Two-Year Preclinical Testing of Perfluoropolyether Polymer as a Corneal Inlay

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PURPOSE. To assess the long-term biocompatibility and optical clarity of a perfluoropolyether (PFPE) polymer as a corneal inlay.

METHODS. A 4-mm-diameter PFPE inlay was implanted under a microkeratome flap in the corneas of rabbits (n = 16) and maintained for predetermined time points of 6, 12, or 24 months. These were compared with normal (n = 5) and time-matched sham-wounded rabbit corneas (n = 8). All corneas were monitored clinically with a slit lamp. Histology was performed on all eyes on termination to assess the tissue response.

RESULTS. Some sham and implanted animals were discontinued from study 1 to 2 days after surgery because of flap dislodgement. Ten animals with PFPE inlays remained in the study, and 7 of these were maintained to their predetermined time point for up to 2 years (3 were discontinued because of peripheral corneal defects). The corneas of these 7 animals remained clear and healthy; tear film remained normal, and there were no signs of inflammation, neovascularization, or increased conjunctival redness. All inlays remained centered and optically clear (clarity 85% or greater). Histology showed PFPE was biostable. The epithelium of operated corneas were stratified but slightly thinned compared with those of normal corneas. Stromal tissue anterior and posterior to each inlay appeared normal. Keratocytes in the vicinity of the inlay were normal in distribution but showed increased vacuolation, indicating tissue repair after the surgery.

CONCLUSIONS. The PFPE polymer maintained a high level of optical clarity and showed long-term biocompatibility for up to 2 years when implanted as an inlay in the rabbit cornea. (Invest Ophthalmol Vis Sci. 2006;47:574–581) DOI:10.1167/iovs.05-0872

There is a growing market for new technologies to correct refractive errors which is stimulated by patient demand for safety, convenience, and cosmesis. Laser-based procedures such as photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), and laser-assisted subepithelial keratomileusis (LASEK) have been meeting much of this demand.1 However, each of these techniques is associated with a range of postoperative complications that include epithelial abnormalities, corneal haze, diffuse lamellar keratitis, flap problems, epithelial ingrowth, corneal ectasia, changes to ocular surface hemostasis, and reduced corneal sensation caused by the damage to corneal nerves (Waring GO, et al. IOVS 1999;40:ARVO Abstract 3088; Restivo L, et al. IOVS 1999;40:ARVO Abstract 4750; Srivannaboo S, et al. IOVS 1999;40:ARVO Abstract 4723).2–15 One newer technique—EpiLASIK, in which an epithelial sheet is separated mechanically from Bowman’s layer before laser ablation and replaced afterward—offers the advantages of the LASIK and LASEK techniques and may address some of the problems arising from either of the original techniques in the treatment of low myopia.14

Another approach is additive refractive keratoplasty. This involves the insertion of a synthetic or biologic material into the cornea to change the refractive power of the eye by altering the curvature of the cornea or by the refractive index of the material itself.15–23 The implanted material may be placed within the stromal tissue or immediately beneath the epithelium. Additive technologies offer several advantages over currently used refractive surgical techniques, paramount of which is that the implant may be removed, giving the procedure the potential to be adjustable and reversible.

Previous efforts at correcting refractive error by implanting materials of biologic origin into the cornea have failed because of remodeling of the implant and difficulty in maintaining a functional epithelium over the implanted material (McCary BE, et al. IOVS 1997;4:ARVO Abstract 2362).24–30 The use of synthetic materials for corneal augmentation has provided an alternative solution. Early attempts at implanting synthetic polymers into the cornea demonstrated the absolute requirement for permeability in the implanted material, the significance of implant thickness and diameter, and the depth at which the implant was placed in the cornea.16–21,22,31–35 Nonpermeable polymers have also been tested as annular ring segments implanted in the peripheral cornea to expand and flatten the corneal surface (Burris TE, et al. IOVS 2000;41:ARVO Abstract 4876).33–36 The long-term success of these implants overall has been thwarted by problems such as dehydration, crystal formation, lipid deposits, opacities, and difficulties with implant edges that have caused thinning, fibrosis, ulceration of the stroma, keratitis, and corneal vascularization.34–42 In recent years, synthetic materials with a high water content and high permeability to nutrient flow have been developed for corneal implantation. One hydrogel material has been tested as an inlay using a microkeratome flap (PermaVision; Anamed Inc., Lake Forest, CA) with encouraging early data, though complications including haze, inlay encapsulation, epithelial opacification, and inlay decentration have since been reported.43–47 Another hydrogel material has been implanted under a corneal flap made in rabbits using the technique of...
photoablative inlay laser in situ keratomileusis (PA-LASIK) with stable outcomes out to 16 months.49
We have developed a different type of material specifically for use as a corneal implant to correct refractive error by altering corneal curvature (additive refractive keratoplasty). The perfluoropolyether (PFPE) material offers many advantages for corneal augmentation in that it is isorefractive, inert, transparent, and chemically and thermally stable. When implanted in the feline cornea during short-term onlay studies, a porous version of PFPE was shown to have sufficient permeability to maintain corneal health.49,50 The present study was designed to test the long-term biocompatibility and optical clarity of the PFPE polymer when implanted as an inlay in the rabbit cornea.

MATERIALS AND METHODS

Inlay Material
PFPE used in this experimental series was formulated for an inlay application and was a high zwiterion-concentration variant of that tested previously for corneal onlay application.49,50 Briefly, a porous PFPE-zwitterion copolymer was made by the UV copolymerization of the PFPE-dimethylacrylate and (2-aminoethyl) dimethyl (3-sulfopropyl) ammonium hydroxide inner salt.51 The porous PFPE-zwitterion copolymer was cast in the laboratory into inlays using polypropylene molds that measured 4 mm in diameter and were approximately 85 mm thick at the center, with tapering edges. The equilibrium water content of the PFPE inlays was 51%. The PFPE formulation used for the inlays had a permeability of 1634 ± 262 µg/hr per cm² to water and 905 ± 46 µg/hr per cm² to tryptophane (used as a model for glucose). Permeability measurements were made using 100-µm-thick PFPE membranes in stirred diffusion chambers with 0.05% solute in PBS at 15 mm Hg pressure applied to the solute chamber.

Surgery
The animal research in this study was approved by the Animal Care and Ethics Committee of the University of New South Wales. All procedures were performed in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Twenty-seven New Zealand White rabbits, aged 1 to 2 years and weighing 2.5 to 3.5 kg each, were used in this study. Nictitating membranes in all rabbits were removed from both eyes at least 2 weeks before surgery, as previously described.52 Animals were anesthetized using an intramuscular injection of ketamine 35 mg/kg and xylazine 5 mg/kg to a depth of stage 3, by a microkeratome (Krumeich-Barraquer; Summit Technology) with the setting of flap diameter, thickness, and hinge, respectively, as 8 to 8.5 mm, 160 µm, and 5 to 7 mm. The corneal flap was rolled over to the nasotemporal plane, with half dedicated to paraffin histology (LM and electron microscopy [EM]) or immunohistochemistry examination. Eyes of the healthy group were used as controls to match the histology of the operated eyes at the three time points.

Clinical Evaluation
Clinical evaluation was performed on each animal at least twice during the first week after surgery, then weekly for the first month, and then every 2 to 3 weeks using a slit lamp biomicroscope until termination. This evaluation included integrity of the corneal flap, assessment of conjunctival redness, appearance of the cornea anterior and posterior to the inlay, position of inlay, and optical clarity and integrity of the inlay. The tear film of the rabbits in our study was assessed with a teardrop, as described elsewhere.53 The uniformity of the lipid layer on the tear film surface was assessed by observing the lipid pattern during the natural opening of the eye. Greater homogeneity of the lipid layer indicated greater uniformity of the tear-film surface. Stability of the tear film was assessed by observing changes in the lipid pattern 10 to 12 seconds after artificial blinking that was necessary because rabbits do not blink as often as humans. Less change in the lipid pattern indicated more stable tear film during the observation period. Oxygen uptake was measured in the implanted and the contralateral eyes in 4 animals 18 months after surgery using a pH/blood gas monitor (PHM73, Radiometer; Copenhagen, Denmark) controlled by customized computer software. Oxygen was supplied to a silicon membrane reservoir within a probe that consisted of a platinum-reducing electrode and a silver reference electrode bathed in a sterile water bath at 37°C. Oxygen tension in the reservoir was set at 155 mm Hg. The probe was touched onto the cornea, central and peripheral to the inlay, respectively. Oxygen tension within the probe slowly dropped as oxygen was consumed by the cornea under the probe when an airtight seal had formed between the tip of the probe and the cornea. This decline in partial oxygen pressure over time (mm Hg per second) was recorded as a measure of the flow rate of oxygen through the cornea. Five readings for each measurement were collected to provide a mean result. The difference in the flow rate of oxygen for the same site of measurements between the operated and control eyes was analyzed (paired t test). Optical clarity of the inlays was assessed using biomicroscopy 30 minutes after the application of a single drop of a topical mydriatic (0.5% wt/vol tropicamide BP), and backscattered light was graded according to the scale shown in Figure 1. Animals were maintained for predetermined times of 6, 12, and 24 months after surgery, at which point they were humanely killed and their eyes dedicated to histology (light microscopy [LM] and electron microscopy [EM]) or immunohistochemistry examination. Eyes of the healthy group were used as controls to match the histology of the operated eyes at the three time points.

Histology (Light and Electron Microscopy)
The eyes from all animals except those of animal 2, dedicated to immunochemistry (see below), were fixed for LM and EM immediately after euthanasia. Eyes were fixed in 4% paraformaldehyde solution for a minimum of 24 hours, and then corneas were excised and placed in fresh 4% paraformaldehyde solution for another 24 hours. Corneas were bisected in the nasaletemporal plane, with half dedicated to paraffin histology (LM), and a 5-µm strip cut limbus to limbus from the other half was dedicated to resin histology (transmission electron microscopy [TEM]). Tissue for LM was processed, and 5-µm sections were cut onto gel-coated slides that were routinely stained with hematoxylin and eosin. These were examined using a microscope (DMIR; Leica, Wetzlar, Germany) fitted with a digital camera. Ultrathin transverse sections 100 nm thick were cut from resin-embedded tissue, stained en grid with uranyl acetate and Reynolds’s lead citrate, and viewed using a transmission electron microscope (CM-100; Philips, Eindhoven, The Netherlands) fitted with a digital camera. Ultrathin transverse sections 100 nm thick were cut from resin-embedded tissue, stained en grid with uranyl acetate and Reynolds’s lead citrate, and viewed using a transmission electron microscope (CM-100; Philips, Eindhoven, The Netherlands) fitted with a digital camera. Ultrathin transverse sections 100 nm thick were cut from resin-embedded tissue, stained en grid with uranyl acetate and Reynolds’s lead citrate, and viewed using a transmission electron microscope (CM-100; Philips, Eindhoven, The Netherlands) fitted with a digital camera.
RESULTS

Clinical Outcomes

At the time of surgery, a PFPE inlay was placed under the corneal flap in the implanted group (n = 16). For the sham group (n = 8), the flap was lifted and replaced with no inlay implanted. During the first 1 to 2 days after surgery, 6 of the animals in the implanted group and 3 in the sham group were excluded from the trial because the corneal flap was irregularly thick, dislodged, or too thin. We noted that the rate of flap dislodgement was the same for the sham (3 of 8 eyes) and implanted (6 of 16 eyes) groups, indicating that the presence of an implanted inlay under the flap was unlikely to be a significant contributing issue to this problem. Most likely, the cause of these surgical failures in the sham and implanted groups was the use of a microkeratome and a suction ring designed for the size and curvature of the human eye, which made it difficult to guarantee a corneal flap of even thickness in the rabbit, especially if the eye was slightly small. The corneal flap in the animals remaining in the trial (10 implanted, 5 sham) remained in place and was observed to be approximately 90 to 120 μm thick. One animal from the sham group died on day 182 of causes unrelated to the ophthalmic surgery. Three animals from the implanted group were terminated earlier than planned because peripheral focal corneal defects developed on days 195, 251, and 553. The remaining 11 animals (7 implanted, 4 sham) were maintained to the original predetermined time points without any problems.

Clinically, the PFPE inlays were well tolerated by the corneal tissue over the 2-year period of the study (Fig. 2). In an early tissue reaction to surgery, some edema was observed at the flap–stromal interface (sham corneas) and the flap–inlay interface (implanted corneas) of operated corneas immediately after surgery that largely subsided within 3 to 7 days. Apart from interfacial debris, all operated corneas remained clear anterior and posterior to the corneal incision; the epithelium remained intact, and there was no evidence of stromal thinning. No infiltration, neovascularization, or increased conjunctival redness was observed in any of the operated corneas for the period of the study. A normal tear film over the cornea in implanted and sham eyes was maintained for the entire duration of the study, as demonstrated by a highly homogeneous lipid pattern in implanted and contralateral (unoperated) eyes. The pattern color of the tear film in both eyes of each rabbit varied slightly from yellow to light brown in different animals, indicating that the rabbits had a thick, even tear film. In addition, little or no change occurred in the lipid pattern in implanted or contralateral eyes after artificial blinking, indicating that the tear film was stable. In the implanted corneas, polymer transparency was maintained between 85% and 95% at the 24-month time point of the study (Fig. 3). During implantation, some inlays were noted to be not completely homogeneous in their transparency, though this did not occur in all cases. Oxygen uptake data at the 18-month time point showed no significant difference between the implanted and the contralateral eyes in either the central or the peripheral cornea (Table 1), though the implanted eye had 12% slower oxygen uptake in the central cornea and 6.4% faster oxygen uptake in the peripheral cornea than the contralateral eye.

Figure 2. Slit lamp biomicrographs. (A) Implanted cornea 742 days after surgery indicating the high level of tolerance of the inlay by the host cornea and the high level of clarity of the inlay (100% in back-scattering). (B) Sham-wounded cornea 727 days after surgery in which the flap edge is not visible and the cornea is clear with no haze, deposits, or other adverse responses.
Histology

In implanted corneas at each time point, an intact polymer inlay with tapered edges was present beneath the corneal flap. In each case, the inlay was intact and undamaged, demonstrating biostability in the corneal environment. In all operated corneas (sham and implanted groups), the original microkeratome incision across the cornea was marked by a fine line of fibrosis, which, in TEM, showed some irregularity of stromal collagens along the original incision line. The epithelium anterior to the microkeratome incision (sham) and polymer inlay (implanted) was stratified but thinned slightly in both groups compared with the central corneal epithelium of normal rabbit (Fig. 4). This was the case at each time point to 24 months. Changed basal cell morphology (cuboidal rather than columnar) and reduced numbers of cell layers (five rather than six) accounted for the epithelial thinning. Local epithelial hyperplasia marked the distal flap edge of sham and implanted corneas at each time point.

Ultrastructural examination (by TEM) of the central portion of each cornea in the study showed that the morphology and distribution of many of the features monitored in the operated groups (implanted and sham) were similar to those of normal rabbit cornea. This was the case for microvilli/microplacae on the anterior ocular surface, which were similar to normal in morphology, distribution, and density (Figs. 5A–C). Desmosomes, the cell–cell junctions responsible for the adhesion between adjacent epithelial cells, were similar in morphology and distribution to those of normal rabbit cornea but fewer in number (Figs. 5D–F). Hemidesmosomes, the cell-matrix junctions responsible for the anchorage of the epithelium to its underlying stroma, were present along the basement membrane with similar morphology and distribution to normal rabbit cornea but fewer in number (Figs. 5G–I). Apart from the fibrosis associated with the microkeratome incision, stromal tissue and keratocyte distribution and density anterior and posterior to the implanted inlay appeared normal at each time point. TEM showed that keratocytes in the region of the original incision line in the sham and implanted corneas were more vacuolated than those in normal cornea, suggesting an increased level of activity (Figs. 5K–L). In implanted corneas, keratocytes were located in places in direct contact with the inlay on anterior and posterior surfaces. Sometimes these were associated with fine cellular processes that had penetrated the surface of the inlay. Extracellular matrix and cell debris that resulted from the degeneration of keratocytes was also evident around the inlay. No inflammatory cells or neovascularization were observed in the vicinity of the microkeratome incision in sham or implanted corneas at any of the time points studied.

Immunohistochemistry

Immunohistochemistry results from the 24-month corneas showed that fibronectin was present in the extracellular matrix along the original incision line in both the sham and the implanted cornea (Fig. 6). No α-smooth muscle actin was detected in the stromal keratocytes or fibroblasts of either sham or implanted rabbit cornea at this time.

DISCUSSION

PFPE inlays were well tolerated by most (7 of 10) rabbit corneas over the 24 months of this trial, demonstrating that it is possible to successfully maintain an inlay under a corneal flap for up to 2 years. In these animals, the inlays were centered under the corneal flap, and the corneas remained clear apart from low levels of interfacial debris with no signs of infiltration or neovascularization in the implanted corneas for the duration of the test period. In each case, the tear film was normal, the epithelium was intact and healthy, and there was no stromal thinning. Problems apparently related to casting imperfections in the inlays and/or to difficulties with consistency of the surgical procedure developed in three animals in the implanted group that then had to be removed from the trial earlier than planned (on days 195, 251, and 553). One animal was discontinued on day 195 because of a small focal defect in the peripheral area of the inlay in the temporosuperior region. Histologic examination of this implanted cornea showed a small, very focal patch of stromal erosion and epithelial thinning anterior to the inlay. This defect was confined, and no other obvious abnormality was observed in the inlay or tissue of this cornea. A second animal was discontinued from the trial on day 251 because of a focal epithelial defect directly above a single split in the inlay. The split was first noted on day 207 and might have resulted from uneven mechanical pressure on the inlay during the period of implantation. A third animal was

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<th>Table 1. Oxygen Uptake in the Corneas of Implanted and Contralateral Eyes 18 Months after Surgery</th>
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<td><strong>Central to Inlay</strong>/<em>Central</em>*</td>
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Oxygen uptake is measured in mm Hg per second.

* Sites of measurement for the contralateral eyes.
removed from the study on day 553 because of a small peripheral focal defect in the nasoinferior region. Histologic examination of this cornea showed focal stromal thinning and erosion anterior to the inlay in that area, and a small foreign body (perhaps a free piece of inlay polymer) was noted on the anterior surface of the inlay in this region. As noted, the use of a microkeratome designed for human eyes in the cutting of a corneal flap in rabbit eyes made it difficult to achieve a flap of consistent depth and thickness on every occasion given the variability in the size and shape of the rabbit eyes and made it difficult to achieve and maintain the desired suction pressure during the cutting of the flap. In addition, casting and molding of the inlays was recognized as significant for achieving a good long-term outcome. All inlays used in this study were prepared under laboratory conditions, and it is likely that some slight irregularities in formulating and casting would be eliminated if these procedures were to be conducted outside a research environment.

**FIGURE 5.** Transmission electron micrographs of the central cornea in (A) normal rabbit, (B) sham-wounded cornea on day 730, and (C) implanted cornea on day 742 (ep indicates corneal epithelium; arrow shows line of original microkeratome cut in sham; polymer is the polymer inlay). Bar, 80 μm; all images are shown at the same magnification.
Comparative clinical and histologic data from normal, sham, and implanted rabbit corneas maintained to their predetermined time points of 6, 12, and 24 months showed subtle responses to the presence of an implanted PFPE inlay. Operated corneas (sham and implanted groups) healed, and the presence of the PFPE inlay was well tolerated in 7 of 10 implanted corneas. The epithelia over the flaps in the sham and implanted groups were similar histologically and differed from that of normal rabbit corneal epithelium only in slightly decreased overall thickness because of a change in the basal cell morphology. Specific epithelial markers (microvilli, desmosomes, hemidesmosomes) monitored during the study were similar in morphology and distribution in sham and implanted groups, but the numbers of desmosomes and hemidesmosomes were slightly lower than those seen in normal rabbit cornea. Despite this slight decrease, the epithelium over the flap in the operated eyes was stratified and maintained a high level of integrity throughout the duration of the study.

The reasons for the epithelial thinning are unclear and may involve several factors, one of which appears to have been species. Other groups have reported long-term epithelial thinning after LASIK procedures in rabbit corneas that were also evaluated by histology after 6 months and 9 months. This differs from reports in human corneas after LASIK surgery, with no change in flap epithelium up to 4 months after surgery as noted by histologic examination or a thickened epithelium for 1 to 12 months after surgery as measured by in vivo confocal microscopy. It is possible that there were differences between histologic and laser confocal data, and we are cautious of direct comparisons with these studies because our study used a microkeratome incision but did not involve the laser ablation used in conventional LASIK procedures. Cutting of the corneal nerves during the microkeratome incision might also have contributed to the epithelial thinning. Postoperative nerve damage and loss of corneal sensation have been reported after various refractive procedures involving the human cornea, including LASIK, LASIK, epikeratophakia, and long-term corneal graft surgery. Concurrent thinning of the central epithelium has been noted in the two latter procedures. Yet another factor involved in the epithelial thinning noted in our study may be the effects of any contour feedback mechanism operant in the corneas; though this phenomenon is not well understood, there has been some suggestion of the eyelid acting as a template for corneal curvature.

Ultrastructural examination of the stroma along the microkeratome incision (sham corneas) and along the incision line and in the vicinity of the inlay (in implanted corneas) revealed keratocytes swollen with vacuoles that were greater in number and size than those of normal rabbit cornea. Confocal microscopy of human corneas has shown a decreased keratocyte density in the stromal flap and anterior retroablation area for up to 3 years after LASIK procedures. This suggests that the increased keratocyte numbers observed in sham and implanted corneas in our study may be related to species and/or to the microkeratome incision without the accompanying laser ablation used in refractive LASIK procedures. The persistent keratocyte activity observed in our study is not an unexpected outcome after wounding of the cornea; rather, such activation is part of the stromal wound healing process in which keratocytes synthesize extracellular matrix to repair damaged tissue. Activated keratocytes have been reported in the vicinity of microkeratome incisions and ablation areas for some months in human and rabbit corneas after LASIK surgery. In our study, a microtome incision was made, but no tissue ablation was performed as would have occurred in a LASIK procedure. Nevertheless, activated keratocytes were present in the vicinity of the wounded tissue at each time point, but this activity did not increase with time during the 24-month period. Keratocytes around the implanted inlays were typically swollen with vacuoles, and there was evidence of cellular degeneration in places. Fine cell processes had penetrated the polymer surface in places around the inlay, as noted at the 12- and 24-month time points. Fibronectin immunodata from our study confirmed that extracellular matrix (ECM) was still being produced in the vicinity of the original corneal incision 24 months after surgery. Interestingly, our concurrent α-sma immunodata showed that the stromal wound healing process did not involve the transformation of keratocytes involved in the wound healing process into a contractile keratocyte phenotype. This indicated that any scar formation was likely to be the result of disorganization in the stromal collagens and proteoglycans, which was consistent with data from our ultrastructural examination along the region of the original microkeratome incision using electron microscopy. The corneas of rabbits implanted with PFPE inlays maintained transparency for the entire period of the study, whereas the clarity of inlays decreased slightly with time (5% to 15% loss over the 24-month period). We do not fully understand the reasons for this. Oxygen uptake on implanted eyes 18 months after surgery was compared with that of their contralateral eyes, and data showed no significant change in the oxygen flow rate. This demonstrated the long-term permeability of the PFPE inlays during the period of implantation. The healthy condition of the stroma and epithelium anterior to the implanted inlays during the 24-month test period was further testament to this. We noted no accumulation of deposits and opacification at the edge or on the surface of the inlays, as reported in hydrogel corneal inlays implanted in human trials. The biologic response in our study was characterized by a low level of keratocyte activity that was localized to the immediate vicinity of the original line of corneal incision and inlay, which might have been the cause of the interfacial debris noted clinically in the sham and implanted groups. It is possible that the penetration of fine cell processes and ECM material into the polymer surfaces might have been responsible for the slight loss in optical clarity and the occasional inhomogeneity of the inlays.

In conclusion, refractive surgical procedures initiate a corneal repair process. The challenge is to minimize the wound healing response and to maximize the refractive outcome for the patient. In this study, PFPE inlays were implanted in rabbit corneas to evaluate the clarity of the polymer and the long-term biologic response. Data demonstrated that the polymer was biostable in the corneal environment over 24 months, with only a slight reduction in optical clarity of the inlays during that time. During the period of implantation, the implanted corneas remained clear, with no infiltration, neovascularization, or increase in conjunctival redness. The polymer elicited only a low-level wound healing response that was confined to the stromal tissue in the immediate vicinity of the inlay and that did not involve inflammatory cells. Keratocyte activity was the key feature of this low-level response and was characterized by...
repair/regeneration and was accompanied by ECM/cellular debris production. Together this constituted an inert foreign body response to the PFPE inlay that was prolonged but benign. Products of this biologic response might, at least partially, have accounted for the slight loss of clarity in the polymer over the 24-month period of this study.

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References


