THE EPIDEMIOLOGY OF CONTACT LENS RELATED DISEASE IN USERS OF DISPOSABLE LENSES

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DECLARATION

Subject to the discretionary powers of the University Librarian, copies of parts of this thesis may be made for the purpose of personal study only.

ABSTRACT

A pilot study identified associations between keratitis and disposable soft contact lens (DSCL) wear (Matthews et al., 1992), and a large series of *Acanthamoeba* keratitis cases showed an increasing frequency in parallel with the growing popularity of these lenses (Bacon et al., 1993). A 12-month prospective case-control study was conducted to establish the relative risks (RR) of microbial keratitis, sterile keratitis and other types of contact lens (CL) complications amongst lens types and wear schedules currently available. A three-year retrospective case-control study was also performed, in order to evaluate lens type and other risk factors for *Acanthamoeba* keratitis (AK).

For both studies, CL wearers presenting as new casualty patients at Moorfields Eye Hospital during the study period completed a questionnaire detailing CL use and hygiene practices. AK cases identified retrospectively were sent a postal questionnaire. Lens-related disorders were classified according to pathogenesis, and patients attending with disorders unrelated to CL wear were used as controls. RR with 95% confidence interval (CI) and p values were calculated, and, for microbial, sterile and *Acanthamoeba* keratitis, multivariable analysis was performed. Daily wear (DW) and extended wear (EW) soft CLs were analysed separately, using conventional soft CL (SCL) as the referent.

In the prospective study there were 94 microbial keratitis cases, 174 sterile keratitis cases, 866 patients with other lens-related complications and 778 patients with disorders unrelated to lens wear. Multivariable analysis showed that, compared to conventional SCL worn with the same wear schedule, both DW and EW DSCL use carried an excess risk of microbial keratitis (RR: 3.51, 95% CI: 1.60-7.66, p=0.002; RR: 4.76, 95% CI: 1.52-14.87, p=0.007, respectively), and EW-DSCL use was also associated with an increased risk of sterile keratitis (RR: 3.53, 95% CI: 1.01-12.28, p=0.048) compared to conventional EW-SCL. Both DW and EW DSCL showed a reduced risk of toxic keratitis compared to DW-SCL (RR: 0.41, 95% CI: 0.18-0.82, p=0.009; RR: 0.14, 95% CI: 0.00-0.84, p=0.023, respectively). For the remaining disease categories there was no significant difference in risk between DSCL and conventional SCL, although small numbers limited statistical analysis. In the retrospective study, 31 AK cases and 240 controls were included in the multivarible analysis of risk factors amongst DW soft CL users. Although an excess risk of AK with DSCL was identified (RR: 3.82, 95% CI: 1.01-14.48, p=0.049), the predominant risk factors were the use of chlorine-based or omitted disinfection (RR: 14.63, 95% CI: 2.8-76, p=0.001; RR: 55.86, 95% CI: 10.0-302, p<0.001, respectively), which were significantly more common amongst DSCL wearers.

These studies show that DSCL are associated with increased risks of suppurative keratitis, including *Acanthamoeba* keratitis, and appear to have a limited protective effect against other types of acute lens-related disorders. Patient and practitioner factors, such as the use of these lenses as a panacea for previous CL complications, and the possibility of poor lens fitting standards as a result of the commercial pressure on practitioners to fit these lenses, may be contributing to these excess risks. It is likely, however, that properties of certain DSCL are partly responsible. Further research needs to be directed at the effects of their fitting characteristics, high level of manufacturing defects, interaction with tear proteins, and increased *in vivo* dehydration on the likelihood of CL-related corneal infection. A UK populattion based incidence study is needed to determine the absolute risk of microbial keratitis with CL wear modalities currently available. Such data would enable practitioners and patients to make informed decisions regarding choice of CL use. Meanwhile, patients should be advised to minimise the risk by employing optimal disinfection and case hygiene routines, and by restricting overnight use to exceptional situations.

KEY TO ABBREVIATIONS

+ve	(Culture) positive
-ve	(Culture) negative
A&E	Accident and Emergency
ACLM	Association of Contact Lens Manufacturers
AK	*Acanthamoeba* keratitis
ARE	(Contact lens related) `acute red eye'
B&L	Bausch and Lomb UK Ltd
BS	Back surface
BVP	Back vertex power
Chi sq.	Chi squared
CI	Confidence interval
CL	Contact lenses
CLPC	Contact lens induced papillary conjunctivitis
ct	Centre thickness
CTRL	Control
D	Dioptre
d.f.	Degrees of freedom
Dk	Oxygen transmissibility
DSCL	Disposable soft contact lens
DW	Daily-wear
DW-DSCL	Daily-wear disposable soft contact lens
DW-SCL	Daily-wear (conventional) soft contact lens
EOP	Equivalent oxygen percentage
EW	Extended-wear
EW-DSCL	Extended-wear disposable soft contact lens
EW-SCL	Extended-wear (conventional) soft contact lens
FDA	Food and Drug Administration (USA)
FS	Front surface
HEMA	2-hydroxyethylmethacrylate
LBPL	Lens-bound protein layer
MEH	Moorfields Eye Hospital
OEH	Oxford Eye Hospital
PBH	Pilkington Barnes-Hind Holdings Ltd
PRS	Planned replacement scheme
RR	Relative risk
SCL	(Conventional) soft contact lens
s.d.	Standard deviation
TD	Total diameter
WC	Water content

GLOSSARY OF EPIDEMIOLOGICAL TERMS USED IN THE THESIS

CASE-CONTROL STUDY:
A study in which individuals with a particular disease (cases) are compared with individuals free from the disease (controls) with respect to characteristics or past exposures thought to be relevant to the development of the disease
COHORT STUDY:
A study in which individuals with differing characteristics are selected, followed over time and compared in terms of their subsequent morbidity
INCIDENCE:
The proportion of a defined group developing a disease within a stated time period
PREVALENCE:
The proportion of a defined group having a disease at one point in time
(RELATIVE RISK: see page 49)

CHAPTER 1. INTRODUCTION

1.1 SUMMARY OF THE BACKGROUND AND AIMS OF THE THESIS

Soft contact lens (SCL) wear is widespread; in 1993 60 to 70% of the estimated 3 million contact lens (CL) wearers in the UK were using this lens type (ACLM, 1994). Ever since the introduction of SCL in the early 1970s, the comfort, flexible wearing schedules, ease of adaptation and simplicity of fitting with these lenses have made them an attractive choice for both practitioners and patients alike. SCL users, however, are at risk of developing complications particularly associated with this lens type: corneal hypoxia can lead to neovascularization and oedema (Holden *et al.*, 1986a; Holden *et al.*, 1985); some SCL care solutions (Morgan, 1979; Wilson *et al.*, 1981a), and bacteria, bacterial toxins or trapped cellular and metabolic debris (Phillips *et al.*, 1986; Josephson and Caffery, 1979; Mertz and Holden, 1981) can cause toxic or inflammatory reactions; and the rapid depositing of SCL with protein and other tear film constituents (Fowler and Allansmith, 1980) is thought to be play a major role in the development of inflammatory diseases such as CL-induced (`Giant') papillary conjunctivitis (Allansmith *et al.*, 1977). Furthermore, for reasons that are still unclear, SCL wearers have an increased likelihood of developing the most serious complication of CL wear: microbial keratitis (Dart *et al.*, 1991).

In 1981 the USA Food and Drug Administration (FDA) approved the first SCL designed for 30-day continuous wear. Following early uncontrolled clinical trials showing no excess of serious complications with these lenses (Stark and Martin, 1981; Lamer, 1983; Binder, 1983), they rapidly grew in popularity until an increasing number of case reports associated extended-wear (EW) SCL with an increased risk of microbial keratitis and less serious complications (Cavanagh, 1987; Schein *et al.*, 1986).

In 1987, in response to these concerns, the manufacturers introduced disposable soft contact lenses (DSCL). These lenses, originally designed for weekly (and initially, fortnightly) extended-wear use, were promoted as a safer, as well as more convenient

alternative to conventional EW-SCL wear; disposal prior to significant surface contamination was expected to reduce the risk of deposit-related complications, and it was thought that the minimizing of lens handling and the abandoning of solutions and storage cases would reduce the risk of both infective and toxic or allergic disorders. In practice, however, numerous subsequent reports of microbial keratitis with EW-DSCL (John, 1991) suggested that, as in the case of conventional extended-wear SCL, uncontrolled clinical trials using carefully selected well-monitored subjects (Donshik *et al.*, 1988; Gruber, 1988) had not provided a true measure of the risks or benefits with the lenses when used in the general population. Subsequently, daily-wear (DW) DSCL were introduced, but these, too, were soon reported in association with severe corneal infection (Efron *et al.*, 1991a; Woods and Woods, 1992) including *Acanthamoeba* keratitis (Sarwar *et al.*, 1992).

A 3 month pilot study conducted at Moorfields Eye Hospital (MEH) in early 1991 (Matthews *et al.*, 1992) identified the presentation of a disproportionate number of Accident and Emergency (A&E) cases with DSCL-related suppurative keratitis. Furthermore, a case series of 72 *Acanthamoeba* keratitis patients presenting to MEH between March 1984 and September 1992 (Bacon *et al.*, 1993) showed a marked increase in cases associated with the growing popularity of DSCL. This thesis describes the first large prospective case-control study comparing the risks of microbial keratitis and less serious acute complications with disposable as opposed to conventional SCL. The second part of the thesis describes a 3-year retrospective case-control study of the risk factors for SCL-related *Acanthamoeba* keratitis; the only previous case-control study of this disease was conducted before the introduction of DSCL (Stehr-Green *et al.*, 1987). For both studies, risks associated with the lens wear habits adopted by DSCL users were separated from the risk due to the lens type itself by the use of multivariable analysis.

1.2 ACUTE COMPLICATIONS OF SOFT LENS WEAR

A case-control study in which subjects are collected in a hospital A&E Department enables assessment of the risks of acute and sub-acute conditions only. This section briefly reviews the characteristics, aetiology and epidemiology of the main acute and sub-acute complications encountered amongst SCL wearers.

1.2.1 (i) Microbial Keratitis

Microbial keratitis is typically characterised by the rapid and progressive onset of pain, corneal suppuration associated with an overlying epithelial defect, hyperaemia, ciliary injection, discharge, and uveitis. It is the most serious complication of CL wear; unlike the majority of other complications it can progress after CL removal, and it has the potential to cause loss of vision due to corneal scarring, corneal perforation or spread of infection to surrounding ocular tissues.

Current laboratory techniques cannot reliably differentiate between microbial and non-infective (`sterile' or `aseptic') suppurative keratitis. It is well established that failure to isolate a pathogenic organism cannot be used to eliminate a microbial cause nor to confirm a non-infective one (Liesegang and Forster, 1980); positive corneal tissue cultures are only obtained in 20-54% of contact lens related cases (Schein *et al.*, 1989a; Galentine *et al.*, 1984; Alfonso *et al.*, 1986). Negative cultures from microbial lesions may occur when there is insufficient material available for culture; when mucous or necrotic material is sampled; when organisms proliferate in deeper corneal layers only, and are therefore not sampled by superficial scraping; and when there has been pre-treatment with antibiotics, reducing the viability of invading organisms. The use of clinical criteria incorporating the severity of signs and symptoms, as well as the size and location of lesions, has been recommended for distinguishing between microbial and `sterile' (non-infective) suppurative keratitis and is supported by epidemiological data (Stapleton *et al.*, 1993a).

Amongst culture-positive cases *Pseudomonas* is the predominant causative organism, other isolates including *S. aureus, S. epidermidis, Serratia* and *Acanthamoeba* (Wilhelmus, 1987). Bacteria causing keratitis in CL users may all be isolated from the ocular surface of normal individuals (Tomar *et al.*, 1986). Although several studies have shown no difference in the ocular flora of CL users compared with non CL-wearing controls (Rauschl and Rogers, 1978; Smolin, 1979; McBride, 1979), others have shown that contact lenses may introduce Gram negative bacteria from contaminated CL storage cases (Morgan, 1979). The contaminated contact lens case (Donzis *et al.*, 1987; Larkin *et al.*, 1990; Wilson *et al.*, 1990; Devonshire *et al.*, 1993) has often been implicated in the pathogenesis of keratitis (Wilson *et al.*, 1981b; Mayo *et al.*, 1986), although an association is not always present (Wilson *et al.*, 1981b; Dart, 1988a). The CL case may amplify the concentration of environmental bacteria, allowing a large inoculum to be presented to the eye by the contact lens.

Adherence of *P. aeruginosa* and *S. aureus* to contact lenses has been demonstrated (Dart and Badenoch, 1986; Duran *et al.*, 1987; Slusher *et al.*, 1987; Butrus *et al.*, 1987; Stapleton *et al.*, 1993b). Deposits on the surface of worn lenses have been shown to increase bacterial attachment *in vitro* (Aswad *et al.*, 1990; Butrus *et al.*, 1987; Butrus *et al.*, 1990), and, in a rabbit model, predisposed the eye to more severe corneal infection (DiGaetano *et al.*, 1986); other investigators, however, have shown no predictable relationship between bacterial adherence and tear film deposits on worn lenses (Dart and Badenoch, 1986; Miller *et al.*, 1988), and epidemiological studies have failed to establish an association between lens aging and keratitis (Schein *et al.*, 1989b; Dart *et al.*, 1991). The clinical relevance of the degree to which bacterial adherence to lenses of different chemical natures and states of deposition has not been shown; adherence merely increases retention of bacteria at the ocular surface by a few hours and will not result in an increase of their numbers unless colonisation of the lens occurs, with the development of a bacterial glycocalyx (Slusher *et al.*, 1987; Dart *et al.*, 1988b;

John *et al.*, 1989; Stapleton *et al.*, 1993b).

Models of keratitis have not resulted in infection in the absence of a corneal epithelial defect (DiGaetano *et al.*, 1986; Solomon *et al.*, 1994); susceptibility of the cornea due to mechanical (Klotz *et al.*, 1989) and, particularly, metabolic effects of CL wear (Lawin-Brussel *et al.*, 1990; Imayasu *et al.*, 1993; Solomon *et al.*, 1994) is important in the pathogenesis of CL-related microbial keratitis.

1.2.1 (ii) Epidemiology of Lens-Related Microbial Keratitis

Microbial keratitis used to be a complication associated with trauma or pre-existing ocular surface disease; CL wear, however, with its increasing popularity, has become the major predisposing factor, accounting for 65% of cases in a recent study (Dart *et al.*, 1991).

In response to concern regarding the apparent excess in cases of microbial keratitis with SCL, particularly when used for extended wear (Mondino *et al.*, 1986; Chalupa *et al.*, 1987; Wilhelmus, 1987), a population-based incidence survey of ulcerative keratitis was conducted in New England (USA) in 1988 (Poggio *et al.*, 1989). Selecting an area in which the likelihood of cross-border treatment was low, all new cases during the study period were identified by surveying all ophthalmologists in the area, and the number of CL wearers in the area was estimated by conducting a household telephone survey. Annual incidence estimates of 4.1:10,000 for DW-SCL and 20.9:10,000 for EW-SCL were established. Similar estimates (6.8:10,000 for rigid gas permeable CL, 5.2:10,000 for DW-SCL, 18.2:10,000 for EW-SCL) were derived from the pooled results of 48 consecutive pre-market approval studies on 22,739 CL wearers for the United States Food and Drug Administration (MacRae *et al.*, 1991), even though the involvement of closely monitored subects would be expected to reduce the risks. These studies, together with the case-control study by Schein *et al.* (1989b) described below, prompted the FDA to reduce the recommended maximum duration of continuous CL

wear to 7 days (Lippman, 1990).

Case-control studies have confirmed the excess risk with extended-wear: Schein *et al.* (1989b), comparing 86 cases with both hospital-based (attending with acute disorders unrelated to CL wear) and geographically matched population-based controls, showed a 10-15 times increased risk with extended wear of SCL; and at MEH Dart *et al.* (1991), comparing 60 cases with two groups of hospital-based controls (one group attending with a disorder other than microbial keratitis, and a subgroup presenting with acute disease unrelated to CL wear) found relative risks with 95% confidence intervals (CI) of 3.6 (1-14) for DW-SCL and 21 (7-60) for EW-SCL compared to rigid CL.

Multivariable analysis has enabled these studies to assess the contribution of other risk factors. In both studies, overnight use of SCL was the dominant risk factor and was shown to increase with the number of nights of continuous wear. Poor hygiene standards amongst DW patients carried a small but significant increased risk, but were not shown to have an effect amongst EW users. The excess risks associated with smoking, lower socioeconomic class and male gender found by Schein *et al.* (1989b) were thought to be related to poor hygiene compliance. Further analysis of the MEH-based study (Stapleton *et al.*, 1993a) showed hydrogen peroxide disinfection to have the greatest protective effect, with preserved chemical systems having a slight but not statistically significant increased risk: with hydrogen peroxide use as the referent, the relative risks (RR) associated with the use of chlorine-release and thermal disinfection systems, were 5.6 (1.02-31.0) and 5.74 (1.0-33.0) respectively. Infrequent use of any system was shown to increase the risk, although this was only significant for hydrogen peroxide (RR:17.46, 95% CI: 2.7-112.0) and chlorine-release (RR:16.38, 95% CI: 1.2-226.0). Failure to employ any disinfection increased the risk by 10.61 times (2.2-52.0).

In view of the introduction of frequent replacement and disposable lenses with the aim

of decreasing the risks of microbial keratitis and other complications, it is interesting to note that lens age was not a significant factor in either of these case-control sudies.

1.2.2 (i) *Acanthamoeba* Keratitis

Acanthamoeba produces some of the most severe cases of keratitis, and, if treatment is delayed, the infection can lead to serious complications such as ring ulcer, hypopyon, scleritis, glaucoma and cataract (Bacon *et al.*, 1993).

Although laboratory techniques may fail to identify *Acanthamoeba* from corneal tissue, particularly in early cases (Bacon *et al.*, 1993), *Acanthamoeba* keratitis can be diagnosed clinically by observation of characteristic features. In early disease these include disproportionate pain and the development, over days or weeks, of punctate epitheliopathy, pseudodendrites, focal and diffuse epithelial and subepithelial infiltrates, perineural infiltrates and limbitis (Moore *et al.*, 1986; Lindquist *et al.*, 1988a; Holland *et al.*, 1991; Bacon *et al.*, 1993); later presentations may show ring infiltrate, frank ulceration and hypopyon (Bacon *et al.*, 1993).

Acanthamoebae are ubiquitous free-living amoebae found in air, dust and, in particular, all kinds of water, including bathroom tap water (Seal *et al.*, 1992). Their ability to encyst under adverse environmental conditions makes them highly resistant to antimicrobial agents; current CL disinfection solutions vary greatly in their effectivity against *Acanthamoeba* (Seal and Hay, 1992), and amoebal contamination, associated with concomitant bacterial colonisation, has been shown to occur in the CL storage cases of 4-7% of asymptomatic CL wearers (Devonshire *et al.*, 1993; Larkin *et al.*, 1990). Adherence of *Acanthamoeba* to used (Lindquist *et al.*, 1988b) and unworn (John *et al.*, 1989; Kilvington, 1993) SCL has been demonstrated, and *in vitro* studies have demonstrated firm epithelial attachment mechanisms (Ubelaker *et al.*, 1991) and penetration of the intact cornea (Moore *et al.*, 1991).

1.2.2 (ii) Epidemiology of Lens-Related *Acanthamoeba* Keratitis

Acanthamoeba keratitis is a very rare disease; although incidence data is not available, the organism is implicated in less than 5% of lens-related microbial keratitis cases in most series (Schein *et al.*, 1989a; Cohen *et al.*, 1991; Stapleton, 1991). There is evidence, however, that the incidence of this disease has been increasing. Stehr-Green *et al.* (1989) estimated the numbers of cases in the USA by combining the results of a survey of members of a corneal specialist society with cases reported to the Centers for Disease Control. The number of cases rose gradually from 1981 to 1984, and then started to dramatically increase from 1985, with a total of over 200 cases having been identified by 1989. This pattern was paralleled by the marked increase in CL wear, particularly SCL wear, during this time; lens wear is associated with 85% of the cases (Stehr-Green *et al.*, 1989). In the UK, an 8 year 6 month study at MEH reported 72 cases, and showed a marked rise in the number of cases during 1991 and 1992 associated with the increasing penetrance of disposable lens wear (Bacon *et al.*, 1993). It has been suggested, however, that increased accuracy of diagnosis by ophthalmologists has contributed to the apparent dramatic rise in incidence; a review of histological specimens obtained before 1983 from the Wills Eye Hospital (Philadelphia, USA) showed that some early cases were missed (Cohen *et al.*, 1985).

The majority of cases have been associated with soft CL, reflecting the greater popularity of this CL type, but rigid and hybrid (soft-rigid combination) CLs have also been associated (Stehr-Green et al., 1989). Stehr-Green *et al.* (1987) in the USA carried out a case-control study of risk factors amongst 27 soft CL wearers and 81 controls matched by CL type, geographic location and CL practitioner. They identified that use of homemade saline, swimming while wearing lenses and irregular disinfection were significantly associated with *Acanthamoeba* keratitis.

1.2.3 i) Sterile Keratitis

CL-related sterile keratitis is a non-progressive form of suppurative keratitis variously ascribed to a delayed hypersensitivity response to thiomersal-preserved CL solutions (Josephson and Caffery, 1979; Mondino and Groden, 1980; Wilson *et al.*, 1981a), a response to tight fitting lenses (Josephson and Caffery, 1979; Zantos, 1984), and hypersensitivity to bacteria or bacterial toxins from the lids or lens case (Josepson and Caffery, 1979; Phillips *et al.*, 1986).

In the absence of laboratory techniques that can reliably differentiate between microbial and non-infective (`sterile' or `aseptic') suppurative keratitis, clinical diagnoses have to be made (Section 1.2.1(i)). Lens-related corneal infiltrates that are central, associated with progressive pain, discharge, epithelial staining or anterior chamber reaction suggest infection (Stein *et al.*, 1988). Sterile infiltrates are less commonly associated with these features, and are usually smaller (less than 1mm) and often multiple or arcuate (Bates *et al.*, 1989). Futhermore, unlike microbial keratitis, sterile keratitis is non-progressive, and despite occasional residual scarring is not associated with visual loss (Bates *et al.*, 1989).

1.2.3 (ii) Epidemiology of Lens-Related Sterile Keratitis

Due to the severity of the potential consequences of untreated microbial keratitis, equivocal cases tend to be classified and treated as infective; sterile keratitis is a diagnosis by exclusion, and its incidence is therefore probably underestimated. In a study conducted at MEH Accident and Emergency Department in 1988-1989, in which sterile keratitis was defined as self-limiting suppurative keratitis in which diagnostic corneal scraping and intensive antibiotic treatment were considered unnecessary according to the criteria described above, sterile keratitis (n=147) was 2.45 times more common than microbial keratitis (n=60) (Stapleton, 1991). Amongst EW CL users the incidence has been estimated at 1.5% per year (Grant *et al.*, 1987).

Stapleton's case-control study showed a significant excess of poor hygiene, contaminated CL storage cases and EW-SCL use amongst the cases (Bates *et al.*, 1989). Further analysis of this study was performed, using new casualty attenders with disorders unrelated to CL wear as controls and employing multivariable analysis (Stapleton *et al.* 1993a). Using rigid gas-permeable CL as referent, both DW-SCL and EW-SCL were associated with an increased risk of the disease, carrying relative risks (95% CI) of 2.31 (1.3-4.3) and 4.65 (2.2-9.9) respectively. Chlorine-release disinfection systems were shown to carry a 2.46 (1.0-6.0) times increased risk when compared to hydrogen peroxide systems, and infrequent disinfection increased the risk by a factor of four to ninefold, depending on the type of system. Other factors shown to significantly increase the risk were the use of aerosol as opposed to preserved saline, higher socioeconomic class, and age less than 24 years. As in the case of microbial keratitis, lens age was not found to be a significant factor.

1.2.4 Toxic and Hypersensitivity Disorders

SCL wearers are particularly prone to toxic and hypersensitivity disorders, due to the care solutions developed for these lenses, SCL fitting characteristics, and the nature of the lens material; analysis of the case-control study by Stapleton at al. (1992) showed that these disorders occurred 5.9 and 4.5 times more often amongst DW and EW SCL users, respectively, than amongst rigid CL users.

Toxic keratopathy, manifest as diffuse corneal punctate stain and conjunctival and/or ciliary injection accompanied by stinging pain, has been attributed to many SCL solution components, including chlorhexidine digluconate (Refojo, 1976; Coward *et al.*, 1984; Fonn, 1991), alkyl triethanol ammonium chloride (Morgan, 1979), and sorbic acid (Simmons *et al.*, 1988). Inadequate neutralisation of hydrogen peroxide (Morgan, 1979), residual enzyme from proteolytic cleaners (Davis, 1983), accidental use of rigid contact lens solutions containing benzalkonium chloride (Chapman *et al.*, 1990) or

application of inappropriate solutions such as surfactant cleaner to the eye will also result in toxic keratopathy in SCL wearers. Solution-related toxic keratopathy usually resolves with lens removal and refraining from lens wear for a few days.

The bacteriostatic mercurial compound thiomersal, used as a preservative in several SCL care solutions, produces potentially more severe inflammatory reactions. Adsorbed and slowly released by hydrogel CL, repeated application produces a local delayed hypersensitivity response (Mondino and Groden, 1980). Inflammatory reactions may include corneal subepithelial infiltrates and superior limbic neovascularization and opacity (Wilson-Holt and Dart, 1989; Wilson *et al.*, 1981a), and in rare cases, severe keratopathy and visual loss may result from permanent stromal opacification and/or corneal epithelial dysplasia (Wilson-Holt and Dart, 1989; Wright and Mackie, 1982; Kenyon and Tseng, 1989).

CL-related `Acute Red Eye' (ARE), an acute inflammatory reaction in which there is pain, limbal and bulbar injection, photophobia, lacrimation, and occasionally peripheral sterile infiltrates, is thought to be due to the toxic effects of trapped cellular and metabolic debris behind the lens (Mertz and Holden, 1981). It is a common and frequently recurrent event amongst EW-SCL patients; in one study it occurred in 27.5% of 400 patients using EW-SCL for up to 57 months (Lamer, 1983), and Sweeney *et al.* (1993) found second and third recurrence rates of 73% and 64% respectively amongst 49 ARE patients followed for up to 45 months. Regular lens replacement and optimal lens care procedures have been shown to reduce its incidence (Kotow *et al.*, 1987a). Chronic discomfort and reduced lens tolerance, in association with conjunctival hyperaemia, corneal staining and papillae or follicles may also occur in response to lens spoilation (Tripathi *et al.*, 1988).

The formation of enlarged upper tarsal conjunctival papillae, associated with hyperaemia, excess mucus, itching and progressive loss of CL tolerance has been termed

`Giant Papillary Conjunctivitis' (Allansmith *et al.*, 1977) or `CL-induced Papillary Conjunctivitis' (CLPC) (Kotow *et al.*, 1987a). There is evidence for the involvement of both delayed (Allansmith *et al.*, 1977) and immediate (Donshik and Ballow, 1983) hypersensitivity reactions to CL deposits (Ballow *et al.*, 1989), as well as a mechanical element (Reynolds, 1978; Greiner, 1988) in its aetiology.

From a large cohort study of 1528 conventional SCL wearers with regular scheduled visits to one of eight private CL clinics, a prevalence of 178.2 and 187.0 per 10,000 eyes was estimated for DW and EW SCL respectively (Poggio *et al.*, 1993a).

Enhanced surfactant cleaning efforts, use of unpreserved care solutions and lens replacement are often prescibed in the management of early cases (Farkas *et al.*, 1986; Grant *et al.*, 1987; Kotow *et al.*, 1987a; Lustine *et al.*, 1991). For more advanced cases a successful return to lens wear after temporarily refraining may often be achieved by refitting with a different lens design or polymer, thereby affecting the type and quantity of protein depositing on the patient's lenses (Donshik *et al.*, 1984). Severe cases may require anti-inflammatory agents, such as mast cell stabilizers, in conjunction with a new lens or during suspension of lens wear (Allansmith *et al.*, 1977; Donshik *et al.*, 1984; Lustine *et al.*, 1991).

Since CLPC is a chronic or sub-acute disorder, the study design employed in this thesis will be limited in its assessment of the relative risks of this disease with different lens wear modalities.

1.2.5 Metabolic Disorders

Acute epithelial necrosis (`overwear syndrome'), is characterised by delayed pain, lacrimation, photophobia, blurred vision due to corneal oedema, ciliary injection, and punctate epithelial erosions which may coalesce into an ulcer. It is thought to occur as a result of hypoxic stress, lactate accumulation and impaired carbon dioxide efflux

(Bonnano and Polse., 1987). Although occasionally occurring following moderate periods of lens wear, it is more frequently reported in association with extended wear (Binder, 1980). Lens tightening, due to dehydration, pH, temperature or osmolarity changes during overnight wear (Mertz and Holden, 1981), can produce a severe form of acute epithelial necrosis accompanied by limbal indentation (`tight lens syndrome'). In several studies of contact lens wearers attending hospital casualty departments acute epithelial necrosis has ranked as the most common presenting disorder (Genvert *et al.*, 1987; Hardman Lea *et al.*, 1990; Stapleton *et al.*, 1992). These conditions resolve with suspension of lens wear until corneal re-epithelialisation is complete, followed by revision of wear schedule advice, refitting with a higher Dk lens material or refitting with a more mobile lens.

Blurring and irritation caused by higher levels of stromal oedema, or brief episodes of pain and epiphora associated with microcystic epitheliopathy, may also prompt CL wearers to attend for emergency consultation (Stapleton *et al.*, 1992; Heaven and Hutchinson, 1993). Stromal oedema at a 5-6% level is accompanied by vertical striae due to fluid separation of collagen fibrils in the posterior stroma (Sarver *et al.*, 1980), and at 10-12% stromal folds may be seen (Holden *et al.*, 1983). Corneal oedema, a response to hypoxia, is related to lens transmissibility and average lens thickness over the central zone (Holden *et al.*, 1983) as well as duration of lens wear, individual patient response, baseline corneal thickness and lens base curve radius (Tomlinson *et al.*, 1981). Although vertical striae are common amongst extended wear patients on waking, they indicate an unacceptable physiological response if seen later in the day or amongst daily wear patients. Acute oedema resolves within hours.

Microcystic epitheliopathy is characterised by small epithelial inclusions, representing disorganized cell growth and accumulations of dead cellular material, which, on reaching and breaking through the epithelial surface, cause staining (Zantos and Holden, 1978). It is thought to be a delayed response to hypoxia (Holden *et al.*, 1985) although

prolonged mechanical pressure may also be a factor (Zantos, 1983). Although reported in daily wear patients (Ruben *et al.*, 1976), they are more commonly associated with extended wear (Zantos and Holden, 1978; Humphreys *et al.*, 1980; Zantos, 1983; Holden *et al.*, 1985; Grant *et al.*, 1987). Microcysts resolve on refitting with a higher Dk material and/or reducing wear time.

1.2.6 Mechanical and Other Disorders

Corneal and conjunctival abrasions due to foreign bodies under lenses, lens defects, lens deposits, poor lens fit or handling problems are amongst the most common acute lens-related complications, but are more frequently associated with rigid CL (Stapleton *et al.*, 1992).

1.3 PLANNED REPLACEMENT SCHEMES

1.3.1 The Introduction of Planned Replacement Schemes

In response to the concern regarding lens spoilation and associated complications, `planned' or `frequent' replacement schemes (PRS) were introduced. A PRS is an arrangement between the patient, practitioner and manufacturer for scheduled lens replacement at a predetermined frequency of between 1 to 12 months. The first PRS, the Fresh Lens Programme by Bausch and Lomb (Hampton, Middlesex, UK) was introduced in 1986. Subsequently, other companies have introduced their own schemes; by 1991 they were offered by 12 CL manufacturers in the UK (Ivins., 1991) and a survey of the prescribing trends of British Contact Lens Association members estimated that 23% of SCL users were on a scheme (Pearson, 1992). This may be an overestimate, however, due to the excess of CL specialists amongst respondents, and the likelihood of response bias. Currently there are no estimates for the penetrance of this mode of SCL use, but the increasing number of companies as well as optical practices offering such schemes suggest that it is becoming more commonplace (ACLM, 1994). With the subsequent introduction of disposable SCL, PRS is usually a term given to replacement cycles of 3 or 6 months (ACLM, 1994).

The theoretical advantages of PRS include improved lens hygiene; encouragement to use high water content SCL, since aging is less important when the lens is to be discarded more frequently; cheaper lens care, since enzymatic cleaning is thought to be unnecessary (Allen *et al.*, 1992); and a constant supply of spare lenses, possibly encouraging patients not to continue to wear damaged ones.

1.3.2 Clinical Performance of Planned Replacement Schemes

Studies of the benefits of PRS have been small-scale and have concentrated on the effects amongst extended-wear users. From multivariable analysis of a masked clinical trial of 20 unilateral EW-SCL wearers, Holden *et al.* (1987) showed that an increased

lens replacement rate, in conjunction with increased lens removal and use of thinner and more mobile SCL, reduced ocular effects of extended wear such as epithelial thinning, stromal thinning and microcystic epitheliopathy. Kotow *et al.* (1987b), however, were not able to show any reduction in the chronic corneal changes during extended wear. They conducted a masked trial in which 48 EW myopes with a lens replaced `as needed' in one eye and a lens replaced at a frequency of 1, 2, 4 or 12 weeks in the other were followed for 48 (+/-19) weeks. They showed a significant difference in the occurrence of ARE, with only one case amongst the lens-replaced eyes compared to 7 cases in the non-replaced lens wearing eyes, despite the absence of clinically significant differences in lens surface depositing. CLPC was the major cause of clinical failure in this study, but the incidence was 15% in both the replaced and non-relaced lens wearing eyes. The authors suggest that the aging non-replaced lens may have acted as a stimulant for development of CLPC in the contralateral eye, in keeping with the proposed delayed hypersensitivity component in the aetiogy of CLPC (Allansmith *et al.*, 1977). Bilateral lens replacement studies may be more appropriate for determining any difference in risk for this disorder, but, due to individual differences in susceptibility (Allansmith *et al.*, 1977) and history, careful selection of a suitable control group is required: Ames and Cameron (1989) found a significant reduction in symptoms and signs of CLPC amongst EW users with a history of ARE and/or CLPC on 3-monthly replacement as opposed to `need only' replacement followed for 9 months (n=80), but the control group was noted to have more subjects with grade 2 tarsal conjunctival changes at initial dispensing. Kaye *et al.* (1988), in a similar study with 72 routine EW-SCL patients, failed to show any significant difference in the incidence of CLPC or other specific EW-SCL related ocular disorders with 3-monthly lens replacement, although the *overall* occurrence of lens related complications was significantly reduced with this regime. In order to establish any significant difference in risk of CLPC with planned replacement a larger comparative cohort study with longer follow-up would be required.

1.4 CHARACTERISTICS OF DISPOSABLE LENSES

1.4.1 Definition of Disposable Lenses

The term `disposable' implies single use followed by disposal; disposable lenses (DSCL), however, are usually defined as lenses designed for regular replacement at a frequency of up to one month, even though continuous DSCL use in excess of 6 nights is not promoted (ACLM, 1994). Occasionally, monthly replacement CL are promoted as PRS instead (David Thomas Contact Lenses Ltd, Northampton). More typically, however, CL replaced at this frequency are dispensed in multipacks (usually consisting of individually foil-sealed blister packs), making fit and quality assessment of individual replacement lenses by the practitioner unfeasible - a factor that may affect the risk of complications. In this thesis DSCL are therefore defined as lenses designed for regular replacement at a frequency of up to one month that are dispensed in multipacks. Lenses dispensed individually at a frequency of one month or less often will be classified as PRS. When the European Medical Device Directives come into force in 1995 it is likely that the term `disposable' will be limited to lenses for single use only, in line with the FDA definition in the USA.

1.4.2 The Introduction and Penetrance of Disposable Lenses

The first disposable lens (DSCL) system, the `Acuvue Disposalens System', was introduced by Vistakon (a subsidiary company of Johnson and Johnson, Jacksonville, Florida) to the USA in 1987, and to the UK in October 1988. Initially these lenses were disposable in the true sense of the word: they were designed for continuous use for one or two weeks followed by disposal. Subsequently, DW use of Acuvue with a simplified care system and fortnightly disposal was introduced, and in 1991 a thicker version, Surevue, was promoted as a monthly replacement DW-DSCL. Although a number of other CL manufacturers have introduced DSCL during the past six years **(TABLE 1.1)**, the Vistakon lenses dominate the disposable lens market in the UK, USA and most of the many countries in which it is available, and are currently worn by approx-

imately 3 million patients worldwide (Davies, 1994). In the UK it is estimated that currently 60-70% of the 3 million CL wearers use SCL, and that 15% of these use DSCL (ACLM, 1994).

TABLE 1.1. DISPOSABLE LENSES AVAILABLE IN THE U.K. (as at July 1994)

MANUFACTURER Lens name (UK introduction)	MATERIAL* Filcon... (%WC)	METHOD OF MANUFACTURE	Dk $x10^{-11}$	PARAMETERS AVAILABLE: BOZR (mm)	TD (mm)	ct# (mm)	BVP (D)	DISPOSAL FREQUENCY (days)
ASPECT VISION CARE LTD								
Frequency 38 (May 1993)	HEMA (38)	Liquid Edge Technology (Cast-moulded)	10.5	8.60	14.0	0.04	-0.25 to -8.00	28
Frequency 55 (May 1993)	HEMA co-polymer	As above (55%)	23.0 23.0	8.60 8.80	14.2 14.2	0.08 ?	-0.25 to -8.00 +0.25 to +8.00	28
BAUSCH & LOMB UK LTD								
SeeQuence (May 1990)	1a (38)	Spun-cast	8.5	Varies with power	14.0	0.035	-9.00 to +4.00	28
Medalist (May 1992)	1a (38)	FS:Spun-cast BS:Lathe-cut	8.5	Varies with power	14.0	0.035	-9.00 to +4.00	28
Medalist 66 (July 1994)	4a	Cast-moulded	30	8.70	14.2	0.11	-6.00 to -1.00	28
BOOTS OPTICIANS								
Frequent Replacement Plan (Dec.1992)	-	Specifications withheld					-	28

* ACLM material classification (Parker, 1990)
\# @ -3.00DS (@ +3.00DS for plus powers listed separately)

TABLE 1.1. (continued)

MANUFACTURER Lens name (UK introduction)	MATERIAL Filcon... (%WC)	METHOD OF MANUFACTURE	Dk x10^{-11}	PARAMETERS AVAILABLE: BOZR (mm)	TD (mm)	ct (mm)	BVP (D)	DISPOSAL FREQUENCY (days)
CIBA VISION UK LTD								
Newvues (Jan.1992 - May 1993)	4b (55)	Cast-moulded	15	8.8	14.0	0.06	-6.00 to +4.00	7,14
Focus Visitint (Jan.1992)	4b (55)	Cast-moulded	20	8.6, 8.9,	14.0	0.10	-8.00 to +4.00	28
Focus Toric (Aug.1993)	4b (55)	Cast-moulded (BS toric)	20	8.9, 9.2,	14.5	0.15	-8.00 to +6.00	28
LUNELLE LTD								
Rythmic (Feb.1992)	4a (73)	Cast-moulded	45	8.9	14.2	0.15	-6.00 to +4.00	28
Zodiac (May 1994)	4a (73)	Cast-moulded	45	8.4 8.6	14.5 14.5	0.14 0.14	-8.00 to -0.25 -8.00 to +8.00	7,14,28
MJS SCIENTIFIC LTD								
ReView (Jul.1993)	4a (73)	Cast-moulded	45	8.4 8.6	14.5 14.5	0.14 0.26	-10.00 to -0.25 +0.25 to +8.00	28
NO 7 CONTACT LENS LABORATORY LTD								
ReVitalEyes (Feb.1994)	4a (73)	Lathe-cut	45	8.4 8.6	14.5 14.5	0.14 0.26	-10.00 to -0.25 +0.25 to +8.00	28

TABLE 1.1. (continued)

MANUFACTURER Lens name (UK introduction)	MATERIAL Filcon... (%WC)	METHOD OF MANUFACTURE	Dk $x10^{-11}$	PARAMETERS AVAILABLE: BOZR (mm)	TD (mm)	ct (mm)	BVP (D)	DISPOSAL FREQUENCY (days)
PILKINGTON BARNES-HIND HOLDINGS LTD [PBH]								
Calendar (Apr.1991)	4a (74)	Cast-moulded	43	8.7	14.4	0.14	-10.00 to +8.00	28
Precision UV (Apr.1993)	4a (74)	Cast-moulded (absorbs 90% UV radiation)	43	8.7	14.4	0.14	-10.00 to +8.00	7,14,28
VISTAKON								
Acuvue (Sep.1988)	1b (58)	Stabilized soft moulding (wet-moulded)	28.0 (18)#	8.8,8.4* 9.1,9.3**	14.0 14.4	0.07 0.15	-9.00 to -0.50 +0.50 to +6.00	7,14
Surevue (Oct.1991)	1b (58)	As above	28.0 (18)#	8.8,8.4**	14.0	0.105	-0.50 to -9.00	28
WESLEY-JESSEN LTD								
Fresh-Look (Apr.1994)	4b (55)	Molded Optical Surface Technology (wet-moulded)	16.1	Median (clear or coloured)	14.5	0.06	-0.25 to -6.00	7,14,30

* Introduced July 1993
** Introduced May 1994
# edge and boundary corrected (Weissman *et al.*, 1990)

1.4.3 The Acuvue Disposable Lens:

1.4.3 (i) Manufacture, Reproducibility and Quality

Aiming to produce a large volume of reproducible lenses at a cost that would make the disposable concept viable, Vistakon developed a revolutionary new manufacturing process: stabilised soft moulding (SSM). In conventional SCL manufacture, lenses are shaped in the dry state before being hydrated. In SSM, a special diluent is added to the monomer, allowing cold polymerisation by ultraviolet rays, and, since the diluent's molecules copy those of water in the polymer network, enabling the lens to come out of its mould already soft and in its final dimensions. The hydration phase is reduced to a simple automated rinsing process, in which water takes the place of the diluent with minimal alterations to the form and dimensions of the lens (Heyda, 1991).

Reproducibility and freedom from defects are very important in disposable lenses: most of these lenses will not be evaluated on the eye, and, since lenses in multipacks are from the same manufacturing lot and therefore likely to share similar faults, any resulting corneal compromise may be perpetuated for up to three months. In a small study of 21 Acuvue lenses from 11 different lots and 3 different sources, Wodis *et al.* (1990) found a high reproducibility in full sagittal height, diameter and power, although centre thicknesses for lenses of the same power showed a variation of up to 38% between different lot numbers. Gundel *et al.* (1993), in a study of 50 Acuvue lenses, found variations in diameter potentially sufficient to affect lens fitting. Both authors, however, concluded that reproducibility of the lenses, especially when compared to conventional SCL, was acceptable.

Several investigators have found a significantly higher level of manufacturing defects amongst Acuvue compared to other disposable lens types (Lowther, 1991; Efron and Veys, 1992; Gundel *et al.*, 1993). Prompted by reports of a high level of edge-induced conjunctival staining with these lenses (Devries *et al.*, 1989; Seger and Mutti, 1991), Efron and Veys (1992) conducted an extensive study of defects in 150 Acuvue, 150

NewVues (Ciba Vision, Southampton, Hants) and 150 SeeQuence (Bausch and Lomb, Hampton, Middx) lenses, together with a simultaneously-controlled, double-masked *in vivo* evaluation of their ocular effects. They found defects in 75% of Acuvue, compared to 5% and 9% in NewVues and SeeQuence respectively, and that subsequently these caused a statistically (but not clinically) significant increase in microcysts, corneal staining and conjunctival staining following one week of continuous wear. It is still not clear whether such a small increase in corneal compromise significantly increases the risk of more serious complications.

1.4.3 (ii) Material

Acuvue lenses are made from Etafilcon A (Filcon 4b), a 58% water content (WC) ionic material. It has been claimed that the unique SSM manufacturing process produces elevated oxygen permeability (Heyda, 1991). Weissman *et al.* (1990), however, using the single-chamber polarographic method corrected for boundary and edge defects, measured the oxygen permeability of these lenses to be similar to that for other SCL of similar water content and thickness. Comparisons of overall oxygen performance, however, are better made by comparing the equivalent oxygen percentage (EOP): an estimate of the *in vivo* oxygen level at the corneal surface beneath the lens which takes lens design, oxygen permeability and back vertex power into account (Efron, 1991b). The EOP profile for Acuvue compares favourably with a standard thickness high WC SCL, being higher centrally but slightly lower peripherally (Jones, 1994). The lens does not, however, provide the EOP sufficient to allow rapid recovery from corneal oedema following overnight wear (Holden and Mertz, 1984). This is in keeping with the results of a study comparing the overnight oedema response with a variety of lenses (La Hood *et al.*, 1988): Acuvue performed relatively well, but the resulting 10.4% (+/-3.2%) oedema shown is in excess of the level usually considered clinically acceptable (Efron, 1991b). Another study concludes that EW-DSCL causes the same metabolic and physiological changes in the corneal epithelium as does conventional EW-SCL (Tsubota and Yamada, 1992). In summary, use of Acuvue is unlikely to

reduce the hypoxic stress associated with overnight wear, and therefore cannot be expected to reduce substantially the risk of microbial keratitis (Dart *et al.*, 1991; Lawin-Brussel *et al.*, 1990; Imayasu *et al.*, 1994; Solomon *et al.*, 1994).

Since high WC, ionicity and reduced centre thickness have each been shown to increase lens *in vivo* dehydration (Kohler and Flanagan, 1985; Efron and Young, 1988; Helton and Watson, 1991), considerable dehydration on the eye with Acuvue is to be expected. This is a potential concern, since lens dehydration is associated with changes in lens parameters, fit and comfort; reduced oxygen transmissibility; and epithelial desiccation (Efron *et al.*, 1987; Efron and Young, 1988; Holden *et al.*, 1986b). In a controlled study Brennan *et al.* (1990) reported an average 6.2% and 10.2% open-eye dehydration after 20 minutes and 6 hours respectively. Other studies have confirmed a significantly greater dehydration with Acuvue than with non-ionic lenses of low and high WC, and an associated reduction in lens diameter (Veys and Efron, 1993; Pritchard and Fonn, 1993), and Helton and Watson (1991) have shown markedly higher dehydration rates for SeeQuence and Acuvue, and lower rates for Newvue, in comparison to averaged results for conventional (non-disposable) lenses in their FDA lens groups. The clinical significance of these findings, however, is unknown; several studies have failed to show correlation between dehydration and Acuvue lens movement or fit (Veys and Efron, 1993; Pritchard and Fonn, 1993; Little and Bruce, 1994), and it has been suggested that, for higher water content ultrathin SCL, parameter changes normally thought to be clinically significant may have a reduced influence on lens movement (Roseman *et al.*, 1993; Little and Bruce, 1994).

High WC ionic hydrogel materials, such as Etafilcon A, show the highest rate of protein deposition (Minarik and Rapp, 1989). Ionicity, however, also affects the characteristics of the lens-bound protein layer (LBPL): the LBPL on non-ionic SCL is invariably thin, mostly insoluble, and consisting of all major types of tear proteins; on ionic SCL, however, it is usually more than 20 times thicker but primarily composed of loosely

bound lysozyme, most of which retains enzymatic activity (Sack *et al.*, 1987). In a study comparing protein deposition on SeeQuence (low WC non-ionic) with that on Acuvue, Lin *et al.* (1991) supported these results and found that the difference in protein accumulation was detectable after 1 minute of wear. Although this study reported that lysozyme accumulation increased with wearing times up to 1 week, other investigators have found no correlation between duration of wear and the spoilage of these two types of DSCL (Tripathi and Tripathi, 1992). The significance of lysozyme accumulation for an immuological response is unknown.

It has been suggested that the lesser attachment by *Pseudomonas aeruginosa* to worn as opposed to unworn Acuvue lenses is due to the retained antibacterial action of lens-bound lysozyme (Boles *et al.*, 1992). Other studies have shown reduced levels of attachment of *Pseudomonas aeruginosa* (Stapleton *et al.*, 1993b) and *Acanthamoeba castellanii* (John *et al.*, 1991) to unworn lenses that are ionic rather than non-ionic. As discussed earlier (Section 1.2.1 (i)), however, the clinical relevance of enhanced or reduced bacterial adherence to lenses has not been shown, since bacterial replication will not occur without the development of a bacterial glycocalyx (Slusher *et al.*, 1987; Dart *et al.*, 1988b; John *et al.*, 1989; Stapleton *et al.*, 1993b). There is no evidence of reduced bacterial colonisation of the Acuvue lens material - Josephson at al. (1990) found no significant difference in the type or extent of microburden of EW weekly Acuvue compared to that of conventional EW-SCL cleaned and disinfected weekly for 6 weeks - and disposability *per se* is unlikely to confer an advantage in this respect, given the failure to show an association between bacterial count and length of lens wear (Barr *et al.*, 1988).

1.4.4 Maintenance of Disposable Lenses

DSCL have been promoted as a more convenient alternative to conventional SCL wear. In EW the greater convenience is obvious: storage cases and lens cleaning and disinfection solutions are no longer needed since the lenses will be discarded on removal.

When DSCL are used for DW, however, they do not offer greater convenience, other than the immediate availability of spare lenses, unless the usual SCL care procedures are simplified. The level of lens hygiene care to achieve safe but convenient lens wear has been the subject of much debate: although enzymatic cleaning is commonly thought to be unnecessary (Kersley, 1991; Allen *et al.*, 1992), different practitioners have suggested that surfactant cleaning should be replaced by a `saline rub and rinse' step, by a 10 second agitation of the lenses in saline, or should simply be omitted altogether (Garwood, 1991). Subsequently, however, anecdotal evidence pointing to the use of chlorine-release systems without prior surfactant cleaning as a possible cause of *Pseudomonas aeruginosa* (Efron *et al.*, 1991a; Woods and Woods, 1992) and *Acanthamoeba* keratitis (Sarwar *et al.*, 1993) has led to a lack of confidence in the practice of omitting the cleaning step; the care instructions with Softab (Alcon Laboratories, UK), the Vistakon lenses, and many other disposable lenses have been changed in order to include the recommendation of surfactant cleaning prior to disinfection. Softab and several of the DSCL manufacturers have also started to encourage regular replacement of storage cases by including them in the product package.

In most of Europe and the USA multi-purpose cold disinfection systems, such as Alcon `Opti-Free' (Polyquad) and Bausch and Lomb's `ReNu' (Dymed) have offered a simple and convenient method of lens maintenance for DW-DSCL (Hannon, 1993). These systems have only very recently become available in the UK. In their absence, chlorine-based systems have been widely used with DSCL, since they are economical, preservative-free and offer relative simplicity of use. The efficacy of these systems, however, has been questioned (Lowe *et al.*, 1992), particularly in the presence of organic debris (Copley, 1989) - which is likely to be considerable on a high WC ionic lens that may not have been cleaned beforehand. Originally, the use of hydrogen peroxide with Acuvue and other DSCL of an ionic material was avoided, since the literature indicated that overnight use of peroxide, even after a 10 minute neutralization, caused significant hydration (Harris *et al.*, 1989) and parameter changes (McKenney, 1990) in

high water content ionic materials. Two recent studies, however, have shown that these changes are reversed within 60 minutes, and if the neutralization time is increased to 20-30 minutes, few patients are likely to experience discomfort on insertion (Veys and Efron, 1993; Jones *et al.*, 1993).

1.5 CLINICAL PERFORMANCE OF DISPOSABLE LENSES

1.5.1 Pre-marketing and Other Early Studies of Disposable Lenses

Results of early studies of the use of DSCL indicated a high level of patient satisfaction and success. A pre-marketing survey of EW use of Acuvue, following 733 mostly experienced patients for 8 months under close supervision, gave a 5.6% incidence of complications including corneal microcysts, oedema, striae, punctate staining and GPC; no serious complications were reported (Donshik *et al.*, 1988). A number of other trials following experienced lens wearers for periods of between 3 and 19 months also found complications with Acuvue to be few and minor in nature (Gruber, 1988; Armitage *et al.*, 1990; Nilsson and Lindh, 1990; Roth, 1990). A lower success rate, but without serious complications, was achieved in a trial in which half of the subjects were novice lens wearers (Michielsen *et al.*, 1990). In a 6 week simultaneously controlled study using 31 successful, very experienced EW-SCL wearers, Josephson *et al.* (1990) found that the Acuvue lens performed better than or equal to the the conventional EW lens in biomicroscopic observation, although no statistical analysis was undertaken.

1.5.2 Microbial Keratitis

1.5.2 (i) Case Reports and Series

In contrast to the optimistic early trials of DSCL use, numerous case reports of DSCL related presumed microbial keratitis appeared once these lenses became widely available **(TABLE 1.2)**. The majority involved EW use of DSCL, and, as for conventional SCL related infections, *Pseudomonas* was the most common organism isolated. Laibson *et al.* (1993), however, in a review of lens related corneal ulcers managed by the Wills Eye Hospital (Philadelphia, USA), reported a greater proportion of less serious Gram-positive infections amongst DSCL users than amongst users of conventional SCL, although small numbers prevented statistical analysis of this trend. Meanwhile an association between DSCL use and *Acanthamoeba* keratitis was identified in a review of 72 consecutive cases managed during the years 1984 to 1992 (Bacon *et al.*, 1993); 28 of

65 (43%) lens-related cases were DSCL users, even though DSCL were only introduced half way through this period and accounted for less than 15% of lens use in the UK by the end of it (ACLM, 1994).

TABLE 1.2. CASE REPORTS OF (PRESUMED) MICROBIAL KERATITIS RELATED TO USE OF DISPOSABLE LENSES

AUTHOR (*et al.*)	NO.	WEAR	DSCL	CULTURE
Dunn, 1989	4	EW	Ac	Propionibacterium acnes Pseudomonas aeruginosa Staphylococcus No growth
Ficker, 1989	1	EW	?	Acanthamoeba
Glastonbury, 1989	1	EW	?	Pseudomonas aeruginosa
Kent, 1989	2	EW	?	P. aeruginosa (2)
Kershner, 1989	1	EW	?	Pseudomonas sp.
Killingsworth, 1989	1	EW	Ac	Pseudomonas aeruginosa
McLaughlin, 1989	1	EW	Ac	No growth
Parker, 1989	1	EW	?	No growth
Rabinowitz, 1989	1	EW	?	Pseudomonas aeruginosa
Heidemann, 1990	3	EW	?	Acanthamoeba (3)
Efron, 1991a	3	DW	Ac	P. aeruginosa (2) No growth
Bacon, 1992	16	EW(3) DW(13)	Ac	Acanthamoeba (8) No growth* (8)
Capoferri, 1992	4	EW	?	Culture +ve for ? (4)
Goyal, 1992	7	EW	?	Staphylococcus spp. (2) No culture / growth (5)
Sarwar, 1993	3	DW	Ac	Acanthamoeba polyphaga No culture* (2)
Woods, 1992	1	DW	Ac	Pseudomonas aeruginosa

*clinically diagnosed as *Acanthamoeba* keratitis

Key:

DW:	Daily wear
EW:	Extended wear
DSCL:	Disposable soft contact lens (type)
Ac:	Acuvue (Vistakon) DSCL
P. aeruginosa:	Pseudomonas aeruginosa

1.5.2 (ii) Cohort Studies

Efron *et al.* (1991a) conducted a practice-based retrospective cohort study in which 120 DW Acuvue patients advised to use Softab without any form of cleaning were followed for an average of 6 months. A 4.8% annualised incidence of corneal ulceration was reported, this being a minimum figure due to the possibility that some patients may have developed corneal ulcers and not reported back to the practice. A similar study of 100 EW users of Acuvue (70), Nuvue [sic] (26) and Seequence (4) DSCL followed for an average of 10.7 months reported an annualised incidence of 2.2% (Maguen *et al.*, 1991). These figures are considerably higher than would be expected from a population-based incidence study of the risk of ulcerative keratitis amongst SCL wearers (Poggio *et al.*, 1989).

Two large retrospective comparative cohort studies of patients from eight and five CL practices respectively have been conducted to compare the risk of complications with DW-SCL, EW-SCL and EW-DSCL (Poggio and Abelson, 1993a) and with DW-SCL and DW-DSCL (Poggio and Abelson, 1993b). In both studies microbial keratitis was not differentiated from sterile keratitis in the analysis presented. Incidence rates for this combined diagnosis (suppurative keratitis) were 38:10,000 for EW-DSCL, and 31:10,000 for EW-SCL in the first study, (in which there were 10 cases), and 47.4:10,000 for DW-DSCL and 43.2:10,000 for DW-SCL in the second study (21 cases). The authors acknowledge, however, that although these large (n=2433 and n=1954 respectively) multi-centre studies are well designed to assess the risk of common CL complications, they did not have the statistical power to detect differences in risk for rare disorders such as microbial keratitis.

Another practice-based historical comparative cohort claims a similar or reduced incidence of corneal ulcers with DW-DSCL compared to DW-SCL (Guillon *et al.*, 1994) although, again, the numbers (n=780 and n=647 respectively) were too small to obtain any statistically significant differences. Use of a very broad case definition based

on corneal scarring with or without infiltrates, however, led to very high annualised incidence rates (88 and 110 per 10,000 for DW-DSCL and DW-SCL respectively) and hindered comparison with other studies. Even the incidence rates of `severe' ulcers (defined as those that had received medical treatment) - 18 and 39 per 10,000 for DW-DSCL and DW-SCL respectively - are 4.4 and 9.5 times higher than incidence estimates for DW soft lens use established in the well-conducted population-based study by Poggio *et al.* (1989), suggesting difficulties with case definition or ascertainment. Furthermore, the exclusion of cases lost to follow-up may have biased the results if severe cases, the most likely to seek emergency medical treatment without consulting their practitioner, were more associated with one lens type than another. The proportion of patients lost to follow-up, and any attempts made to contact them, are not reported by the authors.

1.5.2 (iii) Case-Control Studies

The first case-control studies examining the relative risk (RR) of microbial keratitis in DSCL as opposed to conventional SCL users, simultaneously published in November 1992, suggested that there was an increased risk associated with DSCL. Buehler *et al.*, (1992) in the USA, comparing 42 cases with 210 controls matched by dispensing date and prescribing practitioner, showed DSCL to have an age and sex adjusted RR (95% CI) of 14.34 (5.47-37.63) using DW-SCL as referent, and 7.66 (2.27-25.83) with EW-SCL as referent. At Moorfields Eye Hospital (UK), Matthews *et al.* (1992), piloting the study this thesis describes, compared 10 cases with 273 controls attending the same A&E department as new patients and derived RR of 13.25 (1.52-630) for DSCL using rigid CL as the referent. When compared to DW-SCL and EW-SCL, DSCL are calculated to have a 6.2 and 2.5 times greater risk respectively. Neither study, however, was able to show a significant difference in risk between DSCL and conventional SCL used with the same wear schedule: Buehler *et al.* (1992) categorised their patients according to lens type rather than wear schedule, and Matthews *et al.* (1992) were only able to show a statistically significant excess risk when DW-DSCL and EW-DSCL

users were grouped together, or when EW-DSCL users were isolated. Reanalysis of the Buehler *et al.* study with an increased number of controls (Schein *et al.*, 1994) showed that, after adjusting for the practice of overnight wear, the excess risk associated with DSCL was reduced to 3.21 (1.22 to 14.36), and that in their data overnight use was the predominant risk factor, with a RR of 8.25 (3.33 to 25.58) after controlling for lens type. Another limitation with both studies is the possibility of bias due to the methods in which controls were selected. The USA study's controls were selected from appointment records nearest in date to that of each case patient examined and fitted with lenses; if any CL type was less frequently fitted (or re-fitted) it will have been under-represented in the control group, leading to an overestimate of its RR. In the UK study, patients with acute CL-related disorders were included in the controls; if any CL type was associated with a lesser frequency of complications other than microbial keratitis it will have been under-represented in the control group and its RR for keratitis subsequently overestimated.

The present study has addressed these limitations by collecting enough cases and controls to make direct comparisons between DW-SCL and DW-DSCL and between EW-SCL and EW-DSCL; by performing multivariable analysis to control for other contributing factors; and by limiting controls to those attending with disorders unrelated to lens wear.

1.5.2 (iv) Incidence Studies

Nilsson and Montan (1994a and 1994b) have conducted the first population-based incidence studies examining the risks of microbial keratitis with the range of lens wear modalities now available. In the first study (1994a) they reviewed all hospitalised cases of cosmetic lens-induced ulcerative keratitis in Sweden during the period 1989 to 1991, and for the denominator obtained estimates of the number of wearers of each lens type and wear schedule from a survey of CL fitters conducted by the Swedish Contact Lens Association over a 3 month period in 1990. Annualised incidence per 10,000 for DW-

SCL, DW-DSCL, EW-SCL, EW-DSCL and rigid lenses were 0.51, 0.16, 3.12, 4.17 and 1.21 respectively. Amongst DW users, the smaller incidence with DSCL was statistically significant ($p < 0.05$-0.01), but the two EW groups did not differ significantly ($p > 0.2$).

There are, however, possible sources of bias in both the ascertainment of lens types amongst the cases and the estimate of the penetrance of the different lens types in the population at risk. Lens types for the cases were obtained from medical records; they were not verified with the patient except in the few cases where data was absent. It is possible that for some cases hospital staff may have recorded soft lens use without documenting the disposable regime; this dependence on hospital records for determining lens type may have inflated the number of cases apparently associated with conventional rather than disposable SCL wear. There is also the potential for bias in the manner in which the penetrance of lens types in the population was estimated. CL fitters were asked to count the number of wearers of each lens type and schedule attending the practice during a 3 month period. Adjustment was subsequently made for revisit frequencies greater than one year, but not for less frequent visits. If wearers of some lens types and schedules were more likely to visit very infrequently, they would have been under-represented in this survey and the incidence with their lens type overestimated. The higher relative risk reported with rigid lens wear, contrasting markedly with findings in previous studies (Franks *et al.*, 1988; Schein *et al.*, 1990; Dart *et al.*, 1991) suggests that such a bias may have been operating; rigid lens wearers may have been more likely to attend infrequently, due to the longer average lifespan of their lenses.

In the subsequent three-month prospective study (Nilsson and Montan, 1994b) of *all* cases of CL induced keratitis (defined as stromal infiltrate with overlying epithelial defects) sources of bias regarding lens type ascertainment in the earlier study appear to have been addressed: lens types, wear schedules and other CL use details for the cases

were recorded by ophthalmologists at presentation, and although not clearly described, there appears to have been adjustment for less as well as more frequent patient re-visits to CL practitioners when calculating the estimated number of wearers of each lens type in the country.

The prospective study showed similar risks of ulcerative keratitis for conventional and disposable lenses worn with the same wear schedule, although EW of either modality was significantly associated with an increased risk: annualised incidence per 10,000 for DW-SCL, DW-DSCL, EW-SCL, EW-DSCL and rigid lenses were 2.17, 2.16, 13.33, 10.00 and 1.48 respectively. In both studies severe keratitis was reported as significantly more common amongst users of conventional rather than disposable lenses, although the considerably greater use of conventional rather than disposable SCL amongst EW patients in Sweden is not taken into consideration and may be related to this trend.

In neither study do the authors discuss confounding variables that may have led to bias. In particular, there is no mention of the types of disinfection systems used by disposable as opposed to conventional SCL wearers in Sweden; if DW disposable SCL wearers tended to use a solution with higher relative efficacy than that used by conventional DW-SCL wearers, this may have biased the results. Furthermore, the markedly low incidence and reduced severity of keratitis reported in these studies, compared to that reported in the only comparable studies (Poggio *et al.*, 1989; Schein *et al.*, 1989a), may limit their application to other lens-wearing populations. As the authors suggest, this may be attributable to the Swedish federal regulations requiring CL fitters to inform patients of the risks associated with lens wear and to refer newly fitted patients to an ophthalmologist within 6 months; continued close supervision; and an increasingly cautious attitude to extended wear amongst both practitioners and their patients in Sweden.

1.5.3 Sterile Keratitis

Case reports have concentrated on severe suppurative keratitis **(TABLE 1.2)**, or included both sterile and presumed microbial cases (Mertz *et al.*, 1990). However, both Serdahl *et al.* (1989), in a description of two cases of sterile keratitis, and Mertz *et al.* (1990), in a report of nine cases of culture-negative corneal infiltrates (some of which were associated with features suggesting an infective origin) observed an association with immobile DSCL used for EW. Maguen *et al.* (1991, 1992 and 1994) have commented on the frequent occurrence of non-infectious peripheral corneal infiltrates with EW-DSCL use: in the first two years of their retrospective cohort study of 100 EW-DSCL (Acuvue, NewVues and SeeQuence) patients there were 13 cases during the average follow-up period of 26 months, representing an annualised incidence of 6%. In the third year of follow-up, however, the annualised incidence was reduced to 1.6%, which the authors attribute to a greater lattitude in fitting due to a widening range of DSCL parameters. A comparative retrospective cohort study (Boswall *et al.*,1993) of 65 EW-DSCL (Acuvue, NewVues and SeeQuence) and 61 EW-SCL showed peripheral infiltrates to be the most common cause of failure amongst the DSCL users, but due to small numbers there was no significant difference in the distribution of this disorder between the two groups.

In a case-control study, Matthews *et al.* (1992) showed a 3.93 (1.17-14.38) times increased risk of sterile keratitis for DSCL, rising to 4.24 (1.09-17.21) when EW-DSCL were considered alone, using rigid lenses (which showed a similar risk to that with DW-SCL) as the referent. An excess risk with DW-DSCL failed to reach statistical significance.

1.5.4 Contact Lens Induced Papillary Conjunctivitis

There have been numerous anecdotal reports of the usefulness of DSCL replaced daily (Grant *et al.*, 1988) or weekly (Atwood, 1989; Lowther, 1990; Burnett Hodd, 1991;

Kersley, 1991) in the management of CLPC, and small (n=20) uncontrolled trials have reported a 70-90% success rate amongst mild to moderate cases refit with DSCL for weekly extended wear (Coursaux *et al.*, 1990) or fortnightly daily wear (Hamburg *et al.*, 1991).

In a masked biomicroscopic evaluation of eight patients followed for 6 months wearing a weekly disposed Acuvue in one eye and a weekly cleaned, enzymed and disinfected EW-SCL of the same material in the other, Rumsey *et al.* (1991) found no significant difference in either the progression of papillary hypertrophy or the type and degree of visible lens coating. Bucci *et al.* (1993) conducted a prospective, randomized double-masked trial in which CLPC patients using monthly replaced DW Acuvue in one eye and a DW CSI (Pilkington Barnes-Hind) in the other, with daily cleaning and disinfection and weekly enzyme treatment, were followed for 6 months. The CSI lens is made from a polymer that is non-ionic and has a reduced pore size, providing resistance to deposits up to eight times greater than HEMA (data on file, at Pilkington Barnes-Hind, Southampton, UK). An early and relatively equal improvement in symptoms was achieved with both lenses. Although comfort was significantly greater with Acuvue, handling difficulties prevented any significant overall preference for the lens. It was not clear whether increased comfort with Acuvue was due to the thin lens design reducing mechanical irritation or due to frequent lens replacement periodically reducing the antigenic load. In a similar, further study, Bucci *et al.* (1994) compared the symptoms and overall lens preference, amongst both allergic and non-allergic patients, for monthly and bimonthly replaced Focus (CIBA Vision), fortnightly and monthly replaced Surevue (Vistakon), and the CSI (Pilkington Barnes-Hind) lens. Although the CSI was found to be the optimum lens for non-allergic patients, Focus showed a clinical advantage amongst those with a history of environmental allergies. There was no additional benefit, however, associated with a lens replacement frequency greater than two months.

The results of bilateral (as opposed to simultaneously controlled) comparative studies, have been contradictory and, due to the apparent difficulty of selecting appropriate controls when assessing this disease, often inconclusive. Poggio *et al.* (1993a and 1993b), in their two large cohort studies with average follow-up times of 16.5 and 18 months, found a similar prevalence of CLPC amongst conventional and disposable lens wearers, amongst both the EW and DW users. It was noted, however, that a history of CLPC was much more common amongst DW-DSCL users than DW-SCL users ($p=0.007$), possibly biasing the result against DSCL wear. Another retrospective comparative study (Marshall *et al.*, 1992) has reported similar frequencies of CLPC amongst DW-SCL and DW-DSCL even though 52% of the DSCL users had been fitted with DSCL due to prior CLPC. In this study, however, a bias against conventional SCL users may have occurred. Controls were derived from a random sampling of SCL wearers visiting a contact lens clinic; since patients with lens complications may have been more likely to attend more frequently, and therefore have a greater chance of being selected as a control, patients with chronic lens complications (such as CLPC) may have been over-represented in the controls. In contrast to these studies, Boswall *et al.* (1992) reports a statistically significant reduction in frequency with DSCL, CLPC occurring in only 3 of 65 (4.6%) EW-DSCL users compared to 21 of 61 (34.4%) EW-SCL users followed for approximately 2 years ($p<0.001$). However the DSCL group contained significantly fewer novice EW patients than the conventional EW-SCL group. In summary, there is no conclusive scientific evidence that the DSCL regime reduces the risk of CLPC.

1.5.5 Metabolic and Other Complications

Despite numerous reports of an association between tight lens syndrome and/or micro-cystic epitheliopathy with use of EW-DSCL (Epstein and Donnenfeld, 1989; Josephson *et al.*, 1990; Netland, 1990; Maguen *et al.*, 1991; Boswall *et al.*, 1993), a significantly reduced incidence of `corneal oedema and/or microcysts' with DSCL has been shown

amongst both DW (Poggio *et al.*, 1993b) and EW patients (Poggio *et al.*, 1993a) in large comparative cohort studies. Punctate corneal staining has also been shown to be significantly reduced with DSCL amongst both DW (Poggio *et al.*, 1993b) and EW patients (Boswall *et al.*, 1993). All three retrospective comparative cohort studies (Poggio *et al.*, 1993a and 1993b; Boswall *et al.*, 1993) showed a significant reduction in the total prevalence of complications.

Hamano *et al.* (1994) have conducted the first published comparative study to include an assessment of the performance of daily-disposed DSCL (discarded at the end of each day's use). They reviewed the charts of 23,068 patients wearing PMMA, RGP, acrylelastomer, HEMA, high WC SCL, weekly disposable Acuvue (2,985 eyes) or daily-disposed `One Day Acuvue' (893 eyes) presenting during a 3-month period. Only non-specific corneal signs were documented, and the surprising absence of corneal ulcers and low incidence of infiltrates prevented comparisons of the risks of these disorders. Furthermore, patients are compared according to lens type rather than lens use, limiting true comparisons between most of the lens types. In addition, there may have been a bias in favour of both disposable regimes, since DSCL patients were more likely to be attending the practice for routine rather than emergency examination (with the aim of collecting their 3 months' supply of lenses) than users of non-disposable lens types. The `One Day Acuvue', however, had a markedly reduced complication rate compared to each of the other lens types ($p=0.03236$ to $p<0.000001$).

CHAPTER 2. METHODS

2.1 PROSPECTIVE CASE-CONTROL STUDY OF MICROBIAL KERATITIS AND OTHER COMPLICATIONS AMONG LENS WEARERS

2.1.1 Introduction to Study Design

This prospective, hospital-based study aimed to compare the risks of the various types of CL-related complications associated with disposable as opposed to conventional SCL, and evaluate the relative importance of lens type amongst other risk factors by performing multivariable analysis.

A comparative cohort study would have provided CL complication incidence data for each CL type, but unless the cohorts were unmanageably large, it would not have had the statistical power to detect significant differences in incidence for rare complications such as microbial keratitis (Dart, 1993). A case-control study design was therefore selected; instead of comparing the incidence of disease with each CL type, odds ratios were calculated, giving a measure of how many times more (or less) likely a disease will occur in association with one mode of CL use than another. For rare diseases, odds ratios closely approximate relative risks (Schlesselman, 1982), and are therefore reported as such during this study.

Multivariable analysis was performed in order to evaluate any remaining excess risk with CL type *per se* after adjustment for all other variables. Where appropriate, relative risks (RR) and multivariable analysis were calculated for other variables (such as the type of disinfection).

The study was conducted at Moorfields Eye Hospital (MEH) A&E Department, which provides a 24-hour open access service for ophthalmic emergencies. A nursing triage system is used, whereby senior trained ophthalmic nurses carry out the initial assessment of each patient in order to establish priorities for treatment. Previous studies have shown that between 2.6% (Barry and Ruben, 1980) and 3.8% (Stapleton, 1991) of the

33,000 new patients to A&E each year attend with CL-related problems. A recent succession of studies of CL wearers attending MEH A&E (Franks *et al.*, 1988; Dart *et al.*, 1991; Matthews *et al.*, 1992) has led to familiarity and good cooperation with study protocol among nursing staff, and the establishment of clinical guidelines for the diagnosis and management of CL-related diseases for Casualty Officers.

2.1.2 Data Collection

Data was collected from CL wearers attending the MEH A&E Department as new patients during the 12 month period 2nd March 1992 to 1st March 1993. The majority of patients were self-referred, although a few had consulted their contact lens or general practitioner prior to attending A&E. Nursing staff identified the patients, colour coded their hospital notes for later inspection, and gave them a questionnaire **(APPENDIX 1)** for self-administration. Regular scrutiny of all new patient A&E notes enabled identification of CL wearers who had failed to be identified at the time of their attendence; these patients were either contacted at follow-up visits or sent a postal questionnaire **(APPENDIX 2)**. Non-respondents with a diagnosis of microbial or sterile keratitis were contacted by telephone.

2.1.2 (i) Questionnaire

CL wearers completed a self-administered questionnaire **(APPENDIX 1)** designed to provide data on possible risk factors **(TABLE 2.1)**. Any patients having difficulty remembering the names of their CL solutions were invited to consult an illustrated file at the A&E reception desk. Where necessary, the questionnaire was followed by a telephone or postal interview to the patient and/or his practitioner to clarify any inconsistencies or omissions.

TABLE 2.1. DATA OBTAINED BY SELF-ADMINISTERED QUESTIONNAIRE.

Age
Gender
Occupation (to enable socio-economic classification)
CL type
Length of experience with present CL type
Previous CL type (if any)
Total length of CL wear experience
CL age
Indication for CL wear
Possession of `usable' spectacles
Wear schedule
Frequency of surfactant or `rub and rinse' cleaning
Type and frequency of disinfection
Frequency of enzyme treatment
Use of eye drops and/or other solutions
Frequency of storage case cleaning and replacement
Frequency of planned CL replacement (if any)
Time since the last CL check
Frequency of CL checks advised by practitioner
Wearers of DSCL:
- Reason for DSCL use
- Brand of DSCL
- Frequency of DSCL disposal
- Disposal less frequently than advised
- Re-use of EW-DSCL

2.1.2 (ii) Classification of Patient Lens Use

To be classified as a CL wearer, the patient had to have worn CL within the four week period preceding their presentation to A&E. Patients using CL for aphakia or therapeutic reasons (including keratoconus) were excluded from the study.

Continuous wear of 24 hours or more occurring at least once per week was classified as EW use of lenses, although less frequent `occasional' overnight use among patients categorized as daily-wear was also documented.

Disposable lenses were defined as soft lenses designed for disposal after no more than 4 weeks use, dispensed to the patient in a multipack. Patients were considered to be on a `Planned Replacement Scheme' if a new pair of lenses was dispensed to them at 2 to 6 monthly intervals.

2.1.2 (iii) Socioeconomic Classification

Classification of socioeconomic group and social class based on occupation was carried out according to the new Standard Occupational Classification coding derived for the 1991 Census (OPCS, 1990).

2.1.2 (iv) Evaluation of Patient Lens Hygiene

For each individual a hygiene score for each aspect of CL care was derived **(APPENDIX 4)**. Patients who carried out mechanical cleaning and disinfection with fresh solution on every CL removal, case cleaning weekly, and enzyme treatment, abrasive cleaning or lens disposal fortnightly, would score maximally. Points were deducted for less frequent or sub-optimal attention to these aspects of CL care. Use of non-sterile water for any aspect of soft CL care automatically received a zero score for disinfection. EW patients were judged on lens hygiene practices at the time of lens removal.

2.1.2 (v) Diagnostic Classification

Diagnosis for each patient was derived from the hospital notes. Diagnosis of CL-related disease by attending casualty ophthalmologists was assisted by provision of clinical classification guidelines **(APPENDIX 5)** employed in previous studies in the department (Franks *et al.*, 1988; Dart *et al.*, 1991). To assist subsequent analysis, CL-related complications were classified into the following pathogenic groups:

1. Microbial keratitis:

Suppurative keratitis presumed to be microbial, according to established clinical criteria (see **APPENDIX 5)**, and therefore requiring a diagnostic corneal tissue culture and intensive antibiotic treatment. Microbial keratitis was further classified as:

Severe:

Culture positive (+ve) ulcers OR

culture negative (-ve) ulcers where lesions are > 2mm diameter and within the central 4mm zone

Moderate:

Culture -ve ulcers where lesions are central and < 2mm diameter OR

peripheral (outside the central 4mm zone) lesions > 2mm diameter

Mild:

Culture -ve ulcers, where lesions are peripheral and < 2mm diameter

2. Sterile keratitis:

Suppurative keratitis not defined as microbial

3. Toxic and Hypersensitivity disorders:

Includes CL solution keratopathy, CL-related `red eye', limbitis and CL-related (giant) papillary conjunctivitis (CLPC)

4. Metabolic disorders:

Includes acute epithelial necrosis (`overwear syndrome'), `tight lens syndrome', corneal oedema and microcystic epitheliopathy

5. Mechanical disorders:

Abrasions, foreign bodies and other disorders directly related to the mechanics of CL wear

6. Tear re-surfacing disorders:

Includes 3 and 9 o`clock staining, inferior closure staining and CL-induced `dry eye'

7. Miscellaneous disorders:

Includes non-specific CL intolerance; lost, damaged or dislodged lenses; and CL removal difficulties.

2.1.3 Definition of Cases and Controls

Cases were defined as eligible patients (see 2.1.2. (ii)) attending with a CL-related disorder in the diagnostic classification under assessment; controls were eligible patients presenting with disorders unrelated to lens wear, but not necessarily free from non-acute CL-related disease.

2.1.4 Statistical Analysis

Data from questionnaires and medical notes were entered into a database for analysis.

STATXACT (CYTEL Software Corporation, Cambridge, MA, USA) was used for estimation of `exact' odds ratios (reported as relative risks), 95% confidence limits and p-values, and tests of homogeneity. For comparisons between lens types, conventional DW-SCL were used as the referent with a baseline RR of 1.0, since these are the usual clinical alternative to disposable SCL. In addition, for each disorder a separate RR was

calculated for EW-DSCL using conventional EW-SCL as referent.

The EGRET software package (Statistics and Epidemiology Research Corporation, Seattle, WA, USA) was used to carry out multivariable logistic linear regression analysis of risk factors for microbial and sterile keratitis. The strategy of analysis used was similar to that described by Kleinbaum *et al.* (1982). The first step was to create categorical variables from fields in the database and scrutinize cross-tabulations between them for correlations preventing their inclusion in the same model. Secondly, any interactions between extraneous (potentially confounding) variables were identified and assessed for biological sense; in the presence of meaningful interactions between variables, data was stratified and analysed separately. Odds ratios for the exposure variable (risk factor under analysis) were then calculated, and subsequently adjusted for the possible effect of each extraneous variable, one at a time. Variables that did not materially change the RR but reduced precision (that is, widened the confidence interval) were excluded from the final models. Priority, however, was always given to validity of the RR, in order to give optimal control of confounding.

Statistical comparisons of demographic, lens hygiene or other characteristics amongst lens wearers were made using either the independent t test for comparisons of means (Daly *et al.*, 1991) or the chi squared test (or Fisher' exact test, when numbers were small) for comparing independent proportions (Siegel and Castellan, 1988). The Kruskal-Wallis test (Hollander and Wolfe, 1973) was used to compare the distribution of lens types within each microbial keratitis severity classification.

2.2 RETROSPECTIVE CASE-CONTROL STUDY OF *ACANTHAMOEBA* KERATITIS AMONG LENS WEARERS

2.2.1 Introduction to Study Design

This study aimed to quantify the relative risk (RR) of *Acanthamoeba* keratitis (AK) with disposable as opposed to conventional SCL; to evaluate the relative importance of lens type and other risk factors for AK by performing multivariable analysis; and to calculate, where appropriate, the population attributable risk (PAR%) for prominent risk factors.

Sufficient cases had to be collected, in the limited time available, to have the statistical power for detection of significant differences in risk for such a rare disease; a retrospective case-control study design was therefore selected. Case collection was further enhanced by utilizing MEH's role as a national tertiary referral centre.

2.2.2 Definition of Cases and Controls

Cases were defined as patients presenting to MEH during the three year period 1.9.89 to 31.8.92 with CL-related corneal infections, where *Acanthamoeba* was implicated by microbiological testing of corneal tissue or by the presence of atypical keratitis combined with strongly suggestive diagnostic clinical features such as disproportionate pain, perineural infiltrates, limbitis, ring infiltrates and dendriform ulceration (Bacon *et al.*, 1993). Potential patients were identified retrospectively by records of requests for corneal culture and previous research data (Bacon *et al.*, 1993). Tertiary referrals from other hospitals were included, provided the onset of disease was within the study period and occurred not more than four weeks after the last period of CL wear, the indication for CL use was non-medical, and the patient had presented to the referring hospital as a new patient. Clinical data was derived from the hospital(s) notes. Non-U.K. residents among the cases were excluded, due to the difficulty of verifying CL wear data for these patients.

Controls were CL wearers with non-CL related disease presenting as new patients to MEH A&E (identified as described in section 2.1.2.) during the 6 month period 1.3.92 to 31.8.92.

2.2.2 (i) Study One: The Relative Risk of Each Lens Type for *Acanthamoeba* Keratitis

The RR of each CL type was assessed, using the most commonly worn CL, conventional DW-SCL, as referent. For Study One it was important to keep cases and controls as contemporaneous as possible, since the penetrance of DSCL increased during the three year period **(TABLE 2.2)**. For this reason cases were limited to those presenting to MEH as primary referrals during the latter 12 month period (1.9.91 to 31.8.92).

2.2.2 (ii) Study Two: Multivariable Analysis of Hygiene Practices and Other Risk Factors for Lens-Related *Acanthamoeba* Keratitis

Multivariable analysis of hygiene practices and other risk factors for the disease was undertaken. For Study Two all cases presenting during the three year period (1.9.89 to 31.8.92) were included, since the distribution of different disinfection methods did not change significantly during this time **(TABLE 2.2)**.

TABLE 2.2. DISTRIBUTION OF LENS TYPES AND SOFT LENS DISINFECTION METHODS IN STUDIES CONDUCTED IN 1989 AND 1992

Study:	RADFORD *et al.*, (1993b)	RADFORD (unpublished)
Study time period:	Sep.1989 to Dec.1989	Mar.1992 to Aug.1992
Subjects:	n = 178*	n = 378**
CL TYPE & WEAR SCHEDULE:		
Rigid	53 (30%)	104 (27%)
DW-SCL	120 (67%)	208 (55%)
DW-DSCL	0	37 (10%)
EW-SCL	4 (2%)	18 (5%)
EW-DSCL	1 (<1%)	11 (3%)
SCL DISINFECTION METHOD:		
Hydrogen peroxide	61 (49%)	145 (53%)
Chlorine-release	21 (17%)	49 (18%)
Other chemical	39 (31%)	56 (20%)
Thermal	3 (2%)	5 (2%)
None	1 (<1%)	12 (4%)
Disposal on removal	0	7 (3%)

* CL users from many different practices
** CL users with a non-medical indication for CL wear presenting as new patients to MEH A&E with a disorder unrelated to CL wear

2.2.2 (iii) Study Three: Multivariable Analysis of Hygiene Practices and Other Risk Factors for Lens-Related Culture-Positive *Acanthamoeba* Keratitis

Separate multivariable analysis, in which cases presenting during the three years were restricted to those with a positive corneal culture, was also undertaken.

2.2.3 Data Collection

Patients completed a self-administered questionnaire as described in section 2.1.1 (i). Case patients presenting prior to 2.3.92 were sent a postal questionnaire (as illustrated in **APPENDIX 2**, but replacing the first page with that shown in **APPENDIX 3**). Information received was compared with details in the medical notes and previous research data (Bacon *et al.*, 1993). Where necessary, the questionnaire was followed by a telephone interview with the patient and/or his practitioner to clarify any inconsistencies or omissions. Subjects were classified with respect to lens use, socioeconomic class, and lens hygiene as described in sections 2.1.2 (ii) to (iv).

2.2.4 Statistical Analysis

Statistical analysis was performed as described in section 2.1.4. In addition, PAR% for prominent risk factors was calculated from relative risks determined by multivariable analysis and the proportion of the control population exposed (Schlesselman, 1982).

CHAPTER 3. RESULTS

3.1 PROSPECTIVE CASE-CONTROL STUDY OF MICROBIAL KERATITIS AND OTHER COMPLICATIONS

3.1.1 Subjects

From a total of 32,670 individuals attending MEH A&E as new patients during the 12 month period to 1st March 1993 data was collected for 1912 CL wearers. A further 403 individuals were identified as potentially eligible, but for these patients medical notes could not be traced (n=21), or questionnaires were still incomplete (n=12) or not returned (n=370) when analysis commenced on August 1st 1993. An analysis of a sample of non-respondents is described in Section 3.1.9.

3.1.1 (i) Distribution of Lens Types

The distribution of CL types and wear schedules is shown in **TABLE 3.1**, and the frequency of different DSCL brands in **TABLE 3.2**. The majority of subjects were wearing conventional DW-SCL (1037/1912, 54%). Conventional EW-SCL was the least common schedule (84/1912, 4%), and 20% (17/84) of these subjects were on a PRS. DSCL accounted for 17% (333/1912) of lens use, with just over a third (118/333) wearing them overnight on a regular basis. The Vistakon lenses, Acuvue and Surevue, accounted for 84% (181/215) of DW-DSCL use, and Acuvue accounted for 89% (105/118) of EW-DSCL.

3.1.1 (ii) Demographic Data for Wearers of Each Lens Type

Demographic data for wearers of each CL type is shown in **TABLE 3.3**. Conventional EW-SCL subjects had a slightly older average age than EW-DSCL users. DW-DSCL users were associated with higher social class than users of conventional DW-SCL. Males showed a preference for extended-wear schedules.

TABLE 3.1. DISTRIBUTION OF LENS TYPES

CL TYPE	No. (%)	PRS (2-6 monthly lens replacement)
Rigid	458 (24)	
DW-SCL	1037 (54)	57 (5%)
DW-DSCL	215 (11)	
EW-SCL	84 (4)	17 (20%)
EW-DSCL	118 (6)	

TABLE 3.2. DISTRIBUTION OF DISPOSABLE LENS TYPES

	DW: (n = 215) No. (%)	EW: (n = 118) No. (%)
Acuvue (Vistakon)	150 (70)	105 (89)
Surevue (Vistakon)	31 (14)	
Newvue (CIBA Vision)	10 (5)	5 (4)
Calendar (Pilkington Barnes-Hind)	9 (4)	
SeeQuence (Bausch & Lomb)	7 (3)	4 (3)
Visitint (CIBA Vision)	4 (2)	2 (2)
Medalist (Bausch & Lomb)	1 (1)	
Undetermined brand	3 (1)	2 (2)

TABLE 3.3. DISTRIBUTION OF AGE, GENDER AND SOCIOECONOMIC CLASS FOR WEARERS OF EACH LENS TYPE

	Rigid (n=458)	DW-SCL (n=1037)	EW-SCL (n=84)	DW-DSCL (n=215)	EW-DSCL (n=118)
Age (years)					
mean	34.57	30.02	33.93[a]	30.52	30.75[a]
s.d.	9.84	8.90	12.16	9.28	8.79
range	10-72	14-68	13-68	13-71	16-65
Sex					
(M:F)	134:324	374:663	50:34	71:144	59:59
(%M)	(29)	(36)	(60)	(33)	(50)
Social Class					
1-2:3-5	322:136	631:406[b]	50:34	150:65[b]	84:34
(%1-2)	(70)	(61)	(60)	(70)	(71)

Significant differences between SCL and DSCL users with same wear schedule:
a:Independent t test: t=2.05, d.f.=142, p=0.043
b: Chi squared Test: Chi squared=6.036, d.f.=1, p<0.02

3.1.1 (iii) Lens Use amongst Wearers of Each Lens Type

Characteristics of lens use amongst wearers of each lens type and wear schedule is shown in **TABLE 3.4**. Ninety-one percent (1736/1912) of subjects were myopic. Although the length of CL wear experience was similar amongst the soft lens groups, previous experience of an alternative lens type or wear schedule was significantly more common amongst disposable lens wearers (274/333, 82% compared to 318/1121, 28%). Amongst DW subjects occasional overnight use was a significantly more common habit amongst DSCL users (45/215, 21% compared to 130/1037, 13%). Amongst EW subjects, however, the mean number of consecutive 24-hour periods of CL use was significantly less amongst DSCL users (6.46 compared to 18.0).

3.1.1 (iv) Lens Hygiene amongst Wearers of Each Lens Type

TABLE 3.5 shows the distribution of disinfection methods amongst soft lens wearers. Amongst DW-SCL users the most common disinfection systems were hydrogen peroxide (527/1037, 51%) and thiomersal-preserved products (252/1037, 24%), while DW-DSCL subjects were significantly more likely to be using chlorine-release systems (118/215, 55%) or soaking in saline only (28/215, 13%). Only 63% (72/118) of the EW-DSCL users were disposing of their lenses at every removal, and 19/46 (41%) of those re-using their lenses failed to employ any disinfection.

The distribution of scores for each aspect of SCL hygiene is shown in **APPENDIX 6.** Mean hygiene scores for users of each lens type are shown in **TABLE 3.6**. Although DW-DSCL users had a slightly lower mean score than DW-SCL users the difference was not statistically significant. Amongst EW patients, however, general hygiene standards were significantly higher with DSCL use (mean score 11.93 compared to 3.62).

TABLE 3.4. CHARACTERISTICS OF LENS USE FOR WEARERS OF EACH LENS TYPE

	Rigid (n=458) No. (%)	DW-SCL (n=1037) No. (%)	EW-SCL (n=84) No. (%)	DW-DSCL (n=215) No. (%)	EW DSCL (n=118) No. (%)
Indication					
Myopia	429 (94)	927 (89)	75 (89)	201 (93)	104 (88)
Hyper.	22 (5)	51 (5)	4 (5)	6 (3)	10 (8)
Unknown Rx	7 (2)	56 (5)	4 (5)	8 (4)	4 (3)
Cosmetic	0	3 (<1)	1 (1)	0	0
Experience of lens wear					
0-6mo	11 (2)	67 (6)	1 (1)	13 (6)	4 (3)
7mo-2yrs	25 (6)	226 (22)	17 (20)	39 (18)	23 (20)
3-5yrs	56 (12)	323 (31)	25 (30)	58 (27)	39 (33)
6-10yrs	98 (21)	258 (25)	23 (27)	67 (31)	35 (30)
11yrs+	268 (59)	163 (16)	18 (21)	38 (18)	17 (14)
Previous use of an alternative lens type					
Yes	284 (62)	269[a] (26)	49[b] (58)	177[a] (82)	97[b] (82)
No	174 (38)	768 (74)	35 (42)	38 (18)	21 (18)
Occasional overnight soft lens use (DW patients)					
Yes		130[c] (13)		45[c] (21)	
No		907 (87)		170 (79)	
Extent of overnight use (EW patients)					
Mean no. nights in a row:			18.0[d]		6.46[d]
s.d.			33.78		9.06

Significant differences between SCL and DSCL users with same wear schedule:
a: Chi squared Test: Chi squared=246.879, d.f.=1, p<0.001
b: Chi squared Test: Chi squared= 13.953, d.f.=1, p<0.001
c: Chi squared Test: Chi squared= 14.471, d.f.=1, p<0.001
d: Independent t test: t=3.54, d.f.=200, p<0.001

Key:

Hyper.:	Hypermetropia
Unknown Rx:	Unknown refraction: myopic or hypermetropic
Cosmetic:	Cosmetic (non-medical) only
mo:	months
yrs:	years

TABLE 3.5. DISTRIBUTION OF SOFT LENS DISINFECTION SYSTEMS

	DW-SCL (n=1037) No. (%)	EW-SCL (n=84) No. (%)	DW-DSCL (n=215) No. (%)	EW-DSCL (n=118) No. (%)
Hydrogen peroxide	527[b] (51)	52 (62)	40[b] (19)	11 (9)
Thiomersal*	252[c] (24)	13 (16)	16[c] (7)	5 (2)
Chlorine-release	149[d] (14)	7 (8)	118[d] (55)	9 (8)
Thermal	23 (2)	3 (4)	0	0
Dymed / Polyquad	15 (1)	1 (1)	6 (3)	2 (2)
Chlorhexidine	8 (1)	0	2 (1)	0
Solution for rigid CL	4 (<1)	1 (1)	0	0
`OptimEyes'**	2 (<1)	1 (1)	5 (2)	0
None (no disposal)	57[a] (5)	5 (6)	28[a] (13)	19 (16)
Disposal on removal	0	1	0	72 (63)

Significant differences between DW-SCL and DW-DSCL users:
a: Chi squared Test: Chi squared= 15.942, d.f.=1, p<0.001
b: Chi squared Test: Chi squared= 74.587, d.f.=1, p<0.001
c: Chi squared Test: Chi squared= 30.085, d.f.=1, p<0.001
d: Chi squared Test: Chi squared=174.226, d.f.=1, p<0.001

* Thiomersal-preserved
** Chlorhexidine tablets for use with rising mains tap water

TABLE 3.6. MEAN HYGIENE SCORES FOR EACH LENS TYPE

	Rigid	DW-SCL	EW-SCL	DW-DSCL	EW-DSCL
Mean:	10.22	9.38	9.19[a]	8.95	11.93[a]
s.d.	3.57	3.69	3.62	3.18	4.32

Significant differences between SCL and DSCL users with same wear schedule:
a: Independent t test: t=-4.75, d.f.=200, p<0.001

3.1.1 (v) Distribution of Lens Types Within Each Diagnostic Classification

TABLE 3.7 gives a breakdown of CL types used by patients in each diagnostic category and the frequency of diagnoses within each category is shown in **APPENDICES 7 and 8**. A total of 778 subjects presented with disorders unrelated to CL wear and were therefore eligible as controls.

3.1.2 Microbial Keratitis

There were 98 cases of presumed microbial keratitis amongst the study population during the 12 month period. Data remained incomplete for 4 patients, however: one refused to cooperate, one had died, and two had relocated without leaving a forwarding address. Two had apparently been wearing conventional DW-SCL, and two may have been wearing disposable or conventional SCL. These patients were excluded from the study. The distribution of CL types amongst the 94 cases included in the study are shown in **TABLE 3.7**.

3.1.2 (i) Relative Risk of Microbial Keratitis for Each Lens Type

TABLE 3.8 shows the crude RR for each lens type. DW of disposables was associated with a 3.34 (95% CI: 1.86 - 5.96) times greater risk, and EW of these lenses carried the highest risk, with a RR of 11.46 (5.93 - 22.26). When a direct comparison between EW-SCL and EW-DSCL was made, there was a 3.19 (1.23 - 8.77) times greater risk associated with DSCL.

The preponderance of Acuvue as opposed to other DSCL brands amongst both the cases and controls prevented statistical analysis of risk comparisons between different DSCL types (**APPENDIX 9**).

The pattern of RR persisted when cases were limited to those with a positive tissue culture, although the difference in risk between EW-SCL and EW-DSCL no longer reached significance, probably due to small numbers (**TABLE 3.9**).

TABLE 3.7. DISTRIBUTION OF LENS TYPES WITHIN EACH DIAGNOSTIC CLASSIFICATION

Diagnosis (Totals)	RIGID (n=458)	DW-SCL (n=1037)	EW-SCL (n=84)	DW-DSCL (n=215)	EW-DSCL (n=118)
NON CL-RELATED (778)	212	426	28	86	26
Microbial Keratitis (94)	5	34	8	23	24
Sterile Keratitis (174)	16	98	6	27	27
Toxic & Hypersensitivity Disorders (295)	31	215	11	30	8
Metabolic Disorders (222)	46	116	20	19	21
Mechanical Disorders (274)	114	118	8	24	10
Tear-Resurfacing Disorders (15)	10	3	0	1	1
Miscellaneous Disorders (60)	24	27	3	5	1

TABLE 3.8. RELATIVE RISK OF MICROBIAL KERATITIS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	5	212	0.30	(0.72 - 0.10)	0.0074
DW-SCL	34	426	1.0	(referent)	
DW-DSCL	23	86	3.34	(1.86 - 5.96)	0.0001
EW-SCL	8	28	3.57	(1.43 - 8.28)	0.0068
EW-DSCL	24	26	11.46	(5.93 -22.26)	<0.0001
EW-SCL	8	28	1.0	(referent)	
EW-DSCL	24	26	3.2	(1.23 - 8.77)	0.0231

TABLE 3.9. RELATIVE RISK OF CULTURE-POSITIVE MICROBIAL KERATITIS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	0	212	0.00	(0.00 - 0.81)	0.025
DW-SCL	11	426	1.0	(referent)	
DW-DSCL	10	86	4.49	(1.65 -12.05)	0.003
EW-SCL	3	28	4.13	(0.70 -16.89)	0.116
EW-DSCL	5	26	7.38	(1.87 -25.25)	0.005
EW-SCL	3	28	1.0	(referent)	
EW-DSCL	5	26	1.78	(0.31 -12.60)	0.707

During the study there was considerable interest in the risk of keratitis with DSCL, in both the ophthalmic and lay press (Matthews *et al.*, 1992; Buehler *et al.*, 1992; Anonymous, 1993a; Walsh, 1992a and 1992b). Analysis was undertaken to determine whether, as a result of the impact of these publications, the RR with DSCL changed during the 12 month duration of the study. Homogeneity tests showed that time period variations in RRs for all soft lens types are within sampling variations (**TABLE 3.10**).

3.1.2 (ii) Culture and Severity of Microbial Keratitis Cases

Positive tissue cultures were obtained for 25/80 (31.3%) cases of presumed bacterial keratitis and 4/14 (28.6%) cases diagnosed as *Acanthamoeba* keratitis. The frequency of causative organisms for the culture-positive cases amongst the different lens types is shown in **TABLE 3.11**. *Pseudomonas* was the predominant bacteria, particularly amongst cases using DW-DSCL. Small numbers prevent statistical analysis of the distribution of culture results amongst different lens types, although Acuvue DW-DSCL were associated with *Pseudomonas* (7/16, 44%) (**TABLE 3.11 and APPENDIX 9**).

In total, 44/94 (47%) microbial keratitis cases were classified as `severe', 23/94 (24%) as `moderate', and 27/94 (29%) as `mild', according to criteria previously described (2.1.1 (v)). 16/94 (17%) were admitted, and 7/94 (8%) failed to attain a final Snellen visual acuity of 6/12 or better. **TABLE 3.12** shows the distribution of lens types amongst these severity groups. Amongst DW patients more severe disease, including *Acanthamoeba* keratitis, was significantly more common amongst DSCL users. Conversely, amongst EW patients there was a trend towards *less* severe disease amongst the DSCL users.

In order to test the validity of the inclusion of patients with mild disease the distribution of lens types amongst mild cases of microbial keratitis was compared with the distribution amongst cases of sterile keratitis (**TABLE 3.13**). The distribution of lens types amongst the cases in these two categories was significantly different ($p=0.0033$).

TABLE 3.10. ANALYSIS OF TIME PERIOD VARIATION IN RELATIVE RISK OF MICROBIAL KERATITIS FOR EACH LENS TYPE

	CASE	CTRL	RR	(95% CI)	p VALUE	HOMOGENEITY p VALUE
Presenting 2.3.92-31.8.92:						
Rigid	5	109	0.92	(0.27- 2.96)	0.883	
DW-SCL	11	221	1.0	(referent)		
DW-DSCL	10	38	5.29	(1.92 -14.57)	<0.001	
EW-SCL	6	19	6.34	(1.84 -21.42)	<0.001	
EW-DSCL	10	11	18.26	(5.71 -59.68)	<0.001	
EW-SCL	6	19	1.0	(referent)		
EW-DSCL	10	11	2.88	(0.70 -12.32)	0.098	
Presenting 1.9.92- 1.3.93:						
Rigid	0	103	0.00	?	<0.001	
DW-SCL	23	205	1.0	(referent)		
DW-DSCL	13	48	2.41	(1.07 - 5.42)	0.019	
EW-SCL	2	9	1.98	(0.28 -10.81)	0.393	
EW-DSCL	14	15	8.32	(3.30 -21.11)	<0.001	
EW-SCL	2	9	1.0	(referent)		
EW-DSCL	14	15	4.20	(0.65 -34.16)	0.087	
Stratified (period-adjusted) analysis:						
Rigid	5	212	0.30	(0.10 - 0.81)	0.009	0.005
DW-SCL	34	426	1.0	(referent)		
DW-DSCL	23	86	3.22	(1.76 - 6.07)	<0.001	0.194
EW-SCL	8	28	4.09	(1.55 -10.65)	<0.001	0.230
EW-DSCL	24	26	10.93	(5.59 -23.26)	<0.001	0.251
EW-SCL	8	28	1.0	(referent)		
EW-DSCL	24	26	3.33	(1.10 -10.22)	0.018	0.018

TABLE 3.11. FREQUENCY OF CAUSATIVE ORGANISMS FOR CULTURE POSITIVE MICROBIAL KERATITIS AMONGST DIFFERENT LENS TYPES

ORGANISM	DW-SCL (n=1037)	EW-SCL (n=84)	DW-DSCL (n=215)	EW-DSCL (n=118)	TOTAL
Gram-negative bacteria:					
Pseudomonas	3	3	7	3	16
Serratia	2	0	0	1	3
Acinetobacter	1	0	0	0	1
Gram-positive bacteria:					
Staph. aureus	1	0	0	1	2
Staph. epid.	1	0	1	0	2
Strep. pneu.	1	0	0	0	1
Acanthamoeba	2	0	2	0	4
TOTAL	11	3	10	5	29

Key:
Staph.: Staphylococcus; Strep.: Streptococcus;
epi.: epidermidis; pneu.: pneumoniae

TABLE 3.12. DISTRIBUTION OF LENS TYPES WITHIN EACH MICROBIAL KERATITIS SEVERITY CLASSIFICATION

Daily-wear subjects:

	MICROBIAL KERATITIS				TOTAL
	Mild	Moderate	Severe		
	No. (%)	No. (%)	No. (%)		
DW-SCL	9 (26)	9 (26)	16 (47)	(AK: 3)	34
DW-DSCL	1 (4)	4 (17)	18 (78)	(AK:10)	23
TOTAL	10	13	34		57

Kruskal-Wallis statistic = 6.303 Exact p value = 0.0120

Extended-wear subjects:

	MICROBIAL KERATITIS				TOTAL
	Mild	Moderate	Severe		
	No. (%)	No. (%)	No. (%)		
EW-SCL	2 (25)	2 (25)	4 (50)	(AK: 1)	8
EW-DSCL	12 (50)	6 (25)	6 (25)		24
TOTAL	14	8	10		32

Kruskal-Wallis statistic = 1.957 Exact p value = 0.2267
(not significant)

Key:
AK: *Acanthamoeba* Keratitis

TABLE 3.13. COMPARISON OF THE DISTRIBUTION OF LENS TYPES AMONGST MILD MICROBIAL KERATITIS CASES WITH THAT AMONGST STERILE KERATITIS CASES

	MILD MICROBIAL KERATITIS No. (%)	STERILE KERATITIS No. (%)
Rigid	3 (11)	16 (9)
DW-SCL	9 (33)	98 (56)
DW-DSCL	1 (4)	27 (16)
EW-SCL	2 (7)	6 (3)
EW-DSCL	12 (44)	27 (16)

Fisher's Exact test: p value = 0.0033

3.1.2 (iii) Multivariable Analysis of Lens Type and Other Risk Factors for Microbial Keratitis

Multivariable analysis of risk factors for microbial keratitis was restricted to wearers of SCL and DSCL. DW and EW patients were analysed in separate models. The following variables were included in the analyses:

Age
Gender
Social class
Refraction
CL type
CL age
Length of experience with current CL type
Total length of experience with CL wear
Wear schedule
Occasional overnight use (DW patients)
CL surfactant cleaning score*
CL case cleaning and replacement score*
CL disinfection system & score*
Frequency of enzyme treatment*
Frequency of aftercare advised by practitioner
*or equivalent CL disposal frequency

TABLE 3.14 shows the results of multivariable analysis of risk factors amongst DW users of SCL or DSCL. Even after controlling for other variables, DW-DSCL *per se* carried a 3.51 (1.60 - 7.66) times increased risk of microbial keratitis.

Amongst these DW subjects, disinfection type was also shown to have a very significant effect on the risk. Due to a significant interaction between disinfection type and case cleaning score, data was stratified into `bad' and `good' case cleaners, and re-analysed. Although chlorine-based disinfection carried a 3.77 (1.42 - 9.98) times greater risk than other chemical systems amongst `bad' case cleaners, there was no such association amongst `good' case cleaners **(TABLE 3.14)**.

The inclusion of disinfection type as an extraneous variable hindered multivariable analysis of omitted disinfection as a risk factor; a preliminary multivariable analysis of 6 months' data, however, showed a RR of 4.65 (2.07-10.43, $p<0.001$) for omitted

disinfection with daily disinfection as the referent (Radford *et al.*, 1993a).

Irregular disinfection and occasional overnight use were risk factors of borderline significance **(TABLE 3.14)**. No other variables showed evidence of a significant association with the risk of developing the disease.

Amongst EW patients, controlling for all other variables increased the RR with disposables to 4.76 (1.52 - 4.87) (**TABLE 3.15**). No other variables showed evidence of a significant association.

TABLE 3.14. MULTIVARIABLE ANALYSIS OF LENS TYPE AND OTHER SIGNIFICANT RISK FACTORS FOR MICROBIAL KERATITIS AMONGST DAILY-WEAR USERS OF SOFT LENSES

			RR	(95% CI)	p VALUE
EXPOSURE VARIABLE:					
CL TYPE					
DW-SCL			1.0	(referent)	
DW-DSCL			3.51	(1.60 - 7.66)	0.002
SCL DISINFECTION					
	CASE	CTRL			
Stratum 1: "BAD case cleaners" (case hygiene score <3)					
Hydrogen peroxide / other chemical	11	228	1.0	(referent)	
Chlorine-based	16	69	3.77	(1.42 - 9.98)	0.008
Stratum 2: "GOOD case cleaners" (case hygiene score 3 or 4)					
Hydrogen peroxide / other chemical	15	142	1.0	(referent)	
Chlorine-based	4	40	0.50	(0.13 - 1.90)	0.311
DISINFECTION FREQUENCY					
Daily			1.0	(referent)	
Irregular (score 1 or 2)			2.06	(1.03 - 4.14)	0.041
OCCASIONAL OVERNIGHT USE					
None			1.0	(referent)	
Occasional overnight use			3.95	(1.02 - 15.26)	0.046

TABLE 3.15. MULTIVARIABLE ANALYSIS OF LENS TYPE AS A RISK FACTOR FOR MICROBIAL KERATITIS AMONGST EXTENDED-WEAR USERS OF SOFT LENSES

	RR	(95% CI)	p VALUE
EXPOSURE VARIABLE:			
CL TYPE			
EW-SCL	1.0	(referent)	
EW-DSCL	4.76	(1.52 - 14.87)	0.007

3.1.3 Sterile Keratitis

There were 175 cases of sterile keratitis amongst the study population during the 12 month period, although 1 patient (using SCL) was excluded due to incomplete data. The distribution of CL types amongst the 174 patients in the study is shown in **TABLE 3.7**.

3.1.3 (i) Relative Risk of Sterile Keratitis for Each Lens Type

The risk with DW-DSCL did not differ significantly from that with DW-SCL. EW-DSCL use, however, was associated with a 4.50 (2.41-8.42) times greater risk than DW-SCL and a 4.85 (1.73-13.62) greater risk than EW-SCL (**TABLE 3.16**). Amongst EW-DSCL cases, 26/27 (96%) were using Acuvue.

3.1.3 (ii) Multivariable Analysis of Lens Type and Other Risk Factors for Sterile Keratitis

As for microbial keratitis, multivariable analysis of risk factors for sterile keratitis was restricted to wearers of SCL and DSCL, and DW and EW patients were analysed in separate models. Variables included in the analyses were as listed in Section 3.1.2. (iii).

TABLE 3.17 shows the results of multivariable analysis of risk factors amongst DW users of SCL or DSCL. Due to a significant interaction between current lens type and previous experience of a different lens type, data was stratified according to previous experience and re-analysed. Patients who had switched to DW-DSCL after using a different lens type (or wear schedule) were shown to have an 2.72 (1.15-6.42) times greater risk of sterile keratitis. Amongst patients with no previous lens experience, however, the risk was reduced amongst the DSCL users, although the result was not statistically significant (perhaps due to the small number of DSCL wearers in this group).

Results of the analysis of disinfection system as a risk factor amongst DW patients

showed that inadequate use of disinfection increases the risk two to threefold, but, in contrast to the findings for microbial keratitis, there is no evidence of a difference in risk amongst users of different systems for sterile keratitis **(TABLE 3.17)**.

DW subjects using their lenses for more than 12 hours per day were shown to have a 1.85 (1.19-2.88) times increased risk **(TABLE 3.17)**. No other variables showed evidence of a significant association.

Amongst EW patients DSCL patients were shown to have a 3.53 (1.01-12.28) times increased risk of sterile keratitis **(TABLE 3.18)**. Multivariable analysis of other possible risk factors amongst EW patients was hindered by small numbers.

TABLE 3.16. RELATIVE RISK OF STERILE KERATITIS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	16	212	0.33	(0.18 - 0.58)	<0.001
DW-SCL	98	426	1.0	(referent)	
DW-DSCL	27	86	1.36	(0.81 - 2.26)	0.260
EW-SCL	6	28	0.93	(0.31 - 2.38)	1.000
EW-DSCL	27	26	4.50	(2.41 - 8.42)	<0.001
EW-SCL	6	28	1.0	(referent)	
EW-DSCL	27	26	4.85	(1.73 -13.62)	0.003

TABLE 3.17. MULTIVARIABLE ANALYSIS OF LENS TYPE AND OTHER RISK FACTORS FOR STERILE KERATITIS AMONGST DAILY-WEAR USERS OF SOFT LENSES

	CASE	CTRL	RR	(95% CI)	p VALUE
EXPOSURE VARIABLE:					
CL TYPE					
Stratum 1: No previous lens use					
DW-SCL	317	77	1.0	(referent)	
DW-DSCL	14	1	0.27	(0.03 - 2.36)	0.237
Stratum 2: Previous lens use					
DW-SCL	109	21	1.0	(referent)	
DW-DSCL	72	26	2.72	(1.15 - 6.42)	0.023
SCL DISINFECTION					
Hydrogen peroxide / other chemical:					
optimal use*			1.0	(referent)	
suboptimal use			3.05	(1.18 - 5.13)	<0.001
Chlorine-based:					
optimal use			0.99	(0.51 - 1.94)	0.987
suboptimal use			3.13	(1.44 - 6.79)	0.004
None			2.15	(1.10 - 4.60)	0.048
CL WEAR DURATION					
Upto 12 hours per day			1.0	(referent)	
More than 12 hrs per day			1.85	(1.19 - 2.88)	0.006

*Optimal use: disinfection according to manufacturers' instructions at every CL removal

TABLE 3.18. MULTIVARIABLE ANALYSIS OF LENS TYPE AS A RISK FACTOR FOR STERILE KERATITIS AMONGST EXTENDED-WEAR USERS OF SOFT LENSES

	RR	(95% CI)	p VALUE
EXPOSURE VARIABLE:			
CL TYPE			
EW-SCL	1.0	(referent)	
EW-DSCL	3.53	(1.01 - 12.28)	0.048

3.1.4 Toxic and Hypersensitivity Disorders

The distribution of CL types amongst the 295 subjects in this category is shown in **TABLE 3.7**, and the frequency of specific diagnoses is shown in **APPENDIX 7.**

3.1.4 (i) Relative Risk of Toxic and Hypersensitivity Disorders for Each Lens Type

No significant differences in risk with different soft lens types were shown for toxic and hypersensitivity disorders in general **(TABLE 3.19)**, although more specicific analysis of disorders in this category showed a significant reduction in the occurrence of toxic keratitis amongst DW-DSCL (RR: 0.41, CI: 0.18-0.82) and EW-DSCL users (RR with DW-SCL as referent: 0.14, CI: 0.00-0.84) **(TABLE 3.20)**.

Further analysis of CLPC was undertaken in which data was stratified according to whether an alternative CL type had previously been worn and in which subjects were limited to those with less than 5 years' experience of their present CL type, to allow for the shorter maximum length of experience with DSCL than conventional SCL **(TABLE 3.21)**. The RRs were similar in both strata, and showed no evidence of a protective effect amongst DSCL users.

TABLE 3.19. RELATIVE RISK OF TOXIC AND HYPERSENSITIVITY DISORDERS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	31	212	0.29	(0.19 - 0.44)	<0.001
DW-SCL	215	426	1.0	(referent)	
DW-DSCL	30	86	0.69	(0.34 - 1.10)	0.126
EW-SCL	11	28	0.78	(0.34 - 1.65)	0.619
EW-DSCL	8	26	0.61	(0.23 - 1.42)	0.306
EW-SCL	11	28	1.0	(referent)	
EW-DSCL	8	26	0.79	(0.23 - 2.54)	0.855

TABLE 3.20. RELATIVE RISK OF DIFFERENT TYPES OF TOXIC AND HYPERSENSITIVITY DISORDERS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Papillary conjunctivitis					
Rigid	21	212	0.66	(0.37 - 1.13)	0.141
DW-SCL	64	426	1.0	(referent)	
DW-DSCL	15	86	1.16	(0.59 - 2.18)	0.731
EW-SCL	2	28	0.48	(0.05 - 1.97)	0.479
EW-DSCL	4	26	1.02	(0.25 - 3.09)	1.000
EW-SCL	2	28	1.0	(referent)	
EW-DSCL	4	26	2.13	(0.28 -25.38)	0.671
CL-Related `Red Eye'					
Rigid	1	212	0.07	(0.00 - 0.41)	<0.001
DW-SCL	30	426	1.0	(referent)	
DW-DSCL	5	86	0.83	(0.24 - 2.23)	0.917
EW-SCL	3	28	1.52	(0.28 - 5.37)	0.703
EW-DSCL	3	26	1.64	(0.30 - 7.83)	0.629
EW-SCL	3	28	1.0	(referent)	
EW-DSCL	3	26	1.08	(0.13 - 8.77)	1.000
Toxic keratitis					
Rigid	9	212	0.15	(0.07 - 0.30)	<0.001
DW-SCL	121	426	1.0	(referent)	
DW-DSCL	10	86	0.41	(0.18 - 0.82)	0.009
EW-SCL	6	28	0.75	(0.25 - 1.91)	1.714
EW-DSCL	1	26	0.14	(0.00 - 0.84)	0.023
EW-SCL	6	28	1.0	(referent)	
EW-DSCL	1	26	0.18	(0.00 - 1.67)	0.191

TABLE 3.21. RELATIVE RISK OF PAPILLARY CONJUNCTIVITIS (CLPC) FOR EACH LENS TYPE: STRATIFIED ANALYSIS

	CASE	CONTROL	RR	(95% CI)	p VALUE
Stratum 1: No previous alternative lens use					
Rigid	4	30	0.75	(0.21 - 2.40)	0.603
DW-SCL	38	213	1.00	(referent)	
DW-DSCL	3	14	1.20	(0.26 - 4.77)	0.781
EW-SCL	1	8	0.70	(0.03 - 5.79)	0.740
EW-DSCL	1	3	1.87	(0.07 -20.99)	0.587
Stratum 2: Previous use of an alternative lens type					
Rigid	9	83	0.92	(0.31 - 2.80)	0.874
DW-SCL	8	68	1.0	(referent)	
DW-DSCL	12	71	1.44	(0.51 - 4.14)	0.457
EW-SCL	1	14	0.61	(0.03 - 5.56)	0.649
EW-DSCL	3	23	1.11	(0.21 - 5.19)	0.886
ADJUSTED FOR PREVIOUS LENS EXPERIENCE:					
Rigid	13	113	0.83	(0.38 - 1.83)	0.782
DW-SCL	46	281	1.0	(referent)	
DW-DSCL	15	85	1.35	(0.59 - 3.06)	0.827
EW-SCL	2	22	0.65	(0.10 - 3.14)	0.926
EW-DSCL	4	26	1.26	(0.31 - 4.72)	0.702

3.1.5 Metabolic Disorders

The distribution of CL types amongst the 222 subjects in this category is shown in **TABLE 3.7**, and the frequency of specific diagnoses is shown in **APPENDIX 7**.

3.1.5 (i) Relative Risk of Metabolic Disorders for Each Lens Type

Both EW-SCL and EW-DSCL were associated with significant and similar increases in risk of metabolic disorders in general (RR: 2.62, CI:1.35-5.02 and RR:2.96, CI:1.52-5.69 respectively) **(TABLE 3.22)**). Similar results were obtained for `overwear syndrome', and (not significantly) for hypoxia. There was a trend towards an increased risk of microcystic epitheliopathy and `tight lens syndrome' with EW-DSCL compared to EW-SCL, although small numbers limited statistical analyses. **(TABLE 3.23)**.

3.1.6 Mechanical Disorders

The distribution of CL types amongst the 274 subjects in the mechanical category is shown in **TABLE 3.7**, and the frequency of specific diagnoses is shown in **APPENDIX 7**.

3.1.6 (i) Relative Risk of Mechanical Disorders for Each Lens Type

No significant differences in risk with different soft lens types were shown for mechanical disorders **(TABLE 3.24)**.

3.1.7 Other Lens-Related Disorders

The distribution of CL types amongst subjects in the `tear-resurfacing' and `miscellaneous' categories are shown in **TABLE 3.7**, and the frequency of specific diagnoses is shown in **APPENDIX 7**. Statistical analysis of these two categories was not undertaken: there were insufficient numbers in the `tear-resurfacing' group, and it was considered that meaningful conclusions could not be drawn from any analysis of the `miscellaneous' group due to the unknown pathogenesis of these disorders.

TABLE 3.22. RELATIVE RISK OF METABOLIC DISORDERS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	46	212	0.80	(0.53 - 1.18)	0.279
DW-SCL	116	426	1.0	(referent)	
DW-DSCL	19	86	0.81	(0.45 - 1.41)	0.534
EW-SCL	20	28	2.62	(1.35 - 5.02)	0.004
EW-DSCL	21	26	2.96	(1.52 - 5.69)	0.001
EW-SCL	20	28	1.0	(referent)	
EW-DSCL	21	26	1.13	(0.46 - 2.76)	0.929

TABLE 3.23. RELATIVE RISK OF DIFFERENT TYPES OF METABOLIC DISORDERS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
`Overwear Syndrome'					
Rigid	29	212	0.97	(0.58 - 1.59)	1.000
DW-SCL	60	426	1.0	(referent)	
DW-DSCL	9	86	0.74	(0.31 - 1.58)	0.550
EW-SCL	13	28	3.29	(1.48 - 6.99)	0.003
EW-DSCL	10	26	2.72	(1.11 - 6.20)	0.028
EW-SCL	13	28	1.0	(referent)	
EW-DSCL	10	26	0.83	(0.27 - 2.46)	0.901
Hypoxia					
Rigid	8	212	0.67	(0.26 - 1.57)	0.444
DW-SCL	24	426	1.0	(referent)	
DW-DSCL	4	86	0.83	(0.20 - 2.49)	0.973
EW-SCL	4	28	2.53	(0.60 - 8.12)	0.211
EW-DSCL	3	26	2.04	(0.37 - 7.43)	0.438
EW-SCL	4	28	1.0	(referent)	
EW-DSCL	3	26	0.81	(0.11 - 5.30)	1.000
`Tight Lens Syndrome'					
Rigid	0	212	0.00	(0.00 - 0.46)	0.002
DW-SCL	18	426	1.0	(referent)	
DW-DSCL	5	86	1.38	(0.39 - 3.98)	0.701
EW-SCL	1	28	0.85	(0.02 - 5.76)	1.000
EW-DSCL	6	26	5.43	(1.62 -15.89)	0.006
EW-SCL	1	28	1.0	(referent)	
EW-DSCL	6	26	6.30	(0.69-307.60)	0.136
Microcystic epitheliopathy					
Rigid	8	212	1.46	(0.50 - 4.05)	0.563
DW-SCL	11	426	1.0	(referent)	
DW-DSCL	1	86	0.45	(0.01 - 3.18)	0.762
EW-SCL	1	28	1.38	(0.03 -10.16)	1.000
EW-DSCL	2	26	2.97	(0.30 -14.71)	0.362
EW-SCL	1	28	1.0	(referent)	
EW-DSCL	2	26	2.13	(0.10-131.53)	0.973

TABLE 3.24. RELATIVE RISK OF MECHANICAL DISORDERS FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	114	212	1.94	(1.41 - 2.67)	<0.001
DW-SCL	118	426	1.0	(referent)	
DW-DSCL	24	86	1.01	(0.59 - 1.68)	1.000
EW-SCL	8	28	1.03	(0.40 - 2.40)	1.000
EW-DSCL	10	26	1.39	(0.58 - 3.08)	0.506
EW-SCL	20	28	1.0	(referent)	
EW-DSCL	21	26	1.34	(0.40 - 4.58)	0.786

TABLE 3.25 RELATIVE RISK OF ANY LENS-RELATED DISORDER FOR EACH LENS TYPE

	CASE	CONTROL	RR	(95% CI)	p VALUE
Rigid	246	212	0.81	(0.64 - 1.02)	0.069
DW-SCL	611	426	1.0	(referent)	
DW-DSCL	129	86	1.05	(0.77 - 1.43)	0.833
EW-SCL	56	28	1.39	(0.85 - 2.32)	0.201
EW-DSCL	92	26	2.47	(1.55 - 4.04)	<0.001
EW-SCL	56	28	1.0	(referent)	
EW-DSCL	92	26	1.76	(0.90 - 3.48)	0.105

TABLE 3.26. COMPARISON OF THE DISTRIBUTION OF LENS TYPES AMONGST A SAMPLE OF NON-RESPONDENTS WITH THAT AMONGST STUDY PATIENTS

	NON-RESPONDENTS,* Nov.1992-Feb.1993		STUDY PATIENTS	
Rigid	21	(21.2%)	458	(23.9%)
DW-SCL	64	(64.7%)	1037	(54.2%)
DW-DSCL	8	(8.1%)	215	(11.2%)
EW-DSCL	4	(4.0%)	84	(4.4%)
EW-DSCL	2	(2.0%)	118	(6.2%)
(Undetermined	10)			

Chi squared Test: Chi squared= 5.755, d.f.=4, p=0.2143 (not significant)

* CL type obtained from medical notes only

3.1.8 Relative Risk of Any Lens-Related Disorder for Each Lens Type

EW-DSCL were the only group of lens wearers to show a significant increase in risk for lens-related disorders in general (RR:2.47 (1.55-4.40)) although risks with EW-SCL and EW-DSCL did not differ significantly (**TABLE 3.25**).

3.1.9 Analysis of Non-Respondents

TABLE 3.26 shows that the distribution of CL types amongst a sample of non-respondents (patients failing to return the postal questionnaire) did not differ significantly from that amongst patients included in the study.

3.2 RETROSPECTIVE CASE-CONTROL STUDY OF *ACANTHAMOEBA* KERATITIS

3.2.1 Subjects

3.2.1 (i) Cases

During the three year period 1.9.89 to 31.8.92 47 patients with a diagnosis of CL-related *Acanthamoeba* keratitis (AK) were treated at MEH. Twelve of these patients were excluded from the study: 1 patient had been wearing a bandage CL for pre-existing ocular surface disease; 3 patients, presenting July 1990, February 1991 and August 1991 and wearing RGP, DW-DSCL and DW-SCL respectively, could not be traced in order to verify CL care data; and 8 patients (2 RGP, 3 DW-SCL AND 3 DSCL users) were non-UK residents.

Complete data was obtained for the remaining 35 cases. **FIGURE 3.1** shows how the increasing number of cases each year is paralleled by the increasing proportion of cases associated with DSCL use. Positive tissue cultures were obtained for 14/35 (40%), and *Acanthamoebae* were isolated from the contact lens, CL case or solutions for a further 8/35 patients (23%). Twelve patients presented as primary referrals during the latter 12 month period (1.9.91 to 31.8.92), and were therefore eligible for Study One.

3.2.1 (ii) Controls

During the 6 month period 1.3.92 to 31.8.92 complete data was obtained from 1025 CL wearers attending MEH A&E as new patients. 378/1025 (37%) patients were attending with disorders unrelated to CL wear and were therefore eligible as controls.

Characteristics of the study population are shown in **TABLE 3.27.**

FIG.3.1. LENS TYPES ASSOCIATED WITH
ACANTHAMOEBA KERATITIS, 1989-1992

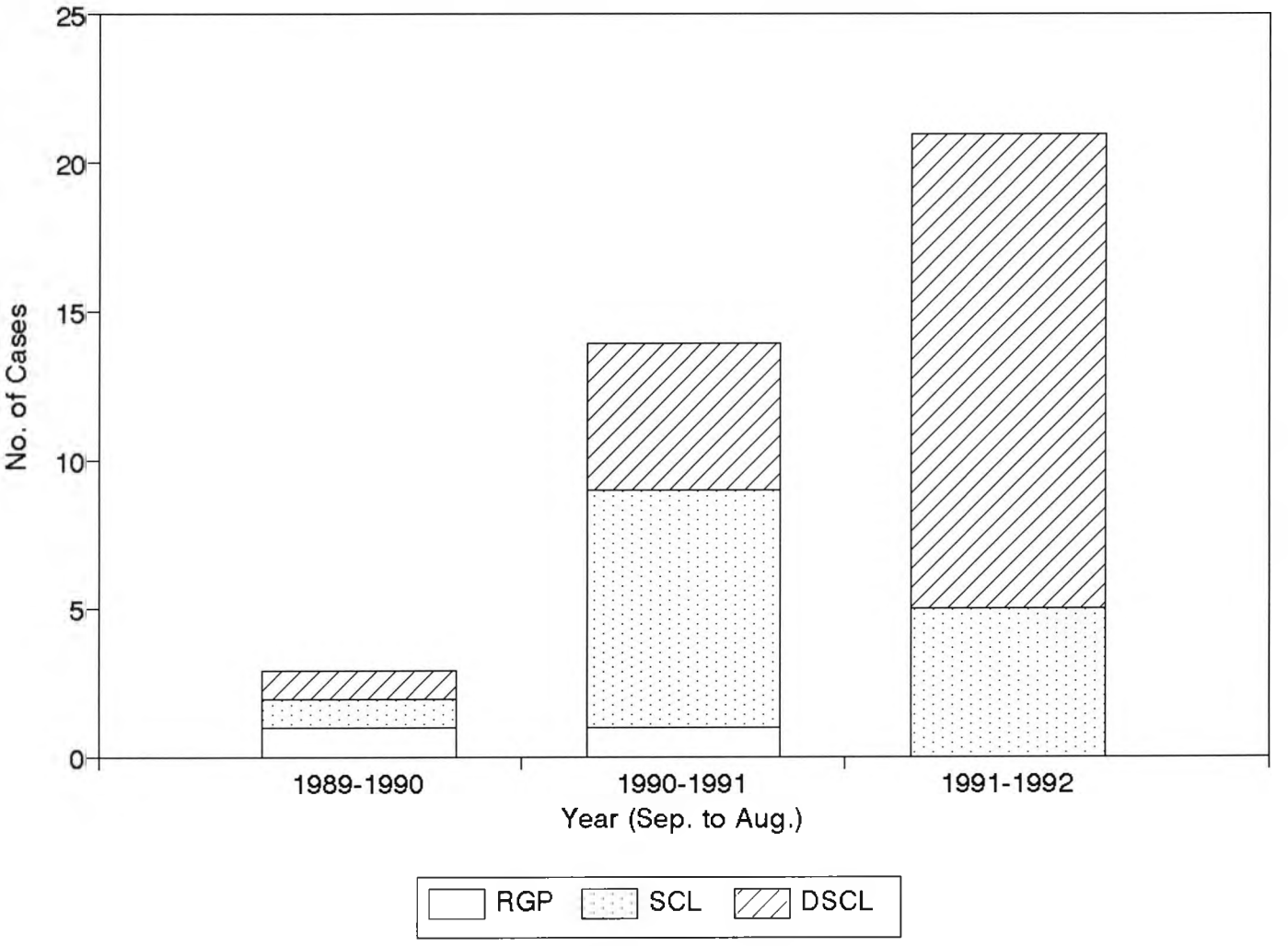

TABLE 3.27. RETROSPECTIVE CASE-CONTROL STUDY OF *ACANTHAMOEBA* KERATITIS: CHARACTERISTICS OF THE STUDY POPULATION.

	STUDY ONE		STUDY TWO	
	CASES n=12	CONTROLS n=378	CASES n=31	CONTROLS 240
Age (years)				
mean	31.50	31.34	31.39	29.89
range	(18-55)	(14-66)	(18-56)	(14-66)
Sex				
(M:F)	3:9	134:244	14:17	90:150
(%M)	(25)	(35)	(45)	(37)
Social Class				
1/2:3/4/5	10:2	238:140	20:11	145:95
(% 1/2)	(83)	(63)	(64)	(60)
Lens type (%)				
DW-SCL	1 (8)	208 (55)	12 (39)	203 (85)
EW-SCL	1 (8)	18 (5)		
DW-DSCL	9 (75)	37 (10)	19 (61)	37 (15)
EW-DSCL	1 (8)	11 (3)		
Rigid CL	0 (0)	104 (27)		
Disposable lens type (%)				
Acuvue	10(100)	35 (73)	19(100)	24 (65)
Surevue	0	7 (15)	0	7 (19)
SeeQuence	0	3 (6)	0	3 (8)
NewVue	0	2 (4)	0	2 (5)
Calendar	0	1 (2)	0	1 (3)
Soft lens disinfection (%)				
None	5 (42)	12 (4)	9 (29)	10 (4)
Hyd. peroxide	1 (17)	145 (53)	1 (3)	132 (55)
Chlorine-based:	6 (50)	49 (18)	19 (61)	47 (20)
Softab*	5 (83)	18 (37)	17 (90)	39 (83)
Aerotab**	1 (17)	2 (4)	1 (5)	6 (13)
`Either'			1 (5)	2 (4)
Other chemical	0	54 (20)	1 (3)	49 (20)
Thermal	0	5 (2)	0	excluded
Rigid CL soln.	0	2 (1)	1 (3)	2 (1)
Disposal	0	7 (2)	0	0

*Sodium Dichloroisocyanurate 0.065mg
**Halazone 0.16mg

Key:
Hyd. peroxide: Hydrogen peroxide
soln.: solution

3.2.2 Study One: Relative Risk of *Acanthamoeba* Keratitis for Each Lens Type

DW-DSCL were used by 9/12 (75%) of the AK cases, but by only 37/378 (9.8%) of the controls. The crude RR associated with DW-DSCL as opposed to DW-SCL (the referent) was estimated as 49.45, with a minimum relative risk of 6.53 ($p<0.001$) **(TABLE 3.28)**. A high prevalence of omitted disinfection (5/12) or chlorine-based disinfection (6/12), however, emphasised the need for multivariable analysis in order to separate the risk associated with DSCL wear from that associated with the CL care habits commonly adopted by these wearers.

3.2.3. Study Two: Multivariable Analysis of Hygiene Practices and Other Risk Factors for *Acanthamoeba* Keratitis

Since DW use of soft CL (disposable or conventional) was associated with 31/35 (88%) of the AK cases, and there were insufficient cases amongst users of other CL types, analysis of further risk factors was restricted to patients using these lenses. The 5 controls using heat disinfection were also excluded, since the absence of this method amongst the cases prevented their contribution to the analysis.

Variables included in the analysis of risk factors for AK amongst these subjects are listed in section 3.1.2 (iii). The use of non-sterile saline/water could not be incorporated into the model, as it was too closely linked with the disinfection score (see **APPENDIX 4**). Separate analysis, however, showed a significantly increased risk of AK (12.51, 95% CI: 1.37-156, $p=0.023$) associated with its use. The risk associated with swimming while wearing CL was not evaluated, since this data was not available for the controls. It was noted, however, that 3/35 (8.6%) of the cases had been swimming while wearing their lenses shortly before developing AK.

The brand of DSCL used was also excluded from the multivariable analysis, due to insufficient numbers using types other than Acuvue: amongst DW-DSCL patients, all 19 cases and 24/37 (65%) of the controls were using Acuvue. A crude minimum RR

for Acuvue compared to other DSCL brands was estimated as 2.63 (95% CI: 2.63 to infinity, p=0.004).

TABLE 3.29 shows the RR and 95% CI for the most important exposure factors. Although Study One's crude analysis showed a 49.5 times increased risk associated with DW-DSCL wear, multivariable analysis showed that the excess risk due to the actual lenses is comparatively small (RR=3.82, 95% CI: 1.01 - 14.48, p=0.049). This RR is probably an underestimation of the current situation, however, due to the increasing penetrance of DSCL in the MEH Casualty population during the three year period in which AK cases were collected (Matthews *et al.*, 1992).

The model factor with the greatest effect on the risk of AK was the type and standard of disinfection used. Failure to disinfect carried a greatly increased risk of AK (55.86, p<0.001), but chlorine-based disinfection, even when used optimally, was also shown to carry a significantly increased risk compared to hydrogen peroxide or other chemical systems (RR: 14.63, p=0.001) **(TABLE 3.29)**.

There was no significant higher-order interaction (effect modification) between CL type and disinfection procedures. This suggests that the RR for different methods of disinfection are good weighted averages that apply to both disposable and conventional DW soft CL wearers. The population attributable risk percentage (with 95% CI), after controlling for CL type, was estimated as 56.3% (27%-86%) for use of chlorine-based disinfection, and 31.8% (8%-55%) for omitted disinfection.

There was a suggestion that surfactant cleaning and receiving of after-care advice each had a small protective effect against the risk of developing the disease, but neither factor reached statistical significance. None of the remaining factors showed evidence of a significant association with the risk of AK in this data.

TABLE 3.28. RELATIVE RISK OF *ACANTHAMOEBA* KERATITIS FOR EACH LENS TYPE (STUDY ONE).

	CASE	CONTROL	RR	(95% CI)	p VALUE
DW-SCL	1	208	1.0	(referent)	
EW-SCL	1	18	11.27	(0.14 - 911)	0.320
DW-DSCL	9	37	49.45	(6.53 - 2227)	<0.001
EW-DSCL	1	11	18.15	(0.22 - 1491)	0.106
Rigid CL	0	104	-----	-----	-----

TABLE 3.29. MULTIVARIABLE ANALYSIS OF LENS TYPE AND OTHER SIGNIFICANT OR MARGINAL RISK FACTORS FOR *ACANTHAMOEBA* KERATITIS AMONGST DAILY-WEAR USERS OF SOFT LENSES (STUDY TWO)

	RR	(95% CI)	p VALUE
EXPOSURE VARIABLE:			
CL TYPE			
DW-SCL	1.0	(referent)	
DW-DSCL	3.82	(1.01 - 14.48)	0.049
SCL DISINFECTION			
Hydrogen peroxide / other chemical	1.0	(referent)	
Chlorine-based:			
optimal* use	14.63	(2.8 - 76)	0.001
suboptimal use	41.05	(7.3 - 232)	<0.001
None	55.86	(10.0 - 302)	<0.001
SURFACTANT CLEANING			
At least 2x per wk.	1.0	(referent)	
< 2x per week	3.50	(0.94 - 13.10)	0.062
ADVICE ON AFTERCARE			
Given	1.0	(referent)	
Not given/recalled	3.49	(0.95 - 12.81)	0.06

*Optimal use: disinfection according to manufacturers' instructions at every CL removal

3.2.4. Study Three: Stratified Analysis of Hygiene Practices and Other Risk Factors for Culture-Positive *Acanthamoeba* Keratitis

A separate analysis was performed in which cases were restricted to those with a positive tissue culture. Due to the small number of such cases (n=13), and since there were no cases amongst the referent groups of some of the key factors, analysis was carried out by stratifying the data by a few important extraneous factors and using Exact procedures for significance tests and estimations of RR. **TABLE 3.30** shows that exclusion of culture-negative cases gives similar or slightly increased lower confidence limits for the excess risks associated with the use of chlorine disinfection and omitted disinfection. With the smaller number of cases, however, the excess risk associated with DSCL failed to reach significance.

TABLE 3.30: MULTIVARIABLE ANALYSIS OF RISK FACTORS FOR CULTURE-POSITIVE *ACANTHAMOEBA* KERATITIS AMONGST DAILY-WEAR USERS OF SOFT LENSES (STUDY THREE).

A) ASSESSMENT OF DISINFECTION TYPE AND USAGE

	CASES	CONTROLS	TOTAL
H. peroxide/other chem.	0	181	181
Chlorine-based: optimal*	7	35	42
suboptimal	2	12	14
None	4	12	16

	RR adjusted for AGE & CL TYPE	95% LOWER CONF. LIMIT	p VALUE
H. peroxide/other chem.	1.0	(referent)	
Chlorine-based: optimal	Infinite	6.49	<0.001
suboptimal	Infinite	7.29	0.004
None	Infinite	15.20	<0.001

	RR adjusted for SEX & CL TYPE		
H. peroxide/other chem.	1.0	(referent)	
Chlorine-based: optimal	Infinite	5.14	0.002
suboptimal	Infinite	5.54	0.006
None	Infinite	8.02	<0.001

	RR adjusted for CLEANING & CL TYPE		
H. peroxide/other chem.	1.0	(referent)	
Chlorine-based: optimal	Infinite	4.43	0.002
suboptimal	Infinite	4.19	0.010
None	Infinite	14.93	<0.001

B) ASSESSMENT OF LENS TYPE

	CASES	CONTROLS	TOTAL
DW-SCL	7	203	210
DW-DSCL	6	37	43

	RR adjusted for CLEANING & DISINFECTION	95% LOWER CONF. LIMIT	p VALUE
DW-SCL	1.0	(referent)	
DW-DSCL	2.19	0.25-14.12	0.589

Key: H. peroxide/other chem.: Hydrogen peroxide / non-chlorine based chemical systems
*Optimal use: disinfection according to manufacturers' instructions at every CL removal

CHAPTER 4. DISCUSSION

4.1 PROSPECTIVE CASE-CONTROL STUDY OF MICROBIAL KERATITIS AND OTHER COMPLICATIONS

4.1.1 Study Design

This study compared the risks of a range of acute and sub-acute lens-related disorders amongst users of different types of SCL in a hospital A&E population. Use of this population enables study of subjects from over 500 different practices in a catchment area estimated at 2.5 million (Stapleton, 1991), thereby avoiding bias due to differing patient management and socioeconomic characteristics between practices.

Despite the exclusion of subjects with a medical indication for lens wear or any previous attendance at the hospital it is still possible that this population may not be entirely representative of lens wearers in general. Controls, however, were limited to those presenting with a disorder unrelated to lens wear, in order to avoid bias due to the inclusion of patients whose condition might predispose to the disease under analysis and/or share similar risk factors. From previous studies it was hypothesized that disposable lenses might reduce some of the less serious complications, whilst failing to protect against or increasing the risk of suppurative keratitis; inclusion of subjects with lens-related diagnoses amongst the control group for such cases might therefore have over-estimated any excess RR of suppurative keratitis with DSCL, due to under-representation of DSCL in other diagnostic categories. It should be emphasised, however, that although controls were patients presenting with a disorder unrelated to lens wear, they were not selected for *absence* of lens-related disease: it is therefore likely that the distribution of minor and/or chronic lens-related disease amongst these patients was representative of the general lens-wearing population.

Lens use, hygiene and personal data were obtained by self-administered questionnaire. Although honest reporting can never be guaranteed, recall and response rates were maximised by giving the questionnaire at the patient's first visit, whenever possible. Fur-

thermore, the stimulus for recall and accurate reporting is unlikely to have varied with case or control status, since all subjects were attending with acute disease (Schlesselman, 1982).

1912 of 2294 (83%) eligible or potentially eligible subjects with hospital notes provided complete data. In a busy A&E Department it is inevitable that some patients will not be offered a questionnaire or will not be reminded if they fail to return it. In view of the ophthalmic and lay press attention to sight-threatening infection associated with DSCL published during the study (Matthews *et al.*, 1992; Buehler *et al.*, 1992, Walsh, 1992a, 1992b; Anonymous, 1993a) analysis of lens types amongst a sample of non-respondents was undertaken. There was no evidence of any increased efforts to recruit DSCL users into the study, or of heightened interest in participation amongst DSCL users. It is therefore reasonable to conclude that exclusion of these nonrespondents is unlikely to have biased relative risk estimates for each lens type.

There are several potential sources of bias associated with comparisons between users of conventional and disposable lenses. Firstly, the use of DSCL as a panacea for poor hygiene compliance and/or depositing problems with other lens types may have increased the number of patients with these characteristics amongst the DSCL users. For microbial and sterile keratitis any trend towards poor compliance amongst DSCL users will have been controlled by the inclusion of hygiene scores for each aspect of lens care in the multivariable analysis. Controlling for history of problems with an alternative lens type was also undertaken for these analyses, albeit indirectly, by including the experience of an alternative lens type as a variable. For the evaluation of lens type as a risk factor for CLPC, stratified analysis with respect to previous lens experience was undertaken. Analyses of other diagnostic groups, however, could be liable to bias associated with the possibility that the DSCL using population differ with respect to their tendency to compliance and lens spoilation.

Another potential source of bias when comparing the two modalities is the limited power range for DSCL compared to conventional SCL: during the study period patients requiring a BVP outside the range of -9.00DS to +6.00DS would not be candidates for DSCL, and therefore may be over-represented amongst the conventional SCL users. The pooled results of three studies of the distribution of ametropia, however, suggest that only 0.3% to 3.2% of individuals have an ocular refraction outside this range (Bennett and Rabbetts, 1989). With respect to hypermetropia bias seems unlikely anyway, since the proportion of hypermetropic patients was small (<8%) and similar amongst DSCL and SCL users. An excess of high myopes amongst the controls may have occurred, particularly in association with retinal disorders. Even if all retinal cases were associated with high myopia, however, these patients only accounted for 18/778 (2.3%) of the controls. Furthermore, patients with high refractive errors are eligible for Hospital Eye Service CL fitting; since all patients in the study were fitted in private practice for non-medical indications the number of high myopes in the study is likely to have been very small. In summary, the likelihood of a marked difference in the distribution of the refractive errors in the two modality groups is unlikely.

Other potential sources of bias for which control was not possible in this study include a number of miscellaneous patient and practitioner factors. For example, the intense marketing of DSCL may have persuaded practitioners to fit patients for whom the limited fitting parameters were less than ideal, perhaps resulting in a lower standard of lens fit amongst DSCL than amongst conventional SCL wearers. Also, the emphasized convenience may have encouraged the fitting of individuals previously thought to be unsuitable for lens wear, and may have encouraged some patients to wear them under adverse conditions.

In summary, this hospital-based case-control study has allowed evaluation of the relative risks of acute complications with different SCL wear modalities amongst a well-

defined population comprising CL wearers from many different practices. Despite the impossibility of controlling for the less tangible patient and practitioner factors possibly associated with DSCL wear, the principal findings of this study, derived from multi-variable and/or stratified analysis, are likely to be applicable to the general CL wearing population in the UK.

4.1.2 Lens-Related Disease in the Hospital A&E Population

The proportion of new A&E attenders presenting with CL-related disease during the study period was between 3.5% (1134 / 32670) and 4.1% (1325 / 32670), the latter figure including the potentially eligible patients for whom lens wear data was incomplete. This is similar to the 3.8% (1104 / 29242) included in the previous study, conducted in 1988-1989 (Stapleton, 1991). In view of the increasing penetrance of lens wear, this may reflect a slightly decreased incidence of lens-related disorders. A reduction in the prevalence of extended-wear would be expected to reduce substantially the incidence of lens-related disease (Stapleton, 1991); however there was no evidence of such a trend in this population **(TABLE 4.1)**.

TABLE 4.1. COMPARISON OF THE DISTRIBUTIONS OF LENS TYPES IN THIS STUDY AND THE PREVIOUS STUDY (STAPLETON, 1991)

Study:	STAPLETON (1991)	THIS STUDY
Study time period:	22.4.88-21.4.89	2.3.92-1.3.93
Subjects with disorders UNRELATED to CL wear:	n = 507	n = 778
CL TYPE:	No. (%)	No. (%)
Rigid	163 (32.1)	212 (27.2)
DW soft	309 (60.9)	512 (65.8)
EW soft	35 (6.9)	54 (6.9)

Note: Stapleton's study included 20 DSCL users, categorized as DW or EW soft according to wear schedule

4.1.3 Demographic, Lens Use and Hygiene Characteristics of Wearers of Each Lens Type

The greater mean age for EW-SCL (and rigid lens wearers) might be explained by these groups containing more experienced lens wearers fitted with PMMA and long-term EW-SCL several years ago when these lenses were more popular.

Although males showed a preference for extended-wear schedules, the proportion of males in conventional and disposable users groups did not differ significantly.

The greater proportion of subjects in social classes 1 and 2 (professional, managerial and technical occupations) amongst DSCL users is unsurprising, given the greater cost of this modality compared to others. Other factors, such as an increased demand for convenience, including the purported reduction in complications, may also be influencing the choice of lens type amongst these social groups.

The increased proportion of subjects with experience of alternative lens types or wear schedules amongst DSCL users may be illustrating the use of DSCL as a problem-solver; this is consistent with findings of a comparative cohort study (Boswall *et al.*, 1993) in which the EW-DSCL users were noted to include a significantly lower proportion of novice lens wearers, and a higher proportion of patients with a history of complications, than conventional EW-SCL users.

Occasional overnight use was significantly more common amongst the DW patients using DSCL than those using conventional DW-SCL. There is a possibility of biased reporting, however: overnight use among DW-SCL may have been underestimated since these patients may have been less willing than DW-DSCL users to be honest about this habit, the latter perhaps being aware they are wearing a lens suitable for EW (70% were wearing Acuvue) and/or having been told that occasional EW with their lenses was acceptable. The high prevalence of unscheduled overnight use amongst DW-

DSCL users is regrettable, since this tendency may negate any positive advantages of frequent lens replacement with DW use. The questionnaire did not enable quantification of occasional overnight use: it is possible that this was not only a more common habit, but also occurred more frequently amongst users of DW-DSCL than DW-SCL (for example, monthly as opposed to just once or twice per year). This would have contributed to the excess risk for microbial keratitis with DW-DSCL.

Amongst EW subjects the extent of continuous overnight use was significantly *less* amongst DSCL patients than amongst conventional SCL users. This is an important result, since continuous overnight wear in excess of 6 nights is associated with an increased risk of microbial keratitis (Stapleton *et al.*, 1993a).

The high proportion of DW-DSCL subjects using chlorine-release systems rather than hydrogen peroxide reflects both the demand for simplicity of DSCL care and the earlier concerns regarding the suitability of the latter system with some types of DSCL (Harris *et al.*, 1989; McKenney, 1990). Subsequently, a new one-step hydrogen peroxide system and a range of multi-purpose chemical disinfectants have been introduced, and are likely to become popular with DSCL users. Only 63% (72/118) of EW-DSCL users were discarding their lenses each time they were removed, and 16% (19/118) failed to use any disinfection before re-using their lenses. In spite of this, the EW-DSCL patients had a significantly higher average standard of hygiene. Despite the omission of surfactant cleaning by the majority of DW-DSCL users, the mean hygiene score for DW-DSCL was not significantly different to that for conventional DW-SCL, due to compensating improved attention to other aspects of lens care amongst these users.

4.1.4 Microbial Keratitis

The use of a clinical case definition for microbial keratitis was based on the need for a diagnostic corneal culture and instigation of intensive antibiotic therapy; this may have led to the inclusion of a few non-infective cases. The validity of this definition, how-

ever, is supported by the consistency of the relative risks when they are re-calculated using only those cases with a positive culture. Furthermore, the differing distribution of lens types amongst cases of mild keratitis as opposed to sterile keratitis supports their classification as different disease entities.

Although positive culture rates of 52%-54% have been reported amongst patients with lens-related microbial keratitis at centres in the USA (Galentine *et al.*, 1984; Alfonso *et al.*, 1986), inclusion of less severe cases in studies at MEH has inevitably led to lower rates: 15% (9/60) in the previous study (Stapleton, 1991), and 31% (29/94) in this study. These lower rates are in keeping with a review of cosmetic CL-related cases in the USA in which a similar case definition was employed (Schein *et al.*, 1989). As in other series of lens-related infections, *Pseudomonas* was the predominant bacterium isolated (Wilhelmus, 1987; Dart *et al.*, 1991). This series, however, contained an unusually large number of cases of *Acanthamoeba* keratitis: only 1 of 60 (1.7%) cases in the previous study (Dart *et al.*, 1991) was attributed to *Acanthamoeba*, compared to 10/94 (10.6%) of cases in this series. This marked increase in frequency, together with the predominance of DW-DSCL use (10/14) and/or chlorine-based disinfection (6/14) amongst these cases, prompted a more extensive evaluation of this trend, using multi-variable analysis (Section 4.2).

Although the threefold reduction in risk of microbial keratitis with rigid CL compared to conventional SCL is in keeping with findings of the previous study (Dart, 1991), the excess risk with extended-wear use of SCL, after adjusting for differing referents, was reduced compared to previous studies (Schein *et al.*, 1989; Dart *et al.*, 1991). This may be due to a reduction in the number of EW patients wearing their lenses continuously for more than 6 days, following the 1989 FDA recommendations of a 7-day continuous wear limit.

Relative risks for DSCL follow a similar trend to that shown in the 3 month pilot study

(Matthews *et al.*, 1992), where DW-DSCL and EW-SCL were shown to carry similar risks and EW-DSCL carried a much higher risk than any other type of lens use. In this earlier study, however, small numbers led to wide confidence limits and hindered detailed statistical comparisons between lens wear modalities. The RR calculated for DW-DSCL compared to DW-SCL in this study is almost identical to that reported by the recently published re-analysis (Schein *et al.*, 1994) of the Buehler *et al.* (1992) study. This is the first study, however, with the power to show a significant excess risk for EW-DSCL compared to conventional EW-SCL.

These increased risks with DSCL contradict the results of previous comparative studies, in which disposables were reported to have a similar or reduced risk of corneal infection to conventional SCL used with the same wear schedule (Poggio *et al.*, 1993a and 1993b; Nilsson and Montan, 1994a and 1994b; Guillon *et al.*, 1994). These studies, however, did not have the statistical power to detect relative risks of the level found in this study (Poggio *et al.*, 1993a and 1993b; Guillon *et al.*, 1994), or were conducted in a country in which patient supervision, and (perhaps consequently) the incidence and severity of ulcers, appears to differ markedly from that in most studied CL wearing populations (Nilsson and Montan, 1994b).

The relative risks for DSCL persist throughout the study, despite considerable ophthalmic and lay press attention to the risks associated with these lenses (Buehler *et al.*, 1992; Matthews *et al.*, 1992; Walsh, 1992a and 1992b) and production of professional guidelines (Anonymous, 1993a) during its course. This suggests that revised recommendations regarding hygiene with DSCL have not reduced the risk associated with these lenses.

DW-DSCL were significantly associated with more severe microbial keratitis, particularly *Acanthamoeba* keratitis. Multivariable analysis results suggest that this association is a consequence of the use of chlorine-based disinfection, saline soaking and occasion-

al overnight use amongst this group. The association between *Acanthamoeba* keratitis and DW-DSCL wear was further explored in the second part of this study.

Amongst extended-wear patients, an association between DSCL and *mild* keratitis, although not statistically significant, is in agreement with trends described in comparative studies (Poggio *et al.*, 1993a; Nilsson and Montan, 1994a and 1994b), a review of cases (Laibson *et al.*, 1993), and clinical observations (Donshik, 1993). The results of this study, however, suggests that this trend cannot be cited in favour of EW-DSCL, since *all* degrees of severity were more common with EW-DSCL than with EW-SCL. It is possible that this preponderance of peripheral ulcers amongst EW-DSCL users may be related to the high incidence of edge defects found in Acuvue lenses, which have been shown to cause statistically significant changes in corneal and conjunctival integrity after 1 week of extended wear (Efron and Veys, 1992); 10/12 of the EW-DSCL patients with peripheral ulcers were using Acuvue.

The excess risk of microbial keratitis with DSCL persisted after multivariable analysis, for both DW and EW patients. As discussed earlier, it is possible that unscheduled overnight use was not only more common, but occurred more frequently, amongst DW-DSCL than amongst conventional DW-SCL. It is also possible that, despite the detailed assessment of hygiene standards, there may have been unidentified aspects of inadequate lens care for which this study has not sufficiently controlled. The most striking result of this study, however, is the excess risk with DSCL amongst *extended-wear* subjects, despite their significantly reduced extent of overnight wear and superior hygiene standards. This result strongly suggests that it is not possible to attribute excess risks of microbial keratitis with DSCL to patterns of overnight use and hygiene factors; one or more properties of the lenses themselves are likely to be contributing to the risk.

The predominance of Vistakon lenses amongst the DSCL prevented analysis of the relative risks with different DSCL brands. Given their predominance, however, toge-

ther with their relatively uncommon ionic material and the revolutionary manufacturing method with which they are produced, it seems possible that an excess risk with DSCL *per se* is attributable to these lenses. Further research needs to be directed at the effects of their apparent tendency to tighten (Maguen *et al.*, 1991) and their increased level of *in vivo* dehydration (Brennan *et al.*, 1990; Helton and Watson, 1991) and manufacturing defects (Efron and Veys, 1992), and the quantity and nature of tear protein deposition on these lenses (Sack *et al.*, 1987; Lin *et al.*, 1991; Tripathi and Tripathi, 1992). These factors may be increasing the frequency of both mechanical and metabolic corneal compromise in these wearers, thereby increasing the risk of corneal invasion by pathogenic organisms (DiGaetano *et al.*, 1986; Klotz *et al.*, 1989; Lawin-Brussel *et al.*, 1990; Imayasu *et al.*, 1993; Solomon *et al.*, 1994). The results of this study suggest that the extent of bacterial adherence, reported as reduced for both new and worn ionic lenses (Stapleton *et al.*, 1993b; Boles *et al.*, 1992), is of limited importance in the pathogenesis of microbial keratitis; study of the process of bacterial *colonisation* of lenses and subsequent invasion of corneas subjected to these factors, ideally in an animal model, may be more appropriate for elucidating the reasons for differing risks.

Lens disposability, however, was only one of several risk factors for microbial keratitis identified by multivariable analysis of DW subjects: the use of chlorine-based disinfection (as opposed to other chemical systems) amongst individuals with poor lens case hygiene, irregular disinfection and occasional overnight use were associated with similar increases in risk.

Chlorine-based disinfection has already been identified as a significant risk factor for microbial keratitis in a recent multivariable analysis of an earlier study at this centre (Stapleton *et al.*, 1993a), although case hygiene standards were not assessed and may have influenced the results; in the present study this type of disinfection only carried an increased risk amongst patients with poor case hygiene, performing as well or better than other chemical systems amongst those who regularly cleaned and/or replaced their

case.

Since organisms responsible for a corneal infection have been isolated from the lens storage cases of the affected individuals (Mondino *et al.*, 1986; Stapleton, 1991; Bacon *et al.*, 1993) this association between an increased risk of infection with chlorine-based disinfection in conjunction with poor case hygiene supports the findings of a large microbiological study in which users of this system had a significantly increased likelihood (RR:2.2, 95% CI: 1.39-3.56) of lens case contamination compared to users of hydrogen peroxide (Devonshire *et al.*, 1993). *In vitro* studies of the relative efficacy of chlorine have been contradictory (Lowe *et al.*, 1992; Rosenthal *et al.*, 1992), perhaps due to interstrain variability in susceptibility to disinfectants. More importantly, these *in vitro* tests probably do not reflect the relative efficacy of these agents *in vivo*, since organisms contaminating CL and cases have been shown to live in biofilms (Wilson *et al.*, 1990) and have increased resistance to disinfectants (Costerton *et al.*, 1987; Gristina *et al.*, 1987). The apparent ability of good case hygiene to reverse the excess risk with chlorine suggests that this system is highly dependent on prior reduction of biofilm, as well as removal of organic debris (Copley, 1989), in order to be effective. Since this study was conducted the leading manufacturer of chlorine-based disinfection systems, Alcon Laboratories UK Ltd, have repackaged their system to include a new storage case with each month's supply. This may reduce the prevalence of case contamination and the excess risk of infection associated with this system.

The other risk factors identified by multivariable analysis have already been established by previous studies; irregular disinfection has been significantly associated with both bacterial (Stapleton *et al.*, 1993a) and *Acanthamoeba* keratitis (Stehr-Green *et al.*, 1987); and overnight lens use has been shown to be the predominant risk factor for corneal infection (Dart *et al.*, 1991; Imayasu *et al.*, 1994; Schein *et al.*, 1994).

Since chlorine-based disinfection, omitted disinfection, and occasional overnight use

were all more common amongst DSCL users, some of these individuals may be increasing their risk of corneal infection by up to thirty times.

Notably, as in a previous study (Stapleton *et al.*, 1993a), lens cleaning was shown to have only a small and statistically insignificant protective effect, despite the proven microbiological effectiveness of lens cleaning and rinsing (Shih *et al.*, 1985). Case hygiene *per se* also failed to emerge as a significant factor. It is possible that the poor technique with which these procedures are frequently carried out by apparently compliant individuals (Radford *et al.*, 1993b) may negate their protective effect; detailed analysis of hygiene techniques was not possible in this study.

4.1.5 Sterile Keratitis

As for microbial keratitis, the reduced risk of sterile keratitis with rigid CL compared to conventional SCL is in keeping with findings of the previous study (Stapleton *et al.*, 1993a). In the present study, however, there was no evidence of an excess risk with EW-SCL compared to DW-SCL. This may be due to a reduction in the number of EW-SCL patients wearing their lenses continuously for more than 6 days and/or the increasing popularity of planned replacement schemes, although neither extent of overnight use or lens age have been identified as risk factors for sterile keratitis. In contrast, EW of DSCL was shown to be associated with a significant fourfold increased risk.

The modelling procedure identified a significant interaction (effect modification) between previous lens use and lens type as risk factors for sterile keratitis: while DW-DSCL users with previous CL experience had a significantly increased risk, `novice' DW-DSCL users showed a trend towards a decreased risk. Although the latter result was not statistically significant, probably due to small numbers, the marked reversal of RR seems to illustrate both the prescribing of DSCL for patients with previous CL complications and possible predisposition to inflammatory disorders (Grant *et al.*,

1987; Sweeney *et al.*, 1993).

Irregular disinfection was also identified as carrying an excess risk of sterile keratitis amongst DW subjects. Stapleton *et al.* (1993a) report an increased risk of borderline significance amongst users of chlorine-based compared to hydrogen peroxide disinfection, although, as discussed earlier, case hygiene standards were not included in the multivariable analysis. In this analysis the quality of disinfection, rather than the method, was important as a protective measure. This is in keeping with the theory that hypersensitivity to bacterial endotoxin is one of the causes of this disease (Phillips *et al.*, 1986).

Finally, a modest increase in risk was shown with daily-wear lens use in excess of 12 hours. This may relate to increased lens dehydration in some SCL after a prolonged wearing time (Efron *et al.*, 1987), perhaps resulting in lens tightening; the latter is thought to be a cause of sterile infiltrates (Josephson and Caffery, 1979). The increased prevalence of hypoxic complications amongst patients with daily wear time greater than 12 hours may also be a factor (Rapkin, 1988).

A strong association between EW-DSCL and sterile keratitis, which persisted after multivariable analysis, confirms the findings of cohort studies (Maguen *et al.*, 1992; Poggio *et al.*, 1993a; Boswall *et al.*, 1993) and the pilot for the present study (Matthews *et al.*, 1992). Several authors have observed tight lens fitting accompanying sterile keratitis with EW-DSCL (Serdahl *et al.*, 1989; Mertz *et al.*, 1990; Maguen *et al.*, 1991; Boswall *et al.*, 1993), and the present study shows an excess of `tight lens syndrome' cases associated with EW-DSCL. This suggests that tight lens fitting, perhaps due to a limited range of available parameters and/or due to increased *in vivo* dehydration with these lenses (Helton and Watson, 1991) is responsible; hypersensitivity to trapped cellular debris, together with epithelial metabolic compromise, are thought to be one of the causes of sterile infiltrates (Josephson and Caffery, 1979).

4.1.6 Toxic and Hypersensitivity Disorders

As in a previous study (Stapleton *et al.*, 1992), toxic and hypersensitivity disorders were significantly less common amongst rigid lens wearers. Amongst SCL wearers, however, DSCL users failed to show a significantly reduced risk, perhaps due to small numbers and the diverse origins of these disorders.

More specific analysis of the more common disorders in this category, however, showed a significant reduction in toxic keratitis amongst DW-DSCL compared to DW-SCL users, perhaps relating to the less common use of hydrogen peroxide (and omitted neutralization `accidents') amongst DW-DSCL. The RR of thiomersal keratopathy was not assessed, since a significantly reduced penetrance of thiomersal-preserved disinfection amongst DW-DSCL users had already been shown.

Although regular lens replacement and better lens hygiene standards have been shown to reduce the occurrence of acute CL-related `red eye' (Kotow *et al.*, 1987a), there was no evidence of this in the present study, although the small number of cases limited statistical analysis. Since DSCL appear to be associated with tight lens fitting (as discussed earlier) it is possible that toxic reactions to trapped cellular debris are counteracting the benefit of frequent replacement for this disorder.

Surprisingly, DSCL also failed to show a protective effect against CLPC, showing similar or slightly higher risks than conventional SCL. Despite the reported use of DSCL in the management of CLPC (Burnett Hodd, 1991; Kersley, 1991), RR were similar amongst patients in the `previous lens use' and `novice' groups, although the need to adjust for lens experience reduced the numbers and limited statistical analysis.

The results of this study, together with the majority of others comparing the frequency of CLPC amongst DSCL and SCL users (Rumsey *et al.*, 1991; Poggio *et al.*, 1993a

and 1993b) suggest that individual susceptibility is a dominant factor in this disease (Allansmith *et al.*, 1977), and that while DSCL may help some CLPC patients (Coursaux *et al.*, 1990; Hamburg *et al.*, 1991) regular but less frequent replacement of alternative lens types may be equally or more effective for others (Bucci *et al.*, 1993 and 1994).

4.1.7 Metabolic Disorders

As reported in an earlier study (Stapleton *et al.*, 1992), metabolic disorders were found to be significantly more common amongst EW subjects, as would be expected due to the hypoxia and sequelae accompanying overnight wear of soft CL (Zantos and Holden, 1978; Holden *et al.*, 1983; Holden *et al.*, 1985). DSCL and conventional SCL users, however, were similarly affected: this is unsurprising, since the oxygen performance of the most commonly used DSCL, Acuvue, is similar (Weissman *et al.*, 1990) or only slightly superior (Jones, 1994) to that for standard thickness high water content lenses, and, as in the case of other soft lenses, is insufficient to allow rapid recovery from corneal oedema following overnight use (Holden and Mertz, 1984).

More specific analysis of the more common diseases in this category revealed that EW-DSCL users carried a sixfold increased risk of developing `tight lens syndrome' compared with EW-SCL users, although small numbers limited statistical analysis. Comparisons of the two EW lens types for the risk of microcystic epitheliopathy were inconclusive due to even smaller numbers. If the two results are viewed together, however, they give some support to the observations of previous authors that EW-DSCL are associated with tight lens syndrome and microcystic epitheliopathy (Epstein and Donnenfeld, 1989; Josephson *et al.*, 1990; Netland, 1990; Maguen *et al.*, 1991; Boswall *et al.*, 1993), perhaps relating to the ultrathin `draping' lens design and/or *in vivo* dehydration characteristics of the Acuvue lens (Helton and Watson, 1991). Manufacturing defects in Acuvue lenses, shown to be significantly associated with the development of microcysts (Efron and Veys, 1992), may also have a role to play in

these findings. Although this finding contradicts that of Poggio *et al.* (1993a), it is possible that by combining corneal oedema with microcysts for their analysis they may have failed to detect an association between EW-DSCL and specific types of metabolic disorders, as occurred in the present study when metabolic disorders were grouped for analysis.

4.1.8 Mechanical Disorders

As in an earlier study (Stapleton *et al.*, 1992), SCL wearers were shown to have a reduced risk of these disorders in comparison to rigid lens wearers, although in the present study this result was not significant for EW-DSCL. Despite the reports of a high frequency of manufacturing defects in Acuvue lenses (Lowther, 1991; Efron and Veys, 1992), there was no significant difference in risk between conventional and disposable lens users for mechanical disorders sufficiently acute to prompt A&E attendance.

4.1.9 (Acute and Subacute) Lens-Related Disorders in General

For acute and subacute disorders prompting A&E attendance there was no significant difference in risk between DSCL and conventional SCL users with the same wear schedule, although EW-DSCL users showed a 2.5 times increased risk compared to DW-SCL or DW-DSCL users. It needs to be stressed, however, that this study was limited in its assessment of less serious acute disorders, which rarely prompt emergency attendance at hospital, and was unable to assess the distribution of chronic CL complications. The relative risks of these more common disorders are better assessed with a large comparative cohort study design (Poggio *et al.*, 1993a and 1993b).

4.2 RETROSPECTIVE CASE-CONTROL STUDY OF *ACANTHAMOEBA* KERATITIS

4.2.1 Study Design

This study assessed the effect of CL type, amongst other risk factors, on the likelihood of developing CL-related *Acanthamoeba* keratitis. In addition to the possible limitations associated with the use of hospital-based controls, as well as the difficulties inherent in comparisons between users of DSCL and conventional SCL wearers (as discussed in Section 4.1.1), this study has additional potential sources of bias due to its retrospective design. The rarity of the disease precluded a prospective design of less than three years' duration, since there would have been insufficient cases to enable detailed multivariable analysis of risk factors. Consequently, due to study time limitations, as well as the need for urgent evaluation of a concerning increase in the number of cases associated with DSCL use, a retrospective study was undertaken.

Retrospective identification and questionnaire surveying of cases can lead to bias associated with excessive missing data from patients who cannot be traced (Lilienfeld and Lilienfeld, 1980) and deteriorating recall with the passage of time (Schlesselman, 1982). In this study, however, 35/38 (92%) of eligible cases patients were traced, and the distribution of lens types amongst the three who could not be contacted (RGP, DW-SCL and DW-DSCL) confirms that their exclusion has not significantly affected relative risk estimates. Furthermore, despite the time elapse between the onset of disease and the questionnaire (a maximum of three years), excellent consistency was observed between questionnaire responses and data from detailed medical notes and recent research in which data was collected at or soon after the time of presentation (Bacon *et al.*, 1993).

Consideration was given to the possibility of using contemporaneous controls, matching cases with patients presenting to A&E with disease unrelated to lens use attending in the same month. It was judged, however, that, while a serious and painful disease

such as *Acanthamoeba* keratitis may stimulate recall (Schlesselman, 1982) the response rate and recall amongst controls with disorders unrelated to lens wear would be greatly reduced with the elapse of time; consequently control patients attending during the latter six months of the study period were identified at or soon after their first presentation. Since the distribution of lens care systems did not change appreciably during the three year study period (Radford *et al.*, 1993b; Pearson, 1992), it is unlikely that the use of non-contemporaneous controls has biased the multivariable analysis of hygiene factors amongst DW soft lens wearers. The distribution of lens types, however, *did* change during the study period, with the relatively recent DSCL steadily growing in penetrance (Matthews *et al.*, 1992); it is possible that some of the cases (attending during the three years to August 1992), were less likely to be fitted with a DSCL than patients attending during the latter six months (March to August, 1992) when these lenses had become more widespread. The multivariable analysis of DSCL as a risk factor is therefore probably an underestimate. For this reason additional assessment of DSCL as a risk factor was conducted, limiting cases to those presenting at A&E during the last year of the study period.

4.2.2 *Acanthamoeba* Keratitis

At MEH, a marked reduction in diagnostic delay, together with improved medical therapy, has resulted in a higher proportion of *Acanthamoeba* keratitis patients with more superficial disease (Bacon *et al.*, 1993); this may explain the low culture positive rate in this study. Although the use of a clinical case definition may have allowed patients with non-amoebal keratitis to be included amongst the cases, this is unlikely since all diagnoses were made by consultants with extensive experience of this disease. Furthermore, this definition seems to be justified by the persistence of the principal new findings of this study when multivariable analysis, albeit limited by small numbers, was performed using culture-positive cases only. Use of the clinical case definition for this disease is not unprecedented (Sarwar *et al.*, 1993; Bacon *et al.*, 1993) and enabled this study to perform the first case-control study using multivariable analysis of

risk factors for the disease.

The increasing number of *Acanthamoeba* keratitis cases presenting to MEH may reflect increasing awareness of the condition and direct referral to a specialist centre. The markedly rising proportion of cases associated with DSCL use, however, parallels their increasing penetrance during the three years; this pattern, together with the considerable crude excess risk estimated for DSCL wearers in this study, suggests that the introduction of these lenses, and/or the hygiene practices associated with them, has greatly increased the incidence of this disease.

Multivariable analysis has shown that there is an excess risk associated with the DSCL *per se*. Risk comparisons between DSCL brands were hindered by insufficient numbers of wearers of DSCL other than Acuvue and the introduction of new DSCL brands during the three year study period. The absence of alternative DSCL brands amongst the cases, and the significant excess crude relative risk for Acuvue compared to other DSCL, however, suggests that the Acuvue lens, rather than DSCL in general, may be responsible for the excess risk with this type of lens use.

Several disposables, including Acuvue, are made from a high water content (WC), ionic material. Although *in vitro* studies of unworn soft lenses have shown significantly more adherence of *Acanthamoeba* trophozoites and cysts to high WC rather than low WC soft lenses (John *et al.*, 1991), less adherence has been observed for ionic soft lenses (John *et al.*, 1991; Kilvington, 1993). It is possible, however, that the greater absorption of protein by ionic materials (Sack *et al.*, 1987; Minarik and Rapp, 1989) may facilitate *Acanthamoeba* adherence to lenses that have been worn. The lens material itself, therefore, may be increasing corneal exposure to *Acanthamoeba* organisms. In addition, manufacturing defects in Acuvue lenses, shown to cause minor but significant changes in corneal integrity (Efron amd Veys, 1992), may predispose the epithelium to invasion by *Acanthamoeba* (Larkin *et al.*, 1991). Use of DSCL in conditions

in which patients might be less willing to use conventional SCL (due to concern over inconvenience in the event of lens loss and delayed replacement) may be contributing to the risk with these lenses: it was noted that 2 of the 3 patients who had been swimming while wearing their lenses prior to developing the disease were DSCL users. Swimming during CL wear has been identified as a significant risk factor for the disease (Stehr-Green *et al.*, 1987).

Multivariable analysis, however, has shown that the predominant risk factors were omitted disinfection and/or use of non-sterile saline (as in the earlier case-control study by Stehr-Green *et al.*, 1987), and the use of chlorine-based disinfection rather than alternative chemical systems; use of a more effective disinfection system would have prevented an estimated 88% of cases.

The disparity in risk between users of chlorine-based disinfection compared to users of other systems was found to be considerably greater in this study of AK than those of microbial (mostly bacterial) keratitis, in which the increased risk with these systems was of borderline significance (Stapleton *et al.*, 1993a) or reversed by good case hygiene (Section 4.1.4). *Acanthamoeba* cysts have been shown to survive at least ten times the theoretical concentration of available chlorine in these systems (Kilvington and Price, 1990), and an association between chlorine-based disinfection and storage case contamination by *Acanthamoeba* has been observed (Devonshire *et al.*, 1993). Other chemical systems are either ineffective against *Acanthamoeba* cysts, or only effective in the absence of organic debris or after a prolonged soaking time (Seal and Hay, 1992). However, since concomitant bacterial contamination is thought to be important for the survival and growth of *Acanthamoeba* in the lens case (Donzis *et al.*, 1989), the relative protection apparently provided by these systems may be due to their having greater anti-bacterial action. As discussed earlier (Section 4.1.4), *in vitro* studies comparing systems have been difficult to reconcile, and probably do not reflect the relative efficacy of these agents *in vivo*.

Other aspects of lens care were found to be of only marginal significance or showed no effect on the risk. The apparently negligible protection provided by surfactant cleaning, previously shown to be one of the most effective methods of removing *Acanthamoeba* cysts and trophozoites from the CL surface if carried out according to manufacturers' instructions (Kilvington, 1993), may be due to small numbers in this study and/or the frequently poor attention to cleaning technique and/or omission of the rinsing step amongst lens wearers using a cleaner (Wilson, 1990).

Although *Acanthamoebae* were isolated from the lens storage case for 16/31 (52%) of the AK patients who had been DW-SCL users, subjective assessment of lens case hygiene did not appear to have any effect on the risk of developing AK. Given the widespread misunderstandings regarding this aspect of lens hygiene (Radford *et al.*, 1993b), it is possible that many individuals were using inappropriate methods that may have increased, rather than decreased, their risk of lens case contamination (Seal *et al.*, 1992). Since this study was conducted, the manufacturers of Softab (Alcon Laboratories, UK Ltd.), whose product accounted for 85% of the chlorine-based disinfection in this study, have repackaged their system to include a new storage case with each month's supply of tablets. This may reduce the prevalence of case contamination, and, possibly, the excess risk associated with this type of disinfection.

The only other factor to show any possible effect on the risk was the patients' receiving of aftercare advice from their CL practitioner. Since compliance with this advice was not directly assessed, responses to this question are likely to be more descriptive of the practitioner, or the patient-practitioner relationship, than the patient. It is possible that practitioners who give clear instructions regarding aftercare visits may also be more conscientious about imparting advice about safe lens use. Additionally, patients with a regular aftercare regime may be more likely to have a better patient-practitioner relationship and/or more frequent revision of lens care procedures, both of which have

been shown to improve lens care compliance (Marren, 1990; Radford *et al.*, 1993b). It appears that practitioners may have a significant role to play in reducing the risk of AK.

CHAPTER 5. CONCLUSIONS

These case-control studies showed significant associations between microbial keratitis and both DW and EW DSCL use; between severe keratitis, including *Acanthamoeba* keratitis, and DW-DSCL use; and between EW-DSCL and sterile keratitis. The study failed to substantiate claims of reduced risks of less serious types of complications with DSCL, except in the case of toxic keratopathy, although it must be stressed that the study design was not well suited to the assessment of less severe or non-acute disorders.

Multivariable analysis of risk factors for microbial keratitis showed that there is an excess risk with disposables *per se*, although other significant exposure variables - poor case hygiene with chlorine-based disinfection, irregular disinfection and occasional unscheduled overnight use - further increase the risk for many DW-DSCL users, since these habits were significantly more common amongst them than amongst conventional DW-SCL users.

Multivariable analysis of risk factors for *Acanthamoeba* keratitis amongst DW users also showed a significant excess risk with DSCL *per se*. For this disease, however, chlorine-based or omitted disinfection were the predominant risk factors; it was estimated that 88% of the cases might have been avoided with adequate use of a more effective system. As for microbial keratitis in general, an association between DW-DSCL and chlorine-based or omitted disinfection augments the excess risk with the lenses themselves; a fifty-fold increased risk amongst DW-DSCL users was shown on crude analysis of the relative risks for each lens type.

Multivariable analysis also identified that use of EW-DSCL carried a significantly increased risk of sterile keratitis compared to conventional EW-SCL users. Although a significant excess risk of sterile keratitis with DW-DSCL compared to DW-SCL was shown for subjects with previous use of an alternative lens type, amongst novice users there was a trend towards a reduced risk. This pattern appears to illustrate the use of

DSCL as a problem solver for patients with a history of inflammatory disorders; it is likely that, amongst new DW patients, disposables may have some protective effect against this type of disorder.

Amongst DW subjects there is a possibility that inadequate control for unidentified aspects of lens use and care may be contributing to the excess risks of infection estimated for these lenses; the excess risks of suppurative keratitis with EW-DSCL (compared to EW-SCL), however, despite their reduced extent of overnight wear and superior hygiene standards, strongly suggests that one or more characteristics of the DSCL lenses themselves are responsible for this increased risk. Laboratory investigations, ideally using an animal model, are required to investigate the effect of characteristics of certain DSCL on corneal resistance to infection.

Although suppurative keratitis is rare, the large number of CL wearers leads to a substantial burden of unnecessary disease in terms of health service resources, time away from work, personal anxiety, inconvenience and discomfort. The findings of this study indicate that with the growing proportion of CL wearers using DSCL this burden is likely to increase. Although many practitioners and patients may feel that the proven benefits of disposable lenses (Poggio *et al.*, 1993a and 1993b; Boswall *et al.*, 1993) outweigh the increased risk of serious but rare and often successfully treated disease, the findings of this study suggest that practitioners and patients should be informed of the risk, and encouraged to minimise it. Practitioners should be encouraged to make a careful assessment of the suitability of a patient for DSCL wear, and to achieve lens fits with adequate movement. Patients should be advised to inspect lenses carefully before insertion, and to discard lenses that may have defects or that cause blurring (due to oedema), since DSCL will not be evaluated on the eye by the practitioner. Practitioners should stress the importance of regular disinfection using a system with a high margin of efficacy. Regular case cleaning and replacement to prevent a build-up of biofilm in the case does not have a proven preventative effect (although there was some

evidence in this study that case hygiene standards can modify the efficacy of disinfection) but in theory should be beneficial. Use of any lens type for use overnight or in adverse conditions such as swimming should be strongly discouraged, and the notion that use of DSCL can reduce the considerable increased risk associated with these practices should be dispelled.

CHAPTER 6. FURTHER STUDIES

6.1 LABORATORY INVESTIGATIONS

These case-control studies, with the use of multivariable analysis, have identified risk factors for microbial and sterile keratitis; only laboratory investigations, however, can elucidate the pathogenesis underlying these risk factors. In particular, the excess risk of microbial keratitis with DSCL use may be attributable to one or more characteristics of these lenses; the effect on the corneal resistance to infection of these characteristics needs to be evaluated, ideally in an animal model of microbial keratitis. Previous such studies have demonstrated the importance of mucin-coated CL (DiGaetano *et al.*, 1986), epithelial trauma (DiGaetano *et al.*, 1986; Klotz *et al.*, 1989; Solomon *et al.*, 1994) and, in particular, corneal hypoxia (Lawin-Brussel *et al.*, 1990; Solomon *et al.*, 1994; Imayasu *et al.*, 1994). Further studies, however, are needed to elucidate the possible roles of lens tightening, lens edge defects, *in vivo* lens dehydration and high levels of loosely-bound protein deposition in the process of CL-induced corneal infection. Subsequently, changes to DSCL design or material may be required; these uncertainties need to be resolved before embracing the concept of *daily* disposal of lenses with confidence.

The relative efficacy of different disinfection systems against sessile as opposed to planktonic bacteria also requires investigation; this study suggests that current testing of these systems may underestimate the biocidal activity required to prevent contamination of the lens environment, even when the system is used optimally.

6.2 ONE-DAY DISPOSABLE LENSES

Vistakon has recently launched a `One-day Acuvue' - a disposable lens for single use followed by disposal at the end of the day - in the USA. The introduction of this regime to the UK has been delayed due to difficulties in setting up a computerised ordering system that will provide patients with flexible use of these lenses (at frequencies of between 1 and 7 days per week) while safeguarding the current control of

supply by ophthalmic practitioners (Vistakon, personal communication). Meanwhile, Award plc of Livingstone, Lothian (Scotland) plans to produce high water content moulded daily disposable lenses for distribution by an undisclosed large multiple ophthalmic company by the end of 1994 (Anonymous, 1993b; Anonymous, 1994).

A large comparative premarket study has indicated a marked reduction in non-suppurative corneal complications with One-Day Acuvue compared to other lens types (Hamano *et al.*, 1994), although, as discussed earlier, there may have been a bias in favour of disposable lenses in this study (Section 1.5.5). A reduced incidence of infection and hypersensitivity reactions to bacteria may be expected with daily disposal due to the obviated need for lens storage cases, which are prone to contamination (Larkin *et al.*, 1990; Devonshire *et al.*, 1993); and cleaning and disinfecting routines, which are often omitted (Radford *et al.*, 1993b) or ineffective in the home environment (Campbell and Caroline, 1990). There is no evidence to suggest, however, that inflammatory disorders in response to lens deposits will be reduced by this regime; a recent study of allergic patients failed to show any clinical advantage in replacement frequencies greater than 8 weeks (Bucci *et al.*, 1994). Furthermore, the daily disposal regime is still subject to the problems of increased susceptibility to infection of the lens-wearing cornea; the possibility of microbial contamination and colonisation of the lens in the eye; and the likelihood of compliance failures, for economic reasons, leading to retention of lenses for use with inadequate hygiene or extended wear.

6.2.1 Proposed Further Case-Control Study including assessment of One-Day Disposable Lenses

A further case-control study will be needed once daily disposables have sufficient penetration amongst the study population to enable statistical comparisons between this regime, other DSCL schedules, and conventional SCL schedules. This would also be an intervention study, allowing assessment of measures recently taken by some manufacturers (Vistakon, Alcon Laboratories UK Ltd) to promote safer use of their products. A

three year case-control study would enable re-assessment of risk factors for *Acanthamoeba* keratitis, including use of the multipurpose solutions for SCL recently introduced to the UK. Use of contemporaneous controls would enable estimates of relative risk that are unaffected by the changing distribution of the lens types and wear schedules.

6.3 THE CURRENT INCIDENCE OF MICROBIAL KERATITIS AMONGST COSMETIC CONTACT LENS WEARERS

In a well conducted population-based study of lens-induced ulcerative keratitis in New England USA Poggio *et al.* (1989) established incidence estimates of 1 in 500 and 1 in 2500 for EW and DW use of soft lenses respectively. Subsequently, a retrospective 3-year and a prospective 3-month incidence study of ulcerative keratitis in Sweden have been conducted to compare the risks with disposable as opposed to conventional SCL (Nilsson and Montan, 1994a and 1994b). As discussed earlier (Section 1.5.2), results of the retrospective study may be subject to considerable sources of bias and must be viewed with caution. The latter study, in which these problems appear to have been addressed, showed no difference in risk between disposable and conventional soft lenses used with the same wear schedule. The markedly low incidence and severity of cases reported in this study (Section 1.5.2), however, may limit the application of this result to other CL wearing populations.

6.3.1 Proposed Incidence Study of Microbial Keratitis amongst Cosmetic Contact Lens wearers in the UK

The feasibilty of a population-based incidence study of microbial keratitis amongst wearers of different lens types now available in the UK is currently being assessed (**APPENDIX 10**). In order to avoid the possible problems of standardization of diagnosis and procedure inherent in a multi-centre study, a single centre with a 24-hour Eye A&E Department that can provide sufficient cases over a three year period has been selected; case collection commenced on October 1st, 1993. In order to define the catchment area (or more precisely, sub-catchment area) of the chosen hospital (Oxford

Eye Hospital [OEH]) as the geographical region in which there is negligible overlap with the catchment areas of surrounding hospitals, sampling of the A&E registers for OEH and surrounding hospitals is currently being undertaken. Only those cases resident in the defined catchment population would be included in the study. To provide the denominator for the estimate of incidence with each CL type and wear schedule, a telephone questionnaire of a random sample of the OEH catchment area would be conducted to estimate the number of persons in the population using each type of contact lens and wear schedule; a pilot study has confirmed the feasiblility of this method.

The size of the proposed study would have a power of 90% to detect a minimum relative risk of 2.8, enabling verification of most of the relative risks for different lens types shown in the present study. Such a study would determine the absolute risk of microbial keratitis to wearers of lens types and wear schedules currently available in the UK.

6.4 SUMMARY

Millions of individuals enjoy the optical, occupational and cosmetic advantages of contact lens wear, and in most countries the comfort, flexible wearing schedules, ease of adaptation and simplicity of fitting of soft contact lenses have made them the preferred lens type. Although serious complications of CL wear are rare, the burden of unnecessary disease is large due to the substantial number of CL wearers at risk. Continued evaluation of the impact of new lenses, wear schedules and care products, as well as efforts to understand the pathogenesis of lens related disease, are needed in order to improve the safety of contact lens wear.

APPENDIX 1: QUESTIONNAIRE FOR PROSPECTIVE CASE-CONTROL STUDY

MOORFIELDS EYE HOSPITAL
CONTACT LENS USER QUESTIONNAIRE

This questionnaire is part of a study at this hospital assessing the risks of contact lens wear. We will be collecting information from all contact lens wearers who attend our casualty department, whether or not their problem is directly related to lens wear. All information is confidential and will not affect your treatment.

If you have any difficulties with the questions, the nursing staff will be happy to assist you. When you have completed the questionnaire, PLEASE HAND IT BACK TO THE CASUALTY NURSE.

Your help with these important investigations is very much appreciated.

Mr.J.K.G.Dart FRCS DM
Consultant Ophthalmologist

Mrs.C.F.Radford MBCO
Optometrist

Please write in CAPITAL LETTERS:

DATE____/____/____

CASUALTY NUMBER _____

HOSPITAL NUMBER (if any) _____

FULL NAME_____

ADDRESS_____

_____Postcode_____

TELEPHONE NO. Home:_____ Work:_____

DATE OF BIRTH____/____/____ AGE_____

SEX: MALE / FEMALE

OCCUPATION
(in detail)_____

Note: If you are a **student**, please note this, and give proposed occupation.
If **temporarily unemployed**, please state usual occupation.
If **unemployed, housewife**, or **under 16 years of age**, please give occupation of the chief wage earner in your household:

_____

WHEN DID YOU LAST WEAR YOUR CONTACT LENSES?_____

PLEASE TURN OVER --->>>

Q 1 What type of contact lenses do you wear?

[ ] Hard

[ ] Gas-permeable

[ ] Soft lenses for daily wear (taken out at night)

[ ] Soft lenses for extended wear (worn overnight at least once per week)

[ ] Disposable lenses for daily wear (taken out at night)

[ ] Disposable lenses for extended wear (worn overnight at least once per week)

Q 2 For how long have you worn this TYPE of lens?

[ ] Less than 1 month

[ ] 1-3 months

[ ] 4-6 months

[ ] 7-11 months

[ ] 1-2 years

[ ] 3-5 years

[ ] 6-10 years

[ ] 11-20 years

[ ] More than 20 years

Q 3 How old are your current lenses?

Right_____Left_____

Q 4 Have you ever worn any other TYPES of lenses?

[ ] No

[ ] Yes

If "YES", which TYPE were you wearing PREVIOUSLY? (If you have tried more than one other lens type, just tick the one you tried LAST)

[ ] Hard

[ ] Gas permeable

[ ] Soft lenses for daily wear

[ ] Soft lenses for extended wear

[ ] Disposable lenses for daily wear

[ ] Disposable lenses for extended wear

PLEASE TURN OVER --->>>

Q 5 For how long have you worn contact lenses (ALL types)?

[ ] Less than 1 month
[ ] 1-3 months
[ ] 4-6 months
[ ] 7-11 months
[ ] 1-2 years
[ ] 3-5 years
[ ] 6-10 years
[ ] 11-20 years
[ ] More than 20 years

Q 6 Why do you wear contact lenses?

[ ] Short-sighted
[ ] Long-sighted
[ ] Poor vision without lenses-don't know why
[ ] Keratoconus
[ ] Cataract removed
[ ] Corneal graft
[ ] Other medical condition requiring lenses

Please state:_____

[ ] To alter eye colour-cosmetic effect
[ ] Any other reason

Please state:_____

Q 7 Do you have a usable pair of spectacles to wear when your lenses are out?

[ ] No
[ ] Yes
[ ] Don't know

PLEASE TURN OVER --->>>

Q 8 Do you ever wear your lenses overnight?

[ ] No, never **Please GO TO Q 9**

[ ] Yes

If "YES" please indicate:

How many nights per week _____

How many nights in a row _____

How many days per week

of daily wear only* _____

How many days per week without lens wear _____

OTHER COMMENTS _____

***If you ever wear your lenses during the day only, please also answer Q 9a):**

Q 9 Wearers of DAILY WEAR lenses, please tick your usual wearing pattern:

a) **HOURS** per **DAY** wearing lenses:

[ ] Less than 4 hours

[ ] 4-8 hours

[ ] 8-12 hours

[ ] 12-16 hours

[ ] More than 16 hours, but taken out at night

b) **DAYS** per **WEEK** wearing lenses:

[ ] 1-2 days

[ ] 3-5 days

[ ] 6 days

[ ] 7 days

PLEASE TURN OVER --->>>

THE QUESTIONS ON THIS PAGE ARE IMPORTANT. PLEASE GIVE FULL NAMES OF YOUR SOLUTIONS. IF YOU ARE UNSURE, ASK TO SEE THE ILLUSTRATED CONTACT LENS SOLUTIONS FILE AT CASUALTY DESK.

Q 10a Do you RUB your lenses with a CLEANING solution?

[ ] No

[ ] Yes **If "YES", WHAT IS THE CLEANING SOLUTION CALLED?**

_____

If "NO", do you clean your lenses by some other means? (eg ultrasound, sponge) Please state how:

_____

Q 10b How OFTEN do you clean your lenses?

[ ] Every time lenses are taken out of eyes

[ ] 2-4 times per week

[ ] Once per week

[ ] Less than once per week

Q 11a Do you use a soaking solution, or other method (eg heat) to disinfect your lenses?

[ ] No

[ ] Yes **If "YES", WHAT IS IT CALLED?** _____

Q 11b How OFTEN do you use it to disinfect your lenses?

[ ] Every time lenses are taken out of eyes

[ ] 2-4 times per week

[ ] Once per week

[ ] Less often than once per week

Q11c How often do you CHANGE the SOLUTION IN YOUR CASE?

[ ] Every time I soak the lenses

[ ] Sometimes I re-use or `top up' the solution

[ ] Other **Please describe:** _____

PLEASE TURN OVER --->>>

Q 12 Do you use a lens wetting solution? (Other than saline)

[ ] No

[ ] Yes **If "YES", what is it called?** _____

Q 13 Do you use saline?

[ ] No

[ ] Yes

If "YES", what type of saline do you use?

[ ] Aerosol

[ ] Preserved

[ ] Single dose units

[ ] Home made

Q 14 Do you use protein remover tablets?

[ ] No

[ ] Yes

If "YES", how many times per MONTH? _____

Q 15 Do you use any other eye drops or contact lens solutions? (eg Optrex, hypromellose, Clerz)

[ ] No

[ ] Yes **If "YES", what are they called?**_____

How often do you use them?

[ ] Several times per day

[ ] Once per day

[ ] 2-4 times per week

[ ] Once per week

[ ] Just occasionally

PLEASE TURN OVER --->>>

Q 16 Do you have a contact lens storage case?

[ ] No

[ ] Yes

If "YES", how often do you CLEAN it?

[ ] Once per week or more

[ ] 2-3 times per month

[ ] Once per month

[ ] Less than once per month

[ ] Never

How often do you get a NEW lens case?

[ ] At least once per month

[ ] Every 2 months

[ ] Every 3 months

[ ] Every 4-6 months

[ ] Every 7-12 months

[ ] Every 1-2 years

[ ] Less than every 2 years

Q 17 Please give name, address and phone number of your contact lens practitioner:

_____

_____

_____

Q 18 When did you last have a routine (non-emergency) check on your eyes by your contact lens practitioner?

_____

Q 19 How often were you advised to have contact lens check-ups?

[ ] Every 3 months or more

[ ] Every 6 months

[ ] Every 12 months

[ ] Every 18 months

[ ] Every 2 years

[ ] No advice given

[ ] Don't know

PLEASE TURN OVER --->>>

Q 20 Do you have a "Planned replacement" scheme arranged with your practitioner?

[ ] No

[ ] Yes

[ ] Yes, for DISPOSABLE lenses (lenses dispensed in a multi-pack) **(GO TO Q 21)**

[ ] Don't know

If "YES", how often are you scheduled to replace your lenses?

[ ] Every month

[ ] Every 2 months

[ ] Every 3 months

[ ] Every 4 months

[ ] Every 6 months

[ ] Every 12 months

[ ] Don't know

WEARERS OF DISPOSABLE LENSES, PLEASE CONTINUE.

WEARERS OF ALL OTHER TYPES OF LENSES MAY STOP HERE. THANK YOU!

Q 21 Why do you wear disposables lenses rather than other types? Tick the MAIN reason only:

[ ] Practitioner advice

[ ] Comfort

[ ] Convenience

[ ] Deposit / tear problems

[ ] Infection risk / "healthier"

[ ] Visual

[ ] Financial

[ ] Other **PLEASE STATE:**

_____

Q 22 What type of disposable lens do you wear?

[ ] Acuvue (Vistakon, Johnson & Johnson)

[ ] NewVues (Ciba Vision)

[ ] SeeQuence (Bausch and Lomb)

[ ] Don't know

[ ] Surevue (Vistakon, Johnson & Johnson)

[ ] Calendar (Pilkington Barnes-Hind)

[ ] Other **PLEASE STATE:**

_____

PLEASE TURN OVER --->>>

Q 23 For how many weeks do you wear each new set?

_____weeks

Q 24 Do you ever dispose of your lenses less frequently than advised?

[ ] No, never

[ ] Yes, occasionally

[ ] Yes, often

Wearers of DAILY WEAR disposables may stop here.
THANK YOU!

Wearers of EXTENDED WEAR disposables only:

Q 25 Have you EVER stored and later re-used your disposable lenses?

[ ] No, never

[ ] Yes, occasionally

[ ] Yes, often

THANK YOU VERY MUCH FOR YOUR HELP!

APPENDIX 2: POSTAL QUESTIONNAIRE FOR PROSPECTIVE CASE-CONTROL STUDY

MOORFIELDS EYE HOSPITAL
CONTACT LENS USER QUESTIONNAIRE

This questionnaire is part of a study at this hospital assessing the risks of contact lens wear. We will be collecting information from all contact lens wearers who attend our casualty department, whether or not their problem is directly related to lens wear. All information is confidential and will not affect your treatment.

To return the questionnaire, please use the stamped addressed envelope provided.

Your help with these important investigations is very much appreciated.

Mr.J.K.G.Dart FRCS DM
Consultant Ophthalmologist

Mrs.C.F.Radford MBCO
Optometrist

Please write in CAPITAL LETTERS:

DATE OF VISIT____/____/____

CASUALTY NUMBER [written in] _____

HOSPITAL NUMBER [written in] _____

FULL NAME_____

ADDRESS_____

_____

Postcode_____

TELEPHONE NO. Home:_____

Work:_____

DATE OF BIRTH____/____/____ AGE AT TIME OF VISIT_____

SEX: MALE / FEMALE

OCCUPATION
(in detail)_____

Note: If you are a **student**, please note this, and give proposed occupation.
If **temporarily unemployed**, please state usual occupation.
If **unemployed**, **housewife**, or **under 16 years of age**, please give occupation of the chief wage earner in your household:

_____

WHEN HAD YOU LAST WORN YOUR CONTACT LENSES?_____

PLEASE TURN OVER --->>>

Q 1 What type of contact lenses were you wearing?

[ ] Hard

[ ] Gas-permeable

[ ] Soft lenses for daily wear (taken out at night)

[ ] Soft lenses for extended wear (worn overnight at least once per week)

[ ] Disposable lenses for daily wear (taken out at night)

[ ] Disposable lenses for extended wear (worn overnight at least once per week)

Q 2 For how long had you been wearing this TYPE of lens?

[ ] Less than 1 month

[ ] 1-3 months

[ ] 4-6 months

[ ] 7-11 months

[ ] 1-2 years

[ ] 3-5 years

[ ] 6-10 years

[ ] 11-20 years

[ ] More than 20 years

Q 3 How old are were your lenses at the time?

Right_____Left_____

Q 4 Had you ever worn any other TYPES of lenses?

[ ] No

[ ] Yes

If "YES", which TYPE had you worn PREVIOUSLY? (If you had tried more than one other lens type, just tick the one you had tried LAST)

[ ] Hard

[ ] Gas permeable

[ ] Soft lenses for daily wear

[ ] Soft lenses for extended wear

[ ] Disposable lenses for daily wear

[ ] Disposable lenses for extended wear

PLEASE TURN OVER --->>>

Q 5 For how long had you been wearing contact lenses (ALL types)?

[ ] Less than 1 month
[ ] 1-3 months
[ ] 4-6 months
[ ] 7-11 months
[ ] 1-2 years
[ ] 3-5 years
[ ] 6-10 years
[ ] 11-20 years
[ ] More than 20 years

Q 6 Why were you wearing contact lenses?

[ ] Short-sighted
[ ] Long-sighted
[ ] Poor vision without lenses-don't know why
[ ] Keratoconus
[ ] Cataract removed
[ ] Corneal graft
[ ] Other medical condition requiring lenses

Please state:_____

[ ] To alter eye colour-cosmetic effect
[ ] Any other reason

Please state:_____

Q 7 Did you have a usable pair of spectacles to wear when your lenses were out?

[ ] No
[ ] Yes
[ ] Don't know

PLEASE TURN OVER --->>>

Q 8 Did you ever wear your lenses overnight?

[ ] No, never **Please GO TO Q 9**

[ ] Yes

If "YES" please indicate:

How many nights per week _____

How many nights in a row _____
How many days per week

of daily wear only* _____

How many days per week
without lens wear _____

OTHER COMMENTS _____

***If you ever wore your lenses during the day only, please also answer Q 9a):**

Q 9 Wearers of DAILY WEAR lenses, please tick your usual wearing pattern at the time:

a) **HOURS** per **DAY** wearing lenses:

[ ] Less than 4 hours

[ ] 4-8 hours

[ ] 8-12 hours

[ ] 12-16 hours

[ ] More than 16 hours, but taken out at night

b) **DAYS** per **WEEK** wearing lenses:

[ ] 1-2 days

[ ] 3-5 days

[ ] 6 days

[ ] 7 days

PLEASE TURN OVER --->>>

THE QUESTIONS ON THIS PAGE ARE IMPORTANT.
PLEASE GIVE THE FULL NAMES OF YOUR SOLUTIONS.
IF IN DOUBT, AT LEAST DESCRIBE THE BOTTLE / CAN / TABLETS!

Q 10a Did you RUB your lenses with a CLEANING solution?

[ ] No

[ ] Yes **If "YES", WHAT WAS THE CLEANING SOLUTION CALLED?**

_____

If "NO", did you clean your lenses by some other means? (eg ultrasound, sponge) Please state how:

_____

Q 10b How OFTEN did you clean your lenses?

[ ] Every time lenses were taken out of eyes

[ ] 2-4 times per week

[ ] Once per week

[ ] Less than once per week

Q 11a Did you use a soaking solution, or other method (eg heat) to disinfect your lenses?

[ ] No

[ ] Yes **If "YES", WHAT WAS IT CALLED?** _____

Q 11b How OFTEN did you use it to disinfect your lenses?

[ ] Every time lenses were taken out of eyes

[ ] 2-4 times per week

[ ] Once per week

[ ] Less often than once per week

Q11c How often did you CHANGE the SOLUTION IN YOUR CASE?

[ ] Every time I soaked the lenses

[ ] Sometimes I re-used or `topped up' the solution

[ ] Other **Please describe:** _____

PLEASE TURN OVER --->>>

Q 12 Did you use a lens wetting solution? (Other than saline)

[ ] No

[ ] Yes **If "YES", what was it called?** _____

Q 13 Did you use saline?

[ ] No

[ ] Yes

If "YES", what type of saline did you use?

[ ] Aerosol

[ ] Preserved

[ ] Single dose units

[ ] Home made

Q 14 Did you use protein remover tablets?

[ ] No

[ ] Yes

If "YES", how many times per MONTH? _____

Q 15 Were you using any other eye drops or contact lens solutions? (eg Optrex, hypromellose, Clerz)

[ ] No

[ ] Yes **If "YES", what were they called?**_____

How often did you use them?

[ ] Several times per day

[ ] Once per day

[ ] 2-4 times per week

[ ] Once per week

[ ] Just occasionally

PLEASE TURN OVER --->>>

Q 16 Did you have a contact lens storage case?

[ ] No

[ ] Yes

If "YES", how often did you CLEAN it?

[ ] Once per week or more

[ ] 2-3 times per month

[ ] Once per month

[ ] Less than once per month

[ ] Never

How often did you get a NEW lens case?

[ ] At least once per month

[ ] Every 2 months

[ ] Every 3 months

[ ] Every 4-6 months

[ ] Every 7-12 months

[ ] Every 1-2 years

[ ] Less than every 2 years

Q 17 Please give name, address and phone number of your contact lens practitioner at the time:

_____

_____

_____

Q 18 When had you last had a routine (non-emergency) check on your eyes by your contact lens practitioner?

_____

Q 19 How often were you advised to have contact lens check-ups?

[ ] Every 3 months or more

[ ] Every 6 months

[ ] Every 12 months

[ ] Every 18 months

[ ] Every 2 years

[ ] No advice given

[ ] Don't know

PLEASE TURN OVER --->>>

Q 20 Did you have a "Planned replacement" scheme arranged with your practitioner?

[ ] No

[ ] Yes

[ ] Yes, for DISPOSABLE lenses (lenses dispensed in a multi-pack) **(GO TO Q 21)**

[ ] Don't know

If "YES", how often were you scheduled to replace your lenses?

[ ] Every month

[ ] Every 2 months

[ ] Every 3 months

[ ] Every 4 months

[ ] Every 6 months

[ ] Every 12 months

[ ] Don't know

WEARERS OF DISPOSABLE LENSES, PLEASE CONTINUE.

WEARERS OF ALL OTHER TYPES OF LENSES MAY STOP HERE. THANK YOU!

Q 21 Why were you wearing disposable lenses rather than other types? Tick the MAIN reason only:

[ ] Practitioner advice

[ ] Comfort

[ ] Convenience

[ ] Deposit / tear problems

[ ] Infection risk / "healthier"

[ ] Visual

[ ] Financial

[ ] Other **PLEASE STATE:**

_____

Q 22 What type of disposable lens were you wearing?

[ ] Acuvue (Vistakon, Johnson & Johnson)

[ ] NewVues (Ciba Vision)

[ ] SeeQuence (Bausch and Lomb)

[ ] Don't know

[ ] Surevue (Vistakon, Johnson & Johnson)

[ ] Calendar (Pilkington Barnes-Hind)

[ ] Other **PLEASE STATE:**

_____

PLEASE TURN OVER --->>>

Q 23 For how many weeks did you wear each new set?

_____weeks

Q 24 Did you ever dispose of your lenses less frequently than advised?

[ ] No, never

[ ] Yes, occasionally

[ ] Yes, often

Wearers of DAILY WEAR disposables may stop here.
THANK YOU!

Wearers of EXTENDED WEAR disposables only:

Q 25 Had you EVER stored and later re-used your disposable lenses?

[ ] No, never

[ ] Yes, occasionally

[ ] Yes, often

THANK YOU VERY MUCH FOR YOUR HELP!

APPENDIX 3: FIRST PAGE OF POSTAL QUESTIONNAIRE TO *ACANTHAMOEBA* KERATITIS CASES IDENTIFIED RETROSPECTIVELY

[MEH headed notepaper]

.....
.....
.....

Extension 2807
or 2320 (message)
.....

Dear.....

I am part of a research group at Moorfields studying contact lens-related complications. We are particularly interested in comparing lens use and care habits of people who have had serious eye infections with those of people who have not.

We would be very grateful if you could spare a few minutes of your time to complete the enclosed questionnaire. All information will be treated confidentially. Don't hesitate to contact me on the above number should you have any difficulty answering the questions. A stamped addressed envelope is enclosed for your convenience.

Your help with these important investigations is very much appreciated.

Yours Sincerely,

Cherry Radford BSc MBCO
Research Optometrist

CONTACT LENS USER QUESTIONNAIRE

NAME_____

ADDRESS (if changed)_____

_____Postcode_____

TELEPHONE NO. Home:_____Work:_____

DATE OF BIRTH____/____/____

OCCUPATION (in detail)_____

Note:
Student: please note this, and give proposed occupation.
Temporarily unemployed:, please state usual occupation.
Unemployed / housewife / under 16 years of age: please give occupation of the chief wage earner in your household

APPENDIX 4: CONTACT LENS HYGIENE SCORING SYSTEM

POINTS	HYGIENE PRACTICE
	LENS CLEANING:
4	Every time contact lenses are removed
2	2-4 times per week
1	Once per week
0	None, or less frequently than once per week

Notes:
Saline `rub & rinse': DEDUCT 1 POINT
Disposal at every CL removal: SCORE 4

LENS DISINFECTION:

5	Every time CL are removed, using fresh solution
2	2-4 times per week
1	Once per week
0	None, or less frequently than once per week

Notes:
Use of non-sterile water / homemade saline with SCL: SCORE 0
Re-use or topping up of solution: DEDUCT 3 POINTS
Disposal at every CL removal: SCORE 5

ENZYMATIC TREATMENT:

2	2-4 times per month
1	Once per month
0	None, or less frequently than once per month

Notes:
Exempt, therefore score maximally:
a) Wearers of PMMA rigid CL
b) Wearers of RGP CL wearers using an abrasive cleaner
c) Patients with an equivalent disposal frequency ie
   disposal every 1-2 weeks: SCORE 2 POINTS
   disposal every 3-4 weeks: SCORE 1 POINT,
   but non-compliance with monthly disposal: SCORE 0

CASE CLEANING:

4	Once per week or more
2	2-3 times per month
1	Once per month
0	None, or less frequently than once per month

Notes:
Case replacement every 6 months or more: ADD 2 POINTS (TO A MAXIMUM OF 4)
Disposal on removal: SCORE 4

Key:
SCL: soft contact lens PMMA: polymethylmethacrylate
RGP: rigid gas permeable

APPENDIX 5: CLASSIFICATION OF CONTACT LENS RELATED DISEASE

CLASSIFICATION	SYMPTOMS	CORNEAL SIGNS	CONJUNCTIVAL SIGNS
MICROBIAL INFECTIONS			
Microbial keratitis	Rapid onset and progression of pain, redness and discharge. Blurred vision	Epithelial ulcer with underlying white stromal infiltrate. *Pseudomonas* common and associated with fulminating course, adherent mucous and gross corneal oedema	Ciliary injection
Microbial conjunctivitis (commonly NOT lens related)	Mild discomfort and mucopurulent discharge	Normal in bacterial infections. PEK and infiltrates in viral infections	Hyperaemia and papillae in bacterial, follicles in viral
TOXIC AND HYPERSENSITIVITY DISORDERS			
Sterile keratitis	Discomfort, redness and discharge	Appearences similar to marginal keratitis. Peripheral infiltrates +/- ulceration	Hyperaemia
Enzyme keratopathy	Severe pain after lens insertion	Widespread punctate stain	Ciliary injection
Thiomersal keratopathy	Chronic irritation and redness soon after lens insertion each day. Vision affected in severe cases	Superior limbal injection and neovascularisation. Opacity, PEK and microcysts affecting superior quadrant in classic cases. Very variable signs in atypical cases	Intense hyperaemia with lens in, without lens, some follicular change

APPENDIX 5 (continued)

CLASSIFICATION	SYMPTOMS	CORNEAL SIGNS	CONJUNCTIVAL SIGNS
TOXIC AND HYPERSENSITIVITY DISORDERS (continued)			
Contact lens related papillary conjunctivitis	Increased discharge and greasing of lenses with itching on lens removal. Later, severe irritation in lenses. Without lens, resolves within days	None	Upper tarsal hyperaemia, and fine papillary response. `Giant' (compound) papillae in advanced cases
Contact lens related red eye	Chronic redness and discomfort. Vision may be blurred	Punctate stain common	Hyperaemia. Papillae and follicles common
METABOLIC DISORDERS			
Acute epithelial necrosis (`overwear syndrome')	Often blurred vision before the onset due to corneal oedema. Delayed pain and epiphora from epithelial necrosis. Resolves in hours (days in severe cases)	Central punctate epithelial erosions may coalesce into an ulcer. Involved area larger in SCL users. Stromal oedema in severe cases	Ciliary injection

APPENDIX 5 (continued)

CLASSIFICATION	SYMPTOMS	CORNEAL SIGNS	CONJUNCTIVAL SIGNS
METABOLIC DISORDERS (continued)			
Tight lens syndrome	As above but starts in morning after overnight anoxia. Vision usually affected	As above but stromal oedema and an epithelial defect common	Ciliary injection and limbal indentation from a tight lens
Microcystic epitheliopathy	Recurrent brief episodes of pain and epiphora	Mini erosions during symptomatic episodes. Clear or opaque epithelial cysts and PEK	None
Epithelial oedema	Blurred vision after some hours of wear. May recover on lens removal or progress to acute epithelial necrosis. Often in new lens wearers	Dull corneal reflex from central epithelial oedema	None
Stromal oedema (striate keratopathy)	Blurring of vision in some cases only	Deep stromal folds from corneal oedema. Occurs in severe acute epithelial necrosis	None, except when associated with acute epithelial necrosis

APPENDIX 5 (continued)

CLASSIFICATION	SYMPTOMS	CORNEAL SIGNS	CONJUNCTIVAL SIGNS
METABOLIC DISORDERS (continued)			
Neovascularization: superficial and deep	None unless lipid keratopathy results from deep vessels when vision is lost	Superficial or deep stromal vessels. Lipid keratopathy associated with deep vessels	None
Endothelial polymegethism	None	Polymegethism	None
MECHANICAL DISORDERS			
Corneal abrasion	Sudden onset of pain and epiphora. Resolves in hours	Linear or sharply circumscribed epithelial defect	Hyperaemia
Anterior stromal opacity	Asymptomatic. Rarely loss of vision	Central superficial stromal opacity	None
Corneal warpage	Uncorrectable spectacle blur but clear vision in lenses	Irregular keratometry and photokeratoscopy	None
Spectacle blur	Spectacle vision blurred for upto 3 weeks after wearing hard lenses	Normal	None

APPENDIX 5 (continued)

CLASSIFICATION	SYMPTOMS	CORNEAL SIGNS	CONJUNCTIVAL SIGNS
TEAR RESURFACING DISORDERS			
Three and nine o'clock stain	Interpalpebral redness. Rarely discomfort	Punctate keratopathy in 3 and 9 positions +/- vascularised superficial stromal scars	Interpalpebral hyperaemia
Inferior closure stain	Inferior redness and discomfort	Inferior or interpalpebral punctate stain	Inferior limbal hyperaemia
Dimple veiling	None or blurred	Flourescein pooling in epithelial depressions	None

APPENDIX 6: DISTRIBUTION OF SCORES FOR EACH ASPECT OF SOFT CONTACT LENS HYGIENE
(See Appendix 4: Contact Lens Hygiene Scoring System)

HYGIENE PRACTICE	POINTS	DW-SCL (n=1037) No. (%)	EW-SCL (n=84) No. (%)	DW-DSCL (n=215) No. (%)	EW-DSCL (n=118) No. (%)
Lens cleaning	4	555[a] (53.5)	37[b] (44.0)	47[a] (21.9)	82[b] (70.0)
	3*	3	2	12	1
	2	126	5	11	0
	1	37	8	6	0
	0	316	32	139	35
Lens disinfection	5	671 (64.7)	61 (72.6)	153 (71.2)	93 (78.8)
	2	217	11	26	4
	1	44	3	3	2
	0	105	9	33	19
Enzymatic treatment or disposal	2	498[c] (48.0)	33[d] (39.3)	157[c] (73.0)	108[d] (91.5)
	1	253	15	57	7
	0	286	36	1	3
Lens case hygiene	4	421 (40.6)	41[e] (48.8)	84 (39.1)	89[e] (75.4)
	2	152	9	59	8
	1	126	5	24	5
	0	338	29	48	16

* `Rub and rinse' cleaning

Significant differences between SCL and DSCL users with same wear schedule:

a: Chi squared Test: Chi squared=71.501, d.f.=1, $p<0.001$

b: Chi squared Test: Chi squared=13.124, d.f.=1, $p<0.001$

c: Chi squared Test: Chi squared=44.616, d.f.=1, $p<0.001$

d: Chi squared Test: Chi squared=63.528, d.f.=1, $p<0.001$

e: Chi squared Test: Chi squared=15.152, d.f.=1, $p<0.001$

APPENDIX 7: DIAGNOSES FOR SUBJECTS WITH LENS-RELATED DISEASE

DIAGNOSIS	FREQUENCY
Microbial keratitis:	
Bacterial keratitis	80
Acanthamoeba keratitis	14
Sterile keratitis:	
Sterile infiltrates	174
Toxic and Hypersensitivity disorders:	
Contact lens related papillary conjunctivitis	106
Thiomersal keratopathy / conjunctivitis	67
Toxic / chemical keratopathy (CL solution related)	57
Contact lens related red eye	42
Limbitis	14
Enzyme keratopathy	6
Superior limbic keratopathy	3
Metabolic disorders	
Acute epithelial necrosis (`Overwear syndrome')	121
Corneal hypoxia / oedema	43
Tight lens syndrome	30
Microcystic epitheliopathy	23
Corneal neovascularization	5
Mechanical disorders	
Corneal abrasion	176
Corneal foreign body	33
Superficial punctate keratitis	24
Conjunctival abrasion / foreign body	14
Poor contact lens fit	13
Traumatic conjunctivitis (poor lens handling)	8
Inflamed pinguecula / canthus	5
Corneal distortion	1
Tear-resurfacing disorders	
Three and nine o'clock staining	6
Inferior closure staining	5
Dry eyes (CL wear related)	4
Miscellaneous	
Contact lens intolerance	30
Lost contact lens	24
Difficulty with lens removal / recentring	4
Contact lens deposits	1
Subepithelial scarring (unknown cause)	1
TOTAL	1134

APPENDIX 8: DIAGNOSES FOR SUBJECTS WITH DISORDERS UNRELATED TO LENS WEAR

DIAGNOSIS	FREQUENCY
Viral / adenoviral / follicular conjunctivitis	132
Conjunctivitis (non-specific)	68
Meibomian cyst / Meibomian gland dysfunction	53
Viral / adenoviral keratoconjunctivitis	47
Anterior uveitis	40
Episcleritis	33
Blepharitis	30
Subconjunctival haemorrhage	30
Corneal abrasion / foreign body (non-lens associated)	27
No abnormality detected	24
Allergic / seasonal conjunctivitis	23
Marginal keratitis (non-lens associated)	18
Posterior vitreous detachment	18
Recurrent corneal erosion syndrome	17
Traumatic iritis / hyphaema	16
Blepharoconjunctivitis / blepharokeratoconjunctivitis	15
Chemical / toxic keratopathy	14
Lid contact / atopic dermatitis	12
Retinal detachmant / tear	11
Herpes simplex virus (HSV) keratitis	10
Conjunctival abrasion / foreign body	9
Preseptal cellulitis	9
Asthenopia	8
Conjunctival concretions / retention cyst	7
External hordeolum	7
Headache / migraine	6
Retinal degeneration	6
Trichiasis	6
Vitreous floaters	6
Anterior scleritis	5
Dry eyes	4
Optic neuritis	4
Thygeson's superficial punctate keratitis	4
Blunt ocular injury (non-specific)	3
Conjunctival chemosis	3
Conjunctival phlycten	3
Exposure keratitis	3
Photokeratitis / Photokeratoconjunctivitis	3
Pinguecula	3
Age-related macular degeneration	2
Conjunctival melanosis	2
HSV conjunctivitis	2
HSV keratouveitis	2
HSV lid disease	2
Herpes zoster lid disease	2
Keratoconus	2
Posterior uveitis	2
Subtarsal foreign body	2
Vitreous haemorrhage	2
Angle recession glaucoma	1
Branch retinal vein occlusion	1
Cataract	1

APPENDIX 8 (continued)

DIAGNOSIS	FREQUENCY
Ciliary injection (unknown cause)	1
Commotio retinae	1
Corneal dystrophy	1
Corneal scar	1
Dacryoadenitis	1
Injected eyebrow follicle	1
Intermediate uveitis	1
Lid laceration	1
Molluscum contagiosum	1
Myokymia	1
Papilloedema	1
Progressive myopia	1
Punctal stenosis	1
Sinusitis	1
Squamous papilloma	1
Thyroid ophthalmopathy	1
Transient ischaemic attack	1
Vertigo	1
TOTAL	778

APPENDIX 9: DISTRIBUTION OF DISPOSABLE LENS TYPES AMONGST CASES OF MICROBIAL KERATITIS

Daily-wear:

DSCL BRAND	CONTROL (n=86) No.(%)	CASE (n=23) No.(%)	CULTURE / DIAGNOSIS
Acuvue	58*(67)	20*(87)	10 *Acanthamoeba* keratitis 6 *Pseudomonas* spp. 4 Culture negative (presumed bacterial)
Surevue	14#(16)	1#(4)	1 *Staph. epidermidis*
Newvue	4 (5)	1 (4)	1 *Pseudomonas* spp.
Calendar	6 (7)	1 (4)	1 Culture negative

* Chi squared = 3.396, d.f.=1, p>0.05 (NOT significant)
\# Chi squared = 2.177, d.f.=1, p>0.10 (NOT significant)

Extended-wear:

DSCL BRAND	CONTROL (n=26) No.(%)	CASE (n=24) No.(%)	CULTURE / DIAGNOSIS
Acuvue	24 (92)	21 (88)	3 *Pseudomonas* spp.; 1 *Serratia* spp.; 1 *Staph. aureus*; 16 Culture negative
Newvue	0	2 (8)	2 Culture negative
Undetermined brand	0	1 (4)	1 Culture negative

APPENDIX 10: PROTOCOL: THE INCIDENCE OF MICROBIAL KERATITIS AMONGST COSMETIC CONTACT LENS WEARERS IN THE U.K.

CF Radford BSc MBCO[1,2]	Research Optometrist
AR Hill PhD FBCO[3]	Principal Optometrist
EG Woodward PhD FBCO[1]	Professor of Optometry and Visual Science
DC Minassian FRCS FRCOphth MSc(Epidem)[4]	Epidemiologist
AJ Bron MD FRCS[3]	Consultant Ophthalmologist
JKG Dart MA MD FRCS[2]	Consultant Ophthalmologist

1. City University, London.
2. Moorfields Eye Hospital, London.
3. Oxford Eye Hospital, Oxford.
4. Institute of Ophthalmology, London.

ABSTRACT

Contact lens (CL) wear has become the major predisposing factor for microbial keratitis[1]. Although the disease is rare, it is estimated that there are currently 3 million CL wearers in the UK at risk of developing this potentially sight-threatening complication[2].

In a population-based study of CL induced ulcerative keratitis conducted in New England (USA) in 1988 annual incidence estimates per 10,000 wearers of 4.1 and 20.9 were established for EW and DW use of soft CL (SCL) respectively[3]. Subsequently, however, disposable SCL have been introduced and currently account for about 15% of SCL use in the UK[2]. Case-control studies have shown a small but significant excess risk of microbial keratitis associated with disposable SCL use[6,7], although overnight use among these wearers has been shown to be the predominant risk factor[6]. A prospective population-based incidence study in Sweden[8], however, found similar risks of microbial keratitis for disposable and conventional SCL, although the markedly low incidence reported may limit the application of these results to other countries.

An incidence study of microbial keratitis among different types of CL wearers in the UK is proposed. All new cases presenting to a single centre (Oxford Eye Hospital) during a three year study period would be identified, and a random sample of the hospital catchment area would be surveyed to estimate the number of persons using each type of CL and wear schedule. This survey would establish the absolute risk of microbial keratitis to the CL user for the different CL types and wear schedules currently available in the UK.

AIMS OF STUDY

1. To produce data on the penetrance of different CL types (rigid, conventional soft, disposable soft) and wearing schedule (daily or overnight wear, and disposal) in the population.
2. To produce estimates of the incidence of microbial keratitis among users of each CL type and wear schedule, enabling informed decisions about lens use among practitioners and patients.

INTRODUCTION

Microbial keratitis is the most serious complication of contact lens (CL) wear; unlike the majority of lens-induced disorders it can progress after lens removal and has the potential to cause loss of vision due to corneal scarring, corneal perforation or spread of infection to surrounding ocular tissues. Although formerly a disease associated with trauma or pre-existing ocular surface disease, CL wear has become the predominant risk factor, accounting for about 65% of cases[1]. Although a rare disease, it is associated with considerable morbidity due to the large number of individuals at risk: currently there are approximately 3 million CL wearers in the UK[2].

The first population-based incidence study of CL induced ulcerative keratitis was conducted in New England (USA) in 1988[3]. Selecting an area in which the likelihood of cross-border treatment was low, all new cases during the study period were identified by surveying all ophthalmologists in the area, and the number of persons wearing cosmetic extended (EW) or daily wear (DW) soft CL (SCL) was estimated by conducting a household telephone survey. Annual incidence estimates of 4.1 and 20.9 per 10,000 wearers were established for EW and DW use of SCL respectively.

Since this incidence study was conducted, disposable SCL have been introduced and have become increasingly widespread; it is estimated that they currently account for 15% of SCL use in the UK[2]. Despite studies showing a reduction in the prevalence of less serious CL complications with these lenses[4,5], case-control studies employing stratified or multivariable analysis have shown a small but significant excess risk of microbial keratitis associated with disposable SCL use[6,7]. Overnight use, however, has been shown to be the predominant risk factor, and in both case-control studies there may have been insufficient controlling for patient characteristics.

The first prospective population-based incidence study of microbial keratitis to include an assessment of the risk with DSCL was conducted in Sweden during a 3-month period during 1993[8]. Every ophthalmologist in the country was asked to report cases treated during this period, and the numbers of wearers of each lens type in the population were estimated from a survey of CL fitters. The study derived annualised incidence estimates per 10,000 wearers of 13.33, 10.00, 2.17 and 2.16 for conventional EW-SCL, disposable EW-SCL, conventional DW-SCL and disposable DW-SCL respectively); although extended wear was significantly associated with microbial keratitis, disposable and conventional SCL were found to carry similar risks. The surprisingly low incidence reported in this study, however, attributed by the authors to close patient supervision and a cautious attitude to overnight use of CL among Swedish CL practitioners, may limit the application of these results to the UK and other countries.

This protocol examines the possibility of conducting an incidence study of microbial keratitis among different types of CL wearers in the UK. To avoid the problems of standardization of diagnosis and procedure inherent in a multi-centre study, a single centre, Oxford Eye Hospital (OEH) has been selected to provide the numerator for each estimate of incidence; OEH should produce a sufficient number of cases within the 36 month period, has a 24-hour Eye Casualty Department (to facilitate case identification), and a reasonably well-defined catchment population. To provide the denominator for each estimate of incidence, a telephone questionnaire of a random sample of the hospital catchment area would be conducted to estimate the number of persons using each type of contact lens and wear schedule. A recent pilot study (**APPENDIX A**), in which the response rate for such a telephone questionnaire was 82%, has confirmed the feasiblility of this method for deriving estimates of the penetration of the different CL types in the population. This survey would establish the absolute risk of microbial keratitis to the CL user for the different CL types and wear schedules currently available in the UK.

PROPOSED PLAN OF INVESTIGATION

1. Defining the catchment population (study population)

The catchment area for Oxford Eye Hospital (OEH) will be assessed by:
i) sampling from the OEH Accident and Emergency (A&E) registers and noting the postcodes from which each new Casualty attender of the relevant age group (12-65 years) has come
ii) surveying emergency attendance for eye problems at surrounding hospitals in the same way
iii) defining the OEH catchment area as the geographical region in which there is negligible overlap with the catchment areas of surrounding hospitals

This part of the study will be completed by April 1995.

2. Determining the number of people (n) in the study population

Population figures for the defined catchment area will be obtained from the most recent census.

3. Collection of cases in the study population (X)

Cases will be defined as patients with clinically diagnosed CL-related microbial keratitis (corneal infiltrate with an overlying epithelial defect, receiving intensive antibiotic treatment) presenting as new cases during the 36 month study period. Case patients resident outside the defined catchment area, or having a medical indication for CL wear, will be excluded from the study.

In order to ensure that no cases presenting to the centre are missed, all CL wearers attending OEH A&E during the 3 year study period will be identified on arrival by the nursing staff and asked to complete a questionnaire **(APPENDIX B)** detailing:
a) Date of presentation
b) Hospital number
c) Name, address and telephone numbers
d) Date of birth
e) Gender
f) Occupation (for hospital audit only)
g) Type of CL worn in the previous 4 weeks, and whether regularly worn overnight (at least once per week)
h) Frequency of lens disposal (disposable CL wearers only)
i) Use of CL for aphakia

Patients will be asked to give the completed questionnaire to the Casualty doctor, who will enter the diagnosis in the space provided. (The additional data provided will be used to assess the proportion of inappropriate A&E attendence by CL wearers for an OEH audit). Regular inspection of the Casualty register will ensure that any cases failing to receive a questionnaire can be swiftly identified and contacted by telephone or letter.

Collection of cases commenced on 1st October 1993. All diagnoses of keratitis are checked with the hospital notes, and, for cases of presumed microbial keratitis (as defined above) the following data is noted:
a) Size and the location of the lesion(s)
b) Corneal culture results
c) Final VA

4. Estimation of the proportion (p) of users of each CL type and schedule in the study population

A random sample of households will be drawn from the postcodes for each of the geographical strata of the study area.

The penetrance of the different CL types and modes of use in each sample will be collected by means of a previously piloted household telephone survey (**APPENDIX A**). The interviews will be conducted half way through the study period, in order to minimize the effect of any changing CL wear patterns during the 36 month period.

Trained interviewers will conduct a telephone questionnaire (**APPENDIX C**) to seek to identify in each household:
a) No. of adults (12 years or over)
b) No. of adults wearing CL within the last 4 weeks
c) Types of CL presently worn by any CL wearers, whether regularly worn overnight (at least once per week), and frequency of CL disposal (disposable CL wearers only)
d) Use of CL for aphakia
e) Age of CL wearers in the household.
f) Gender of CL wearers in the household.
g) Initials of CL wearers in the household.

Upto 4 attempts to obtain complete data from each household will be allowed. As in the pilot study, all telephone calls will be made between 6.30pm and 9.00pm, weekday evenings excluding Fridays.

Data from questionnaire sheets will be entered into a computer database for subsequent analysis.

5. Estimation of required telephone survey sample size
The pilot study (**APPENDIX A**) suggests that the penetrance of CL wear in the general population is approximately 5.7%. An estimate of the distribution of the different CL types and wear schedules may be derived from that among CL wearers attending with disease unrelated to CL wear at Moorfields Eye Hospital Casualty Department (unpublished data). The CL type and wear schedule with the lowest penetrance is EW-SCL (4%), followed by EW-DSCL (6%). Given the size of the adult population for the estimated study area, as suggested by the 1981 Census (approximately 450,000), data from 34,000 persons is required in order to give an estimate of the prevalence of the least common CL type and schedule (EW-SCL) with a precision of +/- 0.05% and in order to have a power (calculated by computer simulation) of 90% to detect relative risks with different daily-wear lens modalities of 2.8 or higher, based on a critical p value of 0.05.

Given an estimated 2.1 persons aged 12 years or more per household, data would have to be complete for 16,190 households. To allow for an 81.6% response rate, as indicated by the pilot study, approximately 19,840 household telephone listings would have to be included in the survey.

6. Estimate of the incidence of CL-related microbial keratitis for the defined period
Estimated annual incidence for each CL type and schedule within the study population will be given as

$$\text{Annual Incidence} = \frac{X / np}{3}$$

where

X = Number of cases of microbial keratitis in wearers of the particular CL type and schedule in the study population, during the three year study period
n = Number of individuals in the study population
p = Proportion of individuals in the study population using the particular CL type and wear schedule

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APPENDIX A

PILOT STUDY (conducted July 1992): A COMMUNITY-BASED SURVEY OF THE PENETRANCE OF CONTACT LENS WEAR

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INTRODUCTION

Prior to the widespread use of contact lenses (CL), microbial keratitis was seldom seen in eyes without a predisposition to infection due to ocular surface disease or trauma. However, soft contact lens (SCL) wear has now become well established as the major predisposing factor for microbial keratitis, a recent study attributing 65% of cases to cosmetic CL use[1]. Although the disease is rare, the large number of CL wearers (over 1.5 million in the UK alone[2]) means that a considerable number of healthy eyes are at risk.

At present, the relative risks of different lens types and wear schedules established in a recent case control study of microbial keratitis[1] have to be viewed in the context of the only well conducted incidence study to date; that of Poggio et al U.S.A. (1989)[3]. This study surveyed all ophthalmologists in the study area (5 states of New England) to identify all new cases over the study period, and conducted a telephone survey of 4178 households to estimate the number of persons wearing cosmetic extended (EW) or daily wear (DW) SCL. Annual incidence estimates of 1 in 500 for EW-SCL and 1 in 2500 for DW-SCL were established.

A new case control study at Moorfields Eye Hospital (MEH), which began in March 1992, is currently assessing the risks associated with the changing CL wearing patterns that have occurred with the introduction of disposable soft contact lenses (DSCL). A pilot case control study[4] has shown both DW and EW DSCL to have a higher relative risk of microbial keratitis than conventional SCL. We are currently investigating the possibility of obtaining our own, UK-based incidence data to which the relative risks of different CL types and wear schedules, including DW and EW-DSCL, may be related.

To help assess the feasibility of an incidence study, a small-scale pilot telephone questionnaire survey was conducted.

AIMS OF PILOT STUDY

1. To estimate the likely response rate for a large scale telephone questionnaire survey.
2. To pre-test the telephone questionnaire script.
3. To estimate the penetrance of CL in the population.
4. To assist costing of the proposed full-scale investigation.

METHOD

Trained interviewers conducted a telephone questionnaire with 500 households. The 500 households were those listed at the top of each of the first five hundred odd-numbered pages of a residential telephone directory (Merton, Surrey, 1992). The questionnaire sought to identify in the household:

a) The number of members at least 12 years of age
b) The number of CL wearers (at least 12 years of age, having worn CL within the last four weeks)
c) Types of CL worn presently by any CL wearers
d) Regular overnight CL wear (at least once per week)
e) Use of CL for aphakia
f) Initials and age of CL wearers.

Telephone interviews were conducted between 6.30pm and 9.30pm, on weekday evenings excluding Friday. Upto 4 attempts to obtain complete data from each household were allowed, each attempt being carried out on different evenings unless there was good reason to try twice in one session (eg engaged tone, respondent request). Households of non-cooperative respondents were not re-contacted.

Data from questionnaire sheets was entered onto a computer database for subsequent analysis.

RESULTS

Sample population and response rate

500 numbers randomly selected from the residential telephone directory were included in the survey; 5 were not households, and no contact could be made with a further 49.

Data was incomplete for 42/446 (9.4%) of the households contacted, chiefly due to respondents refusing to be interviewed (41). A breakdown of the reasons for missing or incomplete data is shown in **TABLE 1**.

Interviews were completed for 404/495 (81.6%) of the telephone numbers presumed to belong to households. These 404 households contained 847 persons aged at least 12 years.

Contact lens wear in the study population

49/847 of persons aged at least 12 years were CL wearers. 1/49 of the CL wearers was wearing a CL for aphakia, so the penetrance of cosmetic CL use among this population was 5.67% (48/846). Soft CL were the most common lens type (27/48, 56.3%), followed by rigid gas permeable (15/48, 29.2%), hard (PMMA) (4/48, 8.3%) and disposable soft CL (2/48, 4.2%). 4/48 (8.3%) were wearing their lenses overnight on a regular basis (at least once per week).

Study duration

A total of 23.75 hours of interviewing time (telephone interview, completion and processing of questionnaires) was required to carry out this survey. Calls to households without any CL wearers lasted an average 30 seconds, while telephoning time for households where there were one or more CL wearers totalled an average 4 minutes.

CONCLUSION

The proportion of listings for whom data was complete was considerably greater in this telephone survey than in that of Poggio et al[3] (81.6% and 59.8% respectively). Despite the differing sampling techniques employed (random selection from a residential directory as opposed to random digit dialling) the proportion of non-residential listings identified was almost identical (10% and 10.5% respectively). The difference in the proportion of households with complete data is due to a better contact success rate (90.1% as opposed to 80%), and a better cooperation rate (90.6% as opposed to 74.7%), among the population in this study.

The survey showed a higher penetrance of CL (5.7%) in the population than previously thought (3 to 4%)[2], although the number of cosmetic CL wearers in the survey (48) was too small to give a reliable indicaton of the distribution of the different CL types and wear schedules in the population.

TABLE 1: Reasons for missing/incomplete data among the 495 listings presumed to be households

Cause	Number	% (n=48)
Respondent refused to be interviewed/withheld some data	41	8.3
Missing data	1	0.2
No English	0	0
No contact: Number unobtainable*	7	1.4
No reply*	42	8.5

* After 4 attempts

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APPENDIX B
OXFORD EYE HOSPITAL
CONTACT LENS USER QUESTIONNAIRE

This questionnaire is part of a study assessing the risks of contact lens wear. We will be collecting information from all contact lens wearers attending Casualty, whether or not their problem is lens-related. All information is confidential, and will not affect your treatment.

PLEASE GIVE YOUR COMPLETED QUESTIONNAIRE TO THE CASUALTY DOCTOR.

Thank you very much for your help.

Dr.A.R.Hill PhD FBCO
(Principal Optometrist)

Mrs.C.F.Radford BSc MBCO
(Research Optometrist)

TODAY'S DATE .../.../... **CASUALTY/HOSPITAL NUMBER** .....

NAME .....

ADDRESS .....

TELEPHONE NO. Home: ..... **Work:** .....

DATE OF BIRTH .../.../... **SEX:** M / F **OCCUPATION**.....

1. Have you worn contact lenses within the last 4 weeks?

[ ] No [ ] Yes

2. What type of contact lenses do you wear?

[ ] Hard / Rigid gas-permeable

[ ] Soft lenses

[ ] Disposable lenses (eg thrown away at least once per month)

If disposable, how often do you throw them away? .....

3. Do you wear your lenses overnight at least once per week?

[ ] No [ ] Yes

4. Do you wear contact lenses because a cataract was removed?

[ ] No [ ] Yes

THANK YOU FOR YOUR HELP

HOSPITAL USE ONLY:

1. DIAGNOSIS: .....

2. COULD THIS DISORDER HAVE BEEN MANAGED BY AN OPTOMETRIST?
(an optometrist may only give chloramphenicol for emergency/prophylactic use)

[ ] No [ ] Yes [ ] Unsure

APPENDIX C

QUESTIONNAIRE FOR INCIDENCE OF MICROBIAL KERATITIS STUDY

TELEPHONE NUMBER: .....HOUSEHOLD NUMBER .....

CONTACT DETAILS:	DATE	TIME	RESULT*	INTERVIEWER
1st attempt:	.....	.....	.....	.....
2nd attempt:	.....	.....	.....	.....
3rd attempt:	.....	.....	.....	.....
4th attempt:	.....	.....	.....	.....

Result*: N = No reply, or answerphone
U = number Unobtainable / out of order
R = further data, Ring again
INC = INComplete (say why, eg no English)
tick = complete data

INTRO:
Good evening. I am calling on behalf of medical researchers at Oxford Eye Hospital. They are studying serious eye disease among contact lens wearers.
May I ask you... > > >

Q.1 Does anybody in your household wear contact lenses?

Ans.:[ ] NO...**O.K., but... > > >** (to Q.2)

Ans.:[ ] YES...**How many have been wearing them in the last 4 Weeks?**

[....] (contact lens) people (to Q.2)

Ans.:[ ] DON'T KNOW...**When would be a good time to ring and speak to someone who would know?**

.....(to Q.2)

Q.2 So that we know how many people we have asked, may I ask how many people aged 12 years or more live in your household?

Ans.:[....] people...**So there are....people aged 12 or more in you household?**
(Correct if necessary)

Household with NO CLs:...**Thank you for your help. Goodbye.**
Household WITH CL wearers: to Q.3.

CL USER HOUSEHOLDS:
Q.3 May I speak to the person/people who wear(s) contact lenses?

Ans.:[ ] NOT IN...**Would you be able to answer some simple questions on her/his/their behalf?**
[ ] NO/DON'T KNOW...**When would be a good time to ring her/him/them?** .....
Thank you for your help. Goodbye.
[ ] YES / I'LL TRY etc...(to Q.4)
Ans.:[ ] YES... (With CL wearer, go to INTRO then Q.4).
FINISHED? FILL IN THE CONTACT DETAILS SECTION ABOVE.

LENS WEARER 1 (Use "her" or "his" if not speaking to CL wearer)
NB SPEAKING TO NEW PERSON: DO INTRO AGAIN!

Q4.1 WHAT TYPE OF CONTACT LENSES DO YOU WEAR, HARD/GAS PERMEABLE, SOFT OR DISPOSABLE?

[ ] Hard / Gas permeable...) Skip to next Q
[ ] Soft...) "
[ ] Disposable...) If disposable:
How often do you throw them away?
[ ] Daily
[ ] Weekly
[ ] Fortnightly
[ ] Monthly
[ ] LESS OFTEN (NOT disposable - TICK SOFT)
[ ] Don't know... **Do you know if they are hard or soft?**
[ ] Hard(/G.P.) type...
[ ] Soft(/Disp) type...
[ ] DON'T KNOW...SEE BELOW

Q4.2 DO YOU WEAR YOUR LENSES OVERNIGHT AT LEAST ONCE PER WEEK?

[ ] NO
[ ] YES
[ ] DON'T KNOW...SEE BELOW*

Q4.3 DO YOU WEAR CONTACT LENSES BECAUSE A CATARACT WAS REMOVED?

[ ] NO
[ ] YES
[ ] DON'T KNOW...SEE BELOW*

Q4.4 MAY I HAVE YOUR INITIALS? .....

Q4.5 AND YOUR AGE? .....

Q4.6 TICK SEX: [ ] Male
[ ] Female

Thank you for your help.

NO MORE CL WEARERS:... **Goodbye.**

FINISHED? FILL IN THE CONTACT DETAILS SECTION PAGE 1.

*DON'T KNOWS FROM FRIEND/RELATIVE OF CL USER:...**When would be a good time to ring her/him?**.....

OTHER CL WEARERS:...(USE EXTRA SHEET & ATTACH TO THIS FORM)
Q.3 May I speak to the person/people who wear(s) contact lenses?

Ans.:[ ] NOT IN...**Would you be able to answer some simple questions on her/his/their behalf?**
[ ] NO/DON'T KNOW...**When would be a good time to ring her/him/them?** .....
Thank you for your help. Goodbye.
[ ] YES / I'LL TRY etc...(to Q.4)
Ans.:[ ] YES... (With CL wearer, go to INTRO then Q.4).
FINISHED? FILL IN THE CONTACT DETAILS SECTION ABOVE.

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