XIII

THE HISTORY OF CORNEAL TRANSPLANTATION

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Evolution of Ophthalmic Surgery

Cataract Surgery

One of the advantages that ophthalmologists enjoy is that they are able to directly view the pathological processes of the eye. Medical observers have been able to document the two most common causes of blindness, cataract and corneal scarring, since records began. Perhaps it was the chance observation that the spontaneous dislocation of a mature cataract from the visual axis gave some restoration of sight that prompted the technique of 'couching', a form of cataract operation first described in Sanskrit manuscripts 2000 years ago. With the aid of a sharp instrument to penetrate the eye and dislocate the lens, navigational vision could be restored in an otherwise blind eye.

Corneal surgery

Effective treatment of corneal scarring was more elusive, since complete removal of a diseased cornea required its replacement with similar transparent tissue if the integrity of the globe is to be preserved. Although the Greek physician Galen (AD 130–200) documented removal of corneal scars by superficial keratectomy, it was not until 1837 that the first successful transplantation of a cornea was recorded by an Irish physician, Bigger.[1] He had been held captive by some Bedouin in the Sahara, during which time he managed to restore the sight of a pet gazelle with a homograft from another animal. It was inevitable perhaps that the earliest corneal transplants attempted in humans were xenografts. Transient success was claimed by Kissam in the U.S., who performed a graft with porcine tissue in 1838. Further experimental work in Germany by von Hippel included a partially successful lamellar xenograft using full thickness rabbit cornea into a lamellar bed. He developed a clockwork trephine with which to cut both donor and recipient cornea.[2] The first successful full-thickness corneal allograft was performed in 1905 by a surgeon named Zirm working near Prague, who restored the sight of a 45-year-old man with bilateral corneal scarring from lime burns.[3] This early success was a spur to further experimentation, but it would not be for another 50 years that corneal transplantation became a reproducible procedure.

Early Surgical Experiences

The introduction of cocaine anaesthesia in the 1884 by ophthalmologist Karl Koller in Vienna, inspired by his colleague in neurology Sigmund Freud, was a potent stimulus to development of ophthalmic surgery. Safe and adequate anaesthesia for corneal and other anterior segment procedures could now readily be achieved, and cataract extraction through a 180° corneal incision became a standard procedure. Iridectomy and other glaucoma drainage procedures were also to become commonplace within a few years. The chief technical problem with early corneal grafting was that of fastening the transplanted tissue in place. Although sharp trephines and scissors could be manufactured to excise the diseased central cornea and to prepare the donor tissue, sutures at that time were not suitable for such fine work, particularly when watertight wound closure was required. The tissue was held in place by 'stay' sutures across the surface of the eye, which was kept closed with padding while the patient rested in bed for many days until wound closure was established. In the absence of an understanding of corneal physiology, many early corneal grafts failed because of corneal endothelial damage. This occurred either during preparation of the donor tissue, or secondary to leaking wounds with a flat anterior chamber as the lens/iris diaphragm pressed forward onto the endothelium. Between 1913 and 1955, some 3500 keratoplasties were carried out by Filatov in Russia with a success rate of around 60%.[4] In France, progress was made particularly in the application of lamellar keratoplasty by Paufique.[5]

Indications for Grafting

The main causes of corneal failure worldwide are trachoma, vitamin A deficiency, herpes simplex and other types of infectious keratitis.[6] These diseases destroy the optical function of the cornea by scarring and opacification, and by stromal melting and thinning that cause surface topographic irregularity. Although the effect of an external keratitis on vision may be profound, on corneal endothelial function it is often minimal. When grafting is carried out in these conditions it is necessary to replace only the diseased superficial stromal layers to restore normal corneal clarity and optical function. By avoiding penetration of the globe, lamellar keratoplasty gives freedom from many of the complications of a penetrating graft.

However conditions that do cause corneal endothelial depletion and failure, such as Fuchs' corneal endothelial dystrophy, and iatrogenic endothelial failure following intraocular surgery, do require endothelial replacement. For such cases a penetrating keratoplasty with transplantation of a viable donor endothelial cell layer has historically been the only effective treatment. In the absence of a clear differentiation of the types of corneal pathology being treated, penetrating keratoplasty became the standard treatment for all types of corneal disease.

Corneal Physiology

Post –war technological advances during the 1950s brought a surge of developments in all areas of medicine. Careful studies of corneal physiology were made by David Maurice that demonstrated the essential role of the corneal endothelial pump function in maintaining

corneal transparency. He observed that the cornea of a whole donor globe held in a refrigerator at 4°C becomes oedematous and hazy as aqueous diffuses amongst the stromal fibres and epithelial cells. As the globe is brought back to room temperature the endothelial pump function recommences, and transparency is restored as the fluid is pulled out of the cornea — the so called 'temperature reversal effect'. Maurice was also a pioneer in specular microscopy, a technique which allowed visualisation of the corneal endothelium both *in vitro* and *in vivo*[7] (Fig. 1). Armed at last with a clear understanding of normal corneal function, clinicians could take rational steps to enhance corneal transplantation technique, and regular success with penetrating keratoplasty became a real possibility.

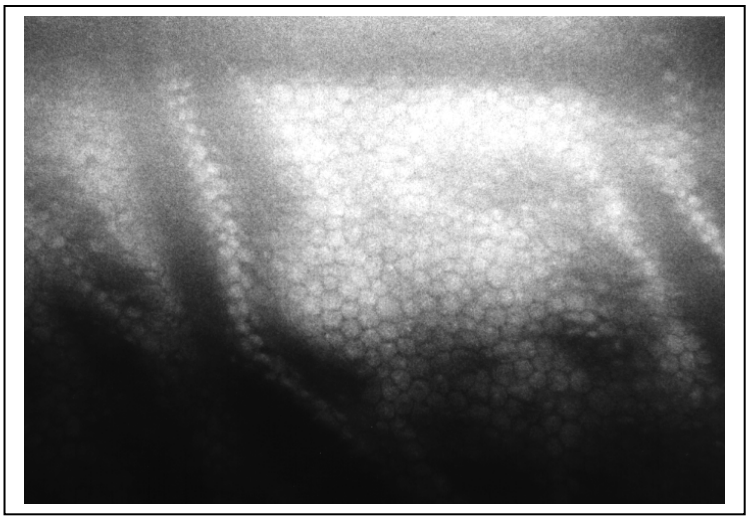

Fig. 1. Specular micrograph of corneal endothelium following penetrating keratoplasty showing a somewhat depleted cell density of 1500 cells/mm^2.

Pharmacological Advances

Pharmacological advances at that time brought the benefits of both antibiotics and steroids. Although iatrogenic infection associated with corneal transplantation is rare, it is a devastating complication because organisms inoculated directly into an eye produce an endophthalmitis which will often destroy the eye before the infection can be brought under control. However, the most important factor in enhancing the success of penetrating keratoplasty has been the introduction of steroids. In the eye it is possible to achieve high local tissue concentrations of topically applied drugs, so that there is virtually no risk of significant systemic side-effects that often occur with the systemic treatment given following solid organ transplant surgery. In the majority of corneal grafts, topical steroids alone are sufficient to control postoperative inflammation and act as prophylaxis against, or if necessary as treatment for, immune rejection. Nevertheless, in high dose or with prolonged use, steroids can take their toll on the eye. Their chief local side-effects are cataract formation, and steroid-induced glaucoma. Both, of course, lead to progressive visual degradation and introduce additional complications when assessing the quality of the outcome of the transplantation procedure.

Advances in Instrumentation

Many small incremental advances in instrumentation and surgical technique were to make substantial impact on graft outcome. Although surgeons had used magnifying loupes from the outset of corneal transplantation, the introduction of the operating microscope gave a new dimension to the accuracy of the technique. Improved microsurgical instrumentation reduced tissue damage during surgery. The introduction of nylon monofilament as a suture material, enabling perfect corneal wound closure with negligible tissue reaction, was a major step forward. Corneal wound healing is slow, and a suture may need to be left *in situ* for as long as 12 to 18 months before adequate wound strength is attained if the healing process has been inhibited by steroid treatment (Fig. 2). Another advance has been the introduction of the viscoelastic substance sodium hyaluronate, which provides ophthalmic surgeons with a method of handling delicate eye tissues with virtually no trauma during intraocular surgery.[8]

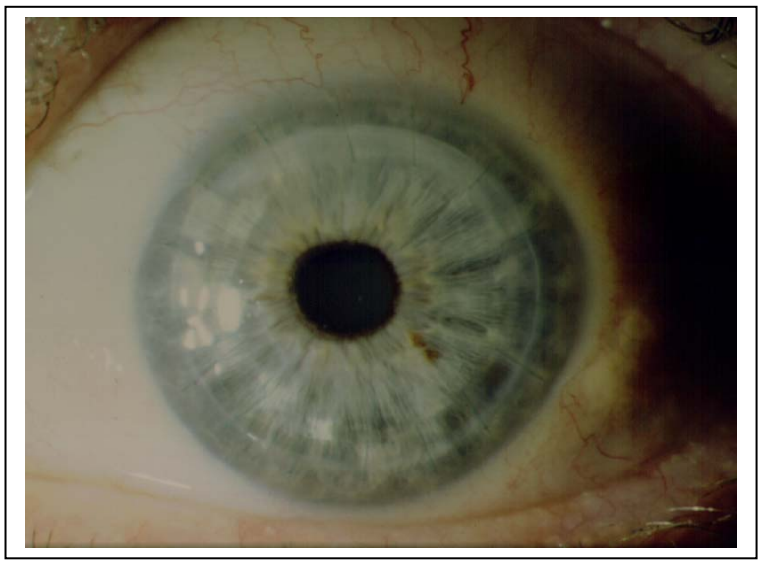

Fig. 2. A penetrating corneal graft with multiple interrupted 11/0 polyester sutures. These have the advantage over nylon of being non-biodegradable, and can give long term support to the wound.

Contact Lenses

The development of contact lenses has also had beneficial effects, both direct and indirect, on keratoplasty. They are now the mainstay in the management of the corneal ectasias such as keratoconus, and are frequently invaluable in correcting post-keratoplasty optical defects. The earliest contact lenses were of glass, with generally extremely limited wearing times. The introduction of molded scleral lenses made from polymethylmethacrylate (PMMA) in the 1930s gave greatly enhanced acceptability, and the subsequent development of the corneal contact lens by Tuohy further extended their use. In the 1970s the ‘gas-permeable’

polymers replaced the impermeable PMMA, but even today the large scleral haptic lens designs are still sometimes required in advanced corneal ectasia.

Eye Banking

Alongside the changes in surgical technique came introduction of eye banking and developments in tissue handling and storage. Historically, donor globes were harvested up to 24 hours post-mortem and the whole eye was then kept in a moist chamber at 4°C for a further 24 to 48 hours, before the corneal button for transplantation was excised for immediate transplantation. In 1974, McCarey and Kaufman in the U.S. demonstrated that by excising the cornea from the globe and placing it in a tissue culture medium at 4°C, that the endothelium could remain viable for several days.[9] Their 'MK medium' which contained TC199, Earle's salts, HEPES buffer and gentamicin remained the standard corneal preservation medium for some 15 years. This was subsequently superseded by other commercial preparations, such as KSol and Optisol, containing osmotic agents to limit corneal tissue swelling, and offering extended preservation times of a week or ten days.[10]

Techniques of Preservation

In the quest for longer term storage, much work has explored the possibility of cryopreservation of the cornea. The first successful graft using cryopreserved tissue was reported by Eastcott *et al*. in 1954.[11] In the 1960s, Casey in England and Kaufman in the U.S. published short series of clinical cases using cryopreserved tissue, with what were reasonable outcomes for the era. However, no further human studies have been published since then, despite extensive laboratory work on the subject. A different approach to extending corneal tissue preservation times is that of organ culture at 34°– 37°C. Pioneering work was carried out by Doughman in Minnesota,[12] and the system further developed by Pels[13] in Holland and Easty in the England. By placing corneas in organ culture, tissue can be preserved for four to six weeks, and the risk of transmission of infective endophthalmitis is probably reduced in comparison to 4°C storage (Fig. 3). However the organ culture system is labour intensive, and whilst it has become the favoured storage method for European eye banks, 4°C storage is still used by most banks in the U.S.

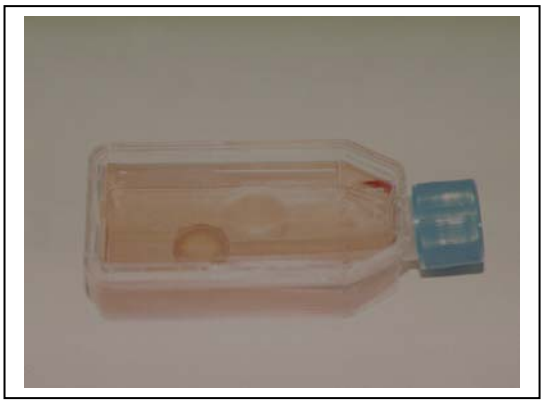

Fig. 3. A corneo-scleral segment held in organ culture medium at 34ºC can be preserved for several weeks, and the corneal endothelium can be examined through the floor of the tissue culture flask.

Eye Bank Associations

The massive increase in cataract surgery in the latter half of the 20th century brought with it a tide of complications. Surgical damage to the corneal endothelium can lead to corneal failure manifest as aphakic and pseudophakic bullous keratopathy, and these became the prime indications for keratoplasty in some the institutions. The development of eye banks and eye bank organizations such as the American and European Eye Bank Associations has done much to improve standards and quality of tissue provided for keratoplasty, and to encourage positive public attitudes towards tissue and organ donation. Eye banks in the U.S. and most European countries currently maintain supplies of corneal tissue at a level commensurate with demand. Globally however, most corneal blindness is found in countries without the resources for transplantation services.

Tissue Matching

With the increasing volume of corneal graft surgery came the possibility of studying the effect of tissue matching. Batchelor and Casey *et al*. in England was the first to show the positive benefits on corneal graft survival of matching HLA Class I in high risk cases.[14] Although these results were subsequently confirmed by other workers, the effect of matching HLA Class II were conflicting.

The high success rate of corneal grafts has been attributed to the apparent 'immunological privilege' that this type of transplant seems to enjoy. When keratoplasty is carried out without tissue-matching into an uninflamed eye with an avascular cornea (as for instance in keratoconus), a two-year graft survival with topical steroid treatment can be >90%. The situation changes dramatically when transplantation is carried out into a recipient where there has been previous inflammation and vascularisation, and in this scenario graft rejection rates can be >50% even with systemic and topical immunosuppression.[15]

Our understanding of the mechanisms of graft rejection has grown considerably in the past 15 years. The immunological privilege of the cornea can be attributed to a constellation of a wide variety of factors including the avascularity of the cornea which

diminishes access of immune cells to the anterior segment, the absence of lymphatic vessels in the cornea, the paucity of Langerhans or other antigen presenting cells, and the low level of expression of MHC antigens in the cornea. In addition, there are active mechanisms by which the immune response is controlled, some of which are unique to the eye. These include factors that inhibit T-cell and complement activation, and others which can induce apoptosis of stimulated T-cells. Presentation of intraocular antigen may also lead to a tolerogenic form of immunity termed anterior chamber-associated immune deviation (ACAID).[16] It has been shown in experimental penetrating keratoplasty that the development of sensitization to donor antigens is virtually universal. The fact that such sensitization does not always lead to rejection indicates the importance of the tolerogenic mechanisms including ACAID.

Sensitization of the recipient in low risk keratoplasty is usually by the 'indirect pathway' in which donor antigens are processed by recipient antigen presenting cells and presented in the context of host MHC to T-cells generating self-restricted or indirect alloreactive T-cells. This explains why minor histocompatibility antigens are a more significant barrier to graft success than MHC antigens in this scenario.

In the high risk setting however, the immune privilege of the cornea is eroded and host sensitization may occur through both direct and indirect pathways. Expression of donor MHC is upregulated and becomes more important in graft rejection. The failure of the American Collaborative Corneal Transplantation Study to show any benefit from MHC matching may have been because the intensive steroid treatment used in the protocol suppressed MHC expression to the extent that it was no longer a significant factor in graft survival.[17]

Refractive Errors after Keratoplasty

The restoration of corneal transparency, although a wonderful achievement, is not synonymous with restoration of vision, as many clinicians have become painfully aware. Keratoplasty may often leave considerable refractive error in the eye. The refractive properties of the cornea, and the possibility of manipulation of the kerato-refractive status of the eye, has been the subject of research for almost as long as the history of keratoplasty itself. In the 1940s, José Barraquer in Colombia devised the operation of keratomileusis to flatten the cornea as a means of correcting myopia, and the operation of keratophakia to steepen the cornea (using donor tissue) as a means of correcting hypermetropia. Because of their complexity, these techniques were never widely adopted. Refractive keratoplasty finally became a reality for corneal surgeons with the introduction of epikeratophakia.[18] In this procedure, a pre-lathed onlay graft is transplanted onto the de-epithelialised surface of a normally functioning cornea. Multicentre trials revealed that for the correction of high hypermetropia, commonly found in aphakia, this procedure effective,[19,20] but that for the correction of myopia it was less satisfactory, due to inaccurate optical outcomes. The procedure was also modified to correct corneal irregularity in early keratoconus by onlaying a graft lathed such that it had no optical power.[21] The multicentre trials of epikeratophakia used freeze-dried corneal tissue. The grafts were transplanted onto corneas which had normally functioning endothelium, and were shown to become covered with host epithelium and repopulated with host keratocytes. No rejection of the transplanted stromal

matrix was seen, and animal studies suggested that although dead donor keratocytes were transplanted, that they did not sensitize the recipient to any donor antigens.[22] Although epikeratoplasty remains an effective treatment for early keratoconus, epikeratophakia has now been supplanted by improved intraocular lens implantation techniques.

Correction of Post-Keratoplasty Refractive Errors

In penetrating keratoplasty, achieving a satisfactory optical outcome remains a challenge. Clinicians continue to be frustrated in achieving the desired optical outcome by primary intention. Part of the problem is the slowness and weakness of the corneal wound healing process. Although per- and postoperative adjustment of suture tension can improve short-term optical performance, the situation can only really be judged finally when all sutures have been removed, and often there will be considerable residual astigmatism. The development of corneal topographic analysis systems has done much to help our understanding and management of post-graft ametropia[23] (Fig. 4). Historically, adjustment of residual astigmatism has been carried out by a variety of approaches, including wound relaxing incisions, tension sutures, and astigmatic keratotomy.[24] In the past few years the introduction of excimer Laser *In situ* Keratomileusis (LASIK) has at last given surgeons the ability to connect residual spherical and astigmatic refractive defects and restore the normal optical function of the eye.[25,26] Nevertheless, this is secondary surgery, which carries the risk of precipitating wound dehiscence or graft rejection, and so cannot be considered ideal.

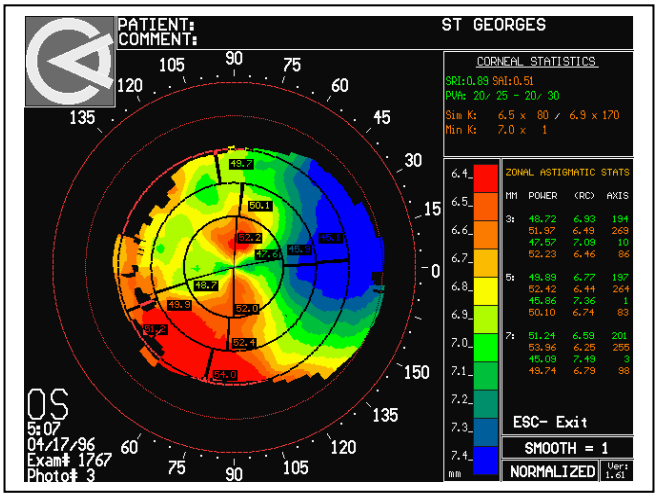

Fig. 4. Corneal topography following keratoplasty for keratoconus showing persistent steepening and irregular astigmatism, although within the optical zone the astigmatism is regular enough to allow good spectacle corrected acuity.

Guided Trephine System

A hi-tech approach to penetrating keratoplasty is exemplified by Krumeich's guided trephine system. This allows extremely accurate trephination of the host cornea with the

trephine system attached and stabilized on the globe by a vacuum suction ring[27] (Fig. 5). The donor cornea is trephined in a similar manner whilst mounted on an artificial anterior chamber. As a final step to try and ensure sphericity of the grafted tissue, a stainless steel ring can be sutured in the wound between graft and host. The added cost and complexity of this approach underlines the problem of achieving not only graft clarity but restoration of effective visual function.

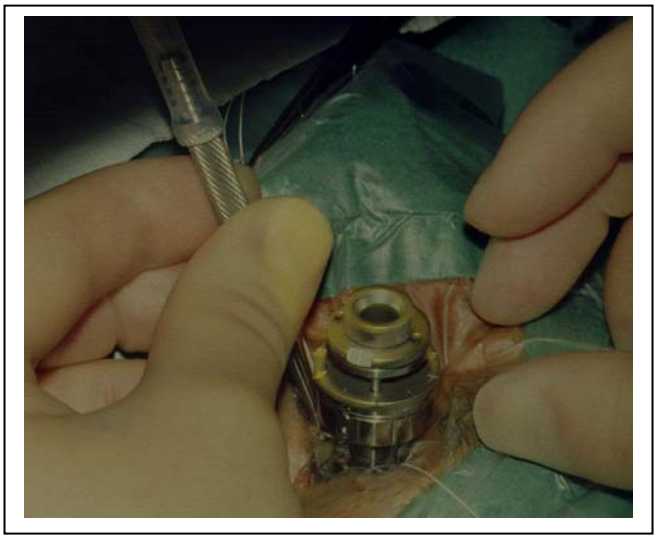

Fig. 5. The guided trephine system is stabilized on the eye by a suction ring, and allows precise vertical trephination of the recipient cornea. The donor is cut in a similar manner whilst the tissue is held in an artificial anterior chamber.

New Lamellar Techniques

Studies of graft survival following penetrating keratoplasty have shown an increased risk of rejection with larger grafts, possibly due to increased proximity of the grafted tissue to the vascular limbus, and to increased donor tissue antigenic load. To enhance graft survival, surgeons try and keep graft size small. However, small grafts create bigger optical problems due to the proximity of the graft wound to the visual axis. This can particularly be a problem when the recipient cornea has an eccentrically situated ectasia, as is commonly found in keratoconus. A new approach to this problem is now offered as surgeons use advances in microsurgical technique to explore the full potential of lamellar keratoplasty. Resection of the recipient stroma can now be made right down to the level of Descemet's membrane, and today the procedure is referred to as deep lamellar keratoplasty. The cleavage of Descemet's membrane from the posterior stroma is achieved by air dissection,[28] hydro-dissection,[29] or visco-dissection[30] (Fig. 6). Deep lamellar keratoplasty is suitable for all corneal pathologies in which endothelial function is intact, e.g. keratoconus, corneal scarring etc. Endothelial rejection is not an issue since the recipient endothelium is not replaced, and large grafts can be used, ensuring complete excision of ecstatic or diseased tissue.

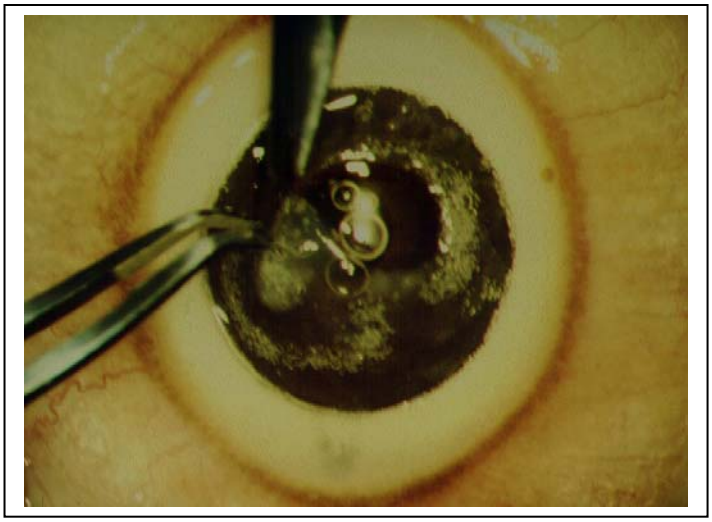

Fig. 6. Deep lamellar keratoplasty: the cornea has been injected with air rendering it opaque (white). The bulk of the central stroma has been resected (a few residual fine bubbles seen). The central stroma is being excised with scissors whilst Descemet's membrane is held clear by viscoelastic. Large bubbles are seen centrally in the anterior chamber beneath Descemet's membrane.

Epithelial Transplantation

The fine optical function of the cornea is dependent not only on the stromal contour but on the health of the corneal epithelium and its overlying tear film. When there is corneal epithelial failure, the surface of the cornea becomes conjunctivalised, vascularised, and irregular. In 1977, Thoft described conjunctival transplantation for ocular surface disease, and in the 1980s devised an operation that he named 'keratoepithelioplasty'.[31] In this procedure, thin lenticules of superficial donor stroma with their overlying corneal epithelium were transplanted to restore normal epithelial cover on the recipient cornea. With the subsequent development of an understanding that the corneal epithelium originates from stem cells located at the limbus, a more rational categorization of the many variants of corneal epithelial and conjunctival epithelial transplantation can be made. Allografts of corneal epithelial stem cells require major systemic immuno-suppression and thus have a more problematical risk/benefit ratio for the treatment of a non-life threatening condition. A recent report from Italy suggest that laboratory cultured epithelial stem cells may in the future be the ideal treatment for stem cell failure.[32] Their technique was based on earlier laboratory work by Lindberg *et al.*[33]

Endothelial Transplantation

The desirability of replacing the corneal endothelium only, when there is endothelial cell failure, has been apparent for some years. The obstacles to this have been the difficulty of getting human corneal endothelial cells to replicate in the laboratory, and the technical challenge of delivering endothelium to the diseased eye. Two recently devised methods of

corneal endothelial sheet transplantation have been described. The first, described by Jones and Culbertson in the U.S., uses a microkeratome to create a large flap in the recipient cornea, and the exposed posterior stroma is then trephined. The donor tissue is also resected with a microkeratome, enabling a 250µ thick button of posterior stroma/Descemet's/endothelium to be prepared and transplanted. The large flap minimizes postoperative astigmatism[34] [Fig. 7(a) and (b)]. The second technique, from Melles in Holland, requires a deep intrastomal pocket to be formed from a limbal wound, and the posterior stroma is then cut out with a low profile intrastromal trephine. The posterior lamellar button is extracted from the wound, and the prepared donor lamella introduced through the same route. This technique gives minimal disruption to the external corneal contour.[35] It is likely that in the future, penetrating keratoplasty will be progressively supplanted by such techniques whereby only the diseased part of the cornea is replaced.

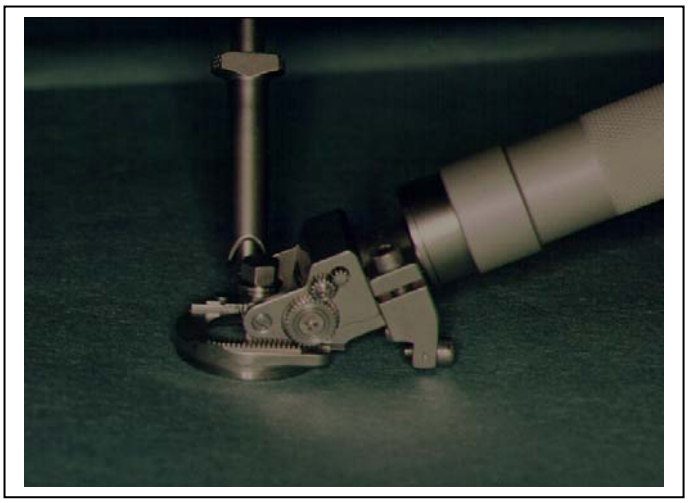

Fig. 7(a). A microkeratome shown mounted on a suction ring. The suction ring is made adherent to the eye before commencing the cut.

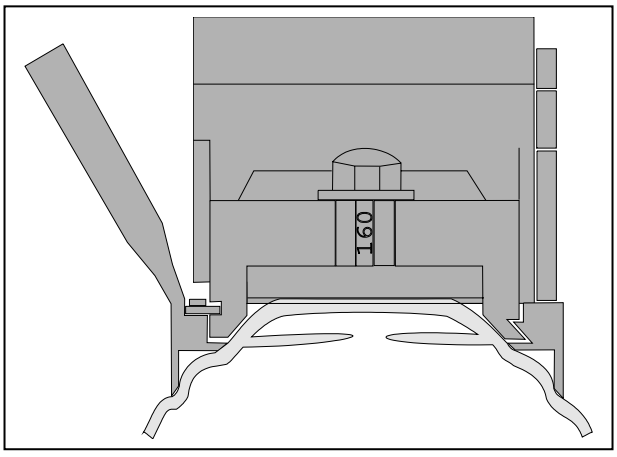

Fig. 7(b). Cross-sectional diagram showing how the microkeratome cuts a lamellar section through the cornea by flattening the central corneal area.

Conclusion

The first hundred years in the history of corneal transplantation have seen huge steps in our understanding of corneal physiology and pathology, the miracle of successful transplantation, and the mysteries of graft rejection. Further scientific advance will no doubt enable even greater success in what we can achieve. The ten million blind from corneal disease globally remain a huge unanswered challenge.[6]

References

1. Bigger SLL (1837). An inquiry into the possibility of transplanting the cornea with a view of relieving blindness. *Dublin J Med Sci* **11,** 408-417.

2. Von Hippel A (1888) Eine neue Methode der Hornhaut transplantation. *Graefes Arch Ophthal* **34,**108-130.

3. Zirm E (1906) Eine erfolgreiche totale Keratoplastik. *Archiv Ophthalmol* **64**, 580-593.

4. Filatov VP (1935) Transplantation of the cornea. *Arch Ophthalmol* **13,** 321-347.

5. Paufique L, Sourdille GP, Offret G (1948) *Les Graffes de la Cornee.* Paris: Masson.

6. Smith GTH, Taylor HR (1991). Epidemiology of corneal blindness in developing countries. *Refract Corneal Surg* **7,** 436-439.

7. Maurice DM (1974). A scanning slit optical microscopy. *Invest Ophthalmol Vis Sci* **13,** 1033-1037.

8. Holmberg AS, Philipson BT (1984). Sodium hyaluronate in cataract surgery. I. Report on the use of Healon in two different types of intracapsular surgery. *Ophthalmology* **91,** 45-52.

9. McCarey BE, Kaufman HE (1974). Improved corneal storage. *Invest Ophthalmol* **13**, 165-173.

10. Kaufman HE, Beuerman RW, Steinemann TL, Thompson HW, Varnell ED (1991). Optisol corneal storage medium. *Arch Ophthalmol* **109**, 864-868.

11. Eastcott HHG, Cross AG, Leigh AG, North DP (1954). Preservation of corneal grafts by freezing. *Lancet* **1,** 237.

12. Doughman DJ (1980). Prolonged donor preservation in organ culture: long term clinical evaluation. *Trans Am Ophthalmol Soc* **78**, 567-628.

13. Pels L, Schuchard Y (1993). Organ culture in the Netherlands. In Brightbill FS (ed.) *Corneal surgery: theory, technique, and tissue*. St. Louis: Mosby, pp. 622-632.

14. Batchelor JR, Casey TA, Werb A, Gibbs DC, Prasad SS, Lloyd DF, James A (1976). HLA Matching and corneal grafting *Lancet* **1,** 551-554.

15. Mader TH, Stulting RD (1991). The high-risk penetrating keratoplasty. *Ophthalmol Clin North Am* **4,** 411-426.

16. Streilein JW (1995). Immunological non-responsiveness and acquisition of tolerance in relation to immune privilege in the eye. *Eye* **9,** 236-240.

17. The Collaborative Transplantation Studies Research Group (1992). The collaborative corneal transplantation studies (CCTS): effectiveness of histocompatibility matching in high-risk corneal transplantation. *Arch Ophthalmol* **110,** 1392-1403.

18. Kaufman HE (1980). The correction of aphakia. XXXVI Edward Jackson Memorial Lecture. *Am J Ophthalmol* **89**, 1-10.

19. McDonald MB, Kaufman HE, Aquavella JV, et al. (1987). The nationwide study of epikeratophakia for aphakia in adults. *Am J Ophthalmol* **103** (3 Pt 2), 358-365.

20. Morgan KS, McDonald MB, Hiles DA, et al. (1987). The nationwide study of epikeratophakia for aphakia in children. *Am J Ophthalmol* **103**(3 Pt 2), 366-374.

21. McDonald MB, Kaufman HE, Durrie DS, et al. (1986). Epikeratophakia for the correction of keratoconus: the nationwide study. *Arch Ophthalmol* **104**, 1294.

22. Moore MB, Gebhart BM, Verity SM, McDonald MB (1987). Fate of lyophilized xenogenic corneal lenticules in intra-stromal implantation and epikeratophakia. *Invest Ophthalmol Vis Sci* **28,** 555-559.

23. Klyce SD (1984). Computer-assisted corneal topography: high resolution graphical presentation and analysis of keratoscopy. *Invest Ophthalmol Vis Sci* **25,** 1426-1435.

24. Troutman RC (1983). Corneal wedge resections and relaxing incisions for post-keratoplasty astigmatism. *Int Ophthalmol Clin* **23**, 161-168.

25. Pallikaris IG, Papatzanaki ME, Stathi EZ, et al. (1990). Laser in situ keratomileusis. *Lasers Surg Med* **10,** 463-468.

26. Guell JL, Gris O, de Muller A, Corcostegui B (1999). LASIK for the correction of residual refractive errors from previous surgical procedures. *Ophthalmic Surg Lasers* **30**, 341-349.

27. Ruhswurm I, Scholz U, Pfleger T, Zehetmayer M, Hanselmayer G, Skorpik C (1999). Three year clinical outcome after penetrating keratoplasty for keratoconus with the Guided Trephine System. *Am J Ophthalmol* **127,** 666-673.

28. Archila E (1985). Deep lamellar keratoplasty dissection of host tissue with intra-stromal air injection. *Cornea* **3,** 217-218.

29. Sugita J, Kondo J (1994). Deep lamellar keratoplasty with complete removal of pathological stroma for vision improvement. *Br J Ophthalmol* **81,** 184-188.

30. Morris E, Kirwan JF, Sujatha S, Rostron CK (1988). Corneal endothelial specular microscopy following deep lamellar keratoplasty with lyophilised tissue. *Eye* **12,** 619-622.

31. Thoft RA (1984). Keratoepithelioplasty. *Am J Ophthalmol* **97,** 1-6.

32. Pellegrini G, Traverso CE, Franzi AT, *et al*. (1997). Long-term restoration of damaged corneal surfaces with autologous cultivated corneal epithelium. *Lancet* **349**, 990-993.

33. Lindberg KL, Brown ME, Chaves HV, *et al.* (1993). In vitro propagation of human ocular surface epithelial cells for transplantation. *Invest Ophthalmol Vis Sci* **34**, 2672-2679.

34. Jones D, Culbertson W (1988). Endothelial lamellar keratoplasty (ELK). *Invest Ophthalmol Vis Sci* **39,** S76.

35. Melles GR, Lander F, Beekhuis WH, Remeijer L, Binder PS (1999). Posterior lamellar keratoplasty for a case of pseudophakic bullous keratopathy. *Am J Ophthalmol* **127** (3), 340-341.