Contact lens wear and its complications
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CHAPTER I

INTRODUCTION
In 1888, Fick, Müller and Kalt were the first to describe contact lenses (CLs), made of blown glass which were placed on the eyes for visual correction (1). Nowadays, a hundred and ten years after the first description, CLs are used by approximately 20% of all individuals who need vision correction (2,3). In the past decade, the number of CL wearers (26.7 million in the USA in 1994 and 1.7 million in the UK in 1988) has grown steadily (4,5).

It has been estimated that ninety-seven percent of the CL wearers use lenses for refractive purposes as an alternative to spectacles (cosmetic CL wearers). The remainder wear their lenses for medical reasons or for the correction of aphakia (6). A rare CL use is to cover a blinded or scarred eye with a coloured lens (prosthetic lens). CL wearers in this thesis are referred to as cosmetic CL users, unless otherwise specified.

**Terminology of CLs**

**Lens type**

CLs can be classified by the lens material, wearing pattern, replacement regimen and gas permeability. The lens material is either hard (rigid) or soft (flexible, hydrogel). Hard CLs are polymethylmethacrylate (PMMA) or rigid gas-permeable (RGP) lenses. Because a PMMA lens does not transmit gas (O₂ and CO₂) through the lens, it has been superseded by RGP lenses, at least in the Netherlands. RGP lenses have been made of various materials, including silicone (or compounds of it), cellulose acetylbutyrate and methylmethacrylate. Since these lens materials are gas permeable, they are able to maintain corneal physiology and minimize corneal hypoxia. The material used to manufacture soft CLs is generally hydroxyethylmethacrylate (HEMA) or a derivative of this polymer such as vinylpyrrolidone. Soft CLs are further subdivided according to the classification of the Food and Drug Administration (FDA) of the USA into 4 groups, dependent on the amount of water content (% of the total weight of the CL) and the surface charge (ionic or nonionic) of the polymer.

**Wearing and replacement schedule**

Lens wearing pattern can either be daily-wear, extended-wear or flexible wear. The first is defined as lens wear less than 24 hours per day and the
second as continuous wear for a minimum of 24 hours (overnight wear), occurring at least once per week. In 1981, the FDA approved extended-wear CL use for up to 30 days of continuous wear. In 1989, this approval was shortened to 7 days and this recommendation (continuous wear for 7 days and 6 nights) is expected to be given by the lens fitters to their purchasers. Flexible wear is not strictly defined. It can refer to occasional overnight wear of daily-wear lens users or to lenses which may be used for either daily or extended-wear as required.

CLs can be replaced within 4 weeks, often before 14 days (disposable) or after more than 4 weeks (conventional lenses) of usage. Daily disposable lenses refer to lenses worn just for 1 day before disposal. Reusable implies that lenses are reworn after cleaning and disinfection. In the USA, disposable lenses can also be defined as lenses limited to one-time use without removal for lens hygiene or reinsertion. Any lens reused (after cleaning) and regularly replaced by a new lens (e.g. 1 or 2 weekly) is a frequent-replacement lens. This relatively new term is (if replacement occurs within 4 weeks) the same as the definition ‘disposable’, used in Europe. Thus, there are many kinds of disposal schedules, such as a 1 day disposal regimen (daily or 1 day disposable lenses) or 1 or 2 weekly disposable lenses. The year in which the specific lens type was introduced, is as follows: PMMA in 1950; soft CLs in 1968; RGP in the mid 1970s; extended-wear soft CLs in 1979; disposable extended-wear soft CLs in 1987 and daily disposable daily-wear soft CLs (1 day wear only) in 1995.

**Corneal physiology and gas permeability**

The thickness and transparency of the cornea is maintained by an active process of dehydration carried out by the epithelium and endothelium. Using an in vitro study, Beekhuis et al showed that 15% of the water that leaves the stroma towards the tears is removed by a chloride-dependent epithelial pump mechanism (7). The cornea extracts its respiratory oxygen from the atmosphere, which is dissolved in the tear film. An aerobic metabolism is necessary for the cornea to preserve its transparent and dehydrated state. CLs act as a barrier to oxygenation by obstructing the gas transmission and by restricting the tear exchange under the lens. Corneal hypoxia initiates anaerobic metabolism. It is now believed that stromal edema and endothelial changes associated with low oxygen permeable CL wear, are caused by stromal acidosis due to the accumulation of lactic acid and CO$_2$ under the lens (8-10). The unobstructed transfer of O$_2$ and CO$_2$ through the CL is of utmost importance in maintaining the normal corneal physiology.

The amount of gas transmission (oxygen) across a given CL is related to
the Dk (gas permeability constant), whereby D is the diffusion coefficient for oxygen movement in the lens material and k is the solubility coefficient of oxygen in the material. Despite of the rapid technological development of the hydrogel CLs, the rate of gas permeability of the new generation soft CLs is far lower than that of RGP lenses. Increased oxygen transfer can be achieved by using high Dk CLs, and also by reducing the lens thickness (L). The ratio of these two properties (Dk/L), termed as oxygen transmissibility, is a better indicator for gas diffusion through the lens. Since the thickness of a CL varies at different positions, the total oxygen that passes through the entire lens and reaches the cornea in vivo, is clinically more important. This measurement is known as equivalent oxygen percentage (EOP), which is expressed as a percentage of the concentration of oxygen in the atmosphere. A given CL that transfers all the oxygen available in the atmosphere (approximately 20% O2) would have an EOP of 20%. The EOP of the currently-marketed soft and RGP CLs ranges from 4% to 14%, and from 6% to 19%, respectively. Thus, low Dk disposable reusable daily-wear soft CLs means that these soft CLs (hydrogels) with a low rate of oxygen permeability should not be worn overnight, expected to be cleaned daily, at least reinserted one time and discarded within 4 weeks.

Prevalence of CL use

Estimates of the number of individuals wearing the specific lens type (prevalence) are generally based on consumer surveys (table 1). Since these market surveys conducted in various countries do not run parallel, and may use different methods and definitions, the data have to be compared with appropriate caution. However, they give a good impression and indicate that the percentage of RGP lens users is the highest in the Netherlands compared with the USA and Sweden, 46.6% versus 10% and 5.2% respectively. It is notable that the percentage of extended-wear in the USA is substantially higher than the two European countries, 25% versus 2.3% and 1.2%. A trend in rising number of disposable/frequent replacement lenses has been shown in these three countries.

CL-induced diseases

Although CLs offer certain visual and cosmetic advantages over spectacles as well as their usefulness in sporting activities, their use is associated with a spectrum of adverse effects. These complications can be classified as metabolic disorders (corneal neovascularisation, stromal edema and endothelial changes), trauma (corneal abrasion), toxic and allergic disorders (toxic keratopathy, giant papillary conjunctivitis), nonmicrobial
Table 1: Prevalence of CL use

<table>
<thead>
<tr>
<th>Distribution of CL wearers</th>
<th>USA</th>
<th>Sweden</th>
<th>The Netherlands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of CL wearers</td>
<td>26.7x10^6</td>
<td>0.44x10^6</td>
<td>1.4x10^6</td>
</tr>
<tr>
<td>Of the total population (%)</td>
<td>9</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Daily-wear CL wearers (%)</td>
<td>75</td>
<td>97.7</td>
<td>98.3</td>
</tr>
<tr>
<td>Extended-wear CL wearers (%)</td>
<td>25</td>
<td>2.3</td>
<td>1.7</td>
</tr>
<tr>
<td>RGP CL wearers (%)</td>
<td>10</td>
<td>5.2</td>
<td>46.6</td>
</tr>
<tr>
<td>Soft CL wearers (%)</td>
<td>89</td>
<td>94.8</td>
<td>53.4</td>
</tr>
<tr>
<td>PMMA CL wearers (%)</td>
<td>1</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Disposable CL wearers (%)</td>
<td>8*</td>
<td>38.9*</td>
<td>17.2*</td>
</tr>
</tbody>
</table>

Reference: USA (11,12), Sweden (13) and the Netherlands (14)

* In the USA, 75% of new fittings are with disposable or frequent replacement CLs, indicates an increasing number of wearers using this disposal regimen (15).

* CL replacement within 4 weeks.

In the Netherlands, virtually all extended-wear users wear disposable soft CLs.

keratitis (sterile corneal infiltrates) and microbial keratitis (16). Most of the ocular changes with the exception of endothelial changes and microbial keratitis, are reversible and recover after discontinuing CL wear. Endothelial morphological changes caused by CL wear can be transient (endothelial blebs), which resolve rapidly after lens discontinuation. Endothelial polymegathism (a variation in cell size) and pleomorphism (a variation in cell shape) associated with long-term low Dk CL wear, are probably permanent, although cases have been described in which marked recovery was observed (17). The functional consequences of these changes are still obscure. Recently, an in vivo corneal stress test showed that the deswelling of the cornea was significantly lower in CL wearers as compared to age-matched non-CL wearing controls (18). This study also demonstrated a downward trend (although statistically not significant) between the degree of endothelial morphological changes, and corneal hydration control. This finding suggests a possible relationship between the increased polymegathism and pleomorphism, and the deterioration of corneal function, although other as yet unknown factors may also be responsible for corneal hydration control. Rao et al demonstrated that corneal edema following intraocular lens implantation was associated with increased corneal polymegathism (19). Whether CL wearers with polymegathism are predisposed to develop endothelial decompensation and corneal edema after intraocular surgery is unknown.

**CL-associated keratitis**

Microbial ulcerative keratitis is the most serious complication of CL wear (20). This disorder is characterized by a defect of the corneal epithelium.
Chapter I

(ulceration) with an underlying stromal infiltrate, which may result in permanent visual loss from corneal scarring or perforation. In contact lens wearers this inflammatory process is presumed to be microbial in origin, mostly caused by bacteria and rarely by fungi and acanthamoebae (21). The diagnosis is made on clinical findings, and in 30-60% of the cases, no organism can be isolated (21-23). Although the microbiological examinations have a moderate sensitivity, *Pseudomonas aeruginosa* is the most frequent pathogen isolated from the culture-positive ulcers (21-23). *Pseudomonas* keratitis is rapidly progressive, is difficult to treat, and is associated with poor visual outcome (23,24). On the other hand, noninfectious keratitis can also occur in contact lens wearers. This sterile keratitis may be caused by metabolic/toxic reactions to preservatives in CL solutions or a hypersensitivity reaction to staphylococcal antigens or disinfectants (25,26). It is of utmost concern to distinguish microbial from nonmicrobial keratitis since the first demands an immediate and effective treatment regimen after performing a microbiological workup. Because of the importance of early treatment of corneal ulcers, it is safer to overtreat some suspicious infiltrates as microbial keratitis awaiting the results of microbiological examinations rather than to risk delaying appropriate treatment (25). All infiltrates suspected to be microbial in origin, should be treated as infected until proven otherwise. Broad-spectrum antibiotics should be initiated. Modifications in this initial therapy are based on the clinical response of the lesion and the identity of the organism and its in vitro sensitivities to a panel of antibiotics (27).

Compared with microbial keratitis, sterile keratitis is associated with minimal pain and minimal anterior chamber reaction, absence of discharge, and epithelial staining limited to superficial punctate keratitis (25). These aseptic infiltrates resolve spontaneously without ocular consequences after discontinuing CL wear.

**Incidence of CL-associated microbial keratitis**

Before the widespread use of CLs, the predisposing factors for ulcerative keratitis were ocular trauma and ocular surface diseases (28). In the past two decades, reports of CL-associated microbial keratitis have increased dramatically, paralleling the rising popularity of CL use. In light of this sight-threatening complication and a very large population at risk, contact lens-associated microbial keratitis becomes an important issue to public health. A single centre case-control study performed in the UK (29) and a retrospective incidence cohort study conducted in the USA (28) have shown that CL wear is now the most common cause of (responsible for 65% and 52%, respectively), and has the highest relative risk (29) for all cases of microbial keratitis. Since the prevalence of CL
use was unknown in these studies, the incidence rates for CL-associated microbial keratitis (the actual risk of developing microbial keratitis to the individual CL wearer over a defined length of time) could not be calculated. A cohort study is normally used to estimate the incidence (ratio of number of all new cases and total number at risk) of a disease. However, this design is inappropriate for assessing a rare disorder, such as microbial keratitis, because the study population has to be too large to provide useful data for statistical analysis (30). This problem can be overcome by identifying all new cases of keratitis diagnosed over a defined period within a demarcated study area (the numerator). The prevalence of CL use (the denominator) can be obtained by sampling the population using a telephone survey. Using these sampling techniques, two incidence studies estimating the magnitude of CL-related microbial keratitis have been carried out in the USA (31) and Sweden (13). In the latter study, the prevalence of lens use was estimated by counting of CL wearers by the lens fitter rather than by population telephone survey. The annual incidence rates for this disease differed in these countries (table 2). Although there are differences in the methods and the results, the common finding in these two studies is the excessive risk of keratitis in extended-wear soft CL users.

To assess the importance of CL-induced microbial keratitis to public health, the ocular morbidity and the health care costs of this disorder have to be elucidated. Despite numerous case series (20,23), describing the morbidity due to keratitis in CL users, there have been no population-based investigations to estimate the morbidity and the costs related to this disorder. Cases included in earlier studies were often hospital-based or referred patients with severe fulminating keratitis in whom the initial treatments failed. The clinical course of these selected patients does not represent that of patients with primary community-acquired corneal infection. Consequently, the morbidity and the medical care costs related to CL-associated microbial keratitis may be different in these two groups. Since the publication of the incidence data of the USA study in 1989 (31), many efforts have been taken to minimize the risk of CL-related microbial keratitis, including reducing the maximal number of consecutive wearing days (from 30 to 7) in extended-wear, improvement in CL materials and in lens-care products and, the introduction of new wearing strategies (disposable CLs). It is not known whether these measures have any

Table 2: Annual incidence of microbial keratitis per 10,000 cosmetic CL wearers

<table>
<thead>
<tr>
<th>Countries</th>
<th>Daily-wear RGP</th>
<th>Daily-wear soft</th>
<th>Extended-wear soft</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>4.0</td>
<td>4.1</td>
<td>20.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.5</td>
<td>2.2</td>
<td>13.3</td>
</tr>
</tbody>
</table>
effects on the incidence rates of this disease. Because of the public health impact, data on the long-term clinical outcome and the related social financial burden of CL-associated microbial keratitis are most desired.

**Pathogenesis of CL-associated microbial keratitis**

Since *P. aeruginosa* is the primary cause of CL-induced keratitis, this bacterium is extensively used in experimental models to study the mechanisms responsible for this disease. The pathophysiology of CL-associated microbial keratitis is thought to be multifactorial in origin. The risk factors include extended-wear (32), lens deposits (33), bacterial contamination of CL care systems and poor patient compliance with the recommendations of lens hygiene (34-36).

The first step of an infectious process is the adherence of bacteria to the target tissue. It is known that *P. aeruginosa* cannot adhere and invade intact corneal epithelium (37). An intact epithelium may protect CL wearers from developing *P. aeruginosa* keratitis since this pathogen is ubiquitously present in our environment and has been isolated from care systems in some asymptomatic CL users (36). Microbial keratitis rarely occurs in healthy eyes (24). However, this pathogen can rapidly attach to the damaged epithelial cells and penetrate the underlying layers (37). Thus, the minimal requirements for infection to occur are trauma to the corneal epithelium and the presence of pathogenic microorganisms. Clinical studies clearly show a strong association between overnight wear and excessive risk of microbial keratitis which is mostly (up to 75%) caused by *P. aeruginosa* (23).

**Extended-wear and *P. aeruginosa***

What is the relationship between extended-wear and *P. aeruginosa* infection?

First, extended-wear induces substantial suppression of epithelial metabolism, and leads to higher corneal hypoxia resulting in damage of the epithelium (38) demonstrated by in vivo tandem scanning confocal microscopy (39). Second, all well-designed case-control studies (29,32,40) demonstrate that the principal risk factor for microbial keratitis is overnight wear of soft CLs, with the risk increasing consistently and incrementally with the increase in overnight wear (32). For the users of extended-wear lenses, every consecutive day of lens use before cleaning is estimated to increase the risk by at least 5 percent (32). Finally, an in vitro study has shown that *P. aeruginosa* adherence to superficial human corneal epithelial cells, is enhanced in extended-wear soft CL users compared to nonlens wearers (41). An in vivo animal model shows that
lenses with lower oxygen transmissibility cause more epithelial damage after overnight lens wear than do lenses with higher oxygen transmissibility. Furthermore, the binding of *P. aeruginosa* to the cornea correlates with the oxygen transmissibility; the lower the oxygen transmissibility of the CL, the higher the attachment of *P. aeruginosa* to the cornea (39). In summary, the extent of hypoxic damage of the epithelium determines the quantity of *P. aeruginosa* adherence to the cornea.

The infectious process involves a sequence of events that begins with bacterial attachment to the host. Bacterial adherence to the host tissue involves specific interaction between an adhesin or ligand of the bacterium and its receptor on the target cell. Various corneal receptors for *P. aeruginosa* have been proposed, including glycoproteins (sialic acid, D-mannose), alpha-D-galactopyranoside and gangliotetraosyl-ceramide (42-44). Recently, an experimental study reported that the lipopolysaccharide outer core of *P. aeruginosa* is a ligand for this microorganism leading to specific binding and invasion into corneal epithelial cells (45). The increased adherence to corneal epithelial cells seen in extended-wear users might be caused by a rise of the number of receptors on the cell surface or/and a decrease of factors that normally prevent bacterial attachment. Studies suggesting a relationship between the alterations of receptors and the increased bacterial adherence include: extended-wear CLs induce changes in carbohydrates on the corneal surface (46), and increased *P. aeruginosa* adherence to the corneas after overnight lens wear is associated with enhancement of the expression of the putative glycoprotein bacterial receptors on the epithelial cells (47). On the other hand, the fact that *P. aeruginosa* does not adhere well to the intact cornea but can bind to corneal epithelial cells in vitro, suggests that there may be some inhibitory factor(s) that prevent adherence in vivo. (41,48). Putative factors are: fibronectin (49), and innate and adaptive immune responses in the tear film (secretory immunoglobulin A[s-IgA], mucin, lysozyme and lactoferrin) (50,51). Until now, little is known about the role of the mucosal immune response in the development of CL-associated microbial keratitis. In mucosal tissues, s-IgA has been shown to specifically inhibit the adherence of certain bacteria to epithelial cells (52). Experimental *Pseudomonas* keratitis studies demonstrate that the activation of the local ocular immune response provides significant protection against corneal damage (53). Recently, inhibition of *P. aeruginosa* adherence to the corneal surface by ocular mucin, human tears (54), and s-IgA (55) has been found in an animal model. It is thought that antiadherence factors (s-IgA) in the tear film bind to this bacterium, prevent the adherence to corneal epithelium by the formation of a s-IgA-
bacterium complex, which is eventually eliminated by tear flow (56). We hypothesized that the decrease of specific anti-\textit{P. aeruginosa} IgA in tears may contribute to the establishment of \textit{P. aeruginosa} keratitis.

\textbf{Lens deposits and microbial keratitis}

Another risk factor for \textit{P. aeruginosa}-induced keratitis in CL users is the presence of lens deposits. The main theory is that deposit formation provides receptor sites for bacteria for their adherence to the lens surface which then acts as a reservoir of microorganisms, that may initiate keratitis if the corneal epithelium is compromised (33,57). The attachment of \textit{P. aeruginosa} to lens deposits might be mediated by ligand and receptor interaction, the same mechanisms as the binding of this microorganism to the corneal epithelium. Sialic acid, a moiety of glycoproteins of tear mucins may be the receptor for \textit{P. aeruginosa} (42,43). This theory is controversial because many studies are contradictory. Studies supporting this hypothesis are: the attachment of \textit{P. aeruginosa} to mucin-coated CLs is significantly greater than CLs coated with saline or human serum albumin (57). A positive relationship has been found between the amount of deposits on patient-worn CLs and an increased adherence of \textit{P. aeruginosa} per lens (58). In an animal model, mucin-coated CLs which were contaminated with \textit{P. aeruginosa} produced more infections than did \textit{P. aeruginosa}-contaminated lenses without mucin coating (33).

In contrast, \textit{P. aeruginosa} can actively attach to new, unworn CLs (59,60). Unexpectedly, worn CLs significantly decrease \textit{P. aeruginosa} adherence compared with new, unworn lenses of the same type (61,62). Using an animal model, no difference in the rate of corneal infection has been found between new lenses inoculated with \textit{P. aeruginosa} versus worn lenses contaminated with this bacterium (63).

In conclusion, \textit{P. aeruginosa} adheres significantly both to new, uncoated CLs and to worn, coated CLs. This finding implies that CL wear is structurally inherent with an increased risk of infectious keratitis. Yet, the role of lens deposits in the development of microbial keratitis is unclear. The conflicting results may be explained by differences in in vitro or in vivo coating of CLs with (constituents of) tears, variation of interindividual tears and variations in the bacterial strains, and the physical characteristics of the CLs such as water content, hydrophobicity and surface charge. Assuming that lens deposits are associated with microbial keratitis (also with giant papillary conjunctivitis), these complications might be reduced by the introduction of disposable, non-reusable extended-wear CLs. During the relative short wearing period (1-2 weeks) extensive deposit build-up will possibly not occur. Theoretically, these lenses should
reduce the risk of microbial keratitis even further, because the additional risk attributed to bacterial contamination of the CL care systems, improper lens handling techniques and noncompliance of lens hygiene would be minimised.

**Therapeutic use of CLs**

Fortunately, CLs are safe for the majority of CL users and offer clearly visual, sporting and cosmetic advantages over spectacles. Besides the rising popularity of CLs for cosmetic use in the past decade, there is also an increasing interest in the therapeutic application of CLs. The medical indications for CLs are: aphakia (severe refractive error), irregular corneal astigmatism (e.g. keratoconus), ocular surface disorders (recurrent erosion syndrome, persistent epithelial defects, filamentary keratitis), dry eye states (keratitis sicca, pemphigoid), traumatic and atraumatic corneal diseases (corneal perforation, Mooren’s ulcer, bullous keratopathy), postoperative adjuncts or complications (band keratopathy, keratoplasty, chemical corneal burn, leakage of filtration bleb), drug delivery (such as a vehicle for delivery of antibiotics, still in experimental phase) and miscellaneous (amblyopia treatment, painted iris for cosmetic purposes or photophobia in aniridia) (64). Recently, successful treatment of complications after trabeculectomy and the treatment of chemical burn-induced symblepharon with a megasoft bandage lens have been reported (65,66). Furthermore, promising results have been reported in the treatment of dry-eye syndrome using high gas-permeable scleral lenses (67). Although bandage soft CLs were effective in decreasing pain after excimer photorefractive keratectomy, their use (as in all cases of extended-wear) can be complicated by microbial keratitis (68).

Aphakia is preferably corrected by RGP lenses because they avoid the limitations created by spectacle-corrected aphakia, such as limited field of view, ring scotoma, magnification and altered depth perception. Soft CLs can also be used for aphakia correction but their use is hampered by the limited capacity to correct severe corneal astigmatism and by their low gas transmissibility due to the thickness of these lenses.

Keratoconus is a well-known corneal disease. In the past, the patients have been fitted with non-gas permeable spherical lenses. The use of these lenses is impeded by both hypoxic and mechanical complications. In this thesis we reported our experience with the fitting of keratoconus with a relatively new lens design and lens materials.

**Keratoconus and CLs**

Keratoconus is a noninflammatory progressive conical deformity of the central or paracentral cornea in which there is bulging and thinning of
these areas with relatively normal curvature in the peripheral cornea. It is often bilateral, but the severity of the involvement can be asymmetrical (69).

In the mildest cases, spectacles can be helpful to correct refractive errors. However, if the condition progresses, the increasing irregular astigmatism can not be adequately corrected by eye glasses. Rigid CLs then become the first choice of treatment. These lenses are able to neutralize the moderate corneal irregular astigmatism, and significantly improve the visual acuity.

Before the introduction of RGP lenses, spherical PMMA lenses were fitted in keratoconus patients with good optical results. However, spherical lenses did not align well with the elliptical conic cornea, resulting in mechanical trauma and scarring at the apex. Lens loss often occurred due to poor fit. More important, this material does not transmit gas through the lens, leading to corneal hypoxia, discomfort and short wearing time. The geometrical problem and the non-gas permeability of PMMA lenses could theoretically be overcome by the development of high Dk, aspherical RGP lenses.

CL fitting in keratoconus is a challenge to the CL practitioners since there are wide range of keratoconic topographies. Because the fitting process is often time-consuming, the development of a fitting technique that shortens the trial-and-error procedure, would be a relief for both the patients and the lens fitters.

1.2 AIMS AND STRUCTURE OF THE THESIS

The primary objectives of this thesis were to investigate the epidemiology of CL-associated microbial keratitis in the Netherlands, and to study the pathogenesis of this disorder.

The prospective epidemiological study described in chapter 2 aimed to answer the following questions:

1. What are the incidence rates for microbial keratitis among CL users in the Netherlands?
2. What is the long-term ocular morbidity related to microbial keratitis in CL users?
3. What are the actual health care costs associated with CL-induced microbial keratitis?

The obtained incidence data were compared with those reported in the well-designed USA study, which was performed in 1987 (31). We wondered whether the continuous laboratory progress in the CL polymers,
the advance of CL care systems, the introduction of a new wearing strategy (disposable lenses), the awareness among physicians of the risk factors, the shortened wearing days of extended-wear, had any effect on the incidence of microbial keratitis in CL users.

To assess the importance of CL-associated microbial keratitis to the public health, the incidence data are best viewed in the context of the morbidity related to this disease.

To gain some insight into the financial social burden of CL-associated microbial keratitis, a cost-of-illness study was conducted (70). The results of this study might also be used as a first step towards cost-effectiveness analyses, whereby the disease costs might serve as a reference point for the analyses. The morbidity and the cost-of-illness study are presented in chapter 2.

With regard to the pathogenesis of CL-associated microbial keratitis, we tested two hypotheses. First, a decrease of specific s-IgA response in tears may contribute to the development of microbial keratitis in CL wearers. Because the presence of specific anti-\textit{P. aeruginosa} IgA in tears of CL wearers had not been investigated, we determined the levels of the specific IgA antibodies against \textit{P. aeruginosa} in tears of various groups of CL users and non-CL wearers. The findings are described in chapter 3. This investigation may offer prospects for further studies which should provide more vigorous evidence for the role of a specific IgA immune response in the pathophysiology of CL-associated microbial keratitis.

The second theory tested in chapter 4, was as follows: the accumulation of tear proteins will not occur during the relative short wearing period of a disposable CL. The time kinetics of lens deposition is important because the expected decrease of the incidence of microbial keratitis rests on the concept that disposable CLs would be thrown away before deposit-related complications developed. In this chapter, we also reported an as yet unidentified tear protein deposited on disposable soft CLs.

In chapter 5, we tested the hypothesis that fitting keratoconus patients with sphero-elliptical lenses with a high oxygen transmeability, would improve the visual acuity and corneal physiology compared with the fitting of spherical low oxygen permeable CLs. We also assessed whether a computer-assisted fitting technique might be helpful in keratoconus patients. The results of this study opened a new perspective to investigate the feasibility of fitting scarred corneas with this lens type. The final chapter provides a general discussion including our view on the sale and possible distribution of CLs through discount houses and mail-order services.
47. Klotz SA, Misra RP, Butrus SI. Contact lens wear enhances adherence of Pseudomonas aeruginosa and binding of lectins to the cornea. Cornea 1990; 9: 266.