-term follow-up data have shown stability of improvement in the refractive outcome of Intacs in the post-LASIK patient. Kymionis et al reported a series of 10 eyes of 7 patients with an average follow-up of 1 year after Intacs for iatrogenic ectasia after LASIK for high myopia.[47] In all cases, the initial refractive procedure was performed at least 1 year before secondary intervention. At the latest follow-up, the UCVA improved from 100% of patients 20/100 or worse to 90% 20/40 or better. All eyes maintained or improved BSCVA by one to two lines and had an improvement in topographic regularity. The authors noted that most eyes of this series experienced a return of BSCVA to their pre-LASIK level.

Pokroy et al reported a series of five eyes of five patients in which the single inferior segment approach to Intacs implantation was employed.[48] An average improvement of four lines of UCVA was noted after surgery; however, one eye experienced no improvement in acuity. More importantly, regularization of the corneal surface as measured by the mean inferior–superior topographic asymmetry improved from 7.88 ± 4.59 to 2.46 ± 2.77 D. This improvement in topographic regularity was associated with an improvement in BSCVA in all eyes.

The techniques of therapeutic indications for Intacs surgery continues to evolve. The ability to use the femtosecond laser for channel creation has allowed for faster surgical procedures, and the ability to customize the channel configuration by software control of the laser. A narrower channel appears to yield a more profound refractive effect and may help to prevent segment migration in the softer tissue of the ectatic cornea. A limitation of laser-created channels at this time is a restricted depth of 400 µm in the stroma.

Given the vast improvements in excimer laser technology including wavefront-guided customized corrections, initial enthusiasm for Intacs to correct low myopia has understandably waned. Nevertheless, the therapeutic indications for Intacs have brought about a resurgence of interest in this technology, and the FDA approved the use of Intacs for keratoconus in July 2004. The ability to defer or potentially obviate the need for penetrating keratoplasty for a patient with keratoconus or iatrogenic ectasia makes this surgical option a valuable resource in our therapeutic armamentarium.

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88 Myopia, hyperopia, and astigmatism

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INTRODUCTION

In humans, the anterior corneal surface provides on average 72% of the eye's total refractive power (43 D of a possible 60 D). Thus, alteration of the anterior corneal curvature represents a good, efficient way to correct refractive errors. The excimer laser can be used to reshape the corneal surface by removing anterior corneal stroma in a microscopically precise process known as ablative photodecomposition. This results in nonthermal, photochemical interactions that break covalent molecular bonds of corneal tissue. Excimer laser-based keratorefractive surgery is a very accurate, precise, and safe means of permanently changing the refractive curvature of the human cornea. It has become the most commonly performed refractive corneal surgery over the last decade, particularly after it was approved by the USA Food and Drug Administration (FDA) in 1995.[1]

HISTORY OF EXCIMER LASERS

In the mid-1970s, researchers first discovered that rare gas and halogen lasers (e.g. argon fluoride (ArF), xenon chloride, and krypton bromide) could be electrically stimulated to form unstable dimers. The photons of energy released from this unstable or excited dimer could then be focused with sophisticated lenses and mirrors to create an ultraviolet (UV) laser beam with considerable energy.[2] The *ex*cited d*imer* (shortened to excimer) laser beam could be shaped to form different treatment profiles or patterns. Trokel and associates showed that the ArF excimer laser could precisely photoablate enucleated bovine cornea by cleaving chemical bonds with no evidence of thermal damage to adjacent tissue.[3] This ability to impart very high energy to corneal stroma without significant thermal effects makes this laser unique among all other ophthalmic lasers. Serdarevic and associates showed that the ArF excimer laser could photoablate a wide area of the optically used portion of the cornea to recontour the cornea and maintain corneal transparency long term.[4] This pioneering work prompted multiple investigations to better understand the use of excimer lasers in keratorefractive surgery. Seiler and Wollensak first used this technology to perform astigmatic keratotomy in 1985 and, subsequently, to perform phototherapeutic keratectomy (PTK) in 1986.[5,6] In late 1986, Marshall and associates used the ArF excimer laser to recontour the anterior corneal surface for myopia in a technique known as photorefractive keratectomy (PRK).[7] Then in 1990, Pallikaris and associates described a technique to recontour the corneal stroma beneath the surface by cutting a lamellar corneal stromal flap first and then photoablating the anterior surface of the residual stromal bed. This became known as laser-assisted in situ keratomileusis (LASIK).[8]

The ArF excimer laser utilizes a 193 nm UV wavelength that produces greater energy, approximately 6.4 eV per laser pulse, than the required 3.5 eV of energy needed to break covalent carbon–carbon bonds. This 193 nm wavelength has been shown to be safe, as it is not mutagenic or cataract forming and creates minimal thermal effects (0–9°C increase in temperature).[9–11] Endothelial toxicity from the ArF excimer laser radiation is also negligible since absorption of radiation occurs within 1 μm of the ablated tissue.[12]

The excimer lasers have evolved, and the effectiveness of laser keratorefractive surgery has markedly improved since 1987. At that time, only two excimer laser systems from two manufacturers, Summit and VISX, were available for FDA studies. Most of the excimer laser systems introduced in the market between 1988 and 1995 consisted of broad-beam lasers with no eye-tracking ability. Broad-beam lasers were the first-generation systems that had large spot diameters (5.0–7.5 mm) and relied on expanding apertures. They were advantageous in that they were fast and effective, but they had the disadvantages of irregular beam profiles or poor homogeneity that would sometimes create rough and irregular surfaces, and they were limited in their inability to create complex ablations profiles without masking devices.

Between 1995 and 1999, small scanning spot excimer lasers with eye-tracking capabilities were introduced. Scanning-beam lasers with fixed or variable size, small-diameter slit beams (0.5–2.0 mm) represented second- and third-generation excimer laser systems. These included flying spot, scanning slit, and variable spot scanning laser systems. All of these systems were an improvement over broad-beam systems, as the laser beam profiles were more Gaussian (more energy centrally than over the edges), produced smoother ablations, and could treat more complex ablation profiles. They had

the disadvantages of longer treatment times since smaller spot sizes require more pulses and of needing sophisticated video or laser radar eye-tracking systems since any misalignment of small-diameter pulses could result in significant alteration from the intended ablation profile.

From 1999 to 2003, newer systems added many upgrades and improvements to make them faster, more reliable, and more precise. They also allowed expandable optical zones and better algorithms for recontouring the cornea and had better tracking systems and faster treatment times. With this level of precision and versatility, these fourth-generation excimer laser systems had become sophisticated enough to support customized or wavefront-guided ablations.

With the advent of wavefront sensors and FDA approval of the first wavefront-guided customized excimer laser platform in October 2002, attention had now focused more on measuring and correcting optical aberrations beyond sphere and cylinder. The ultimate goal has been to achieve an aberration-free correction that is only limited by the resolution of the human retina, which is perhaps around 20/8 vision.

CONVENTIONAL ABLATION PROFILES

The focus of this chapter will be 'conventional' laser-refractive treatments. The conventional ablation profile is mainly used for the correction of spherocylindrical refractive errors: myopia, hyperopia, and astigmatism. Primary input comes from subjective refractive data as measured by manifest and cycloplegic refractions. Laser ablative correction of spherocylindrical refractive errors can be performed as a surface ablation, as in PRK; laser-assisted subepithelial keratomileusis (LASEK); and epi-LASIK or beneath a flap, as in LASIK. Conventional treatments or ablative profiles have evolved considerably over the past two decades to address many of the causes of visual disturbances or complaints, but they do not address or treat higher-order aberrations. These are optical imperfections beyond spherocylindrical refractive errors that might optically limit a patient's quality of vision. This is the realm of wavefront-guided customized laser ablation profiles, which will be discussed in later chapters.

PRINCIPLES OF MYOPIC ABLATIONS

The correction of pure, spherical myopia with the laser requires the removal of a convex lenticule of tissue, where more tissue is removed centrally than peripherally. This was mathematically described by Munnerlyn and associates who took the principles used for creating contact lenses to develop an algorithm to calculate the ablation depths and profiles for both myopic and hyperopic corrections. They developed formulas to guide tissue removal at each point on the corneal surface to change the refractive power of the cornea. The ablation depth proved to be a function of the desired magnitude of refractive power change and the diameter of the ablation.[13]

Munnerlyn equations for myopic corrections

The principle of myopic correction using the excimer laser is based on a graded removal of tissue to decrease the corneal anterior curvature, analogous to the removal of a biologic contact lens from the central corneal surface. In deriving their ablation profile formulas, Munnerlyn[13] assumed the initial and final corneal surfaces to be spherical and the optical power (D) of the excised tissue lenticule to correspond to the intended change in refraction:

$$D = (n-1)\cdot\left(\frac{1}{R_0} - \frac{1}{R_1}\right)$$

where D = change in refractive power of the cornea

n = 1.377 is the index of refraction of the cornea

R_0 = the initial anterior radius of curvature of the cornea

R_1 = the final anterior radius of curvature of the cornea.

Calculation of the ablation profile for the correction of spherical myopia (M) can be performed according to the formula:

$$t(y) = \sqrt{R_0^2 - \left(\frac{S}{2}\right)^2} - \sqrt{R_1^2 - \left(\frac{S}{2}\right)^2} + \sqrt{R_1^2 - y^2} - \sqrt{R_0^2 - y^2}$$

where $t(y)$ = the depth of tissue removal at a distance y from the optical center

y = the distance radially from the optical center

S = the diameter of the treatment zone or the tissue lenticule to be removed

R_0 = the initial anterior radius of curvature of the cornea

R_1 = the final anterior radius of curvature of the cornea.

In myopic corrections, the maximal depth of ablation occurs at the center of the treatment zone ($y = 0$) (Fig. 88.1). By using binomial expansion, this can be approximated from the above equations to the form:

$$\text{maximum ablation depth } (\mu\text{m}) = \text{ablation diameter}^2\ (\text{mm}^2) \times \text{diopters of correction (D)}/3$$

Thus, the maximum ablation depth increases linearly for an increase in diopteric power, but increases at a square exponential rate for the treatment diameter of the optical zone. For an ablation zone of 6.0 mm, a conventional myopic correction would be expected to remove approximately 12 µm/D of correction (Fig. 88.2).

A theoretical approximation of the volume of tissue removed for conventional spherical myopic and hyperopic treatments has also been derived by Gatinel and associates[14] resulting in the formula:

$$\text{volume of ablation } (\text{mm}^3) = (\text{diameter of treatment zone } [\text{mm}]/9)^4 \times \text{diopters of correction (D)}$$

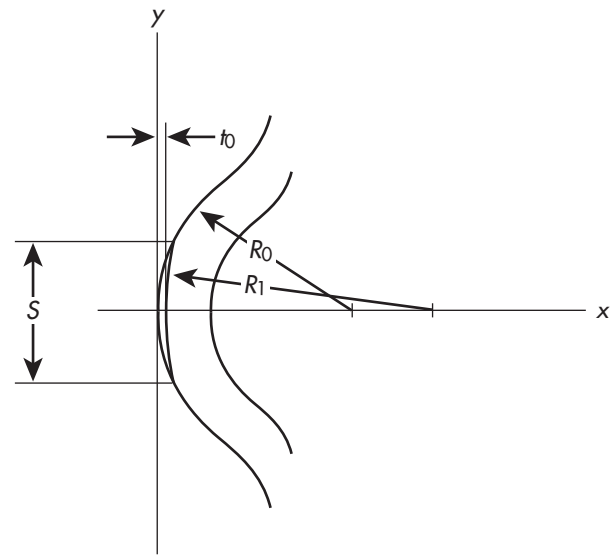

Figure 88.1. Munnerlyn myopic ablation.

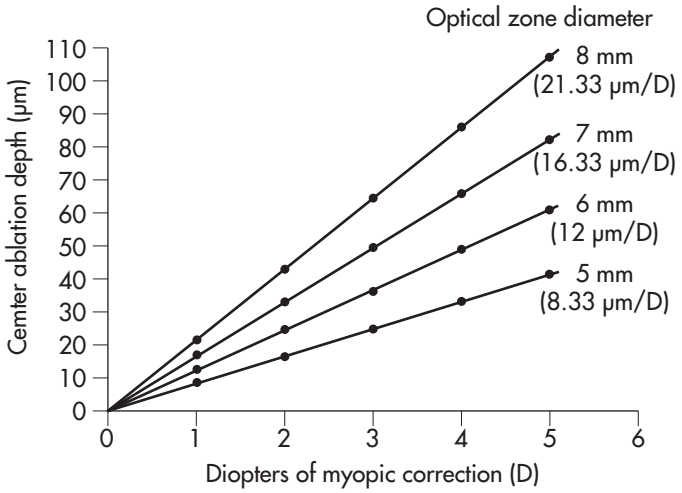

Figure 88.2. Diopters of myopic correction.

Thus, the volume of photoablated tissue also increases linearly for an increase in dioptric power, but by the fourth power for the treatment diameter of the optical zone. Overall, these theoretical, mathematical analyses show that the depth and volume of tissue removal for conventional treatments are mostly dependent on the diameter of the optical zone treatment.

Use of the excimer laser to correct myopia

With the earliest broad-beam excimer lasers, myopic corrections were accomplished with an iris diaphragm that would gradually open as the laser fired a series of pulses. The center of the cornea would receive more laser energy than the periphery and would experience greater tissue removal (Fig. 88.3, *A*). The scanning slit excimer lasers that followed would typically scan the slit across the cornea while increasing a diaphragm aperture to control the amount of laser energy applied centrally. With the subsequent scanning spot lasers, more spots could be applied centrally than peripherally to accomplish the corneal resculpting without the need of an expanding aperture (Fig. 88.3, *B*).

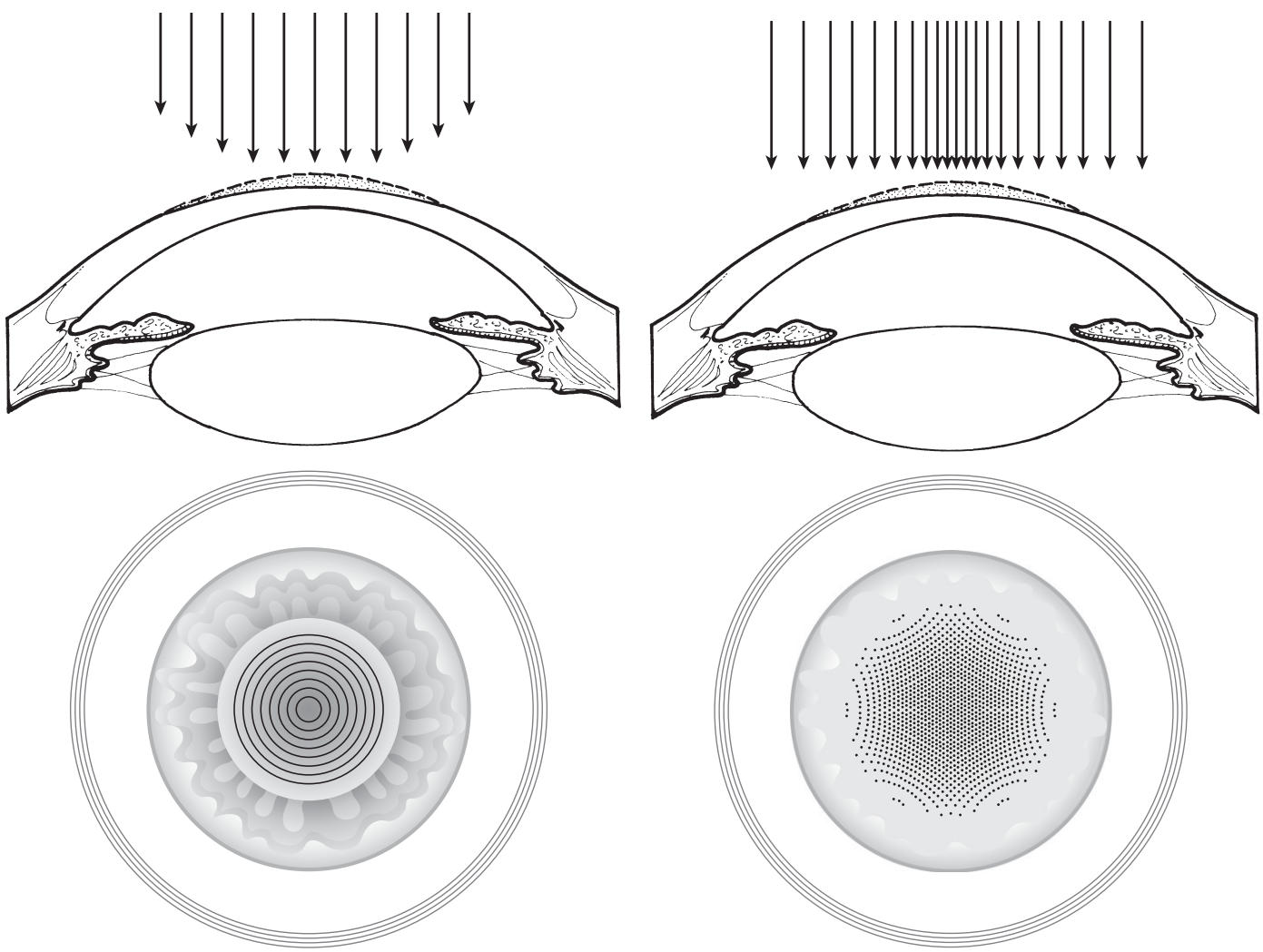

Figure 88.3. *A*, Myopic ablation broad beam. *B*, Myopic ablation scan spot.

These conventional myopic ablation profiles were effective, but were found to occasionally result in loss of visual performance (e.g. reduced mesopic or scotopic contrast sensitivity, increased glare and halos, and increased starbursts). The first myopic ablations were done at smaller diameters (4 and 5 mm in diameter) to minimize ablation depth because of concerns that deeper ablations might stimulate a greater wound healing response and scarring of the cornea. The smaller ablation zone diameters for myopic corrections actually resulted in greater regression and in greater complaints of halos and glare, presumably from the edge effect of the ablation zone with a larger pupil. To optimize visual outcomes and minimize tissue ablation depths, typical optical zone diameters are currently around 6.5 mm.

In addition, the assumptions used to derive the myopic ablation profiles had some shortcomings since the human cornea is not spherical, and this was also felt to contribute to the poor visual performance of some patients. The normal corneal contour is steeper, or has a smaller radius of curvature centrally, and is flatter with a larger radius of curvature towards the periphery. This type of contour is described as being prolate (Fig. 88.4, *A*). With the central flattening effect of a myopic laser correction, the corneal contour would be converted to one that was flatter centrally and comparatively steeper in the periphery, a shape referred to as being oblate (Fig. 88.4, *B*). An oblate corneal surface results in decreased focus on the retina, and this effect is especially pronounced with larger pupils, whether inherent to the patient or due to dim illumination, and with larger myopic corrections. Holladay and colleagues suggested that this might be the predominant factor in the functional decrease in visual performance after excimer laser-based keratorefractive surgery.[15,16]

Another mechanism contributing to the asphericity of the cornea and visual quality is due to the laser interaction with the curved cornea. The peripheral cornea receives less laser energy and less tissue ablation than planned. This is due to the greater distance the laser beam has to travel when ablating the peripheral cornea; the curved contour of the cornea means that the central cornea is closest to the laser source and the peripheral cornea furthest away as it curves posteriorly. In addition, the laser beam hits the central cornea orthogonally or perpendicularly to the surface, whereas it hits the peripheral cornea incidentally or at an angle and is partly reflected with some loss of effect (Fig. 88.5).[17] The newer-generation lasers have incorporated a compensation for this phenomenon, a radial compensation function, and this is no longer a significant source of reduced visual quality.

The ablation profiles for myopic corrections have been modified and have evolved to address all these causes of reduced visual quality in an attempt to give the patient the best and most predictable visual result. This evolutionary process has included the refinement of the excimer lasers with each successive generation to create smoother ablations and enhanced beam homogeneity but also to increase optical zone diameters, to minimize oblate corneal contours, and to add transition zone treatments to smooth and improve the peripheral corneal contour.

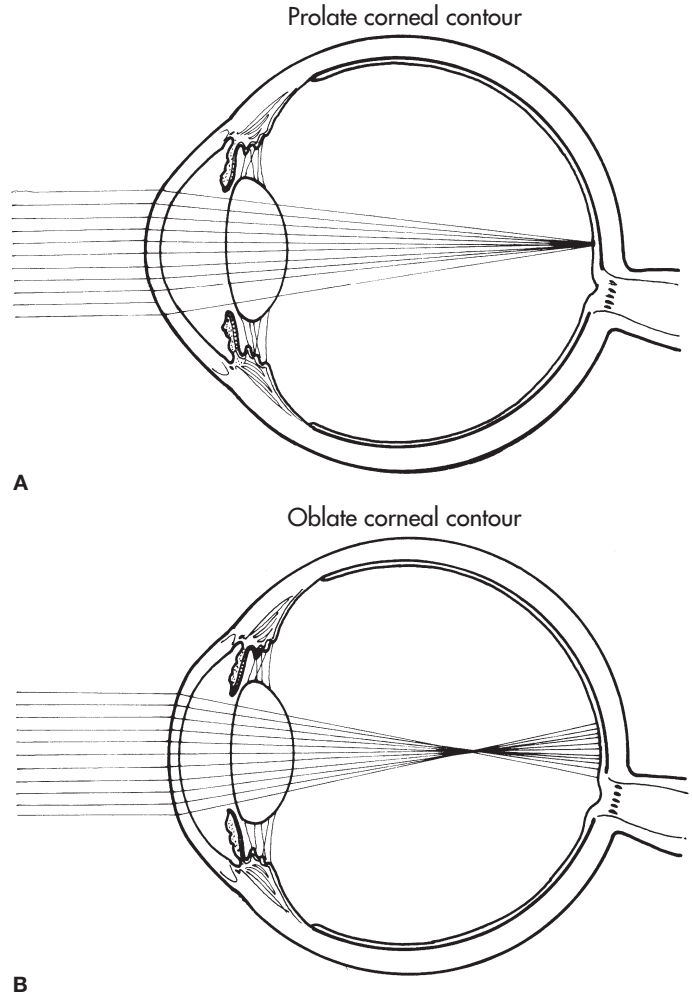

Figure 88.4. *A*, Prolate corneal contour. *B*, Oblate corneal contour.

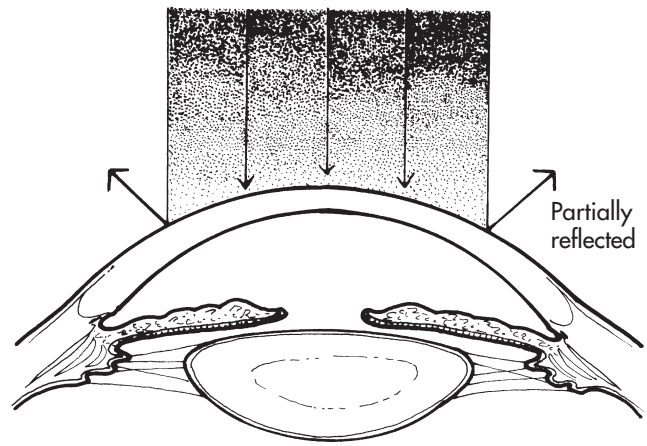

Figure 88.5. Radial ablation efficiency loss causes underablation in the periphery.

PRINCIPLES OF HYPEROPIC ABLATIONS

The correction of spherical hyperopia with the laser requires the removal of a concave lenticule of tissue. Munnerlyn and associates again used the principles that underlie contact lens creation to mathematically describe the dimensions of the lenticule of tissue that would need to be removed in order to accomplish a desired hyperopic correction. The tissue ablation profile was described as a function of initial anterior corneal curvature, corneal refractive index, magnitude of correction desired, and diameter of the lenticule of tissue to be removed, or the ablation zone.[13]

Munnerlyn equation for hyperopic corrections

For the correction of hyperopia, the corneal curvature has to be increased over the ablation zone (or the radius of curvature has to

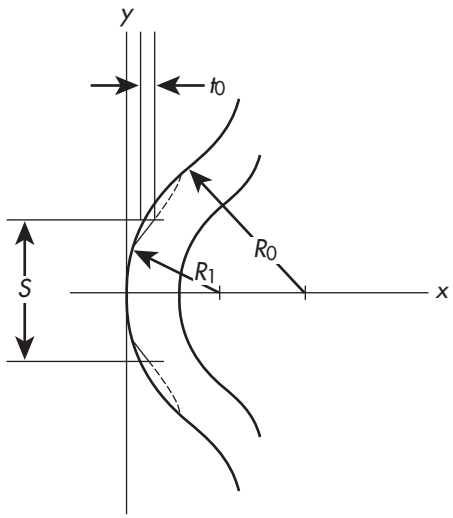

Figure 88.6. Munnerlyn hyperopic ablation.

be decreased). The ablation profile for a hyperopic correction can be calculated by the following equation:

$$t_H(y) = \sqrt{R_0^2 - y^2} - \sqrt{R_1^2 - y^2} + R_1 - R_0$$

where $t_H(y)$ = the depth of tissue removal at a distance y from the optical center

y = the distance radially from the optical center ($y \leq S/2$)

S = the diameter of the treatment zone or the tissue lenticule to be removed

R_0 = the initial anterior radius of curvature of the cornea

R_1 = the final anterior radius of curvature of the cornea.

For hyperopic corrections, the depth of ablation is greatest in the periphery and is negligible centrally and can be determined from Munnerlyn's equations (Fig. 88.6). Again by using binomial expansion, the maximal ablation depth can be approximated as:

$$\text{maximum ablation depth } (\text{mm}^3) = \text{ablation diameter}^2\ (\text{mm}^2) \times \text{diopters of correction (D)}/3$$

Use of the excimer laser to correct hyperopia

With the earliest broad-beam lasers, some of the initial approaches used beam divergers to direct the laser energy to the periphery and masks to control laser energy application. Ablatable masks were made of materials that would photoablate at a known rate. The thinner areas of the mask ablate through quickly and allow passage of the excimer laser energy to the cornea, whereas the thicker areas of the mask shield portions of the cornea from photoablation (Fig. 88.7). Nonablatable masks were also used; these were shaped apertures that allowed passage of laser energy to the cornea and could be rotated to control the ablation pattern applied to the cornea.

With the advent of scanning slit lasers, a slit beam of laser energy could be scanned over the cornea and used with an ablatable mask or a rotating nonablatable mask to ablate the cornea where desired, or the slit beam could be rotated around the periphery obviating the need for a mask. The more recent scanning spot lasers simply apply a greater number of pulses in the periphery than centrally and do not require any masks (Fig. 88.8).

The initial approaches to hyperopic ablations were successful, but again there were reports of regression and poor visual performance. Regression with loss of effect was a greater challenge with

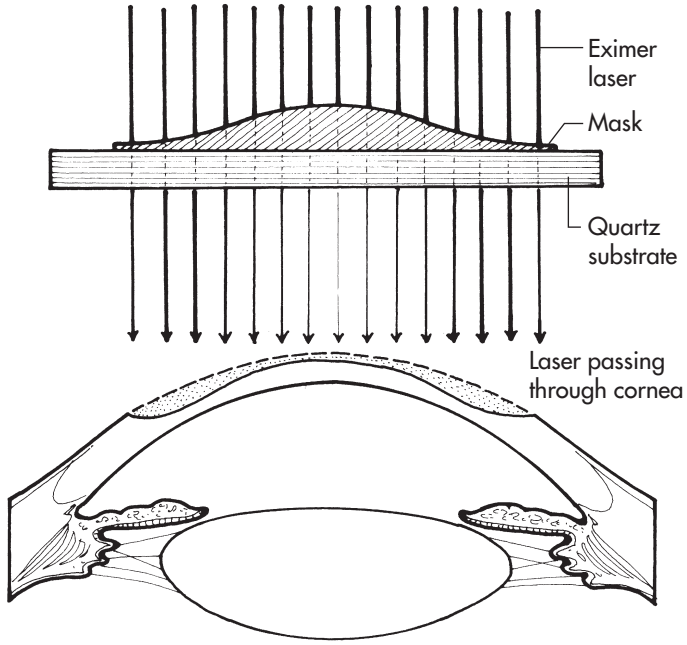

Figure 88.7. Mask for hyperopic ablation.

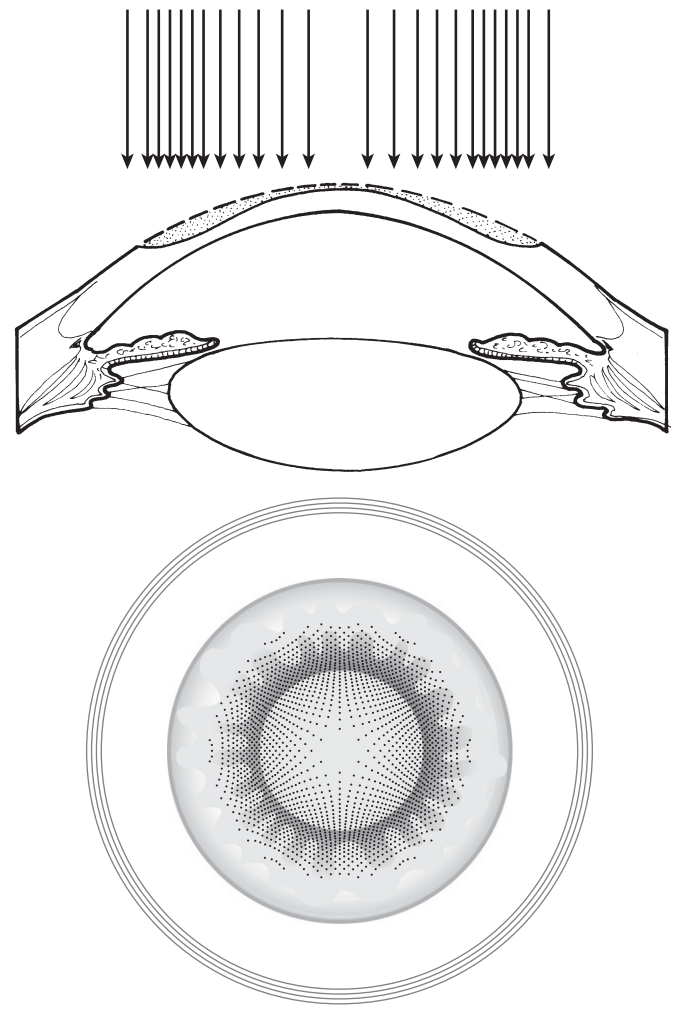

Figure 88.8. Hyperopic ablation scanning spot.

hyperopic ablations compared with myopic ablations. It was physiologically more natural to flatten the corneal center as in myopic corrections, rather than ablate a donut-shaped trough and not have the cornea try to fill the treated areas in with epithelial hyperplasia. Higher hyperopic corrections only required deeper stromal removal with an exaggerated abrupt change in corneal curvature at the edge of the ablation. This was associated with an even more marked healing response with decreased visual acuity under glare conditions.

Similar to earlier myopic correction attempts, the first corrections for hyperopia were done at smaller optical zones. Better visual outcomes and greater stability of result were seen at larger optical zones. In addition, the use of blended transition zones made the recontouring effects more gradual and more stable, and the advent of scanning lasers allowed for smoother ablations.

PRINCIPLES OF ASTIGMATIC ABLATIONS

Astigmatic corrections are more challenging than purely spherical myopic or hyperopic corrections. Astigmatism describes an optical aberration where the refractive power of an optical system varies across different meridians. In stigmatic optical systems, the image of a point source is also a point; in an astigmatic optical system, there are at least two focal points or two focal planes. Conventional laser astigmatic ablations treat regular or symmetric astigmatism, where the two prime meridians of corneal curvature are orthogonal, or 90° apart. Ablation principles for irregular astigmatism will be addressed in the chapters on wavefront- and topography-guided ablations.

Regular astigmatism can be subcategorized as myopic astigmatism, compound myopic astigmatism, hyperopic astigmatism, compound hyperopic astigmatism, and mixed astigmatism. These subcategories describe where the two focal planes created by the astigmatism lie with respect to the retina. This in turn determines the optimal ablation approach to their correction. In myopic astigmatism, one focal plane lies anterior to the retina, and the second focal plane lies on the retina. In compound myopic astigmatism, both focal planes lie anterior to the retina. In hyperopic astigmatism, one focal plane lies on the retina and the second plane lies posterior to the retina. In compound hyperopic astigmatism, both focal planes lie posterior to the retina. Lastly, mixed astigmatism consists of one focal plane anterior to the retina and the second focal plane posterior to the retina (Fig. 88.9, *A–E*).

Use of the excimer laser to correct astigmatism

The goal behind an astigmatic ablation is to resculpt the anterior corneal contour to bring the two focal points to the same plane and then ultimately onto the retina. This requires either selective flattening of the steep meridian or alternatively steepening (or decreasing the radius of curvature) of the flat meridian (Fig. 88.10). The earliest approach with the broad-beam lasers involved flattening the steeper meridian. In 1991, McDonnell and associates proposed passing a large-diameter laser beam between a set of parallel blades.[18] The separation of the blades was controlled by a computer with the slit created gradually increasing in width during the procedure. The mechanical axis (long axis of the slit beam) was rotated and aligned with the astigmatic axis of the patient. No refractive change was intended along the mechanical axis, but the corneal curvature was flattened along the meridian, or 90° opposite of the slit expansion. In a sequential treatment, the cylinder could be treated first and the spherical component next. Elliptical ablations were also employed and were created by having the computer expand both the slit and the iris diaphragms simultaneously; this could treat both myopia and astigmatism concurrently.

Another approach to treating astigmatism was with the use of a mask. The mask was made of an ablatable material and was designed to deliver a graded ablation to the cornea. The thinner areas of the mask would ablate through quickly and allow passage of the excimer laser energy to the cornea, whereas the thicker areas of the mask would shield portions of the cornea from photoablation. The 'steeper' meridian of the corneal surface would receive more treatment and would be flattened.

With the advent of scanning, variable-diameter spot excimer lasers, smaller laser spots could be used to treat astigmatism more directly. Moreover, the laser beam position on the cornea could be altered with scanning mirrors and servo-mechanisms controlled by a computer. The ablation would start with a small-diameter spot along the steep axis, and the spot size would be increased in diameter and continue along the flat axis. This would create a tapered, graded pattern that would flatten the steep meridian (Fig. 88.11, *A* and *B*).

These were appropriate and intuitive approaches to treating myopic astigmatism or compound myopic astigmatism where the steeper meridian could be flattened to the curvature of the flatter meridian, and then the entire cornea could be flattened further with a spherical myopic correction. However, with compound hyperopic astigmatism, this approach meant first flattening the steeper meridian and then attempting to steepen the overall curvature of the cornea with a spherical hyperopic treatment. This required re-steepening of the areas of the cornea that were flattened to treat the astigmatism and thus redundant or excessive removal of tissue was involved. It was a less efficient approach for hyperopic astigmatism.

The more recent scanning-beam lasers use a fixed-diameter spot to rapidly resculpt the cornea as determined by the computer. The beam can be directed to ablate the steep areas more and avoid the flat areas to reshape the myopic astigmatic patient, but can also be used to steepen rather than flatten an axis. The cornea can thus be approached in positive or negative cylinder. This is particularly useful with hyperopic patients with astigmatism where all axes can be steepened but by differing amounts. Not only is it a more direct approach to hyperopic astigmatism and compound hyperopic astigmatism, but it is also much more tissue conserving (Fig. 88.12).

Thus, the most ideal and efficient way to treat any astigmatism is to remove the least amount of tissue and to avoid redundancy. For any myopic astigmatism, this is the minus or negative cylinder format where the steeper meridian is first flattened to create a spherical surface, and then overall corneal surface flattened further to a desired spherical corneal power. In hyperopic astigmatism, it is advantageous to use the plus or positive cylinder ablation approach to first steepen the flatter meridian and then steepen the overall spherical surface further to the desired spherical corneal power.

Mixed astigmatism allows for three possible treatment approaches: minus cylinder format, plus cylinder format, or cross cylinder format. As it turns out, the cross cylinder approach removes the least tissue in mixed astigmatic corrections and is the most ideal and efficient means of achieving the desired refractive and visual outcome. The myopic focal plane in front of the retina is moved posteriorly toward the retina with the minus cylinder ablation, and the hyperopic focal plane is moved anteriorly toward the retina with

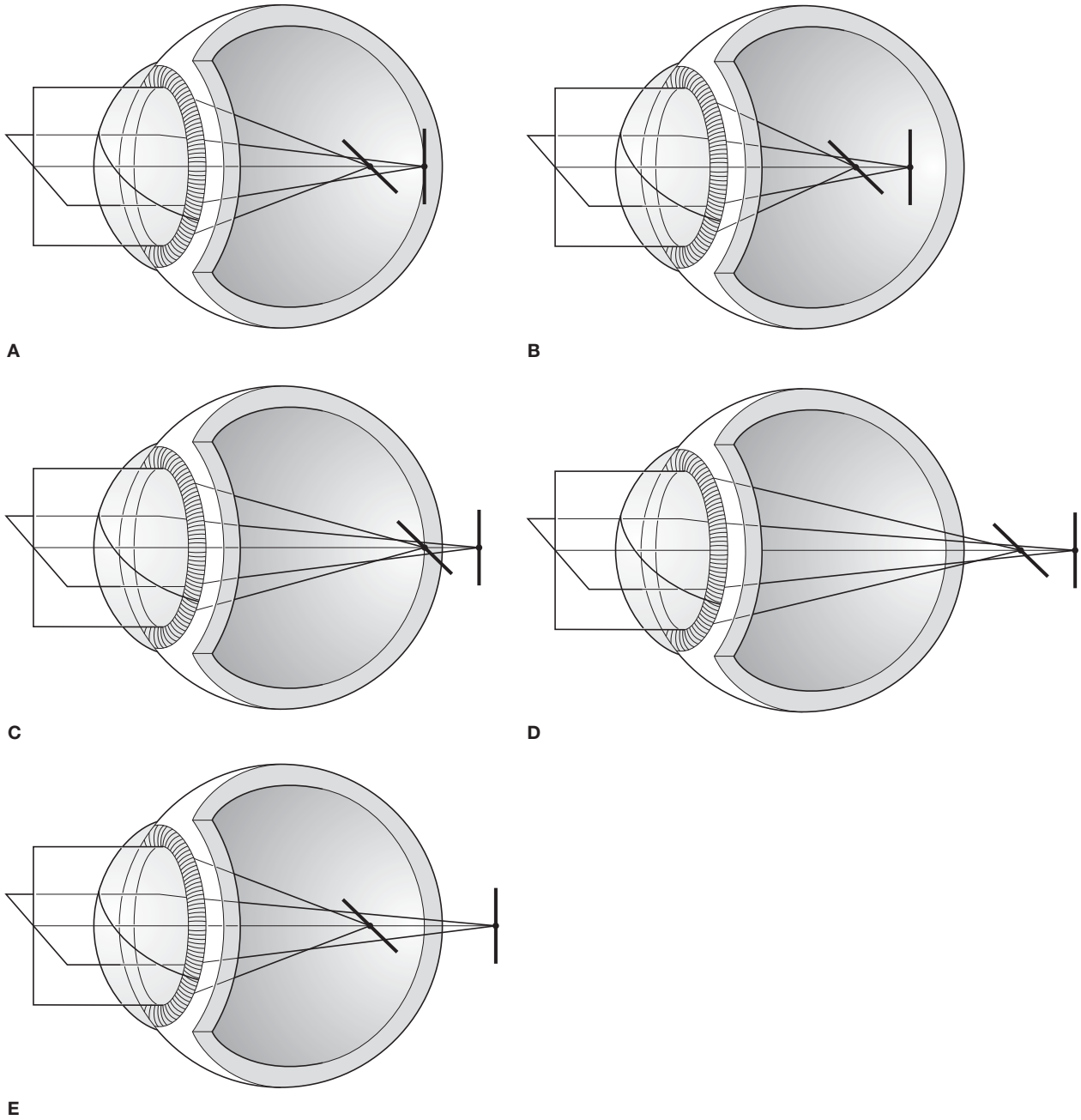

Figure 88.9. *A*, Myopic astigmatism. *B*, Compound myopic astigmatism. *C*, Hyperopic astigmatism. *D*, Compound hyperopic astigmatism. *E*, Mixed astigmatism.

the plus cylinder ablation. No spherical (myopic or hyperopic) ablation is required (Fig. 88.13).

The evolved approach to astigmatic ablation profiles has been increasingly successful, but there are still limits to the degree of correction. Greater regression is still seen with the higher attempted corrections. The regression is perhaps the most common cause of patient complaints of poor visual performance. However, other causes of poor visual outcome include undercorrection seen with any degree of axis misalignment in treating the astigmatism. In addition, as the conventional treatments for astigmatism can only address regular astigmatism, they are not as effective with irregular astigmatism. This requires more customized approaches that will be discussed in subsequent chapters.

BEYOND CONVENTIONAL ABLATIONS FOR MYOPIA, HYPEROPIA, AND ASTIGMATISM

As an introduction to the chapters that will follow, the conventional ablations should be placed into proper context within the spectrum of options that are available and evolving. As stated, conventional laser refractive surgery corrects only myopia, hyperopia, and astigmatism or the lower-order optical aberrations of the eye, and the surgical plan is derived from the patient's manifest and cycloplegic refractions. There are additional optical aberrations or imperfections of the eye that can limit the patient's quality and quantity of vision. These higher-order aberrations can exist before surgery and are typically increased with conventional refractive surgery. And they

are often associated with glare, halos, starbursts, and decreased mesopic or scotopic contrast sensitivity.[19–29]

The current classification of excimer laser ablation profiles can be summarized as follows:

I. Based on the total optical system of the eye:
   A. Conventional ablation profiles: correct lower-order aberrations and are based on the patient's manifest and cycloplegic refractions.
   B. Wavefront-optimized ablation profile: In addition to treating lower-order aberrations, wavefront-optimized treatments attempt to maintain the preoperative prolate shape of the cornea by removing more stromal tissue peripherally than in conventional treatments and adjusts for postoperative biomechanical and biologic effects.[30,31] These extraperipheral laser pulses are derived from the patient's keratometry measurements as well as previous population-averaged preoperative keratometry measurements and postoperative wavefront analyses.[32] The major advantage of this technique compared to wavefront-guided treatment is that the time-consuming wavefront data analysis process is not required. The disadvantages are that it ablates more tissue peripherally than conventional treatments and is perhaps less clinically effective in reducing keratorefractive surgery-induced higher-order aberrations compared to wavefront-guided treatments. One recent randomized prospective study directly compared wavefront-optimized ablations to wavefront-guided ablations using the latest excimer laser platforms. Despite similar keratorefractive surgery-induced increases in spherical aberration (40% increase for wavefront-optimized treatment compared to 46% for wavefront-guided treatment), the total keratorefractive surgery-induced higher-order aberrations were significantly higher after wavefront-optimized treatments (increased by 49%) compared to wavefront-guided treatments (increased by 9%).[33]
   C. Wavefront-guided ablation profile: Wavefront-guided treatments are customized ablations that attempt to reduce the optical aberrations and the total wavefront error of a patient's eye to a reference ideal. The input data are more complex and time consuming to measure as it is derived from objective wavefront sensors (e.g. Hartmann–Shack sensor and Tscherning aberrometer). The wavefront sensor measures the distortion of a planar monochromatic light wave as it is altered by the optics of the eye. Contour irregularities in the cornea or lens typically cause these distortions or aberrations. Although the theoretical advantages of wavefront-guided ablations seem significant compared to conventional ablations, these have only shown marginally better visual results than conventional ablations, particularly in eyes requiring lower degrees of correction or possessing lower preoperative higher-order aberrations.[31,34] Wavefront-guided ablations do generally induce less higher-order aberrations than conventional ablations, and this may correlate to improved visual quality. Since wavefront-guided treatments correct more components of a

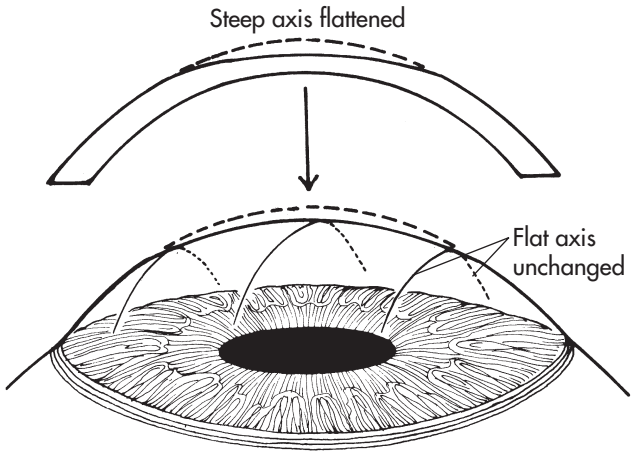

Figure 88.10. Cylindrical ablation.

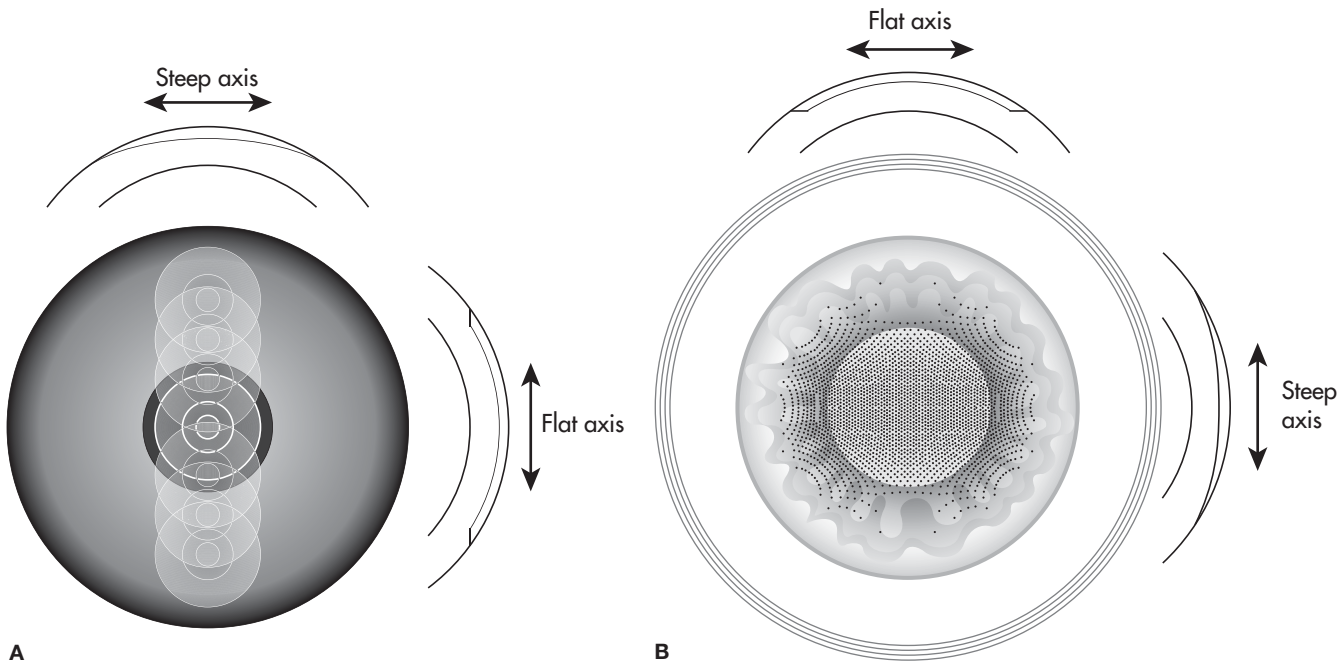

Figure 88.11. *A*, Astigmatic ablation variable spot. *B*, Myopic astigmatic ablation scanning spot.

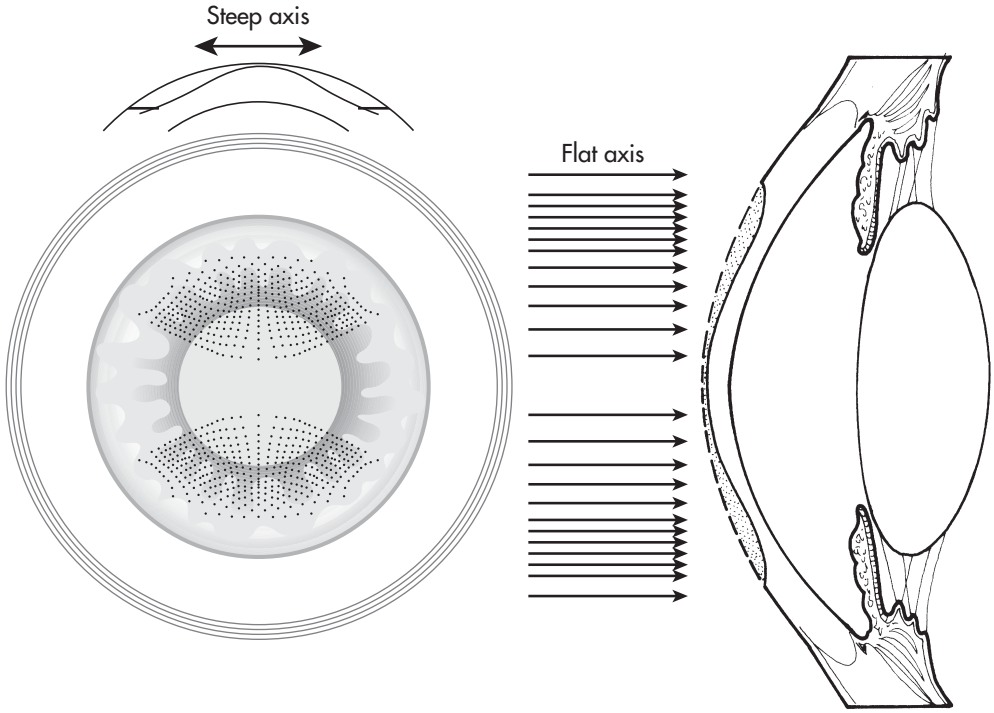

Figure 88.12. Hyperopic astigmatism ablation—scanning spot.

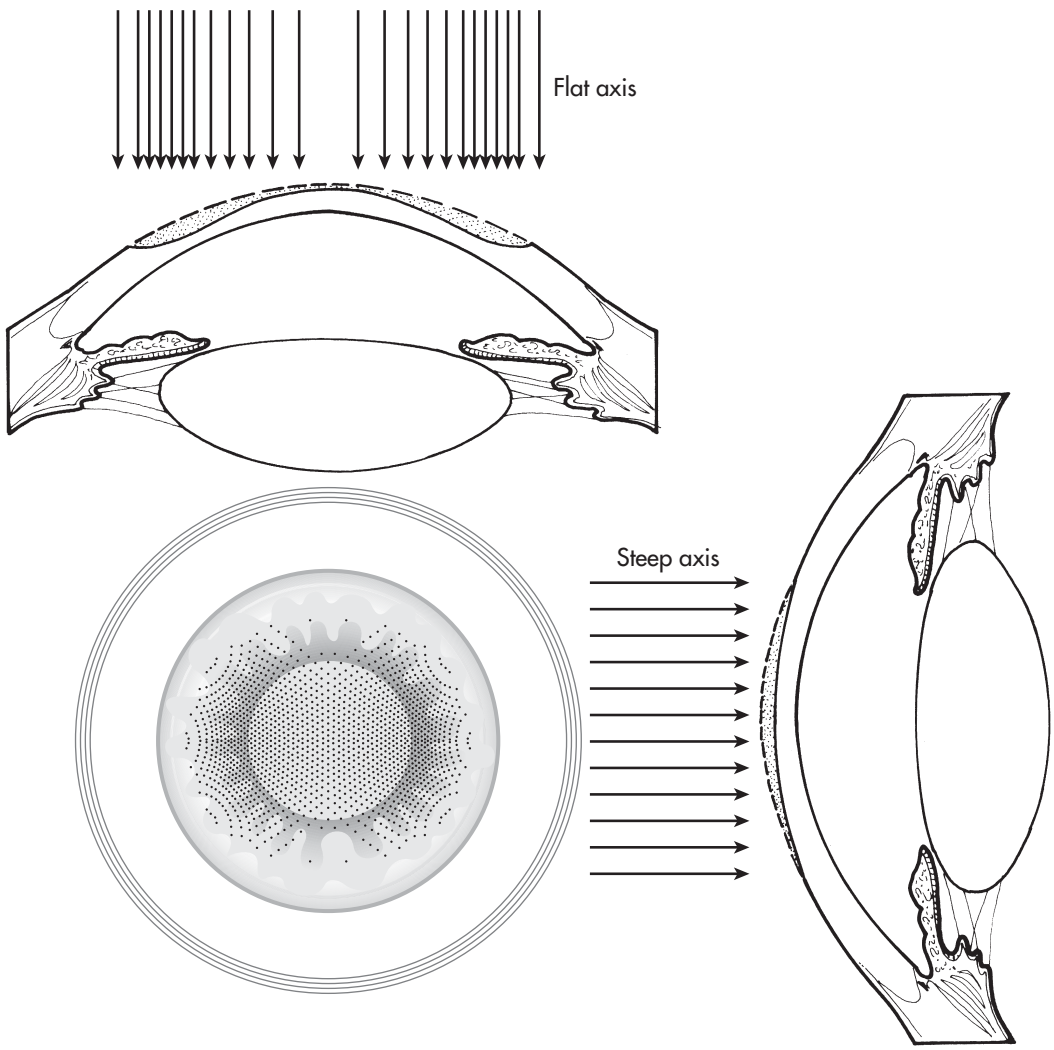

Figure 88.13. Mixed astigmatism ablation—scanning spot.

patient's wavefront error than conventional treatments, it is not surprising that it ablates deeper into the stroma compared to conventional treatments.

II. Based on corneal topography
   A. Topography-guided ablation profile: Topography-guided ablations are an alternative treatment option for patients with irregularities of the corneal surface, particularly those beyond the range of wavefront sensing devices.[35] Input data come from corneal topography measurements, which is then offset to achieve a target asphericity. The major advantage of topographic-guided treatments over wavefront-guided treatments is that they are able to reduce pronounced corneal irregularities that are producing aberrations (e.g. scarring and surgical-induced irregular astigmatism). However, the 'ideal' corneal surface is one that creates balance between corneal and lenticular aberrations, and a one-sided reduction of corneal aberration might even result in an increase of the total aberrations of the entire eye.[31] A major limitation of this technology at this time is that it does not correct refractive spherical error; therefore, a two-stage keratorefractive procedure has been proposed where a topography-guided treatment is followed by a wavefront-guided treatment.[35]
   B. Q-factor adjusted ablation profile: This approach is based on refractive error and corneal topography measurements, and the resultant laser ablation profile corrects the refractive error, while trying to produce a more aspheric corneal shape.[36] The target corneal contour for reducing spherical aberrations is calculated as having a Q-factor of –0.40. The major advantages of this technique compared to wavefront-guided treatments are that it is less time consuming and produces a clinically equivalent reduction in certain postoperative optical aberrations to wavefront-guided ablations.[36] Its disadvantages are that it ablates more tissue centrally than wavefront-guided treatments and does not correct all higher-order aberrations as it predominantly corrects spherical aberrations, similar to wavefront-optimized ablations.

CONCLUSION

Conventional laser ablation treatments with modern fourth-generation scanning-beam excimer laser systems have evolved considerably and are currently sufficient for most keratorefractive surgery candidates. However, patients who have experienced poor outcomes from previous excimer laser or other keratorefractive surgery or who present with greater preoperative optical aberrations would perhaps benefit more from a wavefront-guided treatment. In addition, there are other treatment approaches that are evolving that will be discussed in the chapters to follow.

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89 Comparison of lasers for excimer laser vision correction

David R. Hardten, Scott G. Hauswirth

Surgeons have always been extremely dependent on the tools they use, although at no time has this dependency been more obvious than in laser technology. The field of laser refractive surgery has grown immensely from its initial outset in the early 1990s, and increasing popularity of refractive surgery has increased demands from surgeons on equipment that will provide the best outcomes for their patients. Advancements in laser technology and associated software have attempted to keep pace with these demands.

There are now a wide variety of excimer laser platforms that are used for photorefractive and phototherapeutic keratectomy (PRK/PTK), laser in situ keratomileusis (LASIK), laser in situ epithelial keratomileusis (LASEK), and other associated procedures. The basic premise of the laser's function in each of these surgical procedures is to remove corneal tissue in a specific pattern to correct myopia, hyperopia, and astigmatism or, in nonrefractive cases, to remove corneal scar tissue.

The surgeon can become overwhelmed when trying to assess the relative merits of each of these systems. In addition, each laser model is continuously changing as the manufacturers incorporate updates and advancements in the field into their own systems. It is incumbent on the physician to understand the advantages and limitations of their own specific laser before applying them to patient care. It is also important for surgeons to realize the status of each laser in the USA. Some lasers may be approved for certain indications in the USA by the Food and Drug Administration (FDA) but are not yet approved for other indications, and some may not have FDA approval in the USA at all. Surgeons should contact the company directly to get an update on current regulatory status and features.

This chapter addresses the capabilities of the primary lasers used in refractive surgery and may serve as a guide to provide surgeons with information useful in determining which laser may best suit their specific needs.

ENERGY

Laser systems used in refractive surgery are not merely computer-controlled devices that produce perfectly consistent outcomes. There are several variables that must be controlled or taken into account for the optimal surgical results. Among these factors, a primary consideration is energy.

Energy is used to remove corneal tissue during the photoablative process, and the amount of energy present in a given laser beam can be variable. This amount is expressed in terms of laser fluence (mJ/cm^2). Fluence on a standard excimer laser may vary from 50–500 mJ/cm^2, which is too broad a range to give predictable surgical outcomes. Thus, most lasers available have the ability to modify fluence by adding or subtracting additional energy, usually by means of diluting the ArF gas with another molecule (often He), or by varying the voltage across the laser. These methods control fluence to a more acceptable range between 120 and 180 mJ/cm^2. The ablation threshold for cornea stromal tissue is 50 mJ/cm^2. Below this level, only photochemical changes occur. At very high fluence levels, there is an increase in disruption of surrounding tissue by thermal energy, as well as the acoustical shockwave, both of which may produce undesirable results.

Each of the excimer laser systems has a characteristic energy beam profile. This beam profile may have one of several different patterns. A homogeneous or flat beam profile is present when the energy density at every area along the beam is equal. A Gaussian energy beam profile indicates that there is a greater energy density centrally within the beam. A reverse Gaussian profile is present when there is less energy in the center portion compared to peripheral areas of the beam. Identifying these profiles is extremely important in broad-beam lasers, as the beam profile is repeated many times over the same area, and small irregularities in profile may have undesired effects if not identified preoperatively. It is less critical in smaller beam profiles.

All excimer lasers should be maintained and calibrated regularly for best performance. Beam homogeneity and laser fluence should be checked regularly by surgical staff to ensure optimal surgical results.

LASER ENERGY DELIVERY SYSTEM

Most early lasers used a complicated system of optics to attempt to deliver a large homogeneous beam to the surface of the eye. This method of delivery system is termed broad beam. These early deliv-

ery systems provided surgeons with fairly fast surgery times, but surgical outcomes were subject to beam profile.

Another method is a small spot or flying spot, which delivers the laser energy in a smaller spot (typically 0.5–2 mm), which is moved around the cornea, overlapping in a specific pattern to give the desired ablation profile. The homogeneity of the scanning laser beam becomes less important in small-spot lasers than in broad-beam lasers because each of the spots is overlapped by a different spot. Specificity in ablation profile is theoretically increased, but in early models surgical times also increased significantly. There was also some difficulty ensuring proper distribution of the beam profile to the correct area of the cornea, as each treatment took longer and eyes are subject to saccadic movement or rotation during surgery.

A hybrid of the two types is called a variable-spot scanning laser, which allows for a change in the size of the beam delivered to the cornea as well as the ability to move the beam around to generate the ablation profile.

Aside from the beam type, different delivery systems also vary in the rate in which the laser beam is administered to the cornea. This is termed the pulse rate, or Hertz rate (Hz). Typically this will range from 3 to 200 Hz. Low Hz machines take more time and are undesirable in small-spot scanning lasers because no adjacent spots are treated consecutively. At extremely high frequencies, optics tend to degrade faster, and a problem particular to large beam profiles is that thermal effect increases as less time exists between pulses to allow for heat dissipation.

The majority of excimer lasers currently in use today are using small-spot or variable-spot scanning. Development of eye-tracking devices have drastically improved delivery of the beam to the desired location, as it was noted in early delivery systems using small-spot technology that small saccadic eye movements could alter the desired positioning of the beam. Increase in the delivery rate also decreased surgical time.

ABLATION PATTERN

For myopia, it is necessary for the cornea to receive more energy in the central portion of the cornea than it does in the periphery to create an overall flattening effect. This concentration of energy may be done in several different manners. The broad-beam lasers use some type of a masking device to protect the peripheral portion of the cornea from the laser energy while delivering a larger amount of energy to the central portion of the cornea.

Scanning-slit lasers such as the MEL-60 (Jena, Germany) preferentially ablate different areas of the cornea by using a handheld mask (Fig. 89.1). The flying-spot lasers such as the Bausch & Lomb Technolas 217z Zyoptix laser (Bausch & Lomb, San Dimas, CA) or the Allegretto Wave (WaveLight, Benoptinhagen, Germany) use computer control to preferentially place more spots in the center of the cornea than in the periphery for creation of myopic corrections. Comparisons of astigmatic capabilities are covered in another chapter.

The smaller beam lasers require a less powerful laser head as well as fewer optics to homogenize the beam. The scanning lasers, however, are dependent on an eye-tracking or coupling system. Because the surgeon cannot as accurately follow small saccadic eye movements when the laser is rapidly treating small areas on the cornea, computerized tracking of these small movements is more crucial. Also, because the spot size is much smaller, higher pulse rates are necessary to complete the ablation in a reasonable time.

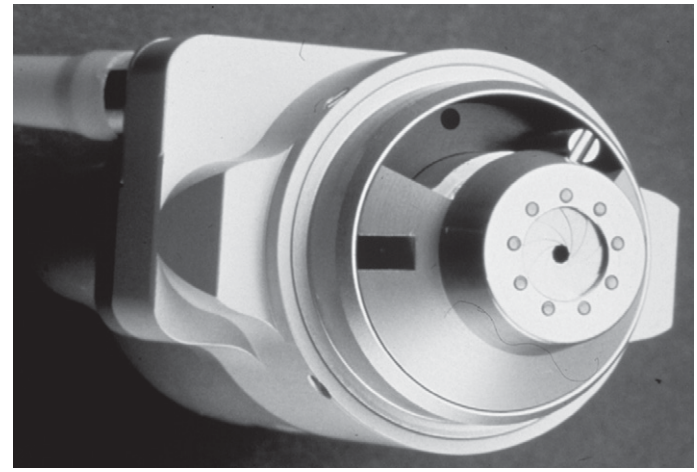

Figure 89.1. Handheld masks used by the Meditec MEL-60 slit scanning excimer laser (Meditec, Jena, Germany). The myopic mask constricts gradually during the treatment to allow more laser treatment to be applied to the central cornea. (Courtesy of Meditec, Jena, Germany.)

Because no one area is treated with two pulses in a row, any thermal energy created is allowed to dissipate between pulses.

VISX STAR LASER

The VISX Star S4 IR excimer laser system (VISX, Santa Clara, CA) is an advancement to the previous models of the VISX excimer lasers (Fig. 89.2). Notably the improvements have come from the integration of a wavefront system and improvements to ensure alignment of the eye-tracking system, which ensures accurate distribution of the laser treatment to the cornea. The Star S4 IR is a variable spot-scanning laser with spot size ranging from 0.65–6.5 mm. Using the WaveScan aberrometer in combination with the laser, surgeons may treat optical zones out to 7 mm using wavefront data and create blend zones as large as 9.5 mm. It also has variable repetition rate (VRR), which allows for variation in delivery times to specific and adjacent sites on the cornea, allowing for improved ejected tissue removal by the vacuum system and thermal dissipation on adjacent sites. The eye-tracking system is a camera-based iris registration (IR) system, which operates on a three-dimensional platform, allowing for adjustment along the *x*–and *y*-axis plus rotation.

The fluence is somewhat in the mid-range of other excimer lasers at 160 mJ/cm^2. The laser operates at speeds up to 20 Hz. A joystick on the control panel allows movement of the patient's bed up, down, to the left, or to the right (Fig. 89.3). The patient fixes on a red flashing He–Ne beam that is coaxial with the excimer laser beam in the standard treatments and aligned with the patient fixation on the WaveScan.

Currently in the USA, the VISX Star S4 IR combined with the WaveScan system is approved to treat up to 11.0 D of myopia, with or without up to 3.0 D of myopic astigmatism, mixed astigmatism up to 5.0 D, and up to 3.0 D of hyperopia with or without 2.0 D of astigmatism. The VISX laser is also being used in a mobile system developed by Laser Vision Centers, Inc. (TLCVision, St Louis, MO).

ALCON LADARVISION LASER

Alcon obtained FDA approval for LASIK with the Apex lasers, and a more recent laser model from Alcon is the LADAR 6000 (Alcon,

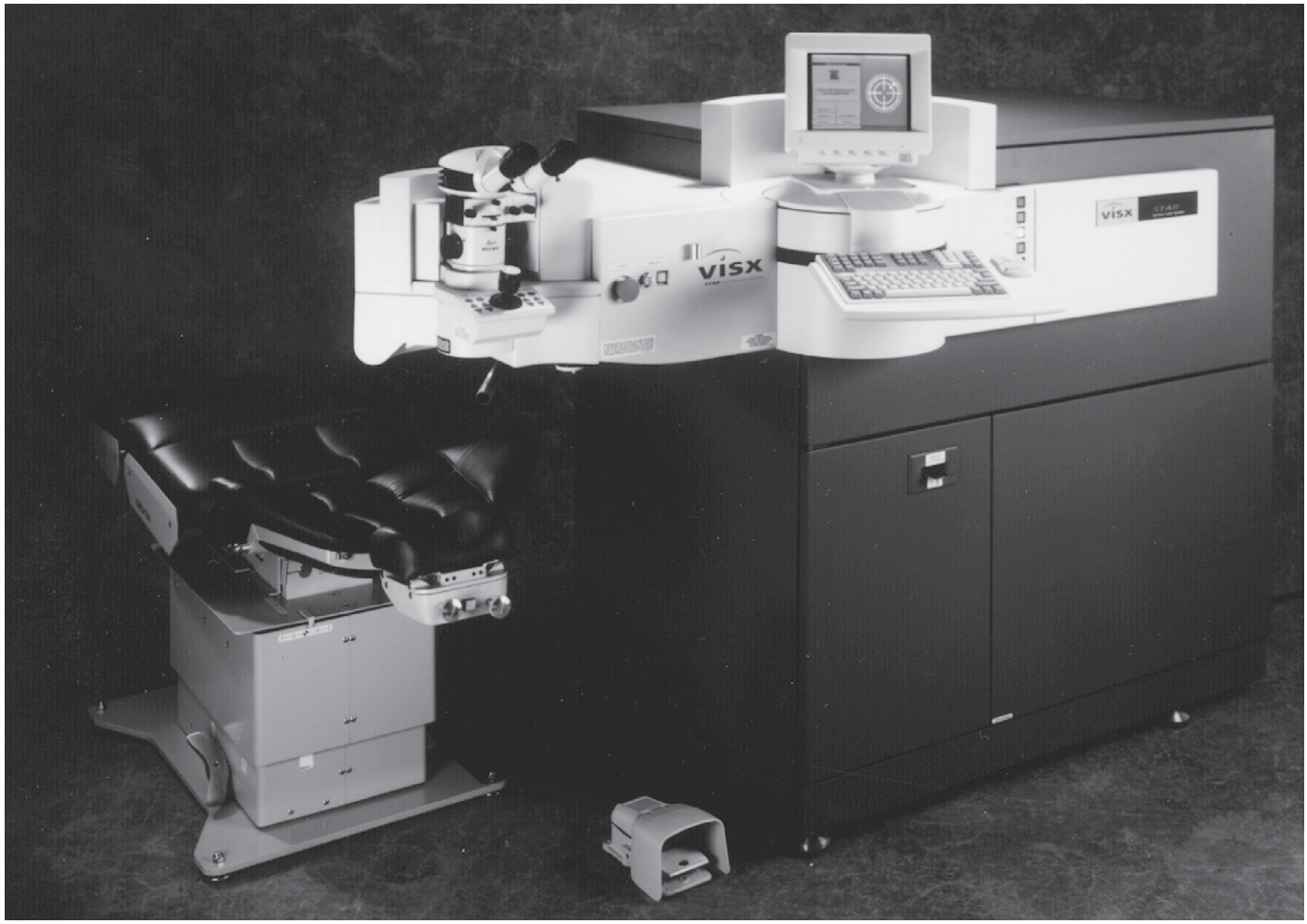

Figure 89.2. The VISX Star laser (VISX, Santa Clara, CA) incorporates a joystick-controlled bed with the excimer laser unit. (Courtesy of VISX, Santa Clara, CA.)

Figure 89.3. The control panel of the VISX Star laser (VISX, Santa Clara, CA) includes a joystick for moving the patient's bed, a Leica Wild microscope (Leica, Inc., Allendale, NJ) and controls for ring and oblique lighting. (Courtesy of VISX, Inc., Santa Clara, CA.)

Figure 89.4. The Alcon LADAR 6000 is a small spot laser with active tracking. (Courtesy of Alcon, Fort Worth, TX.)

Fort Worth, TX), which was developed as a flying small-spot laser (Fig. 89.4). The beam is 0.9 mm wide, has a Gaussian profile, and is fixed in size. It can be used with the CustomCornea software, which allows for wavefront correction. The CustomCornea program also couples the laser delivery with a four-beam infrared eye-tracker functioning at 100 Hz. This makes the tracking system capable of measuring subtle changes in eye position 4000 times/s.

The laser operates at a fluence of 2.7 mJ/cm^2 at the level of the cornea. The treatment rate is 93 Hz with the LADAR 6000 system, an improvement over the 63 Hz found in the LADAR 4000. Optic

zone size is typically 6.5 mm for myopia but can be extended to 9.0 mm (including blend zone) for hyperopia. Blend zone in myopic patients can extend to 11.5 mm.

The FDA has approved the LADAR 4000 and the LADAR 6000 for myopia up to −8.00 D with or without astigmatism up to −4.00 D, hyperopia up to +5.00 D with or without astigmatism of up to −3.00 D, and mixed astigmatism up to 5.00 D of cylinder correction.

ZEISS MEDITEC MEL-80 EXCIMER LASER

Zeiss Meditec (Jena, Germany; Dublin, USA) manufactures the MEL excimer laser. The most recently released model is the MEL-80 laser, which has been approved for use in the USA (Fig. 89.5).

The MEL-80 excimer laser is a small-spot scanning laser with a fixed spot size of 0.7 mm. It operates at a pulse rate of between 10 and 250 Hz. Each pulse duration lasts between 4 and 6 ns. Average fluence level at the cornea is kept in check by diluting the ArF mixture with helium gas. A blend zone can be created out to 10 mm.

A tissue-saving algorithm is used, which results in lower asphericity and preserves more of the corneal tissue for use on thinner corneas. The eye tracker is a high-speed camera-based system combined with an integrated iris-recognition system operating at 250 Hz, which does not require the patient to be dilated.

BAUSCH & LOMB TECHNOLAS EXCIMER LASER

The Technolas 217z with the Zyoptix wavefront system (Bausch & Lomb Surgical, San Dimas, CA) is a small-spot scanning system (Fig. 89.6). It uses a small-size spot with integration of the Zyoptix wavefront software program for treatment of myopia, astigmatism, and hyperopia.

The laser delivery system runs at 50 Hz, with pulse duration of 18 ns. The Technolas 217 laser incorporates an eye tracker with a camera-based iris-recognition system, which runs at 120 Hz. The patient does not need to be dilated to use the eye-tracking system.

The Technolas 217z is approved for myopic LASIK treatments up to −11.00 D with or without astigmatism less than −3.00 D. For hyperopic LASIK, treatments between +1.00 and +4.00 D can be performed with or without astigmatism up to +2.00 D. The 217z incorporates a wavefront system and is approved for myopic LASIK up to −7.00 D with or without astigmatism up to −2.0 D.

NIDEK EC 5000 CX SERIES LASER

The Nidek EC 5000 CX series laser (Nidek, Inc., Fremont, CA) is utilized with the Nidek NAVEX Quest system, which is marketed by

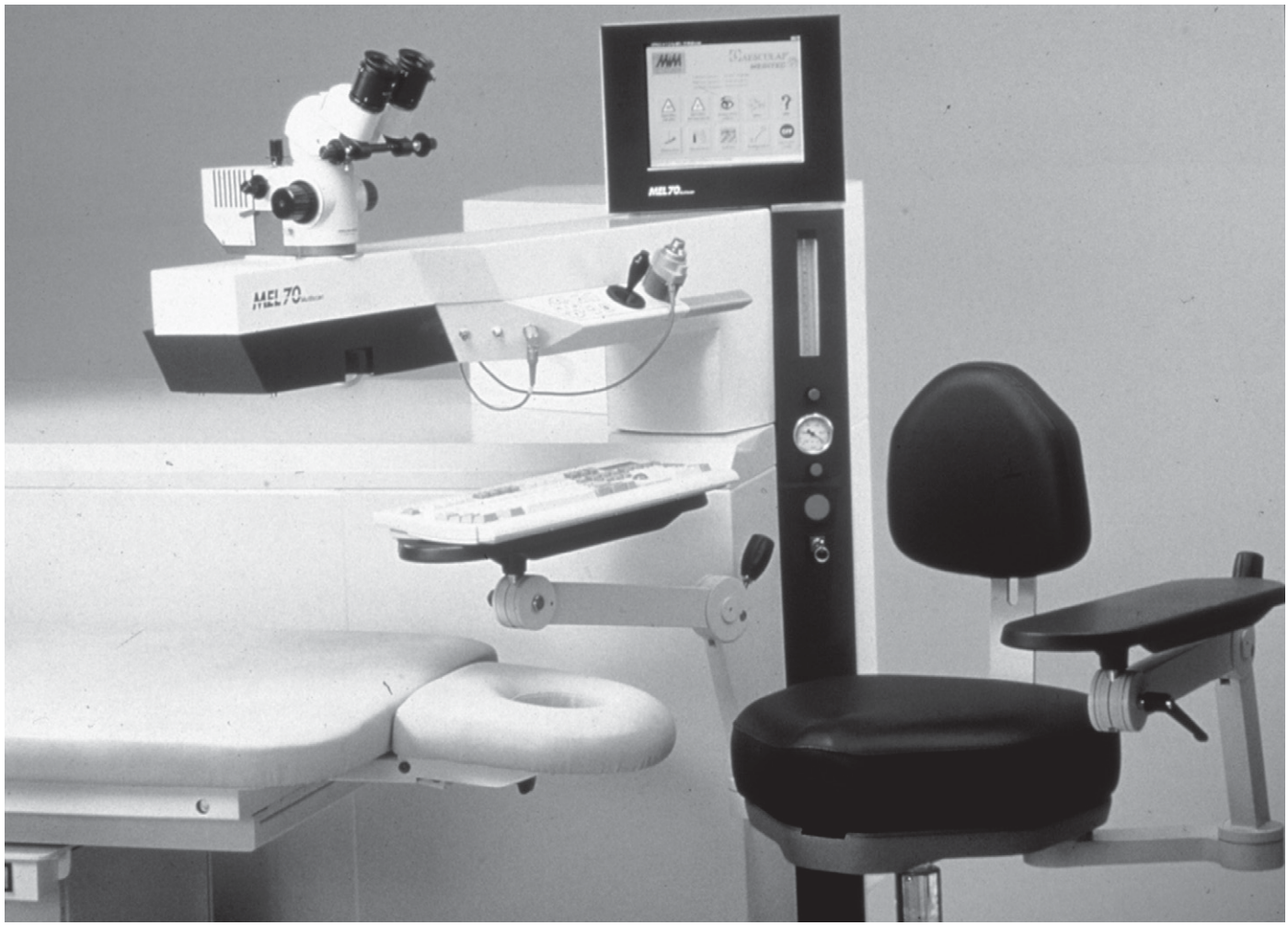

Figure 89.5. The Aesculap-Meditec MEL-80 laser (Aesculap-Meditec, Jena, Germany) has a small flying spot that scans across the cornea for myopic, hyperopic, and astigmatic treatments. (Courtesy of Aesculap-Meditec, Jena, Germany.)

Figure 89.6. The Bausch & Lomb-Technolas 217z Excimer laser with Zyoptix wavefront uses scanning laser technology to treat myopia, hyperopia, and astigmatism. (Courtesy of Bausch & Lomb, Rochester, NY.)

Nidek as a complete refractive surgery package. While the Quest system has not gained approval by the FDA in the USA, the CXII has gained approval status and is available for treatment of myopia and myopic astigmatism. The laser uses a rotating scanning slit to deliver the laser energy. It operates at between 5 and 50 Hz with a pulse duration of 10–25 ns. Fluence averages 360 mJ/cm^2. The laser has an eye-tracking system that operates at 200 Hz and has a torsion control to correct for intraoperative cyclotorsional movement of the eye.

Nidek has FDA approval for the EC 5000, and the CX and CXII systems in the USA but does not have approval for the CXIII as of this writing (Figs. 89.7 and 89.8). Approval for PRK is for treatment of myopia from −0.75 to −13.00 D, and myopic astigmatism from −1.00 to −8.00 spherical equivalents with no more than −4.00 D of cylinder. The FDA has also granted approval for LASIK treatment of myopia from −1.00 to −14.00 D spherical equivalent with no more than −4.00 D of cylinder. Hyperopia has been treated internationally, and the results are still being investigated by the FDA in the USA. This laser is also not yet approved for PTK in the USA.

WAVELIGHT ALLEGRETTO WAVE LASER

WaveLight (Erlangen, Germany) manufactures the Allegretto Wave laser, which is approved in the USA for LASIK treatments of up to −12.00 D of myopia with or without astigmatism up to −6.00 D, and for hyperopic LASIK treatments of up to +6.00 D with or without astigmatism up to +5.00 D. The Allegretto Wave can also treat mixed astigmatism up to 6.00 D. Approved in July 2006 by the FDA is the Wave-Q laser, which is approved for the same parameters of treatment as the Wave, with the exception of mixed astigmatism.

The laser is comprised of a small-spot scanning laser with a fixed spot size of 0.95 mm. Beam profile is Gaussian. The laser operates at a pulse rate of 200 Hz. Fluence at the level of the cornea is measured at 130–140 mJ/cm^2. This system does not use a gas dilution system to control fluence. Instead, the Wave uses a nitrogen-purged optical rail, which reduces the amount of ozone produced during firing of the laser. Optical zones can extend out to 8 mm, with blend zones out to 10 mm.

The eye-tracking system is a camera-based iris-recognition system operating at 200 Hz. Software for the laser also uses a slightly different ablation algorithm, which accounts for normal corneal asphericity, enabling it to minimize spherical aberration and resultant glare or halo.

STUDIES

ALLEGRETTO LIGHT WAVE

FDA clinical trials for myopia and myopic astigmatism were performed with 1-year data available on 780 eyes. Results showed an uncorrected visual acuity of 20/20 or better in 87% of eyes. Loss of two or more lines of best-corrected visual acuity did not occur.

A study appeared in peer-reviewed literature involving 120 patients who were treated for hyperopia or hyperopic astigmatism.[1] They were first divided into three groups based on the degree of refractive error. In the low group (hyperopia 0.00 to +3.00 D and astigmatism <1.00 D; $n = 52$), 92% were within 0.50 D of goal refraction. In the moderate group (hyperopia +3.25 to +5.00 D and astigmatism <1.00 D; $n = 45$), 79% were within 0.50 D of goal refraction. The high hyperopia/toric group (hyperopia >+5.25 D or astigmatism ≥1.25 D) showed 71% of patients achieving within +0.50 D of intended refraction. The high group also noted an increase in higher-order aberrations from 0.47 to 0.94 µm.

In another study, 22 patients underwent LASIK enhancement for residual myopia, hyperopia, mixed astigmatism, or night vision

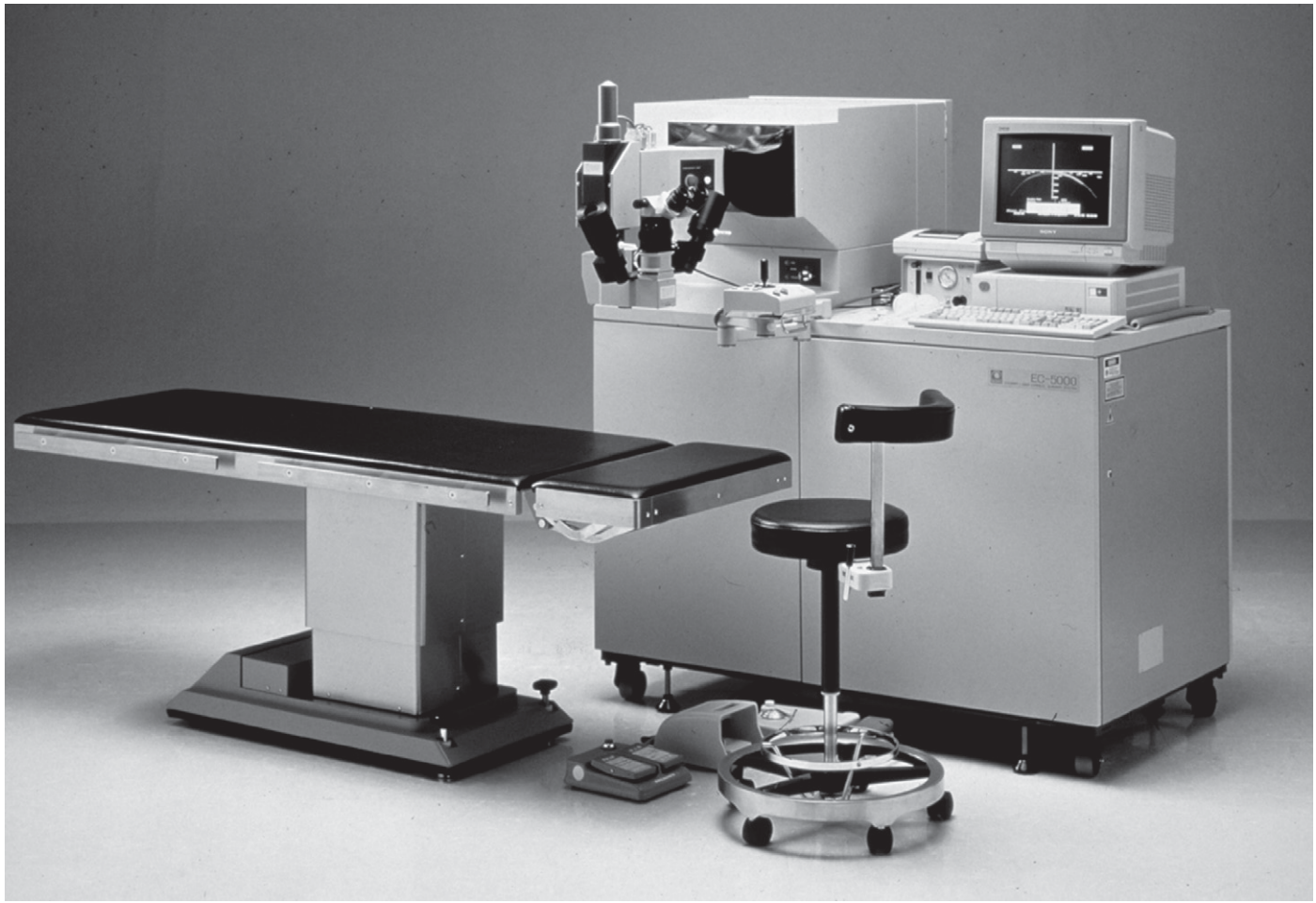

Figure 89.7. The Nidek EC 5000 Excimer laser (Nidek, Japan) uses a scanning slit to create myopic, hyperopic, and astigmatic ablations. (Courtesy of Nidek, Fremont, CA.)

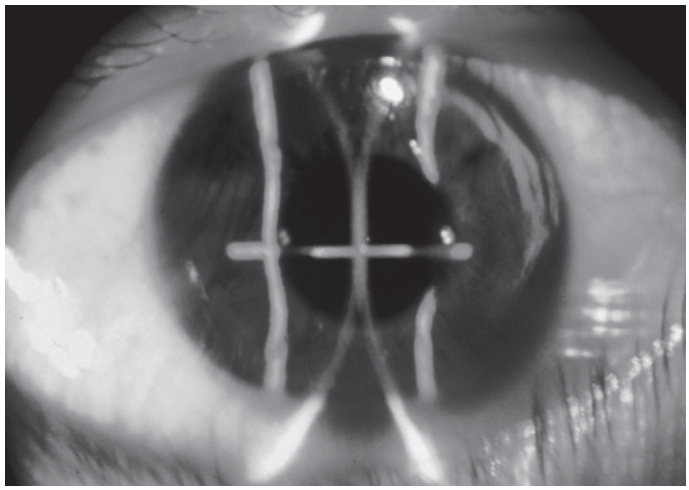

Figure 89.8. The Nidek EC 5000 (Nidek, Fremont, CA.) uses matching projected light images to obtain centration. (Courtesy of Nidek, Fremont, CA.)

problems.[2] All patients postoperatively were within 0.50 D of intended refraction. Mean preoperative BCVA was 20/25 (+0.12), and mean postoperative BCVA was 20/18 (+0.1). No loss of BCVA occurred in any patients. Interestingly, the root mean square (RMS), as an indicator of optical pathways, decreased from 1.04 (+0.22) to 0.46 (+0.14) μm.

VISX STAR S4 WAVESCAN CUSTOMVUE

A retrospective study of 140 eyes that had undergone LASIK for myopia and myopic astigmatism using the VISX CustomVue laser software was performed.[3] Mean preoperative spherical equivalent power improved from −3.89 (+1.48) to −0.21 D (+0.36) at 1 month and to −0.28 D (+0.36 SD) at 3 months. UCVA was measured at 20/20 or better in 84.3% of eyes at 1 month and in 87.9% of eyes at 3 months; 86% of eyes at 1 month and 81% of eyes at 3 months were within +0.50 D of intended goal. RMS values increased slightly from 0.28 (+0.08) to 0.34 (+0.11) μm at 3 months.

Another retrospective study examining the efficacy of the VISX CustomVue treatment for use in enhancements on eyes that had undergone previous keratorefractive surgery was performed.[4] The vast majority (119) of the 120 eyes studied had previously undergone LASIK. Three-month data were obtained. Goal refraction was emmetropia. At 3 months, mean refractive error was −0.20 D, with 100% of eyes being within +0.75 D of intended refraction. RMS values were reduced from 0.39 to 0.34 μm.

In another study, 277 eyes were treated for low to moderate myopia using the VISX S4 laser at six centers around the USA and were available for follow-up at 6 months.[5] UCVA was achieved in 94% of eyes, and 74% of eyes obtained UCVA of 20/16 or better. In this study, 69% of eyes had the same or better postoperative UCVA as their preoperative best spectacle-corrected acuity (BSCVA). Additionally, 90% of eyes were within +0.50 D of intended goal. No

statistically significant ($p < 0.05$) change in higher-order aberrations was noted.

ALCON LADARVISION

A comparison of traditional versus wavefront-guided LASIK was performed on the Alcon LADARVision system.[6] One-hundred forty myopic eyes with maximum level of 7.00 D and maximum astigmatism of less than 2.50 D were assigned to treatment with one of the two systems. At 3 months, 80% of CustomCornea patients had uncorrected vision equal to or better than 20/20, whereas only 45% of the traditionally treated eyes had that level of acuity. In the CustomCornea and traditional treatment groups, 85 and 55% of eyes were within +0.50 D of desired outcome, respectively. Eyes in the CustomCornea group also had statistically significant lower levels of higher-order aberrations ($p < 0.05$).

A recent study examining the results of the LADARVision 6000 for the treatment of myopia and myopic astigmatism was performed.[7] Of the 74 eyes participating, 46 eyes were treated using wavefront-guided software and 28 were treated using conventional methods. At 3 months 93.5 and 89.3% of eyes were within +0.50 D of intended correction in the wavefront-guided and conventional treatment groups, respectively. UCVA of 20/20 or greater was obtained in 97.8 and 92.9% of wavefront-guided and conventional treatment, respectively.

A retrospective, nonrandomized study assessing outcomes on enhancements using the LADARVision 4000 was performed on 97 eyes, which had residual myopia and myopic astigmatism.[8] Conventional LASIK treatment was performed in 74 eyes, and 23 received wavefront-guided treatment with CustomCornea software. Mean pretreatment spherical equivalent was –0.93 D in the conventional treatment group and –0.84 D in CustomCornea group. Post-treatment results (mean follow-up 8.9 months) was –0.19 D in the conventional treatment group and +0.32 D in wavefront-guided group. UCVA of 85 and 35% of eyes was 20/20 or greater in the conventional and wavefront-guided groups, respectively.

ZEISS-MEDITEC MEL-80

Seventy-six eyes with myopia and myopic astigmatism underwent LASIK using the MEL-80 laser.[9] Follow-up data were available to 1 year. Mean uncorrected visual acuity improved from 20/20 preoperatively to 20/18 postoperatively. Ninety-six per cent of eyes were within 0.50 D of intended refractive correction at 1 year. Mean RMS higher-order aberrations increased slightly from 0.20 to 0.28 μm.

Fifty eyes were treated for myopia and myopic astigmatism using aspheric profile PRK on the MEL-80 laser, and 24 eyes were treated using standard PRK ablation profile on the MEL-70.[10] Data were evaluated after 6 months. Postoperatively, there was a greater increase in higher-order aberrations in the traditional PRK group ($p < 0.01$), and a higher percentage of patients in the aspheric treatment group performed better on low-contract visual acuity ($p < 0.05$).

A retrospective study was performed using the MEL-70 laser to examine results of hyperopic correction using PRK and LASIK.[11] One hundred eyes were examined in the PRK group with a mean preoperative correction of +2.85 D, and 100 eyes in the LASIK group with a mean preoperative correction of +4.49 D. Two-year follow-up data were obtained. In the PRK group, mean refractive error was +0.34 D, and 36% of eyes were within +0.50 D of emmetropia. In the LASIK group, mean refractive error was +0.29 D and 70% were within +0.50 D of emmetropia.

NIDEX EC 5000

A retrospective study examining the efficacy of the Nidek EC 5000 CXII system was performed on 100 eyes that had undergone LASIK for myopia and myopic astigmatism. Customized aspheric transition zone profile was used.[12] Preoperative mean correction was –4.70 ± 2.53 D. At 6 months this decreased to 0.12 + 0.53 D. Uncorrected visual acuity was 6/6 or better in 58% of eyes.

Treatment of hyperopia and hyperopic astigmatism using the EC 5000 CXII laser was also performed with three optical zone sizes.[13] A total of 161 eyes, which underwent hyperopic correction with a 7.0 mm optical zone, were examined retrospectively versus control eyes, which used 5.5 and 6.5 mm optical zones. Results showed improved average refractive results and increased stability with increasing optical zone size.

Effectiveness of treatment of mixed and simple myopic astigmatism using the EC 5000 laser was demonstrated using a retrospective study.[14] Forty eyes were examined with data extending to 6 months. Mean postoperative manifest spherical equivalent refraction was +0.30 + 0.46 D. A 77.8% decrease in the magnitude of the cylinder component was present at 6 months, and 50% of eyes were within +0.50 D of intended goal refraction.

COMPARATIVE STUDIES

Several studies comparing laser platforms have been published. Unfortunately, most of these were either not prospective and randomized or utilized older versions of laser hardware or software. These types of studies are difficult to do well because of the rapidly changing technology but are still important.

MEL-70 VS VISX S2 FOR HYPEROPIA AND HYPEROPIC ASTIGMATISM

The right eyes of 43 patients with hyperopia and hyperopic astigmatism were randomly assigned to have LASIK surgery with either the VISX S2 or the Meditec MEL-70 laser, to evaluate increases in corneal aberration.[15] Data were evaluated at 6 months. There were no statistically significant differences in the amount of increase in either group.

LIGHTWAVE VS LADARVISION WITH CUSTOMCORNEA FOR HIGHER-ORDER ABERRATIONS

Thirty patients undergoing bilateral LASIK were randomly assigned to either the Allegretto LightWave laser or to the Alcon LADARVision using CustomCornea software.[16] Of all patients in both groups 90–93% were within ±0.50 D of desired postoperative goal. Subjects who underwent LASIK with the Alcon laser had statistically significant lower amounts of higher-order aberrations ($p < 0.05$).

NIDEK EC5000 VS ALCON LADARVISION4000 FOR LOW TO MODERATE MYOPIA

A retrospective study comparing outcomes on these two lasers was performed on patients who had undergone LASIK for low to

moderate myopia.[17] Results were examined at 6 months. No statistically significant difference in results was obtained with these two systems.

VISX S3 VS TECHNOLAS 217 FOR LOW TO MODERATE MYOPIA

A prospective, randomized trial was performed on patients with low to moderate myopia. Patients were randomized to have surgery on one eye with the VISX laser and on the other with the Technolas.[18] One hundred and forty eyes were enrolled and data were examined at 6 months. No statistical difference was revealed in outcomes on BSCVA or UCVA between groups. RMS of higher-order aberrations was slightly higher in the VISX group (+0.07); however, no subjective difference in satisfaction between eyes was reported by patients.

ALCON LADARVISION 4000 VS VISX STAR S2 FOR BOTH MYOPIA AND HYPEROPIA

A retrospective analysis of 572 sequential LASIK surgeries performed by a single surgeon was performed.[19] The first group consisted of 286 eyes, which were done on the VISX S2 platform. The second group consisted of another 286 eyes, which were performed on the LADARVision 4000. Results were also examined along preoperative ametropia type, and data were evaluated at 3 months. Myopic eyes with uncorrected visual acuity equal to or better than 20/20 were 89% on the LADARVision platform and 63% on the S2. Also for myopia, percentage of patients within +0.50 D of intended correction were 84 and 80% with the LADARVision and S2, respectively. Hyperopic eyes at 3 months showed 74 and 33% for uncorrected visual acuity equal to or better than 20/20 and 69 and 74% were within +0.50 D of intended correction on the LADARVision 4000 and S2, respectively.

DISCUSSION

While there are inherent differences in ergonomics and technical aspects of each laser system, empirically all the excimer laser platforms perform quite well and meet the FDA standards for safety and efficacy. The advances in technology improving ease of use and customization of treatment for each patient seem to be applied in time across most excimer laser systems. It is important for the surgeon to keep up with continued advances and find a system that is flexible and comfortable to use and that provides the best fit for the needs of the surgeon's practice.

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90 Tracking and registration

Natasha L. Herz, Li Wang, Douglas D. Koch

Accurate eye tracking and registration are required for optimal results when applying wavefront-guided laser refractive surgery to the cornea. Because the custom ablation profile is highly specific, it must be applied to the cornea only after achieving precise alignment to the area that was mapped. To optimize this, technology is needed that (1) can identify reliable landmarks in order to link the measured wavefront to the corresponding area on the cornea and (2) can track them as the eye continually moves throughout the treatment.

A well-centered treatment ultimately requires good fixation by the patient. However, natural eye movements and improper fixation cannot be avoided during refractive surgery. Active eye tracking systems were introduced to compensate for these movements in order to decrease the incidence of decentered ablations.

With the emergence of wavefront-guided corneal ablation, one more potentially important step, registration, has been introduced. Registration is the process that links the measured wavefront to the treatment ablation profile on the laser platform, thereby facilitating accurate positioning of the ablation pattern on the cornea. Registration can occur initially at the beginning of surgery but ideally would be an active part of the tracking process to compensate for any eye rotation and pupil size changes that might occur during laser ablation.

This chapter discusses eye tracking and registration with wavefront-guided corneal ablation. The status of eye tracking and registration with four major laser systems is reviewed.

EYE TRACKING

EYE MOVEMENTS

The major eye movements that occur physiologically during fixation for refractive surgery are slow drifts, microsaccades, and tremors.[1] Moving the eye to a new fixation location is a voluntary movement called a saccade. The average velocity of saccades is about 200°/s with peaks up to 500°/s and amplitudes up to 15°.[2]

Schwiegerling and Snyder[3] measured eye motion in patients having laser in situ keratomileusis (LASIK) using a video technique and determined centration and variance of the eye position during surgery. They found the mean centration of the pupil center during the surgery to be within 0.25 ± 0.1 mm of the laser axis.

Porter et al[4] studied offsets and eye movements of 10 eyes during laser refractive surgery and computed the temporal power spectrum of the measured eye movements. The temporal power spectrum takes into account the average incidence, velocity, and amplitude of the eye movements during refractive surgery to determine the necessary closed-loop bandwidth required of an eye-tracker to compensate for them during a conventional or customized procedure. Ninety-five percent of the total power spectrum of the eye movements was contained in temporal frequencies up to 1.4 Hz in the horizontal direction and approximately 0.6 Hz in the vertical direction. More than 99% of the total power spectrum was accumulated in temporal frequencies up to 5.1 Hz in both directions. These results indicate that the majority of eye movements that occur during refractive surgery are caused by relatively slow drifts in eye position.

EYE TRACKING TECHNIQUES

Most tracking systems used in excimer lasers are video-based and track the pupillary margin. These systems capture images of the eye at a certain frequency and then process these images to determine where the laser shots need to be fired to compensate for lateral and rotational shifts of the center of the entrance pupil.

A laser radar eye-tracking system is used by the Alcon LADARVision platform (Alcon Surgical Inc., Fort Worth, TX). This system consists of four 905 nm diode laser sensors that are built into the laser head. These four lasers are aimed at the pupillary margin at the 1:30, 4:30, 7:30, and 10:30 positions. Each of these diode lasers fires at 4000 Hz. As movement of the eye is identified, the mirrors that redirect the excimer laser move in order to compensate for any movement of the eye. In order for the tracker to function optimally, the pupillary margin needs to be stable, which is achieved by dilating the eye pharmacologically.

The sampling rate of the required eye tracking system is primarily determined by the repetition rate of the laser. Based on

the findings by Porter et al,[4] an eye-tracking system with a 1.4 Hz closed-loop bandwidth could compensate for most pupil decentrations that occur during a conventional or customized laser refractive surgery. In general, an eye-tracker would have to sample at least 10–20 times faster than this closed-loop bandwidth, or at 15–30 Hz, to have a sufficient latency time to correct for these movements.[4]

The accuracy of the pupil tracking system depends on several factors:

1. **The contrast between the pupil and the iris provided by the illumination.** Taylor et al[5] examined a pupil tracking system and found an accuracy of 0.06 mm for an intact cornea and 0.1 mm for a cornea with a thin flap removed such as occurs in LASIK.
2. **Parallax.** Geometric parallax occurs when the center of the tracking camera, the center of the pupil, and the corneal apex are no longer aligned. Bueeler et al[6] investigated the theoretical limitations derived from parallax and found that pure lateral shifts of the eye under the tracking device can cause localization errors up to 3% of the detected pupil entrance shift. For ocular rotations, the tracking error can be up to 30% of the detected lateral shift in eyes with a high axial length. These results were calculated for a 500 mm distance of the tracker from the eye. Higher tracking errors result as the camera comes closer to the eye and the axial length of the eye increases.
3. **Processing delay or latency time.** The latency time is determined from the point that the eye position is measured to the time that the laser is adjusted. Eye movements could occur during this latency time. For current laser systems, the latency time ranges from 2–90 ms.[7] The magnitude of latency time that is acceptable is dependent on the frequency and magnitude of eye movements during surgery. Minimum processing delay should be achieved to stabilize the laser at the planned ablation position.

REGISTRATION

With wavefront-guided ablations, tracking the pupil alone during the laser ablation is not enough to predictably correct higher-order aberrations. Wavefront-guided procedures require accurate registration of the treatment ablation profile to the area on the cornea over which the wavefront aberrations have been measured. Sources contributing to the registration error include pupil centroid shift and cyclotorsional rotation of the eye.

PUPIL CENTROID SHIFT AND CYCLOTORSIONAL ROTATION

The pupil centroid shifts in different lighting environments.[8,9] This is relevant to excimer laser corneal ablation since, during the wavefront measurement, the lighting is mesopic whereas, during laser treatment, photopic lighting is typically used. Cyclorotational movements of the eye can occur when body orientation changes from seated to supine, such as occurs between wavefront measurement and surgery.

In 64 eyes of 40 patients treated using the Iris Registration (IR) feature of the VISX Star S4 laser system, Koch and Wang in 2005 (unpublished data) found that the pupil centroid shifted by 0.27 ± 0.14 mm (range 0.04–0.51 mm) and cyclotorsional rotation occurred by 2.1 ± 1.5° (range 0.0–6.6°). Similar findings have been reported in the literature[10–13] (Tables 90.1 and 90.2).

Table 90.1 Pupil centroid shift studies: mesopic to photopic lighting

Study	Eyes	Mean Movement (mm)	Other (mm)
Koch et al[a]	64	0.27 ± 0.14	range 0.04–0.51
Porter et al[10]	65	0.29 ± 0.14	
Yang et al[11]	70	0.13 ± 0.07	

[a] Unpublished data presented at the American Academy of Ophthalmology 2005.

Table 90.2 Cyclotorsional movement studies: upright to supine positions

Study	Eyes	Mean Movement (°)	Other (°)
Koch et al[a]	64	2.1 ± 1.5	Range 0–6.6
Chernyak et al[20]	51	2.2 ± 2.0 excylco	
Swami et al[13]	240	4.1 ± 3.7	8% > 10

[a] Unpublished data presented at the American Academy of Ophthalmology 2005.

IMPACT OF PUPIL CENTROID SHIFT AND CYCLOTORSIONAL ROTATION

Significant reduction in quality of vision occurs when ablation is decentered by 0.2 mm or more[14,15] (Fig. 90.1). The impact of error induced from cyclotorsional movements on the residual point spread function and eye chart letters is shown in Figure 90.2.[16]

Studies by Mrochen et al[17] and Verdon et al[18] showed that decentrations as small as 0.2 mm significantly increase wavefront aberrations and thus decrease the quality of the retinal image. Studies by Bara et al[14] and Guirao et al[15] concluded that lateral displacements begin to be clinically significant when they exceed 0.05–0.1 mm. This agrees with a theoretical study by Bueeler et al[19] where lateral precision of 0.07 mm or better would be necessary to achieve a diffraction-limited retinal image in 95% of normal eyes with a 7 mm pupil. An accuracy of 0.2 mm was required to reach this goal with a 3.0 mm pupil.

To investigate which of these two sources of error had the greatest clinical impact, we evaluated the wavefront aberrations that theoretically would be induced if the ablation was decentered by the mean amount of cyclotorsion and pupil centroid shift found in our study group. To study this, we selected 50 corneal maps of eyes that underwent excimer laser corneal ablation. We used these to do a theoretical ablation with rotation of 2.1° counter-clockwise and a horizontal pupil centroid shift of 0.27 mm, respectively. Using the VOL-CT program (Sarver and Associates), residual wavefront aberrations root-mean-square (RMS) value and Strehl ratio (6 mm pupil) were calculated. In a perfect treatment, the RMS value is 0 and the Strehl ratio is 1. In an imperfect ablation, the RMS value is >0 and the Strehl ratio is <1.

The results of the study showed that total RMS, lower-order RMS, and higher-order RMS values were higher with decentration than with rotational misalignment (Fig. 90.3). The same was true for the

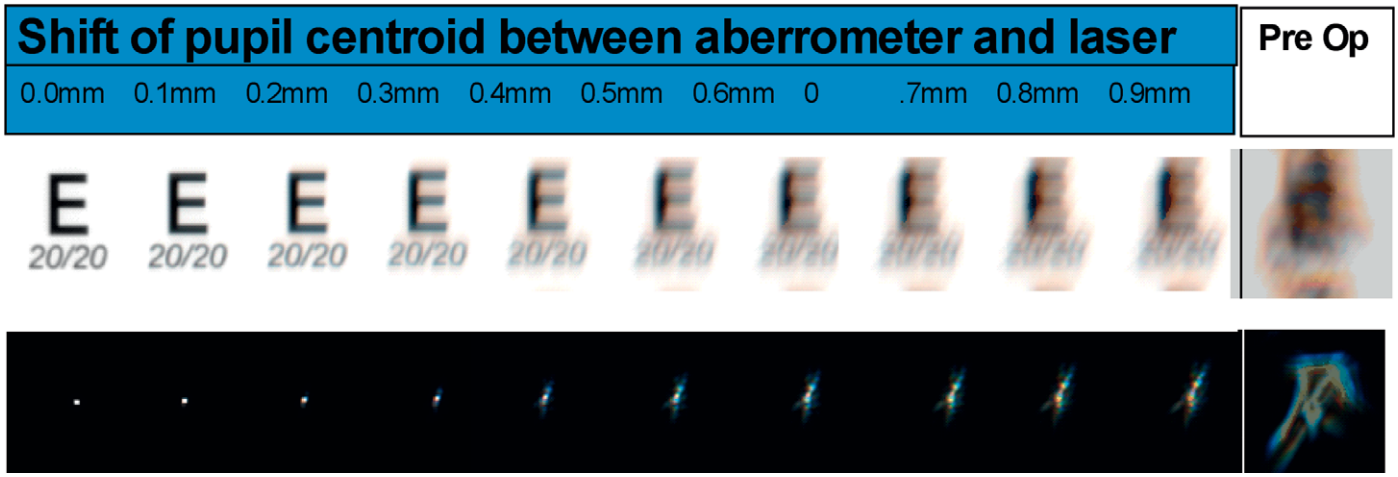


Figure 90.1. The deterioration in the point spread function (PSF) and the appearance of a 20/20 letter 'E' as a function of increasing pupil centroid shift, assuming a 6 mm pupil and using the convolution operation to generate the appearance of the letter chart.[22]

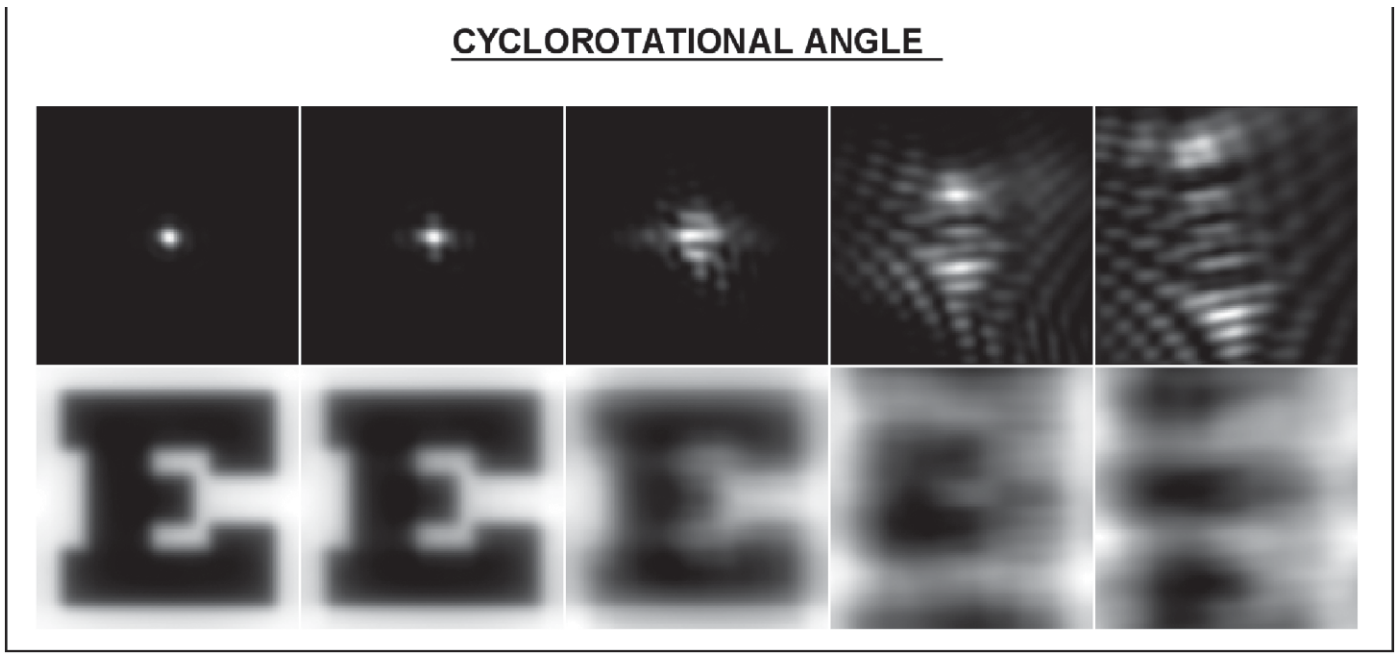


Figure 90.2. Error induced from cyclotorsional movements illustrated by the residual PSF and blurred eye chart letters in an eye with a refractive error of –0.15 DS –1.01 DC × 0°.[22]

Strehl ratio, which was less ideal for pupil centroid shift than it was for rotational misalignment (Table 90.3). Significantly lower Strehl ratio values were induced by decentration of the pupil centroid ($p < 0.001$). This meant the decentered ablations had more aberrations and thus more adverse effect on visual outcome than did the rotational misalignments. With increasing amount of astigmatism, the Strehl ratio values decreased significantly (Fig. 90.4). Once the magnitude of astigmatism was greater than or equal to 2 D, the induced error for rotational misalignment was comparable to that of a decentered ablation.

In another cohort of consecutive cases of 58 eyes treated with the VISX Star S4 IR, based on IR data recorded on the surgical sheet for each eye, residual ocular wavefront aberrations were calculated with cyclorotational error and pupil centroid shift, respectively. Similarly, pupil centroid shift induced significantly higher total RMS and higher-order RMS than did cyclotorsional rotation of the eye. Second-order astigmatism was the largest residual aberration induced by cyclotorsional rotation, whereas coma (third- and fifth-order) was the largest residual aberration induced by pupil centroid shift.

Despite these clear theoretical advantages of compensation for cyclorotational error and pupil centroid shift, we are unaware of clinical studies that validate their importance. However, as laser technology progresses both will almost certainly be essential components of more sophisticated ablation methodologies.

REGISTRATION TECHNIQUES

New technology has been developed to account for pupil centroid shift as well as cyclotorsional rotation. It measures the center of the

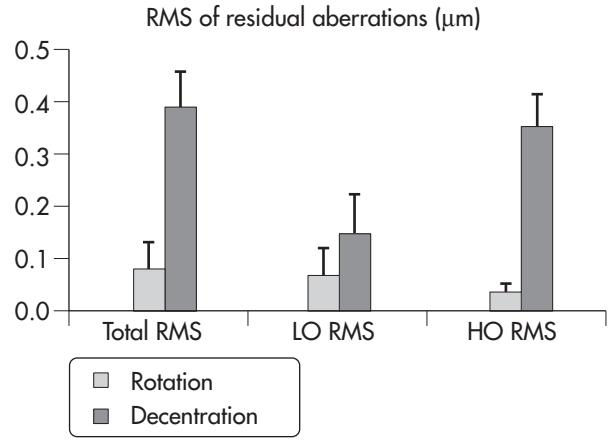


Figure 90.3. In Wang and Koch's study, significantly higher RMS values were induced by decentration of the pupil centroid compared to rotational misalignment (All $p < 0.001$).

Table 90.3 Strehl ratio values induced by rotation and decentration of the pupil centroid in the study by Wang and Koch

	Rotation (2.1°)	Decentration (0.27 mm)
Mean	0.79	0.40
SD	0.17	0.09
Range	0.34–0.98	0.28–0.75

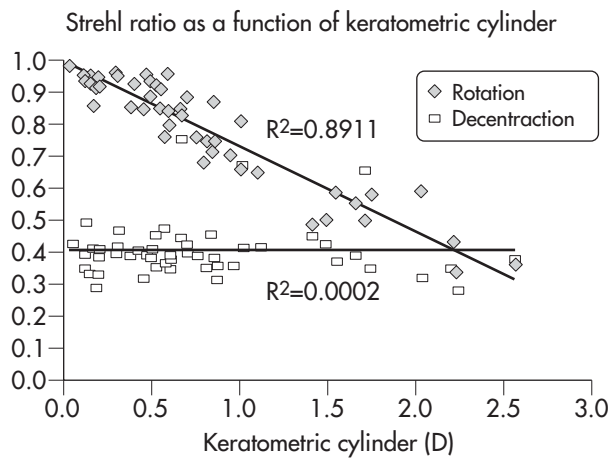


Figure 90.4. In Wang and Koch's study, when astigmatism was greater than or equal to 2 D, the reduction in Strehl ratio was comparable to that induced by pupil centroid shift.

pupil in relation to the limbus or peripheral iris at the time the wavefront measurements are taken and then calculates the adjustment needed at the time of surgery to keep the treatment centered over the original location of the pupil center. It also adjusts for any cyclotorsion that may have occurred during shifting of body orientation from seated to supine. Some systems actively track this during the treatment, while others adjust for it statically before the laser is applied.

REVIEW OF EYE TRACKING AND REGISTRATION WITH DIFFERENT LASER PLATFORMS

AMO-VISX STAR S4 IRIS REGISTRATION EXCIMER LASER SYSTEM

The VISX Star S4 laser system by Advanced Medical Optics has two infrared video-based cameras placed at 90° to each other. Together, they track in the *x*, *y*, and *z* axes. It is an open-loop system that samples at a rate of 60 Hz. Since the laser fires at a rate up to 20 Hz, it acquires a minimum of three consecutive good samples before it allows the laser to fire.

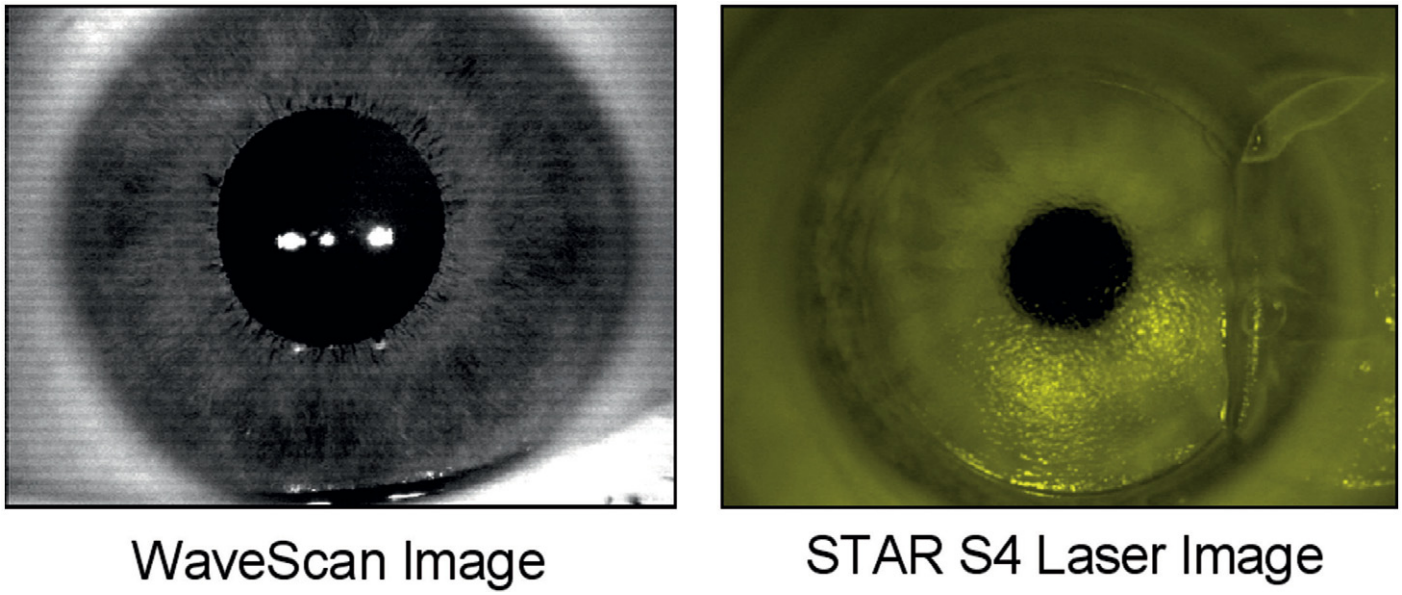
To account for cyclotorsion and pupil centroid shift, the laser uses iris registration software that matches 24 landmarks on the Star S4 IR laser iris image to the 24 landmarks on the WaveScan® iris image (Fig. 90.5, *A–C*). One landmark for each 15° iris sector in each image is identified. A minimum of 21 of the 24 landmarks must match in order to use this feature. The laser also determines the location of the outer iris boundary and determines the centroid of the entrance pupil relative to this landmark. The registration process is typically performed immediately before initiating laser ablation. The laser corrects for cyclotorsional error by internally rotating the ablation. To correct for error introduced by pupil centroid shift (Fig. 90.6, *A–D*), the laser uses the outer iris boundary to shift the center of the ablation from the intraoperative center of the pupil to the centroid of the preoperative WaveScan measurement. Therefore, regardless of location of the pupil centroid at the start of the laser treatment, the ablation pattern is centered over the pupil centroid at the time of wavefront measurement (Courtesy, in part, by Paul Bradford, Technical Support Supervisor-LVC, AMO, Inc.).[12,16,20]

At times, especially with lighter pigmented irides, the software is unable to match the required number of landmarks. It is estimated to occur in less than 10% of eyes.

LADARVISION4000 AND LADAR6000 EXCIMER LASER SYSTEMS

The LADARVision®4000 and LADAR6000™ Systems produced by Alcon use a closed-loop laser radar tracker to track the pupil. Its signal processing time allows minimal latency between acquiring position data and determining where the laser should fire. The tracker samples the position of the eye at 4000 Hz and the system moves to compensate for positional errors at that rate. In order for a closed-loop system to be stable, it must have a sampling rate about 10 times the bandwidth. The LADAR tracker meets this requirement with a sampling rate of 40 : 1.

To register the eye and account for cyclotorsional effects, these systems use the pupil, limbus, and a pair of opposing ink marks on the sclera. For the LADARVision4000 laser, the first step in obtaining an ablation treatment pattern from the LADARWave aberrometer is capturing a photo of the undilated eye. This is used as a reference for the center of the undilated pupil from the limbus. The second step is to obtain five wavefronts of the eye after dilation. This is performed after the ink marks have been placed on the sclera so that the wavefronts can be accurately matched to each other (Fig. 90.7, *A* and *B*). The best three are used to create a composite wavefront for the treatment. This is exported to the laser along with the photo for centration. At the time of surgery, the centration



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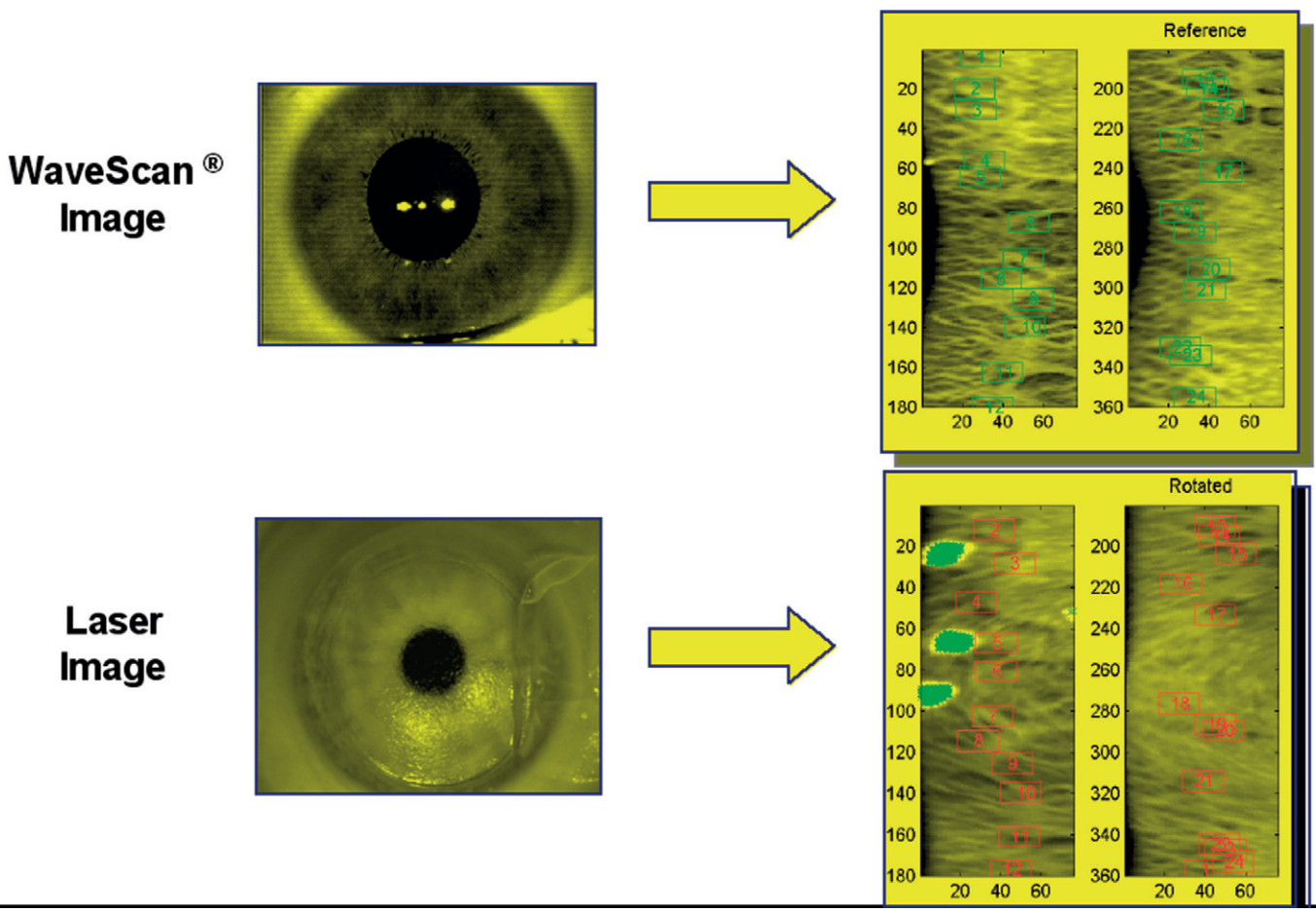
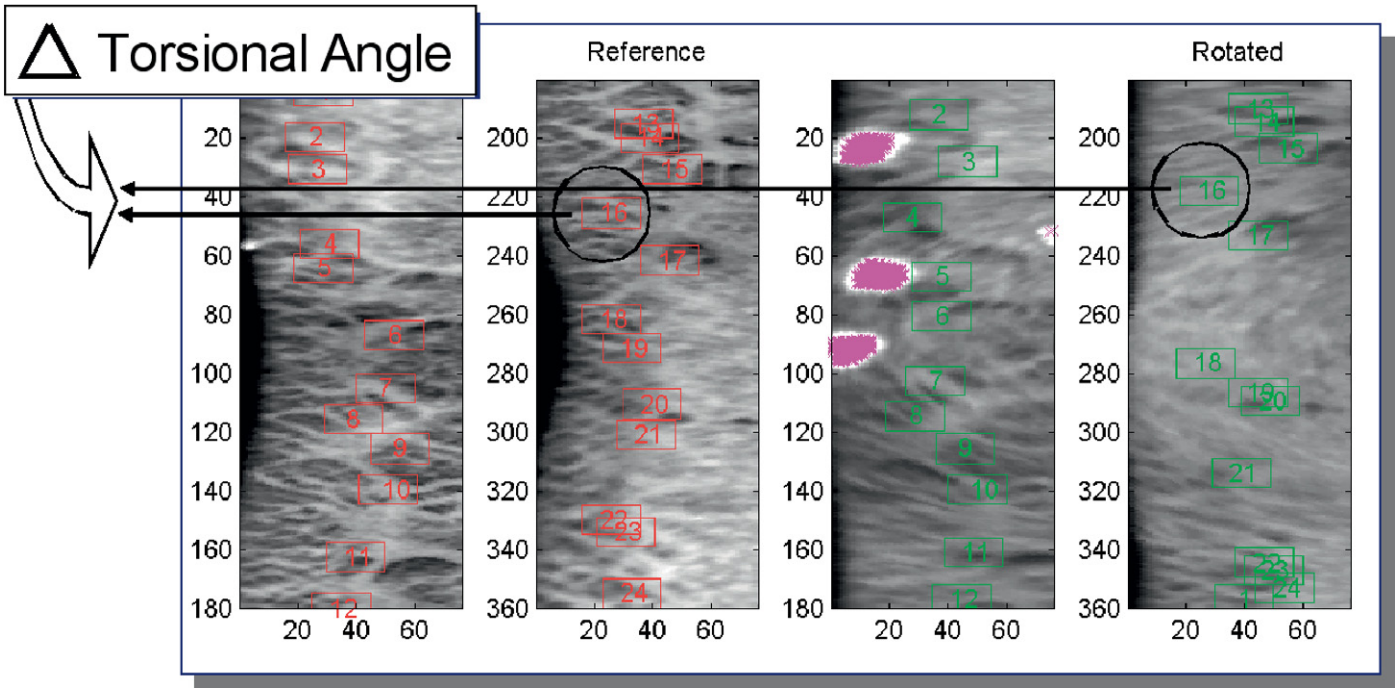


B

Figure 90.5. Iris registration process using the VISX Star S4 IR software. *A*, Comparison of iris images from WaveScan® and VISX Star S4 laser system.[20] *B*, A total of 24 landmarks are located, 1 for each 15° iris sector.[12] *C*, The torsional angle is calculated from the matched landmarks.[12] Courtesy of David R. Hardten, MD, Minnesota Eye Consultants, Minneapolis, MN.



C

Figure 90.5. continued

image is used to statically align the eye with the treatment images, accounting for pupil centroid shift and cyclotorsion by using a limbus ring and scleral ink marks as references. This also allows placement of the hinge mask, which can be accurately positioned to provide software-based hinge protection. The tracker is engaged accordingly. Therefore, the treatment is centered over the position of the undilated pupil center even though the pupil is dilated for the procedure.[21,22]

The LADAR6000 laser uses the same method for controlling for pupil centroid shift but has a greatly simplified process of cyclorotational registration (Fig. 90.8). This laser employs a registration system that uses infrared illumination and digital imaging to track blood vessels in the sclera. These are identified during wavefront capture and are registered by the laser prior to surgery to compensate for cyclorotation. This eliminates the need to mark the eye on the day of surgery to control for cyclotorsion. With this new software, the registration process is entirely automated and can be completed four to five times faster than before. (Courtesy of Rick Potvin and John Campin, Alcon Laboratories, Inc.)

TECHNOLAS 217Z LASER SYSTEM

The Technolas 217Z laser system (Bausch & Lomb, Inc., Rochester, NY) contains a pupil tracker that uses an infrared open-loop video to detect the pupil area from which it calculates the pupil center. The video system samples at a rate of 120 Hz to track the *x*, *y*, and z axes, while the laser fires at 100 Hz. The frequency of 120 Hz means there is 8.3 ms between each capture. The dynamic eye tracking software allows 200 µm of movement over the 8.3 ms, which equals 24 µm/ms. If more than 200 µm of movement has occurred, the next laser pulse is interrupted.

The video system uses the whole pupil area in reference to the limbus to statistically compensate for cyclotorsion and pupil centroid shift that occurs between the Zywave aberrometer diagnostic reference and the laser implementation. In addition to this, the most advanced system, the Dynamic Rotational Eye Tracker (DRET), compensates for dynamic eye rotation during the surgery with a sampling rate of 25 Hz. The DRET received USA Food and Drug Administration (FDA) approval in 2007 and will be incorporated into US lasers later that year. (Courtesy of Brendan B. Sheil, Executive Director, US Refractive Business, Bausch & Lomb, Inc., Rochester, NY.)

ALLEGRETTO WAVE EXCIMER LASER SYSTEM

The Allegretto Wave Excimer Laser System (WaveLight, AG, Erlangen, Germany) uses a video-based eye tracker that samples at 200 Hz using infrared illumination. The system calculates the pupil centroid as the intersection of the maximum X and Y diameters and sends this information to the laser. The spot location for each pulse is then adjusted according to the updated location of the pupillary centroid. The total response time of the system, including aiming of the laser pulse, is approximately 6 ms. With a 200 Hz laser, this allows for near pulse to pulse tracking.

The eye tracker detects movement in two ways: magnitude and velocity. Displacement of the pupillary centroid beyond preset limits (typically 2 mm) causes the laser to stop sending pulses, as does eye movement exceeding preset limits. As a result, factoring the maximal saccadic velocity of eye movements, the most a spot can be displaced with the Allegretto is about 13% of the 0.95 mm pulse diameter. Once the eye has slowed movement and returned to the preset zone, the laser automatically resumes pulsing.

The eye tracker sensing threshold can be adjusted to accommodate a range of iris pigmentation. Pupil sizes from 1–8 mm can be tracked. Dilation is not required, nor is registration of the eye with preoperative photographs.

Registration of treatments based on imaging systems such as aberrometry or topography is done using the eye tracker. Calculation of the pupil centroid is performed from the wavefront or topography image using the same method used by the laser tracker.

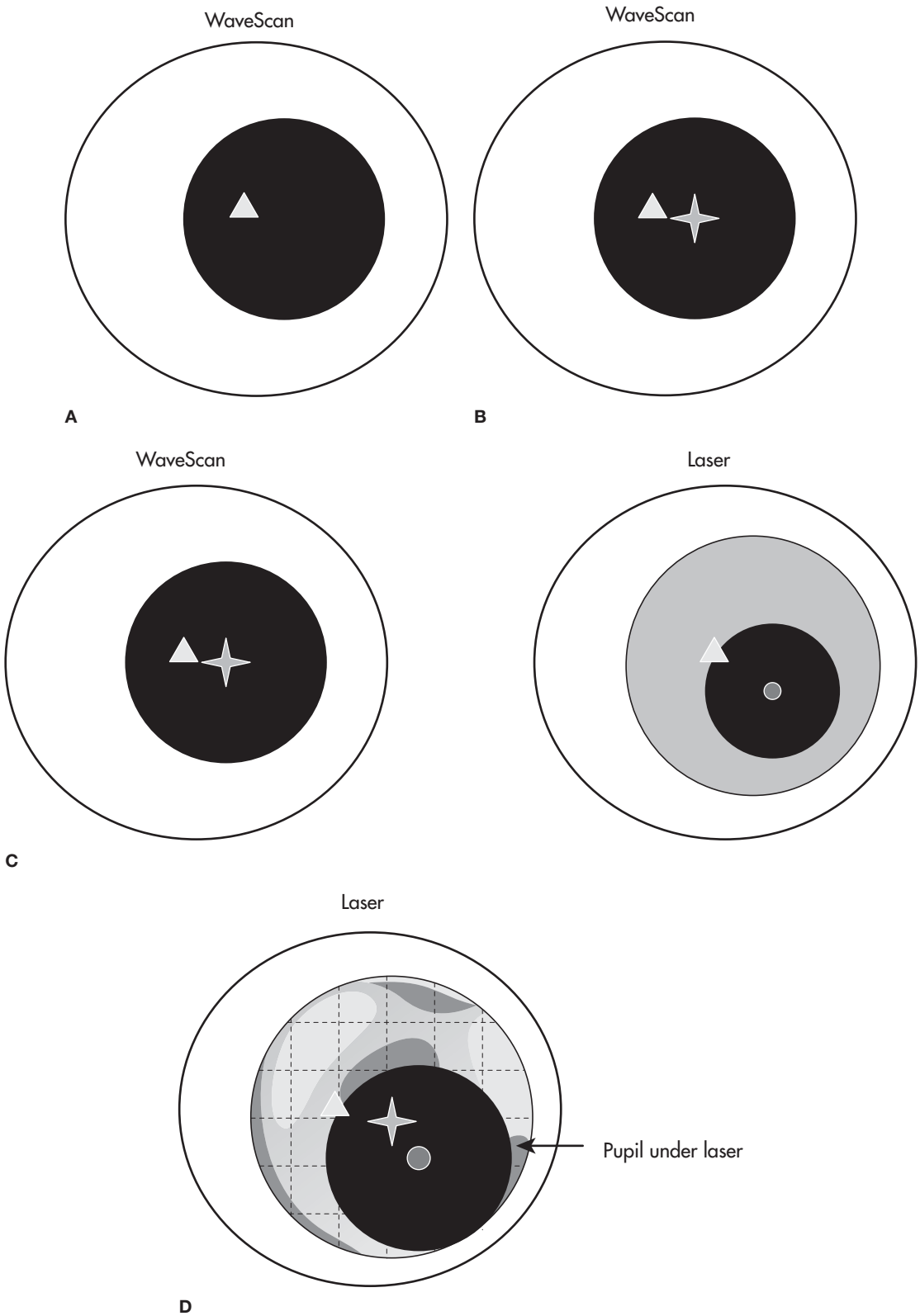
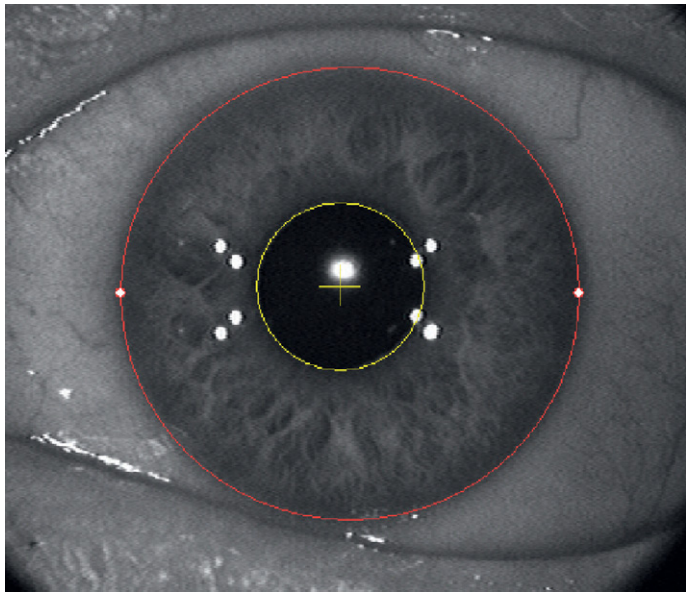


Figure 90.6. Compensation for pupil centroid shift with CustomVue. *A*, Step 1: The center of the outer iris boundary is identified and recorded at the WaveScan®. *B*, Step 2: During the WaveScan® measurement, the pupil centroid is referenced to the outer iris boundary. *C*, Step 3: Intraoperatively, the laser identifies the pupil centroid and references it to the outer iris boundary. *D*, Step 4: Wavefront ablation is centered over the WaveScan pupil centroid (star), not the laser pupil centroid (circle), compensating for centroid shift. Courtesy of David R. Hardten, MD, Minnesota Eye Consultants, Minneapolis, MN.



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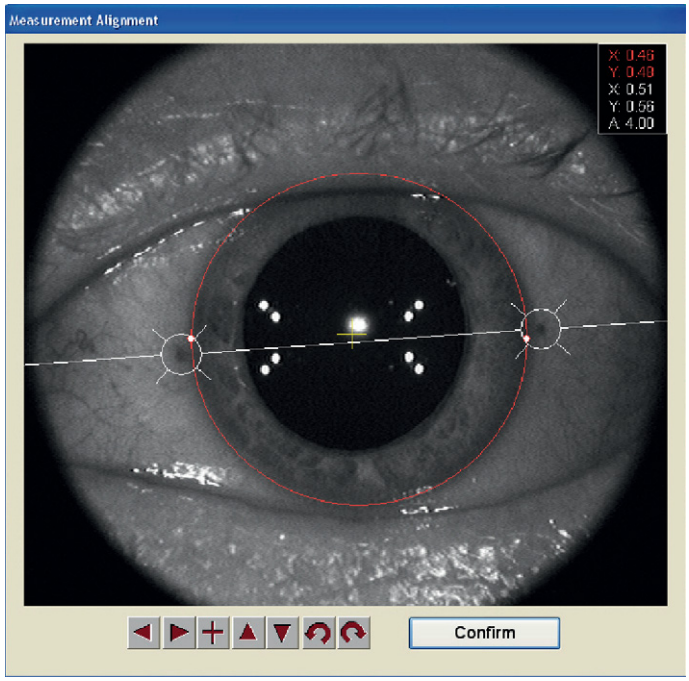

B

Figure 90.7. The LADARWave® Aberrometer: registering the wavefront measurement. *A*, Centration and *B*, wavefront alignment. Courtesy of Rick Potvin and John Campin, Alcon Laboratories, Inc.

Torsional registration at both the imaging device and the laser is done manually by matching bony landmarks with alignment guides. Treatments are performed using a pupil diameter within 2 mm of the diameter of the image used to create the treatment. At the laser, pupil size is controlled by adjusting the illumination lights. (Courtesy of Guy M. Kezirian, MD, FACS, President of SurgiVisionR Consultants, Inc., Scottsdale, AZ.)

CONCLUSION

There has been tremendous progress by manufacturers to reduce the error that results from misalignment of the ablation profile to the mapped area. Pupil tracking systems use high sampling rates to decrease latency times and compensate for eye movements during surgery. For cyclorotational registration, laser systems use landmarks on the eye that do not change with lighting conditions, such as the limbus and peripheral iris, as reference points to compensate for pupil centroid shift and cyclotorsional rotation. Currently, at least one manufacturer is attempting to further increase the level of sophistication by providing active cyclorotational tracking.

To provide even greater accuracy in tracking and registration for customized ablations, research and development should focus on several areas, including more robust registration techniques, faster sensor technology, lower latency times, and, perhaps most importantly, a method to track the corneal surface to eliminate parallax error. Clearly, there will be a point of diminishing return where further improvements in the tracking mechanism will provide no discernible increase in clinical results, and determining this point will require both theoretical and clinical studies.

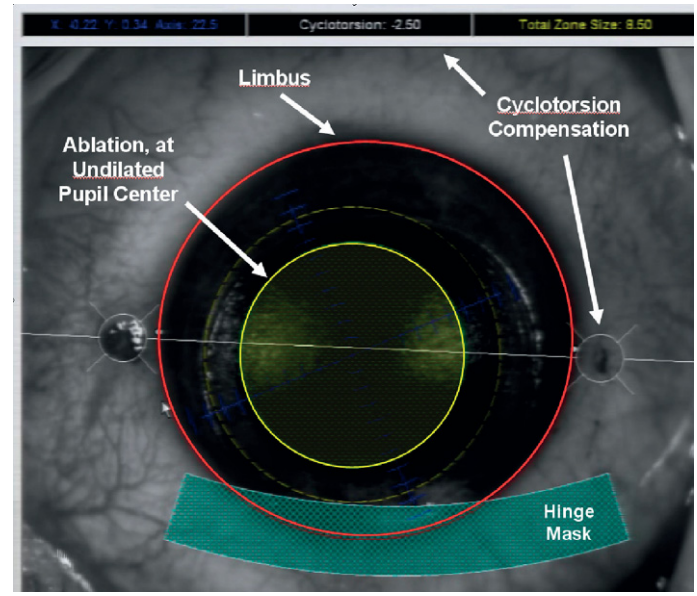

Figure 90.8. The LADAR6000® Excimer Laser System: registering the ablation. Courtesy of Rick Potvin and John Campin, Alcon Laboratories, Inc.

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91 Building a personalized LASIK–laser vision correction nomogram

John F. Doane, Randolph T. Jackson

This chapter is intended to demonstrate to the novice surgeon and, possibly, even to the experienced laser refractive surgeon that understanding the specific laser and software version in use, the laser room environment and the surgeon's technique will determine the refractive success and patient's satisfaction after laser vision correction. It is the hope of the authors that experience from surgical results for six different excimer laser manufacturers, nine different laser models, and innumerable software versions for the treatment of myopia, hyperopia, astigmatism, presbyopia, asymmetric ablations, and customized specialty ablations will provide the beginning laser practitioner with a basis for appropriate surgical decision making and respect for the vast complexity of available systems.

INTRAOCULAR LENS 'A-CONSTANT' VERSUS EXCIMER LASER ALGORITHM

Ophthalmic surgeons are extremely fortunate to be able to use advanced intraocular lens formulas when performing small incision phacoemulsification and intraocular lens placement. In uncomplicated cases, either a novice or an experienced surgeon can obtain excellent refractive results. How is this possible? Doesn't experience matter? Yes, experience matters, but well-defined 'A-Constants' for each commercially available intraocular lens have been determined. Once the 'A-Constant' is obtained the refractive result should be near emmetropia.

As an example, let us propose that the average patient with average keratometry values and axial length measurements is examined by an expert technician shared by an experienced and novice surgeon. If the technician obtains high quality, repeatable keratometry, and axial length values and subsequently enters this data into a modern intraocular lens formula to be used by the two surgeons the lens calculated for emmetropia would be identical. If we then assume a standard cataract procedure is performed with intraocular lens placement in the capsular bag after uncomplicated continuous curvilinear capsulorrhexis, the refractive effect should be identical for the two surgeons.

Why is this? The same intraocular lens placed in the given eye as above will achieve identical results, since it is a fixed optic placed at the same location (within the capsular bag) by both surgeons. With intraocular lens placement in small incision cataract surgery, wound healing is not a big factor in surgical results. Hence, the 'A-Constant' is an invaluable reference number to provide transferable refractive predictability and accuracy to any surgeon who would select a given lens model. We will see with laser refractive surgery (photorefractive keratectomy or laser in situ keratomileusis) that an 'A-Constant' or laser algorithm does not necessarily predict excellent refractive results.

Excimer lasers are not manufactured or shipped with an 'A-Constant' per se, but they are built and tested with a manufacturer-supplied algorithm. An algorithm is similar but not synonymous with a tool familiar to incisional keratotomy surgeons called the nomogram. With incisional keratotomy surgery the surgical plan (number, length, and depth of incisions) is based on the patient's age, degree of ametropia, sex, and other factors. Excimer laser algorithms as originally designed dictated for a given degree of refractive error that a specified number of pulses at selected ablation diameters would be applied to the cornea. The laser algorithm is provided to the laser as a software package that is typically encoded on the central processing unit's hard drive or, less commonly, by an optical reader. The algorithm is unique to a given laser model from a specific manufacturer, and the results from a treatment are based upon the laser being utilized within a set temperature, humidity, and particulate matter environment. The algorithm can be different for the same model from a manufacturer if different software versions are downloaded onto the hard drive for use.

If we are dealing with one patient with, for example, 4 D of spherical myopia, why would the algorithm for different laser models or manufacturers have to be different? There are two main reasons: the beam delivery system and the beam fluence. There is a wide variation in beam delivery systems available for use worldwide. With varying maximal treatment zone diameters, there will be a different number of pulses required for any given refractive error. Virtually all newer lasers incorporate scanning beam delivery. There are two aspects of a treatment that need to be selected; the optical zone and the ablation zone. The optical zone's function is to change the refraction of the eye. The ablation zone, which extends peripherally from the optical zone, functions to minimize

regression of effect from epithelial remodeling as well as to minimize night symptoms. For a given refractive error, using the same laser the software will dictate fewer pulses for smaller diameter optical and ablation zones. Likewise, the smaller the zone, the smaller the central depth of the ablation. As the outer zones of the treatments decrease, the scotopic pupil size and its association with unwanted night symptoms must be recognized. A too small optical ablation zone can be associated with night time dysphotopsia.

We have been discussing only spherical myopia. As we move to the treatment of myopic astigmatism, hyperopia, hyperopic astigmatism, bifocal presbyopic ablations and asymmetric ablations, the variance in pulse number, laser beam aperture size, and orientation becomes exponential.

Excimer laser beam fluence is defined as the amount of energy per pulse that is distributed over a defined area (mJ/cm^2). The laser fluence will determine the overall number of pulses for removing a specific micron thickness of tissue to effect a given refractive error or three-dimensional shape. Two different beam profile characteristics (Gaussian, greater energy density centrally than peripherally, versus table top, relatively even energy distribution across the ablation zone diameter) have been described for excimer lasers. It should also be realized that excimer lasers are not static instruments but ever-fluctuating energy sources. This fact requires frequent calibration so the laser energy is released in a controlled fashion. If different fluences exist between lasers, then differing amounts of tissue will be removed per pulse. It is then clear that, with differing fluence between lasers (Table 91.1),[1] the algorithms for specific refractive errors will be quite different.

It should be obvious at this point that production of excimer lasers and software design can and is highly variable among the different manufacturers. There are additional variables that need to be considered when evaluating the overall performance of a given laser. These include inter-model performance variation, laser room environment, geographic profile of the laser center, and surgeon technique. The performance comparison of lasers within the same manufacturer model number is not always identical. To the beginning surgeon this is probably another confusing and confounding factor. Why would the same model lasers not perform in exactly the same way? There may be true variation among lasers of the same model, despite the best efforts of the ablest engineer and design team and also despite consistent instrument setup and calibration. This variation should not be overly concerning since, as we will describe in the ensuing discussion, the surgeon must define the laser performance to obtain the best surgical outcomes.

Table 91.1 Excimer laser fluence levels[1]

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Please refer to the printed book.

From McDonald MB, Doubrava MW. New developments in excimer laser. In: Pallikaris IG, Siganos DS, eds. LASIK. Thorofare, New Jersey: Slack, Inc; 1997: 8–11.

Maintenance of the laser room environment is critical for laser refractive surgery success. It is critical not only for performing surgery but also for proper laser maintenance. It is felt and recommended by all laser manufacturers that certain conditions should be maintained for optimal laser performance. The laser room should be a closed environment and not be a multipurpose room with open access. Temperature should be controlled between 18 and 24°C. Humidity should be maintained between 30 and 50%. Low particulate matter filtration should be in effect 24 h per day, 7 days per week. This is done to provide each treatment session with a consistent environment, since laser ablation rates are highly dependent on atmosphere in the optical train to the corneal surface. Additionally, it is done to create the most favorable environment to increase the longevity of the optics within the laser. For instance, if high particulate matter is present in the laser room, this matter can coat the lenses within the optical train. When the laser is next fired the particulate matter can be 'burned' into the lens as an imperfection which will subsequently decrease the homogeneity (i.e. the pattern of energy distribution across the ablation zone) of the laser ablation. If this becomes a chronic situation, the life span of individual optics will be reduced leading to increased laser operational costs. Even more important, this could lead to poor ablation pattern on the cornea with possible visual morbidity. Perfumes, deodorants, scents, alcohol, and other combustible liquid vapors should be prohibited from the laser room since they will coat the lenses and potentially affect the same change as particulate matter. Geography also plays a role in laser performance. The relative humidity and altitude will cause variation in laser performance. On average, a high humidity, sea-level locale will realize less refractive effect than the same treatment entered into the laser compared to a low humidity, high altitude locale.

BUILDING THE NOMOGRAM

With the advent of 'custom' laser in situ keratomileusis (LASIK), nomogram development has become less of an issue but for quality improvement reasons adjustments of the 'surgeon' factor for customized ablations becomes the newest incarnation of an individual surgeon nomogram. That being said, reviewing the historical method of conventional adjustments is required to appreciate customized nomogram adjustments.

Success with LASIK is intimately dependent on two important factors: obtaining an excellent keratectomy and performing an accurate ablation. It has been quoted that LASIK is 90% keratectomy and 10% laser. This might more appropriately be termed the novice surgeon mentality or viewpoint. It has also been our observation that there is a patient viewpoint on this topic: a patient is interested in 100% keratectomy success followed by a 100% successful laser ablation. With experience we believe that the surgeon's viewpoint also changes. As he or she becomes comfortable performing the keratectomy, about 5% of his or her time is spent contemplating and performing the keratectomy and 95% of the effort is spent making certain the laser is operating properly and no human errors have been made by the surgical team. The experienced surgeon's success then comes from having a highly predictable nomogram that has been customized to the laser environment and surgical technique. Without a customized approach to a LASIK nomogram by the surgeon haphazard surgery will likely be performed with less than excellent outcomes. One would do equally well if this approach is taken doing haphazard incisional keratotomy or whatever refractive surgical technique is performed. With this being conceptually understood, the next section will describe

the process by which a surgical team approaches the task of delivering accurate and reproducible results.

The process of developing a LASIK nomogram requires four steps: obtaining patient data, formulating an initial nomogram, entering data into the computer of the laser and evaluating data/outcomes and making adjustments based upon this information.

At first glance obtaining patient refractive data seems mundane and not necessarily where the action is. This is a grave error in refractive surgery and especially laser vision correction. LASIK and surface ablation techniques are incredibly powerful. The laser will ablate whatever is entered into the treatment plan. If inaccurate refractive data is entered, the difference between true refraction and that obtained will be the residual refractive error. It is very important to complete several basic refraction principles. For eyes greater than 5 D of refractive error it is important to have proper vertexing to the spectacle plane (12.5 mm) if this is the convention entered into the laser. This can be completed with trial frame glasses. Significant error in refraction outcome can be realized if patients with large refractive errors are refracted at spectacle plane vertex distance and data is entered at corneal plane. Fogging techniques should be utilized, so the least amount of myopia to see the best spectacle corrected line of vision is the refractive endpoint. This minimizes iatrogenic causes for overcorrection. Cycloplegic refraction can also be done to confirm the fogged manifest refraction. Comparison to old or recent refractions should be noted. If large discrepancies are noted, concern for examination error or refraction instability should be considered. For patients wearing contact lenses special consideration should be given in obtaining this data. Soft contacts should be out at least 3 days prior to examination and topography should be obtained to rule out corneal warpage. Rigid contact lenses should be out at least 3 weeks and stability noted with two separate examinations 3 days apart. Likewise, topography should be obtained to rule out abnormalities.

The initial nomogram used should be based upon available data and not a 'shot in the dark' approach. The novice surgeon should utilize all available information to decide on his or her initial surgeon factor adjustments to the laser algorithm. Knowledge of the specific laser's performance with photorefractive keratectomy should be taken into consideration. If the laser is overcorrecting long term with PRK one could anticipate it would do the same with LASIK. If the laser is undercorrecting long term with PRK it can also be assumed that undercorrection will be obtained with LASIK. The difference between what is entered into the laser and that obtained is typically a set percentage difference at all levels of refractive error. Therefore, the individual surgeon should increase or decrease the planned treatment by a set percentage from the manufacturers' algorithm to achieve the target postoperative refraction.

Entering data into the computer ostensibly seems to be the easiest step in laser refractive procedures but this is not always the case. Typing errors on the computer keyboard, incorrect cylinder convention, vertex distance, cylinder axis, wrong patient, or incorrect eye entry are just a few potential errors that can lead to poor outcomes. Calculation of the treatment to be entered into the laser should be checked multiple times by more than one member of the surgical team. One might ask how can an error happen? If the treatment entered differs from the manifest refraction and, certainly, if a percentage difference must be made for the treatment entered, simple math errors can occur. Hence, multiple calculations and checks should be made for each entry. Is the correct patient chart being used for the next patient to be treated? Is data for the correct eye being entered? Is monovision being treated for the eye? These are but a few of the questions that need to be answered for each data entry. The convention by which data is obtained and entered into the laser should be consistent (Table 91.2). Specifically, if refractions are done in plus cylinder convention they should be entered in plus cylinder. Transposition errors will occur, so if the surgical team can completely avoid this step, it is advisable. It is extremely important to check the axis and the cylinder convention on each case. Minus cylinder can be entered when the patient is refracted in plus cylinder and the surgeon will subsequently induce cylinder on the patient's cornea, typically doubling the pre-existing astigmatism. Proper vertex distance entry should also be made. When treating myopia, if the patient is refracted at 12.5 mm vertex distance and the data is entered at the corneal plane, a percentile overcorrection will occur or vice versa. This will be more significant the higher the refractive error treated leading to visual morbidity in some cases. In summary it is extremely important to use a single cylinder convention and enter data the same every time at the same vertex distance. Multiple checks of the calculated entry should be made by more than one person on the surgical team. No member of the refractive surgery team should feel intimidated to announce they have noted an error that can be corrected prior to patient treatment at whatever stage of the process the error is noted. Overbearing egos should be avoided in the treatment of refractive surgery patients. They will be a hindrance to the best care and correction of avoidable human errors.

Table 91.2 Treatment calculation

Line # 1	Refraction	–6.0 D
Line # 2	Target	–1.0 D
Line # 3	Line # 1 – # 2	–6.0 – (–1.0) = –5.0
Line # 4	Multiply Surgeon Factor* by line # 3 and add or subtract as indicated by the specific laser used	–6.0 – (0.1 × –6.0) = –6.0 – (–0.6) = –5.4 D
Line # 5	Number entered as treatment	–5.4 D

* Addition or subtraction will depend if the specific laser is undercorrecting or overcorrecting in relationship to what the algorithm suggests. In the above example, the laser is overcorrecting compared to the algorithm so a set percentage is taken away from the spherical treatment.

For customized ablations in which high-order aberrations are being addressed the custom treatment table can be adjusted with limitations. A reasonable approach to use for these patient treatments is as follows. It is best to not defer all refraction validation to the wavefront analyzer without a manual manifest and cycloplegic refraction. In fact, all manufacturers have set guidelines when to proceed with a custom ablation. For example, if the wavefront sphere is more plus than +0.75 D, or more minus than –0.50 D, or if the cylinder axis is more than 15° off, the recommendation would be to repeat wavefront analysis. If one is unable to achieve this threshold a standard ablation is recommended. Interestingly, if the higher-order aberration root mean square spot size magnitude is large, it may be impossible to capture a wavefront image that would fulfill the lower-order criteria. Once the manual refraction has been obtained comparison to the wavefront refraction can be undertaken. Most custom ablation platforms will not allow the surgeon to alter the lower-order cylinder axis or magnitude, or to adjust the

higher-order ablation. On the contrary, the sphere amount can be adjusted. Why would a surgeon want to adjust the sphere? Currently, wavefront analyzers do not allow for subjective patient approval of the optical correction, but a manual manifest refraction does allow for this critical component for refractive surgery happiness postoperatively. How does one adjust the custom sphere treatment? One approach is to equalize the treatment to the spherical equivalent of the manifest refraction. Let us say the wavefront refraction is $-5.00 + 1.75 \times 090$ and the fogged manifest refraction is $-4.50 + 1.50 \times 090$. The wavefront spherical equivalent equals -4.13 and the manifest refraction spherical equivalent is -3.75. To equalize the wavefront to the manifest refraction the surgeon would reduce the treatment wavefront sphere by 0.38 D or adjust for a more positive refraction treatment. The next step would be to follow the patients to 3 months and assess any discrepancy from the target outcome to that obtained. If there is a discrepancy the surgeon factor adjustment can be modified with all future treatments.

TECHNIQUE CONSIDERATIONS

After the keratectomy is completed the actual ablation is the key factor in determining the nomogram and is the defining act by the individual surgeon, all other preoperative factors being equal. The time to initiate and complete the ablation and the management of the stromal bed during the ablation will determine the amount of dry stroma removed to effect the refractive change. The dryer the bed during the ablation the more dry weight corneal stromal tissue that will be removed.[2] Ablation technique can range from initiating the ablation and completing the pulse count without interruption to stopping at selected intervals to dry the stromal bed with a cellulose sponge or metal spatula, or alternatively wiping the stromal bed only on the appearance of condensation on the stromal bed surface. How does this affect refractive outcomes and dry corneal tissue removal? The dryer the stroma the more dry weight tissue that will be removed for the same number of pulses and, likewise, the wetter the stromal bed less dry weight tissue will be removed for the same number of pulses and, on average, less refractive change than the 'dry ablation' will be obtained. This technique nuance is the reason each surgeon must define their own nomogram since surgeons using the same laser but markedly different technique will obtain completely different surgical outcomes if they enter the same treatment plan for an identical preoperative refraction. For the individual surgeon the lesson to be taken from this discussion is *consistency in technique*. Consistent time to lift, initiate, and complete a case should be a goal as should the frequency of wiping (every 50 or every 100 pulses, etc.). If one elects to have forced air passed over the stromal bed during the ablation, this can be done as long as it is consistent. Two surgeons using the same laser but markedly different ablation techniques can achieve equal results as long as they both understand the tissue effects of their technique and employ their technique in a consistent fashion.

LASIK NOMOGRAM REFINEMENT

LASIK nomogram refinement begins immediately in the postoperative course. Refraction data should be obtained at each postoperative visit. Quality improvement requires evaluation of the postoperative data with adjustment of the nomogram based upon this data. Not obtaining and utilizing postoperative data for improving the individual surgeon's results is as logical as not obtaining a refraction or topography prior to surgery. It is a necessity for the surgeon to provide optimal care and refractive outcomes. Refractive and topographic stability is obtained by virtually every patient by the 3-month examination for LASIK. Surface ablation takes a bit longer to stabilize, sometimes closer to 6 months for myopia and possibly 12 months for hyperopia. This data that should guide precise refinement of the individual surgeon's nomogram. The surgeon's nomogram becomes more powerful the more eyes treated at any given level of ametropia and the further out the postoperative data is obtained. During nomogram development particular attention should be given to secondary refractive surgeries. For example, an enhancement to correct hyperopia following a myopic LASIK usually requires a decreased nomogram adjustment. The technique of retreatment will require a further adjustment of this nomogram subset.[3] If the retreatment is performed after lifting the flap, the stromal bed is likely to be more dry than if a new flap is cut with a mechanical keratome.

SPHERICAL EFFECTS OF ASTIGMATIC ABLATION

It is important to recognize possible spherical refractive effects of astigmatic correction with the particular laser one uses. Most excimer lasers treating myopic astigmatism operate under minus cylinder convention. The author has noted in all systems used to date (large area ablation lasers or scanning spot) that, for each diopter of cylinder ablated, approximately 0.1–0.2 D of overall central corneal flattening will occur, leading to small amounts of hyperopia. If this is not accounted for by reduction of the spherical ablation plan, unwanted hyperopia may be noted postoperatively. Postoperative refractive data will help the surgeon identify this possibility and be a basis to identify the exact correction for each diopter of cylinder ablated.

In conclusion, laser vision correction nomogram development is an individual process in which every surgeon is in essence an island. There are three important elements in the equation: the laser, the laser room environment, and the surgeon's technique. The excimer laser beam is not a static force but an ever-changing one. Likewise, laser refractive surgery is not a static process and requires the practitioner to be an active flexible participant in the process. The process requires ongoing data acquisition, assimilation, and refinement to provide the highest quality postoperative vision that patients are entitled to and demand in the laser refractive surgery era.

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92 Surface ablation: techniques and postoperative management

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HISTORY

The history of the excimer laser began in the 1970s when physicists were interested in developing an excited dimer, or 'excimer', from the combination of an excited rare argon gas atom (e.g. argon or krypton) with a diatomic halogen molecule (e.g. fluorine or chlorine).[1] In 1981, Taboada et al used a 193 nm excimer laser to 'indent' the rabbit corneal epithelium.[2] Subsequently, in 1983 Trokel and associates suggested the use of the excimer laser for corneal surgery.[3] The 193 nm excimer laser accurately ablated tissue by a process labeled as 'ablative photodecompensation' while minimizing thermal damage to adjacent tissues. Later, Seiler in Germany and Puliafito in the USA developed optical delivery systems to convert excimer laser radiation into a homogenous beam with precise ablative profiles.[4] Puliafito et al used high-speed photography to image the laser ablation plume created on the cornea with the excimer laser.[5] Seiler and Wollensak used the excimer laser on a human eye to perform astigmatic keratotomy in 1985 and phototherapeutic keratectomy (PTK) in 1986.[6] McDonald et al performed photorefractive keratectomy (PRK) on a myopic, sighted eye in 1987.[7] These initial studies paved the path for subsequent large, multicenter trials of PRK.

INDICATIONS FOR SURFACE ABLATION

PRK can treat refractive errors with satisfactory visual outcome in myopia up to −12 D, astigmatism up to 6 D, and hyperopia up to +5 D.[8] The most predictable and successful results with lowest incidence of complications occur in lower ranges of myopia, astigmatism, and hyperopia. Treatment of low-to-moderate myopia (−1.5 D to −6 D) is associated with success (defined as achieving 20/40 or better uncorrected vision) in more than 90% of eyes.[9–12] Treatment of larger refractive errors has been associated with higher rates of regression, haze formation, and need for retreatment.

Despite being the first widely utilized laser vision correction procedure, PRK has been largely supplanted by laser assisted in situ keratomileusis (LASIK) as the predominant refractive procedure performed in the USA.[13,14] Maintenance of an intact epithelium in LASIK allows for faster visual rehabilitation, less postoperative discomfort, and less risk of undesired excessive postoperative healing and risk of regression. Nevertheless, there remains an important role for surface ablative procedures like PRK in refractive correction. Current indications for surface ablation include thin corneas, anatomic issues providing difficulty for microkeratome use, previous scleral buckling or trabeculectomy surgery, moderate dry eyes, epithelial disease, high or low keratometric readings, and predisposition for contact injury. Insufficient stromal bed has been implicated in post-LASIK instability and increased risk of progressive corneal steepening and ectasia. Most surgeons agree on a minimal residual stromal bed of 250 μm and surface ablation is usually advised for those with corneal thicknesses below 500 μm. Small interpalpebral fissures, deep-set orbits, and corneal or limbal conditions such as pterygia may hinder correct placement of the microkeratome for LASIK. The presence of a filtering bleb and an anteriorly displaced scleral buckle similarly obstruct the placement of the microkeratome suction ring. Some have shown greater worsening of dry eye conditions in LASIK versus PRK.[15] Although significant topographic abnormalities at baseline preclude many patients from candidacy for refractive surgery, those with very high/low central curvatures would benefit more from surface ablation than LASIK, which bodes a greater chance of intraoperative complications.[16] PRK is recommended for those with anterior basement membrane dystrophy, as LASIK may induce/exacerbate epithelial erosions.[17] In these cases, it may be more favorable to choose PRK to improve epithelial basement membrane healing and prevent future erosions. Some authors believe that realization of the full benefits of wavefront-guided laser vision correction requires the use of surface ablation instead of LASIK, due to concern that unpredictable aberrations from LASIK flaps might confound the desired optimization. Finally, those involved in combat or vocations associated with a high risk of trauma to the head, such as military personnel, benefit from PRK versus LASIK where there is a potential for traumatic flap dislocations.

WOUND HEALING IN SURFACE ABLATION

In surface ablation, epithelium is removed with subsequent laser photoablation of Bowman's layer and the anterior stroma. Removal of the epithelial basement membrane exposes the underlying anterior stromal keratocytes to cytokines produced by epithelial injury, such as interleukin (IL)-1.[18] Epithelial injury or surgical trauma induces keratocyte apoptosis, stimulating the migration of inflammatory cells and surrounding keratocytes. One to two weeks after the initial injury or surgery, myofibroblasts appear in the subepithelial stroma. The epithelially derived cytokine, transforming growth factor-β or TGF-beta, has been shown to activate keratocytes into myofibroblasts.[19] Derived from keratocytes, myofibroblasts have relatively reduced transparency and are considered to be a major contributor to corneal haze. In addition, the collagen matrix produced by activated keratocytes is less organized than normal stroma. It has been shown that the corneal wound healing response, such as keratocyte apoptosis, necrosis, and myofibroblast production, is more intense after PRK than LASIK.[20]

PREOPERATIVE EVALUATION

A full preoperative evaluation includes the following: a complete ophthalmic and general medical history, uncorrected and best corrected visual acuity, manifest and cycloplegic refraction in minus cylinder form corrected for vertex distance, keratometry, computed topographic analysis, ocular dominance, pupil diameter in dim illumination, a complete anterior and posterior segment examination, and applanation tonometry. Specific guidelines regarding discontinuation of contact lens wear should be communicated to the patient. Although no determinant clinical trial has demonstrated the optimal time of contact lens discontinuation before refractive surgery evaluation, recommendations have been proposed based on observational data. Often soft contact lens wear should be discontinued at least 3 days prior to evaluation, rigid contact lenses at least 3 weeks prior to evaluation[21] and hard contact lenses at least a month before initial screening. If contact lens warpage is suspected, surgery should be postponed until topography and refractive error are stable at least 2 weeks apart.

PRK INTRAOPERATIVE TECHNIQUE

LASER CALIBRATION

The following technique can be adopted for all excimer laser systems. The refractive surgical day should always begin with proper system calibration and programming. Beam homogeneity, depth per pulse, and beam alignment should be tested with the appropriate calibration films/sensors. In some geographical regions prone to substantial seasonal variations in humidity, the use of dehumidifiers to control the surgical environment may be helpful in minimizing variation in surgical outcomes (Table 92.1).

PREOPERATIVE MEDICATIONS

As patient cooperation is key to surgical success, if there is much apprehension on the part of the patient, mild sedation with oral diazepam (5 mg) is often offered preoperatively. Some surgeons use anxiolytic agents routinely, while others reserve it only for patients whose natural anxiety cannot be managed by supportive feedback from the surgical team. The patient is brought to the laser room and positioned under the microscope on a reclining chair. The nonoperative eye is patched and the head is draped in the usual sterile fashion. Relevant patient data is checked on the computer. Ocular anesthesia is achieved with topical proparacaine HCl 0.5%. Preoperative medications include topical NSAIDs such as ketorolac tromethamine 0.5% (Acular®, Allergan) or diclofenac sodium 0.1% (Voltaren®, Novartis) and a topical fourth-generation fluoroquinolone antibiotic such as moxifloxacin HCl 0.5% (Vigamox®, Alcon)) or gatifloxacin 0.3% (Zymar®, Allergan). A lid speculum is placed in the operative eye and more topical anesthetic is applied.

Table 92.1 Procedural list for PRK

Administration of preoperative medications
Laser calibration and programming
Patching of nonoperative eye
Ocular anesthesia
Lid speculum placement
Determination of optical center
Delineation of 6 mm ablation or optical zone
Epithelial removal
Ocular fixation
Stromal ablation
Practice pulses
Spheric correction
Instillation of immediate postoperative medications
Placement of bandage contact lens
Postoperative instructions

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BEAM CENTRATION AND DATA VERIFICATION

At this point, the surgeon and his/her team perform a 'time out,' verifying the patient's identity and checking all entered data into the system. PRK laser centration is critical to surgical success. Centration over the pupil is preferred to centration over the corneal light reflex.[22,23] The microscope should also be carefully focused onto the corneal surface. The patient is instructed to look at the aiming beam of the laser, usually a blinking light, to ensure adequate centration of the ablation. To familiarize the patient to the laser apparatus and assure the surgeon of the patient's ability to fixate, test shots can be performed. Communication with the patient throughout the process is helpful for ensuring proper fixation, as patients are calmed by knowing the procedure is progressing appropriately and by positive feedback regarding their ability to maintain fixation. Lasers have incorporated sophisticated tracking systems (either passive or active) to ensure appropriate centration of the laser exposure. Some surgeons still prefer the use of passive, low vacuum suction ring to aid in centration.

DELINEATION OF ABLATION OR OPTICAL ZONE

An optical zone mark 1 mm greater than the desired ablation or optical zone (6 mm) is placed on the epithelial surface and centered over the pupil to set up for epithelial removal.

EPITHELIAL REMOVAL

There are three different methods of epithelial removal for PRK employed by refractive surgeons: mechanical debridement with a spatula, blade, or rotary brush; chemical removal with alcohol; and laser-assisted removal. For each method, epithelial removal should be quick and decisive to avoid corneal hydration changes.

In mechanical debridement, a blunt spatula or Beaver blade is used to scrape from the periphery to the center, the area of the epithelium delineated by the marker. Once the lid speculum is placed and the eye opened under the light of the operating microscope, dehydration and resultant corneal thinning will quickly ensue. Mechanical removal should therefore be performed efficiently and in standardized fashion, not taking longer than 2 min. A sponge impregnated with 1% methylcellulose or balanced salt solution can be used to wipe off residual epithelial debris, leaving a smooth surface of Bowman's layer. An alternative tool used to remove epithelium is the Amoils brush (Innova, Toronto, Canada). This brush has fine hairs that provide a smooth corneal surface that does not disturb underlying Bowman's layer.

Alcohol-assisted epithelial removal has been shown to be a simple and safe alternative to mechanical debridement.[24] An 18–25% concentration of absolute alcohol in balanced salt solution or sterile water is applied to the epithelial surface with a sponge for 2–3 min or in a reservoir centered over the optical zone for 20–30 s. The corneal surface is then washed to remove the alcohol. The central epithelium is then peeled with McPherson forceps.[25]

Finally, the excimer laser can be used to remove the epithelium, essentially as in phototherapeutic keratectomy (PTK). This technique is quite dependent on tear film regularity and a smooth preoperative surface, so patients with an uneven tear film are not ideal candidates for this method. A standard depth of approximately 45 μm of tissue can be programmed into the laser for ablation and the residual debris removed with a spatula. Alternatively, epithelial removal can be assured by performing ablation under blue fluorescence—once the epithelial layer is ablated, blue fluorescence disappears.[26] The appeal of this technique for epithelial removal includes uniformity in time and the precise geometry of the epithelium removed, as opposed to manual removal in which removal of excess epithelium (to ensure that the corneal surface to be ablated is free of epithelium) is common.

STROMAL ABLATION

At this point, the ability of the patient to maintain ocular fixation may be checked by placing practice pulses onto the bare stromal bed and communicating to the patient that the ablation is commencing. The programmed correction for stromal ablation is then performed. The stromal bed is then rehydrated with a wet sponge (Fig. 92.1).

POSTOPERATIVE MANAGEMENT

Adjunctive therapy varies among surgeons. Immediately following stromal ablation, chilled balanced salt solution, topical NSAID, antibiotic, and corticosteroid may be applied to the ocular surface, followed by a bandage contact lens. Postoperative instructions (Table 92.2) include reviewing common postoperative symptoms such as blurred vision, glare, and photophobia.

Our recommended medication regimen is as follows: for the first week, a fourth-generation fluoroquinolone four times a day, an unpreserved topical NSAID four times a day, prednisolone acetate 1% four times a day or fluorometholone 0.1% four times a day, and Vicodin® (acetaminophen/hydrocodone) every 4–6 h as needed for pain. In the first week, re-epithelialization is monitored, with complete healing of a 6.5 mm defect often occurring within 48 h. When the epithelial defect is healed, antibiotic use is discontinued. Postoperative management is summarized by time frame: early, intermediate, and late (Table 92.3).

Topical NSAIDs are used regularly in postoperative management of pain, inflammation, and photophobia after surface ablative procedures such as PRK.[27] Effective in postoperative analgesia, NSAIDs work by inhibiting the cyclooxygenase pathway of arachidonate metabolism. Generally, topical NSAIDs are used four times a day after PRK for up to 4–7 days postoperatively. Our routine is to use the NSAID until the epithelial defect is healed, by which time pain control is no longer a concern. Despite the advantages of NSAID use, such as obviating the need for systemic analgesics in most patients, prolonged or frequent use can cause rare complications, such as subepithelial infiltrates, persistent epithelial defects, corneal ulceration, and corneoscleral melting.[28–30]

The efficacy of steroid use remains to be proven in randomized controlled trials.[31] Studies in the low myopic range (less than –6 D) have shown no significant difference in haze development or refractive outcome between eyes treated postoperatively with steroids or artificial tears. Many surgeons believe, however, that steroids are beneficial in those with high myopia or deep ablations. Thus, there are several approaches to the postoperative application of topical steroids. Some start steroids only if there is significant haze or scarring postoperatively. Some prefer a short course of steroids usually over a month with alteration based on haze severity. Others prefer a longer steroid course over a 4-month period with changes accordingly. Our prednisolone acetate regimen is as follows: four times a day for 2 weeks and then two times a day for 2 weeks. Alternatively, our fluorometholone regimen is as follows: four times a day for the first month, three times a day for the second month, twice a day for the third month, once a day for the fourth month, and stopping at the end of 4 months.

In the intermediate phase (second week to 6 months), uncorrected and best corrected visual acuity, corneal clarity, cycloplegic refraction, corneal topography (looking for decentration or central islands), and intraocular pressure are examined. At 6 months the presence of visually significant haze formation and scarring warrants consideration of reoperation.

ROLE OF INTRAOPERATIVE MITOMYCIN-C

Corneal haze may develop as a fine reticular subepithelial pattern about a month after PRK and usually is not visually significant. Haze usually can appear in 1–2 months, reaching peak intensity in

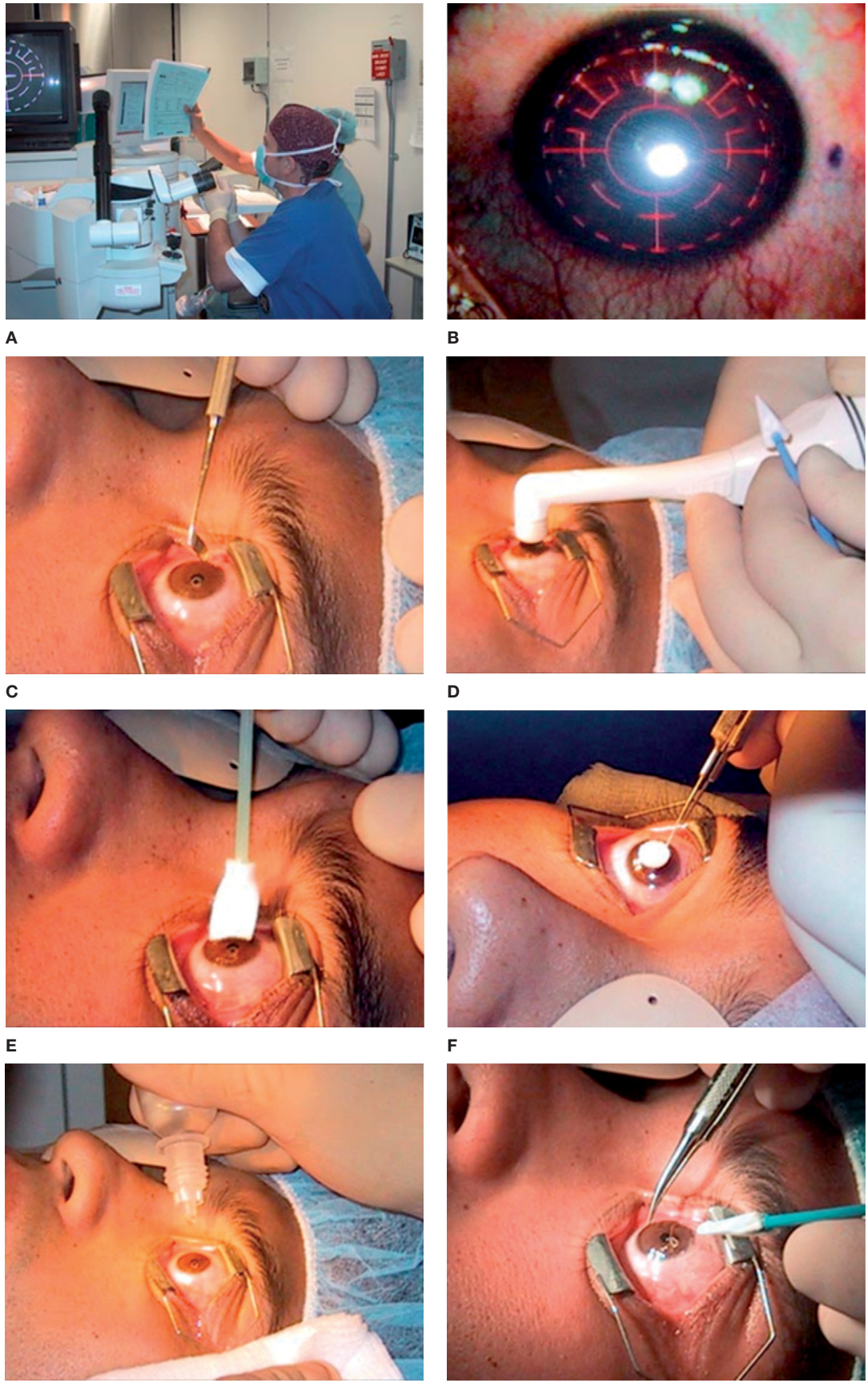

Figure 92.1. Stromal ablation (Images provided by Dr. David Tanzer). *A*, Surgeon and team verifies patient's identity and laser settings. *B*, Laser reticle is centered on pupil. *C*, Mechanical debridement of epithelium with spatula-like instrument. *D*, Mechanical debridement of epithelium with Amoils brush. *E*, Removal of epithelial debris with wet sponge. *F*, If indicated, topical application of 0.02% mitomycin-C in circular sponge on stromal bed after ablation. *G*, Copious irrigation with balanced salt solution. *H*, Placement of bandage contact lens after administration of topical antibiotics, NSAIDs, and corticosteroids.

Table 92.2 Postoperative instructions for excimer laser

Review medication in regimen and dosing frequency
Review common postoperative symptoms (e.g. blurred vision, photophobia, glare)
Instruct patient not to remove contact lens or replace it if it falls out
Encourage rest for first 3–4 days
Refrain from driving for at least 3–4 days
Limit activities leading to ocular drying (e.g. prolonged reading or watching TV)
No swimming or jacuzzi use for at least 7 days
No makeup
Keep eyes closed during bathing
Encourage sunglass use

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3–6 months, and finally resolving by about 18 months.[32] Haze and scarring after PRK have been attributed to corneal wound healing induced by activation and migration of keratocytes and newly synthesized collagen.

A potentially vision-threatening complication of PRK is the development of significant haze affecting vision. In aggressive ablations, in high myopia (greater than −6 D), and in PRK performed after previous keratorefractive procedures (incisional keratotomy, LASIK) haze formation may especially be dense and visually significant. Most strategies for haze reduction have targeted keratocyte activation after wound healing. Topical steroids have been used to inhibit haze formation after PRK. The mechanism is thought to be inhibition of collagen synthesis. Controlled clinical trials, however, have not demonstrated any significant role of haze prevention with steroids.[33,34] Recently, mitomycin-C (MMC), a popular adjunctive treatment to reduce fibrosis after surgery in certain proliferative ophthalmic conditions such as after trabeculectomy and pterygium excision, has also been used for treatment of postoperative haze.

MMC is an antibiotic derived from *Streptomyces caespitosus* with alkylating properties that allow crosslinking to DNA, thereby inhibiting DNA synthesis. Its antimetabolite properties are particularly effective in rapidly dividing cells, such as proliferating keratocytes during post-laser wound healing. Because it is radiomimetic, the effects are long term and not reversible. Keratocyte apoptosis may be the mechanism by which MMC reduces corneal scarring

Table 92.3 Postoperative management after excimer laser PRK

Postoperative Time	Medications	Factor to Monitor	Restrictions
Early (first week)	4th gen. fluoroquinolone q.i.d. Topical NSAID q.i.d. FML 0.1% q.i.d. or prednisolone acetate 1% q.i.d. Bandage contact lens Vicodin every 4–6 h p.r.n.	Re-epithelialization Corneal infiltration	3 days of rest No driving for 3 days No swimming No makeup Limit reading and TV Sunglasses
Intermediate (2nd week to 6 months)			
1st month	FML 0.1% q.i.d. or prednisolone acetate 1% q.i.d. for total 2 weeks, then b.i.d. for total 2 weeks	UCVA, BCVA	
2nd month	FML 0.1% t.i.d.	Corneal clarity	
3rd month	FML 0.1% b.i.d.	Cycloplegic refraction	
4th month	FML 0.1% q.d.	Corneal topography IOP Halo & glare symptoms	
Late (>6 months)		UCVA, BCVA Corneal clarity Cycloplegic refraction Corneal topography IOP Halo and glare symptoms	

FML, fluorometholone, NSAID, non-steroidal anti-inflammatory; UCVA, uncorrected visual acuity; BCVD, best-corrected visual acuity; IOP, intraocular pressure.

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and haze.[35] In 1991, Talamo et al found decreased haze in rabbit corneas treated with MMC before PRK.[36] Majmudar et al have shown reduction in haze formation with topical application of 0.02% MMC after de-epithelialization in corneas with subepithelial fibrosis.[37] In this study, subepithelial fibrosis was first removed with a Beaver blade. A 6 mm circular sponge (Merocel corneal light shield, Xomed Surgical Products, Jacksonville, FL) soaked in 0.02% MMC was applied on the de-epithelialized surface for 2 min and after removal of the sponge the ocular surface was copiously irrigated with balanced salt solution. With a mean follow-up of 13.8 months, all 8 eyes remained clear with no adverse events. A prospective, randomized, comparative study of 60 eyes which received prophylactic use of MMC showed a statistically significant reduction in haze formation in MMC-treated eyes.[38] A prospective, randomized study on highly myopic eyes (greater than 7 D) prophylactically treated with MMC showed again that intraoperative MMC on highly myopic eyes is safe and effective in preventing haze in high myopes.[39]

With these and other studies, intraoperative MMC is now commonly used in deep ablations (greater than 75 μm) and PRK in high myopia (greater than −6 D). When treatment correction is calculated, one must take into account the tendency of MMC to induce hyperopia. MMC prophylaxis has now also been used in higher-risk surface ablations, such as PRK over previous LASIK, radial keratotomy, and penetrating keratoplasty.[40,41]

Despite this expanding usage, there are dangers of MMC use in high concentration or long exposure times. Although a single application of MMC appears to be safe, there is much evidence of MMC toxicity. Corneal edema, glaucoma, and corneal perforation have been described after prolonged MMC use.[42,43] In an animal model, MMC has been shown to cause corneal endothelial apoptosis and subsequent corneal edema in a dose-dependent manner.[44] Another important consideration is the permanent effects of MMC in inhibiting keratocyte repopulation with subsequent decrease in keratocyte density and collagen production.[45] We believe this agent is best used judiciously while data is gathered regarding the long-term safety and efficacy of mitomycin-C.

ADVANCED SURFACE ABLATIONS

INTRODUCTION

Despite the popularity of LASIK, there has been renewed interest in surface ablative procedures for refractive surgery. The creation of the LASIK flap can be associated with significant intraoperative and postoperative complications with a potential for vision loss.[16] Furthermore, there is evidence that wavefront-guided surface ablation may be more accurate in surface ablative techniques over LASIK, as the flap creation during LASIK may affect the preoperative higher-order aberrations.[46–48] More studies are needed to assess if there is a difference in final higher-order aberrations after surface ablation versus LASIK.

As mentioned, patients who have thin corneas, moderate dry eyes, or who work as military personnel are better candidates for surface ablation. PRK, however, has been associated with greater postoperative discomfort and potential complications such as haze formation and regression, especially in high myopia. These limitations have led to the development of alternative surface ablations, also known as advanced surface ablation, in the form of LASEK and epi-LASIK.

LASEK

Laser subepithelial keratectomy (LASEK)[49] was first performed by Azar in 1996 as 'alcohol-assisted flap PRK' and later renamed LASEK by Camellin.[50] As a hybrid of PRK and LASIK, LASEK tries to combine the advantages of PRK and LASIK while avoiding the disadvantages of both procedures, such as flap complications, prolonged postoperative recovery, and development of corneal haze. In LASEK, diluted alcohol is used to loosen the epithelium and create an 'epithelial flap.' Unlike PRK in which the epithelium is removed, in LASEK the epithelial layer is peeled aside in the form of a flap and repositioned back immediately after stromal ablation. There are several variations on the LASEK technique (Fig. 92.2).

LASEK SURGICAL TECHNIQUES

Azar flap technique (Fig. 92.2, *A*)

Azar describes his technique as follows[51]: the cornea is pretreated with topical 0.5% proparacaine and 4% tetracaine, of which the latter may help loosen the epithelium. The corneal surface is marked with overlapping 3 mm circles around the periphery, simulating a floral pattern. A 7–9 mm well with a semi-sharp marker (ASICO, Westmount, IL) is placed over the epithelium and serves as a reservoir for 18% alcohol. After 25–30 s, the alcohol is absorbed through an aspiration hole. Longer times of alcohol exposure (extra 10–15 s) are recommended for young men, postmenopausal women, and long-time contact lens users, who have thicker epithelium.[52] A jeweler's forceps or modified Vannas scissor (ASICO, Westmount, IL) is inserted under the epithelium and traced around the delineated margin, leaving a hinge of 2–3 clock hours, preferably at the 12 o'clock position. A dry Merocel sponge or modified Vannas scissor is used to peel back the epithelial flap. After stromal ablation, an irrigating cannula is used to hydrate the stroma and epithelial flap with balanced salt solution. The epithelial flap is then repositioned using the cannula and intermittent irrigation, carefully aligning with the prior markings. The flap is allowed to dry for 2–5 min. Topical steroids and antibiotics are placed followed by a bandage contact lens. The bandage contact lens may be removed after complete re-epithelialization (usually on postoperative day 3 or 4).

Camellin technique (Fig. 92.2, *B*)

In this technique,[50] a specialized marking trephine of 8–9 mm is used to create a 270° superficial punch of 80 μm on the epithelium (with a 90° hinge at 12 o'clock) (Janach J2900, Como, Italy). The microtrephine is rotated 10° two or three times with constant pressure. Ethanol (20%) is placed in a specialized well of 8.5 mm (Janach J2905, Como, Italy) for 20 s. Thus in this technique, alcohol can penetrate under the flap prior to lifting. The surface is then irrigated with distilled water or balanced salt solution and then with diclofenac sodium. An epithelial 'micro-hoe' (Janach J2910A, Como, Italy) is used to fold over the epithelial flap toward the 12 o'clock position. If the epithelial edges are difficult to lift, additional alcohol treatment is administered for 15 s. After stromal ablation, a blunt instrument, such as the micro-hoe, Barraquer sweep, or a specialized spatula (Janach J2920A, Como, Italy) is used to gently reposition the flap and allowed to dry for a minute. Some advocate irrigating the stroma with chilled balanced salt solution prior to flap replacement in hopes of reducing postoperative inflammation and pain. The surface is smoothed with a masking solution of 0.25% hyaluronic acid using the algorithm of one second of appli-

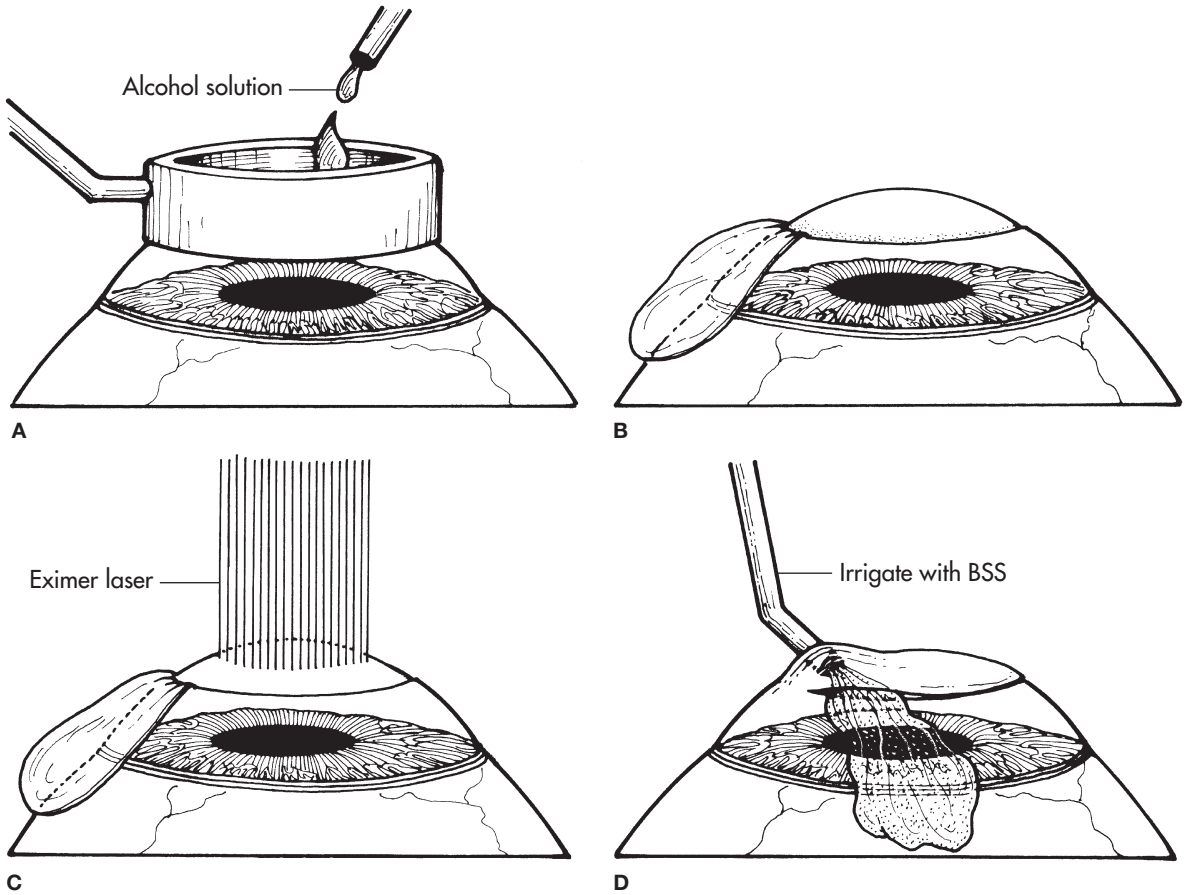

Figure 92.2. LASEK technique. *A*, Azar flap technique. *B*, Camellin technique. *C*, Vinciguerra butterfly technique. *D*, McDonald technique. (Reproduced with permission from Taneri S, Zieske JD, Azar DT. Evolution, techniques, clincial outcomes, and pathophysiology of LASEK: review of the literature. Surv Ophthalmol 2004; 49: 576–602. © 2004 with permission from Elsevier.)

cation for every one diopter of correction. If there is improper flap placement or a nonintact flap, Camellin recommends application of 100% autologous serum, which is continued as a q.i.d. regimen for 1 week postoperatively. A bandage contact lens is then placed and usually can be removed on postoperative day 3 or 4 after re-epithelialization. Topical steroids and antibiotics are also given postoperatively.

Vinciguerra technique (Fig. 92.2, *C*)

In his 'butterfly technique,'[53] Vinciguerra tries to preserve the limbal connection of epithelial stem cells and limbal vasculature. 4% lidocaine drops are instilled on the corneal surface. A thin paracentral line from 8 to 11 o'clock is made with a specialized spatula (Vinciguerra spatula, ASICO, Westmount, IL) and 20% alcohol is placed in a well for 5–30 s. After irrigation with balanced salt solution, the same spatula is used to dissect off the epithelium from Bowman's layer from the center toward the periphery on both sides. The epithelial flap is held in place with a special Vinciguerra LASEK butterfly protector/retractor (ASICO, Westmount, IL). The stromal surface is dried for ablation. A hyaluronic acid solution (Laservis, Chemedica, Munich, Germany) is placed over the stromal surface with a Buratto spatula (ASICO) and further ablation is performed at 30 µm at 10 Hz. The epithelium is repositioned and a bandage contact lens is placed.

McDonald technique (Fig. 92.2, *D*)

Also known as the 'gel-assisted technique,'[54] McDonald uses microkeratome suction and a 3% methylcellulose gel (GenTeal® gel, Novartis Ophthalmics, Duluth, GA) to create the epithelial flap. After topical anesthesia, the cornea is coated with GenTeal gel. The epithelium is marked and is scored down 1–2 mm to Bowman's layer with a 2.25 rounded knife (ASICO). Ten drops of 5% sodium chloride ophthalmic solution are placed to stiffen the epithelium and blotted dry with sponges. A microkeratome suction ring/head is placed and suction applied. A cannula is then slipped under the epithelium and a spatulating motion is made to loosen the epithelium. Suction is released after 30 s and GenTeal gel is injected under the loose epithelium. The raised epithelium is cut in half with Vannas scissors and each half is reflected with a wet sponge. After ablation, the epithelial sheet is repositioned and a bandage contact lens placed.

STATUS OF EPITHELIAL FLAP IN LASEK

Important considerations that arise in LASEK are the viability of epithelial cells in the created flap and the effect of alcohol on epithelial cells. Histological studies of LASEK flaps[49] show an intact epithelial layer with irregularities in basement membrane. No Bowman's layer or stromal cells were present. At the ultrastructural

level, there were normal desmosomes and hemidesmosomes, both of which may help in re-anchoring the epithelium after flap repositioning. The level of separation in LASEK appears to be within the basement membrane.

Chen et al have shown cultured human epithelial cells exposed to alcohol are viable but are significantly reduced in alcohol concentrations above 20% and with exposure times greater than 30 seconds.[55] In rabbit epithelial cells, 20% alcohol exposure caused alteration of surface microvilli, breaks in intercellular junctions, and cellular edema.[56]

CLINICAL RESULTS OF LASEK

With LASEK, there are no microkeratome complications and a reduced chance of epithelial flap complications. The theoretical advantages of LASEK over PRK are less pain, less haze formation, and less regression. Studies have shown reduced formation of TGF-beta in the tear film of LASEK patients compared to PRK patients,[57] thereby reducing the stimulation of haze-causing myofibroblasts. In a rabbit model, Esquenazi et al showed that at higher corrections (–7 D), LASEK-treated eyes had less keratocyte apoptosis and myofibroblast transformation than in PRK-treated eyes.[58]

EPI-LASIK

First described by Pallikaris,[59] 'epipolis' (means 'superficial' in Greek) laser in situ keratomileusis, also known as Epi-LASIK, is an alternative surface ablative procedure to PRK and LASEK. Instead of alcohol, epithelial separation is achieved mechanically with a microkeratome-like instrument with a customized blade design (subepithelial separator). The aim of this method of epithelial removal is to achieve a technique less invasive to epithelial integrity, thereby increasing cell viability and reducing the release of inflammatory cytokines. In contrast to alcohol-treated epithelium, some histological studies show minimal alterations in the epithelial cell layer with areas of intact basement membranes, desmosomes,

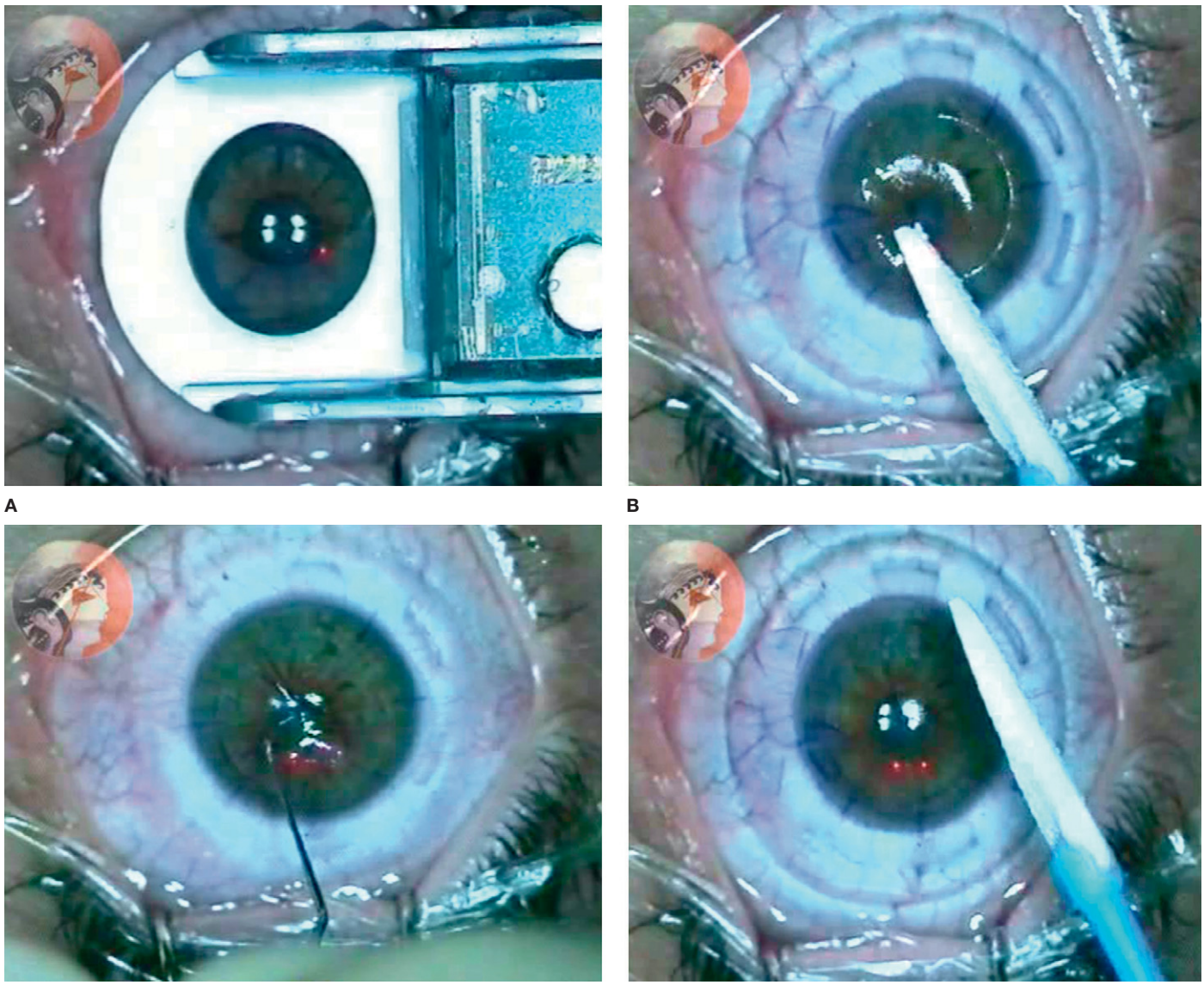

Figure 92.3. Epi-LASIK technique. (Images provided by Dr George Kymionis.) *A*, Microkeratome-like device for Epi-LASIK. *B*, Epithelial flap reflected back with sponge. *C*, Irrigation cannula used to reposition epithelial flap. *D*, Epithelial flap allowed to dry.

and hemidesmosomes.[60] As the basement membrane is believed to provide stability to the epithelial cell layer, preservation of epithelium theoretically can be achieved, if the basement membrane remains entirely intact. Thus, alcohol separation is thought to occur within the basement membrane and mechanical separation in epi-LASIK is thought to be primarily under the basement membrane, but sometimes at other levels.

In this technique, the eye is anesthetized with 0.5% tetracaine hydrochloride. The surface is then irrigated with balanced salt solution and the epithelium is dried with a Merocel sponge. The cornea is marked with a standard LASIK marker. The subepithelial separator is then placed and under suction, an oscillating blade creates an epithelial flap with a 2–3 mm hinge. The flap is reflected back with a wet sponge and the ablation is performed. The stromal bed is then irrigated and an irrigation cannula is used to reposition the flap and flatten any folds or irregularities. The epithelial sheet is allowed to dry for 2–3 min. Topical anti-inflammatory and antibiotic drops are instilled and a bandage contact lens is placed. After re-epithelialization is achieved (usually in 3–4 days), the contact lens is removed and topical steroids are started with tapering over 2 months (Fig. 92.3).

Since the introduction of the epi-LASIK technique, various microkeratome-like devices for epi-LASIK have come on the market such as Centurion SES EpiEdge (Norwood EyeCare, Duluth, GA), Epilift system (Advanced Refractive Technologies, San Clemente, CA), Epi-Blade (Advanced Medical Optics, Santa Ana, CA) for use with the Amadeus II microkeratome, and the Epi-K (Moria USA, Doylestown, PA).

CONCLUSION

The field of surface ablation in refractive surgery has developed significantly since the inception of the excimer laser. Options for patients are ever-expanding within surface ablation, allowing a more tailored procedure for each patient profile. The decision for PRK, LASEK, or epi-LASIK should be determined by the expertise of the surgeon and the needs of the patient, with a thorough discussion of the risks and benefits of each procedure.

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93 Outcomes and complications of surface ablation

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INTRODUCTION

Photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy (LASEK), and Epi-LASIK are currently the three methods of surface ablation. These procedures employ the excimer laser to ablate the most anterior portion of the corneal stroma (including Bowman's layer), and do not require a partial thickness cut into the stroma.[1] This feature allows greater retention of the biomechanical strength of the cornea in comparison to laser in situ keratomileusis (LASIK).[2–7] The visual rehabilitation after surface ablation is associated with more discomfort during the early postoperative period as compared to LASIK. In addition, the wound healing response after surface ablation is associated with increased halos and glare. With recent improvements in new surface ablation, there is an increasing trend for using these procedures to treat specific cases such as thin corneas, recurrent erosions, and topographical abnormalities in patients predisposed to ocular trauma. LASEK, the method of surface ablation introduced by one of the authors (Azar) and popularized by Camellin, creates an epithelial flap using dilute alcohol.[8–10] The flap is replaced after photorefractive ablation to reduce wound healing. Another method of surface ablation, Epi-LASIK, utilizes an 'Epikeratome' to generate an epithelial sheet without using alcohol.[11–13] Technological and methodological developments in surface ablation, wavefront technology, increased comprehension of laser–tissue interactions, increased predictability, and lower complication rates are likely to improve visual outcomes and patient satisfaction after surface ablation.[14–16]

PRK

PRK was the first ablative refractive surgery approved by the USA Food and Drug Administration (FDA). PRK came into some disfavor during the mid-1990s when laser systems did not have the capabilities of current lasers, including advanced software, accurate eye-tracking and larger ablation zones. Large series of reports on PRK often include older data, making comparison with other procedures difficult.

VISUAL OUTCOMES

Outcomes of PRK vary because it was the first procedure of wide area photoablative refractive surgery, and has a long history. Visual rehabilitation after PRK is recognized to be slower than after LASIK. Danasoury et al[2] demonstrated significantly better uncorrected visual acuity (UCVA) and best-spectacle corrected visual acuity (BSCVA) in LASIK patients than PRK patients at 2 weeks postoperatively. These results were consistent with videokeratographic analysis. After 6 weeks, there was no statistically significant difference in the refractive outcomes between LASIK and PRK.[2–5,17–21] In general, available data suggest that PRK achieves results similar to LASIK. Cumulative data with 6 months or more follow-up are shown below.

SAFETY

The percentage of eyes with a loss of two or more lines of best-spectacle corrected visual acuity (BSCVA) varies from 0.2 to 7%[2–5,18–21] and has been decreasing over the years. The data published after 2000 is almost comparable to LASIK safety.[4,5,19–21]

EFFICACY

Efficacy is defined as the percentage of eyes with UCVA of 20/20 and 20/40 or better. The cumulative data demonstrate UCVA of 20/40 or better in 93%[2,4,17–19] and UCVA of 20/20 or better in 68%[2–4,17–20] after 6 months postoperatively.

PREDICTABILITY

The predictability was indicated by the percentage of manifest refraction spherical equivalent (MRSE) within ±0.50 D and within ±1.0 D. At the 6 month follow-up, 71% of eyes were within ±0.50 D[2–4,17,19,20] and 90%[2,4,17,19] were within ±1.0 D of the desired postoperative refractive error.

COMPLICATIONS

Epithelial problems

Epithelial complications include superficial punctate keratitis (SPK), epithelial defects, and recurrent erosions. Medication toxicity is usually the cause of SPK, and discontinuation of the drops and the use of nonpreserved artificial tears should be considered. Rapid re-epithelialization after surgery is desirable for several reasons, including elimination of pain and discomfort, reduced risk of infection, and more rapid improvement of visual acuity. Re-epithelialization is usually completed within 3–4 days. NSAIDs and topical corticosteroids may inhibit re-epithelialization to a small degree and should be used in the minimal effective dose for the shortest amount of time. Persistent epithelial defects after PRK are associated with a higher incidence of corneal haze and scarring. Autologous serum eye drops may encourage healing. Although excimer laser PTK is an effective treatment for recurrent erosions, PRK may be complicated by recurrent erosion. Patients with pre-existing erosions may benefit from epithelial scraping and laser treatment of PTK. In a large series provided by Thompson et al,[22] only 1 of 2000 patients (0.05%) having PRK developed recurrent erosions postoperatively.

Dry eye

A decrease in tear flow and tear film stability has been reported 6 weeks after PRK, and was reduced up to 6 months later.[23] Tear growth factors (such as HGF, KGF, and EFG) are considerably increased after epithelial injury associated with the wound healing process.[24] The extent and duration of corneal hypesthesia depends on the ablation depth.[25] Dry eye symptoms are less common after PRK than LASIK, partially because LASIK reaches deeper into the stroma damaging more nerves than PRK for the same correction. Reduced corneal sensation causes decreased aqueous tear production, increased tear osmolarity, reduction of goblet cell density, and reduced blinking rate. In a comparative study of tear function changes after PRK and LASIK, Lee et al reported a significant reduction in Schirmer test and break up time (BUT) scores and a significant increase in tear osmolarity after 6 months after both procedures but with a greater decrease in tear film functions in LASIK patients.[23] The frequent use of unpreserved artificial tears may be helpful. Application of cyclosporin eye drops may be a good alternative. Salib et al showed that treatment with 0.05% cyclosporin eye drops provided greater refractive predictability 3 and 6 months after LASIK surgery than unpreserved artificial tears.[26] Placement of temporary collagen punctal plugs are also helpful for patients with moderate to severe dry eye patients.

Halos/glare

Glare and halos are night vision disturbances after refractive surgery. Halos may be associated with an ablation zone that is smaller than a pupil diameter in dim light condition. To avoid these problems, the optical zone diameter should match or exceed pupillary diameter in dim light condition. Aspheric corrections and peripheral blend zones help to create minimized halo effects.

Cental islands

Central islands are areas of localized steepening in the central cornea leading to multifocality.[27,28] Symptoms include ghost imaging, halos, glare, night vision disturbance, monocular diplopia and reduced BSCVA and contrast sensitivity, leading to slow visual rehabilitation.[27,28] Central islands occur in up to 70% of cases 1 week after treatment, but tend to resolve with time to an incidence of 2% at 6 months. Treatment for a central island should be delayed 6 months to 1 year.[27,28] Two hypotheses are thought to be responsible for central island formation. One theory involves ablation shock waves that might induce intrastromal shifts of water, leading to different levels of corneal hydration in the center and the periphery. The other theory is that the laser beam might be blocked centrally by the ejected vortex plume of gaseous and particulate debris generated during surgery. Central island formation is observed in some patients after treatment with broad-beam lasers, but rarely with scanning-slit and flying-spot systems.

Undercorrection and overcorrection

Undercorrection and overcorrection are among the most common complications after PRK. Two wound healing processes, including epithelial hyperplasia and stromal remodeling, affect refractive accuracy and stability.[29] The higher the myopia the higher the incidence of undercorrection. In early studies, small diameters of less than 5 mm were ablated based on evidence that postoperative haze was directly related to the size of the ablation zone. These small ablation zones, however, were associated with halos, glare, and more regression. Increased and long-lasting wound healing processes involving epithelial hyperplasia and possible stromal deposition result in undercorrection. The healing response of the epithelium may increase its thickness so that it changes the corneal curvature and reduces the refractive correction. Topical corticosteroids are sometimes used to correct undercorrection, and such treatments have been reported to reverse the effect of regression.[30] However, the long-term effects of corticosteroid therapy on refractive outcomes are not stable.[31] Undercorrection also adversely affects best-corrected visual acuity and can be accompanied by corneal haze, decentered ablation, and irregular astigmatism. Patients with severe myopia should be advised that they are likely to be undercorrected, take longer to stabilize, and may require a second procedure to achieve their optimal outcome. Over 90% of eyes have an initial slight hyperopic correction and then slight regression toward emmetropia.[29] Initial hyperopic overshoot and/or minimal healing response result in overcorrection. Usually there is no haze with overcorrection. They gradually decrease during a period of 3–4 months. The incidence of overcorrection varies with different lasers, in part because the ablation zones have different diameters. The occurrence of overcorrection depends on the magnitude of the attempted correction, even with greater regression.

Haze

Corneal haze is a very important complication of PRK, typically localized to the subepithelial anterior stroma. Two types of haze are observed after PRK. The more common type of haze is the typical transitory haze that is detected between 1 and 3 months after surgery. This type of haze is rarely associated with clinical symptoms and usually disappears within the first year after the surgery. The other type of haze, 'late onset corneal haze,' is much less common and is usually detected between 2 and 5 months after the surgery. Late onset haze affects corneal transparency and refraction. It resolves over time, but in severe cases several years may be required for full resolution.

Subepithelial haze seen after PRK has been associated with increased growth of collagen and extracellular events in the stroma. Keratocyte apoptosis may be triggered by the release of epithelial cytokines. The subsequent wound healing responses are responsible for a hazy appearance to the corneal stroma after PRK. Disappear-

ance of haze is associated with disappearance of myofibroblasts and remodeling of disorganized stromal collagen. Symptomatic haze is reported to occur in a small percentage of eyes, usually less than 0.5–3%.[32,33] The incidence and severity of haze has been shown to increase with the level of attempted correction.[32–35] Other factors such as atopy,[36] autoimmune conditions,[36] and high UV radiation exposure[37] deteriorate haze formation. Corneal haze is much more common after PRK than LASIK, reflecting the different wound healing.

Efficacy of mitomycin C

Mitomycin C (MMC) prevents haze formation after PRK. PRK-induced haze also can be improved by applying MMC. Carones et al randomized 60 consecutive PRK eyes (preoperative myopia range −6.00 to −10.00 D) into two groups: one received a 2-min intraoperative application of MMC (0.2 mg/mL) and the other did not. They concluded that the prophylactic MMC group had lower haze rates (0% of MMC eyes versus 63% of control eyes with haze higher than +1 at 6 months), better UCVA and BCVA results and more accurate refractive outcomes than those achieved in the control group.[38] Special care has to be taken because epithelial healing after MMC is characterized by prolonged latency and decreased migration rate, depending on exposure time. Permanent effects of MMC should be considered. Late side effects are reported, occurring more than 5 years after treatment.

Infectious keratitis

Infectious keratitis is a rare but potentially vision-threatening complication of PRK. Infection should be considered when corneal infiltrates are present in the first postoperative week after PRK. Many of these infiltrates are sterile, contact lens related, or associated with topical nonsteroidal anti-inflammatory agents or antibiotics. The addition of antibiotics with gram-positive coverage and removal of the soft contact lens is recommended. Central or paracentral infiltrates larger than 2 mm or infiltrates associated with significant pain or anterior chamber reaction are serious and should be smeared, cultured, followed closely, and treated aggressively as a sight-threatening condition. In a retrospective review of 25337 eyes that underwent PRK at 6 Army and Navy refractive services, culture proven or clinically suspected keratitis developed in 5 eyes of 5 patients (0.02%).[39] All cases presented 2–7 days postoperatively. Cultures from four cases grew *Staphylococcus*, including two methicillin-resistant *S. aureus* (MRSA). One case of presumed infectious keratitis was culture negative. Bandage soft contact lens use has been reported to be associated with infectious keratitis. Dantas et al evaluated bacterial contamination after 3 days of soft bandage contact lens-use following PRK in 81 eyes.[40] They found 7.4% positive cultures with normal ocular flora, probably related to topical drops and not related to contact lens-use.

LASEK

The initial enthusiasm regarding LASEK was due to the possibility of combining the advantages and minimizing the disadvantages of PRK and LASIK. In LASIK, dilute alcohol solution is used in the loosening of the corneal epithelium and the creation of an 'epithelial flap.' The loosened epithelium is moved aside from the treatment zone as a hinged sheet. The flap is not discarded but replaced immediately after laser ablation. The advantage of LASEK over LASIK is that it is free from any complication related to the 'stromal flap.' Theoretically, the existence of an 'epithelial flap' can be a barrier preventing lacrimal inflammatory cytokines from increasing stromal wound healing and can provide more comfort postoperatively and faster rehabilitation relative to PRK. If the alcohol dilution were optimal, the procedure could be almost harmless to epithelial viability.

VISUAL OUTCOMES

Slow visual rehabilitation is the major drawback of LASEK (in the same way as PRK). Functional visual acuity is obtainable within a week postoperatively, while it takes more than a month for refractive stability. Early stage post-LASEK status is included in the study of Taneri et al.[9] Most eyes had a UCVA of 20/40 or better at 1 week, and only 25% reached 20/20. At 4 weeks, the eyes with a UCVA of 20/20 stabilized at 69–79% until the 1-year visit. Excellent long-term refractive outcomes for LASEK treated eyes were demonstrated by many studies.[9,11,41–49] Anderson et al[44] conducted the largest study of LASEK treated eyes. They treated and followed 343 eyes for up to 6 months. In this study, the authors reported that 85% of LASEK treated eyes were within ±0.50 D and 94% were within ±1.00 D of the intended correction at 6 months ($n = 115$); 98% of eyes maintained UCVA of at least 20/40 through 6 months ($n = 122$). The longest report was provided by Autrata and Rehurek.[47] They treated 92 patients with low to moderate myopia. At 24 months, 73% of eyes and 92% of eyes had UCVA better than 20/20 and 20/40 respectively, with 62% of eyes within ±0.50 D and 92% of eyes within ±1.00 D. From months 12 to 24, there was almost no change in refraction. The cumulative data for a 6-month period is shown below.

SAFETY

In reports mentioning loss of BSCVA of 2 or more lines, the cumulate percentage rate, excluding retreatments, is 0.8%.[9,11,41–49] Kim et al reported that the main reasons for decreased BSCVA were stromal opacity with myopic regression, irregular astigmatism, and eccentric ablation.[48]

EFFICACY

After 6 months postoperatively, 95% and 71% achieved an uncorrected visual acuity (UCVA) of 20/40[9,11,41,44,45,48,49] and 20/20[9,11,41,43–46,48,49], respectively.

PREDICTABILITY

At 6-months follow-up 78% of eyes were within ±0.50 D[9,41,43–46,48,49] and 88% were within ±1.0 D of the desired postoperative refractive error.[9,43–46,48,49]

COMPLICATIONS

Intraoperative complications

Alcohol leakage

This complication may be decreased with improved surgical skill. The incidence of leakage is 1–3%.[43] Excess pressure on the alcohol solution cone and non-cooperative patients are potential causes. Alcohol leaks should be removed immediately and thorough irrigation of the conjunctiva including fornix is required. Patients often complain of pain for several days after alcohol leakage. No addi-

tional complication such as corneal or limbal erosion and limbal deficiency are reported.

Incomplete epithelial detachment

Incomplete epithelial detachments, such as a tear in the flap, buttonhole, or fragmented flap are possible. The incidence of incomplete epithelial flap is less than 5%.[50] The epithelium of contact lens wearers tends to be more adherent and may increase the risk of an incomplete flap.[50] If necessary, alcohol application may be repeated for an additional 10–15 s. If the flap is torn or otherwise damaged, the surgeon can safely revert to PRK.[50]

Postoperative complications

Epithelial problems

Preservation of the epithelial flap is one of the potential advantages of LASEK over PRK. Intact epithelial sheets will settle and adhere by day 3. In Azar's series, 63% of patients had an epithelial defect on day 1, 9% on day 3, and no defect at 1 week.[8] Whether re-epithelialization is faster after LASEK than after PRK is still controversial. Delayed epithelial stability increases inflammatory responses. Treatment for persistent epithelial defects is the same as PRK.

Undercorrection and overcorrection

Residual myopia is caused by insufficient initial treatment, more commonly observed in high myopia. If there is an undercorrection and the patient is not satisfied with the level of vision, additional treatment may be performed. It can be easily managed with an enhancement procedure by removing the epithelium, sometimes without alcohol, and adding the undercorrected value to the laser. This maneuver must be performed within 1 month after the surgery.

Slight overcorrection is observed more often than PRK. Patients with overcorrection may experience blurred vision when viewing objects up close. Dehydration of the stromal bed (by alcohol application) is thought to be the reason. A nomogram adjustment of 5–10% reduction compared to the PRK computed treatment is recommended.

Haze

Haze formation usually peaks at 3 months postoperatively and resolves by 1 year postoperatively. It is postulated that the LASEK flap can reduce stromal infiltration of cytokines from tears, the release of cytokines from damaged corneal epithelium, and subepithelial keratocyte apoptosis. In animal models, LASEK induced less keratocyte apoptosis and myofibroblast transformation.[51,52] Most reports involving LASEK treatment for low to moderate myopia without MMC describe low levels (0–13%) of haze formation. Series involving the treatment of moderate to high myopia report visually significant haze formation in 8–10% of LASEK treated eyes. Risk factors of haze formation after LASEK procedure are almost the same as PRK. Haze tends to be severe in deeper ablation. Lin et al showed that an ablation depth of 100 µm or deeper increases the risk of haze formation.[53] Superiority of LASEK over PRK in haze formation is reported. Lee et al showed a lower haze rate of LASEK than PRK at 1 month after surgery.[54] Autrata and Rehurek demonstrated less haze in 108 LASEK eyes than in 108 PRK eyes at 1–24 months after the surgery.[47] The mechanisms of lower haze incidence is explained by the lower expression of TGF-beta1 in the tear after LASEK than after PRK[54]; TGF-beta1 is a key regulator of wound healing process after refractive surgery.

Dry eye

Postoperative tear function and ocular surface status is similar to that of PRK. Horwath-Winter et al reported that the BUT value and corneal sensation were decreased up to 1 month postoperatively and vital staining scores increased for up to 1 week after LASEK.[55] These tear function and ocular surface test results after LASEK were better than those of other reported results after PRK. Decreased inflammatory reactions after LASEK than after PRK can explain decreased dry eye symptoms.[54]

Glare and halos

The incidence of glare and halos after LASEK seems to be similar to PRK. Halos occur when either the pupil size in dim light exceeds the effective optical zone size or when there is a de-centered ablation. A halo may be a pronounced form of spherical aberration. Persistent halos are rare and diminish with time, if at all.

Pain

A LASEK flap was expected to reduce the postoperative pain covering the ablated surface of the stroma when compared to PRK. Several studies demonstrated less pain associated with LASEK than with PRK.[47,56,57] Mild discomfort and foreign body sensation are seen in LASEK during the first few days postoperatively. The peak time for pain after LASEK is usually on the second postoperative day because discomfort originates from the contact lens, whereas in PRK it is usually on the first postoperative day. Irregular adhesion of the epithelial flap to the stromal bed and occasional sloughing of the flap can induce more pain than PRK. Most postoperative pain is ameliorated after full epithelialization.[29]

EPI-LASIK

Unlike LASEK, epi-LASIK does not use alcohol to remove the epithelium. Therefore, the potential toxic effects of alcohol to the cornea are avoided. Our review of the literature showed a relatively small number of reports.[6,12,15,16,58–60] Further studies are necessary to evaluate the results of EPI-LASIK in comparison to PRK and LASEK.

VISUAL OUTCOMES

Unlike studies in LASEK, improved visual rehabilitation has not yet been demonstrated in Epi-LASIK. Pallikaris et al reported the visual recovery of 44 eyes that received epi-LASIK.[14] They showed that 38% of the treated eyes had a UCVA of 20/40 or better at day 1, 85% of patients had a UCVA of 20/40 or better, and 34% had a UCVA of 20/25 or better at day 3. At the 1-month postoperative visit, 95% of the patients had a UCVA of 20/40 or better and 65% had a UCVA of 20/25 or better. At the 3-month postoperative visit, 96% had a UCVA of 20/40 or better and 92% had a UCVA of 20/25 or better. No eye lost more than 1 line of BSCVA. Seventy-eight percent of treated eyes were within ±0.50 D, and 100% were within ±1.00 D of the targeted refraction.

COMPLICATIONS

Intraoperative complications

As with LASEK, intraoperative complications of Epi-LASIK are rare and are usually not serious. Kim et al reported inadvertent stromal dissection during mechanical separation of the corneal epithelium

using an epikeratome.[15] The reported incidence of the intraoperative complication is 2 out of 91 eyes (2%). In one case, the stromal flap was dislodged during epithelial removal. This may have resulted in uneven photoablation and postoperative irregular astigmatism, according to the thickness and dimension of stromal loss. These cases were retreated with PRK 8 months after the first surgery. Dai et al reported that one case of stromal tissue remained among 289 eyes (0.3%), and free epithelial flaps were made in 12 eyes (4%).[16]

Epithelial viability

Epi-LASIK was developed to reduce corneal epithelial damage caused by alcohol application in LASEK.[13] However, some studies suggest that correct and consistent usage of alcohol for LASEK is not harmful on epithelial viability.[58,59] The plane of dissection is within the basement membrane in LASEK[8,59] but underneath the basement membrane in Epi-LASIK.[6] It is widely accepted that the adherence of the basement membrane to basal epithelial layer is important for the epithelial integrity.

Postoperative complications

Pain

Epi-LASIK is not a pain-free procedure. Dai et al showed that mild discomfort was reported by 93.4% of his 150 patients and moderate symptoms in 6.6% patients.[16] Pallikaris et al[14] showed five (16%) patients reported burning pain that required medication, and the rest of the patients reported no pain (20 patients, 65%) or mild discomfort (6 patients, 19%). By the third postoperative day, there was no pain or discomfort in the eye treated with Epi-LASIK. There is no improvement from LASEK in this regard.

Haze

In comparison with PRK, the incidence of haze after the surgery is less with Epi-LASIK. Recently, Long et al reported that Epi-LASIK reduced the incident of haze formation and lowered levels of TGF-beta1 in tear fluid, compared to LASEK.[60]

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94 LASIK complications

Louis E. Probst

INTRODUCTION

The safety profile of laser in situ keratomileusis (LASIK) has dramatically improved over the last 8 years. LASIK technology has improved with better microkeratomes and scanning excimer lasers that allow for bigger and smoother ablation zones. Surgeon experience has also increased dramatically. These factors have reduced the number of intraoperative contraindications for LASIK. The postoperative complications have also been reduced by the increased awareness of the contraindications for LASIK. LASIK is an elective procedure and, therefore, the complication rate must be low in order for it to be an accepted refractive procedure. Most LASIK complications can be corrected so that no long-term problems persist. However, there are some uncommon complications that can have permanent visual consequences. There are a few LASIK complications that are unique for hyperopic corrections. LASIK complications can be conveniently divided into intraoperative, early postoperative, and late postoperative complications.

INTRAOPERATIVE LASIK COMPLICATIONS

Intraoperative LASIK complications are often preventable with appropriate safeguards of the surgical system. If the equipment is defective or set up incorrectly, a complication is almost certain. Therefore, the key to minimizing LASIK complications is prevention. Proper training and a high degree of focus is essential for both the surgeon and the surgical technicians to minimize operative errors.

A recent retrospective study evaluated the intraoperative flap complications in 84 771 cases of LASIK with the automated corneal shaper (ACS) or the Hansatome.[1] The rate of all flap complications was 0.302%, with failures to achieve intraocular pressure (IOP) in 0.034%, partial flaps in 0.099%, buttonholes in 0.07%, thin or irregular flaps 0.087%, and free flaps in 0.012% of eyes. There were 134 right eye complications and 122 left eye complications. No patient developed an intraoperative flap complication in both eyes. Flap complications have been found to be more common with the ACS as compared to the Hansatome,[2] as success with the ACS is more surgeon experience dependent.

PREVENTION OF INTRAOPERATIVE COMPLICATIONS

Prior to the LASIK procedure, all the equipment should be checked, as any failure of the equipment could result in a flap complication. This is often referred to as the 'preflight checklist.' The microkeratome blade should be checked before every LASIK procedure. The microkeratome blades supplied by the manufacturer can be defective. Nicks or irregularities of the cutting edge will produce a linear ridge through the flap or a split flap.[3] It is difficult to check the microkeratome blade once it is loaded in the microkeratome, as the edge is not well reflected by the light of the microscope. Once the blade is loaded in the microkeratome, it should be checked to make sure it is mobile. It is possible to hear the sound of the microkeratome motor running and have no blade movement if the blade is loaded into the head incorrectly. If a microkeratome pass is made with an immobile blade, a thin irregular flap will result. A test run should then be performed of the microkeratome to ensure that it is running smoothly in the microkeratome track. The resistance level on the Hansatome box gauge should be less than 20. If the gauge is running in the 20–30 range, a drop of proparacaine on the blade and the gears usually causes the resistance to drop into the below 20 range. If the resistance is still in the 20–30 range, the microkeratome should be reassembled as there is excessive blade resistance. Low levels of suction have been experienced when suction tubing was not properly inserted into the suction unit. Therefore, it is important to always check the suction at the beginning of each day to make sure the suction unit is functioning properly. Finally, it is important to confirm the IOP has risen to an adequate level prior to performing the keratectomy. The pressure should be well above 90 mmHg when checked with the 90 mm Barraquer tonometer.

BUTTONHOLE AND IRREGULAR FLAPS

Buttonhole flaps occur when the keratectomy has been performed without adequate suction. The microkeratome produces a meniscus-shaped flap that is thinner in the center so any additional thinning due to the low suction results in a break in the center of the flap creating a buttonhole flap. Although an increased risk of buttonhole

flaps has been suggested with steep corneal keratometry readings (>50 D), this has not been the experience of this author or published in the literature.[4]

Clinical: The buttonhole flap is evident immediately after the microkeratome has completed the reverse pass. The central aspect of the cornea will appear irregular with a 2–3 mm diameter irregular circle in the center representing the buttonhole. If the flap is lifted, it will be thin and difficult to manipulate. The defect through the center of the flap will be obvious (Fig. 94.1). The stromal bed has a clear area in the center about 2–3 mm in size that is slightly elevated representing the uncut area of cornea where the epithelium is still present. After 1 month, haze will form around the edges of the buttonhole (Fig. 94.2).

Management: Performing the laser ablation will result in an irregular astigmatism with central corneal haze. If the buttonhole is identified immediately, the flap should not be lifted. Gentle interface irrigation will allow the flap to be re-floated into position. If the flap has been lifted, the flap should be replaced, and then re-floated into position. This can be difficult as the flap is thin and very unstable. The eye is allowed to heal for at least 3 months. LASIK can be performed again using a deeper plate. Topical steroids are tapered during the healing phase to reduce the risk of haze formation. Although immediate transepithelial photorefractive keratectomy has been reported following flap complications,[5] this technique is not recommended by the majority of refractive surgeons.

Prevention: Buttonhole flaps can be prevented with techniques and precautions discussed above. The keratectomy should never be performed without excellent suction and a perfect blade.

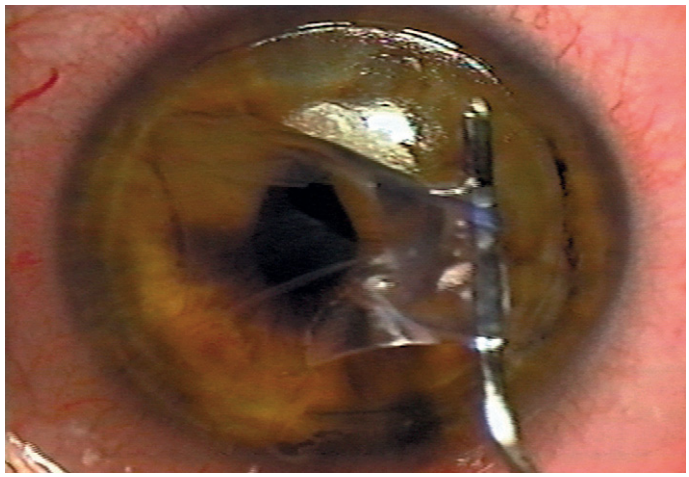

Figure 94.1. Intraoperative view of a buttonhole flap with the cannula protruding through the center of the buttonhole.

THIN FLAPS

The average flap thickness for each microkeratome is variable. The Hansatome generally cuts about 40 μm thinner than the depth indicated on the depth plate. There is also considerable standard deviation in the average cut thickness which is generally about 25 μm.[6,7] Therefore the flap thickness can vary considerably, often between 100 and 200 μm. The Nidek MK-2000 microkeratome also cuts about 20 μm thinner than the depth plate number.[8] Because of this variation, the LASIK surgeon has little room for error if the flap is thin.

Clinical: Thin flaps can be immediately identified after the keratectomy as they tend to role along the distal cut edge. Flaps of 100 μm or more do not demonstrate this pattern. Very thin flaps can be associated with complete buttonhole flaps or partial buttonhole flaps when the central flap is only composed of epithelium. If the suction level was poor or the blade was not moving during the keratectomy the flap and the stromal bed will be irregular. This is best seen with the reflections of the microscope illumination lights. Striae are also more prominent with thin LASIK flaps. The superficial corneal stromal is less hydrated than the deeper stromal so the stromal bed of a thin flap will appear less moist and more reflective. Once a very thin flap has healed a hazy area with irregular striae will form in the center of the cornea (Fig. 94.3).

Management: When a thin flap is achieved the surgeon must evaluate the flap and the stromal bed. If the stromal bed is smooth and the flap itself is smooth, LASIK can still be performed with an excellent outcome. If the stromal bed is not smooth or there are perforations or buttonholes of the flap, then performing the laser ablation will result in irregular astigmatism with central corneal haze.

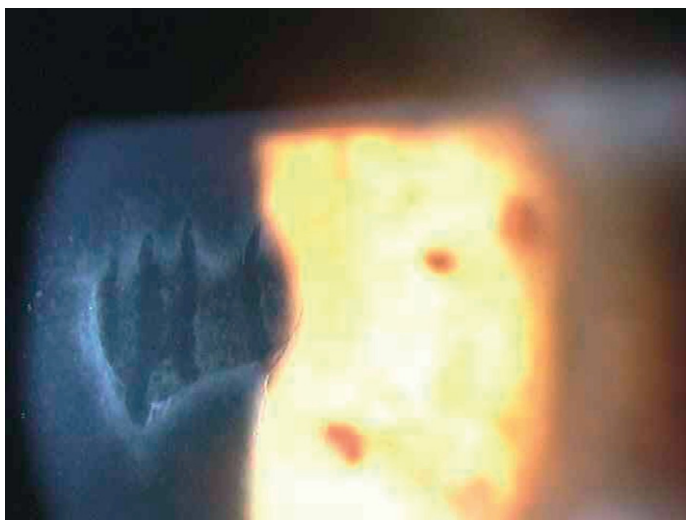

Figure 94.2. One month after a buttonhole with an irregular haze pattern surrounding buttonhole.

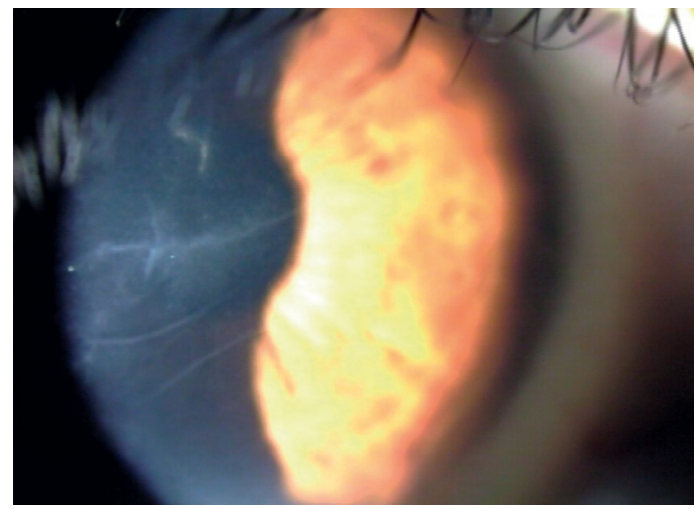

Figure 94.3. Central corneal haze and irregular striae after a thin flap.

In the case of an irregular flap with an irregular stromal bed, the flap should then be replaced and the cornea is allowed to heal for 3 months. LASIK can be performed again using a deeper plate. Topical steroids are tapered during the healing phase to reduce the risk of haze formation.

Prevention: Thin flaps are prevented with the safeguards listed above. The keratectomy should never be performed without excellent suction and a perfect blade.

FREE CAP

A free cap occurs when the microkeratome does not stop to create a hinge but rather continues across the cornea severing the flap from the bed, thereby creating a free cap. Free caps usually occur for two reasons. In eyes with very flat preoperative Ks, a free cap can occur on some microkeratomes such as the ACS when the Ks are less than 41.0 D. A free cap can also occur if there is a very thin flap due to inadequate pressure. This flap would tend to be smaller in diameter, more central in the cornea, with an irregular edge.

Clinical: Free caps are circular and completely separated from the stromal bed. If the free cap is thin, the edges may be irregular and the free cap will fold onto itself when manipulated. If the free cap is of normal thickness, it will maintain rigidity when lifted (Fig. 94.4).

Management: If the suction level was low and the stromal bed is irregular, the flap should be replaced and allowed to heal without performing the excimer laser ablation. If the free cap occurred because of low preoperative keratometry reading, the stromal bed may be smooth and the free cap of normal thickness. In this case, the ablation can be continued with an excellent outcome. The free cap should be carefully placed epithelial side down on a drop of balanced salt solution in the antidesiccation chamber while the ablation is being performed. The antidesiccation chamber should be then covered with a sterile container to ensure that it is not inadvertently knocked off the surgical tray. Once the ablation is performed the free cap can be replaced and aligned using the alignment marks that were placed prior to the keratectomy. It is important to ensure that the epithelial side of the free cap is up and that the epithelial marks are well aligned, otherwise astigmatism will be induced postoperatively because of incorrect flap orientation.

Prevention: In eyes with keratometry readings less than 42.0 D, it is advisable to use the Hansatome or a larger microkeratome head (9.5) on the Nidek Mk-2000. This author has performed LASIK with the Hansatome on Ks less than 37 D and not created a free cap.

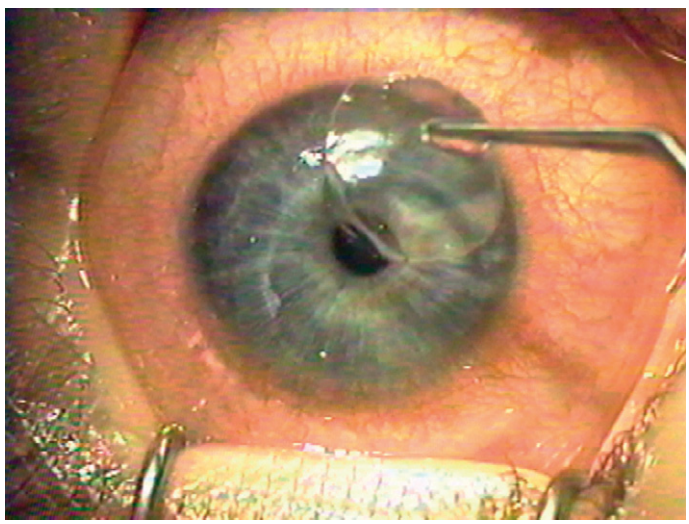

Figure 94.4. This free cap maintains some rigidity as it has a normal thickness.

CORNEAL PERFORATION

Perforation of the cornea during the keratectomy is the most feared and rare complication of LASIK. It was first reported with the ACS microkeratome when the depth plate was not properly screwed into the microkeratome head. Without the depth plate to restrict the cut depth, the blade would cut straight into the cornea causing penetration into the anterior chamber with extrusion of the intraocular contents due to the elevated IOP. When the Hansatome was introduced with a fixed depth plate, this problem was thought to be eliminated. However, this problem was more recently reported during the early introduction of the Nidek MK-2000 microkeratome. Once again, it was the incorrect assembly of the microkeratome that allowed this complication to occur. Nidek has since required that a plastic wedge is placed in the hinge of the MK-2000 that prevents corneal perforation even if the head is not properly assembled.

Clinical: This complication is obvious during the advancement of the microkeratome as there is a sudden release of a jet of fluid as the cornea is penetrated followed by a loss of suction with beeping from the suction pump. The suction should be disengaged immediately. Removal of the microkeratome reveals the penetration which could be associated with extruded iris and/or lens material.

Management: Corneal perforation is managed by preserving as much intraocular tissue as possible, suturing the corneal incision to restore the anterior chamber, and immediate referral for further evaluation/surgery that may be required. An emergency surgical kit that includes a needle driver and sutures should be available in every laser center.

Prevention: Careful microkeratome assembly is critical for successful LASIK. LASIK staff should be well trained for correct assembly as well as the pitfalls of incorrect assembly. The surgeon should always check the microkeratome to insure that it has been properly assembled.

LASER-RELATED COMPLICATIONS

Laser-related complications are perhaps the most frustrating LASIK complication as they are usually completely preventable. The most embarrassing complication is incorrect laser programming. Often this task is left to a technician, who may read a number incorrectly or simply have a typing error. The most insidious programming problems occur with prescription transposition errors. On rare occasions, the excimer laser will actually fail in the middle of a procedure.

Clinical: There is little to warn of incorrect laser programming during the procedure. The result will become obvious postoperatively when the patient does not achieve a good uncorrected visual acuity (UCVA). If there was a transposition error, or an astigmatism axis error the resultant astigmatism may be magnified in a new axis.

Management: Errors in laser programming can be corrected by an enhancement procedure; however the best strategy is prevention with multiple checks. If laser failure occurs, the flap should be replaced and the patient taken from the surgical room. The percentage of the correction performed should be recorded, in case all data

is lost from the laser. The laser company should be called to determine the cause of the failure. Often, with company guidance, steps can be taken that return the laser to full functioning. Most excimer lasers have the procedure in memory so the patient can be brought into the room and the procedure continued from the previous point with no detrimental effect on the outcome. Patient reassurance during this phase is critical to maintain confidence.

Prevention: It is essential to check and double check all programming prior to performing LASIK. One technician can read the programming to the other technician, who verifies the information to ensure that they both have confirmed the numbers. It is very easy to make transposition errors when converting from plus to minus cylinder, therefore the refraction calculations should also be checked. It is helpful to compare the axis and sign of the refractive astigmatism with the astigmatism on the topography to make sure that they are similar. Any discrepancy, particularly those 90° apart may indicate a transposition error.

EPITHELIAL DEFECTS AND ONE-DROP LASIK

Intraoperative epithelial defects (IED) during LASIK can result in a number of highly undesirable complications including prolonged visual recovery, postoperative pain, diffuse lamellar keratitis (DLK), and epithelial ingrowth. Therefore, the LASIK surgeon must strive to avoid this complication in every way possible. A recent study evaluated the risk factors for IEDs during LASIK.[9] IED occurred in 9.7% of 247 eyes. IED significantly increased with older age, preoperative corneal thickness, and maintenance of suction ring vacuum during the reverse pass of the microkeratome. Fewer preoperative drops resulted in fewer IEDs. In patients undergoing bilateral LASIK, the incidence of IED was much higher in the second eye if the first eye developed an IED.

Clinical: IEDs are noted immediately after the keratectomy as irregular areas along the epithelial surface of the cornea. A flap of epithelium can sometimes be seen hanging over the corneal flap (Fig. 94.5). The displaced epithelium is usually edematous and grey in appearance. IEDs can be <1 mm or as large as the entire corneal flap. The flap is usually intact and healthy beneath the defect. IEDs usually occur along the superior edge of the flap where the epithelium is less adherent.

Figure 94.5. Loose flap of epithelium after LASIK.

Management: If an epithelial defect occurs during the treatment of the first eye, the surgeon should continue with the laser treatment, replace the LASIK flap, and place a bandage contact lens over the eye if the defect is greater than 3 mm in size. If the defect is extremely large, it may be elected not to proceed with the treatment of the second eye until the first eye has healed.

The patient must be observed daily for evidence of infection and a prophylactic antibiotic should be used postoperatively at least until the epithelial defect has healed. For small epithelial defects, reassurance that the foreign body sensation will resolve, lubrication, topical NSAIDs to reduce the foreign body sensation, and a topical steroid to control potential interface inflammation may be all that is required. Small epithelial defects will generally heal within 1–3 days. For larger epithelial defects, a bandage contact lens (CTL) should be inserted with care not to disturb the flap. A bandage contact lens with a base curve of 8.4 mm generally fits well. Topical NSAIDs have been associated with sterile corneal infiltrates, therefore they should only be used for 3–4 days.[10,11] Topical steroids should be used at least every few hours as the risk of interface keratitis is higher with larger defects. Oral agents such as sedatives or narcotic agents are required rarely and used only in selective cases as it is far better to have the patient aware of any continued discomfort so that the center can be notified. Pressure patching is contraindicated as patient eye movement against the firmly applied eyelid may create excessive shearing forces and displace the flap. After lubricating drops to hydrate the CTL and topical anesthetic have been instilled into the eye, the bandage CTL can be removed. The ideal technique for CTL removal is to have the patient look up while at the slit-lamp biomicroscope; in this manner the inferior aspect of the CTL is visible and may slide down. Using fine non-toothed forceps, the inferior aspect of the CTL is firmly grasped and the CTL pulled down and away from the eye.

Prevention: One technique that is extremely effective for reducing epithelial defects is 'one drop LASIK'.[12] No preoperative drops are put in the eye prior to LASIK to minimize the toxic keratopathy that greatly increases the risk of epithelial defects. The patient is brought into the laser room and placed under the laser. One drop of topical anesthetic is placed in the eye and then a Murocel sponge soaked in a combination of proparacaine, NSAIDs, steroid, and antibiotic is placed under both lids. In this way we are able to achieve appropriate anesthesia, anti-inflammatory, and antibiotic effect in the eye while reducing the time of exposure so there is limited opportunity for the development of a toxic keratopathy.

Patients that have pre-identified weakness with the epithelium including anterior basement membrane dystrophy or loose epithelium or a skin condition such as acne rosacea are prone to epithelial defects. These patients will be better treated with a nasal hinge flap as the rotary movement of the Hansatome will cause more epithelial friction with a greater incidence of epithelial defects. This author currently uses a nasal hinge flap in approximately 90% of standard myopic LASIK cases and superior hinge flap for hyperopes, wide zone ablations, mixed astigmatism, and large pupils.

LOOSE EPITHELIUM

Loose epithelium may be noted prior to the LASIK procedure or more commonly after the keratectomy. This occurs more commonly in patients over the age of 40 years and those with a history suggesting loose epithelium such as recurrent corneal erosions, previous eye trauma, or obvious anterior basement membrane dystrophy.

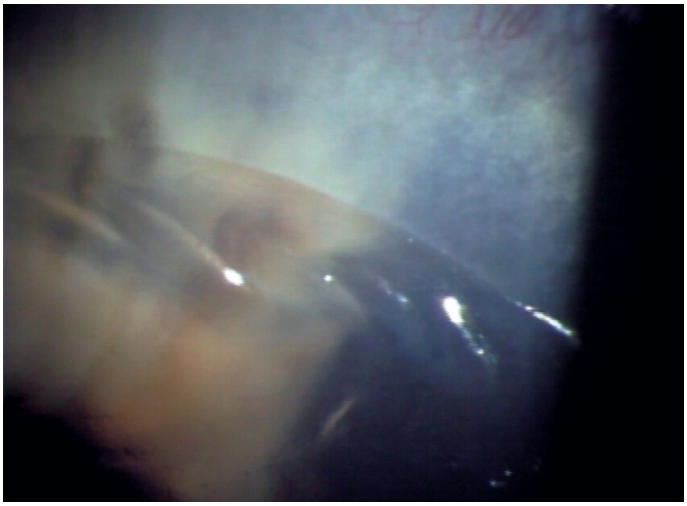

Figure 94.6. Loose superior epithelium immediately after LASIK.

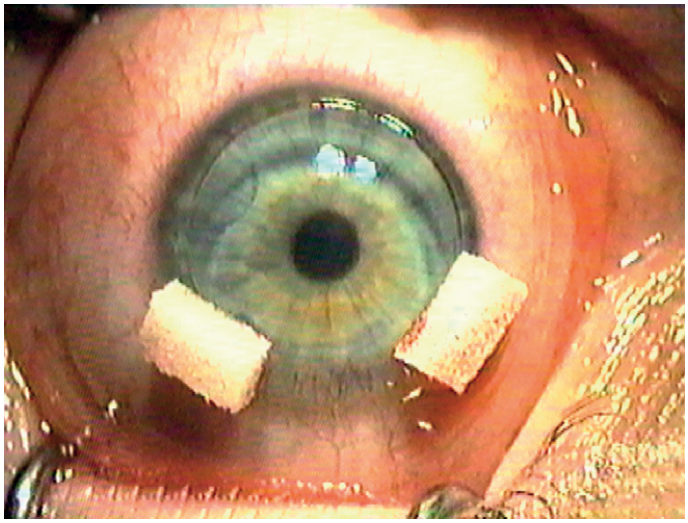

Figure 94.7. Sponges are used to control corneal bleeding during LASIK.

Clinical: Loose epithelium can present in different manners depending on the levels of severity. Mildly loose epithelium will present with a rippled appearance along the cornea surface most commonly seen along the superior flap edge after the keratectomy (Fig. 94.6). Severe loose epithelium can result in large sheets of detached epithelium after the keratectomy with epithelial defects. There is usually some attached epithelium along the inferior flap edge.

Management: Loose epithelium identified after the keratectomy can generally be replaced with gentle pressure along the surface of the flap. Surprisingly, this epithelium will remain in the new replaced position as long as the rest of the epithelium is intact and attached. Large flaps of detached or displaced epithelium are best removed while carefully preserving the remaining attached epithelium. A CTL should then be placed on the eye; this is left in place for 1–3 days to allow the epithelium to attach to the basement membrane of the cornea. Careful removal of the contact lens should reveal healthy attached epithelium.

Prevention: Loose epithelium identified preoperatively should alert the LASIK surgeon to a higher risk of epithelial loss and defects during the LASIK procedure. While the 'one drop LASIK' technique and a careful surgical technique can prevent these complications, photorefractive keratectomy (PRK) or laser assisted subepithelial keratectomy (LASEK) should be considered for low spherical corrections to avoid the risk altogether. If LASIK is still the preferred procedure, a nasal hinged microkeratome will minimize the risk of loose epithelium and epithelial defects.

NEOVASCULAR BLEEDING DURING LASIK

When LASIK was first performed using nasal hinge flaps with the ACS microkeratome, corneal bleeding was not common. The 8.5 mm flap rarely intersected the corneal vessels and if it did, only the superior vessels were involved, which was not a problem to control.

Clinical: With the advent of larger flaps particularly with those created by the Hansatome, it is not uncommon to have corneal neovascular bleeding during the LASIK procedure. Hyperopes tend to have smaller eyes with a greater incidence of neovascular bleeding. Generally, neovascular bleeding occurs immediately after the keratectomy along the superior flap edge. It may be self-limited, lasting for less than a minute or persist for several minutes depending on the size of the vessels cut and the coagulation status of the patient. There are occasions when bleeding occurs 360° around the cornea and can cause difficulties both during the ablation and after the procedure because of bleeding underneath the flap.

Management: Once the flap is cut and it is obvious that there is neovascular bleeding the suction ring can be left in place and downward pressure from the suction ring can tamponade some of the bleeding vessels. The flap is lifted and the bleeding vessels can be dried with a dry Murocel spear.

If there is continued bleeding which could extend into the ablation area then dry rectangles of instrument wipe cut in 2×4 mm segments are placed on the area of bleeding (Fig. 94.7). These are available from Hurricane Medical (Probst LASIK sponge) or can be prepared beforehand by the surgical technician by simply taking an instrument wipe and cutting it into those segments. This allows the ablation to be performed without further interruption. The sponges can be removed and the flap replaced with copious irrigation to make sure there is no further bleeding underneath the flap. The same sponges which have been soaked in Iopidine (apraclonidine HCI) are placed over the areas of bleeding. Iopidine is used as it is an alpha 2 agonist with a vasoconstrictive effect without the pupillary dilation that occurs with phenylephrine. The sponges are left in place for approximately 1 min while the flap is adhering to the stromal bed.

Prevention: There are several maneuvers that can be used to prevent bleeding during the LASIK procedure. When the 9.5 mm suction ring is first placed on the eye, neovascular vessels extending into the exposed cornea will be cut. In this case, the ring can be switched to the 8.5 mm ring so that the neovascular bleeding can be minimized. This author does not use an 8.5 mm ring routinely as this ring more commonly decenters which does not occur to the same degree with the 9.5 mm ring. Pretreatment with Alphagan (brimonidine tartrate) has been suggested to reduce the incidence of intraoperative bleeding; however, this potential benefit must be balanced with the increased width of postoperative slipped flaps.

THE ANXIOUS PATIENT

There is a reasonably high incidence of general anxiety disorder in the population in general which is of course magnified by the normal fears associated with the LASIK procedure. There are also patients who are claustrophobic, who may be fearful if they have had past experience with an MRI. Younger patients are more anxiety prone than the older patients. They have difficulty controlling their anxiety, as well as being extremely sensitive around their eyes, which seems to be a trait particularly common to young males.

Clinical: Anxiety is displayed in countless ways by patients; however, the best measure of identifying the problem is noting increased tension in the surgical suite. As soon as this is noted, the surgeon must make a careful analysis of the source of the problem and address it before further complications arise.

Management: If a patient appears to be anxious, they should be isolated from the other patients so that the anxiety is not propagated throughout the center.

Anxious patients should be evaluated and treated as quickly as possible rather than have them wait while their anxieties build. Preoperative sedation should be used generously whenever someone appears to be anxious. The anxiety prior to LASIK is related to a feeling of helplessness and a loss of control. Patients need to understand that there is no immediate need to do LASIK. Patients should also understand that they can have only one eye treated. Some patients appreciate being able to check their vision with their first eye before continuing with their second eye. Sometimes it is helpful to have the husband, wife, parent, or friend hold the patient's hand during the procedure. If there is any sense of anxiety when the patient is underneath the laser, the procedure should be postponed.

Prevention: Anxiety is demonstrated in many different ways depending on the personality of the patient. Some patients make identification easy by announcing their anxiety as they arrive at the center. Introverted patients will sit quietly in the consultation room; however, they will often leave their coats on, cross their arms and legs, avoid eye contact, and sweaty palms may be noted during the introductory handshake. Extroverted patients will talk in loud tones, pace around the room, make multiple trips to the bathroom, and talk to everyone they can find about the procedure. The challenge for the surgeon and the staff is to identify every anxious patient so they can be appropriately addressed prior to LASIK.

DEEP-SET EYES

Deep-set eyes are more difficult to treat as the palpebral opening is crowded by the prominent orbital bones.

Clinical: Patients with deep-set eyes can be identified preoperatively by their small palpebral fissures, prominent superior orbital rim, and prominent cheek bones. This problem is far more common in men due to a prominent supra-orbital rim but can occur in both sexes. A highly myopic spectacle correction can make the problem appear worse due to the minification effect of the spectacles. Patients with small heads and faces and Asian patients do not generally have deep-set eyes; however, the small palpebral opening introduces similar challenges. Hyperopic patients tend to have small orbits that limit access to the globe for LASIK.

Management: These patients are best avoided until the LASIK surgeon becomes proficient in LASIK. Different techniques can help provide more exposure. Downward pressure on the speculum will often result in slight proptosis. An adjustable wire eyelid speculum usually offers the most exposure with the least interference with the suction ring. Once the speculum has been maximally expanded, a short wait will allow further expansion of a few millimeters. A lateral canthotomy and retrobulbar injection can be performed to increase exposure; however, these aggressive techniques are not well received by the patients. A very effective but technically more difficult technique to perform LASIK in very small orbits is to use the suction ring alone to separate the eyelids without a speculum. Peri-orbital skin can get caught in the microkeratome when LASIK is done without a speculum so caution is required with this technique.

Prevention: If adequate exposure cannot be obtained and the prescription is small, PRK or LASEK may be a safer refractive option in properly informed patients.

EXOPHTHALMIC EYES

Large orbits or exophthalmic eyes are ideal first cases to perform as exposure is maximal. However, there is often considerable orbital fat which allows for a certain amount of spring or ballottement to these eyes when applying the suction ring. This excessive movement can make fixation with the suction ring and the microkeratome pass slightly more difficult as the globe is not stationary. Redundant conjunctiva is often found in exophthalmic eyes which can occlude the suction ring holes without elevation of the true IOP, giving 'pseudo-suction' which is a normal suction pressure reading on the base unit while the IOP remains low.

Management: It is important that the surgeon does not become overconfident and careless because of the excellent exposure. Downward pressure on the speculum can render the eye less mobile in the orbit. Redundant folds of conjunctiva should be pushed away from the limbal region to avoid 'pseudo-suction.' Careful attention to checking the IOP will avoid thin flaps caused by 'pseudo-suction.'

Prevention: In cases when the interaction of the microkeratome and the eye is difficult or the suction level is inadequate, the surgeon should always remember that PRK or LASEK may be safer refractive options in properly informed patients.

EARLY POSTOPERATIVE COMPLICATIONS

FLAP STRIAE

Striae of the LASIK flap occur when it is folded onto itself. Striae generally have three sources: misalignment of the corneal flap after flap replacement, movement of the corneal flap during the first postoperative day, and the 'tenting effect' of the corneal flap over the ablated stromal bed. Obviously, a displaced flap or dislodged flap will also be associated with striae.

Clinical: Normally the striae are oriented horizontally with a nasal hinge and vertically with the superior hinge. Displaced flaps will often have oblique striae. Retroillumination of the fixation light and aiming beam through the dilated pupil provides accurate localization of the flap striae and will help identify striae in cases of unexplained reduction of best corrected visual acuity (BCVA) (Fig. 94.8). Fluorescein staining of the cornea will also assist in identifying subtle striae. If the striae have occurred due to flap movement or displacement after LASIK, the flap may be noted to have shifted 1–2 mm leaving an area of exposed stromal bed. It is helpful to grade striae to assist with the description of their severity and to plan treatment (Table 94.1, Figs 94.9–94.11).

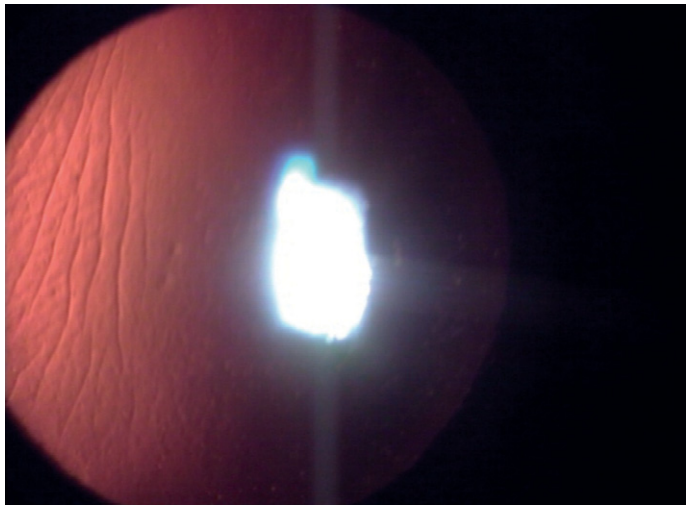

Figure 94.8. Peripheral striae are demonstrated by retroillumination.

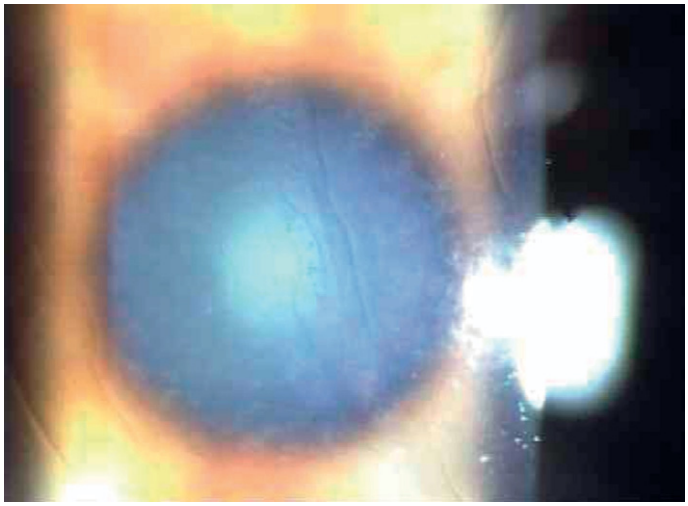

Figure 94.9. Grade 1 mild vertical striae may not affect visual performance.

Table 94.1 Probst classification of flap striae

Grade 1
Fine parallel lines
Difficult to identify
Not in visual axis
No reduction in UCVA or BCVA
No treatment required
Grade 2
Fine parallel lines in flap
Identification obvious
Extent through visual axis
BCVA reduced to 20/25–20/40
Less than one diopter of induced astigmatism
Patient may complain of diplopia
Treatment may be required due to the reduction in the BCVA or the induced astigmatism
Grade 3
Large parallel or 'basket weave' pattern
Identification obvious
Extent through visual axis
BCVA worse than 20/40
One or more diopters of induced astigmatism
Patient may complain of blur, diplopia, and glare
Treatment required to restore BCVA and reduce astigmatism, diplopia, and glare

UCVA = Uncorrected visual acuity.
BCVA = Best corrected visual acuity.

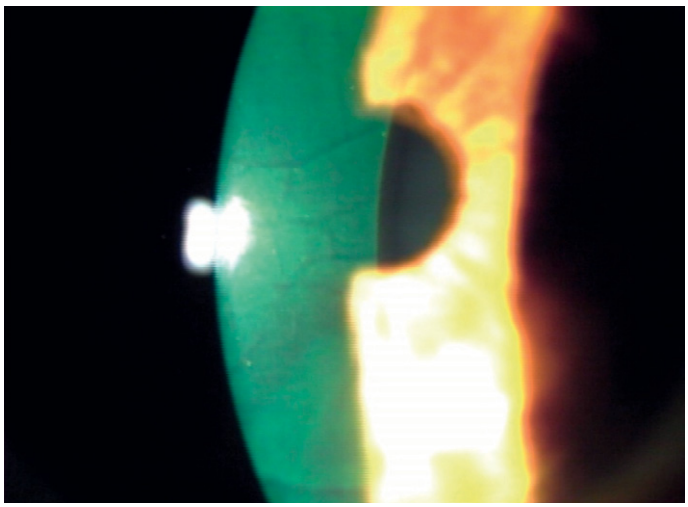

Figure 94.10. Grade 2 striae in a 'basket weave' configuration will reduce the BCVA.

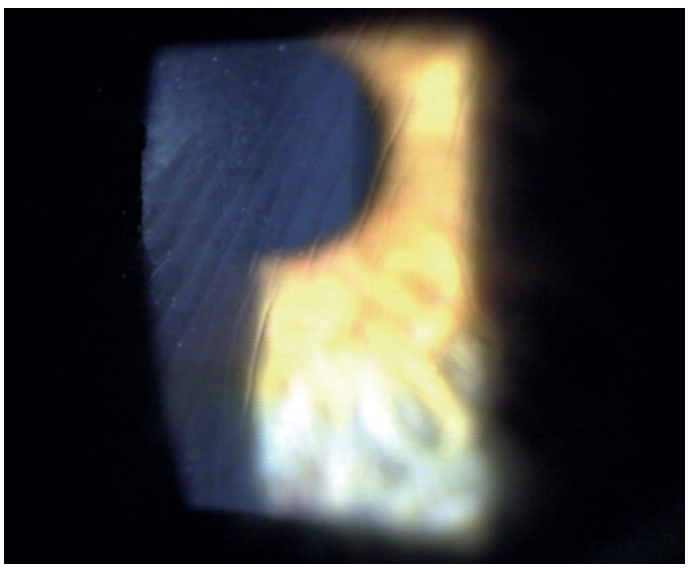

Figure 94.11. Grade 3 severe vertical striae may occur with a displaced flap.

Management: Most flap striae occur within the first hour after LASIK. Flap striae become more difficult to remove as the length of the postoperative course increases, therefore identification of the striae on the first postoperative day is imperative. The indications for the treatment of striae include flap striae that extend through the visual axis, striae causing a decrease in BCVA or diplopia, or striae inducing regular or irregular astigmatism. There have been several techniques described for the removal of flap striae. These include the stretch and smooth technique,[13] flap hydration with hypotonic saline epithelial debridement,[14] flap applanation, photo-therapeutic keratectomy,[15] and flap suturing.[16]

The stretch and smooth technique is the most recognized. The flap edge is first marked at the slit lamp to allow for easy lifting of the flap once the patient is under the microscope. No flap alignment markings are necessary as the flap will be re-aligned in a more correct position when replaced. The flap is then reflected back onto the conjunctiva. The stromal surface of the flap is hydrated with BSS solution for 30–60 s. Some surgeons have suggested the using of a hypotonic irrigation fluid of 80% BSS/20% sterile water mixture to induce flap hydration to assist in flap removal. The flap is replaced in the stromal bed and floated into position with interface irrigation. The flap is left for 5 min to attach to the stromal bed and dry the epithelial surface. The side of blunt forceps is used to stretch the flap perpendicular to the striae for 5–10 min or until epithelial defects start to occur. At the end of the procedure striae will still be visible after stretching; however, will be gone in 24 h. This technique is effective in 90% of striae; however, it can be repeated in 2–4 weeks if necessary.

Prevention: Intraoperative attention to the repositioning of the flap with minimal manipulation once it has been replaced into the correct position. Postoperatively, patients are instructed to avoid rubbing or squeezing the eye. Patients wear eye protection 24 h a day for the first week to prevent any eye trauma while the flaps are healing.

DISLODGED FLAP

A dislodged flap (flap subluxation or dehiscence) occurs when the flap is completely separated from the stromal bed. This most commonly occurs during the first 24 h postoperatively as the flap is still adhering to the stromal bed. Rarely, late dislocation of the flap can occur with corneal trauma.[17,18] With proper LASIK technique and postoperative care, the incidence of flap movement should be less than 1/1000 although an incidence of over 1% has been reported.[19]

Clinical: With nasal flaps, the dislodged flap is found rolled onto the nasal conjunctiva. If the flap has been dislodged for a few hours, it is usually very edematous. The patients are acutely aware of this problem as their vision is extremely blurred (<20/200) and the eye can be painful. With superior hinged flaps, the dislodged flap is usually found 4–5 mm onto the nasal conjunctiva. Epithelium can be seen growing over the area of exposed stromal bed (Fig. 94.12). The flap will have obvious striae and folds; however, they may be disguised by the flap edema.

Management: Patients with dislodged flap should be treated as urgently as possible. Prior to treatment, lubrication and an eye patch can improve the discomfort. Once at the surgical center, the flap is unrolled and smoothed out. The stromal side of the flap and the stromal bed must be thoroughly cleaned of all debris and mucous. The epithelium growing over the area of the exposed stroma should also be removed. The flap is then replaced and allowed to adhere to the stromal bed for at least 5 min because of the edematous state. The flap striae should then be treated as described above. Finally, a CTL should be placed on the eye to safeguard a repeat dislodgement of the flap. When managed properly, the outcome should not be compromised by flap dislodgement.[19]

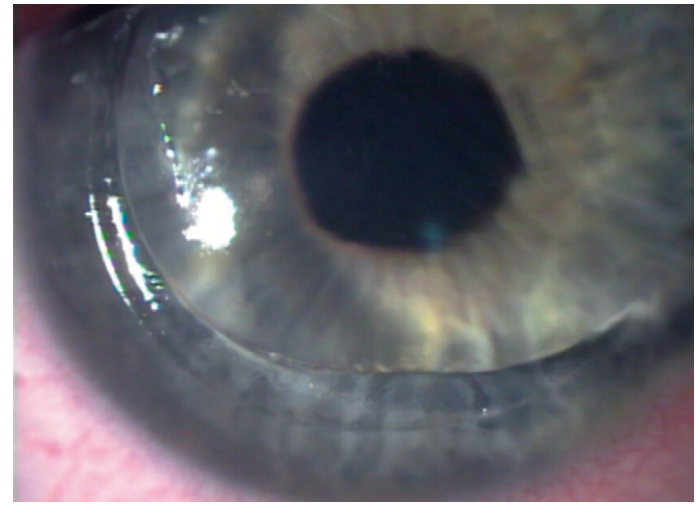

Figure 94.12. Superiorly dislodged flap with exposed stromal bed inferiorly.

Prevention: For the first postoperative day, patients are advised to go home and have a 4 h sleep. This is the critical step to allow their eyes to heal without disturbance immediately after the procedure. For the first postoperative week, patients should be warned not to touch or rub their eyes. Patients should be sent home wearing sunglasses or clear eye shields and instructed to wear these whenever possible. The shields should be worn at night. Patients can participate in any activity that does not involve touching, rubbing, irritating, or squeezing their eyes.

INFECTION

Infections rarely occur after LASIK. However, a recent review of the world literature found that 41 cases have been reported to date.[20] The causative organisms vary from gram positive bacteria to atypical mycobacteria, fungal, and viral pathogens. The infection is usually acquired intraoperatively, but may also be caused by postoperative contamination. While infections are generally unilateral, a bilateral infection after bilateral LASIK has now been reported.[21]

Clinical: The majority of bacterial keratitis patients present within 72 h of the surgery with an acute onset of symptoms.[20] Bacterial infection should be suspected whenever a localized infiltrate is identified either on the surface of the flap or at the flap interface. The infective infiltrate is generally localized, about 1–2 mm in size and white/gray in color with indistinct margins. If located on the surface of the cornea, it may be slightly elevated and associated with an epithelial defect. If allowed to progress without treatment, it will slowly increase in size like an early cornea ulcer. Inflammation of the cornea with surrounding interface keratitis, conjunctival injection, and an anterior chamber reaction may all occur if the infection persists. Reactivation of herpes simplex[22] and zoster[23] viral infections has also been reported after LASIK and presents with corneal dendrites in the postoperative period. Fungal infections after LASIK have a delayed onset and have been related to topical prolonged steroid use after LASIK.[24]

Management: Any suspected corneal infection should be treated immediately. For suspected bacterial infections, hourly topical fluoroquinolones are the obvious first course of treatment. Topical steroids should be discontinued or reduced. Patients should be followed daily. If the infiltrate is larger than 1 mm, increasing in size, or associated with ocular inflammation, a full evaluation by a corneal specialist is recommended. Cultures with microbiological evaluation and fortified antibiotics may be required. If the infiltrate is under the flap, the flap should be lifted, cultures should be taken off the infiltrate from the stromal bed, the infiltrate should be removed, the interface then irrigated, and antibiotics placed in the interface before the flap is replaced. The keratitis can result is some corneal scarring. A BCVA of 20/40 or better can be obtained in the majority of the patients.[20]

Corneal epithelial dendrites that occur in any postoperative LASIK patient, particularly those with a past history of herpes simplex keratitis or herpes zoster, should be treated immediately with the appropriate topical and oral antiviral therapy.

Prevention: Prevention of epithelial defects during and after LASIK should greatly reduce or eliminate the risk of a superficial bacterial corneal infection. Infection at the flap interface is avoided by preventing contamination of the instruments used to treat the interface. Microkeratome heads are sterilized for each patient. New sterile blades are used for each patient. Instruments should also be sterilized. Disposable instruments such as microkeratomes or cannulas ensure the sterility of that step of the procedure. Sterile BSS is used for interface irrigation. While LASIK is not currently a true 'sterile' procedure, all efforts that move in this direction should reduce the risk of infection further.

If a patient had a past history of herpes simplex or zoster infection, a prophylactic course of oral antiviral is recommended 1 week prior and 1 week after the LASIK procedure. Doses of acyclovir from 200–800 mg 5 times per day have been recommended by various LASIK experts. This author treated at least 20 patients with a past history of herpetic keratitis with this regimen and never experienced viral reactivation.

DIFFUSE LAMELLAR KERATITIS (SANDS OF SAHARA)

Diffuse lamellar keratitis (DLK) is referred to by several names, including Sands of Sahara, Sands, nonspecific diffuse interface keratitis, and LASIK interface keratitis (LIK). DLK and Sands are the most common terms. The cause of DLK has remained somewhat of an enigma. Holland et al have demonstrated the risk of DLK from the bacterial cell wall endotoxins that build up in the wet autoclave reservoirs.[25] Epithelial defects have been associated with focal DLK.[26] DLK has been reported months after LASIK associated with ocular inflammation,[27] ocular trauma,[28] and without an obvious etiology.[29] Other causes that have been proposed but remain unproven include cleaning solutions,[30] talc from gloves, Meibomian gland secretions, microkeratome oil, rust on instruments, blade debris, iodine skin cleaners, and carboxymethylcellulose lubrication drops.[31] DLK is a postoperative interface inflammation that occurs in the 24–72 h postoperative period. Late activation of DLK without an identified cause has also been reported.[29] The incidence is thought to be 1:200 to 1:500 cases, but may occur in sequential patients (outbreaks) at a specific location.

Clinical: DLK presents with varying severity, and with patient symptoms ranging from asymptomatic to mild pain, photophobia, and decrease in vision (usually a hyperopic shift). The presentation of DLK can be graded according to the severity of the presentation (Table 94.2, Figs 94.13–94.20).[32] The clinical appearance typically begins in the periphery and is confined to the flap interface without extension into the surrounding stroma. Untreated, this may lead to central inflammation affecting visual acuity secondary to induced hyperopia or irregular astigmatism. It may present with multiple foci, which are diffusely distributed and are often more concentrated around interface debris. Early, subtle DLK may be difficult to differentiate from postoperative superficial punctate keratitis (SPK) or mild interface debris. SPK is always on the corneal surface and will stain with fluorescein. DLK is at the level of the interface and does not stain with fluorescein. There is no anterior chamber reaction in DLK except in the most advanced cases.

Management: Early identification and intervention are the key steps for successful management of DLK. When grades 1 or 2 DLK are identified, the patient should immediately be started on topical steroid every 1–2 h and an antibiotic q.i.d. for prophylaxis against infection.[33] If grade 3 DLK is identified or grade 2 DLK has not resolved after several days of treatment, the flap should be lifted and the interface irrigated. All these measures aim to prevent the progression to grade 4 DLK with central accumulation of cells, central corneal haze and striae, decreased BCVA, and a hyperopic shift. Grade 4 DLK also requires urgent flap irrigation along with flap stretching, and frequent topical steroids after. While PTK has been suggested as another treatment for DLK,[34] this can cause iatrogenic hyperopia.

Prevention: Since epithelial defects have been associated with DLK, the LASIK surgeon should strive to avoid epithelial defects whenever possible. Autoclave reservoirs of wet autoclaves should be drained and cleaned at the end of each day. Instruments should also be cleaned and dried at the end of each day. These maneuvers aim to eliminate the wet environment that could allow the proliferation of gram-negative bacteria that produce the bacterial cell wall endotoxins proposed to be an etiological agent of DLK. Dry autoclaves may offer a safer method of sterilization if DLK becomes recurrent. Disposable instruments offer another method of avoiding a toxic contaminant to the LASIK process. Topical steroids should be used for all patients for a few days after LASIK to suppress any subclinical inflammation.

LATE POSTOPERATIVE LASIK COMPLICATIONS

EPITHELIAL INGROWTH

Carr and coworkers[35] reviewed the risk factors and the incidence of epithelial ingrowth following 1246 consecutive cases of LASIK. Epithelial ingrowth underneath the flap following LASIK was identified in 14.7% of cases. While most of these cases had small amounts of self-limited insignificant ingrowth, 1.7% of all the LASIK cases required flap revision for the removal of significant ingrowth. In another study of 3786 eyes, significant epithelial ingrowth occurred in 0.9% of primary LASIK cases and 1.7% of enhancement cases.[36]

Preoperatively, any factor that contributes to an epithelial defect will increase the risk of epithelial ingrowth. This includes anterior basement membrane dystrophy and a history of recurrent erosions. Helena and colleagues found that ingrowth was associated with some cases of postoperative inflammation.[37] Carr and coworkers[35] found that postoperative epithelial defects, repeat LASIK rather than primary LASIK, postoperative flap slippage within 24 h, and micro-

Table 94.2 Grading of diffuse lamellar keratitis (DLK)

1. Grade 1 DLK

Clinical presentation

- Focal, white to gray, granular material in the LASIK flap interface 1–7 days after LASIK
- No other ocular inflammation/anterior chamber reaction
- Normal visual acuity

Treatment

- Intensive topical steroids every hour with follow-up every 2–3 days to ensure complete resolution

Prognosis

- Excellent after topical steroids and one week for stabilization

2. Grade 2 DLK

Clinical presentation

- Diffuse, white to gray, granular material under the LASIK flap interface 1–7 days after LASIK
- No other ocular inflammation/anterior chamber reaction
- Normal visual acuity

Treatment

- Interface irrigation has an immediate curative effect
- Intensive hourly topical steroids after irrigation
- Follow-up daily to ensure resolution

Prognosis

- Excellent after interface irrigation, topical steroids and 1–2 weeks of stabilization

3. Grade 3 DLK

Clinical presentation

- Diffuse, confluent, white to gray, granular material under the LASIK flap interface 1–7 days after LASIK
- Slight conjunctival injection
- No anterior chamber reaction
- Reduced visual acuity

Treatment

- Interface irrigation has an immediate curative effect
- Intensive hourly topical steroids after irrigation
- Follow-up daily to ensure resolution
- Repeat irrigation in 1–2 days if the inflammation does not resolve
- Topical steroid and antibiotics can been placed on the stromal bed to directly address the area of inflammation

Prognosis

- Excellent after interface irrigation, topical steroids, and several weeks of stabilization

4. Grade 4 DLK

Clinical presentation

- Diffuse, confluent, white to gray, granular material under the LASIK flap interface 1–7 days after LASIK
- Inflammation localized to a 2–4 mm area of intense central inflammation
- Central interface striae in area of inflammation
- Slight conjunctival injection
- No anterior chamber reaction
- Markedly reduced visual acuity

Treatment

- Interface irrigation has an immediate effect
- Wipe the stromal bed with Murocel sponges
- Topical steroid and antibiotics can be placed on the stromal bed to directly address the area of inflammation
- Intensive hourly topical steroids after irrigation
- Follow-up daily to ensure resolution
- Repeat irrigation in 1–2 days if the inflammation does not resolve

Prognosis

- Reduced BCVA and irregular astigmatism with residual hyperopia will persist after the resolution of the inflammation due to the residual interface haze and stromal thinning
- Persistent interface striae may also reduce the final BCVA

BCVA = Best corrected visual acuity.

perforation at the time of simultaneous Arc-T were significant risk factors for epithelial ingrowth after LASIK. Prior surgeon experience was found to be significantly protective against epithelial ingrowth. All of these factors are likely to be related to a disturbance of the epithelial layer during LASIK. Once the epithelium is stimulated to replicate and migrate to heal an epithelial defect, the incidence of epithelial ingrowth will increase.

Clinical: Most commonly, the patient is asymptomatic and the ingrowth is identified on a scheduled postoperative visit as a faint gray line extending less than 2 mm in from the flap edge. The ingrowth can be so discrete that it may be passed over with a quick inspection of the cornea. Epithelial ingrowth can be associated with a mild foreign body sensation that generally indicates an epithelial irregularity along the flap edge associated with the ingrowth. The visual acuity will be unaffected or drop one line of BCVA[37] except in the most severe cases when progression occurs into the visual axis.

The ingrowth is best identified with the direct focal tangential illumination of the slit-lamp biomicroscope. It is generally white to gray in color and can be seen to be located beneath the corneal flap. White to gray areas of stromal haze can occur in areas of previous ingrowth or surrounding an active area of ingrowth. Irregular fluorescein staining and pooling is often identified at the flap edge associated with the ingrowth. Surface irregularities associated with the epithelial ingrowth can be identified with corneal topography.[37] Retroillumination through the dilated pupil can also be useful to delineate the margins of large sheets of ingrowth that have extended near the visual axis. Epithelial ingrowth usually occurs on the superior and inferior regions of the nasal based flap made with the Chiron Vision ACS, although any region of the flap may

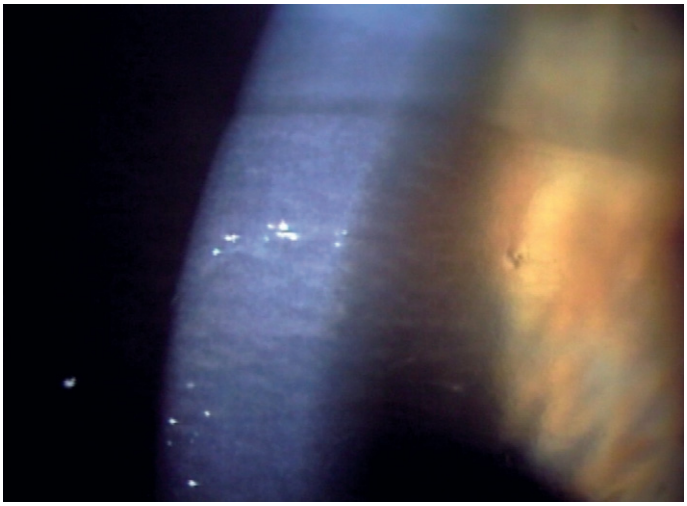

Figure 94.13. Grade 1 DLK underneath a superior epithelial defect one day after LASIK.

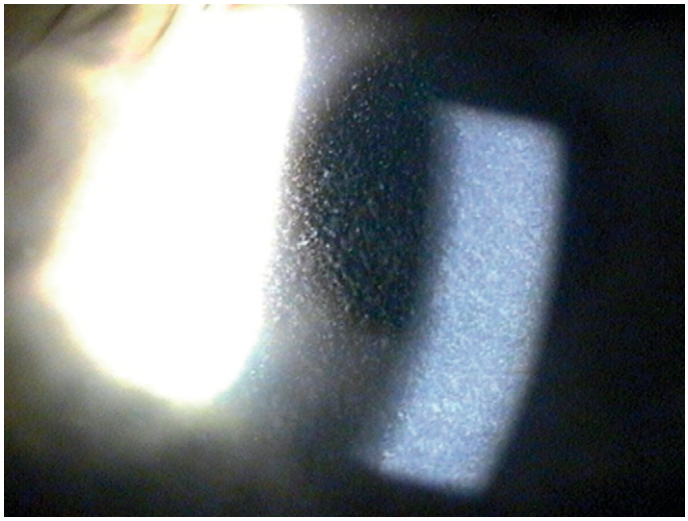

Figure 94.15. Grade 2 DLK 3 days after LASIK.

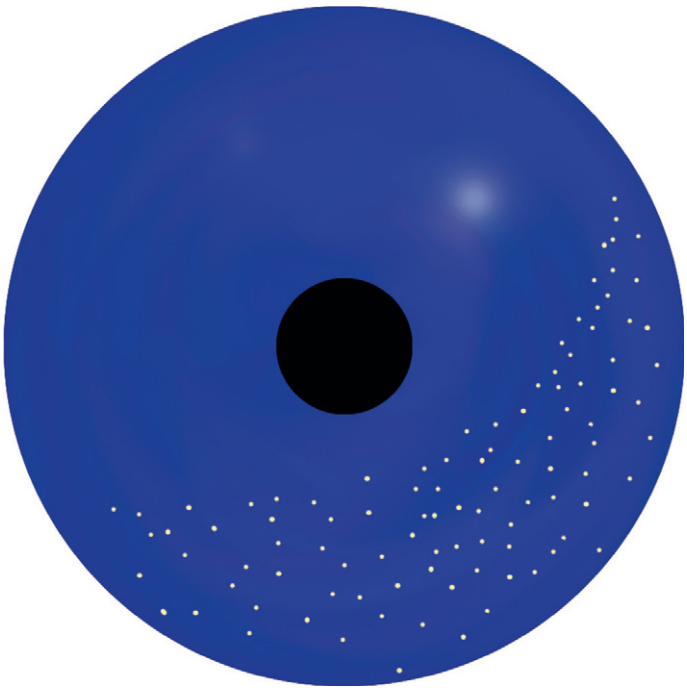

Figure 94.14. Grade 1 DLK illustration. (From Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26: 1072–1077.)

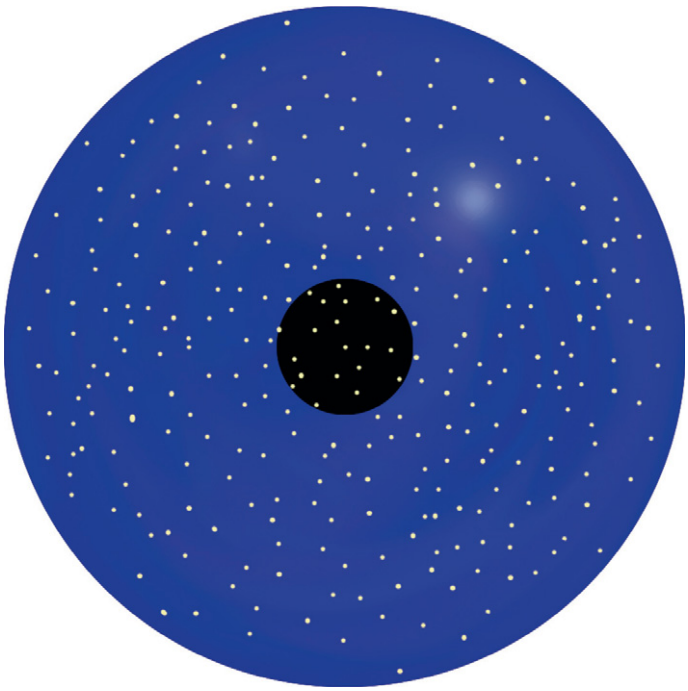

Figure 94.16. Grade 2 DLK illustration. (From Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26: 1072–1077.)

be affected. The Hansatome tends to be associated with inferior epithelial ingrowth.

Epithelial ingrowth following LASIK can occur in a number of different patterns which can be divided into a classification system of grades that assist with identification and treatment (Table 94.3). Grade 1 is the most common pattern with a fine white line 2 mm inside the flap edge, which is seen in up to 10% of patients (Fig. 94.21). This type of ingrowth generally demonstrates very slow progression that arrests without treatment in a few weeks. Grades 2 and 3 ingrowth are more aggressive forms that tend to be progressive and often require treatment. The affected area should have slit-lamp measurements of the extension of the ingrowth from the flap edge. It can occur in patterns with epithelial pearls or nests, strands, or sheets (Figs 94.22 and 94.23). Grade 4 ingrowth is the most aggressive pattern of ingrowth. It is characterized by strands of epithelial cells streaming underneath the flap toward the visual axis often as early as the first 3 weeks following LASIK. This can be associated with flap edge melting (Fig. 94.24). Obviously, this pattern of epithelial ingrowth requires urgent treatment to prevent further progression.

Management: Indications for treatment of epithelial ingrowth following LASIK include greater than 2 mm of ingrowth from the flap edge, documented progression, associated flap melting, or a disturbance of BCVA which can be attributed to the ingrowth.

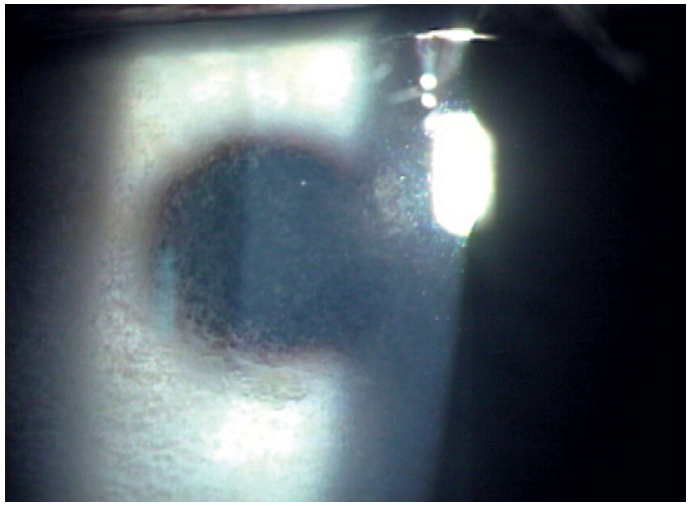

Figure 94.17. Grade 3 DLK with obvious inflammatory diffuse material in the flap interface.

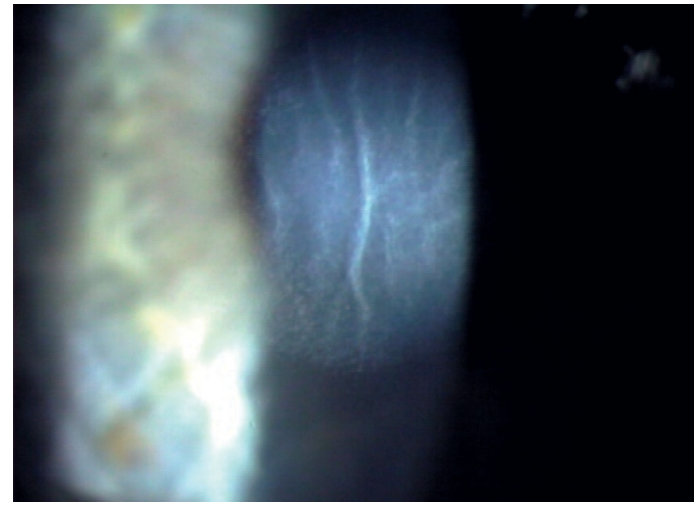

Figure 94.19. Grade 4 DLK with central flap haze and striae.

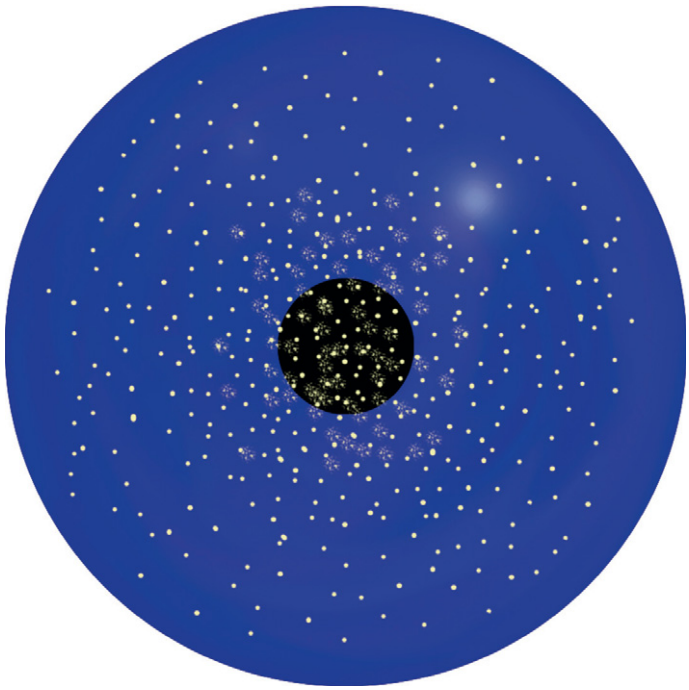

Figure 94.18. Grade 3 DLK illustration. (From Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26: 1072–1077.)

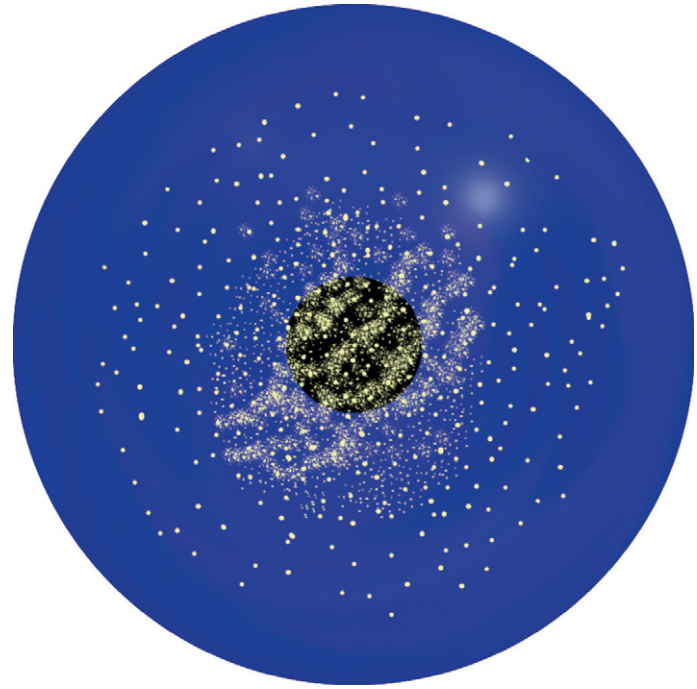

Figure 94.20. Grade 4 DLK illustration. (From Linebarger EJ, Hardten DR, Lindstrom RL. Diffuse lamellar keratitis: diagnosis and management. J Cataract Refract Surg 2000; 26: 1072–1077.)

Epithelial ingrowth removal has been described by several different methods. Generally the flap is lifted and the epithelial ingrowth is removed from the stromal bed and the stromal side of the flap (Fig. 94.25). Since the ingrowth is generally transparent, great care must be used to remove all the ingrowth. Ingrowth that has been present for a short time (<4 weeks) generally slides off the stroma with gentle pressure from a Murocel spear. When the ingrowth has been present for longer, it tends to be more adherent so a dull surgical blade can be used to scrape the ingrowth off the stromal bed. The flap can then be replaced and the interface is generously irrigated to remove any additional epithelial cells. Generally, these two steps are all that is required for complete epithelial removal without recurrence.

Surgeons have suggested that alcohol can be applied to the stromal area of ingrowth to ensure that all the epithelial cells are destroyed.[38] Because alcohol can be toxic to the stroma, this technique should be used sparingly. Phototherapeutic keratectomy of approximately 10 µm has been used by some surgeons to successfully clean the bed after epithelial ingrowth removal.[39] As it may induce a refractive effect, this technique is best reserved for recurrent cases of ingrowth. Suturing of the flap to the stromal bed has also been reported as successful for recurrent cases of epithelial ingrowth.[40] Rarely, epithelial flap removal or corneal transplant may be required.[39]

Prevention: Preoperatively, anterior basement membrane dystrophy, a history of recurrent corneal erosions, advanced age, or a

Table 94.3 Probst/machat epithelial ingrowth classification

Grade 1: thin ingrowth, 1–2 cells thick, limited to within 2 mm of flap edge, transparent, difficult to detect, well-delineated white line along advancing edge, no associated flap changes, nonprogressive
No treatment required
Grade 2: thicker ingrowth, discreet cells evident within nest, at least 2 mm from flap edge, individual cells translucent, easily seen on slit-lamp, no demarcation line along nest, corneal flap edge rolled or gray, no flap edge melting or erosion, usually progressive
Requires non-urgent treatment within 2–3 weeks
Grade 3: pronounced ingrowth, several cells thick, greater than 2 mm from flap edge, ingrowth areas opaque, obvious on slit-lamp, white geographic areas of necrotic epithelial cells with no demarcation line, corneal flap margins rolled with thickened whitish-gray appearance. Progression results in large areas of flap melting from collagenase release from the necrotic epithelium. Confluent haze develops peripheral to the flap edge as flap pulls away leaving exposed stromal bed in contact with surface epithelium
Urgent treatment required with close follow-up, as recurrences are more common due to the altered flap edges

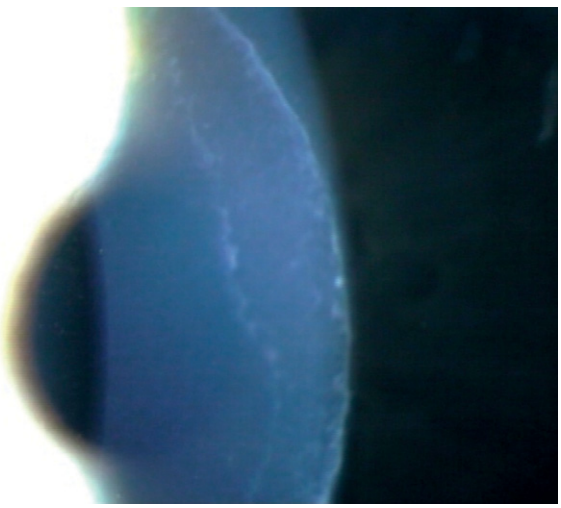

Figure 94.21. Grade 1 epithelial ingrowth with a faint white border inside the flap edge.

history of ingrowth in the other eye would all increase the risk of epithelial ingrowth following LASIK. When one or more of these factors are identified preoperatively, the refractive surgeon must carefully consider whether another refractive option such as PRK would be safer with less potential postoperative complications.

MYOPIC UNDERCORRECTION AND REGRESSION

Ever since LASIK has been performed, enhancements have been required. Due to the normal distribution of LASIK outcomes, some patients will be initially undercorrected. The variability in the corneal healing after LASIK has made LASIK enhancements inevitable. With modern LASIK techniques and excimer lasers the

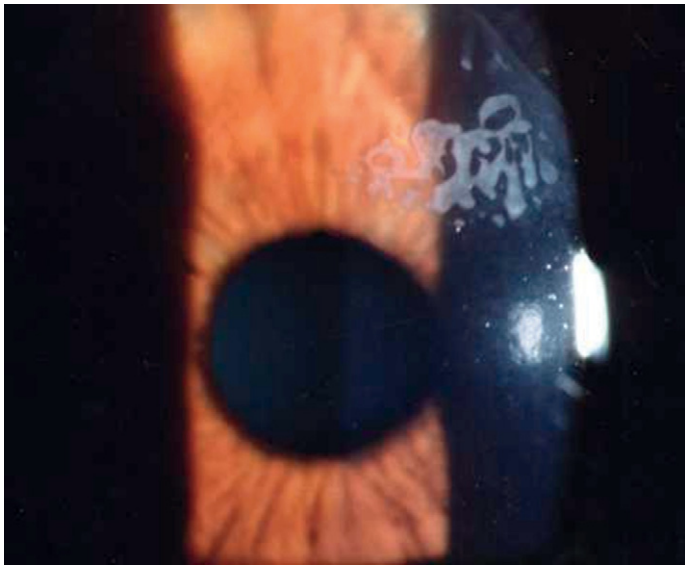

Figure 94.22. Grade 2 epithelial ingrowth with a superior 'grape-like' cluster of epithelium under the flap.

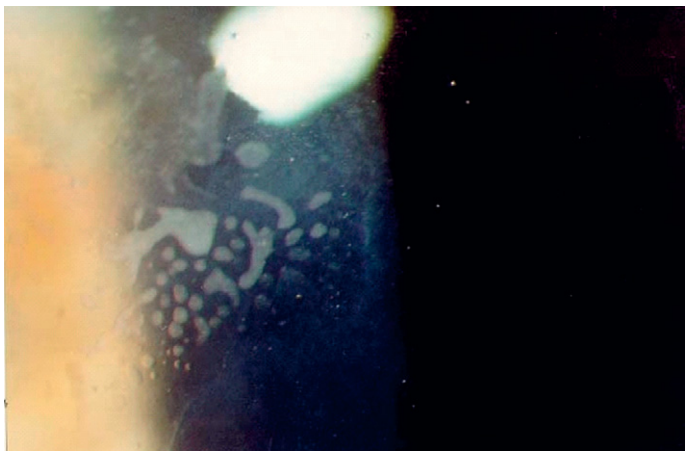

Figure 94.23. Grade 3 epithelial ingrowth with diffuse clusters of epithelial cells extending more than 2 mm from the flap edge.

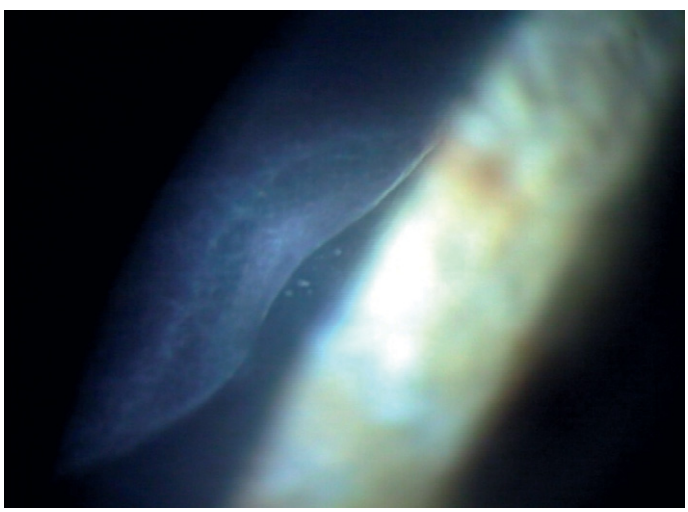

Figure 94.24. Grade 4 epithelial ingrowth is often associated with a flap edge melt.

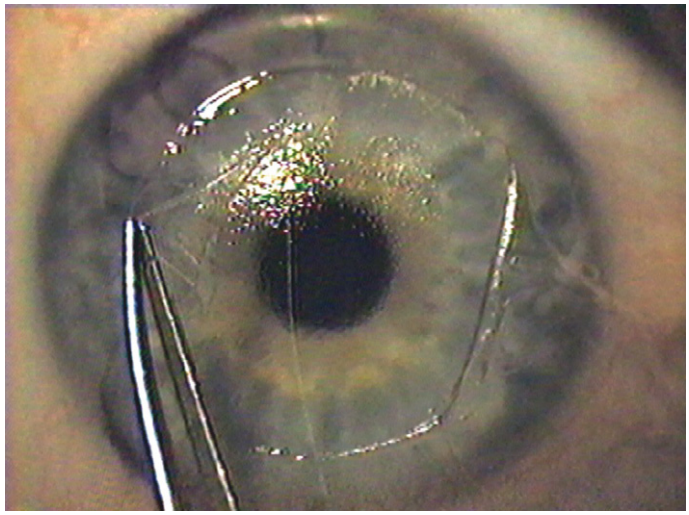

Figure 94.25. The translucent sheet of epithelial ingrowth can be peeled off the stromal bed with forceps.

enhancement rate for myopic LASIK can be generally estimated as 1% per diopter of spherical correction. The enhancement rate for astigmatism is higher at approximately 10% per diopter of astigmatic correction. A patient who has −2.00 D correction would have an enhancement rate of approximately 2% while a patient with −2.00 D of spherical correction and −2.00 D of astigmatic correction would have an enhancement rate of approximately 22%.

Clinical: Myopic LASIK undercorrections are noted immediately as the patient's postoperative UCVA on day 1 will be poor. Regression of the refractive effect usually occurs over the next several months, but rarely can occur years after the primary LASIK. In either case, the patient will be unable to function without glasses or contacts if the undercorrection and regression is significant and bilateral. Patients may also complain of night glare. Presbyopic patients may have their uncorrected near vision restored.

Management: Patients with undercorrections should be prescribed temporary glasses by the end of the first week of surgery or fitted with disposable CTL after 1–2 weeks. Patient symptoms dramatically reduce once some form of temporary correction is obtained pending additional surgical treatment.

Refractive stability should be achieved prior to performing any LASIK enhancement. Generally, it could be estimated that approximately 1 month is required for each diopter of LASIK correction in order to achieve refractive stability. In practice, however, most LASIK enhancements are not performed earlier than the 3–4 month time period, and most large enhancements can be performed at the 6–7 month postoperative LASIK period and achieve excellent results.

Prior to every LASIK enhancement the corneal thickness should be re-measured. The Orbscan will routinely underestimate the thickness of the cornea for LASIK enhancement. This is because this device uses optical pachymetry and will erroneously measure the LASIK flap interface as the posterior edge of the cornea yielding lower corneal pachymetry results. Therefore during LASIK enhancements accurate pachymetry of the cornea is best obtained with ultrasound measurements. As in primary LASIK, at least 250 µm of posterior stroma should be preserved following a LASIK enhancement in order to ensure that the risk of long-term corneal ectasia is minimized. If we assume that the original corneal flap was approximately 160 µm, this means that the minimum corneal thickness that should be preserved after a LASIK enhancement would be approximately 410 µm.

The Orbscan is extremely useful for preoperative evaluation of the LASIK patient as it demonstrates several other conditions that should be monitored prior to performing any additional procedures on the cornea. The anterior flow map of the Orbscan will demonstrate if there are any anterior surface irregularities. More significant, however, is the posterior float map, which can demonstrate any areas of posterior corneal ectasia. If the degree of posterior corneal ectasia on the Orbscan is greater than 50 µm, this indicates that the cornea may be showing some early signs of ectasia and instability as a result of the original LASIK procedure. Furthermore, this ectasia may be contributing to the regressive effect of the cornea. Therefore, large amounts of corneal ectasia, although rarely seen, should be considered a contraindication for a LASIK enhancement procedure. The Orbscan refractive map will demonstrate any irregular topographic patterns. If any irregular patterns are demonstrated on the preoperative LASIK enhancement evaluation the procedure should also be cancelled.

Over the last year and a half, pupil testing has become a standard prior to the preoperative LASIK workup. Prior to this there was really no pupil testing devices available nor was this test regularly performed. It is therefore very important to measure people's pupils prior to the LASIK enhancement to determine whether the original laser settings were indeed appropriate and the feasibility of performing an additional LASIK procedure. The most commonly used device at this time is the Colvard pupillometer. Generally, the blend zone should extend outside the measured pupil size.

For patients who are over the age of 40, the LASIK enhancement often offers an opportunity to revisit the option of monovision. Patients may elect for unilateral LASIK enhancements in order to give monovision a second try. It is important to evaluate older patients with late 'regression' for potential cataract formation because a LASIK enhancement will only temporarily solve their problem, as once the nuclear sclerosis progresses further they will require a cataract procedure.

Prevention: Myopic LASIK undercorrections can be minimized by ensuring a stable refraction preoperatively and careful nomogram adjustment for both the patient's age and the refractive error. The laser room humidity and temperature should also be controlled so the temperature stays between 65°–75° Fahrenheit and the humidity between 30–40%. Although the need for LASIK enhancements cannot be eliminated, the risk can be lowered by careful control of these factors.

ERRORS IN HYPEROPIC REFRACTIVE OUTCOME

The variability in the corneal healing after LASIK has made LASIK enhancements inevitable. With modern hyperopic LASIK techniques and excimer lasers the enhancement rate can be generally estimated as 10% per diopter of spherical correction and 10% per diopter of astigmatic correction. Regression is particularly common with correction over 3.0 D of hyperopia.

Clinical: Hyperopic LASIK undercorrections are noted immediately as the patient's postoperative UCVA on day 1 will be poor. Regression of the refractive effect usually occurs over the next several months, but rarely can occur years after the primary LASIK. In either case, the patient will be unable to function without glasses or contact lenses if the undercorrection and regression is significant and bilateral. Patients may also complain of night glare.

Management: Patients with residual refractive errors should be prescribed temporary glasses by the end of the first week of surgery or fitted with disposable CTL after 1–2 weeks. Patient symptoms dramatically reduce once some form of temporary correction is obtained pending additional surgical treatment. Refractive stability should be achieved prior to performing any LASIK enhancement. Generally, it could be estimated that approximately 1 month is required for each diopter of LASIK correction in order to achieve refractive stability. In practice, however, most LASIK enhancements are not performed earlier than the 3–4 month time period, and most large enhancements can be performed at the 6–7 month postoperative LASIK period and achieve excellent results.

The Orbscan will underestimate the thickness of the cornea for LASIK enhancement; therefore, accurate pachymetry of the cornea is best obtained with ultrasound measurements. As in primary LASIK, at least 250 μm of posterior stroma or a total corneal thickness of 410 μm should be preserved following a LASIK enhancement in order to ensure that the risk of long-term corneal ectasia is minimized. If posterior corneal ectasia on the Orbscan is greater than 50 μm, this indicates that the cornea may be showing some early signs of ectasia and instability as a result of the original LASIK procedure which may be contributing to the refractive regression. Irregular topographic patterns are also a contraindication to LASIK enhancement. The pupil size should be measured to allow for appropriate settings of the ablation zone size.

It is important to evaluate older patients with late 'regression' for potential cataract formation because a LASIK enhancement will only temporarily solve their problem, as once the nuclear sclerosis progresses further they will require a cataract procedure. With eyes less than 410 μm of thickness, the Holmium LTK procedure offers an alternative method of correcting spherical iatrogenic hyperopia for up to 3.0 D.

Lifting the original corneal flap is the preferred technique for enhancement as re-cutting over the original flap can occasionally result in a free wedge of tissue which is difficult to manage.[41] This technique is still effective if a smaller 8.5 mm flap is used as the steepening effective of the hyperopic enhancement is within the treatment optical zone with the blend zone providing no refractive effect.

Prevention: All patients should have a cycloplegic refraction to ensure that accommodation does not occur during the preoperative refraction. Tight control of the operating room environment will improve the consistency of the results. Humidity should be kept in the 30–40% range and the temperature between 65 and 75° Fahrenheit. Low room humidity and high temperatures have been associated with overcorrections. The LASIK nomogram should be set to target slight myopia so that the effect of regression is minimized.

POSTOPERATIVE KERATECTASIA FOLLOWING LASIK

Corneal ectasia following LASIK has been recognized as an uncommon complication of LASIK. In a study of 2873 eyes, 19 eyes (0.66%) developed post-LASIK ectasia.[42] None of the eyes with ectasia had less than 8.00 D of preoperative myopia or a residual corneal bed thickness greater than 325 μm.

Clinical: Corneal ectasia usually presents 1–12 months after the original LASIK procedure.[43–45] The patients often have large LASIK corrections of over 8 D. Most cases involve a final corneal thickness of less than 400 μm associated with the ectasia with less than 250 μm of presumed posterior corneal stroma; however, exceptions to this rule have been reported.[46,47] Ectasia is usually associated with regression of the refractive effect, loss of UCVA and BCVA, and irregular astigmatism. Topography demonstrates irregular astigmatism often with inferior steepening of the cornea. The Orbscan will demonstrate posterior corneal ectasia on the posterior float map with a deep orange to red color in the central area of the cornea with maximum thinning in the same area of the pachymetry map (Fig. 94.26). Furthermore, this ectasia may be contributing to the regressive effect of the cornea.

Management: Any signs of corneal ectasia on the anterior cornea or posterior cornea should preclude any further LASIK as this could exacerbate the ectasia. Patients are best treated with hard CTL if these can be fitted comfortably. Unfortunately, some of these patients must go on to receive corneal transplantation in order to restore functional vision.

Prevention: Patients with keratoconus or other corneal thinning disorders identified on topography should not have LASIK as LASIK will hasten the onset of keratectasia.[48–50] At least 250 μm of posterior stroma should be preserved following LASIK in order to ensure that the risk of long-term corneal ectasia is minimized. If we assume that the original corneal flap was approximately 160 μm, this means that the minimum corneal thickness that should be preserved after a LASIK enhancement would be approximately 410 μm.[51]

LASIK surgeons should carefully calculate the ablation depth per diopter of their excimer laser to determine how many diopters of correction can still be performed while preserving an adequate amount of corneal thickness. Generally, most excimer lasers used at a 6 mm optical zone will remove approximately 13 μm per diopter but as the optical zone or the blend zone are increased this depth can increase to at least 15 μm per diopter and sometimes up to 20 μm per diopter.[51]

NIGHT VISION DISTURBANCES: HALOS AND GLARE

Night vision problems after LASIK have been reported extensively in the media; however, the incidence of significant night vision symptoms is not common. A study of 236 eyes treated on the Bausch & Lomb 217C laser for mild to moderate myopia found that while mild to moderate glare was reported by 10% more patients at the 6 months follow-up, there was no significant increase in marked or severe glare or halos.[52] There were no significant changes in night driving symptoms at any level after LASIK. Hyperopic LASIK tends to be performed on older patients with smaller pupil sizes; however, it also produces a smaller effective optical zone so the incidence of night vision problems is similar.

Clinical: There are two potential night vision problems that occur after LASIK. Halos are the concentric blur circles that surround a point source of light, such as a car headlight, when viewed at night. Halos occur when the optical zone size of the laser treatment are smaller than the mesopic pupil size. Glare is the distortion radiating from light sources at night. Glare occurs because of the optical aberrations of the optical system that are magnified when the pupil dilates at night. Topography can clearly identify the small effective optical zones associated with halos (Fig. 94.27).

Management: Patients who experience night glare postoperatively should be seen immediately as the loss of ability to drive at night can be a very stressful event. Patients are reassured that these symptoms generally abate over 3–6 months. Over the recovery

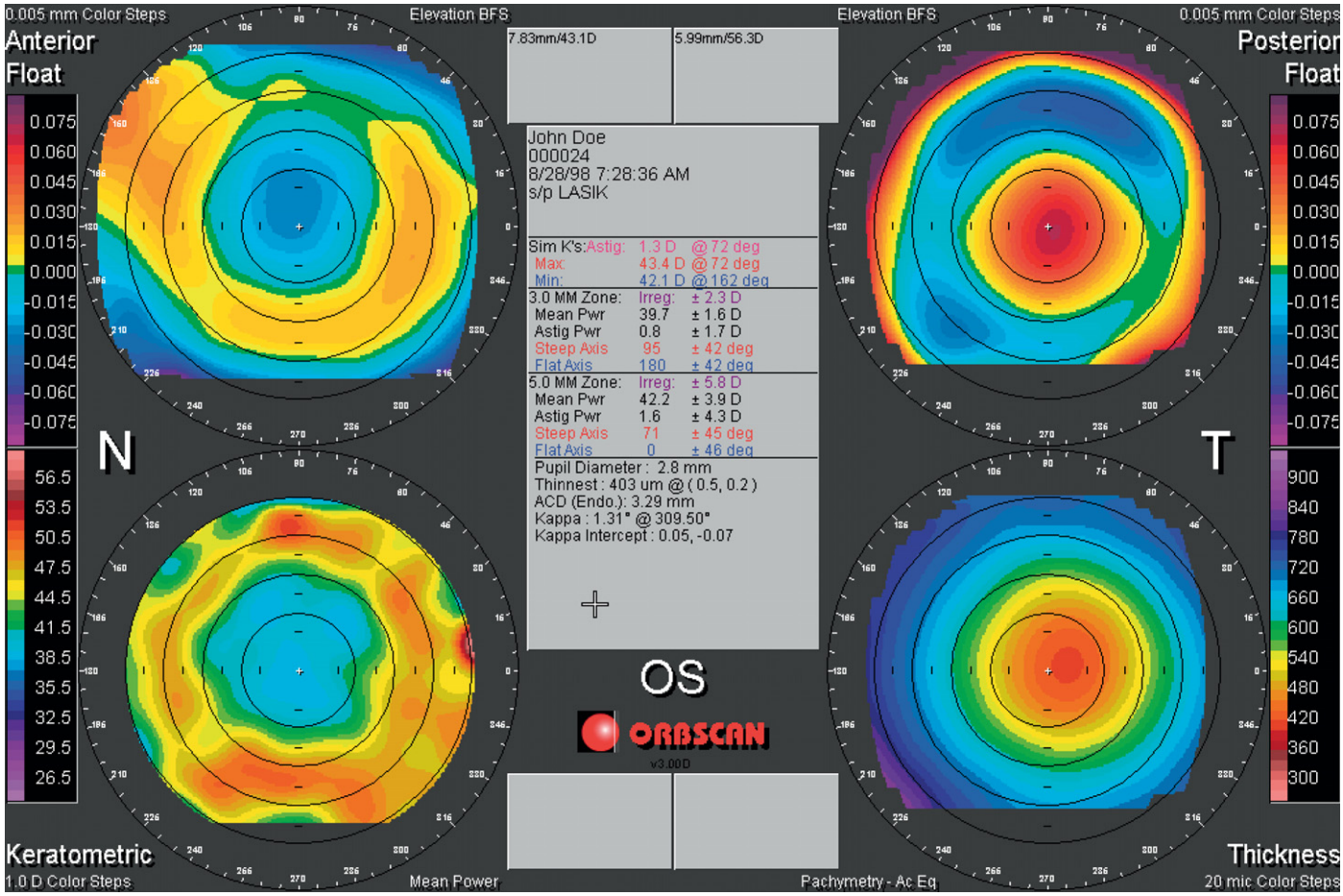

Figure 94.26. Postoperative LASIK Orbscan demonstrating posterior ectasia on the posterior float map.

phase, the treatment of dry eyes and any residual refractive error or monovision often improve the symptoms. For those patients who still have difficulties, night driving glasses, turning on the car dome light when driving, and rarely 1/8% pilocarpine drops just before night driving allow the patients to manage during the recovery phase. Alphagan has recently been found to reduce pupillary dilation at night with far fewer side effects than the pilocarpine.[53] For those rare patients with persistent night glare, custom/wavefront LASIK may offer a more refined method of enlarging the treatment zone.

Prevention: Pupillometry should be performed in all LASIK patients preoperatively to identify those with pupils larger than 6 mm in dim light. While the risks for night glare are multifactorial, the current most accepted treatment is to adjust the blend zone of the treatment correction to cover the measured pupil size.

CENTRAL ISLANDS

The central island is now a rare phenomena after LASIK, which more commonly occurred with broad beam lasers.[54] Central islands occur when the central cornea receives less effect from the excimer pulses than the peripheral cornea. All excimer lasers now use a scanning spot or rotating beam laser delivery system that in effect eliminate the risk of central islands. This author has not had a problem with central islands in the last 4 years with 20 000 LASIK procedures.

Clinical: A central island has been defined as an area of higher refractive power of more than 1.5 D and 2.5 mm or more in diameter[54] or 3.0 D and 1.5 mm in diameter.[55] Postoperative monocular diplopia, visual distortions, and myopia are the main symptoms associated with central islands. Patients with central islands are difficult to refract and have a disproportionately high degree of residual myopia relative to their uncorrected visual acuity. For example, a typical central island patient post-LASIK may have an uncorrected visual acuity of 20/30 with a measured refraction of –2.00 D. Eyes with central islands may also have reduced BCVA, often in the 20/25 or 20/30 range. A central island cannot be identified on slit-lamp examination. Unlike central islands observed with PRK, the topographical abnormalities observed with LASIK do not resolve over time.[56] Topographically, a central island appears as a 2–3 mm area of central steepening, which is red or a lighter shade of blue-green relative to the surrounding area, which is a darker green or more typically blue. The difference in the diopter height of the island compared to the peripheral cornea can range from 3–8 D.

Management: Corneal videokeratography allows the identification of central islands. Central islands are treated by using the Munnerlyn formula (depth of ablation = diameter^2 × diopter correction [height of the island]/3).[57] Computerized videokeratography is used to measure the diameter of the central island, and the height of the island is then calculated by noting the diopter color change between the surrounding ablation and the peak of the island.[55] Central islands

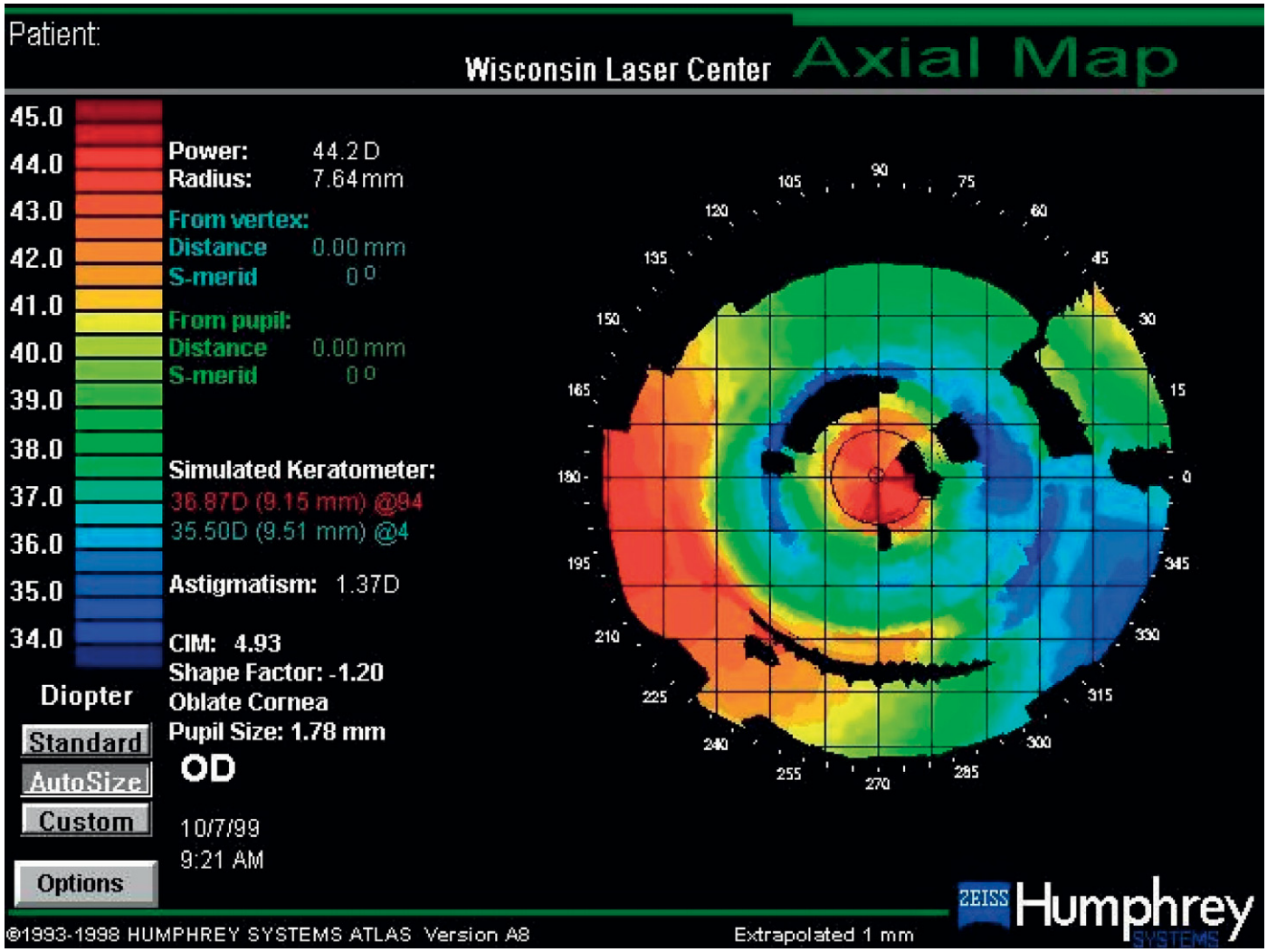

Figure 94.27. Topography after hyperopic LASIK demonstrates relatively small optical effective optical zone.

can be treated using PTK mode of the excimer laser set at the diameter and the height of the central island. Another method involves treating the refractive error with the laser treatment limited to the diameter of the central island. Unfortunately, both these techniques involve estimating the amount of ablation. Too much treatment will result in a central corneal divot with postoperative hyperopia, diplopia, and reduced BCVA. Insufficient treatment will require another re-treatment. With the current advances in customized wavefront laser correction, treatment of patients who are now identified with central islands could be postponed until wavefront technology can accurately identify and treat this problem.

Prevention: The new generation of scanning excimer lasers has effectively eliminated the risk of central islands for standard refractive correction with the excimer laser. However, in the rare circumstance that a central accumulation of stromal hydration is noted during the excimer ablation, this can be removed by wiping the stromal bed during the ablation. Central islands may still occur when performing large (>50 μm) PTK treatments for corneal scars or haze. For these types of treatment, the addition of a small myopic correction of 1–2 D will eliminate the risk for a postoperative central island.

DECENTRATION

Decentration of the excimer laser ablation is much less common now that excimer lasers have eye trackers that allow the center of the laser ablation to be locked onto the center of the pupil. The incidence of decentrations of 0.5 mm or more has been found to occur in 20.8% of eyes after PRK.[58]

Clinical: The patient may be noted to have an undercorrection or induced astigmatism. The patient may complain of diplopia[59] and halos at night. Decentration may produce both a reduction of BCVA secondary to irregular astigmatism and a reduction of uncorrected visual acuity from the associated undercorrection, since the maximally treated area is not aligned. The diagnosis of decentration is made topographically (Fig. 94.28). Nasal decentration is more common with the use of miotics and temporal decentrations with attempts to avoid hitting the nasally hinged flap. Dilatation makes all centration more difficult. When an eye tracker is used most of these difficulties above can be avoided; however, decentrations can still occur when the visual axis of the eye is several millimeters off the center of the pupil. This situation most commonly occurs with a large angle kappa.

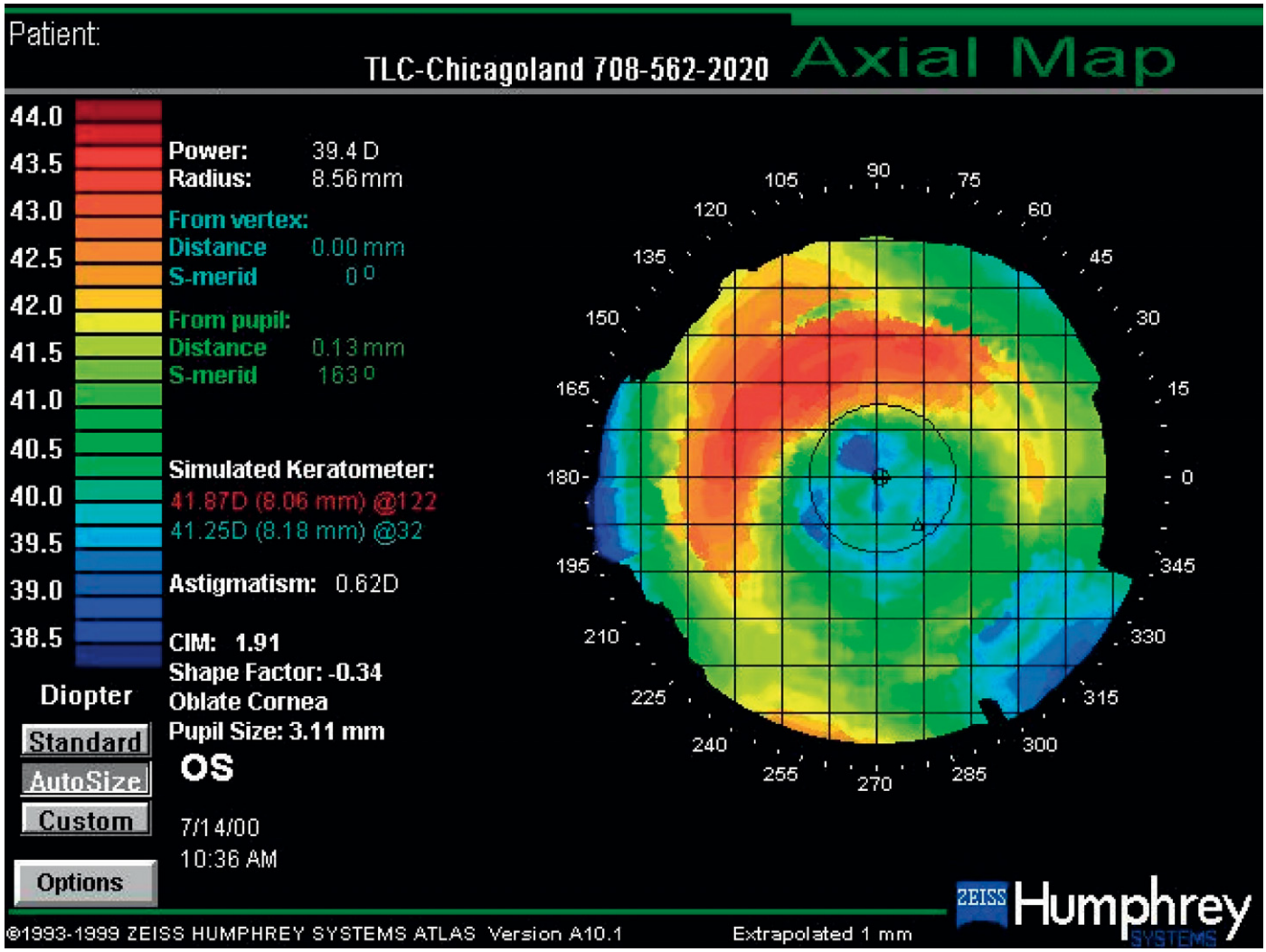

Figure 94.28. Decentered and small zone ablation after hyperopic LASIK will often be associated with night glare.

Management: Various techniques with variable success have been described for the treatment of decentrations including masking techniques to expand the ablation zone, transepithelial ablation opposite to the decentered ablation,[60] or simply correction of the residual refraction with an expanded zone. Custom wavefront LASIK offers the promise of precisely treating the decentered ablation to re-center the ablation and expand the optical zones to improve the night vision problems. Although there is limited experience with this technique at the present time, it offers so much more potential than the previous methods. Therefore, any patient with a decentered ablation at this time should consider waiting for a custom LASIK enhancement.

While patients are waiting for custom LASIK, there are several temporizing measures that can improve the patients' functioning. Although spectacle correction will correct any induced astigmatism, contact lenses will provide better improvement in the quality of the vision. The best improvement will be with a rigid gas permeable contact lens (RGPCTL). Alphagan drops can minimize pupillary dilation at night to reduce night vision symptoms.

Prevention: Decentrations are avoided by appropriate centration of the laser ablation. Generally, the laser ablation should be centered on the center of the pupil unless the patient's fixation, as measured preoperatively or through the operating microscope, is noted to be off the center of the pupil. Most surgeons advise that the laser ablation should then be placed between one half and one third of the distance from the center of the pupil to the visual axis.

IRREGULAR ASTIGMATISM

Irregular astigmatism refers to irregularities identified on corneal topography that do not follow the regular 'bow tie' pattern of astigmatism.

Clinical: Irregular astigmatism can occur alone. However, it usually occurs in association with other LASIK complications such as a flap complication, grade 4 Sands, flaps striae, or a decentered ablation. When irregular astigmatism occurs alone it is often attributed to an asymmetrical healing response of the cornea after LASIK.

Patients will complain of reduced UCVA, blurred vision, diplopia, and glare at night. Irregular astigmatism is often associated with a reduced BCVA. Topography will demonstrate the areas of asymmetrical elevation or depression of the cornea within the visual axis (Fig. 94.29).

If the cause of the lost BCVA after LASIK is unclear, several additional tests can identify the cause. Hard CTL over-refraction will identify subtle corneal pathology. If this over-refraction gives

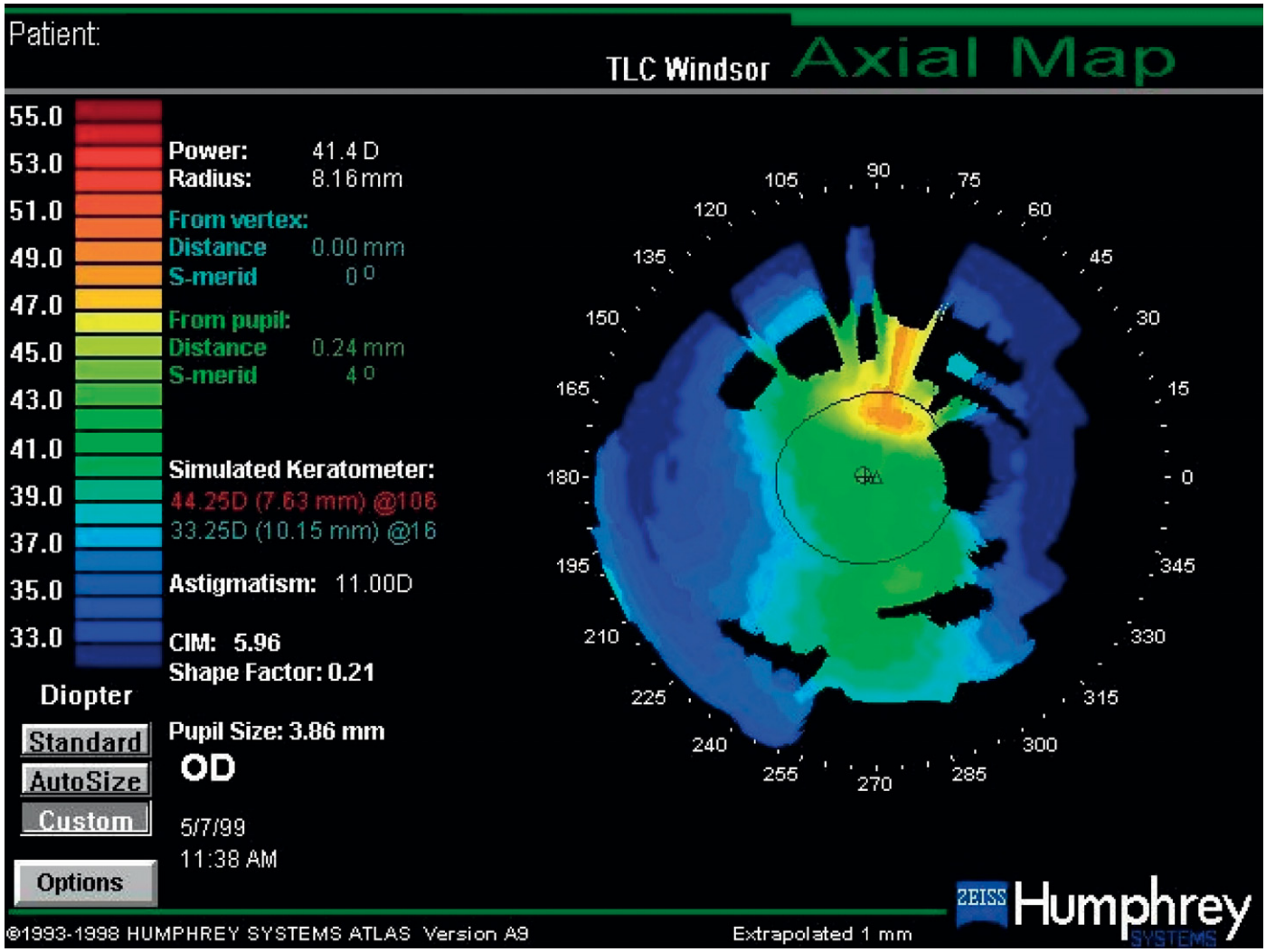

Figure 94.29. Irregular astigmatism on topography 1 year after grade 4 DLK.

a vision of 20/20, the problem is a corneal irregularity. If the BCVA remains reduced, the pathology must involve the lens or the retina. Potential acuity meter (PAM) testing will identify retinal pathology. If the PAM testing is normal, the retinal function is normal and the problem is cornea- or lens-related. If the PAM BCVA is reduced, the problem is retinal. Using these two tests, loss of BCVA related to cornea irregularity can be identified.

Management: Irregular astigmatism associated with other LASIK complications can often be improved or eliminated if the other complication is addressed. Persistent irregular astigmatism or irregular astigmatism that occurs alone is difficult to treat with the current laser systems. Although many techniques have been described using broad beam lasers,[61] they are not recommended. Custom wavefront LASIK offers great promise for the treatment of the few patients with irregular astigmatism. While there has been little experience in this area to date, treatments should be available by this method in the near future.

While patients are waiting for custom LASIK, contact lenses offer the best method for the correction of irregular astigmatism. Soft CTLs will provide up to a 50% improvement in the vision while hard CTLs can offer full improvement if the patient is agreeable to their use.

Prevention: If irregular astigmatism is identified prior to the primary LASIK procedure, it is usually considered a contraindication for standard LASIK as the standard laser ablation pattern cannot correct the irregular pattern. Irregular astigmatism associated with a history of prior hard CTL use may resolve after the contacts have been out for several weeks to months. Irregular astigmatism also occurs with forme fruste keratoconus.

Prior to using the excimer laser, the quality of the laser beam should be tested to ensure that there are no beam irregularities. The LASIK technique should be performed in a manner that allows even application of the laser treatment to avoid irregular astigmatism.

POST-LASIK DRY EYES

Dry eye after LASIK is due to the creation of a temporary neurotrophic cornea by the severing of corneal nerves during creation of the LASIK flap.[62,63] Neurotrophic dry eye is caused by decreased corneal sensation with decreased feedback to the lacrimal gland and reduced tear production.[64] Confocal microscopy has demonstrated that the number of stromal nerve fiber bundles decreases by 90% immediately after LASIK.[65] During the first year after LASIK, the nerve fiber bundles gradually return, although by 1 year their

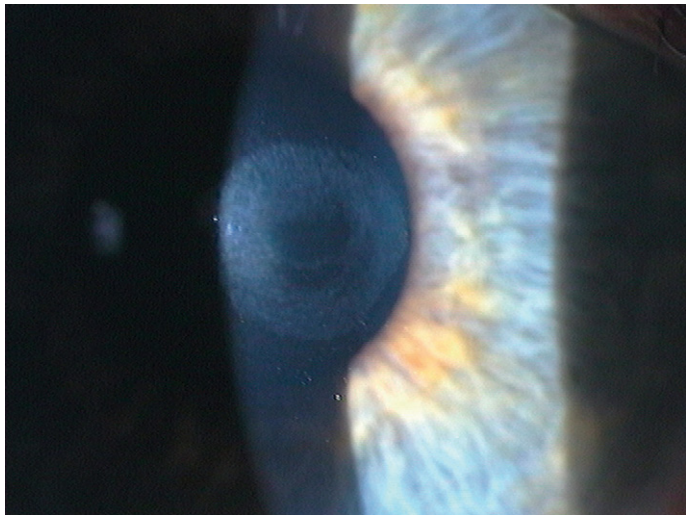

Figure 94.30. Central superficial punctate keratitis after a large hyperopic LASIK correction associated with a reduction in the UCVA and the BCVA.

number remains less than half of that before LASIK. Nasal hinge flaps have been shown by Eric Donnenfeld, MD to sever fewer of these nerves because it preserves the nasal nerves and hence dry eyes are less of a risk because the neurotrophic cornea is less severe.[66]

Clinical: The post-LASIK dry eye presents immediately after the procedure. The patient experiences the 'burning' sensation of the classic dry eye and the vision is often reduced if a dry eye keratopathy affects the central cornea. The symptoms are resolved temporarily with topical lubrication but may return less than 1 h after application. Generally, the symptoms resolve over the first postoperative month but can rarely persist for up to 1 year. Post-LASIK patients are often very frustrated by the dry eye problem as they have usually not experienced it prior to LASIK. After hyperopic LASIK, the dry eye can be caused by both the neutrotrophic cornea and the reduced tear film of the steeper central cornea. This can cause a central SPK that can dramatically affect both the UCVA and BCVA (Fig. 94.30).

Management: The post-LASIK dry eye should be assessed with the same approach used with the classic dry eye patient. Decreased tear secretion can be due to the post-LASIK neurotrophic cornea, but it also can be exacerbated by pre-existing lacrimal gland disease. Large palpebral fissures and Meibomian gland dysfunction can increase the evaporative loss of tears. LASIK patients with dry eyes should be evaluated for all these conditions for the most effective treatment and patient education.

After the LASIK procedure, frequent lubrication is suggested every hour even in normal patients to ensure good healing of the cornea. Punctal plugs are put in the lower punctum if symptoms persist. If the dry eye problems persist after 1 month, silicone plugs should be inserted in the upper punctum. Lubrication should be continued at least 4–6 times a day with nonpreserved viscous artificial tears. Rarely, ointment can be used at bedtime each night. Topical steroid may be useful for treating the inflammatory component of the dry eye as well as any associated eye allergy. Loteprednol etabonate 0.5% is particularly useful, as it is not associated with increased risk of cataract or elevated IOP. In rare instances, bandage contact lenses may be required. Environmental controls for dry eyes, including bedroom humidifiers and protective sunglasses, may also be useful for patients who have chronic dry eye problems. It is important to continue to see the dry eye patient to continue to provide reassurance that the corneal signs and symptoms are resolving.

Prevention: During the preoperative process, it is important to identify patients with dry eyes. If the patient has a history of dry eyes or has evidence of dry eyes, including a small tear meniscus or superficial punctate keratitis, it is helpful to heal their epithelium with lubricating drops prior to the procedure. Dry eyes should be suspected in patients who are already using topical lubrication prior to LASIK or that have skin conditions such as acne rosacea. Another group of patients prone to dry eyes are premenopausal women who tend to have the most complaints with dry eyes after LASIK. Schirmer testing is useful in all patients suspected of dry eyes. Punctal plugs should be used quite liberally in order to minimize the postoperative dry eye. This author prefers to use silicone punctal plugs because they are effective for 1–12 months after the procedure. Collagen plugs are only effective for 1–2 weeks and frequently need replacement.

During the LASIK procedure it is best to use a nasal hinge flap for dry eye patients in order to avoid as much as possible the neurotrophic keratopathy. During the LASIK procedure, every effort should be made to preserve the epithelium as epithelial defects will prolong healing and exacerbate the post-LASIK dry eye symptoms. Other procedures could also be considered such as PRK or LASEK which preserve more corneal sensation and create less neurotrophic keratopathy. These two procedures involve surface ablation of the cornea and therefore should not be performed for corrections greater than −6.00 D, as they would have a greater incidence of corneal haze.

VITREORETINAL COMPLICATIONS AFTER LASIK

There has been a increased theoretical risk of retinal detachment after LASIK caused by alteration of the anterior retina from the suction ring. While the myopic population is already at an increased risk of detachment, no direct relationship has been identified.[67] A recent retrospective review of a large number of LASIK cases (38 823), found that the rate of retinal detachment was 0.08%.[68] Other complications noted to occur at a low frequency after LASIK include lattice degeneration (0.3%), posterior vitreous detachment (0.1%), macular hemorrhage (0.1%), retinal tear without retinal detachment (0.1%),[67] and choroidal neovascularization (0.1%).[69] Although the incidence of vitreo-retinal pathologic conditions in myopic eyes after LASIK is low, it remains important to screen pre- and post-LASIK eyes for complications of lattice degeneration.[67]

COMPLICATIONS UNIQUE TO FEMTOSECOND FLAP CREATION

Opaque bubble layer (OBL)

The bubbles produced during the Intralase flap creation are deposited in the posterior and peripheral stroma.

Clinical: White areas develop during flap creations that vary in size from 1–8 mm in diameter (Fig. 94.31). They have fluffy and almost crystalline borders. The OBL will enlarge and expand as the flap is being created. OBL can make pupil visualization and eye tracking difficult. OBL can make patient fixation on the fixation

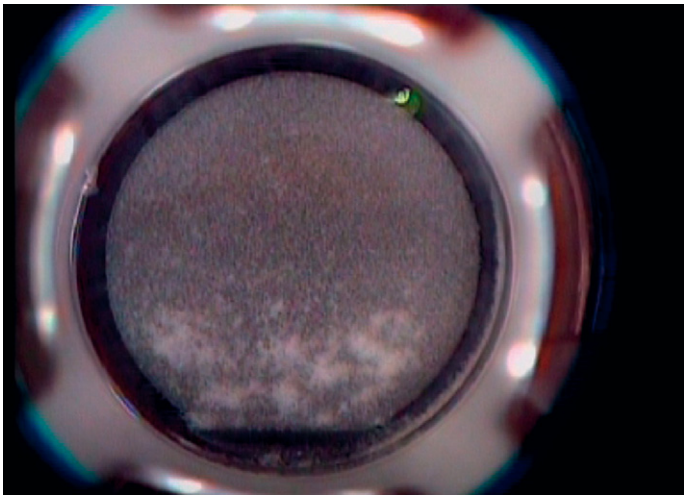

Figure 94.31. White fluffy areas are visible forming during and after flap creation.

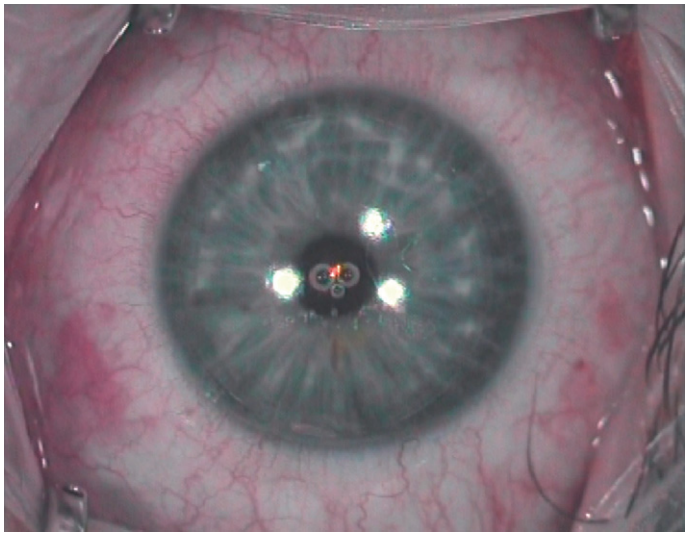

Figure 94.33. Gas bubble in the anterior chamber after Intralase flap creation. This will absorb without treatment over 1–3 h.

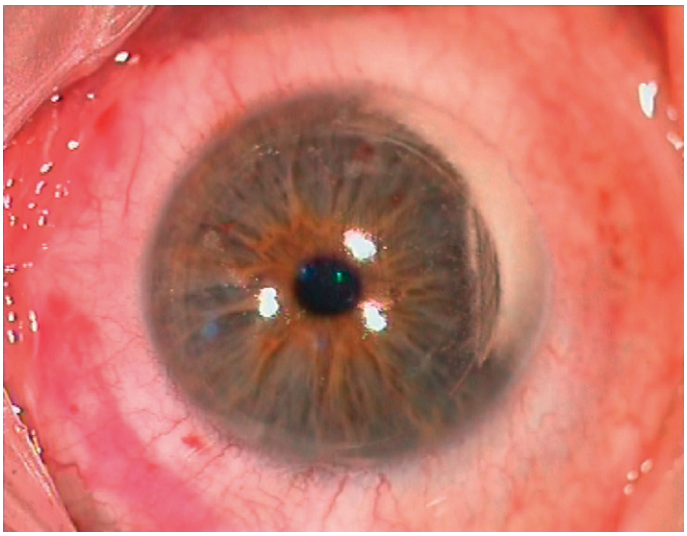

Figure 94.32. Peripheral opaque bubble layer (OBL) can be seen as a white area along the limbus. This is the ideal area for OBL formation as it does not affect the tracker.

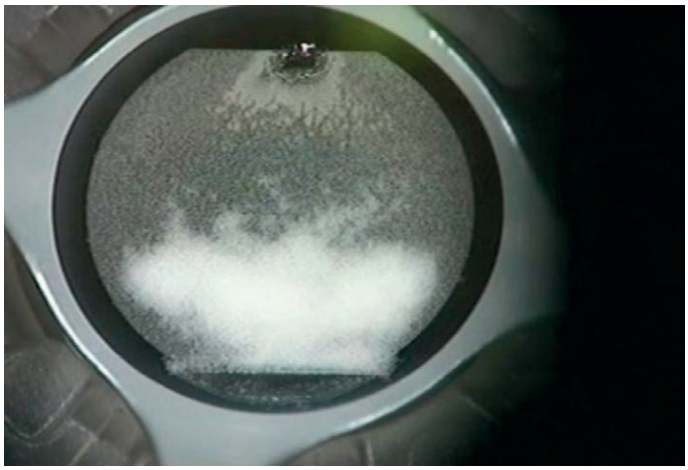

Figure 94.34. Gas breakthrough occurs rarely with Intralase. It appears as a bubble underneath the applanation cone during the flap creation.

target difficult. OBL more commonly occurs in the peripheral stroma (Fig. 94.32).

Management: Mild OBL is common and this degree of OBL can usually be wiped away with a Merocel sponge. Denser OBL will absorb in 20–30 min and the surgeon may wish to wait for resolution of the OBL prior to treatment. OBL does not seem to have an adverse outcome on the results of LASIK, even when the ablation is performed with OBL visible in the stromal bed.

Prevention: OBL is reduced by the faster pulse rate of the 60 KHz laser which allows for reduced energy levels, a denser grid pattern of laser treatment, and less gas production. The technique of 'soft docking' is essential to reduce the incidence of OBL. In this technique, a meniscus is left around the cone edge rather than complete applanation of the cornea. This meniscus is ideally in contact with the area where the 'pocket' of the Intralase flap is created. This meniscus will provide an easier route for the gas to escape so it does not deposit in the posterior stromal bed. Regular laser maintenance also will reduce the incidence of OBL.

Gas breakthrough

Gas created during the flap creation process can be deposited in the stromal bed where it produces the OBL; the peripheral stroma where it produces peripheral OBL; into the anterior chamber where it produces gas bubbles that can disrupt the eye tracker during treatment (Fig. 94.33); or through the flap and under the epithelium or Bowman's layer which is called gas breakthrough.

Clinical: Patients at the greatest risk for gas breakthrough include those with loose epithelium and those who have thin flaps created with the Intralase (<100 μm). Bubbles 1–3 mm in size can be seen forming during flap creation under the applanation cone at the surface of the cornea (Fig. 94.34). They are most often solitary but several bubbles can occur. They are generally small (<1 mm), but (<1/1000) large bubbles can occur. If the bubble is large, the flap cannot be lifted, since the lameller plane is incomplete underneath the bubble.

Management: Small amounts of gas breakthrough do not effect the lifting of the flap or treatment. Large bubbles can make the flap difficult or impossible to lift. If the flap cannot be lifted, the flap

should be replaced and the eye allowed to stabilize for a few weeks. At that time, the flap can be re-cut at a 40 µm greater depth or PRK can be performed with mitomycin C.

Prevention: Maintaining a flap depth of 120 µm considerably reduces the risk of gas breakthrough. The reduced spot size and the higher pulse rate of the 60 KHz laser has allowed for a denser 8 × 8 spot/line separation of the Intralase that has reduced the risk of gas breakthrough.

Transient light sensitivity (TLS)

TLS is thought to be related to higher side-cut energy levels used for flap creation or possibly a higher bed energy used for flap creation.

Clinical: Photosensitivity at day and at night starts 1 month after LASIK with the Intralase laser. There are no ocular abnormalities noted on examination. The uncorrected visual acuity is unaffected.

Management: The patient is prescribed topical steroids on a tapering schedule starting at four times a day over 1 month. This treatment results in resolution of the TLS.

Prevention: The 60 KHz laser allows lower energy levels to be used for flap creation and seems to reduce the incidence of TLS.

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95 Comparative analysis of mechanical and laser microkeratomes

John F. Doane, Randolph T. Jackson, Stephen G. Slade

This is an exciting time for laser in situ keratomileusis (LASIK), with microkeratome modifications making flap creation safer and more predictable. To explore these improvements, this chapter reviews advances in the traditional mechanized microkeratome and the development of a newer alternative, the femtosecond laser, for flap creation. For the patient seeking refractive surgery, the goal is to have excellent vision without spectacles. This consists of two important considerations. Foremost is safety with maintenance or improvement of best spectacle corrected visual acuity, while at the same time having a highly accurate refractive outcome with optimization of uncorrected vision. Advances in both the mechanical keratome and the femtosecond laser seek to meet these criteria.

The original Barraquer microkeratome was an innovative device where the oscillating blade slid over a nongeared suction ring. Many small improvements since then have reduced complications for both the novice and experienced surgeon, so that buttonhole formation, free caps, corneal abrasions, and incomplete flaps are far less common. With the application of the femtosecond laser to create corneal flaps, there is the potential to further reduce complications, improve visual results, and develop new forms of subepithelial, intrastromal, and lamellar corneal refractive surgery. With the evolution of mechanical keratomes corneal refractive surgery has undergone tremendous advances in the past 50 years. The trend toward an increasingly automated process has provided more reproducible results with less dependence on individual surgical technique.

In the early 1960s, Professor Jose I. Barraquer of Santefe de Bogotá, Colombia, was hand-dissecting free caps from the anterior cornea, followed by free-hand dissection of the stromal bed. The first automated microkeratome was developed by Professor Barraquer in the first half of the 1960s.[1] To ensure a uniform flap, the eye needed to be held firmly and the intraocular pressure increased. Professor Barraquer achieved this by developing the suction fixation ring. Even today, the Barraquer tonometer, which is used to quickly check for adequate intraocular pressure during the keratectomy procedure, is still in widespread use.

The basic components of the Barraquer keratome are still present in today's models. These components include the keratome head, blade, depth plate, and vacuum suction ring. The sagittal height of the suction ring and the diameter of the orifice that receives the cornea affect the diameter of the flap. To a beginning surgeon, it would appear that the flap thickness would be controlled solely by the depth plate of the microkeratome and the suction ring parameters would determine the diameter of the flap. While this is valid there are a few other direct correlates to this initial assumption. The steepness of the cornea and the central thickness correlate directly to the end flap thickness. The steepness of the cornea directly influences flap diameter with applanating microkeratomes. The steeper the cornea the larger the resultant flap diameter and likewise the flatter the cornea the smaller the resultant diameter. Steep corneas, for example greater than 47 D, provide a longer arc length of exposed cornea for the microkeratome to engage and, therefore, a larger diameter flap will be created. Conversely, flat corneas (i.e. <42 D) provide a shorter arc length of exposed cornea for the microkeratome to engage and will lead to smaller diameter flaps, and if extremely flat, can lead to free-cap formation.

There are various guidelines for suction ring size based on keratometry and type of ablation. An unusually small corneal diameter or orbital opening can limit the suction ring size that can be used. Regarding flap thickness, the microkeratome depth plate is the starting point, but a few other factors are directly related to outcomes when using an applanating microkeratome. Steeper and thinner corneas tend to produce thinner central flaps, while flatter and thicker corneas tend to produce thicker central flaps, despite using the same depth plate. New blades tend to produce thicker flaps than blades that are sterilized and reused. Low intraocular pressure, or pseudosuction, will lead to thin flaps, while loss of suction during the keratectomy will lead to truncated or free caps.

SHORT-PULSED LASER DEVELOPMENT FOR FLAP CREATION

The term 'photodisruption' was coined by Martin Mainster, MD, PhD in 1983 in an article in which he also described the plasma physics foundations of lasers in the picosecond and nanosecond range.[2] The process involves focusing a large amount of energy into a focused spot in a very short time interval. A key element of this technology is that the laser light must be perfectly focused. If the laser is not

focused, there will be no tissue effect. This is unlike CO_2, argon, or excimer laser delivery systems, which will have tissue effects, albeit suboptimal, even if not focused precisely.

A well-focused short-pulse laser causes an extremely localized temperature increase and electron configuration changes that convert tissue into a matter called plasma. Plasma occurs in nature only under conditions of extreme high temperature, such as lightning strikes, and in the atmosphere of a star such as the sun. The temperatures involved to create plasma are in the range of 10–15 000°C. Amazingly, this is 2–3 times the temperature on the surface of the sun.[2,3] Depending on the time duration or the pulse width, the power created can vary with short-pulsed lasers. The power generated relates to the equation, power = energy/time. For a given amount of energy, decreasing the pulse width increases the power per pulse. Conversely, if you are using ever shorter pulse widths, the amount of energy required to achieve a certain power declines precipitously. With short-pulsed lasers, a microplasma is created and this will vaporize a given sphere of corneal tissue. When photodisruption occurs, there is a plasma expansion followed by a shock wave and the creation of a resultant cavitation bubble (Fig. 95.1). The entire process happens in a very small area and during a very short time period, thus avoiding significant thermal damage to the eye.

This process has been used to great effect with the YAG laser. The YAG laser pulse width is in the nanosecond range. As noted above, by decreasing the time duration of the pulses even further, less energy can be used and the resultant spot size is of smaller diameter with less collateral damage to neighboring tissue (Fig. 95.2).

For corneal surgery, the short-pulsed laser is focused precisely to create the microplasma and cavitation bubble. Microplasma creation vaporizes corneal tissue and creates a bubble of CO_2 gas and water that effectively separates the corneal lamellae. The gas and water are reabsorbed by the endothelial pump with a resultant cleavage plane in the cornea. When thousands of these pulses are connected together, a distinct cleavage plane can be achieved. These spots can be placed horizontally or vertically to achieve desired dissection planes (Fig. 95.3).

The pattern of the cleavage plane is literally at the discretion and creativity of the surgeon and the software written for the specific short-pulse laser system. The wide cavitation spacing of nanosecond short-pulse lasers precluded their use for precise corneal dissection. The subsequent evolution of short-pulsed lasers involved picosecond- and then femtosecond-pulse widths. Two companies produced picosecond lasers designed for intrastromal ablation: Phoenix Lasers, Inc (Phoenix, Arizona). and Intelligent Surgical Lasers, Inc (San Diego, California).[3] Owing to technical difficulties they did not make their way into clinical practice. Notably, the cavitation spacing with the picosecond laser, although closer than with nanosecond lasers, was still not close enough to create

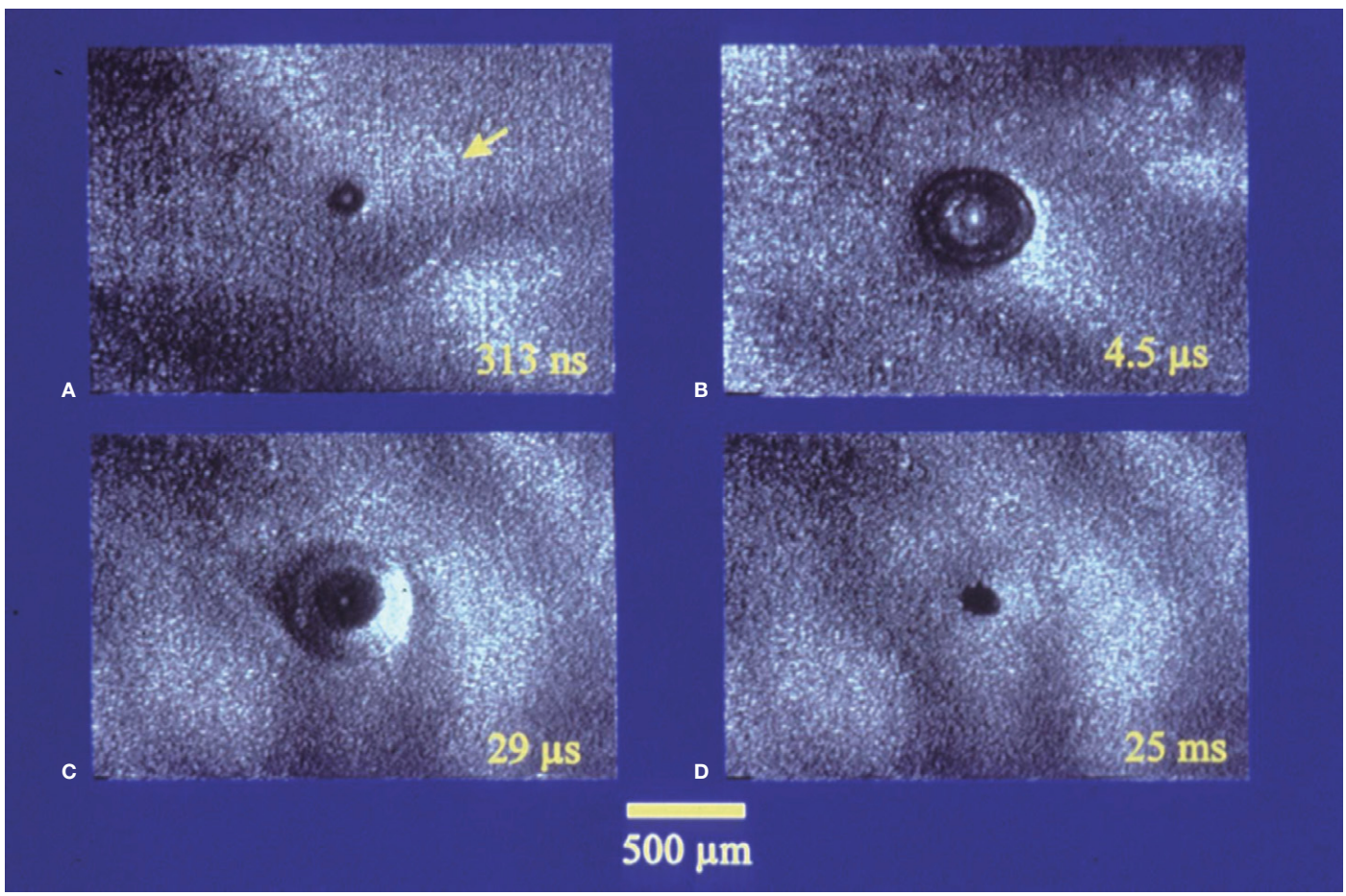

Figure 95.1. Time elapsed photography of short-pulse photodisruption (nanosecond) with three phases of the process. Plasma expansion, shock wave progression, and cavitation bubble creation are evident in this photo series. Photograph courtesy of Intralase®.

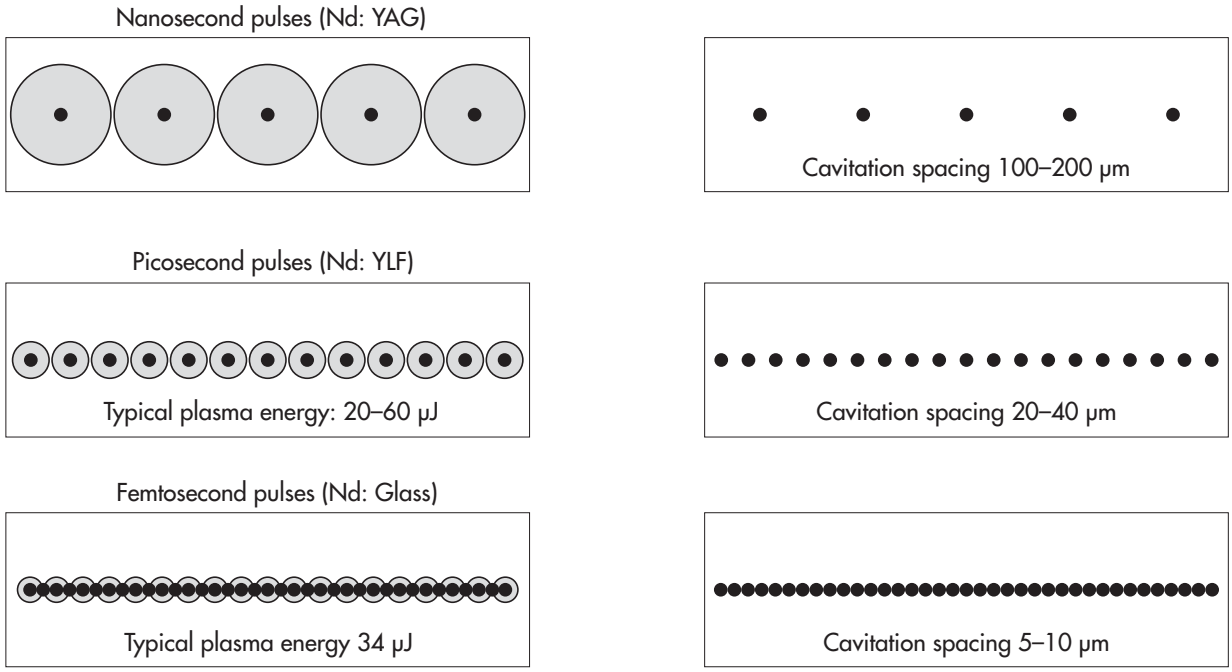

Figure 95.2. Spot energy, spot size, and cavitation spacing for the nanosecond, picosecond, and femtosecond pulsed lasers, respectively. With the nano- and picosecond lasers, the cavitation spacing is so wide that accurate cleavage plane development within corneal tissue is not close enough to create contiguous dissection. With the femtosecond lasers, the cavitation spacing is ideal to create a dissection plane. Note: nanosecond laser energy is in the range of milliJoules whereas picosecond and femtosecond energies are in the microJoule range. Based on photograph courtesy of Intralase®.

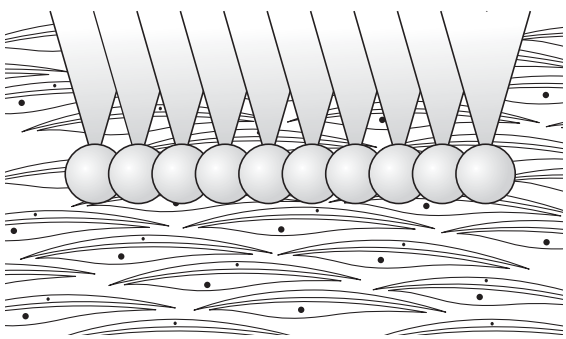

Figure 95.3. Femtosecond pulses connecting to make a horizontal dissection plane. Based on photograph courtesy of Intralase®.

adequate lamellar tissue separation. Research from the University of Michigan published in 1997 found lasers with a pulse duration in the 100 femtosecond range to be well suited for making corneal incisions.[4] One femtosecond is 1×10^{-15} s. To put it in perspective, in 1 second light travels 7.5 times around the globe, while in 1 femtosecond light can travel 30 μm and in 100 femtoseconds light barely has time to make it across the width of a human hair. It was not long after the Michigan researchers developed a laser that worked effectively for corneal dissections that these lasers found their way into clinical ophthalmology practice.

The IntraLase® Pulsion FS (femtosecond) laser was the first commercially available surgical femtosecond laser in 2001. In 2004, the FemTec™ laser from 20/10 Perfect Vision® received US Food and Drug Administration (FDA) approval for LASIK flap creation. The patient–glass interface for the FemTec™ laser is spherical in shape to match the corneal curvature and reducing suction and intraocular pressure requirements, whereas the Intralase Pulsion glass–plate interface is flat. While available in Europe, the FemTec™ laser is not yet being marketed in the USA. More recently, in March 2006, the DA VINCI™ femtosecond laser from Ziemer Ophthalmics© also received FDA approval for use in LASIK. Carl Zeiss Meditec® and WaveLight® are both working on a femtosecond laser and FDA approvals are anticipated in the near future. These instruments are also FDA approved for treatments requiring an initial lamellar resection of the cornea. Corneal transplantation, endothelial transplantation, and insertion of intrastromal rings are other areas where the femtosecond lasers are beginning to prove their effectiveness.

The process of flap cutting with a femtosecond laser is different from the mechanical microkeratome process in a number of ways. A suction ring is still used but with lower pressure. The intraocular pressure increase is reportedly closer to 40 mmHg, instead of the 70 mmHg or slightly more used with the mechanical microkeratome.[5] Note that when the femtosecond flat applanation lens contacts the cornea the intraocular pressure will increase beyond that created with the negative suction created with the syringe system. This reduces the percentage of patients experiencing transient loss of vision during the flap creation. A disposable patient interface which consists of a metal cone with a clear glass applantion lens is used to flatten the corneal dome after the suction ring vacuum is initiated (Fig. 95.4). This glass lens provides a reference plane from which a distance can be chosen where the short pulse laser is to be perfectly focused for maximal photodisruption effects and cleavage plane dissection (Fig. 95.5). A plastic syringe system fashioned after the Hessburg–Barron corneal transplantation suction trephination system is used to create vacuum with a suction ring assembly that acts as the coupler of the cornea to the applanation lens. The applanation lens is lowered over the cornea to achieve the

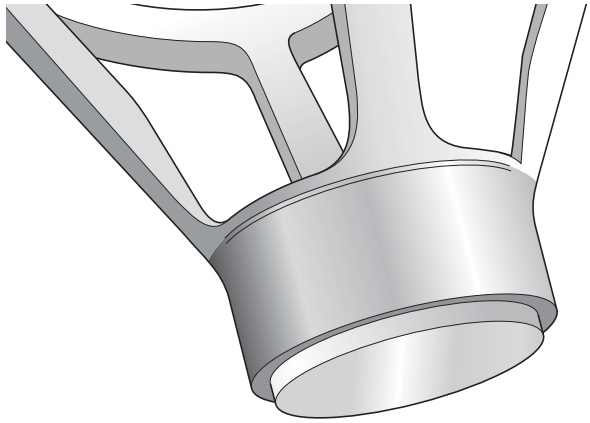

Figure 95.4. IntraLase® disposable patient interface. Based on photograph courtesy of Intralase®.

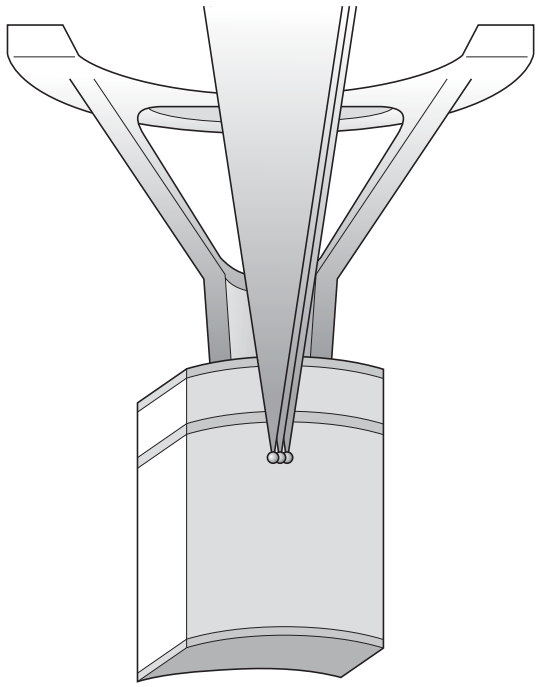

Figure 95.5. The glass lens applanates the cornea to form a reference plane for the laser. Based on photograph courtesy of Intralase®.

exact diameter desired for the corneal flap. The patient's keratometry values are essentially irrelevant compared to mechanical keratome devices. The laser creates the flap by starting at one edge with 1 µm spot placement that expands to create a 2–3 µm cavitation bubble. More bursts create a string of cavitation bubbles back and forth in a raster pattern (or alternatively a spiral pattern) until the base of the flap has been created. The laser then forms the flap edges at an angle selected by the surgeon (Fig. 95.6). The flap diameter and thickness and hinge position are all user adjustable via a graphic user interface (Fig. 95.7). Side-cut angle can be optimized to balance easy repositioning (steep angle) with ease of entry for initial lifting (shallow angle). The width of the hinge is also adjustable to allow the surgeon to balance flap security with exposure for the excimer laser near the flap.

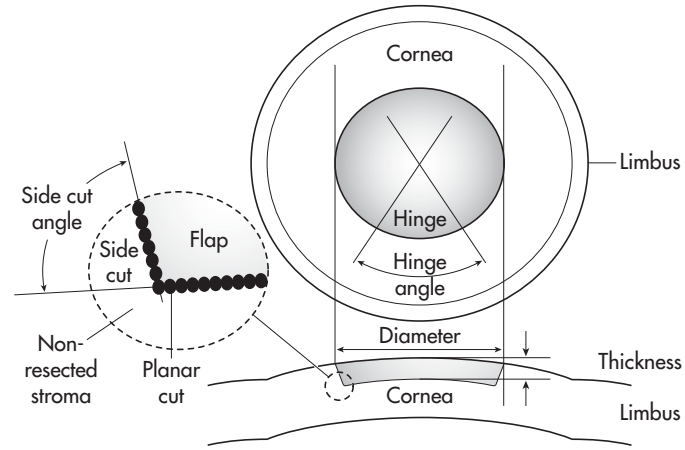

Figure 95.6. Top and cross-sectional views of femtosecond created flap. Based on photograph courtesy of Intralase®.

COMPARISON TO THE COMPLICATIONS POSSIBLE WITH THE MECHANICAL MICROKERATOME

FLAP ANATOMY: MECHANICAL VERSUS LASER KERATOMES

Is the flap anatomy for mechanical and femtosecond lasers the same? From subtraction pachymetry data, our findings suggest that mechanical microkeratomes create a minus meniscus flap[6] (Fig. 95.8). Femtosecond lasers have the capability to create near planar flaps (Fig. 95.9). With steeper and thinner corneas as noted above, mechanical microkeratomes will cut an ever thinner flap. If one checks subtraction pachymetry either at 3 or 5 points on the cornea (one central and four peripherally), the data will be similar to that found in Figs. 95.10 and 95.11. This begs the question as to why mechanical microkeratome flaps are of a meniscus shape. Owing to the 'conservation of arc-length', there has to be central dimpling of the cornea with a microkeratome functioning by applanating the cornea in advance of a cutting blade. With a fixed chord length and compression of the arc to meet this chord length, the cornea has to dimple toward the iris (RJ Sherin, Personal communication). The steeper the cornea the more this dimpling will be, and the worst case scenario would be a buttonhole formation of the flap (Figs 95.12–95.14).[6]

A meta-analysis of studies that include over 1000 eyes reveals that mechanical flap cutting complications such as free caps, buttonhole formation, partial flaps, flap decentration, and epithelial defects occur in 0.3–5.7% of cases.[7] Loss of two or more lines of best spectacle-corrected visual acuity (BSCVA) occurs in 0.5–2% of cases.[8,9] Owing to a learning curve, beginning surgeons have higher rates of complications when compared to experienced surgeons. However, complications occur even in the hands of experienced surgeons.[10] Free caps are a rare occurrence with mechanical microkeratomes. Moreover, the cap normally can be reposited without incident if correct alignment is obtained. If the original alignment is not obtained, regular and irregular astigmatism can occur. The femtosecond laser by design will not create a free cap, and none has been reported to date. Nonetheless, there is still some risk of a torn or free cap following lifting of the flap. If the femtosecond laser does not have near perfect confluence of the bubble layer, adhesions may be present that make flap elevation

Figure 95.7. Graphical user interface of IntraLase® FS laser. Based on photograph courtesy of Intralase®.

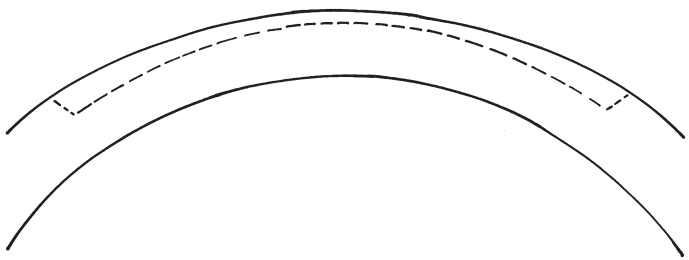

Figure 95.8. Illustration of meniscus shape flap made by a mechanical microkeratome. (Stechschulte SU, Doane JF, Motes S. Mechanical microkeratomes create a meniscus, not a planar flap. ASCRS presentation. San Diego, CA; April 29, 2001.)

difficult. If significant force is required, flap and/or hinge tearing has been reported.

Avoiding partial flaps and buttonholes is arguably the greatest advantage of the femtosecond laser. With mechanical microkeratomes, if there is a laceration through Bowman's layer over the pupillary axis, corneal opacity and/or irregular astigmatism may occur. If a partial flap was created leading to loss of best spectacle corrected vision, the flap can be repositioned, and after 3 months, a new flap can be cut or surface ablation can be performed. The scar may be permanent and can affect best spectacle corrected vision. Suction loss can occur with the femtosecond laser during flap creation. Management of these cases requires the patient to remain at the surgery facility until the opaque bubble layer resorbs in 30–60 min. The patient can then be brought back, and the femtosecond laser can be programmed as if the patient had never had a prior flap formation attempt. In one study, the flaps of four eyes were recut without problems between 5 and 45 min after the initial attempt.[11]

Defects of the epithelium during LASIK are the most common intraoperative complication and these tend to be uncomfortable for the patient at the very least. A study comparing the Carriazo–Barraquer and standard compression Hansatome™ with the IntraLase® included over 100 eyes in each group and found loose epithelium in 9.6% of eyes with the Carriazo–Barraquer, 7.7% with the Hansatome™, and none in the IntraLase® group. Epithelial defects increase the risk of bacterial keratitis and recurrent erosions. Diffuse lamellar keratitis (DLK) has been shown to be 24 times more likely in the presence of an epithelial defect.[12] Epithelial ingrowth, flap

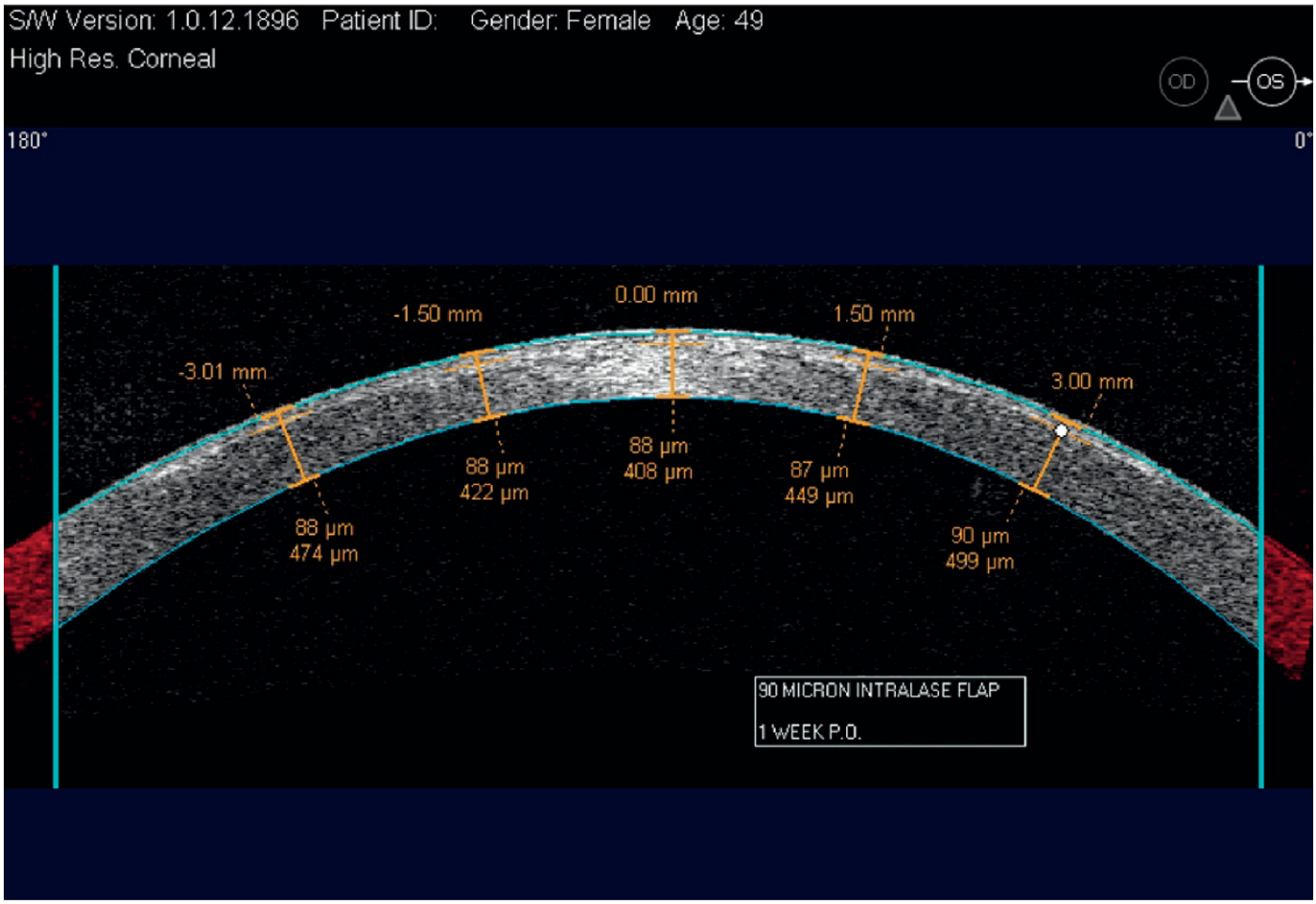

Figure 95.9. Optical Coherence Tomography (OCT) revealing uniform thickness of an IntraLase® generated corneal flap.

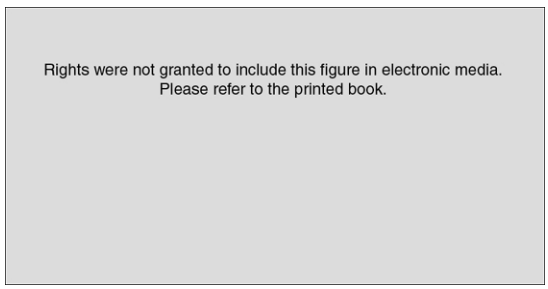

Figure 95.10. Three-point pachymetry of corneal thickness before and after cutting and lifting a Hansatome™ flap. (Stechschulte SU, Doane JF, Motes S. Mechanical microkeratomes create a meniscus, not a planar flap. ASCRS presentation. San Diego, CA; April 29, 2001.)

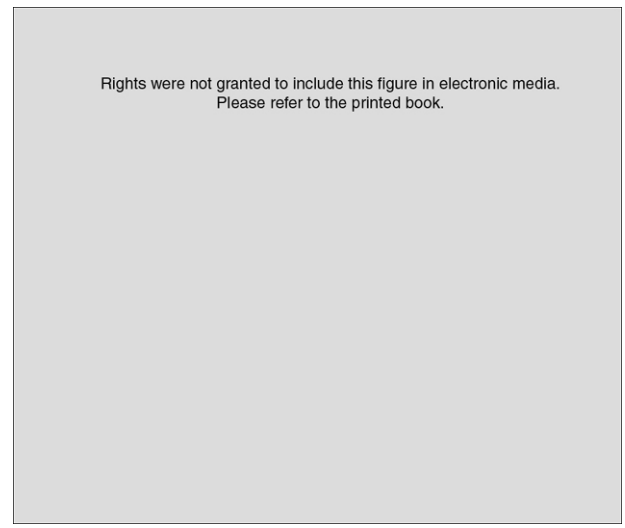

Figure 95.11. Three-point pachymetry subtraction results. This illustrates the typical meniscus shape in mechanical keratome flaps. (Stechschulte SU, Doane JF, Motes S. Mechanical microkeratomes create a meniscus, not a planar flap. ASCRS presentation. San Diego, CA; April 29, 2001.)

melts, and treatment regression all have shown an association with epithelial defects. With the femtosecond laser, no moving parts come in contact with the cornea, greatly reducing the chances of creating an epithelial defect during the cutting of the flap. With the increased effort required to lift a femtosecond-created flap, there is an opportunity to cause epithelial defects during this stage of the

procedure. Avoiding an epithelial defect, probably the most common intraoperative complication, is important, since it is uncomfortable for the patient, and increases the risk of epithelial ingrowth, DLK, and bacterial keratitis.

Late LASIK complications—ectasia

As discussed above, there is a degree of variability in the depth of corneal flaps created with a mechanical microkeratome. The factors of pachymetry, intraocular pressure, and corneal curvature are variable from case to case. The standard deviation of the Hansatome™ and Moria™ microkeratome has been found to be in the 26–29 µm range, but there are clinicians reporting first standard deviation at 10 µm. The femtosecond laser gives a highly precise flap depth with a standard deviation of 14 µm in one comparative study.[13] This precision of the femtosecond laser may eventually decrease the need for intraoperative pachymetry on corneas where there is a concern for adequate residual corneal stromal bed thickness. With a less precise and accurate system, the surgeon has to be ready to abort the case if the residual corneal stromal bed thickness is insufficient. Keratectasia appears to be multifactorial, with some relation to residual corneal stromal bed thickness. Being able to better predict the residual bed depth may help guide the treatment of borderline LASIK candidates.

Corneal sensitivity

There is some evidence that the return of corneal sensitivity may occur more quickly in patients treated with femtosecond created flaps.[14] The mechanical keratome cuts a flap that is meniscus shaped and thus deeper near the edges, thereby cutting more nerve fibers in the peripheral cornea. This explanation for the faster return of corneal sensitivity needs to be confirmed with larger clinical studies, as well as with histologic studies.

Figure 95.12. Illustration of chord length and arc compression. (Stechschulte SU, Doane JF, Motes S. Mechanical microkeratomes create a meniscus, not a planar flap. ASCRS presentation. San Diego, CA; April 29, 2001.)

Figure 95.13. Relationship of chord length and arc compression. (Stechschulte SU, Doane JF, Motes S. Mechanical microkeratomes create a meniscus, not a planar flap. ASCRS presentation. San Diego, CA; April 29, 2001.)

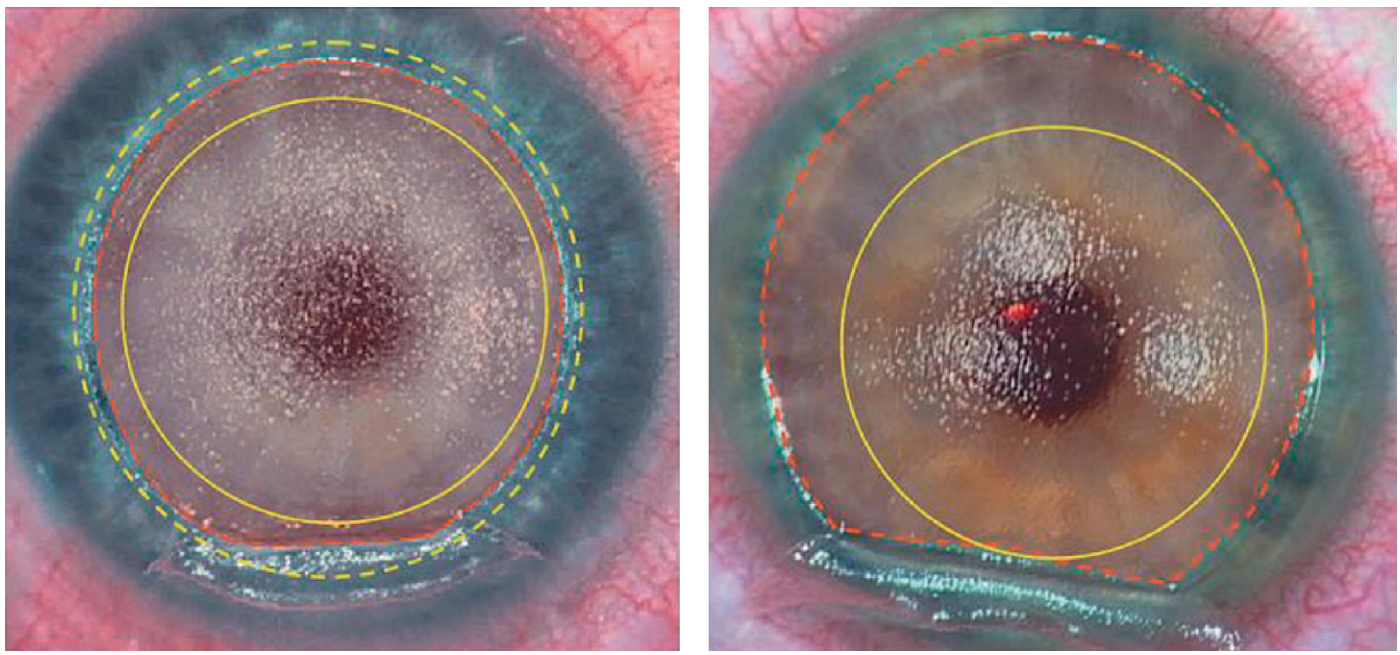

Figure 95.14. Photographic comparison of Hansatome™ and IntraLase® hinge angle. The hinge on the left was created with the IntraLase® and has a diameter of 8.5 mm. The photograph on the right was made with the Hansatome™ and has a diameter of 9.5 mm. Note the larger hinge angle on the right reduces the area available for excimer photoablation. Photograph courtesy of IntraLase®.

Transient light sensitivity syndrome

One complication that is peculiar to the femtosecond patient is the syndrome of transient light sensitivity also known as GAPS (good acuity photosensitivity syndrome). This consists of complaints of severe light sensitivity occurring around 2 to 6 weeks after LASIK. Even low levels of light from television or computer use can be quite uncomfortable for these patients. Visual acuity is generally not affected and the slit-lamp examination does not reveal inflammation. Topical steroid treatment brings resolution without long-term sequelae. Decreasing the laser energy settings appears to greatly reduce the occurrence of light sensitivity.[15]

KERATITIS

Both infectious keratitis and DLK can occur following use of the mechanical microkeratome or the femtosecond laser. Early reports revealed that there may be an increased incidence of DLK following use of the femtosecond laser. This has not been borne out in larger studies to date but most surgeons using femtosecond lasers for flap creation do use topical corticosteroids at a higher frequency and longer duration on average than cases being done with a mechanical microkeratome. There is some advantage to the femtosecond laser in regard to infectious keratitis as it eliminates the keratome and blade as sources of infection.

Visual outcomes

There are some obvious reasons why better vision could be expected when LASIK is performed with a femtosecond flap rather than a mechanical microkeratome flap. The femtosecond flap is highly uniform in thickness (Fig. 95.9). In contrast, mechanical keratome flaps tend to be more meniscus shaped as discussed above. Undercutting of the hinge in femtosecond flaps may contribute to a more uniform mechanical stability.[16] Despite theoretical advantages, research on visual outcomes to this point is mixed.[13,17] The most important measure, uncorrected visual acuity appears to be equal in both groups in most studies to date. Contrast sensitivity appears to be slightly better in the femtosecond group at the 3-month visit.[14] There also appears to be less induced astigmatic refractive error after femtosecond surgery.[5] There are two possible reasons for this. The first reason is that the hinge is undercut on the femtosecond laser, perhaps giving a more uniform, spherical, biomechanical stability of the cornea.[18] The other reason is that the hinge can be made smaller with the femtosecond laser providing more room for ablation near the flap[19] (Fig. 95.14).

Mechanical microkeratomes and femtosecond lasers both appear to be safe and effective for generating LASIK flaps. The femtosecond laser currently holds an edge in appearing to give similar visual results while eliminating or reducing certain types of flap complications. Improved predictability with uniform flap shape may help in patients with thin corneas where residual stromal bed thickness may be inadequate if the flap is inadvertently too thick. It is still controversial whether the femtosecond laser has optical advantages, such as improved contrast sensitivity or better uncorrected distance visual acuity. While not consistently shown in clinical research, there are theoretical visual outcome advantages to having such features as a uniformly dry stromal bed upon flap lifting and an undercut hinge with a small arc length.[20]

In conclusion, for any new device to displace prior technology, typically one or more hurdles need to be overcome. One could look at a comparison of which technology is better, cheaper, and faster as an initial filter. It is not universally believed that laser flap creation is better but this may change with time. At present it is substantially more expensive to use femtosecond technology than mechanical microkeratomes and it is certainly slower although this may eventually be overcome. The last concept to understand is safety. There is substantial controversy regarding safety as there are certainly risks with either technology that are not present with the other. Yet, with technology sometimes you do not have to universally and definitively beat the prior technology to gain traction in the market. It is likely that femtosecond technology will continue to gain market share and utility among ophthalmic surgeons. The time frame to obsolescence of mechanical microkeratomes is not certain as the cost for femtosecond laser technology is prohibitive in many regions of the world currently. But as with most technological evolutions, costs will come down and the technology will find greater geographic adoption.

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96 Femtosecond laser-assisted corneal surgery

Qais A. Farjo, Ayad A. Farjo

INTRODUCTION

The development of femtosecond laser technology has created new opportunities to advance corneal surgery, where the technology can take advantage of the unique anatomy and accessibility of the cornea. These lasers work by creating an extremely short, focused pulse of energy, causing formation of a cavitation bubble.[1,2] As the energy can be focused at a desired depth, even through mild opacities, creation of numerous adjacent cavitation bubbles in a specified pattern provides a precise and powerful tool for tissue dissection. In the cornea, automated planar dissections can be readily created and lamellar flaps are now commonly made with these lasers. With the desire for minimally invasive procedures and predictable outcomes, it is possible this technology will advance the standard of care in corneal surgery in coming years.

CLINICAL APPLICATIONS

LASER-ASSISTED IN SITU KERATOMILEUSIS SURGERY (LASIK)

The primary advantage for the use of femtosecond lasers in corneal refractive surgery is the improved safety over microkeratomes in creation of the lamellar flap.[3] Additional advantages include increased precision,[4,5] customization, and ease of surgery. The chief disadvantage is the cost of purchasing and maintaining the complex equipment. Likewise, it is unclear whether there is a visual advantage to the patient.[6,7] In LASIK, the procedure has also traditionally taken longer to perform than blade-based microkeratome flaps, although increases in laser speed have diminished this difference with the approximate cutting time being 15–20 s for a 60 kHz laser engine.

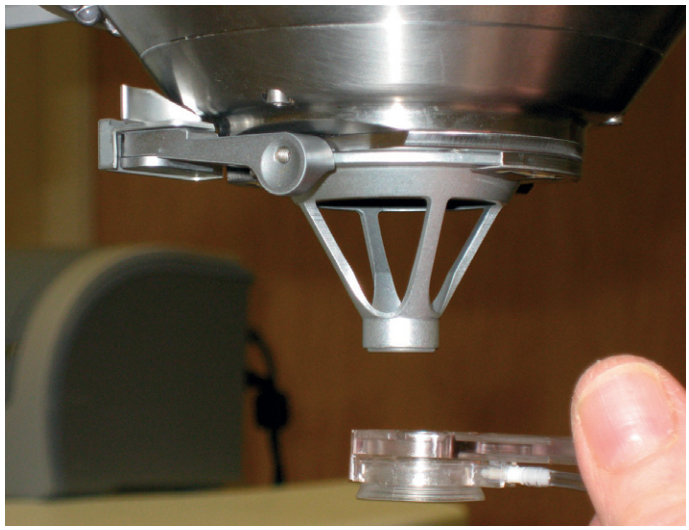
Since the introduction and widespread dissemination of LASIK, the most concerning complications of the procedure involve problems inherent in the creation of LASIK flaps. Although microkeratomes are generally safe with low complication rates,[8,9] most sight-threatening problems associated with LASIK occur as a result of flap complications.[10] The driving force behind the adoption of femtosecond lasers has been to minimize these complications.

The safety and precision of laser-based flap creation results in generally lower standard deviations of the flap thickness relative to those of blade-based flaps,[3–5] although this advantage may be less prominent when compared with newer microkeratomes. Lower degrees of suction are necessary for creation of femtosecond laser-based flaps, with only a spring-loaded syringe necessary to generate adequate suction (Fig. 96.1, *A* and *B*). Additionally, as the flap is cut optically, the entire procedure can be visualized. The ability to focus within the corneal stroma allows the creation of the internal aspect of the flap prior to cutting of the edges (Fig. 96.2, *A–C*). This 'inside-out' cutting approach reduces the concern for problems such as free caps or buttonholes. If a problem is encountered while the cavitation bubbles are being formed, the procedure can be aborted or restarted without concern because the edges have not been cut and the tissue is not displaced. Furthermore, as the flap is often adherent at points between the laser spots, it is not truly free until an instrument is used to bluntly complete the dissection also allowing the procedure to be aborted without fear of visual consequence.

Femtosecond lasers allow for customization of the flap for each patient. In addition to producing reliable flap thicknesses, the flap diameter can be selected to one-tenth of a millimeter. This consistency can be achieved because variations in suction, speed of cutting, and corneal steepness do not affect flap diameter as observed with blade microkeratomes. Flap hinge position can be placed in any axis desired, including temporally hinged flaps that may better preserve corneal nerves and provide improved surgical exposure. The width and angle of the hinge can also be reduced if needed to further enhance surgical exposure. Such hinges allow the LASIK flap to be completely reflected during the excimer procedure, providing protection for the hinge during ablation and placement of the entire excimer treatment within the flap bed. Finally, flap centration is also customizable allowing for precise localization over the patient's pupil, effectively eliminating problems associated with decentered LASIK flaps.

One factor that may also lead to improved accuracy when using femtosecond lasers is the creation of a more consistently hydrated

A



B

Figure 96.1. *A*, The ring is placed on the eye and a spring-loaded syringe is used to generate suction. *B*, The applanation cone is then docked to the ring, which allows for precise delivery of the laser energy to the eye. A side view of the Intralase applanation cone attached to the laser and how the suction ring can be docked is shown.

LASIK bed. Microkeratome blades will generally track moisture and debris from patient tears or from sterile water used to lubricate them into the LASIK bed. This alteration of hydration can have unpredictable effects on the absorption of excimer laser energy. While such effects are generally minimal, they can occasionally result in undercorrections or irregular astigmatism, especially when treating large refractive errors. Because no fluid is generally brought into the interface by the femtosecond laser, a more consistent level of hydration is obtained between procedures, possibly improving the predictability of the excimer ablation.

Technique

The authors use standard LASIK instrumentation, but add an instrument for blunt dissection (e.g. Barraquer spatula), a Sinskey hook, and a nontoothed forceps for flap reflection. In the authors' practice the femtosecond laser is in the same room as the excimer laser, although in other practices these are sometimes in separate rooms. The latter allows the surgeon to create a flap then perform an excimer ablation on another patient while the cavitation bubbles dissipate on the first patient. Generally, the preferred laser settings for the author are a 9.0 mm flap diameter and 120 μm depth, which create a flap that is similar to a 'manhole cover' and allows for better reseating after the excimer ablation, minimizing flap striae.

The general technique is similar to standard LASIK procedures. Anesthetic drops are applied followed by placement of the suction ring with care to center over the pupil. The cornea is applanated and the cone centered on the pupil. Centration of the suction ring on the pupil is important for creation of consistently large and centered flaps. Although the flap can be centered in real time by software, a grossly decentered suction ring may necessitate excessive recentering by this method and results in a reduction of flap diameter. With experience, centration becomes simpler and less software manipulation is required. During the procedure, it is best to encourage patients to raise their eyebrows and avoid head movement to prevent loss of suction. Cavitation gas bubbles can occasionally travel retrograde through Schlemm's canal into the anterior chamber[11] and are of little consequence, though they may require waiting for excimer ablation as they may interfere with pupil tracking. Leaving a small crescent of cornea superiorly that is not applanated may be helpful to allow accumulation of gas bubbles as the flap is cut. For bilateral cases, it is generally easiest to cut flaps on both eyes before performing excimer ablation. After flap creation, it is not necessary to wait for the cavitation bubbles to clear before lifting the flap.

The eye is then prepared in the standard fashion for LASIK. Lifting the flap is generally more difficult than standard microkeratome flaps. The Sinskey hook is used to localize the edge of the flap, followed by insertion and sweeping by the Barraquer spatula. As the flap is thinner than most microkeratome flaps and the underlying adhesion is greater, care should be taken to avoid damaging the flap while sweeping and lifting. The undersurface of the flap tends to appear slightly more irregular than microkeratome-based flaps, but this does not appear to have any detrimental effect on vision (Fig. 96.3). In areas of opaque bubble layer (OBL) formation, the adhesion of the flap tends to be greater and somewhat greater force is required to free the flap. The flap is then reflected and the excimer ablation is performed. After replacing the flap, it is massaged away from the hinge and the gutter margin is inspected for even width to verify proper re-positioning.

Occasionally, suction loss during creation of the flap will occur and, depending on the degree of completion, the procedure can be either repeated or aborted (Fig. 96.4, *A–C*). When attempting a re-cut at the same depth as previously desired, the laser usually will create cavitation bubbles in the plane that was previously intended. However, extra care must be taken during lifting of the flap to avoid entering the incorrect plane. Recognition of the cause of suction loss is important in prevention of recurrence. It is also possible to perform a 'side cut' only procedure, without re-cutting the entire bed, if the procedure aborted during this final phase of flap creation. Recentration of the flap is important and it is recommended to reduce the flap diameter by 0.2 mm to assure that the side cut will fall within the diameter of the previously cut bed. The flap edges can also be cut manually using a surgical blade or curved corneal scissors. When cutting with corneal scissors, it is advisable to cut with a slight pressure radially to ensure the largest possible flap is created.

If the procedure is aborted, the flap can be reattempted once the cavitation bubbles have cleared after several minutes. It may,

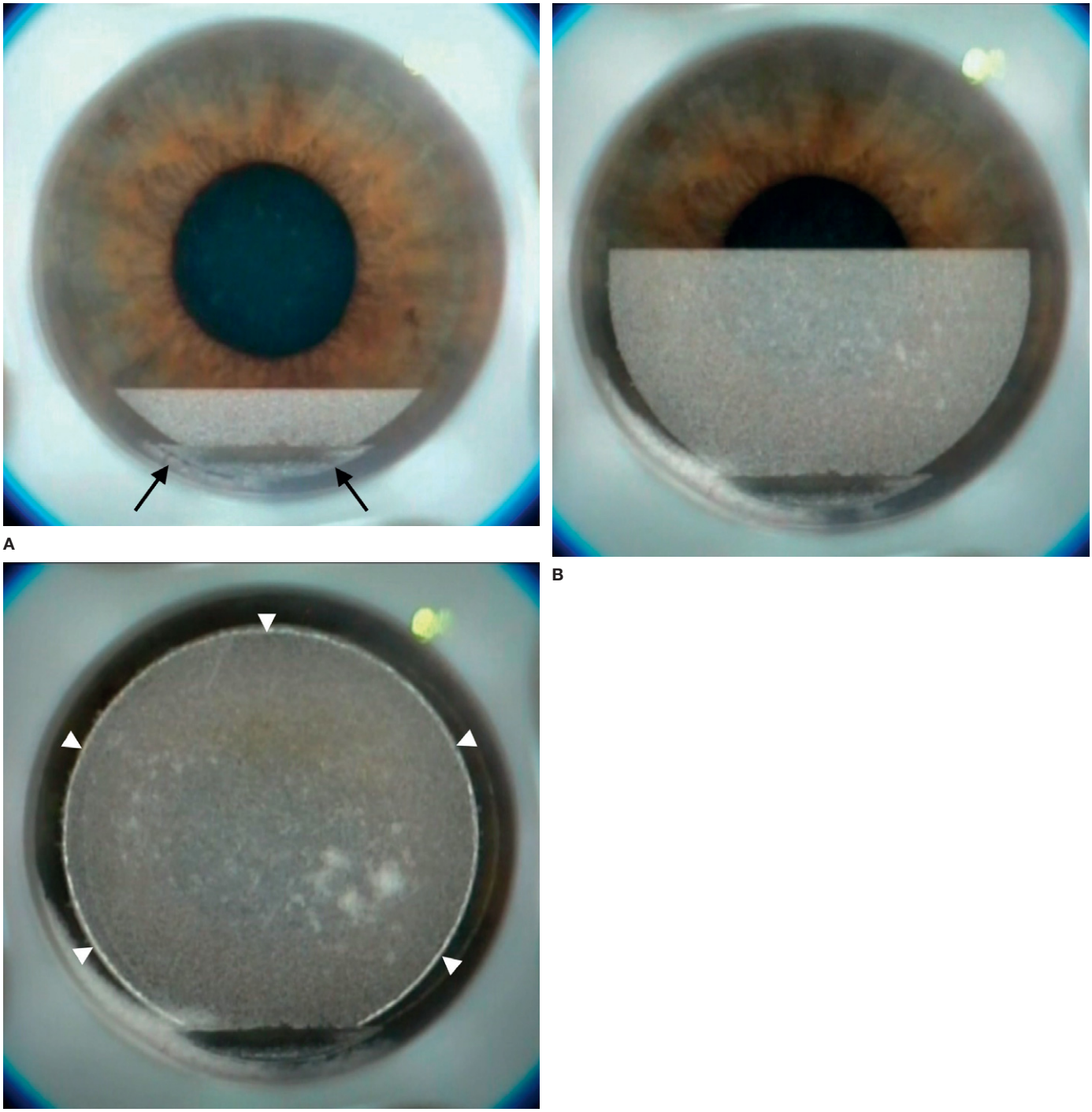


Figure 96.2. *A*, The internal portion of the LASIK flap is cut before the edges. Note the 'pocket' which is created prior to the planar cut in order to act as a reservoir for intrastromal gas (black arrows). Leaving a small meniscus of unapplanated cornea superiorly is recommended to facilitate transit of accumulated gas into the pocket. *B*, A raster pattern of cavitation bubbles creates the lamellar dissection. *C*, The arc of ablation can be seen performing the side-cutting of the flap edges anteriorly (white arrowheads).

however, be advisable to have the patient return in 2–4 weeks to avoid creating multiple planes. Addressing the underlying cause for the aborted procedure is important. For example, if a patient was squeezing excessively during the procedure they should be coached in relaxation of their eyelids or eye brows. Occasionally, injection of local anesthetic into the brows can be helpful for patients who have difficulty relaxing them. Unlike blade-based microkeratomes where head movement will generally not affect suction, subtle head movement can cause a loss of suction and necessitate aborting the procedure. Comfortable and stable head positioning is therefore important before initiating the procedure. As the laser cone may come into contact with the nose, it is recommended that the head be turned slightly in the opposite direction from the eye that is being worked on to reduce this possibility.

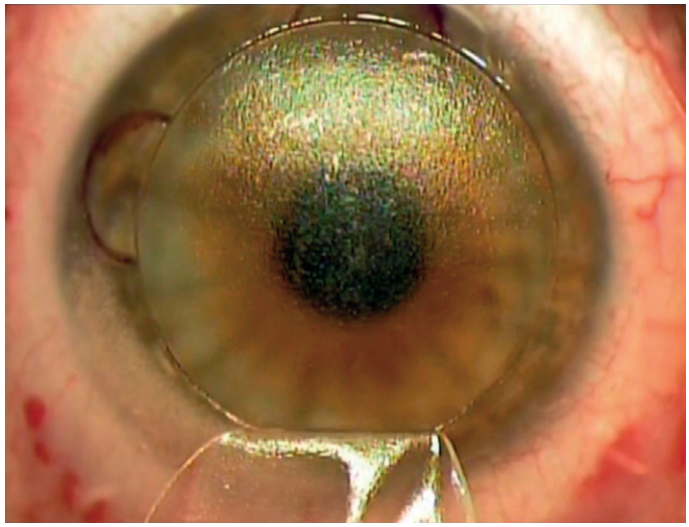


Figure 96.3. Lifting of femtosecond-assisted LASIK flap. Note that the narrow hinge angle allows near total reflection of the flap, allowing complete placement of the ablation. Also note the somewhat more irregular surface of the flap bed compared with blade-based microkeratomes.

Postoperative care

Femtosecond lasers tend to create a greater amount of intracorneal inflammation than microkeratomes. This can lead to more intense postoperative pain and irritation, for which patients should be prepared in advance. Initiation of prednisolone acetate 1% drops and a topical antibiotic immediately after surgery is helpful in controlling this. An oral analgesic may also be necessary for pain control. The pain typically lasts less than 6 h and can be alleviated with application of topical steroids and artificial tears as well as oral analgesics. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) are often useful in treating both the inflammation and pain, although narcotics are certainly more effective in treating the pain. Transient light sensitivity syndrome (TLSS), a condition in which patients suffer significant postoperative photophobia, has been reported to have an incidence of 1.3% after femtosecond laser flap creation and is thought to be related to higher pulse energy settings. The problem is unpredictable but generally self-limited and responsive to early institution of topical steroids.[12,13]

Because of the design of the planar flap with vertical flap edges, healing tends to occur faster and more vigorously than with traditional blade-based microkeratomes. This improved healing is generally advantageous, but it can make lifting flaps for repositioning or enhancement more difficult. Not surprisingly, the longer the time that is allowed to pass the more difficulty there will be in lifting the flap. Although the flap lift procedure does not differ significantly, extra care must be taken to avoid traumatizing the flap which could allow epithelial ingrowth subsequently. Performing enhancements between 3 and 6 months is generally accomplished without too much difficulty. Afterwards, it may be more advantageous to re-cut the flap rather than lift it.

INTRACORNEAL RING SEGMENT IMPLANTATION

Intracorneal ring segments such as Intacs are an accepted treatment for low degrees of myopia[14] and in recent years, they have become recognized as a valuable surgical treatment of ectatic disorders of the cornea such as keratoconus[15–19] and post-LASIK ectasia.[20,21] Insertion of the segments results in central flattening by taking advantage of corneal biomechanical properties. Although manual systems exist for the implantation of intracorneal ring segments, the use of femtosecond lasers offers distinct advantages. These include customization of the axis, depth, and width of the channels, uniform depth of the channels for 360°, and increased speed and safety of the procedure. On the other hand, some disadvantages compared to manual dissection exist in addition to cost. Chiefly, the uniform depth of the channels does not necessarily follow a path between corneal lamellae. Even by increasing the laser ring energy to assure that the dissection is complete, this factor as well as the presence of microadhesions within the channel, can make insertion of the ring segments more problematic.

In the author's and other's experience,[22] intracorneal ring segments have greatest effect in treatment of early keratoconus. In many cases the cone will persist, but will be flattened and centered postoperatively. In patients with advanced keratoconus, distortion and high astigmatism may remain, requiring continued use of contact lenses. Most patients experience improvement in contact lens tolerance associated with the improved corneal contour.[23] With thinner preoperative corneas and central cones, the refractive effect of the segments can be quite dramatic. With diseases such as pellucid marginal degeneration where peripheral thinning can be significant, or with greatly decentered cones, use of a femtosecond laser may not be possible without cutting more at a more shallow depth. In such cases, it may be best to use a manual dissection system to avoid perforation.

Technique

The instrumentation required is less extensive than that needed for manual insertion and include a Sinskey hook, symmetric glide, Intacs insertion forceps, needle driver, and tying forceps. The first step is centration and, although the manufacturer recommends insertion of Intacs on the geometric center of the cornea, the authors advise centration on the pupil. This reduces patient complaints of glare and night vision disturbances and does not seem to have any adverse effect on procedure efficacy. Placement of the Intacs so that the incision is along the steep refractive axis of astigmatism is also recommended. Although this will usually coincide with the topographic incision, occasionally they will be different. In rare cases where the topographic axis is 90° away from the refractive axis, it is best to follow the topographic landmarks to determine optimal placement of incision axis.[24] If a ring illuminating light source is available (as with the VISX laser), the steep axis can often be confirmed by using this as a qualitative keratometer (Fig. 96.5, *A–C*).

Nomograms have been published by the manufacturer for selection of ring sizes in myopia with normal corneas as well in keratoconus (Table 96.1).[24] In considering segment selection for keratoconus, choice of segment thickness is dependent on the severity of the patient cone and patient refractive error preoperatively. Asymmetric implantation with placement of a thicker segment inferiorly and thinner segment superiorly has been generally reported to be effective in treatment of keratoconus.[17,18] Additional reports exist describing implantation of only a single segment inferiorly or adjustment of the procedure by removal of a superior segment.[18,25,26] The authors have found that symmetric segment implantation is generally effective and tends to produce the most flattening of the cone (Table 96.2). Symmetric segment implantation is also effective in recentering the cone. As would be expected,

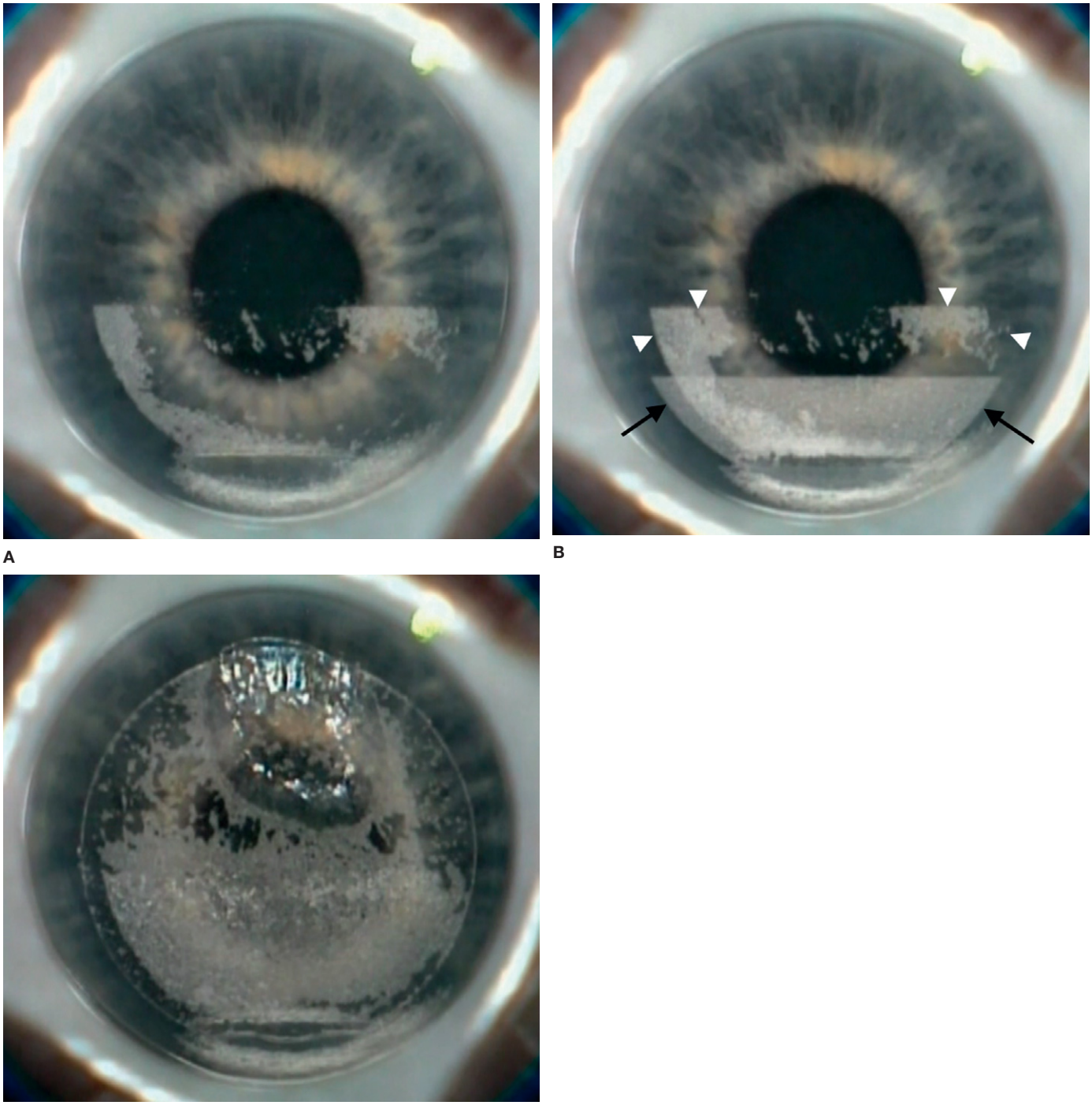
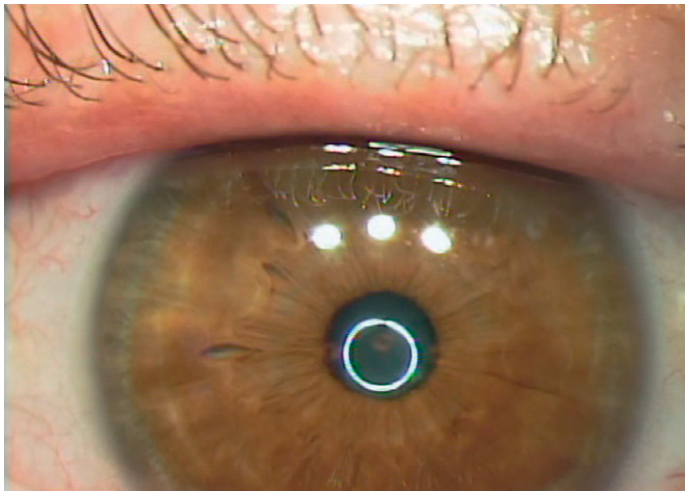


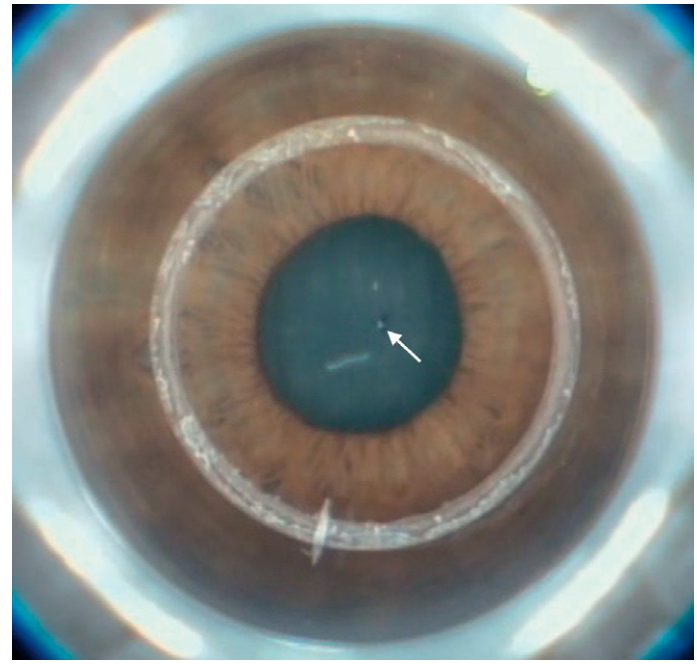
Figure 96.4. *A*, Immediate re-cut of LASIK flap after procedure interruption due to suction loss. *B*, The edges of the previous flap (white arrowheads) are visible during re-cutting of the new flap (black arrows). *B*, Successful re-cut of the flap. Note that the re-cut diameter was slightly larger than the original flap. This may indicate that the original flap attempt may have had poor ring centration, which resulted in software reduction of the flap diameter, and may have been contributed to initial suction loss.

implantation of the thickest segments (0.35 mm in the USA at time of this writing) results in the greatest flattening of the cone and greatest refractive effect.

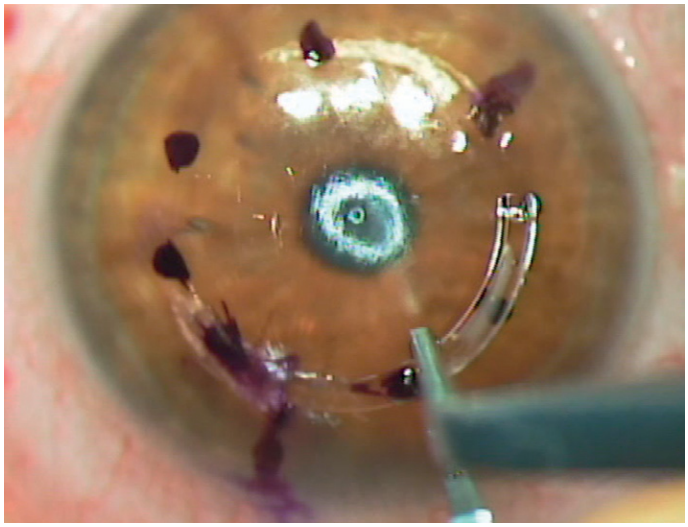
The more narrow the channels, the more difficult the insertion of the segments will be. However, with more narrow channels, the effect of the segments is greatest in the authors' experience. As this can be customized, it is recommended that the channels be made wider for initial cases and gradually decreased as surgeon experience allows. Inner tunnel diameter can vary between 6.6–6.8 mm and the outer diameter can vary from 7.4–7.6 mm. For initial cases, a combination of 6.6 mm inner diameter and 7.6 mm outer diameter is recommended with reduction of the outer diameter with experience. The authors finds the best balance of efficacy with ease of insertion by setting the inner diameter to 6.6 mm and the outer diameter to 7.5 mm, especially when the 0.35 mm segment sizes are used. To insure easiest insertion, the difference between outer and



A



B



C

Figure 96.5. *A*, Ring illumination confirms the steep astigmatic axis on the cornea. *B*, Femtosecond laser channels are created with placement of the entrance incision on the steep topographic axis. Note that channel is centered on the pupil rather than the geometric center of the cornea marked in blue (arrow). *C*, It is recommended that the ring segments be grasped at the midpoint of the exposed segment to maximize insertion force and reduce the chance of fracturing the segment. Direct marking of the segment channels as depicted is not advised as this tends to collapse the channel, making insertion more difficult.

Table 96.1 Intacs manufacturer recommended Intacs nomogram in keratoconus

Preoperative SE	<3 D	>3 D
Intacs size	0.25 superior/0.30 inferior	0.25 superior/ 0.35 inferior

SE = Spherical equivalent.

D = Diopter.

Rapuano CJ, Sugar A, Koch DD, et al. Intrastromal corneal ring segments for low myopia: a report by the American Academy of Ophthalmology. Ophthalmology 2001; 10: 1922–1928.

Table 96.2 Authors' suggested Intacs nomogram in keratoconus (symmetric segments)

Preoperative SE	<1.5 D	1.5–2 D	2–2.5 D	2.5–3 D	>3 D
Intacs size	0.25	0.275	0.30	0.325	0.35

SE = Spherical equivalent.

D = Diopter.

inner diameter should be double the segment size (e.g. 0.6 mm difference for 0.30 mm segment size).

The depth of the cornea should be measured along the path which the Intacs are expected to take. The depths of the channels should be set to approximately $^{2}/_{3}$ of this depth. For standard, healthy corneas, this depth can be approximated by subtracting 90 µm from the central corneal thickness. The manufacturer advises against implantation of ring segments into corneas thinner than 450 µm at the incision site. When inserting the segments, one should be careful

to locate the full depth of the channels in order to avoid creating a false passage. As noted above, insertion of Intacs segments into channels created by femtosecond lasers can be more challenging than implantation into channels created manually. Floating the Intacs in a drop of antibiotic solution makes removal from their protective case easier. In general, if one grasps the midpoint of the segment that is not within the channel and exerts a small rotational force, the segments can be most easily advanced. Other options include increasing ring energy to assure complete dissection, slow insertion of the Intacs, and insertion of a semicircular guide. In most cases, resistance can be overcome with slow and steady pressure and counter pressure with a dry sponge will help open up the incisions. Attention should be paid to try to follow the semicircular pattern of the channels with a small rotational effort. Sometimes removing the segment and reinsertion with emphasis paid to maintaining momentum of insertion also can prove helpful. A dry technique is recommended as hydration of the incision site or channels creates stromal swelling that can make it more difficult to insert the segments. The segments should never be forced into the channel as a false passage may be created and, if the implantation is excessively difficult, the channel should be re-cut. Finally, care should be taken to avoid tracking of epithelium into the channels during insertion and the channels should be checked to be free of epithelium at the end of the procedure, with no gaping of the incision, to reduce the potential of postoperative epithelial ingrowth.

For bilateral cases, although it can be more time efficient to cut the channels in each eye followed by insertion of the segments, the authors advise that each eye be done individually. The primary reason for this is that visualization of the channels, which are filled with air bubbles, is easiest immediately after cutting and that the channels tend to close, if left too long making insertion of the segments more difficult. Although marking of the channels with ink on the corneal surface after cutting can improve visualization, it is advised to avoid this if possible as this can also tend to cause the channels to close at the points of marking (Fig. 96.5, *C*). If implantation is complicated, it allows the surgeon and patient the option of reconsideration of proceeding with the second eye. At the conclusion of the procedure, suturing of the incision is recommended as it can prevent epithelial ingrowth, segment migration, and infection and assure good healing. The suture will generally loosen within 3–6 months and can be removed when this occurs.

Postoperative care

Inflammation following Intacs implantation is moderate with both manual and femtosecond approaches and oral analgesics are recommended. Prednisolone acetate 1% drops and a topical antibiotic are recommended to be used four times daily for 1 week. The drops can be discontinued without taper. Photophobia is not unusual following intracorneal ring segment implantation and may persist for 1–2 weeks in some patients. In rare circumstances, one or both of the segments may need to be explanted.[27] If unsuccessful in improving the patient's visual function, keratoplasty can be performed subsequently. Finally, it is important to counsel patients that the ring segments are used to delay keratoplasty and do not cure keratoconus with likely progression of the disease in the long-term.[28]

FEMTOSECOND LASER-ASSISTED KERATOPLASTY

Femtosecond lasers are also being used for optical lamellar,[29] endokeratoplasty,[30–33] and penetrating keratoplasty.[34–36] At the time of this writing, these techniques are being refined and there is sparse literature on outcomes of these procedures, especially relative to standard manual techniques.

Optical lamellar keratoplasty

The best candidates for femtosecond laser-assisted optical lamellar keratoplasty are those patients with corneal scarring but minimal thinning and generally uniform corneal thickness. The procedure may be especially useful for patients with focal anterior corneal scarring or those with anterior stromal dystrophies who fail therapy with phototherapeutic or superficial keratectomy. The technique and management is similar to standard lamellar keratoplasty except that oversizing of the corneal donor relative to recipient is generally not necessary. An exception is in cases involving severe recipient scarring extending to the limbus, oversizing by 0.25–0.5 mm may be helpful in reducing postoperative astigmatism and induced hyperopia. The procedure can also be performed under topical anesthesia.

Harvesting of the donor is most readily accomplished using a donor globe but, because of hypotony and the fact that the conjunctiva is generally absent, obtaining adequate suction and applanation can be difficult while harvesting the donor. It is important to apply a slight but steady pressure on the posterior aspect of the globe while cutting the tissue. Determining adequate corneal depth for dissection of the host and donor is essential. Estimation of depth of the opacity, coupled with ultrasonic corneal pachymetry measurements can be used to arrive at a setting for recipient dissection. Cutting a donor lenticule 50–100 μm deeper than the recipient can compensate for edema of the donor. One must also consider that if the epithelium is removed from the donor prior to harvesting, this tends to increase effective donor stromal depth by 50–60 μm. Preoperative recipient corneal thinning might also be a factor in determining to create a thicker donor button than that which is excised.

In general, energy settings need to be increased as the laser cuts deeper within the cornea. Because variation in laser energy output exists between lasers, the optimized energy settings for standard femtosecond-assisted LASIK flaps should be used and then adjusted upwards. For every 20 μm over 160 μm depth, the raster pattern needs to be increased by 0.1 J over the LASIK settings. If the laser is focused through a dense scar, the total energy should be increased by 0.2 J in order to create an effective plane of dissection (Fig. 96.6, *A–C*). Side cut energy is generally set 0.5 J greater than the raster energy. Energy adjustments for the harvesting of the donor lenticule are also advised. The settings tend to be similar to the host settings when similar depths are used. After allowing the donor disc to adhere to the corneal bed, placement of a single continuous suture is recommended to secure the graft and reduce induced astigmatism.

Inflammation following lamellar keratoplasty is generally well controlled with topical prednisolone acetate 1% which can be continued for 1–2 weeks. A topical antibiotic is recommended for 1 week. As the procedure can be performed under topical anesthesia, the drops can be initiated immediately postoperatively. Removal of sutures can be completed by 3 months or as the suture loosens.

ENDOKERATOPLASTY AND LASER-ASSISTED PENETRATING KERATOPLASTY

Deep lamellar endothelial keratoplasty (DLEK), posterior lamellar keratoplasty (PLK), and Descemet's stripping endothelial

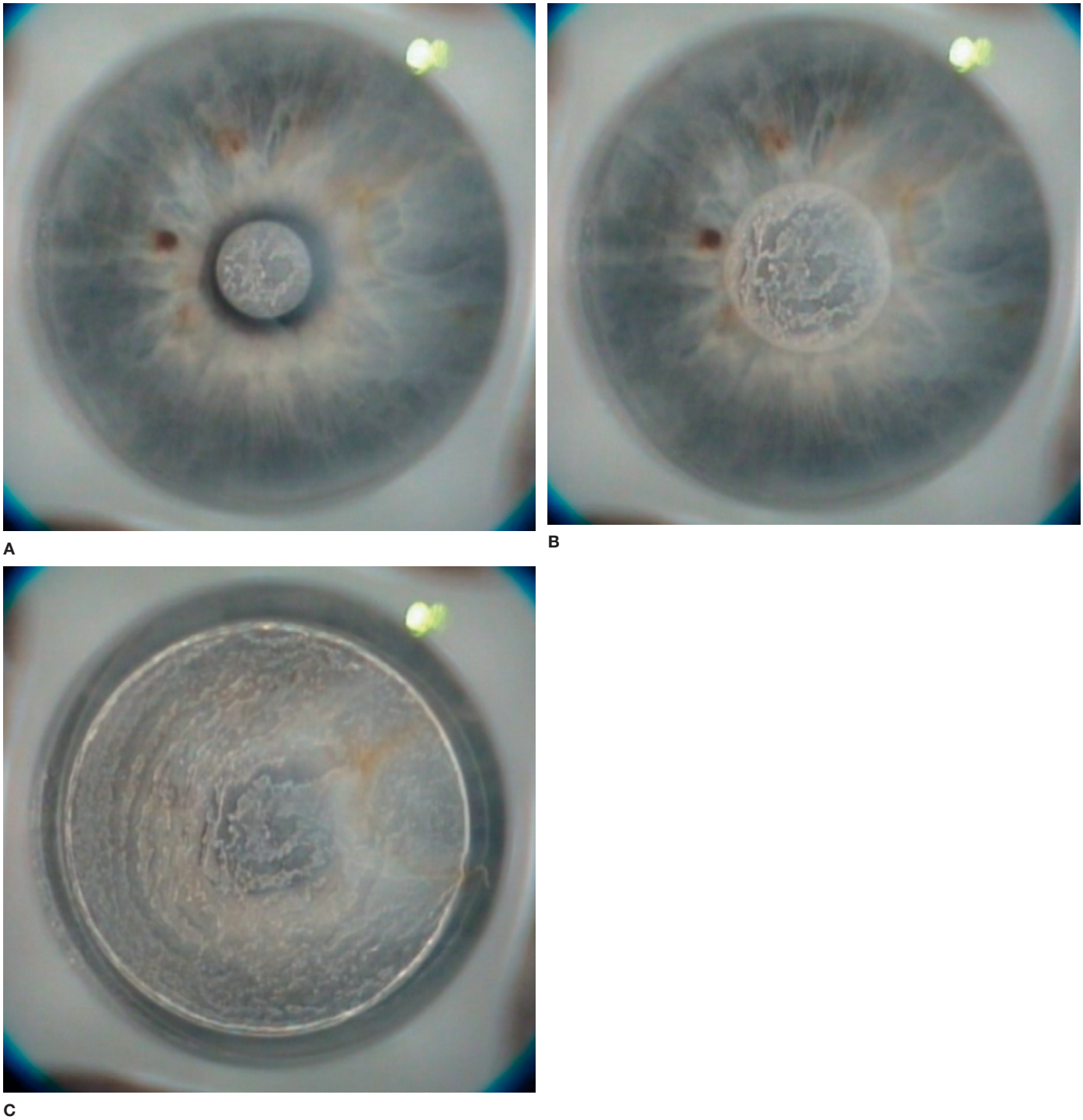


Figure 96.6. *A–C*, A spiral pattern is used to create the lamellar dissection for anterior lamellar keratoplasty in an eye with an arcuate scar bisecting the pupil.

keratoplasty (DSEK) have become more popular alternatives for the replacement of abnormal corneal endothelium. Creation of a posterior lamellar dissection plane in order to remove an endothelial button can be achieved with a femtosecond laser.[31–33] The lamellar button can then be removed through a limbal penetrating corneal incision. Such dissection can be more consistently and reliably achieved with a femtosecond laser than with manual methods and eliminates the risk of anterior or posterior perforation during dissection.

Even with procedures that do not involve significant resection of the host such as DSEK, femtosecond lasers offer potential to improve surgical time and outcomes through more precise creation of donor buttons. Precut donor tissue is now available from many eye banks and more precise depth of dissection may be possible with use of femtosecond lasers.[37,38] There may be improved sterility over a microkeratome given that a blade does not pass through the interface. Microadhesions between the donor disc and the anterior stroma also offer the advantage of prevention of dislocation during

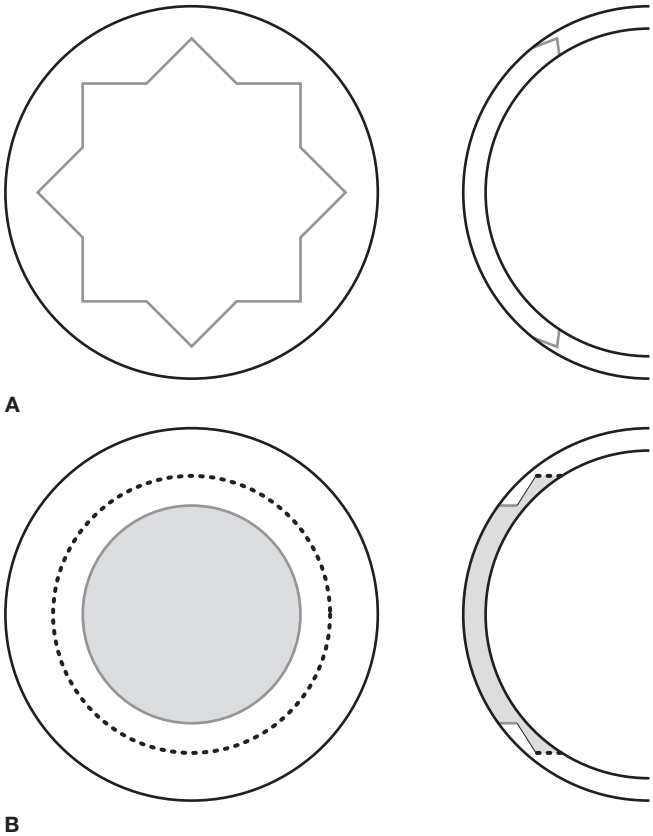


Figure 96.7. *A*, Geometric-shaped penetrating grafts can be fashioned so as to improve wound strength, tissue distribution, and possible postsurgical astigmatism. *B*, 'Top hat' shaped configurations may allow for improved wound strength.

transportation. The bed may not be as smooth as one cut with a microkeratome, which may have an unclear impact on donor adhesion, and intraoperative separation of the donor disc from the donor stroma might be more difficult with this method.

Penetrating keratoplasty with dissection of both donor and recipient by the femtosecond laser has a number of attractions. With the ability to fashion unusually shaped donor lenticules that 'dovetail' with the recipient, the femtosecond laser has the potential of improving healing time and induced astigmatism (Fig. 96.7, *A* and *B*). Inverse-mushroom or 'top-hat' shaped grafts theoretically should be better secured and more resistant to traumatic wound dehiscence. Conical incisions and positional spikes may allow better tissue distribution and wound strength. Fewer sutures would likely be necessary to secure such grafts, reducing operative time and suture-related complications. Likewise, with better healing, the sutures would be able to be removed earlier than with traditional penetrating keratoplasty.

Limitations, however, remain as far as application of this technology to all patients requiring penetrating keratoplasty. Patients with severe disorganization of the cornea or anterior segment may neither see any benefit nor be safe candidates for host dissection. Patients with rupture or corneal perforation of the eye would also not be good candidates given the suction currently required to create dissection planes. It is also unclear whether increased surface area contact with the host would increase the chance of rejection. Notwithstanding this, femtosecond lasers may further refine this procedure which, though currently successful, suffers from numerous technical limitations and unpredictability.

SUMMARY

Femtosecond lasers are instruments that offer more surgical precision than current manual techniques. As time progresses, it will become apparent whether this advantage results in better patient outcomes and offsets the additional cost of the devices. In the meantime, new applications for the lasers continue to appear including glaucoma surgery,[39] wedge resection for high astigmatism,[40] and keratoprosthesis implantation.[41] With time, it would be expected that portability and reduced equipment costs will further expand the application of this technology, perhaps beyond ophthalmic surgery.

The authors do not have a financial interest in any products mentioned.

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97 Excimer laser enhancements

Frederick S. Brightbill

The decision to 'enhance' or further treat the corneal bed after laser assisted in situ keratomileusis (LASIK), laser assisted subepithelial keratectomy (LASEK), and epithelial laser assisted in situ keratomileusis (EPILASIK), or to enhance the corneal surface after photorefractive keratectomy (PRK), is nearly as important as the initial doctor–patient agreement to undertake the first refractive procedure. Enhancement is a mutual endeavor fostered by the ophthalmologist's knowledge and experience, coupled with the patient's desire for the best possible visual outcome.

Modern day refractive surgery with lasers has most certainly received widespread physician and patient approval. Improved procedures over the past 10 years often, but not always, result in 20/20 distance acuity. Immediate factors influencing the degree of improvement in acuity include: (1) the amount of spherical and astigmatic error; (2) the methods of locating and treating both the astigmatic axis and power; (3) tracking devices; and (4) patient cooperation in the laser room. Regression of the ablation effect with time and/or progression of refractive error may lead to a less than ideal result.

DURATION OF EFFECT

With current follow-up of radial keratotomy and both PRK and LASIK eyes reaching more than 10 years, it appears that the majority of patients having either PRK or LASIK with or without early enhancement remain relatively stable, but that stability certainly cannot be guaranteed. In the 10-year progressive evaluation of radial keratotomy (PERK) study,[1] 43% of eyes were changed in the hyperopic direction by 1.00 D or more between 6 months and 10 years after surgery. With care taken not to offer refractive surgery to younger patients who demonstrate progressive myopia >0.50 D within the previous year, this author's late enhancement rate (greater than 2 years) is 2%. These late enhancement procedures most often are performed with a 150 μm microkeratome rather than the 130 μm initial cut using the Moria CB system (Moria, Inc., Doylestown, PA; Antony, France).

For myopic eyes, the greater the amount of spherical error the more difficult it is to achieve 20/20 vision, as there appears to be greater loss of initial effect than in eyes with lower amounts of myopia. If this author limits the LASIK procedure to patients having −3.00 D or less, experience over 10 years indicates a highly successful procedure outcome in 95% of eyes at 20/20. Those with −9.00 D or higher amounts of myopia, given the standard precaution of not exceeding the 50% rule, the incidence of enhancement in this author's practice climbs to between 10 and 30%.

Careful documentation of progressive refractive error in younger myopic patients at the time of screening is useful to protect against operating too soon, although it is never possible to predict future myopic progression. In my own case while editing the second edition of this text, at age 42 and wearing spectacles, I gained −0.50 D of myopia.

The Kleins' Beaver Dam Eye study[2] in adults with 15 years follow-up found that the direction and amount of change in refraction was related to age and that the spherical equivalent became more positive in the youngest participants in the study and more negative in the oldest. This finding would suggest that refractive patients between ages 43 and 59 with an initial plano result could progress to hyperopia via the aging process. This issue raises the question of whether to limit enhancements in mildly undercorrected myopic patients in their late 30s, to avoid inducing early presbyopia.

PRESBYOPIC EYES AND LASIK

Currently, we have no technology to treat bilateral myopia and presbyopia with excellent visual results at both distance and near, but there are encouraging results in managing hyperopic eyes with presbyopia.[3] This can be modified, however, if the patient is willing to have mild undercorrection in a myopic eye or mild overcorrection in a hyperopic eye, so-called monovision. Conductive keratoplasty (CK)[4] can induce corneal steepening with functional corneal multifocality in an emmetropic eye and, if stable, provides temporary improvement at near. Its downside includes repeated applications with time, as presbyopia worsens with progressive distance blurring in the treated eye. In this author's practice, following preoperative discussions of alternatives, 90% of patients either decline monovision or have progressive complaints of monovision intolerance as they approach ages 50–55, because of the increasing blur at distance.

Most postrefractive patients under this author's care want nothing to do with contact lens wear again, especially since the purpose of surgery is to be rid of them. Alternatively, many patients, especially those who complain of glare and starbursting in the undercorrected eye, are willing to accept spectacles for short periods of time; for example, while driving at night, particularly if it is raining, or while attending a sporting event or concert.

For the postrefractive patient with mild residual myopia (–0.50 to –1.25 D) in one eye and good distance acuity in the opposite eye, so that daylight driving with miotic pupils is easily tolerated, spectacle correction in the undercorrected eye combined with a plano opposite lens is an excellent solution that appeals to both patient and doctor for near acuity preservation. Enhancement is thus avoided.

NUMBER OF ENHANCEMENTS

Initial ablation depth, corneal thickness, ease of lifting the flap, and elapsed time since the previous LASIK procedure must all be evaluated prior to enhancement. There is general agreement for LASIK surgery that either 250 μm or one-half of the initial corneal thickness should be preserved to avoid the potential for corneal ectasia, although initial corneal depth alone[5] most likely is not the only factor in its occurrence. Flapless procedures such as PRK obviously allow for more frequent enhancements due to increased residual bed thickness but suffer from the requirement that the entire procedure must be repeated, in addition to the attendant discomfort.

COMPLICATIONS

Complications are somewhat dependent on surgical technique. Preexistent blepharitis is treated appropriately following the screening evaluation prior to LASIK. This author instills fluoroquinolone drops, 1drop hourly times four, given 24 h preoperatively and 72 h postoperatively; and in the laser room use two 4 s surface irrigation rinses with cooled balanced salt solution. Using this treatment protocol, together with betadine lid skin preparation, there have been no instances of infection in 10 years.

Epithelial abrasions always occur at the site at which the flap is lifted. Care must be taken to locate the plane of the bed rather than only epithelium, which results in 'skidding' across the surface and inducing irregular abrasions, causing added discomfort. By far the most bothersome complication of enhancement is that of epithelial ingrowth. Probst and Machat[6] have classified epithelial ingrowth into four stages, ranging from mild cell growth 2–3 mm from the limbus, which becomes inactive but is always visible on slit lamp examination, yet has no apparent effect on visual acuity; to active epithelial proliferation with progressive astigmatism 90° perpendicular to the growth and with significant increasing blurred vision requiring a flap lift and removal of the ingrowth.

AVOIDING ABLATION WITH SIMULTANEOUS INGROWTH REMOVAL

The ophthalmologist should not perform ablation along with ingrowth removal as it is rarely an undercorrection but rather the growth itself that induces myopic astigmatism. One may simply check the initial first postoperative day acuity, which nearly always is good but which deteriorates in subsequent weeks as the ingrowth becomes clinically apparent. Residual epithelial sheets of cells with a gray jelly-like consistency are easily removed, but individual cells are impossible to identify. Laser ablation of the bed, undoubtedly littered with cells, could lead to even further cell proliferation.

WHEN TO ENHANCE

As in strabismus and cataract surgery, in which a subsequent procedure (e.g. suture adjustment or capsulotomy) is not uncommonly required for a better result, patients having LASIK must understand during the evaluation and workup that enhancements are a part of the process rather than a complication. This is usually reflected in the initial global fee quoted to them. When an enhancement is recommended, it is reassuring for patients to understand that it is not only a quicker but a more comfortable event than the primary encounter and that visual recovery occurs more rapidly than following the primary procedure.

Timing the enhancement procedure is quite important for the final outcome and can never come soon enough for the patient. It therefore requires patience from both parties. When the visual acuity at first seems good but at 4–8 weeks has regressed, the ophthalmologist must be on the lookout for a stable postoperative refraction, with the return of the best-corrected acuity to 20/20 or to the best-preoperative acuity. Higher amounts of preoperative refractive error generally require more time to stabilize than lesser errors. LASIK-induced dryness must be monitored and treated and in fact may partially account for postsurgical regression.[7]

For patients with significant regression that affects their ability to drive or read, spectacles should be provided. When possible, conversion to spherical equivalent and the use of old frames, coupled with limiting coatings and bifocals to reduce cost, results in a happier patient. For some patients who exhibit anxiety while waiting for the enhancement, the ophthalmologist may want to consider paying for the interim glasses as a goodwill gesture.

Repeat topography and 'K' readings should be reviewed to rule out early ectasia.

In general, this author prefers never enhancing a patient earlier than 2 months postoperatively and more recently prefer waiting 3 months with two consecutive stable refractions before proceeding.

THE ENHANCEMENT PROCEDURE

Needed equipment includes:

1. Sterile fine-tipped ink marker.
2. Topical anesthetic (0.5% proparacaine is less likely to induce abrasion than tetracaine).
3. Slit lamp microscope.
4. Sharp instrument for locating base of flap potential space (e.g. Storz golf club foreign body spud with triangulated tip #E084).
5. Flap lifting forceps (e.g. Guell LASIK forceps AISCO #AE4358).
6. Speculum.
7. Cheyet drain with long arm removed.

Procedure:

1. At the slit lamp, dry and mark the limbus at 6 o'clock or at 6 and 12 o'clock axes with a sterile ink pen (Fig. 97.1).
2. Then, using both direct and retroillumination of the thin wound scar, reapply the ink pen without drying just distal to the inferior 150° to 180° edge of the flap (Fig. 97.1).
3. Usual lid/skin prep.

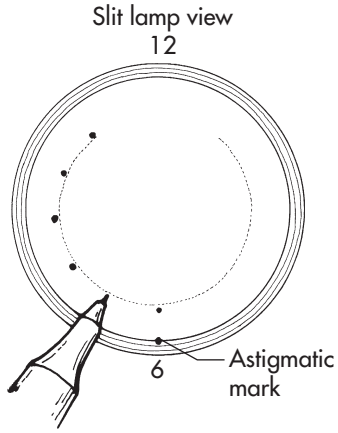

Figure 97.1. At the slit lamp, a sterile ink marker is used to mark the 6 o'clock position for astigmatic alignment and multiple marks over the faint scar at the flap edge using retro and scleral scatter illumination.

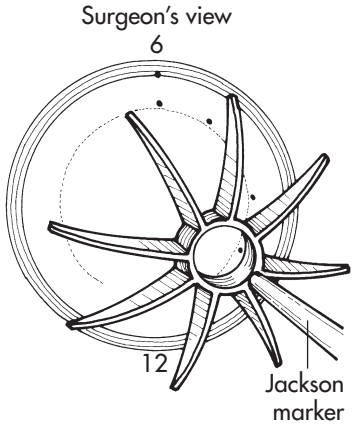

Figure 97.2. At the microscope, the corneal marker is placed overlapping the limbus for flap realignment.

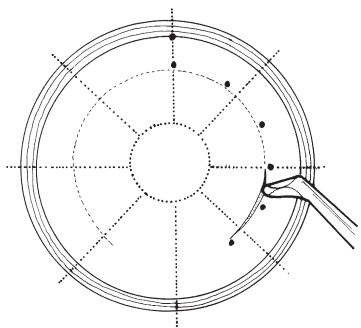

Figure 97.3. Right-handed surgeon's view of 30° angle with slight continuous distal pressure seeking flap 'pocket' with clean, sharp instrument.

4. In the laser room, hold the sharp spud tip at about a 30° angle just distal to flap edge and apply mild inferior pressure, while moving along the wound margin as the tip seeks an opening into the flap space. Care must be taken to angle below the epithelium to avoid large abrasions (Fig. 97.3).
5. Lift 20–25° degrees of the flap edge to facilitate lift with the forceps.

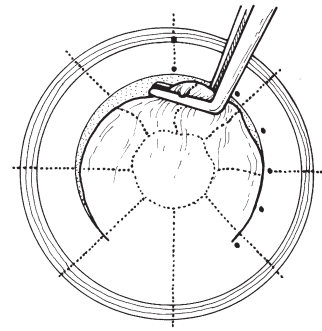

Figure 97.4. Grasp inferior flap edge with forceps pulling towards the superior hinge.

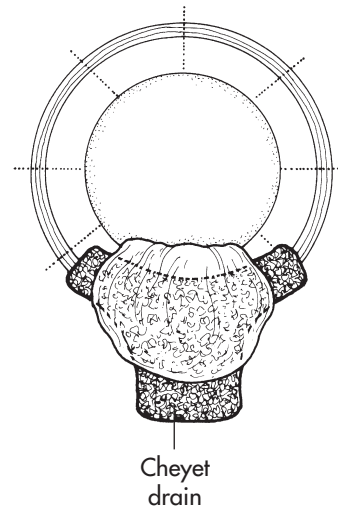

Figure 97.5. Fully expose residual bed up to the edges of the hinge and rest epithelial side down on moistened Cheyet drain.

6. Grasp flap edge gently with forceps and pull towards the flap hinge until the original flap width is reached (video) (Fig. 97.4).
7. Lay flap onto fully moistened partial Cheyet drain to prevent epithelial damage (Fig. 97.5).
8. Check flap edge over all 300° to insure no epithelium overhangs the tear. If present, using a dry cellulose sponge, move distally away from the flap edge so as not to trap it beneath the flap as it is repositioned.
9. Perform laser enhancement and replace flap with usual technique for balanced salt solution irrigation and 'ironing out' epithelial striae with a moistened methylcellulose sponge (Fig. 97.6).
10. Brush distally placed epithelium back across bared Bowman's membrane.

Caution: It is very easy for loose epithelial cells to become trapped beneath the flap, leading to cellular ingrowth. Irrigate copiously beneath the flap; take care to avoid contacting the epithelium with the irrigation tip. Intermittent washing the barrel of the irrigation

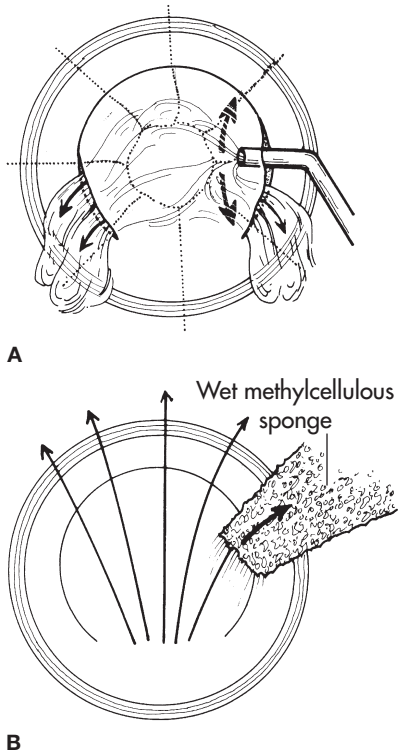

Figure 97.6. Replace aligned flap onto moistened bed and irrigate with balanced salt solution. Care must be taken to avoid excessive rubbing of cannula at flap edge leading to epithelial ingrowth.

tip while operating and careful ultrasonic cleaning with copious irrigation are preventative measures to limit ingrowth*.

**Suggestion*:
A reasonable alternative to post ablation flap-down irrigation is 'flap-up' gentle irrigation of the stromal bed with absorption of the balanced salt solution irrigant using methylcellulose sponges to avoid debris and bacterial contamination.

METHODS FOR INGROWTH REMOVAL

RELIFTING THE FLAP

Active epithelial ingrowth is easily noted on slit lamp biomicroscopy as an amorphous, pearly white, irregular subepithelial opacity that usually, but not always, originates from the flap edge. The ingrowth should be measured in height and width and photographed for comparison several weeks later. A baseline refraction to document astigmatic progression with loss of best-corrected vision is essential for future comparison and for deciding whether to intervene with a second flap lift.

The primary surgical focus with active ingrowth is to avoid stimulating more ingrowth through incomplete removal or inadvertent epithelial cell spreading by instruments placed under the flap. Prior to lifting the flap, the borders of the ingrowth are marked on the epithelial surface with a sterile ink pen at the slit lamp. It is recommended leaving 1.0 mm of clear border from the ingrowth edge. This facilitates visualization of the ingrowth following lifting (and inverting) the flap. The surgeon must remember to mark the flap for enhancements just as in the initial LASIK procedure.

It is prudent to build a platform on which to place the inverted flap, as its removal requires downward pressure to engage the gelatinous clumps of cells. For a superior flap, two stacked, moistened partial Cheyet drains are placed on the superior bulbar conjunctiva. Two sharp #64, #69 or #57 Beaver disposable blades are applied: the first to the inner inverted flap superiorly and the second to remove cells in the stromal bed. Reapplication of the blades is not performed unless they are copiously irrigated and wiped to clean off cellular debris. Both scraped areas are rubbed with non-moistened sterile sponges to remove more cells, but one can never be certain as to how many residual cells remain. The flap is refloated using copious irrigation and smoothed with a wet methylcellulose sponge.

Careful postoperative follow-up, observing for recurrence, is important. It is extremely rare that a second flap lift is necessary; much more commonly, minimal Stage I ingrowth is visible but inactive without progressive astigmatism.

Other methods for removing epithelial cells beneath the flap include: using the YAG laser and flushing cells beneath the flap with irrigation through previously placed flap openings; or flap-up flushing prior to flap replacement.

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98 Intraocular lens calculation

Kenneth J. Hoffer

INTRODUCTION

Since Sir Harold Ridley experienced a 21 D 'surprise' in lens power calculation on his first two cases in 1949–50, we have been seeking ways to calculate intraocular lens (IOL) power with greater accuracy (Fig. 98.1). The science is rather dry and does not stimulate great interest on the part of the majority of cataract surgeons. To make the subject more understandable, it would be advantageous to break it down into its component parts.

The three major components of IOL power calculation are biometry, formulas, and clinical variables. *Biometry* can be divided into its components needed to calculate IOL power: the *axial length*, the *corneal power,* and the *IOL position*. The subject of *formulas* can be divided into their *generations*, their *usage,* and their *personalization*. *Clinical variables* are divided into the topics *patient needs and desires*, *special circumstances,* and *problems and errors*.

When the human lens is replaced with an IOL, the optical status becomes a two-lens system (cornea and IOL) projecting an image onto the fovea. The distance (X) between the two lenses affects the refraction as does the distance (Y) between the two-lens system and the fovea. X is defined as the distance from the anterior surface (vertex) of the cornea to the effective principle plane of the IOL in the visual axis. Y is defined as the distance from the principal plane of the IOL to the photoreceptors of the fovea in the visual axis. It is easy to see that X + Y is equal to the visual axis axial length of the eye (A). Therefore, knowing X and A will allow the calculation of Y (Y = A – X).

Also, to calculate the IOL power (P) we must know the vergence of the light rays entering the cornea (K) (refractive error (R)). For emmetropia, R is zero. The relationship of these factors (X, Y (A – X), P, K, R) are such that a formula can be written to describe it. Knowing the values of any four of these variables will allow for the calculation of the fifth.

BIOMETRY

AXIAL LENGTH

If the crystalline lens (cataract) is to be removed, obtaining an accurate axial length (AL) is mandatory. If the lens has already been removed (aphakia/pseudophakia) or will not be removed (phakic IOL), an AL is not always necessary because the correct implant lens power can be calculated using a refraction formula (see below). Because this formula requires an accurate vertex distance, it is not dependable in cases of aphakia where errors in the vertex distance of a high-powered refraction can have a significant effect.

The important considerations for obtaining accurate ultrasound AL are listed in Table 98.1.

Axial length instruments

Up to 1999, all axial length measuring instruments have been A-scan ultrasound units. There are many A-scan instruments available and it is important to make sure the unit that you are using has been calibrated and is capable of accurate measurements. It is important to be sure that the instrument has a true analog screen such that true echo spikes are observed in determining axiality. Instruments that merely report a numerical reading of the AL ('black box' or spike simulation) do not allow clinical decision making during the examination and are fraught with potential errors. A major step in improving accuracy would be to replace such an instrument with one that has an oscilloscope screen.

A newer methodology for axial length was introduced in 1999 by Carl Zeiss Meditec, Jena, Germany (Fig. 98.2, *A* and *B*.) It uses laser coherent interferometry to measure AL. The instrument, called the IOLMaster® performs four functions: (1) it measures the AL, (2) the corneal power (K or r), (3) the anterior chamber depth (ACD) (the latter two by optical means), and (4) performs the formula IOL power calculations using four modern third generation theoretic formulas. The author has performed side-by-side analysis of the accuracy of this instrument compared to our standard immersion A-scan technique and found the instrument to be comparable to immersion ultrasound. A multitude of reports in the literature con-

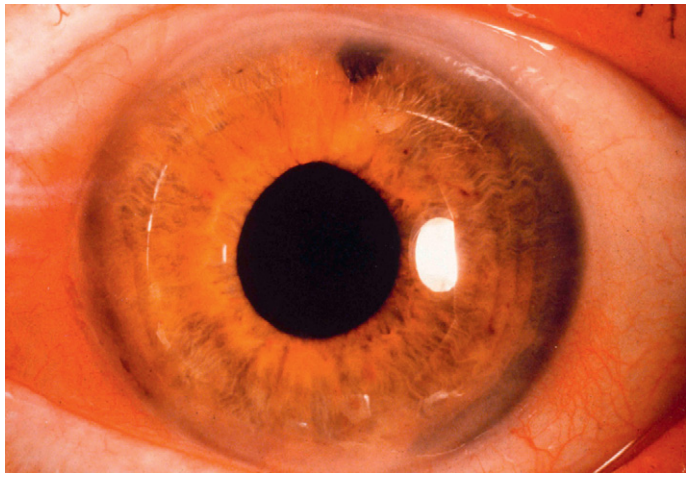


Figure 98.1. Uncorrected 20/20 vision in an eye with a Ridley posterior chamber IOL implanted by Harold Ridley in 1951 (Photograph by author in 1979).

Table 98.1 Considerations for obtaining accurate measurements (in order of importance)

A. Ultrasound axial length	*B. Corneal power*
1. A-scan ultrasound instrument	1. Instrumentation
2. Real-time oscilloscope screen	2. Contact lens wear
3. Immersion technique	3. Astigmatism
4. Experienced technician	4. Previous refractive surgery
5. Appropriate ultrasound velocities	5. Corneal transplant eyes
6. B-scan backup	

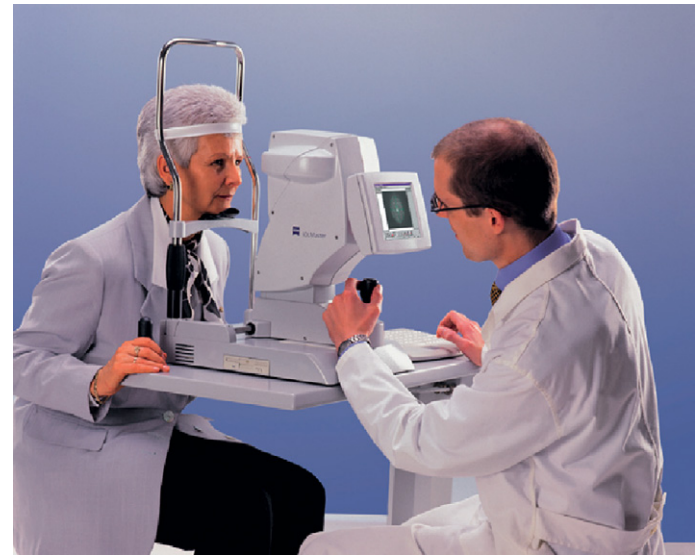
clude that the IOLMaster® cannot obtain results in 10–17% of eyes because of either posterior subcapsular cataract (PSC), the density of a cataract, or the patient's inability to fixate. Our results are similar. We have so far noticed considerable difficulty obtaining an AL measurement in eyes with PSC cataracts but have been impressed with the results up to this point and especially its ease of use and repeatability.

Warning: Be sure the Index of Refraction in the IOLMaster is set to 1.3375 in the Setup screen of the computer for the Hoffer Q formula to operate accurately.

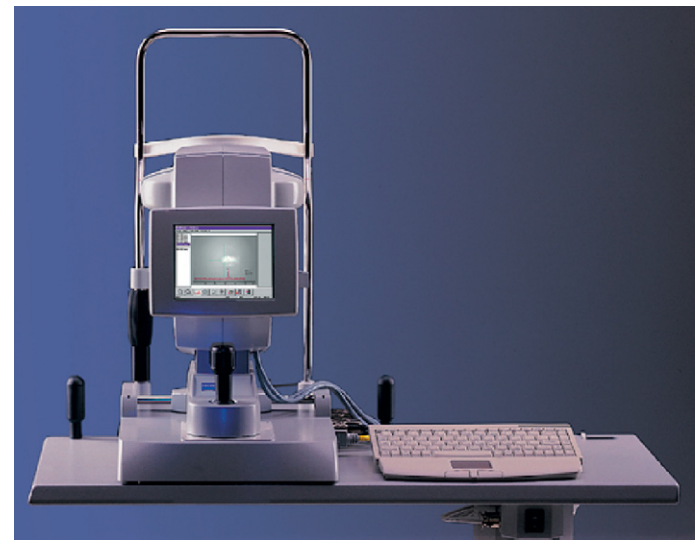
Immersion ultrasound technique

The immersion technique of Ossoinig[1] has been shown to be more accurate than the standard applanation contact technique in several studies[2,3] over the past 15 years. They report a mean average shortening of the AL of 0.25–0.33 mm using applanation compared to immersion. If this shortening error by applanation were a consistent one it could be compensated for by the addition of a correction constant or by IOL power formula personalization. Unfortunately, this is not possible since the error varies from eye to eye.

Arguments against using the immersion technique are that it is time-consuming, more expensive, messy, and requires the patient to be totally supine. On the contrary, the examination can be performed in a standard ophthalmic examination chair reclined back at a 45° angle with the headrest set back so that the patient's AL is perpendicular to the floor (Fig. 98.3). To maintain a non-leaking



A



B

Figure 98.2. The Zeiss IOLMaster laser tomography axial length measurement instrument. *A*, Side view. *B*, Front view.

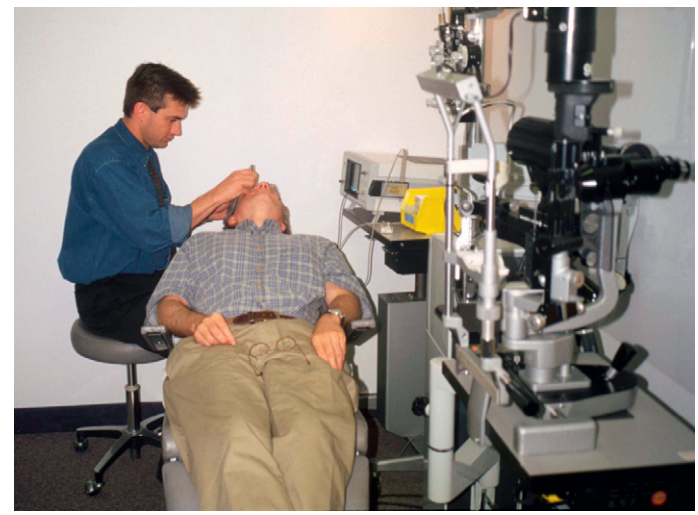


Figure 98.3. Immersion ultrasound technique setup for patient in normal ophthalmic examination chair.

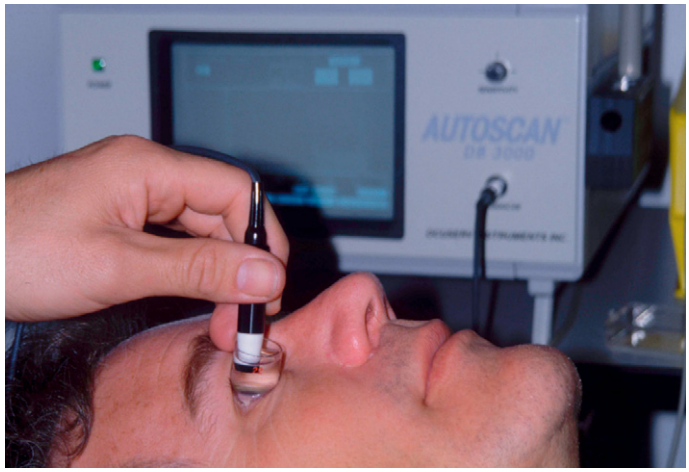
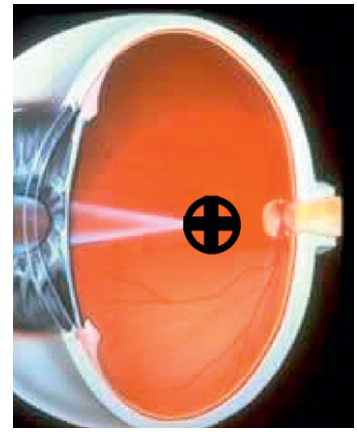
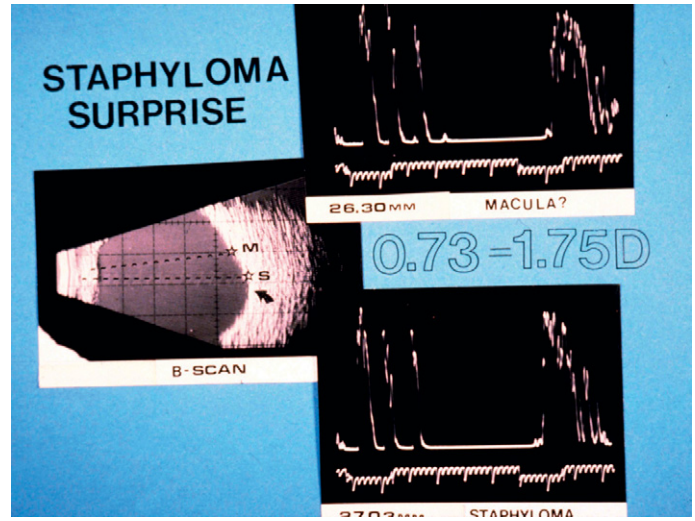


Figure 98.4. Immersion ultrasound technique showing the probe in the Ossoinig shell filled with 50/50 Goniosol/Dacriose solution.



A



B

Figure 98.5. *A*, Direct ophthalmoscope crosshair aimed at fovea by patient fixation. *B*, B-scan (left) demonstrates staphyloma, A-scans (right) show shorter reading at macula (upper) than at posterior pole (lower).

fluid bath in the Ossoinig scleral shell (Hansen Ophthalmic Development Labs, Coralville, IA), we use a 50/50 dilution of 2.5% hydroxypropyl methylcellulose (Goniosol®) in Dacriose® solution. Once the eye is anesthetized topically, the scleral shell is gently placed between the lids and filled 3/4 full with the solution. Any air bubbles should be vacuumed with a short silicone tube attached to a syringe. The latter can also be used to remove the solution at the completion of the procedure. The ultrasound probe is placed into the solution and positioned parallel to the axis of the eye (Fig. 98.4). Axiality is judged by watching for the correct spike patterns on the oscilloscope screen as the probe position is adjusted. First the corneal and retinal spikes must be identified and 'equally' maximized. An undilated pupil aids the examiner by the fact that eliminating the iris spikes improves the chances of being more axial; a dilated pupil eliminates this advantage.

Many find the Prager Shell (ESI, Inc., Plymouth, MN) easier to use for immersion, and studies appear to indicate it being accurate. The author has no experience with it.

Warning: Measuring the AL of *both* eyes is prudent and customary.

Warning: If the AL is very difficult to obtain and the eye appears to have a length greater than 25 mm, suspect a *staphyloma*. Use the IOLMaster or the Shammas method: By direct ophthalmoscopy (with patient fixating on the cross-hair target), measure the distance from the target (macula) to the edge of the optic nerve (in disc diameters). A B-scan exam is then performed to measure the AL at that distance from the edge of the optic nerve shadow (Fig. 98.5).

Warning: When measuring an eye containing an IOL, ignore multiple reduplication echoes caused by the IOL seen in the vitreous space.

Warning: If planning silicone oil injection into the vitreous space, perform an accurate AL measurement before doing so and make this information available to the patient. It is practically impossible to measure a silicone oil eye (try using a velocity of 1000 m/s). The Zeiss IOLMaster is the only way to get an accurate measurement in silicone oil-filled eyes. Alternatively, consider performing a secondary IOL after the aphakic refraction is obtained.

Always measure AL to the nearest hundredth of a millimeter and record it carefully. Errors in AL are the most significant and amount to approximately 2.5 D/mm in IOL power but it is important to be aware that this error drops to approximately 1.75 D/mm in very long eyes (30 mm) but jumps to approximately 3.75 D/mm in very short eyes (20 mm). Greater care must be taken in measuring short eyes.

Ultrasound velocities

The ultrasound velocity[4,5] for the various parts of the eye, IOL materials, and average pseudophakic velocities that the author has calculated are shown in Table 98.2.

Warning: Measuring an eye containing a silicone IOL with standard phakic velocity (1555 m/s) can amount to an error of 3–4 D.

The nominal average velocity for the normal range AL eye is 1555 m/s. Because of the inversely proportional change in the axial ratio of solid to liquid as the eye increases in length, the average phakic velocity of a short 20 mm eye is 1560 m/s and that of a long 30 mm eye is 1550 m/s (Fig. 98.6). This factor only amounts to a small (0.25 D) error in the extremes of AL, but it can be corrected for. The inversely proportional relationship is greater in pseudophakic eyes but is not a factor at all in aphakic eyes (1534 m/s).

Table 98.2 Ultrasound velocities[4,5] (at body temperature)

A. From the following sound velocity values[4,5]

• Cornea and lens	1641 m/s
• Aqueous and vitreous	1532 m/s
• PMMA IOL	2660 m/s
• Silicone IOL	980 m/s
• Acrylic IOL	2026 m/s
• Glass IOL	6040 m/s
• Silicone oil	987 m/s

B. The author calculated average sound speeds[4] *for various conditions of a 23.5 mm eye*

• Phakic eye	1555 m/s
• Aphakic eye	1534 m/s
• PMMA pseudophakic	1556 m/s
• Silicone pseudophakic	1476 m/s
• Acrylic pseudophakic	1549 m/s
• Glass pseudophakic	1549 m/s
• Phakic silicone oil	1139 m/s
• Aphakic silicone oil	1052 m/s

PMMA = polymethylmethacrylate.

If an eye has been measured using the wrong velocity, it can be easily corrected without re-measuring the eye by using Formula 98.1:

$$AL_{CORRECTED} = (AL_{MEASURED}) \times (V_{CORRECTED}) \div V_{MEASURED}$$

where V = ultrasound velocity.

This is because the instrument does not measure length or distance (d) directly. Instead it measures the time (t) it takes the sound to traverse the eye and converts it to a linear value using the velocity (V) formula where $d = V \times t$.

Optional corrected AL factor (CALF) method

Holladay[6,7] has offered an optional method to measure the AL which attempts to decrease the error inherent in changes in average velocity due to the length of the eye. The reasoning behind this method is that, if an 'average' eye velocity is incorrect, it affects the entire AL measurement. However, if the estimate of the CALF value is wrong, it only affects a small percentage of the overall AL, i.e. only the lens portion. The method involves measuring all eyes, regardless of status, at a sound velocity of 1532 m/s (as if the eye was a bag of water) and to this value is added the CALF. The CALF value represents the thickness of a lens in the eye whether it is the crystalline lens or IOL(s). Formula 98.2 gives the CALF value of any lens (including the cornea or IOL):

$$CALF = T_L \times (1 - 1532/V_L)$$

where T_L = the axial thickness of the lens and V_L = the sound velocity through that lens.

Holladay computes the thickness of the human cataractous lens using Formula 98.3:

$$T_L = 4 + age/100$$

and the sound velocity through the cataract using Formula 98.4:

$$V_L = 1659 - [(age - 10)/2]$$

Substituting the above two formulas into the CALF formula above, the CALF formula for the crystalline lens yields (Formula 98.5):

$$CALF = \left[4 + \frac{age}{100}\right] \times \left[1 - \frac{1532}{\left(1659 - \left(\frac{age - 10}{2}\right)\right)}\right]$$

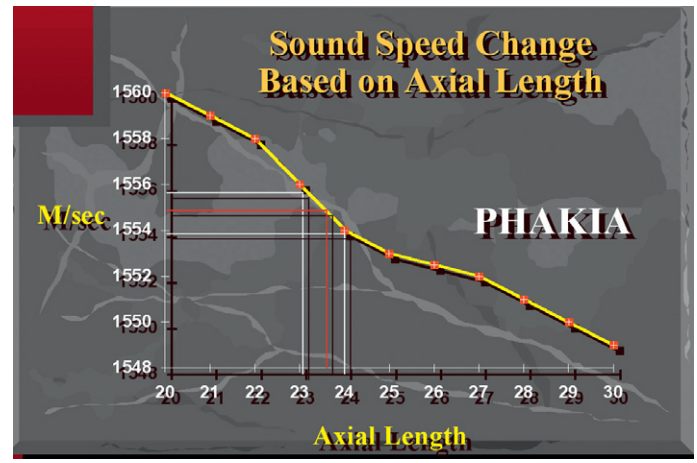


Figure 98.6. Phakic velocity. Graph of decline in average sound velocity of a phakic eye as the axial length increases.

The CALF for the cataractous lens is therefore calculated using only the age of the patient. Holladay recommends using a CALF value of 0.28 (value for 70-year-old) for all ages because the value for a 1-year-old is 0.306 and that for a 100-year-old is 0.224. The maximum error in CALF for those younger than 70 is 0.026 (0.07 D) and for those older than 70 is 0.056 (0.14 D).

His formulation, however, ignores the factor of the corneal thickness (0.55 mm). To correct this, this author recommends using a CALF of 0.32 (0.28 + 0.037). The correction for the cornea is calculated in Table 98.3B. A similar method can be used for pseudophakic eyes using CALF = $T_L \times (1 - 1532/V_L)$ and the known V_L for each IOL material (Table 98.3A). Knowing the thickness of the implanted IOL, the formulas in Table 98.3C can be used. If the IOL thickness cannot be obtained, Holladay[7] has published a table to use. The AL of an eye containing two IOLs of different materials can be obtained using the formula in Table 98.3C.

Biphakic eyes (phakic eye with a phakic IOL)

The problem here is eliminating the effect of the sound velocity through the phakic lens when measuring the AL using ultrasound. This author published a method[8] to correct for this potential error by using Formula 98.6:

Table 98.3 Formulas for calculating biometric parameters

A. CALF factors for pseudophakic eyes (using $CALF = T_L \times (1 - 1532/V_L)$

where V_L = the sound velocity for the IOL material in the eye:

- $CALF_{PMMA} = T_L \times (1 - 1532/2660) = +0.424 \times T_L$
- $CALF_{Silicone} = T_L \times (1 - 1532/980) = -0.563 \times T_L$
- $CALF_{Acrylic} = T_L \times (1 - 1532/2026) = +0.243 \times T_L$

B. The correction for the cornea:

- $CALF_{Cornea} = T_C \times (1 - 1532/1641) = 0.55 \times (0.066423) = 0.037$

C. Knowing the thickness of the implanted IOL, the following formulas can be used:*

- PMMA eye $AL = AL_{1532} + 0.424 \times T_L + 0.037$
- Silicone eye $AL = AL_{1532} - 0.563 \times T_L + 0.037$
- Acrylic eye $AL = AL_{1532} + 0.243 \times T_L + 0.037$
- Piggyback IOLs $AL = AL_{1532} + T_1 \times (1 - 1532/V_1) + T_2 \times (1 - 1532/V_2) + 0.037$

where T_1 and T_2 are the thickness and V_1 and V_2 are the velocity of each IOL.

*The IOL thickness can be obtained from the manufacturer.

PMMA = polymethylmethacrylate.

$$AL_{CORRECTED} = AL_{1555} + (C \times T)$$

where AL_{1555} = the measured AL of the eye at sound velocity of 1555 m/s, T = central thickness of the phakic IOL and C = the material specific correction factor of +0.42 for PMMA, –0.59 for silicone, +0.11 for collamer and +0.23 for acrylic.

The publication[7,7a] contain tables showing the phakic IOL central thickness for each dioptric power for each phakic IOL on the market today.

Retinal thickness factor

Some formula writers add a value to the ultrasonic AL measurement to take into account the additional distance from the surface of the retina to the level of the receptive end of the retinal cones. This value has been estimated to be 0.20–0.25 mm and is automatically added to the AL in some formulas (Binkhorst, Holladay) and not used at all in others (Colenbrander, Hoffer Q).

CORNEAL POWER

The first lens in the eye's optical system is the cornea. We usually think of corneal power in terms of diopters of optical power but really we are measuring the radius of curvature of the anterior surface and making assumptions regarding the curvature of the back surface based on the Gullstrand eye. As newer instrumentation evolves, such as the Pentacam (Oculus, Inc USA, Woodenville, WA), we may be able to use Scheimpflug photography to measure the posterior surface of the cornea and thus the true total optical effect of the cornea. It has been proposed by many that we should convert to using the radius of curvature (*r*) rather than diopters (D) but that may take a long time, especially in the USA.

The important factors to consider in obtaining accurate corneal power are listed in Table 98.1B.

Instrumentation

A manual keratometer measures only the front surface of the cornea and converts the radius (*r*) of curvature obtained to diopters (K) using an index of refraction (IR) of 1.3375 (some units use a different IR). The formula to change from D to *r* is $r = 337.5/D$ and from *r* to D is $D = 337.5/r$. Many postulate that this index is too high and Holladay[6] recommends using 4/3 instead. To make this correction, one can simply multiply the K reading obtained (in D) by the factor 0.98765431. This will result in approximately 0.54 D decrease in corneal power (range; 0.43 D for 35 D cornea to 0.62 D for 50 D cornea). Use the formula $1/3/(IR - 1$ if your keratometer uses a different index of refraction (IR.)

Warning: Before using this refractive index correction factor clinically, test it on a series of previously operated eyes to see what effect it would have had on your accuracy.

To assure accuracy it is important to calibrate all keratometers (including the IOLMaster) on a regular schedule.

Warning: Be sure the index of refraction is set to 1.3375 in the Setup screen of the computer on the IOLMaster for the Hoffer Q formula to operate properly.

Corneal topography units also supply simulated corneal power values. This author performed a prospective comparison study of the manual keratometer (Bausch & Lomb, Rochester, NY) with one such unit (TechnoMed C-Scan, Tubinger, Germany) on 172 cataract eyes. The mean of the central (3 mm zone) readings was 0.24 D flatter with the topography unit (43.55 D vs. 43.79 D), which may be explained by the index of refraction discussed above. When personalization was performed on both instrument data sets, however, IOL power calculation accuracy was statistically equal.

Warning: Hard contact lenses (including gas permeable) should be removed permanently for at least 2 weeks prior to measuring corneal power for IOL power calculation.

Astigmatism

Regular astigmatism is not a factor in IOL power calculation because the goal is to predict the postoperative spherical equivalent refractive error. Therefore, the average of the two K readings is the only value used and should result in mixed astigmatism. If a myopic cylinder were desired, the flattest K reading could be used instead of the average. If astigmatism is surgically corrected at the time of lens implantation, it would be important to know the effect of this surgery on the final average corneal power and adjust the K reading used to calculate the IOL power accordingly. Due to the coupling ratio, this effect is usually zero but an analysis of ones previous cases would be useful. Some have reported higher errors in eyes with severe astigmatism.

Keratoconus eyes

Because a cornea with keratoconus can become very steep, it is important to consider the fact that formulas that use the K reading to estimate the IOL position i.e. the Effective Lens Position (ELP) may overestimate this actual postoperative (PO) position. One should be aware that the K reading has less of this effect in the Hoffer Q formula than the other modern theoretic formulas. It is not a factor at all with the Haigis formula since it does not use the K reading at all in estimating the ELP.

Previous corneal refractive surgery

Previous corneal refractive surgery changes the architecture of the cornea such that standard methods of measuring the corneal power cause it to be underestimated (myopia) and overestimated

(hyperopia). This was first reported by Koch et al[9] in 1989. Radial keratotomy (RK) causes a relatively proportional equal flattening of both the front and back surface of the cornea leaving the index of refraction relationship the same. On the other hand, photorefractive keratectomy (PRK), laser-assisted intrastromal keratomileusis (LASIK), and laser-assisted epithelial keratomileusis (LASEK) flatten only the front surface. In myopic eyes, this changes the refractive index calculation creating an underestimation of the corneal power by about 1 D for every 7 D of refractive surgery correction obtained.

The major cause of error is the fact that most keratometers measure at the 3.2 mm zone of the central cornea, which often misses the central flatter zone of effective corneal power; the flatter the cornea, the larger the zone of measurement. There are at least 22 methods to more accurately estimate the corneal power or adjust the target IOL power in these refractive surgery eyes. To calculate the target IOL power P_{TARG} many of these methods require knowledge of some of the following biometric information:

- Obviously the planned postoperative refractive error desired—Rx_{TARG}
- Refractive surgery preoperative corneal power (K readings)—K_{PRE}
- Refractive surgery preoperative refractive error (spherical equivalent)—R_{PRE}
- Refractive surgery postoperative refractive error (spherical equivalent)—R_{PO}

Methods to estimate true PO corneal power

Clinical history method[10–16]

This method is based on the fact that the final change in refractive error the eye obtains from corneal surgery was due only to a change in the effective corneal power. If this refractive change is added to the presurgical corneal power, we will obtain the effective corneal power the eye has now.

Warning: All patients having corneal refractive surgery should be given the following data to maintain in their personal health records: (1) Preoperative corneal power, (2) preoperative refractive error, (3) postoperative healed refractive error (before lens changes effect it).

They should be told to give it to anyone planning to perform cataract/IOL surgery on them. All attempts should be made to obtain the above information from the refractive surgeon's records. Odenthal et al[17] in 2002 discovered that, though it is optically correct, it is not beneficial to vertex correct the spectacle refraction as was originally recommended. Most recommend not vertexing the refractions because it causes underestimation of the K reading.

For this method, the estimated effective corneal power (K) can be calculated using Formula 98.7:

$$K = K_{PREOP} + R_{PREOP} - R_{PO}$$

where R = refractive error, PREOP = preoperative, PO = postoperative.

Contact lens method[10–19]

The contact lens method was first described in 1948 by Frederick Ridley[18] of England (the inventor of NaOH IOL sterilization), taught by Joseph Soper[19] in 1974, and popularized by Holladay in the 1990s. This method is based on the principle that if a hard PMMA (not rigid gas permeable) contact lens (CL) of plano power (P) and a base curve (B) equal to the effective power of the cornea, is placed on the eye it will not change the refractive error of the eye. That is, the difference between the manifest refraction with the contact lens (R_{CL}) and without it (R_{NoCL}) is zero. To calculate the estimated corneal power use Formula 98.8:

$$K = B + P + R_{CL} - R_{NoCL}$$

where B = base curve, CL = contact lens, P = power of CL, R = refractive error, NoCL = bare refraction.

Again, it is not currently recommended to vertex correct the refractive errors to the corneal plane. Several computer IOL power calculation programs calculate these two methods automatically when needed (Hoffer® Programs and Holladay® IOL Consultant). There are commercially available hard PMMA CL sets in plano powers with appropriate base curves from Ocusoft (Fig. 98.7, *A*) and Eye Scan Consulting (Fig. 98.7, *B*) (Decatur, GA).

Maloney corneal topography method[20]

Based on his analysis of corneal topography central Ks (Kt) on LASIK eyes, Robert Maloney[20] developed a formulation in 1998 to predict true corneal power using only the Kt (Formula 98.9):

$$K = Kt \times (376/337.5) - 5.5 \text{ or}$$
$$K = 1.1141 \times Kt - 5.5$$

where Kt = postoperative topography single central K.

Koch modification of Maloney method[21]

In 2003, Douglas Koch[21] analyzed several of these methods and obtained the best results using the Maloney method but only after increasing the constant from 5.5 to 6.1 (Formula 98.10):

$$K = Kt \times (376/337.5) - 6.1 \text{ or}$$
$$K = 1.1141 \times Kt - 6.1$$

where Kt = postoperative topography central K.

He reported on series of eyes that the best results were obtained using this K estimation and the Aramberri Double-K method with a third generation formula. He also offered a second method to calculate estimated corneal power if the change in refractive error (RC) the patient received is known (Formula 98.11):

$$K = Kt - (0.19 \times RC)$$

where Kt = central average K from corneal topography, RC = refractive change in refractive error from the surgery.

Ronje method[22]

The Ronje[22] method proposes that the corneal power can be estimated by simply adjusting the flattest postoperative manual keratometry (K_{POFLAT}) by 25% of the change in the spherical equivalent refractive error (RC) that occurred from the corneal refractive surgery.

For example (Formula 98.12):

$$R_{PRE} - 5.00, R_{PO} = \text{plano; (thus RC} = -5.00), \text{and } K_{POFLAT} = 42.00$$
$$K = K_{POFLAT} + 0.25 \times RC$$
$$= 42.00 + 0.25 \times (-5.00)$$
$$= 42.00 - 1.25$$
$$= 40.75$$

where R_{PRE} = prerefractive surgery spherical equivalent, R_{PO} = post refractive surgery spherical equivalent, and K_{POFLAT} = flattest measured postoperative manual keratometry.

A

B

C

Figure 98.7. Hard PMMA CL kits in plano powers for the CL method: *A*, Ocusoft kit, *B*, Ocusoft contact lenses and remover, *C*, Eye Scan Consulting kit hard PMMA CL kit in plano powers for the CL method.

Shammas No History Method[23]

Another interesting proposal is by Shammas,[23] who studied a series of eyes that have had LASIK. His results led him to propose a formula, in 2003, to predict the effective power of the cornea without needing any of the patient's clinical history, only the post-operative K reading obtained with manual keratometry (Formula 98.13):

$$K = 1.14 \times K_{PO} - 6.8$$

where K = predicted corneal power, K_{PO} = the average corneal power obtained with manual keratometry after corneal refractive surgery.

Instruments: topographers and pentacam

The first instruments to measure corneal power by topography were the Eyesys, Technomed C-Scan, and Humphrey units. Holladay developed the 'diagnostic summary' for the Eyesys unit (Fig. 98.8) but still most of these measurements fall down in postrefractive surgery eyes.

That brings us to the latest and most promising technology, the Oculus Pentacam, which images the anterior segment of the eye using a rotating Scheimpflug camera measurement providing three-dimensional images (Fig. 98.10, *A–C*). These images provide a topographic analysis of the corneal thickness, its front surface and most importantly its back surface curvature. In conjunction with software provided by Holladay, the Pentacam is touted to have the ability to generate what they call a 'TrueNetPower' map of the cornea and measure the power of the postrefractive surgery cornea within ±0.55 D. This may provide a better estimation of the true corneal power but it has not yet been tested in a large randomized clinical trial.

With consultation from Holladay, the Pentacam produces a 'Holladay Report' which is based on the 4.5 mm zone reading. This was an update from the previous one using the 4.0 zone which was not proven accurate. Many studies using this report have shown the inaccuracy of this report as well and future improvements are expected before this report can be trusted for clinical use in LASIK eyes.

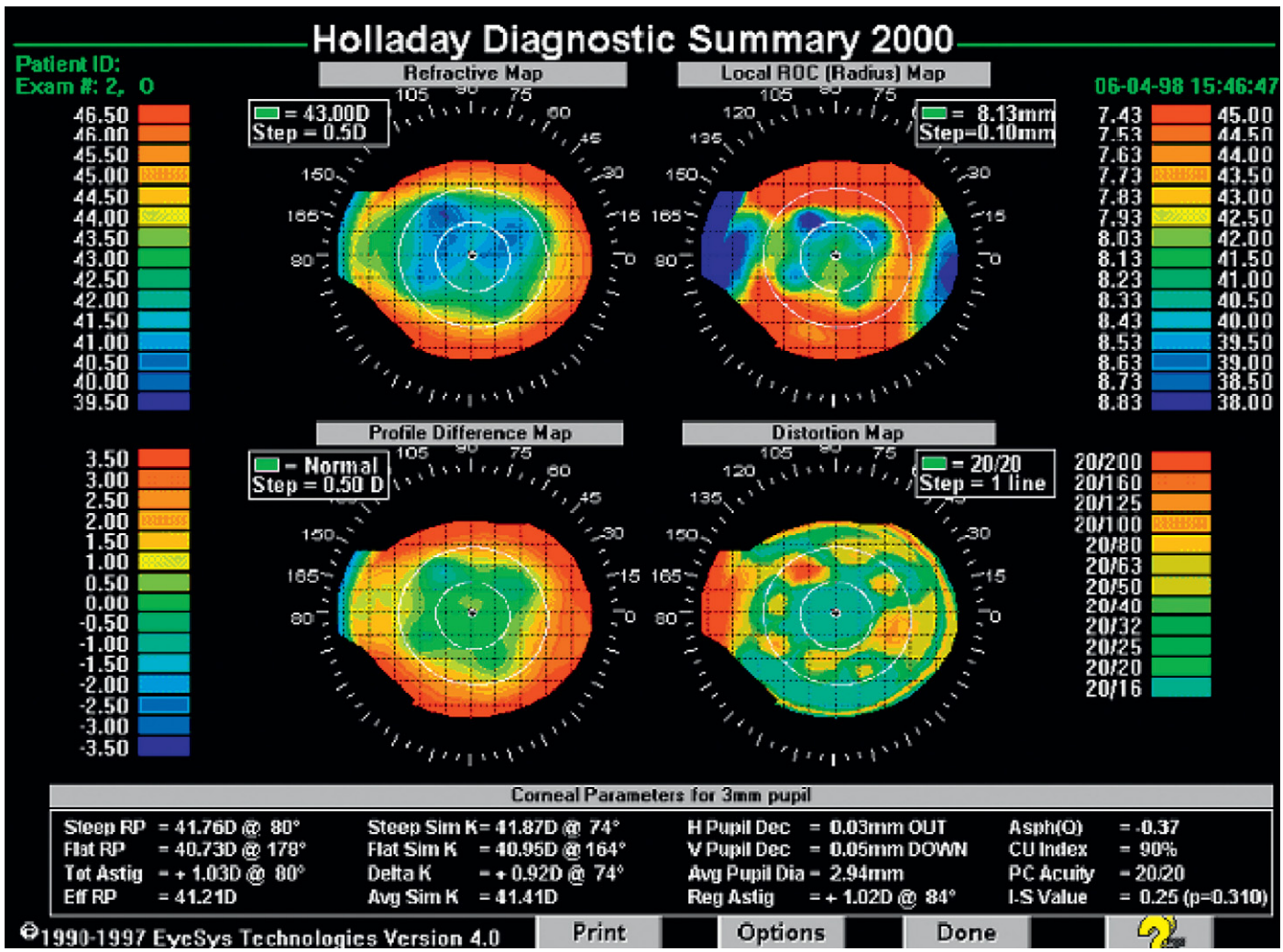


Figure 98.8. Eyesys Holladay diagnostic screen showing corneal power.

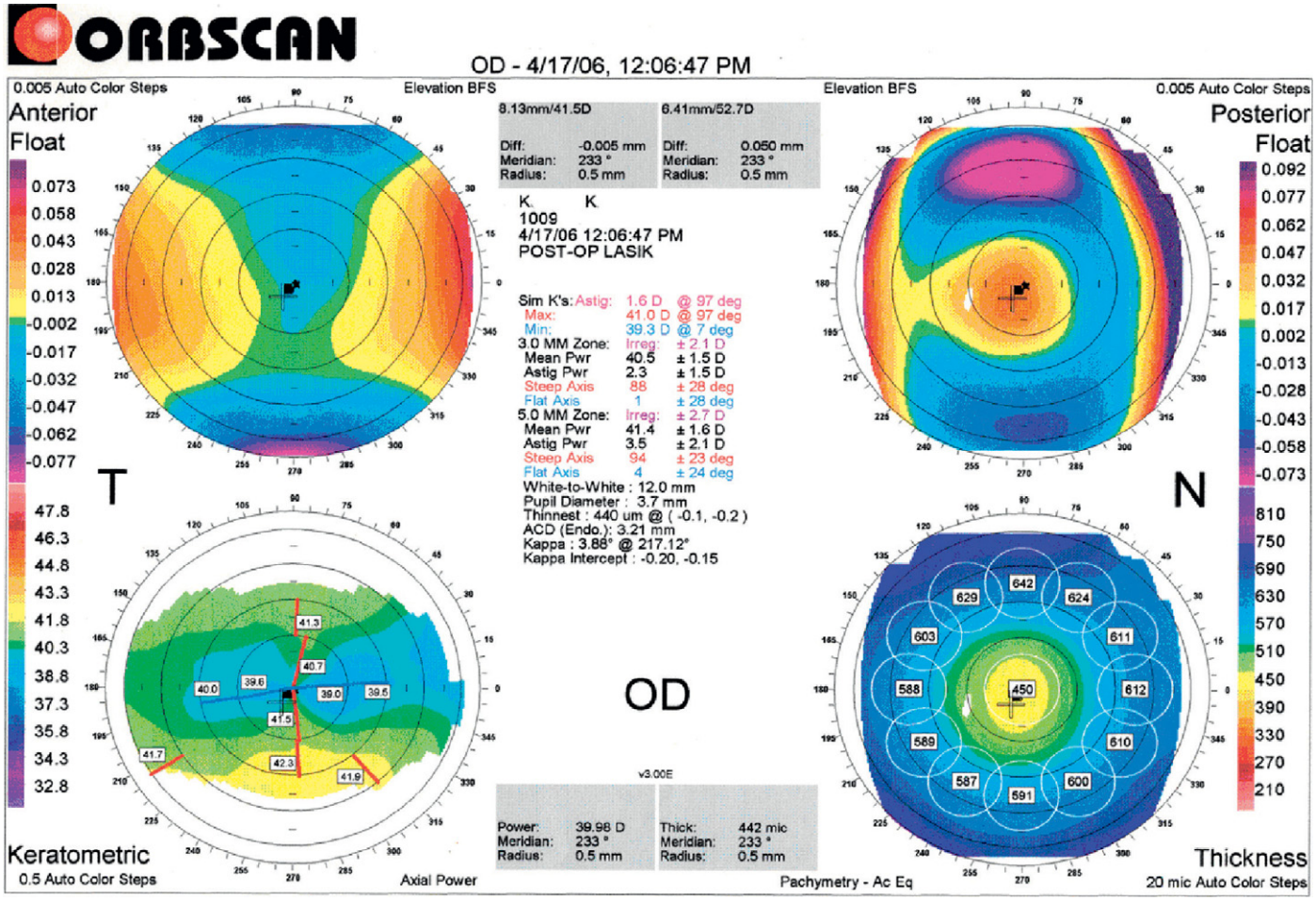


Figure 98.9. Orbscan screen showing corneal power maps.

Corneal power estimation summary

In summary, if the results of the above K estimation methods differ, use the lowest estimated corneal power (highest for hyperopic refractive eyes). Rarely are such eyes myopic after IOL surgery. Obviously, some methods cannot be used if the historical data is not available, and the CL method is impossible if the cataract precludes performing a refraction. In such cases, it might be wise to delay the IOL implantation and calculate the secondary IOL power using the aphakic refractive error in the refraction formula or use a piggyback lens or phakic refractive lens to correct any deficiency. However, there are other methods available; some attempt to calculate the true corneal power while the others fudge the calculated IOL.

Methods to adjust/calculate the target IOL power

Aramberri double K method[27]

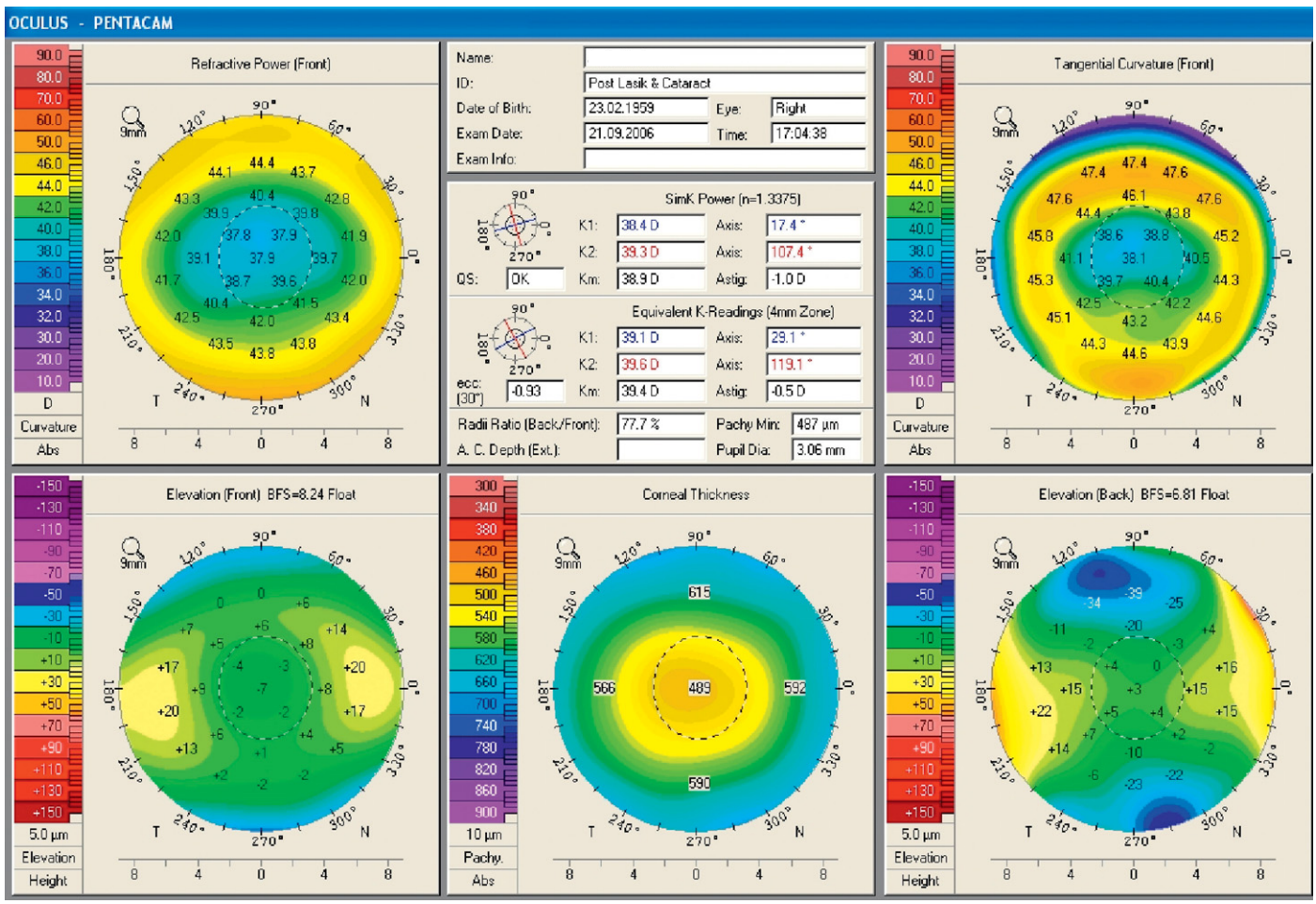
Once you have decided on the 'best' estimated pre-op K, there is one more consideration. It is the Double-K method, one of the most important developments to improve the prediction of corneal power in eyes that have had refractive surgery. It was proposed in 2001 by Aramberri[27] of San Sebastian, Spain. His proposal makes eminent sense. The modern theoretic formulas (except the Haigis) use the corneal power for two purposes: the first is to predict the ultimate position of the IOL (ACD or ELP) and the second (along with AL, target refraction and ELP) is to calculate the power of the IOL. The formulations and algorithms used to predict the ELP are based on the anatomy of the anterior segment which has not been changed by corneal refractive surgery (only the center is flattened and thinned). Therefore, if the PO refractive surgery K reading (which is significantly flatter) is used to calculate the ELP it will produce an erroneous ELP value. Since the anatomy has not changed, Aramberri recommends the use of the preoperative K reading to calculate the ELP. The IOL power is then calculated using the PO K reading, thus the 'Double-K.' His analysis of a small series of eyes proved the benefit of this idea. This method is available for the SRK/T, Holladay and Hoffer Q formulas on the Hoffer® Programs computer system (see Fig. 98.12.)

Feiz method[28,29]

This method was first described in 2001 by Feiz et al.[28] Their formula was developed by comparing manual keratometry values after LASIK and using the SRK/T formula, the IOL power calculated using the historical method, and what they termed the vertexed IOL power method. In this method two assumptions were made. The first was that to achieve emmetropia, the change in spherical equivalent induced by keratorefractive surgery had to be balanced by the change in IOL power. The second assumption was that for every diopter of change in IOL power, only 0.7 D of change will be seen at the spectacle plane.

Performing a linear regression analysis of the vertex IOL power compared to standard keratometry, they developed two linear regression formulas: one for myopic LASIK corneas and the second

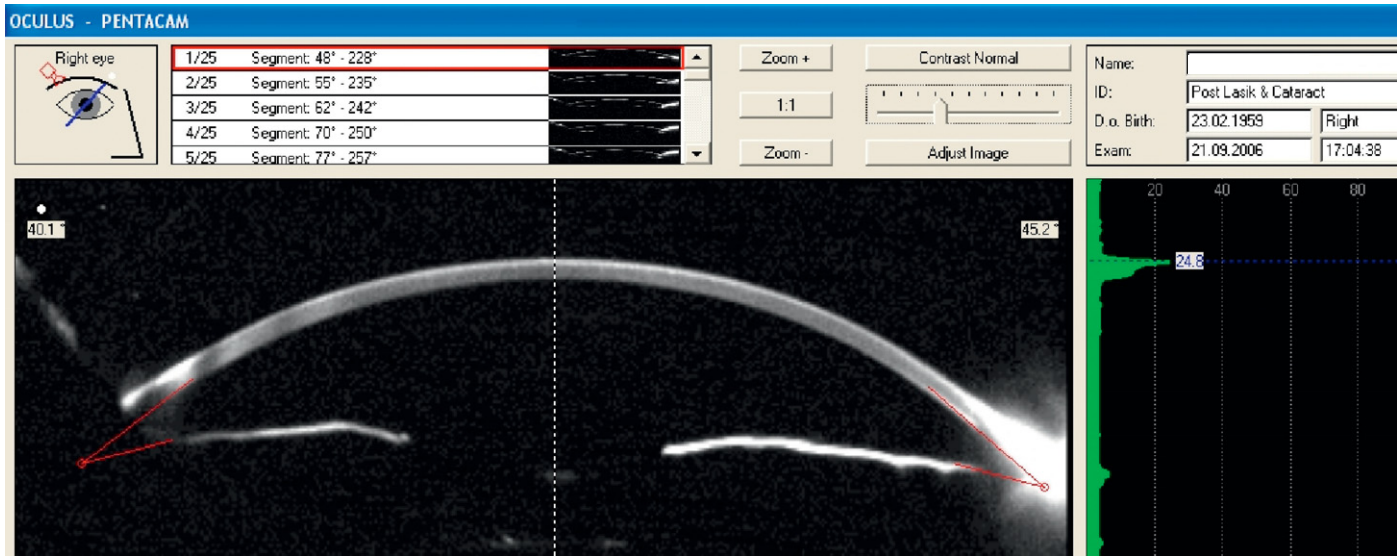
A



B

Figure 98.10. *A*, Oculus Pentacam instrument; *B*, Oculus Pentacam Holladay power map screen showing Sim-K, Equivalent K Reading (EKR).

Continued



C

Figure 98.10. Continued *C*, Pentacam Scheimpflug photo of anterior segment.

BOX 98.1 FEIZ

MYOPIC EYE	HYPEROPIC EYE
SRK/T calculates 16.0 D IOL	Hoffer Q calculates 22.0 D
Change in Rx = –6.0 D	Change in Rx = +3.0 D
$-0.595 \times (-6) - 0.231 = +3.34$	$-0.862 \times (+3) + 0.751 = -1.84$
P = 16.0 + 3.34 = 19.34 D	P = 22.0 – 1.84 = 20.16 D

for hyperopic LASIK corneas (Formulas 98.14 and 98.15):
For myopic LASIK corneas:

$$P = P_{TRx} - 0.595 \times RC - 0.231$$

For hyperopic LASIK corneas:

$$P = P_{TRx} - 0.862 \times RC + 0.751$$

where P = required IOL Power, P_{TRx} = the IOL power calculated for the desired PO Target Rx using the AL and measured (unadjusted) K reading, and RC = the change in refraction (spherical equivalent) caused by the refractive surgery.

In 2005, they reported a comparison of all three methods for IOL calculation[29] in 19 eyes after myopic LASIK or PRK which resulted in consistently higher IOL powers using their formula compared to using the post-LASIK measurements and the historical method. It still resulted in 16% of eyes either moderately over- or under-corrected. The hyperopic formula has not had any reported study demonstrating its validity.

Below are example calculations (Box 98.1).

From their formulas, they produced a nomogram for both types of eyes which might be easier for those without a calculator handy (Box 98.2).

Latkany method[30]

The first proposal by Latkany's group[30] uses the manually measured flattest K of the postoperative cornea in the SRK/T formula. The resulting IOL power is then adjusted by Formula 98.16:

BOX 98.2

FEIZ[29] NOMOGRAM	ADJUSTMENT TO TARGET IOL POWER	
D change in Rx from LASIK (X)	Myopic Eye [–0.595 × –0.231]	Hyperopic Eye [–0.862 × +0.751]
1.00	+0.36	0.00
2.00	+0.96	–0.97
3.00	+1.55	–1.84
4.00	+2.15	–2.70
5.00	+2.74	–3.56
6.00	+3.34	–4.42
7.00	+3.93	–5.28
8.00	+4.53	–6.15
9.00	+5.12	–7.00
10.00	+5.72	–7.87

$$P = P_{FlatK} - (0.47 \times PRx + 0.85)$$

where P = required IOL power, P_{FlatK} = the IOL power calculated by SRK/T for desired PO Rx using the AL and the measured flattest K reading (unadjusted), and PRx = the preoperative refractive surgery spherical equivalent.

The study reported this method to be equal to the historical method for calculation of corneal power. Below is an example calculation (Box 98.3).

Masket refractive history method[31]

In 2005, Sam Masket[31] proposed yet another method which adjusts the power of the IOL calculated using the measured data. Formula 98.17 is used to adjust the IOL power:

$$P = P_{EMM} - 0.323 \times RC + 0.138$$

BOX 98.3 LATKANY

MYOPIC EYE

SRK/T calculates 22.91 D IOL using Flattest K 42.00 D

Pre-LASIK Rx = –5.0 D

–((0.47 × –5) + 0.85)) = +1.50

P = 22.91 + 1.50 = 24.41 D

BOX 98.4 MASKET

MYOPIC EYE	HYPEROPIC EYE
SRK/T calculates 16.0 D IOL	Hoffer Q calculates 22.0 D
Change in Rx = –6.0 D	Change in Rx = +3.0 D
–0.323 × (–6) + 0.138 = +2.076	–0.323 × (+3) + 0.138 = –0.82
P = 16.0 + 2.0 = 18.0 D	P = 22.0 – 1.0 = 21.0 D

where P = required IOL power, P_{EMM} = the IOL power calculated for emmetropia using the AL and measured (unadjusted) K reading, and RC = the change in refraction (spherical equivalent) caused by the refractive surgery.

He recommends using the SRK/T formula for myopic ALs and the Hoffer Q for hyperopic ALs. Here are example calculations (Box 98.4).

In a series of 28 post-LASIK eyes, he reported 43% of the eyes obtaining a postoperative refractive error of plano, 95% being within ±0.50 D of prediction and a total error range from –0.75 D to +0.50 D. These early results in a small series by the author of the method are quite impressive.

Wake Forest method[32]

In 2005, Michael Gagnon[32] presented an alternative calculation method by the group at Wake Forest University, which has been discussed by others over the years. This method simply uses the patient's preoperative refraction before LASIK as the target or 'desired' PO refraction in the calculation and the measured AL and K readings without modification.

Ianchulev intraoperative aphakic refraction method[33]

In 2003, Sean Ianchulev[33] proposed calculating IOL power by performing aphakic refraction on the operating table immediately after the cataract has been removed using a handheld automated refractor. The resultant refraction is modified by Formula 98.18:

$$P = 2.02 \times AR + (A - 118.4)$$

where P = emmetropic IOL power, AR = automated refraction, and A = IOL A constant.

His early results are quite promising. This method would completely eliminate the need for axial length and corneal power measurements and the problems with LASIK and silicone oil-filled eyes. However, it would require a large inventory of IOL powers available in the OR.

Following on this idea, in 2006, Mackool[34] published a small series of patients who had cataract extraction without IOL implantation under topical anesthesia. An aphakic manifest refraction was performed 30 min after the surgery at a vertex distance of 12 mm. The following formula was then used to calculate IOL power (Formula 98.19):

$$P = 1.75 \times AR + (A - 118.84)$$

where P = emmetropic IOL power, AR = aphakic refraction, and A = IOL A constant.

After the IOL calculation, the patient was immediately returned to the operating room for IOL implantation using the calculated power. Using the above formula in 12 eyes, he reported a mean absolute refractive error of 0.30 D, and an average refractive error of –0.18 D. Having two separate surgeries would seem inconvenient.

Hoffer/Savini LASIK IOL Power Tool

In 2006, it became obvious that there were so many methods to perform these calculations that it was becoming very confusing. This author, collaborating with Giacomo Savini of Bologna, Italy, decided to place all the various calculations on one Microsoft Excel spreadsheet so it would be easy to see what data needed to be collected (Fig. 98.11). Once all or most of the data are entered into the appropriate cells, the calculations are performed automatically. Then the results of all the methods are displayed side by side allowing the surgeon to select the most appropriate calculation. Anecdotally, the first use of this spreadsheet (Fig. 98.12) led to a 2 month PO refractive error of –0.25 D (SE) when the target R*x* was –0.50 D (UCVA 20/25; BCVA 20/20). The Tool can be downloaded for free at www.EyeLab.com

Retinal detachment eyes: Hoffer Double-AL method

Just as the Double-K method uses two K readings because the formulas use the K reading to predict the ELP, this method, proposed by the author in 2000, instead uses two ALs. The PO retinal detachment (RD) AL of the eye is used to calculate the IOL power. Since most post-encircling band RD eyes have a 1.0 mm increase in AL, and the ACD is not affected by the encircling band, it would be best to use the AL-1 in the part of the formula that calculates the predicted ELP. This amounts to making the IOL a little weaker than would be predicted using all the modern formulas. Alternatively, one would just lower the power of the recommended IOL power in such RD eyes.

Corneal transplant eyes

A problem also arises when attempting to predict what the corneal power will be after corneal transplantation. Some have suggested using the corneal power of the other eye (if it is available) or using an average of one's post-transplant corneal powers, but published reports show a very large range of prediction and refractive errors using these attempts. Performing the IOL implantation after the corneal transplant has settled down was suggested by this author[35] in 1986, and in 1990 Geggel[36] reported excellent refractive results (Fig. 98.13) using this two-stepped approach (66%, 20/40 or better acuity without correction). A toric phakic IOL or a secondary piggyback toric IOL is another alternative to correct residual ametropia.

Corneal scar eyes

The problem of getting an accurate corneal power measurement in eyes with corneal scarring and irregular astigmatism has not received much attention. Cua et al[37] studied this in two eyes needing IOL exchange due to large 'IOL surprises' of +5 and –7.5 D. They compared six methods to ascertain the corneal power and found

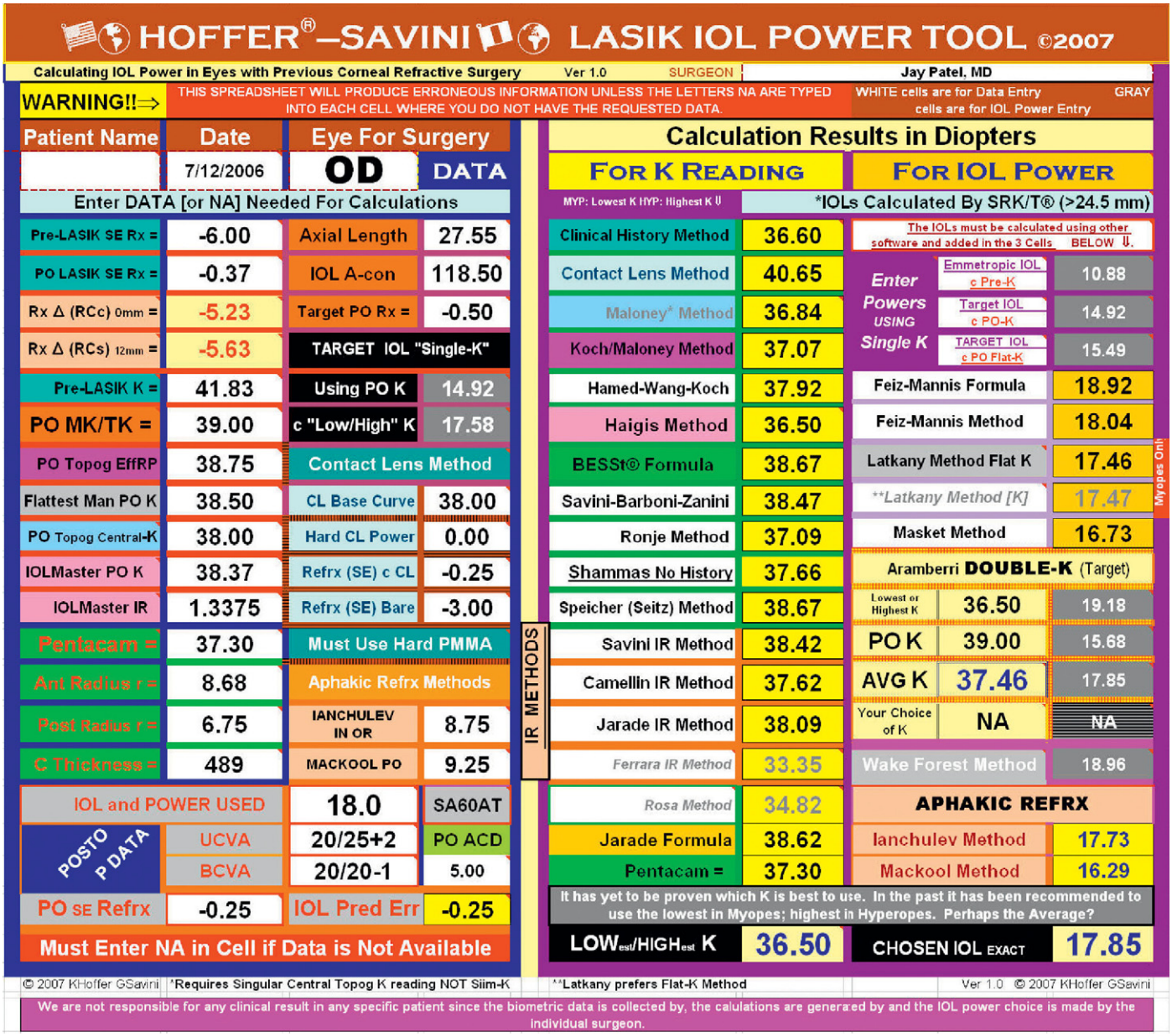


Figure 98.11. Hoffer/Savini LASIK IOL power calculation spreadsheet Tool. Areas for input of biometric data and calculations.

the hard contact lens over refraction method to be the most accurate; decreasing the error they would have obtained with the manual keratometer of +4 to −5 D to −0.4 to −1.6 D. This may be a useful clinical tool in such cases.

IOL AXIAL POSITION

This factor was historically referred to as the anterior chamber depth (ACD) because the optic of all IOLs in the early era was positioned in front of the iris, in the anterior chamber. Because most IOLs today are positioned behind the iris, new terminology has been offered such as ELP by Holladay[6] and Actual Lens Position (ALP) by the US Food and Drug Administration (FDA).

ACD is defined as the axial distance between the two lenses (cornea and lens or IOL) or, more exactly, the distance from the central front surface (anterior vertex) of the cornea to the effective principal plane of the IOL (or front surface of the crystalline lens). This value is required for all formulas and it is incorporated into the A constant specific to each IOL style for regression formulas or as an ACD, both supplied by the manufacturer. Some have proposed that it would be useful to measure the preoperative anatomic ACD (corneal epithelium to anterior capsule) either with an A-scan unit or by optical pachymetry. The author performed such a comparison study on 44 eyes and showed that the optical method resulted in a mean 0.20 mm (±0.35 mm) deeper ACD than obtained by ultrasound using 1548 m/s (3.14 vs. 2.93 mm).

The IOL position has been considered the least important of the three variables as a cause of IOL power error but in 1998, the author saw an early PO IOL patient with a shallowed ACD and myopia of −2.50. After 3 days, the chamber deepened by 2.0 mm and the refractive error changed to plano. IOL position has received the most attention from formula writers over the

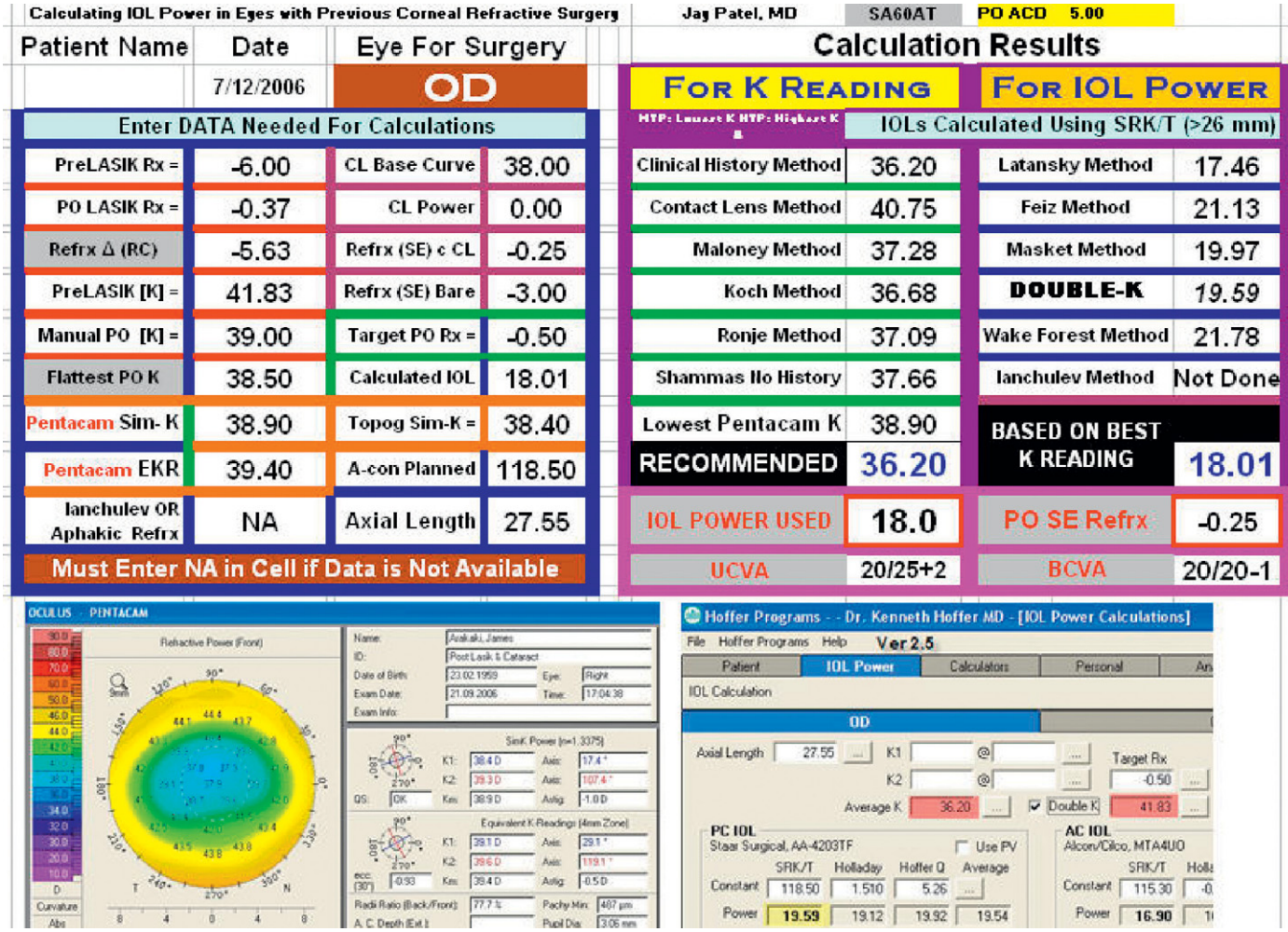


Figure 98.12. Hoffer LASIK IOL power calculation spreadsheet organizer showing all data and PO results.

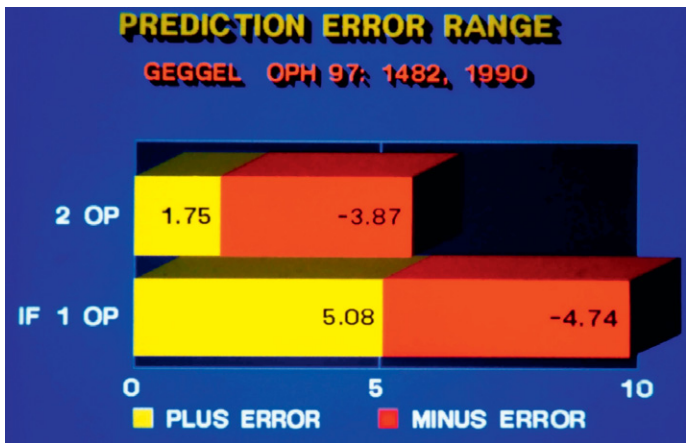


Figure 98.13. Corneal transplants. Dramatic decrease in range of IOL prediction error when IOL is implanted secondarily after transplant heals (5.62 D) vs. a triple procedure (9.82 D).

past 10 years. The major effort has been toward better prediction of where the IOL will ultimately rest. A recent study by the author on a series of 270 eyes receiving a silicone plate haptic lens showed that the IOL shifted a mean of 0.06 mm posteriorly (ACD deepened) at 3 months, compared to its position on the first day after surgery. This was commensurate with a mean 0.21 D shift toward hyperopia.

Warning: An IOL intended for capsular bag placement should be decreased by 0.75–1.00 D (depending upon the IOL power) when placed in the ciliary sulcus.

FORMULAS

GENERATIONS

First generation

The first IOL power formula was published by Fyodorov[38] in 1967. Colenbrander[39] wrote his in 1972 followed by the Hoffer[40] formula in 1974. Binkhorst[41] published his formula in 1975, which became widely used in America. In 1978, first Lloyd and Gills,[42,43] followed by Retzlaff[44] and later Sanders and Kraff,[45] each developed a regression formula based on analysis of their previous IOL cases. This work was amalgamated in 1980 to yield the SRK I formula.[46] All these formulas depended on a single constant for each lens that represented the predicted IOL position (ACD).

Second generation

In 1982, at the Welsh Cataract Congress in Houston, the author[47,48] showed a direct relationship between the position of a PMMA posterior chamber IOL and the axial length, and presented a formula (ACD = 0.282 × AL + 2.83) to better predict ACD. Others (Binkhorst,[49] SRK II[50] (1988)) developed different mechanisms to

apply this predictive relationship which Holladay defined as the second generation.

Third generation

In 1988, Holladay[51] proposed a direct relationship between the steepness of the cornea and the position of the IOL. He modified the Binkhorst formula to incorporate this as well as the axial length relationship. Instead of ACD input, the formula would calculate the predicted distance from the cornea to the iris plane (using a corneal height formula by Fyodorov) and add to it the distance from the iris plane to the IOL. The latter he called the surgeon factor (SF) and it is specific to each lens. Retzlaff[52] followed suit and modified the Holladay I formula to allow use of A constants calling it the SRK/T theoretic formula in 1990. It was intended to replace the previous SRK regression formulas, but some American surgeons still use them. In 1992, Hoffer developed the Q formula[53] using a tangent function of the K to accomplish the same effect.

Fourth generation

In 1990, Olsen[54] proposed using the preoperative ACD and other factors to better estimate the postoperative IOL position and published algorithms for this. After several studies showed the Holladay I formula not as accurate as the Hoffer Q in eyes shorter than 22 mm, Holladay used the preoperative ACD measurement as well as corneal diameter, lens thickness, refractive error, and age to calculate an estimated scaling factor (ESF) that multiplies the IOL-specific ACD. This Holladay 2 formula has been promulgated since 1996 but has yet to be published.

Fifth generation

In 1999, Wolfgang Haigis[55] proposed using three constants to predict the position of the IOL based on the characteristics of the eye and the IOL. The formula calculates the predicted PO ELP by Formula 98.20:

$$ELP = a_0 + a_1 \times ACD + a_2 \times AL$$

where ELP = predicted IOL position, a_0 = a lens-specific constant, a_1 = a constant to be effected by the measured preoperative ACD, and a_2 = a lens-specific constant to be effected by the measured preoperative axial length, ACD = the measured axial distance from the corneal apex to the front surface of the lens and AL = axial length.

As in the Holladay formula, the constants must be optimized (personalized) to each IOL style and surgeon. Single optimization only optimizes the a_0 and creates accuracy equal to the Hoffer Q and Holladay, but triple optimization of all three constants creates additional accuracy. The problem is that triple optimization requires a series of 500–1000 cases of one lens style and the eyes in the series must statistically cover all axial lengths from very short to very long. This may be quite difficult to achieve for the average surgeon.

Refraction formula

Holladay[56] published a formula in 1993 to calculate the power of an IOL for an aphakic eye or ametropic pseudophakic eye (piggyback IOL) or a refractive lens (PRL) for a phakic eye. It does not need the AL but requires the corneal power, preoperative refractive error, and desired postoperative refractive error as well as the vertex distance of both. I do not recommend its use in aphakic eyes because the vertex distance is difficult to measure accurately and due to the high power of their refractive error, greater errors can result. It is, however, a good check against the AL formula calculation.

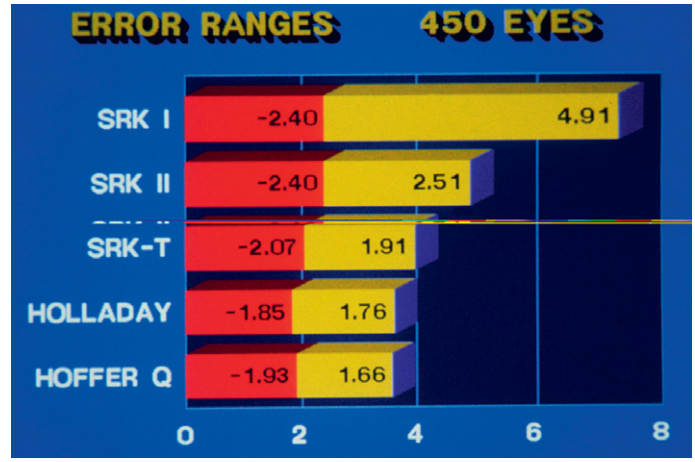


Figure 98.14. Error range. Range of IOL power error in 450 eye study using regression formulas compared to modern theoretic formulas.

USAGE

Based on axial length

This author's study[53] of 450 eyes (by one surgeon using one IOL style) (Fig. 98.14) showed that in the normal range (72%) of axial length (22.0–24.5 mm) almost all formulas function adequately, but that the SRK I formula is the leading cause of poor refractive results in eyes outside this range. It also showed that the Holladay I formula was the most accurate in medium long eyes (24.5–26.0 mm) (15%) and the SRK/T was more accurate in very long eyes (>26.0 mm) (5%). In short eyes (<22.0 mm) (8%) the Hoffer Q formula was most accurate and this was confirmed ($p > 0.0001$) in an additional large study of 830 short eyes as well as in a multiple-surgeon study by Holladay. Holladay has postulated that the other formulas overestimate the shallowing of the effective lens position (ELP) in these very short eyes.

A more recent study[57] this author performed on 317 eyes showed that the Holladay 2 formula equaled the Hoffer Q in short eyes but was not as accurate as the Holladay I or Hoffer Q in average and medium long eyes (Table 98.4). Eyes shorter than 19 mm are extremely rare (0.1%) and may well be benefited by using the Holladay 2 formula. It appears that in attempting to improve the accuracy of the Holladay formula, the addition of more biometric data input has improved the Holladay 2 formula in the extremes of axial length but deteriorated its excellent performance in the normal and medium long range of eyes (22.0–26.0 mm), which is 82% of the population.

Methodology

There are several means by which to use these newer formulas including A-scan instruments, handheld calculators, and computer programs that run on DOS, Windows, and Macintosh systems as well as for the handheld Palm personal digital assistant (PDA) operating system (Fig. 98.15, *A–F*). You can also program the published ones yourself on a spreadsheet program. It is important to check the errata in references 41 and 42. The most popular commercial programs are the Hoffer Programs System* (the first computer program for IOL power in 1994) and the Holladay IOL Consultant* (1997), which

Table 98.4 Results of accuracy of four theoretical formulas on 317 eyes using the Holladay® IOL Consultant for analysis of Mean Absolute Error (MAE)[46]

	MEAN ABSOLUTE ERROR					ALL 317 EYES		
Formula	Short <22.0	Normal 22.0–24.5	M-long 24.5–26.0	V-long >26.0	Long <24.5	All Eyes	Max Error	>±2 D Error
Holladay 2	0.72	0.56	0.51	0.49	0.50	0.55	–1.60	0%
Holladay 1	0.85	0.42	0.37	0.56	0.43	0.43	–1.44	0%
Hoffer Q	0.72	0.43	0.47	0.58	0.50	0.45	–1.61	0%
SRK/T	0.83	0.46	0.35	0.44	0.36	0.44	–1.45	0%
AVERAGE	0.78	0.47	0.42	0.52	0.45	0.47		
BEST	H-Q H-2	H-Q H-1	S/T H-1	S/T	S/T			

M-Long = medium long, V-Long = very long, Long = all long eyes, Max = maximum.

include several formulas and the ability to personalize them as well as routines to deal with odd clinical situations.

(*Available from EyeLab, Inc., Santa Monica, CA)

PERSONALIZATION

The concept of personalizing a formula based on a surgeon's past experience and data was introduced by Retzlaff[52,58] using the A constant to refine the formula. Holladay incorporated this concept into backsolving for the surgeon factor, and Hoffer backsolved for his personalized ACD. Several studies have proved that formula personalization definitely improves formula accuracy significantly.

The following parameters are required from postoperative eyes:

1. axial length (pre-op)
2. corneal power (pre-op)
3. IOL power
4. postoperative refractive error (stable).

The eyes should all contain the same lens style by one manufacturer implanted by one surgeon. The same biometry instruments and technician should also have been used. Eyes with postoperative surprises or acuity worse than 20/40 should not be included in the analysis due to poor accuracy in obtaining refractive error. Personalization involves backsolving for the exact IOL position that would produce the resultant refractive error with that IOL power, AL, and K. Then all the 'ideal' IOL positions are averaged to arrive at the personalized value to use in the future. Personalization can be easily performed using the Hoffer® Programs or Holladay® IOL consultant computer programs.

CLINICAL VARIABLES

PATIENT NEEDS AND DESIRES

Most surgeons have developed their own plan for deciding on the clinical needs of their patients. It has often been recommended to aim patients for mild postoperative myopia (–0.5 to –1.5 D) so if the error is on the plus side, they will be emmetropic and if on the minus side, they will have reading vision. This is necessary because of the larger range of IOL power errors generally experienced. When the bell-shaped curve of prediction error is squeezed down to 67% within ±0.50 D, it is then possible to aim most patients for emmetropia. This is even more important when implanting a multifocal IOL. Senior citizens are much more active today than in the past and in emergency situations it would be a lot safer if they were emmetropic than seeking for their myopic correction to escape to safety.

There are several exceptions, however. Patients who have been life-long myopes are never happy being hyperopes postoperatively. Patients who would wind up with a large anisometropia should be stimulated to be fitted with a contact lens in the other eye prior to deciding on an emmetropic IOL. Monocular CL wearers are more successful than binocular. It is wise to document all discussions regarding unusual situations.

SPECIAL CIRCUMSTANCES

Monocular cataract in bilateral high ametropia

The dilemma is to make the surgical eye emmetropic or match the large ametropia of the other eye, which may never need surgery. Up to now, this author has convinced most patients to accept a monocular CL or ignore the other eye and go for the 'brass ring' of emmetropia. In the future, those who cannot tolerate CLs could have a phakic IOL either placed in the other eye or placed over the IOL to eliminate aneisikonia and have it removed if the other eye ultimately has surgery.

Pediatric eyes

Children have always posed a dilemma[59] in IOL power selection in that the eye will grow in length and become more myopic if a fixed emmetropic power is implanted. The study of pediatric eyes by Gordon and Donzis[60] shows a steep axial length growth rate from premature babies to age 2, increasing by 6 mm (approximately 20 D), while corneal power drops from 54 D to 44 D offsetting 10 D. If IOLs are used in this age group it might be best to place piggyback lenses with the more posterior IOL having the average adult emmetropic power and the anterior IOL being the added power needed to reach emmetropia now. As the children grow, they can be corrected with myopic glasses until they are old enough to have the anterior IOL removed.

Between the ages of 2–5 years, growth slows to about 0.4 mm per year and only increases another 1 mm from age 5–10 while corneal power remains stable. From age 2–10, it might be wise to aim for 1.5–2 D of hyperopia postoperatively which allows for reasonable uncorrected vision and light spectacle correction in amblyopia treatment. When they mature, they will wind up emmetropic or mildly myopic, depending on age at implantation. Growth

slows after age 10–15 and emmetropia can be the aim. Future use of implantable phakic refractive lenses over the top of IOLs may be very helpful in these children since they can easily be exchanged as the eye grows, keeping them emmetropic throughout life.

Plager et al[61] reported on 38 eyes of 27 subjects receiving an IOL in childhood. Based on their results they recommend the following scheme for the refractive goal for children depending upon their age (Box 98.5).

Multifocal IOL

In 1991, the author[62] reported that to obtain –2.75 D myopia (reading at 14″–16″) the IOL power in the near vision region must be about 3.75–4.00 D stronger than the emmetropic power. It was also shown that the amount of this additional power in a bifocal IOL is not affected at all by the axial length and very little by the corneal power. It is affected, however, by the IOL position and an AC lens needs less add power than a PC lens. Obviously, to negate the need for any glasses, it is important to aim for emmetropia, but mild

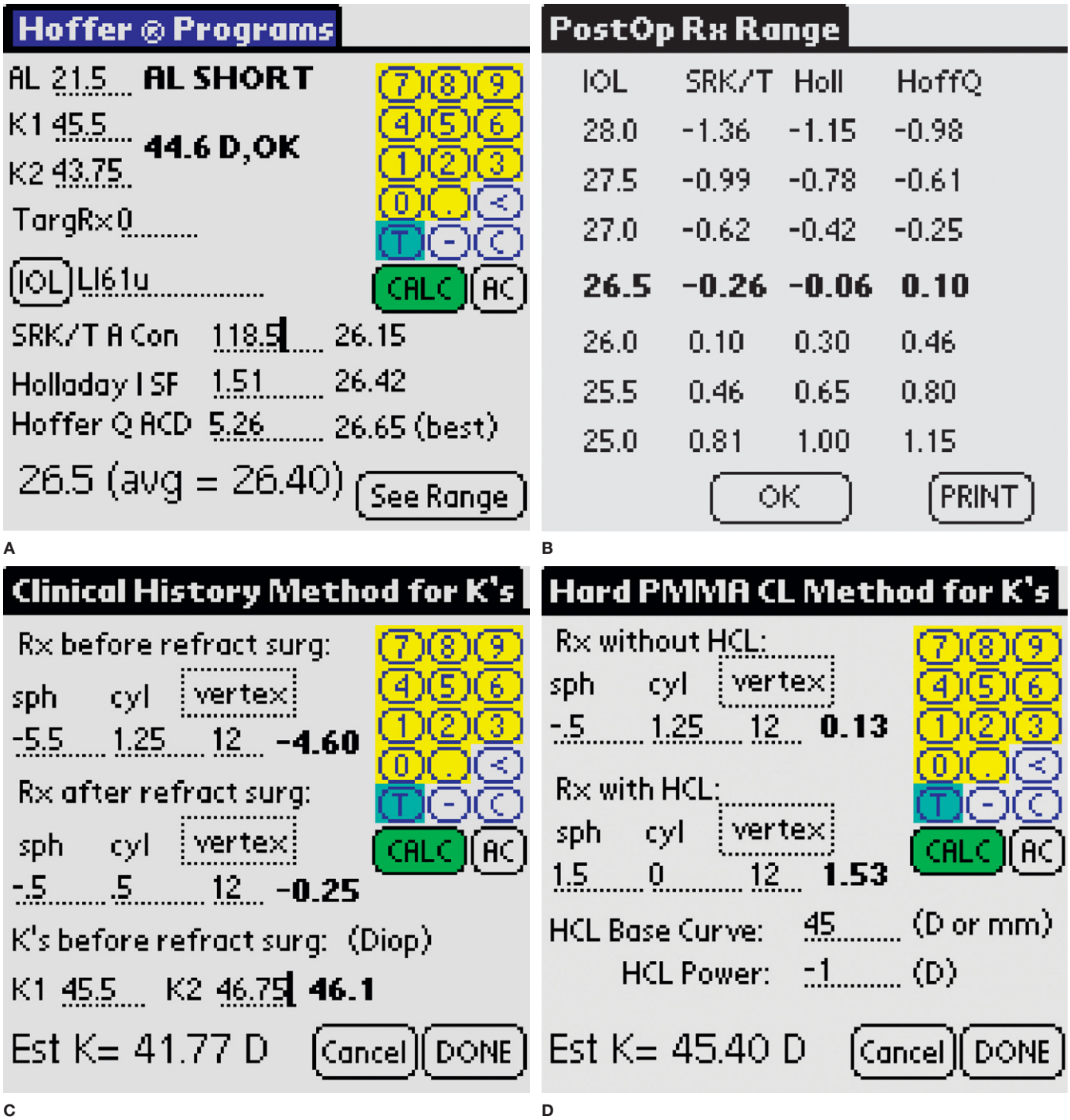
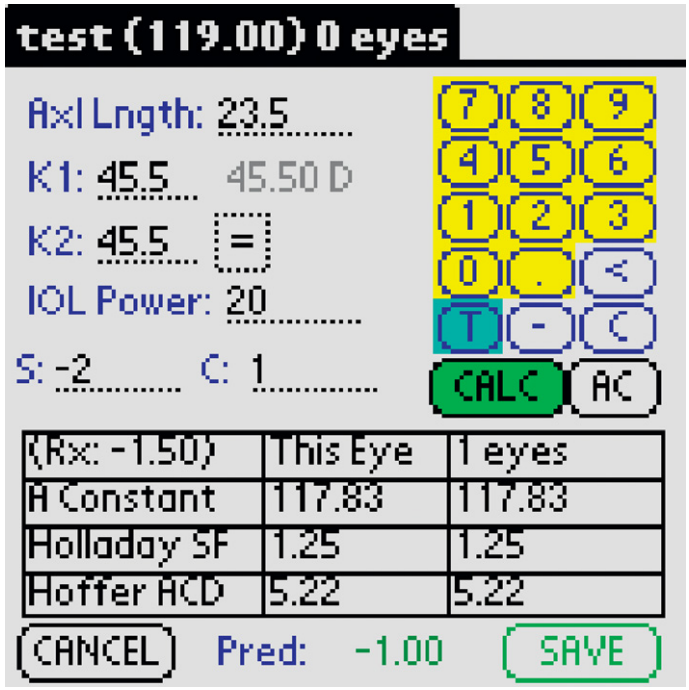


Figure 98.15. Hoffer®Programs IOL power program on a Palm personal digital assistant. *A*, Main calculation screen using Hoffer Q, Holladay, and SRK/T formulas; *B*, Next screen showing refractive results of different IOL powers; *C*, Clinical history method screen; *D*, Contact lens method screen; *E*, Personalization screen for adding new PO eyes; *F*, Personalization screen for various IOLs.



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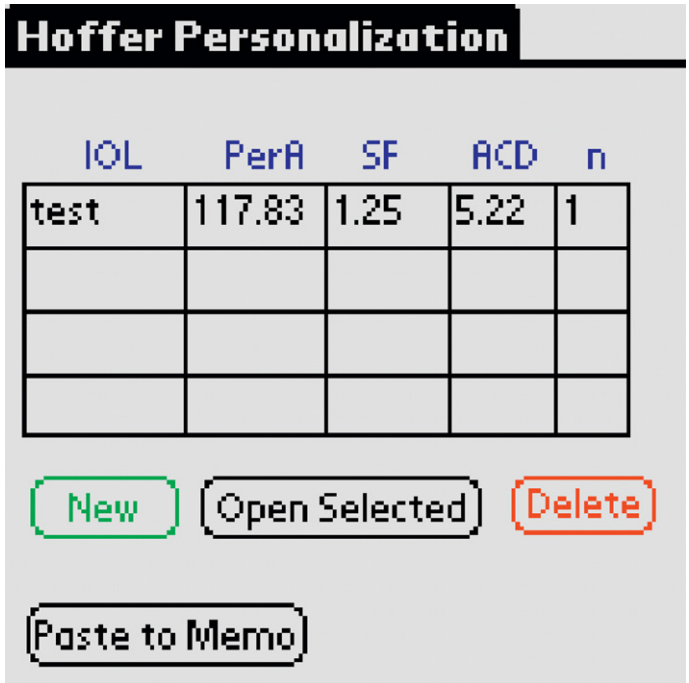

F

Figure 98.15. Continued

BOX 98.5

Age	3	4	5	6	7	8	10	13
Goal	+5.00	+4.00	+3.00	+2.25	+1.50	+1.00	+0.50	Plano

postoperative hyperopia is far better than even the mildest myopia. The distance vision will be reasonable in the former (they can easily obtain readers if necessary); while in the latter it will not. Bifocal IOL patients with myopia are not happy and everything should be done to avoid this situation since minus power 'readers' are not readily available. In the future, a phakic IOL could be implanted over the top of the bifocal to make the eye emmetropic.

Silicone oil refractive effect

The second problem that arises when the vitreous is replaced with silicone oil is that the refractive index of the oil is much less than that of the vitreous and it acts as a negative lens in the eye which must be offset with more power in the IOL. This effect is dependent upon the shape factor of the back surface of the IOL such that a biconvex IOL creates the worst problem and a concave posterior lens (no longer commercially available) causes practically no effect. In between the two is the plano-posterior lens, which is recommended in these cases. With a plano-convex lens, 2–3 D must be added to the IOL power to compensate for this silicone effect.

Piggyback lenses

Either piggyback lenses can be placed primarily or the second lens placed secondarily over a previously healed IOL. In the former, the anterior IOL forces the posterior IOL more posteriorly a distance equal to the central thickness of the anterior lens. This causes the posterior lens (whose focal point is moved more posteriorly) to require more power to maintain the same focus. This effect diminishes the thinner (lower power) the anterior lens is and a thinner lens is easier to remove if that should be necessary. Primary piggyback lenses need special calculations to adjust for the posterior lens shift. One can simply add one-half the central thickness of the anterior IOL to the ACD being used by the formula.

Secondary lenses can be calculated using the refraction formula or by a more simple formulation based on the fact that the healed primary IOL is more stable. Due to the different effect on vertex power changes between plus and minus lenses, the following formulation works well (Formula 98.21).

$$\text{Hyperopic: piggyback IOL} = 1.5 \times \text{Rx}_{\text{ERROR}}$$
$$\text{Hyperopic error: piggyback IOL} = 1.0 \times \text{Rx}_{\text{ERROR}}$$

where Rx = PO spherical equivalent refractive error.

PROBLEMS AND ERRORS

The major problem is an unacceptable postoperative refractive error. The sooner it is discovered, the sooner it can be corrected and the patient made happy. Therefore, it is wise to perform K readings and a manifest refraction on the first postoperative day. The author has long recommended immediate surgical correction[63] (24–48 h). This allows easy access to the incision and the capsular bag, one postoperative period, and excellent uncorrected vision. The majority of medicolegal cases today are due to a delay in diagnosis and treatment of this iatrogenic problem. Up to now, we could only correct this problem by lens exchange which creates the dilemma of determining which factor created the IOL power error: axial length, corneal power, mislabeled IOL, or a combination of all three. Today, with the advent of low-powered IOLs, the best remedy may be a piggyback IOL. When using a piggyback IOL, it is not necessary to determine what caused the error or to

re-measure the axial length of the freshly operated pseudophakic eye. It is possible to confirm the power of an explanted IOL by using the McReynolds lens analyzer (Vision & Hearing Center, Quincy, IL).

It is important to remember that a shallow AC can lead to as much as 3 D of myopia (depending on the power of the IOL) which will disappear when the AC reforms. An RK eye has a propensity for the cornea to flatten postoperatively causing large hyperopic surprises. It may take up to 3 or 4 months for the cornea to re-steepen; therefore, surgical correction should not be attempted until then.

Handling the IOL power surprise

An inappropriate PO refractive result is disappointing to both the patient and the surgeon. It is often difficult to determine what caused this prediction error.

A. According to most studies, the most common cause is an error in measuring *axial length*.

I. This is most commonly seen in eyes longer than 25 mm that have a higher incidence of *staphyloma*. The problem with staphylomas is that they can vary in size and position. If the macula is located at the deepest end of the staphyloma the anatomical AL will equal the visual AL. Most often the macula lies somewhere else along the slope of the staphyloma and the ultrasound measures the anatomical AL which is longer than the true visual AL. Usually these errors are ones of too long AL and too weak an IOL power (hyperopic error).

II. Contact applanation ultrasound artificially shortens the AL and this built-in variable error is worse as the AL becomes shorter. Though this fact has been well accepted, still 70% of clinicians use this procedure and add a fudge factor to correct for it. This would be acceptable if the amount of artificial shortening was approximately the same for every eye, but it is not. Some eyes are shortened by as much as a 1 mm and others are not shortened at all. This shortening leads to a too short AL and too strong IOL power (myopic errors).

III. Technician inexperience or just plain error is another cause for incorrect AL measurements.

IV. Using the wrong average ultrasound velocity is another cause for measurement errors. Many use an average velocity of 1550 m/s which is incorrect. As proven by Hoffer,[42] the correct value to be used for an average phakic cataractous eye is 1555 m/s. The problem is that the average speed for a short 20 mm eye is 1560 m/s and it is 1550 m/s for a long 30 mm eye.

V. Poor IOLMaster readings that are not recognized by the examiner are also a cause of error in AL and are more common as the cataract is more dense or the patient is not able to fixate properly.

VI. Silicone oil-filled eyes are an especially vexing problem since the ultrasound wave is so slowed down crossing the posterior segment that it is often impossible to get a reading at all. It is also difficult to determine what percentage of the vitreous body is filled and what parts the beam is going through.

VII. Lastly there is the problem of the eye that 'just can't be measured'! This situation is rare but unfortunately real. No one has offered a complete explanation for this.

B. Incorrect measurement of the *corneal power* is the second most common reason for IOL power error.

I. Overestimation of the corneal power (K) is the rule in eyes that have had previous corneal refractive surgery. This is due to the fact that there has not yet been a keratometer or keratometer attachment that will allow the measurement of the true central effective corneal power in these eyes. Two factors are at play here. The first is the fact that most keratometers measure at the central 3.2 mm (wider if the cornea is flatter) of the cornea and not able to get the more central flat area that is being used by the eye. The second is the change in the refractive index of the cornea that is difficult to correct for in any individual eye because it is dependent upon the amount that the cornea has been thinned.

II. It is important to have a schedule of calibrating all keratometers to prevent errors in measurement.

III. The IOLMaster has a setup screen that allows the operator to change the index of refraction (IR). Most users are unaware of this. The manufacturer did this to allow the instrument to produce K readings equivalent to that obtained by the manual keratometer used in the clinician's office. American keratometers are set at an IR of 1.3375 and European ones at 1.336. Hoffer recently discovered that if the IOLMaster IR is not set for 1.3375, the Hoffer Q formula will be in error. He has not tested the Holladay 1 and 2 or the SRK/T formulas.

IV. In cataract patients who wear contact lenses, there is a corneal warping factor that produces incorrect K readings compared to what they would be without the CLs (the state the eye will probably be after IOL surgery). This is especially true in eyes wearing hard CLs. Ten years ago a medicolegal case was lost in Louisiana because the judge ruled that the CLs should have been kept out for a minimum of 2 weeks prior to the keratometry examination.

V. Corneal scarring, especially in the center, can cause a great problem in measuring the corneal power.

VI. Eyes that will need corneal transplantation also pose a problem in predicting preoperatively what the ultimate healed corneal power will be.

C. The third and least effective factor in prediction error is the healed *effective position of the IOL* in the eye. This is referred to as the A constant, the surgeon factor (SF), or the Hoffer anterior chamber depth (ACD). Holladay instituted the replacement term, effective lens position (ELP), since most IOLs today are not in the anterior chamber.

I. Errors may occur if the IOL settles in a deeper or shallower position than that predicted by the formula or what would be expected in an eye with that particular IOL, AL, and K. Sometimes this can be a temporary situation in the early PO period.

II. Another cause of error is when the ACD constants have not been personalized to the individual IOL style, surgeon, and clinic.

D. *Formulas* are a cause of IOL power error especially for those using regression formulas and most definitely with those using the SRK I regression formula in eyes outside the normal AL range of 22–24.5 mm. This has been shown in so many studies[14] over the past 12 years it would be impossible to reference them all here.

E. There are other *miscellaneous* causes for IOL power errors that can be just as serious as those mentioned above. A rare manufacturer labeling error can be very serious and very difficult to pick up before the patient is discharged from the facility. If the operating room staff nurse hands the surgeon the wrong IOL power during the surgery this may not be easily recognized in time to correct the error. Lastly, transcription mistakes can cause some of the largest errors seen.

Prevention of common errors:

- Use the IOLMaster or immersion A-scan to measure the AL.
- Suspect a staphyloma in eyes >25 mm: use IOLMaster and/or Shammas A/B-scan technique.

- Use CALF method: measure eye using 1532 m/s and add 0.32 mm to the result to correct for any error in sound velocity.
- Employ a well-trained, experienced technician.
- Regularly calibrate manual keratometers.
- Carefully evaluate the IOLMaster scan for reliability.
- Keep CL out for 2 weeks prior to keratometry (at least in one eye.)
- Silicone oil eyes need the IOLMaster if possible or ultrasound AL multiplied by 0.71.
- Use the Hoffer® Q formula in eyes <22 mm and in post-refractive surgery eyes.
- Use the Holladay® 1 formula in eyes 24.5–26 mm in length.
- Use the SRK/T formula in eyes longer than 26 mm.
- Never use the SRK regression formulas (SRK I or II).
- Personalize your ELP factors in the formulas.
- Surgeon should personally select the IOL power for the individual patient.
- Prepare a sheet with all IOL powers that may be needed and place it on the wall and also on the microscope in the operating room for the surgeon and nurse to verify the correct IOL power. Use red paper for right eyes and yellow paper for left eyes.
- Be sure to set the IR to 1.3375 in the setup screen of the IOLMaster.
- Use the clinical history and contact lens methods (have PMMA CLs in the clinic) for post-refractive surgery corneas and use the lowest calculated K (highest for hyperopes).
  - Consider the Shammas 'No History' Formula: $K = 1.14*K_{PO} - 6.8$ or the Maloney or Koch Corneal topography methods.
  - Use the Aramberri Double K: calculate the ELP using the preoperative K and the IOL power using the PO K.
- Download and use the free Hoffer/Savini LASIK IOL Power Tool www.EyeLab.com.
- Consider delaying the IOL implantation until the cornea has healed after a penetrating keratoplasty rather than performing a triple procedure.

Suggestions for diagnosing and treating IOL power surprises

- Make it a routine to perform a manifest refraction on PO day 1 so as to discover the problem early enough to take the patient back to the operating room and correct the problem in the first 48 h. The patient is immediately pleased and medicolegal actions are completely eliminated.
- Consider the use of a piggyback IOL or phakic IOL if the eye has healed beautifully and removal of the errant IOL would be more traumatic to the eye. For myopic error use 1 multiplied by the error and for hyperopic errors use 1.5 multiplied by the error (or the Shammas formula).
- Consider a minimal 4-incision RK if repeat intraocular surgery is not possible.
- Measure the power of a removed IOL using the McReynolds Analyzer (William McReynolds 217-222-6656) or ask a manufacturer to be present in the operating room to do it.

CONCLUSION

Simple steps and attention to detail can be very useful in preventing IOL power errors, and recent advances in IOL power range availability has made this problem more easily corrected. Since performing the first American ultrasound IOL power calculation[64] in 1974, the past 34 years have seen great improvements in the accuracy of postoperative refractive prediction. Future improvements may someday eliminate the problems we have left.

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99 Anterior chamber phakic intraocular lens

James Lee, Lisa Herrygers

INTRODUCTION

The field of excimer laser refractive surgery has expanded dramatically over the past decade. Laser-assisted in situ karatomileusis (LASIK); photorefractive keratectomy (PRK); and laser subepithelial keratomileusis (LASEK) have been the most popular. Other modalities include corneal inserts, conductive keratoplasty, clear lens extraction with or without intraocular lens insertion, and phakic intraocular lens implants. Corneal refractive procedures account for the vast majority of cases but can be associated with many potential complications including corneal ectasia; diffuse lamellar keratitis; epithelial ingrowth; corneal haze and regression, as well as infection.[1] Excimer laser refractive surgery is capable of inducing irreversible change in cornea shape, inducing optical aberrations resulting in visual disturbances such as glare, halos, starbursting, and loss of contrast sensitivity.[2] In addition, there is also a limit to the amount of refractive correction possible, primarily determined by corneal thickness and high astigmatism.

Phakic intraocular lenses provide certain advantages in refractive surgery. Most of the potential problems associated with corneal procedures are alleviated because the cornea is left mostly undisturbed.[3,4] It is reversible and a greater range of refractive corrections can be treated since it is not dependent on corneal thickness. The amounts of postoperative higher order optical aberrations may be lower than those seen after LASIK. This may result in fewer visual complaints such as glare, halo, and starbursts. However, as with all surgical procedures phakic intraocular lenses can be associated with surgical complications including endophthalmitis, corneal endothelial damage, retinal detachment, glaucoma, and cataract.

LENSES

Phakic intraocular lenses can be placed in the anterior chamber, posterior chamber, or fixated on the iris. Anterior chamber phakic intraocular lens are either angle-supported or iris-fixated.[5] Angle supported models include Vivarte (IOL Tech/Ciba Vision, Atlanta, Georgia), NuVita (Bausch & Lomb, Rochester, New York); Acrys of phakic IOL (Alcon Laboratories, Fort Worth, Texas); whereas the Artisan/Verisyse (Worst-Fechner/Artisan Lens [Ophthtec/AMO, Santa Ana, California]) is iris fixated. These lenses are made using either acrylic or polymethylmethacrylate (PMMA) materials which have been used successfully as intraocular implants in cataract surgery and have been proven to be well tolerated and safe within the eye.

The NuVita is a single-piece angle-supported design with a nonfolding 5 mm optic size diameter. This lens can be used for treating refractive errors in the range of –7.00 to –20.00 D but is only available in Europe. Bausch & Lomb is currently working on a new anterior chamber angle-supported hydrogel foldable lens for the USA market. The Vivarte lens is a single-piece hydrophilic acrylic with angle support. It is foldable and can be inserted into the eye through a small self-sealing corneal incision. It has an optic diameter of 5.5 mm and is supplied in different diameters from 12.00–13.00 mm. The refractive range is from –6.5 to –31.00 D in 0.5 D increments. The Acrys of angle-supported phakic IOL is an acrylic foldable design. It is available in a 5.5 mm or 6.0 mm diameter optics with an overall length of 12.5–14.0 mm. It has a refractive range of –6.00 to –16.5 D in 0.50 D powers. The Artisan/Verisyse lens is made from PMMA material and has an overall length of 8.5 mm and an optic diameter of 5 or 6 mm (Fig. 99.1). It is an iris-fixated lens that attaches to the midperipheral iris. Because PMMA is inflexible, a large incision is required to insert this lens. The lens is available in the myopic refractive range from –5.00 to –20.00 D using a 5 mm optical zone diameter and from –5.00 to –15.00 D using a 6 mm optical zone diameter. Currently, the Artisan/Verisyse lens is the only USA Food and Drug Administraton approved anterior chamber phakic intraocular lens in the USA. There is a foldable version of the Artisan/Verisyse that is currently undergoing clinical trials.

PREOPERATIVE EVALUATION

The Artisan/Verisyse lens is the only phakic anterior chamber intraocular lens currently approved in the USA, and the FDA[6,7] has set specific guidelines for its use. A patient must be at least 21 years old and not pregnant or breastfeeding. The patient's anterior chamber depth must be greater than 3.2 mm and iris configuration

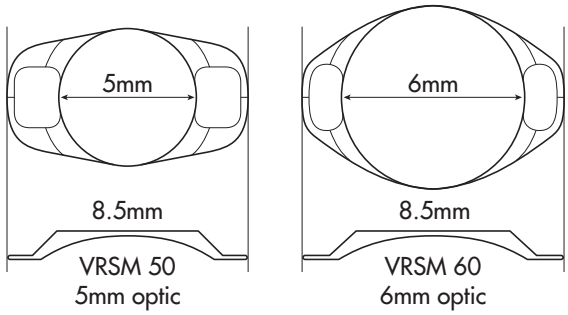


Figure 99.1. Verisyse™myopic phakic lenses.

must be normal. There is also an endothelial cell density requirement that varies depending on age.

CONTRAINDICATIONS

- Cataract
- Retinal detachment or a family history
- Abnormal pupil
- Abnormal cornea
- Endothelial cell count <2000 cells/mm^2
- Anterior chamber depth too shallow
- IOP >21 mmHg

The Artisan lens is approved for a myopic treatment range of −5.00 to −20.00 D with less than or equal to +2.50 D of astigmatism at the spectacle plane. Patients must also document manifest refraction stability for the prior 6 months as defined by a spherical equivalent change of less than 0.50 D.

A careful and thorough patient selection is critical to obtain successful outcomes with phakic intraocular lens. Patient counseling is crucial, as in all refractive surgical procedures. The patient must have realistic expectations and understand that the Artisan lens will not correct astigmatism. The patient must also understand the need for a possible second procedure to correct any residual over- or undercorrection of the refractive error. The preoperative evaluation includes a comprehensive examination including anterior segment evaluation, dilated fundus examination, manifest refraction, cycloplegic refraction, and pupil diameter measurement. Ancillary testing must include measuring anterior chamber depth and the corneal endothelial cell count.[8]

SURGICAL TECHNIQUE

The implantation of the Artisan lens into the anterior chamber is typically performed under topical or peribulbar anesthesia. Preoperative miosis is obtained with topical pilocarpine. Two paracenteses are made at the 10 and 2 o'clock positions. The anterior chamber is then filled with cohesive viscoelastic taking care to avoid injection under the iris. The dispersive and supercohesive viscoelastic materials should not be used. A longer incision is then made at the 12 o'clock position. The length of the incision depends on the lens optic size (5 or 6 mm). The incision can be made corneal, limbal, or scleral, depending on a surgeon's preference. A specialized lens forceps is used to insert the lens. The Artisan lens is attached to the midperipheral iris with an enclavation needle. The needle is inserted through the paracentesis openings and a fold of iris is carefully tucked in between the split haptics. This process, called enclavation, is performed at the 3 and 9 o'clock positions (Figs 99.2–99.6). The wound is then closed using 10-0 nylon or absorbable sutures. The cohesive viscoelastic is completely removed from the eye to reduce the potential for postoperative intraocular pressure elevation. A laser peripheral iridotomy is performed preoperatively or a surgical peripheral iridotomy is made intraoperatively to prevent pupillary block glaucoma. Postoperative medical management consists of a combination of a topical antibiotic, a nonsteroid medication, and a topical steroid. Sutures are removed after 1–2 months or when appropriate as judged clinically by the surgeon. Surgery for the second eye is performed 2 weeks later.

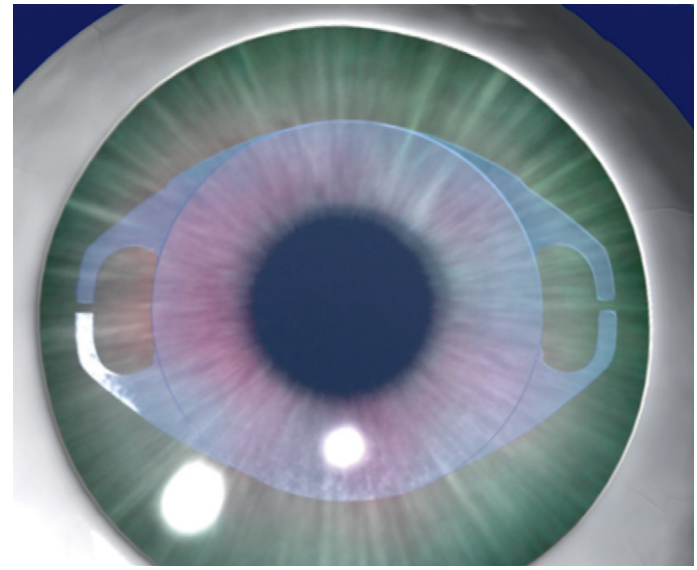


Figure 99.2. Lens positioned in the anterior chamber & aligned with vertical & longitudinal pupillary axis.

RESULTS

The FDA submission data for the Artisan phakic intraocular lens shows very positive clinical results.[9] The procedure is accurate and predictable. Sixty-three per cent of eyes achieved correction within 0.5 D of the target and 87% achieved correction within 1.0 D of the target (Table 99.1). Patients maintained stable correction at 3 years with 96% of patients having less than ±1.0 D of shift.[10] Also at 3 years, 92% had 20/40 or better uncorrected distance visual acuity and 44% had 20/20 or better uncorrected distance visual acuity. Patient satisfaction surveys showed that the majority of the patients did not experience night visual symptom changes such as glare, halo, and starburst (Table 99.2). Contrast sensitivity study showed no loss of contrast sensitivity under mesopic and photopic conditions after Artisan lens implantation.

COMPLICATIONS

During the Artisan phakic clinical study there were several incidences of adverse events (Table 99.3). The incidence rates of three major adverse events were found to be higher or the same when compared to the historical control population. Adverse events included IOL dislocation (0.8%), retinal detachment (0.6%), and surgical reintervention (4.2%), which included lens explants, lens

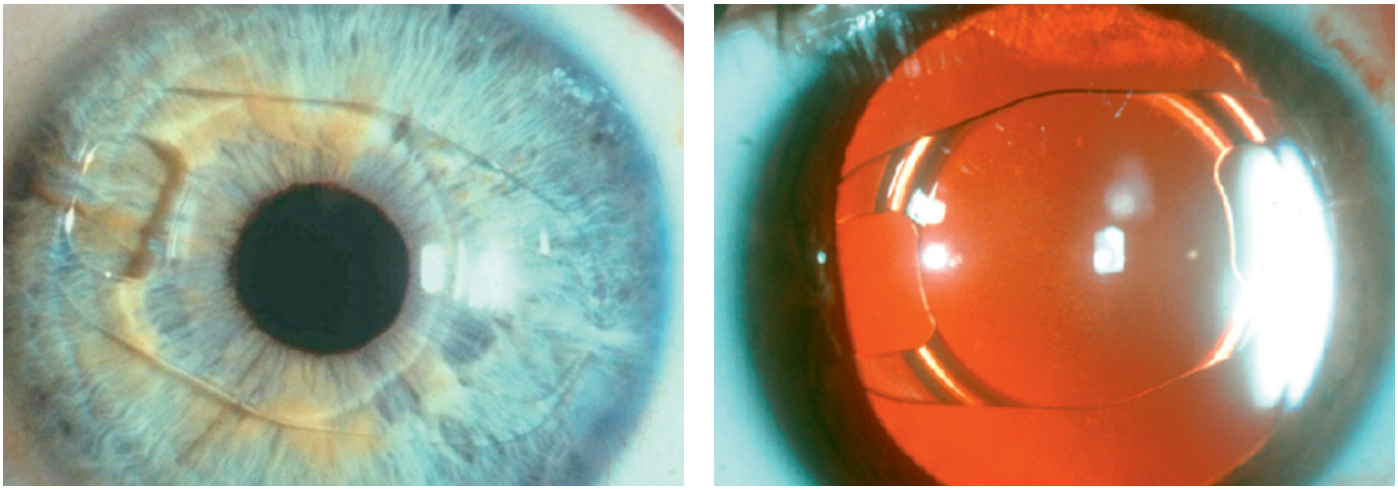


Figure 99.3. Lens position before and after pupil dilation.

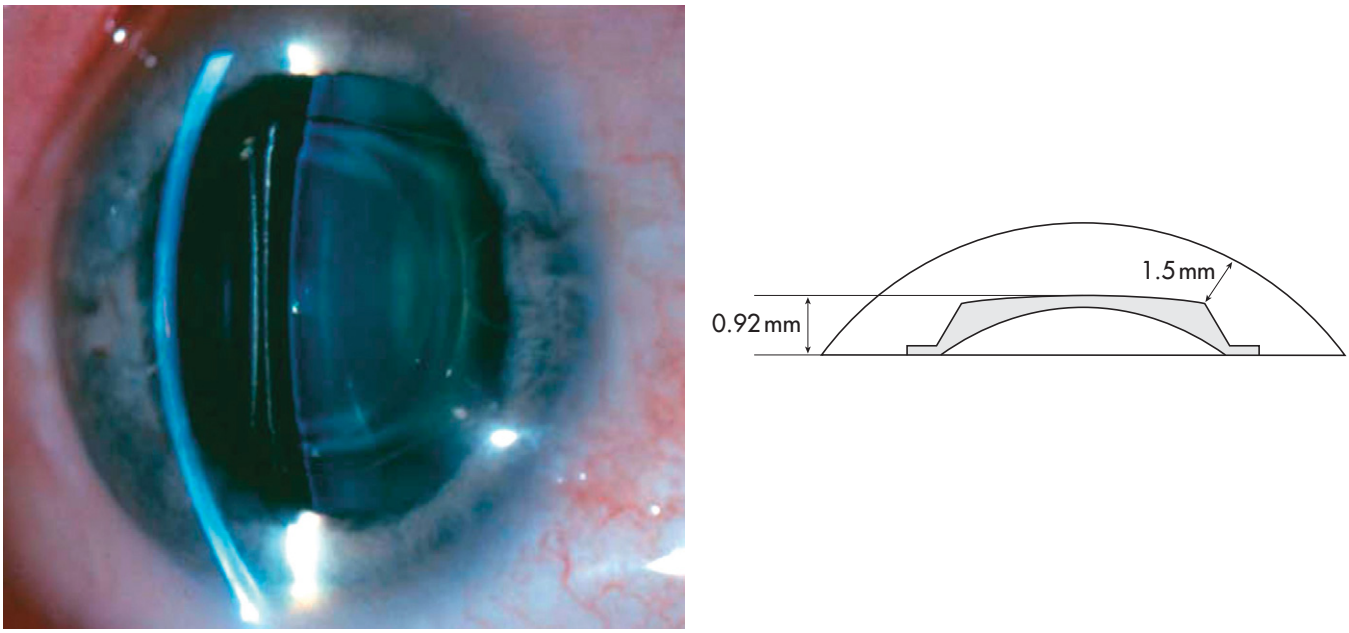
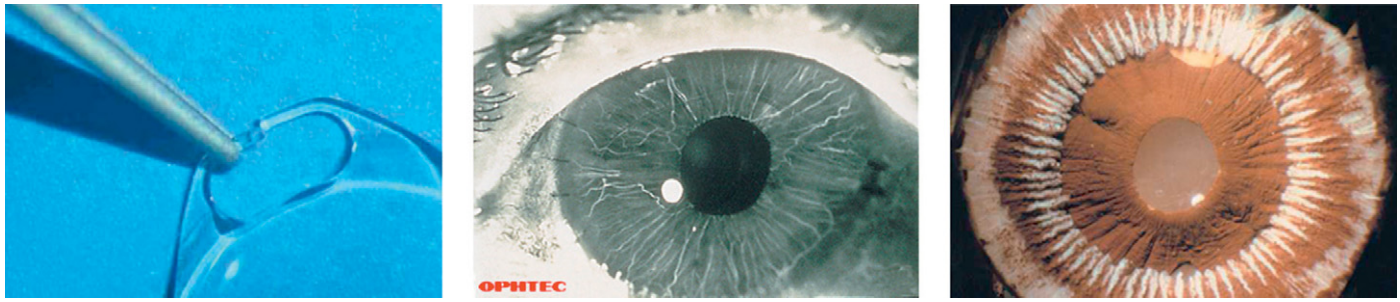
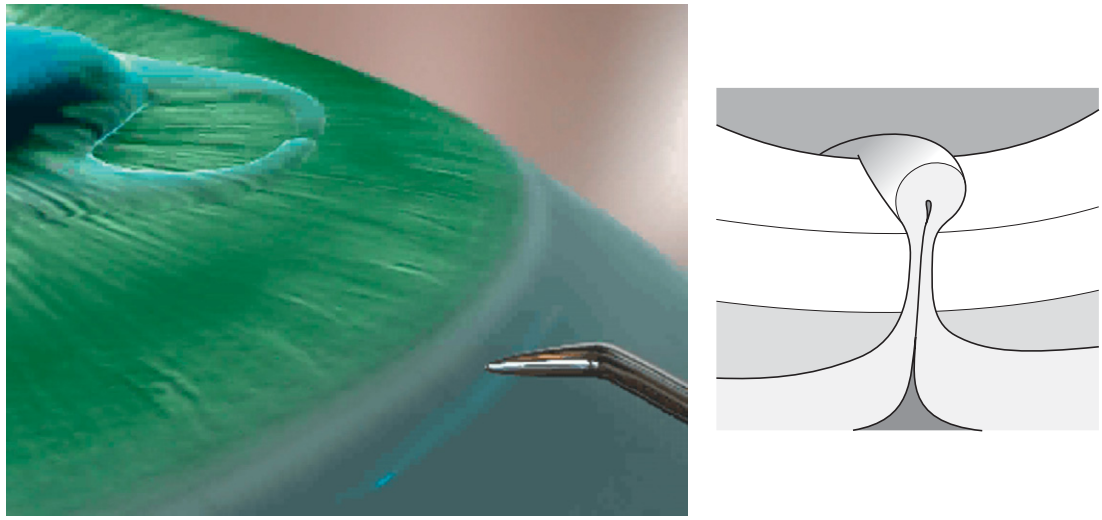


Figure 99.4. Lens size.



A B C

Figure 99.5. Iris attachment *A*, split haptic; *B*, iris angiogram showing perfusion pattern; *C*, 6 years after procedure.



A B

Figure 99.6. *A*, enclavation; *B*, iris captured between split haptic.

Table 99.1 Uncorrected visual acuity of the patient population

	% Each Visit			
Uncorrected Visual Acuity	6 Month	1 Year	2 Years	3 Years
20/20 or better	33.2	35.1	34.6	31.2
20/40 or better	86.7	86.6	87.1	84
20/80 or better	97.9	97.8	98.3	95.2
Worse than 20/80	2.1	2.1	1.7	4.8
No. of patients	581	493	356	231

exchange, lens reattachment, and retinal detachment. The rates of other clinical complications were lower than the incidence reported in the historical control population. These include hyphema, iritis, and wound leak. Complications such as endophthalmitis, cystoid macular edema, pupillary block, corneal decompensation,[11] and elevated intraocular pressure were not observed during the trial. However, other surgeons implanting the same lens in different clinical studies[12] have reported some of these same complications.[11] Treatment-induced astigmatism[13] occurred in 2–3% which was within the study's safety target of less than 5%. In the clinical trial, the incidence of lens opacity was 4.5%, and of these, four were determined to be visually significant and three required cataract extraction. One of the patients lost 2 lines of best uncorrected visual acuity following surgery.

The potential for damaging the corneal endothelium was carefully studied during the trial since anterior chamber intraocular lenses

Table 99.2 Visual symptoms at night

Subjects with at least 1 year follow-up ($n = 412$)	Subjects Response		
Subjects with Change in Symptom:	**Preop = No Postop = Yes**	**Preop = Yes Postop = No**	***p*-value**
Glare (26.4%; 98/371)	51%	49%	0.840
Halo (28.0%; 104/372)	65%	35%	0.002
Starburst (21.5; 80/372)	55%	45%	0.371

*McNemar Chi-square test.

Majority of subjects had no *change*.

Table 99.3 Comparison of adverse events rates reported at 12 months

Adverse Event	Cumulative % (*n*/*N*)
Endophthalmitis	0
Hyphema	0.2 (1/662)
Hypopyon	0
IOL dislocation	0.8 (5/662)
Cystoid macular edema	0
Pupillary block	0
Retinal detachment	0.6 (4/662)
Surgical reintervention	4.2 (28/662)
Corneal edema	0
Iritis	0.5 (3/662)
Raised IOP requiring treatment	0
Preventive lens repositioning	2.1 (14/662)
Refractive procedures	2.6 (17/662)
Nd:Yag peripheral iridotomy	3.0 (20/662)
Aqueous release	1.8 (12/662)
Resuture wound leak	1.2 (8/662)

Table 99.4 Percent cumulative endothelial cell loss for various anterior chamber depths from 6 months to 3 years

Anterior Chamber Depth	Cumulative Cell Loss (%)	Number of Patients
3.0–3.1 mm	9	7
>3.2–3.4 mm	2.9	22
>3.4–3.9 mm	4.1	51
>3.9 mm	6.3	31

have been associated with corneal edema following cataract surgery (Table 99.4). Eyes with anterior chamber depths less than 3.2 mm displayed the greatest endothelial cell loss at 3 years (9.0%), while those with anterior chamber depths greater than 3.2 mm experienced significantly lower endothelial cell loss. The rate of endothelial cell loss was greatest between the second and the third year. The loss rate was lowest during the first 6 months. The rate of endothelial cell density loss in implanted eyes is 1.8% per year based on a regression analysis. If the rate of endothelial cell loss remains the same over years then 25 years after the implantation 39% of patients can be expected to lose 50% of their corneal endothelial cells. At this time there is uncertainty as to the long-term implications associated with this degree of endothelial cell loss. Because the trial was only 3 years in duration, there remains an important need for a study to determine the seriousness of the endothelial cell loss. Meanwhile, it is prudent to regularly assess patients' corneal endothelial cells following implantation of Artisan lenses.

Since FDA approval, numerous papers have been published regarding the efficacy and safety of the Artisan/Verisyse lens. It appears to be very effective in providing a safe and accurate method for correcting myopic refractive error. Early results from hyperopic and astigmatic treatments using Artisan lenses appear promising.[14] Furthermore, patient satisfaction rate following lens implantation appears to be very high.

CONCLUSION

The anterior chamber phakic intraocular lens technology offers many advantages in refractive surgery. It is reversible, accurate, predictable, and patient satisfaction appears to be high. However, it is also associated with certain adverse events that can be potentially serious including endophthalmitis, corneal decompensation, and retinal detachment. Successful clinical outcomes require careful preoperative screening, counseling, and examination as well as diligent postoperative follow-up examinations.

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100 Phakic posterior chamber lens (pPIOL)

Michael A. Lawless, Christopher Hodge

INTRODUCTION

Phakic intraocular lenses offer a number of advantages over competing refractive surgical techniques, spectacles, and contact lenses. Waring,[1] in an editorial in 1991, spoke of the long history of phakic intraocular lenses within ophthalmology, and two papers from as far back as 1990[2,3] both demonstrate the refractive accuracy of phakic intraocular lenses and show their superiority over myopic epikeratoplasty and myopic keratomileusis at that time.

Specifically a phakic intraocular lens has four potential advantages over alternative refractive techniques:[4]

1. The crystalline lens is retained allowing accommodative function in younger patients and protecting against the vitreoretinal side effects of clear lens extraction.
2. There is no disturbance to the natural prolate corneal shape, which has evolved over millennia to provide the best anterior refractive surface of the eye.
3. The phakic intraocular lens is potentially removable and exchangeable.
4. As wound healing is not a variable the refractive result tends to be predictable, and if the desired endpoint is not achieved, it is fairly easily adjustable with modern corneal refractive surgery as a bioptics procedure.

The disadvantages of phakic intraocular lenses relate to the risks of an intraocular operative procedure. In addition there are specific risks and issues related to where the phakic intraocular lens is placed; whether it be the anterior chamber, the iris plane, or behind the iris. One of the advantages of posterior chamber phakic intraocular lenses is that they remain behind the pupil eliminating edge effects as a source of optical aberration. This chapter concentrates specifically on phakic posterior chamber intraocular lenses (pPIOL).

HISTORY TO THE PRESENT DAY

Fyodorov began work in the 1980s at the Moscow Eye Institute, and by 1990 the collar button lens, which was designed to protrude through the iris, was altered so that it could be placed entirely within the posterior chamber.[5] The most frequent complication was decentration because the overall length of 10–11 mm was too short for stable positioning. There were also limitations related to surgical technique at that time with minimal or no ophthalmic viscosurgical device (OVD) used.

Fechner used the Adatomed (Chiron-Adatomed, Munich, Germany) lens entirely within the posterior chamber. The lens had a wide range of powers, an overall length of 12.5 mm and a 5.5 mm optic. This model fell into disuse because of anterior fibrotic damage in the crystalline lens at the contact zones with the thick edges of the pPIOL.[6]

There are three pPIOLs currently in use around the world in any number. These are the phakic refractive lens (PRL), STAAR implantable collamer lens (now known as the Visian ICL), and the Stick lens.

The PRL is made of ultra thin hydrophobic silicone with a refractive index of 1.46. The diameter of the optic is 4.5–5.5 mm depending on the lens power. The posterior base curve aims to mimic the anterior surface of the crystalline lens (10.0 mm of curvature). The front surface curvature varies with correction. The central thickness is less than 0.5 mm, is constant for myopic lenses, and varies with hyperopic lenses. The edge thickness is always less than 0.2 mm. The edge thickness is constant in hyperopic lenses and varies in myopic lenses. The company claims the lens has no anatomical fixation site and floats on a layer of aqueous humor inside the posterior chamber exerting no pressure on the ciliary structures, and without coming into contact with the anterior capsule or the crystalline lens. Generally one single size is used, 11.3 mm for myopic eyes and 10.6 mm overall length for hyperopic eyes. The PRL lens, distributed by Zeiss-Meditec (Carl Zeiss Meditec AG, Dublin, CA), was formally marketed by Ciba Vision (Ciba Vision Corporation, Duluth, GA) after the commercial rights were purchased in 2000 from the developer, Medennium International Vision (Medennium Inc, Irvine, CA).[7]

In the early 1990s, STAAR (STAAR Surgical, Monrovia, CA) patented a material made of 60% poly-HEMA, water (36%), benzophenone (3.8%), and called it a collamer (collagen-copolymer).[8] The lens was called the ICL (implantable contact lens) as initially it was thought that it would come into contact with the anterior surface of the crystalline lens.[9]

In 1993 the first ICL prototypes were implanted.[10] The optic was small (3.5–4.5 mm) and a significant minority of patients developed early glaucoma leading to the subsequent use of two peripheral iridotomies.[11] In 1994 a new version became available with an overall length of 11.5 mm and an optic of 4.5 mm. Decentration was an issue, but the main problem was undercorrection. These early ICL designs had no markings and version 2 (V2) was produced in 1996 with orientation markings on the haptics. Versions V2 and V3 resulted in an unacceptable number of anterior subcapsular lens opacities (9.2% of the US Food and Drug Administration (FDA) cohort V3 series).[12]

The current model is the Visian ICL V4, a rectangular one piece lens 7.5–8.0 mm wide, available in four overall lengths (11.5 mm, 12.0 mm, 12.5 mm, and 13.5 mm for myopia, and 11.0 mm, 11.5 mm, 12.0 mm, and 12.5 mm for hyperopia). The optic diameter ranges from 4.65 mm to 5.5 mm in myopic lenses, depending on the dioptric power, and is always 5.5 mm for hyperopia. The design change has been in the vaulting. The V4 has an additional 0.13–0.21 mm of anterior vault due to the steeper radius of curvature of the base curve which varies depending on the dioptric power. Myopic lenses are plano concave with the plano surface facing anteriorly, and hyperopic lenses are meniscus shaped, being convex on the anterior surface.

The Stick lens (IOL Tech, La Rochelle, France) is the newest of the pPIOLs. It is a single piece lens made of hydrophilic 28% water, soft acrylic material. Its feature is that it sticks firmly to the anterior surface of the crystalline lens, hence the name. The anterior radius of curvature varies, and the overall length of 11.5 mm, posterior shape, and curvature are fixed to match the anterior surface of the crystalline lens. There are four closed loop haptics with large apertures, which it is claimed to allow the maintenance of supply of nutrients to the crystalline lens from aqueous flow, and it is also claimed that this means that vaulting is not necessary to prevent cataract formation.[13]

RESULTS: EFFICACY

The most powerful data comes from the ICL myopia study published in 2004.[14] The efficacy variables are shown in Table 100.1. This study examined 526 eyes of 294 patients with a follow up retention of 77.2% at 3 years. All eyes received the V4 ICL lens design between November 1998 and December 2002. At 3 years 59.3% of eyes had 20/20 or better unaided and 94.7% achieved 20/40 (if best spectacle corrected acuity was 20/20 or better preoperatively and emmetropia had been targeted). A total of 67.5% of patients were within 0.5 D and 88.2% were within 1 D of intended correction. As Table 100.1 shows, for the 7–10 D preoperative myopia level, which would be the commonest range where the lens would be considered as an alternative to corneal refractive surgery, 54.2% achieved 20/20 or better unaided, and 86.9% were 20/40 or better, with 94.3% very or extremely satisfied and no patients unsatisfied.

Figure 100.1 shows the stratified uncorrected acuity for those with less than 7 D of myopia, 7–10 D and greater than 10 D of preoperative myopia where a targeted endpoint was within 0.5 D of emmetropia and preoperative best spectacle corrected acuity was 20/20.

Contrast sensitivity was analyzed at two study sites using the stereo-optical Optec X1600F2 vision tester, performed with best spectacle correction using light levels of 3 candella/m^2 after 10 min of dark adaptation with and without a glare source of 10 lux. Testing was performed at 1.5, 3, 6, 12, and 18 cycles per degree

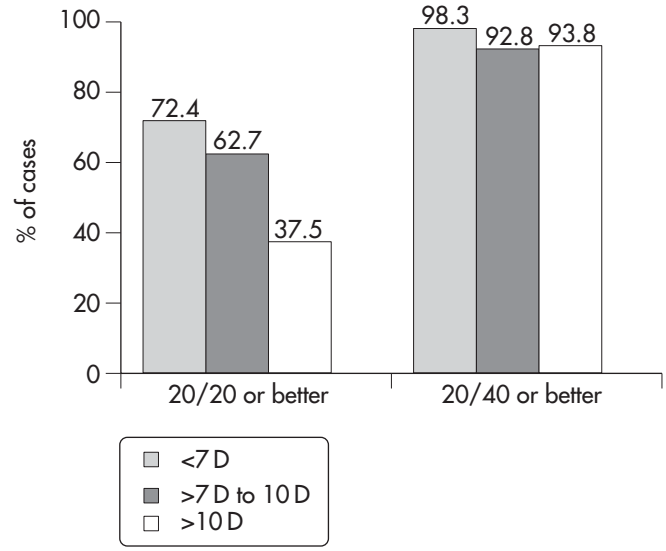

Figure 100.1. Three-year postoperative uncorrected visual acuity stratified by preoperative myopia in the subset of patients with preoperative best spectacle-corrected visual acuity of 20/20 or better and in those targeted to within 0.5 D of emmetropia. Reprinted from Sanders et al. US FDA clinical trial of the implantable collamer lens (ICL) for moderate to high myopia. Three-year follow-up. Ophthalmology 2004; 111: 1683–1692, ©2004 with permission from the American Academy of Ophthalmology.

(cpd). The results are shown in Figures 100.2 (without glare sources) and 100.3 (with glare sources). Under mesopic conditions there was no loss of contrast sensitivity at any spatial frequency, and a statistically significant improvement in contrast at 6 and 18 cpd. When a glare source was used, there was a significant improvement in contrast sensitivity at all spatial frequencies except 1.5 cpd. These excellent contrast sensitivity results are in keeping with clinical observations of others, and are to be expected with the good quality optics of the ICL and the retention of normal corneal asphericity.

Table 100.2 shows the change in subjective patient symptoms before and 3 years after surgery. Across five categories of glare, halo, double vision, night vision, and night driving, the most common subjective response was that there was no change, ranging from a low of 76% for night driving up to 97% for double vision. There was a fairly even spread between improvement and worsening of the five subjective areas.

A comparative multi-center study comparing the ICL with LASIK in eyes with moderate to high myopia (8–12 D) showed the ICL to be superior in both uncorrected visual acuity and best spectacle corrected acuity. The ICL had significantly fewer eyes losing two or more lines of BCVA and significantly more eyes gaining two or more lines of BCVA.[15]

Accurate correction of myopia and hyperopia with the ICL has been confirmed in a study published by Lackner et al, detailed in Figure 100.4.[16] The preservation of excellent visual quality was also confirmed by Jiménez-Alfaro et al[17] in 2001 in a contrast sensitivity study after implantation of 20 eyes in 10 patients with the ICL with a mean preoperative myopia of 14.10 D. The CSV 1000 (Vector Vision Inc, Dayton, OH) was used and showed contrast sensitivity improved after surgery at all spatial frequencies (3, 6, 12, and 18 cpd).

The PRL has shown excellent efficacy data. For uncorrected visual acuity within the range −7.00 to −20 D, 71.2% of eyes were within ±1 D of emmetropia, and 88.5% were within ±1.5 D of emmetropia.

Table 100.1 Summary of key efficacy variables stratified by preoperative spherical equivalent (SE*)

		Preoperative SE			
		≤7 D Myopia (%)	>7–10 D Myopia (%)	>10 D Myopia (%)	TOTAL (3–20 D)
Uncorrected visual acuity	20/20 or better	68.1	48.9	21.9	40.8
	20/40 or better	97.2	86.3	70	81.3
UCVA (if BSCVA >20/20)	20/20 or better	71.4	54.2	32.5	51.6
	20/40 or better	98.4	86.9	83.8	88.8
UCVA for patients with preoperative BSCVA ≥20/20 (for eyes targeting emmetropia)	20/20 or better	72.4	62.7	37.5	59.3
	20/40 or better	98.3	92.8	93.8	94.7
Predictability: attempted vs. achieved	±0.50 D	84.7	71	56.9	67.5
	±1.00 D	97.2	93.1	80	88.2
	±2.00 D	100	100	95.6	98.1
Patient satisfaction	Unsatisfied	0	0	1.4	0.6
	Fairly/ moderately satisfied	4.2	5.7	10.2	7.3
	Very/extremely satisfied	95.8	94.3	88.4	92.1

*Data from 3 years postoperatively.

UCVA = uncorrected visual acuity.

BSCVA = best spectacle-corrected visual acuity

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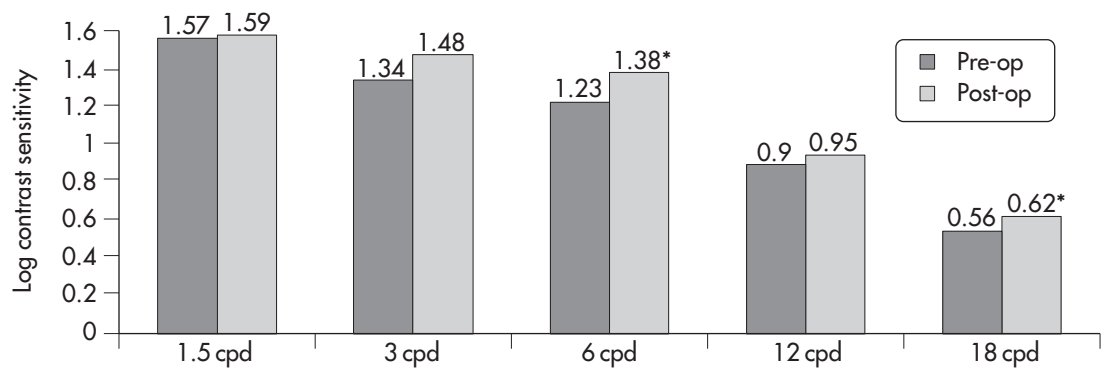

Figure 100.2. Log contrast sensitivity under mesopic illumination (3 candelas/m²) without a glare source. cpd = cycles per degree. *Statistically significantly different at a level of 0.05. Reprinted from Sanders et al. US FDA clinical trial of the implantable collamer lens (ICL) for moderate to high myopia. Three-year follow-up. Ophthalmology 2004; 111: 1683–1692; © 2004, with permission from the American Academy of Ophthalmology.

The preoperative vs. postoperative spherical equivalent is shown in Figure 100.5.[18]

RESULTS: COMPLICATIONS

Making sense of complications of pPIOLs first requires an understanding that the natural history of the average candidates for these lenses, that is the high myopes, have an increased risk of sight-threatening problems during their lifetime even without intraocular surgery. In highly myopic eyes the incidence of retinal detachment is increased, with an increased rate of posterior staphyloma, atrophic thinning of the choroid and sclera with variable degrees of vitreous syneresis and posterior vitreous detachment.[19,20] Highly myopic eyes are also more likely to develop chronic open angle glaucoma and pigmentary glaucoma, and age-related cataract appears earlier than in the normal population.

Highly hyperopic eyes are more at risk of angle closure glaucoma. A list of complications from a meta-analysis of the literature for

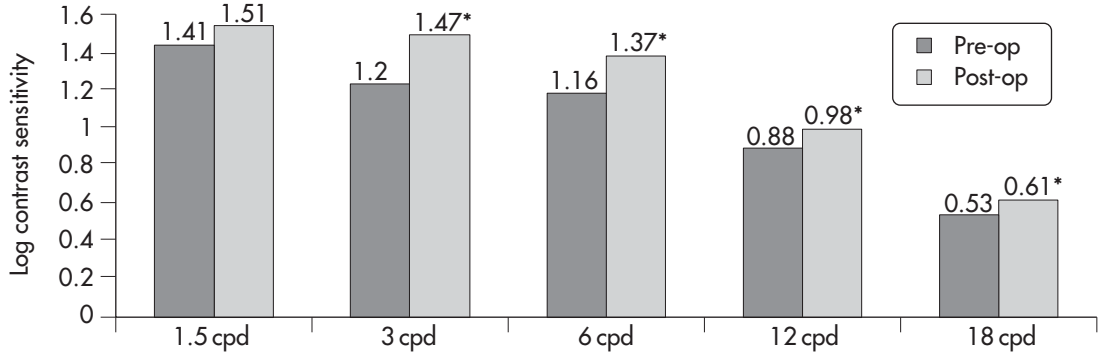

Figure 100.3. Log contrast sensitivity under mesopic illumination (3 candelas/m²) with a glare source (10 lux). cpd = cycles per degree. *Statistically significantly different at a level of 0.05. Reprinted from Sanders et al. US FDA clinical trial of the implantable collamer lens (ICL) for moderate to high myopia. Three-year follow-up. Ophthalmology 2004; 111: 1683–1692; ©2004, with permission from the American Academy of Ophthalmology.

Table 100.2 Change in subjective patient symptoms (before to 3 years after the operation)

	Glare		Halos		Double Vision		Night Vision		Night Driving	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Improved 2 categories	10	2.8	8	2.3	0	0	11	3.1	12	3.6
Improved 1 category	32	9.1	24	6.9	4	1.1	31	8.9	34	10.1
No change	275	78.3	278	79.4	341	97.2	266	76.0	255	76.1
Worsened 1 category	30	8.5	30	8.6	6	1.7	34	9.7	25	7.5
Worsened 2 categories	4	1.1	10	2.9	0	0	8	2.3	9	2.7

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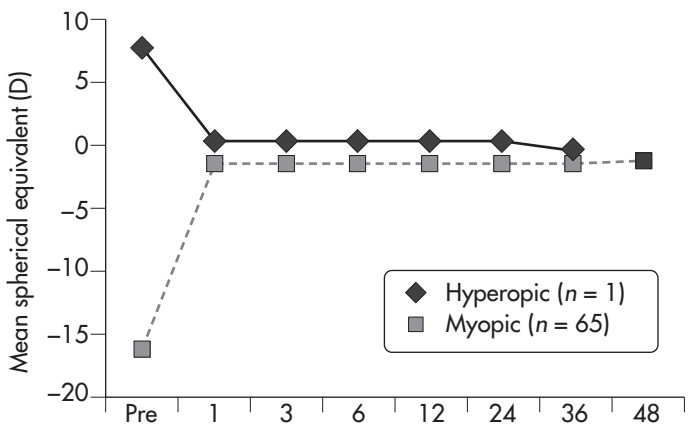

Figure 100.4. Mean spherical equivalent for hyperopic and myopic patients before and after implantable contact lens implantation. D = Diopters. Reprinted from Lackner B, Pieh S, Schmidinger G, et al. Outcome after treatment of ametropia with implantable contact lenses. Ophthalmology 2003; 110: 2153–2161, ©2003, with permission from the American Academy of Ophthalmology.

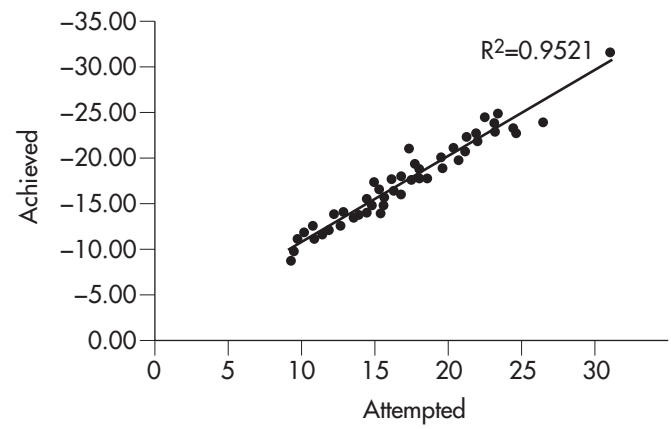

Figure 100.5. Preoperative versus obtained spherical equivalents. Reprinted from Donoso R, Castillo P. Correction of high myopia with the PRL phakic intraocular lens. J Cataract Refract Surg 2006; 32: 1296–1300, ©2006, with permission from ASCRS & ESCRS.

various pPIOLs is shown in Table 100.3. For reliable data with reasonable follow up, the ICL myopia study group gives the most comprehensive analysis. The key safety variables are shown in Table 100.4. In general, the higher the degree of preoperative myopia the greater the incidence of complication or adverse event. In this study all five of the eyes with persistent loss equal to two lines of best spectacle corrected visual acuity occurred in those with greater than 10 D of myopia. All of the subsequent cataract extractions and three of four of the ICL repositioning occurred in those with greater than 10 D of myopia.

The induction of lens opacities or clinically significant cataract is of considerable interest because of the close proximity of these

Table 100.3 Meta-analysis of literature reported complications of available pPIOLs

Chiron Adatomed Phakic IOL

Complications	No. of papers	No. of cases reported	Total no. of eyes	No. of eyes explanted	Percentage Complication of total reported eyes (*N* = 91)
Anterior Sub capsular Cataract (ASCC)	2	40	91	18	44.0%

Fyodorov Phakic IOL

Complications	No. of papers	No. of cases reported	Total no. of eyes	No. of eyes explanted	Percentage Complication of total reported eyes (*N* = 19)
Cataract	1	9	17	8	47.4%
Lens Dislocation	1	2	2	2	10.5%

Staar ICL (All Versions)

Complications	No. of papers	No. of cases reported	Total no. of eyes	No. of eyes explanted	Percentage Complication of total reported eyes (*N* = 1396)
Cataract	7*	20	614	11**	1.4%
ASCC	10*	73	1069	24**	5.2%
Pupillary Block (Glaucoma)	8*	14	125	4**	1.0%
Pigment Dispersion	2	13	21	0	0.9%
Increase in IOP from Preop	1*	18	32	0	1.3%
Retinal Detachment	2*	2	143	2**	0.1%
Retinal Tear	1	2	2	2	0.1%

Phakic Refractive Lens (PRL)

Complications	No. of papers	No. of cases reported	Total no. of eyes	No. of eyes explanted	Percentage Complication of total reported eyes (*N* = 90)
Cataract	2	3	73	3	3.3%
Pupillary Block (Glaucoma)	1*	2	14	2**	2.2%
Retinal Detachment	1	1	1	0**	1.1%
Lens Decentration	2*	4	73	2	4.4%
Lens Dislocation	1	2	2	2	2.2%

*Complications reported in other papers. **No. not available in all papers.

Unknown Phakic IOL

Complications	No. of papers	No. of cases reported	Total no. of eyes	No. of eyes explanted	No. of eyes explanted
Retinal Detachment	1	4	4	4	4
Retinal Tear	1	2	2	0*	0*

**No. not available in all papers

Table 100.4 Summary of key safety variables stratified by preoperative spherical equivalent (SE)

	Preoperative SE			
Safety Events	**<7 D (*n* = 112)**	**>7–10 D (*n* = 174)**	**>10 D (*n* = 240)**	**Total (3–20 D) (*n* = 526)**
Best spectacle-corrected visual acuity worse than 20/40 at 1–3 years postoperatively (if 20/20 or better preoperatively)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Loss of ≥2 lines BSCVA (persistent)	0 (0%)	0 (0%)	5 (2.1%)	5 (1%)
Increase >2 D cylinder (3 years postoperatively)	0 (0%)	0 (0%)	2 (0.8%)	2 (0.4%)
ICL repositioning	1 (0.9%)	0 (0%)	3 (1.2%)	4 (0.8%)
ICL replacement, then removal	0 (0%)	1 (0.6%)	0 (0%)	1 (0.2%)
ICL replacement	3 (2.7%)	4 (2.3%)	1 (0.4%)	8 (1.5%)
ICL removal/cataract extraction/ with/without IOL	0 (0%)	0 (0%)	3 (1.2%)	3 (0.6%)
Lens opacities classification system ≥ trace, anterior subcapsular Clinically significant cataract*	1 (0.9%)	7 (4%)	6 (2.5%)	14 (2.7%)
Anterior subcapsular	0 (0%)	0 (0%)	2 (0.8%)	2 (0.4%)
Nuclear	0 (0%)	0 (0%)	5 (2.1%)	5 (1.0%)
Intraocular pressure >25 mmHg or >10 mmHg. Increase from before the operation (at last visit†)	0 (0%)	0 (0%)	1 (0.4%)	1 (0.2%)
Endophthalmitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increased IOP on medications	0 (0%)	1 (0.6%)	1 (0.4%)	2 (0.4%)
Corneal haze/edema (after 1 week postoperatively)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Retinal detachment	0 (0%)	1 (0.6%)	2 (0.8%)	3 (0.6%)

*Any anterior subcapsular/posterior subcapsular score of trace or more at any postoperative visit with increase in glare, ≥2-line loss BSCVA, or nuclear opalescence ≥2.0 also symptomatic.

†Includes IOP from unscheduled visit 3 months or more after the operation.

BSCVA = Best spectacle-corrected visual acuity; D = Diopters; ICL = Implantable Collamer Lens; IOP = intraocular pressure; LOCS = Lens Opacities Classification System.

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lenses to the natural crystalline lens. Anterior lens opacities (not necessarily clinically significant) were observed in six (2.5%) eyes in the greater than 10 D group, seven eyes (4%) in the 7–10 D group, and only one eye (0.9%) in the less than 7 D group. Of those lens opacities considered clinically significant, both nuclear and anterior subcapsular, all occurred (seven of seven eyes) in the greater than 10 D myopic group. The average age of the study population was 36.5 years (range 22–45) and development of lens opacities may differ in an older population. The three eyes which suffered retinal detachment in this series had preoperative myopia of −9.50, −16.25, and −17.75 D. Perkins[21] has estimated that the expected risk of retinal detachment in phakic myopes is as high as 0.68% per year. Given the follow up in this FDA series of high myopes, as many as nine retinal detachments would be expected, whereas only three were observed. Retinal detachment in one eye produced the only severe nonreversible visual loss in the entire FDA study.

An endothelial cell sub-study was performed in over 200 eyes at each of the preoperative, 3 month, 1 year, 2 year, and 3 year postoperative visits. Sixty-seven eyes were also evaluated 4 years postoperatively. Cumulative cell loss over the first 3 years was 8.4–9.7% depending on the method of analysis. Fifty-seven eyes were examined at both 3 and 4 years postoperatively and the mean endothelial

cell densities were 2354 cells/mm^2 and 2355 cells/mm^2 respectively. The 3–4 year percentage cell change was a 0.1% gain (90% confidence interval, 1.4–1.6%). There was no decrease in percentage hexagonality or increase in co-efficient variation at any interval studied.

Endothelial cell analysis is a relatively controversial issue. It is expected that there will be a small and hopefully insignificant cell loss at the time of surgery, but the area of concern is the possibility of further ongoing cell loss through a patient's life. If this mechanism was due to intermittent mechanical contact, then clearly a lens in the posterior chamber is safer than any other. Dejaco-Ruhswurn and colleagues have suggested in a small study that there may be other mechanisms, specifically a noncontact inflammatory mechanism for ongoing endothelial cell damage.[22] They reported an aggressive loss with rates changing from 5.5% at 1 year, 7.9% at 2 years, 12.9% at 3 years, and 12.3% at 4 years. Only the first year data was statistically significant and the cell morphology indices remained stable. Unpublished data by Reinstein et al[8] on 12 eyes implanted with the ICL in one eye and evaluated for 8 years, with the fellow eye used as control, showed an endothelial cell loss rate similar to that of physiological aging (about 0.7%) per year in the ICL eyes. A complication specific to the PRL was described by Donoso et al.[18] In a series of 53 eyes of 39 patients, there were two cases of inferotemporal subluxation of the PRL through the zonules with no iatrogenic or predisposing factors. Both lenses were explanted through the original clear corneal incision. The authors note that in a personal communication seven PRL dislocations into the vitreous and six PRL subluxations into the anterior chamber were noted in Italy and Spain, and their suggestion was 'until the causes of subluxation are explained, we believe it is prudent to use the STAAR Surgical ICL rather than the PRL IOL.'

Intermittent ICL contact with the crystalline lens during accommodation has been addressed.[23,24] As the sulcus retracts with accommodation no significant changes in distance between the ICL and crystalline lens were found. The ICL vaulting increases as necessary, compensating the 200–600 μm forward movement of the anterior lens surface. Behavior of ICLs in relation to the crystalline lens during accommodation varies with age. The position shift is dependent on the initial vault and the ability of the anterior lens surface to bulge forward. In contrast under photopic environmental conditions or after application of pilocarpine, pupil constriction reduces the vault height, forcing the ICL against the crystalline lens.

ANATOMIC CONSIDERATIONS

Compared with traditional intraocular lenses used with cataract surgery, phakic intraocular lenses have a relatively small anatomic space in which to be placed.[4] Accurate sizing of the pPIOLs is essential for a successful long-term result. Limbal measurements of white to white distance, particularly in the horizontal axis, are commonly used to predict the anterior chamber diameter and ciliary sulcus diameter. This external measure correlates poorly. Werner et al[25] compared vertical and horizontal white to white measurements with direct anatomic measurements in phakic human eye bank eyes and found a positive correlation only between the vertical white to white distance and the anterior chamber angle diameter. There was no correlation between the horizontal white to white distance and the anterior chamber angle diameter; nor was there correlation between either technique of external measurement and the ciliary sulcus diameter.

There are five methods for gaining information about anterior chamber depth and anterior segment configuration:

1. Traditional A-scans ultrasound with an immersion technique giving an excellent measurement of anterior chamber depth.
2. Partial coherence inferometry (PCI) using the Zeiss IOL master for anterior chamber depth.
3. Very high frequency digital ultrasound, which was developed from ultrasound biomicroscopy (UBM). The newest device is the Artemis II, which gives the most useful information regarding anterior segment anatomy.
4. Scheimpflug imaging using the Pentacam system.
5. Anterior segment optical coherence tomography (OCT) using the Zeiss Visante system, which is limited by its inability to directly image behind the iris.

The five modalities are compared in Table 100.5.

Table 100.5 Summary table of methods for measuring anterior chamber anatomy

	Company	Method	Resolution	Imaging Ability
A Scan	Various	Ultrasound	±100 μm	ACD
IOLMaster	Carl Zeiss	Partial coherence interferometry	±10 μm	ACD White to white
Visante	Carl Zeiss	Ocular coherence tomography	Axial ±18 μm Transverse ±60 μm	ACD AC angle Iris and lens position (through pupil)
Artemis 2	Ultralink	Arc Scanning VHF Ultrasound with digital signaling processing	Approx. ±1.2 μm	ACD AC angle Vault Sulcus to sulcus diameter
Pentacam	Oculus	Scheimpflug principle for slit image photography	±39 μm	ACD AC angle Vault

ACD = anterior chamber depth.

Table 100.6 Widely accepted criteria for implanting phakic IOLs

• Ages 21 to 50
• General good health
• Stable manifest refraction (±0.50 D 6 months apart)
• Ammetropia not correctable with excimer laser surgery
• Unsatisfactory vision with intolerance of contact lenses or spectacles
• ACD (endothelium to anterior crystalline central distance) ≥2.8 mm Note: ≥2.5 mm for PRL
• Irido-corneal aperture ≥30° (Shaffer grade 3 and 4 or Scheie grade 0 and 1)
• Endothelial cell count >2500 cells/mm^2 at 20 years of age
• Endothelial cell count >2000 cells/mm^2 at 40 years of age
• No ocular pathology (corneal disorders, glaucoma, uveitis, cataract, maculopathy, etc.)
• No previous ocular surgery

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PATIENT SELECTION

The FDA has approved the Visian ICL for adults 21–45 years of age to correct myopia from −3.00 to −15.00 D with less than or equal to 2.5 D of astigmatism, and to reduce myopia greater than 15 D and up to 20 D with less than or equal to 2.5 D of astigmatism, both with an anterior chamber depth of 3.0 mm or greater and a stable refractive history (within 0.5 D) for 1 year prior to implantation. The generally accepted criteria are shown in Table 100.6. The impact of the rapidly evolving anterior segment imaging techniques is yet to be established in regular clinical practice.

To summarise, ideal candidates are mature young patients, able to make full advantage of the accommodation potential of their natural lens, but having high ametropia not accurately or safely correctable with excimer laser surgery.

SURGICAL TECHNIQUE

The patient is prepped and draped as for routine cataract and lens surgery. Topical anesthesia, with or without sedation, is the standard method, and wide dilatation is required. A week prior to intraocular surgery, two laser peripheral iridotomies at the 11 and 1o'clock positions should be performed.

The lens is placed via an injection technique through a 3.0 mm clear corneal temporal incision. The correct loading of the ICL in the cartridge injector is essential. Using a modified McPherson forceps with long blunt curved tips, the lens is grasped and checked under the microscope. The ICL has two tiny holes on the footplates at the distal right and proximal left to indicate the anterior side. The current PRL has no landmarks. The cartridge is partially filled and lubricated with saline and OVD, and the lens is normally loaded dome up. A piece of soft material (foam tip) is positioned to protect the lens from contact with the plunger of the shooter.

Two side port incisions of 1.0 mm are created and a cohesive OVD substance, such as Ocucoat, is normally used. The cartridge is inserted bevel down. The tip of the injector should only just penetrate the wound. The lens is injected and moves along the funnel in a cylindrical fashion gradually unfolding as it enters the chamber. Retro-pupillary positioning of the footplates involves maneuvering the haptics through the side ports with a sand-blasted 'tucker.' Only a very small degree of dialing is acceptable and manipulations must be smooth and gentle to avoid damage to the crystalline lens and iris.

Once positioned correctly the OVD must be removed as completely as possible using a bimanual irrigation aspiration technique particularly to reach the OVD trapped beneath the ICL. Usually, acetylcholine is injected intraocularly to constrict the pupil, and the wound hydrated.

SPECIAL CLINICAL CONSIDERATIONS WITH THE PHAKIC POSTERIOR CHAMBER INTRAOCULAR LENS

BIOPTICS

Bioptics means combining a phakic intraocular lens with corneal refractive surgery. This is particularly appealing in high ametropia because it combines both a corneal tissue sparing approach with the ability to maximize the effective optical zone. It may be part of a planned procedure, particularly with preoperative astigmatism, or it may be unplanned where there is a residual refractive error after phakic intraocular lens implantation.

Three issues are worth considering. If corneal refractive surgery follows phakic posterior lens implantation, when is the 3.0 mm temporal corneal incision stable enough to withstand the application of a microkeratome or femtosecond suction device? When is the refractive error stable to allow an accurate correction? Thirdly, is the application of a microkeratome with raised intraocular pressure likely to cause damage to the corneal endothelium because of the phakic lens, or is it possible to dislocate the lens?

If bioptics is a planned approach some clinicians suggest the creation of a LASIK flap prior to phakic IOL surgery. We personally do not do this routinely but prefer to wait 2–3 months following surgery and perform corneal refractive surgery on its merits. Two to three months assures both refractive stability and tectonic security of the wound. Often relatively small residual refractive errors need to be dealt with, and surface ablation may be considered as a preferred technique.

ASTIGMATISM

Astigmatism is able to be treated with the Visian ICL but there are no reported cases in the literature. The astigmatic range of treatment is 1–4 D. The surgery is identical to routine ICL implantation but in addition the lens needs to be orientated to the appropriate axis. There are anecdotal good reports but it is reasonable to assume that the ICL will rotate in a significant minority of eyes to make this a less than ideal mechanism for dealing with astigmatism. It is probable that astigmatism, where clinically relevant, will continue to need to be treated with a bioptics corneal refractive approach.

CATARACT AND INTRAOCULAR LENS SURGERY AFTER PHAKIC POSTERIOR INTRAOCULAR LENS SURGERY

It may be the fate of all posterior chamber phakic intraocular lenses to be removed, and/or removed in conjunction with cataract and lens surgery. The largest study in the literature so far is by Morales et al.[26]

Of 215 patients (370 eyes with ICL implantation between 1997 and 2002) 56 eyes (15%) of 45 patients were found to have lens opacities of which 14 eyes (3.8%) of 12 patients had symptoms that required cataract and intraocular lens surgery. Of the 14 eyes 12 had original high myopia and 2 had hyperopia. Axial length was measured using the Sonogauge A scan, and the Hoffer Q formula was used for IOL calculations modified according to the desired postoperative refractive targets. No difficulties were encountered measuring the axial length in any way. The patients were prepped in the normal manner, and following injection of OVD the proximal haptics of the ICL were dislocated into the anterior chamber using a Bechert lens manipulator. The ICL was then grasped with forceps and extracted from the anterior chamber through a 3.2 mm incision. The anterior chamber was refilled with OVD and cataract surgery completed in a routine manner. No adverse events were observed. One eye had a tear in the posterior capsule unrelated to the ICL manipulation. The final manifest spherical equivalent was 0.30 D (standard deviation 1.07) and a range of +2.38 to −2.00 D. Ten eyes (71%) were within ±1 D of the calculated target. Since the speed of sound through the various materials of phakic intraocular lenses is widely different, and is not the same as the average velocity used to measure the eye, a variable but definite error occurs. Hoffer[27] concluded that the greatest effective error will occur with a silicone IOL in an eye with very high hyperopia, and the least effect will occur with a collamer lens (Visian ICL) in an eye with very high myopia.

CONCLUSION

Phakic posterior chamber intraocular lenses are approved for use within the USA, and will be part of the refractive surgery portfolio. They bridge the gap between corneal refractive surgery and cataract and lens surgery, requiring skills from both subspecialties. Specifically the highly developed surgical skills, which are an essential component of cataract and lens surgery, and also the perioperative decision making, most often associated with corneal refractive surgery. Given the success both in efficacy and safety of corneal refractive surgery (but also its definite limits) phakic intraocular lenses will form a minority of refractive surgical procedures in adults below the age of 50 years. The placement of a phakic intraocular lens in the posterior chamber is particularly appealing esthetically and from the viewpoint of protecting the endothelium and anterior chamber angle, and the main complication is cataract development. At least this is a complication that is amenable to effective treatment. Issues of particular lens design, and better methods of optimizing a lens size and shape to an individual anterior segment anatomy, will improve both the accuracy and safety, and therefore the popularity of this type of surgery over the next few years.

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101 Multifocal, pseudo-accommodative, and accommodative intraocular lenses

Jesse Chew, Liliana Werner, Randall J. Olson

Intraocular lenses (IOLs) are a standard part of cataract surgery and their rapid evolution over the last few decades has led to significant advances in their design. Today they not only restore the refractive power of the eye after surgery but also may provide special features to address presbyopia.

Presbyopia is an age-related process that can be described as a decrease in amplitude and speed of accommodation.[1] Accommodation occurs by contraction of the ciliary body and subsequent relaxation of the lens zonules resulting in increased lens curvature and hence optical power. Physiologic changes in the lens capsule, lens, ciliary muscle, and zonules have all been implicated as factors causing presbyopia.[2]

One means of achieving good distance and near vision after cataract surgery is with multifocal IOLs which use simultaneous vision. Separate near and distance images are superimposed on the retina. In this setting the optical power of the eye is not changed but the brain must interpret the images as separate, selecting the one related to the object of regard and suppress the other.[3] The other mechanism to achieve good distance and near vision in the eyes is to actually change the optical power of the eye, true accommodation, by having an IOL that moves or changes shape during contraction and relaxation of the ciliary muscle.

Accurate biometry is essential to obtain appropriate visual results for all types of IOL implantation. Axial length can be measured with immersion A-scan ultrasonography or laser interferometry. Contact A-scan ultrasonography should be avoided as it is prone to compression errors with resulting underestimation of true axial length. Similarly, manual keratometry is recommended as automated keratometers often lack the accuracy desired. Topography derived keratometry also lacks the accuracy of manual keratometry and is not recommended.

Previous corneal laser refractive surgery is not a contraindication to multifocal or accommodative IOL implantation. However, because of greater potential error in the keratometry readings, patients should be warned there is a higher chance of missing the target refraction and needing a secondary procedure to achieve emmetropia.

Patients with macular pathology and limited potential acuity after cataract surgery are not likely to gain sufficient benefit from a multifocal or accommodative IOL compared to a monofocal IOL. Patients who are at risk of having retina surgery/silicone oil should obviously not be implanted with any of the new lenses manufactured from silicone-based materials. All the pseudophakic lenses mentioned in this segment require precise centration and capsular bag support. They are not recommended for use without an intact capsulorrhexis and posterior capsule.

In this text, we describe some of the new IOLs currently available or under development, which are designed to relieve patients of presbyopia. It should be noted that none of the IOLs mentioned correct pre-existing astigmatism, which should be addressed with some form of refractive procedure for optimal visual results.

MULTIFOCAL INTRAOCULAR LENSES

Multifocal IOLs have multiple optical foci (typically two: one distance and one near) and thus even under the best of conditions one image will be in sharp focus, and one image will be blurred by a defocus aberration. By their very design, this lower optical quality as compared with monofocal IOLs is measured as lower contrast sensitivity in patients.[4] However, most published studies confirm that multifocal IOLs lead to good near visual acuity with distance correction. Still, they often fail to satisfy highly demanding patients, with an explantation rate of up to 7% for the Array IOL.[5] The presence of halos around image borders could outweigh the advantages of spectacle independence. As the strength of these halos depends on the luminance of the defocused image, multifocal IOLs can be distance dominant or near dominant, or even change dominance with pupil size.

Current multifocal optics address distance and near, but this may not meet the visual needs of all patients. An intermediate focal length is desired by some. Adding an intermediate distance to current diffractive designs would add greater complexity to an already complex manufacturing process that may degrade the optical quality of the lens.

Before choosing a multifocal IOL, precise biometry as well as careful patient selection are required. This is especially important because of concerns related to the possibility of higher incidence of decreased contrast sensitivity and glare with these lenses. Success

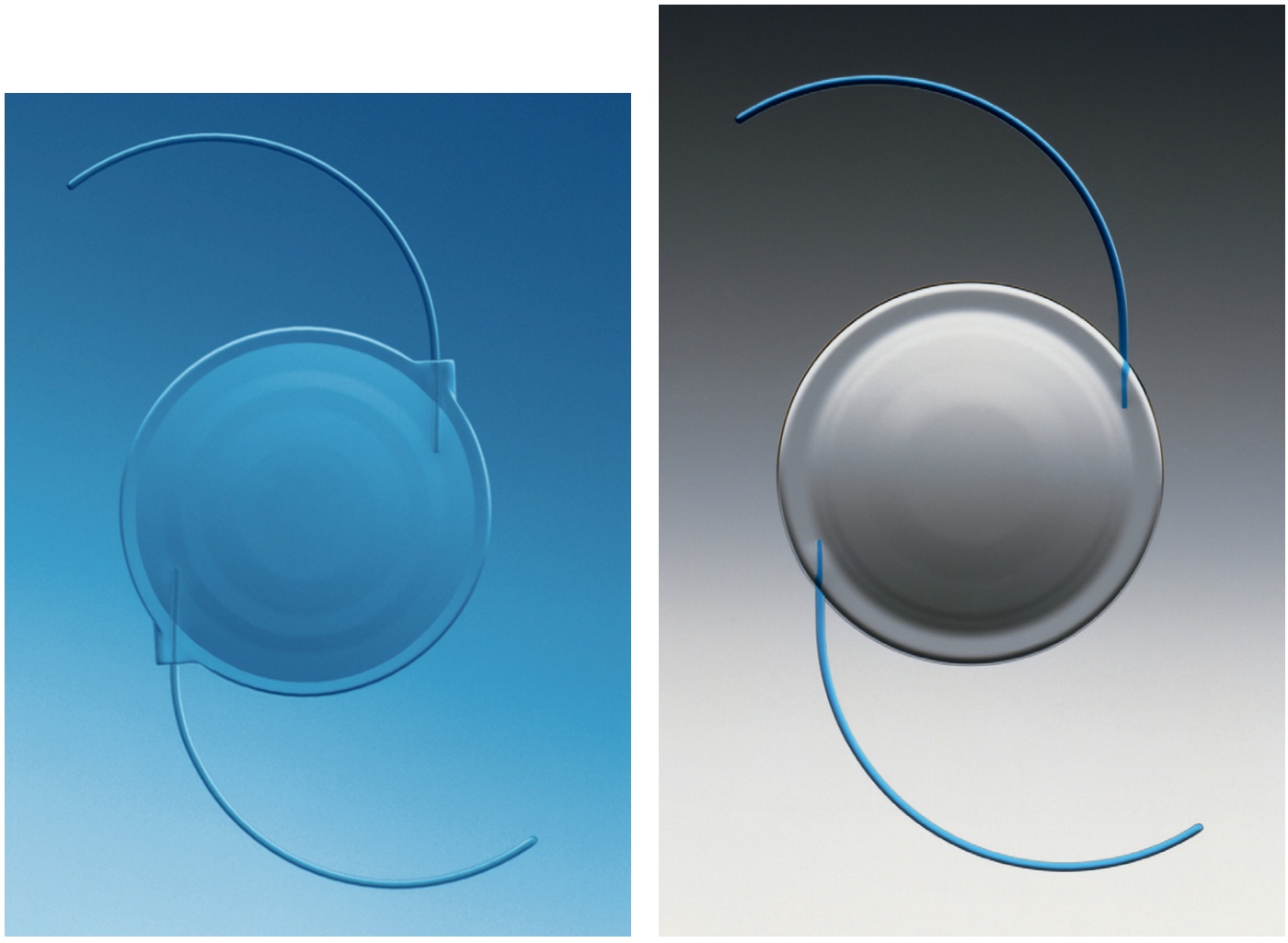
is also dependent on surgical technique: in-the-bag implantation and appropriate capsulorrhexis are necessary to ensure good centration, avoid myopic shift, and reduce posterior capsule opacification (PCO).[6] It is generally recommended by all manufacturers that multifocal IOLs be implanted bilaterally for better patient satisfaction.

PSEUDOPHAKIC MULTIFOCAL IOLs

The Array lens (Advanced Medical Optics, AMO, Santa Ana, CA) is a three-piece multifocal IOL manufactured from a silicone material having a refractive index of 1.46 (Fig. 101.1, *A*). It has angulated 'C' haptics made of extruded polymethylmethacrylate (PMMA). The optic is 6.0 mm in diameter with total length of the lens measuring 13.0 mm. It is the first multifocal IOL approved by the Food and Drug Administration (FDA). The optical design of this lens is a zonal-progressive multifocal optic with five concentric zones. The center of the lens is primarily for distance. All the other zones have distance and near in different proportions—approximately 50% of the light at distance, 37% at near, and approximately 13% for intermediate vision. The optical zone is 4.7 mm in diameter. No available light is lost as the optic is refractive and not diffractive. The addition power is +3.5 D at the lens plane and it is available from +6.0 to +30.0 D in 0.5 D steps.

Javitt et al compared bilateral implantation of the Array lens versus a monofocal lens with respect to visual function, patient satisfaction, and quality of life.[7] They found that those patients who had bilateral implantation of the Array obtained better uncorrected and distance-corrected near visual acuities and reported better overall vision, less limitation in visual function, and less spectacle dependency than patients with bilateral monofocal lenses. In the study by Schmitz et al reduced contrast sensitivity was found in the multifocal group (also implanted with the Array) only at the lowest spatial frequency without halogen glare.[8] The monofocal and multifocal groups of patients studied by them had no statistically significant differences in contrast sensitivity with moderate and strong glare. Their results suggest no difference in glare disability induced by halogen light similar to oncoming vehicle headlights for patients implanted with monofocal and multifocal IOLs.

More recently, AMO launched the ReZoom lens (Fig. 101.1, *B*). This is a second-generation, refractive, multifocal IOL, manufactured from a hydrophobic acrylic material with a refractive index of 1.47. It has angulated (5°) modified 'C' haptics made of 60% blue core PMMA monofilament. The overall diameter of the lens is 13.0 mm, with an optic diameter of 6.0 mm. The optical design of this lens features the Balanced View Optics Technology, with five concentric zones modified from the Array design to enhance func-



A B

Figure 101.1. Multifocal intraocular lenses manufactured by Advanced Medical Optics: *A*, Array. *B*, ReZoom.

tion and decrease glare (Fig. 101.2, *A* and *B*). Zones 1, 3, and 5 are distance dominant, while zones 2 and 4 are near dominant. The latter provide +3.5 D near add power at the IOL plane translating to +2.57 D add power in the spectacle plane and a near point of 39 cm or 16 inches. There is an aspheric transition between the different zones. The area of zone 4 was decreased by 55%, zone 3 was increased by 80%, and zone 2 was increased by 2% in relation to the Array™. The IOL is also available from +6.0 to +30.0 D in 0.5 D steps. It incorporates the new OptiEdge design, which combines three elements: a rounded anterior edge, a sloping side edge that is frosted, and a sharp, vertical posterior edge. The rounded anterior edge and frosted sloping edge were designed to minimize glare. It spreads out rays that pass through its surface and disperses light rays reflected from the edge. This is especially important with IOLs manufactured from hydrophobic acrylic materials, which have a higher refractive index than silicone materials. The frosted sloping side edge is designed to reduce the area of the surface that can cause internal reflections and to scatter internal reflections away from the retina. The squared posterior optic rim design has proven to be effective in the prevention of PCO. FDA approval came in March 2005. Clinical experience suggests that emmetropia should be targeted; however, any error in the refractive target that must occur should be on the side of hyperopia (±0.25 D) to provide good near vision as well as good distance vision for driving.[9]

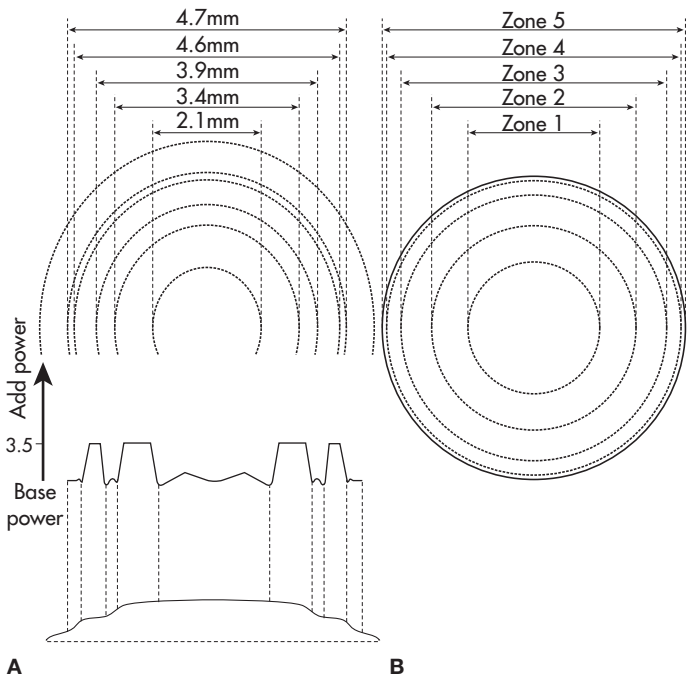


Figure 101.2. Schematic drawings showing the distribution of refractive power in the Array (*A*) and the ReZoom (*B*) lenses according to the different zones.

Clinical trials showed significantly better mean binocular and monocular distance corrected intermediate visual acuity in subjects with bilateral multifocal IOLs when compared with subjects with bilateral monofocal IOLs. A recent study by Longhena and associates compared the ReZoom IOL with the Array IOL.[10] Thirty patients (60 eyes) received a ReZoom or an Array after cataract surgery. Six month data showed 80% of ReZoom patients were spectacle independent compared to 60% of Array patients. No glare or halos were reported by 80% of ReZoom patients compared to 40% of Array patients.

Dick, in a study, compared visual acuity, photic phenomena, and defocus acuity curves of the ReZoom IOL and the Array IOL. Similar defocus curves were noted with both lenses, indicating good near and excellent intermediate vision. ReZoom patients reported spectacle independence 100% of the time for distance, 95% for intermediate, and 71% for near vision. There was also a lower incidence of photic phenomena with the ReZoom when compared to the Array IOL.[11]

Another currently available multifocal IOL is the ReSTOR lens (Alcon Laboratories, Fort Worth, TX). This apodized, diffractive IOL received FDA approval in March 2005, and is manufactured by using the platform of the hydrophobic acrylic single-piece AcrySof lens (Fig. 101.3, *A*). The lens has a length of 13.0 mm and the optic is 6.0 mm in diameter. The design incorporates 12 diffractive grating zones present on the anterior surface in the central 3.6 mm of the optic. Apodization is the gradual tapering of the diffractive steps from the center to the periphery. The largest diffractive step is at

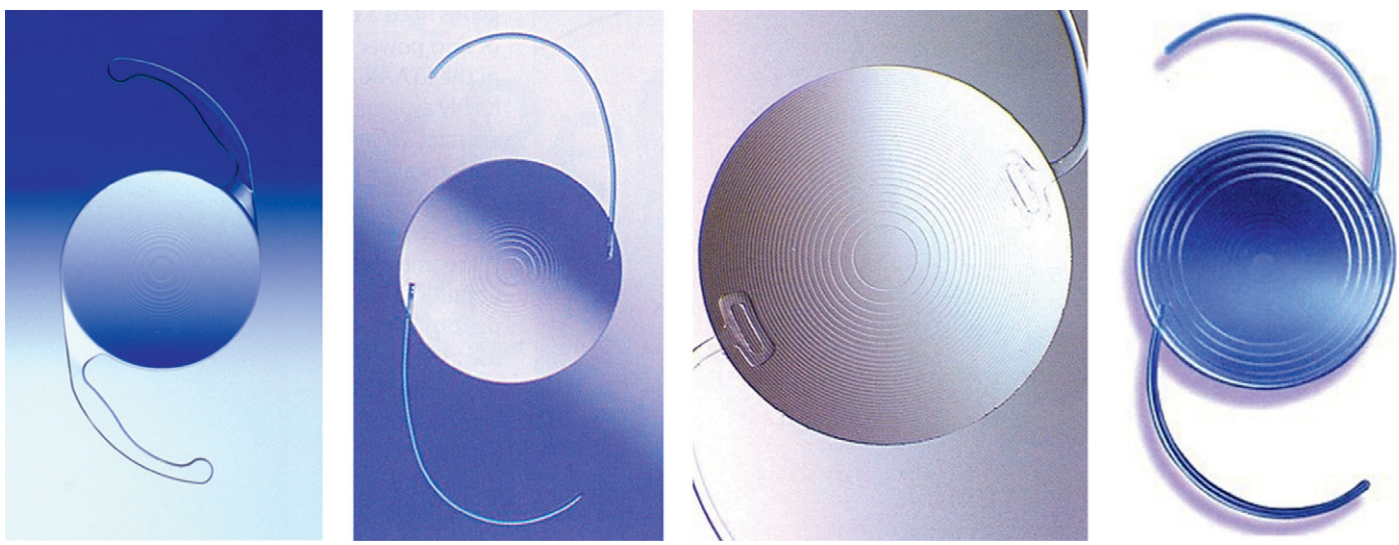


Figure 101.3. Photographs showing other currently available (or under evaluation) multifocal lenses. *A* and *B*, single-piece and three-piece ReSTOR lenses (Alcon). *C*, Multifocal Tecnis lens (AMO). *D*, Acri-Twin (Acri.Tec).

the lens center (about 1.3 μm) and sends most of the light to a near focus. As the steps move away from the center, they gradually decrease in size, blending into the periphery, and sending a decreasing proportion of light to a near focus. As a result of this design, when the pupil is small, such as during reading tasks, the lens provides appropriate near and distance vision (the Array multifocal IOL provides no near image if the pupil is approximately 2.5 mm or smaller). However, in large pupil situations, such as at night, the ReSTOR lens becomes a distant-dominant lens, providing appropriate distance vision while reducing unwanted visual phenomena, as the defocused near image has less signal strength. The add power is +4.0 D at the lens plane, which provides approximately 3.2 D of add power at the spectacle plane. It should be noted that with a diffractive approach there is a resultant 15–17% of the light being lost attributable to random scatter.[12]

In FDA clinical trials, bilateral implantation of the AcrySof ReSTOR IOL into 566 patients provided uncorrected visual acuity of 20/40 or better throughout the distance to near visual range with no restrictions on pupil size.[9] Following cataract surgery 80% of patients with bilateral implantation achieved total spectacle independence and 17% reported only occasional use of spectacles. There were significantly more glare, night vision problems, and halos for subjects implanted with the ReSTOR lenses when compared to a monofocal IOL control group. However, this was observed only in the 'mild' or 'moderate' symptoms category whereas no significant differences were noted in the 'severe' symptoms when compared to the control group.

A study by Rocha et al compared the visual acuity, total and high order wavefront aberrations (coma, spherical aberrations, and other high-order aberrations), and contrast sensitivity in 105 eyes implanted with four different lenses: the ReSTOR, 3-piece and single-piece monofocal AcrySof lenses, and a single-piece hydrophilic acrylic monofocal lens.[13] They observed that the ReSTOR induced significantly less spherical aberration compared to the monofocal lenses, but the contrast sensitivity was better with the monofocal AcrySof lenses.

More recently Alcon has produced the ReSTOR, model MA60D3, which is a three-piece multifocal hydrophobic acrylic lens, with PMMA haptics (Fig. 101.3, *B*). The optic has the same apodization design as its predecessor. Early clinical trials have shown 88.0 and 84.6% spectacle independence for distance and near vision. Unwanted photic phenomena has been described as clinically acceptable.[14]

The Tecnis lens with the Z-Sharp Optic Technology (AMO) has an anterior aspheric surface that compensates for the natural positive aberration of the cornea. The manufacturer is also working on a multifocal lens, which incorporates a diffractive posterior surface to the Tecnis design (model ZM001). In theory, the Tecnis multifocal lens would compensate for the decrease in contrast sensitivity that may be associated with multifocal lenses, by an increase in contrast sensitivity due to the aspheric characteristics of the lens. Peer-reviewed articles on the Tecnis multifocal IOLs are not yet available in the literature (Fig. 101.3, *C*).

Different clinical studies on the three above-mentioned multifocal designs have been presented at the latest annual symposiums and meetings of the European and American Societies of Cataract and Refractive Surgeons, as well as the American Academy of Ophthalmology. The three designs were generally associated with appropriate near, intermediate, and distance vision, as well as spectacle independence. To date, superiority of one design over the other is yet to be determined. Many have presented using a refractive multifocal in one eye and a diffractive in the second to optimize the best features of both. Peer-reviewed studies are currently being carried out.

The newly developed Acri.Twin (Acri.Tec, Hennigsdorf, Germany) bifocal diffractive 3-piece lens has a 6.0 mm silicone optic and PMMA monofilament haptics with 5° angulation (Fig. 101.3, *D*). The overall diameter is 12.0 mm. The central thickness of the IOL is reduced by peripheral fresnel structures. These structures are not responsible for near focus. The two focal points are created by central diffractive steps on the anterior surface of the IOL. There are two models: the Acri.Tec 733D and the Acri.Tec 737D. The Acri.Tec 733D has a 30% to 70% light distribution between distance and near focus while the Acri.Tec 737D has a 70% to 30% light distribution between distance and near focus. The IOLs are designed to be implanted binocularly (one model in one eye, the other model in the fellow eye). According to the manufacturer, both IOLs have a near addition of +4.0 D in the lens plane. A recent study by Schmidinger et al suggests that binocular implantation of the Acri.Twin system may be beneficial for visual acuity, near contrast sensitivity function, and distance contrast sensitivity function compared with a diffractive bifocal IOL.[15] Currently, this system is available in Europe but has yet to be approved for use in the USA.

PHAKIC MULTIFOCAL IOLs

IOL technology encompasses not only pseudophakic patients but phakic patients as well. Most degrees of myopia, hyperopia, and astigmatism, can be corrected with refractive surgery. Available techniques include excimer laser treatment, phakic IOLs, and clear lens exchange. The development of phakic multifocal IOLs give refractive surgeons yet another tool to add to their armamentarium for treating refractive errors, including presbyopia. The obvious advantage of a phakic multifocal IOL is, of course, the reversibility.

The bifocal refractive phakic IOL, known to most as the Baikoff IOL, is marketed under the trade names of Newlife (IOLtech, La Rochelle, France) and Vivarte Presbyopic (Ciba Vision, Duluth, GA). This is a hydrophilic acrylic lens manufactured through a process named selective polymerization, which allows the manufacture of a one-piece IOL with flexible and rigid areas anywhere needed to optimize the mechanical properties of the lens (Fig. 101.4, *A*). The lens thus has soft hydrophilic acrylic (38% water content) optic and footplates, while the haptics have a rigidity similar to that of PMMA lenses. This foldable angle supported lens has a 5.5 mm diameter optic which is divided into three concentric zones. The center and periphery are for distance vision and the middle periphery is for near vision. The central zone diameter is 1.5 mm, the intermediate zone is 1.1 mm wide, and the remaining 2.9 mm makes up the peripheral zone. The haptic is shaped like the number '2' and is available in overall diameters of 12.0 mm, 12.5 mm, and 13.0 mm. The lens comes in powers between −5.00 D and +5.00 D for distance vision with an addition of +2.50 D for near vision.

In the first trial study of phakic multifocal IOLs, Baikoff and his associates looked at 55 eyes of 33 patients with this lens implanted.[16] Although the results were satisfactory with fewer than 10% needing glasses in mesopic conditions, there were some findings which should be addressed. Slight pupil ovalization was seen in 10% of eyes under high light conditions, with fewer being noted in normal light conditions. Endothelial cell loss was not significant. No cataract or ocular hypertension was observed although the follow up time in the study was limited to only one year. In general, patients who reported halos tolerated them well. The authors suggested strict anatomic and psychological inclusion criteria for patient selection. The lens requires an anterior chamber depth (ACD) of 3.0 mm or

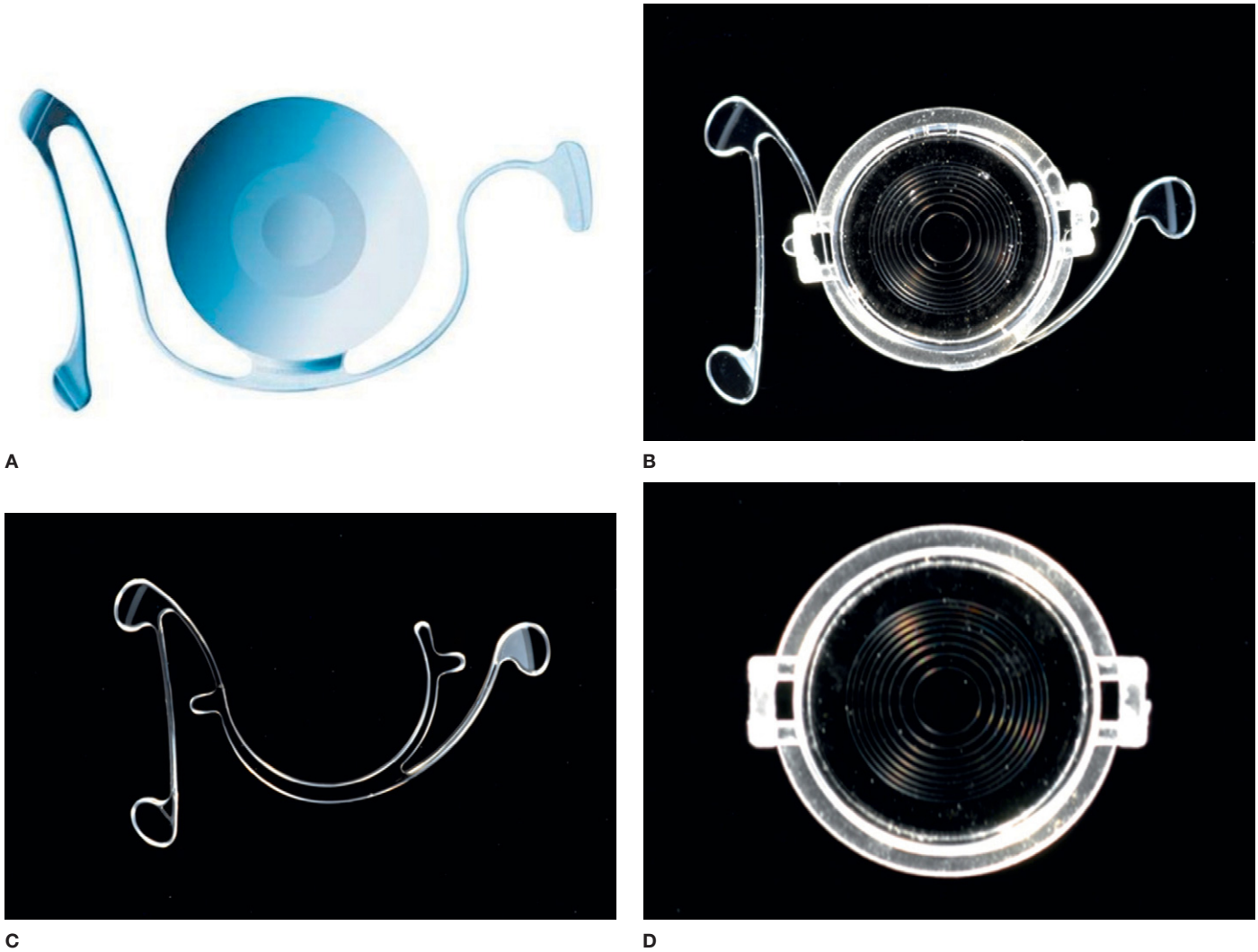


Figure 101.4. Examples of phakic, multifocal intraocular lenses. *A*, Newlife lens (Ioltech). *B–D*, Presbyopic phakic multifocal version of the Kelman Duet lens (Tekia). The two components of this lens are shown separately in *C* and *D* (haptic and optic, respectively).

deeper, an open angle, healthy endothelium, and no anterior segment or retinal disorders. Any astigmatism must be corrected before or after implantation of the phakic IOL. Patients who are too demanding and those whose profession require them to drive at night must be excluded.

In another pilot study, this one by Alio and Mulet, a multifocal phakic IOL prototype by Advanced Medical Optics was implanted into 34 eyes of 17 patients.[17] This one piece, angle supported, PMMA anterior chamber IOL is designed to maximize the physical distance from the IOL to both the cornea and the iris. The lens has a meniscus shape with a diameter of 12.5 mm and an optic diameter varying between 5.8 mm (myopic) and 6.0 mm (hyperopic), depending on the implant power. The anterior surface includes a multifocal design similar to that of the Array lens, with an add power of +1.75 D at the lens plane. This low power add was chosen apparently to minimize postoperative night vision photic phenomena. The design has five concentric zones: 1, 3, and 5 being distance dominant, and zones 2 and 4 being near dominant. The lens is available in powers ranging from +5.0 D to −15.0 D in 0.5 D increments. Because it is not foldable, a larger incision is necessary for implantation. In this study, wounds were 6.5 mm wide. Results showed that 65% of patients did not require reading glasses after surgery. However, the lens did not always allow comfortable extended reading or the ability to read small print clearly without spectacles for more than 20 min without visual fatigue. Findings concerning endothelial cell count and anterior segment complications correlate with previously published data on other angle-supported phakic IOLs.[16,18] As with the Newlife/Vivarte Presbyopic IOL, there were several cases of pupil ovalization but these resolved after 1 month of miotic treatment. No cases of ocular hypertension or cataract were noted although follow-up time was once again only for 1 year.

The very nature of multifocal lenses makes patient selection extremely important no matter what lens is chosen. There will almost undoubtedly be some compromise in visual quality when compared to best spectacle corrected vision. Patients must be made aware that spectacle independence may come at the cost of excellent preoperative vision for good postoperative vision.

Another multifocal phakic IOL being developed uses the platform of the Kelman Duet implant (Tekia, Inc., Irvine, CA). This is a foldable, phakic, angle-fixated anterior chamber IOL (Figs 101.4, *B–D*). The lens has two components: an independent Kelman tripod PMMA haptic, with an overall diameter of 12.0, 12.5, or 13.0 mm, and a 6.3 mm silicone optic, with an incorporated glare shield. The haptic of this lens is implanted first into the anterior chamber through an incision inferior to 2.0 mm. The multifocal optic is then inserted using an injector onto the previously implanted haptic, and then

fixated to it by the means of the optic eyelets and haptic tabs using a Sinskey type hook. The optic can be exchanged as the refraction of the patients evolves, e.g. in case of progressive presbyopia.

The last phakic multifocal IOL has a slightly different approach to the correction of ametropia and presbyopia. The Vision Membrane (Vision Membrane Technologies Inc., Carlsbad, CA, Apollo Optical Systems LLC, Rochester, NY, and Millennium Biomedical Inc., Pomona, CA) is a thin, vaulted, angle fixated diffractive IOL with a 6.0 mm optic. Its thickness ranges from 450 to 600 μm compared to 800 to 1200 μm for a standard refractive IOL. According to Lane et al it can be implanted through a 2.60 mm wide incision.[9] With an optic of 6.0 mm there should be less halos and glare effect when compared to anterior chamber IOLs of lesser diameter. No peripheral iridotomy is necessary because of the very flexible vaulted design which optimizes distance away from both the pupil and the corneal endothelium. Currently, the lens is manufactured from a silicone material.

Conventional diffractive optic lenses use a single diffraction order in which the optical power of the lens is directly proportional to the wavelength of light. A white light will project as different wavelengths focusing at different distances from the lens. The Vision Membrane is described as having multi-order diffraction (MOD) designed to bring multiple wavelengths to a common focus. This principle allows the IOL to be of a constant thickness for all refractive powers, and eliminate chromatic aberrations.

There are two forms of the Vision Membrane lens available. One is intended for correction of near or farsightedness (single power). The other is for the correction of near or farsightedness plus presbyopia. These are available in powers from −15.0 D to −1.0 D, and from +1.0 D to +6.0 D in 0.5 D increments. Patients are recommended to be over the age of 18 years, with stable refraction. Previous posterior chamber IOL implantation is not a contraindication.

ACCOMMODATIVE INTRAOCULAR LENSES

In the past few years there have been several accommodative IOLs developed. Some have single optics designed to move along the visual axis during accommodative efforts, thus changing the effective power of the eye. Others have a dual optic design where the contraction and relaxation of the ciliary muscle causes change in the separation distance between the two lenses.

When evaluating near vision for any accommodative IOL, remember that beyond movement, pseudoaccommodative factors such as increased depth of focus from small pupil size, residual myopia and astigmatism, and high contrast settings can contribute to improved near vision.

SINGLE OPTIC

The Eyeonics Inc. (Aliso Viejo, CA) CrystaLens (model AT-45) is a modified plate haptic lens manufactured from a third generation silicone material (Biosil) with a refractive index of 1.43 and has an integrated UV-absorbing chromophore (Fig. 101.5, *A*).[19] It is the first accommodative IOL based upon movement in the capsular bag secondary to accommodative effort and has been FDA approved for use in the USA since November 2003. It is hinged adjacent to the optic and has looped polyimide haptics. Grooves, which run across the plates adjacent to the optic, make the optic–haptic junction flexible. The overall length of the lens is 11.5 mm, corner to corner, while the straight length is 10.5 mm. The biconvex square-edged optic has a diameter of 4.5 mm and a manufacturer's recommended A-constant of 119.24 when placed in the capsular bag. Theoretically, when there is accommodative effort by the ciliary body mass, there is increased vitreous pressure which will move the optic forward along the visual axis creating increased effective lens power. It has been recommended that one drop of atropine be administered at the time of surgery and one drop the first day after surgery to allow the lens to remain in the most posterior possible position within the capsular bag and prevent forward movement until a certain amount of fibrosis surrounds and stabilizes the haptics. This should result in greater potential forward movement upon ciliary muscle contraction. The hinges are intended to facilitate forward movement of the optic by minimizing the resistance to the pressure exerted on the lens by the forward movement of the vitreous body during accommodative effort.

This IOL is intended for placement in the capsular bag only. The recommended capsulorrhexis size is 5.5 mm. This allows the plate haptics to be posteriorly vaulted in the right position. A large capsulorrhexis or a wound leak at the end of the surgery potentially allows the lens to vault anteriorly. This position inhibits movement of the lens and would likely require surgical repositioning.

Unfolded, the lens can be inserted through a 3.2 mm incision, and slightly less than 3.0 mm with the injector system. Uniplanar clear corneal incisions are not recommended because of potential early postoperative wound leakage.

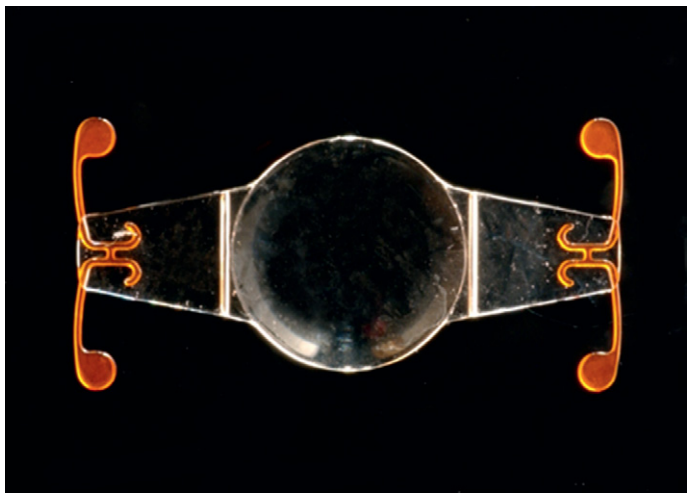
The lens is claimed to give 1 D of additional power during accommodation. In the investigational FDA clinical trials, 497 implantations were done with the CrystaLens allowing approximately 73% of subjects to remain essentially free of spectacles. However, other studies have not been able to show good correlation between the objective measurement of the anterior shift of the lens and the reported near vision of the patients.[20,21] In some cases posterior movement was actually observed. Therefore, it is likely that pseudoaccommodation or IOL arching inducing added power may play a role in the reading performances of patients implanted with this lens design.[22]

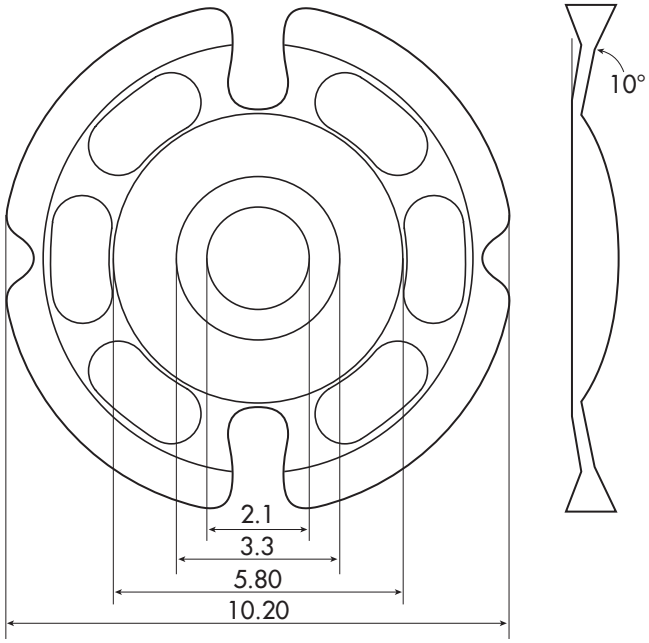
There is some concern with regards to patients with large pupils. The scotopic results achieved in clinical trials were excellent; however, the average age of the patients was approximately 70 years. Dysphotopsias, because of a comparatively small optic measuring only 4.5 mm in diameter, may be of concern when using such a lens on younger patients with larger pupils.

The CrystaLens is very flexible and can bend more easily than a standard IOL in response to capsular contraction. Because of unpredictable capsular contraction in pseudoexfoliation patients, manufacturers recommend the lens not be used in patients with this condition.

Other concerns about the CrystaLens include the accommodative potential after Nd:YAG capsulotomy. Over 50 eyes in the USA clinical trial have undergone laser capsulotomy and their accommodative abilities have not diminished. If needed, posterior capsulotomies are recommended to be small, approximately 3 mm or less, to avoid vitreous herniation around the optic and to preserve the mechanism responsible for accommodation in this lens. Capsular fibrosis syndrome has also been discussed with dislocation of the IOL or induced 'Z' syndrome (one haptic up and one back). Some have recommended 100% prophylactic laser capsulotomy, which raises concerns about retinal detachment and cystoid macular edema.

Three year data for the eyes in the USA clinical trials demonstrate no loss of accommodative performance over time, which suggests IOL movement is probably not important for near vision even after





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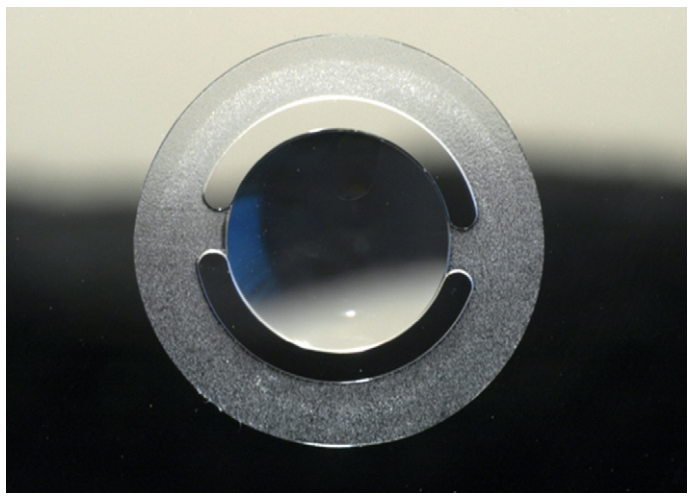

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Figure 101.5. Examples of mono-optic, accommodative intraocular lenses. *A*, CrystaLens (Eyeonics). *B*, Earlier BioComFold design (Morcher). *C*, Akkommodative 1CU (HumanOptics). *D*, Tek-Clear (Tekia).

typical capsular fibrosis. Similar findings have been observed in longer-term follow-up in overseas trials.[23]

Other single optic accommodative IOLs have been more popular in the European market. The first was a ring-haptic IOL designed by Payer (Fig. 101.5, *B*).[24,25] Models BioComFold 43A and 43E were marketed in the 1990s. This is a foldable hydrophilic acrylic single piece lens, which has a disk-like shape with a peripheral ring. The ring is connected to the central optic by an intermediate forward angled perforated ring section. The optic sits anterior to the ring haptic plane to allow forward shift of the optic during ciliary muscle contraction and hence ring haptic compression. Available now is the Biocomfold 43S which is an accommodative IOL with refractive multifocal optic.

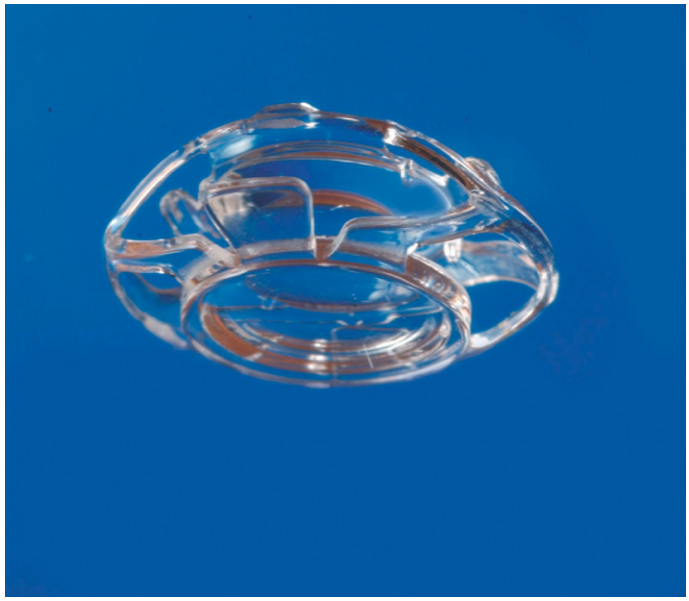
Yet another accommodative IOL is the Akkommodative 1CU made by HumanOptics (Erlangen, Germany). This is also a hydrophilic acrylic single optic posterior chamber lens (Fig. 101.5, *C*). The optic is 5.5 mm in diameter with biconvex shape and an ultraviolet filter incorporated. There are four haptics tapering at the optic–haptic junction, which act as hinges, giving the lens an overall diameter of 9.8 mm. The refractive index is 1.46 with a recommended A-constant of 118.1. The lens is available in powers between +16.0 to +26.0 in 0.5 D increments. The design is often assumed to function similar to the CrystaLens. This is actually not the case. Relaxation of lens zonules during ciliary body contraction leads to relaxation of the capsular bag and forward movement of the IOL at the hinges of the four haptics.[26] This would suggest that the flexibility of the capsular bag is critical to its performance, which has yet to be proven in large peer-reviewed studies. It has been suggested that an IOL of this design characteristically moves less than 1 mm anteriorly on accommodative effort as determined by ultrasound biomicroscopy.[3] As with all accommodative IOLs that are intended to shift position with accommodative effort, the effective lens power increase varies with the power of the lens. High-powered lenses typically used for hyperopes will show greater change in diopter power when compared to weaker powered lenses of the same design. For high myopes who generally have

lower-powered IOLs implanted, the potential add will be more limited.

The Tek-Clear (Tekia, Inc., Irvine, CA) accommodative IOL was also designed to take advantage of the natural accommodating process of the human eye (Fig. 101.5, *D*). This is a single-piece, disk-shaped lens, with an overall diameter of 10.0 to 11.5 mm, manufactured from a hydrophilic acrylic material, which can be fully injected through an incision of 3.2 mm. The lens design incorporates a 'bending-beam' approach, to optimize the IOL movement as the ciliary muscle contracts during the accommodation process. Its full bag haptic design incorporates a square edge for PCO prevention.

DUAL OPTIC SYSTEMS

Theoretical studies using model eyes demonstrate that dual-optic IOL systems may have an advantage over single piece accommodative lenses in terms of amplitude of optical power gained with optic movement during ciliary muscle contraction.[3,27] This is particularly true if there is anterior movement of the anterior optic with an unchanged position of the posterior optic. The Synchrony IOL (Visiogen Inc., Irvine, CA) is a one-piece, dual optic lens manufactured from silicone (Figs 101.6, *A–C*).[28] The optics have a general design of a plate haptic silicone lens and they are connected by a bridge through the haptics, which act like a spring. The 6.0 mm posterior aspect of the lens has a larger surface area than the 5.5 mm anterior, which allows better stability within the capsular bag during contraction and relaxation of the ciliary muscle. The anterior optic has two expansions oriented parallel to the haptic component that lift the capsulorrhexis edge and prevent complete contact of the anterior capsule with the anterior surface of the lens. The anterior optic has high +32.0 D power while the posterior lens has a patient-dependent minus power to return the eye to emmetropia. Theoretical accommodation is 3.3 D, with 1.5 mm of anterior



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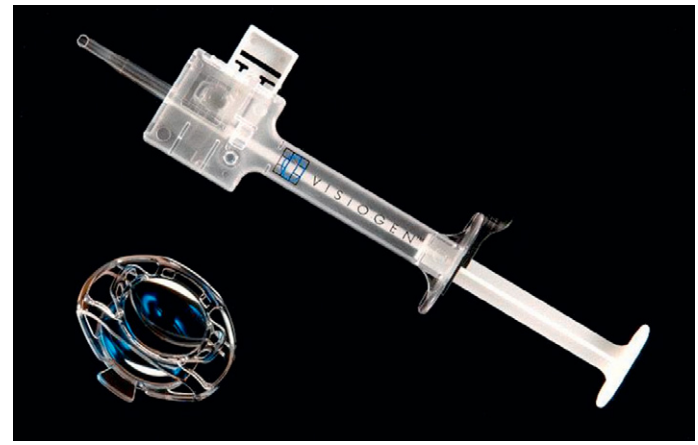

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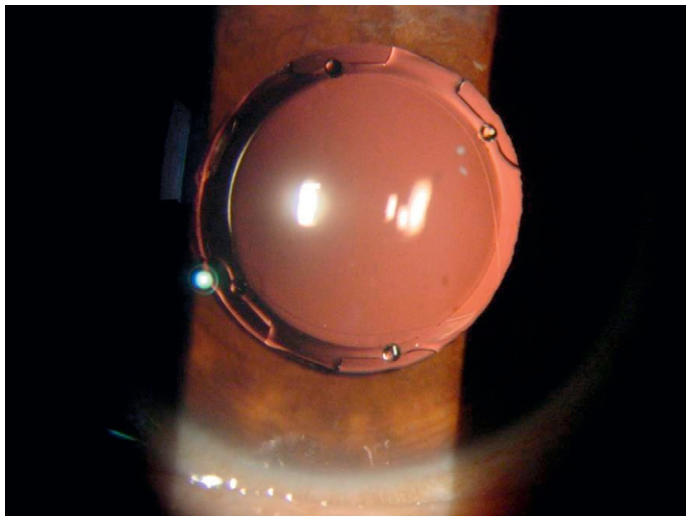

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Figure 101.6. Dual-optic accommodative intraocular lenses. *A*, Photograph of the Synchrony lens (Visiogen). *B*, Gross photograph of the lens, and the injector, which was designed to be pre-loaded with the lens. *C*, Slit-lamp photograph of a patient implanted with the Synchrony lens, taken 12 months postoperatively (retroillumination; courtesy of Dr Ivan Ossma, Cali, Colombia). *D*, Photograph of a prototype of the lens invented by M. Sarfarazi, currently being developed by Bausch & Lomb.

lens movement. The lens is designed to work within the capsular bag according to Helmhotz's theory of accommodation. The distance between the two optics is stated to be at a minimum in the unaccommodated state and at a maximum in the accommodated state, with the anterior optic displaced forward. Stoppers are incorporated to maintain a minimum separation of the lenses which sets the resting distance refraction at emmetropia. With accommodative effort and zonule relaxation, the tension of the capsular bag is released, which allows the interoptic spring-like articulations to displace the anterior optic forward. Rabbit studies by Werner et al demonstrated that significantly less anterior capsule opacification and PCO were observed in eyes implanted with the Synchrony™ lens when compared to eyes implanted with plate haptic silicone lenses.[29,30] They also demonstrated that interlenticular opacification (ILO) was significantly associated with pairs of hydrophobic acrylic lenses implanted in the bag, but not with the Synchrony. The Synchrony is currently under clinical trials. Since the last quarter of 2005, it is being implanted through a 3.6–3.8 mm incision, by using a preloaded injector that only requires balanced salt solution for IOL lubrication. The suggested continuous curvilinear capsulorrhexis size is between 4.5 and 5.0 mm. A recently reported series of 24 patients implanted with this lens showed 100% distance corrected visual acuity of greater than or equal to 20/40. Defocus curve analysis showed a mean accommodative range of 2.83 ± 0.16 D.[31] Actual anterior lens movement has been documented by ultrasound analysis.

Another dual-optic accommodative IOL system is now being developed by Bausch & Lomb (Rochester, NY). It was invented by Dr Faezeh M. Sarfarazi and is composed of a single-piece molded silicone lens (Fig. 101.6, *D*). There are two optics connected by three haptic components. The design also uses a high-powered positive anterior lens and a low-powered posterior lens. It has Bausch & Lomb's patented Aspheric Advanced Optics platform, which reduces aberrations and makes the lens system less prone to optic–optic decentration and tilting. The haptics act to center the lens as well as provide the spring-like resistance that separates the two optics. The posterior surface of the posterior lens has a square edge to reduce PCO. The continuous silicone lens is designed to match the size and characteristics of the human eye to achieve accommodation through the natural contraction/relaxation of the capsule by the ciliary muscle. According to its inventor, measured accommodation closely matches the theoretical optical design of 2.2 D per mm of lens translation for a total accommodation of 4.0 D. Clinical trials show the lens can be inserted through a 4.0–4.5 mm incision and into the capsular bag with good centration. It is currently under clinical studies being conducted by Bausch & Lomb. So far safety has clearly been demonstrated with good patient acceptance.[32]

NEWER CONCEPTS

With such huge efforts being put forth toward designing an IOL that 'cures' presbyopia, we are bound to come across some innovative ideas, which take a different approach to addressing the problem. What if instead of a multifocal IOL, or an IOL that moves with accommodative effort, we could have an IOL which mimicked the natural crystalline lens during ciliary muscle contraction?

One approach may be to place a malleable material inside the capsule to produce a situation very close to our pre-presbyopic state. At Medennium Inc. an IOL with such potential capabilities is being developed. This lens uses a thermodynamic hydrophobic acrylic material that is packaged as a solid rod approximately 30 mm long and 2 mm wide.[6] The refractive index of the material is 1.47, and the softening temperature is 20–30°C. When implanted through a small incision, body temperature transforms the rod into a soft gel-like material, which has the shape of a full-size biconvex lens that completely fills the capsule. The entire transformation takes about 30 s and the result is a 9.5 mm wide lens having 2–4 mm thickness at the center depending on thickness (Fig. 101.7, *A–D*).

Besides being implanted through a very small incision, another potential advantage is to restore accommodation. By combining a full-sized optic with a flexible material, the hope is that the lens will be able to mimic the accommodative action of a young, natural lens. Complete filling of the capsular bag may eliminate the space for cell growth (Fig. 101.8). The hydrophobic material of this lens exhibits a tackiness, which might promote its attachment to the capsular bag, enhancing PCO prevention. A new design of this lens is being developed, which is a three-piece lens with PVDF haptics. This potentially will eliminate problems related to varying capsular bag sizes in different eyes. Dealing with after-cataract formation, refractive precision, and whether or not the anterior capsule needs to be largely intact to transmit accommodative effort are still unresolved issues. It is also not clear how well accommodative forces can act on such a lens with the anterior capsule open due to capsulorrhexis.

Yet another design for an accommodative lens originates from the thought that when a flexible material is pressed between two hard planes, one of which has a central aperture, the flexible material will follow the path of least resistance through that aperture. If that flexible material is transparent, this bulge acts as a lens that changes in radius and power according to the pressure applied. This is the concept of the NuLens (NuLens Ltd, Herzelia Pituach, Israel). In theory, the IOL power would change with ciliary body action and generate an add power of up to at least 8.0 D by manipulation of a flexible material between a sulcus-fixated rigid plate and a ciliary muscle operated capsular diaphragm.[33] This diaphragm would consist of the collapsed capsular bag, zonules, and ciliary processes. It would provide the force transfer from the ciliary muscle to the diopter-generating device placed adjacent to it.

To complete the concept, there would be a need for a stable reference plane in front of the diaphragm to turn those forces into physical changes in curvature of a flexible lens material. Once the rigid reference plane is fixated, a contained flexible material could be placed between the rigid plane and the capsular diaphragm. Movements of the diaphragm would then deform that flexible material through a hole in the rigid anterior reference plane or through a posterior pushing piston to create a secondary lens.

The original design used accommodation effort for distance vision, which raises issues of patient acceptance and induced esotropia due to the accommodative convergence mechanism. Another design gets around this issue if it were to prove to be a problem. Thus far a second generation lens has been developed, which is designed to be fixated in the ciliary sulcus via micropins, and the dynamic surface is in the posterior part of the lens near the nodal point of the eye. Ongoing development for safe insertion and fixation techniques into the ciliary sulcus are being tested for structural assessment and further modification of the lens components (Fig. 101.9, *A* and *B*).

Early laboratory studies, including in primates have been done with promising results. The feasibility of the concept has been demonstrated; however, further analysis along with the continuing development of this lens is necessary before any clinical conclusions can be made about the future use of this IOL in humans.

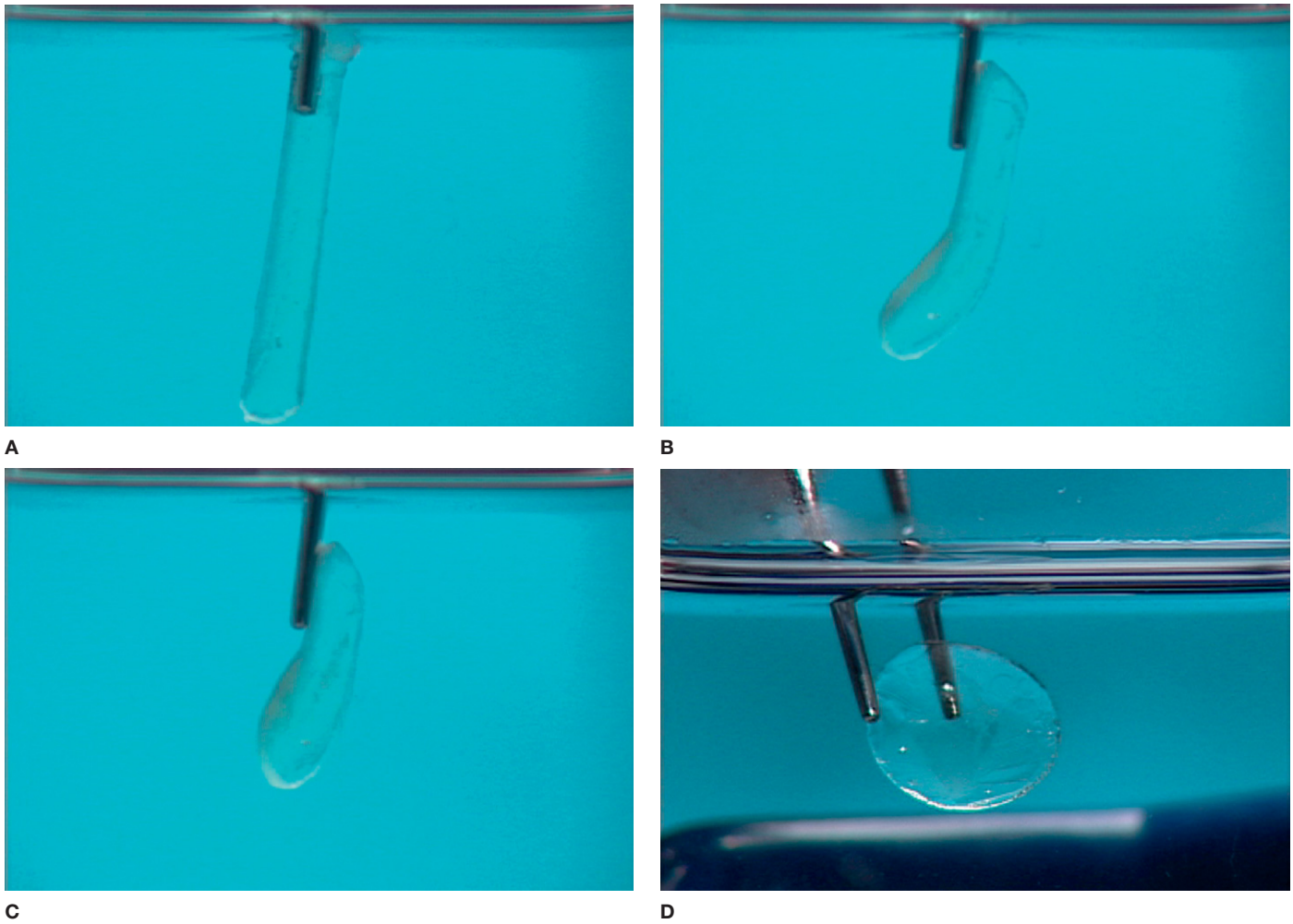

Figure 101.7. Photographs showing the transformation of the solid rod into a biconvex lens (*A–D*), after immersion in balanced salt solution at body temperature. (Courtesy: Medennium).

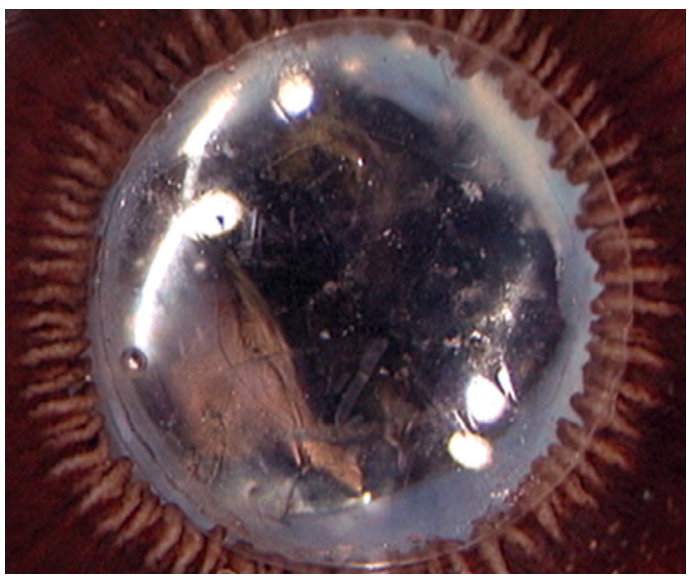

Figure 101.8. Gross photograph of a human eye obtained postmortem (Miyake-Apple posterior view) implanted with a prototype of the single-piece SmartIOL (Medennium). The rod gradually transformed into a full size lens, after instillation of balanced salt solution at body temperature, which in this case completely filled the capsular bag.

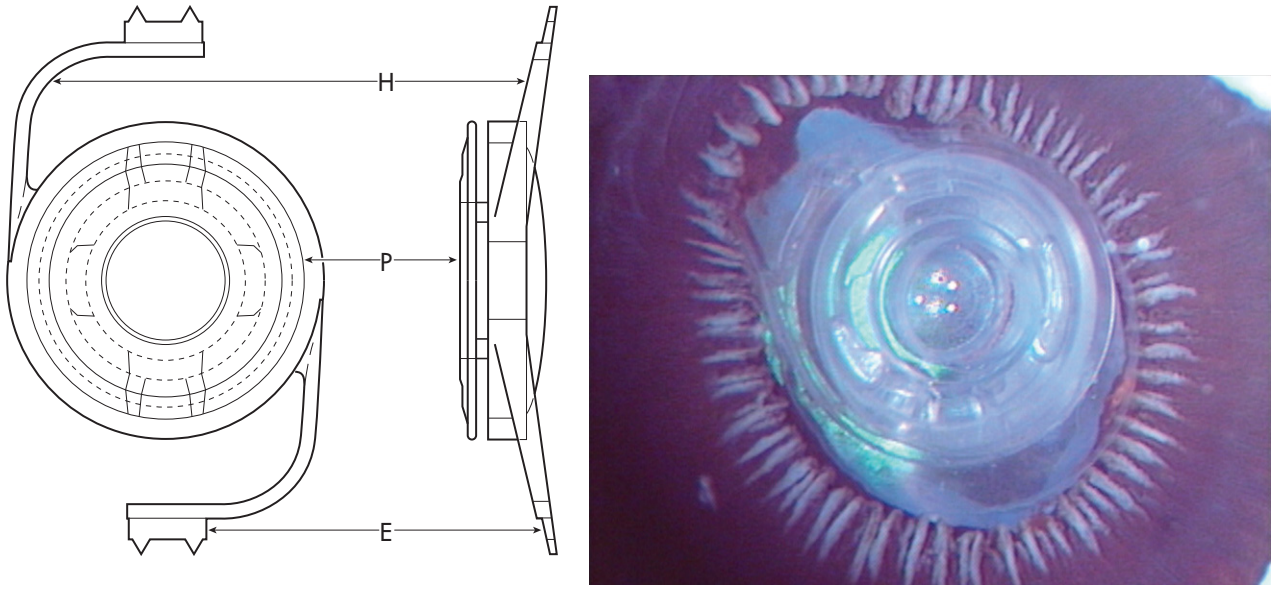

Figure 101.9. Example of a deformable accommodative intraocular lens. *A*, Schematic drawing showing the NuLens (left: posterior view; right: side view). H = haptics; E = end plates with micropins; P = piston (from Ben-Nun J, Alio JL. Feasibility and development of a high-power real accommodating intraocular lens. J Cataract Refract Surg 2005; 31: 1802–1808). *B*, Experimental implantation of the NuLens in a human eye obtained postmortem (posterior view of the anterior segment).

In summary, we have been witnessing an incredible evolution in the world of IOLs, much of it driven by the quest to treat presbyopia. The interest in this field continues to grow as manufacturers aim to meet the visual needs of patients while maintaining high standards of safety and quality. Whether it will be pseudoaccommodative or accommodative, the innovative designs of IOLs are a trend sure to expand. Which design will provide the best patient satisfaction is not clear at this time.

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