Although refractive errors are extremely common, their pathogenesis remains undetermined; both genetic and nongenetic factors appear to influence an individual's risk for myopia and the severity of the myopia. The pursuit of good visual acuity without corrective spectacles or contact lenses has spawned a large number of surgical procedures designed to correct myopia, hyperopia, and astigmatism, with the first published descriptions of corneal incisions for this purpose appearing 100 years ago. Two thirds of the refractive power of the eye resides within the cornea, so most of these procedures involve surgical manipulation of the cornea (keratorefractive surgery). Exciting new technologies are being developed for use in refractive surgery, but variability in wound healing remains an old enemy. Predictability of keratorefractive surgery would be greatly improved by a better understanding of corneal biomechanics and by effective strategies for pharmacologic manipulation of wound healing within the cornea. The global public health and socioeconomic implications of safe, effective, and predictable refractive surgery are enormous; about one fourth of the United States population has myopia, and in other regions of the world the prevalence of myopia may reach 70%. If a cost-effective surgical procedure were developed, the avoidance of decades of contact lens or spectacle wear could save billions of dollars.

HISTORICAL ASPECTS

A century ago, experimental and clinical studies demonstrated the feasibility of surgical alteration of corneal refractive power, and various surgical procedures have been proposed for the reduction of myopia, hyperopia, and astigmatism. The goal of these procedures is to permit excellent visual acuity without spectacles or contact lenses, or to reduce a very large refractive error (such as high surgically induced astigmatism after cataract extraction or corneal transplantation) to a level that enables the patient to tolerate corrective lenses.

The strategies proposed for altering corneal shape have been varied, but most refractive surgical procedures fit into one of three categories: incisional procedures (such as radial keratotomy), lamellar procedures (such as epikeratophakia), and heat-induced shrinkage (such as thermokeratoplasty). In the United States, radial keratotomy is the most commonly performed of these procedures; estimates are that 250,000 such procedures are performed annually. In radial keratotomy, a diamond blade is used to make four to eight incisions through approximately 80% to 90% of the corneal thickness. The incisions extend radially in spoke-like fashion from the paracentral cornea (usually 1.5 to 2 mm peripheral to the center of the entrance pupil) to the peripheral cornea. Greater corneal flattening is achieved if the number of incisions is increased and if the incisions are placed closer to the center of the cornea. Lamellar procedures generally involve the addition of tissue to the cornea, or the removal of tissue from the cornea, so as to flatten or steepen the center. In an early form of this approach, a high-speed oscillating blade (microkeratome) was used to excise the anterior stroma, which was then frozen, carved on a lathe, and sutured back into place on the patient's cornea. Thermokeratoplasty has been used to achieve thermal shrinkage of stromal collagen to flatten keratoconic corneas, to steepen normal corneas for hypermetropia, or to steepen selected corneal meridians to treat astigmatism.

Limitations of Keratorefractive Procedures

The success with incisional procedures such as radial keratotomy has been limited by several factors. The predictability of the acute response of the cornea to surgery is limited by our ignorance of the important biomechanical properties of the cornea that determine the magnitude of its immediate deformation in response to surgery. As a material, the cornea has...
characteristics of nonlinear behavior, viscoelasticity, and anisotropy that complicate prediction of its response to surgery, so nondestructive techniques for measuring the material properties of individual corneas are needed. In addition, early success may turn to failure weeks to months after surgery as the incisions heal, and the final refractive outcome cannot be predicted because of interindividual variability of wound healing. Finally, the “ultimate” outcome of radial keratotomy may never be known in many or even most patients because of a long-term (over years) refractive shift toward increased flattening of the cornea. This phenomenon of long-term instability is a major weakness of the radial keratotomy procedure performed in the 1980s.

Lamellar refractive surgical procedures have historically been limited by lack of accuracy, opacity within the interface, and irregular astigmatism. Procedures that rely on thermal shrinkage of collagen have been limited by short-lived refractive effects and complications related to excessive thermal damage to the epithelial basement membrane-Bowman's layer complex.

EXCIMER LASER CORNEAL SURGERY

The excimer laser has generated tremendous interest as a new device for refractive modification of the cornea. The term excimer laser refers to a family of lasers that can operate with a number of different gas mixtures to produce intense pulses of radiation in the ultraviolet region of the spectrum. The name excimer, a misnomer, is a contraction of excited dimer, which refers to the bonding of a rare gas and a halogen atom. The resultant molecule exists transiently in an excited state before dissociating with the emission of a highly energetic photon of ultraviolet radiation. The energy of the emitted photon, and thus the wavelength of the laser, depends on the gas mixture employed. Clinical lasers for corneal surgery use argon and fluorine, with wavelength of 193 nm and a photon energy of 6.4 eV, which is sufficient to break carbon-carbon single bonds (3.6 eV), carbon-nitrogen bonds (3.1 eV), and carbon-hydrogen bonds (4.3 eV). The radiation is absorbed within a thin surface layer of the cornea, with 67% of the incident energy at 193 nm absorbed within a path length of 4 μm. The absorbed photons rupture the intramolecular bonds of the long-chain polymers to produce smaller volatile fragments that are ejected from the surface at velocities up to 2000 m/second. Examination of the wound surface with transmission electron microscopy demonstrates a narrow electron-dense zone approximately 100 to 200 nm in width. Beyond this zone, the corneal tissue appears to be undisturbed, suggesting that this procedure may elicit a minimal healing response on the part of the corneal stromal cells.

Wide Area Surface Ablation

The excimer laser was offered initially as an improved “scalpel” for creating narrow linear excisions of corneal tissue. As experience was gained with the laser for creation of linear radial keratectomies (for myopia) or transverse keratectomies (for astigmatism), however, it became clear that this approach did not improve on results obtained with the diamond blade. The strategy was then advanced to ablate a wide area of the corneal stromal surface to change central curvature, using the laser to reduce the anterior convexity of the cornea over the pupil. With this technique for correcting myopia, a maximal amount of tissue is removed centrally, with progressively less tissue removed toward the periphery of the ablation zone (Fig. 1). The radius of curvature of the cornea is increased, the refractive power is decreased, and the focal point of the optical system of the eye is thereby moved posteriorly onto the retina. The ablation zone diameter usually measures approximately 5 to 6 mm, and the maximal central depth of an ablation to correct myopia can be approximated using the following formula:

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\text{Central ablation depth (μm)} = \frac{(\text{number of diopters of myopia})}{3 \times (\text{ablation zone diameter in mm})^2}
\]

Inspection of this formula makes clear that increasing ablation zone diameter substantially increases central ablation depth.

To correct hyperopia, a minimal amount of tissue is removed centrally, and progressively more stroma is ablated toward the corneal periphery so that the central cornea is steepened. To correct astigmatism, a different amount of tissue is ablated in the steep meridian than in the flat meridian, so that the preoperatively steep meridian is selectively flattened or the preoperatively flat meridian is selectively steepened. In the typical situation, cylindrical and spherical refractive errors coexist, and an ablation may be designed to correct both components of the ametropia.

This wide area, surface ablation of the cornea for the correction of refractive error has been termed photorefractive keratectomy. Photorefractive keratectomy remains under investigational status in the United States, whereas in Europe, Canada, Australia, and some Asian nations it is reportedly in wide use. The laser may also be used to excise superficial corneal scars, other opacities, or surface irregularities; when used for this purpose, the procedure is termed phototherapeutic keratectomy. Currently, the largest cate-
FIGURE 1. Schematic illustration of wide area surface ablation (photorefractive keratectomy) for myopia. Selective removal of anterior corneal stromal tissue increases the radius of curvature of the cornea, moving the focal point posteriorly onto the retina. The magnitude of tissue loss is exaggerated for purposes of illustration.

FIGURE 2. Dense, subepithelial corneal opacity 6 months after photorefractive keratectomy to correct 20 D of myopia. This patient’s best visual acuity, with spectacles, is reduced to 20/70 from a preoperative level of 20/40. Opacity of this severity is very rare.

category of patients treated has been those with myopia, followed by those with astigmatism, and lastly those with hyperopia.

Photorefractive Keratectomy Surgical Technique

The patient is placed supine under the laser delivery system. The patient’s refractive error is programmed into the computer, which calculates the number and distribution of pulses required to produce the desired refractive change, and the laser typically is calibrated by performing the ablation in an appropriate test material, such as polymethylmethacrylate. Topical anesthetics are applied to the ocular surface, the lids are retracted with a speculum, and the epithelium is removed from a circular area approximately 6 to 7 mm in diameter around the apical cornea. With the patient fixating on a target that is coaxial with the surgeon’s view and with the laser beam, the surgeon centers the laser over the entrance pupil and precisely focuses the laser on the surface of Bowman’s layer. The laser is then activated by the surgeon, who monitors progress of the procedure through the operating microscope. The laser ablates tissue for about 30 seconds at the rate of about 0.2 μm per pulse; the distribution of laser pulses across the cornea and, hence, the induced change in refractive power, is controlled by passing a large-diameter beam through an iris-diaphragm or by scanning a small-diameter beam across the corneal surface. After surgery, topical antibiotics are used as a prophylaxis against infection until the corneal epithelium heals over the ablation zone (usually within 48 to 72 hours). Visual acuity is limited immediately after surgery because the exposed corneal stroma absorbs fluid from the precorneal tear film. After the epithelial defect has healed, the stromal edema subsides and visual acuity improves.

Results With Photorefractive Keratectomy

Results of excimer laser photorefractive keratectomy have been encouraging. For patients with myopia between -2.00 and -6.00 D, 90% to 96% have achieved postoperative visual acuity of 20/40 or better without correction, and approximately 50% of patients have achieved 20/20 or better visual acuity without correction. Patients often experience a transient hyperopia or regression of initial effect and the length of time required for stabilization of the refractive error are functions of the amount of myopia the procedure was intended to correct; the greater the intended refractive correction, the greater the amount of regression and the longer the time interval required for stability.

Early in the clinical trials with the excimer laser, it became apparent that many patients experience extremely severe pain during the first 24 hours after surgery. This pain appears to be related to an increase in corneal levels of prostaglandin E2, a potent sensitizer of pain fibers. The use of a topical cyclooxygenase inhibitor, plus a therapeutic soft contact lens, blunts the postoperative rise in prostaglandin E2, thereby reducing postoperative discomfort.

Visual Loss After Excimer Photorefractive Keratectomy

As part of the healing process after surgery, corneal opacities typically appear beneath the epithelium in the region of the ablation. These opacities are first
Recent Developments

visible with the biomicroscope approximately 4 weeks after surgery and usually become maximal by 3 to 6 months. In only a small minority of patients are these opacities of sufficient magnitude to reduce visual acuity or contrast sensitivity, and in most patients they resolve spontaneously over time. In some individuals, however, the opacities persist and degrade visual acuity (Fig. 2); in the Food and Drug Administration-supervised trials within the United States, 1% to 3% of patients lose two or more Snellen lines of visual acuity with spectacle correction. The frequency of visual loss increases as the amount of preoperative myopia increases, presumably because the depth of the ablation is greater in these eyes, so more corneal lamellae are severed and greater numbers of keratocytes are stimulated.

Thus, despite the early success with the high technology (and high expense of approximately $500,000) of excimer laser wide area surface ablation, and the relative lack of trauma to the underlying cornea, variability in wound healing limits predictability of the refractive outcome and results in a small percentage of eyes that lose corneal clarity and visual acuity. Keratocytes migrate to the region of the ablation and synthesize new collagen and glycosaminoglycans. Immunohistochemical studies indicate the newly formed collagen to be type III collagen. Proteoglycans are produced in response to the injury, including keratan sulfate and hyaluronic acid. Hyaluronic acid deposited in the area of ablation may change the water balance in the cornea, creating disruptions in the lamellar arrangement. Because these newly synthesized macromolecules lack the organized, crystalline arrangement seen within the corneal lamellae, they reflect and scatter more light than does normal corneal stroma. Regression of the initial refractive correction may be attributable to at least two mechanisms: synthesis of collagen and glycosaminoglycans by keratocytes and increased thickness of the corneal epithelium in the ablation zone. Central thickening of the cornea because of one or both of these phenomena by only approximately 5 μm may be sufficient to result in the loss of 1 D of the initial refractive change. Furthermore, keratocytes in the wounded cornea may exert contractile forces that might influence corneal topography. If the postoperative wound healing process is not uniform and the resultant central corneal topography is irregular, optical aberrations may limit postoperative visual function. Research into the consequences of these surfaces on visual performance, image distortion, night vision versus day vision, exacting visual tasks, and so on, is needed. Understanding the biomechanics of corneal wound healing would clarify the factors that determine the long-term results of excimer photorefractive keratectomy and other keratorefractive procedures.

CURRENT RESEARCH CHALLENGES: CENTER STAGE FOR WOUND HEALING AND THE KERATOCYTE

A prime focus in keratorefractive surgery, therefore, is the control of wound healing. The cell of interest in the loss of corneal clarity is the keratocyte, a fibroblast-like cell of neural crest origin located between corneal lamellae. Normally considered fairly inactive, these cells are distributed in a neural-like network, with each keratocyte in communication with several of its neighbors through long cytoplasmic extensions and intercellular gap junctions. Injury to keratocytes in one location results in dramatic changes in neighboring keratocytes: retraction of cytoplasmic extensions, incorporation of DNA precursors, increase in rough endoplasmic reticulum, and migration to the site of injury. These so-called activated keratocytes synthesize collagen and glycosaminoglycans, which give rise to the opacities observed clinically. Thus, the keratocyte is the target cell of therapies designed to limit corneal opacification and refractive regression after excimer keratectomy.

Numerous therapies have been explored experimentally and clinically for limiting superficial stromal opacification after excimer ablation. These include topical corticosteroids, which are used routinely as part of the FDA-supervised U.S. clinical trials. The use of postoperative corticosteroids has been common since initial small studies in animals suggested that they limit subepithelial deposition of new collagen and ground substance and since initial clinical observations of the effects of topical and periocular steroids in blind and sighted human eyes. Unfortunately, their efficacy has not been demonstrated in prospective clinical trials in which steroids or placebo were administered for 3 months after surgery, and complications of their use have included substantial elevations in intraocular pressure. Others, however, claim that corticosteroids are of value in selected patients to prevent regression after surgery or to reverse regression once it occurs. The value of corticosteroids after excimer laser surgery is therefore in dispute.

Nonsteroidal anti-inflammatory agents are used commonly to control postoperative pain after excimer corneal ablation. Although some of these drugs have been shown to limit fibroblast proliferation in vitro, and possibly to affect postoperative corneal clarity in animals, evidence of their effectiveness in humans is lacking.

Antimitotic agents (such as mitomycin), inhibitors of collagen cross-linkage, and topical interferon-α 2b have also been reported to be beneficial in vitro and in animals, but none of these agents have been tested in clinical trials, and potential toxicity is of serious concern.
The cellular events that trigger dramatic morphologic, functional, and biosynthetic changes in stromal keratocytes adjacent to the wounded stroma are incompletely understood, and roles of growth factors and growth factor antagonists need further investigation. Targeting of the stromal keratocytes through specific cell-surface receptors is an appealing alternative to current nonselective, and fairly ineffective, therapeutic options and is a technology that warrants further investigation.

**FUTURE OF KERATOREFRACTIVE SURGERY**

Many observers anticipate increased consumer demand for a surgical alternative to glasses and contact lenses; industry estimates suggest that nearly 1.5 million Americans have undergone radial keratotomy, and this number might increase by an order of magnitude during the next decade if the FDA determines excimer laser photorefractive keratectomy to be safe and effective. In addition to radial keratotomy and excimer laser photorefractive keratectomy, new refractive procedures that involve manual techniques or lasers are being investigated or contemplated. This competition will continue until one or more procedures is proven safe, highly predictable, potentially adjustable, and stable for decades.

**References**