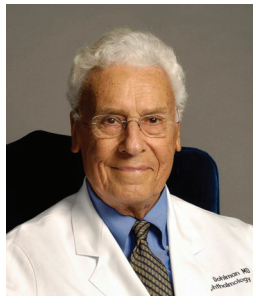

Claes H. Dohlman

ANNUAL REVIEWS

Annual Review of Vision Science

The Boston Keratoprosthesis—The First 50 Years: Some Reminiscences

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corneal blindness, corneal transplantation, keratoprosthesis, Boston KPro, Dohlman, autobiography

Abstract

Millions of people worldwide are bilaterally blind due to corneal diseases including infectious etiologies, trauma, and chemical injuries. While corneal transplantation can successfully restore sight in many, corneal graft survival decreases in eyes with chronic inflammation and corneal vascularization. Additionally, the availability of donor cornea material can be limited, especially in underdeveloped countries where corneal blindness may also be highly prevalent. Development of methods to create and implant an artificial cornea (keratoprosthesis) may be the only option for patients whose eye disease is not suitable for corneal transplantation or who live in regions where corneal transplantation is not possible. The Boston Keratoprosthesis (B-KPro) is the most commonly implanted keratoprosthesis worldwide, having restored vision in thousands of patients. This article describes the initial design of the B-KPro and the modifications that have been made over many years. Additionally, some of the complications of surgical implantation and long-term care challenges, particularly complicating inflammation and glaucoma, are discussed.

1. PRELUDE

The concept of replacing an opaque cornea with a transparent artificial "window" to restore vision is obvious. However, to make such an intervention work—being practical, long-term safe, at affordable cost—is not so easy!

It is now 230 years since attempts at creating a useful artificial cornea first appeared in the ophthalmic literature (Dohlman 1999, Parel 1999). Since then advances have been made, but it is fair to say that in spite of substantial effort by a number of excellent surgeons of very sharp mind, progress has been slow (**Figure 1**). Substantial obstacles still exist and an unmet need for a totally safe device remains. The artificial cornea concept that we call the Boston Keratoprosthesis (B-KPro), with its unique surgical and postoperative management requirements, is a late step in this continuous development and while only a half-century old still warrants some pause and reflection on where we stand at this moment. Here will be attempted a brief sketch of the scientific and clinical background from the beginning of our efforts in the 1960s, starting with small-scale animal experiments with a group of collaborators on corneal physiology at the Retina Foundation laboratories in Boston. We adopted and modified a design, followed by initial clinical applications on a few patients with "hopeless" corneal pathology in the newly established Cornea Service at the Massachusetts Eye and Ear Infirmary (MEEI)/Harvard Medical School (HMS).

With apologies, this narrative will be distinctly personal.

A brief comment on the background for our move to Boston in 1958: I was given a recruitment offer by Drs. Schepens, Balazs, and Dunphy (Chair, HMS; Chief, MEEI) to come to Boston and "do cornea work" for three years, preceded by six months of corneal surgery apprenticeship at any center in the world of my choosing. My position as "docent" (assistant professor) of ophthalmology in Lund, Sweden, was very satisfying but three years of additional academic training in Boston was seen as valuable for my aspirations for an eventual professorship in Sweden—so I accepted. Drs. Schepens (famous retina surgeon) and Balazs (equally famous biochemist) were the prime movers but Dr. Dunphy was in the end the one who could support me the most.

Of the six months of cornea training, I used three months for an apprenticeship with Professor Louis Paufique in Lyon, France—perhaps the world's foremost cornea surgeon at the time. Then in October 1958

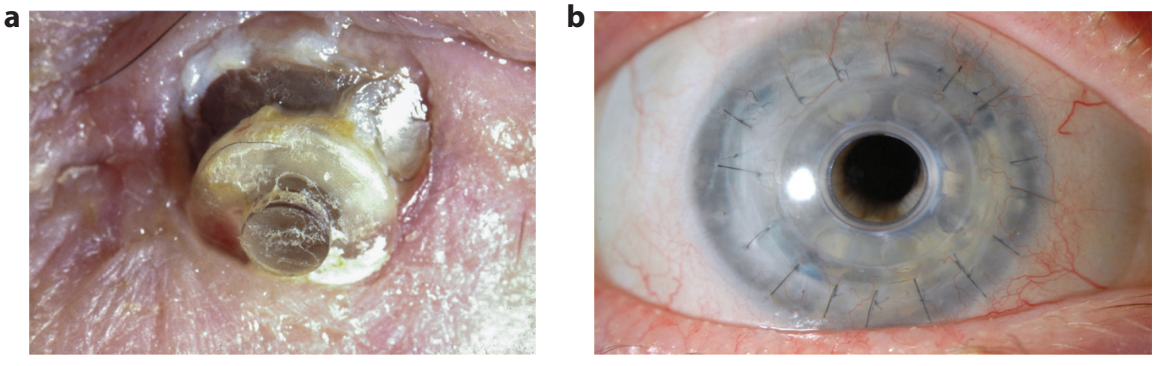

Figure 1

(*a*) A telltale example from the past: a one-eyed 80-year-old woman with blindness from pemphigoid, treated with the early model Type II B-KPro. 20/40 vision for nearly a year—then tissue melt, sudden extrusion, endophthalmitis, and enucleation. In retrospect: too large of a back plate (11 mm), without holes, blocking nutrition—in autoimmune disease. No prophylactic antibiotics. (*b*) In contrast: a middle-aged woman with herpetic keratitis, followed by three failed penetrating grafts, then Type I B-KPro. Little inflammation, adequate tears, and normal lid function. About 20/25 uncorrected for 15 years, still doing well. Prophylactic Polytrim® and Pred Mild®, once daily.

we arrived in Boston. I was given a small laboratory at the "Retina Foundation" (later renamed "Schepens Eye Research Institute") and later a 10′ × 10′ room off the General Eye Service at the Infirmary, for cornea patients.

After my arrival it turned out that Dr. Schepens rather would have me work with him on retina research, and Dr. Balazs wanted me to do biochemistry with him. However, after a half year of adjustments, I was given the green light for full-time cornea work and I was off and running. With Dr. Dunphy's blessings I started and developed the world's first formal Cornea Service for patient care, teaching, and research. My personal relationships with my three supporters remained excellent throughout.

A career in academic medicine was not lucrative at the time: My first year's total income was $10,000, my second was $11,000, and my third was $13,000. But with a strong and supporting wife, no problems!

In the 1960s, when we started our laboratory activities at "the Foundation" with newly recruited fellows and PhDs, we had some fading interest in proteoglycan biochemistry and corneal histochemistry. Our focus gradually shifted to the physiology of the cornea: edema, tear film, and dry eyes, as well as the role of collagenases in corneal ulceration—all with translational potential. We were not as focused as we should have been but we had to make some accommodations to the individuals who wanted to join us.

With regards to recruitment of scientists and clinical fellows, we quickly became lucky. We managed to attract individuals with excellent credentials and ambition, aided by generous funding from the rapidly expanding National Institutes of Health. The PhDs were the backbone of the lab and among them we counted Miguel Refojo, Marshall Doane, Michael Berman, Frank Holly, Charles Cintron, and Stephen Klyce, and, later, Arthur Neufeld, Ilene Gipson, and David Sullivan. David Maurice, PhD, from the Eye Institute in London, was a frequent visitor and an exceptional thought leader. The full-time research staff also included a long line of foreign academic ophthalmologists, led by the brilliant Saiichi Mishima (future "Shogun" of Japanese ophthalmology), likewise Kinoshita, Itoi, Gnädinger, Kitano, Iwata, Payrau, Reim, Anseth, Hedbys, Ytteborg, Khan, Praus, and others who stayed for many years. Also, US ophthalmologists of future academic fame like James Aquavella, Peter Laibson, Deborah Langston, Harvey Slansky, Jules Baum, Stuart Brown, Herbert Kaufman, Mathea Allansmith, Mark Abelson, Anthony Gasset, David Miller, Richard Thoft, Kenneth Kenyon, Michael Lemp, Robert Webster, Michael Wagoner, Roswell Pfister, Dwight Cavanagh, Gary Foulks, Ira Udell, James McCulley, Melvin Freeman, Donald Doughman, Jonathan Lass, Elizabeth Cohen, Peter Donshik, Henry Perry, Allan Jensen, and many others belonged to this highly productive early group. This, with time, became a large, diverse and very stellar department (**Figures 2** and **3**) (for the full list of names of the individuals who contributed so much, see the **Supplemental Bibliography**).

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On the clinical side, we tried to build a Cornea Service for patient care and teaching of fellows as well as residents. My first clinical associate was Edward Sweeby, a very talented recent graduate of the residency who tragically died from Hodgkin's disease two years later. Also, Eeva-Liisa Martola spent three very helpful years with us. Then Arthur Boruchoff, a very experienced clinician and a very kind man, became my main clinical associate for many years—a very fruitful collaboration. Michael Wiedman and Eleanor Mobilia contributed as well. Clinical research was very much a part of the program and keratoplasty was a foremost subject—but herpetic keratitis and antivirals, as well as treatment of edema and other pathologies, were also priorities. Subsequent Directors of the Infirmary's Cornea Service were or became great leaders in the field (Langston, Kenyon, Steinert, Wagoner, Talamo, Adamis, Azar, and Dana).

Here I should pay special tribute to our Clinical Cornea Fellows. The Fellowship Program has been the Prize of our academic activities since its inception. About 300 graduated ophthalmologists have come for one or two years (some even longer) of Cornea Subspecialty training throughout the years. Their contributions and collective impact have been immense. On average, they spent half their time on investigations, often with

Figure 2

The Cornea Lab (at the "Retina Foundation") in the early 1960s: (*from left*) visitor, me, Saiichi Mishima, Miguel Refojo, Stuart Brown, and Jules Baum.

a PhD collaborator, or on KPro research. They were uniformly ambitious and academically successful and many sooner or later started their own Cornea Service elsewhere in the United States, or abroad. About a hundred have reached the rank of Full Professor. It is impossible here to give full credit to the many excellent Fellows who gave so much over the years (***Figure 4***) *(for full list of contributors, see the* ***Supplemental Bibliography***).

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2. THE B-KPro STORY

We were already at an early stage, on and off, interested in adhesives and particularly various devices that might help restore vision in severe corneal disease. Gradually a picture began to emerge of how they could affect corneal physiology, for good or bad—insights that would become crucial for later developments. Here we realized that we very much had to stand on the shoulders of our predecessors.

As for general background at the time, industry had already in the 1940s introduced the virtually nontoxic transparent plastic polymethylmethacrylate (PMMA), which subsequently became used for the optical portion of most artificial corneas. Around that time also antibiotics

Figure 3

The cornea group (most of them—clinical and lab) in 1982 in front of Schepens Eye Research Institute (formerly the Retina Foundation).

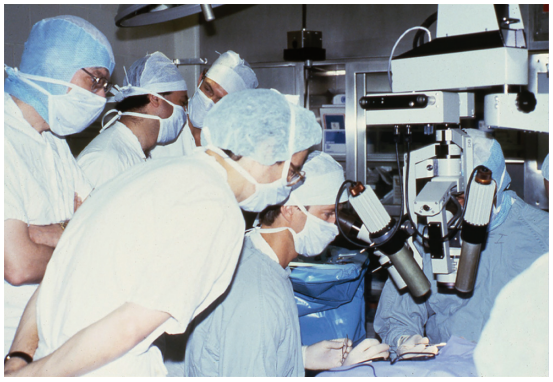

Figure 4

Endless hours spent in the operating room. . . .

and corticosteroids revolutionized medicine, and benefitted keratoprostheses as well. Those developments stimulated some very distinguished cornea surgeons and investigators elsewhere (1950–1960) to propose a number of KPro designs that served as inspiration for subsequent developments by us as well (Cardona, DeVoe, Stone, Castroviejo, Choice, Aquavella, Strampelli, Falcinelli, Barraquer, Girard, Pintucci, Crawford and Hicks, Lacombe, Legais, Parel, Moroz, Yakimenko, and many others) (Cardona 1962). Most proposed designs had a supporting plate (haptic) to be inserted into the recipient's corneal stroma, or in front of it, but a few had some kind of collar button design or pulley shape, with anterior and posterior plates [Dorzee, Franceschetti, Györffy, Baron, Barraquer, and Cardona (Cardona 1962)] (**Figure 5**). Most of their clinical applications were short-lived with the exception of those by Cardona and DeVoe, the osteo-odonto keratoprosthesis, the AlphaCor®, and a few others. The entire field definitely moved forward but the clinical applications were not widespread. For a more complete history of keratoprostheses, see several reviews (Cardona 1962, Dohlman 1999, Mannis & Dohlman 1999).

This was the clinical starting point for us (1960s). We experimented with a number of designs and materials, among them a collar button device similar to what had been suggested by Barraquer and Cardona, and attached it to a carrier corneal graft with the aid of cyanoacrylate adhesive. The adhesive was later abandoned due to unreliable long-term efficacy. Since that time we slowly, stepwise, improved the design, surgery, postop management, etc., and applied our procedure as we saw it at the moment. We devoted great time and effort, searched for clues in the clinical exam (slit lamp), learned from the complications, changed approach accordingly, and, in general, did the best we could for our patients.

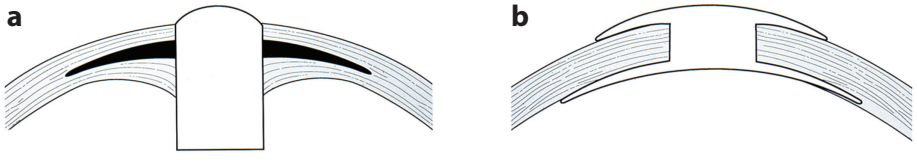

Figure 5

Two designs have dominated the keratoprosthesis field since its beginning: (*a*) The most common has had the bearing plate (haptic) placed in the middle of the patient's cornea—in the stroma or in some cases even in front of the cornea, with additional tissue. (*b*) In the second design ("the collar button") the haptic ends up behind the cornea—behind Descemet's membrane.

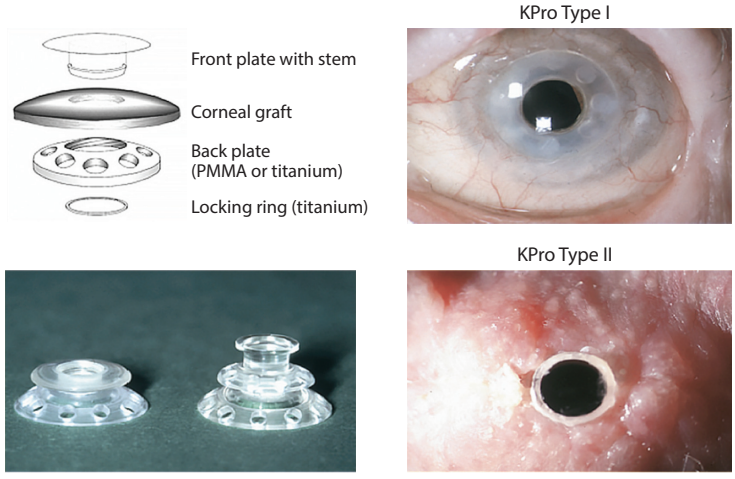

Figure 6

The principle of assembly of the early model Boston Keratoprostheses Type I and Type II (the latter with a nub protruding through the covering lid skin). Both devices are first implanted into a fresh corneal graft, the combination then sutured into the patient's cornea like a standard graft. Figure adapted with permission from Sayegh et al. (2008). Abbreviation: PMMA, polymethylmethacrylate.

During 1965–1974 the first models were implanted in 36 patients with very advanced pathology (Dohlman et al. 1969, 1970, 1974) (**Figure 6**). Although most failed in the end, some had long-lasting visual improvement and made us realize the potential for further improvements. We also painfully realized that for achieving any success with artificial corneas with its decades-long prospects, we had to keep trying for a long time—a very long time!

A major career deviation unexpectedly delayed further progress, however. I became sidetracked with academic administration for 15 years, a task which at that time was so heavy and poorly paid that serious research was out of the question. It took until 1989 until research could be effectively resumed again—now almost full time.

Over the next 25 years improvements developed gradually (**Figures 7** and **8**). Personally, I did or supervised about 450 B-KPro implantations of various designs, materials, surgical procedures,

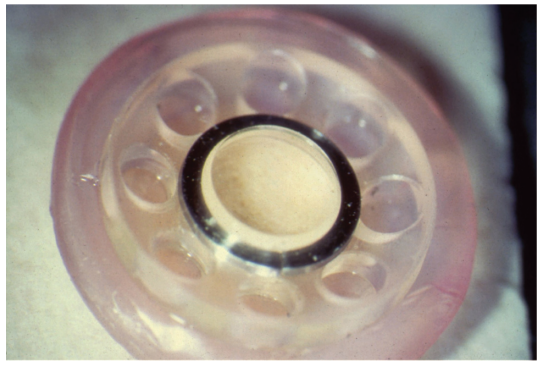

Figure 7

A B-KPro implanted into an 8.5 mm fresh cornea graft, viewed from behind. Back plate of polymethylmethacrylate (PMMA), with locking ring of titanium.

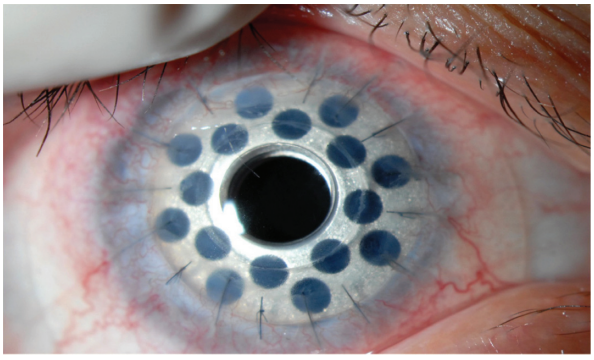

Figure 8

B-KPro Type I with a back plate of titanium in a recently operated patient. With time the carrier corneal graft becomes somewhat scarred and grayish.

or postoperative regimens. The rest of the cornea world began to take notice as we proceeded and we were asked to arrange for distribution of the device, with appropriate instructions. Expert machinists, first Adolph Holmberg and George Bearse and, since 1998, John Graney with his colleagues and daughters, handled the manufacturing in machine shops. Ms. Larisa Gelfand, a key individual for the organization and a great leader, has for over two decades managed the regulatory issues and the distribution under the auspices of the Infirmary. Ms. Rhonda Walcott-Harris has typed and organized an endless number of manuscripts and bibliographies and junior secretaries and assistants also added to the effort.

Most importantly, however, clinical cornea colleagues like Kathryn Colby, James Chodosh, Joseph Ciolino, Miguel Gonzalez, Roberto Pineda, Samir Melki, and Ula Jurkunas of the Cornea faculty of the MEEI joined the effort to a varying degree and continued the clinical and research initiatives and leadership. A long string of Cornea Fellows (see above) were instrumental in the progress—in fact, they have been the backbone of the B-KPro effort over the years. Not only did they take care of the patients, many also contributed very substantially with ideas and scholarship (again, too many individuals to list here; see the **Supplemental Bibliography**). Reza Dana and his large laboratory provided much basic information necessary for progress. Demetrios Vavvas helped us greatly to understand retinal biology once we realized that the ganglion cells were so vulnerable after any corneal trauma. Also Lucy Young guided us in the field of retinal detachments. Likewise Lucy Shen, Cynthia Grosskreutz, and Teresa Chen helped us with glaucoma aspects—the most important KPro complication. Marlene Durand, Irmgard Behlau, Michael Gilmore, and Paulo Bispo were the infectious disease experts and Stephen Foster and George Papaliodis were leaders on uveitis.

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Most important of all factors in the progress has been the relatively recently established Keratoprosthesis Laboratory at Schepens Eye Research Institute, de facto supervised by Eleftherios Paschalis, PhD, and home to a number of innovative postdoctoral fellows such as Steven Zhou, Dylan Lei, Wallace Hui, Mirazul Islam, Sina Sharifi, and others. All in all it was a very fruitful translational collaboration where everybody was important. Senior scientists and scholars from outside the group also gave very valuable guidance: Ilene Gipson, Eli Peli, Frederick Jakobiec, Daniel Kohane, Dimitri Azar, Shigeru Kinoshita, Stephen Foster, Jan Dohlman, Francois Delori, Pablo Argueso, David Sullivan, and others.

All financial proceeds from the sale of the B-KPros (about $35 million gross, up to the year 2020) have been kept by the Department of Ophthalmology and most of the profit could be spent

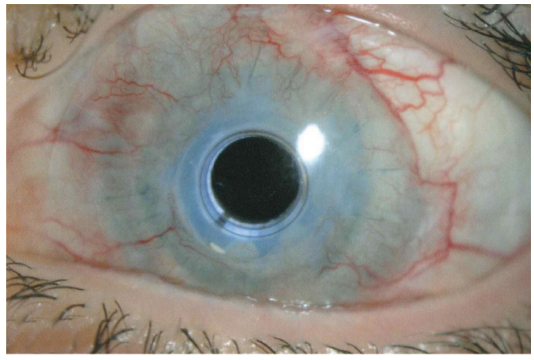

Figure 9

A middle-aged woman with one eye lost. The eye depicted above had suffered several severe episodes of different diseases: herpes zoster, severe Stevens-Johnson syndrome, a ruptured globe with loss of the lens and vitreous hemorrhage, retinal scarring, glaucoma, and keratoplasty failures. B-KPro and Ahmed shunt 16 years ago. Present vision 20/125. (Polytrim®, Pred Mild®, vancomycin 1.4 mg/mL, all once daily, plus Cosopt® twice daily.)

on further B-KPro research. We, the staff, clinical investigators, PhDs, and fellows, have received standard salaries for our full-time academic work but no additional benefits.

Since we started in earnest, about 16,000 B-KPros have been implanted worldwide. The visual results, modest in the beginning, have improved markedly as a result of focusing, widening insights, and resulting changes in device, in materials, and particularly in postoperative management (see the **Supplemental Bibliography**). It gradually became apparent that the roles of design and materials of KPros have been overestimated in the past and that the reactive biology of the surrounding tissues (cornea, eye, and beyond) has been correspondingly underestimated. Thus, the clinical outcome of a KPro is clearly very dependent on the type and degree of previous pathology and the response of the surrounding tissue in terms of inflammation, enzymological tissue melt, nutrition, vulnerability to infection, evaporation from the ocular surface, and particularly glaucoma. Therefore, prognostic markers such as inflammatory cytokines, their effect on the retina and role in glaucoma, scarring and resulting glare, etc., will have to be much more profoundly considered than in the past. Responding with prophylactic postoperative measures such as daily low-dose topical antibiotics, antifungals, increased dosage of anti-inflammatories (corticosteroids and biologics such as anticytokine antibodies), protective soft contact lenses, etc., has become very important (**Figures 9** and **10**) (Dohlman et al. 2006, 2014, 2018).

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The one obvious reason for trying to develop a well-functioning artificial cornea is to provide the means to restore vision in corneal blindness when standard keratoplasty [penetrating keratoplasty (PK)] cannot be sufficiently successful. A KPro outcome will always have to be compared with a PK not only in terms of visual acuity but also in terms of practicality, low cost, and long-term safety. Here a comparison in outcome between the two approaches is crucial. PK and KPro surgeries are now hardly different in terms of demand for effort, time spent, or skill. The trajectory of postoperative visual acuity restoration, however, is markedly different between the two procedures. A PK may take several months to reach maximum possible vision and the patient may then have to struggle for life with astigmatism, spherical correction, and sometimes graft opacity—but vision will likely remain on the same level for a long time with minimum maintenance. A KPro on the other hand can rapidly reach a spectacular level of correction-free vision, even by the next day, but it can suffer a sudden severe complication or a long-term attrition, as well as a need for more demanding postop care.

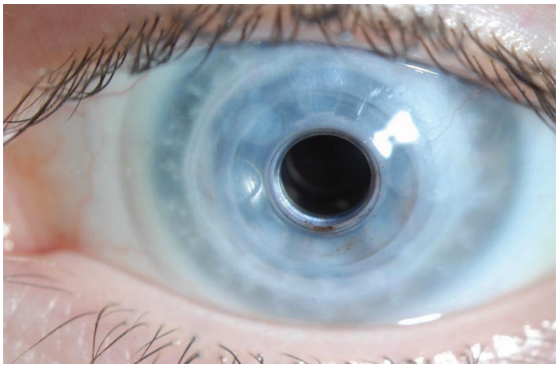

Figure 10

A B-KPro in the remaining eye of a young woman with corneal hereditary endothelial dystrophy (CHED) and 13 failed standard penetrating keratoplasties bilaterally. Little inflammation and good tear production. After the B-KPro, uncorrected vision 20/25 for 15 years and counting. (Should be on Polytrim®, vancomycin 1.4 mg/mL, and Combigan® once daily.)

Under the circumstances, do we need keratoprosthesis at all in the future? It has been argued that the world lacks donor material and that the keratoplasty needs will continue to outnumber available corneas. This is questionable since about 50 million people globally die every year, most of them carrying two clear corneas to the grave. The ratio of potential donor corneas to the number of PKs (about 200,000 yearly worldwide) would be about 500:1 and it can be argued that a better eye bank network should easily be able to satisfy the needs—thus an administrative and cultural problem, not an absolute deficiency.

On the other hand, it is clear that standard PKs are not all successful in restoring the desired vision—for immunological and other reasons. Advances in contact lenses, layer-by-layer corneal surgery (sequentially), prophylaxis against transplantation immunology, especially for xenografts and for biological constructs, suppression of inflammation, etc., can all be expected in the future but the time and scope for this to happen are highly uncertain, especially when compared to the exceptional transparency and rapid rehabilitation of a successful KPro.

Here the B-KPro is clearly gaining by comparison. Over 500 papers have been published—about 200 of them from Boston. Mostly, outcome studies have been published from outside Boston, whereas our papers have primarily focused on mechanisms. Most of them reflect the slowly increasing visual success and long-term safety. Evidence is mounting in favor of B-KPros having a better long-term visual outcome than standard PKs (Ahmad et al. 2016; Akpek et al. 2015; Chang et al. 2015; Y. Chen et al. 2020; Driver et al. 2018; Fadous et al. 2015; Kang et al. 2012, 2018; Ma et al. 2005; Ono et al. 2020).

By reviewing the existing KPro literature, the correlation between corneal pathology and complications (risk factors) is becoming more discernable. In the "old" KPro literature, preoperative "vascularity" of the patient's cornea often resulted in sudden infections or extrusions. Most likely such cases have been inflamed or autoimmune, prone to tissue melt. On the other hand, outcomes after bullous keratopathy, treated, for instance, with Cardona's interlamellar or nut-and-bolt devices, have done quite well, undoubtedly due to minimal levels of inflammation (Donn 1976). We, as well as many KPro surgeons elsewhere (see the **Supplemental Bibliography**), have expanded on these comparisons and trends and found a remarkable difference in risk in B-KPro retention and visual acuity between gross categories of corneal disease (Yaghouti et al. 2001):

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1. Autoimmune diseases such as Stevens-Johnson syndrome, ocular pemphigoid, graft-versus-host disease, chronic uveitis, etc., are by far the most likely to respond with inflammation, tissue melt, glaucoma, uveitis, intraocular membrane formation, retinal detachment, etc.
2. Chemical burns, especially alkali, initially become heavily inflamed and can then be prone to long-term glaucoma.
3. Non-inflammatory conditions (corneal edema, etc.), with intact lid function and normal tear secretion, have indeed the best prognosis.
4. Age of the recipient affects outcome. Thus, KPro surgery in children is difficult, not only from a management point of view but also because of a more explosive postoperative inflammation (Aquavella 2008, Aquavella & Wozniak 2018, Aquavella et al. 2007, Botelho et al. 2006, Brown et al. 2016, T. Dohlman et al. 2016, Fung et al. 2018, Haugsdal et al. 2016). Aquavella has the leading experience. Elderly people, on the other hand, with their fading immune response, often do very well (Homayounfar et al. 2017).

These categories require different approaches and prophylactic treatment. Two summarizing reviews on the B-KPro progress have already been published (Dohlman et al. 2006, 2014). Below, I discuss further in more detail the steps of improvements that have been taken during this long journey, with comments on presently ongoing research directions.

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For references on autoimmune cases, see the **Supplemental Bibliography**, References 8, 9, 34, 67, 82, 110, 165, 210, 250, 283, 303, 313, 341, 359, 367, 374, 471, and 474.

2.1. Carrier Tissue

It gradually became clear that the surgical B-KPro procedure became much easier and safer to carry out by routinely implanting the device into a fresh corneal graft, followed by transplanting the graft–device combination into the patient's cornea and suturing it in place like a standard PK (Dohlman et al. 1969). The New York City surgeons had already made occasional use of fresh corneal support for the Cardona device with an intralamellar plate (Castroviejo et al. 1969). It also became clear that the previous practice of implanting the KPro device directly into a patient's cornea that had earlier undergone a severe disease process would make that cornea more vulnerable to later aseptic necrosis ("tissue melt"), whereas a healthy cornea from an eye bank as a carrier seems to be more resistant. If the cause of the corneal disease is edema only from a poorly functioning endothelium, or a failed graft having an essentially healthy stroma, that cornea can still be used as a carrier graft (trephined out, B-KPro inserted, sutured back) (Ament et al. 2010, Cruzat et al. 2013b, Kyrillos & Harissi-Dagher 2011, Wang et al. 2012). Another good alternative is to use a frozen stored donor cornea (Muzychuk et al. 2017b, Robert et al. 2012).

Prior gamma radiation of the graft may also confer further resistance. This technique, previously introduced by the International Tissue Bank and Esen Akpek et al., has been proven suitable for B-KPro surgery (Akpek et al. 2012, Fadlallah et al. 2014). Recently a multi-institutional group led by Joseph Ciolino has been further investigating this resistance-to-melt issue. We also feel that gamma radiation can allow a more practical and safe in-house assembly of device and graft by a technician, followed by gamma irradiation, which allows longer shelf storage for years in a small vial of fluid (Gonzalez-Andrades et al. 2018). Another way to reduce melt of the carrier cornea is to crosslink it by standard means (Kanellopoulos & Asimellis 2014, Tóth et al. 2016, Zarei-Ghanavati & Irandoost 2015).

For references on carrier tissue, see the **Supplemental Bibliography**, References 105, 122, 159, 167, 181, 238, 244, 248, 265, 308, 351, 381, 415, and 461.

2.2. Design of the B-KPro

It seemed to us that a collar button–shaped device (Type I), similar to what had been previously suggested by several surgeons (see above), would be a suitable starting point (**Figures 5** and **6**). The anterior and posterior plates give the optical stem great stability. In addition, the position of the posterior plate (the haptic), behind the sturdy hard-to-digest Descemet's membrane, would be expected to enhance retention of the device.

Since the implantation of the KPro into a carrier corneal graft turned out to be also surgically practical, it followed that the device had to be manufactured in two parts: the front membrane (now of 5 mm diameter) combined with the optical stem (about 3.35 mm diameter) as one part, and a separate back plate (now sized 7.0–8.5 mm outer diameter). The back plate was originally designed to be *screwed* on to the back of the stem after the latter's insertion through the trephined hole (3.0 mm) in the graft (Dohlman et al. 2006). However, after several instances of loosening of the plate postoperatively, a posterior locking ring of titanium was added (Dohlman et al. 2007). This was again later improved in some models by having the back plate (with a slit) directly snapped into a groove on the posterior stem.

There was initially another more severe design problem that required correction. In a large number of the B-KPro Type I patients, the corneal tissue next to the stem necrotized soon after surgery and melted away, often creating aqueous leak, and even infection (Dohlman 1983, 1993) (**Figure 11**). This phenomenon could be due to dehydration or to lack of nutrition for the adjacent graft keratocytes (see below). It had been earlier shown in animal experiments that the cornea, including its epithelium, receives its nutrition practically in its entirety from the aqueous humor, not from the tears or the limbus (Turss et al. 1970). (O_2 and CO_2 exchange occurs across the epithelium.) The large solid back plate of a KPro therefore blocks necessary access of nutrients from the aqueous fluid to the overlying cornea, resulting in cell death and aseptic necrosis (melt). Instituting large holes into a smaller-diameter back plate dramatically improved the situation and tissue melt around the KPro stem became a rarity (Harissi-Dagher et al. 2007). The cosmetic appearance of the back plate could also be improved by coloring the plate [blue or brown (Paschalis et al. 2013)] or by changing the size and configuration of the holes (Bakshi et al. 2019, Traish & Chodosh 2010).

The diameter of the back plate may influence the outcome in another way. Formation of a retroprosthetic membrane is a common complication after B-KPro implantation (**Figure 12**) and

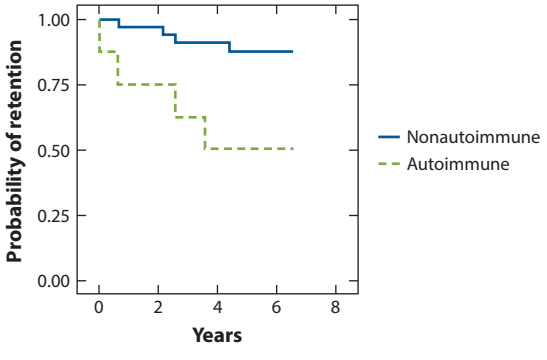

Figure 11

While relatively uninflamed eyes have had good retention over the years, chronically inflamed eyes (autoimmune diseases, chemical burns, etc.) fare much worse.

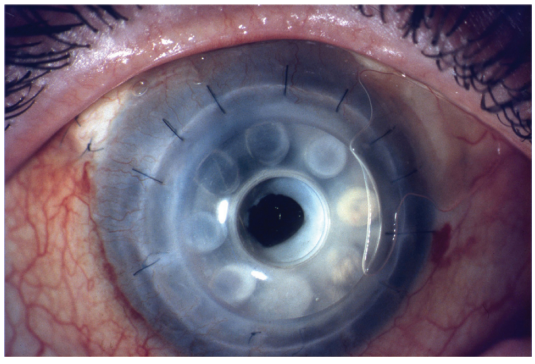

Figure 12

Eye with a retroprosthetic membrane—originating from the cornea graft wound in inflamed eyes. A modest opening has been created with a YAG laser.

it seems to have its physical origin primarily in the wound between the carrier graft and recipient cornea—the wound often gaping posteriorly because of tight anterior suturing (Stacy et al. 2011). Postoperative intraocular inflammation is definitely an additional promoting factor. Enlarging the diameter of the B-KPro back plate to 9.5 mm to clamp the posterior wound area (but still preserving holes) blocked the tissue escape from the wound and the membrane formation, but unfortunately it also was followed by retinal detachments in some of these eyes and the approach had to be temporarily abandoned (Cruzat et al. 2013a, Kaufman et al. 2018). Intensified anti-inflammatory medication with biologics postoperatively may ameliorate this problem.

The B-KPro Type II has an added anterior nub that can transverse lid skin or buccal mucous membrane coverage (**Figure 6**; see also **Figure 21** below). It is much less in demand than the Type I and is usually reserved for end-stage dry eyes in severe autoimmune diseases, such as Stevens-Johnson syndrome, ocular pemphigoid, etc. The tissue response in these systemic inflammatory diseases is often severe with skin retraction, necrosis, and melt of the carrier cornea that can result in extrusion of the KPro, but systemic administration of TNF-α antibody can give dramatic protection (see below, Section 2.6.4).

Two more recent designs promise increased applications. One called "Lucia" is a modified Type I B-KPro with different-sized holes (Bakshi et al. 2019). The other is a Type II modification ("Lux") with a titanium-clad stem (Bakshi et al. 2020).

Supplemental Material >

For references on design and fabrication, see the **Supplemental Bibliography**, References 10, 64, 115, 223, 365, 396, 404, 446, 456, 470, and 474.

2.3. B-KPro Materials

Most keratoprostheses have been made of rigid transparent PMMA—so also the B-KPro. However, after a while we questioned whether the back plate, which does not have to be transparent, might be replaced by medical-grade titanium (actually 90% titanium, 6% aluminum, and 4% vanadium) with its superior reputation for inertness. Also, its lack of transparency might have an additional virtue in that it screens out some of the scattered light, which causes glare (see below). Since 2005 we have offered a titanium back plate option, which has become standard (Ament et al. 2009, Todani et al. 2011, Zhou et al. 2016). It is still somewhat controversial, however, and some prominent surgeons still prefer the original PMMA plate (which also is cosmetically less conspicuous).

The rigidity of the KPro has been another controversy. Which is preferable, a rigid haptic plate or a flexible one? Soft dacron mesh, silicone rubber, soft acrylics, etc., have been introduced by other investigators but no unanimity has been reached.

However, the most important aspect of KPro materials relates to the interface between the optical stem and the surrounding tissues—the "biointegration" of the device. A penetrating KPro creates a hole in the cornea, connecting the outside world with the inside of the eye, facilitating the travel of microbes and debris. It has been observed that a narrow cleft easily develops between the PMMA stem and the abutting cornea tissue, especially in inflamed situations, maybe as a result of upregulation of matrix metalloproteinases—clearly a risk for infection (Dudenhoefer et al. 2003, Grassi et al. 2015). Covering the stem with titanium [by Salvador-Culla et al. (2016), in animal experiments, in collaboration with MIT] showed considerably improved adhesion of the corneal tissue to the covered stem, which should result in less exposure to microbes or debris (sterile vitritis). Clinical applications have been started by Salvador-Culla et al. (2016) and by Chodosh and colleagues (Bakshi et al. 2020) using devices with these titanium-clad stems.

There have been numerous attempts at covering the stem with stable biologic substances like hydroxyapatite (HyAp), which can possibly "heal" into the surrounding cornea. The HyAp can be firmly anchored to the PMMA stem with a molecular bridge of dopamine (Dong et al. 2014, Jeong et al. 2011, Sharifi et al. 2020, Wang et al. 2011, Yang et al. 2013, Zhou et al. 2016). This combined coating is somewhat fragile in handling but promising. Other recent attempts have included certain polypeptide coatings, which may provide a sufficient degree of biointegration (Camacho et al. 2020, Riau et al. 2017). These approaches are all promising and may result in a welcome biointegration of sufficient strength and durability to be a game changer for KPros.

For references on B-KPro materials, see the **Supplemental Bibliography**, References 81, 89, 133, 146, 147, 211, 232, 249, 338, 354, and 477.

Supplemental Material >

2.4. Optics. Imaging

The design of any keratoprosthesis must also conform to the requirements of optical quality and maximal transparency. The patients must have the ability to read a fine line on the vision chart, if the rest of the eye allows, without astigmatism or excessive refractive correction need, and with sufficient peripheral visual field. The present dimensions of the stem (about 3.35 mm diameter and about 2 mm length for the Type I device) seem to be an acceptable compromise between postsurgical device retention on one hand and optical performance on the other. Thus the narrower the stem is, the better the retention and the depth of focus, but the narrower the visual field—versus a wider stem with better field and easier wide-field photography of the retina, but riskier retention. The visual field of the present Type I B-KPro reaches about 60° from the center toward the temporal side—sufficient for everyday living. For the Type II device, the field is about 40° from the center (**Figure 13**).

Our evolving B-KPro device has several times been the subject of optical analysis and increasingly detailed description (often supervised by Professor Eli Peli) and also correlated with the machining technique, refractive power corrections, etc. (Abdelaziz et al. 2017; Chaudhary & Shamie 2012; Helms et al. 2018; Karas et al. 2019; Khalifa & Moshirfar 2010; Langenbucher et al. 2013; Pineles et al. 2010; Salvador-Culla et al. 2014; Sayegh et al. 2010, 2015). Clinically, 20/20 vision has been rapidly achieved in many cases, assuring us of the sufficient optical performance of the device. Any subsequent reduction of vision, which is unfortunately not uncommon, is not related to optical quality but rather is due to biological complications. One residual problem at the present time is making the central area of the anterior device surface appropriately aspheric to allow central vision of more uniform quality. This adjustment will probably have to be combined with the switch in the manufacturing from machining and polishing to molding of the anterior PMMA part.

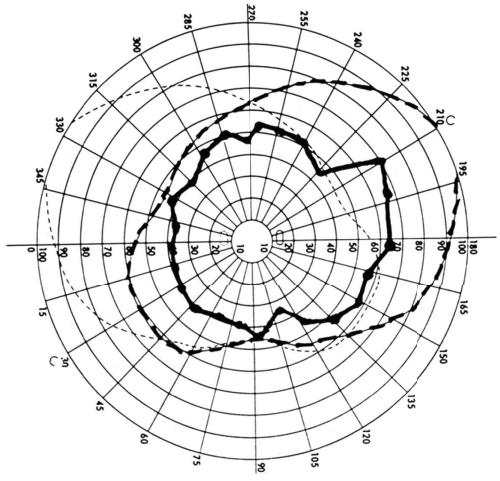

Figure 13

Visual field of eye with a B-KPro Type I (*solid line*, allowing about 60° of the field temporally from the center) versus control (normal eye, without KPro; *interrupted line*). The fine dotted line represents the field of the opposite, normal eye, superimposed. The maximum field through a B-KPro Type II (not shown) is about 40° from the center.

In the early days of the distribution of B-KPros, we took pains to deliver devices made to within one diopter of calculated refractive need of the recipient's eye, based on axial length measurement of the patient's eye. We now realize that only a few axial lengths need to be in stock, which reduces cost. The pinhole effect of the narrow stem provides an increased depth of focus and reduces the need for optical precision. If a substantial dioptric correction is still necessary postoperatively, it can easily be accomplished by choosing a soft contact lens (which will be used for protective reasons anyway) with the needed dioptric power. This has worked very well in practice.

Then there is the problem of postoperative glare, which can be very bothersome for the patient. In a standard B-KPro Type I situation, light enters the eye not only via the KPro stem but also around it, through the scarred carrier cornea and PMMA back plate. Light transmitted through a scarred cornea gets severely scattered forward, resulting in a wide area of spread points on the retina, causing the glare, which can be quite debilitating. A back plate of titanium can block about half the light bearing on its area but still leaves the holes that are filled with translucent scar tissue. On the other hand, in the Type II situation the lid skin around the front nub prevents any light at all from passing, and glare is totally eliminated and vision can be very sharp. A correction-free vision of 20/10 has been recorded from a Type II patient with Stevens-Johnson syndrome!

Internal reflexes do not constitute much of a problem. Only in the pseudophakic situation are there some reflexes that can be mildly confusing during the slit-lamp examination. In general, if the patient's eye ends up aphakic, with appropriate B-KPro power, it will be optically "cleaner" than the corresponding pseudophakic situation.

Supplemental Material >

For references on the optics of B-KPro, see the **Supplemental Bibliography**, References 95, 111, 170, 200, 225, 243, 287, 288, 389, 413, and 442.

2.4.1. Imaging. Modern imaging methods have proven to be very effective in pinpointing morphological changes that can explain leaks, the development of glaucoma, and other complications after B-KPro. Particularly, high-resolution spectral domain anterior segment optical coherence tomography (AS/OCT) and ultrasound biomicroscopy have been widely used. Some work has

been done in Boston but most has been generated in Chicago (University of Illinois), Montreal, Los Angeles (UCLA), New York City [New York Eye and Ear Infirmary (NYEEI), Cornell], University of California Davis, Cologne, and São Paulo (Ali et al. 2018; Fernandez et al. 2012; Garcia et al. 2008, 2010; Kang et al. 2013a,b; Kiang et al. 2012; Poddar et al. 2013; Qian et al. 2015; Shapiro et al. 2013; Siebelmann et al. 2016; Silva et al. 2018). Particularly, imaging of tissue melt around the device and anterior chamber angle closure has been clinically valuable. External photography at every patient visit is now routine and wide-angle fundus photography has become well developed (Kornberg et al. 2016, Sayegh & Dohlman 2013). Teresa Chen and colleagues have shown that three-dimensional spectral domain OCT volume scans of the optic nerve head and the peripapillary area can be very useful in the management of glaucoma after B-KPro (Khoueir et al. 2019).

2.5. Surgical Technique

Already in the early days of B-KPro, the actual surgery proved to be relatively easy for the experienced cornea surgeon. The technical details have been repeatedly published (e.g., Dohlman 1997; Dohlman et al. 1974, 1996). Developments of the specific operating room techniques followed from the desirability of incorporating a corneal graft as a carrier in the implantation. Thus, a fresh eye bank cornea is requested and delivered to the operating room. As mentioned, the present procedure starts with the surgeon implanting the device into the graft. The latter has to be trephined to a suitable outer diameter, usually 8.5 mm, which leaves a sufficient rim of tissue outside the 5 mm anterior plate of the device to allow for easy final suturing of the graft. A central hole is trephined to allow for the stem to be inserted (decentration can be mildly disturbing). Here the choice of dimension of the hole had to be adjusted to the availability of very inexpensive disposable biopsy trephines (available in 2.0, 2.5, 3.0, 4.0, etc., mm diameter). As mentioned, a 3.0 mm hole was chosen as the most practical and, to allow for a snug fit, a stem diameter of 3.35 mm became routinely manufactured. (A 3.0 mm disposable trephine and a 16 mm diameter soft contact lens are routinely shipped with the B-KPro to the requesting surgeon.)

After pushing the graft over the stem, the back plate is pressed up the posterior stem where it is snapped into a groove, or is stabilized with a locking ring, depending on the model. The graft–KPro combination is then stored in a beaker of saline with antibiotics until the patient's eye has been trephined (usually 8.0 mm) and is ready for the implantation after 5–10 minutes. Suturing of the graft–device combination is usually done with 12 9-0 nylon sutures or 16 10-0 nylon sutures. Postoperatively, I prefer to leave the sutures in place indefinitely unless loosened, for extra security.

2.6. Complications and Prophylaxis

In the short term after a B-KPro, often excellent astigmatism-free vision can be achieved if the rest of the eye allows—even for years. However, as mentioned above, in the long run "real world" experience has taught us that complications can result in a downward visual attrition slope that wipes out the initial gains and can even result in total failure. In a large number of outcome studies from Boston and the rest of the world, these complications and their impact have been gradually identified. As mentioned, especially autoimmune diseases, chemical burns, and chronic inflammation categories—cases that need help the most—have proven vulnerable (Yaghouti et al. 2001). Efforts to develop prophylactic methods to prevent glaucoma, infection, and inflammation were therefore given top translational research priority. This resulted in a gradual but very marked improvement of outcomes in the long term and the B-KPro has become widely accepted as a rescue procedure after severe graft failures. Still, postoperative management is at the present time somewhat logistically complicated, burdensome, and dependent on patient compliance, and costly for

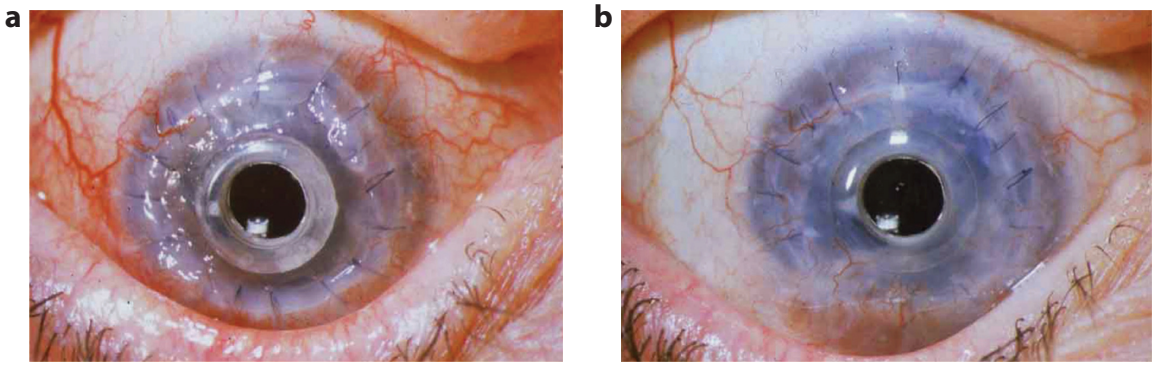

Figure 14

(*a*) A woman with somewhat reduced tear secretion had B-KPro surgery bilaterally (no soft contact lens). Please note the dehydration of the cornea and the irritation of the surface. (*b*) The same eye as depicted in panel *a*, but one week after a soft contact lens had been added for permanent wear (Kontur® 16 mm lens, barely visible). The cornea has become fully hydrated and the surface irritation is gone.

developing countries to routinely adopt. It is clear at this point that in spite of all progress it is necessary to continue to improve long-term safety, simplification, and reduction of cost. Here will be summarized some remaining postoperative problems with specific B-KPro issues, as we presently see them, and what is attempted to make the procedure safer.

2.6.1. Corneal surface exposure. In many early B-KPro cases, the corneal surface around the device appeared dry, thinned, and irritated, with tear film breakup and dellen, all indicating that evaporation from the surface is being too slowly replaced by fluid from the tears by blinks, or from the tissue behind (**Figure 14**). Low tear secretion as well as a large KPro back plate without holes are aggravating factors. In addition, lower blink rate resulting from reduced innervation in bilateral corneal pathology, or bilateral KPros, can lead to enhanced evaporation and reduced stimulation of tear secretion. All this can result in epithelial defects, sometimes persistent with stromal ulceration. However, solutions for these problems gradually developed.

A total conjunctival flap of the Gundersen style, used commonly in corneal surgery, can dramatically protect the B-KPro-holding cornea from postoperative surface problems and ulceration (Adesina et al. 2013, Al-Merjan et al. 2000, C.H. Dohlman et al. 2016, Eghrari et al. 2016). A broad, loose flap can be mobilized from the temporal side (better than from above because of the lid movements), with the vascularized bases above and below intact, and slid over the cornea to be firmly anchored at the limbus with 10-0 nylon sutures. There is no buttonholing, and the corneal epithelium must have been previously removed completely (chemically, e.g., with 70% ethanol) to secure healing connective tissue to connective tissue without cysts or fistulas. The drawbacks are the time it takes for this extra procedure (5–10 minutes) as well as the occasional problem of the original poor condition of the conjunctiva. However, a complete vascularized flap invariably provides an intact surface epithelium and immediately stops stromal ulceration (anticollagenase effect of blood α_2-macroglobulin?).

The introduction of a soft contact lens, to be worn routinely around the clock postoperatively, revolutionized the situation (Dohlman et al. 2002b). Although not universally accepted, we became impressed by the ability of a large soft lens (especially the 16 mm Kontur® lens) to serve as a substitute for a stable tear film and to diffuse the evaporation forces, thereby reducing chronic irritation. It serves the same purpose as a total conjunctival flap but it is easier and faster to handle (Harissi-Dagher et al. 2008, Kammerdiener et al. 2016, Nau et al. 2014). We recommend replacement of the

lens only if lost, or if deposits have formed, which is relatively rare (Beyer et al. 2011, Farooq et al. 2018, Kruh et al. 2015). The lenses add somewhat to the cost but we have had lenses stay in place, clean, for over five years without replacement. In markedly nonblinking or dry eyes, lenses of central rigid water-impermeable material, but with a soft skirt, are recommended (Beyer et al. 2011).

Supplemental Material >

For references on contact lenses in B-KPro, see the **Supplemental Bibliography**, References 36, 68, 86, 90, 129, 142, 202, 241, 258, 282, 300, 332, 373, and 443.

Scleral lenses of large or small dimensions, particularly the PROSE type pioneered by Drs. Rosenthal and Jacobs of Boston, are often very effective in protecting and restoring vision in eyes that are very dry from autoimmune disease. They can also be effective post-B-KPro although their handling is not always easy (Papakostas et al. 2015).

2.6.2. Tissue melt, extrusion. Epithelial defect, necrosis of the stroma surrounding the KPro, deepening melt, and final extrusion of the device, with or without accompanying endophthalmitis, were frequent end-stage experiences of the pioneers in our field. Such final outcomes must be judged in the context of the severity of the corneal disease in those patients who were later selected for a KPro procedure—often end-stage autoimmune disease with chronic inflammation, prone to ulceration, and often after several failed PKs.

Our own experience did not differ much from this pattern in the beginning. However, one single patient in the 1990s changed our approach and thinking entirely (Dohlman et al. 2002a). This middle-aged woman from Chicago had severe burned-out Sjögren's syndrome with end-stage rheumatoid arthritis and a severely ulcerating cornea with light perception vision in her only remaining eye (**Figure 15**). We performed a B-KPro Type I procedure, which resulted in a vision of 20/50–20/20 for many years. However, eventually a severe melt occurred in the very inflamed eye, with perforation, and the device partly extruded after a month. Several repair procedures failed and we had to give up. Independent of the eye problem, however, the patient's rheumatologist in her city started her on the TNF-α antibody infliximab (Remicade®) intravenously. The result was miraculous: At her next visit in Boston the eye had calmed down and the leak healed spontaneously, and the B-KPro had somehow regained its original position (**Figure 15*b*,*c***) (sadly the eye considerably later succumbed to retinal detachment). However, she became the index patient for our 20-year research approach on biologics, primarily in the form of TNF-α inhibitors, in a variety of inflammatory settings.

Unfortunately we could only treat a few more patients with biologics due to the expense and the reluctance of the insurers to allow reimbursement at the time, but most experienced spectacular healing.

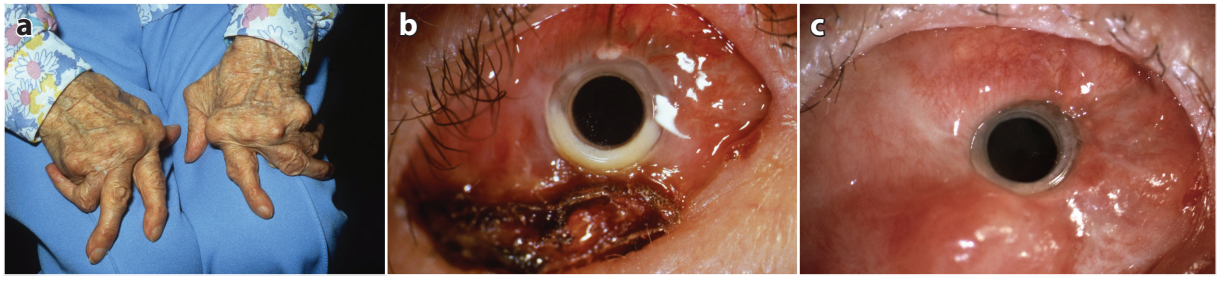

Figure 15

(*a*) Severe rheumatoid arthritis in a middle-aged woman. (*b*) One eye lost, the other heavily inflamed, relentlessly ulcerating. A B-KPro gave years of good vision but eventually did not help and severe ulceration and continuous aqueous leak could not be repaired. (*c*) Intravenous infliximab (antibody against TNF-α) dramatically decreased inflammation and allowed spontaneous healing in a month.

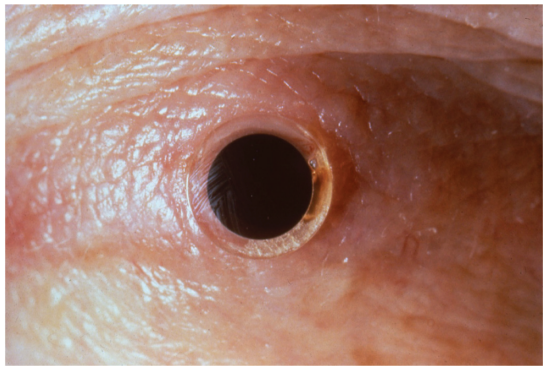

Figure 16

A B-KPro Type II in a woman with Stevens-Johnson syndrome and an eye enucleated (see Section 2.6.2). After two previous failed similar operations followed by rapid tissue melt and threatening extrusion, a third could be remarkably protected with monthly intravenous infliximab (the TNF-α antibody). During seven postoperative years, not a trace of inflammation was visible and vision was 20/50–20!

One more example: A young woman with severe Stevens-Johnson syndrome having already lost one eye had, after five years of observation, a B-KPro Type II implanted by us. The skin around the device soon started the characteristic melt and retraction, and the device had to be replaced. The new one melted even more rapidly and lasted only a year before the third Type II had to be implanted. However, this time we had the resources to provide intravenous Remicade® (infliximab) postoperatively. *For seven years she did not have a trace of inflammation or skin retraction*—and had full vision (**Figure 16**)—until we believed that we could begin to taper off the biologic (Dohlman et al. 2009)!

These patients and a few others convinced us that TNF-α inhibitors should be routinely applied after B-KPro in inflamed, autoimmune diseases—made possible when the price comes down and the insurance companies loosen up. These initial clinical observations, however, stimulated our subsequent laboratory activity applying cytokine inhibitors, particularly for their role in prophylaxis against post-KPro glaucoma (see below).

Supplemental Material >

For references on melt and ulceration, see the **Supplemental Bibliography**, References 99, 137, 140, 204, 207, 219, 245, 260, 268, 270, 276, 304, 350, 387, and 469.

2.6.3. Infection. Devastating keratitis and endophthalmitis have been complications of artificial corneas since their introduction 230 years ago. As every ophthalmologist knows, bacterial endophthalmitis (usually streptococcus, staphylococcus, or pseudomonas) often results in total destruction of the eye within 24 hours (**Figure 1**). A fungal etiology means a somewhat slower progression but often has bad outcomes as well. The latter is common in the developing world, often in agrarian settings in a hot humid climate, and often diagnosed and treated too late.

As mentioned, throughout the history of artificial corneas the first clinical applications were usually performed on patients with the worst prognosis, often autoimmune, usually without prophylactic antibiotics, and therefore resulting in a high incidence of endophthalmitis and enucleation. Our initial results did not differ much. It seemed intuitive, however, that chronic prophylactic antibiotics might give some long-term protection despite the possibility of developing bacterial resistance. Embarking on a double-blind study many years long to get statistical significance appeared too complicated and time-consuming to be practical. Therefore, a guesswork regimen of daily installation of low-dose antibiotics was instituted early and routinely in

our cases, to be evaluated anecdotally and long term. This approach turned out to be surprisingly effective. Although the choice of drug and dosing was initially wild guesswork, the incidence of endophthalmitis fell dramatically—practically without side effects—in some outcome series to zero while followed for many years.

Further clinical experience indicated that broad-spectrum polymyxin B/trimethoprim/BAK (Polytrim®) drops, or fluoroquinolones, in regimens of once or twice daily, for life, were quite effective in most cases—with Polytrim® by far the least expensive. In a large B-KPro series from Boston, a subgroup of nonautoimmune cases treated with Polytrim® drops once daily were followed for 30 cumulative years without a single infection (Behlau et al. 2014). In very vulnerable situations, such as autoimmune diseases or severe chemical burns, the addition of low-concentration 1.4 mg/mL vancomycin once or twice daily blocks gram-positive infection very effectively (Durand & Dohlman 2009). There has been a tendency among some surgeons to give much higher doses of prophylactic drops—to be on the safe side. Four times a day is not only distressing for the patient, in my opinion, but potentially damaging to the ocular surface, and too much steroid can push up the intraocular pressure (IOP).

This leaves antifungal prophylaxis as an unmet need, however, especially in low-resource countries. Recent efforts have been made to identify antibiotics or antiseptics suitable for the purpose, with low cost, good availability, and chemical stability as requirements. Polytrim®, povidone-iodine, hypochlorous acid, and ionic liquids have emerged as safe and mostly low-cost candidates (Kim et al. 2020).

A general problem with antimicrobial prophylaxis after B-KPro implantation is the *compliance* with the daily self-medication, for life—a regimen that is difficult to adhere to for most people. There remains a clear need to dissociate the patient from the medication. A drug-eluting contact lens (Ciolino et al. 2009, 2011, 2014), or a similar device implanted subconjunctivally (Robert et al. 2016), might provide a solution. A polymer, capable of eluting a well-tolerated antiseptic for months and placed in the lower lid fornix (like an Ocusert®), possibly anchored by a fine nylon suture, is presently under development by us. Another promising approach is to cover the KPro stem with an antimicrobial that is covalently bound to the stem PMMA (Behlau et al. 2011).

Supplemental Material >

For references on infections after B-KPro, see the **Supplemental Bibliography**, References 29, 31, 58, 72, 83, 87, 91, 106, 113, 143, 153, 156, 157, 161, 162, 163, 173, 189, 194, 195, 201, 202, 218, 221, 224, 229, 256, 290, 308, 309, 314, 325, 337, 342, 357, 359, 367, 372, 373, 402, 417, 423, 437, 443, 471, and 481.

2.6.4. Glaucoma, inflammation. Long-term glaucoma is, in my opinion, the most consequential and severe complication after any type of KPro (Baratz & Goins 2017, Cade et al. 2011, Črnej et al. 2014b, Dohlman et al. 2020a, Kamyar et al. 2012, Kwitko 2019, Netland et al. 1998, Talajic et al. 2012), actually after any type of acute trauma or complex surgery. This is well documented in numerous clinical outcome studies although the magnitude has not always been appreciated. The gradually worsening glaucoma is manifested by the characteristic disc (**Figures 17** and **18**) and field changes and, in the long run, as an attrition of the visual acuity. These changes are difficult to prevent by standard glaucoma medication and they can lead to total blindness in the most vulnerable cases, particularly after chemical burns and autoimmune diseases.

The visual consequences of glaucoma following surgery or acute trauma have invariably been blamed on the IOP, whether recorded as elevated or not. During the healing stage after severe ocular injury or surgery, aqueous outflow resistance is well-known to often increase (from angle closure, trabecular meshwork scarring, etc.), to lead to IOP rise and damage to the retinal ganglion cells, and to result in glaucomatous neuropathy. Although the exact mechanism is still obscure, this pathway has been accepted for centuries.

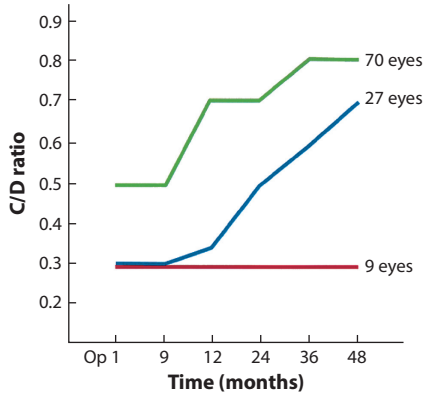

Figure 17

Long-term glaucoma is the most consequential complication after B-KPro. Shown here is the cup:disc (CD) ratio (now visible through the cleared media) in a series of 106 sequential postoperative severe cornea cases of different etiologies. Two-thirds had glaucoma before the B-KPro operation—they could worsen. Also many could develop glaucoma de novo afterwards. Only a minority remained glaucoma-free after 4 years. Figure adapted with permission from Črnej et al. (2014b).

However, recent experiments in our laboratory have indicated that there may be additional elements to the story, mediated by intraocular inflammation and inflammatory cytokines (Dohlman et al. 2019). Thus, after a chemical burn to the cornea in rabbits or mice, cytokines such as TNF-α can promptly become massively upregulated in the anterior segment and rapidly diffuse posteriorly to cause apoptosis of the retinal ganglion cells, which in turn is known to lead to glaucoma (Cade et al. 2014, Paschalis et al. 2017). These rapid developments occur while IOP is still within normal limits (Dohlman et al. 2019). The concept of this rapid, inflammatory, and IOP-independent pathway is strongly supported by the fact that prompt delivery after the trauma of anti-TNF-α antibodies (infliximab, adalimumab) is very effective in protecting the ganglion cells against apoptosis (Cade et al. 2014, Paschalis et al. 2017, Zhou et al. 2017). These findings have gradually opened up exciting possibilities of powerful anti-inflammatory treatment and

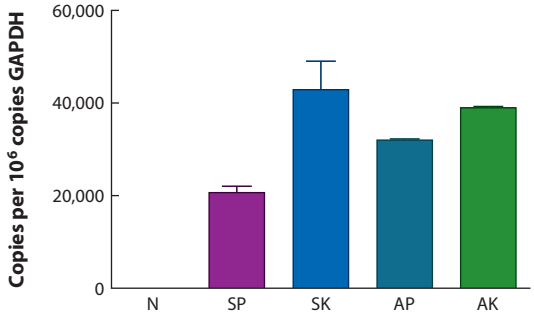

Figure 18

TNF-α in corneal grafts (syngeneic, allogeneic, with or without miniature B-KPro) in mice, 8 weeks postop. TNF-α is markedly upregulated after all surgeries compared to naive cornea (N). Figure adapted with permission from Črnej et al. (2014a). Abbreviations: AK, allogeneic KPro group; AP, allogeneic penetrating keratoplasty group; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; N, naive group; SK, syngeneic KPro group; SP, syngeneic penetrating keratoplasty group.

antiglaucoma prophylaxis (Dohlman et al. 2018). This insight should also be juxtaposed to a recent clinical finding that TNF-α levels in blood can be elevated for years following B-KPro implantation (Paschalis et al. 2019b). Although the full relevance of these findings is not yet clear, it is possible that TNF-α in blood can serve as a useful marker for inflammation and as an indicator for further prolonged anti-inflammatory treatment.

Supplemental Material >

For references on glaucoma after B-KPro, see the **Supplemental Bibliography**, References 15, 33, 42, 88, 96, 107, 125, 131, 135, 141, 144, 154, 164, 166, 169, 184, 187, 228, 231, 233, 237, 241, 246, 251, 253, 254, 259, 269, 284, 292, 296, 321, 347, 363, 364, 370, 379, 380, 394, 400, 414, 421, 436, 444, 448, 450, 454, 458, 459, 463, 464, 465, 478, 479, 483, and 484.

These conclusions are based on some recent papers that promise to be game changers for our field. The first was by Cade et al. (2014). What started out as a routine project for a clinical fellow increased in significance when Drs. Regatieri and Vavvas taught us histochemical staining techniques for the retina. It then became apparent that injury to the cornea rapidly resulted in inflammation of retinal elements, including the ganglion cells (the hallmark of glaucoma). Ocular burn to the surface does not result in direct pH damage to the retina—the alkali is effectively buffered at the iris-lens level. Rather, the inflammatory cytokine TNF-α is clearly a prominent mediator, demonstrated by the highly protective effect of its antibody infliximab. Thus the link between damage to the ocular surface and late glaucoma (via TNF-α and ganglion cell apoptosis) became established in animals. It had already been shown in Kinoshita's laboratory that a chemical burn to the corneal surface in mice could result in elevation of IL-1α, IL-1β, and IL-6 in the retina (Miyamoto et al. 1998).

This connection was more firmly established by Paschalis et al. (2017). The damage to the ganglion cells was caused by TNF-α, and probably other cytokines as well, originating in the anterior segment and rapidly diffusing posteriorly. Again, the antibody inhibition was markedly protective.

The third paper zeroed in on chemical burns in humans (Dohlman et al. 2018). This paper formulated prophylactic treatment against long-term glaucoma in patients who are victims of a burn to the eye. Increased, prompt administration of anti-inflammatory medication after such acute event may diminish or prevent later glaucoma. If confirmed in patients, such prophylactic treatment promises to be clinically widely useful.

*Finally, as mentioned, a new, additional pathway to glaucoma may have been identified (Dohlman et al. 2019). This paper describes the possibility of a non-IOP-related inflammatory cause of secondary glaucoma in animals (**Figures 19** and **20**).*

These experiments need further confirmation, of course, but they already suggest that after KPro surgery—in fact after any surgery or acute trauma—it would be advisable to promptly institute sufficient anti-inflammatory drugs for a sufficient length of time to protect against the "time bomb" of later glaucoma. These requirements need further definition but it is clear that corticosteroids cannot completely fill the gap due to their known complications. Biologics, with their very good safety record and precise mechanism of action, are expected to take up the slack to a great extent. Thus, expanded use of anti-inflammatories instituted promptly after surgery or other acute events, and kept up until cytokine levels in the patient's blood have been reasonably normalized, might be effective as prophylaxis against the long-term secondary glaucoma. If these results are confirmed, the identification of this pathway to glaucoma may have an impact on clinical ophthalmology even beyond keratoprostheses.

Glaucoma is so prevalent and severe in some instances of trauma, e.g., after chemical burns, that we generally recommend that a valved glaucoma drainage device (Ahmed®) be implanted before or simultaneously with the B-KPro in patients who have glaucoma clearly diagnosed beforehand. The clinical outcome of such intervention is quite beneficial (Črnej et al. 2014b).

A rare circumstance is epithelial downgrowth into the anterior chamber from complications after ocular surgery or trauma, usually with disastrous outcomes from resulting corneal edema

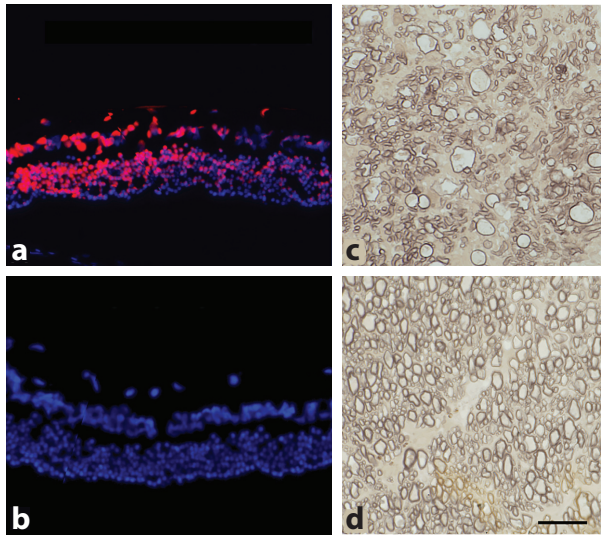

Figure 19

Injury to the cornea can rapidly result in damage to the retina, including the ganglion cells. After alkali burn to the cornea of mice or rabbits, the retinas were subjected to TUNEL stain for cellular apoptosis. The left panels show the retinal stain in rabbits 72 hours after exposure, (*a*) without and (*b*) with infliximab administration promptly postburn—while the intraocular pressure (IOP) remained essentially normal. The right panels show (*d*) a normal optic nerve compared with (*c*) a nerve three months after a corneal burn, indicating permanent loss of the axons. Infliximab is very protective against axon degeneration as well (not shown). Original earlier experiments in mice had given similar results. Figure reprinted from Zhou et al. (2017) (CC BY-NC-ND 4.0).

and glaucoma (Anseth et al. 1991). Here a combination of IOP-lowering measures and a B-KPro can give sight-saving results (Bielory et al. 2012, Rachitskaya et al. 2015, Sa-Ngiampornpanit et al. 2009).

2.6.5. Further complications. There are other complications after B-KPro implantation, which are of less threat or which can be expected to decrease in frequency and significance as

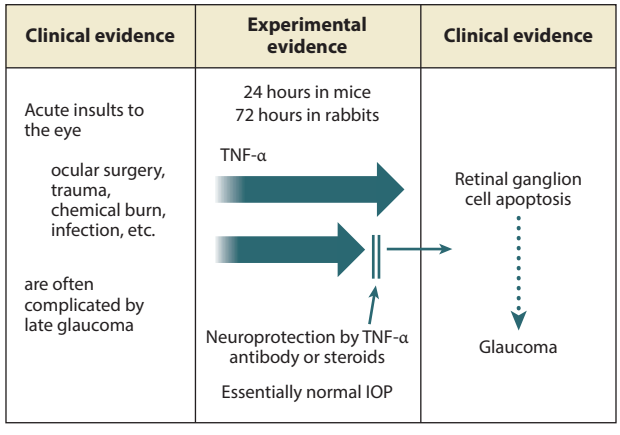

Figure 20

Schematic illustration of glaucoma after corneal trauma or surgery: a rapid, inflammatory intraocular pressure (IOP)-independent pathway. Figure adapted from Dohlman et al. (2019).

a consequence of improved and more sustained anti-inflammatory prophylaxis, particularly with biologics. Melt of the cornea around the device in autoimmune diseases is clearly one of them (see above). Retroprosthetic membranes, which seem to result from intraocular inflammation, likely aided by a gaping cornea wound (see above, Section 2.5), are diminishing in frequency and may disappear altogether with more available and more intensive anti-inflammatory treatment (**Figure 13**). The same gradual disappearance may happen to the phenomenon of sudden, sterile vitritis (see above). These episodes almost invariably clear up in a month on corticosteroids but can be difficult to initially distinguish from bacterial endophthalmitis and thereby cause confusion in treatment. A better "biointegration" between corneal tissue and the B-KPro stem may also help.

Likewise, retinal detachments, initially not uncommon after B-KPros in autoimmune diseases, have been reported much less frequently lately (Goldman et al. 2013, Jardeleza et al. 2015, Modjtahedi & Eliott 2014, Moshiri et al. 2019, Rishi et al. 2016). Even though the incidence of such detachments is now rare, they are still difficult to repair with preserved vision. Ironically, quite a measure of success has been achieved with B-KPro in the most severe category of retinal detachment where silicone oil fill is necessary (Chan et al. 2011; Iyer et al. 2019, 2011; Toygar et al. 2019; Utine et al. 2010). Dr. Iyer in Chennai is the pioneer in treating various vitreoretinal conditions with silicone oil (hypotony, uveitis, ruptured globe, chemical burns, detachments, etc.). The oil is usually incompatible with a clear cornea or graft and therefore needs a KPro, which can give excellent vision for a considerable time (Iyer et al. 2019). Increased prophylactic use of anti-inflammatory drugs, particularly biologics, is again expected to be useful. The same can be predicted for chronic uveitis, of whatever noninfectious etiology, where substantial progress has already been made (Levy-Clarke et al. 2014).

Supplemental Material >

For references on retinal complications, see the **Supplemental Bibliography**, References 22, 35, 177, 203, 217, 272, 310, 324, 327, 331, 349, 386, 408, 449, and 462.

For references on sterile vitritis, see the **Supplemental Bibliography**, References 46, 286, 304, and 441.

2.6.6. Sidelines. It is not surprising that with our long-lasting translational research effort on B-KPro, some unexpected insights into related problems have surfaced. One of these sidelines pertains to the immune response in the retina during intraocular inflammation from ocular trauma, led by Drs. Paschalis, Vavvas, and Zhou, who, by using the model of alkali burn to the cornea in mice and rabbits, identified blood-derived monocytes invading the retina and becoming permanently engrafted (Paschalis et al. 2018b, 2019a). These cells retain a distinct signature that promotes continuing inflammation even long after the noxious stimulus has been removed—ultimately contributing to progressive neurodegeneration (Paschalis et al. 2018a). This includes the retinal ganglion cells, the pathway to glaucoma. These events can also occur after everyday surgical procedures like PK or even ocular suturing, and are amenable to prevention with cytokine inhibitors (X. Chen et al. 2020).

2.6.7. Treatment of chemical burns. Another initially unsuspected insight of potential clinical interest resulted from outcome studies of severe chemical burns (also see above) (Cade et al. 2011; Črnej et al. 2014b; Dohlman et al. 2018, 2019). Such bilateral corneal burns in humans, whether from industrial explosions, household accidents, or criminal activity, are not uncommon, particularly in developing countries, and often happen to young males. Later implantation with B-KPro in such cases has resulted in surprisingly good immediate postoperative vision but then it became apparent that many of them had already developed severe glaucoma (Cade et al. 2011, Muzychuk et al. 2017a) (**Figure 17**). Thus, a majority of these patients did have glaucoma even before the B-KPro and many worsened afterward (Črnej et al. 2014b).

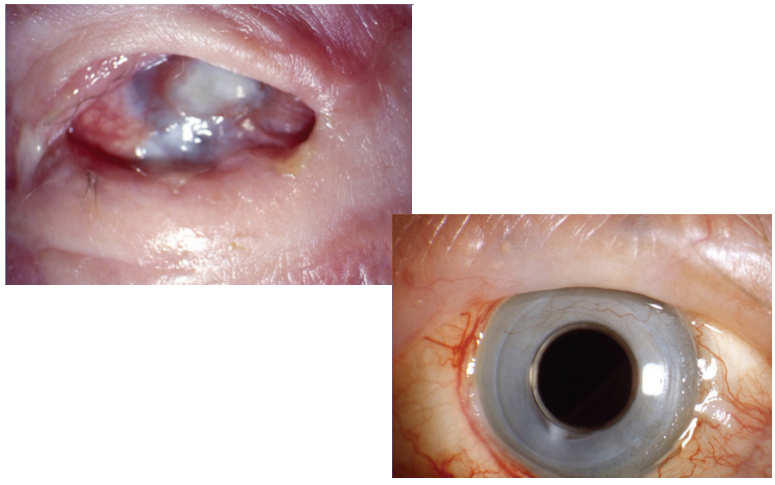

Figure 21

Acid burn, pre- and postoperatively with B-KPro (early model) since 15 years. Vision 20/40—but with glaucoma. Figure adapted with permission from Dohlman et al. (2020b).

It is now clear from clinical experience and from our animal studies, combined, that chemical burns create a storm of TNF-α in the anterior segment, which diffuses rapidly posteriorly and causes apoptosis of the retinal ganglion cells within hours or a few days—which is expected to result in progressive glaucoma. Treatment with anti-inflammatory drugs (corticosteroids and biologics) is remarkably effective in protecting the ganglion cells from apoptosis and the optic nerve from axon degeneration in animals and might be considered to be given promptly also to patients on arrival in the emergency room—and for sufficient time afterwards (e.g., Kenalog® plus Humira®). For details on such a proposed regimen for chemical burns, see a recent review (Dohlman et al. 2020b) (**Figure 21**).

2.7. General Considerations, Summary

Supplemental Material >

As mentioned, the overall outcome picture of the B-KPro is reflected in about 500 publications produced so far by the community of KPro surgeons (see the **Supplemental Bibliography**). A large percentage of these papers have emanated from Boston but even more from elsewhere, contributing major progress particularly from great academic B-KPro "hot spots" like the University of Montreal (Harissi-Dagher, Robert), UCLA (Aldave, Deng), Wilmer Institute (Akpek), Rochester (Aquavella), University of Illinois (Chicago) (Cortina, de la Cruz, Djalilian, Rosenblatt), NYU (Colby), University of Michigan (Mian), Cincinnati (Holland), Cleveland (Sayegh), Iowa (Wagoner, Goins), Miami (Parel, Perez, Alfonso), Cornell (Sippel, D'Amico, Ciralsky, Starr), NYEEI (Ritterband, Seedor), Pittsburgh (Dhaliwal), Tucson (Belin), University of California Davis (Mannis), Wills Eye Hospital (Cohen, Ayres, Rapuano, Hammersmith, Laibson), Toronto (Slomovic, Chan, Rootman, Ma, Odorcic), Edmonton (Rudnisky), Medellin (Abad), Mexico City (Graue), São Paulo (Oliveira, Regatieri), Victoria (Cade), London (Wilkins), Brighton (Liu), Barcelona (Barraquer, Salvador Culla, de la Paz, Alvarez de Toledo, Güell), Bilbao (Etxebarria), Cologne (Cursiefen), Erlangen (Kruse), Salzburg (Grabner), Munich (Neuhann), Athens (Kanellopoulos), Chennai (Iyer, Srinivasan), New Delhi (Tandon, Sangwan), Hyderabad (Basu), Singapore (Mehta, Tan), Beijing (Wang), Bangkok (Lekhanont), and many others. The

details cannot be included here. However, in summary, we can proudly point to successes in thousands of patients, many dramatic, lasting for a long time. Particularly important is the solid demonstration that in many situations a B-KPro will have better prognosis for long-term success than a classic PK. Although B-KPros have been followed for much less time than PKs, it is clear from a number of studies with recent techniques and follow-up of at least 5–8 years that retention and visual acuity results of the B-KPro are substantially superior to those of PKs performed under similar circumstances (Ahmad et al. 2016, Akpek et al. 2015, Y. Chen et al. 2020, Ma et al. 2005, Ono et al. 2020). This trend is valid whether the B-KPro is implanted as a primary procedure in corneal opacity or following one or more failed PKs (Chang et al. 2015; Driver et al. 2018; Fadous et al. 2015; Kang et al. 2012, 2018). It is also valid for severe autoimmune indications such as Stevens-Johnson syndrome (Alexander et al. 2015, Sayegh et al. 2008). However, there has been a question as to whether the failures after B-KPros, when they do occur, can be more severe and definitive than after PK—a point that deserves further analysis (Muzychuk et al. 2017a). There should also be strong hope for other ultrasevere corneal diseases (chemical burns, war trauma, etc.) by employing well-timed prophylactic treatment against inflammation, glaucoma, infection, etc., following the implantation of the device.

All this progress is welcome news—but not good enough. At present only about a thousand KPros (mostly B-KPros) are implanted per year worldwide—which constitutes only a half percent of penetrating keratoplasties of all permutations (about 200,000 PKs—185,000 identified in 2013) (Gain et al. 2016). This in spite of the fact that KPro of virtually any design can result in immediate spectacular, astigmatism-free vision, if the condition of the rest of the eye allows. As described, there are still unpredictable residual problems with long-term safety, particularly caused by glaucoma—coupled with somewhat heavy postoperative management demands, and expense. These issues are of particular importance for the developing world where reportedly about 90% of the cornea blind reside. In our Western world, most visual problems from the cornea are due to edema (with swollen but otherwise normal stroma) from a faltering endothelial pump function. With modern layer-by-layer surgery, the isolated endothelium can effectively be replaced. In the developing world, on the other hand, scarring of the stroma from agrarian infections, etc., is much more prevalent and makes the availability of a safe KPro more urgent.

We will never be able to completely prevent calamities like chronic inflammation, autoimmune diseases, chemical burns, severe infections, disastrous surgery, violent trauma, etc. It is particularly for situations where there is bilateral corneal involvement that we have to continue our efforts to elevate the B-KPro to a safety level above a desperate final attempt as a rescue procedure. For the B-KPro and for any other improved KPro in the future, it seems logical to continue to strive for increased long-term safety and simplicity by improving prophylaxis against postoperative glaucoma, inflammation, and infection, in particular, and preferably with preventative therapy administered locally. It seems that control of inflammation by biological means is an imperative. Science has recently given us more powerful weapons to help to keep inflammatory responses down for prolonged periods and we are well advised to apply them fully, within the limits of safety. Thus, controlled studies on using biologics in addition to standard corticosteroids after all B-KPro surgery—but particularly in autoimmune diseases and after chemical burns—are urgently needed. The ultimate reward will be our increased ability to help the large number of patients worldwide with severe corneal pathology to regain a life of safe vision.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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