WOUND HEALING ANOMALIES AFTER EXCIMER LASER PHOTOREFRACTIVE KERATECTOMY: CORRELATION OF CLINICAL OUTCOMES, CORNEAL TOPOGRAPHY, AND CONFOCAL MICROSCOPY*

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ABSTRACT

Purpose: To further the understanding of wound healing anomalies affecting visual function after myopic photorefractive keratectomy (PRK).

Method: Analysis of a clinical database of PRK on 133 eyes with myopia of -1.5 to -7.0D and 43 eyes with myopia of -6.0 to -12.0D. Visual function was analyzed by subgroups of 1) no topographic anomalies; 2) topographic central islands; and 3) topographic keyhole patterns. The natural course of healing was documented over 6 months with visual acuity measurements, clinical observation, and corneal topography. In vivo clinical-pathologic correlations were made by scanning confocal microscopy.

Results: Topographic anomalies were identified 1 month post-PRK in 48 eyes (40.3%) with low-moderate myopia and in 14 eyes (32.5%) with moderate-high myopia. For patients with 6 month follow-up, these rates declined to 25% and 23%, respectively. At 1 month post-PRK, topographic anomalies significantly reduced uncorrected and best-corrected visual acuity and refractive predictability. By 6 months post-PRK, the small number of eyes with persistent anomalies had visual outcomes similar to patients with normal topography. A simple approach to anti-island pre-treatment reduced islands slightly and keyhole anomolies significantly (anti-island pre-treatment vs no pretreatment: islands 25% vs 31.8%; keyholes 2.3% vs 17.6%; p=0.021) but with decreased predictability of induced refractive change at 1 month post-PRK. Confocal microscopy *in vivo* demonstrated prominent deposition of subepithelial extracellular material 1 to 2 months after PRK that diminished by 6 to 8 months, but persisted in the presence of central islands. Scar formation appeared to represent an elevated plaque of new collagen with active keratocytes.

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Conclusions: Topographic anomalies of wound healing are common after PRK. Vision and predictability are reduced by anomalies 1 month post-PRK but anomalies often resolve by 6 months. Marked improvement of vision occurs even when anomalies persist. Central islands appear to consist of persistent dense subepithelial extracellular deposits. Local scars are caused by new collagen deposition.

INTRODUCTION

Following the introduction of the excimer laser as a potential corneal surgical device by Trokel and associates in 1983,[1] numerous investigations examined the laser-tissue interaction of the excimer laser with the cornea, the corneal wound healing response, and therapeutic and refractive clinical applications. With the general availability of commercial excimer laser refractive surgical systems internationally and, more recently, in the United States, patterns of anomalous wound healing with clinically undesirable optical effects have emerged.

This thesis reviews current knowledge of the corneal wound healing response to the excimer laser, as developed in laboratory investigational studies by the author and his group as well as at numerous other centers. The author's current clinical data base then serves as the basis for exploring the most common patterns of anomalous wound healing after myopic photorefractive keratectomy (PRK). Case studies with clinical histories, topography data, in vivo confocal microscopic examination, and operative findings are presented in an effort to advance the understanding of these anomalies and their treatment.

PRE CLINICAL STUDIES

Laser-Tissue Interaction

Initial investigations determined that high-power, pulsed, ultraviolet radiation from excimer lasers can precisely etch the cornea.[1-4] Argon-fluorine gas mixture as an excimer laser medium produces 193-nm radiation, capable of creating corneal incisions with sharply defined margins and a minimal zone of adjacent damage.[2] In contrast, longer wavelength excimer laser ablations at 248, 308, and 351 nm produce incisions with irregular margins and the wider zone of damage, apparently thermal in nature, to the adjacent nonirradiated tissue.[2,5]

Although the precise photobiology of 193-nm radiation and its interaction with biologic macromolecules, in particular collagen, remains to be determined, the most commonly accepted hypothesis is that ultraviolet photons at 193 nm directly rupture the peptide bonds.[6] The energy of a single photon of 193-nm light exceeds the bond strength of the carbon-carbon-nitrogen links. Although the laser energy is largely converted to

heat, with typical thermal changes seen in the ejected protein fragments,[7] minimal thermal injury to the adjacent tissue is seen, presumably owing to both the highly specific and effective photon absorption and the extremely fast photoablation process.[8] In large-area photoablation, measurement of intrastromal thermal gradients demonstrates that local temperature elevation increases with laser repetition rate, drops exponentially with increasing distance from the edge of the ablation zone, and does not exceed 5°C at the edge of the keratectomy.[9]

Epithelial Healing

Numerous laboratory investigations, principally utilizing rabbit and monkey models, have generally demonstrated rapid and stable re-epithelialization over the area of excimer laser ablation. After injury, re-formation of the basement membrane and anchoring fibril network is necessary for tight adhesion of the epithelium to the stroma, and the healing epithelium must synthesize and assemble these structures.[10,11] After mechanical keratectomy wounding, full reassembly of the adhesion complex generally requires 1 to 2 months in rabbits and 3 months in monkeys.[11]

Nevertheless, early instability of the epithelium over the area of excimer laser ablation was not observed in preclinical animal investigations, and normal patterns of rapid re-epithelialization were demonstrated.[12-19] Several immunohistochemical studies demonstrated rapid deposition of fibrogen and fibronectin 1 day after excimer surface keratectomy in monkey eyes.[15,16] Marshall and coworkers[20,21] have postulated that the electron-dense layer of material observed adjacent to the ablation zone, generally referred to as a "pseudomembrane," may contribute to initial surface healing.[22] Basal lamina and hemidesmosomes are seen within 1 week in rabbit eyes[13] and in monkey eyes.[17] Synthesis of type VII collagen, a major component of anchoring fibrils, was also evident at 7 days in monkey corneas, and a nearly continuous anchoring fibril zone is present by 12 weeks.[18]

In a study of green monkeys followed up to 18 months, Beuerman and colleagues[23] found that the percentage of intact basal lamina regenerated under the ablated area averaged 86.3% intact compared with 99.2% for intact basal lamina in the untreated areas, although this difference was not significant. The numbers of hemidesmosomes did not change after the fourth month, and was significantly reduced in the treated areas compared with untreated areas (1.85 versus 2.44 hemidesmosomes per micrometer).

Hyperplasia of the healed epithelium in the center of the ablation zone has been widely observed.[12-17,23] Hyperplasia reduces the corneal flattening induced by the laser ablation, which would lead to regression of the initial hyperopic shift.

Stromal Response

In both rabbit and monkey eyes, the ablation zone is initially clear, but a diffuse reticular haze, sometimes accompanied by a localized or diffusely dense scar, has been commonly observed.[12-18,23] Loss of transparency peaks at approximately 1 month and then slowly diminishes over 6 or more months. Opacification may completely disappear, but some degree of light scattering persists throughout a follow-up period in most animal studies.

During the brief period of de-epithelialization, there is a transient disappearance of keratocytes from the anterior stroma to a depth of approximately 40 μm.[15] Although it was first observed in excimer laser studies, a subsequent study has confirmed this phenomenon after simple scrape injury in rabbits.[24] Within several weeks, activated keratocytes return as fibroblasts with the appearance of vacuolization.[12-17] Dilated rough endoplasmic reticulum is evidence of a high level of keratocyte activity.[13,15,17]

Both rabbit and monkey models show evidence of new collagen deposition under the epithelium in the ablation zone, demonstrated by the fluorescent dye dichlorotriazinyl aminofluorescein (DTAF),[14] entrapment of type VII collagen, presumably from broken-down anchoring fibrils, within the anterior stromal bed,[18] and immunofluorescent histopathologic staining for type III collagen.[16,18] There was intense staining for type III collagen in the bed of the ablation zone, but not in the underlying untreated corneal stroma. A tissue culture study of stromal keratocytes showed no evidence of transformation induced by 193-nm excimer light, with normal growth patterns and contact inhibition of treated cells found to be identical to those of controls.[25] Deposition of new collagen in the ablation zone may lead to corneal opacification, regression of the induced optical change, or both.

Extracellular matrix may also be initially deficient in normally sulphated keratan sulphate,[16,18] although a mild persistent increase in the density of keratan sulphate is seen for as long as 18 months in monkey corneas.[18] Abnormally large proteoglycans are seen within the area of new collagen deposition in the rabbit, most prominent after 2 weeks but persisting up to 45 weeks.[26] In the hazy rabbit stroma, collagen fibrils are notably disorganized,[26] and variable diameter collagen fibrils are seen in healing monkey corneas.[27] Ramirez-Florez and Maurice[28] used a quantitative measurement of corneal haze intensity in a rabbit study of fibroblast proliferation, connective tissue formation, and corticosteroid treatment. They found a high correlation of haze intensity and fibroblast density but a poor correlation of haze intensity and the thickness of newly deposited connective tissue.

Fitzsimmons and colleagues[29] studied hyaluronic acid deposition in the rabbit cornea after excimer laser superficial keratectomy and conclud-

ed that the water balance may be altered following ablation, creating disruptions in the lamellar stromal organization.

Restoration of Corneal Innervation

In addition to providing reflex protection against external injury, corneal innervation is believed to have an important role in epithelial integrity and healing after injury.[30-33] Tervo and coworkers[34] studied reinnervation of rabbit corneas after PRK. The initial laser treatment eliminated the epithelial and subepithelial nerve plexus, leaving sharply cut stromal nerves. The epithelium became reinnervated essentially completely within 3 months, with the innervation originating at the epithelial nerve plexuses at the wound margins. In contrast, stromal nerves showed abnormal morphology, including coiling and abnormal branching of the regenerating axons emerging from the cut stromal nerves. They hypothesized that haze, particularly in the center of the cornea, where denervation is the most prolonged and pronounced, may be related to the destruction of stromal nerves. In a similar study, however, Ishikawa and coworkers[35] were impressed at the relative hypersensitivity of the rabbit epithelium after laser ablation, with a decline back to normal levels occurring only after 210 days. Mechanically debrided corneas exhibited a lower level of hypersensivity compared with the excimer-treated eyes at each of the follow-up intervals.

Summary of Preclinical Studies

Reduction in corneal stromal transparency and increased light scattering may therefore be due to one or more of the following factors: increased density of keratocytes and fibroblasts; vacuoles and stromal debris; disruption of collagen fibril size, alignment, or spacing; abnormality in the type or density of anterior stromal proteoglycans; and the deposition of new connective tissue. Many of the abnormalities diminish or resolve over time, consistent with the observed reduction of the presence of reticular haze in the months after PRK. Permanent dense scar formation, on the other hand, is most likely due to new collagen deposition.

The factors potentially contributing to anterior stromal haze may also disturb the corneal topography and optical performance of a cornea treated by PRK. Differential epithelial thickening or thinning may either be the source of topographic irregularity or mask irregularities in the underlying stroma.

WOUND HEALING AFTER HUMAN PHOTOREFRACTIVE KERATECTOMY

Corneal Opacification: Haze and Scarring

With the nearly universal finding of at least transient haze in animal corneas after PRK, and a disturbing rate of persistent opacification,

human clinical trials of excimer laser surface ablation appropriately emphasized the rate and severity of transient haze and permanent scarring. In general, corneal clarity after PRK in humans is notably better than in animal studies, including nonhuman primates. Some of this improvement may be attributed to the improved lasers and delivery systems of commercial ophthalmic excimer lasers compared with early studies performed with scientific excimer lasers on an optical bench or using prototype ophthalmic devices. As Cintron[36] noted, however, "Rabbit corneas are known to respond vigorously to wounds by synthesizing scar tissue. However, higher vertebrates, such as humans and monkeys, are more sluggish in healing."

Early human trials of PRK utilized optical zones as small as 4.0 mm, because animal studies had suggested that increased haze and scarring occurred with deeper ablations.[37-40] The depth of the ablation for myopic correction increases linearly for the dioptric power but as a square exponential function of the optical zone diameter.[41] Indeed, early clinical experience indicated that the frequency and severity of corneal opacification increased with the amount of attempted correction, particularly over 6 D.[42-45] Recently, Taylor and his group[46] demonstrated a nearly linear relationship of mild corneal haze to dioptric correction, but haze at a more severe level (grade II or more) was infrequent and rare in corrections under 10 D of myopia. Similarly, in a study with the Summit Technology laser utilizing a 5.0-mm optical zone, Dutt and associates [47] reported only mild early haze and complete resolution of all haze by 1 year in corrections up to 6.1 D of myopia, while Ditzen and coworkers[48] found a marked correlation of the severity of haze to dioptric correction for treatments exceeding 15 D of myopia, utilizing the Aesculap-Meditec laser with a 5.0 mm treatment zone.

The human cornea exhibits less dense opacification than animal corneas, but a similar time course of onset and resolution. Most clinical series report maximal, although generally mild, haze having developed within 1 to 2 months after treatment; marked improvement in haze by 6 months; and even further improvement with little or no haze by 12 months.[44,47,49-53]

Despite the results with animal studies, and the early experience suggesting that haze in humans was indeed correlated with ablation depth, difficulties with smaller optical zones became apparent. In particular, patient complaints about halos and glare under dim illumination, and the lack of any margin for error in centration of the ablation zone, led clinicians to expand the treatment zone to 6.0 mm. Surprisingly, the human cornea tolerated the increased ablation depth associated with a larger optical zone with an overall reduction in haze as well as less refractive regression and improved predictability.[52-60] Abundant anecdotal and limited pub-

lished evidence[57] suggest that improved results are obtained with a large optical zone in conjunction with an aspheric peripheral "blend" zone, but other reports fail to confirm a beneficial effect from a multizone peripheral contour.[60] At least in the human cornea, therefore, unanticipated beneficial effects on corneal haze and refractive predictability and stability occur with a 6.0 mm treatment zone, despite the increased ablation depth necessitated.

Utilizing techniques for quantification of light scattering based on the Scheimpflug principle, Lohmann and associates[61,62] demonstrated excellent visual function in patients after PRK compared with spectacle and contact lens wear, and illustrated the importance of differentiating "back-scattering" of light, which is visible to an observer, from "forward-scattering" of light, which is potentially bothersome to a patient. Harrison and coworkers[63] found no evidence of forward light scattering 1 month after PRK in 24 normal myopes, utilizing 3 objective techniques for measuring light scattering; no patient had a haze score greater than 0.5, however. In contrast, Lohman and associates did find significiant forward light scattering 1 month after PRK, although their patients had been treated with an early 4.0 mm optical zone compared with the 6.0 mm optical zone in the Harrison study.

Braunstein and coworkers[64] measured the back-scattered light and found objective verificiation that back-scattering of light correlated with the clinical haze grading, and particularly that ablations with depth greater than 80 μm produce significantly higher levels of back-scattering than PRK with central depth less than 80 μm. The authors did not specify the optical zone. In another objective measurement of light scattering after PRK, Schallhorn and coworkers employed the stray-light meter developed by van den Berg and IJspeert[65] to measure the forward-scattering of light onto the macula caused by an off-axis annular light ring glare source.[66] On the average, there was a 5% increase in forward light-scattering at 1 month, but the forward-scattering at 3, 6, 9, and 12 months was unchanged from preoperative levels. With the pupil dilated, however, increased light scatter compared with preoperative levels was present through the sixth postoperative month, but by the 12th month, values had once again returned to baseline. The treatment zone was 6.0 mm. In all cases, the forward-scattering values after PRK remained markedly lower than in control patients having had previous radial keratotomy. Of particular interest was 1 patient who described poor night vision after PRK with the perception of an "annular mist" surrounding light in the operated eye. Corneal topography appeared normal, and contrast acuity at all levels with and without glare were all normal. The forward-scattering values at 6 and 12 months with the undilated pupil were also normal, but with the pupil dilated, light scattering was markedly increased through the 12th

postoperative month in this patient.

Maldonado and colleagues[67] utilized a computerized system to digitally analyze the anterior slit-lamp photographs of 40 eyes after PRK. This measurement of back-scattered light also showed a weak but positive association of the amount of haze and the attempted level of correction for myopia between -6.0 and -22.0 D. Interestingly, they documented that the initial appearance of the corneal haze was essentially uniform throughout the ablation zone, but as the haze diminished postoperatively, there was a statistically significant trend toward greater reduction in the central corneal haze compared with the peripheral haze.

The distinction between the frequently reported phenomenon of "haze" and the less common complication of "scarring" is unfortunately subjective and variable. In general, most clinicians use the term "haze" for a diffuse reticular opacity of no more than mild or 1+ density on clinical grading schemes and causing little to no objective or subjective visual impairment. The term "scar" tends to be employed for diffuse opacities of greater density (2+, moderate, or higher), often accompanied by impairment of subjective or objective vision. "Scar" is also used to describe more localized dense opacities with or without impact on the patient's vision. In their early report of PRK, Seiler and Wollensak[51,68] reported scarring in 2.8% of treated corneas. Risk factors included noncompliance with postoperative steroid medication, higher levels of myopic correction (up to -9.25D), steroid-induced intraocular pressure response (requiring discontinuation of steroid medication), and collagen vascular and other autoimmune diseases. This report did not differentiate between their initial 26 patients treated with only a 3.5-mm optical zone and the subsequent 255 eyes treated with varying sized optical zones up to 5.0 mm. Later, Seiler and coworkers[42] estimated a 1% incidence of corneal opacification of sufficient density to reduce visual acuity by two or more lines. Moderate to severe haze is generally reported more commonly with higher levels of intended myopic correction (Table I). Durrie and colleagues[69] first called attention to the tendency for a small group of patients to exhibit both increased haze and increased regression compared with the average. In a study where 73% of patients were treated with only a 4.5 mm optical zone, they reported that 4.3% of their patients displayed above-average regression of the initial correction, and 80% of those patients also exhibited moderate to severe haze. Only a total of 4 patients were included in this group, however. Reoperations are frequently performed for excessive opacification as well as regression, although most reports of reoperations include a variety of indications. Table II summarizes 4 series with reoperation rates between 0.81% and 3.7%.[42,70-72]

TABLE I. MODERATE TO SEVERE HAZE AS A FUNCTION OF AMOUNT OF MYOPIC PRK

SERIES REFERENCE	LOW CORRECTION RANGE (D)	% HAZE	HIGH CORRECTION RANGE	% HAZE
43	5 - 8	9	9 - 12	17
45	2 - 7	0	7 - 13	3
68	<6	0.5	>10	10

TABLE II. RATES OF REOPERATION AFTER PRK

SERIES REFERENCE	TOTAL NO. OF PATIENTS	NO. OF REOPERATIONS	% REOPERATION	FOLLOW-UP (MO)
42	298	11	3.7%	Not reported
70	255	4	1.6%	12
71	162	4	2.5%	6 - 12
72	124	1	0.81%	6 - 24

Human Histopathology

Histopathologic studies of human corneas after PRK are understandably few. No published case of penetrating or lamellar keratoplasty following PRK on a previously normal cornea has been found. Several reports do exist, however, of patients who went on to penetrating keratoplasty after previous excimer laser phototherapeutic keratectomy.

The acute morphology several weeks after excimer laser treatment in blind eyes undergoing planned enucleation was first reported by Aron-Rosa and coworkers,[73] who produced partial-thickness incisions with an excimer laser. L'Esperance and coworkers[74] first described histopathology of 3 human corneas from blind patients who had undergone surface ablation 12 or fewer days prior to enucleation. Both of these reports were notable for the essentially normal appearance of the stroma adjacent to the ablation zone, with absence of inflammation or evidence of new collagen deposition acutely.

Wu and colleagues[75] performed a detailed histopathologic examination on 4 patients undergoing penetrating keratoplasty 6 to 15 months after phototherapeutic keratectomy for macular dystrophy, recurrent keratoconus in a previous corneal transplant, and 2 cases of corneal scarring. Ultrastructural examination showed the persistence of abrupt transection of collagen bundles at the margin of the ablation with minimal remodeling. An apparent laser-induced scar with increased numbers of fibrocytes and loss of the normal lamellar structure was present in layers 10 to 15 μm thick in the 2 corneas that had not been scarred prior to ablation. Subsequently, Fountain and colleagues[76] reviewed the same corneal specimens to perform morphometric analysis of the extent and pattern of reformation of the hemidesmosomes, anchoring fibrils, and basal laminae. Although the epithelium was intact, the epithelial basement membrane had focal discontinuities recognized in the original report. In the follow-up study, only 8% of the basal epithelial cells had normal anchoring fibrils present at 6 months, compared with 35% at 15 months. In contrast, the percentage of the basal cell membrane occupied by hemidesmosomes was essentially identical at both postlaser intervals (35.2% versus 37.7%). The cross-sectional area of the basal lamina increased slightly with longer duration of wound healing, but never achieved normal levels. Chan and associates[77] reported marked scarring in a 35-year-old man with previous penetrating keratoplasty who underwent PRK for compound myopic astigmatism twice in the graft. Fifteen months after the second PRK, a dense subepithelial scar in the ablation zone prompted a second penetrating keratoplasty. Light microscopic examination of the initial graft showed anterior stromal scarring, characterized by a loose arrangement of the collagen fibers and a persistent increase in the number of keratocytes. In addition, irregularity in the thickness of the epithelium and localized absence of

basement membrane formation were also noted.

Binder and coworkers[78] had the opportunity to examine 12 corneal specimens obtained 5 to 15 months after lamellar or penetrating keratoplasty following prior phototherapeutic keratectomy for a variety of degenerations and dystrophies. This type of series may be biased by the underlying corneal pathology as well as the failure of the phototherapeutic keratectomy, which led to the subsequent keratoplasty. Nevertheless, evidence of disorganized stromal lamellae in the subepithelial ablated areas was seen in some specimens. In some specimens, newly synthesized collagen was detected by differential trichrome staining. The epithelium showed focal hyperplasia and areas of abnormal epithelial attachment. In a follow-up study, 6 of these corneas were further examined with immunohistochemistry.[79] In addition, 4 corneas from 2 donors were treated with an excimer laser within 96 hours of death and then maintained in organ culture for 3 weeks. Details of the specific laser treatment were not given. Three weeks after laser treatment, the cultured corneas showed heavy deposits of fibronectin, and patchy distribution of elements of epithelial attachment complexes were seen (beta^4 integrin and types IV and VII collagen). In addition, keratocytes stained for prolyl^4-hydroxylase and type I procollagen, indicative of keratocyte activation and the beginning of new collagen formation. In the corneal specimens submitted 5 to 16 months after phototherapeutic keratectomy, a thin layer of type III collagen was found in the anterior subepithelial stroma of the ablation zones up to 16 months after laser treatment; the untreated areas did not respond to the type III collagen antibody. There was no staining indicative of ongoing new collagen production in the corneal specimens 5 months or later after laser treatment.

Fibronectin deposition in response to the PRK wound may occur as excretion in the tear film as well as a local cellular response.[80]

These human studies all show a high degree of similarity to the more extensive literature on animal histopathology, particularly the studies of nonhuman primates.

In efforts to further study the wound healing response in normal human corneas, Cavanagh and coworkers[81] and Corbett and coworkers[82] both employed the tandem scanning confocal microscope manufactured by Tandem Scanning Corporation, Reston, Va. This device allows visualization of the corneal cellular and extracellular structures in vivo. In the Cavanagh study,[81] a 42-year-old woman who had undergone a -2.5 D PRK 6 weeks earlier was found to have evidence of keratocyte activation and up to 20 μm of new collagen deposition. In addition, there was increased reflection of light from the extracellular matrix. No epithelial basal laminar region could be detected, and no subepithelial nerve plexi had regenerated in the treatment zone.

Corbett and coworkers[82] followed 10 patients who had undergone a -6.0-D 6-mm optical zone PRK with sequential examination over 12 months. Visual performance was measured by conventional high-contrast acuity, contrast sensitivity, and glare testing. Corneal haze was objectively measured from retroillumination images and back-scattering from the cornea determined from gray-scale analysis of video slit images. Confocal microscopy was performed at each of the follow-up intervals. By day 2 post-PRK, keratocytes in the anterior stromal immediately underneath the wound had doubled in size, and density had increased by 50%. At 1 month, the cell size had peaked at 3 times normal and cell numbers had peaked at double the preoperative density. The number of cells had returned to normal density by 6 months, but even at 1 year the keratocytes were still double normal size. Presumed subepithelial deposits of extracellular material were judged by the appearance of a bright heterogeneous layer. This peaked at 3 months and then steadily declined, but remained above the preoperative level at 1 year. The time line of the confocal microscopic changes and the visual function tests indicated that the presence of large and more numerous keratocytes may play a role in early visual dysfunction, but it was the postoperative production of extracellular materials that most likely caused mild but persistent loss of contrast sensitivity and persistent glare-induced dysfunction after the sixth postoperative month.

Topographic Irregularities

Visual dysfunction after PRK may be due to focal or diffuse corneal opacification and light scattering, abnormality of the corneal contour in the optical zone, or both . Irregularity in the contour of the ablated corneal stroma may be reflected through the contour of the overlying epithelium, but several clinical series have questioned whether the epithelial healing itself is a primary contributor to irregular corneal postoperative topographies.[83,84] Gauthier and colleagues[85] measured corneal thickness with an optical pachometer and determined epithelial oxygen uptake in a subgroup of eyes. The epithelium was 24% thicker than control eyes when PRK was performed using ablation zones of 4.1 to 5.0 mm, compared with 7% thinner than controls when the ablation zone diameter was 6.0 mm.

Grimm and associates[86] first called attention to the topographic patterns that frequently correlate with regional variations in corneal wound healing. In a retrospective study of 17 eyes with regional variation in wound healing, the clear areas in the ablation zone tended to correspond with flatter areas on videokeratography, whereas areas of subepithelial haze corresponded to areas of topographic relative steepness.

Lin[87] reviewed the corneal topography analyses of 502 consecutive eyes having undergone PRK; most cases were with a 6.0 mm optical zone.

Three principal patterns of nonuniform ablation were identified: "semicircular " crescentic patterns extending 90° or more; "keyhole" ablations with the nonuniform pattern extending less than 90°; and "central islands" with a central elevation whose diameter was at least 2.5 mm. In all cases, a disparity of at least 1.5 D between flattest and steepest area was required for inclusion in a category. The central islands had the most marked deleterious impact on best corrected visual acuity, but a pronounced reduction in the frequency of the islands and the impact on visual acuity occurred over 12 months (26% of patients showing central islands at 1 month compared with 2% at 12 months). Utilizing the "surface irregularity index" of the topography system employed (Computed Anatomy Inc, New York), the study demonstated that reduction in irregularity occurs throughout the 12-month follow-up period for the patient population as a whole. Hersh and colleagues[88] analyzed computer-assisted videokeratography data from 181 patients after PRK with a 5.0 mm optical zone. With the smaller optical zone, no central islands were seen, and other irregular patterns were infrequent.

The topographic phenomenon of "central islands" and the attendant deleterious impact on visual function were not detected in animal studies or early clinical trials, but appeared abruptly when investigators of the VISX system discontinued the practice of blowing nitrogen gas across the operative field during the procedure.[89] Topographic steep central islands are exceedingly rare except with large-area (diaphragm) excimer laser systems with optical zones of 6.0 mm. Spontaneous improvement in the severity and visual impact of these areas of central steepening occurs over time, although re-treatment is occasionally necessary.[88-90]

The following theories have been proposed to explain the occurrence of central islands:

- Laser optics. Differences in laser emission may result in differential increased central ablation due to a "Gaussian" beam profile, automatically avoiding central islands. The VISX laser beam is reported to be highly uniform or "flat-top" in energy density, in contrast to the Summit system, which has a slightly more Gaussian profile.[91] The appearance of central islands with the Summit system when the optical zone was expanded to 6.0 mm argues against this theory.
- Degradation of laser optics. Degrading quality of laser optics might reduce energy density centrally compared to peripherally. This theory would explain sporadic, maintenance-related topographic anomalies but not the consistent occurrence of steep central islands nor sporadic appearance of central islands in some patients but not others who were treated during a single laser session.
- Vortex plume. The ejection of ablated material from the cornea at high speed results in a central particulate "cloud" over the ablation zone [8,92]

that may absorb some of the central energy of the next laser pulse. The appearance of steep central islands with the elimination of the nitrogen gas blow is consistent with this theory, but the lack of any central islands with a 5.0 mm ablation is difficult to explain.

- Vortex debris. Thomas Neuhann has recently produced ultra-high-speed photographic evidence of vortex air currents that draw the particulate debris toward the center of the cornea and deposit it on the corneal surface so that the debris acts like a central mask, which must be ablated by each successive laser pulse (video presentation, Annual Meeting of American Society of Cataract and Refractive Surgery, Seattle, Wash, June 1996). Different vortex currents with 6.0 mm ablation zones compared with 5.0 mm zones have not been demonstrated, however.
- Differential hydration. The nitrogen gas blow had been discontinued by VISX because of reports of increased rates of corneal opacification and less predictable outcomes. VISX investigators had noted a uniformly "frosted" or dry appearance to the cornea with the nitrogen blow, compared with the appearance of central moisture when the nitrogen blow was eliminated.[93,94] A dry stroma will ablate more tissue per pulse than a moist cornea. Maguen and Machat[94] further proposed that the laser pulse–induced pressure waves force water out of the stroma and differentially toward the center of the cornea.
- Epithelial thickening. Greater epithelial hyperplasia centrally than peripherally might result in central steepening. Although epithelial hyperplasia is commonly seen in animal and human histopathology after PRK, central elevation has never been demonstrated. In addition, central steep islands have been detected immediately following PRK.[95]

In this thesis, we are particularly interested in the implications of the progressive improvement in central islands over time with regard to the healing of the human cornea after myopic photorefractive keratectomy.

Biologic and Environmental Factors Effecting Wound Healing

Increasing age is correlated with reduced predictability of refractive outcome and, most prominently, a tendency toward overcorrection. Seiler and Wollensak[51] first noted a tendency to overcorrection in older patients during the first 6 months of surgery, although they reported that this effect was no longer seen at longer follow-up intervals. Dutt and colleagues[47] next reported observing this finding of overcorrection in older patients, except that the overcorrection persisted through the 1-year follow-up of their study.

Hersh and coworkers[96] examined the preoperative and intraoperative characteristics associated with outcomes in the 612 patients of the Phase III multicenter clinical trials of the Summit Technology excimer laser. Older age was independently associated with reduced predictability and

poorer uncorrected visual acuity, with a specific trend toward overcorrection. Other biologic factors associated with reduced predictability and poorer uncorrected visual acuity were lighter-colored irides and increased intraocular pressure. The poorer outcomes associated with increased intraocular pressure may have been due to direct effects of pressure on the cornea, but might also reflect alterations in the postoperative treatment with topical steroid medication necessitated by the pressure elevation. The poorer outcomes with light-colored irides remain to be further studied; perhaps there is some racial effect on corneal wound healing. The tendency for overcorrection in older patients is well known in incisional keratotomies, where diminished healing and contraction of the incision leads to a markedly greater refractive response to surgery in older patients.[97]

Corbett and colleagues[98] investigated biologic and environmental risk factors in the British population having undergone PRK for low to moderate myopia 3 months previously. The tendency for regression was increased significantly in higher dioptric corrections (-6 D compared with -3 D), smaller-diameter treatments (5 mm optical zone versus 6 mm optical zone) and in patients who had shown higher regression after treatment of the first eye. Although there was no statistically significant difference between male and female populations, there was a marked increased risk of regression in women taking oral contraceptive medication. In addition, exposure to ultraviolet radiation in the follow-up period was correlated with a higher degree of regression, whether the exposure was in outdoor activities or artificial, such as welding or using a sun bed. No significant assocation of regression was found with previous contact lens wear, swimming, cigarette smoking, or incidental minor ocular trauma.

POSTOPERATIVE MODULATION OF WOUND HEALING

Pharmacologic Intervention

Despite very limited animal studies demonstrating efficacy of topical corticosteroids for reduction of scarring after PRK,[14] the theoretical desirability of limiting inflammation and wound healing after PRK led all major groups performing early investigations of PRK in sighted eyes to use a topical corticosteroid regimen for many months postoperatively.[49,51,53,99-101] Later laboratory studies continued to demonstrate reduction in inflammation, keratocyte activity, and deposition of new collagen in the highly reactive rabbit cornea following PRK when topical corticosteroids were administered.[102-104]

In a prospective, randomized, double-masked trial by Gartry and coworkers[105] comparing topical corticosteroids and placebo, no lasting benefit was demonstrated in the steroid-treated group, however. This

study had several limitations, notably the use of a 4.0 mm optical zone and the relatively abrupt discontinuation of the steroids after the third postoperative month. Benefit for both -3 D correction and especially -6 D corrections was, in fact, present through the third month but had disappeared by the sixth month, when all patients had been off steroid medication for at least 3 months. Tengroth,[106] Fagerholm,[107] and colleagues reacted to these findings by discontinuation of the routine use of topical dexamethasone in their postoperative PRK patients. Their group experienced a dramatic onset of myopic regression not previously seen. The regression largely reversed with the resumption of steroids. They also reported that patients who showed the onset of regression 15 to 18 months after surgery responded favorably to topically administered steroids. However, O'Brart[108] reported a follow-up prospective, randomized, masked study of 86 patients with 12 months' follow-up, treated with a 5.0 mm optical zone and a slow reduction in topical steroids over a 6-month period. This study also utilized the weaker steroid fluorometholone 0.1%, attempting to approximate the most widely employed current clinical regimens at that time. Statistically significantly less regression was now seen through the sixth postoperative month in the steroid-treated group, but the effect had disappeared 3 months after discontinuation of the topical steroids. There were no significant differences in best corrected visual acuity, clinical haze gradings, objective measurements of forward- or back-scattered light, or perception of halos.

The routine use of topical corticosteroids after PRK remains controversial, without any clear consensus. Influenced by the Gartry[105] and O'Brart[108] studies, however, many clinicians avoid the routine use of topical corticosteroids, at least for lower levels of intended myopic correction. No large, prospective, and well-controlled study has yet addressed the efficacy of topical corticosteroids in patients with a 6.0 mm optical zone PRK, nor the impact of topical steroid medication on topographic abnormalities such as central islands.

In addition to the studies by Tengroth,[106] Fagerholm,[107] and colleagues, several other centers have also reported that topical corticosteroids can induce partial or complete reversal of early and late regression after PRK, as much as 33 months after treatment.[109-111] Moreover, abrupt discontinuation of topical steroids appears to trigger the onset of regression, sometimes accompanied by haze; reinstitution of the topical steroids sometimes successfully reverses these changes.[99,109,112]

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are also frequently employed after clinical PRK, particularly for the control of acute postoperative pain. Szerenyi and coworkers[113,114] used a rabbit model to investigate production of prostaglandin E_2 (PGE_2) and the effect of topical diclofenac sodium 0.1% after laser and mechanical superficial keratec-

tomy. They found that both mechanical and excimer laser superficial keratectomies induced elevation of PGE_2, but the increase was greater for the laser-treated corneas. Hourly treatment with topical diclofenac for the first 3 hours after laser injury significantly reduced the corneal levels of PGE_2 compared with placebo, but presurgical treatment with the topical diclofenac did not result in any further suppression of PGE_2 production. The diclofenac-treated corneas also showed significantly less ingress of polymorphonuclear leukocytes. Nassaralla and associates[115] reported on further rabbit studies from this group, investigating the long-term effect of topical diclofenac compared with topical fluorometholone and placebo in rabbits treated 4 times daily for 1 month and twice daily for the second month. After 2 months, both the steroid and NSAID corneas exhibited less haze than the control group, but the difference was slightly greater and became significantly different for the diclofenac-treated group. Combination treatment with diclofenac and fluorometholone did not result in further decrease in haze, however. Most recently, Phillips and colleagues[116] reported a comparison of the effect of topical diclofenac, ketorolac, and fluorometholone on the production of both PGE_2 and leukotriene B_4 and leukocyte infiltration in rabbit corneas following excimer laser phototherapeutic (disc) ablation. Neither the laser treatment nor the postoperative medications resulted in a significant change in the detected level of leukotriene B_4. Curiously, although both the steroid and NSAIDs resulted in partial suppression of the production of PGE_2 after the laser treatment, the corneas treated with diclofenac exhibited increased density of polymorphonuclear leukocytes, compared with marked reduction in leukocyte invasion in the ketorolac- and fluorometholone-treated corneas. An increase in leukotriene levels, as one of the metabolites of the lipo-oxygenase pathway that stimulates chemotaxis of polymorphonuclear leukocytes, would be expected to account for the increased leukocytes. Because diclofenac is believed to indirectly reduce the products of the lipo-oxygenase, as well as the cyclo-oxygenase pathways, further study is required to understand these inconsistent findings.

In humans, Arshinoff and colleagues[117] assessed postoperative pain and the effect of topical NSAIDs in combination with a bandage soft contact lens after PRK. The investigation was prospective but not masked, and 97 consecutive patients were examined with a postoperative pain survey. Significant and apparently equivalent pain reduction occurred with either topical diclofenac or topical ketorolac in combination with the bandage soft contact lens. Interestingly, although less effective in pain control, topical flurbiprofen sodium, when added to topical steroid, appeared to significantly reduce myopic regression in 68 patients studied prospectively. In a paired-eye study, Ferrari[118] treated 1 eye with topical dexamethasone and the fellow eye with topical diclofenac in 10 patients. No

difference was found in up to 12 months' follow-up, but the series is small.

Lohmann and Marshall[119] measured the concentration of plasmin in the tear fluid of 21 patients prior to photorefractive keratectomy and observed that the 3 patients with the highest levels of plasmin also regressed more than other patients after photorefractive keratectomy, in a sample of a total of 21 patients prior to surgery. Because plasmin degrades many proteins, including fibronectin and laminin, it might impair rapid and stable healing after photorefractive keratectomy. In a prospective, randomized trial of aprotinin, a polypeptide that inhibits plasmin, however, O'Brart and colleagues,[108] including Lohmann and Marshall, could not demonstrate any difference in postoperative healing compared with controls.

Other agents are being examined for their ability to modulate the wound healing response. The cytotoxic agent mitomycin C, when used in rabbits, was reported to reduce the level of haze and reduce the amount of new collagen synthesis and ground substance deposition.[120,121] Follow-up studies demonstrated substantial toxicity from mitomycin C, however, with delayed re-epithelialization and without substantial improvement in corneal clarity.[122] In another rabbit study, idoxuridine and 2 inhibitors of collagen cross-linkage, beta-aminoproprionitrile, and D-penicillamine were not demonstrated to reduce corneal haze.[123]

One study[124] has suggested that basic fibroblast growth factor, in a rabbit model, accelerated re-epithelialization and was associated with a 50% reduction in corneal haze during the first 2 postoperative months. This study emphasized the importance of the interaction of the epithelium and stroma in surface ablation. Follow-up study is needed.

Topical application of interferon-alpha 2b was discovered to inhibit production of glycosaminoglycan by fibroblasts in tissue culture.[125] Subsequently, interferon-alpha 2b was applied topically 4 times daily for 5 weeks in a rabbit model, which led to a statistically significant reduction in corneal haze.[126] This effect was amplified by concomitant use of topical dexamethasone. Haze was observed to continue to improve during 7 further weeks of follow-up after discontinuing the interferon-alpha 2b, and no toxicity was observed. A subsequent study from this group reported a prospective, double-masked, placebo-controlled, randomized study of 31 patients undergoing photorefractive keratectomy.[127] The topical interferon-alpha 2b was applied four times daily for 4 weeks. In this human study, re-epithelialization was delayed by an average of 3 days. There was a tendency for slight reduction in corneal haze grading scores, but this achieved statistical significance only for corrections higher than -5.0 D. There was a small but not statistically significant trend toward better uncorrected visual acuity, associated with final refractions closer to emmetropia and less variability in the postoperative refractive outcome.

This agent deserves further follow-up study, addressing both efficacy and appropriate administration, including evaluation of the ability of interferon-alpha 2b to penetrate intact epithelium.

Thermal Cooling

Although preclinical investigations indicated that a temperature elevation of only about 5°C should be expected in the course of large-area PRK, [9] several surgeons have speculated that temperature elevation during PRK may play a role in abnormal postoperative healing. Niizuma and coworkers[128] investigated the effect of preoperative and postoperative cooling on enucleated pig eyes, rabbit eyes, and 3 human cases of keratoconus undergoing PRK. Five hundred laser pulses resulted in attempted increase of up to 10° in rabbit eyes, and 300 pulses in the human cases of keratoconus caused increases of up to 7°C. The authors reported 1 case of human photorefractive keratectomy, which showed less haze in the eye receiving preoperative cooling compared with the eye that had been treated without cooling. This report is clearly preliminary and requires considerable further investigation. The concept of potential of reduction of thermal injury has been one of the factors prompting increased interest in scanning small-spot laser systems, where cumulative thermal effects would be minimized.

Postoperative Mechanical Debridement

Loewenstein and associates[129] reported some degree of improvement in postoperative undercorrection, haze, and loss of best corrected vision when patients were manually debrided. Their series of 21 eyes of 20 patients centered on moderately high corrections (mean -9.93 D) with a 5.0 mm optical zone. Hyperplastic epithelium and underlying superficial cloudy cornea were scraped with a Beaver blade, with use of topical anesthesia, at the slit lamp. The time between photorefractive keratectomy and scraping ranged from 4 to 10 months, averaging 6.7 months. Twelve treatments were successful, with final refraction between -1.0 and +1.0 D. Ten eyes nevertheless demonstrated persistent unsatisfactory loss of best corrected visual acuity. Cherry[130] reported the opposite effect, however, with worsening of undercorrection by epithelial debridement. He was unable to remove any underlying hazy stroma. In contrast, however, Cherry reported improvement in overcorrected eyes, when they were debrided and the exposed underlying stroma further abraded with a scalpel blade. Mean overcorrection in 19 eyes was reduced from +2.77 D to +0.68 D 12 months after the scraping. He postulated that the debridement caused inflammation and stimulated deposition of new collagen, resulting in regression of the initial overcorrection.

Excimer Laser Re-treatment

Seiler and coworkers[131] first reported successful excimer laser re-treatment after photorefractive keratectomy. In a series of 298 patients, reoperation was performed because of scarring in 11 eyes and undercorrection in 27 eyes (baseline myopia of -6.0 D or less). Only 1 of the 11 eyes showed mild scar reformation after the re-treatment, and 63% of the undercorrected patients had a stable postlaser refraction between -1.0 D and +1.0 D 6 months after re-treatment. Pop and Aras[132] reported re-treatment of 90 eyes with myopic regression; they subdivided these patients into those with minimal haze and those with haze clinical gradings greater than 1. As in the Seiler series, repeated photorefractive keratectomy was performed a minimum of 6 months after the primary treatment. All the patients showed improvement in the uncorrected visual acuity, best corrected visual acuity, and residual refractive error. Re-treatments were less predictable in the patients with greater levels of haze before re-treatment. In particular, the patients with greater haze had a 40% rate of overcorrection. In this series, it is impossible to distinguish whether the overcorrection was due to differential ablation rate of the hazy material or whether these patients have a propensity to anomalous wound healing. In both Seilers series[131] and a later series by Lawless and coworkers,[133] the re-treatment technique included laser ablation of the epithelium utilizing a phototherapeutic keratectomy disc ablation. Observing the pattern of fluorescence of the epithelium, they consistently found the thinnest epithelium at the edge of the ablation zone and the thickest epithelium at the center, consistent with the preclinical observations of epithelial hyperplasia after photorefractive keratectomy. Subsequent large series have continued to demonstrate the usefulness of treatment of undercorrection and excessive haze with repeated photorefractive keratectomy, typically a minimum of 6 months after the initial treatment.[134,135] The predictability of re-treatment is less than the predictability in successful initial treatments, however. Kalski and colleagues[136] published a case of 2 re-treatments over 38 months in a patient exhibiting excessive regression after a photorefractive keratectomy with a 5.0 mm ablation zone. After the first re-treatment, scarring and regression recurred 13 months after a re-treatment with a 5.0-mm optical zone. After a second re-treatment with a 6.0 mm ablation zone, however, clarity improved and the refraction remained stable for at least 12 months, consistent with the many clinical series showing less regression and haze when a 6.0 mm optical zone is used in the primary photorefractive keratectomy.

In addition to the use of photorefractive keratectomy algorithms to guide re-treatment for regression, 2 series have reported phototherapeutic techniques to reduce the undesirable optical side effects of decentered ablation zones.[137,138] Methylcellulose or the epithelium itself can be used as

a masking agent to protect the already flat ablated area while performing further ablation of the undertreated area adjacent to the decentration.

METHODS AND MATERIALS

Wound healing anomalies after PRK were identified from the author's database of personal PRK treatment results and from patients treated elsewhere referred for consultation.

Low-moderate Myopia

In a 1-year period ending November 17, 1996, 133 eyes of 93 patients with preoperative myopia between -1.5 D and -7.0 D were treated. The database was closed at that time to allow at least 1-month follow-up refractive and topographic data on all patients. The database was restricted to patients treated after the FDA granted premarket approval to the Summit Technology laser, because postoperative treatment was altered from investigational protocols, with institution of the use of bandage soft contact lenses and topical nonsteroidal anti-inflammatory agents on all patients after premarket approval from the Food and Drug Administration (FDA).

All patients were treated at a single site with a Summit Technology Apex excimer laser with a 6.0 mm single refractive optical zone. Preoperative evaluation included a comprehensive ophthalmic examination, manifest and cycloplegic refractions, and corneal topography. Attempted correction was usually based on manifest refraction corrected for vertex distance to the corneal plane. Patients with more than 0.5 D disparity of the manifest and cycloplegic refractions underwent a second postcycloplegic manifest refraction, and then a "consensus" refraction was used as a basis for the laser treatment.

Arcuate astigmatic incisions at an optical zone of 7.0 mm were placed in the steep meridian for astigmatism greater than 1.25 D. The incisions were made outside the zone of de-epithelialization, either preoperatively or immediately preceding the PRK.

Three methods of removing the epithelium were employed: (1) marking with a 7.0 mm optical zone marker followed by mechanical debridement with a No. 64 Beaver blade; (2) laser-assisted transepithelial ablation, stopped at the first sign of epithelial perforation as judged by the disappearance of fluorescence from the epithelium, then wiping the base lightly with a No. 64 Beaver blade and cellulose surgical spear; (3) full transepithelial ablation with the excimer laser, having first thinned the central epithelium with "anti-island" central laser pulses. Anti-island pretreatment was instituted in late August 1996 and used on all subsequent treatments. The anti-island pretreatment usually consisted of 30 pulses of the program designated as "Patient Training A." In that mode, the

diaphragm opens to 3.0 mm diameter over the 30 pulses. With method 2 of epithelial removal, the anti-island treatment is performed after epithelial removal; with method 3, the anti-island treatment is applied to the central zone prior to epithelial ablation.

The PRK treatment was centered on the entrance pupil without the use of pharmacologic miotic agents.

After the completion of the PRK, 3 drops each of diclofenac 0.1%, ofloxacin 0.3%, and fluoromethalone 0.1% were administered. A bandage soft contact lens was then applied with sterile technique using 2 cellulose surgical spears. Initially, SeeQuence 2 lenses (Bausch & Lomb) were employed; because of sporadic corneal hypoxia postlaser, the lens was changed to ProTek (Ciba Vision) in February 1996 with no further episodes of hypoxia.

Patients were instructed to apply a single drop of ofloxacin and fluorometholone 4 times daily, and to use the diclofenac drops up to 4 times daily for pain. The diclofenac drops were to be used on an ongoing basis only if they provided pain relief. Oral demerol 50mg/promethazine 25mg combination tablets were prescribed as a pain "escape" medication.

Patients were examined daily until re-epithelialization occurred; this was usually at 48 hours, and in no case longer than 72 hours. The diclofenac drops were confiscated from the patient on the first posttreatment day. After re-epithelialization, the bandage soft contact lens was discarded and the ofloxacin drops were discontinued. For corrections of -3.0 D or less, the fluorometholone was also discontinued. For corrections of -3.1 D or greater, fluorometholone drops were applied 4 times daily for the first month, 3 times daily for the second month, twice daily for the third month, once a day for the fourth month, then discontinued. If a patient was judged to be overcorrected, the fluorometholone was more rapidly tapered or abruptly discontinued. If excessive regression of the optical correction occurred or haze at the 2+ (moderate) or greater level developed, the patient was given a course of prednisolone acetate 1.0% drops at a rate of every 2 hours while awake for 2 weeks, followed by 4 times daily for the third and fourth weeks. Subsequent tapering of the steroid drops was determined by the initial response to steroid treatment and the subsequent course.

The minimum schedule of follow-up examinations with refraction and corneal topographic analysis was at months 1, 2, 4, 6, and 12.

Moderate-high Myopia

Forty-three eyes of 26 patients underwent PRK by the author for correction of preoperative myopia between -6.0 and -12.0 D under an FDA Investigational Device Exemption protocol sponsored by Summit Technology. All treatments were between August 1995 and December

1996. Patients with more than 1.5 D of astigmatism were excluded. Patients were randomly assigned to either a single-zone 6.0 mm spherical correction or a multizone correction consisting of a 5.0 mm optical zone spherical correction with an automated aspheric blend zone between 5.0 and 6.0 mm performed as a single pass, utilizing a Summit Technology Apex laser equipped with modified software for this investigation. The investigation was approved by the hospital Investigational Review Board; the laser and the site differed from that for the low-moderate patient group.

The treatment technique and postoperative follow-up were identical to those for the low-moderate group with the following exceptions. In all cases, the protocol required manual epithelial debridement with a No. 64 Beaver blade at a 7.0 mm outer diameter marked with a surgical optical zone marker. The base was cleaned and wiped with a cellulose surgical spear lightly moistened with carboxymethylcellulose 0.5% drops. After the PRK, dexamethasone/tobramycin combination ophthalmic ointment was applied followed by a pressure patch; use of a soft contact lens was not allowed under the protocol.

Patients were examined on the first and third postoperative days. The patients applied dexamethasone/tobramycin ointment and reapplied the pressure patch 4 times daily. On the third postoperative day, all patients were re-epithelialized. Medication was changed to prednisolone acetate 1.0% drops 4 times daily for the first month, then fluorometholone 0.1% drops 3 times daily for the second month, 2 times daily for the third month, once daily for the fourth month, then discontinued. The prednisolone drops were continued and the dose was adjusted at the surgeon's discretion for evidence of excessive regression or haze higher than a mild level.

Patients were evaluated monthly for the first 6 months, and then at 9 and 12 months and every 6 months thereafter.

Corneal Opacity

Corneal opacification after PRK was graded according to the following commonly employed scale:

Trace:	Opacity visible only by careful inspection with a broad oblique slit-lamp beam
Mild:	Opacity faint but readily seen with diffuse illumination
Moderate:	Easily seen opacity that partially obscures visualization of fine iris and retinal details
Severe:	Dense opacity that markedly interferes with visualizing iris and retinal details

The pattern of the opacity was described as diffuse, localized, ring, arcuate, or focal. The texture was described as reticular or uniform.

Topographic Analysis

All patients were evaluated by computer-assisted videokeratography preoperatively, and postoperatively beginning with the first postoperative month. Placido-disc-based computerized videokeratographic analysis was performed with an EyeSys system, Humphrey Master Vue, or both. In 1 case (case history 2), the patient also had an Orbtek Orbscan slit projection topographic analysis performed at a single postoperative examination.

Topographic irregularities were defined as follows in order to maximize identification of "mild" irregularities:

Islands:	Central elevation > 2.0 D with a diameter of >1.0 mm
Keyhole:	Steepening > 2.0 D compared with the hemimeridian 180° opposite, extending from the periphery to within a 4.0 mm diameter central zone, but not crossing the center, and with a width < 90°
Semicircle:	Steepening >2.0 D compared with the hemimeridian 180° opposite, extending from the periphery to within a 4.0 mm diameter central zone, and with a width > 90°
Focal irregularity:	An area of steepness > 2.0 D compared with the surrounding treated zone, neither central in location nor connected to the margin of the treated zone

Confocal Microscopy

A Confoscan scanning confocal microscope for analysis of patients with healing anomalies was kindly loaned by Tomey Corporation (Cambridge, Mass), for 4 months, allowing examination of a subgroup of patients after PRK. During examination, the objective lens was not in contact with the cornea but rather at a free distance of 1.8 mm spanned with ultrasonic gel. The field width was 330 µm, which corresponds to a magnification of 40x. Optical sections of the cornea were approximately 10 µm in depth. The resolution was approximately 1 µm.

The image was grabbed by an S-VHS recorder with a resolution of 640x480 pixels and recording 25 frames per second.

Statistical Analysis

The contingency tables were analyzed using the program StatXact, providing *P* values for the hypothesis of independence of the classifications.

RESULTS

The demographics of the 2 treatment groups are given in Table III. A total of 119 mild-moderate myopia eyes and 43 moderate-high myopia eyes had a minimum of 1 month follow-up with refractive and topographic examination.

The incidence of wound healing anomalies is given in Table IV for 1 and 6 months postoperatively. Only 2 types of topographic anomalies occurred in either group: central islands and keyhole patterns. Although the incidence of central islands was slightly higher in the moderate-high myopia group at both 1 and 6 months, this difference did not achieve statistical significance (P=0.170). Keyhole patterns were significantly more common in the low-moderate myopia eyes than in the moderate-high myopia eyes at 1 month postlaser (15 [12.6%] versus 1 [2%], P<0.001). The difference between groups was not statistically significant by 6 months, with a small number of patients in either group showing persistent keyhole patterns (5 [15%])versus 1 [4%]).

TABLE III. PATIENT DEMOGRAPHICS

	LOW-MODERATE MYOPIA	MODERATE-HIGH MYOPIA
Total	93	26
No. of Patient eyes	133	43
Age (years):		
Mean	39	38
Range	21 - 66	21 - 53
Sex:		
Male	43 (64 eyes)	11 (19 eyes)
Female	50 (69 eyes)	15 (24 eyes)
Range of attempted correction		
1.5 - 3.0	31	
3.1 - 5.0	60	
5.1 - 7.0	44	7
7.1 - 9.0		12
9.1 - 12.0		22
Combined astigmatic incision	5	
Preop spectacle best-corrected vision		
20/20 or better	127	39
20/25	4	4
20/30	2	

Table IV. Incidence of Wound Healing Anomalies

	1 mo°		6 mo†			
			Persistent anomaly		Resolved anomaly	
	Low-moderate myopia n=119 eyes	Moderate-high myopia n=43 eyes	Low-moderate myopia n=40 eyes	Moderate-high myopia n=26 eyes	Low-moderate myopia	Moderate-high myopia
Topographic						
Central islands	33 (27.7%)	13 (30.2%)	4 (10%)	5 (19.2%)	6 (15%)	3 (11.5%)
Keyhole	15 (12.6)%	1 (2.2%)	5 (15%)	1 (3.8%)	4 (10%)	0
Opacity						
Haze > mild	1 (0.8%)	0	0	0	1 (100%)	—

° Low-moderate versus moderate-high Pearson chi-square = 3.63; exact *P*-value = .170.

† Low-moderate versus moderate-high Pearson chi-square = 2.32; exact *P*-value = .333.

All of the keyhole anomalies were in the inferior half of the ablation zone; all but one occurred between the 240° and 300° hemimeridians. As shown in Table V, at 1 month postlaser, the low-moderate myopic eyes with peripheral keyhole patterns showed a small trend toward increased astigmatism compared with patients with normal topography, but a central topographic island was associated with statistically significantly increased astigmatism of patients (P=0.003). Moderate-high myopic corrections had significantly more induced astigmatism than mild-moderate myopia eyes overall (P=0.044).

Table VI shows the evolution of the refractive cylinder in the limited number of patients with at least 6 months follow-up who had induced refractive cylinder > 0.5 D at 1 month postlaser. Overall, approximately half of the eyes showed spontaneous reduction in refractive cylinder to within ± 0.5 D of the preoperative value. Partial or complete resolution of the central topographic island had occurred at 6 months in all the low-moderate myopia eyes with 1 month induced astigmatism >0.5 D; in 4 of these eyes, the astigmatism simultaneously improved to within ± 0.5 D of the preoperative value, but in 1 eye, the astigmatism persisted even though the island fully resolved, and in another eye, the island improved but persisted and the astigmatism remained > 0.5 D. The small number of patients with induced astigmatism > 0.5 D and 6 months follow-up precludes meaningful statistical analysis.

Only 1 eye in the low-moderate myopia group had haze rated greater than mild at 1 month. In that case, by 6 months the haze had improved to mild and visual acuity was 20/25. This haze was associated with the steep area of a topographic keyhole pattern, which had nearly resolved at the 6-month interval.

The impact of topographic anomalies on visual acuity at 1 month postlaser is shown in Tables VII and VIII and Figs 1 and 2. The relationship of topographic anomalies to the predictability of refractive change at 1 month is analyzed in Table IX and Fig 3. There is a clear tendency for topographic anomalies to reduce uncorrected and best corrected visual acuity and to reduce predictability with several differences achieving statistical significance (Tables VII through IX). Excellent visual acuity and predictability do occur in the presence of some anomalies, however, and some eyes with normal topographic patterns nevertheless experience some loss of vision at the 1-month period.

By 6 months postlaser, many of the anomalies have spontaneously resolved. Moreover, improvement in visual outcomes is seen for both the topographically normal group and those eyes with persistent anomalies (Tables X through XII and Figs 4 through 6). The small numbers of patients with residual topographic anomalies at 6 months postlaser reduces the power of the statistical analysis for those patients There is a

TABLE V. ASTIGMATIC CHANGE AT 1 MONTH POSTLASER IN PATIENTS WITH PREOPERATION ASTIGMATISM OF 1.25 D OR LESS

	NO. OF EYES (% OR SUBGROUP)					
	NO TOPOGRAPHIC ANOMALY		TOPOGRAPHIC "KEYHOLE" PATTERN		TOPOGRAPHIC CENTRAL ISLAND	
	+/- 0.5 D	>0.5 D	+/- 0.5 D	>0.5 D	+/- 0.5 D	>0.5 D
Low-moderate myopia*	57 (87.7)	8 (12.3)	14 (82.4)	3 (17.6)	17 (56.7)	13 (43.3)
Moderate-high myopia†	17 (68.0)	8 (32.0)	1 (100)	0 (0)	10 (76.9)	3 (23.1)

*Low-moderate myopic: No anomaly versus keyhole versus central island; Pearson chi-square = 11.91; exact *P*-value = 0.003.

†Moderate-high myopic: No anomaly versus keyhole versus central island; Pearson chi-square = 0.74; exact *P*-value = 0.795.

Low-moderate versus moderate-high myopia; Pearson chi-square = 11.30; exact *P*-value = 0.044.

TABLE VI. REFRACTIVE CYLINDER AT 6 MONTHS POSTLASER IN PATIENTS WITH INDUCED ASTIGMATISM >0.5 D AT 1 MONTH POSTLASER, GROUPED BY TOPOGRAPHIC PATTERN AT 1 MONTH

NO. OF EYES (% OF GROUP)

	NO TOPOGRAPHIC ANOMALY		TOPOGRAPHIC "KEYHOLE" PATTERN		TOPOGRAPHIC CENTRAL ISLAND	
	+/- 0.5 D	>0.5 D	+/- 0.5 D	>0.5 D	+/- 0.5 D	>0.5 D
Low-moderate myopia	1 (50%)	1 (50%)	—	2 (100%)	4 (66.7%)	2 (33.3%)
Moderate-high myopia	3 (50%)	3 (50%)	—	—	—	1 (100%)

TABLE VII. UNCORRECTED VISUAL ACTIVITY 1 MONTH POSTLASER

	NO. OF EYES (% OF GROUP)									
	NO TOPOGRAPHIC ANOMALY*				TOPOGRAPHIC "KEYHOLE" PATTERN			TOPOGRAPHIC CENTRAL ISLAND†		
	Low-moderate myopia (n=71)‡		Moderate-high myopia (n=21∏)§		Low-moderate myopia (n=15)‡		Moderate-high myopia§	Low-moderate myopia (n=33)‡		Moderate-high myopia (n=12)§	
20/15	3	(4.3)	1	(4.8)	—		—	1	(3.0)	—	
20/20	20	(28.2)	4	(19.0)	3	(20.0)	—	1	(3.0)	1	(8.3)
20/25	14	(19.7)	2	(9.5)	1	(6.7)	—	5	(15.2)	1	(8.3)
20/30	13	(18.3)	—		5	(33.3)	—	9	(27.3)	1	(8.3)
20/40	6	(8.5)	4	(19.0)	3	(20)	—	7	(21.2)	6	(50)
20/50 - 20/70	13	(18.3)	9	(42.9)	1	(6.7)	—	5	(15.2)	—	
20/80 - 20/100	2	(2.8)	1	(4.8)	2	(13.3)	—	5	(15.2)	3	(25)

∏Excludes two (2) patients deliberately undercorrected.

‡Low-moderate: No anomaly versus keyhole versus central island - Pearson chi-square = 20.35; asymptotic *P*-value = .061.

§Moderate-high: No anomaly versus keyhole versus. central island - Pearson chi-square = 13.05; exact *P*-value = .020.

*No topographic anomaly: Low-moderate versus moderate-high - Pearson chi-square = 11.29; exact *P*-value = .076.

†Topographic central island: Low-moderate versus moderate-high - Pearson chi-square = 7.47; exact *P*-value = .291.

TABLE VIII. SPECTACLE-CORRECTED VISUAL ACUITY ONE MONTH POSTLASER COMPARED WITH SPECTACLE-CORRECTED PREOPERATIVE VISUAL ACUITY

		NO. OF EYES (% OF GROUP)									
		NO TOPOGRAPHIC ANOMALY*				TOPOGRAPHIC "KEYHOLE" ANOMALY			TOPOGRAPHIC CENTRAL ISLAND†		
		Low-moderate myopia (n=71)‡		Moderate-high myopia (n=23)§		Low-moderate myopia (n=15)‡		Moderate-high mopia§	Low-moderate myopia (n=33)‡		Moderate-high myopia (n=12)§	
Gain	2 Lines	—		—		—		—	—		—	
	1 Line	5	(7.0)	6	(26.1)	1	(6.7)	—	1	(3.0)	1	(8.3)
	No change	39	(54.9)	8	(34.8)	6	(40.0)	—	9	(27.3)	5	(41.7)
Loss	1 Line	20	(28.2)	6	(26.1)	2	(13.3)	—	11	(33.3)	3	(25.0)
	2 Lines	6	(8.5)	2	(8.7)	5	(33.3)	—	8	(24.2)	3	(25.0)
	3 Lines	1	(1.4)	1	(4.3)	1	(6.7)	—	3	(9.1)	—	
	4 Lines	—		—		—		—	—		—	

*No topographic anomaly: Low-moderate versus moderate-high - Pearson chi-square = 7.53; exact *P*-value = .116.

†Topographic central island: Low-moderate versus moderate-high - Pearson chi-square = 2.80; exact *P*-value = .782.

‡Low-moderate: No anomaly versus keyhole versus central island - Pearson chi-square = 18.82; asymptotic *P*-value = .043.

§Moderate-high: No anomaly versus keyhole versus central island - Pearson chi-square = 3.34; exact *P*-value = .532.

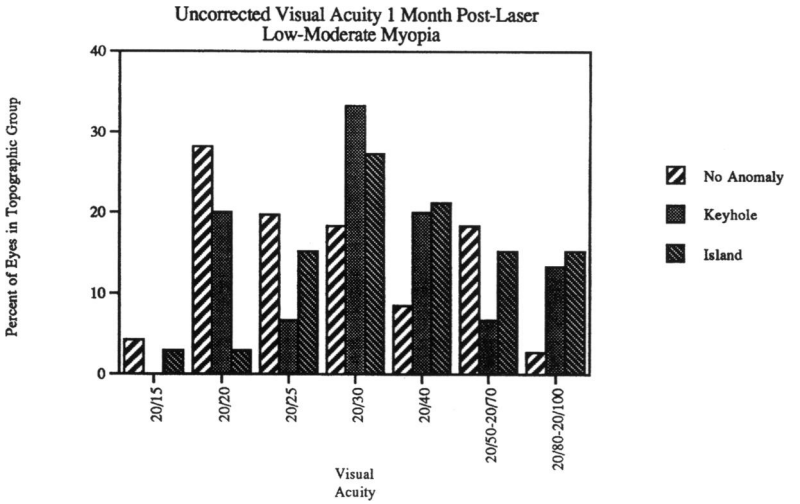

FIGURE 1A
Uncorrected visual acuity 1 month postlaser for low to moderate myopia patients.

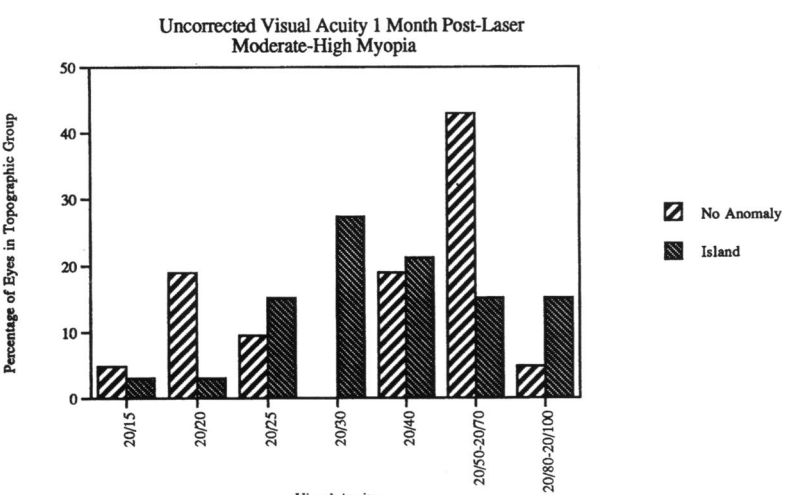

FIGURE 1B
Uncorrected visual acuity 1 month postlaser for moderate to high myopia patients.

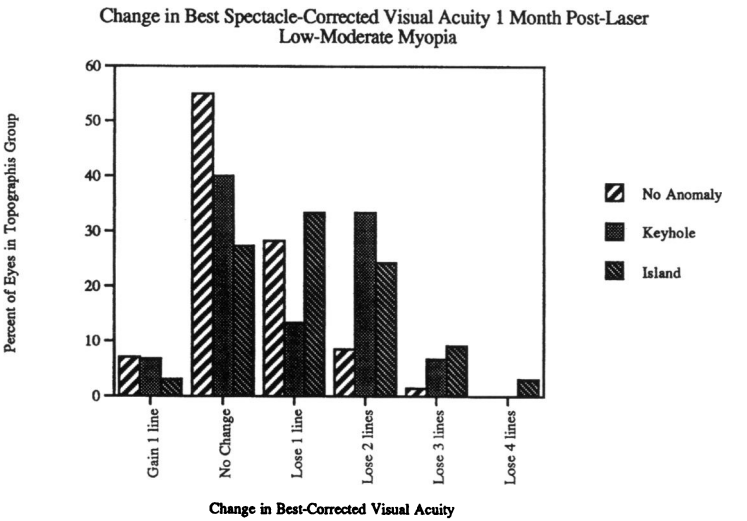

FIGURE 2A

Change in best spectacle-corrected visual acuity 1 month postlaser compared with preoperative best spectacle-corrected visual acuity, for low to moderate myopia patients.

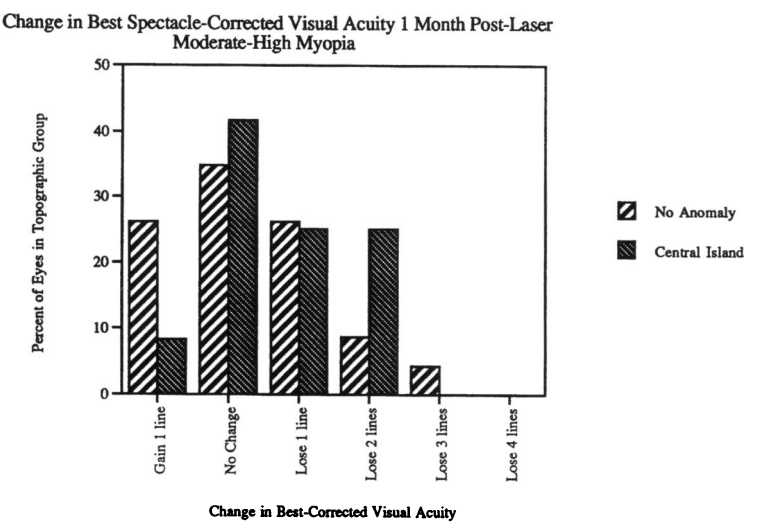

FIGURE 2B

Change in best spectacle-corrected visual acuity 1 month postlaser compared with preoperative best spectacle-corrected visual acuity for moderate to high myopia patients.

TABLE IX. PREDICTABILITY OF LASER-INDUCED RETRACTIVE CHANGE AT 1 MONTH POSTLASER

NO. OF EYES (% OF GROUP)

	NO TOPOGRAPHIC ANOMALY*				TOPOGRAPHIC "KEYHOLE" ANOMALY		TOPOGRAPHIC CENTRAL ISLAND†			
	Low-moderate myopia (n=71)‡		Moderate-high myopia (n=23)§		Low-moderate myopia (n=15)‡		Moderate-high myopia§	Low-moderate myopia (n=33)‡		Moderate-high myopia (n=12)§	
+/- 0.5D	33	(46.5)	6	(26.1)	6	(40.0)	—	16	(48.5)	3	(25.0)
+/- 0.51 - 1.0 D	14	(19.7)	9	(39.1)	3	(20.0)	—	11	(33.3)	5	(41.7)
+/- 1.1 - 2.0 D	16	(22.5)	7	(30.4)	6	(40.0)	—	5	(15.2)	2	(16.7)
+/- 2.1 - 3.0 D	8	(11.3)	—		—		—	—		2	(16.7)
> +/- 3.1 D	—		1	(4.3)	—		—	1	(3.0)	—	

*No topographic anomaly: low-moderate versus moderate-high - Pearson chi-square = 10.54; exact *P*-value = .026.

†Topographic central island: low-moderate versus moderate-high - Pearson chi-square = 7.20; exact *P*-value = .115.

‡Low-moderate: No anomaly versus keyhole versus central island - Pearson chi-square = 12.85; asymptotic *P*-value = .117.

§Moderate-high: No anomaly versus keyhole versus central island - Pearson chi-square = 4.95; exact *P*-value = .292.

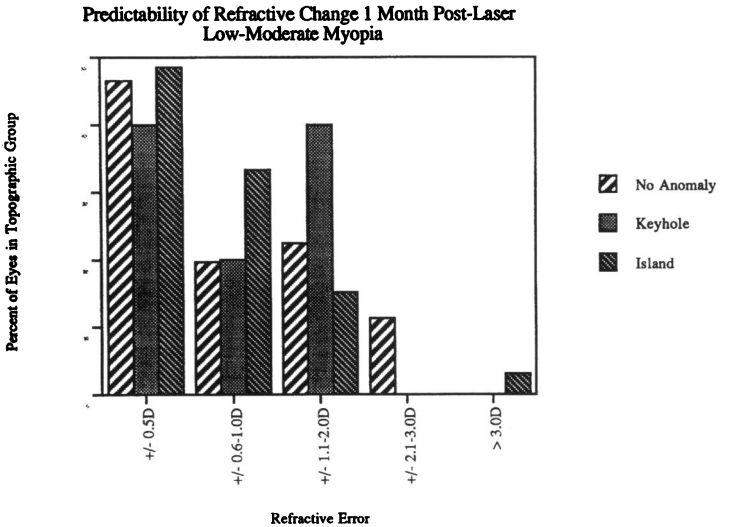

FIGURE 3A
Predictability of refractive change 1 month postlaser for low to moderate myopia patients.

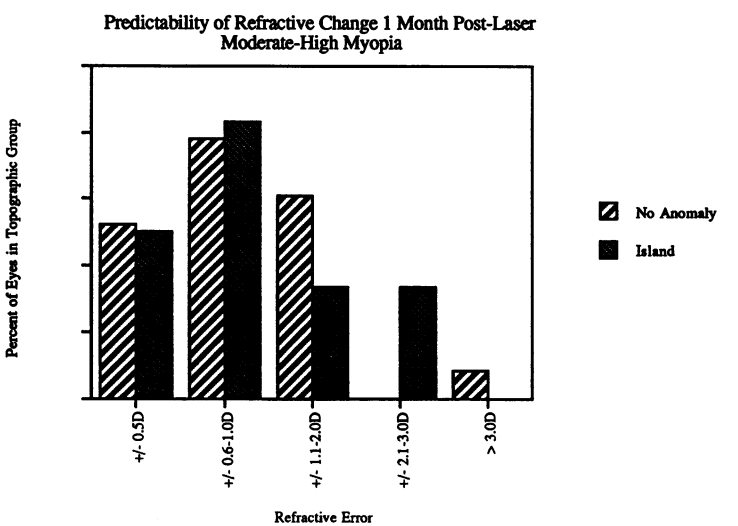

FIGURE 3B
Predictability of refractive change 1 month postlaser for moderate to high myopia patients.

TABLE X. UNCORRECTED VISUAL ACUITY 6 MONTHS POST-LASER

	NO. OF EYES (% OF GROUP)							
	NO TOPOGRAPHIC ANOMALY				PERSISTENT TOPOGRAPHIC "KEYHOLE" PATTERN†			
	Low-moderate myopia (n=37)‡		Moderate-high myopia (n=20)§		Low-moderate myopia (n=9)‡		Moderate-high myopia (n=6)§	
20/15	4	(10.8)	5	(25)	—		1	(16.7)
20/20	13	(35.1)	3	(15)	1	(11.1)	1	(16.7)
20/25	9	(24.3)	6	(30)	6	(66.7)	1	(16.7)
20/30	8	(21.6)	1	(5)	1	(11.1)	1	(16.7)
20/40	2	(5.4)	2	(10)	—		1	(16.7)
20/50 - 20/70	1	(2.7)	2	(10)	1	(11.1)	1	(16.7)
20/80 - 20/100	—		1	(5)	—		—	

*No topographic anomaly: Low-moderate versus moderate-high - Pearson chi-square = 7.75; exact *P*-value = 0.170.

‡Persistent island or keyhole pattern: Low-moderate versus moderate-high - Pearson chi-square = 5.18; exact *P*-value = 0.525.

‡Low-moderate: No anomaly versus persistent island or keyhold pattern - Pearson chi-square = 8.40; exact *P*-value = 0.140.

§Moderate-high: No anomaly versus persistent island or keyhole pattern - Pearson chi-square = 1.57; exact *P*-value = 0.974.

TABLE XI. SPECTACLE-CORRECTED VISUAL ACUITY 6 MONHTS POSTLASER COMPARED WITH SPECTACLE-CORRECTED PREOPERATIVE ACUITY

		NO. OF EYES (% OF GROUP)							
		NO TOPOGRAPHIC ANOMALY*				TOPOGRAPHIC KEYHOLE OR ISLAND†			
		Low-moderate myopia (n=37)‡		Moderate-high myopia (n=20)§		Low-moderate myopia (n=9)‡		Moderate-high myopia (n=6)§	
Gain	2 Lines	1	(2.7)	1	(5)	—		1	(16.7)
	1 Line	4	(10.8)	8	(40)	—		—	
	No change	18	(48.7)	5	(25)	3	(33.3)	3	(50)
Loss	1 Line	11	(29.7)	5	(25)	4	(44.4)	2	(33.3)
	2 Lines	3	(8.1)	1	(5)	2	(22.2)	—	

*No topographic anomaly: Low-moderate versus moderate-high - Pearson chi-square = 7.53; exact *P*-value = 0.098.

†Topographic keyhole or island: Low-moderate versus moderate-high - Pearson chi-square = 3.19; exact *P*-value = 0.590.

‡Low-moderate: No anomaly versus persistent island or keyhole pattern - Pearson chi-square = 3.40; exact *P*-value = 0.527.

§Moderate-high: No anomaly versus persistent island or keyhole pattern - Pearson chi-square = 4.57; exact *P*-value = 0.429.

TABLE XII. PREDICTABILITY OF LASER-INDUCED REFRACTIVE CHANGE 6 MONTHS POSTLASER

	NO. OF EYES (% OR GROUP)							
	NO TOPOGRAPHIC ANOMALY*				TOPOGRAPHIC KEYHOLE OR ISLAND†			
	Low-moderate myopia (n=37)‡		Moderate-high myopia (n=20)§		Low-moderate myopia (n=9)‡		Moderate-high myopia (n=6)§	
+/- 0.5 D	22	(59.5)	10	(50)	8	(88.9)	3	(50
+/- 0.6 - 1.0 D	12	(32.4)	6	(30)	1	(11.1)	3	(50)
+/- 1.1 - 2.0 D	3	(8.1)	3	(15)	—		—	
+/- 2.1 - 3.0 D	—		1	(5)	—		—	

*No anomaly: Low-moderate versus moderate-high - Pearson chi-square = 2.67; exact *P*-value = .525.

†Keyhole or island: Low-moderate versus moderate-high - Pearson chi-square = 2.78; exact *P*-value = .235.

‡Low-moderate: No anomaly versus keyhole or island - Pearson chi-square = 2.86; exact *P*-value = .247.

§Moderate-high: No anomaly versus keyhole or island - Pearson chi-square = 1.73; exact*P*-value = .585.

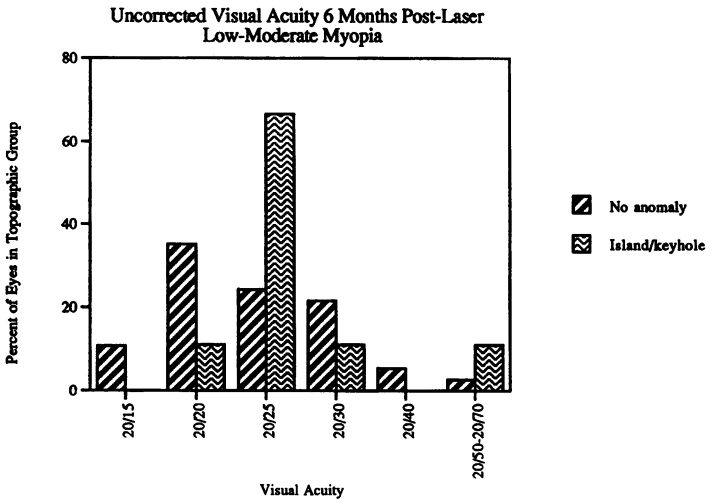

FIGURE 4A
Uncorrected visual acuity 6 months postlaser for low to moderate myopia patients.

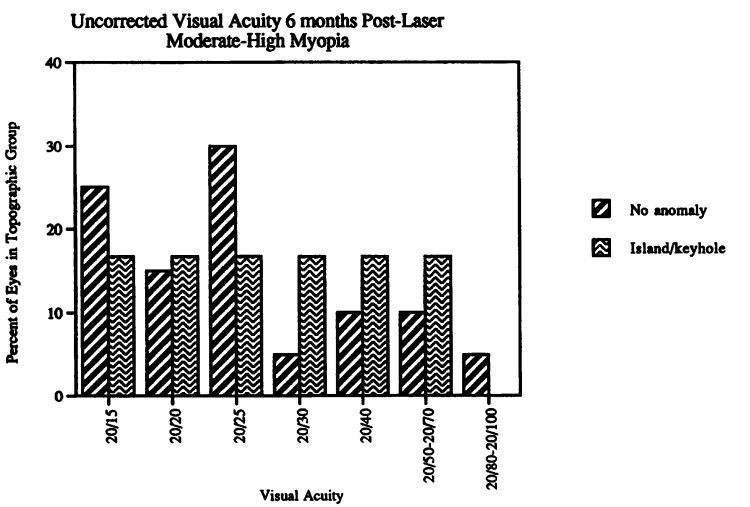

FIGURE 4B
Uncorrected visual acuity 6 months postlaser for moderate to high myopia patients.

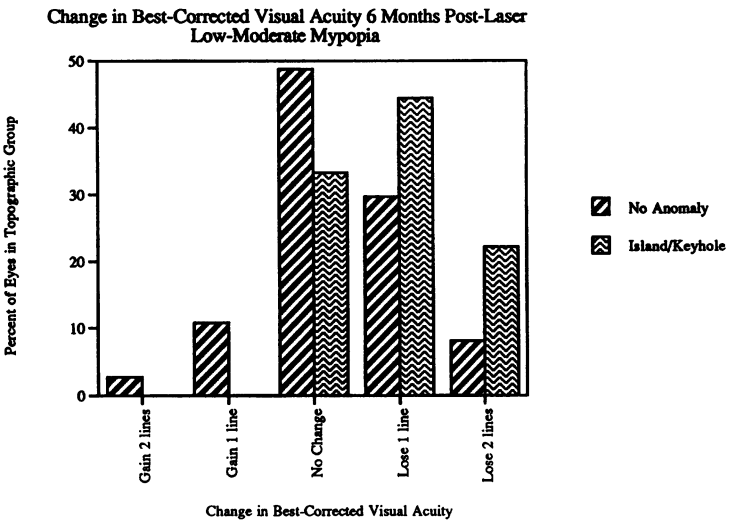

FIGURE 5A

Change in best spectacle-corrected visual visual acuity 6 months postlaser compared with preoperative best spectacle-corrected visual acuity for low to moderate myopia patients.

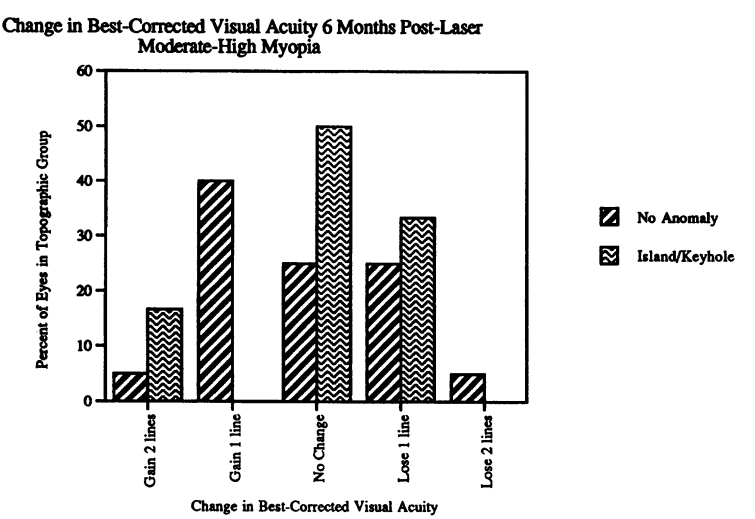

FIGURE 5B

Change in best spectacle-corrected visual acuity 6 months postlaser compared with preoperative best spectacle-corrected visual acuity for moderate to high myopia patients.

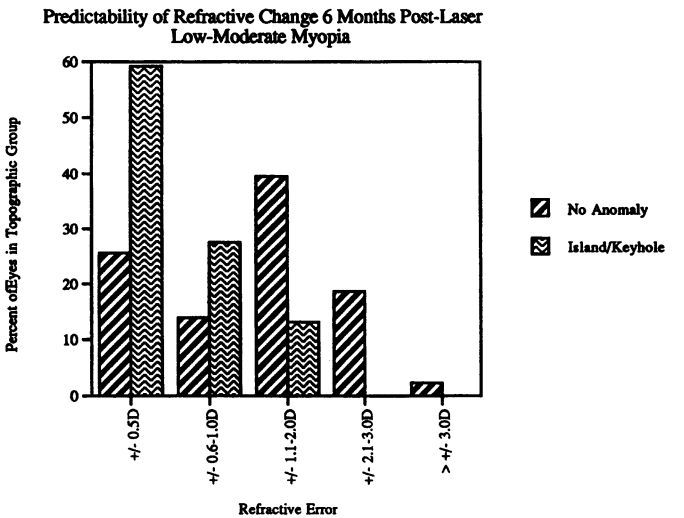

FIGURE 6A
Predictability of refractive change 6 months postlaser for low to moderate myopia patients.

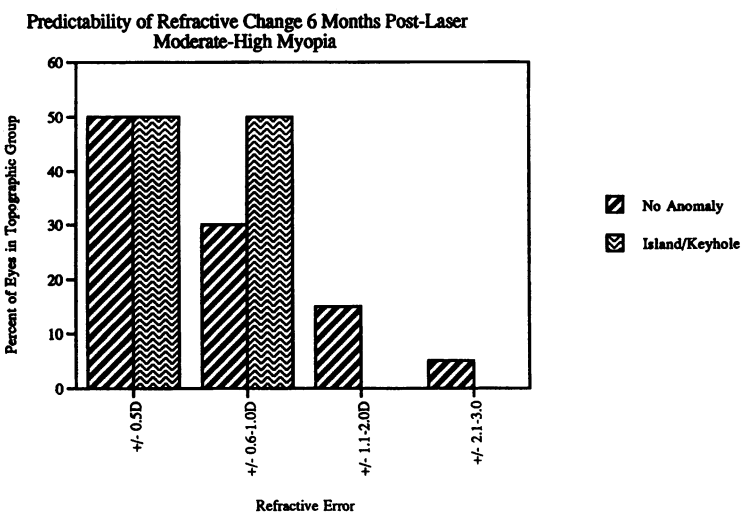

FIGURE 6B
Predictability of refractive change 6 months postlaser for moderate to high myopia patients.

nonsignificant trend for better vision outcomes for low-moderate myopia than for moderate-high myopia.

Because anti-island pretreatment was only begun 3 months prior to database closure, and only on low-moderate myopia patients, only 1 month postlaser results are available for a limited number of eyes. As shown in Table XIII, this particular anti-island regimen reduced but did not eliminate topographic central islands (keeping in mind the "low threshold" definition employed in this study for identifying topographic anomalies). Key anomalies were significantly reduced by anti-island pretreatment, however (P=0.021).

Tables XIV through XVI demonstrate, however, that this particular anti-island protocol reduced predictability at 1 month postlaser (P=0.000), principally due to overcorrections.

REPRESENTATIVE CASES AND CONFOCAL MICROSCOPY

Case 1: Four Months and 1 Month Post-PRK

A 46-year-old man underwent PRK in the left eye on June 25, 1996, for correction of -3.5 D of myopia and on September 24, 1996, in the right eye for -3.8 D of myopia. The corneas were spherical preoperatively.

On November 1, 1996, uncorrected vision was 20/25+1 on the right and 20/25-1 on the left. Refraction was +0.50 -0.50 x165 on the right with 20/20 acuity and -0.50 -0.25 x180 on the left with 20/15 visual acuity. Mild reticular haze was present centrally in the right cornea and zero to trace haze centrally in the left cornea. Corneal topography shows well-centered ablation zones bilaterally, with a smooth contour on the left and a small, low, central island on the right (Fig 8). Fig 9, A through C, shows representative confocal microscopic findings in the left cornea 4 months post-PRK and Fig 10, A and B, shows confocal microscopic findings in the right cornea 5 weeks after PRK. The more recently operated right cornea shows a higher amount of bright extracellular subepithelial material compared with the left at 4 months. Figure 11, A through C, shows confocal microscopy of a normal untreated cornea as a control.

Case 2 (right eye): Central Island Resolution

A 45-year-old white man underwent PRK in his right eye. Preoperative evaluation showed uncorrected visual acuity of count fingers at 10 feet. Best corrected preoperative high contrast visual acuity was 20/15-1 with a contact lens and spectacles. Refractive correction was -4.0 D with a spectacle lens of vertex distance 14 mm and -3.75 D with a soft contact lens. Contrast sensitivity with Regan charts was 95% 8.3; 50% 8.0, 25% 6.3, and 11% 4.4. Baseline topography revealed a normal pattern with 0.36 D of steepening vertically.

PRK was performed with a Summit Technology Apex laser, -3.8 D

Table XIII. Effect of Anti-Island Pretreatment on the Occurrence of Topographic Anomalies in Low-Moderate Myopic Eyes at 1 month PostLaser

	no. of eyes (% of treatment group)					
	no topographic anomaly*†		topographic central island*†		topographic keyhole pattern†	
Anti-island pretreatment n=44	32	(72.7)	11	(25)	1	(2.3)
No anti-island pretreatment n=85	43	(50.6)	27	(31.8)	15	(17.6)

*Anti-island pretreatement versus no anti-island (without keyhole); Pearson chi-square = 2.01; exact *P*-value = 0.218.

†Anti-island pretreatment versus no anti-island (no topographic and topographic central island versus keyhole); pearson chi-square = 6.31; exact *P*-value = 0.021.

Table XIV. Effect of anit-island pretreatment on uncorrected visual acuity 1 month postlaser in low-moderate myopia patients

	No. of eyes (% of group)			
	Anti-Island* N=44		No Anti-Island* N=76	
20/15	—	—	4	(5.3)
20/20	7	(15.9)	17	(22.4)
20/25	5	(11.4)	15	(19.7)
20/30	11	(25.0)	17	(22.4)
20/40	7	(15.9)	9	(11.8)
20/50 - 70	10	(22.7)	9	(11.8)
20/80 - 100	4	(9.1)	5	(6.6)

*Anti-island versus no anti-island; Pearson chi-square = 6.82; exact *P*-value = .346.

TABLE XV. EFFECT OF ANTI-ISLAND PRETREATMENT ON BEST SPECTACLE-CORRECTED VISUAL ACUITY 1 MONHT POSTLASER COMPARED WITH PREOPERATIVE VISUAL ACUITY IN LOW-MODERTE MYOPIA PATIENTS

		NO. OF EYES (% OF GROUP)			
		ANTI-ISLAND		NO ANTI-ISLAND	
Gain	2 Lines	0	(0)	0	(0)
	1 Line	0	(0)	7	(9.2)
	No change	22	(50)	32	(42.1)
Loss	1 Line	15	(34.1)	18	(23.7)
	2 Lines	6	(13.6)	13	(17.1)
	3 Lines	0	(0)	5	(6.6)
	4 Lines	1	(2.3)	1	(0)

Anti-island versus no anti-island; Pearson chi-square = 8.80; exact *P*-value = .107.

TABLE XVI. EFFECT OF ANTI-ISLAND PRETREATMENT ON PREDICTABILITY OF INDUCED REFRACTIVE CHANGE 1 MONTH POSTLASER IN LOW-MODERATE MYOPIA PATIENTS

	NO. OF EYES (% OF GROUP)			
SE	**ANTI-ISLAND***		**NO ANTI-ISLAND***	
≤ +/- 0.50	11	(25.6)	45	(59.2)
+/- 0.51 - 1.00	6	(14.0)	21	(27.6)
+/- 1.10 - 2.00	17	(39.5)	10	(13.2)
+/- 2.10 - 3.00	8	(18.6)	0	(0)
> +/- 3.00	1	(2.3)	0	(0)

*Anti-island versus no anti-island; Pearson chi-square = 33.19; exact *P*-value = .000.

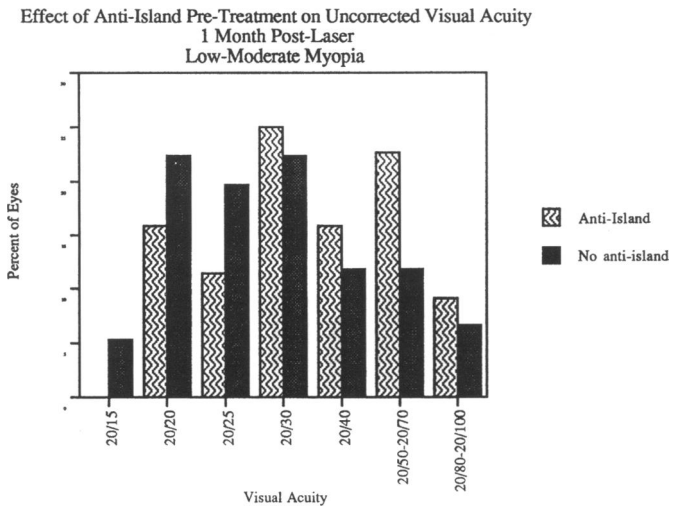

FIGURE 7A

Effect of anti-island pretreatment on uncorrected visual acuity, 1 month postlaser for low to moderate myopia patients.

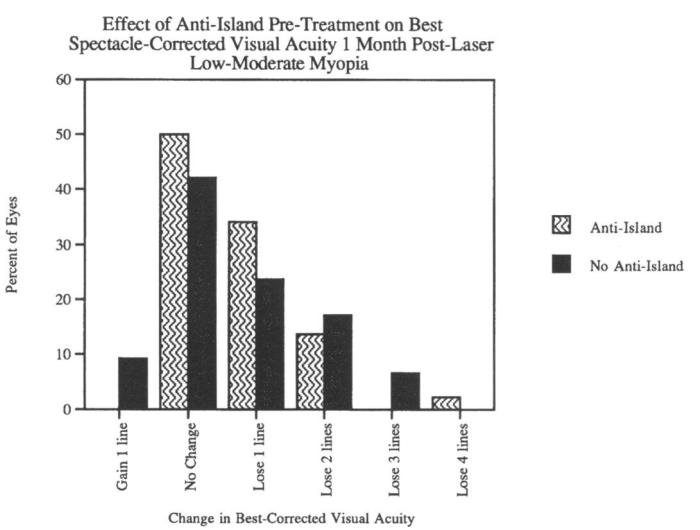

FIGURE 7B

Effect of anti-island pretreatment on best spectacle corrected visual acuity, 1 month post-laser for low to moderate myopia patients.

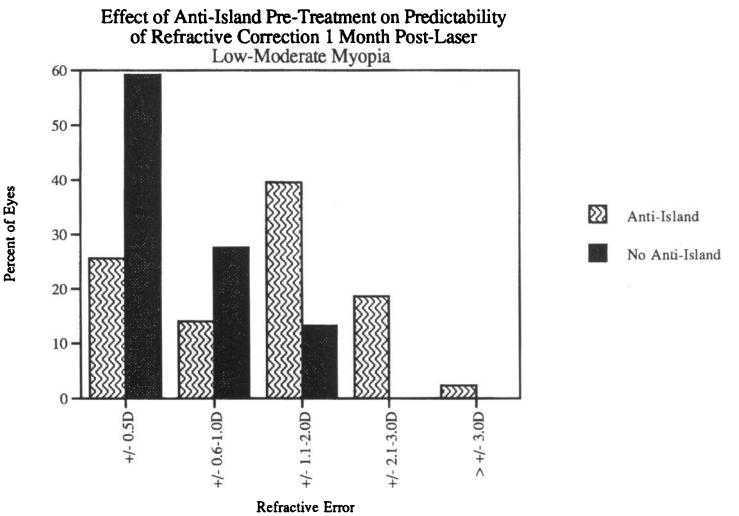

FIGURE 7C
Effect of anti-island pretreatment on predictability of refractive correction 1 month postlaser for low to moderate myopia patients.

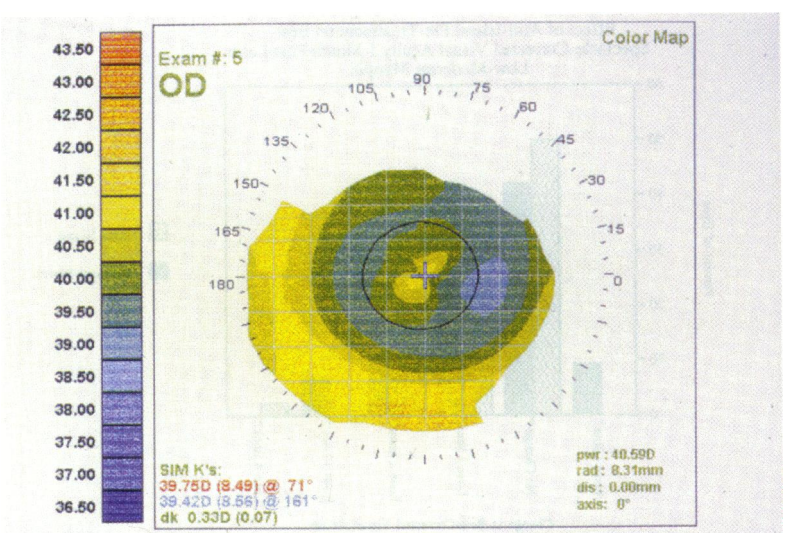

FIGURE 8
Case 1 (right eye). One month postlaser, topography shows well-centered PRK with central island of approximately 1.5 D central power and 2-mm maximal width.

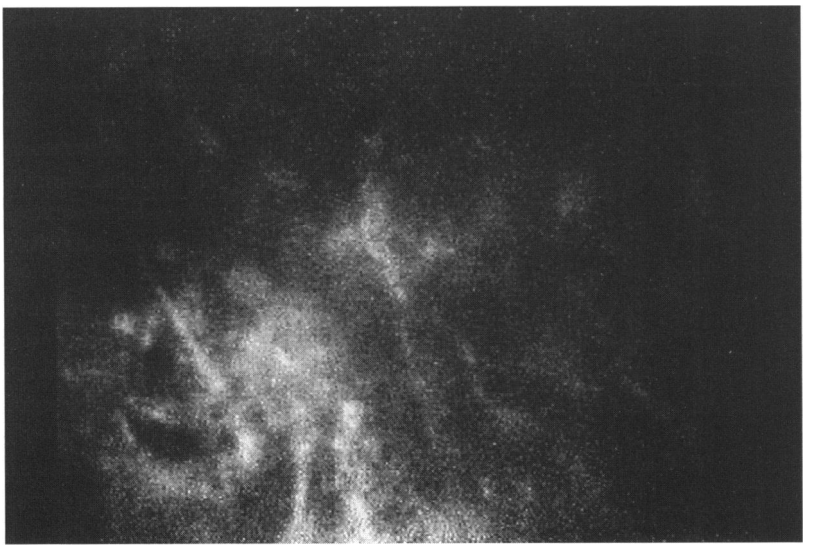

FIGURE 9A

Case 1, confocal microscopy of left eye 4 months postlaser. A, Slight increase in highly reflective extracellular matrix is seen in center of treatment zone. Linear structure toward left may represent regrowth of anterior stromal nerves. This modest increase in extracellular matrix correlates with clinical appearance of bare trace haze on slit-lamp examination.

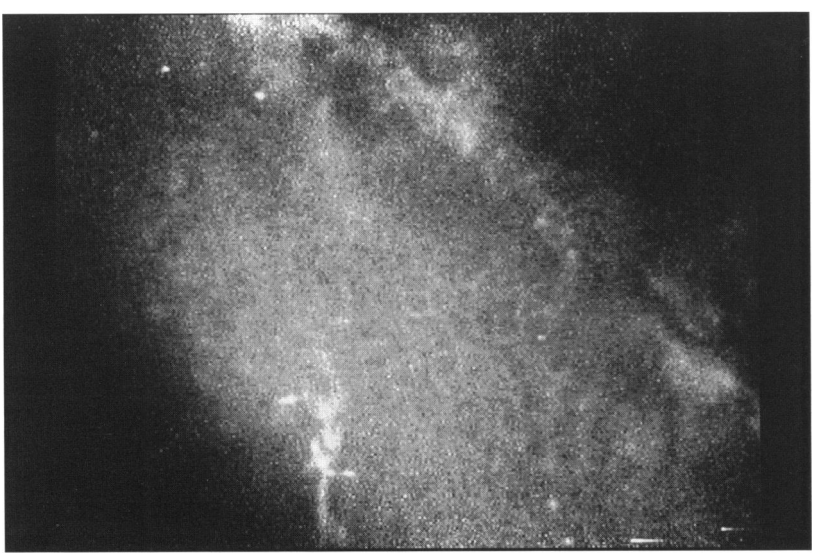

FIGURE 9B

At level of basal epithelium in ablation zone, several highly reflective dots are seen. Identity of these dots is unknown, but they are frequently seen in ablation zone after PRK.

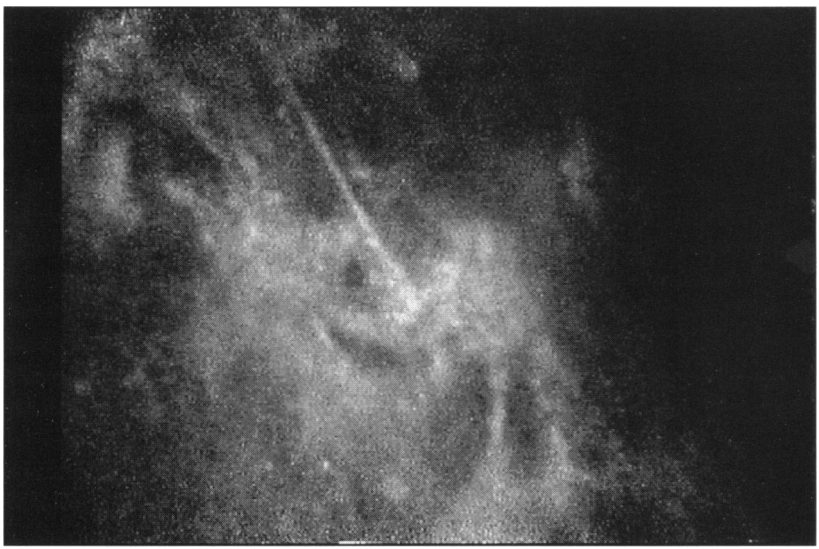

FIGURE 9C
Edge of ablation zone, with untreated anterior stroma shown as dark area to upper right. Moderately dense deposition of extracellular matrix is seen as indistinct, highly reflective material centrally and inferiorly. Portions of keratocytes are visible, as is one linear corneal nerve.

FIGURE 10A
Case 1 (right eye) 5 weeks after PRK. Dense and highly reflective extracellular material is seen centrally, corresponding to area of topographic central island.

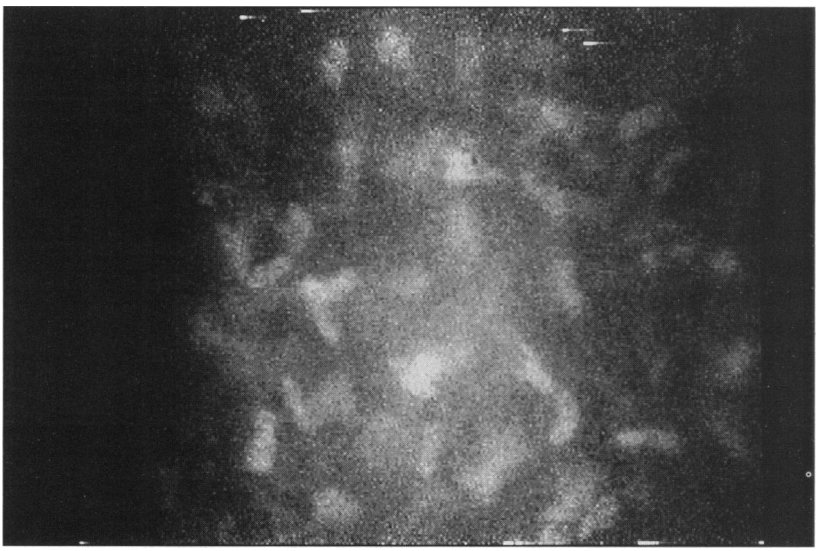

FIGURE 10B
Slightly deeper, anterior stroma shows numerous cells, whose shape suggests that they are predominantly keratocytes. They are enlarged compared with normal keratocytes.

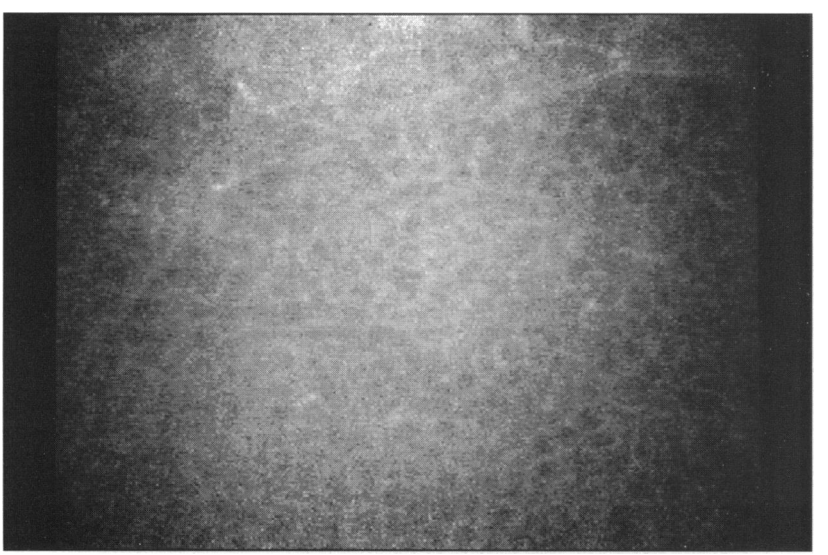

FIGURE 11A
Comparison confocal microscopy from cornea of 45-year-old woman with negative ocular history and absence of contact lens wear. A, Basal epithelium. Branching nerve is seen in upper right.

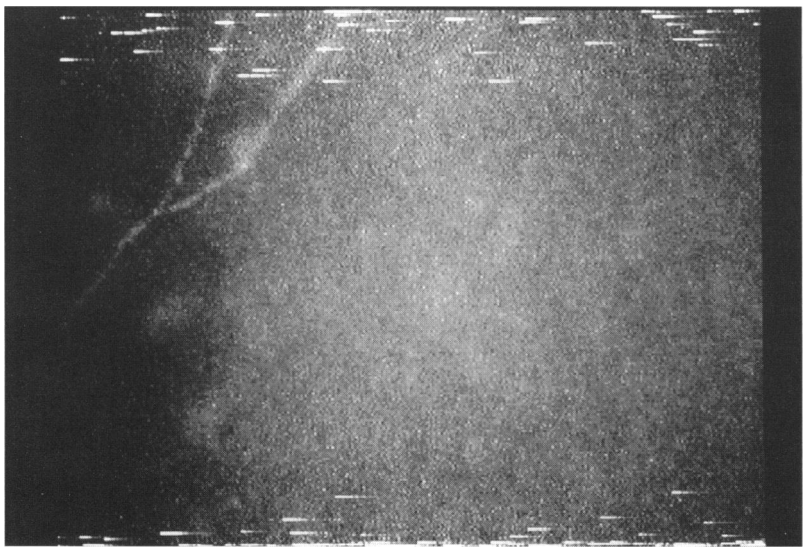

FIGURE 11B
Prominent branching nerve is seen in upper left, located at level of Bowman's layer. Note absence of epithelial cells and keratocytes. Linear white streaks are electronic artifact.

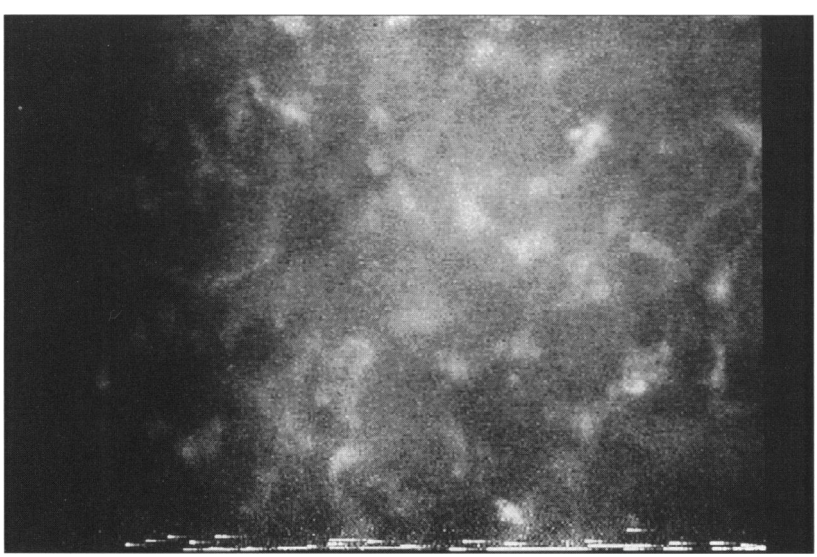

FIGURE 11C
Anterior stroma showing normal size and density of keratocytes. Keratocyte density diminishes in deeper layers of stroma.

correction, 6.0 mm optical zone. The epithelium was manually debrided. Immediately at the completion of the PRK, topical diclofenac, fluoremetholone 0.1%, and ofloxacin drops were administered followed by a ProTek (Ciba Vision) bandage soft contact lens.

Postlaser, fluorometholone and ofloxacin drops were administered 4 times daily until re-epithelialization was complete and the bandage lens removed on the third postoperative day. The ofloxacin drops were discontinued and the fluorometholone drops tapered and then discontinued by the sixth week.

Ten days postlaser, the patient complained of ghost images and blurred vision. Uncorrected acuity was 20/30 and could not be improved with refraction. Corneal topographic analysis with the EyeSys system showed an elevated central island with a vertical length of 2.5 mm, a horizontal maximal width of 2.0 mm, and approximately +2.75 D central power compared with the midperiphery. The ablation zone was slightly decentered nasally. A Humphrey MasterVue topography was similar.

One month postlaser, uncorrected Snellen visual acuity was 20/20+1, but the patient reported a "fuzzy edge" to the letter. There were no other visual complaints other than reduced edge definition; no halos or glare occurred even with pupil diameter exceeding 6 mm. Refraction was +0.50 -0.25 x180 with 20/15 Snellen acuity. Slit-lamp examination showed trace haze in a vertical streak nasal to the center.

Corneal topography at 1 month showed persistence of the central island. A difference display (STARS) clearly showed the initial flattening of the ablation zone with a central island 10 days after PRK, and partial resolution of the island 5 weeks after PRK.

Seven weeks postlaser, the patient reported resolution of the perception of fuzzy edge definition. Uncorrected visual acuity was 20/15, and refraction was +0.25 -0.50 x180 without further improvement. The cornea was entirely clear on slit-lamp examination. Topographic analysis showed a persistent, although diminished, central island (not shown).

Eight months postlaser, the patient reported "the best vision I have ever had." Uncorrected high-contrast Snellen acuity was 20/15, and a refraction of +0.25 -0.25 x180 yielded 20/15+3. Regan contrast sensitivity measured 95% 10.0, 50% 9.3, 25% 8.5, and 11% 6.4. Nevertheless, placido-disc corneal topography showed persistence of an apparent central island, although markedly diminished in height and diameter. At that time, the opportunity to examine the patient with a non-placido disc topography system (Orbscan) became available. This system failed to document a central elevation; rather, a slight central depression was measured.

Eight months postlaser, confocal microscopy at the level of the basal lamina discloses branching highly reflective structures consistent with

regrowth of corneal nerves (Fig 12A). In the center of the ablation zone, patchy areas of increased reflectivity without cellular structure suggests mildly increased extracellular matrix (Fig 12B). Keratocytes appear mildly enlarged but not increased in density compared with control anterior stroma.

Case 2 (left eye): Anti-island Treatment

The patient underwent PRK in his left eye 7 months after the treatment of the right eye. As with the right eye, preoperative topography showed a normal pattern with 0.36 D of vertical steepening. Preoperative uncorrected acuity was count fingers at 10 feet. Best corrected vision was 20/15 with a -4.75 D spectacle lens at a vertex distance of 14 mm and -4.25 D at the corneal plane with a soft contact lens. Regan contrast sensitivity was 95% 8.0, 50% 7.4, 25% 6.3, and 11% 4.3.

PRK was performed with a Summit Technology Apex laser. The epithelium was removed by applying PTK disc ablation pulses with a 6.0 mm optical zone until disappearance of fluorescence at the superior periphery indicated the beginning of epithelial perforation. The remaining basal material was debrided with a technique identical to that used in the patient's right eye. Because of the central island in the right eye, the

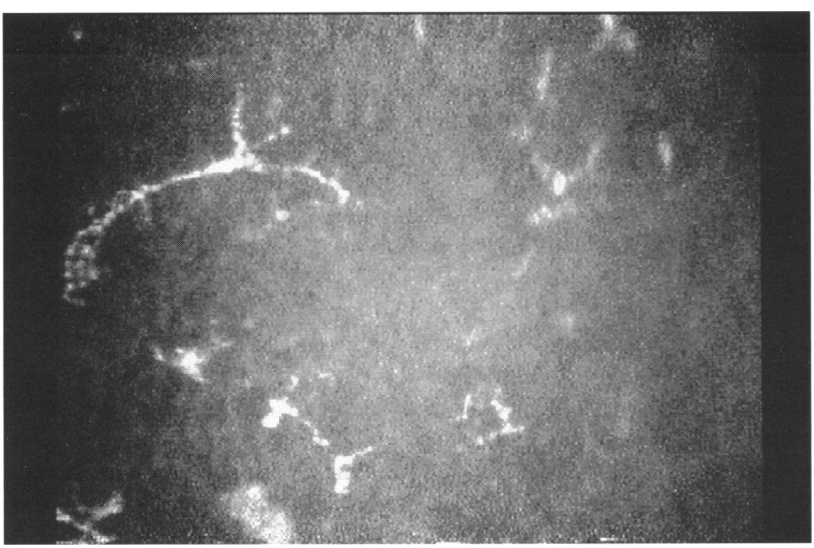

FIGURE 12A

Confocal microscopy of case 2 (right eye) 8 months after PRK. A, Highly reflective, branching structures just beneath basal epithelium suggest regrowth of corneal nerves.

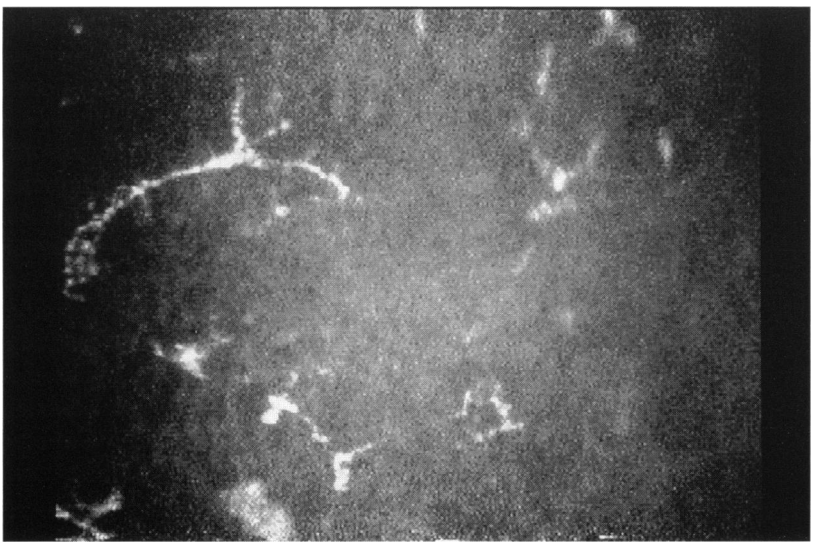

FIGURE 12B
In center of ablation zone, a mild increase in extracellular matrix is suggested. Keratocytes appear normal in density but mildly enlarged compared with controls.

left cornea then received 20 pulses of "Patient Training A" (approximately 2-mm diameter). PRK with a -3.2 D correction and optical zone of 6.0 mm was then performed with a postlaser goal of -1.0 D for "monovision" undercorrection.

The immediate postlaser regimen was identical to that used in the right eye. After re-epithelialization was completed, all topical medications, including steroids, were discontinued.

At 2 weeks postlaser, the patient reported excellent vision with absence of the fuzzy edge definition present at the same postoperative stage in the right eye. Uncorrected visual acuity was 20/30, and a refraction of -0.25 -1.00 x15 yielded 20/15+1.

At 1 month postlaser, uncorrected distance visual acuity was 20/20, although slightly blurred. A refraction of -0.50 -1.00 x5 yielded 20/15+3 visual acuity. Regan contrast sensitivity testing results were 95% 10.4 , 50% 10.5, 25% 9.7, and 11% 7.5. Slit-lamp examination showed a clear cornea.

Placido-disc corneal topography showed slight with-the-rule astigmatism. No central island or keyhole was detected. Scanning topography with the Orbscan system suggested mild central depression, very similar to that in the right eye.

Confocal microscopy 5 weeks post-PRK showed increased levels of extracellular material and increased numbers and size of keratocytes (Fig 13, A and B). The most basal epithelial layer showed highly reflective linear structures with the suggestion of early branching, perhaps representing early nerve regrowth at an earlier stage than seen in Fig 12A.

Case 3: Late Resolution of Central Island

A 38-year-old white man underwent PRK in his right eye on December 1, 1995. Preoperative refraction was -3.50 -0.50 x30 with 20/16 acuity. A -3.7 D PRK was performed on December 1, 1995, with use of manual debridement of the epithelium. The PRK procedure and postoperative regimen utilized the standard protocol described under Materials and Methods. Re-epithelialization occurred in 3 days.

The patient returned at 6 weeks postlaser, with uncorrected acuity of 20/30+2 and a refraction of +1.00 -1.25 x180 yielding 20/25+3 visual acuity. A small but definite central island was present. Fluorometholone drops were tapered and discontinued by 4 months postlaser. The central island persisted essentially unchanged through the 10th postlaser month.

FIGURE 13A

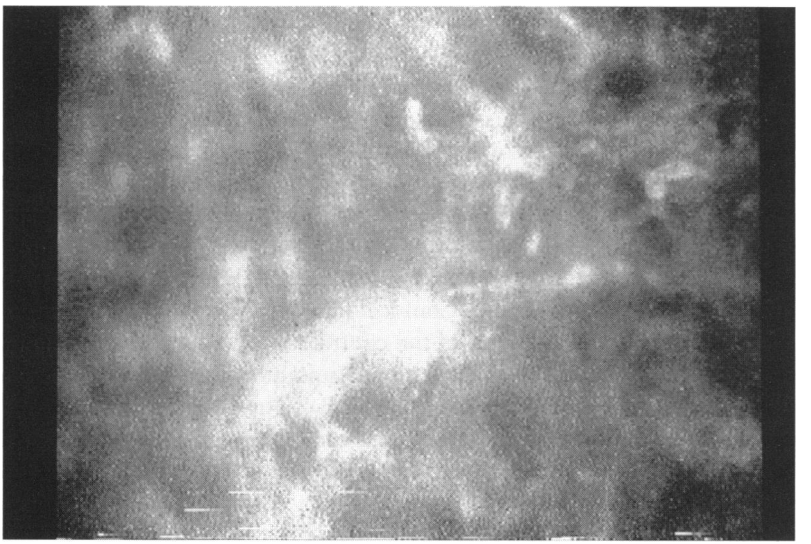

FIGURE 13B

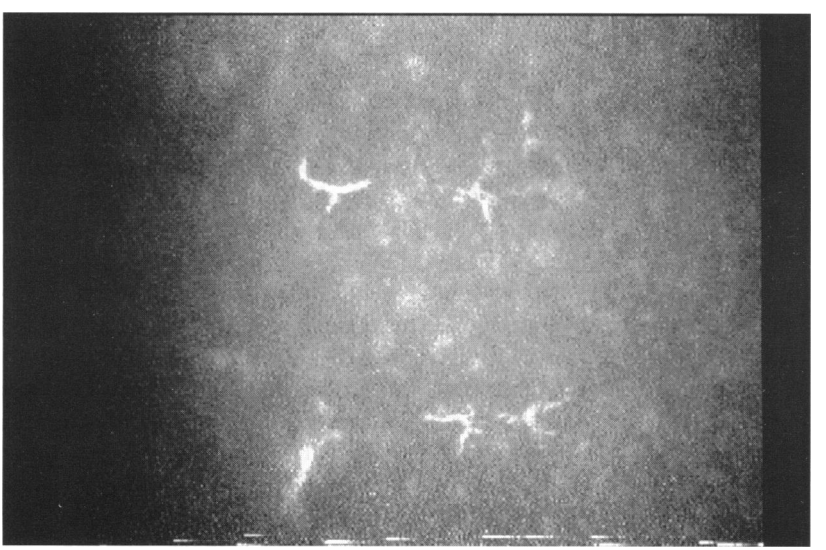

FIGURE 13C

Confocal microscopy of case 2 (left eye). Increased density of extracellular material, increased numbers of keratocytes, and increased keratocyte size are all evident in A and B. This pattern was essentially uniform throughout the ablation zone. Slit-lamp appearance showed only trace reticular haze.(C) At level of basal epithelium, in addition, some small branching highly reflective linear structures are seen. These may represent early stage of nerve regrowth.

Although best corrected acuity was 20/20+2 with a refraction of +1.25 -1.25 x175, uncorrected vision was 20/40 and the patient perceived "poor quality" near vision with or without spectacle correction. He requested re-treatment at that time. The cornea was entirely clear upon slit-lamp examination. Confocal microscopy was performed. Re-treatment was deferred for 3 months, however. The patient returned with a slight improvement of distance vision to 20/30+2, and a sharper end point of 20/15-1 Snellen visual acuity with a refraction of +1.00 -1.25 x180. Corneal topographic analysis showed apparent resolution of the island, with a pattern of regular with-the-rule astigmatism. Confocal microscopy was repeated.

At the time of persistence of the central island, 10 months post-PRK, confocal microscopy detected prominent amounts of extracellular material in the area of the island (Fig 14, A and B). The anterior stroma immediately beneath this region showed abnormally large and numerous keratocytes (Fig 14C). Three months later, when the topographic island had spontaneously improved, confocal microscopy continued to find evidence of increased levels of extracellular material (Fig 14D). However, the anterior stroma immediately beneath this region now showed more normal-sized keratocytes with a density expected for normal anterior stroma (Fig 14E).

Case 4: Resolution and Reappearance of Central Island
A 46-year-old woman underwent PRK as a participant in the moderate myopia investigational protocol on April 16, 1996. Preoperative refraction was -8.25 -0.50 x10 with 20/16 high-contrast acuity. The PRK was a -8.5 D correction at a 14.0-mm vertex distance, and the treatment was multizone with an aspheric blend between the 5.0 mm optical zone and the 6.0 mm total ablation. An approximately 2 D central island was noted on the 1-month postlaser topography. A refraction of +1.25 -0.75 x60 yielded 20/25 visual acuity. At 2 months post-PRK, only a trace residual inferior keyhole irregularity was present, and this had fully resolved by 4 months post-PRK. At that time, uncorrected acuity was 20/25 and the patient refracted with -0.25 sphere to 20/16. The patient was instructed to taper the fluorometholone drops over the subsequent 2 months.

However, at an 8-month follow-up examination, she reported she was still taking the drop once daily. Vision was unchanged, although the refraction was now -0.25 -0.75 x170. Slit-lamp examination showed minimal haze in a small central area. Corneal topography showed return of a vertically oriented central island. This persisted for the following month. Confocal microscopy was obtained at that time.

Confocal microscopy was performed in an effort to identify factors that might have accounted for the late reappearance of the central island. As seen in Fig 15A, there may be some inflammatory cells in addition to

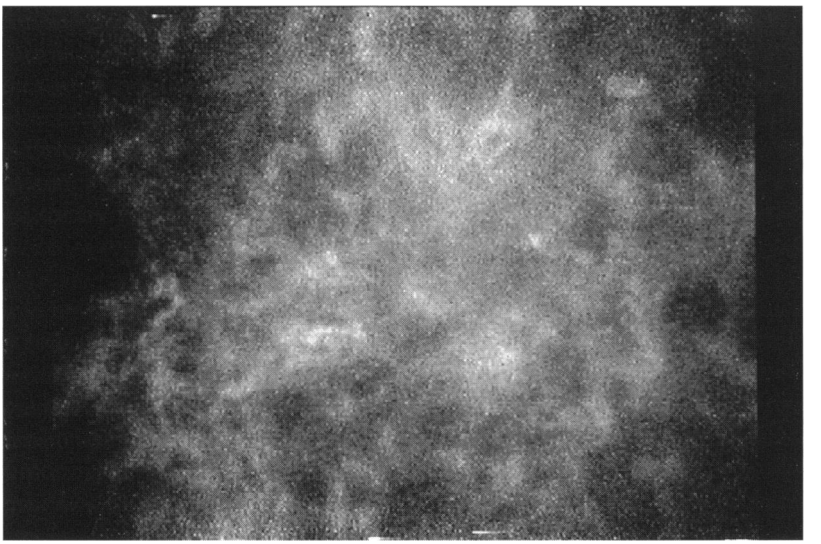

FIGURE 14A

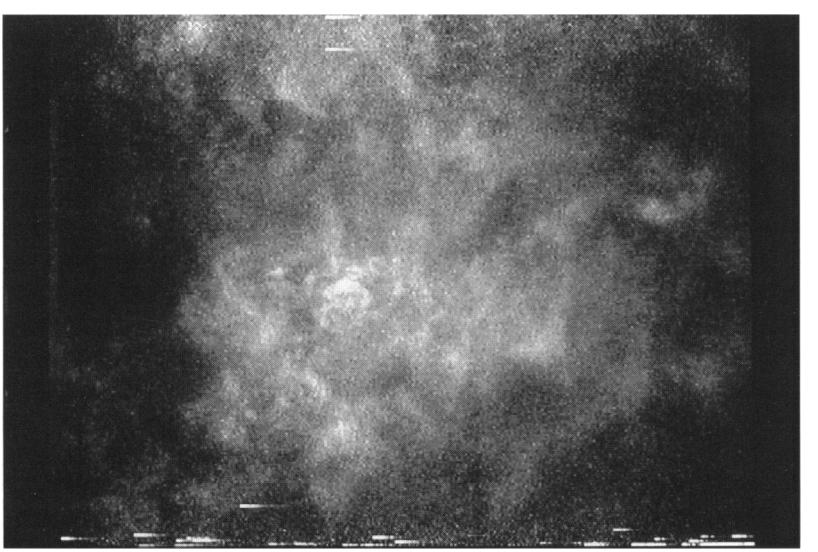

FIGURE 14B

Case 3. Confocal microscopy of right eye. A and B, Ten months post-PRK, at time of unchanged persistent central island on corneal topography, prominent bright extracellular material was seen centrally. Cornea was entirely clear on slit-lamp examination at this time

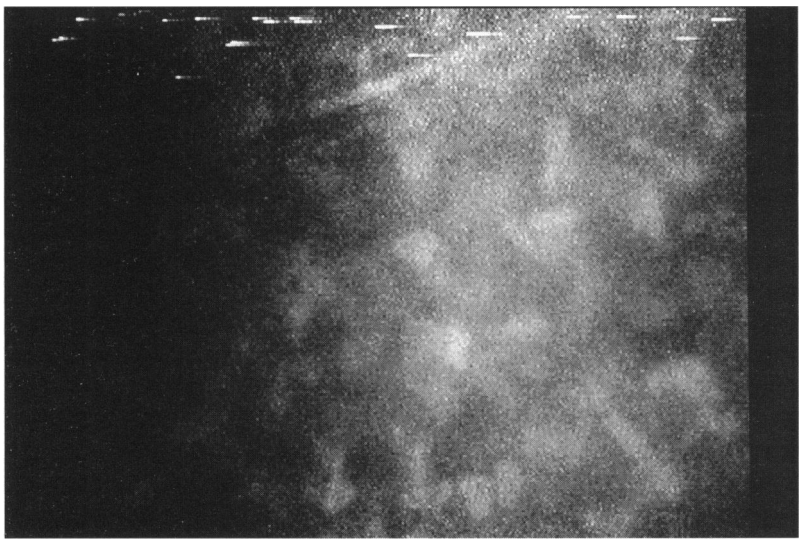

FIGURE 14C
Just beneath dense extracellular material, anterior stroma exhibited increased density and increased size of keratocytes.

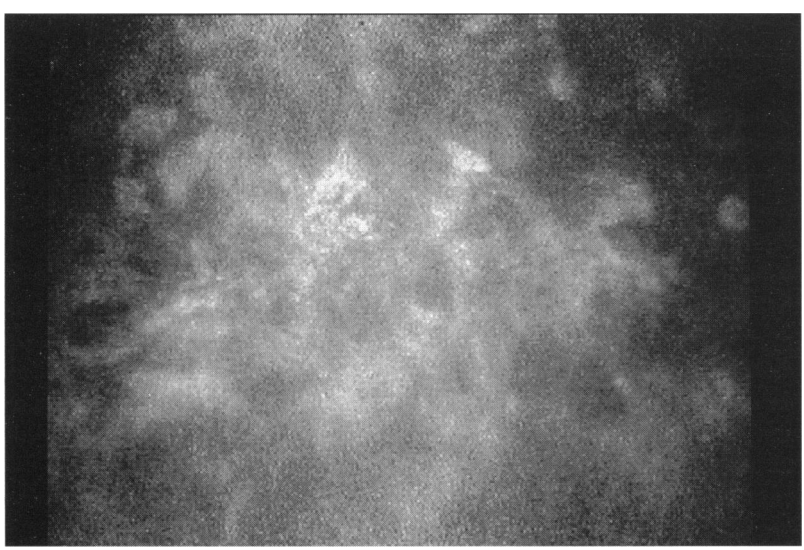

FIGURE 14D
Three months later, with marked improvement in central island on corneal topography, confocal microscopy continued to detect moderately prominent extracellular matrix just beneath epithelium.

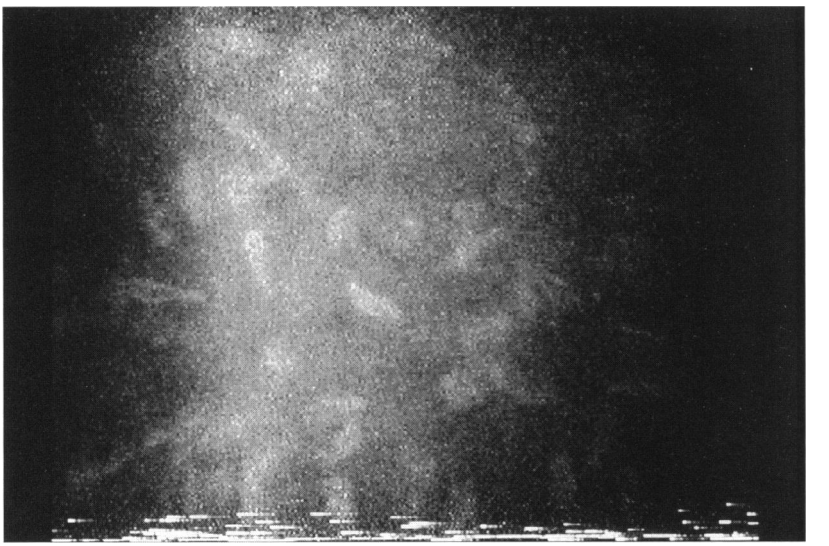

FIGURE 14E

Slightly deeper, however, anterior stroma showed decreased density and size of keratocytes, more typical for normal healing pattern 13 months post-PRK.

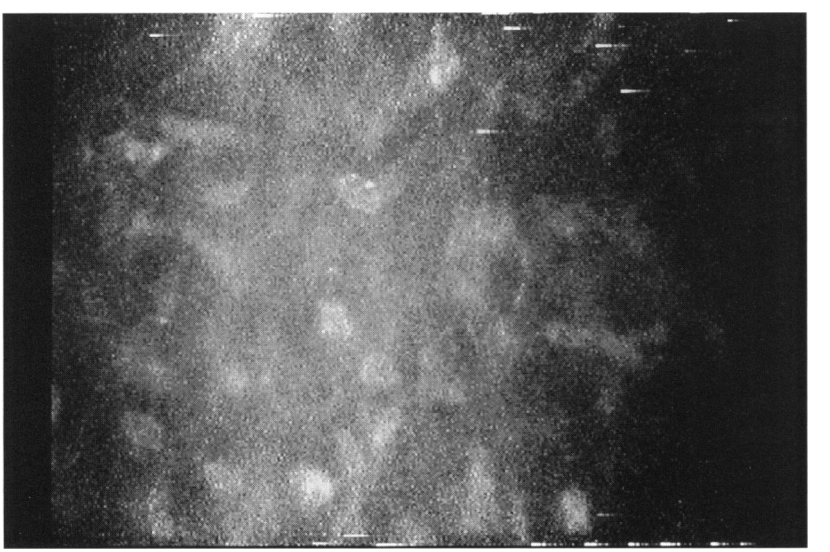

FIGURE 15A

Case 4 (1eft eye). Confocal microscopy was performed 9 months post-PRK in an effort to identify causes for reappearance of central topographic island seen in early postoperative phase. A, Only a mild increase in extracellular matrix is seen in anterior stroma of central cornea. Several round cells are present in addition to more elongated appearance customarily seen with keratocytes; round cells may represent inflammatory cells or enlarged portions of keratocytes whose long processes are outside image plane of microscope.

keratocytes in the anterior stroma. Fig 15C showed persistence of increased size of keratocytes, as well as some evidence of nerve regrowth; the density of keratocytes is not notably increased compared with normal for this postoperative interval, however. Fig 15B shows highly reflective dotlike bodies of unknown etiology, frequently found after PRK. In this case, confocal microscopy was not helpful in determining a cause for the return of the central island, other than the possible presence of inflammatory cells.

Case 5: Debridment for Post-PRK Hyperopia

A 29-year-old white man underwent PRK on February 20, 1996, with a -5.3 D ablation. Epithelium was removed with transepithelial ablation and wiping of the base; no anti-island treatment was performed. Preoperative manifest refraction was -5.00 -0.50 x180 with 20/15-1 acuity and cycloplegic refraction was -5.25 -0.50 x005 with 20/15 acuity. Two months after PRK, uncorrected acuity was 20/60 and refraction was +1.75 -0.50 x5 with a 20/25+2 visual acuity.

FIGURE 15B

At level of basal epithelium, highly reflective dotlike bodies are seen.

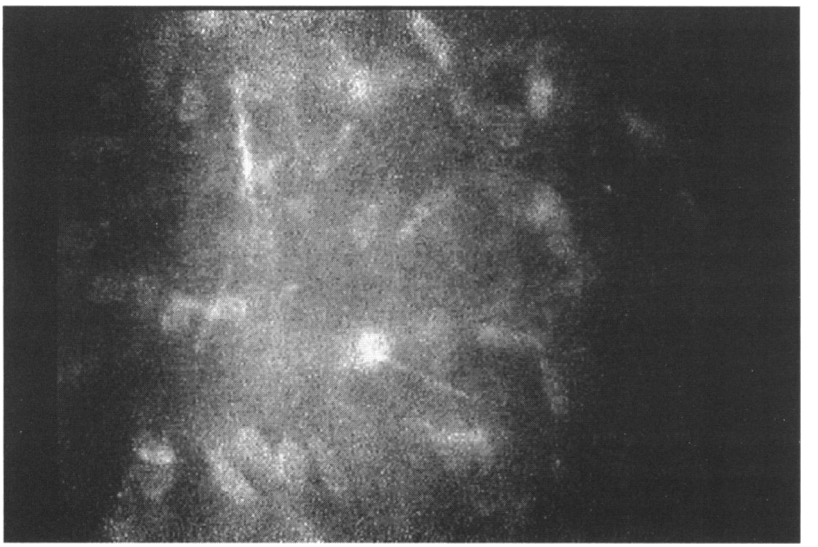

FIGURE 15C
Early regrowth of nerves appeared to be present. Keratocytes appear enlarged, although not unusually dense for this location and phase of healing.

Because the spherical equivalent refraction was +1.25 D at the first postoperative month, the fluoremetholone drops were rapidly tapered and discontinued at the second month. A refraction at the 2-month visit was +1.75 -0.50 x5 with a 20/25+2 acuity; uncorrected visual acuity was 20/60. Corneal topographic analysis showed an inferior keyhole pattern.

Five months after PRK, the haze had diminished to trace level but refraction remained hyperopic. Although uncorrected vision was 20/30, a refraction of +2.00 -0.50 x140 could only improve visual acuity to 20/25. An Acuvue soft contact lens was worn without interruption for 1 month in an effort to stimulate regression, but there was minimal improvement. Refraction after removal of the lens remained hyperopic, at +1.50 sphere, and visual acuity remained 20/25. The patient was unhappy with the quality of vision, and therefore epithelial debridement was performed at the slit lamp after topical anesthesia. The epithelium was easily removed, atypical for an ablation zone. The base of the ablation was scraped aggressively. The immediate regimen was identical to that after PRK, except that steroid was omitted.

One month after debridement, the left eye remained hyperopic, with a refraction of +3.50 -0.75 x125 yielding 20/30+3 visual acuity. Slit-lamp

examination showed trace to mild haze. Corneal topography showed central corneal power 0.63 D steeper than prior to the scraping. Confocal microscopy was performed. Confocal microscopy 1 month after the epithelial debridement showed a dense layer of highly reflective extracellular material (Fig 16). This appearance is similar to that seen 1 month after initial PRK.

At the most recent follow-up, 3 months after debridement, the patient reported improvement in the quality of vision, although he still perceived that he was far-sighted. A refraction of +1.00 -2.00 x175 yielded a 20/15 level of visual acuity. Corneal topography continued to show the inferior keyohle pattern. There was a slight increase in the central corneal power, to 40.68 D.

Case 6: Re-treatment for Symptomatic Keyhole Irregular Astigmatism
A 58-year-old white man underwent PRK in the left eye on June 25, 1996. He was programmed for an intended correction of -3.0 D. Epithelial removal was with the transepithelial laser technique with wiping of the base. No anti-island treatment was peformed. Preoperative refraction was -3.75 -0.50 x45 with 20/20 acuity. Re-epithelialization occurred within 2 days and was stable.

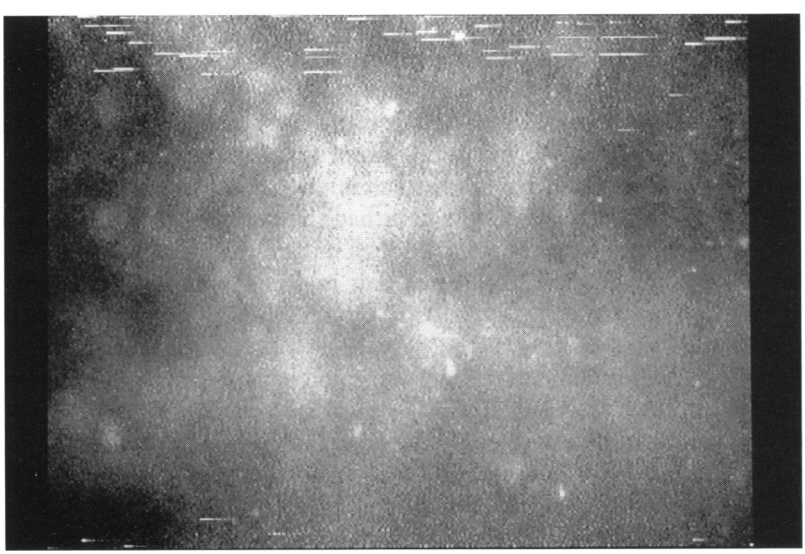

FIGURE 16
Case 5 (left eye) 1 month after epithelial debridement. Confocal microscopy showed highly reflective extracellular material, similar to appearance 1 month after laser PRK in case 1 and case 2.

Four months post-PRK, the patient felt that the quality of postoperative vision was inferior to the results of subsequent PRK in the right eye. The right eye was 20/20-2 uncorrected, but the uncorrected vision in the left eye was 20/40, and best corrected visual acuity was 20/25 with refraction of -0.75 -0.50 x 90. Slit-lamp examination showed barely visible trace haze in a diffuse pattern without any localized, more dense haze. Corneal topography disclosed an inferior keyhole pattern, steepest at approximately the 300° hemimeridian.

Approximately 6 months after the original PRK, the left eye was retreated. Confocal microscopy was performed over the topgraphically steep area inferotemporally prior to re-treatment with the laser. Keratocytes in this area appear mildly enlarged (Fig 17), as expected for this stage of healing,. The density of keratocytes appeared typical for a cornea 5 months after PRK. There was no increase in detected extracellular material, nor any difference between the steeper interferotemporal zone and the remainder of the flatter optical zone.

Epithelial debridement was performed with a 6.0-mm optical zone PTK program. Breakthrough of the epithelium, as judged by the disappearance of epithelial fluorescence, first occurred as a peripheral ring, and

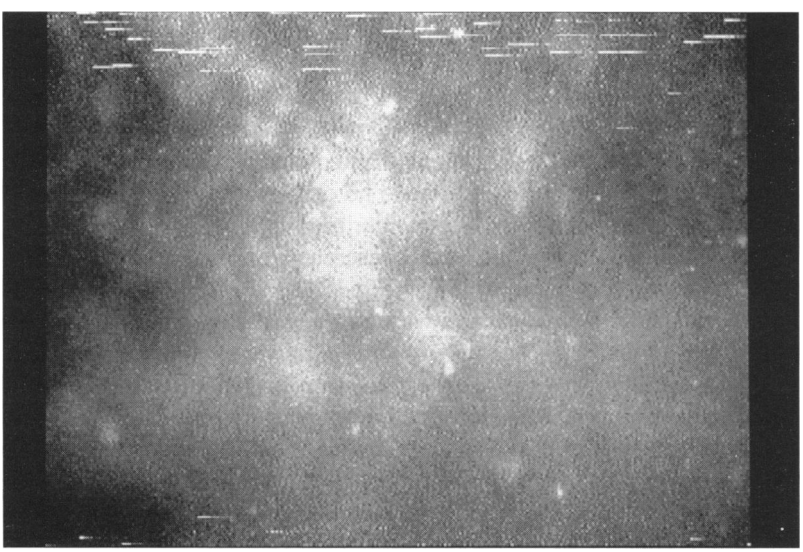

FIGURE 17

Case 6 (left eye). Confocal microscopy of inferotemporal steep zone obtained prior to retreatment shows mildly enlarged keratocytes, but density of keratocytes appears typical for this stage of healing after PRK. There is no evidence of prominent extracellular matrix in steep zone compared with remainder of flatter optical zone.

next occurred centrally at a total of 186 pulses. There was no early breakthrough in the steep quadrant. The remaining basal epithelium was therefore debrided in the inferotemporal quadrant. Forty-two further PTK pulses were then applied to the exposed steep quadrant, with protection of the remaining cornea utilizing methylcellulose 1% artificial tear-drop solution applied with a cellulose surgical spear. The number of pulses was calculated from the Munnerlyn formula.[41]

Six weeks after re-treatment, the topographic appearance showed improved regularity of the corneal contour. As of this most recent examination, however, visual acuity remains mildly reduced, with a refraction of +1.00 -0.75 x30, giving 20/30 acuity.

Case 7: Localized Dense Scar

A 43-year-old white man was referred for re-treatment. He had undergone PRK elsewhere with a 6.0 mm optical zone for correction of approximately -6 D of myopia on March 29, 1996.

He related a history of having lost his postoperative bandage soft contact lens on the first postoperative night. He was seen the next day and instructed to pressure-patch for 2 more days, but was not seen again until 1 week postoperatively. At that time, an epithelial defect remained. A bandage soft contact lens was reapplied and ultimately removed at the end of the second week. Inflamase Forte drops were applied 4 times daily for 2 months, twice daily for 1 month, and then discontinued. The patient developed a localized corneal scar.

On initial evaluation on August 19, 1996, uncorrected visual acuity in the treated right eye was 20/40+2. The patient refracted with plano -1.50 x37 to an acuity of 20/20-2. He complained of a perception of haze with disruptive glare and halos. At distance he perceived a vertical monocular diplopia and at near a vertical monocular triplopia.

Slit-lamp examination disclosed a discrete, approximately 1 mm diameter scar within the pupillary zone (Fig 18A). Corneal topography disclosed a marked keyhole pattern with a steepening corresponding to the area of scar formation, extending into the pupillary center (Fig 18B).

Confocal microscopy of the discrete scar was able to detect the transition between the scar and the adjacent treatment zone. In Fig 21A, basal epithelium is seen superiorly and to the left, while extracellular material is evident inferiorly and to the right. In the center of the scar, keratocytes are both enlarged and more numerous, consistent with formation of new collagen in the region of the scar (Fig 21B).

A 1-month course of intense topical corticosteroids did not alter the scar. On October 15, re-treatment was performed. With the laser programmed for PTK at a 6.5 mm optical zone, transepithelial ablation was performed in a zone centered over the scar, and therefore decentered

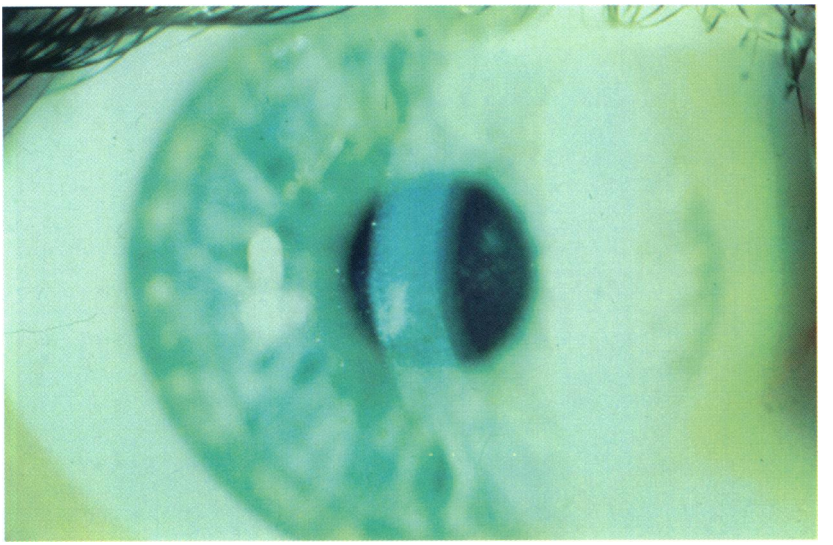

FIGURE 18A

Case 7 (right eye). A, Slit-lamp photomicrograph prior to re-treatment shows dense localized corneal scar in inferotemporal pupillary zone.

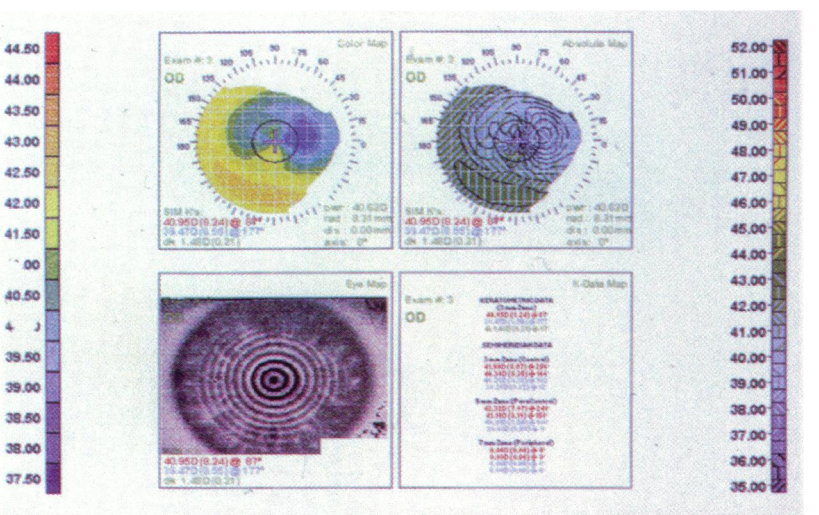

FIGURE 18B

Corneal topography of right eye prior to re-treatment shows steepening over area of scar located inferiorly and slightly temporal topupillary center.

FIGURE 21A

Case 7 (right eye). A, Confocal microscopy at edge of scar prior to re-treatment is consistent with presence of extracellular material. Note presence of basal epithelium superiorly and to left of extracellular material. This suggests that extracellular material is elevated.

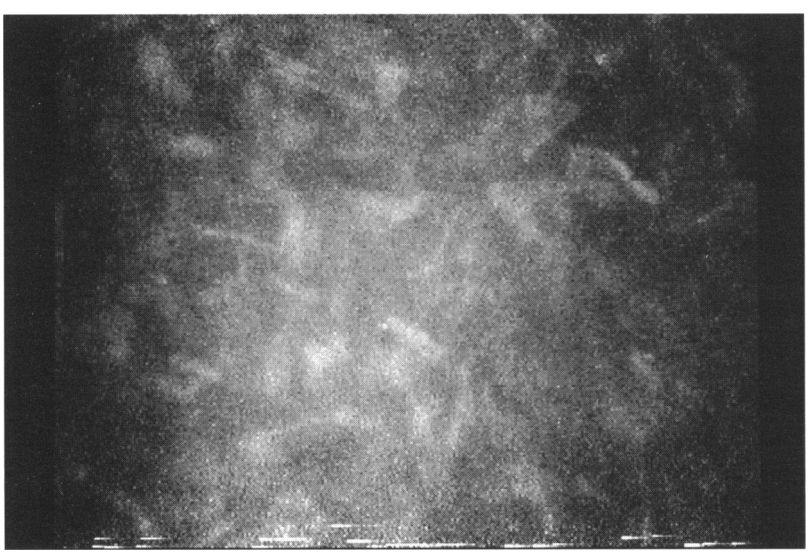

FIGURE 21B

In center of scar, increased density of enlarged keratocytes is evident, consistent with new collagen formation.

inferiorly relative to the pupil. The pattern of epithelial fluorescence was recorded on S-VHS video. Fig 20 demonstrates the pattern of disappearance of epithelial fluorescence as the underlying scar tissue was exposed. The scar broke through first, followed by the appearance of the rim of the inferior ablation zone. This pattern was consistent with thinning of epithelium over an elevated subepithelial scar, correlating well with the topography and confocal microscopy findings. After exposure of the subepithelial zone in the area of the scar, 32 further PTK pulses were applied to the steep scarred zone, while masking of the cornea outside the steep keyhole area, utilizing methylcellulose 1% artificial tear fluid applied with cellulose surgical spears. Two months after re-treatment, the patient reported marked improvement in the subjective multiplopia. Uncorrected acuity remained 20/40. Refraction with +2.50 -3.50 x175 yielded 20/20+1 visual acuity. Corneal topographic analysis (Fig 19B) was consistent with the refraction, showing 2.4 D of astigmatism. The topography showed alteration in the topography of the superior cornea, even though this area was untouched during the re-treatment. Slit-lamp examination showed trace reticular haze inferiorly, with complete resolution of the localized scar.

DISCUSSION

This investigation utilized scanning confocal microscopy to obtain in vivo histopathologic correlations of clinical and topographic measurements. Only one previous study, recently published, has employed tandem confocal microscopy to systematically evaluate corneal haze and its effect on visual function after PRK.[82] Wound healing anomalies were not addressed. The principal findings of that study are in agreement with observations of normally healing eyes in the present study:

- In the superficial stroma of the ablation zone, keratocyte numbers and size are increased within 1 month after PRK and return toward normal levels in most subjects by 6 months post-PRK. This time course is in general agreement with some but not all laboratory studies and parallels the course of mild transient haze frequently observed after PRK.[12,14,23-28]
- A highly reflective "bright layer" develops at the epithelial-stromal junction after PRK. Immunofluorescence histopathology of rabbit and monkey eyes has demonstrated the appearance of a range of extracellular substances at the base of the ablation zone, including fibronectin, laminin, type III collagen, and hyaluronic acid; keratan sulfate may either be altered or initially depleted.[16,18,29] Histopathology has suggested that these deposits may occur within small vacuoles, as optically disruptive deposits between collagen lamellae[12,14,17,20,74,75,140,141] or as a dense subepithelial layer.

  While the source of these substances is unknown, candidates include

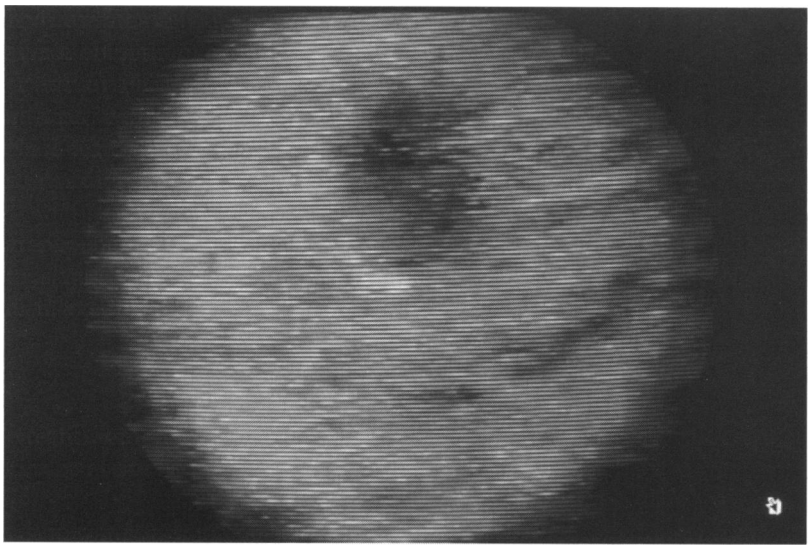

FIGURE 20A

Case 7 (right eye). Segments from videotape of laser re-treatment showing epithelial fluorescence pattern. Images are oriented to match slit-lamp micrographs and corneal topography, with superior cornea at top of photograph and inferior cornea at bottom of photograph. A, First area of disappearance of fluorescence, indicating breakthrough from epithelium to stroma, occurs over scar, just superior to center. Inferiorly, ridge at edge of ablation zone begins to break through as arcuate dark area to right of center. Location of red He-Ne aiming beams shows deliberate decentration of reablation zone.

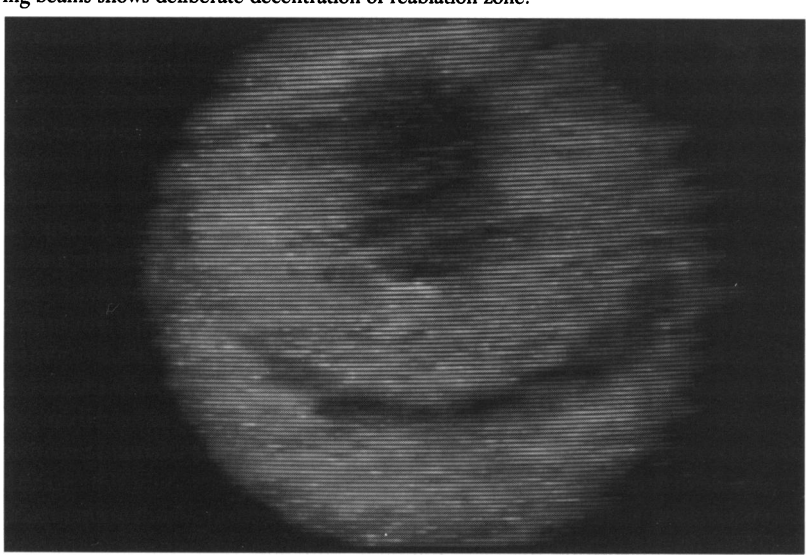

FIGURE 20B

In last frame prior to discontinuing transepithelial ablation, base of scar is seen to be more exposed, and inferior rim of ablation zone is easily seen.

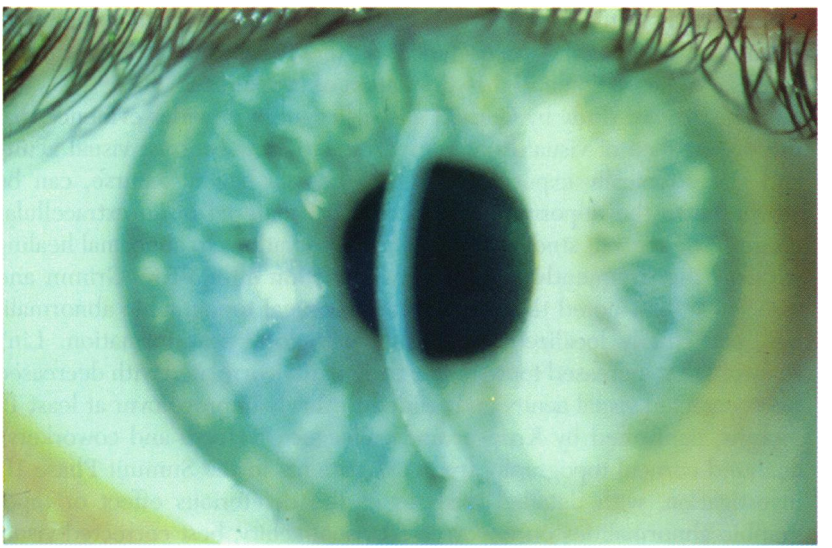

FIGURE 19A
Three days after re-treatment, re-epithelialization had occurred. Scar had been completely removed.

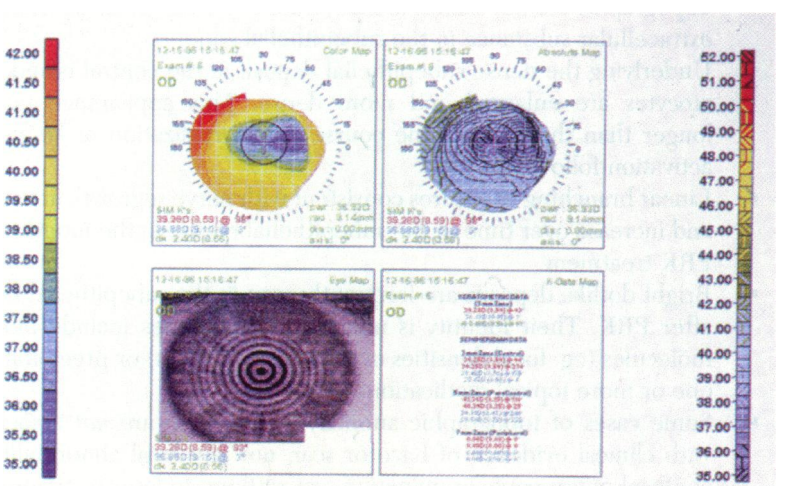

FIGURE 19B
After re-treatment, steep area over previous scar has resolved. At this measurement, 2 months after re-treatment, overall optical zone has diminished in vertical size, however, both superiorly, where no treatment was undertaken, as well as inferiorly.

metabolically active keratocytes, epithelial cells, or their interaction. Possible other factors in formation of these deposits include trophic effects of denervation and the stimulation of cytokines.[33-35,114,123-127]

The elegant study by Corbett and colleagues[82] provides evidence that the disturbance of visual function, particularly low-contrast visual acuity and glare, typically experienced in the normal healing course, can be attributed to the deposition of subepithelial material of an extracellular nature. The current study extends those observations to abnormal healing patterns that frequently disturb visual function after PRK. Grimm and associates[86] first noted the correlation of corneal topographic abnormalities, particularly localized steepening, with local scar formation. Lin[87] reported that increased topographic irregularity correlated with decreased best corrected visual acuity and tended to slowly improve over at least 12 months, confirmed by Krueger and colleagues.[90] Hersh and coworkers[88] analyzed corneal topography from 181 patients in the Summit Phase III investigation, with detailed analyses of the deleterious effect of topographic abnormalities on uncorrected visual acuity, best corrected visual acuity, and predictability. The Hersh study was limited by the use of a 5.0 mm optical zone, with the absence of central islands, however.

To the best of my knowledge, the current study is the first series that provides in vivo histopathologic correlation by confocal microscopy of patterns of clinically significant healing anomalies. The principal new observations are as follows:

- Topographic central islands are associated with an excess of the bright extracellular substance in the subepithelial zone.
- Underlying the dense subepithelial deposit at the central island, keratocytes are enlarged and more dense. This appearance persists longer than the typical time course for normalization of keratocyte activation following PRK.
- Linear branching structures consistent with nerve regrowth are visible and increase over time in the subepithelial region in the months after PRK treatment.
- Bright dotlike deposits are frequently seen in the subepithelial region after PRK. Their identity is unknown. Possibilities include biologic molecules (eg, focal densities of glycosaminglycans) or precipitates of one or more topical medication.
- Some cases of topographic anomaly (eg, case 6) are *not* associated with clinical evidence of haze or scar, nor any local abnormality on confocal microscopic examination, yet respond to laser re-treatment.

Local dense scar formation may represent new collagen deposition with or without other extracellular substances. Confocal microscopy of such a scar (case 7) provided an opportunity to visualize the presence of keratocytes within the scar and demonstrated the

apparent elevation of the scar relative to the adjacent treated zone. The operative finding of epithelial thinning over the scar, as judged by the epithelial fluorescence, both confirms that the scar tissue was elevated, matching the topographic pattern, and demonstrates that the epithelial thickness can vary in order to reduce the optical effect of local stromal irregularities. This pattern is also seen when central islands are re-treated with laser ablation.

- Topographic anomalies are associated with poorer uncorrected and best corrected visual acuity as well as reduced predictability, in agreement with previous studies.[81-85] The current study documents several further observations, however. There is considerable overlap in outcomes between topographic subgroups, with some patients who have "normal" topography and clear corneas nevertheless experiencing unexplained reductions of visual function compared with other patients with apparent major topographic anomalies. Moreover, a simple approach to anti-island pretreatment reduced the frequency of topographic anomalies, particularly keyhole patterns, but with poorer early predictability. An intriguing and unexplained finding was the dramatic reduction of keyhole-shaped peripheral topographic anomalies with the anti-island pretreatment, an effect larger than the effect on the central islands themselves (Table XIII).

Both corneal topography systems and confocal microscopy have limitations that reduce our ability to better understand these healing patterns and anomalies. Current clinical topographic systems do not necessarily give the same results in comparative tests, and even the same system can give remarkably different results utilizing different analytical approaches.[142-146] Case 2 vividly demonstrates that 2 different systems can analyze the same cornea as having a central elevated island or a central depression. At least one explanation of this phenomenon is that placido-disc-based systems, the most common systems in clinical practice and the systems used in all clinical reports of central islands,[87,89,90,146] may reflect in identically appearing rings from the corneal surface whether a slope is rising or falling (Charles Rauch, Orbtech Corp, and Joseph Wakil, EyeSys Corp, personal communications). The system algorithm makes a determination of the direction of the slope change based on adjacent rings, and therefore misinterpretation may occur.

Confocal microscopy allows resolution of cellular structures in vivo, of particular importance in studying the healing response of the cornea in a clinical setting where opportunity for conventional histopathology is extremely limited. The first confocal microscope was developed by Minsky in 1955 to visualize neural networks in the living brain.[147] The term "confocal" refers to the design principle that the microscope condenser and objective lenses had the same focal point. More recently, Wilson and

Sheppard[148] developed the basis for modern confocal microscopy. A single point in a specimen is simultaneously illuminated by a point light source and imaged by a point detector. Because of highly limited optical spreading, both lateral and axial resolution increases. The field of view is correspondingly highly limited. Scanning of the target is therefore used to give a field of view. The scanning confocal microscope loaned by Tomey Corporation (Cambridge, Mass) has specifications of a minimum resolution of 1 μm, optical section depth of 10 μm, and a field width of 330 μm, giving an effective magnification of 40x.

Confocal microscopy has some inherent limitations. Structures are visualized because of different refractive indices. As pointed out by Corbett and associates,[82] regular cell systems and boundaries such as epithelium and endothelium are imaged well, but less organized structures such as the cornea are more difficult to visualize, with complex irregular images. The long processes of keratocytes cannot be visualized. With our current level of knowledge, we are unsure whether the elongated objects being interpreted as keratocytes represent the cell nucleus, cell body, or adjacent extracellular material. Inflammatory cells should be present in some sections, but cannot be clearly differentiated. The highly reflective subepithelial deposit is presumed to be extracellular material because of the lack of defined structure, but collagen cannot be differentiated from other biologic or extrinsic macromolecules or materials. Nevertheless, the images found in the current study are consistent with the limited published literature on corneal stromal confocal microscopy.[81,82,149]

The specific commercial model of confocal microscope available for this investigation is still under development, and accordingly had some limitations. Most notably, the software to allow simultaneous imaging and measurement of reflected signal strength on rapid axial scanning (the "Z scan") was not yet available. We had the microscope available for only a 4-month period. Longer-term longitudinal follow-up of multiple patients would increase the accuracy of interpretation of these findings as well as improve our understanding of long-term healing patterns.

The current study, as well as virtually all other reports on healing patterns after PRK, documents the trend toward improved visual function over time, particularly during the first 6 postlaser months.[42-59,87-90] If the metabolic and cellular activity of the wounded corneal surface is the "curse" of PRK, then the tendency for a normative healing of the surface with improved corneal optical function is the "salvation" of PRK. In contrast, in LASIK where the corneal surface remains largely undisturbed, little or no normative healing responses are seen. For example, central topographic islands, when they occur, tend to persist unchanged (Daniel Durrie, MD, and Michael Knorz, MD, personal communications).

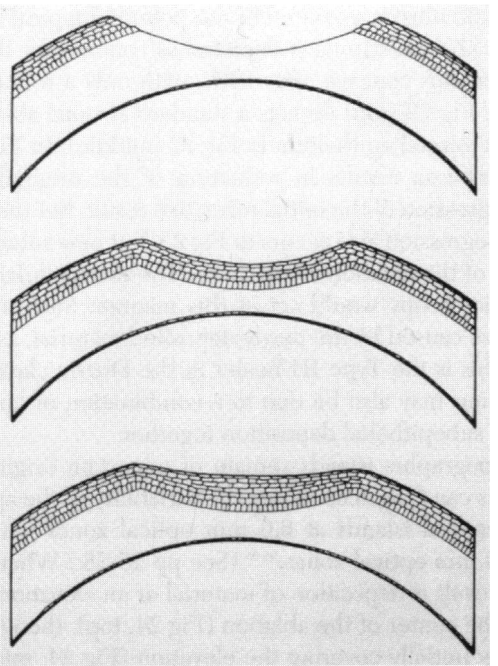

FIGURE 22

Top, Schematic diagram of cornea after PRK. Concavity is for illustrative clarity; actual clinical treatment only reduces convexity of anterior cornea. Middle, Normal-thickness re-epithelialization after PRK. Bottom, Epithelial hyperplasia reduces optical effect of laser stromal ablation.

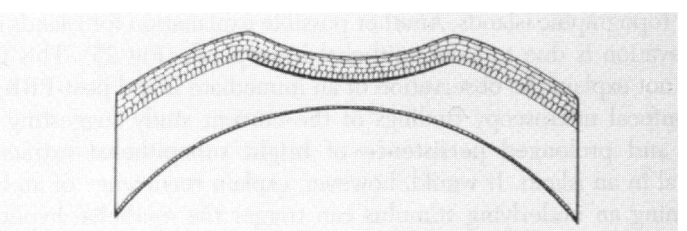

FIGURE 23

Deposition of new material in subepithelial region of ablation zone also causes regression of initial refractive correction.

Fig 22 and 23 illustrate several of the potential typical wound healing responses. The ablated stroma is depicted as concave for illustrative purposes, but it remains concave after PRK, with only a reduction of curvature, of course. Fig 22 (top) depicts a standard stromal ablation, followed by healing with normal epithelium in Fig 22 (middle). In Fig 22 (bottom), epithelial hyperplasia results in reduction of the original contour; this would cause regression of the initial refractive result, but the cornea would remain clear. Regression also occurs in Fig 23, but new subepithelial material at the base of the ablation is the cause. The extracellular material seen on confocal microscopy would act in this manner. Such a cornea might have visible haze caused by the newly deposited material, as well as exhibit regression (this is the Type III healer in the Durrie classification[69]). Of course, regression may also be due to a combination of epithelial hyperplasia and new subepithelial deposition together.

Central topographic islands remain of uncertain origin; none of the current theories can fully account for the variability of the appearance and frequency of central islands at 6.0 mm optical zones while islands are absent with 5.0 mm optical zones.[91-95] (See pp 25-28.) Whatever the etiology, if the net result is deposition of material or an elevation of the stroma at the base of the center of the ablation (Fig 24, top), then the epithelium may respond by initially covering the elevation (Fig 24, middle) but then slowly filling in around the island so that the island disappears as the "ocean of epithelium rises up to flood over the island" (Fig 24, bottom). If this were the case, however, topography would be expected to show overall steepening, and refraction would show regression. If, on the other hand, the elevated subepithelial material is gradually removed and remodelled by keratocytes and inflammatory cells, the contour would eventually be restored to the originally intended shape, the topography would demonstrate uniform flattening, and the refraction would not show regression. Continuing the island metaphor, the island would have "sunk into the epithelial ocean," not have been flooded by a rising epithelial ocean. Current measurements cannot differentiate between these mechanisms with adequate accuracy to fully resolve the roles that they have in resolution of topographic islands. Another possible explanation for islands is that the elevation is due to local epithelial hyperplasia (Fig 25). This theory would not explain the observation of an immediate island post-PRK,[95] nor the confocal microscopy findings of the current study suggesting more dense and prolonged persistence of bright subepithelial extracellular material in an island. It would, however, explain recurrence of an island, presuming an underlying stimulus can trigger the epithelial hyperplasia reaction long after the PRK.

The current study showed deleterious effects of a simple anti-island pretreatment. Why should this be unexpected? Applying the anti-island

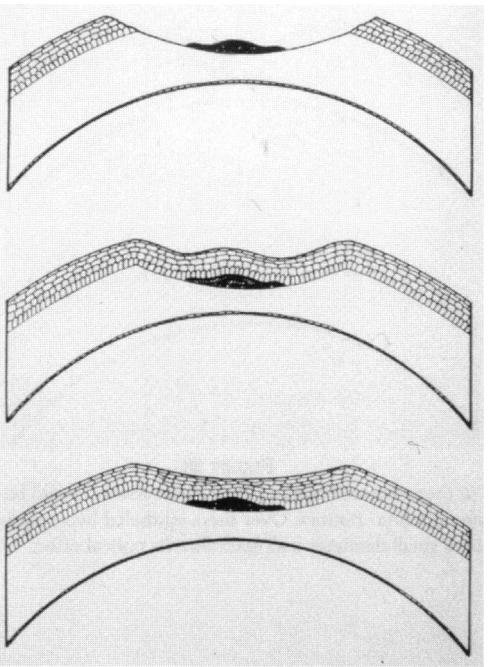

FIGURE 24

Top, Residual stroma or deposits at center of ablation zone may be responsible for central islands. Middle, Epithelium follows contour of ablation, with topographic central island. Bottom, Over time, epithelial hyperplasia around central island may mask presence of island. Partial regression of initial correction and final undercorrection would be expected.

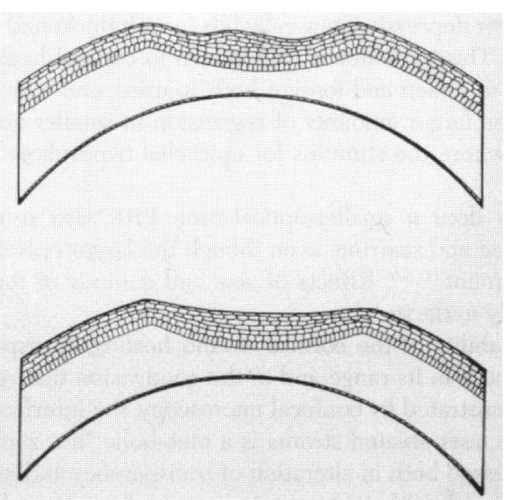

FIGURE 25

Top, Central topographic island could be caused solely by local epithelial edema or hyperplasia. Bottom, Island could then resolve by further hyperplasia of peripheral epithelium.

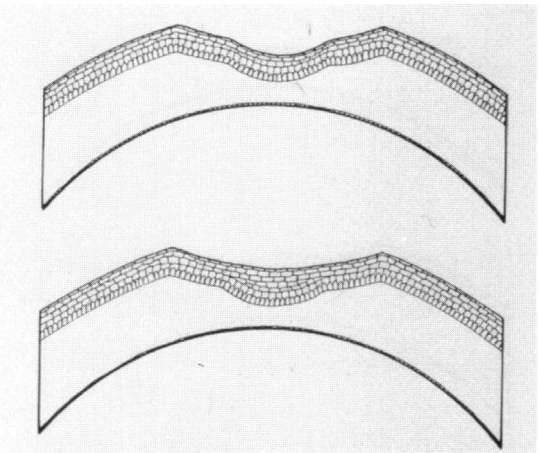

FIGURE 26
Top, Initial effect of excessive central anti-island pretreatment would be a central depression and refractive overcorrection. Bottom, Over time, epithelial hyperplasia may "fill-in" a central depression with a small diameter and neutralize its optical effect.

treatment to all patients will inevitably overtreat eyes that were going to have little or no central islands in any case. As shown in Fig 26 (top), a small central depression might cause visual disturbance at the onset, but a small-diameter depression generally fills in with thickened epithelium (Fig 26, bottom). This tendency is well known in corneal healing of localized defects such as dellen and foreign-body injuries, and may account at least in part for the larger amounts of regression in smaller-optical-zone PRK treatments, where the stimulus for epithelial hyperplasia may be greater (Fig 27).

But why does a smaller-optical-zone PRK also result in a higher degree of haze and scarring, even though the larger optical zone requires deeper treatment?[41,59,60] Effects of size and contour of the ablation zone remain poorly understood.

The variability of the corneal wound healing in response to PRK is impressive, both in its range and in the good vision that results nevertheless. As demonstrated by confocal microscopy, the interface of the epithelium and the laser-ablated stroma is a metabolic "hot zone," with wound healing expressed both in alteration of transparency and in surface optics. Further studies should yield important new information about the regulatory processes in the epithelium and stroma.

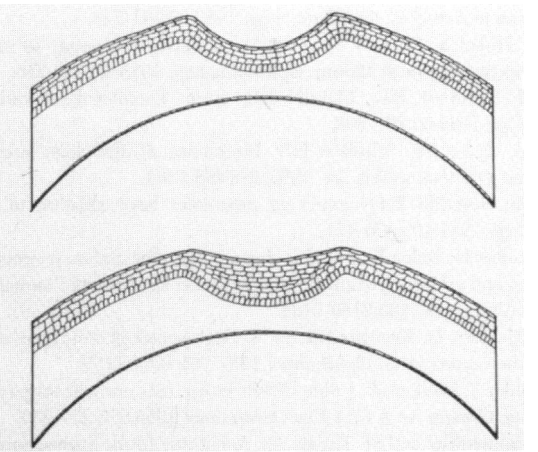

FIGURE 27
Top, Laser ablation with small optical zone. Bottom, Epithelial hyperplasia may be more pronounced with small optical zone diameters, leading to increased postoperative regression of initial correction.

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