Refractive surgical techniques

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Publication date:
1995

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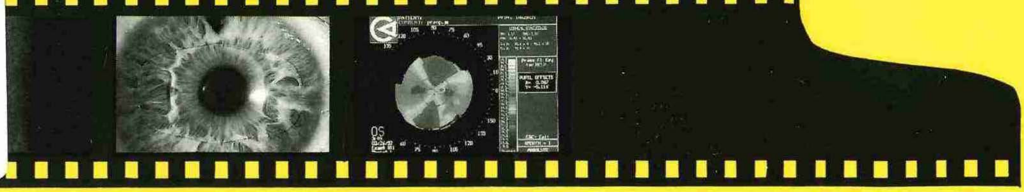
Evaluation of clinical studies on the Phakic Iris Claw Lens and on the applications of the 193-nm Argon Fluoride Excimer Laser

Monika Landesz



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Stellingen behorend bij het proefschrift

Refractive surgical techniques.

Evaluation of clinical studies on the phakic iris claw lens and on the applications of the 193-nm argon fluoride excimer laser.

I. Het corrigeren van hoge myopie met een iris claw lens van negatieve sterkte resulteert in een stabiele en voorspelbare postoperatieve refractie.

II. Om de configuratie van de fotorefractieve ablatie van de cornea met de 193-nanometer Argon-Fluoride excimer laser te beoordelen is het gebruik van een video keratograaf onontbeerlijk.

III. Het endotheelcelverlies van de cornea na implantatie van de Worst Myopia Claw Lens is vergelijkbaar met het endotheelcelverlies na phacoemulsificatie.

IV. Om het cornea-endotheel tijdens het implanteren van de Worst Myopia Claw Lens te beschermen is het gebruik van een viscoelasticum noodzakelijk.

V. De voornaamste reden dat hoog myope patienten kiezen voor een chirurgische correctie van hun refractieafwijking is het verbeteren van hun visuele functie.

VI. Bij follow-up studies van de morfometrie van het cornea-endotheel is het raadzaam steeds dezelfde endotheel microscoop te gebruiken, bij voorkeur gecombineerd met een computer gestuurd beeldbewerkingsprogramma.

VII. De beste indicatie voor phototherapeutische keratectomie met de excimer laser voor de behandeling van therapie resistente recidiverende erosies van de cornea is wanneer deze in de visuele as zijn gelocaliseerd.

VIII. Het grootste nadeel van het implanteren van de Worst Myopia Claw Lens is de implantatie zelf.

IX. Bijziendheid is geen maat voor kortzichtigheid.

X. Bij het veranderen van het AIOstelsel, waarbij de AIO de studentenstatus krijgt, wordt het begrip 'eeuwige student' weer actueel.

XI. Kaalkopshampoo is een contradictio in terminis.

XII. Volgens de kleurenaanduiding van de videokeratoscopie voor de verschillende cornea radii, waarbij de blauwe kleuren de lange radii weergeven en de de rode kleuren de korte radii, zou de kleurencirkel van Goethe heel goed bij een keratoconus kunnen passen.

Rijksuniversiteit Groningen

Refractive Surgical Techniques.

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Proefschrift

ter verkrijging van het doctoraat in de
Geneeskunde
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus Dr F. van der Woude
in het openbaar te verdedigen op
woensdag 20 december 1995
des namiddags te 4.00 uur

door

Monika Landesz

geboren op 16 december 1963
te Budapest, Hongarije

Promotores: Prof.Dr G. van Rij
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Paranimfen	mw. drs. J.I. Schut-Adema R.P. Nieman

Szüleimnek
(aan mijn ouders)

The research presented in part I of this thesis was financially supported by SENTER and was in cooperation with Ophtec B.V.. The research presented in Part III was financially supported by the 'Prof. Mulder Stichting'.

The printing of this thesis was financially supported by the 'Prof. Mulder Stichting' and Oculenti B.V..

Cover design: E. van Ommen

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PREFACE

Refractive surgery is an operation to alter the refractive state of the eye. It has become one of the subspecialties in Ophthalmology during the last decades. The best known and most accepted refractive surgical technique is implantation of an artificial intraocular lens after cataract extraction. For many patients the conventional optical devices such as glasses or contact lenses to correct myopia, hyperopia, and astigmatism prove to be an intolerable hindrance and therefore ophthalmic surgeons have been searching for new techniques that will allow patients to discard the prosthetic devices.

The pursuit of good visual acuity without corrective spectacles and contact lenses has resulted in a large number of surgical procedures. The improvement of surgery in general and the increasing understanding of the physiology and wound healing of ocular structures are contributing factors to this continuing quest for new techniques and reintroduction of old abandoned procedures. Most of these procedures involve surgical manipulation of the cornea, because two thirds of the refractive power of the eye resides within the cornea. Yet, variability in wound healing limits the predictability of the refractive outcome in these keratorefractive procedures. Other non-corneal techniques that have been developed involve implantation of intraocular lenses into phakic eyes and removing the clear crystalline lens, both for the correction of high myopia. However, there is general concern about progressive endothelial cell loss in the former, and retinal detachment in the latter. Other procedures to alter the axial length of the eye to halt the elongation of the eye globe are still in elaboration. The quest for new refractive surgical procedures will continue, until a safe, predictable, and stable refractive surgical technique is found.

Aim of the study.

The aim of this thesis is to contribute to further evaluation of the efficacy and safety of two recently developed refractive surgical techniques: 1) phakic iris claw lens implantation for the correction of high myopia, and 2) altering the shape of the cornea with the 193-nm argon-fluoride excimer laser. Because of the diversity of the subjects treated in this study this thesis is divided into four parts.

General Introduction: A general survey on the background of phakic anterior chamber lenses, specular microscopy and excimer laser is given.

Part I. Phakic Worst Myopia Claw anterior chamber lens. This part begins with the description of a case with one of the first occlusive phakic iris claw lenses (chapter 2). The next two chapters describe the refractive results and morphometry of the corneal endothelium of patients with the biconcave and convex-concave iris claw lens for the correction of high myopia (chapters 3 and 4). In chapter 5, a psychosocial study on patients with a convex-concave iris claw lens will be discussed.

Part II Specular Microscopy. Chapter 6 deals with the computerized technique we developed to analyze automatically the corneal endothelium in patients with a phakic iris claw lens. In chapter 7, we compare the endothelial morphometry performed with three different specular microscopes.

Part III 193-nm Argon-Fluoride Excimer Laser. Chapters 8 and 9 deal with therapeutic applications of the excimer laser for the treatment of corneal epithelial dysplasia and recurrent corneal erosions. Chapter 10 describes the correction of astigmatism, combined with myopia and hyperopia, by consecutively toric and spherical photo refractive ablation of the cornea with the excimer laser.

CHAPTER 1

General Introduction

1.1 SURGICAL CORRECTION OF HIGH MYOPIA.

1.1.1 Anomalies of the optical system of the eye.

The types of ametropia.

In the physiologically normal eye parallel rays of light converge upon the retina. When this ideal optical condition occurs within the eye in a state of rest the condition is termed emmetropia (εν, within; μετρον measure; ωψ the eye)[1]. The opposite condition is ametropia (α privative; μετρον measure; ωψ the eye), when parallel rays of light are not focused exactly upon the retina. There are three main types of ametropia: a focal point may be formed by the refractive system of the eye, but instead of being situated on the retina, it may be situated either behind it or in front of it. Alternatively, the refractive elements may not be spherical so that no single focal point is formed.

Myopia.

Myopia (μυω I close; ωψ the eye) is defined as ..."*that form of refractive error wherein parallel rays of light come to a focus in front of the sentient layer of the retina when the eye is at rest.*"...[1]. The refractive power of the eye is determined by the cornea, the anterior chamber depth and the crystalline lens (Figure 1). Refractive myopia occurs when the overall refractive power of the cornea and crystalline lens is excessive in relation to a normal axial length (21.5-25.5mm)[2]. Yet, myopia is usually axial (Figure 2).

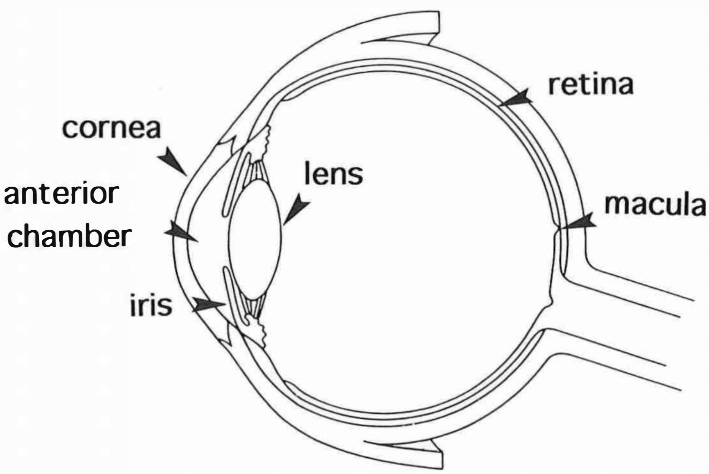

Figure 1. Schematic drawing of a cross section of the eye.

Hyperopia.

Hyperopia (hyper, in excess) is defined as ...'*that form of refractive error wherein parallel rays of light are brought to a focus some distance behind the sentient layer of the retina when the eye is at rest.*"[1](Figure 2). The formation of a clear image of any kind is impossible unless the converging power of the optical system is increased either by the eye it self by an effort of accommodation, or by artificial means with a convex lens (Figure 3).

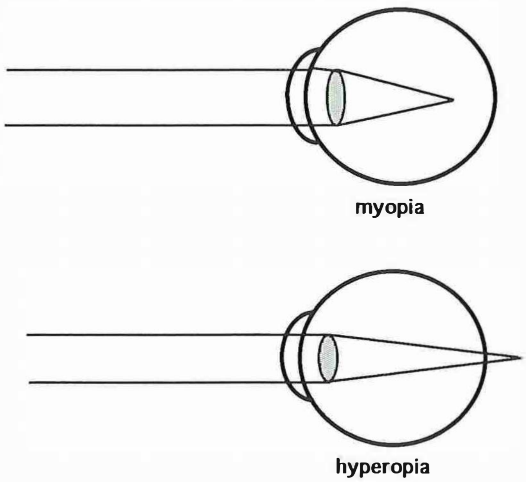

Figure 2. Myopia and hyperopia

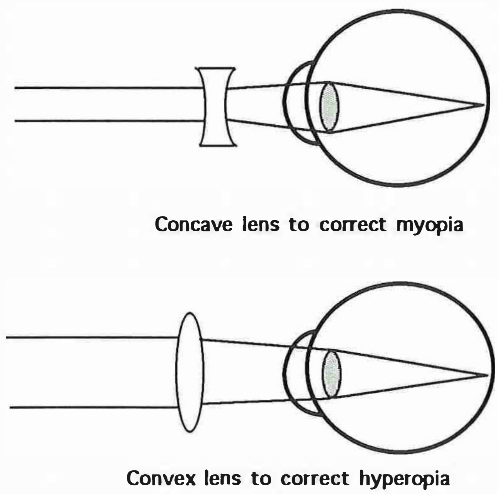

Figure 3. Correction of myopia and hyperopia.

Astigmatism

Regular astigmatism is that type of refractive anomaly in which no single focal point is formed owing to the unequal refraction of the incidence light by the dioptric system of the eye in different meridians[1]. It may also be caused by irregularities in curvature, decentering of the optical surfaces of the eye, or by inequalities in the refractive index of the lens (irregular astigmatism).

Regular astigmatism depends on the presence of toroidal instead of spherical curvatures of the refracting surfaces of the eye (Figure 4). Regular astigmatism is a condition where the refractive power changes gradually from one meridian to the next by uniform increments, and can be corrected by a cylindrical lens. When there are irregularities in the curvature of the meridians, the condition is called irregular astigmatism and cannot be corrected by spectacles, but sometimes, in so far as it is corneal, it can be corrected by contact lenses.

Curvature astigmatism of the anterior surface of the cornea occurs physiologically up to 1 diopter and is thus responsible for the majority of cases of astigmatism.

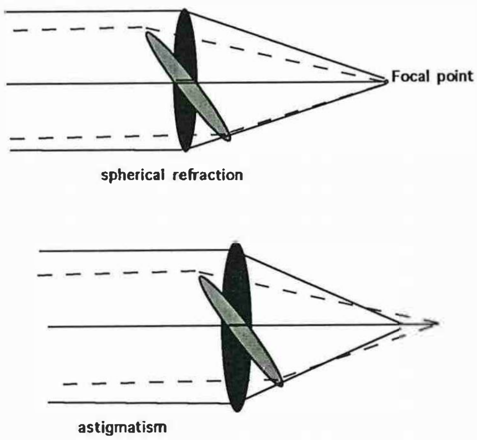

Figure 4. Astigmatism.

High myopia.

High myopia is defined as myopia of more than 6 D[1]. This refractive anomaly is relatively rare. Incidence rates of about 2 to 8%[1,3] of the total population have been described. Especially in high myopia the axial component plays an important role.

Pathological myopia is that type of high myopia with degenerative changes on the posterior pole[4] due to the elongation of the eye, which is almost confided to the posterior globe solely. In such long eyes the sclera is stretched out which results in thinning of the scleral wall with formation of staphylomata. Degenerative processes are noticed not only in the posterior globe (myopic maculopathy), but also in the periphery (myopic lattice). The choroidea may show signs of degeneration and atrophy. Consequently, high myopes suffer from a considerable visual disability. They rarely attain a visual acuity of 20/20.

Persons with myopia exceeding -5 diopters accompanied by lattice degeneration of the retina have an extraordinarily high risk of detachment during their life time[4]. Regardless his or her age, an emmetropic person without lattice degeneration would have an annual risk of detachment of 2×10^{-6}. This increases 3 to 5 times in low to moderate myopia and increases 15 times or more in high myopia[4].

1.1.2 Correction of Myopia.

1.1.2.1 Spectacles and contact lenses.

The traditional correction of myopia consists of spectacles or contact lenses. The optical correction with spectacles have several disadvantages, particularly for the higher degrees of myopia. The minus lenses cause minification of the image and aberrations in the thick edges of the glasses[2]. These aberrations have important effects on the visual field of a high myope[5]. Progressive blurring and deformation of the image towards the periphery of the lenses occur.

An alternative is the use of contact lenses. One major advantage is the decrease of the image minification because of the increase in retinal image, by moving the vertex of the negative lens to the corneal plane, which also yields less peripheral distortions[2]. But the thick edges of the contact lenses can cause considerable discomfort. Since high myopes are very dependent on wearing contact lenses, contact lens intolerance can give serious problems in the patient's functional visual ability.

1.1.2.2 Refractive Surgery.

Refractive surgery is an operation which alters the refractive state of the eye. Since the number of surgical techniques to correct refractive errors is so tremendous[6], it would be beyond the scope of this introduction, to discuss them all. Hence I will restrict myself only to the approaches seeking to correct high myopia (Figure 5). The refractive condition of the eye is an equilibrium between the axial length, the corneal curvature and the crystalline lens power[1]. Therefore I will discuss the refractive surgical techniques performed on these three levels.

Axial Length.

Scleral reinforcement.

Scleral reinforcement is ..."*the only surgical technique which attempts to correct a cause rather than an effect.*"...[7]. With this technique the sclera is reinforced by overlying collagen grafts[7] or synthetic graft material[9] to steady the elongation of the posterior globe. The long-term results of homologous grafts are not very promising[7], because the progressive increase in myopic refraction does not stabilize postoperatively. New synthetic graft materials are currently under investigation[10].

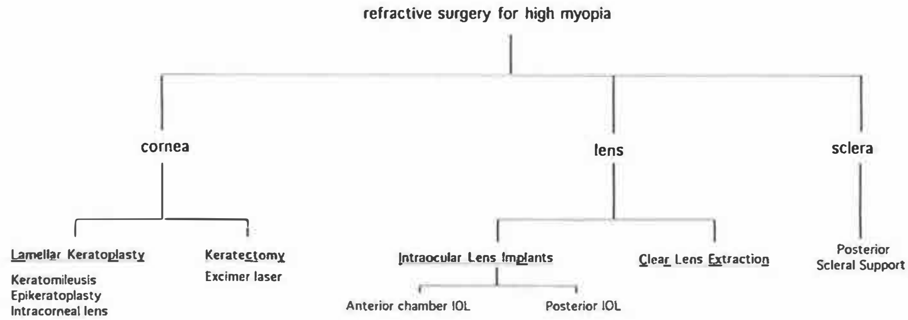

Figure 5. Surgical techniques for the correction of high myopia.

Cornea

Refractive keratoplasty.

Most of the refractive surgical techniques involve the cornea[6]. The objective of the procedure is to alter the corneal curvature and therefore the corneal power. Because of the large difference between the refractive indices of the air and the corneal tear film small changes in corneal radius, i.e., curvature, will result in relatively large changes of its dioptric power. There are many types of refractive keratoplasty techniques, not only to correct (high)myopia but also for the correction of aphakia, astigmatism, hyperopia and keratoconus. At present, the approaches to correct high myopia comprise lamellar techniques and keratectomies (Figure 6).

Lamellar techniques.

Myopic keratomileusis was introduced by Barraquer in 1964[11] and consists of removing a corneal disc with a microkeratome (Figure 6). The initial approach comprised freezing and reshaping the disc with a cryo lathe, after which the disc was defrosted and resutured on the patient's cornea. Alternative approaches include non-freezing techniques[12] and the use of donor corneas[13].

The results in refractive outcome, however, are moderately accurate[13-15], with possible haze formation on the interface (Table 1). An additional difficulty is the high demand of the surgeon's skills.

Recent studies on the use of the excimer laser (details will be described later in part 3) to modify the corneal cap, or the stromal bed after making a corneal flap, show promising results[17-19] (Table 1). The main advantages over the original keratomileusis technique is that more precise amounts of tissue can be removed and that Bowman's layer remains intact. Ablating the stromal bed with the flap technique does not induce astigmatism when the flap is repositioned without sutures. A major disadvantage in the technique where the button is treated with the excimer laser is the possibility of perforating the eye with the microkeratome. One disadvantage of a more practical nature is the application of two sterile surgical suites; one for the lamellar surgery and one for the excimer laser surgery.

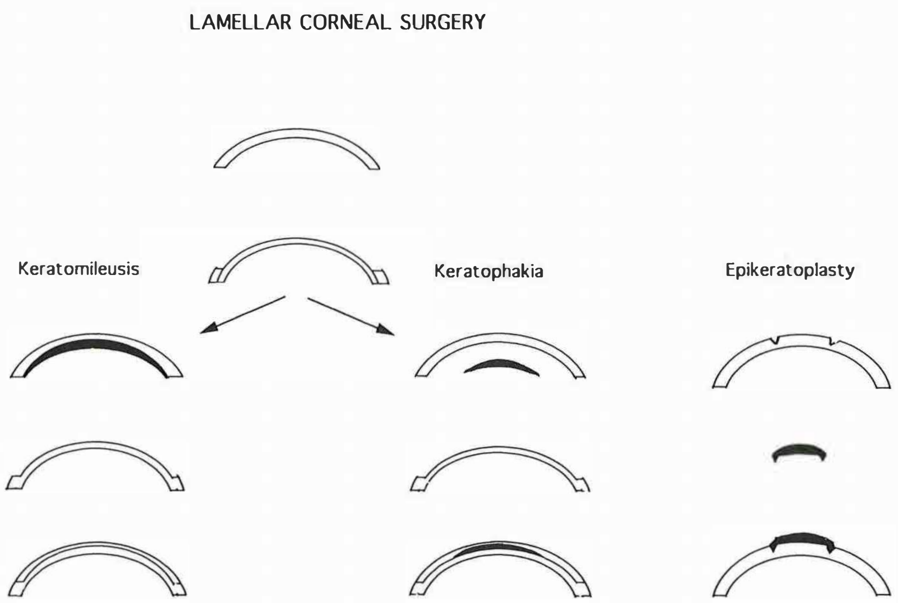

Figure 6. Keratorefractive techniques for the correction of high myopia.

To simplify the technically difficult procedure of keratomileusis and to make it safer, the procedure of epikeratoplasty was originated in 1979[20], primarily for the correction of aphakia. In 1985 the first attempts were made to use this new technique for the correction of high myopia[21]. As in keratomileusis the effect of epikeratoplasty is creating a new anterior surface of the cornea (Figure 6). The recipient cornea is de-epithelialized and with a trephine a circular groove is created. A commercially available frozen lyophilized lathed donor cornea is then sutured on the recipient cornea.

As in keratomileusis, the refractive outcome is unsatisfactory[14,20,22] (Table 1). A great deal of postoperative problems concern the wound healing[23]. However, recent

Table 1. Summary of literature on surgical correction of high myopia.

source	n	follow-up	preoperative myopia	outcome	comments
Scleral reinforcement					
Curtin et al.(6) 1987	40	5 years	_	43% stable refraction 57% increase of myopia by more > 1 D 90% increase in axial length by >0.3 mm	anterior uveitis, motility disorders retinal detachment progression in myopic fundus disorders
Whitmore et al.(8) 1990	2	10 years	_	localized supportive effect overall progression of posterior staphyloma	
Jacob-Labarre et al.*(10) 1993	_	5 months	_	no difference in globe lengths	venous beeding in fundo
Keratomileusis					
Swinger et al.(15) 1984	38	> 1 year (n=17)	_	82% within 3D	epithelial problems stabilization after 3 to 6 months
Colin et al.(14) 1990	26	_	_	61% within 3D 31% loss of VA	slow visual recovery 80% small interface opacities delayed epithelial healing
Keratomileusis in situ					
Buratto et al.(16) 1993	30	24 months	11.25 to 24.5	63% within 1 D	stable postoperatve refraction
Siganos et al.(18) 1993	9	6 months	8.75 to 25 (mean ±11.7 D)	achieved mean 11.34 D	_
Epikeratoplasty					
McDonald et al.(21) 1985	352	> 1 month		35% within 10% of attempted correction 86% within 40%	3% loss of VA 36 lenses removed because of wrong power and/or reepithelialization problems
Colin et al.(14) 1990	29	26 months	12 to 28	66.6% within 3 D 33.3% within 1 D	change in refraction by more than 1D in 32.2% 14.3% loss of VA melting, haze, delayed epithelialization
Baikoff et al.(22) 1990	21	1 to 2 years	11 to 21	43% more than 3 D	melting/ulceration poor refraction, no improvement VA

Keratophakia					
Werblin et al*(22a) 1984	9	1 to 2 years	5 to 20	70% of attempted correction	
McDonald et al.*(22b) 1993	29	3 to 43 months	6 to 21	overall successrate 83%	17% extrusion 17% deposits on interface
Photorefractive keratectomy					
Buratto et al.(31) 1993	40	2 years	6.6 to 9.64	35% within 1 D	unstable refraction 84% persistent haze progressive regression in 72.4%
Seiler at al.(30) 1994	52	1 to 2 years	>6.0 D	50 to 52% undercorrected by >1D	myopic regression 17.3% scar formation
Dausch et al.(32) 1993	6	12 months	12 to 24	41.7% within 1 D	longer healing time epithelium
Clear lens extraction					
Goldberg(37) 1987	4479	3 years	> 10 D	19% more than 4 D	opacification posterior capsule loss of accomodation 9.6% retinal detachment
Lyle & Jin(40) 1994	31	6 to 57 months	8 to 20.5	68% within 1 D 90% within 2 D	58% posterior capsule opacification no retinal complications
Colin et al.(39) 1994	52	1 year	12 to 23.75	63.5% within 1 D 92.3% within 2 D 88.5% VA of >20/40	7.6% posterior capsule opacification treated with YAG laser no retinal complications
Barraquer et al.(36) 1994	165	4 to 14 years	_	_	7.3% retinal detachment posterior capsule opacification

*=non-human eyes
n= number of eyes

results on new synthetic lenses seem to be more promising[6].

Another technique to correct high myopia is the implantation of intraocular lenses in the cornea, or keratophakia. After a lamellar dissection of the cornea a synthetic corneal inlay is implanted within the patient's cornea (Figure 8). However, the existing soft (hydrogel, which changes the corneal curvature)[13] and rigid (polysulfone with high refractive indices)[24] corneal implants have been assessed with less than satisfactory refractive results. Interface problems, undercorrections and subluxations have been reported[13,25] (Table 1).

Photorefractive Keratectomy.

The 193-nanometer Argon Fluoride excimer laser was developed in 1983 by Trokel et al.[26] This laser emits light at 193 nm wave length, which permits a spectacularly precise ablation of anterior corneal tissue without damaging adjacent structures. Since the first successful clinical use in 1989[27,28], various applications for keratorefractive procedures have been developed for the excimer laser[6,29]. More details on this subject will be given later in the introduction and part III.

Although low to moderate myopia has been successfully corrected with photorefractive keratectomy (PRK), the correction of high myopia is inaccurate and unstable, with high rates of scar formation and regression[30,31]. But, some investigators claim a more successful approach[32].

Lens

Clear lens extraction.

High myopes are known to be contented aphakes, because of the low residual myopia after cataract extraction[33]. Considering this "aphakic happiness", Fukula[34] advocated to extract the clear lens to correct high myopia in 1890. Because of the enormous complications that occurred this approach was soon abandoned. In 1985 renewed interest in clear lensectomy[3], with or without implantation of an intraocular lens[35,36], was generated, because of the improved techniques in cataract surgery. However, most surgeons are still reluctant to use this technique, not only because of loss of accommodation, and opacification of the posterior capsule, but especially because of the potential risk of retinal detachment in these fragile high myopic eyes[37,38]. Nevertheless, prospective studies were started recently on clear lensectomy to study the risk/benefit ratio[39,40]. The main advantages of clear lens exctraction combined with posterior chamber lenses is a stable refractive outcome without endangering the corneal endothelium.

Phakic Intraocular Lenses (IOL).

The first lens implantation in cataract surgery was performed by Ridley in London in 1949[41]. The material he choose to be used for these lenses was polymethylmetacrylate (PMMA), based on the inertness of this material in the eyes of Spitfire pilots in World War II, whose integument's were shattered during fighting. This choice was a prosperous one, since PMMA is still the standard material used today to manufacture IOLs.

In the 1950s Strampelli and Barraquer were the first surgeons to use angle fixated anterior chamber lenses for the correction of high myopia[42,43]. Unfortunately, all the lenses had to be explanted because of major complications such as corneal decompensation, mainly due to the imperfection of manufacturing[44]. The lenses were solid and extremely thick at the periphery. Another factor contributing to the termination of the procedure was the inferior surgical technique. There was no concept of endothelial vitality, and the crystalline lens was subject to enormous trauma. Because of this disastrous experience, it took 30 years before the correction of high myopia with intraocular lenses was reconsidered. New surgical techniques with lens glides, the use of viscoelastics and the improved manufacturing techniques allowed the development of new types of phakic anterior chamber lenses[5,45].

Because of the disasters which plagued these lenses in the past, a reluctance exists in the ophthalmic community against new lens designs for high myopia [45-47]. The risks and benefits can only be evaluated by studying these new phakic lenses very carefully in a selective population.

Spider lens.

Momose developed a phakic angle supported IOL with a glass optic and polyamide haptics in 1987[48], the "spider lens". The results described are very concise. They show a predictable refractive outcome, an increase in visual acuity, and an acceptable amount of endothelial cell loss. No serious complications have been reported. Long term follow-up data have not been yet published. What remains unclear is the stability of the fixation with the flexible polyamide haptics.

Baikoff ZB lens.

The first myopic implant Baikoff developed was based on the PMMA Kelman multiflex anterior chamber lens, an angle-supported lens with foot plates. The refractive results were satisfactory and accurate [14,22]. However, further studies showed a marked decrease in endothelial cell density particularly in the mid-periphery, especially at the site of the optical rim of the lens[49,50]. The investigators hypothesized that there might be intermittent touch between the corneal endothelium and the IOL, and that eye rubbing and contact specular microscopy would increase the chance of this endothelial touch. Other complications that were described related to the haptics of this angle support lens, like synechiae, pupillary deformation, iris atrophy[51] and glare.

Because of the proximity of the Baikoff ZB lens to the endothelium a second generation myopic implant (Baikoff ZB 5M) was developed with a lower vault[52]. Also, the shape of the optic was modified to reduce thickness of the rim. This new lens is still under restricted clinical investigation, but recent reports on the endothelial cell loss seems to be more acceptable (Baikoff, presentation at the European Society of Refractive Surgeons, Innsbruck, 1993). No reports on the specific results have been published yet.

Silicone disc posterior chamber lens.

The silicone lens of Fyodorov is placed behind the iris in contact with the crystalline lens capsule. There are no reports available on the results. However, some opacification of the anterior part of the natural lens and the tendency for decentration have been described[5,24].

Iris claw lens.

In 1978 Worst developed the lobster claw lens in the Netherlands to be implanted after cataract extraction[53]. This anterior chamber lens is fixated on the iris, leaving the chamber angle free. The diametrically opposed haptics can be "pinched" on the midstromal iris tissue, as "claws". In this way the lens stays fixated on the immobile part of the iris. Many of these lenses have been implanted in Europe and India during cataract surgery with good results [41].

In part I of this thesis I will discuss the results of our retrospective and prospective studies on several modifications of the iris claw lens; namely the occlusion lens and the biconcave and convex concave models for the correction high myopia.

In 1980 a modified lobster claw lens was implanted for the first time in a phakic eye of a patient suffering from untreatable diplopia after trauma. This lens is still *in situ* today (1994) and the patient has a clear cornea and no lens opacification (Chapter 2).

Biconcave Worst-Fechner lens.

In 1987 Worst and Fechner developed a phakic anterior chamber lens based on the iris claw lens[54,55]. This new Worst-Fechner lens has a biconcave optic and has the same fixation mechanism as the lobster claw lens, that is enclavation on the midperipheral iris tissue. A few hundred of the Worst-Fechner lenses were implanted with good refractive results[56,57](Chapter 3). However, some reports described corneal endothelial damage[56].

Worst Myopia Claw Lens.
The design of the optic was altered in 1991 into a convex-concave shape. The main advantages of the new model are the increase in the diameter of the optic from 4.5 mm to 5.0 mm to reduce glare, and the reduction of the height of the optical rim. In theory this would reduce problems of glare and lower the chance of intermittent endothelial touch. Because of the general reluctance to operate on high myopic eyes a carefully designed prospective study has to evaluate the risk/benefit ratio of the use of phakic anterior chamber lenses. Not only is the risk for retinal detachment higher in high myopic eyes, the presence of an anterior chamber lens may also cause chronic subclinical inflammation[58]. These subclinical inflammatory reactions can at the end damage the corneal endothelium or cause cystoid macular edema.

To evaluate the efficacy and especially the safety of this new lens a prospective multicenter study was started in several European clinics in 1991. In Chapter 4, I will present the preliminary results of the patient population operated by Worst in Groningen.

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1.2 SPECULAR MICROSCOPY.

To patients with an intraocular lens for the correction of high myopia one of the quintessential questions is to what extent the endothelium will be damaged. To examine the corneal endothelium a specially designed instrument, the specular microscope, is imperative. The specular microscope has become the standard mean to study the corneal endothelium *in vivo*.

1.2.1 Morphologic characteristics of the corneal endothelium.

The normal human endothelium and aging.

Corneal transparency is necessary for clear vision. The corneal endothelium is the most posterior layer of the cornea (Figure 1) and is essential for the maintenance of its thickness and transparency[1].

The barrier and pump function of the corneal endothelium mediate a delicate balance of fluid movement across the posterior corneal surface by limiting the movement of fluid into the hydrophilic corneal and by removing excessive fluid[2,3]. With this mechanism a continuous relative deturgescent state of the cornea, with a hydration rate of 78%, is persevered and corneal transparency is maintained. When the rate of fluid leak exceeds the corneal endothelium pump activity, corneal edema will occur. This destroys the orderly arranged collagen fibers of the stroma, and vision will be impaired[2] because of the corneal opacity.

At birth the corneal endothelium consists of approximately 400,000 cells arranged in a monolayer of a thickness between 4 to 6 μm. The corneal endothelium is composed of a tessellated mosaic of polygonal cells, predominantly hexagonal in shape[2]. The hexagon is physically and geometrically the most stable shape to form a plane, because the minimal perimeter produces the least surface tension energy[4].

The corneal endothelial cells have an average diameter of 20 μm and a surface area of about 250 μm^2[1,5]. Corneal endothelium cell density decreases with age throughout life, due to cell loss without replacement by cell division. The endothelial cells enlarge and migrate to replace the lost cells[6,7]. Mean cell losses of 0.5%[8] and 0.8%[9] per year have been reported. There is a wide individual variation of mean cell density but in general one can say that in infants the mean cell density is approximately 4000 cells/mm^2[10] and that it declines rapidly till the age of 25[13] to a mean cell density of 2850 cells/mm^2. The population over 25 becomes increasingly heterogeneous and cell densities can vary between 1000 to 3500 cells/mm^2 at the age of 50 and between 900 to 3300 cells/mm^2 at the age of 80[6,12,13]. Hence we cannot predict a person's age by looking at the endothelial cell density alone.

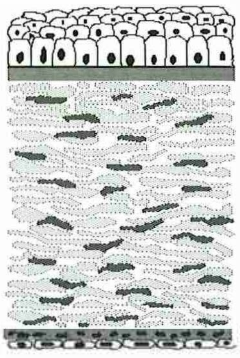

Figure 1. Schematic cross section of the cornea.

Endothelial wound healing.

Endothelial damage is repaired primarily by cells in that region, leaving more remote areas undisturbed[14]. Although cell migration with mitotic proliferation has been described in non-primate corneas[15] and in organ-cultured human corneas[15,16], in the human the healing efforts occur by cellular reorganization, enlargement, and migration[4,14,17]. Endothelial cell division is a minor component of the repair response[18]. Even if mitosis has been documented, it is insufficient to keep up with the attrition from aging and trauma. For clinical purposes we consider the human endothelium a non-replicating tissue[5,15].

Even with reduced endothelial cell densities the human cornea can maintain its clarity[19,20]. This can be illustrated by the development of more pump sites in corneas with a low cell density[3]. In general there is no correlation between cell density and cell function, but when a cell is larger than 3300μm^2 (300 cells/mm^2), on the average, the cornea becomes cloudy[4]. We once photographed the corneal endothelium of a patient 6 years after penetrating keratoplasty and found a mean cell density of 600 cells/mm^2, without signs of corneal edema (Figure 2).

1.2.2 Specular microscopy

The corneal endothelium is the only human tissue that can be observed on a cellular level *in vivo*, without disturbing its surroundings. The first report on visualizing the corneal endothelium by using specular illumination dates from 1920 when Vogt[21] observed several endothelial disorders by slit-lamp biomicroscopy. In 1968 Maurice[12] introduced a microscope for *in vitro* examination of whole enucleated eyes, using the reflection principle of Vogt, and proposed to call this microscope 'specular microscope'.

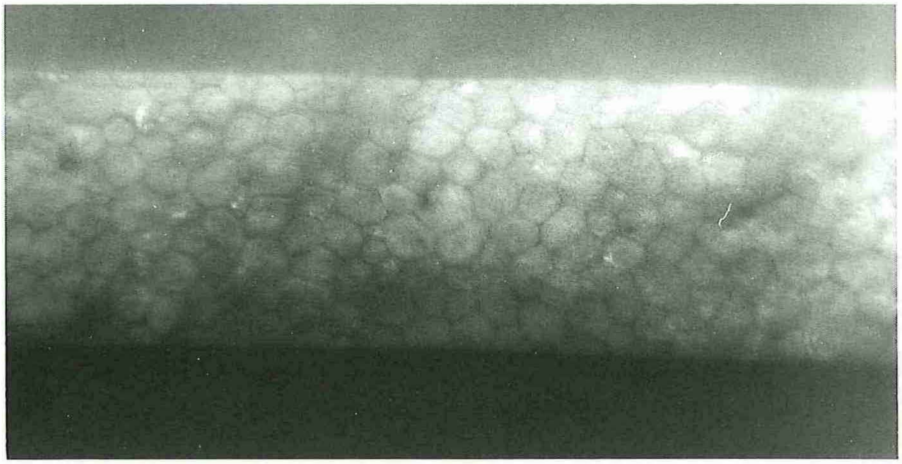

Figure 2. Specular microscopy of a corneal graft 6 years after surgery.

In the 70s several clinical specular microscopes were developed to examine and photograph the corneal endothelium *in vivo*[6,7]. These early contact microscopes applanated the cornea, but later also non-contact microscopes were developed[13,23]. To enhance the field of view, wide-field specular microscopes were developed, which allow both qualitative and quantitative examinations of a greater surface area of the cornea [19,24,25]. Because early analyzing methods of the endothelium were time-consuming and tedious, due to manual tracing of cell boundaries or cell apices[26], sophisticated computerized image processing methods have been developed for more automated morphometrical analysis of the corneal endothelium[27,28]. Recently, commercially available specular microscopes have been elaborated with autofocus devices and additional incorporated analyzing software, for a quick assessment of the endothelial morphometry[29,30]. In part II of this thesis I will discuss the computerized specular microscopy analysis we developed for clinical purposes and compare it with commercially available microscopes.

Specular microscopy has been shown as a safe, reliable and effective mean to ascertain the endothelial cell density and to provide information on the functional status (morphometry). It has increased our knowledge and understanding of the corneal endothelium.

1.2.3. Confocal microscopy.

A new development in assessing the corneal endothelium and other structures of the cornea is the tandem scanning confocal microscope[31,32]. The viewer sees thin slices of the cornea, which are parallel to the epithelial surface. This instrument gives a dynamic look at the corneal structures as in conventional microscopy. The confocal microscope is able to assess all cell layers of the cornea under a variety of conditions, whereas with the specular microscope only the surface epithelium and endothelium can be imaged. A major advantage is that with the confocal microscope the images can be detected better through a cornea that is partially opaque, due to edema and scarring. However, the technique is still difficult because of the low signal to noise ratio.

1.2.4 Morphometric characteristics.

Because the corneal endothelium is amitotic, quantitative analysis has become an important approach to document the endothelial viability. The number of cells per square millimeter has become widely used in the assessment of preoperative and postoperative corneas [9,33-37]and has been recommended by the American Academy of Ophthalmology[19]. Because there is no linear correlation between cell density and cell function full assessment of the endothelium is provided with three additional parameters[4,15,19]: (1)the coefficient of variation in cell size (polymegathism), which is the ratio of standard deviation of the cell sizes to the mean cell size; (2) the hexagonality (pleomorphism) expressed as the percentage of six-sided cells, which is a measure of variation in cell shape; and (3) the heterogeneity of the population of the different cell sizes in one sample, in terms of coefficient of skewness [5,9].

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1.3 193-NM ARGON-FLUORIDE EXCIMER LASER.

History.
In 1983 Trokel et al.[1] were the firsts to describe the interaction of the new 193-nm Argon-Fluoride excimer laser and the cornea. Because of its extraordinary precision of corneal tissue ablation, this new laser held great potentials to be used in superficial corneal surgical procedures. Trokel suggested to use photoablation for the correction of optical errors and superficial corneal pathology.

Since the first successful clinical utilization of the excimer laser in the late 1980s[2,3] this new technology still rides the wave of popularity in keratorefractive surgery. Many applications of this powerful instrument have been developed and are still under investigation, of which some will be presented in this thesis (Chapters 7 through 10).

1.3.1 The 193 nm argon-fluoride excimer laser.

The term *excimer laser* is the contraction of two words (*excited dimer*) which describes the physical state of the lasing media used. Noble gas atoms in metastable excited states can react with halogen gasses to form diatomic rare gas halides in bound excited state. Decay of these excimer molecules to a weakly bound ground state is accompanied by emission of photons with ultraviolet frequency. The noble gas Argon and the halogen gas Fluoride excimer laser produces high power UV radiation with 193 nanometer (i.e., 6 eV per photon) emission wavelength[4].

Because far ultraviolet light of 193 nm is absorbed very strongly by the cornea, the penetration depths of the pulses are of sub micron magnitudes. This makes the 193-nm excimer laser clinically very useful[5,6]. Ninety percent of the photons at 193 nm will be absorbed by the first micrometer of the tissue surface. The longer wavelength of the secondary fluorescence has greater penetration and may be biologically active. However, it would take hundreds of thousands of pulses to lead to sufficient secondary fluorescence to induce photokeratitis or cataract[7].

The 193 nm ultraviolet light acts on tissue by a process described as 'ablative photo-decompensation' or more properly photodissociation. The target molecules are broken into smaller vaporous fragments by direct photochemical interaction (ablation) without heating the remaining adjacent tissue, due to the short pulse duration (about 10 ns). Ablation occurs within the time span of the laser pulse[8]. During the ablation process, products are ejected from the irradiated target, and an ablation crater is created[9]. The limiting value of energy density was studied histologically and was found to be 1 J/cm^2, since higher values cause thermal effects[10].

Table 1. Summary of clinical results on myopic photorefractive keratectomy.

Source	n	follow-up (months)	refractive correction(D)	% within 1 D of near emetropia	V.A.
Gartry et al.[12] 1992	120	12 to 22	2 3 6 7	95 70 40 20	18% loss of BCVA
Seiler et al.[13] 1994	193	12 to 24	up to 3 3.0 to 6.0 6.0 to 9.0 >9.1	97,6 91,8 44,4 25	1.2% loss of BCVA
Salz et al. [14] 1993	160	3 to 24	1.25 to 7.5	73 to 91.6	18.3 % to 53 % loss of BCVA
Kim et al.[15] 1994	45	24	2.0 to 6.0	91,1	4.4% loss of BCVA
Piebenga et al.[16] 1993	133	6 to 36	1 to 6	58 to 88	67 to 100% uncorrected VA was 20/40 or better

VA= visual acuity

BCVA= best-corrected visual acuity

Table 2. Summary of literature on phototherapeutic keratectomy in anterior corneal pathology.

Source	n	follow-up months	disease	result	problems/complications
O'Brart (18) 1993	122	3 to 60	band keratopathy	>8% recurrence >88% improved vision >95% improvement of ocular discomfort	hyperopic shift in 33 eyes of 1.4D
Campos et al.(19) 1993	18	2 to 18	>corneal dystrophy >scars >band keratopathy	>77.7% improvement of corneal clarity >61.1% VA improved	>irregular astigmatism(n=2) >hyperopic shift (n=10)
Fagerholm et al.(20) 1993	166	6 to 28	>opacities >irregularity >recurrent erosions	goal achieved in 84.2%	hyperopic shift correlated with number of pulses.
Stark et al.(12) 1992	27	24	>corneal dystrophy >corneal degeneration >scars	improvement of visual function in 78%	mild to severe hyperopic shift in total group
Sher et al.(22) 1991	33		corneal scars		50% hyperopic shift

Photoablation in several tissues results in an extremely smooth surface[2]. The longitudinal excisions by the 193 nm excimer laser are very smooth compared to the ones made with traditional diamond and steel knives[11].

1.3.2 Applications.

Photorefractive Keratectomy (PRK).
PRK is the most frequently used modality of the excimer laser today, for thousands of patients have been treated world-wide. In the early stage Trokel[3] has already proposed to use excimer laser ablation for the correction of refractive errors, as in myopia, astigmatism, and hyperopia. Many trials on the correction of myopia are currently under investigation. The results of the studies with a longer follow-up are summarized in Table 1.

Myopic PRK results in a central disciform photoablation varying between 5 and 6 mm in diameter, with a depth up to 50 or 80μm[13]. Most of the problems encountered until now are related to the wound healing and decentration of the ablation. Problems of haze formation and gradual regression of the refractive outcome have not been solved yet. Also, the habitual use of steroids postoperatively can result in some serious, well-known, side effects.

Recently, other refractive applications of PRK have been developed. Studies on the correction of astigmatism and hyperopia are currently in progress.

Phototherapeutic keratectomy (PTK).
The capability of the 193 nm excimer laser to remove precise amounts of tissue has generated therapeutic use in anterior corneal pathology and is called 'phototherapeutic keratectomy'. Experimental therapeutic keratectomy was first performed in 1984[17] followed by the use in human eyes by Seiler in 1986[3]. Studies on the different corneal pathologies treated with photoablation are summarized in Table 2. PTK can offer a significant number of patients an alternative to penetrating or lamellar keratoplasty. Chapters 9 and 10 deal with the treatment of recurrent corneal epithelial erosions and a case of intraepithelial dysplasia. The postoperative flattening of the cornea can cause induced hyperopia, which can affect the favorable outcome of the surgery. Further attempts to minimize this postoperative hyperopic shift would be appropriate.

1.3.3 Wound healing.

After histological studies revealed a maintenance of transparency and retention and stability of the anatomic features[23] the excimer laser was applied to functional human eyes. However, with photorefractive keratectomy one is concerned of the possible scar formation in the visual axis, producing vision loss and glare, and the stability of the procedure[24,25]. A common clinical response in myopic PRK is regression of effect, due to epithelial hyperplasia and/or corneal wound healing[26]. Haze formation generally occurs during the first 6 months, after which it gradually disappears. The decrease in epithelial anchoring fibers[27], an increased epithelial thickness, and an increased fibroblastic activity[28] seem to correlate with haze formation and regression of refractive effect after photoablation.

The use of topical steroids after excimer laser keratectomy is widely spread, since it is thought to successfully reduce the amount of corneal haze and regression[29,30]. The inhibiting activity of steroids on immune reactions and collagen synthesis could limit the stromal changes responsible for haze formation and/or regression. With respect to refractive surgery one might ask if the use of steroids is acceptable in view of the serious side effects.

Only recently a controlled prospective study on the effects of steroids in PRK has been published[31]. The investigators did not find a significant difference in haze formation between a non-steroid group of patients and patients using high-dose dexamethasone, nor did they find a significant change in refractive outcome. The use of steroids induced a greater refractive effect, which completely regressed when medication was discontinued. These results were confirmed by Piebenga et al.[32]. Nevertheless, other investigators advised the use of topical steroids[33-35]. The role of corticosteroids remains an unresolved issue in reducing the wound healing response. Alternatives, as interferon-alpha 2b, appear to reduce the corneal haze in experimental studies[36]. However, this new possibility has to be explored yet.

The formation of haze seems to be dependent on the ablation depth[12,28]. Seiler[13] found a significantly increased scar formation in patients with higher degrees of myopia where more tissue was ablated (up to 80 μm).

The principle effects of photoablation on the tissue described in the literature usually relate to the epithelial and stromal histological changes [23,26,37]. The effect on the corneal endothelium remains unclear and there are a great deal of discrepancies in investigative results on the morphometric outcome. While some investigators claim that photoablation did not affect the endothelial cell density and morphology[11,23] up to one year after treatment and that there is no correlation between cell loss and ablation depth, others[38] did find a mean cell loss of 17% after 1 year or cell damage when the ablation depth was within 40 μm of the endothelium.

Although the excimer laser holds great potential, increased insight into the multi-facet wound healing response to photorefractive keratectomy and its modulation will define the future success of this powerful instrument. The excimer laser has certainly a place in ophthalmology but not without further examination. The long-term effects should be examined carefully.

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PART I

Phakic Worst Myopia Claw anterior chamber lens

CHAPTER 2

Nontransparent Iris Claw Lens in a phakic eye to correct acquired diplopia. 14 years after implantation.

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(submitted)

Acquired incomitant strabismus frequently results in diplopia, which is often experienced as chronically uncomfortable by the patient. Therapy has usually been aimed at either to restore binocularity by using prisms or vision training, or by eliminating one image through occlusion [1]. Herein we present a case 14 years after implantation of an occlusive intraocular lens for treating acquired diplopia.

Report of a case. In 1975 a 26-year-old white man was referred to our clinic because of an abducens nerve paresis on both sides after cranial injury. Surgical correction resulted in a primary position of the fixating right eye and, after repeated surgery, a final position of 15° of his left eye.

Because of the patient's complaints on persistent diplopia and affected cosmesis, he was referred to another clinic in 1980. A specially manufactured tinted Iris Claw Lens was implanted by one of the authors (JGFW) in the left eye (Figure 1), with the crystalline lens in situ. The following years the crystalline lens remained clear. Slit-lamp biomicroscopy did not reveal apparent inflammatory symptoms in the anterior chamber or decompensation of the corneal endothelium. The patient's complaints on persistent diplopia disappeared. Through the opaque intraocular lens he is still able to perceive lightness and darkness.

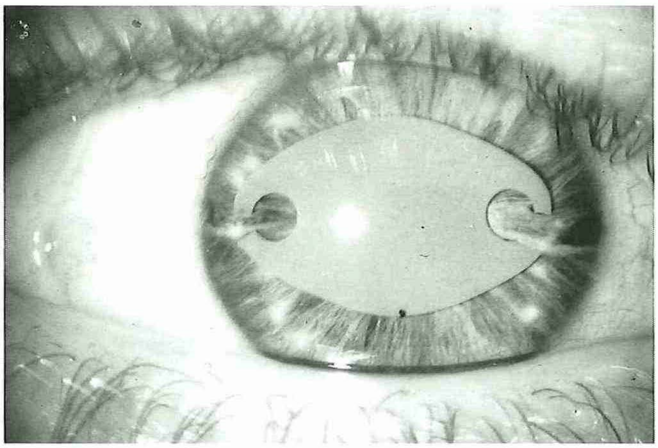

Figure 1. Tinted Iris Claw Lens in the left eye 14 years postoperatively. The haptics are fixated, diametrically to each other, on the midstromal iris tissue. No signs of iris atrophy was noticed.

In June 1994 the patient's corneal endothelium was examined in our clinic with a contact wide-field specular microscope (Keeler Konan sp3300) in combination with a semi-automated computer-assisted video image analyzer. The mean endothelial cell density in the right eye was 2480 cells/mm^2 and in the left eye 2018 cells/mm^2 (Figure 2). The coefficient of variation in cell size was RE: 0.39 and LE: 0.36, the hexagonality was RE: 62%, and LE: 69%, and the coefficient of skewness was RE: 0.33 and LE: 1.47.

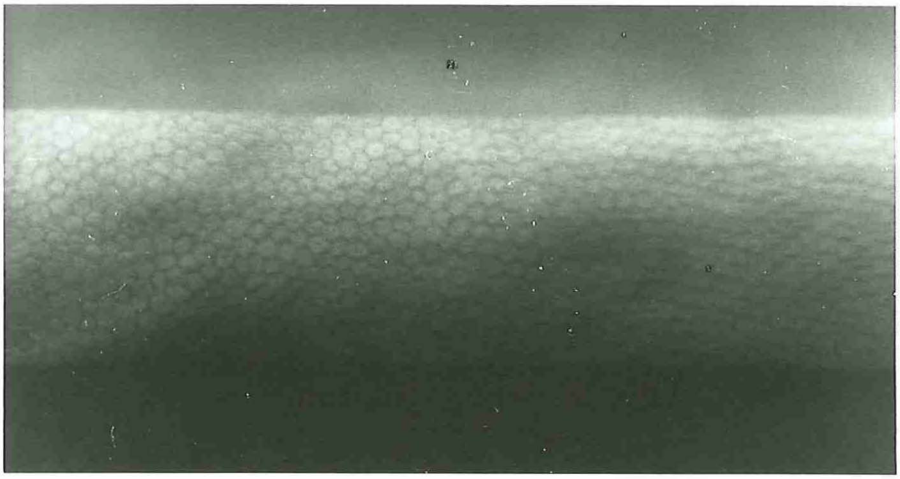

Figure 2. The specular photograph of the corneal endothelium of the left eye 14 years postoperatively.

Comment.

When there is no possibility to restore binocularity in patients with acquired diplopia, occlusion may be the only device left to relieve annoyance[1]. Because an occlusive contact lens was ineffective in our patient, a modified iris fixated anterior chamber lens, the Iris Claw Lens [2], was used for monocular occlusion.

To our knowledge no report has been published previously on a patient with a phakic anterior chamber lens with such a long follow-up. One of the major concerns of (phakic) anterior chamber lenses is the effect on the corneal endothelium because of possible chronic subclinical inflammatory reactions[3]. Therefore, we examined the corneal endothelium in both eyes of this patient. Since there is a high correlation in endothelial cell density between fellow eyes in one individual[4], we can only appraise that the cell loss in his left eye was approximately 18.6% after 14 years, without knowing if stabilization had occurred. The larger coefficient of skewness in the left eye indicates a cell population with larger cells due to the varied increase in cell size caused by cell loss. The morphological parameters in terms of variation in cell size and hexagonality[5] seem not to differ significantly in both eyes, indicating a sufficient endothelial functioning.

The iris fixated Lobster Claw Lens was modified in 1987, to some extent based on the case described above, into a biconcave model for the correction of high myopia in phakic eyes[6]. Later, in 1991, the convex-concave Worst Myopia Claw Lens was developed and is currently under investigation for the correction of high myopia.

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CHAPTER 3.

Negative implant: a retrospective study.

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(Documenta Ophthalmologica 1993;83:261-270.)

Abstract.

Implantation of a negative power intraocular lens in a phakic eye is one of the options for surgical correction of high myopia. We studied 36 eyes with a Worst-Fechner Claw Lens, implanted in Groningen between March 1987 and November 1991. The preoperative myopia ranged from -7.00 to -30.00 diopters. Twenty one eyes had a follow-up period of more than 12 months. Correction within 1 diopter of emmetropia was achieved in 55.5% of the cases. Deviation of more than 2 diopters occurred in 25%. In 24 eyes the best corrected postoperative visual acuity improved. In none of the cases complications were encountered during surgery. In the postoperative period one intraocular lens had to be replaced because of an error made in the calculation of the lens power. In one case endothelial decompensation occurred, probably due to a combination of compulsive eye rubbing and a preexisting corneal guttata. The rim of the optic is the part which is the closest tot the corneal endothelium. Our recommendation would be that one should avoid indentation of the cornea. No other serious complication occurred in this study.

Introduction.

Inserting a negative intraocular lens in the phakic myopic eye is one of the modalities in the field of refractive surgery. In the 1950s Strampelli and Barraquer attempted to implant negative intraocular lenses (IOL) in the anterior chamber of myopic eyes[1,2]. These implantations were unsuccessful, partly due to the poor quality of the lenses and the chamber angle support of the IOL, causing various severe complications. Therefore Barraquer had to remove the majority of the 239 lenses he had implanted[3]. Nowadays, the quality of intraocular lenses has improved, which reduced the problems due to manufacture imperfections.

In 1986 Worst and Fechner developed a biconcave anterior chamber lens for high myopia[4,5]. This lens is based on the iris claw lens which was developed in the 1970s for cataract surgery by one of the authors (J.G.F.W.). The haptics of these lenses are diametrically opposed to each other and fixate the lens with "claws" at the midperipheral iris stroma. Since 1979 some 33.000 of these lenses have been implanted during cataract surgery[6]. In this retrospection we will discuss the results and safety of the negative iris claw lenses implanted by Worst between March 1987 and November 1991 in Groningen.

Patients and methods.

Patients.

We studied the records of all the patients who underwent an implantation of a biconcave negative iris claw lens performed by one of the authors (J.G.F.W.) between March 1987 and November 1991. Only patients with normal intraocular pressure and deep anterior chambers were operated. The original total number of patients in this group was 20. To be able to compare the results with the literature, we excluded 2 patients, one minor and a mentally retarded child. Therefore we studied 18 patients, who were all operated on both eyes. The mean age was 40.5 (±11.2) years and the follow-up ranged from 60 to 2 months (Table 1). In 21 eyes the follow-up period was at least 12 months (Table 2). The anterior chamber depth ranged from 3.1 mm to 4.1 mm.

Table 1. Population characteristics.

patients	18
eyes	36
mean age	40.5 years (sd: 11.2
mean follow-up	19.97 months (sd: 15.3)

sd=standard deviation

Table 2. Results.

nr.	eye	sex	age (years)	refraction@ pre	refraction@ post	bcva* pre	bcva* post	implant	follow-up (months)	acd** (mm)
1	OD	M	23	-19.00	-3.25	0.4	0.5	-15.00	60	3.3
	OS			-19.00	-4.00	0.4	0.2	-15.00	53	3.2
2	OD	M	59	-16.50	-1.00	0.3	0.6	-16.00	43	--
	OS			-17.75	-1.25	0.5	0.8	-17.00	42	--
3	OD	M	37	-15.25	--	0.3	--	-14.00	46	3.5
	OS			-12.25	-0.25	0.15	0.5	-14.00	36	3.5
4	OD	M	54	-13.50	-1.50	0.4	0.4	-13.00	36	3.8
	OS			-15.50	-1.00	0.4	0.4	-15.00	36	3.8
5	OD	F	37	-09.00	0.00	0.3	1.0	-10.00	34	3.8
	OS			-09.50	-0.50	0.4	1.0	-09.00	30	3.7
6	OD	M	58	-20.00	0.00	0.25	0.5	-19.00	29	3.6
	OS			-19.75	0.00	0.5	0.7	-19.00	27	3.8
7	OD	M	38	-08.50	0.00	0.8	1.0	-09.00	30	3.6
	OS			-08.75	-0.50	0.8	1.0	-09.00	28	3.7
8	OD	M	32	-14.00	-0.75	0.3	0.8	-14.00	30	3.1
	OS			-14.00	0.25	0.8	1.0	-14.00	26	3.3
9	OD	F	43	-10.25	-0.75	–	1.0	-11.00	25	3.3
	OS			-10.75	0.00	–	1.0	-11.00	23	3.3
10	OD	F	43	-14.25	1.25	0.6	0.8	-16.00	17	--
	OS			-17.00	0.50	0.6	0.8	-18.00	17	--
11	OD	F	39	-26.25	-3.75	0.07	0.15	-20.00	13	3.9
	OS			-24.25	-3.00	0.033	0.1	-20.00	12	3.9
12	OD	F	41	-12.75	0.00	0.8	1.0	-14.00	12	4.1
	OS			-15.00	0.00	0.8	1.0	-16.00	07	4.0
13	OD	M	56	-30.00	-4.00	0.25	0.2	-20.00	10	3.7
	OS			-30.00	-3.25	0.3	0.2	-20.00	06	4.0
14	OD	F	35	-07.00	-3.50	–	1.0	-06.00	09	--
	OS			-07.00	-2.00	–	1.0	-06.00	03	3.3
15	OD	F	41	-19.00	-0.50	0.2	0.3	-19.00	06	3.4
	OS			-19.00	-0.25	0.7	0.8	-19.00	05	3.5
16	OD	M	24	-17.00	1.50	0.3	0.6	-20.00	08	3.7
	OS			-18.50	-0.25	0.3	0.6	-19.00	04	3.6
17	OD	F	47	-20.25	-6.50	0.8	0.8	-20.00	04	3.8
	OS			-23.00	-8.25	0.3	0.4	-20.00	04	3.6
18	OD	F	23	-18.25	-0.25	0.6	–	-20.00	03	4.0
	OS			-15.50	-1.25	0.6	–	-18.00	01	4.1

@ spherical equivalent in diopters
*bcva=best corrected visual acuity
**acd= anterior chamber depth

Biconcave iris claw lens.

The Worst-Fechner negative iris claw lens has a biconcave optical part (Figures 1 and 2). The lens is made of one single piece of perspex CQ-UV absorbing PMMA, by Ophtec B.V. in Groningen, the Netherlands. The total length of the lens is 8.5 mm the optic has a diameter of 4.5 mm. The total height of the lens is 1.2 mm with a vault of 0.5 mm. Because the concave side faces the crystalline lens there is a space of approximately 0.8 mm between the natural lens and the IOL.

The lens is manufactured in 1 diopter steps and the power ranges from -5.00 to

-20.00 diopters. Van der Heijde developed a formula for the calculation of the power of the negative lens to be implanted[7]. The anterior chamber depth, the refractive power of the cornea, and the preoperative refraction are the parameters required for this formula.

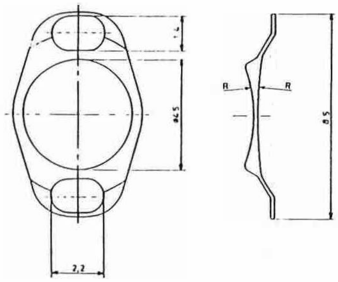

Figure 1. The biconcave Worst-Fechner Iris Claw Lens.

Surgical technique en medication.

During two days before the operation indomethacine 0.1% was administered twice a day. The pupil was constricted with pilocarpine 2.0% one hour before surgery. As retrobulbar anesthesia xylocaine 2%, with 1:80.000 adrenaline (ASTRA Pharmaceutical), and Hyason (Organon), was used. Sometimes oxybuprocaine 0.2% was added topically.

Two traction sutures were placed in the intramuscular quadrant for stabilization. Two corneoscleral incisions were performed in patients #1 to #8, a large one from 9 to 12 o'clock and a small one from 1:30 to 2:30 o'clock. In the other patients one large corneoscleral incision of a quarter of the circumference was performed. Pilocarpine chlorhydrate (Laboratoires Meran) was used for myosis.

Sodium hyaluronidate 10 mg/ml (Healon, Kabi-Pharmacia) was introduced in the anterior chamber and the IOL was inserted through the large incision at 12 o'clock. The lens was rotated into the horizontal position, bringing the enclavation sites to 3 and 9 o'clock. The lens was held with a iris claw lens fixation forceps. Small folds of iris tissue were enclavated with an enclavation forceps, introduced through the small incision at one side and through the large incision at the contralateral side, while the IOL was kept fixated. In the eyes with only one large incision, special enclavating needles were used instead of forceps.

Finally, a peripheral iridectomy was performed to prevent pupillary block. All the viscous material was carefully rinsed out. The incisions were closed with interrupted stainless steel sutures.

Garamycine 40 mg with Celestone 4 mg (Schering) was injected subconjunctivally immediately after surgery. Postoperatively tropicamide 1% and acetazolamide 250 mg were administered in the first two days, Timoptol and Cyclogyl during the first week, and Decadron and Indocid during the first 5 weeks.

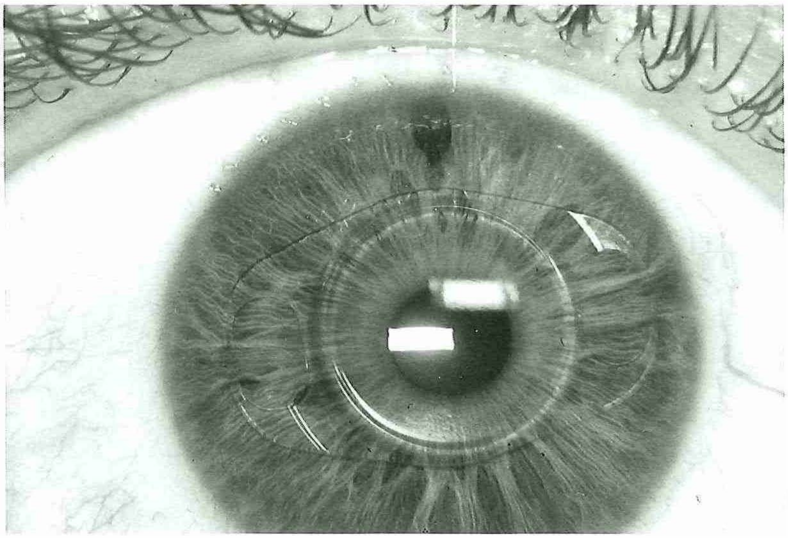

Figure 2. The Worst-Fechner Iris Claw Lens in situ.

Patient examination.
The manifest refractive error and the best corrected visual acuity were measured under standard conditions. Keratometry was performed with a Javal keratometer. The anterior chamber depth was measured with ultrasound.

We evaluated the central corneal endothelial cell counts in 13 patients at the University Eye Clinic in Groningen. The endothelial cell counts were performed in patients #9 and #12 with a Zeiss specular microscope mounted on a Zeiss slitlamp. Video images were transmitted directly into a computer. The images were processed semi-automatically with the use of a software package (TIM, Difa Measuring Systems b.v., Breda, Netherlands). In the other 11 patients a Keeler Konan sp3300 wide-field specular microscope was used in a contact mode, with oxybuprocaine 0.2% as local anesthetic. The cell counting was performed with the aid of a grid.

Results.

Refractive outcome.
The baseline refraction varied from -7.00 to -30.00 diopters (Table 3). It was not possible to obtain emmetropia in each patient because of the limitations in the power of the IOL. Nevertheless, in 20 eyes (55.5%) of the 36 eyes near emmetropia (i.e.,

between -1.00 and +1.00 diopters) was achieved (Table 4). In 25% of the eyes the myopia was undercorrected with more than 2 diopters (table 4). The undercorrection in 6 eyes was due to a high myopia of 20.00 D or more. In patients #2 and #16 the calculation of the lens power turned out to be wrong, resulting in replacement of the IOL in patient #16. For patient #13 the postoperative goal was -2.00 D in both eyes. The postoperative refractions in the 10 eyes, where the calculated powers of the IOLs were available, were all within 1 diopters of emmetropia. In general the patients were very pleased with the results of the operation.

Table 3. Baseline refraction.

myopia	range	n	%
low	-07.00 to -10.00	6	16.6
middle	-10.12 to -15.00	9	25.0
high	-15.12 to -20.00	15	41.6
higher	-20.12 to -25.00	3	8.3
very high	-25.12 to -30.00	3	8.3

The best corrected visual acuity was improved in 24 (60%) of the 36 eyes (Table 2). This can be explained by the magnification of the retinal image. In 4 (10%) eyes the visual acuity decreased. Patient #2 showed lacquer crack lesions and macular degeneration in both eyes. The reason of the decreasing visual acuity in patient #12 is probably due to cataract formation, which already was present before the operation. In 4 (10%) eyes the visual acuity remained stable. Because of the incompleteness of some records we could not determine the difference in the preoperative and postoperative visual acuity in 8 eyes.

Preoperative endothelial cell counts were performed in 4 eyes only (Table 5). No serious cell losses occurred in these eyes, after 6 and 12 months. Because of the non-compliance of some patients, postoperative endothelial cell counts were performed only in 21 out of 32 eyes. In patient #3 the endothelial cell count of the left eye was 715 cells/mm^2 (figure 3). At the time that we examined this patients' endothelium, the cornea of the contralateral eye had become dystrophic after a 22 months follow-up. Therefore a penetrating keratoplasty had been performed and the IOL has been removed. The low endothelial cell count was probably due to a combination of compulsive repeated rubbing of the eyes and a preexisting cornea guttata. The postoperative endothelial cell density in the remaining 16 eyes varied between 2200 and 3180 cells/mm^2. The follow-up period varied between 42 and 5 months.

In patient #10 the IOL in the right eye was slightly decentered and caused monocular diplopia. The lens was recentered and the diplopia disappeared.

Table 4. Refractive outcome.

spherical equivalent (diopters)	n	%
+2.00 to +1.12	2	5.5
+1.00 to +0.25	2	5.5
0.00 to -1.00	18	50.0
-1.25 to -2.00	4	11.0
-2.25 to -3.00	1	2.7
-3.25 to -6.00	6	16.6
-6.25 to -10.00	2	5.5

Table 5. Preoperative and postoperative endothelial cell count.

nr.	eye	cell density*		
		preoperative	postoperative	
			6 months	12 months
9	OD	3008	2745	----
	OS	3193	3296	----
12	OD	3175	3085	2649
	OS	2829	3089	2693

*coeff. var. of method is 4.2%.

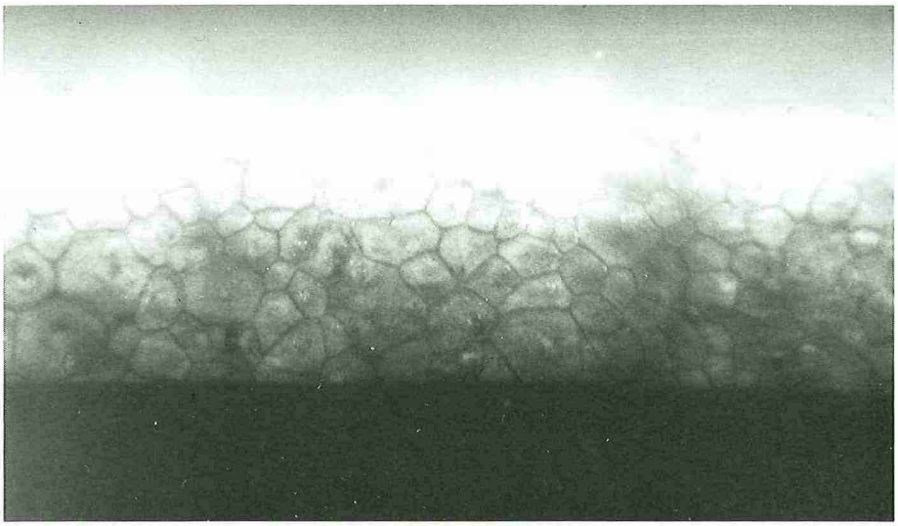

Figure 3. Wide-field specular microscopy of the endothelium of the left eye in patient #3 (716 cells/mm²).

Other phenomena that are ascribed to the prismatic effect of the optic are glare and halos, especially at night when the pupil is dilated. Therefore two patients had to be treated with pilocarpine, while in 25% of the patients halos occurred in the early postoperative period, which gradually disappeared. There were no other complications in this population. The iris did not show any signs of atrophy or other abnormalities at the sites of the enclavation.

Table 6. Postoperative endothelial cell density.

nr	eye	cell density*	follow up (months)
2	OD	2633	42
	OS	2200	41
4	OD	3080	37
	OS	3100	36
3	OS	716	36
5	OD	2733	34
	OS	2900	30
7	OD	2700	30
	OS	2741	28
8	OD	2383	31
	OS	2750	27
10	OD	2900	18
	OS	2725	18
11	OD	2833	13
	OS	2650	12
12	OD	2966	12
	OS	3180	06
15	OD	2566	06
	OS	2900	05
19	OD	2900	04
	OS	2760	04

*coeff.var. of method is 10.9%.

Discussion.

This study indicates that the implantation of a negative iris claw lens gives satisfactory results in correcting high myopia. Bearing in mind the fragility of myopic eyes, inclusion criteria must be handled with care to ensure satisfactory results and a safe procedure. Patients with shallow anterior chambers, low endothelial cell counts, raised intraocular pressure, or a bad motivation should be excluded.

The shortcoming of the Van der Heijde formula is the use of the subjective preoperative refraction. Patients with high myopia may have a myopic maculopathy, which makes it difficult for them to cooperate. The accuracy of the refractive correction in our population was less impressive than in the study of Fechner et al. [10] (125 eyes), where the postoperative correction was within 1 diopters of emmetropia in 68.8% of the cases, and deviated with more than 2 diopters of emmetropia in 9.2% of the cases (respectively 55.5% and 25% in our study).

The main point for attention in using anterior chamber lenses in phakic myopic eyes is the corneal endothelium. Fechner et al. [10] reported endothelial damage in 10 eyes, in 5 eyes this was due to traumatic surgery, in the other 5 eyes the endothelial damage was unexplained by operation. Studies on the angle supported minus power anterior chamber IOLs designed by Baikoff and Joly[11,12] revealed a significant endothelial cell loss especially in the paracentral area.

We are aware of the limited endothelial morphometry in our study, most of the patients were examined only postoperatively and merely in the central area. Nevertheless, severe endothelial cell loss occurred in one patient. This was probably due to a failure to diagnose a cornea guttata preoperatively. We also assume that compulsive eye rubbing in this patient was an additional factor for the endothelial cell loss. Whenever anterior chamber lenses are implanted in the phakic eye the endothelium must be respected at all time. Endothelial touch must be avoided during surgery. As a precaution patients should not rub their eyes and avoid any ocular trauma. Until now we do not exactly know what the impact of corneal indentation is on the endothelium in eyes with these anterior chamber lenses. Like Mimouni et al.[11] and Saragoussi et al.[12] we also think that rubbing of the eye and using a wide-field specular microscope in a contact mode may be harmful to the corneal endothelium in phakic eyes with a negative anterior chamber lens.

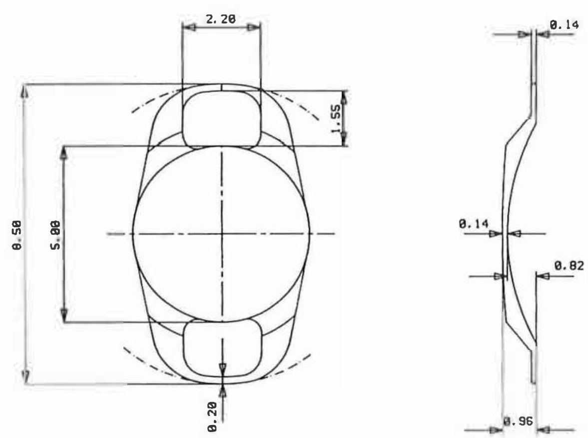

Figure 4. Design of the new convex-concave Worst Myopia Claw Lens.

We did not encounter any of the complications Fechner et al.[10] describe such as severe traumatic iritis, cystic wounds, postoperative temporary glaucoma, postoperative atonic pupil, and retinal detachment. We believe that the loss of the best corrected visual acuity in the left eye of patient #2 is not related to the implantation of the IOL. No damage or disturbances of the iris were noticed in this patient group. Fluorescein angiography of the iris did not show any vascular leaks[13]. A core group of Fechners patient population (109 eyes) was examined for signs of chronic uveitis[14] by means of a laser flare cell meter, resulting in a very low protein content and cell counts in the anterior chamber.

In 1991 the design of the biconcave lens was altered (figure 4). The optical zone is now convex-concave without a high optical rim, thus providing a greater distance between the IOL and the corneal endothelium and probably also reducing the prismatic effect causing glare. A prospective clinical trial has started at the beginning of 1992 to study the efficacy, safety, stability and predictability of this new type of lens.

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CHAPTER 4

Correction of high myopia with the Worst Myopia Claw Intraocular Lens.

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(Journal of Refractive Surgery 1995;11:16-25)
(Troutman Medal Paper Award 1995)

Abstract.

Background: Phakic anterior chamber lenses are one of the modalities used to correct high myopia. We report the initial results of our prospective study on the Worst myopia claw intraocular lens.

Methods: We studied 35 eyes in 18 patients with a preoperative myopia ranging from -6.00 to -28.00 diopters (D). The follow-up ranged from 6 months (n=15) to 12 months(n=20).

Results: In 26 (74.3%) eyes, the postoperative residual myopia was within one diopter of emmetropia. The mean refraction was stable between 1 to 2 months and 12 months. The mean best corrected visual acuity improved from 20/50 to 20/40. The straylight measurements did not show a significant increase postoperatively (p=0.64). The mean endothelial cell loss was 5.6% (range, +6.3% to -22.6%) at 6 months, and 8.9% (range, +0.77% to -23.5%) at 12 months. We did not encounter major complications.

Conclusion: Implanting a Worst myopia mlaw IOL in high myopic eyes resulted in a stable, reasonably accurate refractive outcome. This group of patients will be followed longer because of concern over ocular complications with this technique

Introduction.

Implanting an anterior chamber intraocular lens (IOL) in phakic high myopic eyes has been proposed as one of the most satisfactory surgical techniques for the correction of high myopia[1-3]..Several models of anterior chamber lenses, mainly based on existing IOLs for aphakia, have been designed and implanted during the last few years with accurate refractive results[4-6]. In 1986 Worst and Fechner modified the existing iris claw lens, used in cataract surgery, into a negative biconcave lens[7,8]. Since that time this biconcave Worst-Fechner lens has been successfully used and has provided accurate, predictable and stable refractive results[9-13]. In 1991 the optical part of the lens was altered into a convex-concave model. The new design of the lens was changed in two respects: 1) the optical part was increased from 4.5 to 5 mm, and 2) the somewhat prominent rim of the biconcave lens was lowered. The intention of the changes was to decrease possible danger to the endothelium, as well as subjective symptoms of glare and halos.

To perform intraocular surgery on eyes with extreme axial myopia raises many questions concerning the potential hazard to the fragile myopic eye. Therefore, we started a prospective study on this lens in 1991 to investigate these risks. In this study we report the preliminary results of the implantation of the Worst Myopia Claw Lens in high myopes, performed by J.Worst in the Refaja Hospital in Stadskanaal between September 1991 and March 1993.

Patients and methods.

Patients.

All patients were operated in Stadskanaal and sent to the Department of Ophthalmology at the University Clinic in Groningen, for independent preoperative and postoperative examinations. A total of 48 eyes in 25 patients were operated on, but for this report we excluded all patients with a follow-up period of less than 6 months and one patient with a previous corneal graft. Therefore, the final patient group we studied was comprised of 35 eyes in 18 patients (11 men and 7 women). Each patient was informed of the investigative nature of the procedure and received a detailed oral and written informed consent. Patient ages ranged from 17 to 52 years (mean, 35.4 years; standard deviation, 9.7), with a preoperative refraction range from -6.0 to -28.0 diopters, of which the majority had a myopia between -10.12 and -20.00 diopters (Table 1). The follow-up period was 6 months in 15 eyes and 12 months in 20 eyes.

Table 1. Preoperative refraction of the total patient population.

Refraction (D)	Number of eyes (n=35)
- 06.00 D - -10.00 D	8
-10.12 D - -15.00 D	12
-15.12 D - -20.00 D	12
-20.12 D - -28.00 D	3

Range -6.00 to -28.00

Worst Myopia Claw Lens.

The convex-concave Worst myopia claw IOL is made of one-piece CQ-UV absorbing polymethylmetacrylate, and manufactured by OPHTEC B.V. in Groningen, The Netherlands. The total length of the lens is 8.5 mm with an optic of 5 mm in diameter (Figure 1). The height of the lens does, regardless of power not exceed 0.96 mm. The lens power ranges from -5.0 to -20.0 diopters and is manufactured in 1-diopter steps. The two diametrically opposed haptics fixate the lens on the iris by enclavation of midperipheral iris stroma (Figure 2).

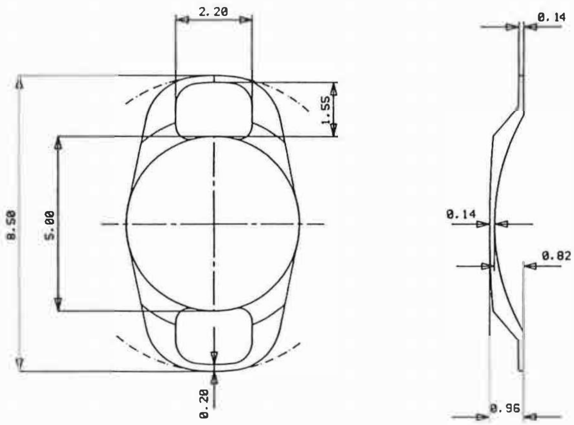

Figure 1. Schematic drawing of a -20.00 D convex-concave Myopia Claw Lens.

Surgical technique and medication.

Two days prior to surgery, indomethacin 0.1% was administered twice a day topically. One hour before surgery, pilocarpine 2 % was instilled to constrict the pupil. Due to the relatively large size of the globe, the surgeon (JGFW) preferred general anesthesia, which was only performed upon patients' request. When patients were operated under local anesthesia, lidocaine 2%, with 1:80,000 adrenaline was used peribulbarly, with additional oxybuprocaine 0.4% in some eyes. The local anesthesia was given progressively through the eyelids and, if technically possible, retrobulbarly. Due to the thinness of the scleral wall, the risk of perforation had to be taken into account. Nine of the 18 patients were operated under general anesthesia.

Two episcleral traction sutures were placed at both sides of the rectus superior muscle. A large corneoscleral incision of a quarter of the circumference was made at 12 o'clock. The anterior chamber was filled with the viscoelastic substance sodium hyaluronate (Healon, Kabi-Pharmacia) before implanting the IOL. The IOL was inserted in the anterior chamber with a special implantation forceps and was then released. One stainless steel suture was placed at 12 o'clock with one suture on each side to prevent extrusion of Healon from the anterior chamber. The lens was rotated into the horizontal position, bringing the enclavation sites to 3 and 9 o'clock. Small folds of iris tissue were enclavated with the iris "crochet" needle. Subsequently, a peripheral iridectomy was performed. All the viscoelastic material was carefully removed with Balanced Salt Solution, after which the incision was closed with interrupted stainless steel sutures.

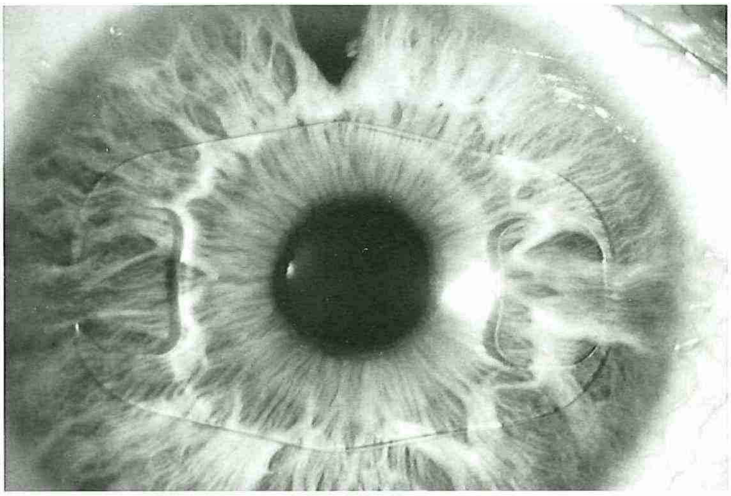

Figure 2. The Myopia Claw Lens after implantation. Small folds of midperipheral iris tissue are enclavated in the two haptics, by which the lens is fixated. A peripheral iridectomy is performed to prevent pupillary block.

Gentamicin 40 mg with betamethasone 4 mg was injected subconjunctivally immediately after surgery. Postoperatively, tropicamide 1% eye drops and acetazolamide 250 mg tablets were administered in the first two days, timolol 0.5%, and cyclopentolate 1% during the first week, and prednisolone, neomycin, and indomethacin during the first 5 weeks topically.

Patients ' examination.

Preoperatively. all eyes were carefully examined by slit-lamp microscopy and funduscopy. To determine the power of the IOL, we measured the subjective refraction, the corneal curvature with the Zeiss keratometer, and the anterior chamber depth with ultrasound. These three parameters are used in the Van der Heijde formula[14]. To determine the predictability of the refractive outcome we converted the Van der Heijde formula in such a way that we could calculate the expected correction for each implantation preoperatively. For the measurement of the visual acuity we used the modified Bailey-Lovie chart[15], which is currently used in the Early Treatment of Diabetic Retinopathy Study and the Prospective Evaluation of Radial Keratotomy Study[16], placed in a box with standardized direct illumination[17]. The visual acuity is expressed in the logarithm of the minimal angle of resolution (logMAR) and was converted into Snellen notation.

We assessed disability glare by measuring the intraocular light scatter with the straylight meter by Van den Berg[18,19]. With this instrument the amount of forward scattered light is measured by a direct compensation method. The measurements are made in a dark room while the subject's head rests on a chin rest above a black screen. Four different ring-shaped straylight sources, with angles of 3.75°, 7.5°, 15°, and 30° between the optical axis and the middle of the rings are presented in front of the patient. A central light patch flickers in counterfase of 8 Hz with the eccentric rings. The disappearance point of the central flicker light is measured for each scattering angle and subsequently averaged. Because of their high myopia, patients wore a trial frame or spectacles during these measurements preoperatively. Otherwise they could not distinguish the central flicker light.

For the examination of the corneal endothelium we used a Zeiss non-contact specular microscope in seven patients, and a Keeler Konan sp-3300 wide-field contact specular microscope in all the other patients, in combination with a video camera and a frame grabber. The specular images were analyzed semi-automatically with image processing software. We only examined the central cornea because of the arduous technique and the difficulty for the patients to keep their eyes still while fixating one point. Three images were made of each eye during each session and were all processed. The weighted average of the three processed images are presented as the mean endothelial cell density.

All patients were asked to respond subjectively to their satisfaction with the visual outcome, hindrance of night glare, distortion, and imbalance.

Statistical calculations were performed with Systat Software (Systat, Inc., Evanston, U.S.A.). A two-tailed probability of 0.05 or less was considered statistically significant. In 16 patients both eyes were operated on. Because the Pearson correlation matrix with the Bonferroni-adjusted probabilities did not show any significant correlation for the variables we measured between the left and right eyes (1.0>p>0.14), we will discuss the results of all eyes in this report.

Results.

Refraction and visual acuity.
The mean preoperative spherical equivalent myopia was -14.7 D (sd=4.9 D) and the mean postoperative refraction was -0.93 D (sd=2.9 D), measured at the last follow-up visit for the entire group. In figure 3, we represented the individual refractive outcome in a scattergram. In 26 (74.3%) eyes, the postoperative spherical equivalent residual myopia was within 1.00 D of emmetropia (Table 2). Undercorrection of more than 2.00 D occurred in 4 (11.4%) eyes, while in 3 eyes an overcorrection was noticed. One severe overcorrection of 3.50 D is probably due to an incorrectly calculated IOL power. Because the IOL is available in diopter powers up to -20.00 D, patients with a higher myopia could only be undercorrected. If we excluded the three "over 20 diopters" patients, the results would be: 81.3% of the eyes within one diopter of emmetropia and only one undercorrection of more than 2 diopters, and again 3 overcorrections.

Table 2. Refractive outcome.

Interval of spherical equivalent (D).	Number of eyes with residual refractive error.	Number of eyes with a difference from calculated outcome.
>+3.12	1	1
+2.12 to +3.00	0	4
+1.12 to +2.00	2	3
+1.00 to +0.62	3	6
+0.50 to +0.12	1	4
-0.50 to -0.00	18	7
-0.62 to -1.00	4	3
-1.12 to -2.00	2	6
-2.12 to -3.00	1	1
>-3.00	3	0

In figure 4, we plotted the time course of the mean postoperative refraction of the 20 eyes with a follow-up of 12 months to demonstrate the stability in refractive outcome. The mean spherical equivalent refraction at 4 to 8 weeks was -1.30 D, at 6 months -0.80 D, and at twelve months -0.98 D. The paired Student's t-test did not show any significant difference between these three periods (p>>0.05). In 4 eyes the postoperative refraction changed by 1.00 D or more, to a maximum of 1.50 D, between 4 to 8 weeks and 12 months.

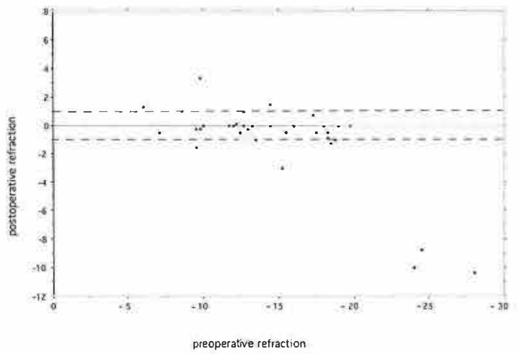

Figure 3. Preoperative and postoperative spherical equivalent refraction of the total group. Near emmetropia between +1.00 and -1.00 D (horizontal lines) was achieved in 26 eyes.

Figure 5 is a scattergram representing the deviation of the achieved correction from the calculated correction for each IOL. The mean deviation of the refractive outcome was 0.18 D (ranging from -3.62 D to +3.77 D). Eleven eyes (i.e., 31.4%) deviated by more than 10% of the calculated correction. The difference around the calculated outcome was within 1.00 D in 20 (57.1%) eyes (Table 2). The 90 percent-confidence interval of the deviation in predicted outcome was between -0.34 and +0.58 D.

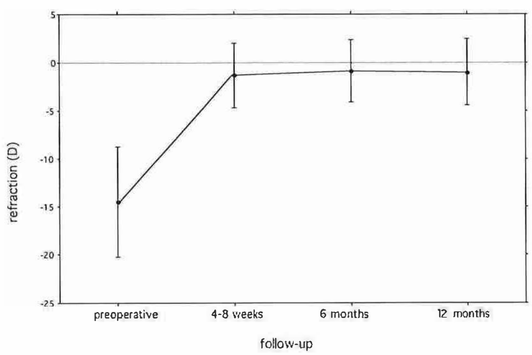

Figure 4. Time course of the refractive outcome in 20 eyes.

The mean spectacle-corrected visual acuity increased from 20/50 preoperatively to 20/40 postoperatively. However, the eye that was overcorrected with 3.50 D lost two lines (Figure 6). The mean uncorrected visual acuity postoperatively was 20/60. The cumulative number of eyes with an uncorrected visual acuity was: 20/20 or better in 1 (2.8%) eye, 20/25 or better in 3 (8.6%) eyes, 20/30 or better in 10 (28.6%) eyes, and

20/40 or better in 13 (37.1%) eyes. The spectacle-corrected visual acuity was 20/20 or better in 4 (11.4%) eyes, 20/25 or better in 9 (25.7%) eyes, 20/30 or better in 22 (62.8%) eyes, and 20/40 or better in 28 (80.0%) eyes. The visual acuity of these patients is often affected by other pathological states such as myopic chorioretinal degeneration.

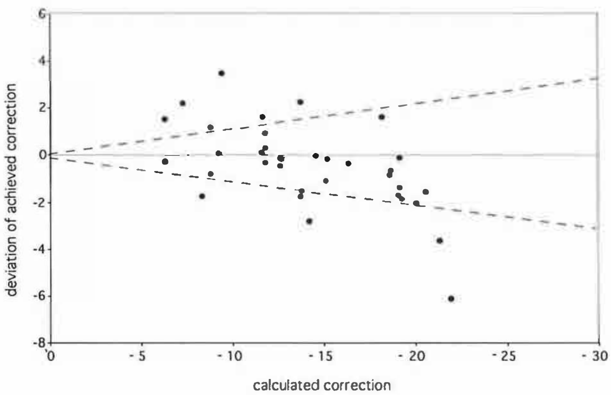

Figure 5. Deviation of the achieved correction from the calculated refraction at the last follow-up visit. Results above or below the oblique lines deviate by more than 10% of the predicted correction.

Glare and Halos.

The straylight measurements did not show a significant increase postoperatively (Figure 7), even though some patients complained about occasional halo's. At 6 months, 8 out of 18 patients did report halo's but were not disturbed by them. Six of those 8 patients still perceived halos at 12 months. In none of these eyes the visual acuity has decreased. The severity of halos and glare disappeared gradually within six months after surgery in the majority of patients.

Corneal endothelium.

We could only perform preoperative specular microscopy in 32 of the 35 eyes. Figure 8 represents a bar diagram of the endothelial cell densities at 0 and at 6 months in 32 eyes (group 1), and of the 17 eyes with a follow-up of 12 months (group 2). The mean cell loss in all 32 eyes at 6 months was 5.3% (ranging +6.3% from to -22.6%). The mean cell loss at 12 months was 8.9% (ranging from +0.77% to -23.5%) in 17 eyes, which is significantly different (p=0.003) from the cell loss at 6 months. The two eyes with the highest cell losses, one at 6 months (22.6%) and one at 12 months (23.5%), did not show any sign of corneal edema.

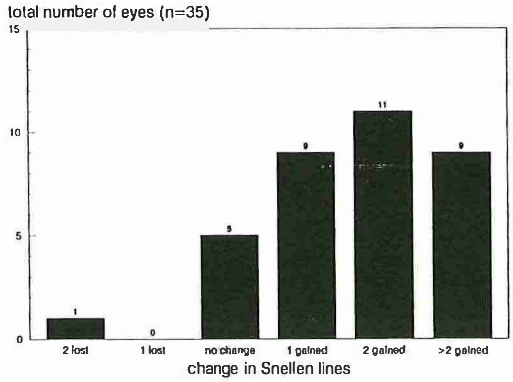

Figure 6. Change in best corrected visual acuity expressed in loss or gain of one or more Snellen lines. Most of the patients showed an increase in visual acuity postoperatively.

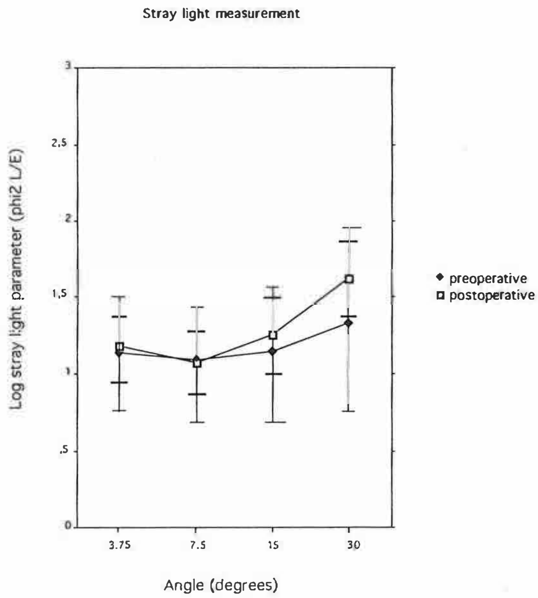

Figure 7. Stray light parameter values and standard error of the means as a function of light incidence angle preoperative and postoperative. Student's t-test did not show a significant difference (p=0.64).

The mean anterior chamber depth of these 32 eyes was 3.7 mm (ranging from 3.1 to 4.1 mm). We did not find any correlation between the anterior chamber depth and the amount of cell loss. Because 9 patients were contact lens wearers, we tested to determine if the cell loss was significantly different. At 6 months, the mean cell loss in contact lens wearers was 6.3 % and in non-contact lens wearers 4.9 %, which was not significantly different (p=0.6). In 3 eyes we could only examine the corneal endothelium postoperatively. The cell densities at six months were 2826, 2698, and 3025 cells/mm^2, and at twelve months 2919, 2509, and 2844 cells/mm^2, respectively. The mean cell loss between these two postoperative periods was 3.7%. One patient

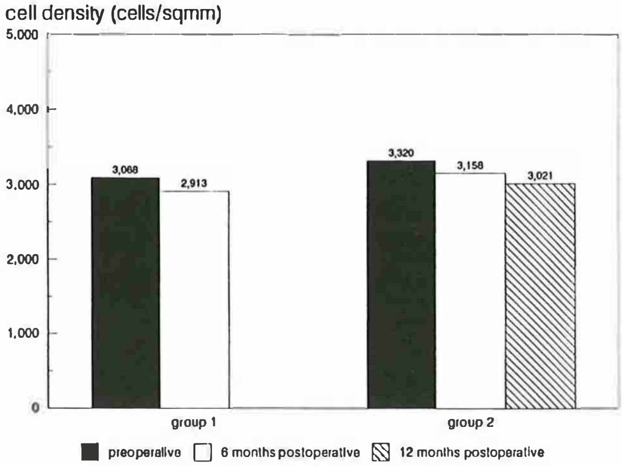

Figure 8. Mean endothelial cell densities in all the patients (group 1, n=32) and in those patients with a follow-up of 12 months (group 2, n=17).

Figure 9. Specular microscopy of one of the eyes with corneal guttata of a mean cell density of 2844 cells/mm^2.

developed corneal guttata in both eyes (Figure 9). We performed preoperative specular microscopy on his left eye only, in which the mean cell loss was 11.8% after 12 months. The endothelial images of this eye did not show any guttata preoperatively.

Complications.

Examination by slit-lamp microscopy did not reveal any apparent flare in the anterior chamber, nor did we see damage to the iris tissue. During surgery we noticed corneal touch in one eye. In the same eye the IOL had to be recentered 4 months after surgery, because of distorted images. Unfortunately, we could not perform endothelial cell count prior to the second surgical intervention, but the mean endothelial cell densities preoperatively and 6 months postoperatively were 3274 cells/mm^2 and 3046 cells/mm^2. One patient received a blunt trauma in his left eye, four and a half months after surgery, without any obvious ocular damage. The endothelial cell counts in that eye were 3751 cells/mm^2 preoperative, 3385 cells/mm^2 after 6 months, and 3332 cells/mm^2 after 12 months. In the left eye of one patient a, severe inflammatory response was observed during the early postoperative period, which disappeared during the first week. The mean endothelial cell loss at 6 months was 18.7%.

Subjective response.

In general, the patients were very satisfied with the results. For most of the patients, a new era has started. They felt less handicapped without spectacles or contact lenses. On a scale from 1 to 10, with 1 meaning very poor and 10 excellent, the mean score of satisfaction on the visual outcome in these patients was 7.5 (ranging from 5 to 10). On a scale from 1 to 10, where 1 means no disturbance and 10 means very much disturbed, the subjective response with respect to the disturbance of glare, distortion, and imbalance was 2.7 (ranging from 1 to 9), 1.1 (ranging from 1 to 3), and 1.0 (ranging from 1 to 3), respectively.

Discussion.

Despite a variety of surgical procedures to treat high myopia, no consensus exists on the optimum procedure yet. Keratorefractive surgical techniques to correct high myopia, such as epikeratoplasty and keratomileusis, have shown unpredictable results in refractive outcome and a delayed regression of lens power compared to phakic anterior chamber lenses[4,5]. Excimer laser photorefractive keratectomy seems to be effective to correct low to moderate myopia. However, with regard to correcting high myopia, several authors described a significant increased rate of refractive regression and scar formation up to 1 to 2 years after surgery[20-22]. The results of excimer laser keratomileusis, however, seem promising[22-24].

Clear lensectomy to correct high myopia is still considered controversial[25,26], due to the increased incidence of retinal detachment in patients with high myopia. Even though a recent study[27] did not reveal retinal detachment one year after clear lens extraction, other investigators[28,29] described an incidence of 7.3%, and observed that 30% of the complications consisted of retinal detachment.

Based on the preliminary results of the present study, we deduce that correcting high myopia with the Worst Myopia Claw Lens gives accurate refractive results. The high percentage of achieved near-emmetropia, as well as accuracy, stability, and predictability of the refractive outcome in our study confirm findings of other investigations on phakic anterior chamber lenses[4-13]. We did not aim for emmetropia in all eyes to avoid aniseikonia. Consequently, some patients have been undercorrected intentionally. The mean increase in best corrected visual acuity that occurs in correcting high myopia with an IOL[14] was ascribed to the increase in the retinal image by moving the myopic correction from the trial frame plane to the iris plane[30]. The decrease in best corrected visual acuity in one eye of our series is possibly due to macular degeneration.

Intraocular light scatter causes glare and can be measured with a straylight meter by Van den Berg[18]. Although patients complained about halos occasionally, the straylight measurements did not show a significant increase postoperatively. The severity of halos and glare seems to diminish considerably during the first three to six months. But we must bear in mind that even if we were not able to measure the straylight scatter objectively, patients could suffer from decreased visual function under certain lighting conditions, when the pupils are dilated[31].

Despite the effectiveness of correcting high myopia with a phakic anterior chamber lens, the long term safety of this technique has yet to be determined[32-34]. The potential hazard of the anterior chamber lens for the fragile surrounding ocular tissue in the anterior chamber has full attention in all of these studies. There is a significant concern for the long-term effect of phakic anterior chamber lenses on the endothelium.

In our population group the mean endothelial cell loss after 6 months was 5.3% and 8.9% after 12 months. This was in agreement with other investigators[6,35] who found an acceptable mean endothelial cell loss of 5.3% and 7%, respectively. However, certain studies on other phakic anterior chamber lenses showed a marked decrease in cell density after one year with a mean cell loss of 16.6%, ranging from 0 to 53.2%[36,37]. Fechner et al.[10,11] encountered severe endothelial cell loss in three eyes, which had to be treated with corneal transplantation. Bour et al.[38] found a mean endothelial cell loss of 8.2% at 6 months and 15.5% at 12 months (going up to 29% and 58% respectively). In an experimental study on angle support phakic anterior chamber lenses in monkey eyes, Peiffer[39] reported a mean cell loss of 31% after one year.

Various reports have been written on the long-term effect of cataract surgery on the corneal endothelium. The Oxford Cataract Treatment and Evaluation Team[40] reports a mean cell loss ranging from 8.2% to 13.9% at 6 months and from 13.6% to 19.3% at 12 months, depending on the surgical technique. Psilas[41] reported a mean cell loss of 26.6% at 6 months in anterior chamber IOLs and 23.8% in posterior chamber IOLs, whereas Schultz et al.[42] reports a mean cell loss of 7.5%. Werblin[43] found a mean cell loss of the central corneal endothelium of 8.8% one year after phacoemulsification. A long-term study on these patients showed plateauing of cell loss during the first three postoperative years at 11.5%, after which the total cell loss did not increase. In our study, we only examined the central corneal endothelium, which may not reflect the actual cell loss until the endothelium has equilibrated after several years. Therefore we have to examine these patients for an extended period of time, until a plateauing of cell loss or an equilibration level is obtained.

Werblin[43] suggests to compare the effect of a phakic IOL on the endothelium with the "acceptable" amount of cell loss seen with routine phacoemulsification surgery. After one year, we found a mean cell loss of 8.9%, which compared to the 8.8% of Werblins[43] study seems not to be significantly different. If 50% of the total cell loss occurred in the first three months[43] after intraocular surgery, then likewise, the mean cell loss at three years in our population would be 10.6%. Since we did not examine the endothelium at three months, we took the results at 6 months, 5.3%, as reference. Again, this was not significantly different from the 11.5% Werblin found in his study. Although some of studies on phakic anterior chamber lenses showed a significantly larger endothelial cell loss than in cataract surgery, we may conclude that in our patient population the mean cell loss is not significantly different from the cell loss which occurs in phacoemulsification.

We are aware that reporting on the mean cell loss alone does not reflect complete assessment of the vulnerability or functional reserve of the corneal endothelium. An accurate cell density, coupled with the coefficient of variation in cell area and the percentage of hexagonal cells would be more informative[44]. However, we thought that an extensive study on the morphometry of the endothelium was outside the scope of this work. Furthermore, the references cited in this study did not perform such analysis, hence it would not have helped our comparative discussions.

Although we did not detect flare in our patients by biomicroscopy, anterior chamber lenses may lead to important blood-aqueous-barrier changes, producing subclinical uveitis, which may cause chronic endothelial cell loss[45]. Recent studies[46,47] on phakic anterior chamber lenses using cell flare photometry revealed increased flare and cell measurements both in angle supported IOLs (n=9[47], and n=17[46]) and the biconcave Worst-Fechner lens (n=9[47]), with a significant higher level in the latter[47], without clinically apparent inflammatory reactions. However, Strobel and Fechner[48] retrospectively examined the protein and the cell concentrations in the anterior chamber of 68 eyes with a biconcave Worst-Fechner Lens. They found a slightly raised protein concentration which, compared to other IOLs, was situated between the capsular bag IOL and the sulcus fixated IOL. The concentrations of cells in the anterior chamber were also elevated, but 100 times less than one would expect in chronic or active iridocyclitis. Because we could not perform laser flare photometry, the concern about an ongoing inflammatory response creating chronic progressive endothelial cell loss in these phakic IOLs[39,43,45-47] can only be excluded in our patient population by a long-term study on the endothelium.

High myopia has a notorious reputation for causing blinding complications, even when such eyes are not operated. One of the serious complications that has been related to phakic anterior chamber lenses is retinal detachment. Two reports[49,50] on this subject have described retinal detachments in six eyes with a phakic anterior chamber lens, within 1.5 to 13 months after implantation. We do not know the exact incidence and prevalence of retinal detachment in phakic anterior chamber lenses. However, Fechner et al.[10,11] reported one case of a flat retinal detachment in his study of 123 eyes. Barraquer[1] reported 2 detachments in 236 eyes, and Baikoff and Joly[4] one in 163 eyes. In our entire group of 48 eyes we have not encountered one retinal detachment; nor did we see cystoid macular edema, which might be considered in this type of lens.

Additional complications that have been described in other phakic anterior chamber lenses are early postoperative iritis[10,11], iridocyclitis[10,11], cystic wounds[10,11], temporary raised intraocular pressure[10,11,5], and Urrets-Zavalia syndrome[10,11]. Saragoussi et al[51] reported on specific complications in patients with an angle supported lens, like inflammatory reactions, pupillary deformations and adherence of the iris to the implant. An early postoperative inflammatory reaction occurred in only one case of our series. We have not noticed any sign of iris atrophy or other abnormalities at the enclavation sites.

Our preliminary results on the Myopia Claw Lens confirm earlier findings on the effectiveness of the refractive results in phakic anterior chamber lenses.

Because of the general concern over the hazardous effect of a phakic anterior chamber lens, we have to apply strict inclusion criteria. The patients operated on to date must carefully be examined in due course so that we may gain a better indication on the occurrence of possible complications and on the final endothelial outcome. It would also be of interest to conduct a more detailed study on the psychosocial findings, because of the positive subjective response in these patients.

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CHAPTER 5

Evaluation of psychosocial findings and satisfaction among patients with a Worst Myopia Claw Lens.

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Abstract

The Worst Myopia Claw Lens is a phakic anterior chamber lens for the correction of high myopia which is currently under investigation. This study describes the questionnaire data collected on patients with a Worst Myopia Claw Lens and compared with a control group consisting of high myopic contact lens wearers. In general, patients with a Worst Myopia Claw Lens are very satisfied with the surgical outcome 6 to 24 months after surgery. These patients experience more aversion against contact lenses than the control group. The main reason for seeking surgery was improvement of vision and independence of corrective lenses. There is no evidence that the patients are socially or psychologically different from the control group.

Introduction

Implanting anterior chamber lenses in phakic high myopic eyes is an elective surgical procedure to reduce the refractive error. In the late eighties, a renewed interest in phakic anterior chamber lenses led to the development of several new types of intraocular lenses, which are currently under investigation to analyze the risk/benefit ratio. In 1987[1] the iris fixated biconcave anterior chamber lens was developed and in 1991 changed into a convex-concave Worst Myopia Claw Lens, the latter being under investigation in a prospective multicenter trial. At our hospital we are clinically evaluating a group of high myopic patients with the Worst Myopia Claw Lens, who are operated elsewhere, and who are included in the prospective study.

Reports on the results of studies on phakic anterior chamber lenses have never included a systematic approach to assess the psychosocial findings in these patients. Only some anecdotal patients' commentaries have been cited, like..."until now, I have always felt that there was a wall between myself and the outside world"[2], and..."The operation has me made me the happiest of humans. I cannot express in words my emotions when I open my eyes in the morning. I feel as if I have just started a real life."[3]...

Because we noticed a very positive response of the patients in our population we wanted to evaluate their experience, expectations, satisfaction, improvement of lifestyle, and define their psychosocial characteristics.

Patients and method

Patients

From a total group of 40 consecutively referred patients we excluded 2 non-native Dutch speaking patients and one illiterate. Two patients were lost at follow-up. Finally, 35 patients were handed a questionnaire prior to their ophthalmologic examination. The postoperative period ranged from 6 to 24 months, with an average of 12 months. All patients, but one, were operated on both eyes. Preliminary clinical outcome has been reported previously[4]. The questionnaires were completed anonymously. We also provide the contact lens department with questionnaires to be handed out to high myopic contact lens wearers who were unaware of the possibility of this surgery. We matched a subgroup of 10 patients to a control group of 10 consecutive referrals of our contact lens department on the grade of myopia (Table 1), since we wanted to examine the difference in psychosocial status and well-being in patients who are contact lens wearers and in patients who are willing to undergo surgery.

Table 1. Demographic characteristics

	Total group (n=35)	subgroup* (n=10)	control group** (n=10)
age	35.4±9.8	30.5±9.5	40.4±14.7
sex	16M, 19F	3M, 7F	2M, 8F
unmarried	38.30%	70.00%	50.00%
married	52.90%	30.00%	40.00%
widowed	8.80%	--	10.00%
education			
University, college	28.50%	40%	40%
High school	48.50%	60%	50.0%
elementary school	20.6%	--	10%
employment			
full-time	50.0%	60%	20%
part-time	17.6%	20%	40%
unemployed	5.9%	10%	--
retired	--	10%	10%
housewife	11.8%	--	10%
student	14.7%	10%	20%
grade of myopia			
mean±sd	14.6 ±4.9	10.6±3.1	10.2±2.5
range	5.5 -28.0	5.5 - 14.19	7.5 - 15.0

* Subgroup from total patient group, matched on grade of myopia with control group.
** Control group of contact lens wearers.

The questionnaires were developed by the first two authors (M.L. and T.K.B.) through interviews with patients and a review of the literature and other questionnaires. The preoperative questionnaires and those handed out to the control group contained 39 questions on demographic characteristics, on the surgery itself, expectations, motivation, preoperative correction, and 10 on general psychological well being. The preoperative questionnaires were handed out on the preoperative examination in our out patient clinic. Because we started this study much later than the study on the surgical technique itself, we could hand out preoperative questionnaires to 17 patients only. The postoperative questionnaires contained 30 items on demographic characteristics, subjective visual abilities, rating of satisfaction lifestyle, 10 items on general psychosocial well-being, and were handed out during the patient's last visit to our clinic.

The majority of the patients (68.6%) wore contact lenses prior to surgery, of which 68.8% consisted of hard gas permeable lenses, and 31.2 % of soft lenses. The other 31.43% wore spectacles, of which 40 % had tried to wear contact lenses without success. The problems patients encountered in wearing contact lenses and spectacles are presented in Table 2. The majority of the contact lens wearers complained about red, dry, painful eyes and all spectacle wearers complained about the weight of high negative powered spectacles.

Table 2. Subjective perceptives on contact lenses

	total group (n=24)	subgroup (n=10)	control group (n=10)
rating on cl as visual aid*	7.9±1.6	7.3±1.7	8.9±1.1
satisfaction on vision with cl**	3.7±0.85	3.9±0.9	3.6±1.1
complaints***			
red, irritated eyes	68.8%	60%	10%
problems with sport	18.8%	30%	--
maintenance	12.5%	10%	30%
dust	12.5%	30%	50%
miscellenous	12.5%	20%	30%

cl=contactlenses
* ranging from 1 to 10 (1=very bad, 10=excellent)
** ranging from 1 to 5 (1=not at all, 5 =very much)
*** subjects could indicate one or more complaints

Results

Expectations of the surgery.

The majority of the patients (67.7%) first heard about the possibility of this operation through their own ophthalmologist. A reasonable number (16.1%) heard about it through their optometrist, and a smaller percentage heard about it through friends, relatives or others. More than half (62.5%) of the patients decided to have the surgery immediately after having heard about it. The majority of the patients (79.2%) discussed the procedure with family, relatives or friends, and/or physician before deciding to undergo surgery.

Patients were asked to name only one reason for having surgery. By far the most important reason was to have permanent good vision or to improve vision (Table 3). The least important reason was cosmetic improvement and self-confidence.

Table 3. Most import reason of undergoing surgery

	total group (n=35)	sub group (n=10)
to have a good vision always	34.6%	40%
better vision	26.9%	20%
convenience not to wear cl or spectacles	11.5%	10%
sport/employment	7.8%	10%
freedom in	7.8%	10%
self confidence	3.8%	10%
cosmetics	3.8%	-
other	3.8%	-

Subjective experience of surgical outcome

On a scale from 1 to 5 (ranging from 1= bad to 5= good) the mean response to the question how well they were prepared for the procedure in terms of explanation by the ophthalmologist was fairly good (mean 4.4 ±0.8, range 3 to 5). With respect to their

PART II

Specular Microscopy

CHAPTER 6

Automated video image morphometry of the corneal endothelium.

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(Documenta Ophthalmologica 1993;85:35-44)

Abstract.

The central corneal endothelium of 13 eyes in 13 subjects was visualized with a non-contact specular microscope. This report describes the computer-assisted morphometric analysis of enhanced digitized images, using a direct input by means of a frame grabber. The output consisted of mean cell area, cell density, frequency distribution of the individual cell area, and cell polygonality. Results showed that the mean coefficient of variation of images analyzed three times consecutively was 0.95%. The cell analysis of three different images of the same subject was accurate, with a mean coefficient of variation of 4.2%.

Introduction.

The introduction and development of several contact and non-contact specular microscopes in the 1960s and 1970s has enabled examination and photography at high magnification of the human corneal endothelium in vivo[1-7]. Morphometric analysis has become an accepted practice both clinically and in research to provide information on the corneal viability after surgery, trauma, disease or other stresses on the endothelium[8-10].

Manual methods of cell analysis, counting, planimetry, and digitization, are time-consuming and liable to human error and bias[6,11]. To overcome these problems sophisticated computer technology has been developed in order to determine cell boundaries directly from the original photograph or video image, although some manual involvement may still be required[12-18]. This computerized technology not only quantifies cell densities but also determines the frequency distribution of cell areas and analyzes the polygonality[19].

The purpose of this study was to describe the system we use in computerized cell analysis by transporting specular microscopic images directly into the computer by means of a video digitizer, in combination with a modified general image software program.

Subjects and methods.

Subjects.
We recorded the central corneal endothelium in 13 right eyes of 13 subjects (8 males, and 5 females) with normal corneas. None of the eyes had a history of trauma, ocular disease, or surgery. All eyes appeared normal by biomicroscopy. Three recordings were made of each endothelium and the images obtained were analyzed with the method described. The subjects' ages ranged from 21 to 71 years (mean, 38.1 years). The results were statistically analyzed with SPSS/PC+ (SPSS Inc., Chicago, USA).

Recording technique.
A clinical non-contact specular microscope (Zeiss) in combination with a photo slit lamp (Zeiss SL75) was used to visualize the corneal endothelium. The images obtained were recorded with a black-and-white video camera (HTH MO High Technology Holland BV, Eindhoven, The Netherlands), fixed on the slit lamp. A frame grabber (PC Vision) digitized the images. The clearest images were selected with the use of its snap-function, input in an image analyzer (TIM, Difa Measuring Systems BV, Breda; The Netherlands), and processed with a microcomputer (PC AT 486, 33 MHz) where the

images were stored on the harddisk.

Image analysis.

A movable box frame can be placed arbitrarily on the image to determine the area to be analyzed (Figure 1). High frequency noise and differences of brightness are excluded with 3x3 pixels filters, and subtracted from the original image. To improve the quality of the image, the contrast is normalized and the cell boundaries sharpened. All small intracellular inclusions are eliminated. The gray-value dilatation reconnects small breaks of the cell boundaries, creating enhanced boundaries on the processed image.

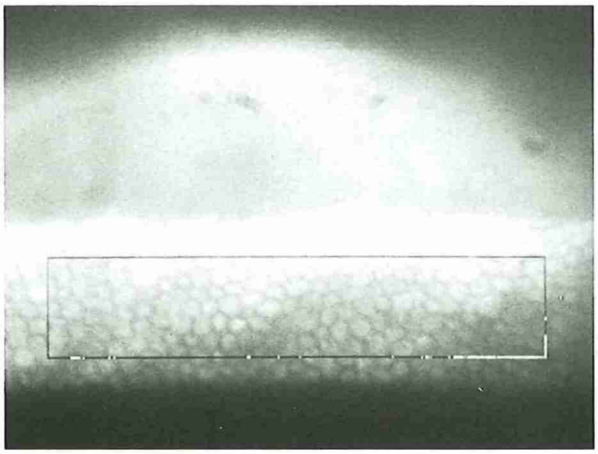

Figure 1. The non-contact specular microscope (Zeiss) of the endothelium with the box frame superimposed.

With the use of a minimum and maximum threshold value the gray-values are transformed into (i.e. black and white) binary images. The image considered to be the most suitable for processing is selected. The accuracy of the analysis of the cell boundaries depends on the determination of the optimal threshold value. The binary image is skeletonized into 1-pixel-width cell boundaries creating closed contours only, depicted in red, and superimposed on the original black-and-white image (Figure 2).

The processed image is placed next to its original for comparison. Missed or wrongly determined boundaries can be corrected or restored manually by means of interactive processes such as erasing, dilatation, and drawing. Cells touching the sides of the box frame are rejected because of incomplete visibility. When the correction is completed the cell boundaries are again skeletonized and the image analyzer automatically labels the cells for measurement.

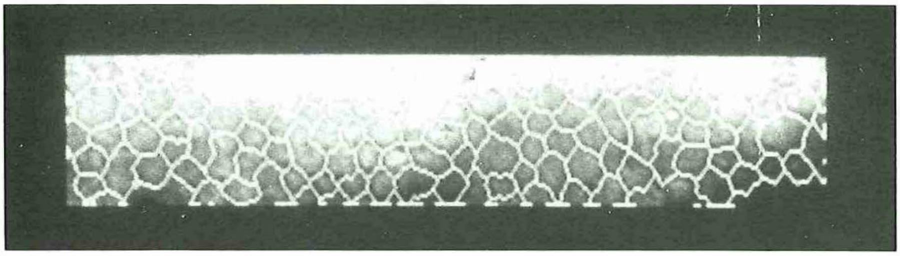

Figure 2. Endothelial image after digitized enhancement with the inverted binary image superimposed.

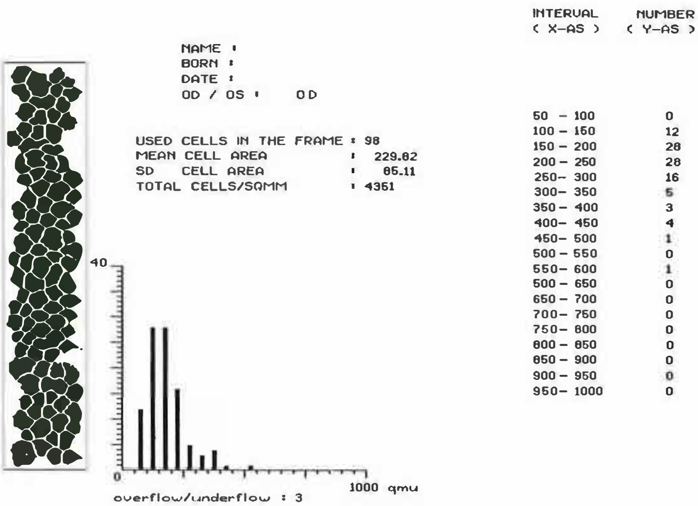

Figure 3. The monitor display after image analysis with the mean cell area, cell density and histogram.

All structures smaller than 50 μm^2 are automatically rejected, being considered as debris. The individual cell areas are calculated, resulting in the mean cell area, standard deviation, and cell density. The frequency distribution of cell areas are represented in a histogram (figure 4). All data can be transported to SPSS, through an ASCII file, which enables the calculation of the skewness, curtosis, and other statistic values.

The polygonality of the cells is determined by framing each cell with a rectangle. With this algorithm the pixels of the analyzed cell boundary create triangles with those belonging to the neighboring cells. The number of triangles calculated determines the polygonality of the analyzed cell. In this way each cell is analyzed. As a consequence the cells that are not completely surrounded by other cells, such as on the margin of the image, are incorrectly analyzed.

Results.

To measure the reproducibility of the image analysis we selected 5 pictures of 5 subjects at random and measured the mean cell area. One of us (M.L.) processed each picture three times according to the method described. The mean coefficient of variation of the measured mean endothelial cell area was 0.95%. (Table 1).

Table 1. Reproducibility analysis of the mean cell area (μm^2) in 5 images analyzed 3 times consecutively.

	Analysis					
Picture	1	2	3	Mean	SD	CV
1	251.86	261.19	258.48	257.18	4.80	1.86
2	518.26	514.05	512.92	515.07	2.81	0.50
3	308.73	302.67	306.43	305.94	3.06	1.00
4	298.49	290.94	297.40	295.61	4.08	1.20
5	305.40	305.86	304.60	305.28	0.64	0.21
						Mean:0.95

SD=standard deviation; CV=coefficient of variation.

To measure the variability of our analysis, we analyzed three different pictures of each subject. The coefficient of variation varied between 0.4% and 9.7% with a mean of 4.2% (Table 2). To determine differences between the results of the three measurements we used a one-way Analysis of Variance (ANOVA), which showed a significant difference in two out of thirteen cases ($p<0.05$).

There was a significant negative correlation between age and endothelial cell density ($r=-0.804$, $p<0.01$) (Figure 4). Measurements of the polygonality showed there was a majority of hexagonal cells. The variability in measuring the polygonality was significantly large in four cases (chi-square test, $p<0.05$). The chi-square test was performed on all forms of polygonal cells, however in table 2 we only represent the percentage of the hexagonal cells for reasons of clarity. The recording and processing of one image was approximately of 15 minutes' duration.

Discussion.

For most of the automated or semi-automated processes described to analyze endothelial cells photography or video tapes have been used to record specular images[12-14,18,19]. However, transporting specular images directly into the computer with a frame grabber has great advantages[16]. With this direct image input into the computer, circumventing photographic processes, we avoided magnification errors. A relative disadvantage of using the frame grabber in our system is the limited number of

Table 2. Cell analysis of 3 different images in each subject.

	Mean cell area					*Polygonality*	
Subject	N (cells)	Mean ($\mu m2$)	CV (%)	SD ($\mu m2$)	ANOVA p	Hexagonality (%)	Chi-square test p
A1	75	254		87		43.2	
2	76	254	1.84	78	0.78	35.6	0.75
3	83	246		80		46.7	
B1	28	495		181		35.0	
2	34	522	4.63	186	0.60	45.2	0.15
3	32	543		179		34.8	
C1	61	306		94		44.3	
2	67	269	2.51	114	0.75	55.4	0.22
3	59	311		126		49.1	
D1	93	228		71		57.7	
2	88	233	1.26	91	0.90	45.7	0.28
3	93	228		70		57.9	
E1	62	288		124		34.1	
2	65	288	0.40	116	0.99	49.6	0.13
3	68	286		103		42.8	
F1	76	271		81		57.3	
2	72	282	8.24	91	0.006	44.1	<0.01
3	84	240		81		47.1	
G1	59	308		87		50.8	
2	60	303	2.72	103	0.64	33.3	0.28
3	66	292		104		41.7	
H1	69	284		101		46.9	
2	57	321	9.70	116	0.012	58.3	0.14
3	56	345		129		54.1	
I1	64	325		113		54.5	
2	64	321	2.80	91	0.66	54.4	0.23
3	62	308		113		41.3	
J1	66	304		103		40.4	
2	57	337	5.62	91	0.15	57.2	<0.01
3	67	309		107		49.3	
K1	54	345		91		29.0	
2	52	368	5.79	126	0.13	49.6	0.06
3	56	328		81		44.2	
L1	55	336		157		18.5	
2	65	318	3.54	113	0.62	31.7	0.01
3	58	340		138		34.8	
M1	50	381		141		47.3	
2	49	344	5.48	153	0.41	40.5	<0.01
3	49	351		138		27.3	

pictures that can be recorded and stored. The use of a video tape recorder allows a long recording time, so that it is readily to obtain sharp and well-focused images[18]. Whereas with our system we grab the images during the real-time recording period. The non-contact specular microscope is subject to eye movements which can sometimes affect the quality of the images. These images of a less quality can elongate the processing-time, because more manual corrections are required.

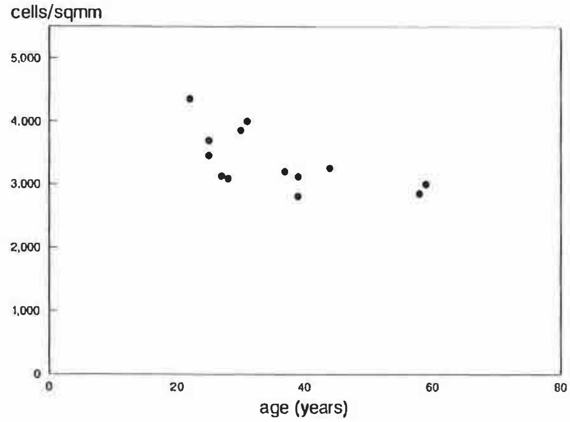

Figure 4. Correlation between age and cell density in 13 subjects (r=-0.81, p<0.01). The intercept of the regression line is 4467 cells/mm2 with a slope of -32 cells/mm² per year.

We analyzed 49 to 92 cells per image, while recommendations have been madeto use a sample of at least 75 or 100 cells[6,10]. The relatively small sample sizes in our study can be explained by the fact that the box frame, of a fixed size, determines the area to be analyzed. Properly speaking, our system consists of a variable frame analysis enclosed in a fixed frame, resulting in a sample size which is inversely proportional to the cell size. To exclude any magnification differences between the center and the periphery of the image, the box frame was intended to be smaller than the whole endothelial image and was always positioned in the center. In addition, the non-contact specular microscope visualizes only a small central field of the endothelial layer[7,8]. With wide-field specular microscopy pictures can be obtained up to 3000 cells per photography[20]. For these microscopes automated or semi-automated processes are indispensable for cell analysis, otherwise it becomes very expensive and time consuming.

The automated determination of the polygonality showed a lower percentage of hexagonality than Nishi and Hanasaki reported in their study[19] (between 27.3 % and 58.3% vs. 43.0% and 63.6%). This was probable due to our smaller sample sizes and the incorrect analysis of the cells at the exterior edge. Because for the analysis of the polygonality neighboring cells are required. The polygonality of the cells at the edge is therefore less than the real polygonality. As in other studies on the endothelial changes as a function of age, we also found a statistically significant decrease in the central endothelial cell density[3,4,21]. The corneal endothelium does not regenerate by cell division and it would be expected that some decline in cell counts might occur with age.

Although the cell morphometry is performed by the computer, the operator must always verify whether the cell boundaries are detected correctly[14,16-18]. Human judgment and manual intervention are still required.

The advantage of using a frame grabber is saving time by circumventing photography or video recording[16]. In addition, adjusting courant multi-purpose equipment to a specific image analysis makes this system relatively inexpensive. In combination with a microcomputer and an image processing software this procedure provides accurate cell analysis, with a total processing and recording time of approximately 15 minutes. Since the mean coefficient of variation of the cell analysis in our study was 4.2%, we can suffice with the analysis of one image per eye. However, the accuracy of the measurements depend on the quality of the image. Adjusting a contact wide-field specular microscope to our system in the future may increase the sample size and resolve the problem of eye movements, resulting in images with a higher resolution.

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CHAPTER 7

Comparative study of three different semi-automated specular microscopes.

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(Journal of Cataract and Refractive Surgery 1995;21:409-416)

Abstract.

We compared two clinical video-assisted specular microscopes (Zeiss, non-contact, and the wide-field Keeler Konan sp 3300, contact) with an autofocus microscope (Konan noncon Robo-ca sp 8000, non-contact) with built-in analyzing software. by studying the morphometry of the central corneal endothelium of 12 eyes in 12 subjects. The mean coefficient of variation of the cell size analysis of three successive images per cornea for the three method were 3.9%, 4.0%, and 2.2%. One-way analysis of variance showed a significant difference in the mean cell area measured with the three methods; there was no significant difference in the results of hexagonality (pleomorphism) and coefficient of variation (polymegethism). Although each microscope showed a high reproducibility, we do not recommend using the three interchangeably. The Konan noncon Robo-ca sp 8000 specular microscope provides a rapid morphometric endothelial analysis. The Keeler Konan sp 3300 is better for more detailed studies and photography of the corneal endothelium.

Introduction.

Vogt was the first to describe the corneal endothelium *in vivo* by using the specular reflection of the slit-lamp biomicroscope in 1920[1]. To examine the corneal endothelium *in vitro*, Maurice introduced the specular microscope in 1968[2]. Since then several clinical contact and non-contact specular microscopes have been developed to study the corneal endothelium *in vivo* [3-6]. Because the human corneal endothelium is considered to be amitotic, this new development enabled ophthalmologists to study the viability of the corneal endothelium during aging[4,7], after anterior segment surgery[8-10], and during contact lens wear[11] by quantifying the endothelial morphology.

The early processing methods to analyze the corneal endothelium morphometrically were tedious and time-consuming[12,13]. They were performed with digitizers or image analyzers, which required manual tracing of the cell boundaries or cell apices was. Relatively small fields were viewed with the early contact and noncontact microscopes. The introduction of the wide-field specular microscopy[14] significantly increased the number of cells that could be photographed per image. Because more than thousand cells per image could be visualized, this development demanded a more automated cell analysis. Computer technology to determine cell boundaries directly from the original photomicrographs was developed[13-15]. To enhance the efficiency, photography was later omitted and cell analysis can now be performed directly from video recordings in combination with a frame grabber[16-19].

This computerized cell analysis not only provides in the mean cell density but also quantifies the frequency distribution of the individual cell sizes, and analyzes the polygonality. New specular microscopes include an autofocus device to record the specular images readily and have an incorporated semi-automated image analyzing program.

We studied our two video-assisted specular microscopes (one contact and one noncontact), adapted to a computerized image processor[20], and a noncontact autofocus microscope and evaluated the similarities and dissimilarities.

Subjects and methods.

Subjects.

We recorded the central corneal endothelium in 12 right eyes of 12 individuals (5 females, and 7 males) with healthy corneas, that appeared normal by biomicroscopy. None of these eyes had a history of trauma, ocular disease, or surgery. Three images of each eye were recorded with each specular microscope and were analyzed with the techniques described. Subjects' ages ranged from 24 to 48 years (mean: 31 years). The results were analyzed with StatView 4.01 (Abacuse Concepts Inc., Berkeley CA, USA). For parametric values we used one-way analysis of variance (ANOVA) and for non-parametric values the Friedman test. A two-tailed probability of 0.05 or less was considered significantly different.

Recording methods.

Zeiss. This is a clinical non-contact specular microscope used in combination with a photo slit lamp (Zeiss SL75) to visualize the corneal endothelium. The images were recorded with a black-and-white video camera (HTH MO High Technology Holland BV, Eindhoven, The Netherlands), also fixed on the slitlamp. A frame grabber (PC Vision) digitized the images, which were displayed on the monitor (Sony, PVM 1442QM). The clearest images were selected with the use of its snap function, put into an image analyzer (TIM, Difa Measuring System BV, Breda, The Netherlands), and processed with a microcomputer (PC AT 486, 33 MHz) where the images were stored on the hard disk.

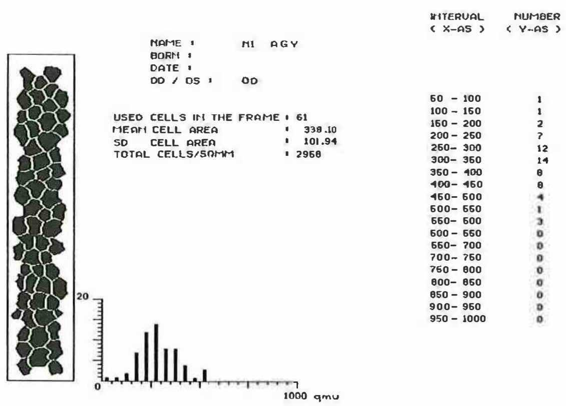

Figure 1. Output after video image analysis with the Zeiss noncontact specular microscope, displaying the mean cell area, cell density, and a histogram.

Keeler Konan sp 3300. This is a contact wide-field specular microscope also used with the video recording technique described above. Although this microscope can be provided with different magnification cones, we only used the 40x cone, which applanates the central part of the cornea. The eyes were instilled with oxybuprocain hydrochloride 0.2% eye drops; methocel was used as a lubricant on the cone.

Konan noncon Robo-ca sp 8000. This is a non-contact specular microscope with an autofocus device. The endothelium is visualized on an incorporated screen. The images cannot be stored, so the analysis must be performed immediately after each recording session. (New recordings overwrite the previous ones.) A video printer prints the images.

Image analysis.

We used the same semi-automated image analysis for both the Zeiss and the Keeler Konan sp 3300 specular microscopes. Both microscopes were calibrated with a haematocytometer before the computer program was adapted. The image processing software has been described elsewhere[19]. This software can determine cell boundaries on specular video images. During the processing, missed or wrongly determined boundaries can be corrected and restored manually. The individual cell areas are calculated, resulting in the mean cell area, standard deviation, and mean cell density. The frequency distribution of cell areas are represented in a histogram (Figures 1 and 2).

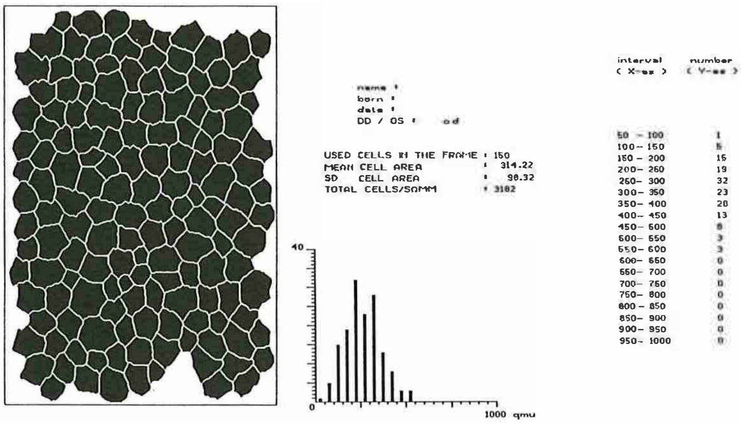

Figure 2. Output after video image analysis with the Keeler Konan sp 3300 contact specular microscope, displaying the mean cell area, cell density, and a histogram.

The polygonality of the cells is determined by framing each cell with a rectangle. With this algorithm the pixels of the analyzed cell boundary create triangles with those belonging to the neighboring cells. The number of triangles calculated, determines the polygonality of the analyzed cell. As a consequence the cells that are not completely surrounded by other cells, e.g. in the margin of the image, are incorrectly calculated. Therefore a manual correction is needed.

The Konan noncon Robo-ca sp 8000 has a built-in software program which has two analyzing modalities. To calculate the cell density, a rectangular area can be determined manually. All the cells within the border of the rectangle, as well as those touching two adjacent borders, are marked with a mouse according to Gundersen[20] (Figure 3). Another method is to mark the center of adjacent cells (Figure 4). The mean cell area, mean cell density, hexagonality, and coefficient of variation is than calculated. We used the latter method in this comparative study.

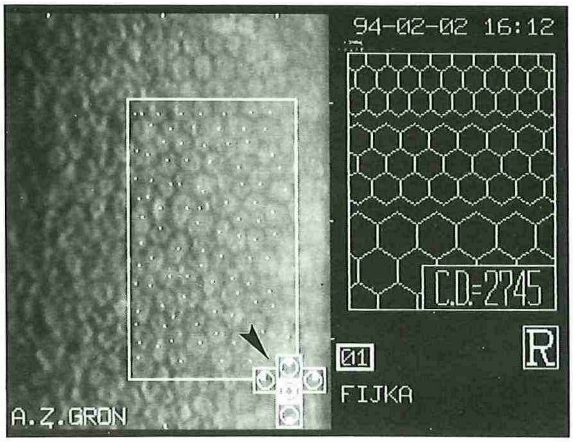

Figure 3. Video print of the simple fixed frame analysis of the corneal endothelium resulting in the mean cell density with the Konan noncon Robo-ca sp 8000. The cross-like figure (arrow) indicates the position of the image taken (center and four peripheral positions).

Results.

Mean cell area.

The mean cell area of the twelve corneas that was determined by the three methods (Tables 1 and 2) differed significantly (one-way analysis of variance, $F=44.9$, $p<0.0001$). The mean cell size measured with the Zeiss microscope was smaller than those measured by the other two methods. The difference in mean cell size between the Zeiss and the Keeler Konan sp 3300 was 15.8% and between the Zeiss and the Konan Robo-ca, 12.5%. The difference between the two Konan microscopes was 3.8%.

When the individual mean cell density was plotted against the age, the average cell size was again smaller for the Zeiss microscope (Figure 5). Even if all three methods show a positive correlation with age, only the results of the Zeiss measurements indicate a significant correlation with age. Remarkably, the curves of the three methods were fairly parallel. There was also a heterogeneity in cell size in the individuals between 24 and 30 years old.

Repeatability.

We calculated the coefficient of variation for all measurements (Table 1). Table 3 shows that the mean coefficient of variation of three measurements per eye is the lowest for the Konan noncon Robo-ca sp 8000. To analyze the significance of the difference in the three measurements per eye, we needed the individual cell sizes per image. The software of the Konan noncon Robo-ca sp 8000 only gives the means of the calculations as a result, without giving access to the raw data. Therefore, we could only perform a one-way analysis of variance on the three measurements per eye made with the Zeiss and Keeler Konan sp 3300.

Figure 4. Video print of the complete quantitative cell analysis with the Konan noncon Robo-ca sp 8000, displaying the mean cell size, mean cell density, number of cells, and polygonality. The adjacent cells are marked in the center with a mouse .

Hexagonality and coefficient of variation.

Because we could solely measure the hexagonality instead of the total polygonality with the Konan noncon Robo-ca sp 8000, we included only the hexagonality in our comparison (Table 4). The Friedman test for non-parametric values did not show a significant difference in the three methods for the hexagonality (p=0.46) and the coefficient of variation (p=0.67).

Table 1. Mean cell size of each measurement per cornea and per method.

subject	*Zeiss*			*Keeler Konan sp 3300*			*Keeler Konan Robo-ca*		
	cell size	n	cv	cell size	n	cv	cell size	n	cv
A1	395.3	55		507.0	71		450	64	
2	434.9	41	6.1	500.2	82	5.2	447	71	1.4
3	389.6	36		459.9	81		438	82	
B1	301.4	63		340.4	88		316	121	
2	282.2	51	3.6	357.7	98	2.6	316	100	4.3
3	284.4	66		354.6	110		293	87	
C1	364.1	45		420.4	89		436	112	
2	341.3	39	5.8	387.1	103	5.1	412	77	3.2
3	324.4	46		426.1	81		413	82	
D1	259.5	41		336.6	109		323	111	
2	275.1	48	4.6	361.6	94	3.7	339	71	2.5
3	284.6	49		355.8	105		334	82	
E1	356.6	60		394.8	109		433	84	
2	391.4	49	5.1	426.1	97	10.0	433	89	0.3
3	361.4	56		348.9	119		435	89	
F1	335.2	41		375.3	93		344	84	
2	344.6	36	2.3	400.1	93	4.2	345	92	0.4
3	329.0	46		406.3	98		347	97	
G1	258.0	80		317.5	135		284	80	
2	258.4	76	0.97	307.8	141	1.6	285	87	0.5
3	253.9	76		314.5	127		287	83	
H1	269.3	82		337.4	128		337	71	
2	273.5	73	0.89	365.6	102	4.2	319	74	3.1
3	273.5	77		345.5	124		337	70	
I1	247.6	73		299.7	120		353	85	
2	251.5	71	4.1	298.6	138	2.9	349	90	3.1
3	267.5	76		284.3	149		353	97	
J1	335.7	69		383.1	112		304	81	
2	309.1	68	5.1	365.9	108	2.4	293	87	1.9
3	306.3	66		369.3	107		296	78	
K1	338.1	61		381.7	90		360	72	
2	351.6	55	2.0	401.7	100	3.2	370	61	0.7
3	344.5	53		379.3	114		403	63	
L1	259.7	78		320.5	130		339	78	
2	258.7	74	6.6	329.5	126	2.9	332	85	6.0
3	290.1	72		340.0	125		345	73	

A-L=12 subjects, measured three times
n= number of cells analyzed.
cv= coefficient of variation (%).
cell sizes are in μm^2

Table2. Mean cell area for each specular microscope in 12 individuals.

	Zeiss	Keeler Konan sp 3300	Konan noncon Robo-ca sp 8000
Mean	311.16	369.78	355.58
SD	49.18	51.24	53.02
Range	255.53-406.57	294.20-489.19	285.00-445.00

All measurements are in μm^2.
SD=standard deviation

Table 3. Repeatability.

	Zeiss	Keeler Konan sp3300	Keeler Konan Robo-ca sp 8000
Mean c.v.	3.9%	4.0%	2.2%
ANOVA p>0.05*	11/12	11/12	n.p.

c.v.= coefficient of variation.
* Number of corneas out of twelve with no significant difference between three measurements.
n.p.=not performed.

Table 4. Percentage of hexagonal cells and coefficient of variation.

	Zeiss		Keeler Konan sp 3300		Konan noncon Robo-ca sp 8000	
Subject	(%)	cv	(%)	cv	(%)	cv
A	57.7	0.28	64.7	0.27	62.0	0.33
B	64.3	0.40	58.3	0.31	62.7	0.30
C	64.3	0.27	57.7	0.31	77.0	0.37
D	59.7	0.29	60.0	0.31	77.0	0.37
E	61.7	0.34	59.3	0.38	62.3	0.32
F	59.7	0.27	56.3	0.28	61.0	0.29
G	57.0	0.33	61.3	0.33	61.7	0.31
H	64.0	0.42	55.7	0.39	62.0	0.33
I	65.7	0.29	65.7	0.31	56.7	0.31
J	64.7	0.26	57.7	0.28	62.3	0.28
K	58.3	0.29	70.0	0.29	62.0	0.31
L	57.3	0.42	61.7	0.34	59.3	0.30

(%)=percentage hexagonal cells
cv=coefficient of variation

Discussion.

The specular microscope is a unique instrument because living human tissue can be examined without disturbing its environment. The first clinical microscopes applanated the cornea, resulting in a good resolution and a high magnification[3-5]. However, manipulation of the cornea may cause artifacts and is disfavored in fragile diseased corneas. Therefore, noncontact microscopes were developed; these were better tolerated by patients and provided a broader view[23]. Because of uncontrolled eye movement, it is difficult to maintain a focused view, and the images have a lower resolution and a lower magnification. The quality of the images is also affected by a distortion caused by the corneal curvature[24]. The wide-field microscope combines some advantages of both microscopes. The field of view is large, depending on the magnification; the resolution high and the image quality is less susceptible to eye movements[25].

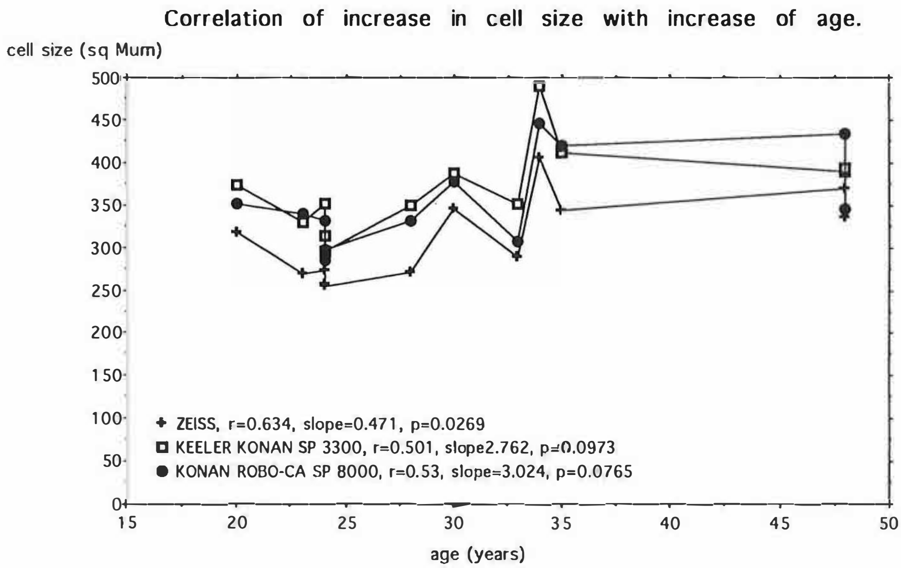

Figure 5. Mean cell density of each cornea plotted against the age. Regression analysis was performed for all three methods. The increase in cell size was only significantly correlated with the Zeiss measurements.

In our comparative study, the accuracy of measuring the mean cell size of the corneal endothelium with the Zeiss, Keeler Konan, and Konan noncon Robo-ca sp 8000 microscopes was practically the same. The reproducibility was highest with the latter, perhaps because the autofocus device only focuses on the same area of the corneal endothelium, while the other two microscopes require manual focusing. This was difficult to achieve with the noncontact Zeiss microscope. The measurement of the mean cell size was significantly different among the three devices. The mean cell size was the smallest, i.e., the mean cell density the largest, measured with the Zeiss microscope. This may have been because the horizontal distortion of the images caused by the corneal curvature was not calibrated accurately[24].

Alteration in morphology such as abnormalities in cell size (polymegethism), cell shape (pleomorphisme), and the heterogeneity or asymmetry of the cell population in terms of coefficient of skewness, may be more reliable indices of endothelial distress than the mean cell density alone[8,22]. The advantage of using a computerized system is the possibility to calculate the individual cell area, with which the coefficient of variation can be deduced, as a degree of polymegethism. In addition, the modality of analyzing the polygonality (i.e., the percentage of hexagonality) measures the variation in cell shape. The results of these two parameters were not statistically different among the three different techniques. Additional information on the coefficient of skewness can only be calculated with the computerized video analysis.

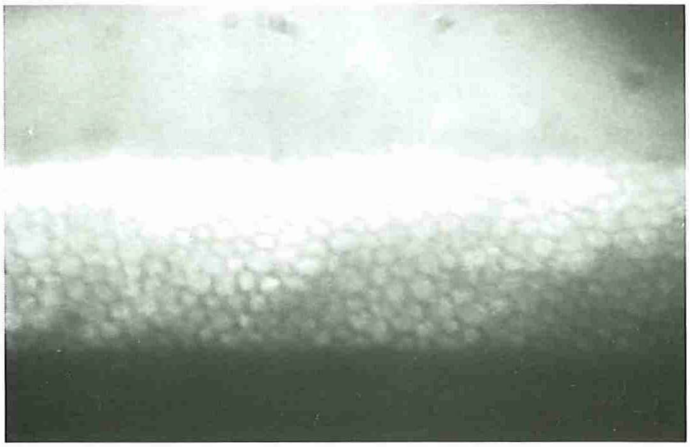

Figure 6. Specular photograph of the corneal endothelium with the noncontact Zeiss microscope.

The number of cells analyzed was 39 to 82 with the Zeiss, 81 to 149 with the Keeler Konan sp 3300, and 61 to 121 with the Konan noncon Robo-ca sp 8000 (Table 1). A sample of at least 75 to 100 cells was recommended[8,22]; this was achieved with both Konan microscopes. In general, the non-contact specular microscope visualizes a small central field of the endothelium[24]. The Konan noncontact microscope, however, had a wider view than the Zeiss noncontact camera (Figures 3 and 6).

The automated determination of the hexagonality showed about the same percentage of hexagonality as Nishi and Hanasaki[19] reported in their study on automated video assisted morphometry of the endothelium (between 48% and 70%).

In accordance with other studies we found a positive correlation between the cell size and increase in age,[7,26] although this correlation was only significant with the Zeiss microscope. Converting the cell size in cell density, the ranges in our study, for an age from 22 to 48 years, were 2460 to 3913 cells/mm^2 with the Zeiss, 2044 to 3399 cells/mm^2 with the Keeler Konan sp 3300, and 2249 and 3509 cells/mm^2, with the Konan noncon Robo-ca sp 8000. This agrees with other studies[12,18] in which average cell densities were found varying between 2200 and 4000 cells/mm^2 for ages from 20 to 64 years.

Although we found a statistically significant difference in the results of mean cell size for all three analyzing methods, we do not think this is clinically meaningful. However, for research purposes, where precise measurements are demanded, the three microscopes should not be used interchangeably. Various morphometric parameters can be analyzed with all three microscopes, but the most complete analysis (coefficient of variation, polygonality, and coefficient of skewness) can only.be achieved with the two video-assisted methods.

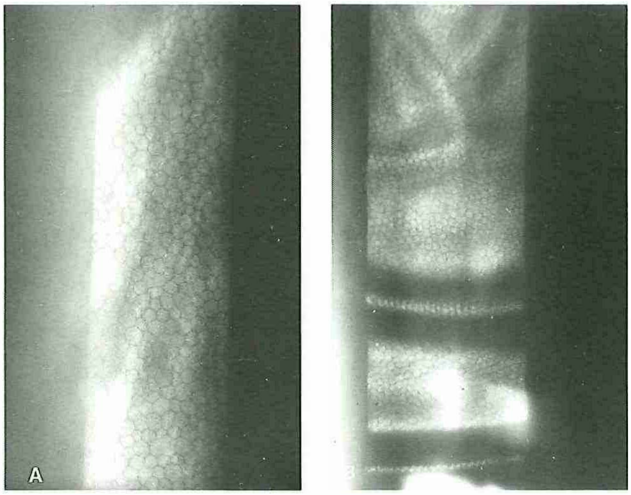

Figure 7. Specular photograph with the Keeler Konan sp 3300 using a (A) 40x magnification cone, and a (B) 22x magnification cone.

Another autofocus noncontact specular microscope (Topcon sp 1000,a small field camera) showed the same level of accuracy as contact wide-field specular microscopy[26-28], although there was a discrepancy in the results of polymegethism in patients with contact lenses[26]. We do not know whether this discrepancy would occur with our microscopes in nonhealthy corneas. The small sample sizes in noncontact specular microscopy may be adequate to quantify normal corneal endothelium but inadequate for corneas with low density and variable cell size[29]. This has been confirmed by other investigators reporting on uncertain coefficient of variation estimates in polymegathous corneas, even with 100 cells analyzed[30].

Different specular microscopes fill different clinical needs. Because of its high reproducibility and safety, the new noncontact Konan noncon Robo-ca sp 8000 is clinically very useful. The autofocus device facilitates the recording technique and the incorporated cell analyzer allows quick, almost real-time, morphometry of the endothelium. Although the field of the images obtained is comparable with that of wide-field microscopy, the contact wide-field microscope has more advantages for detailed studies of the corneal endothelium. Different magnification cones can be used to study the endothelial morphology (Figure 7). It is also possible to study precisely the epithelium, the iris, the anterior surface of the lens, and the surface of intraocular lenses. The entire cornea can be examined by moving the cone manually over the corneal surface. This is more complicated to achieve with the noncontact Zeiss microscope, because of prompt defocusing. With the Konan noncon Robo-ca sp 8000, only four fixed peripheral areas of the cornea can be examined (Figure 3). The use of a separate computer in our video assisted system allows the images and the raw data to be stored on the hard disk, so more complete statistical analysis can be performed.

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PART III

193-nm Argon-Fluoride excimer laser

CHAPTER 8

Phototherapeutic keratectomy in recurrent corneal intraepithelial dysplasia.

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(Archives of Ophthalmology 1994;112:22-23)

The argon-fluoride excimer laser has gained a lot of interest as a treatment modality for superficial ocular abnormalities. We report a case of recurrent corneal intraepithelial dysplasia treated with phototherapeutic keratectomy.

Report of a case.

A conjunctival squamous cell carcinoma with corneal involvement developed in the right eye of a 65-year-old woman. Because of a recurrence 4 months after epithelial abrasion, penetrating keratoplasty was performed in April 1988 in another clinic. The margins of the excised cornea were free of dysplastic epithelial cells. However, the neoplasia recurred repeatedly on the corneal graft with a 3-month interval. Each recurrence was treated with abrasion followed by histologic examination, which time and again showed an intraepithelial dysplasia, stage III.

In November 1989, slit-lamp microscopy of the right eye showed a superficial dot-shaped epitheliopathic lesion on the nasal half of the corneal graft, paracentral midstromal scars, and peripheral superficial vascularisation (figure 1). On examination, visual acuity was hand motion at 9 feet in the right eye.

The patient was admitted to our clinic in March 1990, where we applied 193-nm argon fluoride excimer laser (MEL 50 Aesculap-Meditec, Heroldsberg, Germany) photoablation to the four quadrants of the graft at the sites of the recurrence in four sessions, without manual removal of the epithelium prior to the operation. The laser was set in spot mode, with a 1.5-mm-diameter circular spot. Each pulse ablated roughly 1 μm, according to our own experience. The firing rate was 3 Hz, with a high energy density of 800 mJ/cm^2. For normal refractive purposes we use a much lower energy density of 250 mJ/cm^2. A total of 750 pulses was delivered. Three weeks after laser treatment, the corneal clouding had decreased and the corneal vascularisation had diminished. During the first 26 months, the cornea has remained clear (figure 2) and the visual acuity improved to 20/100.

Comment.

Conjunctival and corneal intraepithelial neoplasm (CIN) include each form of conjunctival and corneal intraepithelial dysplasia. When such a dysplastic process breaks through the basement membrane, the diagnosis is squamous cell carcinoma. The most common therapy of conjunctival and corneal neoplasia is radical excision in combination with cryotherapy[1]. Recurrences develop most often in the first two years and do not necessarily show the same cell pattern. Dysplastic epithelial cells have often been treated successfully with lamellar keratectomy combined with limbal autotransplantation. To our knowledge, this is the first reported case of excimer laser keratectomy in recurrent corneal intraepithelial dysplasia.

Figure 1. Slit-lamp photograph of the right eye with recurrent intraepithelial dysplasia that had involved the cornea and the corneal graft.

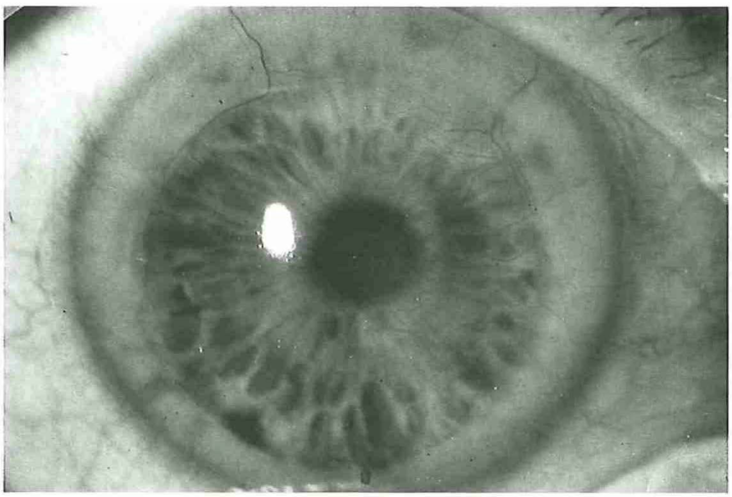

Figure 2. The same right eye 26 months after phototherapeutic keratectomy of the pathological tissue with the argon fluoride excimer laser.

The far-ultraviolet radiation of the excimer laser is capable of removing precise amounts of corneal tissue without thermally damaging the adjacent structures[2]. This process allows a sharply defined photo ablation of the cornea in a non-contact mode, thus avoiding the risk of spreading tumor cells. To debulk abnormal areas and to smooth an irregular surface of the cornea, the excimer laser provides a simpler and safer alternative to procedures such as lamellar or penetrating keratoplasty. The laser ablation allows a smooth surface after therapeutic keratectomy[3]. The drawback of this technique is that no histologic examination can be performed on the ablated tissue after the operation. Histologic examination can be helpful in determining the origin of the dysplastic tissue and if the margins of the resection are clear and free of diseased tissue. The examination also provides prognostic value depending on the degree of dysplasia.

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CHAPTER 9

Phototherapeutic keratectomy in recurrent corneal epithelial erosion.

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(Journal of Refractive and Corneal Surgery 1994;10:419-424)

Abstract.

Background: Excimer laser phototherapeutic keratectomy has generated considerable interest in treating superficial corneal and scleral pathology. The excimer laser is also used to treat recurrent corneal epithelial erosions.
Method: With the MEL 50 Aesculap-Meditec 193-nm argon-fluoride excimer laser, we treated 74 eyes of 73 individuals, who suffered from post traumatic, therapy-resistant, recurrent corneal epithelial erosions. We used the excimer laser in spot-mode under manual guidance. Only in those cases where the erosion was covered with loose bullous epithelium did we remove the epithelium mechanically prior to surgery. The postoperative follow-up period ranged from 6 months to 4 years.
Results: Of the 74 eyes, 55 (74.43%) eyes were recurrence-free. One eye developed superficial haze in the treated area. No other complications occurred.
Conclusion: Phototherapeutic keratectomy in recurrent epithelial erosions is a promising treatment, specially in recalcitrant cases overlying the entrance pupil. Photoablation allows a fast re-epithelialization of the affected area and a quick relief for painful symptoms.

Introduction.

Recurrent corneal epithelial erosion was originally described by Hansen[1] in the last century, while Von Arlt[2] introduced the term "recurrent erosion" for the first time. The classical story is that after a traumatic abrasion of the cornea the patient wakes in the morning with acute symptoms of pain, lacrimation, and photophobia. Once new, apparently normal, epithelium has been reformed it may erode again months or even years after the initial trauma for no obvious reason. Although eyes with recurrent corneal erosions usually respond to simple and conventional therapy, it may be very frustrating to treat this disorder because of its recalcitrant nature. The exact pathogenesis is still under investigation. However, we know that hemidesmosomes, anchoring fibrils, and the basement membrane play an important role in the maintenance of an intact corneal epithelium[3,4]. The formation of hemidesmosomes requires proper apposition between the basal cell plasma membrane and the basement membrane.

The excimer laser was used for therapeutic purposes the first time in an experimental *Candida* keratitis in 1985[5]. This encouraged us to use the 193-nanometer excimer laser for a wider range of corneal and scleral pathology. The first time we applied the excimer laser for therapeutic keratectomy was in 1988, when we removed tumor tissue from the cornea and sclera[6]. This taught us more on the reaction and healing of ocular tissue after phototherapeutic keratectomy. One striking feature was the increased rate of re-epithelialization after one to four days. With this in mind, we decided to treat a patient with a history of recurrent corneal erosion with the excimer laser in April 1988. At that time, no reports had been published on the treatment of epithelial defects in recurrent corneal erosions with the excimer laser. As a consequence, we did not know whether the epithelium would grow tightly on the basement membrane. Trokel et al's[7] and our[6] observation on the behavior of the epithelium encouraged us to use the excimer laser for refractive purposes. We did not have much experience with photorefractive keratectomy at that time, and we feared that re-epithelialization would be inadequate after excimer laser photoablation of the cornea.

Because of the good result of our first case, we started to treat other eyes with therapy resistant recurrent corneal epithelial erosions systematically with phototherapeutic keratectomy in July 1988. In this study, we describe the management of recurrent corneal erosions in seventy-three patients by means of phototherapeutic keratectomy with the 193-nm ArF excimer laser.

Patients and methods.

Patients.

Patients who suffered from one or more episodes of recurrent corneal epithelial erosions were treated with the technique described, between April 1988 and February 1992. In total, we treated 97 eyes, but for this study we included compliant patients with a minimum follow-up of 6 months. Finally, we studied 74 eyes of 73 patients, 36 men and 37 women. Their age varied between 27 and 67 years (mean; 38.6 years, standard deviation, 10.04). The follow-up period ranged from 6 to 50 months with a mean of 21.1 months (standard deviation, 10.7).

All of the patients studied had a history of corneal trauma and were presented during the acute stage of the recurrence. There was no evidence of basement membrane disorders. All 74 eyes were treated with non-hyperosmotic topical lubricants during the previous episodes with recurrences. In 10 eyes, the erosions had additionally been treated with abrasion, and in 6 eyes with a therapeutic soft contact lens. Three eyes received a combination of abrasion and therapeutic contact lens. In one eye the abrasion had been repeated six times. The localization of the corneal erosions was in the lower half of the cornea in all eyes. In five eyes, the erosion was located before the pupil entrance partially. We also asked the patients for their subjective response. We present one case report that is representative of our series of 74 eyes.

Surgical Technique.

All patients were in supine position under the laser. The operated eyes were anesthetized with a topical anesthetic. We used a commercially available ArF-excimer laser (MEL 50, Aesculap Meditec, Heroldsberg, Germany) that emitted laser light at 193 nanometers with a radiant exposure at the cornea of 800 mJ/cm^2, which is much higher than for refractive purposes. We set the laser in spot-mode with a spot size of 1.5 mm in diameter, using a low repetition rate of 3 Hz. The pulse duration was 20 nanoseconds. During keratectomy, the laser beam was moved manually over the cornea with a joystick, while the patient's head was fixated, without using a suction mask to grasp the eye.

The aim of the laser treatment was to ablate the epithelium completely and, in some eyes, Bowman's layer to some extent. We did not mechanically remove loose epithelium in every case prior to performing phototherapeutic keratectomy. Our aim was to remove epithelial tissue with laser ablation only. The circular laser beam was moved with a joystick over the loosely attached epithelium and the edges of the erosion, to prevent circular punching. Only when the erosion was covered with loose bleb-like epithelium did we use a sponge to remove it. We ascertained the areas with loose epithelium and epithelial defect by slit-lamp microscopy and topical fluorescein.

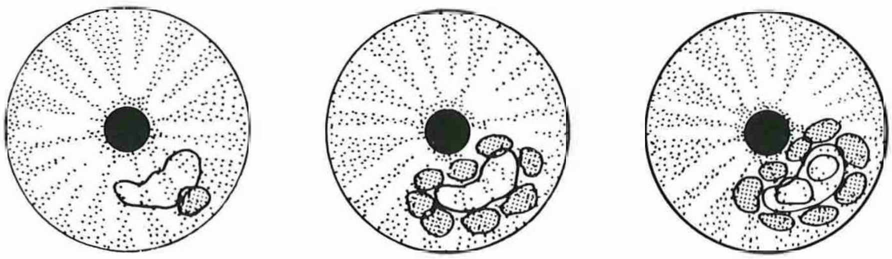

Figure 1. Diagram of the procedure in recurrent corneal epithelial erosion. The marginal epithelium is ablated to a depth of 30 μm. The center of the defect is ablated superficially to a depth of 3 μm, only to smoothen the surface.

The ablation depth of each pulse was roughly 1 μm, according to our own experience. The phototherapeutic ablation depth for loose epithelium and epithelium at the margins, within an area of one spot size (i.e., 1.5 mm) beyond the margins, was 30-40 μm (Figure 1). Areas not covered with epithelium, were treated superficially to an ablation depth of approximately 3 μm, only to smooth the surface, interfering as little as possible with Bowman's membrane and the anterior stroma. We preset the number of pulses for each area before starting phototherapeutic keratectomy. The total number of laser pulses depended on the size of the erosions and varied from 100 to 1000 pulses. At the conclusion of the surgical procedure the patients received a combination of antibiotic (gentamicin) ointment and pressure patching for the next 12 hours. Topical lubricants were prescribed for the first 6 weeks.

Case report.

A 29-year-old man suffered from a posttraumatic corneal erosion of his right eye in January 1988. Despite conventional treatment with lubricants, recurrences occurred every 3 weeks during the next 7 months. On August 16, 1988, patient suffered from a new painful attack of his right eye and was sent to our clinic. Slit-lamp microscopy revealed an erosion with a partial bullous epithelial detachment in the lower half of the cornea (Figure 2A). The erosion was immediately treated with the ArF-excimer laser. Instead of removing the loose epithelium at the margins, we removed it with laser ablation and smoothened the marginal epithelium to a depth of 30 μm (Figure 2B). The next day, the patient was symptom-free and the epithelium intact except for some punctata defects (Figure 2C). Three days after the laser treatment, the epithelium was completely healed (Figure 2D). No recurrences occurred the following 4 years.

Results.

In all eyes, the erosions healed within 4 days, while the majority of the patients was symptom-free the first day after laser treatment. Of the 74 eyes treated with phototherapeutic keratectomy, 55 (74.32%) eyes remained free of recurrences with a follow-up period varying from 6 to 50 months (Table 1 and figure 3). New recurrences occurred 1 to 22 months (mean, 8.42; standard deviation, 9.3) after phototherapeutic

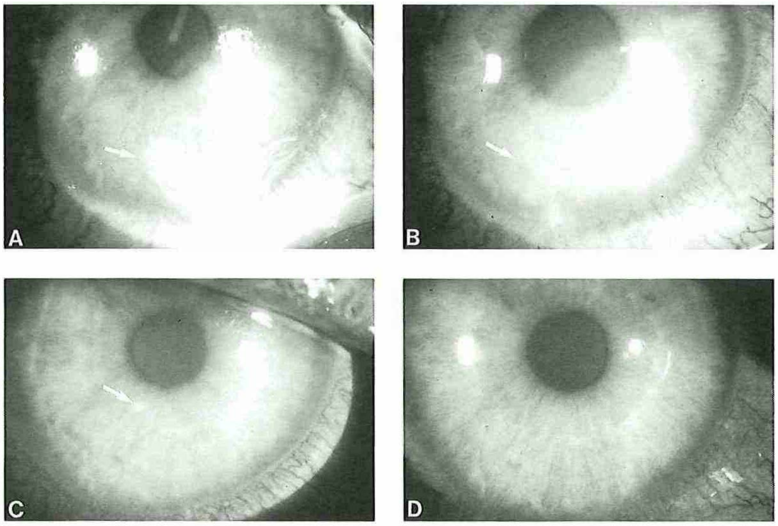

Figure 2. Recurrent corneal erosion with bullous epithelium (A) preoperatively, (B) immediately after phototherapeutic keratectomy,(C) one day postoperatively, and (D) 3 days postoperatively.

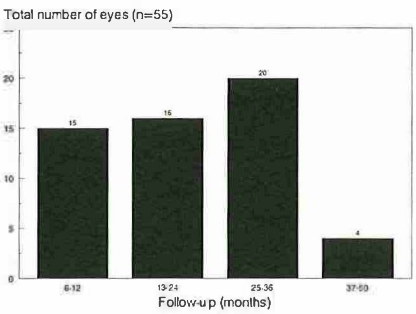

Figure 3. Bar-diagram representing the frequency distribution of the recurrence free eyes.

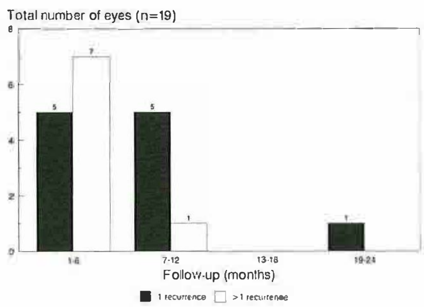

Figure 4. Bar-diagram representing the periods when new recurrences occurred for the first time after surgery.

keratectomy in 19 eyes, of which 8 suffered from more than 1 recurrence (Figure 4). The patients with new recurrences were treated conventionally with pressure patching and topical medication. Superficial haze grade 1 was present in one case, after 9 months, which we ascribe to a postoperative infection. Visual acuity was not influenced in this patient. In all other eyes, including those where the central cornea was involved, the treated area was not visible on slit-lamp microscopy. Because the majority of the patients were referred to us by other clinics, we did not have the preoperative refractive data available in all patients. Therefore, we could not compare the pre- and postoperative refractive outcome. However, our impression is that no severe hyperopic optical shift occurred.

In the recurrence-free group, 19 patients were still using topical lubricants occasionally, varying between once a day, before sleeping, to once a week. Four patients still complained about a dry eye sensation, whereof three showed some corneal punctata (Table 2). In the other group, 12 patients were still using lubricants. Fourteen patients complained about some discomforting sensations. However, this was negligible compared to the preoperative symptoms.

Table 1. Results

Recurrences	Number of eyes (n=74)
0	55 (74.32%)
1	11 (14.86%)
>1	8 (10.81%)

Table 2. Subjective response.

	no recurrence group (n=55)	recurrence group (n=19)
dry-eye sensation	4	7
pain	10	4
miscellaneous	5	3

Discussion.

Based on our experience so far, we think that phototherapeutic keratectomy in recurrent corneal epithelial erosions is promising. The overall success rate in our patient group was 74.32% with a mean follow-up period of 21.1 months. We emphasize the fact that all these patients suffered from recalcitrant cases of recurrent erosions that did not respond to any conventional approach until phototherapeutic treatment. Our intention in our first patients was only to treat the acute symptoms. Meanwhile, we learned that the raised marginal epithelium particularly should be ablated within a zone of at least one spot-size, to prevent recurrences. When we started phototherapeutic keratectomy, we treated eyes with erosions covered with loose bleb-like epithelium with photoablation only. After this treatment the epithelium simply fell off instead of re-attaching to the underlying structures. For this reason we removed the bullous epithelium mechanically before surgery in these cases. We think that abrasion of the cornea, in order to have the stem cells at the limbus regenerating healthy epithelium, is not necessary. In our opinion the margins should only be smoothed to have the epithelial cell migrate to the center of the defect. We have observed that the epithelium heals within one to four days and that in the majority of the cases the symptoms disappeared during the first day.

Except for one case with postoperative haze, we did not encounter other complications. Most of the new recurrences occurred during the first 12 months postoperatively. The patients who were still complaining about painful sensations did not show evident erosions. They probably suffered from subclinical signs, which did not result in the classical symptoms of corneal erosions. Because of our incomplete data on the pre- and postoperative refractive errors, we could not conclude on hyperopic optical shift. Phototherapeutic keratectomy has been commonly associated with induction of hyperopia[8]. However, our impression is that no major shift in refraction did occur in our patients.

Anterior stromal puncture[4,9,10] is an alternative treatment that appears to be successful with recurrence free periods from 18 to 39 months[10], and from 5 months to 12 years[9]. This method consists of puncturing loose epithelium and the anterior stroma with a hypodermic needle or with the aid of the Nd:YAG laser[11]. This brings the corneal epithelium in close contact with the anterior stroma, resulting in a strong adhesion between the basal epithelial cells and the underlying tissue. This procedure has the advantage of being simple to perform at low costs. However, the drawback of this technique is the possible risk of fine residual anterior stromal scarring that could affect vision if too many marks are clustered over the visual axis. With the hypodermic needle, there is also an eventual risk of corneal perforation. Although surgeons have applied needle punctures within the visual axis successfully, the shallow application of the excimer laser technique provides more satisfying results.

Other studies imply the usefulness of the excimer laser to treat superficial ocular pathology[7,8,12,13,]. Ultrastructural studies of the cornea after laser keratectomy showed an extremely smooth surface in the irradiated areas[14-16]. We presume that a smooth and clean surface stimulates centripetal migration of the epithelial cells. Lubatschowski et al.[17] found a significant correlation between the fluence and the intensity of the measured acoustic shock wave of the 193-nm argon-fluoride-excimer-laser, by means of piezoelectric transducers. Such a shock wave exerts a potential mechanical stress on the corneal surface. Although the mechanism by which stromal punctures actually improve epithelial adhesion is unknown, we presume that the shock wave of the excimer laser excerpts a similar effect on the epithelium. For this reason, we used such a high energy density of 800 mJ/cm^2.

Probably phototherapeutic keratectomy of loose epithelium and epithelial defects modifies biomechanically the surface structure of basement membrane and the Bowman's layer, allowing a stronger cell anchorage. New epithelium requires a re-establishment of the underlying anterior stroma. The anchoring fibers (of which type VII collagen is a major component), basement membrane, and hemidesmosomes are important structures for a strong epithelial adhesion. Histological studies of laser-ablated monkey corneas[18,19] showed linear and regular alignment of the basal epithelial cells, and an evident linear anchoring fibril zone. An increased accumulation of type VII collagen and hemidesmosomes along the basal membrane of the basal epithelial cells were present postoperatively. However, in some eyes the basement membrane was devoid of anchoring fibrils and the epithelium appeared to be less firmly attached. This finding might partially explain the painful sensations that some of our patients experienced, and also that the treatment was not successful in every case.

Even though we can only hypothesize on the mechanisms of phototherapeutic keratectomy in recurrent erosions, the excimer laser is great promising. One of the potential benefits of the expensive excimer laser technology is the possibility of treating recalcitrant corneal erosions located in the visual axis.

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CHAPTER 10

Photorefractive keratectomy for the correction of astigmatism combined with myopia and hyperopia.

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(Journal of Cataract and Refractive Surgery 1994;20:252-257)

Abstract.

Excimer laser photorefractive keratectomy as a means to flatten the central cornea has generated considerable interest. With this technique radial symmetric ablations can be performed to correct myopic refractive errors and to excise superficial corneal pathology. We developed a new technique of toric ablation for the correction of astigmatism. A new mask was designed for the MEL 60 Aesculap-Meditec excimer laser. This mask can be rotated regularly over 360 degrees. By varying the angular distances, the surgeon can increase the ablation depth in any desired meridian. As a result, both cylindrical and spherical errors can be corrected in one procedure. Seventy-three eyes with either simple, myopic, mixed, or irregular astigmatism were treated. In each category of astigmatism, the surgery reduced the spherical component as well as the overall mean preoperative cylindrical refraction. Our findings suggest that this technique is a safe and effective procedure for correcting different types of astigmatism.

Introduction.

The excimer laser has generated considerable interest as a means to reshape the anterior corneal surface, as is done in photorefractive keratectomy (PRK). Furthermore, the laser can be used to treat superficial ocular pathology. The 193-nm wavelength allows a superficial ablation of the corneal tissue. By controlling the size, shape, and energy of the laser beam, the cornea can be molded into various shapes. To date, this possibility has been used to correct myopia and hyperopia with good results[1-3]. However, astigmatism has remained a major problem, both in PRK and in conventional ophthalmic surgery.

Surgeons have used PRK to perform radial symmetric ablation depths to correct the spherical component of refractive errors. Because astigmatism often occurs in combination with myopia and hyperopia, we tried to find a solution to treat both cylindrical and spherical refractive errors in one procedure.

Excimer laser techniques have been described to correct astigmatism with toric ablations only[4]. The use of a specially designed laser mask enabled us to perform toric ablations as well as a combination of toric and spherical ablations. In this article, we describe our technique and the results of our first group of patients treated with this method.

Subjects and methods.

We used a 193-nm argon-fluoride excimer laser (Aesculap-Meditec MEL 60, Heroldsberg, Germany). This laser emits laser light through a computer-controlled slit profile, 1 mm by 7 mm in size. Each complete exposure was created using a scanning process rather than one single exposure. The slit profile was moved uniformly in such a way that a circular area up to a maximum diameter of 7 mm was exposed to the laser light. The exposures for large-area photoablation were performed with a repetition rate of 0.5 Hz. The energy density of the individual laser beam was 250 mJ/cm^2, resulting in a corneal ablation depth of 0.5 μm per pulse. At a repetition rate of 20 Hz, however, the scanning process was adjusted in order to achieve considerable overlap of adjacent laser shots. Therefore, the total effect of one scanning process was an ablation of 1 μm. This overlap also ensured that the ablation procedure created a smooth surface. The techniques to correct myopia and hyperopia have been described elsewhere[1-3].

We modified the laser hardware for the correction of astigmatism. The laser beam remained in scanning-mode, but the ablation profile was altered by a rotating mask with an hour-glass-shaped opening, 5 mm and 7 mm in diameter (Figure 1). The mask was inserted into a suction ring, which was first adjusted and then fixed to the patient's eye. After each angular step of the mask opening the laser beam scanned the aperture.

After the mask was rotated with equidistant angular steps over 360 degrees, the profile of the ablated tissue proved to be symmetrical with the steepest part in the center, thus correcting the myopia (Figure 2). The angular steps do not have to be equidistant. By varying the angular distances, the ablation depth can be increased in any desired meridian during the rotation, resulting in a profile with a myopic and an astigmatic component (Figure 2).

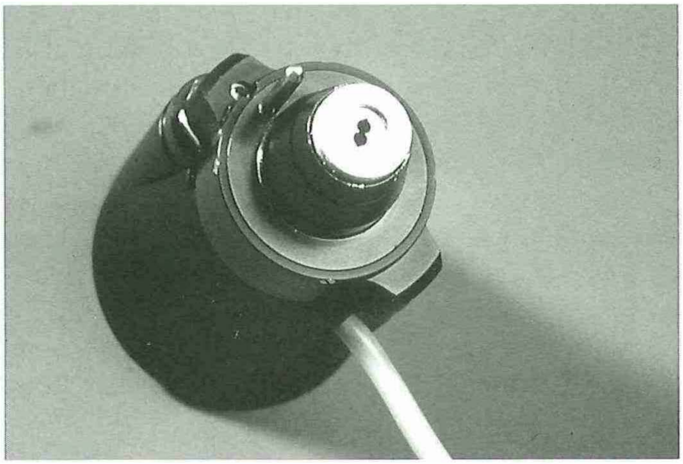


Figure 1. The rotating mask with an hour-glass-shaped opening.

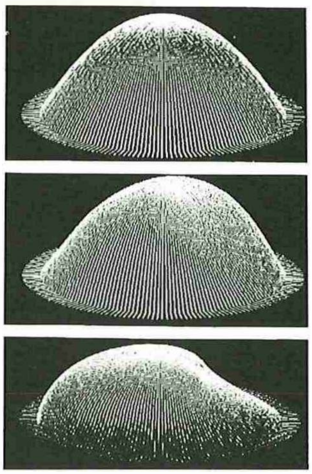


Figure 2. Computer simulated profile of the ablated tissue for correcting myopia (upper), astigmatism (middle), and irregular astigmatism (lower).

The nomogram to correct the cylindrical component was the same as the one used for the spherical correction. However, the laser was used only in the meridian which had to be ablated. In the orthogonal meridian, no refractive ablation was intended. Ablations were performed with the same fluence and repetition rate as the ones used for the correction of simple spherical refractive errors.

Two surgeons (Dausch and Klein) performed the ablations using the same type of excimer laser. The investigative nature of the procedure was discussed with the patients; the risks, side effects, possible complications, and alternative treatment were emphasized. A competent ethics committee was informed of the study.

Seventy-three eyes (of 66 patients, aged 18 to 85 years) were treated. The patients were divided into four groups (Table 1). In the first group of 30 patients, we only treated the astigmatism, not the spherical errors. Among these patients, three had postoperative astigmatism after penetrating keratoplasty and one had astigmatism after cataract extraction. The second group consisted of 29 patients with myopic astigmatism. The third group consisted of five patients with mixed astigmatism. The fourth group consisted of two patients who had irregular astigmatism. In one case the astigmatism was caused by an epidemic keratoconjunctivitis, in the other by a pterygium excision.

Table 1. Patient characteristics.

Group	eyes (n)	M	F	age (years) (mean, ± sd)	follow-up (months) (mean, ± sd)
I	30	13	17	40.6 (18.7)	10.4 (2.45)
II	36	12	17	35.8 (9.4)	6.4 (2.69)
III	5	3	2	48.4 (21.1)	4.2 (2.68)
IV	2	2	0	37.0 (2.83)	3.0 (0.00)

In Group 1, the 7-mm mask was used; the axis and the diopter-value to be ablated were entered into the computer. In this group we had to correct extremely high cylinders. Because of our previous experience with myopic PRK, we selected a large treatment zone of 7 mm in diameter in order to reduce the amount of regression as much as possible. In Group 2, the standard 5-mm mask was used; the axis and the desired refractive change were entered into the computer in minus cylinder and minus spherical forms. In Group 3, we first used the 5-mm mask and we immediately switched to the mask we used for correcting hyperopia[5] to correct the plus spherical refractive error. To perform asymmetrical ablations in Group 4, we designed a special asymmetric mask based on the videokeratographic images.

Patients were placed in supine position under the excimer laser. Topical anesthesia was instilled. The corneal epithelium was removed with a blunt knife blade prior to surgery. The center of the hourglass-shaped excimer ablation was determined by marking the entrance pupil as the patient fixated on the light of the operating microscope. During the ablation procedure, the eye was stabilized with the mask and the suction ring. We did not take into account a possible cyclotorsion of the globes.

Gentamicin ointment was applied postoperatively to all patients until the epithelial defect healed. Patients were then given 0.1% fluormetholone, according to a standardized schedule: four times daily during the first month, three times daily during the second month, and then twice daily during the third month. The follow-up period varied from three to twelve months. Refraction and computer-assisted video-keratography (Corneal Modeling System, Computed Anatomy, Inc., New York) were performed in the fourth week and subsequently in the third, sixth, ninth, and twelfth month after surgery. Data were processed with dBase IV and Systat, and were presented as means with one standard deviation error bars. Changes in refraction were considered non-significant when P-values were greater than 0.05.

Results.

Refractive outcome.

Group I (simple astigmatism) comprised 30 patients with astigmatism up to -11.00 diopters (D). Mean preoperative refractive cylinder was -3.30 D ± 2.40 (ranging from -1.00 to -11.00 D). One month after treatment this value averaged -0.19 D ± 0.48 (ranging from 0.00 to -2.00 D); three months after treatment the average was -0.22 D ± 0.59 (ranging from 0.00 to -2.75 D). In 19 eyes, overall mean postoperative residual cylindrical error after 12 months was -0.3 D ± 0.58, which was significantly different from the preoperative cylinder (paired *t*-test, $P<0.05$).

Overall mean spherical equivalent change measured in all 30 eyes during the last visit was non-significant (+0.68 D ±1.4, ranging from +4.0 to -2.0 D). Figure 3 shows the time course of the spherical and cylindrical outcome.

We also calculated the predictability of the correction at 6 months. Regarding the refractive cylinder, 83.3% of the treated eyes were corrected within half a diopter, and 86.7% within one diopter.

In Group II (myopic astigmatism), mean preoperative cylindrical refraction was -2.10 D ± 0.93 (ranging from -1.00 to -5.00 D). After 1 month this value averaged -0.10 D ± 0.41 (ranging from 0.00 to -2.25), and after 3 months -0.11 D ±0.37 (ranging from 0.00 to -2.00 D). Overall mean residual cylindrical outcome, measured in all 36 eyes during the last visit, was -0.08 D ± 0.23 (ranging from 0.00 to -2.25 D), which was significantly different from the preoperative cylinder ($p<0.05$).

Mean preoperative spherical refractive error was -6.10 D ± 3.70 (ranging from

-0.50 to -16.00 D); after 1 month this value averaged + 0.44 ± 1.05 (ranging from +4.00 to -1.00 D), and after 3 months -0.05 D ± 1.39 (ranging from +3.00 to -4.00 D). The overall change in mean spherical refraction was significant (-0.12 D ± 1.04, $p<0.05$). The time course of the refractive outcome shows a slight undercorrection (Figure 4).

As for the predictability of the correction of the cylindrical error in this group, 80.6% of the eyes were corrected within half a diopter, and 83.8 within one diopter. The spherical component was corrected within a half a diopter in 50.0% of the eyes, and within one diopter in 84.6% of the eyes.

From 5 patients in Group III (mixed astigmatism), we present one patient as an example. The patient's preoperative manifest refraction was +3.75 x -5.5 x 165°. Three months after ablation the manifest refraction was +0.75 D. The cylindrical component was completely corrected.

Group IV (irregular astigmatism) comprised two patients only. The first patient had a preoperative refraction of +2.0 x -1.25 D x 90°. Three months after photoablation the refraction was +0.75 x -0.5 x 168°. The other patient's refraction changed from +1.25 x -7.0 x 130° to +0.5 x -1.5 x 180° after 3 months.

Visual acuity.

In Group I, the goal of surgery was to reduce the cylindrical error. Mean uncorrected visual acuity improved from 20/125 preoperatively to 20/40 postoperatively. In 33.3% of the cases the uncorrected visual acuity was 20/20 or better; 66.7% had an uncorrected visual acuity of 20/30 or better and in 80.0%, 20/40 or better.

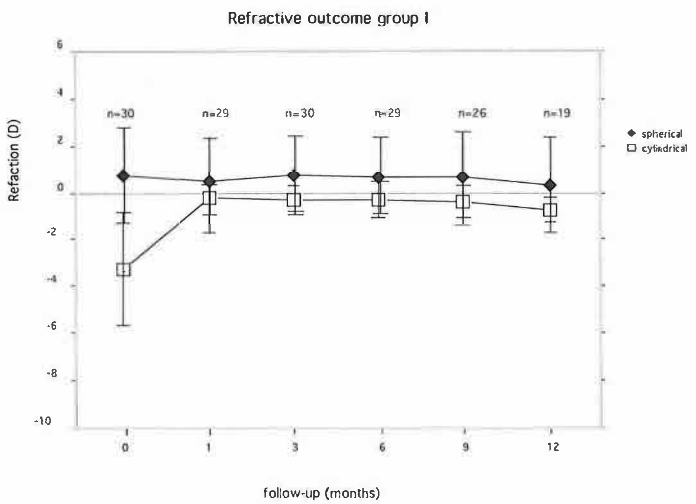


Figure 3. Plot of mean refractive sphere and cylinder error before and after toric excimer laser ablation in group I.

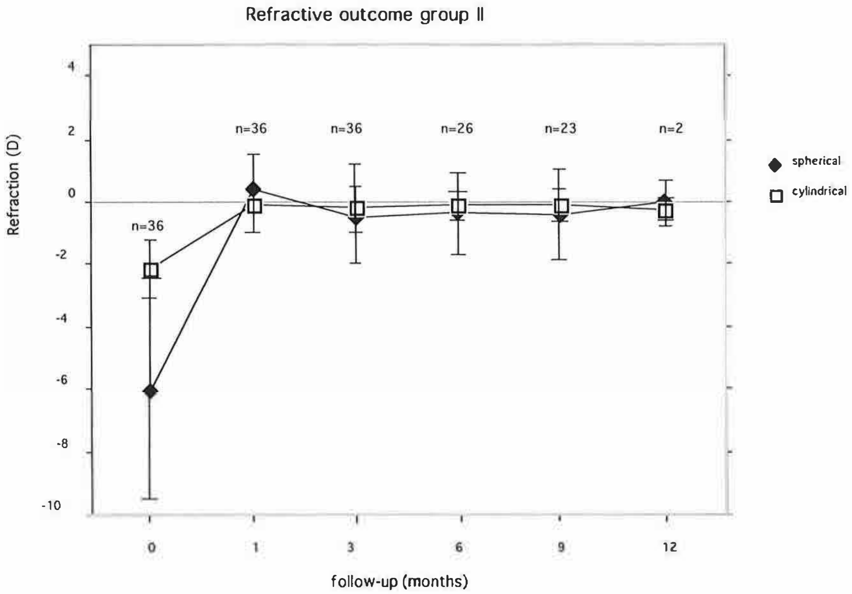


Figure 4. Plot of mean refractive sphere and cylinder error before and after excimer laser ablation in group II.

Mean best spectacle-corrected visual acuity improved slightly, from 20/35 before to 20/30 after surgery. Figure 5 shows the results of the change in best corrected visual acuity after 9 months.

The aim in Group II was to improve the uncorrected visual acuity. Visual acuity had a mean overall increase from 20/180 to 20/25. The uncorrected visual acuity was 20/20 or better in 21.6% of the eyes, 20/30 or better in 45.9%, and 20/40 or better in 54.1%. Figure 6 shows the results of best corrected visual acuity six months after ablation.

Three months after ablation the patient in Group III had an improvement in uncorrected visual acuity from 20/200 to 20/40. Best corrected visual acuity remained 20/30.

In Group IV, one patient's uncorrected visual acuity improved from 20/100 to 20/40; best corrected visual acuity improved from 20/50 to 20/40. In the other patient these values changed from <20/400 to 20/50 and from 20/400 to 20/30 respectively.

Cylindrical axis.

The postoperative axis of astigmatism was within 15° of the preoperative axis in most eyes, and was not significantly different (paired Student t-test, t=0.745, p=0.46) for the group as a whole. In Group I, the difference between the axis of refractive cylinder preoperatively and the last follow-up ranged from 1° to 39° with a mean shift of 2.5° ± 23.6°. In Group II, this difference ranged from 1° to 19° with a mean shift of 2° ±13.3°. We noted a shift of more than 10° in the two patients in Group IV without visual acuity being affected.

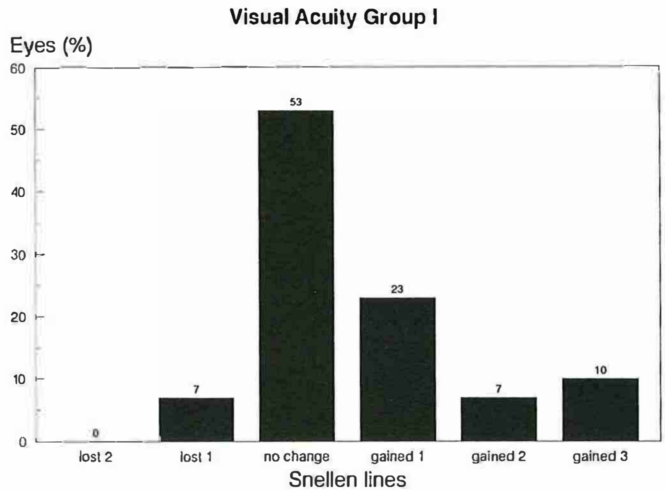


Figure 5. Change in best corrected visual acuity between the baseline and 9 months after PRK (n=26).

Topographic findings.

In this study all but two patients had regular astigmatism. In these patients, computer assisted topography revealed a bow-tie pattern, in which the colors green or blue represent the flattest meridians, which are about 180 degrees apart; red or orange represented the steepest meridians, (Figures 7,8, and 9).

We used the videokeratograph to visualize the topographic outcome of the cylinder's photoablative correction and to reveal any residual astigmatism. For this purpose, we subtracted the preoperative from the postoperative pictures. The difference obtained is equal to the profile of the ablated corneal tissue. The ablation was performed correctly if the preoperative bow-tie profile matched the subtracted picture (Figure 7A). We also found that in patients with asymmetric astigmatism, one of the hemimeridians was much steeper than the other (Figures 10A, and 10B). We tried to flatten the steepest meridian only, which resulted in an elliptical ablation zone.

Complications.

In two of the 73 eyes, the ablation zone was poorly centered. In two other eyes, a postoperative mild superficial haze was noticed after 6 and 9 months. In all cases, the epithelial defect healed within five days. We have not encountered any persistent epithelial defects.

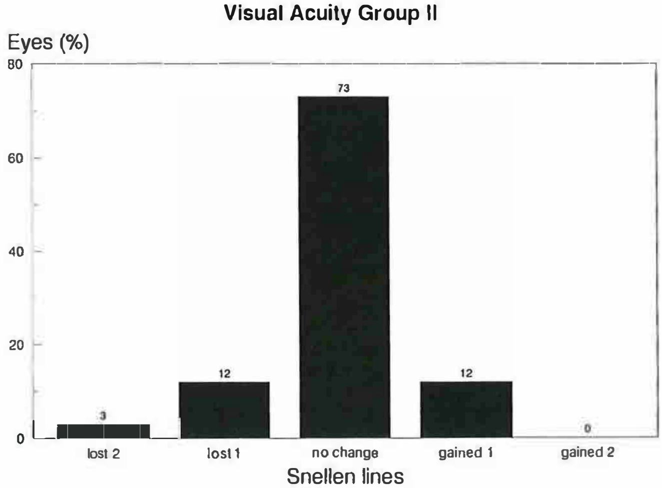
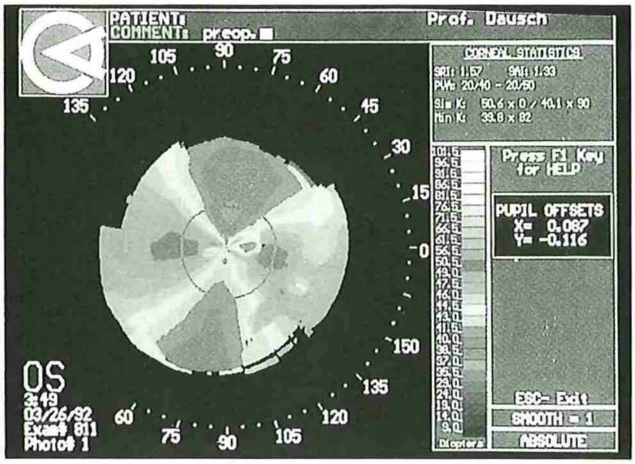


Figure 6. Change in best corrected visual acuity between the baseline and 6 months after PRK (n=26).

Conclusion.

Modification and control of astigmatism have been a long-term goal in ophthalmology. Since the development of the excimer laser, only a few studies have used the apparatus to correct astigmatism[6-8].

The excimer-laser technique described is not specifically designed for the correction of regular astigmatism with symmetrical steepening in the two steepest hemimeridians. With the new rotating mask, spherical myopic components can be corrected as well. Other laser techniques that have been described to correct astigmatism by means of toric ablations[7-8] merely allow cylindrical correction in regular astigmatism in one session. Therefore, a superimposed ablation has to be performed to correct any spherical errors.



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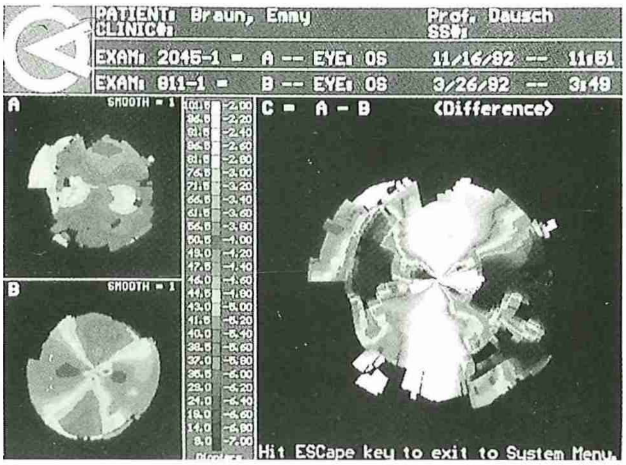


B

Figure 7. Color-coded keratograph of a group-I patient. The bow-tie configuration represents the degree of astigmatism before surgery (A), and six months after toric ablation to correct refractive cylinder of 11 diopters (B). The ablated corneal tissue in the difference-image has the same pattern as the preoperative topography. The steep meridian has been flattened.

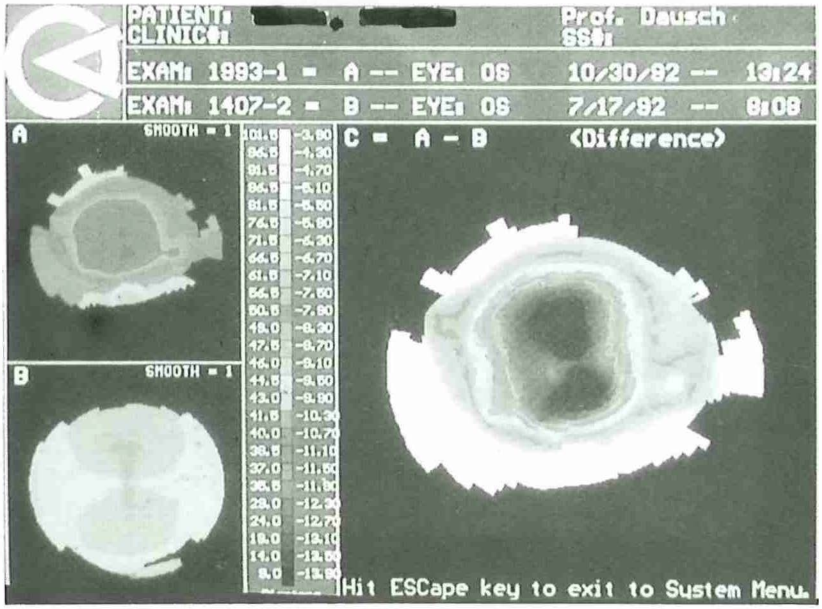


Figure 8. Color-coded keratograph of a group-II patient three months after toric and spherical ablation for the correction of a -9.5 diopter myopia and a -2.25 diopter astigmatism. The steepest meridians have been flattened and a central spherical ablation has been performed.

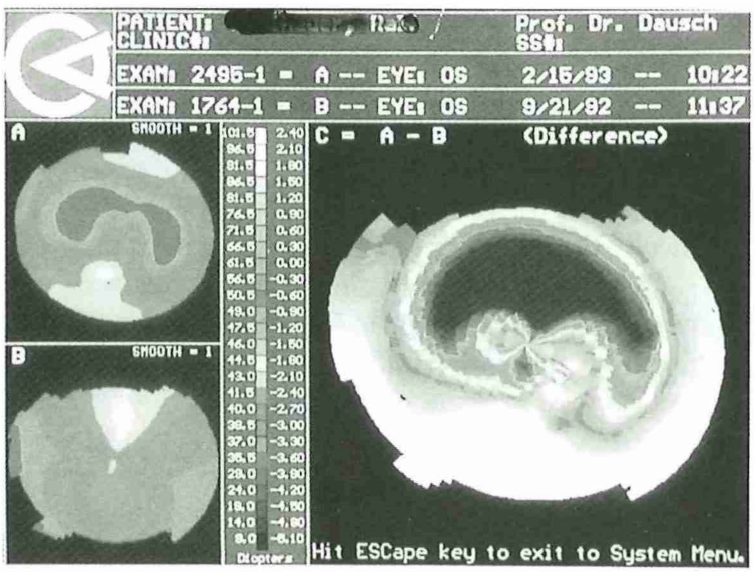
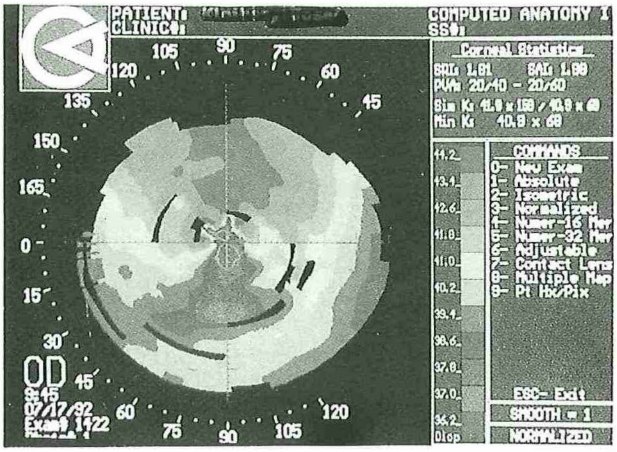


Figure 9. Color-coded keratograph of a group-III patient five months after toric ablation for the correction of a 6-diopter cylinder with an elliptical ablation zone.



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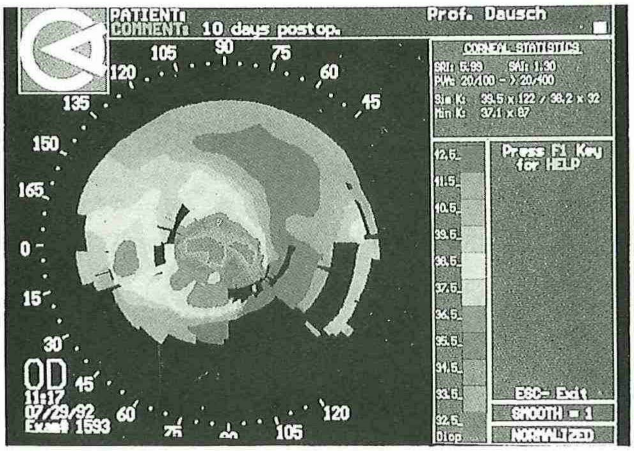

B

Figure 10 Color-coded keratograph of a patient with irregular astigmatism as a result of an epidemic keratoconjunctivitis. The upper hemimeridian is steeper than the lower one (A). One week after surgery (B).The upper meridian has been flattened.

In this article, we reported a study of a total of 73 human eyes followed up from 3 to 12 months after excimer laser PRK for simple astigmatism, for astigmatism in combination with spherical errors, and for irregular astigmatism. Although the follow-up period of the whole group of patients may not seem long enough, a preliminary assessment of the method's effectiveness seems justified.

Photorefractive keratectomy to correct myopia, appears to be relatively safe[1-5].

Patients with haze and decentered ablation zones did not suffer from decrease in visual acuity. We have not yet found an explanation for the 7 cases that showed a decreased corrected visual acuity.

To assess the efficacy and safety of PRK, it is important to evaluate the topographic alterations using computer-controlled videokeratography[9]. Subtracting the preoperative images form the postoperative images provides visualization of the final result of the ablation profile and, therefore, verifies the procedure. The final image serves as a way to verify any correspondence between the refractive axis and the final topographic correction. It also shows any decentration of the ablation zone.

Although corneal flattening induces a shift of the spherical component to hyperopia[8], we have not noticed a hyperopic shift in patients in Group I. In Group II, we first overcorrected the spherical error on purpose because, from our experience with previous studies[4], we anticipated a regression . Even high astigmatism and astigmatism induced by penetrating keratoplasty can be treated adequately, as in Group I. Furthermore, no significant regression of the cylindrical correction was noticed in any of the patients. We therefore conclude that this method may be useful for treating different types of astigmatism in one session. To evaluate the efficacy and safety of this technique, a multicenter study has been started.

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SUMMARY

Replacing glasses or contact lenses by an operation is called refractive surgery and has become one of the subspecialties in Ophthalmology. This thesis deals with two new developments in the field of refractive surgery and their clinical evaluation.

The first technique discussed is the negative iris claw lens for the correction of high myopia. This lens is implanted in high myopic eyes without removing the natural crystalline lens. One important aspect of this procedure is the effect on the inner layer of the cornea, the endothelium, which can be studied with a specially designed microscope, the specular microscope. The other refractive surgical technique studied is the Argon-Fluoride 193-nm excimer laser. The radiation of this laser is completely absorbed by the anterior layers of the cornea, which, therefore, allows a superficial removal of corneal tissue.

Chapter 1 is a review of the literature and historical background on phakic anterior chamber lenses in phakic eyes, specular microscopy of the corneal endothelium, and the Argon-Fluoride 193-nm excimer laser.

After the introduction of intraocular lenses (IOL), attempts were made in the 1950's to correct high myopia with IOLs leaving the natural crystalline lens in place. The implantation of these lenses was soon abandoned, because of severe complications. New developments in ophthalmic surgery and lens manufacturing techniques led to the reintroduction of these IOL's in the mid 1980's.

One of the main concerns in phakic IOLs is the effect on the corneal endothelium, since this tissue is considered amitotic. To examine the corneal endothelium, specular microscopy is a prerequisite. The first specular microscope was developed in the 1960's and was used in vitro. In the 1970's, in vivo specular microscopes were developed for more clinical purposes, such as evaluation of surgical trauma and disease of the endothelium.

The effects of the Argon-Fluoride 193-nm excimer laser on the cornea was reported for the first time in 1983. This technique allows a superficial ablation of corneal tissue without damaging adjacent structures. Therefore the excimer laser seems to be ideal to remove corneal tissue in superficial corneal diseases and to alter the corneal curvature for the correction of refractive errors.

The first part of this thesis deals with anterior chamber lenses fixated on the iris in phakic eyes. Chapter 2 describes a case with an occlusive iris claw lens because of concomitant strabismus fourteen years after implantation. No effect on the iris has been noticed. The cell density of the operated eyes was 18.6 % less than of the contralateral eye.

Chapters 3 and 4 describe the refractive and visual outcome, and the effect on the corneal endothelium in high myopic patients with a negative iris claw lens. The refractive outcome is stable and fairly predictable. In 55.5% and 74.3 % respectively of the eyes a residual refraction between +1 and -1 diopters was achieved. The endothelial cell loss seems to be stable after 12 months. However, the patients should be followed in due course to fully assess the long-term effect on the corneal endothelium and the stability of the refraction.

In Chapter 5 a psychosocial study on patients with a negative iris claw lens is described. In general, the patients were very satisfied with the optical results. Compared to high myopic contact lens wearers, their psychosocial well-being does not differ significantly. The only difference was a higher rate of complaints on the contact lenses themselves.

The second part deals with the semi-automated technique developed by us to study the corneal endothelium. Chapters 6 and 7 describe our modification of two specular microscopes in order to analyze the corneal endothelium semi-automatically with an image processing computer program. We also compare these two microscopes with one commercially available autofocus microscope. The accuracy of each microscope is comparable, but should not be used interchangeably in morphometric studies of the corneal endothelium.

The last part deals with therapeutic and refractive applications of the excimer laser. In Chapter 8, a case of recurrent corneal epithelial dysplasia treated with the excimer laser with a 26 months recurrence-free period is described.

In chapter 9, a group of 73 patients with recurrent corneal epithelial erosions was treated with the excimer laser. The overall success rate was 74.3%. Especially for cases where the erosion is located on the visual axis this treatment could be beneficial. The superficial removal of corneal tissue causes less scarring than more conventional techniques as in anterior stromal puncture.

Chapter 10 deals with the correction of astigmatism, combined with myopia and hyperopia, with the excimer laser. This report is the first on a combined toric and spherical ablative technique. The refractive results are satisfactory, although the follow-up period is limited to a maximum of 12 months.

SAMENVATTING.

Refractie chirurgie is een operatie met als doel de refractie van het oog te veranderen om daardoor het dragen van de bril of contactlenzen overbodig te maken. In de laatste jaren is refractie chirurgie een opkomend subspecialisme van de Oogheelkunde geworden. Dit proefschrift beschrijft de klinische evaluatie van twee nieuw ontwikkelde technieken op dit gebied.

De eerste techniek bestaat uit het implanteren van een kunstlens in het oog, waardoor hoge bijziendheid (myopie) wordt gecorrigeerd. Nadat Ridley in 1949 de eerste kunstlens met positieve sterkte had geimplanteerd in het oog na verwijderen van staar ging de ontwikkeling van implantlenzen zeer snel vooruit. Tegenwoordig is het vervangen van staar door een kunstlens de techniek lege artis geworden in de Westerse wereld. Eigenlijk is deze procedure de meest geaccepteerde en toegepaste refractie chirurgische techniek in de Oogheelkunde. In de jaren 50 waren Strampelli en Barraquer de eersten die kunstlenzen implanteerden ter correctie van hoge myopie. Bij deze techniek wordt niet, zoals bij staaroperaties de natuurlijke lens verwijderd, maar wordt deze juist in het oog gelaten en wordt de kunstlens in de voorste oogkamer (ruimte tussen het hoornvlies (cornea) en de iris) geplaatst en in de kamerhoek gefixeerd. Dit soort kunstlens wordt een voorste oogkamerlens met negatieve sterkte ter correctie van bijziendheid genoemd. Echter, wegens een aantal zeer ernstige complicaties heeft men deze techniek snel verlaten. De oorzaken van deze problemen waren enerzijds de slechte afwerking van de kunstlens en anderzijds de onwetendheid van de reactie van het oog op schade ontstaan door chirurgisch ingrijpen. In de loop der jaren werd het fabriceren van kunstlenzen met steeds meer geavanceerde technieken gedaan, waarbij de lensranden veel gladder werden afgewerkt. Tevens nam de wetenschap over de pathofysiologie van de verschillende structuren van het oog toe. Deze ontwikkelingen leidden in de jaren 80 ertoe opnieuw kunstlenzen te maken ter correctie van hoge myopie. Een van de doelstellingen van dit onderzoek is het bestuderen van de implantatie van deze kunstlenzen bij patiënten.

De belangrijkste aspecten om de effectiviteit en veiligheid te bestuderen van refractiechirurgie zijn de postoperatieve residuele brekingstoestand van het oog (meestal uitgedrukt in het percentage patiënten die een refractie tussen +1.0 en -1.0 dioptrie overhouden), de stabiliteit daarvan, het verlies in gezichtsscherpte en schade aan weefsels van het oog.

Een van de belangrijkste aspecten bij het bestuderen van een voorste oogkamerlens is de eventuele schade toegedaan aan de cornea. De meest kwetsbare structuur van de cornea is de binnenste cellaag, het corneaendotheel. In deze cellaag vindt na de geboorte van de mens geen of bijna geen celdeling meer plaats, zodat bij beschadiging van het corneaendotheel de dichtheid van de endotheelcellen vermindert. De functie van het endotheel is het wegpompen van vocht uit het hoornvlies. Bij een te laag aantal endotheelcellen wordt de pompfunctie aangetast, en treedt er zwelling (oedeem) van het hoornvlies op, waardoor de gezichtsscherpte sterk kan verminderen. Om het endotheel te kunnen bestuderen bestaat een speciale microscoop, de spiegelmicroscoop. In dit proefschrift wordt de semi-automatische techniek beschreven die wij op onze oogheelkundige afdeling hebben ontwikkeld om de endotheelcellen morfometrisch te kunnen analyseren.

De andere refractie chirurgische techniek die bestudeerd werd in dit proefschrift is de 193-nanometer argon-fluoride excimer laser. In 1983 werden door Trokel de eerste bevindingen gepubliceerd over de reacties van corneaweefsel op straling van deze excimer laser. Het feit dat de laserstralen volledig door de buitenste lagen van het hoornvlies geabsorbeerd worden, biedt de mogelijkheid zeer nauwkeurig weefsel te verwijderen op submicrometer niveau, zonder omliggende structuren te beschadigen. Hierdoor is deze techniek geschikt voor fotorefractieve keratectomie waarbij dunne lagen hoornvlies verwijderd worden om de breking van het hoornvlies te veranderen. Tevens is deze techniek geschikt om oppervlakkige hoornvliesaandoeningen nauwkeurig te verwijderen. Op deze twee toepassingen van de excimer laser zal in dit proefschrift nader ingegaan worden.

Het proefschrift begint in hoofdstuk 1 met een overzicht van de literatuur en geschiedenis van voorste oogkamerlenzen ter correctie van bijziendheid, de bestudering van het corneaendotheel met de spiegelmicroscoop en de excimer laser.

Het eerste deel beschrijft de klinische evaluatie van patienten met een iris claw lens, die gefixeerd wordt aan de iris. In hoofdstuk 2 wordt een patient beschreven 14 jaar na de implantatie van een occluderende iris claw lens wegens hinderlijke dubbelbeelden na een ongeval. De lens is nog steeds in situ, zonder complicaties, met een endotheelceldichtheid die 18.6% procent lager is dan in het niet geopereerde oog.

De hoofdstukken 3 en 4 beschrijven de resultaten van de negatieve iris claw lens ter correctie van hoge myopie. Hoofdstuk 3 beschrijft een retrospectieve studie van hoog myope patiënten na implantatie van het eerste model negatieve iris claw lens, met een biconcave optiek. De vervolgperiode varieerde tussen de 1 en 60 maanden. Postoperatief was de resterende refractie in 55.5% van de gevallen tussen de -1 en +1 dioptrie. Het postoperatief getelde endotheel liet geen beduidend lage celdichtheden zien. In één geval echter, trad corneaoedeem op, waarschijnlijk door compulsief in het oog wrijven.

Hoofdstuk 4 beschrijft een prospectieve studie naar het nieuwe type convex-concave negatieve iris claw lens in 35 ogen van hoog myope patienten. De refractie was in 74.3% van de gevallen tussen -1.0 en +1.0 dioptrie. Het gemiddelde endotheelcelverlies was 5.6% na 6 maanden en 8.9% na 12 maanden. Voor een uiteindelijke conclusie over de stabiliteit van de optische resultaten en het endotheelcelverlies moeten deze patiënten nog een aantal jaren gevolgd worden. Hoofdstuk 5 is een psychosociaal onderzoek naar de patiënten genoemd in hoofdstuk 4, waarbij een groep contactlensdragers als controle groep fungeert. De psychosociale karakteristieken van deze twee groepen waren niet significant verschillend. Het enige grote verschil was dat het draagcomfort van de contactlenzen bij de geopereerde patiënten aanmerkelijk lager was. De tevredenheid was in de groep van geopereerde patiënten zeer hoog. Wat opviel was dat de reden van operatie bijna uitsluitend het optimaliseren van de gezichtsscherpte was en niet cosmetisch van aard.

In deel twee, hoofdstuk 6 en 7, wordt de bestudering van de morfologie van het corneaendotheel met de spiegelmicroscoop beschreven. Hiervoor werd op onze afdeling een aanpassing van een computer gestuurde beeldbewerkingsprogramma ontworpen. Tevens werden de metingen verricht met onze techniek vergeleken met die verricht met een commercieel verkrijgbare camera, waaruit bleek dat de nauwkeurigheid van de metingen vergelijkbaar is.

Deel 3 beschrijft verschillende therapeutische en refractie chirurgische toepassingen van de excimer laser. Hoofdstuk 8 beschrijft een geval van epitheeldysplasie van de cornea in een patient 26 maanden na behandeling met de excimer laser, bij wie ziek weefsel verwijderd werd. Tot nu toe is er geen recidief waargenomen.

In hoofdstuk 9 wordt een studie beschreven naar 74 ogen met recidiverende epitheelerosies van de cornea die met de excimer laser behandeld werden. In een periode variërend tussen 6 en 48 maanden na behandeling trad in 74.43% van de gevallen geen recidief op. Het voordeel van deze methode tegenover andere conventionele therapieën is dat een erosie gesitueerd op de visuele as minder kans op littekenvorming geeft, wat het optisch resultaat begunstigt.

Het laatste hoofdstuk (10) beschrijft een studie naar de correctie van astigmatisme gecombineerd met myopie en hypermetropie. Door een toepassing aan de excimer laser kan er tegelijkertijd een sferische en een torische correctie verricht worden. In 73 ogen werd deze techniek toegepast met een maximale vervolgperiode van 12 maanden. De postoperatieve correctie binnen 1 dioptrie van emmetropie varieerde tussen 83.8% en 86.7%.

Met het hier gepresenteerde onderzoek werd getracht meer inzicht te verschaffen in de veiligheid en effectiviteit van de klinische toepassingen van de negatieve iris claw lens ter correctie van hoge myopie en van de excimer laser. Om aan dit onderzoek een uiteindelijke conclusie te kunnen verbinden zullen deze patiënten nog een aantal jaren vervolgd moeten worden. De korte termijn resultaten laten een bevredigend optisch resultaat zien, maar de veiligheid van de technieken zal in de loop der jaren moeten blijken.

DANKWOORD

Dit proefschrift zou niet tot stand zijn gekomen zonder de hulp en ondersteuning van velen. Mijn dankbaarheid gaat dan ook uit naar allen die op enigerlei wijze betrokken zijn geweest bij mijn onderzoek.
In de eerste plaats wil ik Prof. Dr G. van Rij bedanken voor zijn zorgvuldige en kritische analyse van de manuscripten van dit proefschrift. Als begeleider van mijn promotieonderzoek kon ik altijd een beroep op hem doen en heb daar dankbaar gebruik van gemaakt. Onze wekelijkse besprekingen zorgden ervoor dat ik altijd weer met frisse moed het onderzoek voortzette.
Prof. Dr J.G.F. Worst wil ik bedanken voor de talloze keren dat ik met hem mee mocht kijken tijdens het implanteren van de negatieve iris claw lens. Het was een genoegen hem bezig te zien in de operatiekamer en ik heb met veel plezier met hem samengewerkt.
I would like to thank Prof. Dr. med. D. Dausch, who gave me the opportunity to write with him on several aspects of the excimer laser. It was always a pleasure to spend time at his clinic in Amberg and I appreciated his and his wife's great hospitality.
Prof. Dr J.W.F. Beks, Prof. Dr A.F. Deutman en Prof. Dr W.F. Treffers dank ik voor de bereidheid zitting te nemen in de promotiecommissie en voor het beoordelen van het manuscript.
Helaas heeft Jaap Siertsema de voltooiing van dit proefschrift niet meer mee mogen maken. Jaap overleed op 4 september 1994. Als fotograaf van de afdeling heeft hij veel bijgedragen aan de beeldbewerkende ondersteuning van mijn onderzoek. Zonder zijn hulp en medewerking had ik nooit de endotheelfotografie op deze wijze kunnen uitvoeren. Winy Biewenga en José Eisses wil ik bedanken voor hun inzet om het endotheelonderzoek na het overlijden van Jaap draaiende te houden.
Er is bijna niemand van de vakgroep die niet direct of indirect betrokken is geweest bij mijn onderzoek. Er zijn een aantal medewerkers die ik met name wil danken:
Fenna Fonck-Pot, Ella Oosterhuis en Wim Berghuis, voor het oplossen van de (financieel-) administratieve beslommeringen; Henry van den Brom voor het bijbrengen van de strooilichtmeting, tijdens zijn promotie heb ik als één van zijn paranimfen tevens een soort generale repetitie gehad; Albert Damhof voor het oplossen van alle problemen op het gebied van de informatica; Aart Kooijman voor zijn meetkundige adviezen. Alle andere medewerkers en arts-assistenten bedankt voor de samenwerking en voor jullie tolerantie.
Mevr. A.E.D. van Rij-de Jong ben ik erkentelijk voor de tijd die zij heeft besteed om het Engels te corrigeren en Albert Breekveldt dank ik voor het leesbaar maken van het Nederlands.

Tot slot wil ik mijn ouders bedanken, voor de warme belangstelling en steun tijdens mijn studie en promotie.

Curriculum Vitae

The author of this thesis was born on December 16th 1963, in Budapest, Hungary. After receiving secundary education at the Huygens Lyceum, Voorburg, the Netherlands; the Lycee International, St. Germain-en-Laye, France; and the Lycee Francais Van Gogh, The Hague; she received her French Baccalaureat in July 1982.

Medical education was attended at the Free University in Amsterdam (1982-1988) and the University of Amsterdam(1989-1991), where she did her general internship. During her medical studies she participated in clinical research projects at the Morse Laser Laboratory, Harvard Medical School, Boston, U.S.A. (dr. C.A. Puliafito) and at the department of Ophtalmology of the University of Utrecht (dr. O.P. van Bijsterveld).

After receiving her medical degree, she worked as a research fellow at the department of Ophthalmology of the University Hospital in Groningen between 1991 and 1994 under guidance of Prof. G. van Rij. She enrolled in the residency program at the same institute in September 1994.