Clinical and Experimental Ophthalmology 2005; **33**: 642–657

Perspective

Centennial review of corneal transplantation

S Louise Moffatt BSc, Victoria A Cartwright BA and Thomas H Stumpf PhD FRCOphth
Department of Ophthalmology, University of Auckland, Auckland, New Zealand

Abstract

One hundred years ago, on 7 December 1905, Dr Eduard Zirm performed the world's first successful human corneal transplant. This significant milestone was achieved only after many decades of unsuccessful trial and error; however, it did not lead to relatively 'routine' keratoplasty success for several more decades. The idea of replacing an opaque cornea had been suggested for centuries, and had stimulated theoretical approaches to the problem by many esteemed physicians throughout history. However, little practical progress was made in the ultimate realization of the dream until the 19th century when pioneering surgeons pursued extensive studies in relation to both animal and human 'keratoplasty'. Clinical progress and scientific insight developed slowly, and it was ultimately due to parallel advances in medicine such as anaesthesia and antisepsis that Zirm's success was finally achieved. Key concepts were enshrined such as the use of fresh tissue from the same species, careful placement and handling of tissue, and the development of specialized instrumentation such as the circular trephine. In the latter half of the 20th century, many 'masters' of corneal surgery evolved significant refinements in technique and instrumentation with the development of corticosteroids, antibiotics, surgical microscopes, improved trephines, viscoelastics and suture materials, that enable this delicate procedure to be routinely performed with the prospect of success. There are still limitations to corneal transplantation, and corneal allograft rejection still poses the greatest challenge to the modern corneal surgeon. In the foreseeable future it may be in the laboratory, rather than the theatre, that further milestones will be achieved. This review aims to highlight the significant milestones in the rich history of corneal transplantation, and to pay tribute to the many inspired and dedicated individuals involved in the development of keratoplasty to a point where the procedure is now a standard tool in the repertoire of ophthalmic surgery and more than a million people have enjoyed restoration of useful sight.

Key words: cornea, history, keratoplasty, review, transplant.

Introduction

> '. . . Eduard Konrad Zirm produced, after decades of stellar theory but mediocre clinical results, the first truly successful graft: a small but brilliant torch to inspire his successors.'[1]

One hundred years ago, on 7 December 1905, Czech ophthalmologist Dr Eduard Zirm finally achieved success where those before him had failed, an event that was the culmination of centuries of theories and experimentation. He reported the world's first successful corneal transplant using human tissue that remained clear and functional. There is no doubt that this milestone was significant, and worthy of celebration in this Centennial year, but both before and after this event, the history of corneal transplantation provides one of the most enthralling dramas in medicine. Although a review can only highlight the most significant breakthroughs and the major players, the rich story of the trials and tribulations of keratoplasty serves to inspire and amaze us even today. Indeed, the contemporary field of keratoplasty is the culmination of novel ideas, perseverance, experimentation and therapies that have evolved over more than 200 years and continue to evolve today.[1] In-depth historical reviews have already been thoroughly and elegantly written by others and, where appropriate, reference is made to these.[1–5] This review primarily aims to highlight and pay tribute to the insight and skills of the surgeons, scientists and 'eye bankers' involved in the development of corneal transplantation.

In the beginning: ideas and inspiration

The earliest written references to transplantation (of skin and corneas) can be found in Egyptian manuscripts dating from around 2000 BC. Blindness from corneal scars and infection due to trachoma, smallpox, staphyloma or injury had been known since the earliest times; however, treatments for cor-

■ *Correspondence:* Ms Louise Moffatt, Department of Ophthalmology, University of Auckland, Private Bag 92019, Auckland, New Zealand. Email: l.moffatt@auckland.ac.nz

neal disorders involved the topical application of elaborate mixtures of exotic ingredients and were part of a complex medical belief system involving religious omens, spirits and healing rituals. One common treatment involved rubbing soot onto the eye as a 'cure' for corneal scarring.

Hippocrates (BC 460–375), the father of medicine, described ulcers and scars of the 'transparent membrane', but it was the Greek physician Galen (AD 130–200), the founder of experimental physiology, who first suggested the concept of restoring the transparency of an opaque cornea (Fig. 1). He also advocated '*abrasio corneae*' (superficial keratectomy) by tattooing corneal scars using 'copper sulphate reduced with nutgall' to achieve a better cosmesis. There was, however, limited surgical knowledge and no mention made of 'transplantation' as a therapeutic treatment.[2,4]

In medieval times, no significant surgical advances were made in respect to the cornea, although the concept of ocular transplantation was promulgated through allegory and legend. References to 'eye transplants' were made with the mythical restoration of new eyes to St Lucy (Fig. 2), and, less miraculously, with the feline eye transplant of the army surgeon in Grimm's fairy tale. Sir Hans Sloane, a distinguished English physician, described the use of ointments to 'heal' scarring and assuage pain, with ingredients such as viper's lard, aloe and zinc or iron oxide. However, very little progress was made in the treatment of corneal disorders until the 18th century when interest in corneal pathology was awakened, including the pioneering work of Antonie van Leeuwenhoek (1632–1723) and his microscopic observations of the cornea.

Nonetheless, despite this new enlightenment, Galen's concept of *abrasio corneae* was still pursued in the 18th century. Indeed, in 1775, some 30 years after the introduction of extracapsular cataract surgery, Robert Mead wrote: 'The use of equal parts of powdered glass and sugar levigated into an impalpable powder, put into the eye every day gradually absterges and wears off the spot by its inciting quality'.[2] It was only in the latter half of the 18th century that the idea of completely replacing the dysfunctional cornea began to gain support.

Erasmus Darwin (1731–1802), grandfather of Charles Darwin, first suggested the removal (trephination) of an opaque cornea in 1760: 'Could not a small piece of cornea be cut out by a kind of trephine about the size of a thick bristle, or a small crow quill, and would it not heal with a transparent scar? . . . If the scar should heal without losing its transparency, many blind people might be made to see tolerably well by this slight and not painful operation. As an experiment, I wish strongly to recommend some ingenious surgeon or oculist.'[6]

Guillaume Pellier de Quengsy (1750–1835), a distinguished cataract surgeon, published the first monograph devoted to ophthalmic surgery in 1789.[7] It contained the earliest description of a method of treating scarred corneas by 'keratoprosthesis'. The artificial cornea was suggested to be made of glass placed in a silver ring and stitched to the sclera with cotton thread. The book contains illustrations of the materials and technique, but it is highly doubtful de Quengsy ever attempted this procedure (Fig. 3).

In the late 1700s, many eminent ophthalmologists in Europe described an alternative approach to corneal blindness using sclerotomy techniques, attempting to create a scleral 'window' through which light rays could pass to the inner eye. The sclera was excised and covered with a conjunctival flap. However, in both animals and humans, the scleral window typically closed with an opaque scar, and the technique was largely abandoned.[2]

The cornea became the chosen tissue for early pathologists to study the fundamental processes of inflammation and

Figure 1. Galen (left) and Hippocrates (right). Reproduced with permission from Albert and Edwards.[2]

Figure 2. St Lucy – patron saint of sight and sufferers from eye diseases.

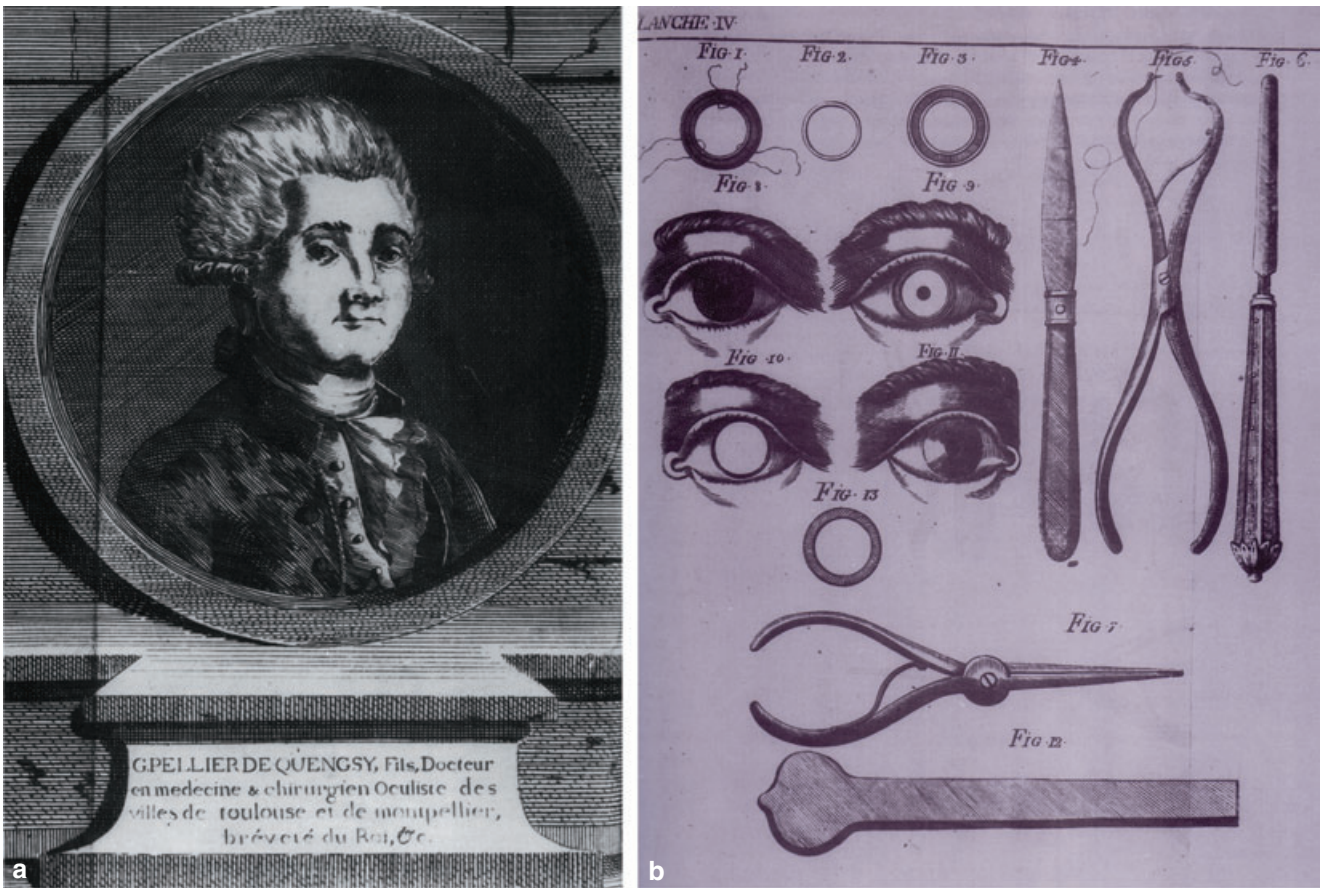

Figure 3. (a) Guillaume Pellier de Quengsy and (b) a sketch of the proposed keratoprosthesis and instruments.

repair. However, despite earlier suggestions of theoretical approaches, corneal transplantation did not begin in earnest until the 19th century. The impetus for this renewed interest was the great increase in corneal disease and blindness caused by smallpox, Egyptian ophthalmia (trachoma) and eye trauma from the Napoleonic wars.[4]

The 19th century: experimentation and frustration

In 1813 Karl Himly (1772–1837) first suggested the replacement of opaque animal corneas with transparent corneas from other animals. However, it was Franz Riesinger (1768–1855), a student of Himly, who was the first to propose replacing opaque human corneas with transparent animal corneas in 1824.[8] He had witnessed an attempt at skin grafting in England, and said: 'This case gave me excellent encouragement to attempt similar experiments with the cornea'.[1] He performed experiments in rabbits in which he excised the host cornea with a cataract knife and scissors and sutured in place a corneal graft. Although healing occurred, none of the corneas remained clear. Riesinger coined the term 'keratoplasty'.

Reisinger's report attracted the attention of several ophthalmic surgeons who undertook further animal trials to study techniques, unfortunately, the outcome of most of this work was failure due to corneal oedema or panophthalmitis.[3] Notable among these surgeons was Johann Dieffenbach (1792–1847), the founder of plastic surgery and the first to perform strabismus surgery. He attempted to replace the entire cornea in many species of animals by suturing the donor tissue to the conjunctiva. However, all the grafts contracted or sloughed off, leading him to conclude in 1831 that keratoplasty was simply 'an audacious fantasy'.[9] However, an event of considerable serendipity and importance occurred a few years later. Samuel Bigger was an Irish surgeon interested in blindness from staphyloma. On his travels, he was held captive for ransom by Bedouins in Africa, where, in 1837, he performed the first reported successful penetrating allograft in animals – on a pet gazelle with corneal scarring. He subsequently noted: 'The cornea was taken from another animal of the same species brought in wounded but not quite dead; adhesion took place and ten days after the operation, the animal gave unequivocal signs of vision, and the upper part of the transplanted cornea remained perfectly transparent.'[10]

His success did much to rekindle the dwindling hope that optically clear corneal grafts might be achieved. Richard Sharp Kissam, following Bigger's promising report, attempted to transplant an animal cornea into a human eye

in New York in 1838 (reported in 1844).[11] Because of the difficulties encountered with the penetrating procedure, he recommended replacing only the anterior layers, hence the advent of the lamellar technique. Without anaesthesia, he transplanted a portion of the cornea of a pig into the eye of a young man, practically blind from leucomatous cornea. He used a Beer's knife to remove a portion of the patient's cornea and attach the animal's cornea by means of two sutures at the three and nine o'clock positions. Vision improved immediately, but the cornea became opaque within 2 weeks, and within a month the graft was absorbed.

Thus, the promise of the first decades of the 19th century gave way to despair, as transplanted corneas invariably became infected and opaque, and proponents failed to realize the importance of allograft compared with xenograft tissue. However, in 1830, the Medical Faculty of the University of Munich offered a prize for the best work on keratoplasty, which served to stimulate much of the experimentation that followed over the next decades. Awareness developed of the importance of careful handling, placement and suturing of tissue. Developments favourable to success then occurred in collateral branches of surgery. Most significantly, in 1846 and 1847, ether and chloroform anaesthesia were introduced, followed two decades later by Lister's principles of antiseptic surgery, both improving the prospects for successful corneal transplantation.[2]

Phillip Franz von Walther (1782–1849), a distinguished Professor of Surgery in Munich, having pursued penetrating keratoplasty without success, recommended excision of the anterior layers only, with the deeper layers and Descemet's membrane left intact. His experimental grafts were cut in the form of isosceles triangles and held in place with a suture and eyelid pressure. Konigshofer published a monograph in 1841 entitled 'De Transplantatione Corneae' in which he also endorsed the lamellar technique.[12]

The following decades brought increasing awareness of the importance of asepsis, careful handling and placement of the graft, and the use of allograft tissue. In addition, the knowledge of corneal anatomy was greatly increased through the work of Sir William Bowman (1816–1892), who provided an accurate microscopic description of the tissue in 1847.

Arthur von Hippel (1841–1916) reported the first partially successful lamellar graft in 1886. A professor at various German universities from 1868 to 1890, he performed classic research on corneal repair and pioneering experiments on corneal transplantation using hundreds of animal and human subjects. Although impressed with the suggestion of Theodor Leber (1840–1917) that the transparency of the cornea depended on the integrity of the endothelium and Descemet's membrane, he erroneously believed that the membrane was a 'glass' membrane and could not unite after being cut.[2–4] He attributed the failure of heteroplastic transplants (cross-species) to oedema and abandoned transplanting the entire corneal thickness, believing the endothelium and membrane must be left in place. In turning to lamellar grafts, the first series from dogs became opaque, which he attributed to excessive trauma while dissecting. However, in using smaller animals such as rabbits, the entire thickness of the cornea was removed. Using cocaine anaesthesia and iodoform antiseptic, he transplanted the full-thickness rabbit cornea into the lamellar bed of a young girl – her vision improved and he subsequently reported the case.[13] von Hippel also invented the circular 'clockwork' trephine, which was used for more reproducible excision of both the graft and host window, and proved to be a major advance in keratoplasty technique (Fig. 4).

Henry Power (1829–1911), an English ophthalmologist, was a pioneer whose views were opposite to von Hippel's. He favoured penetrating keratoplasties, and reported his extensive work on animals and humans in 1872.[14] Unlike von Hippel, he believed small grafts, and those of animals, failed to heal satisfactorily. However, his preference for allograft tissue was related to matching of corneal thickness rather than to an understanding of antigenic differences between species. He was the first to give importance to the use of fresh allograft tissue with minimal trauma, exact graft placement and freedom from infection.

Scientific battles continued to rage between the two opposing 'camps' with von Hippel defending his use of animal tissue, which slowed the development of keratoplasty

Figure 4. Use of the von Hippel clockwork trephine.

for several decades. However, observations of the healing of penetrating keratoplasties set the stage for success.[2] August Wagenmann (1862–1955) performed rabbit experiments that demonstrated that a portion of the cornea excised in entire thickness could heal when re-inserted and remain transparent. He recognized that, contrary to von Hippel's claims, the gap in Descemet's membrane was bridged by newly formed endothelium.[15] Ernst Fuchs (1851–1930) reported a series of 30 experiments with generally disappointing results. He used both animal and human material, recognizing the superiority of the human tissue. He studied the physiology and pathology of penetrating grafts, noting that oedema occurred 4 days or longer after the transplant. He disagreed with von Hippel's assertion that opacification resulted from the entrance of aqueous humour, instead attributing it to vascularization, cell multiplication and cellular migration into the graft. Indeed, a study of a human graft removed 2 years postoperatively showed permanent healing of the donor tissue occurred as opposed to gradual substitution by host tissue.[16]

Almost a century of keratoplasty failure was, therefore, not caused by a lack of ideas on how to replace a dysfunctional cornea, but rather due to a lack of knowledge of the basic science and medicine that would prevent graft failure, that is, the physiology and immunology of the cornea, antisepsis and germ theory, appropriate anaesthesia and a limited knowledge of microsurgical techniques.[5]

Keratoplasty success and refinement: 1900–1950

Eduard Konrad Zirm (1887–1944) finally succeeded where all others before him had failed. On 7 December 1905 in the small town of Olmutz near Prague, Zirm performed the first successful penetrating keratoplasty in a human where the graft remained clear. The patient was Alois Glogar, a 45-year-old farm labourer who had sustained severe bilateral alkali burns 16 months earlier while cleaning his chicken coop with lime. The donor tissue came from an 11-year-old boy with a blind eye due to a penetrating scleral injury. The eye was enucleated immediately prior to transplantation. Two 5-mm buttons were removed with the von Hippel trephine from one donor cornea, and bilateral transplants performed with chloroform anaesthesia and strict asepsis. He also used overlay sutures and preoperative miotics. Despite the high-risk recipient corneas, although one graft failed the other remained clear, with visual acuity of 6/36 at 6 months. Zirm suggested the following points were essential for the success of keratoplasty: exclusive use of human corneas, preferably young and healthy; use of the von Hippel trephine; profound anaesthesia; strict asepsis and avoidance of antiseptic; protection of the graft between pieces of gauze moistened with sterile salt solution and kept warm; use of overlay sutures; and use of agents to maintain the anterior chamber.

Zirm reported the case in 1906,[17] and although he performed more corneal transplants, they were not always successful and, interestingly, after this initial success he never published any further work on keratoplasty (Figs 5,6).[1]

While Zirm's case attracted much interest, it did not herald an era of consistent success, and the lamellar graft remained the dominant form of surgery for the next two decades. Direct tissue apposition was still unappreciated and penetrating grafts usually failed. For the next 30 years, transplants were performed largely using tissue from the enucle-

Figure 5. Eduard Konrad Zirm.

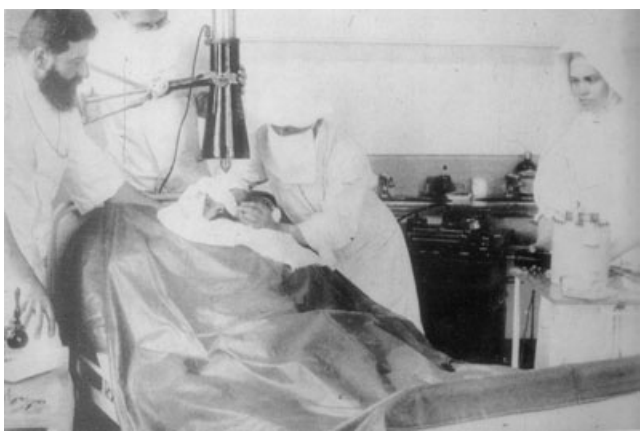

Figure 6. Eduard Zirm at work in his surgery.

ated eyes of living donors.[5] Few penetrating keratoplasties were reported during the period 1921–1939. A review by Gradle in 1921, in which only seven of 54 grafts performed remained clear, described the main causes of failure as separation of lamellar tissue from the bed, failure of tissue to adhere and subsequent opacity.[18]

There was little published in English on the subject of keratoplasty until the 1920s, when Tudor-Thomas from England published his seminal clinical work.[19] With the problems of unsatisfactory anaesthesia and antisepsis solved, clinical experimentation was directed primarily towards the refinement of instrumentation and operative techniques including experimentation with graft shape, size and fixation methods, and a variety of suturing methods, including both overlay-retention type sutures and direct sutures, were developed (Fig. 7).[3]

Anton Elschnig (1863–1939) was considered a master of corneal surgery in his day, when Prague was the world centre of corneal transplantation. By 1914, Elschnig reported his first successful penetrating keratoplasty, and during the next two decades a series of reports defined the optimal operative technique, case selection, cause of clouding and other complications. He used various overlay suture patterns and encouraged the use of full-thickness inlay grafts. He performed 180 corneal transplants, 22% of which showed optical improvement, a success rate considered remarkable for that time.[20,21]

In 1939, Wiener and Alois described a new trephine that created a beveled edge to assist in maintaining correct tissue coaptation, and great advances were made in elucidating the corneal anatomy and pathological disorders with the development of the slit-lamp biomicroscope in the 1930s.[2]

Vladimir Filatov (1875–1956), a Russian Ophthalmologist from Odessa, was encouraged by Elschnig's reports and began a systematic study of keratoplasty such that by 1955 he had performed more than 3500 human corneal transplants with increasing success rates. He overcame many technical problems and complications and devised numerous instruments and surgical innovations.[22] Considered by many as the 'grandfather' of eye banking, Filatov advocated the use of fresh cadaver corneas, and used an egg membrane to fix the graft.[23] He highlighted the key importance of direct corneal suturing and protecting the intraocular tissues while trephining the host cornea (Fig. 8).

In the 1940s, corneal transplant surgery evolved dramatically with the availability of antibiotics and would benefit further from the introduction of steroids in the subsequent decade. However, corneal tissue for transplantation was always in short supply. Enucleated eyes from living persons remained the major source of limited material.[5] In the 1940s supplies of donor tissue became more readily available because of the development of eye banking. Richard Townley Paton (1901–1984) founded the world's first eye bank in New York – the 'Eye Bank for Sight Restoration' in 1944.[24] Initially using corneas from executed prisoners, his vision was to set up a regular supply of quality, viable tissue for the large numbers of patients waiting for corneal transplants. This grew quickly into a network of eye banks throughout the USA and internationally, making tissue more readily available for surgeons, who previously had to wait for tissue as it became (infrequently) available in their own hospitals. So began the world's first 'anatomical gift' donation programme, where people could pledge their eyes for the good of others when they died. Thus, although Filatov is credited with popularizing the use of cadaveric corneas, it is Paton who established the system to supply these with regularity throughout the developed world. Paton's techniques and writings on keratoplasty also deserve note (Fig. 9).[4,25]

Ramon Castroviejo (1904–1989), a Spanish ophthalmologist practising in the USA, initiated detailed studies of surgical techniques and made numerous innovations in instrumentation, many of which still bear his name.[26] These were the fine, delicate instruments that corneal transplantation required, and he popularized the use of direct sutures. Over the course of his career he also experimented with different-shaped grafts, including a series of 'square' grafts, mainly for keratoconus, which, although many survived, proved to be less than satisfactory from an optical perspective (Fig. 10).[26]

At the same time, the Frenchmen Paufique and Charleux repopularized lamellar grafting, and also introduced limbal and eccentric grafts, as well as advocating the use of tectonic grafts in restoring structure to the compromised globe.[27] They also drew attention to corneal immunology and the possibility of graft rejection. From a statistical study presented at the first American Academy of Ophthalmology and Otolaryngology Symposium on corneal transplantation in 1947, Owens discussed 417 grafts where 36.5% remained clear.[5]

Contributions to the development and refinement of keratoplasty techniques were increasingly made from all parts of the world by prominent ophthalmologists, who became champions of corneal transplantation, including: Arruga[28] and Barraquer[29] (Spain), Tudor-Thomas[30] and Rycroft[31] (UK), Imre[32] (Hungary), Fine[33] and Paton (USA), Franceschetti[34] (Switzerland) and Vannas (Finland). Based on the progress achieved by these early 'masters', the greatest advance to corneal transplantation following World War II was achieved by Frederick Stocker in his classic treatise of 1953, where he elucidated the structure and function of the human corneal endothelium.[35] This coincided with major developments in technology, understanding of immunology and development of therapeutic drugs. In the 1950s, fine 'atraumatic' needles were used for the first time for suturing. Until this point, various forms of splints and straddling sutures were principally used to fixate the graft. These developments, combined with advanced instrumentation, led to a great increase in the prognosis for clear grafts recorded from the 1950s onwards.[4,36]

Corneal allograft rejection was, and remains, the greatest limitation in corneal graft survival. Following the classic work by Sir Peter Medawar and colleagues, immunologically mediated graft rejection was clearly recognized for the first

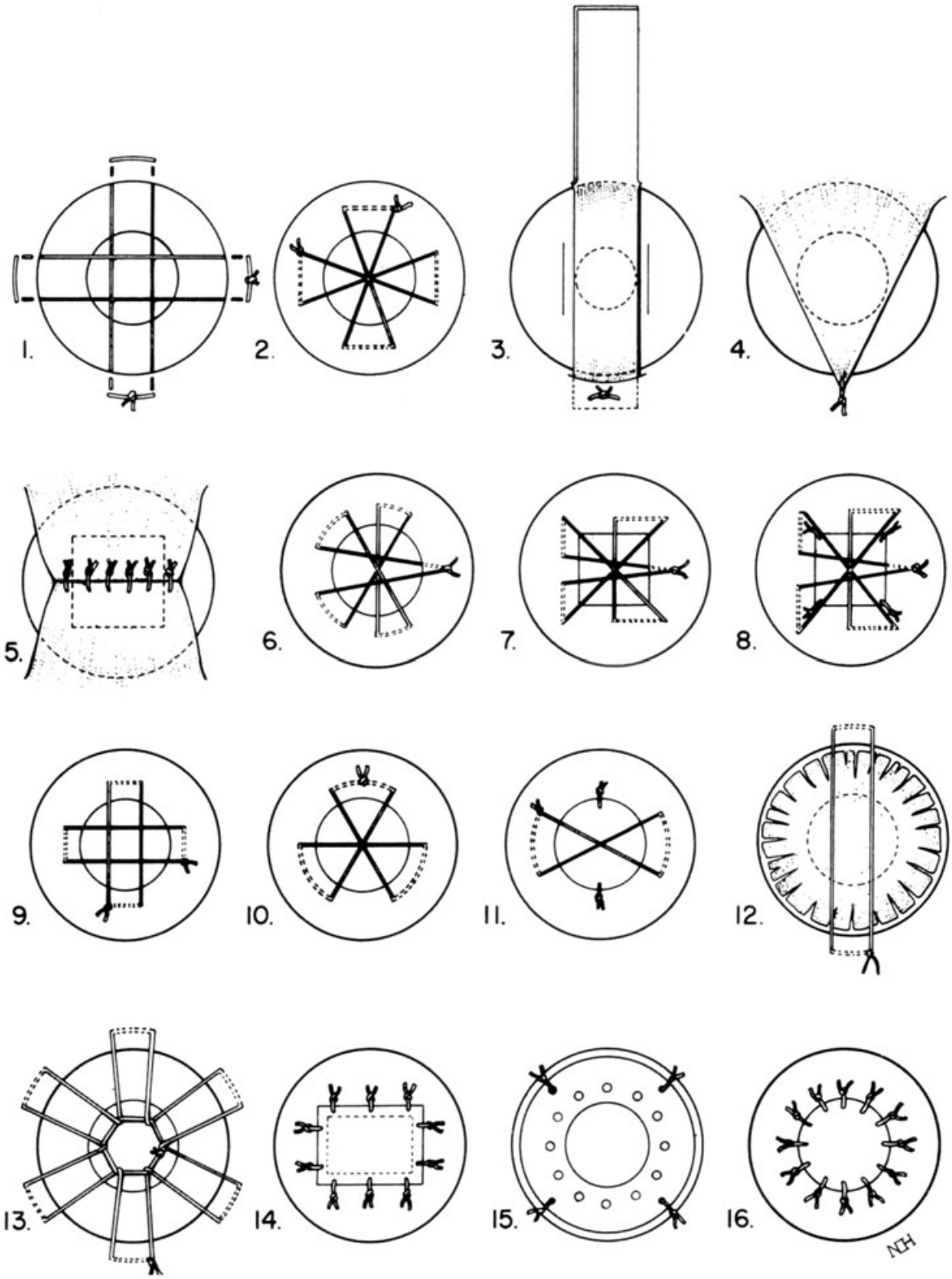

Figure 7. Various early suturing techniques in keratoplasty.

time in the 1950s. This in turn led to the development of immunosuppressive agents such as corticosteroids and cyclosporin A, and interest turned to the antigenic status of corneal tissue. Edward Maumanee was the first to report corneal graft rejection as a clinical entity,[37,38] and classic scientific description and experimental models were elegantly designed by Khodadoust, whose name was given to the endothelial rejection line.

Other significant developments were achieved by Richard Troutman[39] and Dermot Pierse (who brought the surgical microscope to ophthalmology); David Maurice[40] (who developed the specular microscope and studied the endothelium in great detail) and Herbert Kaufman (who developed antiviral agents and corneal storage medium).[4]

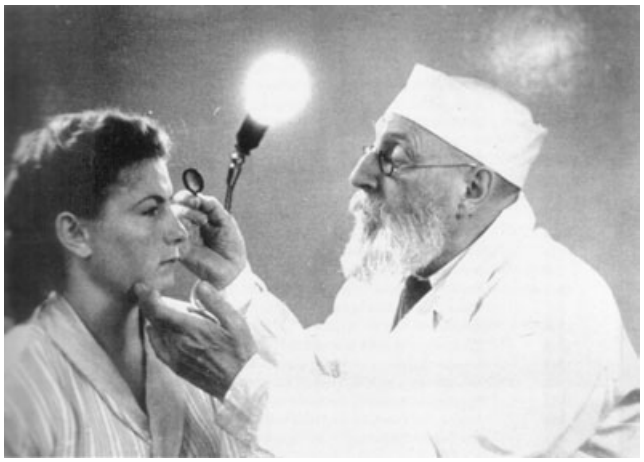

Figure 8. Vladimir Filatov examining a patient.

CONSOLIDATING KERATOPLASTY SUCCESS: 1950–PRESENT

Since the development of the successful techniques of corneal transplantation by pioneers in the first half of the 20th century, numerous refinements have improved success rates (Fig. 11). These range from careful patient selection to improved surgical techniques and better postoperative management, particularly in cases of allograft rejection and astigmatism.

Patient selection

The indications for keratoplasty have changed over the last 50 years. In the first half of the 20th century the majority of grafts were performed for infections, trauma and chemical and thermal burns, often in the presence of acute disease. The management of many of these conditions improved dramatically with the introduction of antibiotics and antiviral agents as well as corticosteroids, and improvements in contact lens technology. Fewer of those patients now require a corneal graft for visual rehabilitation in the acute stages of disease.

In addition, the increase and evolution of cataract surgery in the second half of the last century led to a dramatic

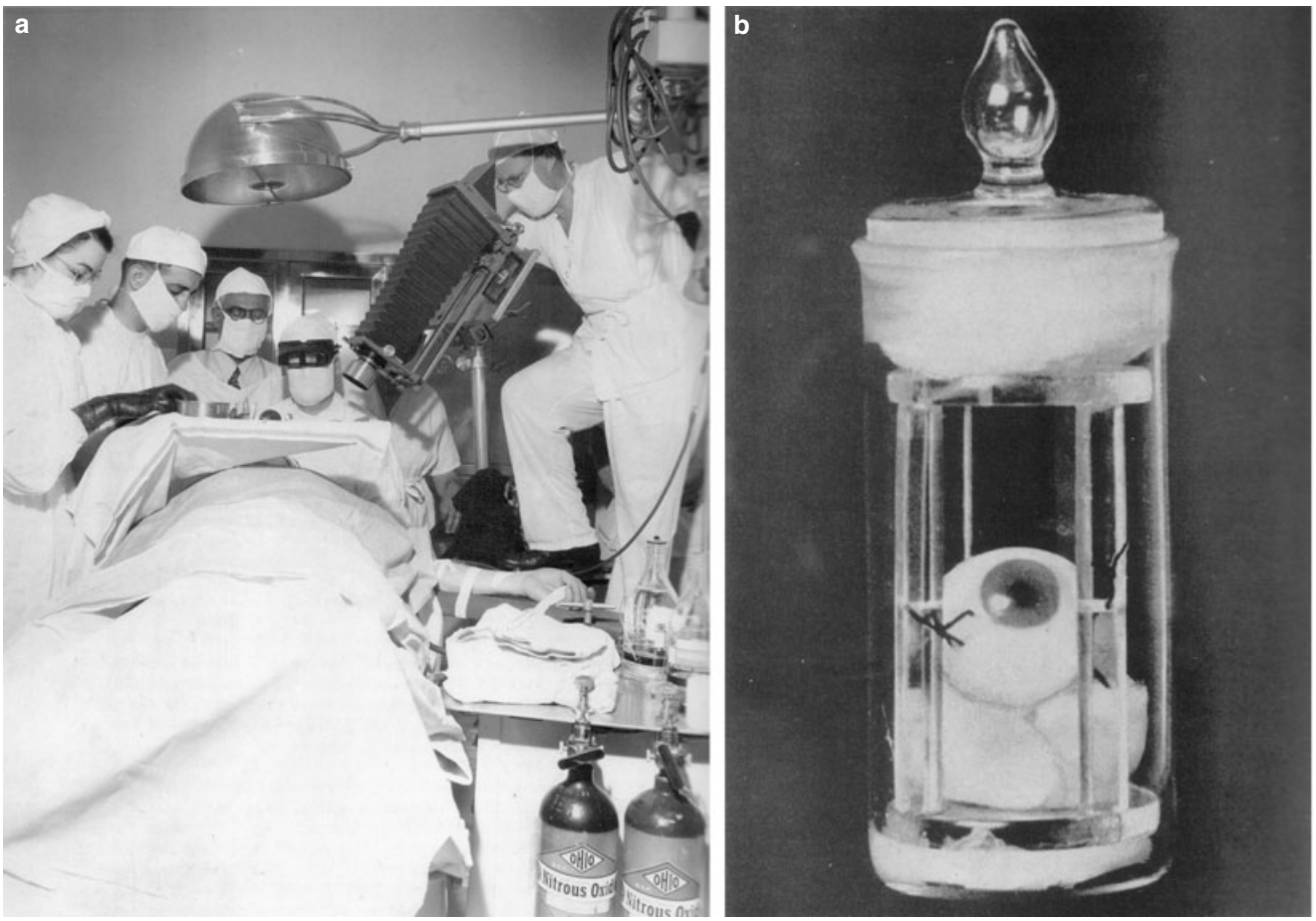

Figure 9. (a) Dr Townley Paton, performing one of the first corneal transplants in New York, 1937 and (b) a donor eye in moist pot storage.

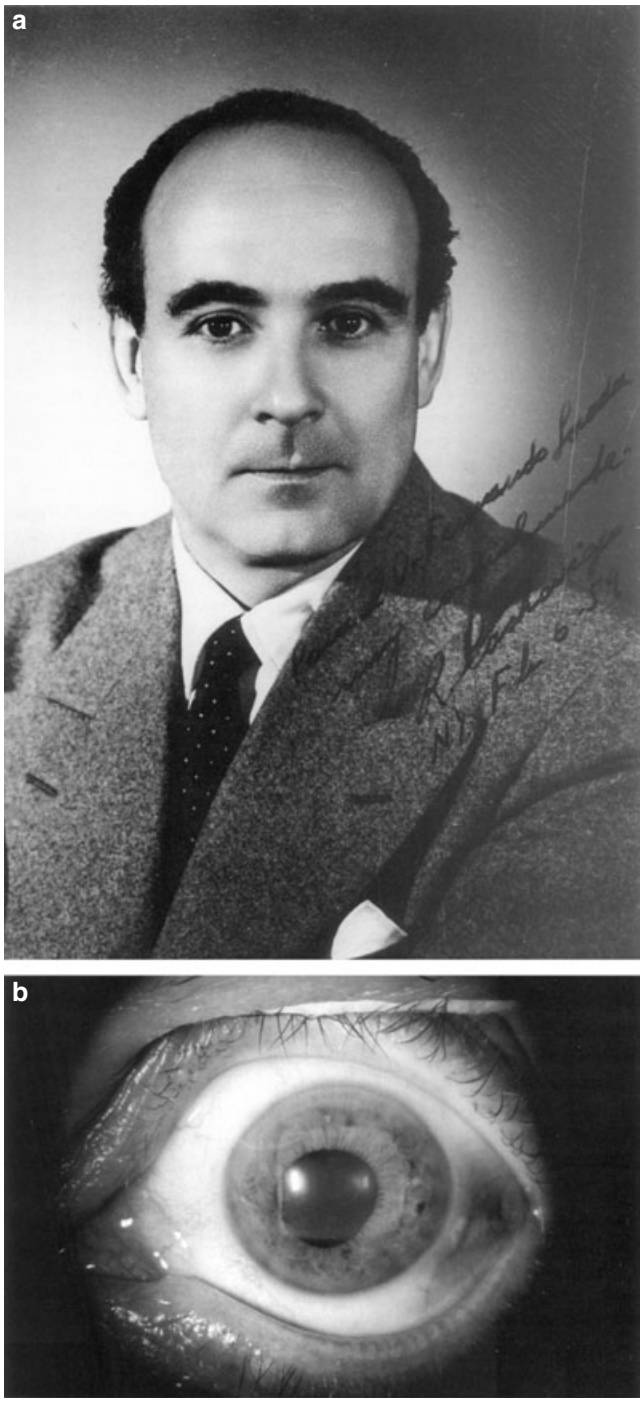

Figure 10. (a) Ramon Castroviejo in 1950 and (b) Castroviejo's signature square graft.

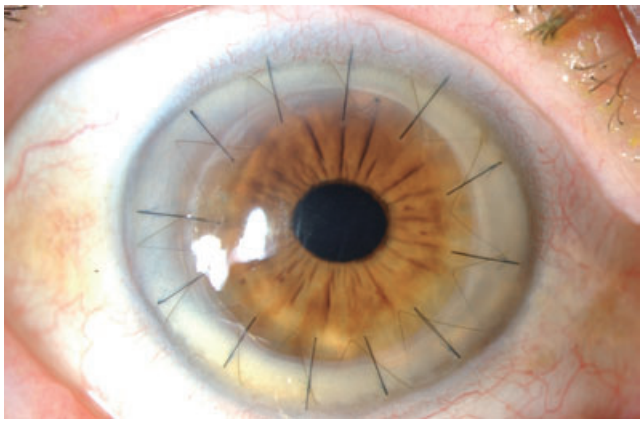

Figure 11. Photograph of a modern, successful, clear corneal penetrating keratoplasty with sutures in place.

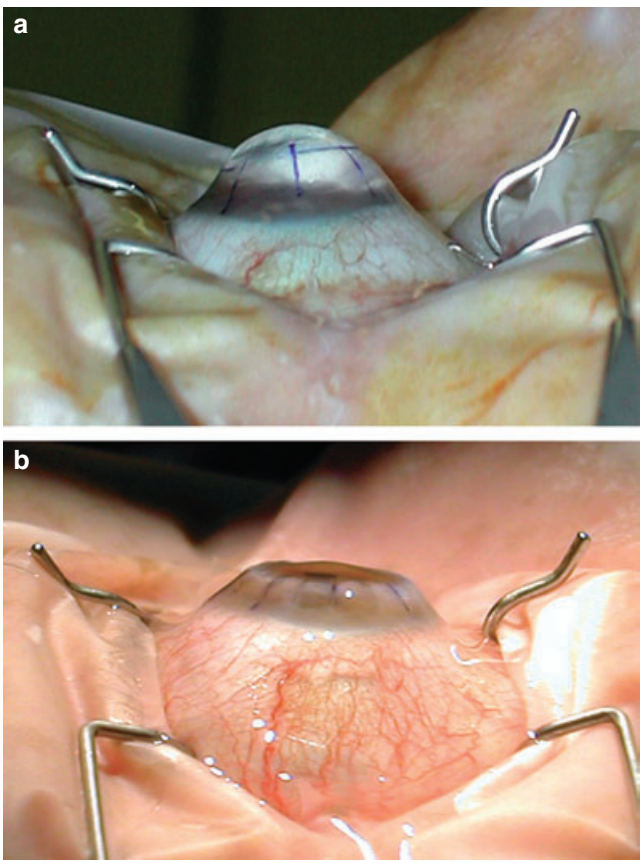

Figure 12. Profile of an eye with keratoconus immediately (a) before and (b) after penetrating keratoplasty.

increase in the number of patients developing iatrogenic bullous keratopathy, which remains the most common indication for penetrating keratoplasty in many countries, such as France, Singapore, Canada and the USA. More recently, with improving techniques for cataract surgery, the incidence of this condition has been falling and has been overtaken by keratoconus (Fig. 12) as the main indication for penetrating keratoplasty in Australia, New Zealand, Sweden and Germany and corneal dystrophies (including Fuch's endothelial dystrophy) in the UK (Table 1).

The change in indications over the years from acute inflammatory and infectious conditions, often in the presence of a hostile ocular surface, to the chronic non-inflammatory conditions that predominate today, has no doubt contributed to the improved success of corneal transplantation.

Table 1. International variability in the indications for penetrating keratoplasty (see references 41–50; Armitage J. pers. comm. 2005)

Country	Year	Keratoconus (%)	Bullous keratopathy (%)	Regraft (%)	Corneal dystrophies (%)
Australia	1995	30.0	25.0	18.0	–
Canada	1997	10.0	34.6	22.4	7.6
France	2003	25.3	27.7	14.1	9.1
Germany	1998	20.9	17.0	15.5	14.9
Israel	2005	28.4	8.4	13.4	–
New Zealand	2002	45.6	17.9	8.7	–
Singapore	1997	9.8	26.3	11.9	10.4
Sweden	2002	29.0	21.0	10.0	18.0
Taiwan	2001	2.5	17.6	21.0	4.5
UK	2004	24.1	17.4	13.9	25.1
USA	2002	15.4	27.2	18.1	15.2

Technological developments

Today, it is difficult to imagine having to perform a keratoplasty without the aid of modern instruments and techniques. Some of the most important developments have included: (i) the introduction of the surgical microscope and microsurgical instruments; (ii) improved methods of trephination; (iii) atraumatic needles and sutures and new suture materials; and (iv) newer techniques to improve lamellar keratoplasty.

Where the pioneers of corneal transplantation used low magnification loupes (×2–×4) under poor illumination to perform their surgery, modern technology has provided high-quality operating microscopes with good coaxial illumination, easily adjustable magnification (×6–×20) and focus. This has allowed the development of microsurgical instruments, finer and stronger needles and sutures. Furthermore, the development of specular, confocal and electron microscopy led to improvements in the understanding of the structure and function of the corneal cells, from both *in vivo* and laboratory studies. This highlighted the importance of the endothelial cell layer in maintaining transparency of the cornea and the need to protect it during surgical procedures.

The concept of a round trephine is well established and the basic principles of trephination today remain remarkably similar to those pioneered by von Hippel. However, there have been significant improvements in the quality, design and sharpness of the blades providing better and more consistent surgical wounds. In the early 1970s the standard for corneal trephination was the hand-held Castroviejo trephine developed in the 1930s. Extensive experimentation led to the oversizing of the donor button, in relation to the recipient, because donor buttons were usually punched from the posterior (endothelial) surface and recipient corneas were trephined from the anterior (epithelial) surface. By 1980, the Hessburg–Barron suction trephine was introduced,[51] and is still widely used today. The Hanna trephine was introduced 5 years later to improve the fit of same-sized buttons, thereby reducing the myopia induced by donor oversizing.[52,53] More recently, Hessburg–Barron have introduced a disposable artificial anterior chamber, to allow same-sizing of donor and recipient corneas using their suction trephine. However, conceptually, the greatest change in corneal trephination was introduced in the late 1990s, when Naumann and his group showed that using a 193-nm excimer laser to cut both donor and recipient corneas might induce lower myopia and astigmatism than mechanical trephination.[54]

The awareness of protecting the endothelium during intraocular surgery led to the introduction of viscoelastic substances in the 1970s. Initially introduced mainly for use in cataract surgery, soon the benefits of viscoelastics in penetrating keratoplasty became clear.

Although the pioneers of keratoplasty used non-apposition overlay sutures to secure the cornea, appositional sutures were introduced in the 1950s. Initially these were made of silk but since the 1970s, monofilament 10/0 and 11/0 nylon sutures remain the most frequently used suture material in corneal surgery. However, unlike polyester (Mersilene) and polypropylene (Prolene), nylon tends to slowly hydrolyse, which can lead to changes in astigmatism or a microbial keratitis associated with loosening sutures. Contemporary needles are finer and stronger, and with sharper and wider tips they also allow easier tissue penetration with less traction and easier knot rotation.

Much discussion has surrounded suturing techniques, with advocates for interrupted, continuous, mixed, and double continuous with antitorque technique. With interrupted and mixed suturing techniques, selective suture removal has allowed early management of postoperative astigmatism. This has been associated with a higher rate of irregular astigmatism in some studies,[55] but not in others,[56] and there have been few studies comparing the results of different suturing techniques after all sutures have been removed. Consequently, there is still no universally accepted technique for keratoplasty suturing.

As previously noted, the first successful lamellar keratoplasty was performed before penetrating keratoplasty, and there has been a recent resurgence of interest in lamellar keratoplasty. In theory, lamellar surgery offers several advantages over penetrating keratoplasty by replacing only the diseased layer of the cornea. However, in practice the interface between host and donor cornea has limited the use of this procedure. Traditionally, lamellar keratoplasty has been used predominantly to provide tectonic support or provide

clear tissue replacement for anterior corneal dystrophies or anterior stromal scars. With improving techniques at the end of the 20th century, lamellar surgery has experienced somewhat of a revival with the introduction of deep anterior and posterior lamellar keratoplasties, where the lamellar dissection is performed at the level of Descemet's membrane. A recent study of 40 keratoconic patients confirmed good visual results from both penetrating and deep anterior lamellar keratoplsty with a similarly high percentages of eyes achieving a corrected visual acuity of 6/9.[57]

Eye banking

> 'It was the basic premise of the program that an appeal to the public could bring the requisite increase in donor tissue, a view which has been borne out.'[25]

Although the establishment of eye banks in the 1940s greatly increased the supply of tissue, storage time of the tissue was limited to 2–3 days, and corneal transplants were still 'urgent' surgical procedures. Prolonged corneal storage was achieved in 1974 by McCarey and Kaufman who developed the M–K preservation medium.[58] This allowed the storage of corneas for up to 5 days, greatly increasing the availability and supply of tissue. Subsequent variations of hypothermic storage medium (K-Sol, Dexsol, Optisol) provided further longevity and efficacy of antibiotics, thereby increasing storage time to 7–10 days, and the outcomes were demonstrated to be as good as fresh tissue.[59] This enabled transplants to become largely scheduled, resulting in major cost and efficiency benefits to surgeons, hospitals and patients. Eye banks in Europe and the UK further developed the organ culture corneal storage technique originally developed by Doughman,[60] where tissue can be stored at physiological temperature for up to 30 days, and where microbiological surveillance and tissue typing can be performed.[61]

Advances in eye banking were made with the establishment of the Eye Bank Association of America in 1961. The standards determined by this organization had considerable influence on the procurement, preservation, storage and use of donor tissue in the USA, and throughout the world, where many international eye banks followed their lead. Medical Standards and contraindications to eye donation defined by the Association have been used as a model for other eye and tissue banking organizations, and led to improved safety and quality of corneas.[62] Although the list of contraindications has grown over the years because of possible transmission of emerging pathogens such as HIV and Creutzfeldt–Jakob disease, and the emergence of refractive corneal procedures, donation of ocular tissue is still the most common form of donation, and very few cases of transmission of infectious disease or endophthalmitis have occurred.[63]

In 1961, the Eye Bank Association of America reported 2000 transplants – today there are more than 40 000 transplants performed each year in the USA. Eye banks today are professional service organizations with extensive donor programmes, and advanced instrumentation to evaluate tissue. The recent requirement for compliance with regulatory 'therapeutic goods' agencies has ensured eye banks formally meet the highest standards for quality and safety, although considerable negotiation has occurred to ensure recognition of the unique nature of the cornea and the limited ability to test for function and sterility. Eye banks also strive to maintain the profile and value of eye donation since the advent of organ donation and transplantation.

Artificial corneas

Although penetrating keratoplasty is by far the most successful transplantation surgery, the outcomes in high-risk patients, such as those with severe ocular surface diseases, multiple graft failures and in paediatric patients with congenital corneal opacities, are often disappointing. Furthermore, the shortage of donor corneas, the risks of disease transmission (in particular Creutzfeldt–Jakob disease) and the difficulties with eye banking, particularly in the developing countries where corneal blindness is most prevalent, has encouraged the development of artificial corneas.

Although described over 40 years ago by Strampelli,[64] the osteo-odonto-keratoprosthesis remains the keratoprosthesis of choice for end-stage corneal blindness not amenable to penetrating keratoplasty (Fig. 13). It is particularly resilient to a hostile environment such as the dry keratinized eye resulting from severe Stevens–Johnson syndrome, ocular cicatricial pemphigoid, trachoma and chemical injury. Its rigid optical cylinder gives excellent image resolution and quality.[65] More recently, early results suggest that the AlphaCor, previously known as the Chirila keratoprosthesis (Chirila KPro), has a low incidence of the complications traditionally associated with keratoprostheses and can effectively restore a degree of vision in patients considered untreatable by conventional corneal transplantation. Importantly, the device can be replaced with a donor graft in the event of the development of a significant complication.[66] Although several different devices are available, none has yet shown to be

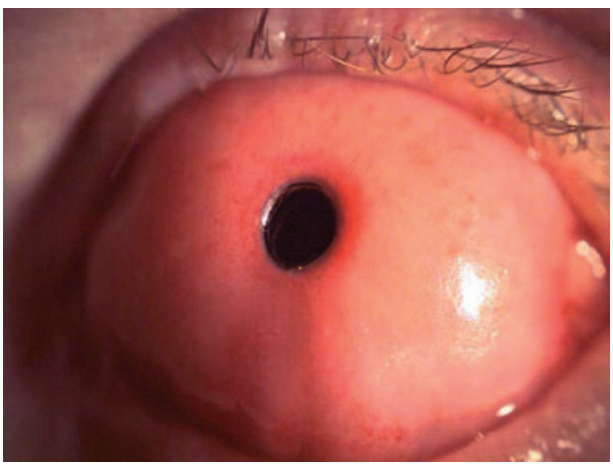

Figure 13. Photograph of an eye after osteo-odonto-keratoprosthesis.

clinically superior and further evaluation and development is required.

Advances in postkeratoplasty management

The technological advances over the last century have substantially reduced the early postoperative complications, but infection, rejection and corneal astigmatism still remain problematic.

Postoperative infection

Since the widespread introduction of antibiotics and antivirals, fewer penetrating keratoplasties are performed for acute infectious keratitis and their prophylactic use has practically eliminated early postoperative infections, particularly in the presence of epithelial defects. However, microbial keratitis associated with corneal suture erosion remains a problem.[67] Similarly, although fewer penetrating keratoplasties are performed for herpetic keratitis since the introduction of antivirals in the 1980s,[68] the use of postoperative topical steroids to prevent rejection can potentially exacerbate viral recurrences. Many surgeons now use long-term prophylactic oral acyclovir to prevent such serious complications that may jeopardize the survival of the graft and the eye.[69]

Management of rejection and outcome

Although the introduction of topical corticosteroids markedly improved the outcome of penetrating keratoplasty, the results have not paralleled the improvements seen in solid organ transplantation over the last 30 years,[70] and immune mediated corneal graft rejection remains the single most important cause of corneal graft failure. The reasons for this are not clear but may be related to the relatively complacent attitude by both ophthalmologists and patients to corneal allograft immunosuppression, by virtue of the non-life-threatening consequences of keratoplasty failure. Furthermore, some studies have suggested that there may be a benefit in major histocompatibility complex class I tissue matching,[71] whereas others suggest that it does not reduce the likelihood of corneal graft failure.[72] However, ABO blood group matching, which can be achieved with relatively little effort and expense, may be effective in reducing the risk of graft failure.

Several host factors have been identified as conferring a 'high risk' status to the recipient. These include vascularization, which augments the afferent and efferent arc of the immune response; herpes simplex keratitis; uveitis; previous failed (rejected) grafts; 'hot eyes'; young recipient age; and multiple surgical procedures at the time of grafting. Large grafts, by virtue of being closer to the recipient limbus, are more susceptible to rejection.[73]

Although graft rejection can lead to graft failure, the majority of allograft rejections can be controlled if appropriate management is commenced as soon as possible after rejection develops. Topical corticosteroids are the mainstay of graft rejection management; however, systemic steroids and other immunosuppressive drugs such as cyclosporin A and tacrolimus are of proven benefit, both for the treatment and prevention of rejection in high-risk grafts.[74]

Despite the problems with infection and rejection, corneal transplantation remains one of the most successful transplant procedures. Some large studies have suggested survival rates of 90% at 1 year and between 60% and 90% at 5–10 years,[41,75] with higher success rates (97% at 5 years) for keratoconus.[76] In the latter group, 91% of patients achieved 6/12 or better visual acuity. However, in the Australian corneal graft register of 4499 grafts, only 43% of all recipients achieved a best-corrected acuity of 6/12 or better, and 20% had acuities of less than 6/60. The reasons for poor postoperative acuity included graft failure and ocular comorbidity.[41]

Management of astigmatism

Although corneal transparency has always been a primary measure of the success of penetrating keratoplasty, the quality of vision and corneal astigmatism, have become increasingly important with improving graft survival rates. Trephining methods, graft size, suturing technique and postoperative suture adjustment all contribute to the management of postkeratoplasty astigmatism.

Initially, refraction and keratometry were the only tools available to measure astigmatism; however, computerized corneal topography has been shown to be beneficial when compared with keratometry and refraction alone in the management of high postkeratoplasty astigmatism (Fig. 14).[77] Although many variables of suture removal remain unpredictable, the selective removal of interrupted sutures postkeratoplasty can improve the recovery of vision after corneal transplantation without subjecting the eye to increased risks.[78] In addition, there appears to be no advantage of single continuous suturing over interrupted sutures in terms of fewer manipulations or less astigmatism.[56] However, a suturing technique using two continuous sutures with 16 bites each can minimize irregular postkeratoplasty astigmatism as long as sutures are in place, when compared with interrupted sutures or double-running sutures of less than 16 bites.[55] Although larger corneal grafts tend to be associated with lower astigmatism and higher rejection rates, smaller grafts result in lower rejection and higher degree of topographic irregularity, but not in higher net astigmatism.[79]

Persistent astigmatism after suture removal can be improved with the placement of paired arcuate incisions in the graft–host junction with paired augmentation sutures, guided by corneal topography. This has been shown to reduce the amount of cylinder in proportion to the magnitude of the preoperative cylinder and effectively reduces postpenetrating keratoplasty astigmatism.[80,81] More recently, LASIK was shown to be superior when compared with incisional or surface-based excimer laser methods, and has the advantage of reducing the myopic spherical equivalent in addition to astigmatism, thus improving the uncorrected

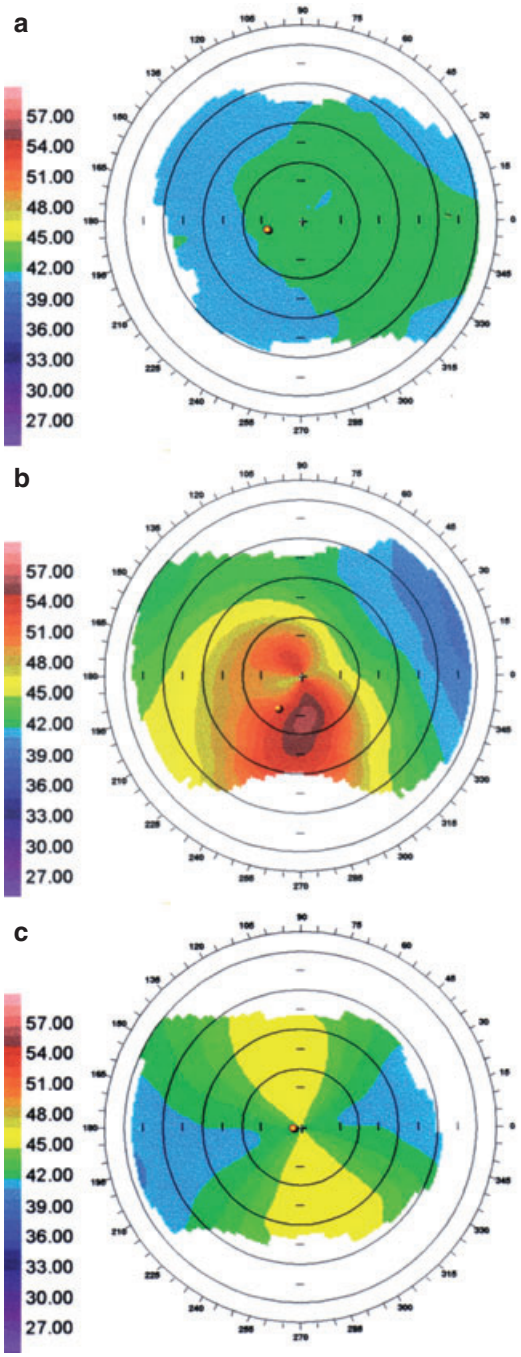

Figure 14. Orbscan topographic maps of (a) normal (b) keratoconic and (c) postoperative astigmatism.

visual acuities.[82] However, the results of LASIK after penetrating keratoplasty are not as predictable as in normal corneas and complications are more common.[83]

Notwithstanding these technological developments in the management of astigmatism, the visual rehabilitation of most subjects following penetrating keratoplasty remains spectacles or contact lenses. The latter have been shown to improve visual function in patients with irregular astigmatism and anisometropia after penetrating keratoplasty (Fig. 14).[84]

The future of keratoplasty

In the century that has elapsed since the first successful penetrating keratoplasty there have been many changes that have contributed to the improved success of the procedure. However, there are still many limitations both in terms of graft survival and visual outcome.

Several factors need to be addressed to improve the outcomes of corneal transplantation. As endothelial rejection is the most important reason for graft failure, selectively inhibiting the immunological responses to corneal antigens may improve graft outcomes. The use of antibody fragments to block pro-inflammatory mediators, such as interferon-γ,[85] immunoregulatory proteins or gene fragments that code for such proteins, for example the use of CTLA4-Ig or cDNA in blocking the CD28-mediated T lymphocyte costimulation,[86] among others, has shown promise in the treatment of corneal allograft rejection.[87] An alternative method may be the induction of specific tolerance to donor antigens prior to transplantation.

However, the ideal cornea would be an acellular stromal scaffold with *ex vivo* colonization of host endothelial cells, keratocytes and epithelium. These cells could be bioengineered to have the original disease characteristics removed and they should have the same long-term biological properties after transplantation as a healthy cornea. Hopefully it will be much sooner than another century before such advances become reality.

Conclusion

Corneal transplantation is now a standard tool in the surgical repertoire of ophthalmology, and the dream as old as medicine itself has been largely realized. One hundred years after performing the first successful corneal transplant, what would Eduard Zirm think if he witnessed a modern keratoplasty procedure?

In all fundamental ways, the operation remains remarkably similar: the use of viable, healthy allograft tissue, handled with care and free of infection; the use of a circular trephine to excise the tissue; the practice of profound anaesthesia and aseptic technique; the precise coaptation and suturing of tissue; and careful postoperative management.

However, he would notice remarkable differences in the technological developments, instrumentation and perioperative management of cases. Zirm would be envious of the delicate nature of the instruments, sutures and needles. He would marvel at the surgical stereomicroscope, the excimer laser, the orbscan and the confocal microscopes. He would covet the aid of antibiotics, anti-inflammatories and immunosuppressives. He would be greatly appreciative of the safe, quality tissue that arrived with near certainty by the efforts of his local eye bank. And he would be aided immensely by the cumulative knowledge obtained from hundreds of thousands of transplants performed by others that described, refined and improved the best procedures to be utilized in each, unique, case. He would envy and harvest the extensive

knowledge that now details the structure, biology, physiology and immunology of the cornea, and would in many instances now be able to reverse the complications of infection and rejection following surgery.

There are undoubtedly still limitations in corneal transplantation. As Sir Benjamin Rycroft said in his acclaimed Doyne Memorial Lecture to the UK Ophthalmological Society in 1965: 'Indeed, it is in the biological laboratory rather than in the operation theatre that further knowledge is likely to be gained; at present in corneal graft surgery the surgeon has outstripped the biologist'.[88] This statement remains true 40 years later, but nevertheless for hundreds of thousands of people, restoration of useful sight by corneal transplantation is a daily 'miracle' enabling renewed quality of life that did not appear possible until one momentous day in 1905.

ACKNOWLEDGEMENTS

The authors wish to thank Jean-Paul Wayenborgh (http://www.history-ophthalmology.com) for granting permission to reproduce Figures 3–10, sourced from 'Corneal Transplantation: A History in Profiles' by Mannis and Mannis (Wayenborgh Press 1999).

REFERENCES

1. Mannis MJ, Mannis AA. *Corneal Transplantation: A History in Profiles*. Oostende, Belgium: Wayenborgh Press, 1999.
2. Albert DM, Edwards DD. *The History of Ophthalmology*. Massachusetts: Blackwell Science, 1996.
3. Mannis MJ, Krachmer JH. Keratoplasty: a historical perspective. *Surv Ophthalmol* 1981; **25**: 333–8.
4. Casey TA, Mayer DJ, eds. *Corneal Grafting*. Philadelphia: WB Saunders, 1984.
5. Laibson PR, Rapuano CJ. 100-year review of cornea. *Ophthalmology* 1996; **103**: S17–28.
6. Darwin E. *Zoonomia, or the Laws of Organic Life*. London: J Johnson, 1796.
7. Pellier de Quengsy G. *Precis au cours d'operations sur la chirurgie des yeux*. Paris: Didot, 1789.
8. Reisinger FR. Die keratoplastik, ein versuch zur enweiterund der augenheilkunde. *Bayerische Annalem* 1824; **1**: 207.
9. Dieffenbach JB. Beitrage zur Verpflanzung der Hornhaut. *Festschr Ophthalmol (von Ammon)* 1831; **1**: 172–6.
10. Bigger SLL. An inquiry into the possibility of transplanting the cornea with a view to relieving blindness. *Dublin J Med Sci* 1837; **11**: 408–17.
11. Kissam RS. Ceratoplastics in man. *NY J Med* 1844; **2**: 281–2.
12. Konigshofer T. De transplantatione corneae (Opus praemio ornatum, Monachii, 1841). In: Schmidt CC, ed. *Jarbucher der in- und auslandischen gesammten Medicin*. Leipzig: Otto Weigand, 1843; 128.
13. von Hippel A. Uber transplantation der cornea. *Arch Ophthalmol* 1878; **24**: 235–56.
14. Power H. On transplantation of the cornea. IV International Congress of Ophthalmology. **Vol. IV.** London 1873; 172–6.
15. Wagenmann A. Experimentalle untersuchungen zur frate der keratoplastik. *Arch Ophthalmol* 1888; **34**: 211–69.
16. Fuchs E. Uber Keratoplastik. *Wein Klin Wehnschr* 1894; **7**: 843–5.
17. Zirm E. Eine erfolgreiche totale keratoplastik. *Arch Ophthalmol* 1906; **64**: 580–93.
18. Gradle HS. The present status of keratoplasty. *Am J Ophthalmol* 1921; **4**: 895–9.
19. Tudor-Thomas JW. Transplantation of the cornea: a preliminary report on a series of experiments in rabbits, together with a demonstration of four rabbits with clear corneal grafts. *Trans Ophthalmol Soc UK* 1930; **50**: 127–41.
20. Elschnig A, Gradle HS. History of keratoplastic operations to date. *Am J Ophthalmol* 1923; **6**: 998.
21. Elschnig A. Keratoplasty. *Arch Ophthalmol* 1930; **4**: 165–73.
22. Filatov VP. Transplantation of the cornea. *Arch Ophthalmol* 1935; **13**: 321–47.
23. Filatov VP. Transplantation of the cornea from preserved cadavers' eyes. *Lancet* 1937; **1**: 1395–7.
24. Paton D. The founder of the first eye bank: R. Townley Paton, MD. *Refract Corneal Surg* 1991; **7**: 190–5.
25. Paton RT. *Keratoplasty*. New York: McGraw-Hill, 1955.
26. Castroviejo R. Keratoplasty. *Am J Ophthalmol*, 1941; **24**: 1–20.
27. Paufique L, Sourdille GP, Offret G. *Les Greffes de la Cornee*. Paris: Masson and Cie, 1948.
28. Arruga H. La greffe corneene. *Arch D'opht* 1939; **3**: 289–313.
29. Barraquer JIJ. Technique of penetrating keratoplasty. *Am J Ophthalmol* 1950; **33**: 6–17.
30. Tudor-Thomas JW. The results of corneal transplantation. *Br J Med* 1937; **1**: 114–16.
31. Rycroft BW. The scope of corneal grafting. *Br J Ophthalmol* 1954; **38**: 1–9.
32. Imre J. *Klinische und histologische Erfahrungen mit der Hornhautubertragung*. Stuttgart: Enke, 1942.
33. Fine M. Techniques of keratoplasty. *Int Ophthalmol Clin* 1970; **10**: 271–96.
34. Franceschetti A, Kiewe P. Greffe corneene dans une cas de degenerescence familiale de la cornee. *Bull Mem Soc Franc d'Opht* 1936; **49**: 102–6.
35. Stocker FW, King EH, Lucas DO, Georgiade NA. The endothelium of the cornea and its clinical implications. *Trans Am Acad Ophthalmol Otolaryngol* 1953; **51**: 669–786.
36. Forstot SL, Kaufman HE. Corneal transplantation. *Ann Rev Med* 1977; **28**: 21–35.
37. Maumanee AE. The influence of donor-recipient sensitisation on corneal grafts. *Am J Ophthalmol* 1941; **34**: 142.
38. Maumanee AE, Kornblueth W. Symposium: corneal transplantation. IV. Pathophysiology. *Trans Am Acad Ophthalmol* 1948; **52**: 331–40.
39. Troutman RC. *Introduction and Basic Techniques*. St Louis: CV Mosby, 1974.
40. Maurice DM. The location of the fluid pump in the cornea. *J Physiol* 1972; **221**: 43.
41. Williams KA, Muehlberg SM, Lewis RF, Coster DJ. How successful is corneal transplantation? A report from the Australian Corneal Graft Register. *Eye* 1995; **9** (Pt 2): 219–27.
42. Liu E, Slomovic AR. Indications for penetrating keratoplasty in Canada, 1986–1995. *Cornea* 1997; **16**: 414–19.
43. Poinard C, Tuppin P, Loty B, Delbosc B. [The French national waiting list for keratoplasty created in 1999: patient registration indications, characteristics, and turnover.] *J Fr Ophtalmol* 2003; **26**: 911–19.

44. Cursiefen C, Kuchle M, Naumann GO. Changing indications for penetrating keratoplasty: histopathology of 1250 corneal buttons. *Cornea* 1998; **17**: 468–70.
45. Yahalom C, Mechoulam H, Solomon A, Raiskup FD, Peer J, Frucht-Pery J. Forty years of changing indications in penetrating keratoplasty in Israel. *Cornea* 2005; **24**: 256–8.
46. Edwards M, Clover GM, Brookes N, Pendergrast D, Chaulk J, McGhee CN. Indications for corneal transplantation in New Zealand: 1991–1999 *Cornea* 2002; **21**: 152–5.
47. Chan CM, Wong TY, Yeong SM, Lim TH, Tan DT. Penetrating keratoplasty in the Singapore National Eye Centre and donor cornea acquisition in the Singapore Eye Bank. *Ann Acad Med Singapore* 1997; **26**: 395–400.
48. Claesson M, Armitage WJ, Fagerholm P, Stenevi U. Visual outcome in corneal grafts: a preliminary analysis of the Swedish Corneal Transplant Register. *Br J Ophthalmol* 2002; **86**: 174–80.
49. Chen WL, Hu FR, Wang IJ. Changing indications for penetrating keratoplasty in Taiwan from 1987 to 1999. *Cornea* 2001; **20**: 141–4.
50. Cosar CB, Sridhar MS, Cohen EJ *et al.* Indications for penetrating keratoplasty and associated procedures, 1996–2000. *Cornea* 2002; **21**: 148–51.
51. Hessburg PC, Barron M. A disposable corneal trephine. *Ophthalmic Surg* 1980; **11**: 730–3.
52. Spadea L, Bianco G, Mastrofini MC, Balestrazzi E. Penetrating keratoplasty with donor and recipient corneas of the same diameter. *Ophthalmic Surg Lasers* 1996; **27**: 425–30.
53. Pouliquen Y, Ganem J, Hanna K, Saragoussi JJ. New trephine for keratoplasty (Hanna trephine). *Dev Ophthalmol* 1985; **11**: 99–102.
54. Seitz B, Langenbucher A, Kus MM, Kuchle M, Naumann GO. Nonmechanical corneal trephination with the excimer laser improves outcome after penetrating keratoplasty. *Ophthalmology* 1999; **106**: 1156–64; discussion 1165.
55. Busin M, Monks T, al-Nawaiseh I. Different suturing techniques variously affect the regularity of postkeratoplasty astigmatism. *Ophthalmology* 1998; **105**: 1200–5.
56. Karabatsas CH, Cook SD, Figueiredo FC, Diamond JP, Easty DL. Combined interrupted and continuous versus single continuous adjustable suturing in penetrating keratoplasty: a prospective, randomized study of induced astigmatism during the first postoperative year. *Ophthalmology* 1998; **105**: 1991–8.
57. Funnell CL, Ball J, Noble BA. Comparative cohort study of the outcomes of deep lamellar keratoplasty and penetrating keratoplasty for keratoconus. *Eye* 2005.
58. McCarey B, Kaufman HE. Improved corneal storage. *Invest Ophthalmol* 1974; **13**: 165–73.
59. Lindstrom RL. Advances in corneal preservation. *Trans Am Ophthalmol Soc* 1990; **88**: 555–648.
60. Doughman DJ, Harris JE, Schmidt MK. Penetrating keratoplasty using 37oC organ-cultured corneas. *Trans Am Acad Ophthalmol Otol* 1976; **81**: 778–93.
61. Anderson J, Ehlers N. Corneal transplantation using long-term cultured donor material. *Acta Ophthalmol (Copenh)* 1986; **64**: 93–6.
62. Chu W. The past twenty-five years in eye banking. *Cornea* 2000; **19**: 754–65.
63. O'Day DM. Diseases potentially transmitted through corneal transplantation. *Ophthalmology* 1989; **96**: 1133–8.
64. Strampelli B, Valvo A, Tusa E. [Osteo-odonto-keratoprosthesis in a case treated for anchylobepharon and total simbleraphon.] *Ann Ottalmol Clin Ocul* 1965; **91**: 462–79.
65. Liu C, Paul B, Tandon R *et al.* The osteo-odonto-keratoprosthesis (OOKP). *Semin Ophthalmol* 2005; **20**: 113–28.
66. Hicks CR, Crawford GJ, Lou X *et al.* Corneal replacement using a synthetic hydrogel cornea, AlphaCor: device, preliminary outcomes and complications. *Eye* 2003; **17**: 385–92.
67. Dana MR, Goren MB, Gomes JA, Laibson PR, Rapuano CJ, Cohen EJ. Suture erosion after penetrating keratoplasty. *Cornea* 1995; **14**: 243–8.
68. Kaufman HE. Antimetabolite drug therapy in herpes simplex. *Ophthalmology* 1980; **87**: 135–9.
69. Tambasco FP, Cohen EJ, Nguyen LH, Rapuano CJ, Laibson PR. Oral acyclovir after penetrating keratoplasty for herpes simplex keratitis. *Arch Ophthalmol* 1999; **117**: 445–9.
70. Coster DJ, Williams KA. Management of high-risk corneal grafts. *Eye* 2003; **17**: 996–1002.
71. Vail A, Gore SM, Bradley BA, Easty DL, Rogers CA, Armitage WJ. Conclusions of the corneal transplant follow up study. Collaborating Surgeons. *Br J Ophthalmol* 1997; **81**: 631–6.
72. The collaborative corneal transplantation studies (CCTS). Effectiveness of histocompatibility matching in high-risk corneal transplantation. The Collaborative Corneal Transplantation Studies Research Group. *Arch Ophthalmol* 1992; **110**: 1392–403.
73. Dua HS, Azuara-Blanco A. Corneal allograft rejection: risk factors, diagnosis, prevention, and treatment. *Indian J Ophthalmol* 1999; **47**: 3–9.
74. Sloper CM, Powell RJ, Dua HS. Tacrolimus (FK506) in the management of high-risk corneal and limbal grafts. *Ophthalmology* 2001; **108**: 1838–44.
75. Thompson RW Jr, Price MO, Bowers PJ, Price FW Jr. Long-term graft survival after penetrating keratoplasty. *Ophthalmology* 2003; **110**: 1396–402.
76. Kirkness CM, Ficker LA, Steele AD, Rice NS. The success of penetrating keratoplasty for keratoconus. *Eye* 1990; **4** (Pt 5): 673–88.
77. Karabatsas CH, Cook SD, Figueiredo FC, Diamond JP, Easty DL. Surgical control of late postkeratoplasty astigmatism with or without the use of computerized video keratography: a prospective, randomized study. *Ophthalmology* 1998; **105**: 1999–2006.
78. Binder PS. Selective suture removal can reduce postkeratoplasty astigmatism. *Ophthalmology* 1985; **92**: 1412–16.
79. Seitz B, Langenbucher A, Kuchle M, Naumann GO. Impact of graft diameter on corneal power and the regularity of postkeratoplasty astigmatism before and after suture removal. *Ophthalmology* 2003; **110**: 2162–7.
80. Koay PY, McGhee CN, Crawford GJ. Effect of a standard paired arcuate incision and augmentation sutures on postkeratoplasty astigmatism. *J Cataract Refract Surg* 2000; **26**: 553–61.
81. Koffler BH, Smith VM. Corneal topography, arcuate keratotomy, and compression sutures for astigmatism after penetrating keratoplasty. *J Refract Surg* 1996; **12**: S306–9.
82. Koay PY, McGhee CN, Weed KH, Craig JP. Laser *in situ* keratomileusis for ametropia after penetrating keratoplasty. *J Refract Surg* 2000; **16**: 140–7.

83. Hardten DR, Chittcharus A, Lindstrom RL. Long term analysis of LASIK for the correction of refractive errors after penetrating keratoplasty. *Cornea* 2004; **23**: 479–89.
84. Wietharn BE, Driebe WT Jr. Fitting contact lenses for visual rehabilitation after penetrating keratoplasty. *Eye Contact Lens* 2004; **30**: 31–3.
85. Skurkovich S, Kasparov A, Narbut N, Skurkovich B. Treatment of corneal transplant rejection in humans with anti-interferon-gamma antibodies. *Am J Ophthalmol* 2002; **133**: 829–30.
86. Comer RM, King WJ, Ardjomand N, Theoharis S, George AJ, Larkin DF. Effect of administration of CTLA4-Ig as protein or cDNA on corneal allograft survival. *Invest Ophthalmol Vis Sci* 2002; **43**: 1095–103.
87. Thiel MA, Coster DJ, Williams KA. The potential of antibody-based immunosuppressive agents for corneal transplantation. *Immunol Cell Biol* 2003; **81**: 93–105.
88. Rycroft BW. The corneal graft – past, present and future. The Doyne Memorial Lecture. *Trans Ophthalmol Soc UK* 1965; **135**: 459–517.