The Challenge of Corneal Wound Healing After Excimer Laser Refractive Corneal Surgery

Three articles in this issue emphasize that subepithelial stromal corneal wound healing affects the amount of corneal haze and the refractive outcome after photorefractive keratectomy for myopia. Durrie and colleagues describe the spectrum of spectral wound healing responses, aggressive healing being associated with increased haze and a myopic refractive shift, and inadequate healing being associated with a persistently clear cornea and residual hyperopia. Grimm and colleagues describe regional variations in stromal wound healing within the ablation zone, areas of haze being associated with steeper corneal curvature and clear areas being associated with flatter corneal curvature. Corbett and colleagues review the basics of corneal wound healing and the role of topical corticosteroids in its modulation. (Epithelial wound healing probably plays a role in the refractive outcome, hyperplasia being associated with a loss of the initial refractive effect, but there is currently no practical clinical method for measuring epithelial thickness.) This variability in corneal wound healing may be affected before surgery, during surgery, and after surgery. How can the surgeon control these factors to increase the predictability of refractive outcome and the uniformity of corneal clarity and curvature? Let's examine a few of these factors.

Factors Before Surgery

Before surgery, the energy distribution in the laser beam may be variable, giving variable impact on the cornea that could stimulate variable wound healing. Hot spots in the beam give greater ablation. Before surgery, manufacturers must develop methods to accurately measure the pulse energy and beam energy distribution of the excimer laser—methods that can be used immediately before treatment to control the symmetry of radiation exposure. This technology is in evolution. Manufacturers currently provide test materials (which must be accurately made and calibrated themselves) to quantify the pulse energy, determining the number of pulses needed to penetrate or shape the material. Beam quality and energy distribution are more difficult to measure and usually require special techniques, such as profilometry of ablated plastic surfaces; because the testing is performed by the manufacturer, it is not practical to use before treating each patient. Gottsch and colleagues have described a practical method of clinically measuring energy distribution over the laser beam using digital imaging of ablated test materials. Beam uniformity is a very important factor in large area ablations with a single laser beam (eg, Summit, VISX, Chiron) but may be less important in systems that use a smaller scanning beam (eg, Nidek, Meditec, Novatec) where hot spots and cold spots can overlap and create more uniformity. Until excimer laser beams can be calibrated reliably before each procedure, as is commonly done in radiation therapy of neoplasms, the surgeon will have a difficult time determining the effect of variations in beam quality on corneal wound healing.

Factors During Surgery

During surgery, variations in epithelial removal, corneal hydration or patient movement, may distribute the energy unevenly in the stroma, resulting in variable wound healing. Mechanical removal of the corneal epithelium must be uniform and gentle to avoid damage to Bowman's layer. The surgeon who uses either a gentle brushing or whisking motion with a blade or a soft rotating brush will accomplish this better than a surgeon who roughly scrapes off the epithelium. Because the epithelium is not uniformly


thick over the ablation zone, it is difficult to reliably remove all of the epithelium with the excimer laser prior to commencing the stromal photorefractive keratectomy. Variations in stromal hydration during ablation may be responsible for steep central topographic islands postoperatively. These could be prevented by creating a laser beam with the appropriate shape or multizone software with the appropriate steps, or surgical intervention such as wiping away the fluid areas. Conditions over the cornea are important, such as avoiding the blowing of gas over the surface. Centration of the laser beam and stability of the eye will place the ablation zone over the pupil; eye tracking devices are under investigation to see if they can maintain centration and improve outcome.

FACTORS AFTER SURGERY

Variability in the wound healing response of individual eyes cannot be controlled, but it can be influenced by topical drugs, most commonly corticosteroids; however, Corbett and colleagues emphasize the general inadequacy of this approach. Even if corticosteroids can modulate wound healing after photorefractive keratectomy, the process lasts for 6 to 18 months—a long time to wait for refractive stability. Subepithelial wound healing can be effectively eliminated by performing the excimer laser ablation within the stroma, either on the back of the disc or in the stromal bed (laser in situ keratomileusis [LASIK]). Apparently, one of the triggers for stromal wound healing is communication from a healing epithelium, which elaborates cytokines such as interleukin-3, to send a message to the stroma. "I've been hit—you'd better fight back." This stimulates the keratocytes to turn into fibroblasts and elaborate new extracellular matrix consisting of "corneal wound healing molecules" such as type III collagen and hyaluronate proteoglycan. We do not know how this communication occurs, but it seems to require close approximation and direct communication between epithelial and stromal cells. If the epithelium is left undisturbed, if Bowman's layer is left intact, and if a distance of 100 μm or more is left between the epithelium and the ablation site, there seems to be minimal stimulation of stromal wound healing with the absence of haze after surgery. This presumably decreases the effect of individual biological variability. Whether LASIK and other laser keratomileusis techniques will produce more accurate and stable refractive results awaits documentation in the peer-reviewed literature.

Of course, around the edge of the flap or disc, the epithelium is in touch with the stroma because Bowman's layer is cut, so a circumferential stromal scar results. This reduction of wound healing has an additional advantage: it allows the surgeon to break through the scar at the edge of the flap and easily lift the flap from the bed for repeated ablation (enhancement, adjustment).

Intrastromal photorefractive keratectomy with a Nd:YLF picosecond laser has the same advantages of surgery done intrastromally with an intact epithelium and Bowman's layer, with minimal stromal wound healing. Whether this technique can create predictable refractive change is unknown.

Jean and colleagues, in this issue, used the fundamental mode of an erbium:YAG laser for photorefractive keratectomy. This infrared laser produces more collateral stromal damage than the ultraviolet 193 nm excimer, and further clinical trials will be necessary to determine if this leads to more pronounced stromal haze postoperatively. If it is comparable, the "3-second" erbium:YAG PRK may represent a technical advance, but it will not address the fundamental problem of stromal wound healing.

Ariyasu and colleagues emphasize the plasticity of stromal wound healing after holmium laser thermokeratoplasty in human eyes by demonstrating variability in refractive effect over 3 months. These laser burns changed corneal curvature acutely; variable amounts of regression occurred from wound healing and remodeling, especially when there was an attempt to steepen the central cornea. Surgeons have abandoned other methods of thermokeratoplasty, such as the superficial treatment of Gassett and Kaufman for keratoconus or the hot needle of Fyodorov, because the corneal wound healing response produced postoperative scarring and instability. Whether the more subtle approach of holmium:YAG thermokeratoplasty can reduce corneal wound healing to a subclinical level and produce refractive stability remains to be demonstrated.

Postoperatively, if the epithelium is not intact, molecules in the tears have direct access to the stroma and which may produce variable wound healing. Procedures that leave the epithelium intact eliminate this variable. The absence of an epithelial defect also minimizes pain postoperatively and reduces the need for antiinflammatory and analgesic medications, which could also afford stromal wound healing. All of these factors tilt the balance in favor of laser corneal surgery beneath an intact epithelium.

SYNTHETICS—A DIFFERENT APPROACH

A different category of refractive surgery—the use of synthetic implants—may eliminate the refractive effects of corneal wound healing. Procedures such as phakic intraocular lenses, intracorneal ring, or onlay synthetic epikeratoplasty are under investigation. Each will bring other clinical and biological challenges.

Refractive surgery is developing in the direction of procedures that minimize or eliminate mechanical destabilization of the cornea and corneal stromal wound healing, with the goal of a more accurately predictable refractive outcome.