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LITERATURE REVIEW

Eye Banking in the 21st Century: How Far Have We Come? Are We Prepared for What's Ahead?

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ABSTRACT

PURPOSE: This review of milestones in eye banking describes efforts by the eye banking community to ensure the quality and quantity of corneal tissue over the last century and anticipates key challenges going forward.

METHODS: This account draws on a review of the scientific literature, public documents, and eye banking statistics and is augmented by the recollection of the author, discussions with eye bankers, and an analysis of pressing medical and nonmedical issues that will bear on the future success of eye banking in the United States and internationally.

RESULTS: The author identifies five eras of eye banking, highlighting scientific breakthroughs in surgical techniques, storage, and instrumentation; the professionalization of eye banks through development of medical standards and accreditation programs; and the advent of laws and regulations leading to reimbursement changes and donor legislation. The author next identifies five strengths exhibited by the community to achieve those milestones and delineates crucial questions posed by an ever-expanding array of unprecedented demographic, socioeconomic, geopolitical, biological, regulatory, technological, cultural, and ethical challenges.

CONCLUSIONS: Technological advances and collaborative efforts have brought the eye banking community to the enviable position it enjoys today. Only by building on its historical strengths can eye banking professionals worldwide successfully evolve their role in an increasingly complex future.

KEYWORDS: corneal endothelium, corneal preservation, corneal transplantation, eye banks, eye donation, healthcare economics

Preserving and restoring vision impaired by corneal disease, disorder, or injury have never been so routine as they are today in the United States, more than 100 years after the first successful penetrating corneal transplant was performed in 1905[1] in Europe. Indeed, for most affluent countries throughout the globe, healthy donor tissue and surgical services are readily available and, for many patients, reasonably accessible. Emerging advances in instrumentation, surgical technique, and new materials hint at more options and better outcomes for patients and more efficient use of donor tissue by eye banks and surgeons. However, against a backdrop of shifting demographics, economic uncertainties, and pressures on the healthcare delivery system in the United States and elsewhere, the picture is about to change. Add to this mix an array of differing cultural expectations, religious practices, and ethical frameworks, not to mention differing stages of economic development in less affluent countries, and the context for corneal transplantation internationally becomes even more complicated. Are eye bank and medical professionals prepared for what lies ahead?

Given the numerous variables in play at this moment in history, the launch of the *International Journal of Eye Banking* provides an opportune time to take stock of where we have been, where we are, and where we are going. To this end, this paper (1) reviews the

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technological advances of the last 100 years in tissue procurement, storage, and surgical techniques and describes how they led to the proliferation of eye banks and medical standards, (2) mentions promising developments in the field, and (3) identifies future challenges, including demographic, socioeconomic, geopolitical, ethical, and regulatory issues, made all the more complex by differences among nations, regions, and cultures. A review of this nature, of course, could fill a book; however, the purpose here is to sufficiently set the stage for the eye banking community to consider what questions must be asked and answered as we move into an uncertain future.

HOW FAR HAVE WE COME?

The trajectory of eye banking as a professional focus has spanned not only many decades but also many countries, and it represents the contributions of countless individuals dedicated to the mission of preserving and restoring sight. It is perhaps simplest to summarize that history by differentiating key periods of growth.

The formative years: 1935–1944

Until the 1930s, surgeons had but one source for procuring tissue when they needed to perform a corneal transplant: the eyes of living donors who had been enucleated as the result of posterior segment pathology.[2] Eyes had to be removed and corneas transplanted immediately, owing to concerns regarding donor tissue death. Although surgeons used only clear corneas, outcomes were relatively limited due to factors such as primitive surgical techniques, intraoperative and postoperative complications, and limited pharmaceutical agents, among others.

The event that changed the course of penetrating keratoplasty (PK) and broke ground for what would become eye banking occurred in 1937, when Russian ophthalmologist Vladimir Filatov reported that cadaver tissue stored in a moist chamber at 4°C could successfully be used as donor material.[3] Simple, convenient, and relatively inexpensive, this storage method was a marked advance over using tissue from live donors. Nevertheless, it had significant limitations, particularly the short-term survival of endothelial cells, a critical factor in maintaining cornea transparency. As a result, corneal transplant surgery continued to be an emergency procedure. Surgeons grafted corneas stored at 4°C as soon as possible, usually 24−36 hours post mortem.[4]

Patients undergoing ophthalmic surgical procedures such as corneal transplants benefited from the introduction of antibiotics in the 1930s and corticosteroids in the 1940s, as well as the development of more refined surgical instruments and techniques. In 1939, Weiner and Alois added a beveled edge to the trephine, which was first developed by von Hippel around the turn of the century, thus providing surgeons with a tool for better dissection of donor tissue.[5] In Spain, the United Kingdom, Hungary, the United States, Switzerland, and Finland, prominent ophthalmologists championed corneal transplantation and continued to refine procedures. Technological advances led to finer sutures and needles; the introduction of the surgical microscope, a major contributor to improving PK outcomes; and a more sophisticated understanding of the role of the cornea's anatomy and physiology, including the critical nature of the endothelium.[5]

The organizing years: 1945–1970

The ability to store donor corneas even for a short period of time allowed for the establishment of eye banks in which tissue could be collected and distributed. The first of these organizations, the Eye-Bank for Sight Restoration, Inc., in New York, was founded in 1944 by Richard Townley Paton to "supply donor material to qualified surgeons, to support research in and teaching of surgical techniques, to provide ocular tissue for experimental work, and to stimulate research in the causes of blindness."[6] Thus, the concept of the eye bank came to be pioneered in the United States; by 1956, the cities of Boston, Philadelphia, Winston-Salem, New Orleans, Chicago, San Francisco, and Los Angeles had established eye banks. Moist-chamber storage at 4°C continued to be the preservation method of choice, while research into alternatives[7] (e.g., drying, formalin fixation, freezing, freeze-drying, and liquid paraffin storage) did not produce satisfactory results.

During these organizing years, most of the development of eye banks individually as well as nationally continued to take place in the United States. Alson Braley, the physician-founder of an eye bank in Iowa, is credited with stepping up eye banking to a new level of efficiency and reach when he organized volunteer ham radio operators into a national network focused on procurement and placement of eye tissue in the United States.[2] Given the urgency of transplanting corneal tissue as quickly as possible after donor death, the ham radio network offered the most expedient method of communicating between eye banks.[8] Within 1 year of its founding in 1962, the Eye Bank

Emergency Network had expanded to 60 operators working in 47 cities throughout 26 states.[6]

The proliferation of eye banks, run almost entirely by highly committed volunteers, also galvanized medical individuals involved in corneal transplantation around the goals of (1) ensuring quality, (2) maintaining a high level of trust among eye bankers, medical professionals, and the patients they served, and (3) establishing themselves (rather than government) as the standard bearers of quality control for their field. Toward that end, a group of leading ophthalmologists met in 1955 during the annual meeting of what was then the American Academy of Ophthalmology and Otolaryngology (AAOO); they formed a Committee on Eye Banks with the intent to standardize procurement, preparation, and distribution procedures in the United States. In 1961, this committee led to the establishment of the Eye Bank Association of America (EBAA), bringing together "lay and professional individuals dedicated to the advancement of worldwide eye banking"[2] and heralding a new era in corneal transplantation. (For a complete account of the history of this first eye bank association, see the related article in this issue, "The Evolution of Eye Banking in the United States: Landmarks in the History of the Eye Bank Association of America.") In the field of medicine, ophthalmology as a practice attracted bright students to fellowships and residencies, in which physicians were required to enucleate eyes as a part of their program.

Meanwhile, the supply of donor tissue—still being transplanted on an emergency basis—was not sufficient, and the list of patients waiting for corneal transplants grew longer. Before 1968, no federal laws existed to address organ, tissue, and eye donation, and laws differed at the state level. To attempt to make the process of organ donation easier—and the same from state to state—the United States Congress enacted the Uniform Anatomical Gift Act in 1968, historic legislation that allowed citizens to declare themselves donors for the first time.[9]

A surgical breakthrough occurred when Richard Troutman integrated the use of the operating microscope during corneal transplants.[10] This instrument became the standard of care for intraocular procedures, providing surgeons with greater magnification capability, but it also created a need for more precise surgical instruments. Troutman miniaturized and angled existing surgical tools to make microsurgery possible and reduce trauma to tissue.

By this time, PK had become the standard procedure for corneal transplants. Lamellar procedures had been tried in the 1950s, but until recently they have had limited success in restoring useful vision and were used primarily as a tectonic procedure to repair perforated corneas and globes. Meanwhile, Stocker[11] reported the importance of the endothelium to corneal hydration while Harris and Nordquist established its role as an active metabolic pump,[12] thus building the body of knowledge that, among other things, would inform a resurgence of interest in lamellar surgery decades later.

The scientific years: 1971–1999

The word "transformative" best describes the impact of this time period on eye banking and on the surgeons who transplanted corneas. The confluence of 3 drivers propelled the field into a new era: (1) *scientific breakthroughs* – a series of advances in corneal preservation that broke new ground and built one upon another; (2) *professionalization of eye banks* – a rapid change from volunteerism to professionalism when eye banks employed executive directors, technical directors, and certified technicians and when medical standards required medical directors to take a more active role in eye banking; and (3) *new laws and regulations* – federal legislation prompting the emergence of a strong leadership able to advocate for the eye banking community.

Scientific breakthroughs

McCarey-Kaufman (M-K) medium. The first significant breakthrough in short-term preservation of donor corneas emerged in the mid-1970s, some 40 years after Filatov's seminal finding. McCarey and Kaufman[13] reported the development of a modified tissue medium (McCarey-Kaufman [M-K] medium) in which human corneas with viable endothelium could be preserved at 4°C for at least 4 days. The finding hinted at the possibility for corneal transplantation to become a scheduled surgery. Wilson and Bourne[7] made note of this milestone in their 1989 major review on corneal preservation, as "this allowed the patient to better plan for the transplant and for the surgery to be performed when a well-trained regular team of operating personnel were available to assist a well-trained surgeon." Corneas stored at 4°C in M-K medium remained thin and clear and could be transported in polystyrene containers with ice. While surgeons largely accepted the method, a preference for transplanting corneas within 48 hours persisted.

Corneal storage media. Meanwhile, Doughman and colleagues[14] at the University of Minnesota, in collaboration with the Minnesota Lions Eye Bank, pursued a line of investigation that would change the

corneal storage paradigm from preventing cell death to extending the viability of the critical endothelial layer. Beginning in the 1970s, they pioneered the use of 34°C organ culture as an attempt to reduce corneal antigenicity and to lengthen the period of time that donor tissue could be stored. Over the next 2 decades, the development of the Minnesota Corneal Storage System enabled the preservation of corneas at 34°C (a temperature comparable to corneas *in vivo*) in sterile, closed containers for at least 35 days. Although reduced antigenicity was never demonstrated, extension of endothelial viability made this medium the first successful long-term donor cornea storage model.

The addition of chondroitin sulfate to organ culture in 1985 also made storage at 4°C possible, eliminating the need for serum, which was required at 34°C.[15] Further improvements to this simpler storage system led to the commercial production of Optisol by Bausch + Lomb,[4] boosting its use among United States eye banks and firmly establishing corneal transplantation as a procedure that could be scheduled. Later enhancements included the addition of the antibiotics gentamycin and streptomycin, producing a medium marketed as Optisol-GS; in recent years the Food and Drug Administration (FDA) began asking the United States eye bank community whether an antifungal agent should be added. Eye banks in the United Kingdom, the Netherlands, Denmark, and France[16] continued to use organ culture for extended preservation of corneas at 34°C; this storage method has the potential to be used in developing countries in which there are shortages of cornea donors.

Specular microscope. Until the 1980s, eye banks evaluated the suitability of donor corneas for transplantation using slit-lamp biomicroscopy. Introduction of the specular microscope and closed-chamber containers to safely hold corneas separated from globes enabled eye bankers to more carefully screen donor tissue.[4] Equipped with a new tool for viewing corneas at the cellular level, eye bank technicians were able for the first time to visualize cell morphology, measure endothelial cell loss, and consistently compare the effects of new storage techniques.[17,18]

Professionalization of eye banks

Eye banking standards. The 1970s saw the proliferation of highly organized eye banks and a technically skilled workforce that could apply new techniques for corneal preservation, including the growing use of Optisol for interim storage of donor tissue and the monitoring of disease transmission. For example, in 1974, the possible transmission of Creutzfeldt-Jakob Disease (CJD) from a donor to a healthy recipient was first reported.[19] Subsequently, the donor was identified as a 55-year-old who died due to clinical symptoms of CJD at a medical center in New York and whose corneas were delivered directly to the center's eye institute, never having passed through an eye bank. Nevertheless, the incident caused great concern within the transplant community and among eye bankers. To ensure the safety of healthy donor tissue, the EBAA adopted stringent quality standards in 1978 that became the EBAA Medical Standards. The act established the organization as the standards-setting agency for eye banking in the United States.[20] These standards continue to be updated semi-annually by the EBAA's Medical Advisory Board, a collaboration of medical and lay professionals that remains unique among professional medical organizations and is characterized by an equitable sharing of power and mutual respect.

The EBAA also launched efforts to standardize eye banking techniques, provided an intensive training course to certify technicians, and began a program for accreditation of eye banks. (These initiatives are more fully described in "The Evolution of Eye Banking in the United States" in this issue.) The organization also initiated scientific symposia that feature original peer-reviewed research papers focused on eye banking techniques and procedures; these sessions are held twice annually in association with EBAA conferences, including one held in conjunction with the Cornea Society.[21]

New laws and regulations

Reimbursement changes. With Frederick Griffith at the helm, a bold move by Medical Eye Bank (MEB) Inc. in Baltimore, Maryland, permanently changed the business model for eye banks in the United States. In 1971, faced with budget constraints, MEB recognized the potential inherent in the passage of the United States entitlement act that established the Medicare program.[6] The field of kidney transplantation had already tapped into the new stream of federal reimbursement for organ processing fees, opening the possibilities for other transplant fields. MEB's Medical Director, John W. Payne, wrote in a 1980 review describing the new directions in eye banking, "Agreements were reached with the local Blue Cross and Medicare officials to accept reasonable fees billed through local hospitals for our services. Several years later, similar arrangements were made in most of the other states where the MEB sent donor tissue. In 1979 the MEB, which previously had depended totally on

fund raising and charity support, derived 75% of its operating budget from fees paid by third-party insurers for processing costs."[6]

Medical examiner laws. With a short-term method to store corneas available using M-K medium, the Maryland eye bank decided to boost its supply of donor tissue by working with medical examiners. A collaboration that included Payne, the state medical examiner, and concerned ophthalmologists advocated for and won passage of landmark state legislation that allowed the immediate removal of corneal tissue from the eyes of cases under the medical director's jurisdiction requiring autopsy—unless the next-of-kin had specifically expressed objections to donation. In essence, this legislation made it unnecessary to obtain consent, and most autopsied individuals could serve as donors.

Similar legislation was passed by 23 states by 1997, each with varying provisions for contacting next-of-kin; collectively, the laws were credited with eye banks receiving 15,527 corneas.[22] (Morticians had already been found to be valuable enucleators, with successful outcomes using corneas for transplantation from the eye tissues they had recovered.[23,24]) These laws have been declared constitutional in the states in which they have been passed, even when they do not contain a clause requiring the medical examiner to make a "good faith" effort to notify next-of-kin.

Presumed and expressed consent. The matter of "presumed consent" is not without controversy,[25] as it typically implies that a person may be considered a donor only if he or she has not declared otherwise. Many members of the transplant community argue that the principle of "gifting" one's eyes (indeed, any organ or tissue) implies either an active decision by the deceased made known through a will, advance directive, donor card (including a driver's license in the United States), or donor registry or else the direct permission of the next-of-kin. When the state intercedes in this principle, thereby removing actual consent, it raises ethical implications, even as proponents of presumed consent legislation —sometimes called "opting-out" legislation—intend to ensure the most equitable distribution of organs, tissues, and eyes. A discussion of the complex medical, legal, and ethical issues surrounding donation and transplantation is beyond the scope of this discussion, especially since they remain unresolved. Many European countries and Singapore have moved toward an opt-out system, while the United States and the United Kingdom operate under a model of expressed, or first-person, consent. Some studies suggest that countries with presumed consent have generally higher rates of donation,[26] yet others dispute that conclusion; a systematic review of studies on the impact of presumed consent legislation from 8 electronic databases, including MEDLINE, found that presumed consent alone is unlikely to explain the variation in organ donation rates between countries with and without presumed consent systems.[27]

Required request law. To further remove barriers to donation, the United States Congress, following the lead of states, enacted in 1987 a revised Uniform Anatomical Gift Act. Among its amendments was one requiring hospitals that accept Medicare reimbursements to notify next-of-kin of the option to donate appropriate organs and tissues or to decline. The impact on the donor supply came to depend on the how effectively hospital personnel, particularly nurses, carried out the provisions in collaboration with donation organizations; the impact of the change on donor pools is unclear, with some institutions originally reporting increases and others no change.[28] In 1997, Doughman[2] reported that the Minnesota Lions Eye Bank experienced a tripling of cornea donations following passage of the law.

In the United States, most states have passed first-consent legislation and established online donor registries. Donate Life America, a nonprofit alliance of national organizations and state teams, reported in 2011 that registrations had passed the 100 million mark (42% of the adult American population). Also in 2011, the EBAA began tracking the number of corneal tissues recovered from donors found on a registry or who had given first-person consent through some other means; nearly 40% of recovered corneas came from such donors (Table 1).[29]

FDA regulations. More than a decade after the EBAA established standards to ensure safety of donor tissue and had begun credentialing eye bank technicians and accrediting eye banks, federal agencies began to impose regulations on eye banks. The FDA proposed a series of regulations during the 1990s that were scientifically inappropriate for corneal tissue, nearly failed to include eye banking in provisions that would have boosted the supply of corneal tissue to eye banks, and came close to changing reimbursement formulas based on erroneous assumptions.[4] In response, leaders in the corneal transplant community increased their efforts to provide the education and expert authority to avert or redirect the more onerous aspects of the regulatory effort, acquiring the experience and expertise to successfully represent the new field in the face of regulatory threats.

Table 1. Eye Banking Statistics Reported by U.S. Eye Banks: Donations, Recoveries, and Tissues Suitable for Transplantation

Donations	2011	2010	2009	2008	2007
Number of Eye Banks Reporting	79	79	78	77	76
Total Whole Globes and Corneas Donated	114,348	110,630	107,289	94,864	82,741
Total Number of Donors	57,835	55,913	53,786	47,776	41,672

Death Referrals	2011	2010
Total Death Referrals	745,405	821,011
Death referrals determined eligible	170,388	216,653
Tissue Recoveries		
Total Donors	57,835	55,913
Donors recovered not found on donor registry or known to have first person consent	35,144	-
Donors recovered found on donor registry or known to have first person consent	22,691	-
Eyes or Corneas Recovered with Intent for Surgical Use	101,533	98,053
Eyes or Corneas Recovered for Other Uses	12,815	12,577

In 2011, the consent type is measured for the first time using the same measurement method used by Donate Life America. Eye bank policies around the country vary with respect to applying donor registry documentation as consent. When interpreting this data, it is important to note that six eye banks reported that none of their donors were found on a donor registry. This data does not represent the number of donors recovered using donor registry documentation as *consent to recover.*

Transformation of the industry

As the 20th century drew to a close, eye banking and corneal transplantation professionals had achieved a successful collaboration that made PK the most common and successful form of solid tissue transplantation.[30] In a comprehensive review published in 2000, Chu[4] named 3 major milestone achievements in the history of eye banking:

1. Corneal transplants could be scheduled; surgery is no longer considered an emergency. Chu credited improved corneal storage, better instrumentation, "remarkably improved" procurement programs, and a network of eye banks characterized by efficient communication and transportation.
2. Surgeons could be assured of the quality and safety of corneal tissue. Chu cited the EBAA's history of promoting training and certification programs for eye bank technicians, preparing written policy and procedure manuals for operating eye banks, accreditation of individual eye banks, and vigilance in evaluating and revising its medical standards document.
3. The eye banking community proved that it could work with federal regulatory agencies in a constructive manner to establish proper oversight.

The modern era: 2000–present

By 2000, more than 30,000 corneal transplants a year were being performed within the United States, with PK making up the majority of the procedures, according to records kept by the EBAA.[31] But full-thickness corneal transplants, while capable of restoring vision, had limitations, including increased risk of postoperative complications such as wound dehiscence with blunt trauma, suture-related infections, disabling astigmatism, and graft rejection. Lamellar procedures to replace diseased *layers* of the recipient's cornea, including the endothelial layer, rather than the entire cornea, had been attempted in the 1950s[32] and had continued to be of interest in Europe; however, they were technically difficult, relied on sutures, and did not have good long-term outcomes. The first decade of the new century has been notable for a series of advances in surgical techniques that made use of emerging technology, improved instrumentation, and deepening knowledge regarding the structural, genetic, and molecular makeup of corneas. Characteristically, entrepreneurial eye banks have ensured that skilled technicians can provide surgeons a safe supply of precut tissues to keep pace with the demand for these new precise procedures, which constitute various approaches to lamellar keratoplasties.

Lamellar corneal surgery

Posterior lamellar corneal surgery. The introduction of posterior lamellar keratoplasty (PLK) by Melles et al[33] in the Netherlands in 1998 has been a significant advance in corneal surgery. Indeed, for many surgeons, it ranks as highly as the discovery of the viability of cadaver tissue as a source for donor tissue, the operating microscope, and storage media allowing elective scheduling of corneal transplants. PLK uses an air bubble to support the posterior lamellar graft, thus allowing the new tissue to adhere to the graft recipient's tissue, avoiding a through-and-through, 360-degree, full-thickness corneal wound, which, as previously noted, requires multiple sutures, yields unpredictable visual results, and always presents a risk for wound rupture with trauma. The evolving techniques that resulted are briefly discussed below.

Deep lamellar endothelial keratoplasty. Terry and Ousley[34] performed the first endothelial keratoplasty in the United States in 2000; they called it deep lamellar endothelial keratoplasty (DLEK) and

also used an air bubble to support the posterior lamellar graft, as do all other posterior lamellar techniques. Both PLK and DLEK procedures led to faster visual rehabilitation than traditional PK and avoided many of its complications, although the techniques were technically difficult,[35] particularly posterior trephination of the recipient cornea.

Descemet stripping endothelial keratoplasty. In 2004, Melles et al[36] refined the DLEK technique by peeling the recipient Descemet membrane and endothelial layer, exposing a smooth stromal posterior bed on which to place the posterior lamellar graft. The technique, Descemet stripping endothelial keratoplasty (DSEK), was technically simpler than DLEK and required a smaller incision.[37] Additionally, visual rehabilitation time proved to be shorter.

Descemet stripping automated endothelial keratoplasty. In 2006, Gorovoy[38] produced a smoother donor surface using the microkeratome to dissect donor tissue, a technique he called Descemet stripping automated endothelial keratoplasty (DSAEK). Visual recovery following DSAEK has been shown to be faster (weeks) compared with PK (months).[35] Use of the microkeratome in the operating room, however, lengthened the time in surgery, involved the use of expensive equipment, and required the surgeon to have specialized skills. The drawbacks presented an opportunity for eye banks to streamline the process by training technicians to prepare precut tissue specifically for endothelial keratoplasty (EK). A retrospective study of 913 corneal tissues prepared by trained technicians in Tennessee during a 12-month period between 2007 and 2008 showed a successful preparation rate of 98.5%.[39] In a study from Iowa, precut tissue was found to improve safety while increasing surgeon efficiency.[40] Lamellar dissection of donor tissue is also possible with the more expensive femtosecond laser, which can produce the most precise dissection depths; however, the femtosecond's dissection plane is not as smooth as the microkeratome cut.[30] Due to the higher costs and unproven outcomes associated with use of the laser for corneal surgery,[41] as well as unresolved concerns expressed by surgeons,[42] the femtosecond laser has so far seen limited use for corneal transplantation.

Descemet membrane endothelial keratoplasty. In an attempt to improve visual outcomes, Melles et al[43] reported successfully transplanting bare endothelium on a recipient Descemet membrane in 2006. The technique, called Descemet membrane endothelial keratoplasty (DMEK), holds great promise if a number of technical challenges can be overcome. In their review on EK, Price and Price[30] noted, "The technique provided superior visual outcomes but raised the bar in terms of difficulty, both in harvesting donor endothelium and Descemet membrane as well as implanting it into the eye in the correct orientation with minimal trauma."

Anterior lamellar corneal surgery. The use of the microkeratome for posterior lamellar procedures has been adapted for anterior lamellar keratoplasty, which also is becoming an alternative to PK.

Deep anterior lamellar keratoplasty. For individuals with healthy endothelium and Descemet membrane layers but whose vision has been impaired by keratoconus, stromal dystrophies, or scarring, deep anterior lamellar keratoplasty (DALK) shows promise. In 2002, Anwar and Teichmann[44] reported a technique using a "big bubble" (of air) to separate the Descemet layer from the deep corneal stroma. DALK patients retain their own endothelium and Descemet membrane; only the anterior portion of the cornea is transplanted. DALK requires more time in surgery than other procedures and is technically challenging; however, it appears to result in less postoperative endothelial cell loss.[45] A potential disadvantage to this technique is that, as with PK, it requires multiple sutures along with their potential complications.

Keratolimbal allograft transplantation

The success of a corneal transplant depends upon obtaining healthy donor tissue. For posterior corneal disease, the endothelium is critical and is not replaced by the recipient. However, for any transplant to be truly successful, the surface epithelial cells must be replaced by the recipient's epithelial cells. These cells come from the stem cells located at the ocular limbus. The causes of stem cell deficiency include chemical burns, thermal burns, aniridia, Stevens-Johnson syndrome, ocular pemphigoid, chronic contact lens wear and trauma, and multiple surgeries involving the limbus. Although the endothelium is healthy, these conditions will not allow successful corneal transplantation unless the stem cell deficiency is corrected, allowing the cornea to regain its normal surface.

A procedure developed and popularized by Holland,[46,47] as well as others, recovers stem cell tissue from the limbus of healthy donors and transplants them directly to that of the recipient after removal of diseased stem cells. Known as keratolimbal allograft transplantation (KLA), the procedure requires systemic immune suppression since the grafted tissue does not share the immune privilege afforded by a central corneal graft. Therefore, the patient must be healthy enough to tolerate the regimen, although the level of immunosuppression can be justified for this

group of patients, as they are highly dependent on the survival of their grafts for functional vision.[48] KLA has been able to restore useful vision for patients with severe ocular surface disease who have no other options.

Recently, eye banks have explored the possibility of conserving donor tissue by splitting a single cornea into 2 sections, the first consisting of the Descemet membrane and endothelium for a patient requiring DMEK and the other providing the epithelium and stroma for a patient undergoing DALK on the same day. In 2011, Heindl et al[49] published promising results using this strategy. This technique could prove especially useful for regions in which the need for corneal tissue is greater than the supply.

Innovations notwithstanding and yet to come, PK still accounts for 53.5% of corneal transplants reported by United States eye banks, according to the EBAA's most recent statistical report[29] covering the year 2011 (Table 2). However, a preference for EK procedures is clearly trending. The number of penetrating grafts for corneal disease in the United States (figures not shown in Table 2) decreased for the sixth straight year, from 42,063 in 2005 to 21,620 in 2011. The number of EK procedures rose to 21,555, a 12.5% increase over 2010 and 18.3% over 2009. EK has become the surgical treatment of choice for corneal endothelial failure and is expected to exceed the number of PK procedures within the United States in 2012.[29]

The unknown future: present–?

This trend appears to be continuing with the introduction of Descemet membrane automated endothelial keratoplasty (DMAEK).[50,51] Furthermore, rapidly expanding research into surgical and nonsurgical techniques involving artificial corneas, xenotransplantation, collagen cross-linking, amniotic membranes, stem cells, genetic engineering, or cutting-edge pharmaceuticals such as vaccines and eye drops promises even more dynamic advances for treating corneal patients, some of which may preclude the need for surgery as we now know it. These innovations will inevitably have a dramatic impact on eye banking.

Table 2. Eye Banking Statistics Reported by U.S. Banks: Distribution of Tissues

Distribution	2011	2010	2009	2008	2007
Corneal Grafts Total	67,590	59,271	59,784	52,487	50,122
Penetrating Keratoplasty	36,144	21,970	23,269	32,524	34,806
Anterior Lamellar Keratoplasty	1778	1,041	774	1,072	950
Endothelial Keratoplasty	23,287	19,159	18,221	17,468	14,159
Keratolimbal Allograft	95	130	120	173	207
Keratoprosthesis (K-Pro)	358	342	222	-	-
Tectonic	-	-	-	1,250	-
Glaucoma Shunt Patch or other non-keratoplasty use	604	-	-	-	-
Other keratoplasty (experimental surgery)	14	-	-	-	-
Unknown or Unspecified	2,223	-	-	-	-
Sclera	5,507	6,746	7,634	5,374	4,698
Long-Term Preserved Corneas	4,409	3,518	2,053	989	-
Keratoplasty	276	-	-	-	-
Glaucoma Shunt Patching	3,802	-	-	-	-
Other Surgical Uses	331	-	-	-	-
Research	19,230	17,260	14,547	13,730	13,824
Training	6,940	5,726	7,113	5,385	4,801

The highlighted numbers reflect tissues distributed and used within the U.S. only. Data for tissue distributed internationally in these years did not include by surgery type. Data from previous years included U.S. and international distribution of tissues.

In 2010, Corneal Grafts Total did not include long-term preserved corneal tissue. In 2011 and progressing, long-term preserved corneal tissue is included in the total.

ARE WE PREPARED FOR WHAT'S AHEAD?

In reviewing the last 100 years of milestones in eye banking and corneal transplantation, 5 strengths emerge that distinguish the community. These can be summarized as follows:

1. Commitment to the highest standards. The internal drive of eye banking and medical professionals to hold ourselves to the highest possible standards is second to none and imbues the field with authority.

2. Cooperation. Mutual trust and respect between medical professionals and eye bankers have fostered the productivity to which private enterprises aspire.

3. Innovation and application. Our field has a long and rich tradition of innovating and moving advances into practice for the benefit of patients.

4. Global mindset. Long before "globalization" became a buzzword, eye bankers and medical professionals were sharing information,

discoveries, and resources across borders while remaining realistic about our capabilities.

5. Leadership and advocacy. Challenges and threats have galvanized the field, allowing our leaders to speak with credible authority.

These strengths provided a strong foundation upon which our field could mature, and they will be profoundly needed as we enter the next era.

For all of the progress of the past century, the fact remains that millions of men, women, and children worldwide experience blindness from corneal disease or injury, the largest proportion of whom live in countries with developing economies. In one estimate of the number of blind people in the world—some 50 million—corneal diseases ranked as the second most important cause.[52] And of an estimated 1.4 million children globally who are blind, corneal pathology was reported to be the cause for 20% of them.[53] How do we bring the benefits of cornea transplantation to a greater proportion of patients, especially in these times of economic upheavals, not to mention unprecedented demographic, socioeconomic, geopolitical, biological, regulatory, technological, cultural, and ethical challenges?

The intent of this section is to raise the important questions that must be addressed and to point to any strengths and assets available to the eye banking community as we attempt to answer these questions. Every effort has been made to present the challenges ahead from an international perspective wherever possible and when verifiable information has been available. That said, examples from the United States, as they are familiar to the author, play a large role in the following discussion.

Healthcare economics

The complexity of healthcare economics is beyond the scope of this review, although the topic can be ignored only at our own risk. Internationally, the World Health Organization (WHO) is advocating for universal healthcare coverage in all countries.[54] In the United States, such a goal gained traction in the healthcare reform measures passed in March 2010 ("Obamacare"). These reforms have been a lightning rod for political opposition, with a sizable number of Congressional representatives elected in 2010 having campaigned on overturning the measures. The current political climate, characterized by intense opposition to federal spending (i.e., the Tea Party movement) and mounting frustration with economic disparities (i.e., the Occupy Wall Street movement), is bringing more and more scrutiny to how revenue in the United States is generated and spent, and it is safe to say that the American healthcare system will continue to be in the political crosshairs for a long time to come.

At the same time, the fragility of the current economic recovery from an unprecedented period of economic volatility, unemployment, mortgage industry collapse, and sovereign debt crises leaves few untouched financially. Who in the long run will be able to afford to receive—or deliver—healthcare is an open question. What will be the impact of the worldwide economic crisis, the pace of economic recovery, unchecked healthcare costs, and fluctuations in the political will to fund (or not fund) breakthrough research? Who will be able to afford new technology, new drugs, and new procedures in the years to come? How will the business of eye banking and the profession of ophthalmology change in the next 5 or 10 years?

Government efforts to impose regulations in the field of cornea transplantation warrant close scrutiny. Regulations can increase costs, particularly administrative and reporting costs, without improving quality. Legislation that increases the availability of donor tissue has merits, as do training programs that enhance the ability of hospital and hospice staff to encourage families to allow donation of loved ones' corneas.

Demographic trends

The situation is further complicated by an aging population, certainly within the United States. By 2030, the proportion of the American population in the working age group (ages 21–64) will drop to 55% from 60% in 2010.[55] The numbers of Medicare recipients will increase commensurately, driving up costs, unless politically unpopular measures to the contrary are taken. What affects Medicare coverage in the United States inevitably affects reimbursement at large. Whether or not Medicare covers corneal transplantation procedures in the future, federal spending on healthcare is a powerful force in the United States, influencing everything from funding for research, specialties selected, the balance of preventive care vs. treatment, which pharmaceutical advances are developed, and more.

The aging of the baby boomers could also have an impact on the donor pool. For 2011, the EBAA[29] reported the donation of 114,348 whole globes and corneas to United States eye banks, compared with 110,630 in 2010 and 107,289 in 2009; this was the third year in a row that more than 100,000 recoveries were made in a single year. Fully 70% of donors were between the ages of 51 and 80 years old at the time of their death. In 2011, the "leading edge" of the baby boomers entered the 65- to 69-year-old age

group, according to the Census Bureau.[55] This same age group forms a portion of the age category (ages 61–70) that accounted for 32% of cornea donors in 2011.[29]

As the bulge of baby boomers advances, the Census Bureau projects that by 2030, nearly 1 in 5 Americans will be age 65 or older. Will they be donors, recipients, or both? Eye banks would be well advised to (1) ensure this population group is well informed about their ability to donate corneas, (2) encourage agreement about a donor's wishes among family members, who are often conflicted and may refuse to donate tissue if they are unsure of a relative's wishes, and (3) work collaboratively with professionals involved in the donation process such as healthcare professionals, medical examiners, and funeral directors.

Corneal surgeons and eye bank professionals should continue to examine the data regarding the viability of transplanting older corneas,[56,57] particularly in light of evidence suggesting that surgeons continue to show a preference for corneas from younger donors. A 2008 report[58] from the Cornea Donor Study Investigator Group noted that whether donor age should be used to determine suitability of a cornea for transplantation has been an area of considerable controversy among corneal surgeons in the United States, and it analyzed whether graft survival over a 5-year period using corneal tissue from donors older than 65 years is similar to graft survival using corneas from younger donors. The primary finding was that clear graft rates at 5 years were the same for both older and younger donors (86%). A recently released report from the same study group retrospectively evaluated whether these findings had led to changes in transplantation of corneas from older donors and concluded there had been a modest overall increase in the donor age of corneas transplanted in the United States from 1998 to 2009; the authors argue for wider acceptance of older tissue.[59] Continuing to build the body of knowledge around this question should be a priority.

Another factor that will limit the donor pool is the prevalence of donors who have undergone laser *in situ* keratomileusis (LASIK), a commonly performed refractive surgery, which restricts the suitability of corneas for use in certain types of transplant procedures. LASIK correction for myopia, for example, flattens the surface of the cornea and thins the stroma. Thus, corneas that have undergone LASIK are unsuitable for PK due to potential splitting of the corneas during surgery; even if corneas do not split, flattening of the anterior surface creates unpredictable visual results. LASIK-treated corneas also cannot be used for DALK or artificial corneas. However, they can be used for endothelial lamellar keratoplasty, KLA, or patch grafts.

Unfortunately, refractive procedures cannot always be detected in donor eyes, and families may not remember or know whether the donor had LASIK.[4] The EBAA 2011 Statistical Report notes that LASIK is expected to have an impact on the donor population, although at this time a large percentage of LASIK patients are living.[29] If LASIK continues to grow in popularity and affordability, so will its impact on the donor supply. As yet unanticipated innovations in corneal surgery may have similar inhibitory impacts on the donor supply.

Add to the demographic situation the fact that, due to a lack of financial support, there has been no appreciable expansion in ophthalmology residencies for years. A highly discussed report from the RAND Corporation in 1998[60] concluded that ophthalmologists were in "oversupply," but did not take the baby boomers into account. Will there be enough physicians trained in corneal transplantation—and specifically in eye banking—to meet the needs of greater demand? All of the advances in surgical techniques will not help if there are too few surgeons to use them. Efforts need to be undertaken to (1) ensure funding to train physicians and (2) recruit highly talented students into the specialty, particularly those students interested in the kind of collaboration with eye bank professionals that has made the field so strong.

Diversity of beliefs

Immigration issues within the United States and elsewhere have been growing more contentious in recent years, with some factions arguing that a country is strengthened by a diversity of beliefs and cultural practices and other voices expressing concern about refugees and undocumented workers taking jobs that might otherwise go to native citizens. Europe has repeatedly grappled with the issue, watching violence erupt when such tensions heated up. Any resolution of immigration matters may be a long time in coming. Meanwhile, it would be wise for eye banking and medical professionals to (1) be familiar with the variety of groups and related belief systems comprising the population of their geographic region and (2) help professionals who are securing donation agreements when known concerns about donation are due to the influence of faith-based, ethnic, or cultural groups.

It is critical to guard against misunderstanding or misinterpreting convictions held by individuals with different worldviews. In South Texas, for example, *The Texas Tribune*[61] featured a report noting that a

common practice among the large Hispanic population in the area is to honor the deceased and their families with open-casket viewing. A barrier to organ and tissue donation has been a deeply imbedded cultural fear that donation will render a body unsuitable for viewing. To boost donation rates, the federally funded Texas Organ Alliance determined its target audience to be 18- to 36-year-olds, who were perceived to be young enough to entertain a fresh point of view.

Donate Life America has taken steps to raise awareness about such multicultural issues related to donation.[62] Its primary goals are to facilitate high-performing donor registries, develop and execute multimedia donor education programs, and motivate Americans to register as organ, eye, and tissue donors. In May 2011, Donate Life partnered with Facebook in an effort to dramatically increase the number of Americans who officially designate themselves as donors.

On the other side of the planet, Yew et al[63] found that 67% of participants in randomly sampled households in Singapore were willing to donate their corneas. Chinese ethnicity and religious affiliation with Christianity, Hinduism, or no religion were associated with increased willingness to donate. Respondents least willing to donate were Malays and Muslims. Among respondents unwilling to donate, 73.2% said they believed it was important for the body to remain intact after death.

Shaheen and Souqiyyeh[64] addressed Islamic views and specific barriers to donation among Muslim donors in Saudi Arabia. Although selling organs is forbidden, donating to genetically related individuals or spouses is permitted. The authors said obstacles to donation include (1) inadequate numbers of emergency rooms, paramedics, and neurologists, (2) late reporting of deaths for fear of uncovering medical mistakes, and (3) pervasive lack of awareness about brain death.

Many religious groups support organ and tissue donation so long as it does not hasten the death of the donor. Buddhism, for example, teaches that, in his previous lives, the Buddha repeatedly gave his body or parts of his flesh to others.[65] Sri Lanka, where about 70% of the population is Buddhist, has become an exporter of corneas; many Sri Lankans believe that surrendering their eyes at death completes an act of "dana," or giving, which helps them to be reincarnated into a better life.[66] In South Korea, a celebrated Roman Catholic cardinal who died in 2009 donated his eyes; subsequent media coverage was shown to increase cornea donation, according to a recent modeling analysis, which concluded that religious leaders who achieve celebrity status can positively affect public health.[67]

A summary of the views on donation and transplantation from prominent as well as lesser-known religious groups can be found in *Organ and Tissue Donation: A Reference Manual for Clergy,* developed for transplant professionals and clergy who work in the hospital, parish, clinic, or classroom setting.[68] A recent report from the United Kingdom provides an overview of key issues related to death rituals and religious faiths and how they impact donation, with the goal to help procurement staff deal more effectively with recently bereaved families.[69] A WHO report released in October 2003 mentioned religious, cultural, and ethnic factors that influence corneal transplantation rates in African, Asian, and Latin American countries and at the same time examined more "scientific" issues such as the infrastructure and paucity of trainer personnel, oversight mechanisms, and lack of legislation and research.[70]

Natural and man-made disasters

Clearly, the challenges ahead will vary by culture and by region, although we must also keep in mind that we live and work in a world of unprecedented interconnectedness. Moreover, economies throughout the world are linked, and volatility and uncertainties in one region will, sooner or later, touch another. While advanced surgical techniques may be more accessible in countries with developed economies, for example, such surgeries depend on the availability of pharmaceuticals with ingredients increasingly produced in countries with developing economies. All it takes to interrupt a precarious supply chain is a natural disaster, civil unrest, or even the discovery of contamination of a critical ingredient. This occurred in 2008 when the FDA[71] alerted healthcare providers of the recall of the critical anticoagulant heparin, most of which was produced in China. Ultimately, a reduced heparin supply became dire enough that the United States General Accountability Office (GAO) was asked to investigate the crisis. In its report to Congress, the GAO pointed out that the FDA had "faced some limitations in its efforts to inspect heparin firms in China and collaborate internationally."[72]

An example from the eye banking community occurred when Bausch + Lomb ran low on corneal viewing chambers (CVCs) and eye banks had to resort to using vials to store corneal tissue, which had become an outdated practice given the preference to use CVCs to measure corneal layer thickness after precutting. The situation points out how reliant eye banks are on very few suppliers for key products that are unique and necessary for eye banking. Yet to control

spending, healthcare facilities (like all big industries) have moved away from stockpiling regularly used supplies (e.g., pharmaceuticals, electronics, infection control equipment, even food).

As a result of globalization, just-in-time ordering[73,74] keeps inventory costs down and is generally more efficient. However, this trend puts critical supplies needed for surgery in jeopardy, as what have become "long and thin" supply chains could be easily interrupted by disasters brought on by nature, human activity, or accidents. The 2009 H1N1 influenza pandemic, for example, created a worldwide shortage of N-95 respirators and surgical masks. A more devastating pandemic could affect the supply of electrical power, making rationing necessary.[75] The 2011 earthquake, tsunami, and resulting nuclear disaster in Japan brought manufacturing of some cars to a standstill. Intentional acts of terrorism, such as the 9/11 disaster, stopped air transport for days. The impact of disasters on elective surgeries such as corneal transplants could be chilling.

Ethical dilemmas

As advances in gene therapy, xenotransplantation, and stem cell use continue, the eye banking community will encounter ethical concerns that have yet to rise to a contentious level. Additionally, as cost-control pressures squeeze healthcare delivery further, rationing of care may become an increasingly important issue, especially as accelerating demographic changes drive up utilization rates. The growth in medical tourism also poses ethical concerns, as patients from affluent countries travel to countries with emerging markets that offer modernized healthcare facilities at lower cost. Some observers question whether it is fair or appropriate for wealthier patients to save money by utilizing medical resources that should be directed toward a country's native population.

DISCUSSION

The numerous advances in corneal transplantation and eye banking over the last century have produced—for most developed countries—a plentiful supply of safe donor tissue, the ability to schedule surgery rather than react on an emergency basis, and new and better tools. However, those advances have yet to reach all of the patients who could benefit from them, and the humanitarian goal to deliver safe corneas and ever more sophisticated surgical techniques to far-flung regions of the world is hampered by 21st century forces that threaten to restrict access to care and limit the donor pool.

Are we prepared for the complex challenges ahead? They seem daunting and unpredictable, with permutations few of us might even be able to imagine. The answers surely lie in the traditional strengths of our community: commitment to the highest standards, innovation, cooperation, leadership, and advocacy. As this discussion hopes to make clear, we must further develop our global mindset, and we must develop it aggressively and quickly.

While eye banking and medical professionals, long united in the pursuit of high quality and accessibility, should build on that history of collaboration, taking steps to preserve and protect it, it is likely that each eye bank will prepare for our uncertain future in its own way, depending on its size and location. But make no mistake: each eye bank must prepare. Perhaps the launch of the *International Journal of Eye Banking* will provide eye banking and medical professionals with a valuable forum for discovering and discussing cost-effective, regionally useful solutions, not only over time but even—through electronic media—in real time. Our goal as a community should be to tackle the compelling questions head on, not shirking from them but seeking profoundly new avenues to restore eyesight whenever and wherever we can.

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