AN ANALYSIS OF CORNEAL ENDOTHELIAL AND GRAFT SURVIVAL IN PSEUDOPHAKIC BULLOUS KERATOPATHY*

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INTRODUCTION

PSEUDOPHAKIC BULLOUS KERATOPATHY (PBK), THE DEVELOPMENT OF LASTing corneal edema in an eye with an intraocular lens (IOL), has become a major complication of cataract surgery. As such, it is an important cause of visual loss and discomfort in the elderly population undergoing cataract extraction. Because widespread use of IOLs has developed only in the past 15 years, development of treatment strategies for PBK has also occurred recently and is still in the process of refinement. With IOL type changes, therapy for PBK in eyes with differing IOL types has also changed. This study was designed to utilize information developed prospectively on the surgical management of PBK over a 6-year period as the basis for evaluating surgical approaches to PBK.

Prior studies have led to conflicting advice on surgical management of PBK. In particular, the timing of keratoplasty[1] and the wisdom of implant retention or removal at keratoplasty have been debated.[2-6] The hypothesis to be tested in this study is that the approach to the implant at keratoplasty has a significant effect on graft and visual success. While this hypothesis can be tested by analysis of graft survival, such analysis is limited by the delayed time frame of graft failure and the influence of the number of failure events on the statistical power of studies to distinguish between graft survival rates. A clinical laboratory technique, specular microscopy, is therefore used as a proxy measure for graft survival. It will be demonstrated that the rate of endothelial cell loss measured by specular microscopy correlates with late graft failure and can be used as a predictive measure, shortening the necessary follow-up time for evaluation of keratoplasty results. Groups of patients having various forms of surgical therapy can be compared by life-table analysis of clinical outcomes. Specular microscopic results can be described by relatively simple regression models. Life-table survival curves and regression slopes for

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various treatment groups can be compared to evaluate the significance and magnitude of differences, and thus to derive the preferred treatment strategies for various clinical situations. This study attempts to link clinical data, clinical laboratory data (specular microscopy), and descriptive models of their behavior by the application of modern biostatistical methods.

HISTORICAL AND LITERATURE REVIEW

PSEUDOPHAKIC BULLOUS KERATOPATHY — INCIDENCE

Cataract surgery has undergone dramatic changes over the past two decades. The most important change has been the popularization of IOL insertion and its continued refinement. This change occurred during a period of rapid growth in the number of cataract surgeries performed annually in the United states, from about 400,000 in 1965 to over 1,000,000 in 1986.[7] This increase is related to the aging US population, improved surgical success, broad insurance coverage for the elderly, and improved access to ophthalmologists. In recent years over 90% of patients having cataract extraction have had IOL insertion. In 1985, 888,000 IOLs were inserted. From 1978 through 1985, 3,261,000 were inserted.[8] In 1987, 1,367,000 IOLs were inserted.[9]

Increased IOL use has been accompanied by a corresponding increase in the frequency of complications of IOLs.[10] PBK is a major complication, resulting in significant visual loss and discomfort. The incidence of PBK was as high as 50% over 5 years in some early European series; that experience delayed IOL development and introduction in the US.[11-15] Barraquer[11] had inserted nearly 500 anterior chamber IOLs in the late 1950s and had removed half of them by 1970 because of corneal edema or chronic inflammation, complications which had not been recognized until several years after implantation. Binkhorst[11] noted some degree of corneal endothelial decompensation in 9.2% of 694 early iris-clip lenses, occurring an average of 3 years following implantation; in 5.5% useful vision was not regained. No PBK was found in a later, short-term series,[16] but in another Binkhorst series PBK occurred in more than 9% of 354 patients with intracapsular cataract extraction and iris-clip IOL insertion.[17] A 4-year follow-up of Binkhorst iris-clip lenses inserted by Pearce[18] revealed a 2.7% incidence of permanent PBK. American studies using the Copeland iris plane implant demonstrated central corneal edema in 5 of 81 early cases followed for 5 years and in 3 of 81 in a later series followed for 19 months.[14] By meta-analysis combination of several reported series from the literature, Drews[19] derived an incidence of 3.2% ± 4.3%

corneal decompensation in 8515 cataract extractions with implant done in the 1960s and early 1970s. The majority of these were iris-supported or anterior chamber IOLs with intracapsular extraction, although Tennant[20] had reported an incidence of about 15% in a small series of anterior chamber IOLs with extracapsular extraction.

Good data are not available on the current incidence of PBK. The US Food and Drug Administration (FDA) follow-up of 409,000 lenses inserted in the US from 1978 through 1982 found 0.06% corneal decompensation at 1 year for posterior chamber IOLs, 1.2% for anterior chamber IOLs, and 1.5% for iris-fixated IOLs.[21] This is likely to be an underestimate because of underreporting to the FDA.[22] Even some "modern" IOLs have been associated with excessively high PBK rates. The Azar 91Z flexible closed-loop anterior chamber lens, for example, has been reported to have the "highest postoperative complication rate of any implant of contemporary design and manufacture."[23] A 5.1% incidence of bullous keratopathy has been reported at 1 year and an increasing cumulative incidence thereafter.[24] This lens was withdrawn from the market in 1983. The Leiske closed-loop lens has been associated with 5.5% incidence of PBK at 41 months' follow-up.[25-27] This lens and the stableflex lens,[28] another popular flexible closed-loop anterior chamber lens, were put on "core restrictions" by the FDA, effectively removing them from use,[22] and a similar style was recently withdrawn.[29] Some large series of extracapsular cataract extractions with posterior chamber IOL insertion, the most frequent form of cataract surgery in present use, have had remarkably low PBK rates. Stark and associates[30] reported only a 0.1% rate in 1041 cases. In a retrospective comparison Taylor and associates[15] reported PBK in 4.3% of 800 intracapsular cataract extractions with iris-supported IOL, aphakic bullous keratopathy in 0.8% of 3000 intracapsular cataract extractions without IOL, and PBK in 0.3% of 300 extracapsular cataract extractions with posterior chamber IOL. A similar estimate was derived from 15,500 cataract extractions in Switzerland in 1986.[31]

With a decreasing incidence of PBK for recently performed procedures, and an increasing frequency of cataract extraction, PBK is likely to remain an important problem. If a long-term rate of 0.5% is hypothetically used to estimate the incidence of of PBK (and it is assumed that at least 1,300,000 IOLs are inserted each year), then 6500 PBK cases would be generated annually in the United States. This is a significant proportion of the 36,000 transplants performed in the US annually[32] and approaches the estimate of 9000 cases if about 25% of grafts are currently performed for PBK.[33] The large number of cataract extractions with IOL done in the past, the increasing life expectancy of these patients, and the present high

rate of cataract surgery have created a large pool of patients with patient-years at risk for PBK.

An alternative approach to estimation of the magnitude of the PBK problem is to determine the number of penetrating keratoplasties (PKP) done for this indication. Prior to the mid 1960s, the success rate for PKP in eyes with aphakic bullous keratopathy was low.[34,35] In the 1970s the success rate improved and aphakic bullous keratopathy became a major indication for keratoplasty.[36,37] With the development of PBK, the number of keratoplasties increased and PBK became the leading indication for PKP in the United States.[33] In one report PBK accounted for 2% of keratoplasties in 1976 and had increased to 26% by 1984.[38]

ETIOLOGY OF PSEUDOPHAKIC BULLOUS KERATOPATHY

The causative factors in development of PBK have not been fully defined. Potentially the etiologic factors can be separated into preoperative, intraoperative, and postoperative.

Preoperative factors associated with PBK development are primarily preexisting corneal endothelial pathologies. Waltman[39] found unexpectedly low endothelial cell counts, less than 1000 cells/mm^2, in the unoperated eyes of 17% of patients having PKP for PBK; another 8% had counts between 1000 and 1500, suggesting a role for prior endothelial disease. Rao and associates[40] did not find a correlation between preoperative endothelial cell density and PBK. They did, however, find a correlation between preoperative variation in cell size and development of later PBK. Bates and Cheng,[41] however, examined preoperative and postoperative cell morphology in patients in a randomized trial of IOL use. They found no evidence that risk of developing PBK could be predicted by preoperative specular microscopy. It appears that in recent series of patients with PBK following posterior chamber IOL insertion, the onset of corneal edema is early. Many of these patients show histologic[42] or clinical[43] evidence of underlying corneal endothelial dystrophy.

Potential intraoperative factors are many. Intracapsular cataract extraction alone was shown to cause a significant long-term increase in corneal thickness, presumably secondary to endothelial damage.[44] Instrumentation, irrigating solutions, medications, corneal bending, and mechanical factors related to IOL insertion itself may be important. Irrigating solutions were shown by Edelhauser and associates[45] to have potentially toxic effects, leading to improvement in solutions and limitation of flow rates. Bourne and Kaufman[46] in 1976 demonstrated that cataract extraction with IOL insertion caused a 62% reduction in central corneal endothelial cell

density. This remarkable finding spurred interest in the endothelial effects of IOL surgery and led to improved surgical techniques. Kaufman and associates[47] showed that surface contact between IOLs and endothelium caused severe endothelial damage. The endothelial protection demonstrated by air and, later, viscoelastic substances confirmed mechanical factors for damage at the time of surgery.[48-50] The degree of cell loss has varied from a few percent to 62% with different techniques. Current methods of extracapsular cataract extraction or phacoemulsification, with posterior chamber lens insertion, yield about 10% cell loss, although the variance is large.[51-53] Eyes with eventual cell loss have greater corneal thickness in the early postoperative period, indicating functional significance to cell loss.[54]

Postoperative factors in PBK development, presumably mediated by endothelial cell loss, are even more difficult to define in the usual case. Some obvious mechanical factors can occur, such as anterior chamber flattening or IOL subluxation with IOL to endothelial touch.[18,55] Severe postoperative uveitis has also been a probable factor.[14] Increased inflammatory reactions to ethylene oxide sterilization and to residual polishing compounds may have been factors in the past,[56,57] as were problems related to poor lens surface polishing.[10,58] Less obvious mechanical factors have been related to lens movement within the eye, as demonstrated photographically by Miller and Doane[59] and seen in an exaggerated form in the "intermittent touch syndrome" described by Drews.[60] These are problems related primarily to iris-supported IOLs and are not as likely to be factors with stable anterior chamber and posterior chamber lenses, although iris chafing can occur.[10] It has been demonstrated, however, that continuing endothelial cell loss can be a problem, not only with unstable lenses.[61] Continuing cell loss has been shown up to 3 years after implanting of iris-supported IOLs.[62] This is of relevance to keratoplasty performed over such lenses. Of greater current concern is the demonstration by Liesegang and associates[51] that eyes with extracapsular extraction and posterior chamber IOLs also showed continued cell loss at 2 years. A similar phenomenon has been demonstrated for intracapsular extraction without IOL, suggesting that IOL presence is not solely responsible.[51,63] Other morphologic findings suggest that closed-loop anterior chamber lenses are more likely to cause long-term changes than posterior chamber IOLs.[53]

Long-term "toxic" effects of IOLs have also been postulated. These could be from monomers or other compounds in polymethylmethacrylate or from added ultraviolet filtering compounds. Studies to date suggest both sources are unlikely.[64,65] Other chemical factors have been postu-

lated. Prostaglandin-mediated breakdown of the blood-aqueous barrier has been suggested by the role of nonsteroidal anti-inflammatory drugs in preventing post IOL cystoid macular edema.[66,67] The development of corneal edema has been linked with cystoid macular edema through a common mechanism of mechanically stimulated release of inflammatory mediators.[68] The role of IOLs in blood barrier disruption has also been studied with anterior segment fluorophotometry.[69] Other forms of inflammatory reaction may be mediated by activation of the complement system by intraocular plastic materials. Galin and associates[70] demonstrated stimulation of chemotaxis of white cells by IOLs, confirmed to be a complement-mediated reaction.[71] The alternative complement pathway may also be involved.[72] Wolter[73] reported that a macrophage and protein membrane develops routinely on the IOL surface. In a cornea removed for early PBK, a similar macrophage reaction appeared to be destroying the endothelium. It was postulated that the reaction was stimulated by IOL-induced complement activation.[74]

The several mechanisms of endothelial damage postoperatively are of particular concern in the management of PBK. If they can be better understood, then a more etiologic rather than an empirical approach can be taken to management of the IOL at keratoplasty. If an IOL is present after keratoplasty and it continues to cause endothelial damage, then the survival of the graft may be significantly limited. Prior to the IOL era, Stocker and Irish[75] postulated that grafts for bullous keratopathy in aphakic eyes had a limited life span, probably only 8 or 9 years, because of poor host endothelium and decline of donor endothelium. Additional effects of IOL presence could then potentially further shorten this course.

CLINICAL SPECULAR MICROSCOPY

Clinical specular microscopy is a means of examining, photographing, and quantitatively evaluating the corneal endothelium. Its application to the study of the cornea after IOL insertion and its relevance to PBK development have already been discussed. This section briefly reviews the diagnostic technique and some factors in previous studies relevant to keratoplasty for PBK. Previous reviews by others provide more detail.[76,77] Post keratoplasty specular microscopy is described.

The techniques used for specular microscopy were developed by Maurice[78] for laboratory use and were modified by Laing[79] and by Bourne and Kaufman[80] for clinical application. Modifications since then have allowed examination of large fields of endothelial cells.[81] Most studies of the endothelium have used quantitative measures of endothelial size, or the inverse, cell density. These can be derived from either fixed- or variable-

frame analysis of photographs or video images. Sophistication of these methods requires tracing of cell outlines and computer digitization. With such methods the cell shape and size and their variance can be analyzed. Matsuda and associates[82] called attention to the importance of the proportion of hexagonal endothelial cells as a measure of endothelial stability. The precision and reliability of specular estimates of endothelial cell parameters have been evaluated in several studies.[76,83-86]

The usefulness of specular microscopy in evaluating the effects of surgery on the cornea is dependent on the permanence of endothelial cell loss. The failure of adult human endothelial cells to divide in vivo makes cell size an appropriate measure.[87] When endothelial cells are lost, the resulting defect is filled by enlargement and sliding of surrounding cells.[88,89] The process of cellular pattern reorganization initiated by an acute major injury takes about 3 months to stabilize, as measured by change in the central endothelium.[90-92]

Decline in endothelial cell count with age has been documented in normal human subjects.[80,83,86,93] Decline after surgical and nonsurgical trauma has been the subject of numerous studies.[77] The importance of declining endothelial density is both as a marker of past or continuing trauma and as a predictor of endothelial failure. The cell density necessary for maintenance of corneal deturgescence is unknown, although cell counts below approximately 600 cells/mm^2 suggest extreme vulnerability. A mean cell density of 515 cells/mm^2 was found at the time of diagnosis of bullous keratopathy in a study serially following postsurgical cataract patients.[94] Descriptive deterministic mathematical models predict exponential cell loss following surgery.[76,94]

SPECULAR MICROSCOPY OF POST KERATOPLASTY CORNEAS

The original applications of specular microscopy to keratoplasty were in cross-sectional surveys of clear grafts.[95-97] These showed mean cell densities of about one-fourth to one-third of normal. Some retrospective studies failed to show a relationship between postoperative time and cell loss, and others found a decline with time beyond that expected for aging alone.[97] Attempts were made to relate endothelial status in the graft to the endothelial status of the host, but no difference was found between grafts in eyes with good host endothelium and those with poor host endothelium.[95-99] This suggested that there is little spread of endothelium across the graft-host junction, although such spread can be demonstrated in animal models.[100,101]

Prospective studies of the donor endothelium post keratoplasty have all shown a decline in cell density with time.[76,99] Bourne[99] showed a mean

cell loss of 46% at the end of 1 year and no difference between phakic and aphakic grafts. In his comprehensive thesis he showed a 21% cell loss per year for the first 3 years following grafting, but no significant further loss.[76] This stabilization was confirmed in a study by Matsuda and Bourne[102] showing 57% cell loss over the first 2 years, followed by 3.5% loss each year thereafter. The reduced rate of cell loss was attributed to the reestablishment of hexagonal patterns in the endothelium.[38] Others[103,104] have shown 32%, 34%, and 21% to 39% loss at 1 year. A single report, using direct measurements from three clear grafts removed 1 to 11 months after keratoplasty, found a maximum of 5.6% cell loss; but this finding is clearly different from the majority experience and was based on very few observations.[105]

Other specular microscopic studies have been used to evaluate keratoplasty techniques, showing the benefits of preoperative hypotony, ring support, and viscoelastic agents in endothelial protection.[106,107] The only study of the effects of implant retention or removal on endothelial cell loss favored IOL removal from this standpoint.[38]

Specular microscopic studies of donor tissue had been performed prior to specular studies in living eyes[108] and since,[109,110] but guidelines for their use in donor selection were not established. The effects of donor age, storage time, and storage medium have been evaluated.[111-114] Donor age has been correlated with donor cell count[97,102] but not with postoperative cell count.[98,101] There have been suggestions of decreased cell change with decreased recipient age.[102,103] Using their observed rate of cell loss over 5 years, Matsuda and Bourne[102] suggested 1600 cells/mm^2 as a minimum count for corneas suitable for transplantation.

KERATOPOLASTY FOR PSEUDOPHAKIC BULLOUS KERATOPATHY

The first series of keratoplasties for PBK was reported by Fine[115] in 1978. Fifteen of 16 grafts remained clear at 6 to 12 months. Eleven of the iris-supported implants were retained and five removed at keratoplasty. Subsequently, multiple series have had largely good anatomic results but only fair visual results. The issue of advisability of IOL retention or removal has not been fully resolved, and the more recent approach of IOL exchange has not been adequately scrutinized.

The early reports of PKP for PBK urged IOL retention for optical purposes. Taylor and associates[116] believed that PKP over an IOL was similar to PKP in a phakic eye. Kok-VanAlphen and Volker-Dieben[1] in 1979 presented a series of 31 grafts for PBK with iris-supported IOLs. Ninety percent remained clear at 1 to 2 years' follow-up, and most IOLs were retained. Their most important findings were that delayed onset of

corneal edema after cataract extraction had a favorable visual prognosis, while visual results of PKP are improved if the time from onset of edema to PKP is short (less than 10 months). These significant findings have not been tested since. Waltman[39] preferred IOL retention in 31 of 36 PBK grafts, with 92% clear; 54% had 20/40 or better vision at 1 year. Taylor and associates,[15] in a later series, retained the IOL in 35 of 42 caes, with 88% clear at 18 months. Meyer and Sugar[117] also had 88% clear grafts in 25 cases at 20 months; half of their IOLs had been removed and half retained, with no difference in clarity or visual results. Charlton and associates[118] likewise found no difference in results whether an IOL was retained or removed, but they felt visual rehabilitation was accelerated by the presence of an IOL. Arentsen and Laibson[6] advised retaining all stable IOLs at PKP, if possible, because of their finding in a nonrandomized series of 40 cases of 20/100 or better visual acuity in 86% of those with IOLs retained and 20/100 or better in 47% of those with IOL removed. Terry and associates[2] retained all Copeland IOLs in a series of 20, with 90% of first grafts clear at 2 years. Kozarsky and associates[5] likewise found no adverse effects of retaining stable IOLs in 26 eyes with 2-year follow-up. Eighty percent of their grafts were clear, and 38% of eyes had 20/40 or better vision. Samples and Binder[119] retained 41 of 76 IOLs at PKP and found slightly better acuity for those with IOL retention, although those with IOL removed had a slightly greater proportion (83% versus 76%) of clear grafts.

All of these series had relatively short-term follow-up. With longer follow-up (usually beyond 2 years), however, it became apparent that retained IOLs, at least those with iris support, may have a detrimental effect on the graft. Volker-Dieben and colleagues[3] had noted slowly progressive corneal edema without signs of graft rejection in 7 of 78 grafts with retained IOLs. She found significantly decreased survival at 2 years (48.5%) for such grafts compared with 72.5% survival at 2 years for aphakic bullous keratopathy without an IOL. Sugar and associates[38] documented the phenomenon of late graft failure with IOLs. They used specular microscopy to support the contention that this was related to an accelerated rate of endothelial cell loss. They found 39% cell loss 1 year after grafts with iris-supported lenses retained, and 21% with iris-supported lenses removed. Findings with retained and removed anterior chamber lenses were similar. Alpar[120] confirmed these findings in a series of 53 cases.

For a brief time the phenomenon of late graft failure, as well as studies confirming continuing endothelial cell loss after iris-supported IOL insertion in eyes with normal corneas, led to IOL removal without replacement

at PKP. Waring and associates[4] removed all IOLs (85% iris-supported) from 35 eyes having keratoplasty. Ninety-one percent of grafts were clear at a mean follow-up of 15 months, but visual acuity was not as good as in a comparison series of aphakic bullous keratopathy eyes. This difference was attributed to 43% maculopathy in the PBK eyes and 22% in the aphakic bullous keratopathy eyes. Schanzlin and associates,[121] however, found no difference in visual acuity of PBK and aphakic bullous keratopathy eyes at 1 and 2 years after PKP and no significant effect of IOL removal on acuity or maculopathy. Larger, more recent series[122] have had good anatomic results but less favorable visual improvement. Cohen and associates[123] found 77% of 189 grafts clear at a mean follow-up of 15 months. At 1 year 11% had 20/40 or better acuity, but this improved to 31% by 2 years. A long-term follow-up study showed the greatest graft failure over retained anterior chamber IOLs (60%) and exchanged IOLs (20%) at 2 years, and the best vision with retained iris-supported, posterior chamber, or rigid anterior chamber IOLs.[124] Vision and graft success have both been good when grafting over retained posterior chamber IOLs.[43]

Several investigators have commented on the functional difficulties of the aphakic graft patient after IOL removal,[5,38,118-121] creating a dilemma between the choices of (1) improved expectation of graft clarity but decreased functional vision when aphakic spectacles were used or a contact lens could not be tolerated and (2) decreased chance of graft success but better visual function.[122] Some surgeons had been exchanging iris-supported IOLs for anterior chamber or posterior chamber IOLs since the late 1970s.[124,125] In 53 eyes Hall and Muenzler[124] exchanged iris-supported or anterior chamber IOLs for sutured posterior chamber IOLs. Eighty-eight percent were clear with 3-year average follow-up and 38% had 20/40 or better visual acuity. Polack[125] found no difference in visual acuity or graft clarity between 65 grafts with IOL removed (93% clear, 50% 20/100+) and 25 grafts with IOL exchange for flexible anterior chamber lenses (96% clear, 50% 20/100+). Waring and associates,[126] who had previously advocated IOL retention, then IOL removal,[4,5] studied 25 PBK eyes with flexible-loop anterior chamber IOL exchange, or a sutured posterior chamber IOL exchange at a mean of 19 months postoperatively. Eighty-eight percent were clear, and 32% had 20/40 or better vision. Waring[127] has described their technique in detail. A similar technique for exchanging iris-supported or closed-loop anterior chamber lenses for one-piece flexible anterior chamber lenses has been used by others with good results.[128] There is no agreement on the choice between these alternatives of anterior chamber and posterior chamber lens insertion for IOL

exchange at keratoplasty. The anterior chamber lens is technically easier to insert, but it may compromise areas of angle in an eye with previous IOL-related angle damage.[129] Posterior chamber lenses are more difficult to insert in eyes with compromised or absent posterior capsule but are further from the donor endothelium. Techniques for IOL insertion in such eyes have been described.[122,130-134] Published results of these techniques of sutured posterior chamber lens exchange showed clear grafts in 95% and 20/40 or better vision in 43% on short follow-up of 44 cases.[135]

An alternative approach to keratoplasty and IOL exchange for PBK has been suggested by Hoffer.[136] He believes that three procedures—initial IOL removal, later keratoplasty, and final secondary lens insertion—offer the greatest safety and probability of good uncorrected visual acuity. No evaluation of grafts using this technique has been reported.

STUDY DESIGN AND JUSTIFICATION

The purpose of this study is to evaluate and compare the results of keratoplasty for PBK using the various approaches to the IOL described above. This is a cohort study with prospective generation of specular microscopic data but retrospective collection of clinical data. The patients with specular data have been entered consecutively since 1981 and are divisible into five groups on the basis of whether their IOL was retained, removed, or exchanged for one of three IOL types at keratoplasty. Selection of patients for each treatment was not made on a randomized or arbitrary basis, but rather reflected changes in experience and historical trends over the 6 years during which data were generated. An initial approach was to retain all stable IOLs, if possible. Initial data from these patients and from the literature, however, suggested that the risk of late graft failure was increased if the original IOL was retained. Implants were then removed more frequently for a period, and the technical results appeared improved in terms of graft clarity; however, the functional results were believed to be poor, in that these eyes were not visually useful if no appropriate means of optical correction was available. The original IOLs were then exchanged successively for flexible closed-loop anterior chamber IOLs, one-piece semiflexible anterior chamber IOLs, and, most recently, posterior chamber IOLs. Data on graft clarity and specular microscopy were developed prospectively as part of a long-term effort to evaluate the endothelium of corneal transplants for all indications. The present study is nonconcurrent in the sense of following each cohort by retrospectively determining the group designation.

To perform this study as a randomized trial would not have been feasible from both ethical and practical standpoints.[137] It would not have

been ethical to randomize, because the surgeon believed at surgery, or study entry, that the specific procedure performed was the best available for each given patient at that time. *The goal of this study is to determine the validity of those judgments*. Randomization regarding IOL use would not likely have been acceptable to a large enough portion of the study patients to allow accrual of adequate sample sizes. Randomization would also have been hampered by historical changes occurring during the study period. Persistence with the use of older techniques when newer techniques, believed to be improvements, became available would potentially have withheld appropriate therapy from the study patients. The only randomized trial of IOL use, which was not associated with keratoplasty, was performed in Great Britain and reached conclusions of questionable external validity, suffering from the latter defects.[62,138]

As the primary outcome measures in this study are graft failure and endothelial cell loss, it would have been possible to derive a nested case-control study from these cohorts. Patients having graft failure could be compared with those not having graft failure for presence of potential risk factors (eg, IOL status, rate of endothelial cell loss). The rate of cell loss, however, is probably an intervening variable for nonrejection graft failure. Comparison of the regression slopes of endothelial cell loss allows for large samples and is postulated to be a predictor of late graft failure that may occur beyond the follow-up time of this study.

A case-control study to examine factors in initial development of PBK would be useful in determining etiologies, but such a study would require a control population not available for the current study. An appropriate control group would be age-matched patients with similar follow-up to the PBK patients, but in whom PBK had not yet developed. Because the PBK patients in this study were referred by their original surgeon and may not represent a cross section of all PBK patients, a comparison group must be derived from the practices of the same referring surgeons. Such a study could answer etiologic questions, but it would not answer the questions posed here regarding the approach to the IOL at PKP.

The use of a cohort study to approach this problem has advantages. The greatest is the availability of data on the largest group of PBK patients yet studied. The potential disadvantages are many. The PBK population in this study is a referral population but is probably representative of PBK patients requiring keratoplasty. The surgeons caring for these patients perform a large proportion of the keratoplasties in their catchment area. Because of the historical trends discussed previously, however, all study groups may not be comparable in many respects. Comparative demographic data will be presented. But the type of original IOLs present were

predominantly iris-supported IOLs early in the study and anterior chamber IOLs later in the study. Stratification of data on the basis of original IOL type was performed, but numbers in many subgroups are too small for meaningful statistical comparisons.

Potential biases exist because of the nonrandomized, nonmasked group assignments. Observation bias is limited by masking of specular photographs, and adherence to careful definitions of graft failure. Follow-up bias is a more difficult problem. Most patients have at least 1 year of follow-up; comparisons for longer periods are more subject to bias and may be less valid. The use of life-table methods and contacts of referring ophthalmologists for patients lost to follow-up attempt to limit these defects.

While the external validity of this study may be somewhat limited by the referral population studied, most PBK patients are referred to corneal transplant specialists. The results of this study should allow refinement of approaches to surgery in such patients.

MATERIALS AND METHODS

STUDY POPULATION

Patients

All patients who had keratoplasty for PBK on the corneal service from 1976 through 1986 were identified from the corneal surgeons' transplant logs; 469 such patients were identified. Of these, 390 keratoplasties for PBK, done between January 1981 and December 1986, had preoperative donor and postoperative serial graft specular microscopy performed. Several patients who had grafts prior to 1981 had partial postoperative specular microscopy follow-up. No patients were excluded from initial review unless they had no specular data; 44 such patients were found. Patients without specular data, but with clinical data, were included in clinical analyses. Patients were categorized as belonging to one of five groups: (1) IOL retained, (2) IOL removed, (3) IOL exchanged for flexible-loop anterior chamber IOL, (4) IOL exchanged for one-piece semiflexible anterior chamber IOL, or (5) IOL exchanged for posterior chamber IOL. All patients were referred for keratoplasty by their cataract surgeons. No information was available on the size of the cataract surgery population from which they were derived.

Although the sample sizes for each group were restricted to those accrued in the study period, sample size calculations were performed to determine whether these groups were appropriately large for parametric

statistical analysis. Calculating sample sizes to detect a 20% difference in failure rate, with a baseline rate of 5% failure, at a power of 80% and significance level of 5%, 49 cases were needed per group. If the baseline failure rate were 10%, each group would require 62 patients.[139-141] The numbers of patients available in each group were appropriate for such comparisons, except for the group with exchange of the original IOL for a one-piece anterior chamber IOL.

Four hundred sixty-one patients had PKP for PBK performed in one eye, and eight had keratoplasty for PBK in both eyes. To avoid the possibility of covariance between two eyes of the same patient, that is, the possibility that two eyes of the same subject are more likely to behave similarly than two eyes of different subjects (between and within subject variance differ), the first operated eye of each subject was used.[142-144] The small number of bilateral grafts, however, makes this correction trivial. Fifty-four grafts (11.5%) were done in eyes having two or more keratoplasties.

Clinical data were obtained from patient records in two ways. Abstracted data from clinical records have been recorded and stored prospectively in a corneal transplant registry. Data are stored in 120 fields, and the registry includes demographic information, preoperative and operative details, and extensive follow-up data for the first postoperative year. Data are reviewed annually after the first year. A manual of procedures for the data registry defines the classification of variables and outcomes. All patient records were also reviewed directly to ensure that data were current. The referring physicians of patients lost to follow-up were contacted by letter. The referring physicians were asked to complete a form detailing specific information on date of last visit, graft clarity, vision, and other outcome variables. Very few data, however, were added in this way. Initial clinical data were recorded from the preoperative examination. Follow-up data were recorded at 1 week, 3 months, 6 months, and 1 year postoperatively, and then annually.

Definition of outcome variables was determined prior to record review. Keratoplasties were considered to be clear if they were thin centrally and believed on slit-lamp examination to be optically consistent with good visual acuity. Graft rejection was defined by increased inflammation, keratic precipitates limited to the graft endothelium, and peripheral graft edema. Other features of graft rejection were recorded.[145] Visual acuity was measured by Snellen acuity with best refracted spectacle correction. Cystoid macular edema was defined on the basis of the clinical appearance of the macula by ophthalmoscopy and contact lens examination. When fluorescein angiography was available, results of angiography determined

the diagnosis. Because visual fields were not consistently obtained, glaucoma was considered to be the presence of elevated intraocular pressure requiring long-term medical or surgical treatment. Information for reliable determination of preoperative glaucoma was usually not available; this designation was based on use of glaucoma therapy at the time of referral.

DONOR CORNEAS

Donor corneas were obtained from the state eye bank. All were stored in McCarey-Kaufman medium (M-K).[146] Corneas with a scleral rim were removed from enucleated eyes and transferred to M-K after a period of moist chamber storage or were placed directly in M-K on removal from the donor. If they were received in a glass M-K vial, they were transferred to modified storage and viewing chambers as described by Bourne.[147] All were examined at the slit lamp by eye bank personnel and again by the surgeon. Donors greater than 65 years old were excluded, as were corneas from patients with sepsis, neurologic disease of unknown cause, or prior ocular surgery.[148] Donor corneas with visible guttae, signs of corneal infection, or scarring were also excluded. Although donors were examined by specular microscopy, no donor corneas were excluded on the basis of the specular findings. Specular microscopy was performed for the purpose of obtaining data for postsurgical follow-up. Donor cell counts were not made available to the surgeons until after operation and were recorded separately from the recipient medical records. Corneas were used within 96 hours of donor death.

KERATOPLASTY TECHNIQUES

All keratoplasties were performed by three experienced, fellowship-trained corneal surgeons or by fellows (15% to 20%) under their direct supervision. Surgery was performed using local anesthesia. Globes were stabilized with modified scleral support rings. All donor buttons were hand-punched on a Teflon block.[149] The patient's cornea was then incised with a disposable trephine, directly entering the anterior chamber in most cases. The recipient trephine was 8 mm in more than 95% of eyes, and the donor cornea was 0.5 mm larger in almost all cases.[150] After trephination the IOL present was inspected. In the initial cases the IOL, usually iris-supported, was retained unless it was unstable or was associated with chronic inflammation. If there was vitreous presenting around the IOL, a vitrectomy was performed through the pupil or through an iridectomy using a vitreous suction cutting device.[3] If the implant was forced forward

by vitreous pressure, but the vitreous remained behind the iris-IOL plane, a vitreous aspiration was performed through the pars plana. When iris-supported IOLs were removed, adhesions to iris and vitreous were carefully lysed with scissors. A vitrectomy was usually then performed. The first type of IOL used for exchange at the time of IOL removal was a flexible closed-loop anterior chamber IOL (ORC stableflex). This lens was abandoned after early verbal and then published reports of difficulties with this lens style.[151] Later a single-piece polymethylmethacrylate semi-flexible "multiflex" anterior chamber lens was used (IOLAB 85J). Most recently a Sinskey modified J-loop posterior chamber lens (IOLAB 107G) was used to replace removed IOLs. It was sutured to the iris in a mattress fashion similar to that described by others.[135,152] In cases with adequate posterior capsule present after IOL removal, an angled-loop Sinskey posterior chamber lens was inserted into the ciliary sulcus and not sutured. When closed-loop anterior chamber IOLs were removed, the lens loops were cut from the optic and carefully pulled through the tunnels of iris tissue binding them to the angle.[153,154] Peripheral anterior synechiae were lysed by blunt and sharp dissection with a spatula or scissors when necessary in all cases.[127] The remaining implant was covered with a viscoelastic substance, sodium hyaluronate, in all cases. A viscoelastic was not used if IOL was absent. In 68.5% of all cases a viscoelastic was used.

Grafts were sutured with 16 to 24 interrupted 10-0 nylon sutures, a combined running 10-0 and 11-0 nylon suture, or combined 10-0 interrupted and 11-0 running sutures.[155] Subconjunctival antibiotics were given at the end of surgery in all patients. Most patients also received subconjunctival steroid injections. Patients were treated with frequent topical steroids postoperatively.

SPECULAR MICROSCOPY

Donor specular microscopy was performed using an eye bank microscope (PRO). Donor corneas were examined in Bourne chambers[147] after arrival from the eye bank and warming to room temperature. All donor counting was done from images recorded on videotape using fixed-frame analysis. At least three fields were counted, and the resulting cell densities were averaged. The technician doing the counting was not aware of the recipient diagnosis. Cell counts were not used for donor or recipient selection.

Postoperative specular microscopy was performed at 1 week, 3 months, 6 months, 1 year, and then annually. A contact specular microscope (Syber) was used to photograph the central cornea. At least six photos were taken of each eye at each session. Cell counts were determined by fixed-frame analysis, counting at least three frames and averaging the

results. Counts were made directly from negative film. The cell counter was masked as to patient grouping. Magnification for specular microscopy was calibrated by measurement of a micrometer grid.

Cell density was the only variable derived from the specular microscopic photographs. Cell tracing to estimate parameters of cell shape and size distribution was not performed. Hexagonality and its change could therefore not be determined for these populations. Cell counting is essentially a population sampling technique, subject to the errors of sampling. Larger cells, thus lower cell counts, would cause a smaller number of cells to be counted for each frame and for the total count. The smaller the number of cells counted for a given patient, the greater would be the variance of the mean of multiple measurements and its standard error. Bourne[76] calculated that 50 cells should be analyzed to allow a narrow 95% confidence interval for the estimate of the true mean cell size. This calculation was based on the standard deviation for digitized cell border analysis. Sperling and Gundersen,[85] however, studied the precision of cell counts by fixed-frame analysis and determined that two frames and counts of 20 to 80 cells were sufficient for estimates with 95% confidence. Errors due to changes in magnification induced by corneal thickness variation are negligible.[96,156,157] Errors due to positioning may exist in the normal cornea[157,158] and are greater when localized endothelial damage has occurred.[159] While features of the endothelium such as variation in shape and size add valuable information,[160] cell density, as will be shown, is still of value in analyzing corneal graft endothelium.

STATISTICAL ANALYSIS

Statistical analysis was performed by the author using one statistical package, Systat,[161] on a microcomputer and another, BMDP,[162] on an IBM 3090-400 mainframe computer.

Comparisons of demographic variables with continuous distribution were made using Student's *t*-test and the standard normal (*z*) distribution. For simultaneous comparison of multiple groups, analysis of variance (ANOVA) was performed. Pearson product-moment correlations were calculated. Categorical variables were analyzed by chi-squared methods using Cochran-Mantel-Haenszel methods for analysis of multiple tables.[163] Where necessary, Fisher's exact test was used in preference to the more conservative Yates' correction.

Analysis of specular microscopic data was performed using parametric and nonparametric techniques. Liesegang and associates[51] and Bourne[76] have argued that the distribution of cell size data is not normal and nonparametric techniques are necessary. But Rose[164] has argued that

these nonparametric tests are less sensitive than parametric tests. In fact, both the Wilcoxon rank sum test (Mann-Whitney test) and the *z* tests are fairly robust in the ranges of deviation from their assumptions that we have encountered in specular data.[165] While sampling means should be normally distributed in accordance with the central limit theorem, the distributions of cell count data were examined by determination of skewness and kurtosis[166] and the Lilliefors modification of the Kolmogorov-Smirnov test.[167] When multiple groups were compared nonparametrically, the Friedman two-way ANOVA was used for related samples and the Kruskal-Wallis test for independent samples.[162,165] Spearman rank correlations were used for nonparametric analysis.

The key approaches to analysis of data in this thesis involved descriptive modeling of the rate of endothelial cell loss and graft survival. Endothelial cell loss was described by modeling the slope of cell loss over time for each group. This was done using least square estimator techniques of linear regression.[168] Slopes were then compared by derivation of a *z* statistic for differences. A nonlinear exponential survival function was also fit to these data, and rates of decrease were compared. Graft survival was analyzed using product-limit life-table methods.[169,170] Such methods allow the description and comparison of groups with variable lengths of follow-up. They have been used very little in analyzing corneal grafts.[3,171] Kaplan-Meier curves were derived for survival of each group,[172] and differences were compared using the Breslow (generalized Wilcoxon) and Mantel-Cox (generalized Savage) tests.[162,173]

Differences between groups were considered statistically significant at an alpha or probability level of .05 or less using two-sided tests. Confidence intervals (CI) are presented where appropriate.[174]

RESULTS

PREOPERATIVE DETAILS — DEMOGRAPHY

Of the 469 patients in this study, 94 were in the IOL-removed group, 170 in the IOL-retained group, and 180 in the IOL-exchanged groups. Twenty-five additional patients had an IOL removed as a separate procedure prior to keratoplasty and are not included in most comparisons. Mean age at PKP was 73.5 years (standard deviation [SD], 9.0; 95% CI, 72.7 to 79.4), with a range from 39 to 97 years; 61.2% were female. These figures did not differ significantly between groups. The right eye was treated for PBK in 52.2%. Prior intracapsular cataract extraction had been performed in 71.6% and extracapsular extraction in 28.4%. Information on details of extracapsular technique was not adequate for analysis.

Mean time from cataract surgery to PKP was 50.8 months (SD, 32.9) for the total group. This period was 45.3 months in the IOL-removed group, 37.9 in the IOL-retained group, and 63.9 in the IOL-exchanged groups. Within the IOL-retained group those with posterior chamber IOLs had keratoplasty 17.9 months post cataract extraction, those with anterior chamber IOLs 36.8 months, and those with iris-supported IOLs 49.5 months after surgery. These differences were significant ($P < .005$). In the IOL-exchanged groups those receiving posterior chamber IOLs were operated on 71.5 months, those receiving closed-loop anterior chamber (ORC) IOLs 61 months, and those receiving one-piece (85J) IOLs 54.6 months after cataract extraction. The original IOL types are given by group in Table I.

TABLE I: ORIGINAL INTRAOCULAR LENS TYPE (NO.)

POST PKP* GROUP	ANTERIOR CHAMBER	POSTERIOR CHAMBER	IRIS-SUPPORTED
IOL removed	17	4	73
IOL retained	56	47	67
IOL exchanged PC	40	1	30
IOL exchanged 85J	12	1	6
IOL exchanged ORC	14	0	75

*PKP, penetrating keratoplasty; PC, posterior chamber.

Time from onset of corneal edema to surgery averaged 16.7 months overall (SD, 17.7) and was significantly shorter ($P = .029$) in the exchange groups (13.5 months) than in the IOL-removed (16.6 months) and IOL-retained (19.4 months) groups. Inadequate information was present on preoperative retinal disease. Glaucoma, designated on the basis of therapy at referral, was present in 34.5%. In 33.5% of patients, some ocular surgical procedure was performed between cataract extraction and keratoplasty; most procedures were for capsulotomy or IOL repositioning. This figure was significantly lower in the IOL-exchanged group (23.9%). Medical IOL repositioning had been performed in 7.4% of the IOL-removed group and in less than 2% of the other groups.

OPERATIVE DETAILS

Vitrectomy was performed at keratoplasty in 72.5% of cases. As expected, those with IOLs retained had vitrectomy significantly less often (45.9%) than those with IOLs removed (86.2%) or exchanged (91.1%). Viscoelastic material was used in 68.5% overall: 16.1% in IOL-removed, 73.2% in IOL-retained, and 97.2% in IOL-exchanged grafts. IOL type inserted on exchange was sutured posterior chamber lens in 60, unsutured posterior

chamber lens in 11, closed-loop anterior chamber lens (ORC) in 90, and one-piece anterior chamber (85J) lens in 19.

POSTOPERATIVE RESULTS

Follow-up

Mean follow-up time was 27.1 months (SD, 20.4; 95% CI, 25.3 to 28.9), with a range of from 1 to 101 months. As expected, the duration of follow-up differed significantly ($P < .005$) between groups. It was 35.4 months in IOL-removed, 30.1 in IOL-retained, and 19.5 in IOL-exchanged groups. (Survival comparisons will be discussed.) Follow-up time was measured to graft failure or last visit. Ninety-three patients (19.8%) were lost to follow-up. Twenty of these were known to have died at a mean of 21.8 months after PKP. The other 73 were followed a mean of 21 months prior to loss to follow-up. Mean follow-up in the 376 not lost was 28.6 months. The age, sex, type of cataract extraction, and group distribution did not differ between those followed and those lost. Because of the age distribution of these patients, it is presumed that many had died. One hundred thirty forms seeking additional follow-up information were sent to referring ophthalmologists. Ninety-six (73.8%) were completed, but many patients lost to follow-up had not seen the referring ophthalmologist since about the time of their last study visit.

Graft Clarity

Ninety-four of the 469 grafts (20%) failed during the study period. Overall failure rates were 20.2% in the IOL-removed group, 23.5% in the IOL-retained group, and 16.1% in the IOL-exchanged groups. Because of the relation to follow-up time, these differences were not significant ($P = .516$). If failure was stratified by subgroup, however, there were marked differences. The failure rate for retained IOL was 33.6% for anterior chamber lenses, 28.9% for iris-supported lenses, and 6.4% for posterior chamber lenses. The rate for posterior chamber lenses was significantly less. In the IOL-exchanged groups the failure rate was 8.3% for sutured posterior chamber, 11.1% for unsutured posterior chamber, 5.3% for one-piece anterior chamber, and 24.4% for closed-loop anterior chamber lenses. Within these groups it is notable that failure rates were equal to or less than rejection rates for IOL-removed, IOL-exchanged, or IOL-retained posterior chamber lenses and IOL-exchanged one-piece anterior chamber lenses. Failure rates were significantly greater than rejection rates for retained iris-supported lenses (28.9% *vs* 19.5%), retained anterior chamber lenses (33.6% *vs* 16.9%), and exchanged closed-loop anterior

chamber lenses (24.4% *vs* 14.4%). This confirms an excess of nonrejection failure in these groups.

Survival Analysis

Graft survival was analyzed by the product-limit method. The overall survival function is shown as a modified Kaplan-Meier curve in Fig 1. Overall cumulative survival at 1 year was 93.3%, at 2 years 83.6%, at 3 years 72.8%, at 4 years 66.9%, at 5 years 65.55, and at 6 years 62.2%. Cumulative mean survival time was 72.6 months (standard error [SE], 2.75).

When removed, retained, and exchanged groups were compared by survival curves (Fig 2), the curves did not differ ($P = .80$, Breslow; $P = .45$, Mantel-Cox). When stratified by subgroups for anterior-chamber, posterior-chamber, or iris-supported IOLs for retained and exchanged lenses, however, the groups differed significantly by a generalized test ($P = .037$, Breslow; $P = .034$, Mantel Cox). The survival was lowest for the retained anterior chamber and iris-supported lens and exchanged closed-loop anterior chamber lens groups.

When the exchanged IOL groups are compared separately (Fig 3), differences are not detectable ($P = .65$ Breslow; $P = .79$, Mantel-Cox). This result is biased greatly, however, by the low event rate, 1 early failure out of 19, for the one-piece anterior chamber group, and the small numbers with long follow-up in the sutured posterior chamber IOL group. Because the one-piece anterior chamber and the posterior chamber IOL- exchanged groups have the shortest follow-up, their comparison beyond the 15-month point is difficult. In the closed-loop anterior chamber IOL-exchanged group the numbers are large enough to make the continued decline in survival from 2 to 4 years noteworthy.

Other Complications

Rejection episodes occurred in 26.6% of the IOL-removed, 15.3% of the IOL-retained, and 13.3% of the IOL-exchanged groups. The differences between the IOL-removed group and those with IOLs remaining were significant ($P = .018$) and were not explained fully by the longer follow-up time. In all groups combined, 17.7% of grafts had at least one rejection episode.

Postoperative glaucoma occurred in 46.8%. Although this was greater than the initial 34.5% present preoperatively, this is somewhat misleading. Many patients considered to have glaucoma preoperatively on the basis of glaucoma medication use did not require medications postoperatively. The postoperative increase is therefore greater than the difference between the preoperative and postoperative rates.

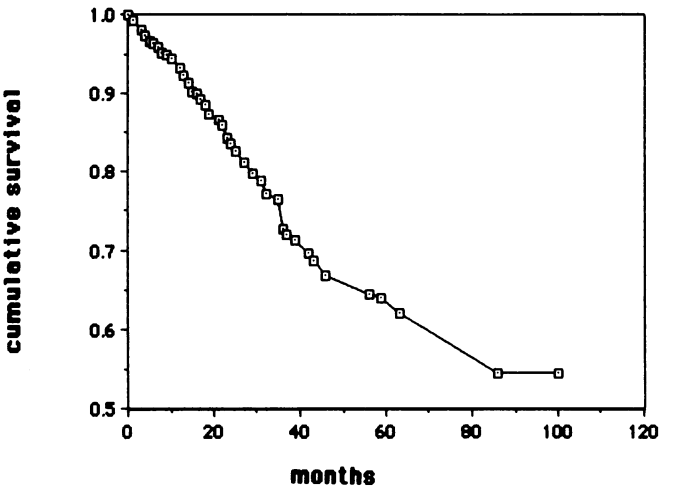

FIGURE 1
Modified Kaplan-Meier curve for graft survival in all groups combined.

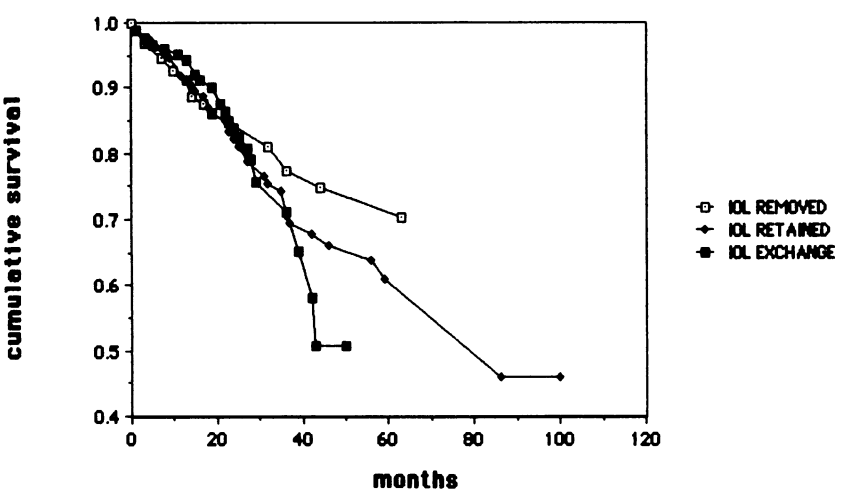

FIGURE 2
Modified Kaplan-Meier curves for graft survival by group.

Visual Results

Visual acuity results were tabulated by proportion with 20/40 or better vision and by mean visual acuity. Mean acuity was calculated as the mean of the denominator of the Snellen fraction, with a numerator of 20. Vision of finger counting was given a denominator of 800, and hand motions or less a denominator of 1600. At 1 year, all three groups had 50% to 56% of patients with 20/40 or better acuity, and at 2 years 41% to 46% with 20/40 or better acuity, with no significant differences between groups. Mean visual acuity at 1 year was 20/203 for removed, 20/181 for retained, and 20/164 for exchanged IOLs, but these differences were not significant ($P = .24$). Mean visual acuity declined thereafter at a slow rate in all groups, with no significant differences. For subgroups the mean visual acuity in the retained lens group was best for those with retained posterior chamber IOLs and was significantly better than in other IOL-retained subgroups or in the IOL-removed group. In the IOL-exchanged groups the best visual acuity was for exchange for unsutured posterior chamber lenses, and next best was for exchange for one-piece anterior chamber lenses. These were both significantly better than the other two IOL-exchanged groups.

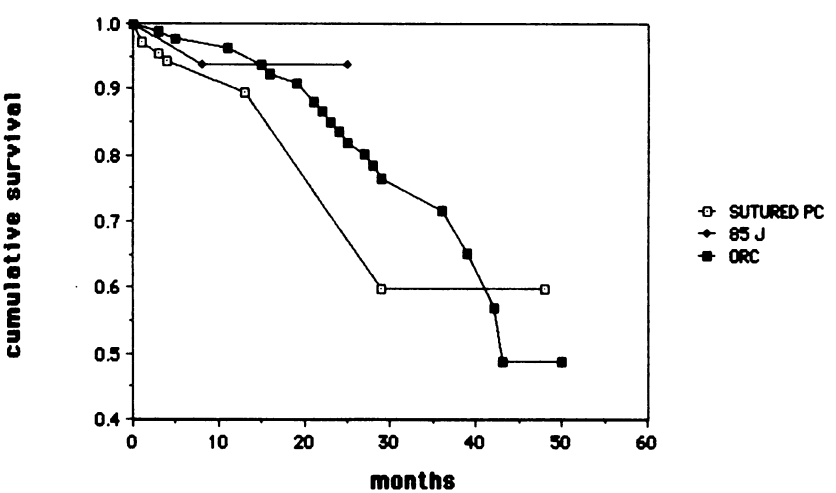

FIGURE 3
Modified Kaplan-Meier curves for graft survival in exchanged IOL subgroups. PC, posterior chamber; 85J, flexible one-piece anterior chamber lens; ORC, closed-loop anterior chamber lens.

When vision was related to duration of preoperative corneal edema, the differences were small and not statistically significant.[1] In those with corneal edema duration of less than 10 months prior to PKP, 44% had 20/40 or better visual acuity, and in those with greater than 10 months' duration, 34% had 20/40 or better visual acuity. The Pearson correlation between edema duration and visual acuity denominator was low (.08). The Spearman correlation, a nonparametric technique, was higher (.215).

Vision-limiting factors were primarily retinal. The most common was cystoid macular edema, occurring in 62% of those with visual acuity of less than 20/40 and in 36% of all study patients. Macular degeneration occurred in 22.4% of those with limited acuity and in 13% of the total study group. There were 13 retinal detachments, 2.9% of the total study group. A capsular membrane dense enough to cause decreased acuity was present in 17 patients. Eleven patients (2.4%) had glaucomatous optic atrophy.

Specular Microscopy

Specular microscopy results are based on mean cell counts for each time period by group and subgroup. Mean endothelial cell densities are shown in Table II. Combined cell density over time is shown in Fig 4. Percentage cell loss by group at each time is shown in Table III. Percent cell loss is derived by subtracting cell density at a given time from the donor

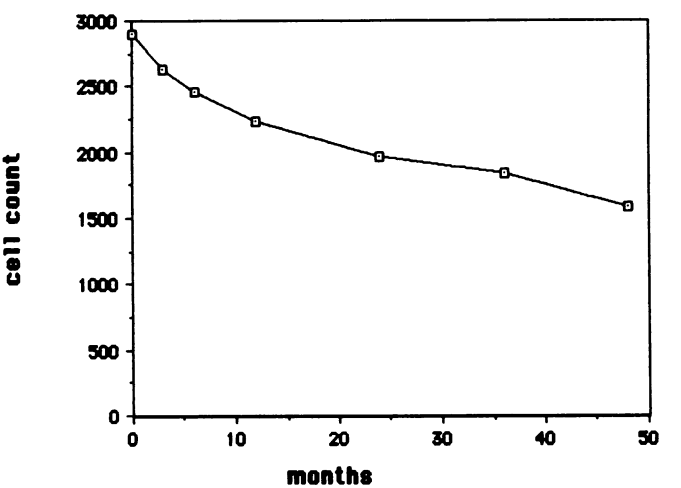

FIGURE 4
Mean cell loss over time for all groups combined.

TABLE II: MEAN ENDOTHELIAL CELL DENSITY* (NO.)

INTRAOCULAR LENS GROUP†	DONOR	3 MO	6 MO	1 YR	2 YR	3 YR	4 YR	5 YR
Removed	2,897 (62)	2,640 (61)	2,466 (51)	2,241 (57)	1,968 (34)	1,834 (19)	1,580 (18)	1,331 (17)
Retained (total)	2,945 (129)	2,521 (123)	2,343 (120)	2,139 (109)	2,011 (51)	1,559 (33)	1,240 (23)	1,301 (13)
PC	2,810 (42)	2,580 (42)	2,447 (39)	2,347 (32)	2,121 (17)	1,796 (10)		
AC	2,944 (45)	2,457 (40)	2,258 (43)	2,035 (39)	2,117 (19)	1,372 (9)	817 (5)	
Iris	3,060 (42)	2,478 (39)	2,301 (36)	2,016 (32)	1,770 (16)	1,516 (15)	1,149 (16)	1,434 (9)
Exchanged (total)	2,934 (169)	2,513 (147)	2,409 (129)	2,240 (126)	1,802 (64)	1,686 (29)	1,600 (3)	
PC	2,957 (65)	2,570 (60)	2,478 (49)	2,394 (42)	1,826 (7)			
AC 85J	2,844 (18)	2,285 (14)	2,350 (15)	2,374 (16)	2,036 (5)			
AC ORC	2,932 (84)	2,512 (71)	2,369 (63)	2,104 (66)	1,762 (50)	1,670 (26)		

*Cells/mm^2.

†PC, posterior chamber; AC, anterior chamber; Iris, iris-supported.

TABLE III: PERCENT ENDOTHELIAL CELL LOSS

INTRAOCULAR LENS GROUP*	3 MO	6 MO	1 YR	2 YR	3 YR	4 YR	5 YR
Removed	8.9	14.9	22.6	32.1	36.7	45.5	54.1
Retained (total)	14.4	20.4	27.4	31.7	47.1	57.9	52.4
PC	8.2	12.9	16.5	24.5	36.1		
AC	16.5	23.3	30.9	28.1	53.4	73.9	
Iris	19.0	24.8	34.1	42.2	50.5	62.5	53.1
Exchanged (total)	14.3	17.9	23.7	38.6	42.5	45.5	
PC	13.1	16.2	19.0	38.2			
AC 85J	19.7	17.4	16.5	28.4			
AC ORC	14.3	19.2	28.2	39.9	43.0		

*PC, posterior chamber; AC, anterior chamber; Iris, iris-supported.

density for that group or subgroup and then dividing by donor density. The aggregate differences between cell counts for each time period were highly significant until year 5. The difference between year 4 and year 5 was not significant by parametric tests but was by nonparametric tests. All differences were significant through year 6 for the IOL-removed group, and through year 5 for the IOL-retained group, using the parametric ANOVA. For the exchanged groups, cell loss continued to be significant at 3 years for closed-loop anterior chamber lenses, but 85J and posterior chamber exchanges were not followed longer than 2 years. Similar results were obtained with the Kruskal-Wallis nonparametric ANOVA, with highly significant P values ($< .005$). The Friedman two-way ANOVA for related groups confirmed this result.

Evaluation of skewness, kurtosis, and Lilliefors comparison to normal distributions all showed the distribution of endothelial cell count data within groups and times to deviate somewhat from Gaussian normal distributions. Bartlett's test also showed significant differences between group variances. These tests suggested that the nonparametric comparison techniques were more appropriate.

For the overall groups there was no statistically significant difference between cell densities at any time period (Fig 5). The differences within groups, however, were highly significant. At 1 and 2 years, retained posterior chamber IOLs had less cell loss than retained iris-supported or anterior chamber IOLs. At 1 year, cell loss was 17%, 31%, and 34%, respectively; and at 2 years it was 25%, 28%, and 42% (Fig 6). For exchanged IOLs, both posterior chamber and one-piece anterior chamber IOLs had less cell loss than closed-loop anterior chamber IOLs. Cell losses were 19%, 17%, and 28%, respectively. At 2 years, however, the differences were not significant, but the numbers were very small (Fig 7).

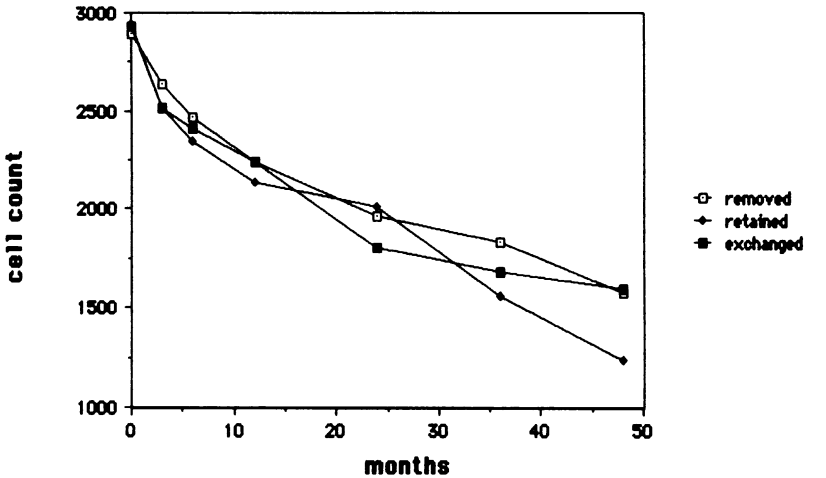

FIGURE 5
Mean cell loss over time by group.

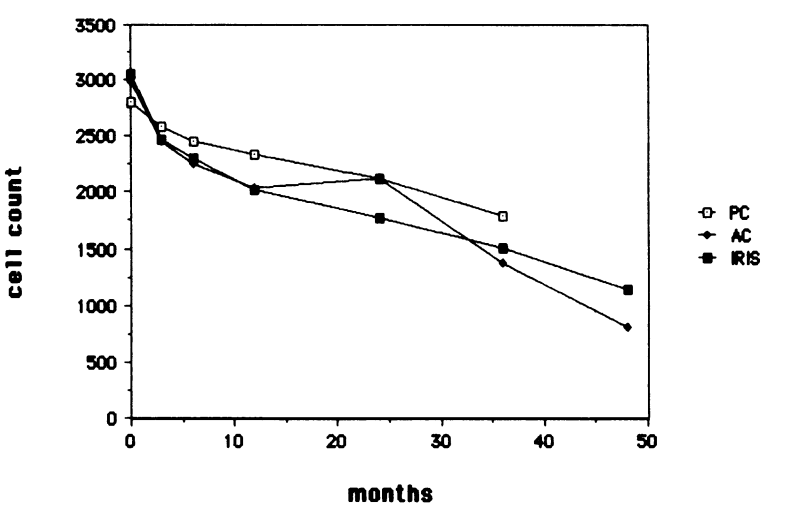

FIGURE 6
Mean cell loss over time for retained IOL subgroups. PC, posterior chamber; AC, anterior chamber; IRIS, iris-supported.

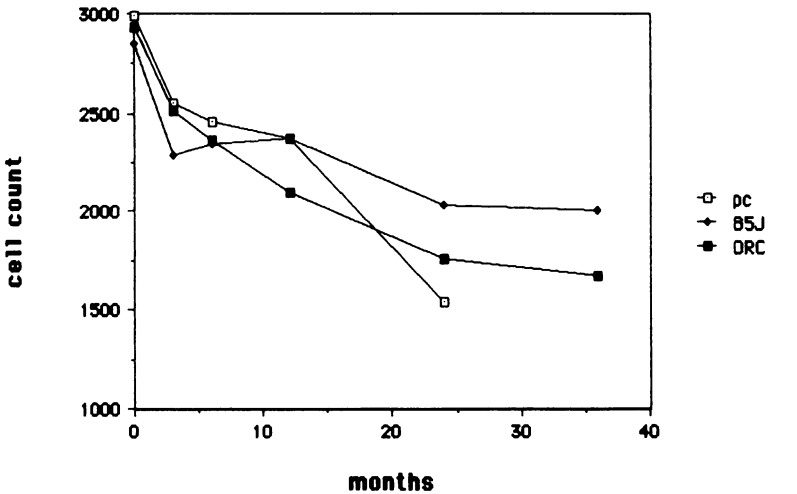

FIGURE 7
Mean cell loss over time for exchanged IOL subgroups. PC, posterior chamber; 85J, flexible one-piece anterior chamber lens; ORC, closed-loop anterior chamber lens.

Descriptive Mathematical Modeling

Another approach taken to comparison of cell loss was to derive mathematical models to describe the rate of cell loss for each group. This was done first by least-squares estimator linear regression. This method determines the slope of the straight line that best describes the data. The slope of the regression line is a measure of the rate of cell loss. These slopes were essentially the same, −24.3 to −28.6 cells/mm²/mo, for the removed and retained groups and the posterior chamber and one-piece anterior chamber exchange groups. The slope of the closed-loop anterior chamber exchange group was significantly different, −37.4 cells/mo. Expressing slope in percentage terms, all groups lost 11% to 12% per year except the closed-loop anterior chamber exchange group, which lost 16.5% per year. These losses are less than those actually seen, because the linear model only approximates what appears to be initially a nonlinear function. Thus, the cell loss by the regression model is distributed evenly throughout the period for which there are data. All regression coefficients were highly significant (Table IV). The correlation coefficient, R, ranged from .324 to .564. The R squared values, the coefficients of determination, were moderately low, however, indicating that the linear models only accounted for between 11% and 32% of the variance in the observed values.

TABLE IV: LINEAR REGRESSION PARAMETERS*

INTRAOCULAR LENS GROUP†	CONSTANT	SLOPE (B)	SE (B)	NO.	*R*	R^2	*P*
Removed	2,697	−24.3	2.05	305	.56	.32	< .005
Retained	2,645	−26.1	1.69	600	.53	.29	< .005
Exchanged							
PC	2,790	−28.6	5.48	234	.32	.11	< .005
AC 85J	2,614	−24.5	8.66	69	.33	.11	.006
AC ORC	2,726	−37.4	3.45	360	.50	.25	< .005

*Cell loss = constant + B months.
†PC, posterior chamber; AC, anterior chamber.

Because the cell loss appears to be greatest in the earliest time periods, and then lessens, a nonlinear exponential model was fit. This model was fit as an iterative semi-Newton least-squares fit for the following equation:

$$\text{Cell count} = \text{constant A} + \text{constant B} \times \text{loss rate}^{\text{time}}$$

This is one form of a survival function with a rate parameter raised to the power of time in months. A similar equation with only one constant gave very similar results. Nonlinear regressions derived values for the constants and the rate. If the constants are similar between groups, then the rate parameter is a measure of cell loss. The results were similar to those for the linear regressions with all rate parameters, in terms of proportion of cell surviving per month, between .96 and .97, except for the flexible anterior chamber exchange group, with a cell survival rate of .93. The *R* squared values for these regressions were about .35, indicating that they were only slightly better models than the linear regressions. These models also only approximate the data. It appears that an exponential loss exists for the early time, and then slows but approximates linearity. A combination of these two models might better describe the data, with early exponential cell loss followed later by slow linear loss.

DISCUSSION

In comparing nonrandomized, largely consecutive treatment groups, the influence of original group differences on outcomes is a critical issue. It was shown that the groups in this thesis were demographically similar. The main differences were in length of follow-up and type of original IOL. Iris-supported IOLs predominate in the IOL-removed and closed-loop exchanged groups, while anterior chamber IOLs predominate in the IOL-retained and other exchange groups. It is difficult to conceive of a mechanism whereby the original IOL, once removed, would have more effect on

the graft than the final IOL, but such effects have not been fully measured here. Potential biases from loss to follow-up did not appear to exist.

The success of keratoplasty for PBK was confirmed in this study. Eighty percent of 469 grafts were clear with a mean follow-up of 27 months. This is comparable to previous smaller series.[1,15,39,117] It is important, however, to distinguish the success rate differences on the basis of the IOL present after keratoplasty. In IOL-retained groups, grafts over posterior chamber IOLs were 93% successful, compared with 66% and 71% success for grafts over anterior chamber and iris-supported lenses. This difference remained when compared by survival analysis. Likewise, the exchanged groups showed greater success for sutured and unsutured posterior chamber IOLs (92% and 89%) than for closed-loop anterior chamber IOLs (76%). The smaller, one-piece anterior chamber IOL group did as well as any group, with 95% success.

The survival analysis showed continued decline in graft clarity throughout a 6-year period, although the rate was slowed after 4 years. The 62% graft survival at 6 years may be considered to be reasonable in an elderly population. The survival analysis of subgroups must be considered cautiously. While this method allows description and comparison of patients with variable length of follow-up, the plots are influenced greatly by the results in relatively small numbers in the later time periods. A follow-up bias related either to graft success or graft failure could potentially exist. In comparison to these PBK patients, the life-table survival of first keratoconus grafts is 91% at 4 years.[171] Whether this difference reflects the role of aphakia, recipient endothelial status, or the role of prior surgery is not clear. The success of the triple procedure, keratoplasty combined with cataract extraction and posterior chamber IOL insertion, suggests that IOL presence alone does not explain late failure within this time frame.[175]

It is important to distinguish between graft rejection and graft failure. Failure rates significantly exceed rejection rates for groups with retained iris-supported or anterior chamber lenses, and those with exchange for closed-loop anterior chamber lenses. This phenomenon of late endothelial failure, especially in these groups, is in part described by the analysis of cell loss. This linkage between cell loss and survival, and their similar conclusions, is important.

The visual results in the patients studied were moderately good, with about 50% having 20/40 or better vision. The mean vision was best in those with IOLs exchanged, but was still far from ideal (20/164). The devastating role of cystoid macular edema, which limited vision in 36% of all patients, cannot be underestimated. Unlike the study of Kok-Van-Alphen and Volker-Dieben[1] this study did not find a detrimental effect of

delaying keratoplasty after the onset of corneal edema. Factors related to acuity post keratoplasty, and possible means of limiting cystoid macular edema, require further study. Issues related to refractive error and IOL power calculations were not considered.

Specular microscopic findings paralleled the survival results. As reported by others, cell loss at 1 year was greatest for retained IOLs.[38] Patients with retained posterior chamber lenses, however, had 16.5% cell loss at 1 year, as did those with exchange for one-piece anterior chamber lenses. The cell loss for sutured posterior chamber IOL exchanges at 1 year (19%) was not significantly different. The numbers with specular microscopy at 2 years were too small for comparison of the exchanged posterior chamber and one-piece anterior chamber lenses. Those with retained posterior chamber lenses, however, did significantly better than any other group at 2 years. Comparisons using parametric and nonparametric statistical tests reached the same conclusions, although the assumptions of normal distribution and equal variance were not met for parametric tests.

The use of mathematical models to describe endothelial cell loss over time has been attempted in the past.[76,94] The models tried here were only moderately successful, explaining about one third of the cell density variance. Introduction of covariate factors into the models may help. Further exploration of modeling techniques should improve the predictability of endothelial cell loss, and thus prognostication in regard to endothelial and graft failure over new types of IOLs. The results of the models used here would suggest that a model combining an exponential rate of cell loss for the first few years, followed by linear cell loss, could be fit to the data. The limitation of cell loss to the first 3 years following keratoplasty, suggested by Bourne,[76] does not appear to be confirmed by this study. By comparison, a linear model fit to data from triple procedures predicts a 9.1% annual cell loss continuing through 4 years, with confirmation by the data (unpublished observations). A comparison between PBK and triple-procedure grafts may not be appropriate, however, as the PBK eyes may have been preselected for particular sensitivity to corneal damaging effects of IOLs. Similar specular observations in prospectively followed keratoconus patients confirm roughly linear cell loss through 5 years (unpublished data).

The hypothesis of this study was that specular microscopy could be used to predict graft outcome. If the 1-year data for cell loss are compared to the results of survival analysis, this appears to be the case. The lowest cell loss was for retained and exchanged posterior chamber IOLs and one-piece anterior chamber IOL exchanges. These were the groups with the best graft survival. At 2 and 3 years the retained posterior chamber lens

grafts continued to have the lowest cell loss. Long-term specular results for the posterior chamber and 85J anterior chamber IOL exchanges cannot be evaluated because of small numbers. Linear regression slopes suggest the same correlation with long-term clinical outcome. This predictive value of specular microscopy may be useful in the future evaluation of IOL-related graft procedures. The poor graft outcome following closed-loop anterior chamber IOL insertion at PBK might have been predicted from the early specular results. This IOL type, as a class, was used for several years before adverse effects were noted in cataract patients. Careful specular follow-up studies may be useful in the future to give early warning of such late complications.

The combined clinical, survival, and endothelial analyses suggest reasonable grounds for IOL management at PKP. The best vision, graft survival, and endothelial survival were in those patients with retained or exchanged posterior chamber IOLs and exchange for one-piece anterior chamber IOLs. Our decision to remove iris-supported and closed-loop anterior chamber IOLs appears to have been validated. The decision, for a time, to use closed-loop anterior chamber IOLs for exchange, however, was clearly a mistake. There is no evidence from this study to favor either one-piece semiflexible or sutured posterior chamber IOLs over one another; both offer good alternatives for maintenance of vision, graft clarity, and graft endothelium. From a visual, functional, graft survival, and endothelial maintenance standpoint, it would be reasonable to recommend that posterior chamber IOLs be retained at PKP, that flexible one-piece anterior chamber IOLs be retained if they are stable and well positioned, and that all other IOLs be removed and replaced with posterior chamber, sutured if necessary, or one-piece flexible anterior chamber IOLs at keratoplasty for PBK. These data suggest that further studies are indicated. A prospective trial comparing anterior and posterior chamber exchange lenses is needed and is now under way.

SUMMARY

PBK has become an important complication of cataract surgery and a leading indication for keratoplasty. While there are many potential causative factors, erroneous concepts of IOL positioning and design appear to have led to PBK with many iris-supported and anterior chamber lens styles. Underlying host endothelial abnormalities are an important risk factor with posterior chamber lenses. Previous studies of keratoplasty for PBK have shown variable early results in terms of graft clarity and visual rehabilitation. Specular microscopy and life-table survival analysis have been infrequently used to study endothelial and graft survival after

keratoplasty. This study combined these techniques to evaluate several approaches to the original IOL at PKP for PBK.

Four-hundred sixty-nine patients having PKP for PBK between 1976 and 1986 were studied in five retrospective cohorts on the basis of whether their IOL was retained, removed, or exchanged. Specular microscopy was performed prospectively on 390 patients.

Survival analysis showed overall failure in 20% of IOL-removed, 24% of IOL-retained, and 16% of IOL-exchanged grafts, without significant differences. Within the retained group, however, graft failure rate for posterior chamber IOLs (6%) was significantly less than for anterior chamber (34%) and iris-supported (29%) lenses. With lens exchange, the failure rate was 8% for sutured posterior chamber lenses, 5% for one-piece anterior chamber lenses, and 24% for closed-loop anterior chamber lenses. Graft failure rates exceeded rejection rates for retained iris-supported and anterior chamber lenses, and exchanges for closed-loop anterior chamber lenses, suggesting nonimmunologic causes. The survival curve for all groups combined showed cumulative survival of 93% at 1 year, decreasing to 62% by 6 years. Survival was lowest for retained anterior chamber and iris-supported lenses and exchanged closed-loop anterior chamber lenses.

Visual acuity results were best for retained posterior chamber IOL eyes and exchange for one-piece anterior chamber IOLs. Exchange for one-piece anterior chamber IOLs gave significantly better visual acuity than exchange for sutured posterior chamber IOLs. There was not a significant relationship between duration of corneal edema prior to PKP and visual outcome, refuting earlier findings.[1] Cystoid macular edema was related to poor vision in 62% of those with visual acuity of less than 20/40 and in 36% of all patients.

Specular microscopy findings at 1 year were predictive of longer term survival results. The least cell loss was for retained and exchanged posterior chamber lenses and exchange for one-piece anterior chamber lenses. Mathematical models attempting to describe the rate of cell loss were only partially successful. Cell loss appeared to continue at a slow rate throughout the period of study, with linear decline beyond the 3-year stabilization point described by Bourne.[76]

While survival, endothelial, and visual data confirm the value of IOL exchange for posterior chamber and one-piece anterior chamber lenses, prospective randomized trials will be necessary to distinguish between these options. The use of prospectively generated specular microscopy data, as demonstrated here, may help to shorten the follow-up time needed for such trials.

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