
THE BOWMAN LECTURE

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PART I. HISTORICAL NOTES

SOME ASPECTS OF BRITISH, GERMAN AND EUROPEAN OPHTHALMOLOGY AROUND BOWMAN'S TIME

Sir William Bowman gave Albrecht von Graefe a portrait photograph of himself at the age of 42, signed 'To Dr Albrecht von Graefe from his sincere friend William Bowman, May 14, 1858' (Fig. 1). This picture, and another one showing Donders, were the only pictures on von Graefe's desk. At this time, Bowman was already a man of recognised accomplishments: his studies on the skeletal muscles prompted his election as Fellow of the Royal Society at the age of 25; his research on the anatomy of the kidney earned him the Royal Medal a year later (Table 1). His observations (1847) on the ciliary muscle (independently of von Brücke) and even more so those on the 'anterior elastic lamina of the cornea' have made his name a household word in ophthalmologic practice to this day and reveal his capacity for precise detailed observation, quantification and convincing interpretation. The eponym of Bowman for the corneal lamina in fact made me choose this topic for the Bowman Lecture.^{56,57} (Details of previous Lectures are given in the References.¹⁻⁵⁵)

In 1851, Albrecht von Graefe visited the United Kingdom and Ireland, meeting Mackenzie in Glasgow and Wilde in Dublin. At Moorfields Hospital in London, Donders, Bowman and von Graefe discussed the exciting opportunities the newly developed ophthalmoscope provided. Bowman generously invited the 23-year-old von Graefe to stay for a month at his home Joldwynds in Dorking.

In a letter to his friend Waldau, Albrecht von Graefe gave the following impressions of this visit to London: 'I must praise the local scientists. It is a small circle of people working with iron industriousness and penetrating thoroughness . . . As far as true lust and love of science is concerned, they certainly exceed the French and perhaps the Germans' . . . and, this I really can confirm from my own

experience. 'the English physicians excel in collegiality to foreigners and also – oh miracle – among themselves'.^{58,59} Later in the year, on 7 November, von Graefe wrote a letter to Hermann von Helmholtz asking for three of the latest version of his ophthalmoscope, not only for himself but also for Bowman in London and Desmarres in Paris, stressing 'particularly the first one [Bowman] is very interested in the scientific culture of his field and has extensive practical facilities at Moorfields Hospital; he would look forward to receiving your apparatus as soon as possible'.⁶⁰ This is quite remarkable evidence of constructive international



Fig. 1. Bowman's photograph signed 'To Dr A. von Graefe from his sincere friend W. Bowman, May 14, 1858'. This and one of Donders were the only photographs on von Graefe's desk. (Courtesy of W. Jaeger, von Graefe Collection, Heidelberg.)

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Table I. Sir William Bowman: some aspects of his life

| | |
|-----------|---|
| 1816 | 20 July, born in Nantwich, Cheshire |
| 1838 | Visited Hospitals in Holland, Germany, Vienna and Paris |
| 1841 | Fellow of the Royal Society, for studies on skeletal muscle histology |
| 1842 | Royal Medal, for research on kidney histology |
| 1847 | 'Anterior elastic lamina' of the cornea; ciliary muscle (with Brücke) |
| 1851 | Welcomed Donders and von Graefe at Moorfields Hospital |
| 1859 | Attended Heidelberg Meeting (7 of 19 from abroad) on 'The Conical Cornea . . .' |
| 1857–1862 | Supports von Graefe's iridectomy (but in a superior location) |
| 1880 | Founder and First President of the Ophthalmological Society of the United Kingdom |
| 1884 | Sir Jonathan Hutchinson delivers the Bowman Lecture ¹ |
| 1888 | Bowman Testimonial Fund established |
| 1892 | 29 March, died from pneumonia in London |

co-operation in the middle of the last century.

Bowman apparently shared this sentiment of respect and appreciation. In his remarks from 1857 and 1863 accompanying the translation (by Mr Windsor of Manchester) of Albrecht von Graefe's paper on glaucoma and the results of iridectomy, Bowman defended the new approach in the treatment of glaucoma with great emphasis. He also modified the location for iridectomy: instead of the original temporal location he recommended a superior location.^{61–63}

After he had already visited hospitals in Holland, Germany, Vienna and Paris in 1838, Sir William Bowman attended the Third Ophthalmological Society Meeting in Heidelberg in 1859. There were a total of 19 participants, seven of them from abroad, among them Donders and Arlt. It was the third informal meeting of the society. The 'Ophthalmological Society of Heidelberg' was actually founded in 1863 and is the first specialty society to have detached itself from general surgery. At the above-mentioned meeting, ten colleagues presented 17 papers. Bowman talked about orbital tumours, ethmoid exostosis and ptosis surgery. Albrecht von Graefe discussed Bowman's therapy of lacrimal sac diseases.⁶⁴

One of the many rewards associated with the privilege of giving the Bowman Lecture is the unexpected but great pleasure of studying his publications. They not only reveal the towering scientist the world knows,^{56,64–66} but also show an amazing human being with a great heart and soul who, in language still vivid, seems to speak to us to this day. He was truly a '*magnanimus*'. He went out of his way to praise the work of others. In '*On the "Immortal Helmholtz"*' – a particularly touching headline in a paper presented at the Thirtieth Meeting of the British Medical Association, 5–8 August 1862 (published only 8 weeks later in October 1863) he said: 'We are fallen on a time that will be for ever memorable in the history of

ophthalmic science, the epoch of the invention of the ophthalmoscope . . . So long as there are human eyes to suffer from disease or are cultivators of the fine art of healing, so long will the ophthalmoscope be in universal use and the name of Hermann von Helmholtz held in honour among mankind'.⁶³ And in giving a eulogy on the '*Splendid Researches of Albrecht von Graefe on Glaucoma and Iridectomy*' in 1881, at the opening of the International Medical Congress in London – 11 years after von Graefe's death! – he called him 'that bright spirit, whose premature death we have not ceased to mourn for ourselves and for science.'⁶⁷

In 1869 Bowman met von Graefe for the last time in Naples, Italy, a meeting recorded in a photograph of them both. von Graefe, though 12 years younger, is obviously suffering from the advanced stages of the tuberculosis that killed him in the following year (Fig. 2).

In 1880, Sir William Bowman was instrumental in founding the Ophthalmological Society of the United Kingdom and was its first President for three years. In 1881,^{68,69} Bowman had to write an obituary for his friend Franz Cornelius Donders: 'He had the fortune to have contributed to the advancement of his specialty and lived long enough to see the fruit of

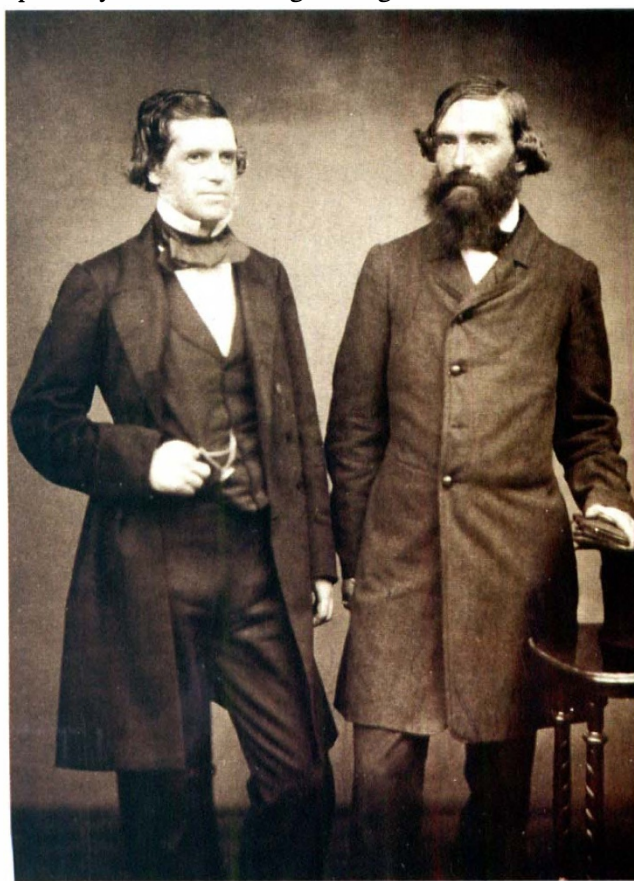


Fig. 2. Sir William Bowman and Albrecht von Graefe in 1869 at their last meeting in Naples. von Graefe, who was 12 years Bowman's junior, died from tuberculosis in 1870. (Courtesy of W. Jaeger, von Graefe Collection, Heidelberg.)

his work universally recognised'. Hirschberg is quoted by M. Amsler³² (in the Thirty-second Bowman Lecture, 1948) as saying that this would have been a very fitting obituary to Sir William Bowman himself, who died on 29 March 1892.

At the Twenty-second Annual Meeting of the Ophthalmological Society in Heidelberg, Wilhelm von Zehender read Bowman's obituary during its first session on 8 August 1892: 'Bowman once attended our meeting during the early years of our society. He was, as you all know, *primus omnium* among English ophthalmologists; nobody would have dared to challenge him for this position. Everyone who knew him will always remember his fine, noble, kind and pious character. Our Society can be proud to count among its members, in addition to Albrecht von Graefe and Donders, also William Bowman'.⁶⁴

The Ophthalmological Society of the United Kingdom inaugurated the Bowman Testimonial Fund in July 1888. The list of contributors from all over the world in September 1892 reveals the obvious admiration and affection the leaders of the international medical scientific community had for Bowman.⁵⁶ Among the 442 international contributors, 33 were from Germany and represented the elite of medical science in my country; I am happy to note that three were from Erlangen (Michel, Rosenthal and Sattler). Four of these German contributors were also Fellows of the Royal Society (Du Bois-Reymond and von Helmholtz from Berlin, Ludwig from Leipzig and Pflüger from Bonn).

ESTABLISHMENT OF THE BOWMAN LECTURE

At meetings of the Council of the Ophthalmological Society of the United Kingdom on 18 September and 11 October 1883, Dr Stephen Mackenzie moved and Dr Spencer Watson seconded the following resolution, which was unanimously agreed on, to establish the Bowman Lecture:⁷⁰ 'That in recognition of Mr Bowman's distinguished scientific position in ophthalmology and other branches in medicine and in commemoration of his valuable services to the Ophthalmological Society of which he was the first president, the Council shall each year or periodically nominate some person to deliver a lecture before the Society to be called "The Bowman Lecture" which shall consist of a critical résumé of recent advances in ophthalmology or in such subjects as the Council shall elect or in any original investigation and shall be delivered at a special Meeting of the Society held for the purpose at which no other business shall be transacted.' The Bowman Lecture served as an example to establish other lectureships.^{71,72}

Donders was invited to give the first lecture but declined (M. Hallendorff, personal communication).

In 1884 Sir Jonathan Hutchinson¹ initiated The Bowman Lecture with a paper on 'Certain Diseases of the Eye to Gout'. Four of the first 19 Bowman Lecturers were from Germany. In the third lecture, in 1886, Wilhelm von Zehender of Rostock, the co-founder (with Albrecht von Graefe) of the journal *Klinische Monatsblätter für Augenheilkunde*, which is one of the first ophthalmologic journals, talked about 'Parasitic Diseases of the Eye'. In the eighth Lecture, held in 1892, Theodor Leber of Heidelberg spoke on the 'Present Position of our Knowledge of Inflammation'.⁸ In 1907, Hubert Sattler of Leipzig in the sixteenth Lecture discussed 'The Pathology and Treatment of Myopia'.¹⁶ I particularly enjoyed his introductory comments – not only because he was originally from Leipzig (where I went to medical school) but also because he served in Erlangen as the second Chairman of the Department of Ophthalmology and is thus one of my predecessors. His vivid account of a visit to Bowman recalls 'the privilege of seeing Sir William Bowman at work on Tuesday and Friday in Moorfields Ophthalmic Hospital' and admires him as a 'scientific practitioner' and 'surgeon of unequalled skills', also stressing the 'winning kindness he bestowed on me, a young man without merit at that time'.

In 1914, W. Uthoff of Breslau in the nineteenth Bowman Lecture discussed 'Ophthalmic Experiences and Considerations on the Surgery of Brain Tumours and Tower Skull'. He characterised Bowman as follows: 'for him there existed no territorial boundaries in science, a circumstance which was ever gratefully recognised in foreign countries. Both at home and abroad, he was considered a man of learning and a gentleman in the truest sense of the word'. And Uthoff expressed the wish that in Bowman's spirit 'many individuals as well as nations be ever ready to acknowledge without envy the merits of others and be ever willing to learn one from the other'.¹⁹ Only a few months after this sincere declaration, Europe drowned in catastrophes for several decades.

The sentiments voiced by these four former Bowman Lecturers from Germany are shared by my colleagues and myself, while we all work together with our fellow ophthalmologists for closer co-operation in ophthalmology within the European Union. Since 1986, the European University Professors of Ophthalmology (EUPO) and, since 1992, the European Board of Ophthalmology (EBO) have tried to be constructive elements in advancing this spirit. Their goal is to associate and include European ophthalmologists still outside the European Union for the sake of the patients. It is to be hoped that European ophthalmologists will then be able to contribute even better to international ophthalmology.

PART II

CORNEAL TRANSPLANTATION IN ANTERIOR SEGMENT DISEASES

The special immunological privileges of the cornea allowed Zirm,⁷⁴ as early as 1905, and many others in ophthalmology following him, to be pioneers in human transplantation – so it is an old-established procedure and there are numerous experts.^{75–98} An encyclopaedic approach is neither intended nor possible here, but I shall attempt to touch on the following four aspects of the subject in an eclectic fashion:

1. Spectrum of indications for corneal transplantation: Why are optical indications only part of the wide spectrum of different reasons for performing a corneal graft? (Figs. 3, 4)
2. Some aspects of surgical technique: How does Bowman's lamina represent a 'critical structure' in corneal surgery? Are there advantages to a non-mechanical trephination of the cornea in penetrating keratoplasty, e.g. with the 193 nm excimer laser?
3. Corneal graft-versus-host effects: What can we learn from looking more closely at the often disregarded effects of the corneal transplant on the recipient's cornea?
4. New approaches to some old problems in corneal transplantation.

SPECTRUM OF INDICATIONS FOR CORNEAL TRANSPLANTATION

Obviously corneal transplantation is usually done for optical indications and the graft is placed in the centre of the cornea. Tectonic corneal transplants at an eccentric location are less often discussed – although they are essential for preservation of the globe.

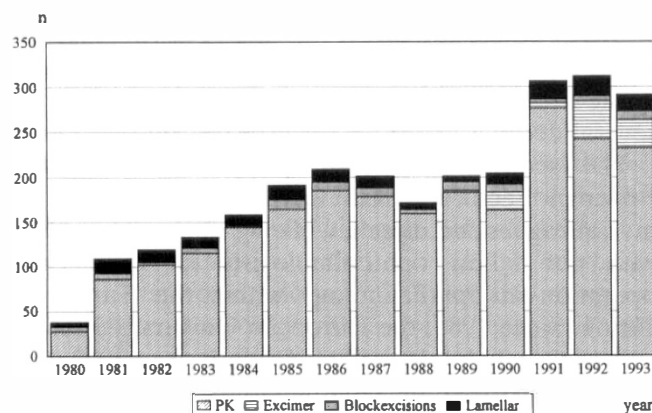


Fig. 3. Corneal transplantations performed at the Department of Ophthalmology, University Erlangen-Nürnberg in Erlangen 1980–1993. PK, conventional penetrating keratoplasties. 'Excimer' indicates non-mechanical trephination in PK with the 193 nm excimer laser along a metal mask; this was first performed on two patients in June 1989. Block excision includes eccentric tectonic corneoscleral grafting.

Tectonic Eccentric Corneoscleral Transplantation

Corneoscleral Graft after Block Excision for Anterior Uveal Tumours

Full-thickness grafts are necessary to close iatrogenic defects in the eye wall following block excision.^{100–104}

If anterior uveal tumours involve the angle of the anterior chamber, it is impossible to detect the degree of scleral invasion clinically, especially if the tumour cells are not pigmented. But we must be certain that the tumour is indeed strictly localised and that there is no evidence of tumour cell shedding into the aqueous. An effort must be made to assess the 'biocytology' of cells on the surfaces of the lens, iris and angle structures. This is worthwhile and it is also possible to study individual cells at the slit lamp with $\times 40$ magnification in order to distinguish malignant from benign melanocytic cells.

'Biocytology' should be attempted in every examination of tumour of the anterior uvea. The sometimes loosely used term 'pigment dispersion' actually covers several entirely different phenomena. We can recognise with relative ease, particularly on light-coloured irises, the following morphological elements. (Unfortunately due to physiological pulsation and microneystagmus they are rather difficult to photograph!) *Mature benign melanocytes* are an everyday sight on the central anterior lens surface as remnants of the pupillary membrane and at the margins of naevi of the iris. These obviously benign melanocytes show bulging nuclei and a dendritic pattern. *Malignant melanocytes* look quite different, are more fusiform and reminiscent of those growing

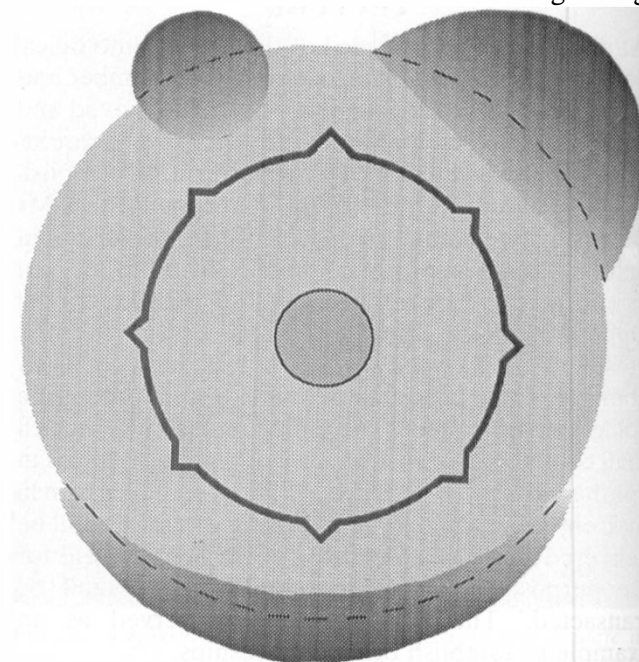


Fig. 4. Spectrum of corneal transplantation: central optical indication, and various tectonic corneal grafts at the limbus.

in tissue culture. *Melanin granules* from the iris pigment epithelium are also familiar. They float freely in the anterior chamber or are phagocytosed in corneal or trabecular endothelial cells as part of juvenile pigmentary glaucoma, pseudoexfoliation syndrome, diabetic pigment epithelial iridopathy, or following contusion or local long-term mydriatic therapy. *Melanophages* containing mainly uveal melanin granules are evident in areas of iris stroma necrosis following pupillary block in angle closure glaucoma, zoster ophthalmicus or herpetic keratouveitis. *Macrophages* containing haemosiderin or lipofuscin are more difficult to make out as they show less contrast to the surrounding iris tissue.¹⁰⁵

Our technique of block excision for uveal tumours¹⁰⁰⁻¹⁰⁴ and epithelial ingrowth has been modified only in minor details: Prophylactic retinopexy is not indicated if the area of resection does not reach 4-5 mm behind the limbus. If the block excision reaches more posteriorly, cryocoagulation or laser coagulation of the peripheral retina is necessary to prevent retinal detachment after excision. As the ciliary muscle is completely removed in the sector of resection, separation of the anterior uvea from the sclera in the sense of a cyclodialysis does not occur. Intraoperatively temporary controlled arterial hypotension¹⁰⁶ reduces the haemorrhage from the wound edges of the ciliary body – as does bipolar cautery of the ciliary artery using minute forceps. The composite sclerocorneal graft is as reliable as the pure corneal transplant formerly used. It is fixed with direct 8-0 or 10-0 interrupted sutures at the scleral wound edges, with running 10-0 nylon at the corneal cuts.^{103,104}

Results. Wound leaks have never been observed in our total series of more than 140 block excisions followed by an eccentric tectonic corneoscleral graft. Immune reactions of the eccentric grafts occur in almost all eyes after varying intervals with a few notable exceptions (Figs. 5, 6). Mortality after 90 block excisions for tumours compares favourably with series of enucleations; the functional results are acceptable.

Corneoscleral Graft after Block Excision for Diffuse and Cystic Epithelial Ingrowth

This approach is used in analogy to excision for anterior uveal tumours to prevent recurrences.^{103,107-109} With the exception of small epithelial implantation cysts within the iris stroma, the delicate lining of the cyst, which is sometimes made up of only one or two layers of epithelial cells, is always fused to the anterior ciliary body face and is so friable that it cannot be separated – even by the most skilful microsurgical manoeuvre – from the adjacent tissues of the anterior segment of the eye. Therefore the neighbouring cornea and sclera are used as a ‘shell’

for complete block removal of the invading epithelium. With the exception of a grossly visible external fistula, the sometimes labyrinthine course of the invading epithelial strands cannot be detected by clinical means as is evident from histopathological examination. In our view, the only approach to removing all non-pigmented transparent ducts between surface epithelium and intraocular cyst is to remove the adjacent cornea and sclera.

At present the resulting defect in the eye wall can be closed only by a *full-thickness corneoscleral graft* (Fig. 6). We have learned to decrease the size of the defect in the eyewall by shrinking the diameter of the cyst by a combination of draining it externally (through a transcorneal stab incision involving tissue later removed) and compressing it with Healon injected into the anterior chamber.

Results. In our experience with more than 60 block excisions for cystic and diffuse epithelial ingrowth, no recurrence was seen and the functional results are acceptable.¹⁰⁸ We therefore suggest that our approach currently seems to be the therapy of choice.

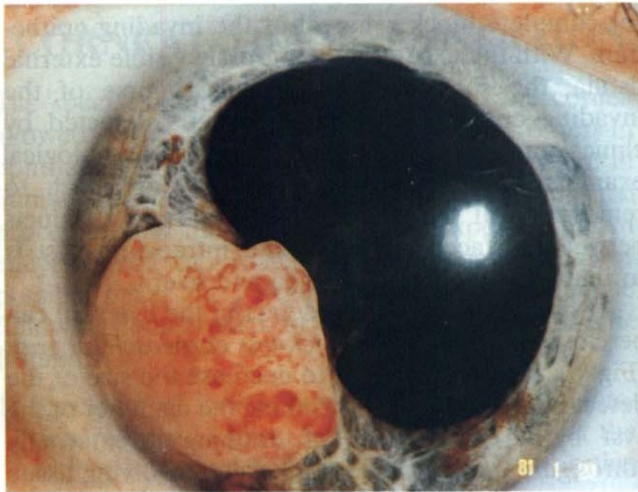
Corneoscleral Graft after Block Excision for Congenital and Infantile Cysts of Iris and Ciliary Body

Congenital ‘iris cysts’ are practically always attached not only to the retrocorneal surface but – very much like cystic epithelial ingrowth – to the anterior ciliary body face.^{109,110} Some can be traced to amniocentesis.¹¹¹ We are therefore convinced that these processes require the same approach as cystic epithelial ingrowth, even though at first sight this may be judged radical!

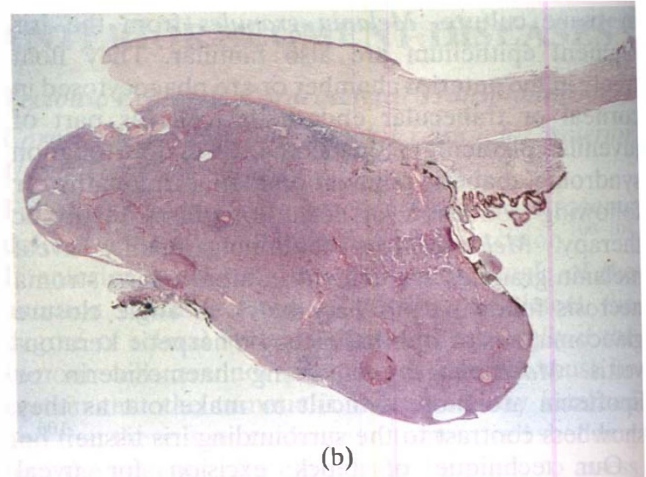
Results. In our small series of 7 patients treated by block excision and full-thickness corneal graft, we achieved a cure without recurrence.^{110,111} Less radical measures may be followed by a 25% enucleation rate, in addition to other evidence of incomplete removal.^{112,113}

Other Indications for Eccentric Tectonic Corneal Transplantation

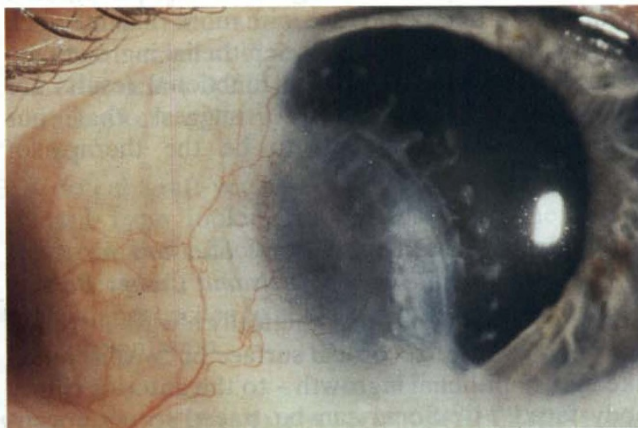
Simultaneous ‘Direct Cyclopexy’ and Patch Graft for Persisting Ocular Hypotony Syndrome. Indications for patch grafts are a combination of external fistula and extensive cyclodialysis after trauma: We treated in this way 3 eyes from a series of 40 consecutive patients with traumatic cyclodialysis. A full-thickness corneal graft is fixed in a deep lamellar scleral bed. Our technique of direct cyclopexy¹¹⁴ is a modification of the approach used by McCannel and Mackensen. The critical reapposition of the severed ciliary muscle to the scleral spur can be performed under direct microscopic control through the remaining deep scleral layers after a thick lamellar limbus-based flap has been made.



(a)

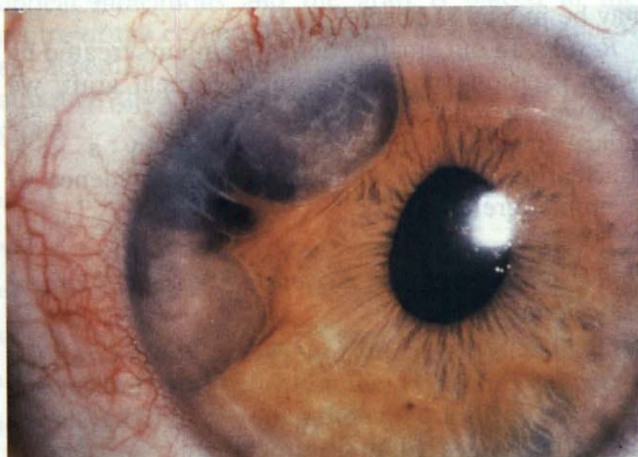


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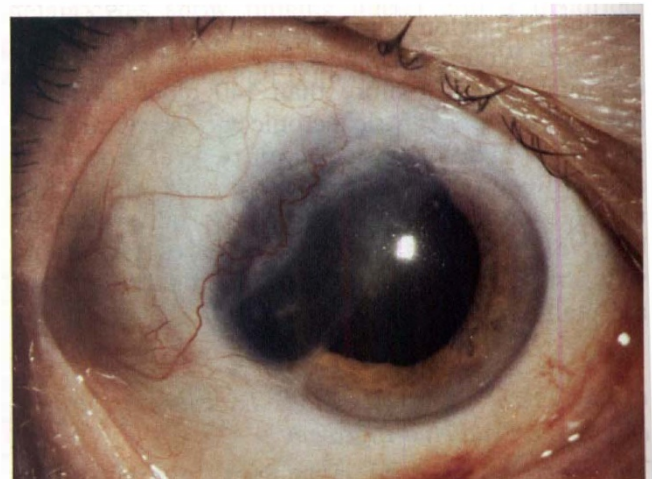


(c)

Fig. 5. Tectonic corneoscleral graft after block excision for malignant melanoma of the iris and ciliary body. (a) Pre-operatively, after recurrent anterior chamber haemorrhage in a 47-year-old man. (b) Histology: mixed malignant cell melanoma (PAS-haematoxylin). (c) Thirteen years after block excision and tectonic corneoscleral graft of 7.5 mm diameter reaching 3.5 mm behind the limbus: the graft is vascularised and opaque.



(a)



(b)

Fig. 6. Tectonic corneal graft after block excision for a rapidly growing cystic epithelial ingrowth 2 years after puncture trauma in a 45-year-old man. (a) Pre-operatively. (b) Nine years after 10 mm block excision and tectonic corneoscleral graft: as an exception to the rule, the corneal transplant remains clear.

Results. In our total series of 50 eyes, persisting peripheral anterior synechiae did not develop; there was a transitory post-operative pressure rise for a few days, but no persisting secondary glaucoma occurred.¹¹⁵

Patch Graft in Peripheral Corneal Defects. Peripheral marginal degeneration, Fuchs–Terrien's keratolysis or peripheral corneal perforations, and both infectious and other ulcers following trauma,^{116–118} are indications for using this technique. The eccentric

full-thickness crescent graft is fixed end-to-end to the central corneal wound edge and placed in a very deep lamellar scleral bed. Preservation of the scleral spur appears to be crucial.¹¹⁷ Removal of the scleral spur might result in cyclodialysis. The corneal graft is then fixed in the lamellar bed overlying the scleral spur using interrupted sutures. The suturing is facilitated by undermining the posterior scleral wound edges by means of lamellar dissection.

Neglected, Perhaps New Optical Indications for Corneal Transplantation

The usual optical indications for corneal transplantation are known to all ophthalmologists and do not need to be mentioned here. Technical details are discussed in the section on Aspects of Surgical Technique. Here I will focus on new entities.

Endothelial Keratopathy in Pseudoexfoliation Syndrome ('PEX Keratopathy')

In 1917, before slit lamps were in general use, Lindberg¹¹⁹ described pseudoexfoliation syndrome as characterised 'by peculiar deposits on the anterior lens surface, resembling the changes seen in glass blower's cataract'. Its clinical significance as a vicious type of glaucoma was stressed as early as 1925 by Vogt, who called it 'glaucoma capsulare'.¹²⁰ The exact role of the pseudoexfoliation material among other types of chronic to subacute glaucoma is still controversial.^{121,122} Recently, interest in pseudoexfoliation syndrome has been renewed by observations of a markedly increased risk of vitreous loss in extracapsular cataract extraction explained by the diminished mydriasis or mainly by the instability of the zonular apparatus, clinically often recognisable as phacodonesis.¹²³ The reasons for zonular instability have been demonstrated electron-microscopically by striking alterations at three crucial regions: (1) at the anchoring of the zonular fibres in the non-pigmented ciliary epithelium, (2) the enzymatic erosion at the tips of the ciliary processes and (3) enzymatic erosion at the insertion in the anterior lens capsule.¹²⁴

As was first shown in our laboratory¹²⁵ – and quickly confirmed by others¹²⁶ – pseudoexfoliation syndrome is not exclusively an intraocular process, but also involves extraocular muscles, the walls of vortex veins, meninges of the optic nerve, and is, in fact, a *systemic alteration* involving heart, lung, liver, kidney, skin, meninges and gallbladder.

Corneal Endothelial Decompensation. In view of the systemic findings, it is no longer surprising that our clinical observation of corneal endothelial decompensation in pseudoexfoliation syndrome – even with moderate rises in the intraocular pressure, e.g. with diagnostic mydriasis¹²⁷ – is indeed caused by direct involvement of the corneal endothelial cells (Fig. 7). This has quantitative and qualitative aspects: (1) The

number of corneal endothelial cells is significantly decreased, even without increased intraocular pressure, and these cells show alterations.^{128,129} (2) There is clear evidence of direct *production of pseudoexfoliative material* by corneal endothelial cells themselves^{130,131} (Fig. 8).

The capacity of the corneal endothelial layer to compensate for corneal hydration is apparently enormous even if the number of cells decreases and individual endothelial cells are sick (Fig. 8). Clearing of the cornea by reduction of a moderate intraocular pressure rise from approximately 30 mmHg to about 20 mmHg is often striking. However, the limits of compensation are reached if the affected endothelial cells are additionally damaged by intraoperative traumatic manipulation. The surgeon can therefore be unpleasantly surprised by a cloudy cornea in eyes with pseudoexfoliation syndrome on the first post-operative day even following gentle glaucoma or cataract surgery.^{127,130} In the advanced stages of pseudoexfoliation syndrome, the corneal endothelial decompensation may become irreversible and may thus present an indication for keratoplasty, above all in very old patients. We performed penetrating keratoplasty in 7 such patients. Three of these showed clear evidence of local production of pseudoexfoliative material in the remaining endothelial cells.¹³¹

Differential Diagnosis: Cornea Guttata. Pseudoexfoliation syndrome keratopathy can be associated with cornea guttata (as an unspecific alteration, e.g. after stromal keratitis, iritis or contusion). The differential diagnosis has to deal with idiopathic 'cornea guttata' and Fuchs' endothelial-epithelial corneal dystrophy.¹³²⁻¹³⁶ There are obvious similarities and differences: Both are not confined to the cornea. Aside from the corneal endothelial decompensation, both develop a nuclear cataract sooner or later. But in classical Fuchs' corneal dystrophy, the iris stroma and epithelium are not affected, there is no phacodonesis, the incidence of open-angle glaucoma is not significantly increased and pseudo-uveitis is absent (Table II).

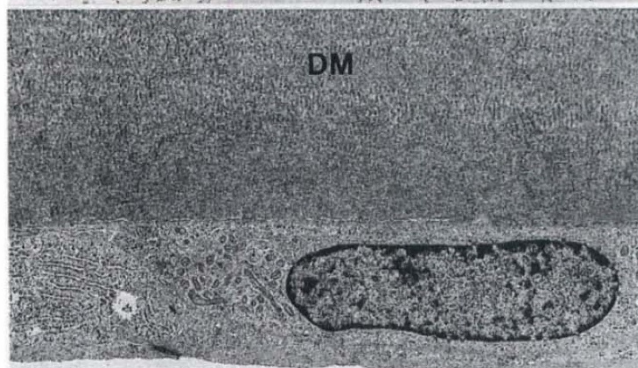
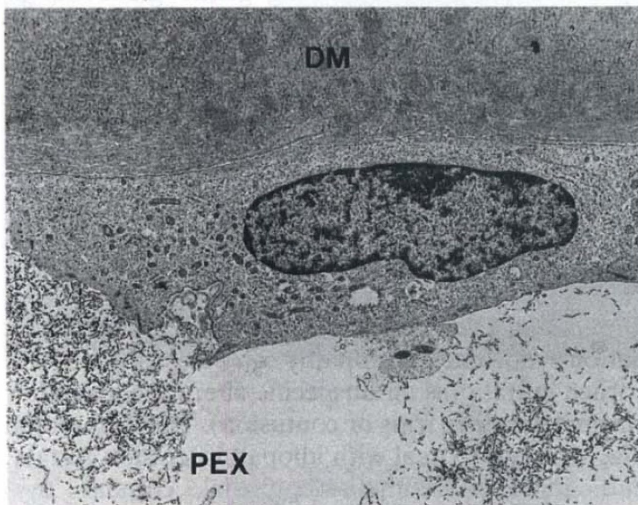
Melanin Dispersion. Trabecular pigmentation with corneal endothelial decompensation should alert the ophthalmologist to the possibility of (*PEX*) keratopathy if other reasons for pigment dispersion, such as poorly controlled diabetes mellitus, can be ruled out. Perhaps PEX keratopathy covers the entity '*atypical Fuchs*' as used in the past. As life-expectancy increases, I suspect that we are going to see the diffuse corneal endothelial decompensation caused by PEX keratopathy more often. We should then pay special attention to the surgically relevant phacodonesis and open-angle glaucoma. Clinically, this endothelial decompensation can be distinguished from the corneal oedema in cornea guttata and



(a)



(b)



(c)

Fig. 7. Corneal endothelial decompensation with massive intraocular in pseudoexfoliation syndrome (PEX keratopathy) in a 78-year-old man with normal intraocular pressure before penetrating keratoplasty. (a) Opaque, diffuse oedematous cornea: note the small round pupil without evidence of pupillary block. (b) Slit lamp view. (c) Above: Electron micrograph of the corneal button obtained at penetrating keratoplasty. The PEX fibres (PEX) are locally produced by endothelial cells in surface pits of the cell membrane. No PEX fibres are seen inside cells. Below: A neighbouring endothelial cell may be normal in contact with Descemet's membrane (DM). (From Naumann and Schlötzer-Schrehardt.¹³¹)

Fuchs' corneal dystrophy, which starts centrally and moves peripherally, as well as from bullous keratopathy, e.g. following anterior chamber lens implantation, spreading from the periphery to the centre (Fig. 9). Finally, PEX keratopathy may coexist with other diseases of the corneal endothelium, which explains the spectrum of decompensations.

Nuclear Cataract. As the keratopathy in PEX syndrome is often associated with a nuclear cataract, simultaneous corneal transplantation and extracapsular cataract extraction is required. Here it is important to make the diagnosis and be especially aware of the instability of the zonular apparatus in this condition.¹³⁷⁻¹⁴⁰

results of penetrating keratoplasty are extremely disappointing. In spite of numerous corneal transplantations and countless post-operative examinations – under general anaesthesia! – too many of the eyes end in atrophy of the globe.¹⁴⁴ We have therefore performed in 22 eyes just a simple optical sector iridectomy with no intra- or post-operative complication and gained gratifying functional results.¹⁴⁵ As all these patients were first seen with manifest nystagmus the functional results are not fabulous, but much better than the reported results after penetrating keratoplasty. Perhaps the situation can be summarised by stating that ‘the better can be the enemy of the good’.

SOME ASPECTS OF SURGICAL TECHNIQUES

Nuances of surgical technique are of particular importance in the delicate procedure of corneal transplantation.⁹³ The principal goals are: (1) ensure water-tight wound closure at the end of the procedure to restore the anterior chamber completely without obtaining anterior synechiae, (2) to keep damage to the graft endothelium to a minimum, and (3) to reduce the risk of post-operative complications such as wound dehiscence, immunological allograft reaction and suture-induced short-term and long-term residual astigmatism.

Surgical Significance of Bowman's Lamina in Corneal Surgery

In Bowman's own words, written in 1847, ‘the anterior elastic lamina of the cornea is 1/1200 to 1/1000 inch thick and the maintenance of its exact curvature is of primary importance to vision’; ‘this arrangement might, I imagine, be shown on mechanical principle to be the best possible for the maintenance of the convexity of the front of the cornea’.⁵⁷ Consequently, it is a determining factor for the refractive power of the cornea and particularly of any astigmatism. It is the most important structure to be considered in the inevitable scarring after photorefractive keratectomy.¹⁴⁶ It is also resistant to corneal oedema, such as in bullous keratopathy, and is long preserved in proliferative and even neoplastic processes originating from the limbus cornea.⁹³

The fact is sometimes overlooked that the presence or absence of Bowman's lamina also determines the anchoring of the 10-0 nylon sutures.^{147,148} If post-operatively a loosening of the 10-0 nylon suture occurs it is always in areas where Bowman's lamina was absent. If Bowman's lamina is missing in parts of the patient's cornea, this is considered a contraindication for a *running* suture and we try to modify the width of the suture bite for *single* interrupted sutures in such a way that the suture runs through areas of Bowman's lamina if

possible. In preparatory lamellar keratoplasty also, Bowman's lamina seems to be the most important structure.⁹³ The anchoring of 10-0 sutures may be deficient in its absence, particularly in children.^{149,150}

Non-mechanical Trephination with the 193 nm Excimer Laser in Penetrating Keratoplasty

Disadvantages of Mechanical Trephination

All methods of mechanical trephination are associated with three principal disadvantages: (1) The mechanical force leads to deformation of the tissue and therefore to some degree of deviation of the intended cut. (2) This deformation differs between donor and recipient cornea, resulting in a ‘vertical tilt’ (Fig. 10). (3) As all surgeons know, the fitting of the donor tissue into the malleable recipient cornea is extremely difficult to achieve in perfect symmetrical fashion. Therefore some degree of asymmetrical placement and rotation of the donor tissue *in situ* of the patient's cornea leads to ‘horizontal torsion’ (Fig. 10). Since von Hippel (1888) developed a trephine with a clockwork motor¹⁵¹ many other manual and motor-driven trephines have been developed.^{152–154} However, the principal difficulty remains. We therefore disagree with Olson,¹⁵⁵ who believes that ‘future

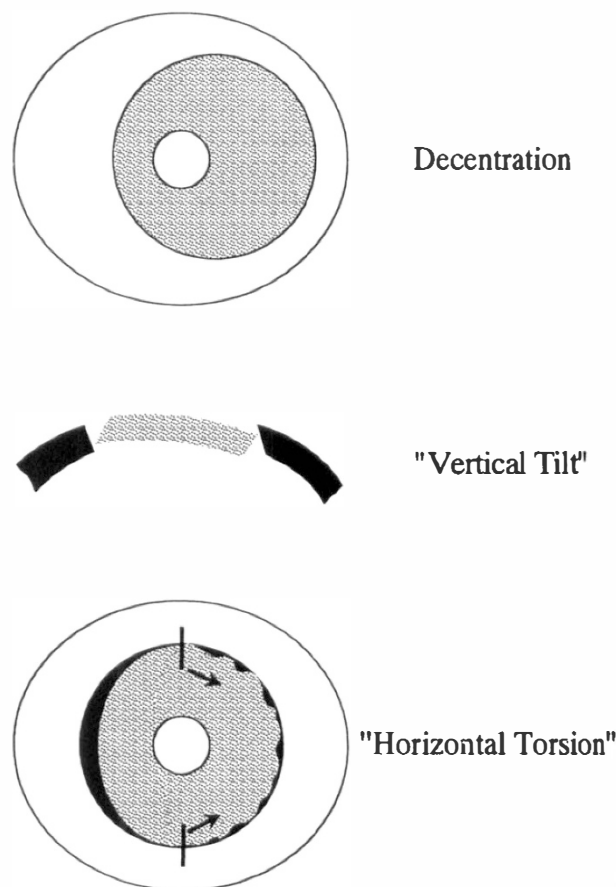


Fig. 10. Typical deformations in conventional penetrating keratoplasty. Mechanical trephination by hand or motor-driven may lead to decentration of the graft, ‘vertical tilt’ and/or ‘horizontal torsion’ (bottom).

development in penetrating keratoplasty may move in the direction of greater mechanisation'. On the contrary, we suggest that on theoretical grounds alone, the future will be reached by non-mechanical methods of trephination.¹⁵⁶

Arguments for and Principles of a Non-mechanical Approach with 193 nm Excimer Laser Trephination

For our experiments and later applications to patients, we used the Meditech 193 nm excimer laser.¹⁵⁶⁻¹⁶⁰ Tissue behind a metal mask is protected

from the effects of the excimer laser (Fig. 11). Exposed tissue evaporates without mechanical or thermal effects. The invisible laser beam is guided by a red helium-neon aiming laser beam, but the effect of the excimer laser itself is visible at the edge of the metal mask by its fluorescence. Exposure of the corneal tissue at the edge of the metal mask is under direct microscopic control and the procedure can be interrupted at any stage.

Arguments for using the excimer laser are the following: (1) As there is no mechanical contact

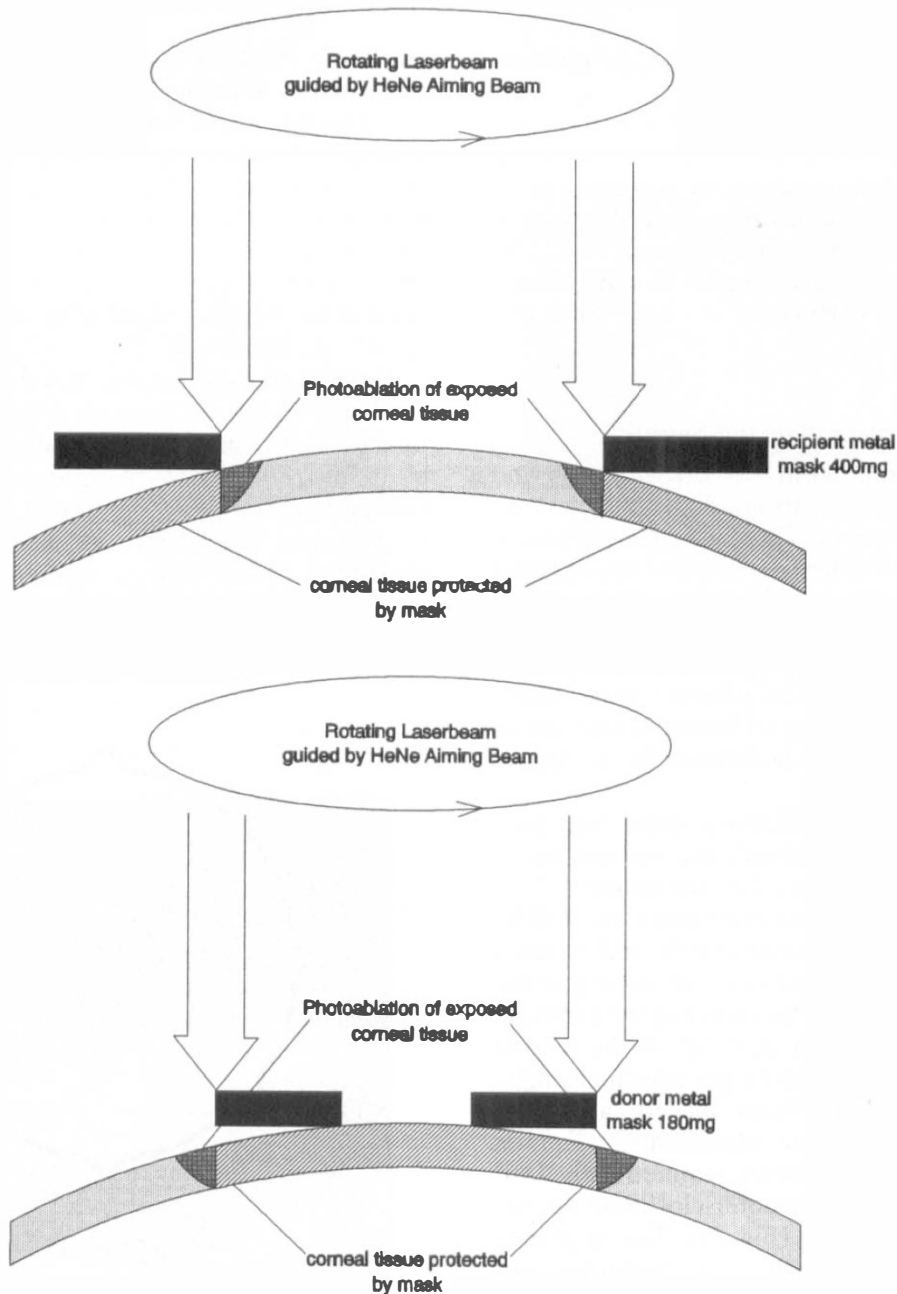


Fig. 11. Principle of non-mechanical trephination with the 193 nm excimer laser along a metal mask. Half of the 1.5 mm beam is on the mask, the other half on exposed cornea. Tissue behind the mask is protected. Features of the cut are practically identical for the patient's and the donor cornea. Above: Patient's cornea with open recipient mask. Photoablation of corneal tissue at the inner edge of the metal mask results in a penetrating cut until aqueous prevents further penetration. Below: Donor cornea (from a whole eye or a corneoscleral ring fixed in an artificial anterior chamber) with donor mask. Photoablation is performed at the outer edge of the mask.

during cutting, practically no deformity of the tissue is possible (the weight of the metal mask ranges from 90 to 400 mg). (2) If the donor and recipient corneas are each placed horizontally beneath the perfectly horizontally placed metal mask, the wound surfaces of graft and patient are practically identical. (3) As the entire procedure is visible under the microscope, centration is facilitated. (4) Any shape of the trephine opening can be chosen. This is in contrast to mechanical methods that favour a circular outline of trephination. (5) As soon as the anterior chamber is opened, the cutting process is stopped by the outflow of aqueous.¹⁵⁶⁻¹⁶⁰

Before the procedure was applied to patients, extensive animal experiments on pigs' eyes were performed to verify the technical details; trephination had to be checked, mutagenic effects on corneal tissue had to be ruled out, both on corneal and on other extra- and intraocular tissues, and the wound-healing mechanism had to be analysed.¹⁵⁷⁻¹⁵⁹ On 16 June 1989 non-mechanical trephination by 193 nm excimer laser was performed on the first two patients.^{160,161}

Non-mechanical Trephination and Suturing

Trephination is possible from both the whole eye and a corneoscleral ring measuring 16 mm, fixed in an artificial anterior chamber. The metal mask is placed on the centre of the donor cornea and the excimer laser guided along the outside of the mask, which today has seven orientation teeth of 0.15–0.2 mm, in addition to a more prominent orientation tooth of 0.2–0.4 mm (Figs. 12–14). The patient's mask shows eight corresponding notches of identical size on its inner side. Centration is facilitated by a central opening in the donor mask.

Non-mechanical trephination is possible only until the anterior chamber is opened; the outpouring of aqueous stops further cutting. The remaining 0–10% of the deeper corneal stroma must therefore still be cut by scissors. The orientation teeth and notches allow fitting of the transplant tissue according to the 'key-lock principle'.¹⁶²⁻¹⁶⁷ Placement of the principal sutures is greatly facilitated, particularly the second principal suture. After the first eight principal single, interrupted sutures have been placed, a double running suture according to Hoffmann^{156,168,169} is inserted. The knots are placed symmetrically 180° apart after clockwise and counter-clockwise adjustment of the running sutures (Fig. 14). This approach also allows a combination with extracapsular cataract extraction as a 'triple procedure'.

We used a slow 'step-by-step' and 'wait-and-see' approach in the clinical application of non-mechanical trephination to our patients. Since 1989 numerous details have been further refined (Table III). These concern changing the shape of the trephina-

Table III. Steps in the development of non-mechanical trephination with the 193 nm excimer laser

| | |
|------------|---|
| 1989–90 | <i>Elliptical mask, MEL 50, repeat rate 30/s</i> |
| Nov. 1991 | <i>Add 4 orientation teeth, MEL 60, repeat rate 25/s</i> |
| Jan. 1992 | <i>Round, 4 orientation teeth (0.15 × 0.3 mm)</i> |
| Feb. 1992 | <i>Double running suture (Hoffmann)</i> |
| Apr. 1992 | <i>Artificial anterior chamber (Krumeich)</i> |
| May 1992 | <i>Round, 8 orientation teeth (0.15 × 0.3 mm)</i> |
| June 1992 | <i>Add 1 'marker' (0.2 × 0.4 mm)</i> |
| Sept. 1992 | <i>Automatic rotation of donor tissue</i> |
| Sept. 1992 | <i>Double running suture with knots 180° apart</i> |
| Oct. 1992 | <i>Excimer vs conventional penetrating keratoplasty in Fuchs' dystrophy and keratoconus</i> |
| Oct. 1993 | <i>Horizontal positioning of the limbal plane</i> |
| Dec. 1993 | <i>Harmonising of donor/recipient corneal topography</i> |

tion from elliptical to circular with orientation teeth, the number and shape of the orientation teeth and notches, the proper diameters, the use of an artificial anterior chamber, the automatic rotation of the donor tissue, the achievement of perfect horizontal placement of the donor and patient's cornea by the focusing device of the excimer laser and of the mask by total reflection of the coaxial microscope light. It is obvious that the 'devil is in the details' and the details are important.

Patients and Indications. Between June 1989 and 1994 a total of 124 patients with avascular corneal opacities and (since 1993) keratoconus were treated as described below. A prospective randomised clinical trial comparing results of transplantation for keratoconus (8.0/8.1 mm in diameter) and Fuchs' dystrophy (7.5/7.6 mm in diameter) was started in 1993 and is in progress.

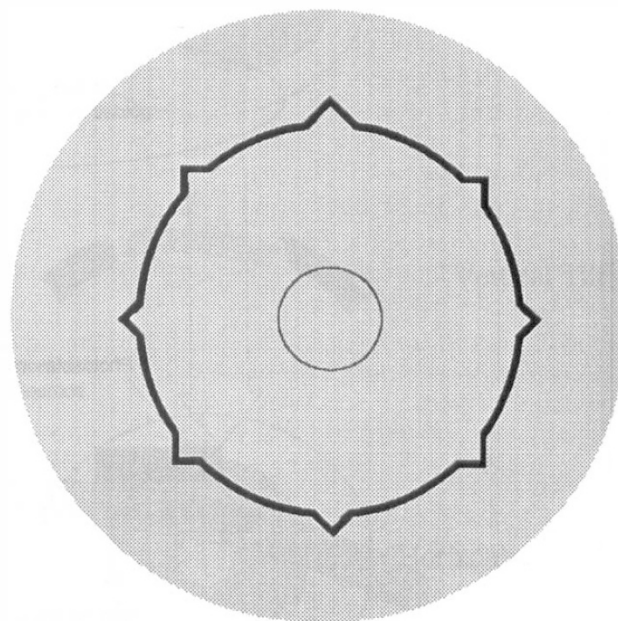
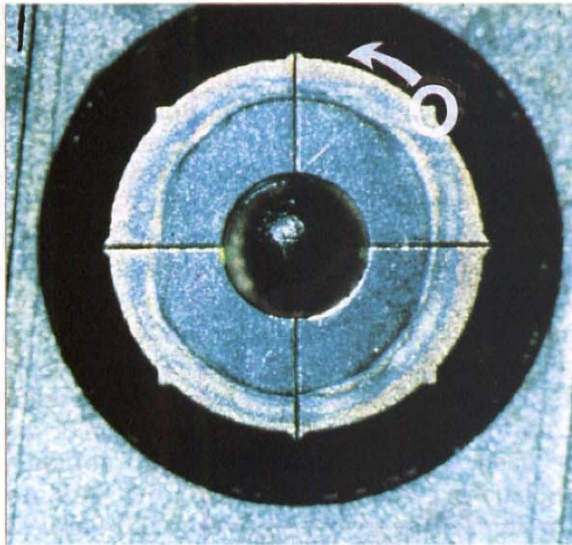


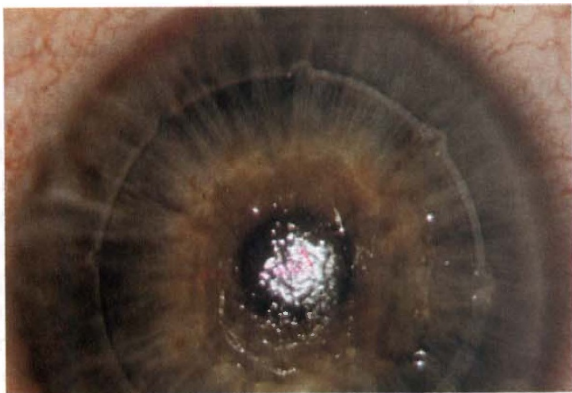
Fig. 12. Principle of non-mechanical trephination with the 193 nm excimer laser along the edge of a metal mask in penetrating keratoplasty. The horizontal schema showing eight orientation teeth/notches (one 0.2 × 0.4 mm and seven 0.15 × 0.3 mm). Currently the graft diameter is 0.1 mm larger. Standard diameter for keratoconus is 8.0/8.1 mm; for Fuchs' corneal dystrophy 7.5/7.6 mm.



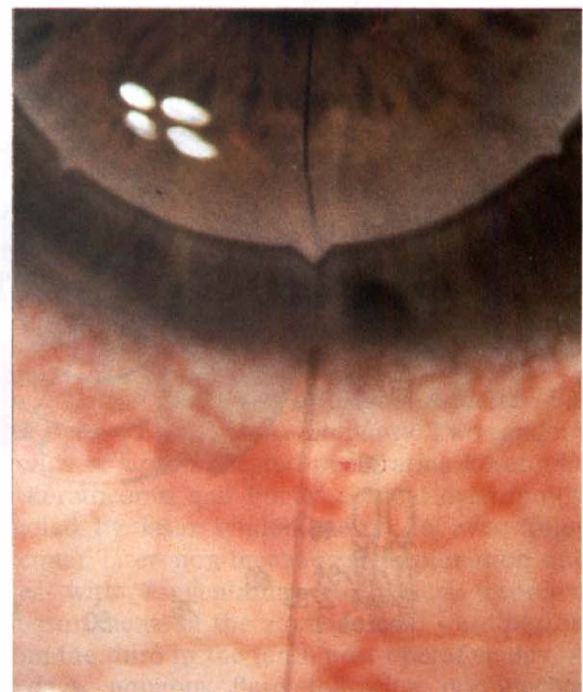
(a)



(b)



(c)

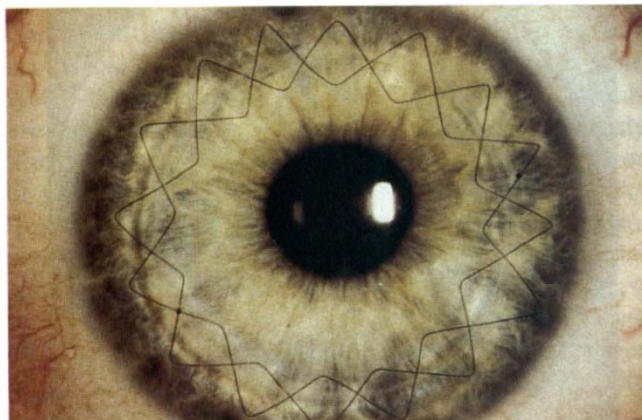


(d)



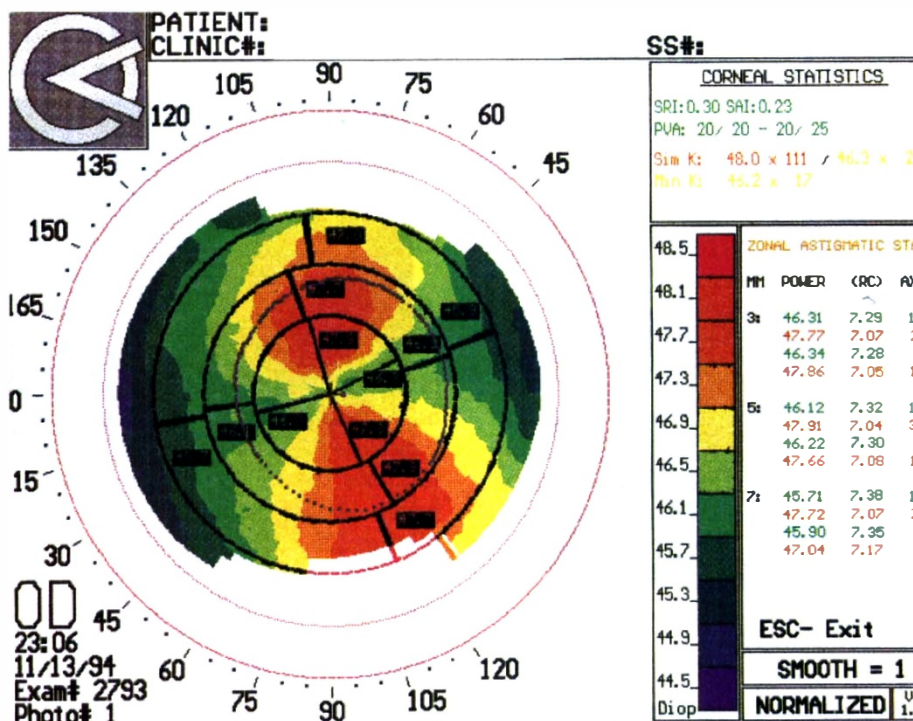
(e)

Fig. 13. Practical steps of non-mechanical trephination with the 193 nm excimer laser along a metal mask. (a) Donor metal mask with eight orientation teeth on a corneoscleral ring fixed in an artificial anterior chamber. The white ring indicates the 1.5×1.5 mm laser beam on the outer edge of the mask automatically rotating (arrow). (b) The patient metal mask. The invisible 193 nm excimer laser beam width of 1.5 mm is rotated manually along the inner edge of the mask by the surgeon using a joy-stick. The location of the beam is indicated by the red helium-neon laser guiding beam and/or fluorescence from the mask surface. The open mask is 8.0 mm in diameter and has eight corresponding orientation notches. (c) The patient's cornea shows the orientation notches at the end of trephination. (d) Placement of a 10-0 nylon suture through the principal orientation tooth-notch (0.2×0.4 mm). (e) Typical orientation tooth-notch (0.15×0.3 mm) combination post-operatively with double running suture in place.



(a)

Fig. 14. Corneal graft (8.0/8.1 mm) for keratoconus after non-mechanical trephination with the 193 nm excimer laser using eight orientation teeth-notches in a 16-year-old patient. Pre-operatively the ophthalmometer showed more than 60 dioptres irregular, visual acuity $-9.0 = -3.0 A90^\circ 0.1$. (a) The double running suture in place; knots are 180° apart. $-3.0 \text{ sph} = \text{cyl. } -1.0 A40^\circ = 0.8$. (b) Corneal topography after suture removal; $-2.0 \text{ sph} = \text{cyl. } -0.5 A10^\circ = 1.0$.



(b)

General Surgical Aspects. All 124 penetrating keratoplasties were done by myself – with the exception of cases 3 and 10. Non-mechanical trephination using the 193 nm excimer laser was performed along a metal mask. General anaesthesia was used except for one patient. After insertion of a lid speculum sutures were placed into the superior and inferior rectus muscles. Since November 1993 horizontal positioning of the limbal plane of the patient’s cornea has been achieved with the help of the focusing device of the excimer laser. Horizontal positioning of the metal mask was evident when there was total reflection of the coaxial light from the OPMI-IV Zeiss operating microscope.

Technical Data. From June 1989 to October 1990 we used the Aesculap-Meditec (Heroldsberg, Germany) Phönix MEL 50 193 nm excimer laser with a repetition rate of 30/s. Since November 1990 we have

used the Phönix MEL 60 with a repetition rate of 25/s. The invisible $1.5 \times 1.5 \text{ mm}$ excimer laser beam is marked by the red helium–neon guiding beam and moved with a micromanipulator (joy-stick) along the outer edge (donor) or inner edge (patient) of the mask. The process is done under direct optical control and can easily be interrupted by a foot switch.

Pulse Energy to Corneal Perforation. Donor: 15–22 mJ; 9000 ± 3000 pulses. Patient’s cornea: 15–25 mJ; 6500 ± 2000 pulses. (Measurement by pyroelectric measuring device PM 50M, Radiant Dyes Laser Accessories, Germany.)

Non-mechanical trephination with the 193 nm excimer laser takes about 5–7 minutes. As aqueous prevents the ultraviolet light from penetrating the cornea further, the remaining 0–10% of the deep corneal stroma has to be cut by scissors. Eight

principal sutures, later removed, are placed through the orientation notches and teeth and a double running suture after Hoffmann with opposite symmetrical knots is placed.

Configuration of the Metal Mask. The weight of the donor mask is 90–180 mg and it is 0.25–0.5 mm thick. The weight of the patient's mask is 200–400 mg and is 0.25–0.5 mm thick. Between June 1989 and December 1990 a total of 22 elliptical masks between 6×7 and 7×8 mm diameter were used.¹⁶¹ After November 1991 only circular masks 6.5–8.0 mm in diameter with changes in the direction and configuration of the orientation teeth and notches were used. Since summer 1992 only outward-directed orientation teeth and notches have been used: seven 0.15×0.3 mm teeth and one 'principal' tooth measuring 0.2×0.4 mm.¹⁶² For reasons of wound safety the outer diameter of the donor mask edge is 0.1 mm larger than that of the patient's cornea.

Preliminary Results

Between 1989 and 1994 non-mechanical trephination has been performed using the 193 nm excimer laser in 124 patients who required corneal transplantation for non-vascularised corneal processes. To avoid any unpleasant surprises, in the first year only 2 patients and in the second year only 20 patients were operated on. In the course of the 5 years no unexpected complications developed and the results are at least as good as those achieved by mechanical trephination.

Intra- and Post-operative Complications. With higher energy levels insignificant thermal epithelial changes can occur; this does not happen with the application of 25 hertz. Minimal traces of iris microhaemorrhage may be observed at the site of corneal perforation.

Wound Healing. Re-epithelisation requires an average of 2 days and wound closure is unremarkable.

Due to our very slow eclectic approach only a relatively small number of consecutive prospective penetrating keratoplasties comparing mechanical and non-mechanical methods have been performed. Two patients showed a reversible immunological graft reaction after an average follow-up of 2 years. Two diabetic patients developed transitory bacterial ulcers under sub-optimal post-operative care elsewhere with contact lenses. In the initial phase, for the most part very old patients were considered as candidates for the procedure, but since 1993 patients with keratoconus have been included. Centration of the graft is superior to that achieved with mechanical trephination. A learning curve for reduced astigmatism can be demonstrated. Post-operative astigmatism, even with

sutures still in place, seems to be more regular than after mechanical trephination (see below).

Further Potential Advantages

'Open Eye'. Trephination of an extremely soft eye makes mechanical trephination difficult or even impossible – even when using a really sharp mechanical trephine. If the anterior chamber is filled with Healon and seeping of aqueous out of the defect is prevented, the placement of the almost weightless mask (200 mg) on this eye facilitates the edging of an outline for the trephination and has obvious advantages.

Infectious Processes of the Cornea. 'Disinfection' of the cut edges in e.g. amoebic keratitis may be possible. As Garner¹⁷⁰ has pointed out in his clinico-pathological correlation of 30 cases of amoebic keratitis, it is impossible to determine clinically the extent of invasion of the amoebae into the patient's cornea.

In 4 patients we used non-mechanical trephination in order to avoid smearing of the infectious elements with a mechanical trephine, gaining excellent results. The same holds true for other forms of infectious keratitis which do not respond to medical therapy.^{93,171–173}

Reduction of Leakage of Blood–Aqueous Barrier Following Penetrating Keratoplasty. Two randomised groups of uncomplicated penetrating keratoplasties in keratoconus and Fuchs' corneal dystrophy were studied by laser tyndallometry: 26 eyes following excimer laser non-mechanical trephination and 26 eyes with conventional mechanical trephination. Measurements of the aqueous flare were performed from the third to the tenth post-operative day. After 6 days, aqueous flare following non-mechanical trephination by excimer laser keratoplasty was significantly less pronounced than with conventional mechanical trephination (Table IV). Comparison of the advantages and disadvantages of conventional and non-mechanical trephination has confirmed our working hypothesis that non-mechanical trephination has potential for the future.

Table IV. Aqueous flare following excimer laser versus conventional mechanical penetrating keratoplasty: early post-operative course

| Post-operative follow-up | Aqueous flare (photon counts/ms) | | |
|--------------------------|----------------------------------|-----------------------|------------------------|
| | Excimer (n = 26) | Conventional (n = 30) | Significance (p value) |
| 3rd day | 21.1 ± 5.4 | 25.9 ± 8.9 | 0.06 |
| 5th day | 16.1 ± 4.9 | 21.2 ± 5.7 | 0.02 |
| 7th day | 12.6 ± 3.4 | 17.5 ± 5.5 | 0.005 |
| 9th day | 9.3 ± 2.2 | 12.8 ± 3.2 | 0.001 |

After Küchle *et al.*²⁰⁹

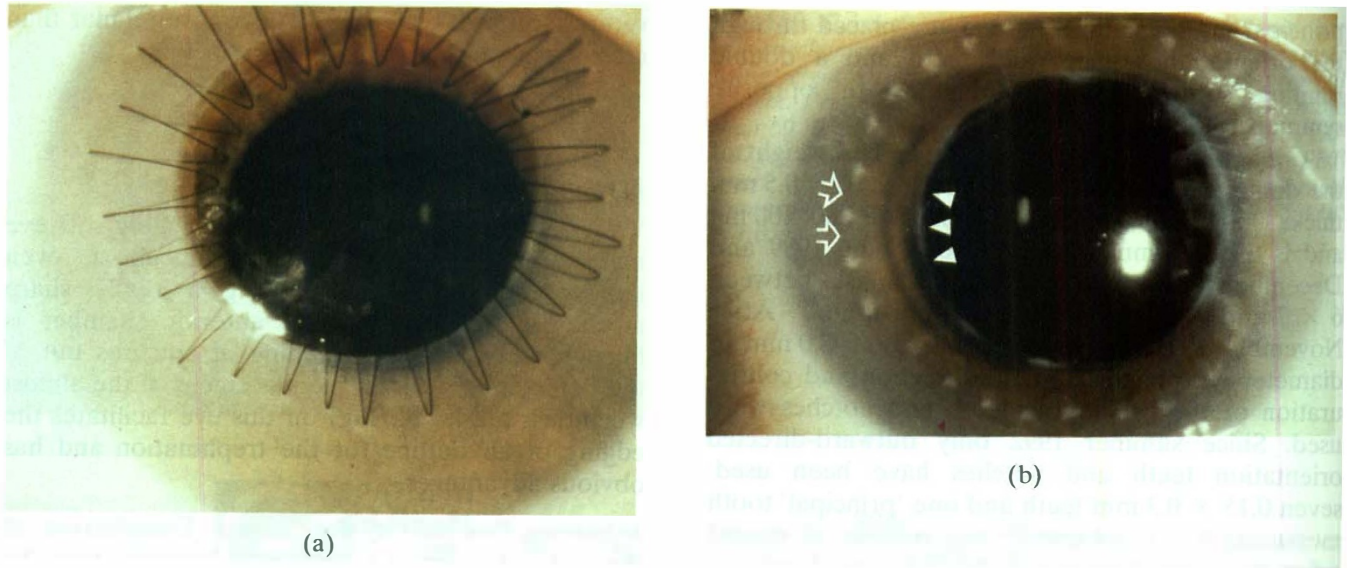


Fig. 15. Clearing of the cornea following penetrating keratoplasty in Maroteaux–Lamy mucopolysaccharidosis VIA in a 7-year-old girl. (a) Clear corneal graft of 6.2 mm with a running suture in place 3 months after surgery. Note that the patient's cornea is dense and opaque up to the wound edge. (b) After 2.5 years there is distinct clearing of the patient's cornea beyond the area of suture tract (arrows). The graft edge is indicated by arrowheads. (From Naumann and Rummelt.¹⁷⁷)

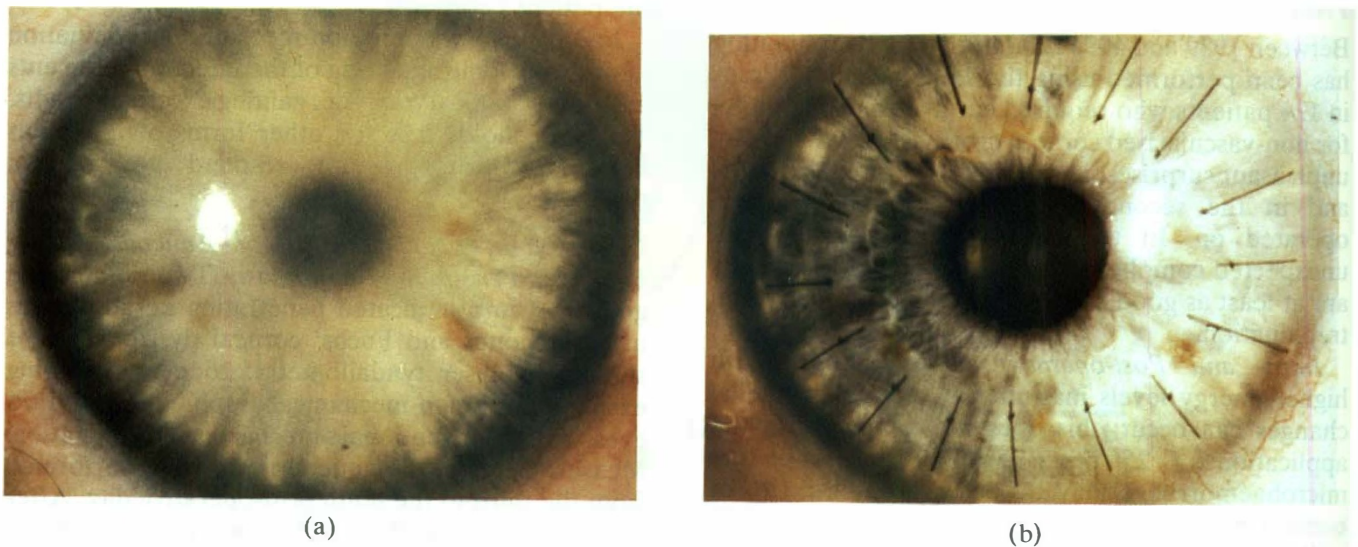


Fig. 16. Clearing of a patient's cornea following elliptical penetrating keratoplasty (PK) for diffuse corneal endothelial decompensation. This was the first case done with non-mechanical trephination in June 1989. (a) Diffuse corneal oedema from limbus to limbus. (b) Two years after elliptical PK (8.0 × 7.0 mm/8.1 × 7.1 mm) by non-mechanical trephination with the excimer laser the patient's cornea had cleared completely. (Ophthalmometer +2.0 = cyl -2.0 A70°). (Same patient as reported by Lang and Naumann.¹⁶⁰)

GRAFT-VERSUS-HOST EFFECT IN CORNEAL TRANSPLANTATION

Clearing of the Patient's Cornea

Our medical colleagues in liver transplantation today talk about 'chimerism', that is the distribution of donor cells away from the location of the main bulk of the transplanted organ.^{174,175} We usually do not pay much attention to these effects of the corneal graft on the patient's cornea. But as ophthalmologists, we are able to observe both the graft and the adjacent host tissue and the interface under high

magnification: By observing more closely we may learn more about the interaction between graft and host following corneal transplantation.

Maroteaux–Lamy Mucopolysaccharidosis VI

After penetrating keratoplasty in 4 eyes of 3 patients the corneal grafts remained clear in a follow-up of from 2½ to 5 years. We observed in 3 of these patients after 2 years a striking clearing of the cornea adjacent to the graft.^{176,177} This phenomenon, so evident biomicroscopically, has not been studied histopathologically. The following possibilities might

be discussed as a potential explanation: migration and proliferation of corneal endothelium and/or stromal keratocytes from the graft into the patient's cornea, or seeping of enzymes from the same type of cells from the graft to the donor tissue (Fig. 15).

Diffuse Bullous Keratopathy from Limbus to Limbus
Photographs of 38 patients before and from 4 to 47 months after penetrating keratoplasty¹⁷⁸ showed a striking clearing of the patient's cornea in 31 (81%) cases (Fig. 16).

Immunological Allograft Reaction

Immunological allograft reaction would be expected in all eccentric tectonic grafts. However, in some of these eccentric grafts, immunological graft reactions do not develop (Fig. 6b). All the other eccentric graft locations allow us to study the typical chronic endothelial immune reactions attacking the graft corneal endothelium, leading to corneal oedema due to endothelial decompensation, until vascularisation results in complete scarring and full integration of the tectonic graft into the eye wall (Fig. 5c).

Pseudoexfoliation Syndrome Following Penetrating Keratoplasty in Young Patients with Keratoconus

Pseudoexfoliation syndrome following penetrating keratoplasty in young patients with keratoconus has been reported in 3 eyes of 2 patients.¹⁷⁹ The patients' ages at keratoplasty were 37, 40 and 31 years and pseudoexfoliation was first observed 5, 4 and 6 years following keratoplasty, respectively. The respective donor age was in the eighth decade. Possible explanations include mere coincidence, some sort of non-specific reaction to surgery or to post-operative medications, or an immunogenic reaction to transplanted corneal tissue. Finally, the very hypothetical speculation cannot be ruled out that we might be dealing with a completely unknown induction process or even an obscure infection.

As the need for corneal transplantation increases, more attention needs to be paid to the effect of the corneal graft on the host tissue. We may learn that these are not just esoteric observations but of clinical significance.

NEW APPROACHES TO OLD PROBLEMS IN CORNEAL TRANSPLANTATION

The results of corneal transplantation in the standard situations are better than in any other type of transplantation in humans. However, as the total number of corneal transplantations is large, problems of even relatively low frequency affect many patients. I shall touch here only on selected aspects in the following five problem areas:

Shortage of Donor Material

A worldwide shortage of suitable donor tissue is the main obstacle to treating corneal blindness.¹⁸⁰

Autologous Donor Tissue

One alternative option in case of shortage of donor tissue is the use of autologous tissue via *ipsilateral* rotation of the opaque central parts of the cornea to the periphery (Fig. 17). Another option is the use of patients' *contralateral* cornea from an amaurotic eye, due to optic nerve or retinal disease.^{181,182}

Phototherapeutic Keratectomy (PTK)

Superficial corneal processes removed by 193 nm excimer laser may be an alternative to conventional lamellar or penetrating keratoplasty.¹⁸³ Currently this is our preferred method in superficial non-vascularised scars of the cornea and in superficial corneal dystrophies such as granular or Reis-Bückler's corneal dystrophy.¹⁸³⁻¹⁸⁵

Keratoprosthesis

Methyl acrylate and other plastic material usually proves to be an unsatisfactory keratoprosthesis in the long run, particularly as a result of late epithelial ingrowth and irreversible secondary glaucomas.^{186,187}

Experimental Seeding of Corneal Endothelial Cells

Injection of suspensions of corneal endothelial cells is not yet a realistic approach to replace the loss of corneal endothelial cells in Fuchs' dystrophy and secondary corneal endothelial decompensation. It is still not applicable to the clinical situation because, for example, the spread of endothelial cells cannot be

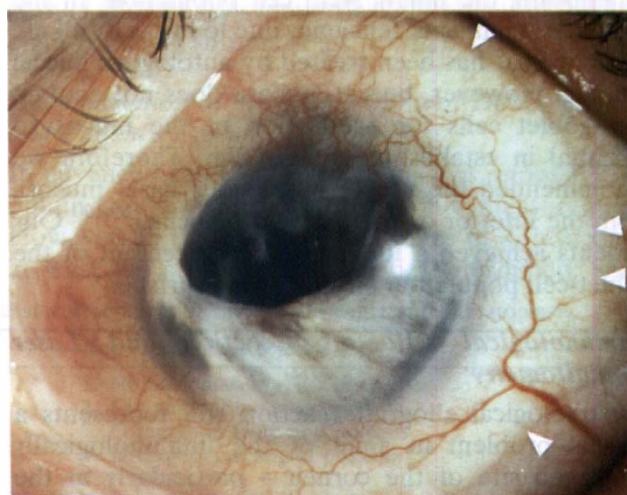


Fig. 17. Oversize 15 mm corneoscleral graft in deep lamellar scleral bed, for acute severe melting of the anterior segment due to lye-burn in a 50-year-old woman (*oculus ultimus*). Following systemic therapy with cyclosporin A for 20 months, extracapsular cataract extraction and continuous local corticosteroid therapy the cornea remains clear after 7 years. Laser tyndallometry facilitates monitoring and titration of minimal doses of effective immunosuppressive therapy.

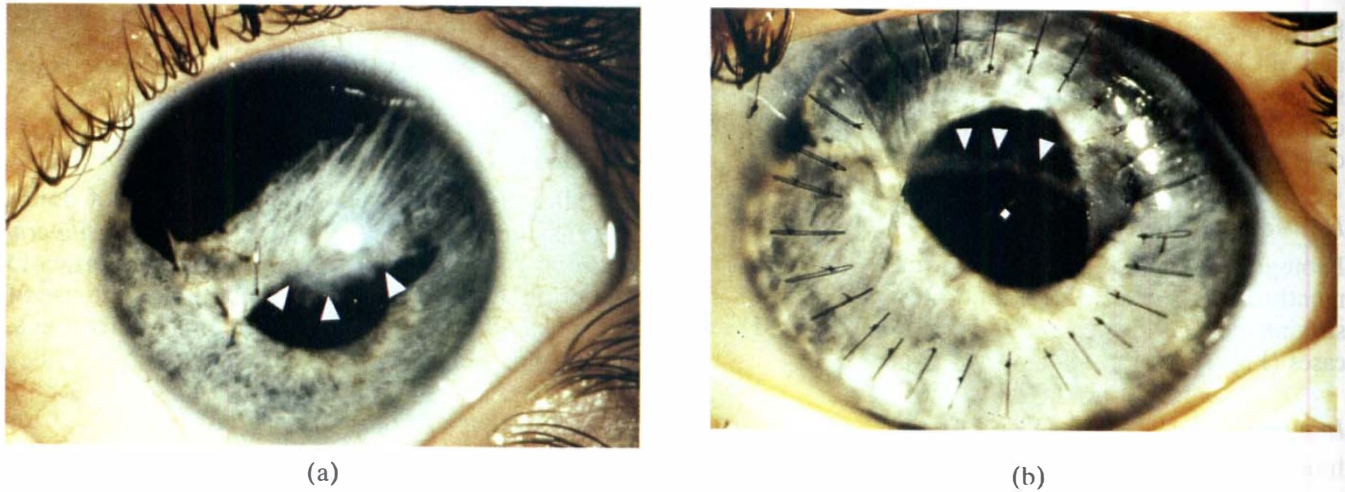


Fig. 18. Ipsilateral autologous rotational keratoplasty after perforating corneal injury with traumatic iridodialysis and cataract in a 10-year-old boy. (a) Central corneal scar (arrowheads). (b) Six months after eccentric 7 mm perforating keratoplasty. The scar is rotated from the centre of the cornea (diamond) superiorly (arrowheads). Iridopexy and extracapsular cataract aspiration with posterior chamber lens implantation: visual acuity score 0.8 20 months later.

confined to the back of the cornea within Schwalbe's line.¹⁸⁸ Finally, the idea of seeding a collagen gel with the recipient's fibroblasts is currently only a hypothetical approach. In the best of circumstances, this could lead to a synthetic 'tectonic biograft'. Even more futuristic is the idea of covering one surface with viable endothelial cells with the goal of producing transparent features for synthetic grafts.

Surface Problems

Various chronic surface processes leading to unilateral mucus deficiency syndrome may be amenable to autologous limbal grafts with the goal of re-establishing the limbal stem cell population. In the past bilateral mucus deficiency due to burns by alkali, acids or heat has been treated by autologous buccal mucosa. However, buccal mucosa does not contain any goblet cells for production of the mucus so essential in establishing a tear film. Therefore we recommended the use of autologous nasal mucosa from the inferior or middle nasal concha.^{189,190} Our patients achieved a long-lasting replacement of the goblet-cell population on the ocular surface.

Immunological Allograft Reaction and Laser Tyndallometry

Immunological allograft reaction still represents a serious problem in spite of the immunologically privileged site of the cornea – particularly in the vascularised cornea associated with surface problems.^{191–208} Kühle *et al.*²⁰⁹ have shown that quantifying defects in the blood–aqueous barrier by laser tyndallometry can be of help for the follow-up of patients after corneal transplantation. This allows the early diagnosis of an immune reaction and the monitoring and titrating of local and systemic

therapy. Measurement of the aqueous flare appears particularly useful in the following situations: (1) early diagnosis of the beginning of a corneal graft reaction; (2) follow-up of high-risk patients (Fig. 18); (3) monitoring therapeutic effect and titrating the maintenance dosages of corticosteroids or immunosuppressive agents in eyes with manifest or past corneal graft reactions. Of course, the best way to avoid the problem of immunological allograft reaction is to use the patient's own cornea, as in ipsilateral rotational grafts or contralateral autografts (Fig. 16).

Recurrences

Corneal Stromal Dystrophies

Recurrences of the original corneal disease on the graft can be a problem in Reis' granular and Bücklers' lattice dystrophy. Superficial photokeratectomy may be an alternative to regrafting.^{183,184,185}

'Reinfection' of the Graft

As mentioned above, we think that in infectious processes non-mechanical trephination with the excimer laser may offer the advantage that wound margins are 'disinfected' and the danger of smearing of infectious agent to as yet uninfected parts of the patient cornea is reduced. The recurrence of viral diseases in corneal transplantation following herpes corneae may still be problematic.^{210–213} Viral antigen can be demonstrated in excised corneal specimens, especially if the patient's cornea is not vascularised. This may indicate a higher risk for reinfection. Excised corneal tissue after regrafting for herpes corneae showed viable virus elements in 50%, although the non-vascularised grafts were clinically

Table V. Graft decentration (\pm SD) after non-mechanical trephination with the 193 nm excimer laser in penetrating keratoplasty compared with that after conventional motor-driven trephination ($n = 50$)

| | Excimer laser | Motor trephine |
|-----------------------------|-----------------|-----------------|
| Relative to the pupil (mm) | 0.33 \pm 0.26 | 0.64 \pm 0.24 |
| Relative to the limbus (mm) | 0.23 \pm 0.25 | 0.58 \pm 0.27 |

After Langenbucher *et al.*²²⁴

interpreted as suffering from immune reaction.²¹² Vascularised scars after herpes corneae are more vulnerable to an immune reaction. Immunohistological evaluation of the excised corneal tissue in herpes corneae can be helpful in the post-keratoplasty follow-up.²¹¹⁻²¹³

Astigmatism after Penetrating Keratoplasty

Even in 1859, Sir William Bowman was trying to improve the life of patients with keratoconus by transforming the pupil into a vertical slit by 'iridesis' with apparent stenopodic effects. He also thought that this would reduce the curvature of the eye in patients with keratoconus.⁷³

Astigmatism after an otherwise successful corneal transplantation resulting in a clear graft is still an unsolved and serious problem, particularly in keratoconus, and more than an annoyance to the patient.²¹⁴⁻²²³ Short-term post-operative astigmatism is obviously determined by the sutures. Bigar⁷⁹ reported persisting post-keratoplasty astigmatism of over 8 dioptres in 10% of keratoconus patients, Kirkness *et al.*¹⁹⁶ reported 18% 'intolerable' astigmatism. Persisting long-term astigmatism after removal of the suture, however, seems to be influenced by the following factors:

Decentration of the Graft

Tissue excised eccentrically from the donor eye and decentration of the patient's corneal trephine opening can lead to marked discrepancies of the opposing wound edges and distortion to the corneal surface topography. The centration can be related to the corneal apex, the pupil, optical axis and to the limbus. Only some of the motor-driven mechanical

trephines satisfactorily allow centration during trephination. The most problematic indication is keratoconus, as extreme corneal astigmatism leads to additional prismatic 'shift of the pupil'.

In a group who had excimer laser trephination there was a statistically significant improvement of the centration of the graft in relation to the pupil and also to the limbus compared with the centration of the graft following motor-driven mechanical trephination (Table V).²²⁴

'Vertical Tilt'

As a consequence of mechanical trephination, the angles of cut usually deviate from the perpendicular vertical direction. In addition, the cut angle *differs* in the donor's and in the patient's cornea. In order to achieve water-tight closure, the sutures must be pulled, causing a marked distortion of the corneal surface topography. This can be improved by non-mechanical trephination under the condition of perfectly horizontal positioning of the patient's cornea and the mask. Horizontal positioning of the limbal plane is easily achieved if the focusing device of the excimer laser is similarly placed at the 3, 6, 9 and 12 o'clock position. Horizontal positioning of the metal mask is achieved by observing total reflection of coaxial light by the surgical microscope.

'Horizontal Torsion'

Horizontal torsion follows asymmetrical suturing of the donor cornea into the patient's cornea. Ideal symmetrical placement after circular trephination is very difficult to achieve. The apposition of the eight orientation teeth on the donor button with the corresponding orientation notches on the patient's cornea allows easy symmetrical placement of the first eight principal sutures (Figs. 10, 12).

Harmonisation of the Topography of Donor Cornea and Patient's Cornea

In advanced cases of keratoconus it is impossible to obtain any satisfactory topographic measurement. However, in the intermediate stages of keratoconus at least the steepest axis can be determined. Seitz

Table VI. Advantages and disadvantages of mechanical and non-mechanical trephination methods in penetrating keratoplasty

| | Mechanical trephination | Non-mechanical trephination |
|---------------|--|---|
| Advantages | <ol style="list-style-type: none"> 1. Feasible also in vascularised scars 2. Less expensive (currently!) | <ol style="list-style-type: none"> 1. No deformation 2. Cut angle same in donor/host 3. Orientation teeth and notches 4. Divergent cut angles possible 5. 'Open eye' 6. 'Disinfection' in ulcers (?) 7. Better centration 8. Post-operative astigmatism more regular, less asymmetrical 9. Reduced aqueous flare |
| Disadvantages | <ol style="list-style-type: none"> 1. Deformation of wound edges: 'vertical tilt', 'horizontal torsion' 2. Centration more difficult | <ol style="list-style-type: none"> 1. Currently not feasible in vascularised scars 2. Stop by aqueous exit |

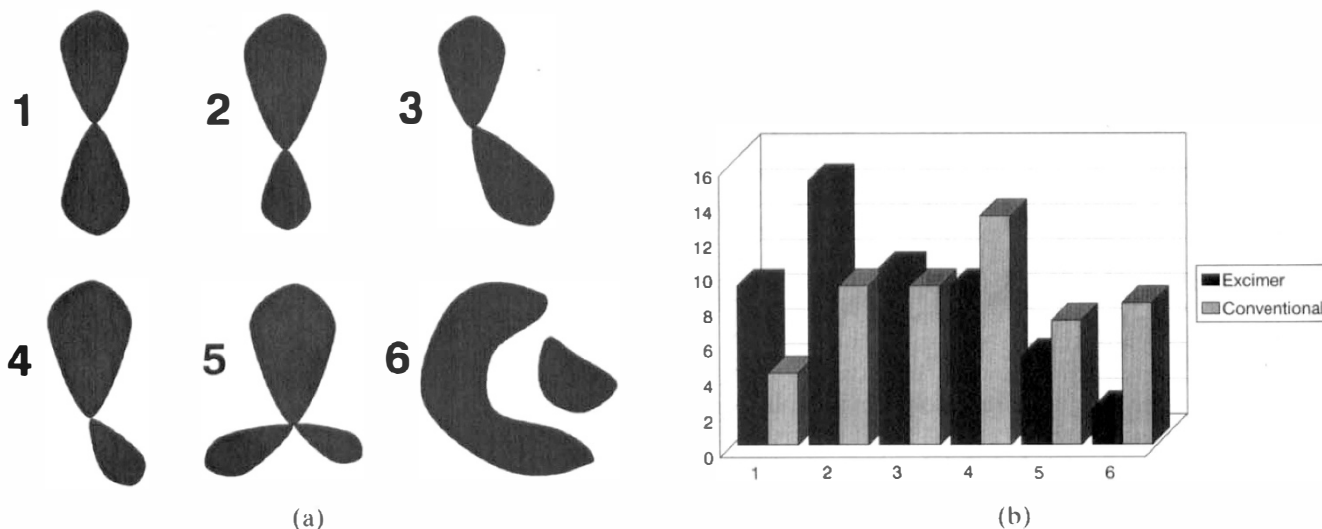


Fig. 19. Post-keratoplasty astigmatism: 'degree of irregularity' in corneal topography. (a) Definition: six groups according to the location of the steepest axis. (b) Preliminary results of a prospective randomised clinical study comparing two groups of 50 patients following penetrating keratoplasty after either conventional motor-driven trephination or non-mechanical trephination with the 193 nm excimer laser along a metal mask with eight orientation teeth/notches and with double running sutures in place. There is less irregularity in the excimer group and visual acuity is better (0.61 compared with 0.39).

et al.^{225,226} have developed a method for measuring the topography of the donor tissue after it is fixed in the artificial anterior chamber. Using as orientation the largest orientation tooth, the steepest axis of astigmatism of patient and cornea can be 'harmonised'. This should help to avoid one aspect of the discrepancy between patient's and donor cornea.

Preliminary Results of a Prospective Randomised Clinical Study

Since 1993, I have treated two groups of 51 patients using mechanical and non-mechanical trephination. Greater numbers and a longer follow-up will be needed to obtain better information. Table VI summarises our observations so far.

Patients. Each group consisted of 32 patients with keratoconus (using graft diameters of 8.1 mm for a recipient opening of 8.0 mm) and 19 patients with Fuchs' dystrophy (using 7.6 mm graft diameter for a 7.5 mm recipient opening). All patients treated by excimer laser trephination had the eight orientation teeth and notches on donor button and host cornea respectively; a double running suture was used to secure the graft.

Astigmatism. As long as both sutures were in place there was no significant difference in astigmatism between the mechanical and non-mechanical trephination groups, although there is a positive learning curve for the entire excimer trephination group. There is a trend for reduced astigmatism after removal of sutures in the excimer group (though the numbers of patients are still too small) and increased astigmatism in the conventional group. Finally a statistically significant difference is observed as regards the regularity of the astigmatism in favour of non-mechanical trephination: this

may explain the fact that the best corrected visual acuity is 0.6 in the excimer group and 0.4 in the conventional group (Fig. 19).

I will conclude with the words of Sir William Bowman from his Address on Surgery 1866: 'I have endeavoured to give you – I fear at too great length – my general impression on this head – I hope without offence to anyone and with sincerity and very inadequately'.²²⁷

SUMMARY

The following aspects have briefly been touched upon in this Bowman Lecture:

Indications

Ninety years after its introduction penetrating keratoplasty is today the oldest and most frequently performed and most successful transplantation in humans. It is indicated not only for the obvious optical reasons, but also for a wide spectrum of tectonic indications.

Tectonic full-thickness corneal scleral grafts in an eccentric position are essential for closing iatrogenic defects in the eye wall following *block excision* for tumours of the anterior uvea, cystic and diffuse epithelial ingrowth and congenital cysts of iris and ciliary body. Corneal transplantation in these indications is a prerequisite for the preservation of the globe with as much vision as possible. The *scleral spur* is a critical structure in any peripheral corneal degeneration treated by limbal corneal graft fixed in a deep lamellar scleral bed and should be preserved.

Ipsilateral autologous corneal transplantation may be the best access for lens surgery in patients with extreme microcornea.

Corneal transplantation is *contraindicated* in all patients with sclerocornea and many with Peters' anomaly associated with microcornea; optical sector iridectomy appears to be a better option in the latter.

New indications for corneal transplantation may be 'PEX keratopathy' (corneal endothelial involvement and decompensation in pseudoexfoliation syndrome) and corneal scarring as part of Münchhausen syndrome.

Surgical Technique

Bowman's lamina is a critical structure to be considered in all corneal surgery and details of suturing.

Non-mechanical trephination with the 193 nm excimer laser around a metal mask was done in 124 eyes of 124 patients between 1989 and 1994 without any unexpected complications. It offers the following advantages over mechanical trephination. As mechanical deformation of the donor's and patient's cornea is avoided, problems of decentration, 'vertical tilt' and 'horizontal torsion' can be reduced. Eight orientation teeth and notches allow better placement of the principal sutures and running sutures, and are a prerequisite for orienting the donor tissue into the patient's cornea following 'harmonisation' of the corneal topography in donor and host. Centration of the graft is significantly improved. These factors offer the potential to reduce the persisting post-operative astigmatism following corneal grafting after suture removal. The surgical technique is simple and can be performed under direct control through the operating microscope. Six days after non-mechanical trephination the breakdown of the blood-aqueous barrier is less pronounced than after conventional trephination.

Non-mechanical trephination may also offer advantages in situations of 'open eye', if the patient's cornea is non-vascularised. *Infectious processes* in non-vascularised corneas not responding to medical therapy may benefit from a '*disinfection*' of the wound margins by non-mechanical excision with the 193 nm excimer laser patterned after the location of the infiltrate.

Effects of the Donor Tissue on the Patient's Cornea

The effects of donor tissue on the patient's cornea deserve more attention and promise a better understanding of the interaction between donor and host. Clearing of the patient's cornea can be striking after penetrating keratoplasty in Maroteaux-Lamy syndrome and in diffuse endothelial decompensation.

Old Problems and New Approaches

Ipsi- and contralateral *autologous keratoplasty* avoids an immune reaction. It should be considered more often, particularly in children.

Autologous nasal mucosa transplants are suggested to reduce mucus deficiency syndromes in desperate bilateral ocular surface problems preceding keratoplasty. They appear to be superior to conventional buccal mucosa transplants.

Laser tyndallometry allows early diagnosis of corneal graft immune reaction, monitoring and titration of local and systemic therapy with immunosuppressive medications.

Preliminary results from a prospective randomised study of two groups of 51 patients (since 1993) reveal that with non-mechanical trephination there is a trend for less *astigmatism* and a statistically significant reduction in the irregularity of post-keratoplasty astigmatism. With sutures still in place, the post-keratoplasty astigmatism is significantly less irregular and visual acuity is significantly better than after conventional trephination.

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Key words: Block excision, Bowman Lecture 1994, Excimer laser 193 nm, Graft-versus-host effects, Non-mechanical trephination, Pseudoexfoliation keratopathy, Spectrum of corneal transplantation.

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