2.6 Corneal transplantation; developments

Corneal transplants are aimed to improve vision or to relieve pain. Other benefits for patients include saving the eyeball in case of a corneal perforation or improving the cosmetic aspect of the eye. The evolution of corneal transplantation has had an impact on eye banking, the processing and selection of donor tissue.

International developments

Despite attempts since the early 1800s[285,286] it was not until the beginning of the 20th century that success in corneal transplantation came in sight. In December 1905, in the former Moravia now Czech Republic, the first successful human corneal transplant was performed by Dr Eduard Zirm on a 45 year old farm hand. The patient suffered from lime burns and both corneas were severally scarred in the centre. At present this patient would be considered a poor candidate for corneal transplantation.[75,76] His preoperative visual acuity was hand movements in both eyes. The donor was an 11 year old boy. He lost vision following an intraocular metallic foreign body injury. Zirm enucleated the blind eye and used its clear cornea for two 5.0 mm buttons. He removed the tissue with a von Hippel trephine, developed in 1888. Zirm kept the transplants in place with a bridge of conjunctiva sutured over the corneas. One of the grafts failed, the other cleared and 15 weeks after surgery the patient was sent home. A year later an ophthalmologist checking the patient's visual acuity found it to be 6/36 with a stenopeic disc. The patient lived for 3 years after surgery. Zirm died in 1944, he did not record any other corneal transplant in his 45 publications.

The evolution of keratoplasty is divided by Rycroft into four periods,[287] and recently a fifth period has been added.[288] We in turn have added a sixth period; because of the renewed interest for lamellar grafting, due to the development of special instruments, it is very likely that the eye banks will be involved in the production of lamellar grafts.

1. Inspiration (1789 - 1824)
2. Trials and frustration (1825 - 1872)
3. Conviction (1873 - 1905)
4. Achievement (1906 - mid 1970s)
5. Refinement (mid 1970s - late 1990s)
6. Revival of lamellar grafting (late 1990s - today)

Inspiration period

At the start, a French surgeon, de Quengsy, proposed in 1789 to replace the human cornea with a piece of glass. He illustrated what was perhaps the first keratoprosthesis but the surgery itself was never performed. In 1797, Erasmus Darwin, grandfather of Charles Darwin, suggested that the cornea might grow back clear after surgical removal of a scar.[288,289,290]

Period of trials and frustration

In 1824, Reisinger suggested that living tissue grafts might be used to perform a corneal transplant. Most attempts at transplantation in the 19th century were done with corneas of different species and they failed. The first successful transplant was performed by James Bigger in 1837 with a homograft. He was captured by Sahara Bedouins and the story goes that he achieved his freedom by transplanting the opaque cornea of the pet gazelle of the sheik using another gazelle's cornea. In 1844, Kissam discussed guidelines for keratoplasty, which are still accurate today, 165 years later.[288]

Period of conviction

Power was the first who recommended transplantation with tissue from the same species.[291] In 1877, von Hippel published the use of circular trephines to remove the donor and recipient corneas. This principle is still used today. The development of general anesthesia was one of the other helping factors to achieve the success of corneal grafting. Ether was used since 1846 and chloroform since 1867. Lister brought to the attention that an aseptic setting was essential for successful surgery.[288]

Period of achievements

This started with the successful transplantation performed by Eduard Zirm. Most research in keratoplasty was carried out in Europe. Freshly enucleated donor corneas from eyes with pathology were the source for the corneal transplant. Elschnig was the first who reported approximately 20 years of corneal transplantation experience.[292] He also advocated careful cleaning of the conjunctival fornix to prevent infection. By the mid 1930s, transplantation became a less elective procedure. Filatov published the successful use of cadaver corneas in an ice chest at 4°C.[83,84] Later on, the development of new surgical techniques improved the outcome of transplantation. Castroviejo developed unique surgical instruments and techniques.[293,294] Small grafts (less than 4 mm) were used, mostly fixated with overlying sutures. The most commonly used technique was the creation of square corneal transplants with a parallel razor blade. Surgical techniques and instruments were further improved by Barraquer in the 1950s.

He used donor tissue up to 6.5 mm in diameter and sutured donor to recipient with silk sutures with sharp Grieshaber needles.[295] Nylon sutures were introduced in the late 1950s by Mackensen and Harms.[288] The introduction of wide spectrum antibiotics and steroids soon after World War II provided a simple method for combating the sepsis and the antigenic response, the combination of which had frustrated the large majority of transplants in the past.

Stocker in 1952 was the first to call attention to the donor endothelium in keratoplasty.[208,296] Bourne started research after the longevity of the corneal endothelium.[249] As corneal transplantation became more successful, the demand for donor corneas increased. Eye banking began in the 1940s when Paton established the first eye bank in New York.[297] The primary goal at that time was collection of donors and donor tissue. The introduction of preservation media for the storage of corneoscleral discs in the mid 1970s increased the availability of donor tissue (see chapter 2.2 and 2.5) and the number of transplants increased. With the delivery of stored corneoscleral discs, the surgeon became more dependent on the procedures and selection procedures performed in the eye bank (see chapter 2.2).

Period of refinement and innovation

Postoperative rejection was first recognized as a distinct clinical entity by Paufique in 1948. It was further described by Maumenee in the 1960s.[298] The term low "immune privilege" was introduced to describe the low frequency of corneal transplant rejection rates. Medawar provided evidence that this is primarily due to the lack of direct vascular supply. More recently, there is evidence that the lack of antigen (Langerhans) presenting cells in the central cornea may be an important reason for the low immunogenicity. Studies, mainly carried out in Europe, demonstrated that the risk of an allograft rejection can be reduced by the use of HLA matched donor tissue.[228,299,300,301,302,303] The results of these studies had an impact on the preferred preservation method in eye banks in Europe as OC facilitated the use of HLA matched tissue.[117,212,304,305]

The number of corneal grafts continued to increase in the 1980s while the indications for grafting changed.[306,307,308] In the USA a higher proportion of pseudophakic bullous keratopathy and re-grafts were found than in Europe, probably related to the type of intraocular lenses implanted in cataract surgery.[308,309]

With the results from corneal graft registries in the 1990s (see chapter 2.7) the risks and benefits were better defined and this has had an impact again on the distribution of indications.[225,304,310,311,312] The reasons for grafting have been categorized in visual, tectonic, therapeutic and cosmetic indications. Visual indications were and still are the principal reason for grafting.[309]

New therapeutic modalities (antiviral drugs, immunosuppressive therapy), surgical refinements as trephination modification, suture techniques, astigmatism procedures and the developments of contact lens fitting[313,314,315] improved the visual outcomes during the end of the 1980s. Later modifications as toric Artisan lens implants behind the keratoplasty increased visual outcomes.[316] This changed the expectations of patients and with the revival of lamellar grafting, a new period started.

Revival of lamellar procedures

In the 1960s lamellar techniques, anterior[317] as well as posterior[318,319] have been described as alternatives for penetrating procedures. They did not become popular despite the fact that many advantages were recognized by clinicians. The procedure was very time consuming and results were disappointing due to interface haze.

At the end of the 1990s, the topic received renewed interest for several reasons. An anterior lamellar keratoplasty evolved from a very time consuming manual procedure into a microkeratome assisted surgical procedure. With this change results improved and indications for anterior grafting increased[320,321] although the numbers performed are still small compared to those of the posterior keratoplasty (personal communication Cornea Bank Amsterdam). Laboratory experiments concerning posterior lamellar keratoplasty,[322] new manual surgical approaches introduced by Melles[323,324,325] and the introduction of new surgical equipment (microkeratome, artificial anterior chamber, femtosecond laser) resulted in a tremendous increase of these procedures in the last 4-5 years. In addition to the numbers, the procedure developed from a macro- to a micro invasive surgical procedure. At first, donor tissue is mainly prepared by the surgeon. Because of the growing number of procedures, the demand for pre-cut tissue in eye banks has increased. Tissue may be prepared by hand, by microkeratome or by femtosecond laser.[326,327] The first publications show that pre-cut tissue is of good quality and safety.[328,329,330] Complications described can be attributed to the surgical technique and not to the tissue.[264,265,331]

Future of keratoplasty

Techniques for keratoplasty are continuously evolving. Surgical techniques are still developing. Laser trephination helps to improve visual outcomes with improved wound apposition and reduced astigmatism.[332,333] Sutureless or near sutureless surgery with the help of bioadhesives,[334,335] tissue welding or photochemical keratodesmos may possibly improve visual outcomes and reduces rates of neovascularisation, rejection and infection by sutures.[336] Alternatives to human donor tissue keratoplasty, as keratoprosthesis and tissue engineered corneal equivalents, might be further developments. The development of epithelial stem cell transplantation is very successful. In the furture it will be necessary to focus not only on better identification of cultured epithelial stem cells but also on their

application. Research into endothelial cell transplantation focuses on the preparation of primary or transfected human corneal endothelial cells and the development of an appropriate carrier for the cells. In all these fields, a support of the eye bank may be expected. Concomitant with the developments in grafting technique, eye banks have changed and will change from collection to storage to tissue engineering facilities.

Developments in the Netherlands

The national history of corneal grafting started in 1939. Much about the start may be found in the theses of Deutman and Kok van Alphen.[79,80] Inspired by the experiences of Castroviejo, the first transplantation in the Netherlands was performed by Deutman on June 10, 1939 in Leiden. The patient was a 54 years old male with an infection of the eye and a vascularised cornea. Surgery was performed with a surgical magnifier (x 22.5). The square graft was fixed with overlying sutures. Another two grafts followed that same year. Indications for treatment were infections with vascularisation, which today are prognostically poor cases.

During World War II not much happened, but in 1946 Pieck together with Kok van Alphen continued their transplantation efforts in Leiden. In 1953 the square grafts were replaced and the "double bladed von Graefes knife" was substituted by the Elliott trephine of 5 mm. Flieringa introduced his ring to stabilize the eye. New suture material, virgin silk was brought to the Netherlands by Hoppenbrouwer.

In 1962, Kok van Alphen was the first surgeon to perform a graft with a surgical microscope. During the 1970s Crone in Amsterdam and van Loenen Martinet in Rotterdam brought the manual lamellar grafting to perfection. Van Rij paid a lot of attention to the trephination and the model of the trephines with the objective to reduce astigmatism and improve the result of grafting. Völker-Dieben and van Rood did a lot of work to demonstrate the beneficial effect of HLA matching on the outcome of corneal grafting.

Donor tissue became more and more stored as corneoscleral discs, in MK in Rotterdam, Leiden and Groningen, in Doughman's organ culture for short-term storage in Nijmegen. Völker-Dieben transplanted the first long term preserved corneas in 1982, imported from Denmark at first and later in the year the first donor that has been stored in the Netherlands. Ever since, organ culture has been used to prolong the storage of donor tissue collected all over the Netherlands. With the realization of the risks of communicable diseases, the necessary serological screening of the donor tissue and the risks of stored corneoscleral discs in tissue culture medium require professional eye bankers. A research activity of the Netherlands Ophthalmic Research Institute aiming at the development and optimalisation of OC resulted in the sole Cornea Bank in the Netherlands for all the tissue collected by Eurotransplant and later on by Bio Implant Service Foundation.

Over the years, Völker-Dieben showed the importance of a follow-up registry which resulted

in a national Corneal Follow-up Registry in 1995. Beekhuis started corneal fellowships for young ophthalmologists in 1988 and it was his merit that the overall national level of corneal surgery increased. Melles in 1998 introduced the internationally important new technique of posterior lamellar keratoplasty and finally Nuijts introduced femtosecond corneal surgery in the Netherlands in 2007.