Copyright Undertaking

This thesis is protected by copyright, with all rights reserved.

By reading and using the thesis, the reader understands and agrees to the following terms:

1. The reader will abide by the rules and legal ordinances governing copyright regarding the use of the thesis.

2. The reader will use the thesis for the purpose of research or private study only and not for distribution or further reproduction or any other purpose.

3. The reader agrees to indemnify and hold the University harmless from and against any loss, damage, cost, liability or expenses arising from copyright infringement or unauthorized usage.

If you have reasons to believe that any materials in this thesis are deemed not suitable to be distributed in this form, or a copyright owner having difficulty with the material being included in our database, please contact lbsys@polyu.edu.hk providing details. The Library will look into your claim and consider taking remedial action upon receipt of the written requests.
AN EVALUATION OF
COMMON STANDARD DIAGNOSTIC TESTS
FOR DRY EYE

KWONG YEE MAN

M. PHIL.
THE HONG KONG POLYTECHNIC UNIVERSITY
2002
Abstract

Abstract of thesis entitled "An evaluation of common standard diagnostic tests for dry eye"

Submitted by Kwong Yee Man

For the degree of Master of Philosophy

At the Hong Kong Polytechnic University in June of 2002.

Introduction

Dry eye is a common complaint in patients attending eye clinics. It is characterised by a variety of ocular surface abnormalities and has typical symptoms of dryness, foreign body sensation and discomfort.

Although a number of clinical tests and techniques are available for the diagnosis of dry eye, such as the Cotton Thread Test (CTT), the Schirmer Test (ST), Rose bengal staining, fluorescein staining, tear meniscus height (TMH) measurement and the Mc-Monnies' dry eye questionnaire (Mc-DEQ), the condition is nevertheless difficult to diagnose.

Most research findings related to dry eye have been on Caucasian eyes and recent studies have shown that the tear stability and tear volume of Hong Kong (HK)-Chinese are significantly less than those reported for Caucasians. In view of the differences in tear characteristics between Caucasians and Chinese, the internationally used Mc-DEQ (whether in English or Chinese (the Mc-DEQC)) may not be applicable to Chinese, and the effectiveness of the
commonly used tear assessment tests for discriminating between normal and dry eye in Chinese is unknown.

Results

The prevalence of Chinese dry eye was determined by a retrospective survey of patient files (dry season 741 subjects, humid season 857 subjects) from a private eye centre in HK. The prevalence of dry eye was about 3% and was not affected by mean humidity within the range of 60% to 72%. Foreign body sensation was the most common ocular symptom, and dryness was also commonly reported. Based on ten ocular symptoms, high specificities (>83%) but poor sensitivities (<65%) were obtained from the predictive equations. The poor sensitivity was influenced by the relatively small number of dry eye subjects (n=25).

We found no statistically significant relationship between the results of the SP-CTT and the TMH, or between the findings of the PRT Test and the TMH. Our results showed that most responses to the questions in the Mc-DEQC could not discriminate between normal and dry eye subjects. Neither the total scores nor the discriminant scores of the Mc-DEQC were able to discriminate between normal and dry eye.

The SP-CTT, the PRT Test and the Mc-DEQC were unable to discriminate between normal and dry eye subjects and had poor specificities and sensitivities. When more stringent diagnostic criteria were applied, the specificities and sensitivities of the SP-CTT and the PRT Test did not improve, however the specificity and sensitivity of the Mc-DEQC did somewhat.
The sensitivity of the TMH as a diagnostic tool for dry eye was found to be over 80% at a cut-off value 0.21 mm, however the repeatability of measures is such that one measure could indicate normal and a repeated measure on the same eye could indicate dry eye.

Neither the Mc-DEQC nor the SD-DEQC was a good screening test for Chinese dry eye. Both DEQ had poor specificity and sensitivity when we used less stringent diagnostic criteria. When more stringent criteria were used, both the specificity and sensitivity of the SD-DEQC were improved somewhat.

Conclusions

The predictive equations developed show potential for the diagnosis of dry eye. The SP-CTT and the PRT Test were unable to discriminate between normal and dry eyes. Results from these tests are not related to tear volume. TMH measurement using a photo-slit lamp in conjunction with the IMAGEnet System was not sufficiently repeatable, however, it is a potentially useful test for the diagnosis of dry eye as it is the only test that we used which can discriminate between normal and dry eye.

Based on the scoring system, the Mc-DEQC and SD-DEQC are poor screening tools for Chinese dry eye, however discriminant analysis may be a better method than the scoring system to analyse their results. Neither the Mc-DEQC nor the SD-DEQC could effectively discriminate between the normal and dry eye subjects.

Clinically, in the absence of better tests, we therefore recommend use of the fluorescein inferior corneal staining and the presence of ocular symptoms. The tests described here are in common use around the world and used universally
for dry eye assessment. Our work indicates that the value of these tests is extremely limited in a Chinese population.
PART A: LITERATURE REVIEW

Abstract i
Acknowledgements v

Chapter 1 Introduction ......................................................... 1
  1.1 Background ............................................................... 1
  1.2 Statement of the Problem ............................................... 2
  1.3 Research Questions .................................................... 3
  1.4 Objectives ............................................................... 4

Chapter 2 Tear Film and Tear Assessment Techniques .................. 5
  2.1 Introduction ............................................................. 5
  2.2 Tear Film ............................................................... 5
    2.2.1 The Physiology of the Tear Film ............................... 6
    2.2.2 Tear Layers ........................................................ 7
      (i) Superficial Lipid Layer ........................................... 7
      (ii) Aqueous Layer .................................................... 8
      (iii) Mucous Layer .................................................... 8
  2.3 Dry Eye ................................................................. 9
    2.3.1 Classification of Dry Eye ....................................... 11
      (i) Tear Deficient Dry Eye .......................................... 11
      (ii) Evaporative Dry Eye ............................................. 11
  2.4 Prevalence of Dry Eye ................................................ 12
  2.5 Approaches in Diagnosis of Dry Eye ................................ 14
2.5.1 Symptoms of Dry Eye ........................................... 15
2.5.2 Clinical Signs ..................................................... 15
2.6 Diagnostic Tests for Dry Eye ..................................... 17
2.6.1 Clinical Diagnostic Tests ....................................... 17
   (i) Fluorescein Corneal Staining Test ............................ 17
   (ii) Rose Bengal Staining Test .................................... 18
   (iii) Fluorescein Tear Break Up Time (TBUT) .................... 19
   (iv) Schirmer Test (ST) ............................................. 20
   (v) Cotton Thread Test (CTT) .................................. 20
   (vi) Dry Eye Questionnaire (DEQ) ............................... 21
   (vii) Tear Meniscus Height (TMH) Measurement .............. 21
2.6.2 Laboratory Tests ............................................... 22
   (i) Tear Protein Concentrations ................................ 22
   (ii) Tear Film Osmolarity ........................................ 23
   (iii) Examination of Conjunctival Cells ......................... 23
2.7 Comments .................................................................. 24

Chapter 3 The Cotton Thread Test, Tear Meniscus Height and Dry Eye Questionnaire ................................................. 25
3.1 Introduction .................................................................. 25
3.2 Cotton Thread Test (CTT) ......................................... 26
   3.2.1 Types of Developed Cotton Thread Test (CTT) .............. 26
       (i) White Cotton Thread Test (WCTT) .......................... 26
       (ii) Phenol Red Thread (PRT) Test ............................. 27
       (iii) The Self-Prepared Cotton Thread Test (SP-CTT) .......... 28
3.2.2 Factors Affecting CTT ........................................... 32
(i) CTT Measurement................................................. 32
(ii) Testing Periods.................................................... 34
(iii) Humidity.......................................................... 34
(iv) Consecutive Measurements............................... 35
(v) Age and Gender................................................... 36
(vi) Local Anaesthetic............................................... 38
(vii) Racial Differences.............................................. 38

3.2.3 Pros and Cons of CTT........................................... 39

3.2.4 Reliability....................................................... 40

3.2.5 Validity.......................................................... 42

3.2.6 Statistical Considerations................................. 44

3.2.7 Comments....................................................... 46

3.3 Tear Meniscus Height (TMH)................................. 46

3.3.1 Methods for Assessing Tear Meniscus Height (TMH)..... 46

(i) Slit Lamp Observation (SLO)................................ 47

(ii) Photographic and Computer Analyses (PCA)............. 49

(iii) Videography and Rule Scale Measurement............... 50

3.3.2 Factors Affecting TMH Measurement....................... 50

(i) Fixation Position of the Eye................................. 50

(ii) Age and Gender................................................ 51

(iii) Ocular Conditions............................................. 51

3.3.3 Reliability of TMH Assessment............................ 51

3.3.4 Validity of TMH Assessment............................... 52

3.3.5 Comments....................................................... 53

3.4 Dry Eye Questionnaire(s) (DEQ).............................. 54
3.4.1 Types of DEQ ......................................................... 55
(i) Simple DEQ ......................................................... 55
(ii) Complex DEQ ...................................................... 56
3.4.2 Symptoms of Dry Eye ........................................... 57
3.4.3 Reliability ......................................................... 60
3.4.4 Validity .......................................................... 60
3.4.5 Comments ......................................................... 62

PART B: EXPERIMENTAL METHODS

Chapter 4  Introduction to Experimental Studies and Research Aims...... 64
  4.1 Introduction ....................................................... 64
  4.2 Research Aims ................................................... 65

Chapter 5  Investigation Techniques ..................................... 67
  5.1 Tests Used ......................................................... 67
  5.2 Materials Used and Procedures of Each Test ....................... 67
    5.2.1 SP-CTT ....................................................... 67
    5.2.2 PRT Test .................................................... 70
    5.2.3 TMH Measurement with Topcon IMAGEnet System ............. 71
    5.2.4 Dry Eye Questionnaire (DEQ) ................................ 73
    5.2.5 Ocular Examination Using Slit-lamp Biomicroscope .......... 75
  5.3 Subject Criteria .................................................. 76
  5.4 Ethical Approval and Subject Consent ................................ 76
PART C: EXPERIMENTAL STUDIES

Chapter 6  Prevalence of Dry Eye in an Eye Clinic Population in Hong Kong

6.1 Introduction ........................................................................................................ 78
6.2 Procedure ............................................................................................................. 79
6.3 Results ................................................................................................................... 80
6.4 Discussion ............................................................................................................. 83
6.5 Conclusions ......................................................................................................... 87

Chapter 7  A Study of the Specificity and Sensitivity of a Self-prepared Cotton Thread Test and the Phenol Red Thread Test in the Diagnosis of Dry Eye ................................................................................................. 88

7.1 Introduction ........................................................................................................... 88
7.2 Subjects .................................................................................................................. 89
7.3 Procedure ............................................................................................................. 89
7.4 Results .................................................................................................................. 91
7.5 Discussion ............................................................................................................. 92
7.6 Conclusions ......................................................................................................... 97

Chapter 8  Tear meniscus height in normal and dry eyes ......................................... 98

8.1 Introduction ........................................................................................................... 98
8.2 Subjects ................................................................................................................ 99
8.3 Procedure ............................................................................................................ 100
8.4 Results .................................................................................................................. 102
8.5 Discussion .......................................................................................................... 104
8.6 Conclusions ....................................................................................................... 109
Chapter 9  Performance of Mc-Monnies Dry Eye Questionnaire, a Self-designed Dry Eye Questionnaire, and Cotton Thread Tests . 111

9.1 Introduction ................................................................................................................. 111

9.2 Subjects ............................................................................................................................ 112

9.3 Procedure ........................................................................................................................ 115

9.4 Results .............................................................................................................................. 116

9.4.1 Evaluation of the tests used .......................................................................................... 117

(i) SP-CTT and the PRT Test ......................................................................................... 117

(ii) Mc-DEQC and SD-DEQC ......................................................................................... 118

9.4.2 The change in optimum cut-off values when using more stringent criteria for dry eye and normal groups ................................................................. 119

9.4.3 Correlation of the TMH and CTT ............................................................................. 123

9.5 Discussion ......................................................................................................................... 123

9.5.1 Classification of Subjects .......................................................................................... 123

9.5.2 Evaluation of CTT ..................................................................................................... 125

9.5.3 Evaluation of Mc-DEQC and SD-DEQC ................................................................. 126

9.6 Conclusions ..................................................................................................................... 130

Chapter 10  Conclusions ................................................................................................. 131

10.1 Summary of current study ............................................................................................. 131

10.2 Implication of the results .............................................................................................. 134

10.3 Further investigations .................................................................................................... 135

References ............................................................................................................................ 137

Appendices ............................................................................................................................ 153

List of Abbreviations ........................................................................................................... 163
Acknowledgements

It is my greatest honour to thank those who gave me tremendous support and assistance. First, I would like to thank Dr. Pauline Cho for her stern encouragement and guidance. She gave me invaluable advice and support in this study, and taught me the concept of proper scientific research. As I was a part-time student, she sacrificed most of her non-office hours to teach me how to think logically and independently, to make my own decisions and to prepare this thesis. Her patience and guidance helped me all the way. Therefore, this thesis would not have existed without her.

I am also sincerely grateful to Professor Marion Edwards, my co-supervisor, for her invaluable comments on the published papers and for her support in the preparation of this thesis. I thank her for her advice on the analysis of my results and for the long hours spent on reading my thesis.

I also thank the staff of the General Eye and Low Vision Centre, Ms Katherine Li, Susanna Lee, Joseph Cho, Kong Wai Chi, Ng Wing Shuen and Andrew Au Yeung for their assistance and support.

This work would not have been possible without the moral support of my mother, Ms Mak Choi Yau, and my husband, Mr. Lee Chun Cheong. Last but not least, I would like to thank Miss Lee Hoi Wun, my daughter (seven years old), for her understanding and moral support.

This research was supported by The Hong Kong Polytechnic University (GV453).
Chapter 1

Introduction

1.1 Background

The percentage of patients visiting eye clinics complaining of dry eye has been reported to average 20-25\% (Lyle 1982). Dry eye is a term used to describe a variety of ocular surface abnormalities of different causes, with symptoms of discomfort, dryness and foreign body sensation. It also includes the condition in which there is a deficiency of any layer of the tear film, such as aqueous deficiency, mucin deficiency or lipid abnormality (Lemp 1992, Nelson 1994, Sindt 1999). It is a frustrating problem for eye care practitioners due to the difficulty in its diagnosis and management (Robboy and Orsborn 1989), and diagnosis is complicated by a lack of effective discriminatory diagnostic tests (Holly and Lemp 1977).

Laboratory tests such as measurement of tear protein concentrations, tear film osmolarity or examination of conjunctival cells require sophisticated and expensive equipment. There are a number of clinical tests available for the diagnosis of dry eye, the commonly used clinical tests being fluorescein staining, the Schirmer Test (ST) and the Cotton Thread Test (CTT). However, the results of the ST have been shown to be unreliable, and as a result the CTT has become more popular for tear volume tests, although its use in dry eye to date is limited. Rose bengal stain is less commonly used, as it causes
significant patient discomfort. Other clinical tests reported to be effective screening tools for the presence of keratoconjunctivitis sicca (KCS) are tear meniscus height (TMH) assessment (Sargent et al. 1988, Mainstone et al. 1996) and the Mc-Monnies’ dry eye questionnaire (Mc-DEQ) (McMonnies and Ho 1987, Robboy and Orsborn 1989, Golding and Brennan 1993, McMonnies et al. 1998).

Recent research studies have shown that the tear stability of Hong Kong (HK)-Chinese is significantly less than that of Caucasians (Cho et al. 1992, Cho and Brown 1993, Cho and Yap 1993b) and the tear volume of HK-Chinese is also significantly less than that of Caucasians (Cho and Douthwaite 1994, Cho and Kwong 1996). Although there are many reports of the performance of the various clinical tests for dry eye, most, if not all, were of findings for Caucasian eyes.

1.2 Statement of the Problem

Reports of the prevalence of dry eye and dry eye assessment in Chinese patients are scarce. The self-prepared Cotton Thread test (SP-CTT) and the Phenol Red Thread (PRT) Test have been reported to be repeatable on Chinese subjects (Cho 1993, Cho and Kwong 1996) but to our knowledge, the specificity and sensitivity of the CTT for the diagnosis of dry eyes are unknown for Chinese subjects. To our knowledge, there has been no report of the effectiveness of TMH assessment or of any dry eye questionnaire (DEQ) in the diagnosis of Chinese dry eye. In view of the differences in tear characteristics between Caucasians and Chinese, the internationally used Mc-
DEQ may not be applicable to Chinese, in which case there is a need to design a DEQ specially for Chinese. Therefore, the specificities and sensitivities of these tests in the diagnosis of dry eye in Chinese should be evaluated.

1.3 Research Questions

The questions addressed in this work in relation to Chinese subjects were

1. What is the prevalence of dry eye in an eye clinic population in HK?

2. What is the best model to predict whether a patient with particular symptoms has dry eye?

3. What are the specificity and sensitivity of the above model for classification of normal and dry cases?

4. How effective are the SP-CTT, the PRT test and the Mc-DEQC in discriminating between the normal and dry eye?

5. What are the specificities and sensitivities of the above tests in the diagnosis of dry eye?

6. How are the specificities and sensitivities of the above tests affected by the criteria used to define dry eye?

7. How repeatable is TMH determination, using the TOPCON IMAGEnet system, in normal and dry eye subjects?

8. What is the average TMH value in normal and dry eye subjects?

9. How effective is the self-designed DEQC for the diagnosis of dry eye?
1.4 Objectives

We estimated the prevalence of dry eye in a private eye centre in HK, determined a model to predict whether a patient with particular symptoms has dry eye, and explored the clinical tests for dry eye on Chinese subjects. We determined the specificities and sensitivities of a SP-CTT, the PRT test, TMH test and Mc-DEQ (translated into Chinese) for the diagnosis of the dry eye. We also evaluated the efficacy of a self-designed DEQC for Chinese.
Chapter 2

The tear film and tear assessment techniques

2.1 Introduction

Abnormality of the tear film, cornea or lids can lead to dry eye (Lemp 1992). Clinical and laboratory tests can be used to diagnose dry eye and in this chapter, a detailed review of the work previously carried out on tear film, and some of the more common tests used for assessing the tear film, are presented.

2.2 Tear Film

The tear film has six important functions which contribute to vision and corneal health (Stein and Hurwitz 1996). It provides a smooth surface thereby improving the optical characteristics of the eye. It also acts as a lubricant between the lid and the corneal surface during blinking and provides a moist environment for the eyeball. The tear film provides a medium for the transmission of oxygen from the atmosphere to the corneal and conjunctival epithelial cells, and provides glucose to the corneal epithelium. Desquamated corneal cells and bacteria can be removed by the tear film during blinking. Antibacterial substances in the tear film help to maintain corneal health. The stability of the tear film is therefore essential to the well-being of the corneal and conjunctival epithelia (Holly and Lemp 1977, Lamberts 1987) and
abnormalities in the tear film can cause dry eye and may disrupt vision (Holly and Lemp 1977). The stability of the tear film and the adequacy of the tears also play important roles in successful contact lens wear (Holly 1981).

- SUPERFICIAL LIPID LAYER $\sim$0.1 μm
  Consisting mainly of waxy and cholesteryl esters and some polar lipids

- AQUEOUS LAYER $\sim$7 μm
  Containing in dissolved form inorganic salts, glucose, urea, and surface active biopolymers, proteins and glycoproteins

- MUCUS LAYER $\sim$0.02 – 0.05 μm
  A hydrated layer of mucoproteins rich in sialomucin

1 μm

Figure 2.1. Structure of the tear film (adapted from Holly and Lemp 1977).

2.2.1 The Physiology of the Tear Film

The precorneal tear film is a thin fluid film, which covers the exposed part of the ocular globe (Holly 1987). The most widely accepted model for the tear film is that proposed by Wolff (1976). According to Wolff's model, the tear film consists of three layers: a superficial lipid layer, an aqueous layer and a mucus layer (see Figure 2.1). The mean thickness of the tear film is generally
accepted to be about 7 μm (Holly and Lemp 1977) but has been reported to be as little as 3 μm (King-Smith et al. 2000) and as great as 40 μm (Prydal et al. 1992). In this study, we adopted the widely-accepted Wolff's model in which the thickness of the tear film is about 7 μm.

The normal total ocular tear volume includes the exposed tear volume and the unexposed tear volume under the eyelids (Port and Asaria 1990). The exposed tear volume consists of tears on the cornea, on the exposed bulbar conjunctiva and in the tear menisci. Tear volume has been determined by the fluorescein dilution method in a number of previous studies (Mishima et al. 1966, Scherz et al. 1974). Mishima et al. (1966) found that the average tear volume was approximately 7.0±2.0 μl. Based on anatomical considerations, Mishima and his co-workers (1966) calculated the tear volume to be 8.5 μl (4.5 μl for unexposed tear volume, 1.1 μl for tear film in the normal palpebral fissure and 2.9 μl for the tear menisci).

2.2.2 Tear Layers

2.2.2 (i) Superficial Lipid Layer

The superficial lipid layer, about 0.1 μm thick, is the outermost layer, and consists of low and high polarity lipids. Most of the lipids are secreted by the meibomian glands, which have openings along the upper and lower lid margins. The glands of Zeis, which are located at the base of the lashes, also secrete some lipids. The main function of this layer is to retard the evaporation of the underlying aqueous (Blades and Craig 1997) and another important
function is to spread the tear film. Therefore, the stability of the tear film is directly affected by this layer (Holly and Lemp 1977).

2.2.2 (ii) Aqueous Layer

The aqueous is the middle layer, and is secreted by the main and accessory lacrimal glands. This layer consists of dissolved inorganic salts, glucose, urea, and surface active biopolymers, proteins and glycoproteins (Holly and Lemp 1977). It maintains the optical quality of the corneal surface and lubricates the lid movements. It also provides nutrition and immune defense for the cornea and conjunctiva, and removes foreign material (Dilly 1994). The range of thickness of this layer in normal eyes is from 6 to 7 μm (Holly and Lemp 1977).

2.2.2 (iii) Mucus Layer

The mucus layer is the innermost layer, and is mostly produced by the conjunctival goblet cells. The lacrimal gland and the superficial epithelial cells also secrete some mucus glycoproteins (Holly 1987). Non-goblet epithelial cells which contain mucus secretory vesicles are secondary sources of mucin (Blades and Craig 1997). The superficial epithelium of the cornea is covered by the mucus layer which is a hydrated layer of mucoproteins. The mucus material provides a foundation for the tear film (Holly and Lemp 1977). The main function of this layer is to reduce the surface tension of the tear fluid, so that the tear film can spread, stabilize and cohere to the epithelial surface (McKee and Keetch 1988). The thickness of this layer is only a few hundredths of a micron, about 0.02 μm to 0.05 μm.
2.3 Dry Eye

De Roetth (1950) called the condition in which ocular irritation occurs along with symptoms of burning, smarting, grittiness and tiredness, with or without signs of KCS “dry eye”. Holly and Lemp (1977) classified tear abnormalities into five categories: (i) aqueous deficiency, (ii) mucin deficiency, (iii) lipid abnormality, (iv) impaired lid function and (v) epitheliopathy. A workshop (the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes) was held in 1992 to identify important aspects of the design and interpretation of the results of clinical trials investigating dry eye. A report of the outcomes of this workshop was published in 1995 (Lemp 1995). Since there are various etiologies of dry eye, an all-embracing definition of dry eye was needed. A global definition was agreed by the Classification Study Group at this workshop, namely, “Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.” Four features characterize most forms of the dry eye, namely (i) symptoms, (ii) interpalpebral surface damage, (iii) tear instability and (iv) tear hyperosmolarity.
Figure 2.2. Classification of dry eye by the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eyes (adapted from Lemp 1995)
2.3.1 Classification of Dry Eye

The Dry Eye Classification Study Group also defined the different classes and types of dry eye (Lemp 1995). Dry eyes can be divided into two major classes; tear deficient and evaporative (see Figure 2.2).

2.3.1 (i) Tear Deficient Dry Eye

In tear deficient dry eye, a reduction of the tear flow and tear volume in the conjunctival sac may be caused by a disorder of the lacrimal function or problems in transferring lacrimal fluid into the conjunctival sac (Lemp 1995). Lemp (1995) reported that this is the largest category of dry eye. Two major classes of the tear deficient dry eye are Sjögren Syndrome tear deficiency (SSTD) and non-Sjögren tear deficiency (NSTD) (see Figure 2.2). The presence of systemic signs or clinical manifestations of autoimmune disease in SSTD can be used to differentiate SSTD and NSTD. NSTD can be due, for example, to lacrimal disease or reflex hyposcretion, or may be of uncertain etiology.

2.3.1 (ii) Evaporative Dry Eye

In this case, the lacrimal function is normal but increased tear evaporation causes tear abnormality (Lemp 1995). It can be divided into four sub-classes: lipid deficient, lid related, contact lens related and ocular surface change related (see Figure 2.2).

---

1 Sjögren’s syndrome comprises KCS, xerostomia and arthritis, and is often associated with rheumatoid arthritis.
2.4 Prevalence of Dry Eye

Previous authors (Khurana et al. 1991, Hikichi et al. 1995, Schein et al. 1997, Doughty et al. 1997, Bjerrum 1997, McCarty et al. 1998, Albietz 2000, Moss et al. 2000), have reported values for the prevalence of dry eye ranging from <1% to 25%, depending on the criteria used to diagnose the condition.

The prevalence of dry eye, clinically diagnosed by tear function tests, in 21,683 ophthalmic outpatients was found to be 0.46% (Khurana et al. 1991), however, the tear function tests used were not described.

Hikichi et al. (1995) estimated the prevalence of dry eye in eight Japanese centres. The investigators performed double vital staining tests, tear break up time (TBUT) tests, basal tear tests and tear clearance tests on 2,127 consecutive new out-patients (aged from 10 to 92 years). They concluded that the prevalence of dry eye was 17% in this clinical sample. However, as the dry eye patients were diagnosed by 15 different investigators, there might have been diagnostic variability between investigators.

Schein et al. (1997) studied the prevalence of dry eye among the elderly in a population-based sample (aged 65 years and older). When dry eye was defined based on the symptoms alone, the prevalence was found to be 14.6%. When the definition was based on the presence of symptoms plus one or more clinical signs, the prevalence was only 3.5%.

Doughty et al. (1997) collected questionnaire data from 13,517 patients from different optometric practices in Canada. The prevalence of self-reported symptoms (not taking into consideration the severity) of dry eye was found to be 25%. Considering severe symptoms only, the prevalence of dry eye became just 0.44%. 
Bjerrum (1997) investigated the presence of KCS in a sample of 504 Danes (aged from 30 to 60 years). The prevalence of KCS was estimated to be 8% and 11% applying the European criteria and Copenhagen criteria respectively. The Copenhagen criteria are less stringent than the European criteria which include additional criteria such as ocular symptoms, oral symptoms and presence of autoantibodies, and this may explain why the prevalence of KCS was lower using the European criteria.

A population-based study was performed on 926 patients in Australia to study the prevalence of dry eye (McCarty et al. 1998). Dry eye was assessed by symptoms, ST, TBUT, rose bengal staining and fluorescein corneal staining. The prevalence of dry eye was found to vary from 1.5% to 16.3% depending on the diagnostic criteria used.

Albietz (2000) reported that the prevalence of dry eye subtypes in 1,584 patients (aged from 3 to 98 years) from an optometry practice in Australia were: lipid anomaly dry eye - 4%, allergic/toxic dry eye - 3.1%, lid surfacing/blinking anomalies - 1.8%, aqueous tear deficiency - 1.7% and primary epitheliopathies - 0.2%. The overall prevalence of dry eye was found to be 10.8%. She explained that the relatively low prevalence found in her study when compared with previous studies (Hikichi et al. 1995, Doughty et al. 1997, Shimmura et al. 1999) was probably due previous investigators using less specific criteria in their studies. The current authors suggested it was possible that patients with symptoms of dry eye tended to present at ophthalmological rather than optometric practices, thus reducing the prevalence of this condition in an optometric practice sample.
Moss *et al.* (2000) studied the prevalence of dry eye in 3,722 subjects (aged from 48 to 91 years). Based on self-reported dry eye symptoms, the prevalence of dry eye was found to be 14.4%.

In conclusion, the prevalence of dry eye reported varied considerably from study to study, depending on the diagnostic criteria used. As the prevalence of dry eye in some studies was estimated from patients in clinics or hospitals, the selected group of patients usually had moderate to severe dry eye condition with intolerable symptoms. The mild dry eye was not included in these selected populations. Therefore, the prevalence of dry eye may be underestimated in these studies as the selected patients were not representative of the whole population. Many of the studies reported above were of ophthalmic clinical population. The results of these studies will be compared to our own, presented in Chapter 6, of a clinical population in HK. McCarty and co-workers (1998) have pointed out that the prevalence of dry eye is still unknown. Determination of the prevalence is complicated by the fact that, as yet, there is no universally accepted set of criteria for dry eye diagnosis, and the use of different criteria lead to different prevalence estimations.

### 2.5 Approaches in Diagnosis of Dry Eye

One of the most common presenting complaints is ocular irritation (Pflugfelder 1996). Many cases are due to tear abnormalities and are diagnosed as dry eye, however other eye diseases may have symptoms and signs in common with dry eye (McMonnies and Ho 1986), and proper diagnosis must be the first step in solving dry eye problems (McKee and Keech 1988). The complaint of dry
eye symptoms, along with the clinical signs and results from diagnostic tests can differentiate dry eye from other eye diseases.

2.5.1 Symptoms of Dry Eye

Dry eye patients are symptomatic (Whitcher 1987). Dry sensation, foreign body sensation and red eye are the typical complaints (Toda et al. 1993). These symptoms are the most important information to obtain in diagnosing mild or early dry eye conditions (Lowther and Malinovsky 1988). McMonnies (1986) has developed a dry eye questionnaire (Mc-DEQ) which consists of questions on previous history of dry eye, primary symptoms and their frequencies, secondary symptoms and systemic and ocular conditions associated with dry eye. The Mc-DEQ has been found to be a useful diagnostic tool for the identification of dry eye patients (McMonnies and Ho 1987). Details of the various questionnaires will be given in the next chapter (Section 3.4.2).

2.5.2 Clinical Signs

Clinical signs can be observed by slit-lamp examination. The most helpful diagnostic clinical sign in the tear deficient dry eye is the absence or diminution of the tear meniscus (TM) (Whitcher 1987, McKee and Keech 1988). A decrease in the TM indicates a reduction in the tear volume (Whitcher 1987). Some dry eye patients present with an irregular edge to the inferior TM along the lid margin (Holly and Lemp 1977, Lowther and Malinovsky 1988). Chronic conjunctival hyperemia is commonly found

15
(Whitcher 1987) and excess mucus or an increase in tear debris may be noted (Whitcher 1987, Lowther and Malinovsky 1988, McKee and Keech 1988). Loss of corneal and conjunctival luster, abnormal blinking and meibomian gland dysfunction may be also found in dry eye patients (Lowther and Malinovsky 1988). Other signs include corneal staining (with fluorescein or rose bengal), unstable tear film and reduced tear volume. Tests of these parameters are discussed in more detail in the next Section.

Figure 2.3. Fluorescein corneal staining patterns of dry eye of varying degree of severity (adapted from Lowther and Malinovsky 1988).

Figure 2.4. Grading scale (0-3) for corneal staining, and the 5 corneal locations to be observed for staining (adapted from Lemp 1995).
2.6 Diagnostic Tests for Dry Eye

Many clinical and laboratory diagnostic tests are available to aid the diagnosis of dry eyes.

2.6.1 Clinical Diagnostic Tests

The fluorescein corneal staining test, the rose bengal staining test, fluorescein TBUT, ST, CTT, DEQ and TMH are commonly used as clinical diagnostic tests for dry eye.

2.6.1 (i) Fluorescein Corneal Staining Test

Fluorescein stains the denuded epithelium by penetrating intercellular spaces (Whitcher 1987). A typical punctate staining pattern can be found in the inferior cornea of KCS patients (Lowther and Malinovsky 1988, Michelson 1997, Yokoi and Kinoshita 1998). The degree of staining varies with the severity of the dry eye (see Figure 2.3). In mild cases, small scattered spots can be found on the inferior cornea or interpalpebral area. In moderate cases, the area of small scattered spots may cover up to half of the inferior cornea and larger patches of stain may appear in the inferior cornea. In severe cases, the small scattered spots may cover the whole cornea with larger patches of stain especially in the inferior cornea.

In Lemp’s grading system, corneal staining is graded from 0 to 3 (as shown in Figure 2.4) at 5 corneal locations (Lemp 1995) and the sum of the grades from these locations recorded as the corneal staining score. For example, if a grade 3 corneal staining is observed at each of the 5 locations of an eye, a score of 15
is recorded for this eye. Corneal integrity is classified as abnormal when the score is greater than 3 out of 15. So, according to Lemp's grading system (Lemp 1995), an abnormal score can be obtained even if the inferior cornea is not involved. Hence Lemp's staining score is not ideal as a typical sign of dry eye is inferior corneal punctate staining (Whitcher 1987, Lowther and Malinovsky 1988, Michelson 1997).

Figure 2.5. Rose bengal staining patterns of dry eye of varying degree of severity (adapted from Holm 1949).

2.6.1 (ii) Rose Bengal Staining Test

Rose bengal stains devitalized cells, mucus, mucus strands and filaments (Whitcher 1987). Reduced tear volume associated with dry eye results in degenerative changes in the conjunctival and corneal epithelia (Doughman 1973), resulting in staining of the bulbar conjunctiva and cornea in the exposed
intrapalpebral areas (Yokoi and Kinoshita 1998). Rose bengal staining in dry eye patients can be classified into 3 types (see Figure 2.5) according to the severity of the disease (Holm 1949). In staining type A, which is found in mild cases, small, irregular patches of staining are found in the exposed interpalpebral area and inferior cornea. In staining type B, which is found in moderate cases, there is in addition ribbon-like staining in the conjunctiva and corneal staining is found in the limbal area between 2 and 4 o’clock and between 8 and 10 o’clock. In staining type C, which is found in severe cases, diffuse staining is found in the inferior corneal surface and in the exposed interpalpebral areas and bulbar conjunctiva, forming a wedge-shape.

2.6.1 (iii) Fluorescein Tear Break Up Time (TBUT)

Norm (1969) used a slit lamp to observe the tear break up with the aid of fluorescein dye. After instillation of fluorescein dye, the patient is asked to blink and to keep the eyes open. The time from the last blink to the appearance of random dark spots in the tear film is measured by the examiner. A TBUT of 10 seconds or less is indicative of instability of the tear film and may be related to mucus deficiency (Lemp et al. 1971, Lemp and Hamill 1973, Holly and Lemp 1977).

Some investigators have found large individual variability of TBUT (Vanley et al. 1977, Chopra et al. 1985, Cho and Brown 1993). Racial differences also appear to exist and Cho and co-workers found that over 70% of asymptomatic HK-Chinese have TBUT less than 10 s (Cho et al. 1992, Cho and Brown 1993, Cho and Yap 1993b). This suggests that TBUT of 10 s or less cannot be used as a criterion for dry eye in HK-Chinese.
2.6.1 (iv) Schirmer Test (ST)

The most commonly used clinical test for the assessment of tear quantity or adequacy in HK is probably still the ST, which was introduced by Schirmer in 1903 (Bennett and Gordon 1989, Sorbara and Talsky 1989, Jaanus 1990, Korb 2000, Nichols et al. 2000). The ST assesses tear volume using 35x5 mm strips of blotting/filter paper, and has been criticized by many investigators as being a crude, unreliable and highly invasive test (Henderson and Prough 1950, Wright and Meger 1962, Pinschmidt 1970, Frankel and Ellis 1978, Feldman and Wood 1979, Sorbara and Talsky 1989, Cho and Yap 1993a). As a result of the large variability of results reported (Wright and Meger 1962, Pinschmidt 1970, Patel et al. 1987), some practitioners are now using other clinical tests to replace the ST.

2.6.1 (v) Cotton Thread Test (CTT)

Kurihashi et al. first introduced a CTT using fine white cotton threads (WCTT) to assess the tear volume of human subjects in 1975 (Kurihashi et al. 1975). The wetted length of thread can be measured with the help of fluorescein. With the cooperation of the Yokota Company, Hamano developed a specially designed cotton thread which was impregnated with phenol red dye, and their PRT Test was introduced in 1983 (Hamano et al. 1983). Phenol red dye is pH sensitive and changes colour from yellow to red over a pH range of 6.6 to 8.2. The pH of the tears is in the range of 7.4 – 7.5 (Duke-Elder 1968), and the change in thread colour from yellow to red allows the wetted length of PRT to be easily measured. In 1993, when the PRT Test was not available in HK, Cho (1993) used a self-prepared orange-red cotton thread (SP-CTT), to assess tear
volume. The thread used was commercially available sewing thread. When wetted, the wetted length of the thread appears darker than the dry portion and can be quite easily measured. Details of these CTT will be given in next chapter (Section 3.2).

2.6.1 (vi) Dry Eye Questionnaire (DEQ)
A detailed ocular and systemic health history is crucial in diagnosing dry eye (Jaanus 1990) and patients are typically asked a series of questions relating to ocular symptoms, systemic disease and medication taken. The Mc-DEQ was developed in the mid 1980's and consists of questions on previous history of dry eye, primary symptoms and their frequencies, secondary symptoms and systemic and ocular conditions associated with dry eye. There are also other DEQ available (Anderson et al. 1972, Sargent et al. 1988, Doughty et al. 1997, Schein et al. 1997) but the most commonly used is the Mc-DEQ. The Mc-DEQ has been found to be a useful diagnostic tool for the identification of dry eye patients (McMonnies and Ho 1987). Details of the different questionnaires will be given in the next chapter (Section 3.4)

2.6.1 (vii) Tear Meniscus Height (TMH) Measurement
It has been suggested that the tear menisci contain about 2.9 µl of tears (see Section 2.1.1), representing more than 70% of the exposed tear volume. A diminished TMH represents a decreased tear volume, and indicates a marked reduction in the aqueous portion of the tears (Whitcher 1987). TMH measurement has been suggested as a useful diagnostic test of tear deficient
dry eye (Scherz et al. 1974, Lim and Lee 1991, Mainstone et al. 1996). Details of TMH measurement will be given in the next chapter (Section 3.3).

2.6.2 Laboratory Tests

Tear protein concentrations, tear film osmolarity and examination of conjunctival cells are laboratory tests for diagnosing dry eye.

2.6.2 (i) Tear Protein Concentrations

Tear protein concentrations can provide indirect measurements of lacrimal gland activities (Jaanus 1990, Craig and Blades 1997). Lysozyme and lactoferrin are two major protein components of human tears, and significant reductions of tear lysozyme and lactoferrin have been found in dry eye patients (Regan 1950, Velos et al. 1985, Boersma and van Bijsterveld 1987).

Lysozyme and lactoferrin have bacteriolytic ability (Regan 1950, Lupelli 1986) and this property is utilized in the lysozyme agar diffusion test to assess the concentration of lysozyme. A small filter paper disc is placed in the lower cul-de-sac for one minute. The saturated disc is then placed on an agar plate which has been inoculated with a suspension of Micrococcus lysodeikticus. The antibacterial activity of tear lysozyme will result in a zone of lysis. After 24 hours of incubation, the diameter of lysis is measured and a zone of <21.5 mm is an indication of dry eye (van Bijsterveld 1969, Lupelli 1986).

Lactoferrin can be assessed in a similar way using the Lactoplate test (Jannsen and van Bijsterveld 1983, Jaanus 1990, Craig and Blades 1997). The tear sample is obtained by placing a small filter paper disc in the lower cul-de-sac for 3 minutes. The disc is then transferred to a gel. After 3 days of incubation,
the zone of colour change on the gel shows the presence or otherwise of lactoferrin. The results are read from the chart provided with the test kit. A reading of $\leq 0.9$ mg/mL is suggested to be abnormal (Lemp 1995).

2.6.2 (ii) Tear Film Osmolarity

The tear osmolarity of dry eye patients is significantly higher than that of normal patients (Gilbard et al. 1978). A tear sample is obtained by a capillary tube via capillary action. The tear osmolarity can be measured using a nanolitre osmometer and is determined by freezing-point depression (Benjamin and Hill 1983, Farris et al. 1983). Gilbard et al. (1978) measured the tear osmolarity of 33 normal eyes and 30 KCS eyes. KCS was diagnosed based on the presence of ocular symptoms and at least one of the following clinical signs: (1) debris in the tear film, (2) more viscous tear film, (3) diminished TM or (4) fluorescein corneal staining. They used 311 mOsm/litre as the upper limit of normal. With the cut-off value of 312 mOsm/litre, the sensitivity and specificity of diagnosing KCS were found to be 94.7% and 93.7% respectively. Based on this finding, it has been suggested that a tear osmolarity of $\geq 312$ mOsm/litre should be regarded as abnormal (Farris et al. 1983, Lemp 1995).

2.6.2 (iii) Examination of Conjunctival Cells

Several studies have found a decrease in the number of goblet cells in dry eye patients (Agarwal and Malhoutra 1955, Ralph 1975, Nelson et al. 1983). Impression cytology is used to evaluate the morphologic features of the epithelial and goblet cells on the conjunctival surfaces (Nelson et al. 1983). A
5x10 mm strip of Millipore filter is gently pressed onto the bulbar or palpebral conjunctiva. A specimen containing broad sheets of cells is obtained on the rough surface of the filter paper. The filter paper is then treated and stained and the morphological appearances of conjunctival epithelial and goblet cells are graded. Nelson et al. (1983) found that KCS patients had abnormal epithelia and decreased, abnormal or absent goblet cells in the bulbar conjunctiva, but normal epithelial and goblet cells in the palpebral conjunctiva.

2.7 Comments

Primary eye care practitioners would prefer quick and inexpensive tests for diagnosing dry eye. Laboratory tests are therefore not commonly used in private practice because of the expensive equipment and expertise required. The DEQ is an inexpensive assessment tool and has been found to be an effective screening tool for diagnosing dry eye. The questionnaire can be administered with or without supervision. Due to significant irritation, rose bengal is less commonly used. Although the TBUT test is quite commonly used, a number of investigators have reported poor repeatability of results, and its usefulness on Chinese eyes has been reported to be limited. The ST has been shown to be unreliable and the CTT was developed as an alternative test for assessing tear volume. TMH measurement was found to be correlated with tear volume and has been suggested to be a good diagnostic tool for tear deficient dry eye. A detailed review of the CTT, TMH and DEQ will be presented in the next chapter.
Chapter 3

The cotton thread test, tear meniscus height
and dry eye questionnaire

3.1 Introduction

There are two major classifications of dry eye: tear deficient and evaporative dry eye (see Section 2.3.1). Tear volume tests can be used for diagnosing tear deficient dry eye, however evaporative dry eye can only be diagnosed via a DEQ, the appearance of interpalpebral staining or testing the tear osmolarity (Lemp 1995). Laboratory tests such as tear osmolarity, tear protein measurement and examination of conjunctival cells are also available but these are not commonly used clinically due to the requirement of expensive and sophisticated equipment. The ST has been the main clinical test for years, although it has been widely criticized for its inaccuracy and invasiveness (see Section 2.6.1 (iv)). Due to its less invasive nature, the CTT has been suggested as an alternative to the ST for assessing tear volume. The TMH has been found to be strongly correlated with tear volume (Scherz et al. 1974). In the work described in this thesis, three clinical evaluation tests for the diagnosis of dry eye, namely the CTT, TMH measurement and the DEQ, were used and are now described in detail.
3.2 Cotton Thread Test (CTT)

Three main types of CTT have been developed since 1975 (Kurihashi et al. 1975, Hamano et al. 1983, Cho 1993). Basically, the CTT is similar to the ST except that a thin cotton thread is used instead of a piece of filter paper, and the testing period for a CTT can be much shorter than that for the ST. The CTT is thus less invasive than the ST.

3.2.1 Types of Cotton Thread Test (CTT)

3.2.1 (i) White Cotton Thread Test (WCTT)

Kurihashi et al. (1975) reported the use of a white cotton thread (#40/2) to assess the tear volume. In 1982, they reported the use of a better quality cotton thread (#82/3) made of American pima cotton (Yokota Co.). The thread used was more than 60 mm in length and about 0.2 mm in diameter, and approximately 5 mm was inserted into the lateral conjunctival sac and then removed 3 to 7 seconds later.

Kurihashi proposed three methods of using the WCTT. In method 1 (M1), the end 5 mm of a thread was stained with 10% solution of fluorescein and then inserted into the lower conjunctival sac. The wetted length of the white cotton thread became yellow and was measured. In method 2 (M2), the inferior conjunctival sac was stained with fluorescein before the insertion of the thread. The stained tears were absorbed by the white cotton thread and the wetted length (yellow in colour) was measured. In method 3 (M3), a white cotton thread was inserted without any dye. After removal, the boundary between the dry and wetted portion of the thread was blotted with a fluorescein paper to
allow easier determination of the end point of the wetted portion of the thread for measurement.

3.2.1 (ii) Phenol Red Thread (PRT) Test

Hamano et al. (1983) pointed out several drawbacks of using fluorescein to mark the wetted length. First, it was difficult to produce an exact segment (5 mm) stained with fluorescein. Second, the wetted lengths showed no color change in some cases. Third, the fluorescein may elute into the conjunctival sac and could stain the lenses of soft contact lens wearers. Lastly, the eluted fluorescein may induce reflex tearing in some patients.

Hamano and co-workers (1983) suggested that commercially available cotton thread contains too many impurities. With the cooperation of the Yokota Company, they used a specially designed cotton thread which was impregnated with phenol red dye (phenosulfophthalein) which is non-reactive and has been used for renal function tests. Their phenol red thread (PRT) test was introduced in 1983, using a two-ply, high quality cotton thread with a diameter of about 0.2 to 0.3 mm and cut into equal lengths of 70 mm.

Hamano and co-workers performed a series of studies using their PRT test on normal subjects, and recommended a standardized test procedure. One end (3 mm) of the thread was bent and crimped to form a hook. The bent end was inserted into the inferior conjunctival sac, and the testing period recommended was 15 s. The wetted length of a PRT can be easily measured as it changes colour from yellow to red when wetted with tears. They claimed that this improved thread has greater absorbency and gives more reproducible results than CTT tests utilizing fluorescein.
Blades and Patel (1996) produced a self-prepared PRT (SP-PRT) test in which commercially available white cotton thread was soaked in phenol red solution for 48 hours. The thread was then air-dried for 8 hours and was cut into lengths of 100 mm. After sterilized under ultraviolet light for 60 min, the threads were sealed in plastic envelopes. Blades and Patel studied the dynamics of tear flow with this thread, and Patel et al. (1998) also used a SP-PRT to differentiate aqueous and non-aqueous deficient dry eye.

3.2.1 (iii) The Self-Prepared Cotton Thread Test (SP-CTT)

As the PRT Test was not available in Hong Kong in 1993, Cho and co-workers also used commercially available coloured cotton thread to prepare their own CTT. Cho (1993), having observed that wetted cotton threads became darker in colour, selected an orange-red thread (Brand ‘555’, made in China) which was about 0.2 mm thick to prepare the SP-CTT. The thread was boiled in water for 30 min to improve its absorbency by removing wax, and then air-dried. The air-dried thread was then sterilized by soaking in 90% alcohol for 3 hours.

The treated thread was then cut into 70 mm lengths and stored in a sterile plastic bag. The measurement method was the same as the PRT Test.

Table 3.1. Summary of the results of cotton thread tests obtained by previous investigators.

<table>
<thead>
<tr>
<th>Investigator(s) (Year)</th>
<th>Type of thread test</th>
<th>Testing period(s)</th>
<th>No. of subjects (eyes)</th>
<th>Location of insertion</th>
<th>Mean (SD) (mm/testing period)</th>
<th>Eye posture</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurashi et al. (1977)**</td>
<td>WCTT (M1) 3x on each eye</td>
<td>5, 10, 30</td>
<td>56 (112) 49 (98) 50 (100)</td>
<td>Upper temporal</td>
<td>RE: 19; LE: 18 RE: 19; LE: 19 RE: 22; LE: 22</td>
<td>Closed</td>
<td>Entire wet length</td>
</tr>
<tr>
<td></td>
<td>PRT Test</td>
<td>15</td>
<td>1890 (3780) non CLW (3336) CLW</td>
<td>Inferior temporal</td>
<td>5-25 at 30 s</td>
<td>Closed</td>
<td>Entire wet length</td>
</tr>
<tr>
<td>Hamano et al. (1983)**</td>
<td>SP-PRT</td>
<td>5, 10, 15, 20, 30, 60, 120</td>
<td>(8)</td>
<td>Inferior temporal</td>
<td>Non CLW: 16.7 CLW: 16.9</td>
<td>Closed</td>
<td>Entire wet length</td>
</tr>
<tr>
<td>Kurashi (1986)**</td>
<td>WCTT M1: 3x on each eye</td>
<td>3-7</td>
<td>(100)</td>
<td>Inferior</td>
<td>1st: 22.5 (5.9); 2nd: 21.0 (5.9); 3rd: 21.4 (6.3) overall: 22.5 (7.5)</td>
<td>Closed</td>
<td>Entire wet length</td>
</tr>
<tr>
<td></td>
<td>M1: 3x on each eye M2</td>
<td>3-7</td>
<td>(3000) 62 (124)</td>
<td>Inferior</td>
<td>24.9 (7.0) Inferior</td>
<td>Inferior: 21.0 (6.2) Inferior 1st: 23.3 (7.4) 2nd: Upper 25.7 (8.1) Inferior</td>
<td>Inferior: 25.9 (10.7)</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>5-7</td>
<td>105 (210)</td>
<td>Inferior</td>
<td>Inferior</td>
<td>Inferior: 25.9 (10.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M2 2x on each eye</td>
<td>5</td>
<td>105 (210)</td>
<td>Inferior</td>
<td>Inferior</td>
<td>Inferior: 25.9 (10.7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>5</td>
<td>(112)</td>
<td>Inferior</td>
<td>Inferior</td>
<td>Inferior: 25.9 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Chiang et al. (1988)</td>
<td>PRT Test</td>
<td>30</td>
<td>(66) Normal (14) Dry eye</td>
<td>Inferior</td>
<td>20.3 (8.7) 8.1 (8.0)</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Key:
SD - standard deviation
WCTT - white cotton thread test
M1, M2, M3 - different test procedures used by Kurashi (see Section 3.2.1 (i))
M1 - test procedure not specified (data collected from patient’s records from different clinics from 1984-1987)
SP-PRT - Phenol red thread using commercially-available cotton thread dyed with phenol red dye
PRT - Phenol red thread
CLW - contact lens (soft, PMMA or RGP) wearers
? - not specified or not clear
** - presumably on Japanese subjects
Table 3.1. Summary of the results of cotton thread tests obtained by previous investigators (continued).

<table>
<thead>
<tr>
<th>Investigator(s) (Year)</th>
<th>Type of thread test</th>
<th>Testing period (s)</th>
<th>No. of subjects (eyes)</th>
<th>Location of insertion</th>
<th>Mean (SD) (mm/testing period)</th>
<th>Eye posture</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho (1993)</td>
<td>SP-CTT</td>
<td>60</td>
<td>54 HK-Chinese</td>
<td>Left infero temporal</td>
<td>22.8 (9.4)</td>
<td>Closed</td>
<td>From the 5 mm bend</td>
</tr>
<tr>
<td>Sakamoto et al. (1993)</td>
<td>PRT Test</td>
<td>15</td>
<td>Japanese:</td>
<td>Inferior temporal</td>
<td>17.7 (8.5)</td>
<td>Opened</td>
<td>Entire wet length</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250F (500)</td>
<td></td>
<td>19.8 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250M (500)</td>
<td></td>
<td>18.8 (8.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 500 (1000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>US-Caucasians:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250F (500)</td>
<td></td>
<td>22.8 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>250M (500)</td>
<td></td>
<td>25.0 (9.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total 500 (1000)</td>
<td></td>
<td>23.9 (9.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 Dry Eye</td>
<td></td>
<td>20 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[presumably Caucasians]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho &amp; Yap (1994)</td>
<td>SP-CTT</td>
<td>60</td>
<td>91 HK-Chinese</td>
<td>Left infero temporal</td>
<td>17.5 (8.1)</td>
<td>Closed</td>
<td>From the 5 mm bend</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35 S-Chinese</td>
<td></td>
<td>19.6 (12.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pooled:</td>
<td>18.1 (9.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cho &amp; Douthwaite (1994)</td>
<td>SP-CTT</td>
<td>60</td>
<td>15 HK-Chinese</td>
<td>Right infero temporal</td>
<td>22.5 (10.7)</td>
<td>Closed</td>
<td>From the 5 mm bend</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>13 UK-Caucasians</td>
<td></td>
<td>25.8 (9.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 HK-Chinese</td>
<td></td>
<td>22.7 (9.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key:

SD - standard deviation
PRT - Phenol red thread
SP-CTT - Self-prepared cotton thread test
CLW - contact lens (soft, PMMA or RGP) wearers
M, F - male, female subjects respectively
? - not specified or not clear
** - presumably on Japanese subjects
<table>
<thead>
<tr>
<th>Investigator(s) (Year)</th>
<th>Type of thread test</th>
<th>Testing period (s)</th>
<th>No. of subjects (eyes)</th>
<th>Location of insertion</th>
<th>Mean (SD) (mm/ testing period)</th>
<th>Eye posture</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little &amp; Bruce (1994)</td>
<td>PRT Test (on 2 consecutive days)</td>
<td>15</td>
<td>17 Caucasians</td>
<td>Right inferior temporal</td>
<td>2 consecutive days: 27 (8) on day one 27 (7) on day two</td>
<td>Opened</td>
<td>Entire wet length</td>
</tr>
<tr>
<td>Cho &amp; Kwong (1996)</td>
<td>SP-CTT PRT Test</td>
<td>15</td>
<td>15 HK-Chinese</td>
<td>Inferior temporal</td>
<td>SP-CTT: 11.8 (4.4) PRT: 15.4 (4.9)</td>
<td>Closed</td>
<td>From the 3 mm bend</td>
</tr>
<tr>
<td>Cho et al. (1996)</td>
<td>PRT Test</td>
<td>15</td>
<td>22 HK-Chinese</td>
<td>Inferior temporal</td>
<td>19.6 (6.8)</td>
<td>Closed</td>
<td>Entire wet length</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14 HK-Chinese</td>
<td></td>
<td>19.0 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiu et al. (2000)</td>
<td>SP-CTT PRT</td>
<td>15</td>
<td>55 HK-Chinese [non CLW]</td>
<td>Right inferior temporal</td>
<td>SP-CTT: 10.9 (6.2) PRT: 14.4 (5.6)</td>
<td>Opened</td>
<td>Entire wet length</td>
</tr>
<tr>
<td>Tomlinson et al. (2001)</td>
<td>PRT</td>
<td>15</td>
<td>20 Normal [10F, 10M]</td>
<td>Left inferior temporal</td>
<td>PRT: 17.3 (6.7)</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

Key:
- SD - standard deviation
- PRT - Phenol red thread
- SP-CTT - Self-prepared cotton thread test
- SP-PRT - Phenol red thread prepared by using commercially-available cotton thread dyed with phenol red dye
- M, F - male, female subjects respectively
- CLW - contact lens (soft, PMMA or RGP) wearers
3.2.2 Factors Affecting CTT

Because of the small size and absorbency of the thread, different testing methods will yield different results. Different aspects of the CTT were studied by previous investigators and Table 3.1 shows a summary of the results. The wetted length of SP-CTT was relatively short when compared with those of CTT, PRT and SP-PRT. More details about previous studies on CTT will be presented in the following sections.

3.2.2 (i) CTT Measurement

CTT measurement may be affected by the location of insertion of the thread, the testing method and measurement of the wetting length.

3.2.2 (i)(a) Location of Insertion

Hamano et al. (1983) performed a SP-PRT test at two different insertion locations, namely the superior temporal and the inferior temporal regions of the conjunctival sac, on 10 eyes. The wetted thread length in the superior conjunctival sac was greater and Hamano and co-workers suggested that this could be explained by the anatomy of tears production and commented that it was difficult to insert the thread into the superior conjunctival sac. Kurihashi (1986) also reported longer wetted lengths when WCTTs were inserted in the superior conjunctival sacs of 210 eyes (105 subjects) than when inserted in the inferior conjunctival sacs.

Hamano et al. (1983) also compared the wetted length of the threads at different locations (temporal, central & nasal) in the inferior conjunctival sacs.
of 12 eyes (six subjects). There was no statistically significant difference* in the results from these locations, and due to the ease of insertion, they suggested that this test should be carried out at the inferior temporal conjunctival sac.

3.2.2 (i)(b) Testing Method

Kurihashi (1986) used different testing methods (M1, M2 & M3) (see Section 3.2.1 (i)) to compare the (WCTT) wetted length. They found that the mean wetted length using M2 was significantly greater than that using M1, while that using M1 was significantly greater than that using M3. Fluorescein was involved in M1 and M2 which may explain why the mean wetted length using M3 was the smallest.

In the original CTT, subjects were required to close their eyes during the measurement (Kurihashi et al. 1977, Hamano et al. 1983, Kurihashi 1986). However, some investigators asked the subjects to blink normally instead of closing their eyes (Hamano et al. 1990, Little and Bruce 1994), and there has been no report on the difference in results with the eyes open compared with closed.

3.2.2 (i)(c) Measurement of the Wetted Length

The whole wetted length was measured in most reported studies (see Table 3.1). However, Cho and co-workers measured the wetted length from the bend

---

* The statistical analysis of their data is queried (see Section 3.2.6)
in a number of their studies (Cho 1993, Cho and Douthwaite 1994, Cho and Yap 1994), in order to be consistent with the measurement using the ST.

3.2.2 (ii) Testing Periods

Kurihashi et al. (1977) conducted WCTT (M1) (see Section 3.2.1 (i)) on both eyes of three groups of normal subjects (n=56, 49 and 50) using different testing periods (5 s, 10 s, 30 s) respectively (see Table 3.1). They found no statistically significant difference in the values between the three groups. They commented, however, that there was considerable within-subject variation with longer testing periods and repeated measurements.

Hamano et al. (1983) performed a SP-PRT test (see Section 3.2.1 (ii)) on eight normal eyes. In seven out of eight eyes the wetted length did not increase after 30 s. In another study, they performed the PRT Test on 455 normal and 76 dry eye subjects using testing periods of 5-60 s. They defined ‘dry eye’ as eyes showing <6 mm of wetted length in 15 s. The distribution histograms for wetted length at different testing periods were similar in shape for normal and dry eye subjects. The dry eye subjects consistently gave the shortest wetted length with a testing period of 15 s and above. Therefore, Hamano et al. (1983) suggested that a testing period of 15 s was sufficient to differentiate dry eye patients and longer testing periods might be valuable to assess the degree of dryness.

3.2.2 (iii) Humidity

The following studies showed that ambient conditions do not significantly affect CTT values.
Hamano et al. (1983) reported an in vitro study of the effect of changes in relative humidity on the wetted lengths of SP-PRT. The upper end of 20 suspended threads were dipped into 2 µl of the dye solution. The wetted lengths were measured at relative humidity of 35%, 60% and 80%, at an ambient temperature of 25°C with testing periods of 5-60 s. No statistically significant difference was found in wetted length with testing period <20 s. In considering the wetted length in different testing period (see Section 3.2.2 (ii)), they suggested that 15 s was an optimal testing period for the thread test.

Sakamoto et al. (1993) studied the effect of different temperatures (Japan: 18-33°C, United States: 20-29°C) and humidities (Japan: 27-84%, United States: 42-81%) on the PRT values on both eyes of 500 Japanese and 500 American subjects. They found no significant effect of temperature or humidity on PRT values.

3.2.2 (iv) Consecutive Measurements

Hamano et al. (1983) studied the absorbed amount of fluid for a given wetted length for SP-PRT and ST filter paper strips. For 20 mm of wetted length, the ST paper strip absorbed about 10 µl while SP-PRT absorbed only 1 µl. They suggested that, if desired, the SP-PRT test could be repeated several times on a given eye, due to the small amount of tears required.

Cho and Douthwaite (1994) performed their SP-CTT with a testing period of 1 min on 15 HK-Chinese and 13 UK Caucasian subjects (baseline measurement). The test was repeated in three different intervals at 5, 10 and 15 min. The second measurement was performed 5 min after the first, the third measurement was taken 10 min after second measurement and so on. They
found that the mean wetted length of SP-CTT thread obtained after 5 min was significantly less than the mean baseline value at 0 min, and there was no statistically significant difference in wetted length between the mean baseline value at 0 min and the mean wetted length obtained after the 10 and 15 min intervals. They concluded, therefore, that 10 min was sufficient for tear recovery after a SP-CTT with a testing period of 1 min.

3.2.2 (v) Age and Gender

A number of investigators studied the effect of age and gender on CTT values. Kurihashi (1986) used the WCTT (M1) on 3,000 normal eyes (544 males, 956 females). The wetted length for the age groups between 0 and 19 years and between 80 and 89 years were found to have significantly higher values* than those of the other age groups. They explained that this might be due to apprehension regarding the test in the young subjects, and lacrimal drainage dysfunction in the older subjects. The mean wetted lengths for female subjects were found to be significantly shorter* than those for male subjects in all age groups, except in the age groups of the range of 20 to 49 years. However, they did not suggest why this was the case. It might be due to periodical hormonal changes.

Hamano et al. (1990) used the PRT Test to study the relationship between age and wetted length. They performed the test on 11,336 eyes of contact lens subjects aged from 10 to 59 years. The results showed that (i) the percentage of eyes with PRT value ≤9 mm/15 s increased from teens up to their thirties

* The statistical analysis of their data is queried (see Section 3.2.6).
(from 1.2% to 9.1%) and decreased from their thirties to their fifties (from 9.1% to 0.2%); (ii) the percentage of eyes with PRT value ≥15 mm/15 s decreased with increasing age (from 92.9% to 67%).

Sakamoto et al. (1993) studied the PRT wetted length obtained from 1,000 Japanese and 1,000 Caucasian eyes of age 0 to >60 years. They found no statistically significant correlation between age and the PRT wetted length was found in both groups of subjects although they found a tendency for the wetted length to decrease with age. The mean PRT value was found to be significantly lower in females than in males in both groups of subjects. The mean (SD) PRT values for the Caucasian subjects were 22.8 (9.5) mm/15 s (female) and 25.0 (9.4) mm/15 s (male). Those for the Japanese subjects were 17.7 (8.5) mm/15 s (female) and 19.8 (8.6) mm/15 s (male).

Cho and Yap (1994) performed their SP-CTT using a testing period of 1 min on 91 HK-Chinese of age 8 to 70 years (46 females, 45 males) and 35 Singapore (S)-Chinese of age 7 to 65 years (21 females, 14 males). There was no statistically significant difference in the mean SP-CTT values between two groups. After pooling the data, they concluded that there was no significant effect of gender on the wetted length, but the wetted length decreased with increasing age.

Blades and Patel (1996) carried out a SP-PRT test on the right eyes of 40 normal subjects aged 18 to 86 years (26 females, 14 males). Significant age difference in wetted length was found only with testing periods of 30, 60 and 90 s but not with other testing periods (15, 45, 75, 105 and 120 s) — the correlation between age and wetted length was not consistent in different age
groups. There was no gender difference in wetted length. The authors concluded that the wetted length of the thread was not related to age or gender.

3.2.2 (vi) Local Anaesthetic

Hamano et al. (1983) assessed the measured tear volume after adding local anaesthetic, using their SP-PRT test. One drop of either oxybuprocaine or normal saline was instilled to the eyes of the subjects\(^\text{\textsuperscript{v}}\). In both cases the wetted lengths showed a sudden increase but returned to the pre-drop level after 5 min. They concluded that this test was extremely sensitive to a change of tear volume. They also applied oxybuprocaine (0.4%) to the right eyes of six subjects with the left eyes acting as controls. Five minutes after the instillation, the SP-PRT test was performed three times on both eyes at 1 min intervals. There was no significant difference in the wetted lengths between the right and left eyes. They suggested that it was not necessary to use an anaesthetic with this thread test as the test did not cause great reflex tearing in the short testing period.

3.2.2 (vii) Racial Differences

The following studies shows that the wetted length of CTT is lower in Chinese than in Caucasians.

Sakamoto et al. (1993) reported that the mean wetted length of Japanese subjects was significantly lower\(^*\) than that of American subjects (see Sections

\(^\text{\textsuperscript{v}}\) The number of eyes was not clearly stated.

\(^*\) The statistical analysis of their data is queried (see Section 3.2.6).
3.2.2 (iv)). The mean (SD) wetted length of the Japanese and the American were 18.8 (8.6) mm/15 s and 23.9 (9.5) mm/15 s respectively.

Cho and Douthwaite (1994) found that the mean SP-CTT value of 15 HK-Chinese was lower than that of 13 UK-Caucasians. The mean (SD) SP-CTT values of the HK-Chinese and UK-Caucasians were 22.5 (10.7) mm/60 s and 25.8 (9.7) mm/60 s respectively.

Cho and Kwong (1996) found the mean PRT value of 15 HK-Chinese to be significantly lower than those of Caucasian subjects obtained in the studies of Little and Bruce (1994) and Sakamoto et al. (1993).

3.2.3 Pros and Cons of CTT

The advantages of CTT over ST in measuring the tear volume are many and may be summarized as follow:

(i) the CTT is easier to carry out and needs a short testing time (Kurihashi et al. 1977, Hamano et al. 1983, Chiang et al. 1988, Cho 1993);

(ii) there are minimal environmental factor effects due to the short testing time of CTT (Hamano et al. 1983);

(iii) there is minimal reflex tearing due to minimal discomfort of CTT (Hamano et al. 1983);

(iv) the small size of the thread minimizes apprehension, so that the test can be applied to children (Kurihashi et al. 1977, Cho 1993);

(v) CTT is less injurious to eye (Kurihashi et al. 1977);

Nevertheless, the CTT has a few disadvantages:

(i) the accuracy of the test has been queried due to the relatively low absorption capacity of the thread (Holly and Lamberts 1984);

(ii) the test may be measuring the residual tears in the cul-de-sac rather than the secretion (Tomlinson et al. 2001);

(iii) phenol red dye requires to be purified before impregnating the threads (Hay and Stevenson 1996).

### 3.2.4 Reliability

Measurements with the CTT have been found to be reliable in previous studies (Kurihashi 1986, Cho 1993, Little and Bruce 1994, Cho and Kwong 1996). In a recent study (Kinney 1999), the repeatability of the PRT Test was found to be poor.

Kurihashi (1986) reported a study in which the WCTT (M1) was carried out repeatedly on a 44 year-old female subject with right epiphora due to lacrimal drainage dysfunction. A total of 54 measurements were obtained on 18 occasions. The diseased eye consistently had longer wetted length than the normal eye. He suggested that the result proved good reproducibility of the test.

In another case, a 60 year old woman who suffered from Sjögren’s syndrome, was tested 16 times by WCTT (M1) over 14 months. Three consecutive measurements were taken each time and a total of 48 measurements were obtained. The drier eye was found to have consistently shorter wetted length than the fellow eye.
Chiang et al. (1988) performed the PRT Test on 28 normal eyes on two consecutive days. They reported that the PRT Test was reliable* based on Pearson Product Moment Correlation.

Cho (1993) performed the SP-CTT eight times on the left eye of seven normal HK-Chinese on separate days over a period of two weeks. There was no statistically significant difference* in the SP-CTT values taken on different days. It appeared that the repeatability was good. However, not finding a statistically significant result might be due to lack of power, rather than no difference.

Little and Bruce (1994) carried out the PRT Test on the right eyes of 17 normal Caucasian subjects on two consecutive days. No statistically significant between-day difference was found and moderate repeatability was shown. The 68% and 95% confidence limits for between-session repeatability were 5 mm/15 s and 10 mm/15 s respectively.

Cho and Kwong (1996) performed the SP-CTT and the PRT Test on 15 normal HK-Chinese on six different days over a period of two weeks. One eye of each subject was measured with the SP-CTT and the other eye was measured with the PRT Test. The eye to be tested first and which eye received which test were randomized. There was no statistically significant between-day difference for either test. They concluded that both SP-CTT and PRT were reliable for normal HK-Chinese subjects.

* The statistical analysis of their data is queried (see Section 3.2.6).
Kinney (1999) conducted the PRT Test on 75 dry eye patients on two occasions. Up to 16 mm difference was found between visits, indicating poor repeatability of this test. However, Kinney did not provide any details about the methodology used in the study.

3.2.5 Validity

Kurihashi (1977) performed the WCTT (M1) on both eyes of eight patients with unilateral extratemporal facial nerve paralysis and lagophthalmos or weakness of the orbicularis oculi muscle in order to test the validity of the procedure. These patients had unilateral impaired lacrimal drainage function but bilateral normal tear secretion. The diseased eye should have greater tear volume than the other eye, and indeed, longer wetted lengths were consistently found for the diseased eyes. Seven patients with unilateral acoustic tumors and one patient with cholesteatoma in the left petrous apex were also assessed, shorter wetted lengths were also consistently found in the diseased eyes. WCTT had a high validity as a reduction in wetted length of WCTT could reflect a reduction in the tear volume. Chiang et al. (1988) performed the PRT Test on 66 normal eyes and 14 dry eyes. The mean wetted lengths of the dry eye subjects were significantly shorter than those of normal subjects. It is not clear from the paper whether they were taken from one eye or both eyes of a subject. "Low" specificity (67%) and sensitivity (67%) of the PRT Test at testing period of 15 s has been reported for the diagnosis of KCS (referent value <20.5 mm) (Golding and Brennan 1993). These authors also reported a statistically significant correlation between the ST and the PRT Test results, but this is an
expected finding, as these tests are intended to measure the same variable.
With the moderate diagnostic accuracy and the advantages of the PRT Test (see Section 3.2.3), Golding and Brennan (1993) suggested that it was time for the PRT Test to replace the ST.
Patel et al. (1998) investigated the SP-PRT test using a testing period of 120 s for differentiating aqueous and non-aqueous deficient dry eye subjects. The mean wetted length of aqueous deficient subjects (n=35) was significantly shorter than those of non-aqueous deficient (n=24) and normal subjects (n=38), however no statistically significant difference was found between all dry eyes and eyes of normal subjects. With an arbitrary cut-off value of 20 mm, the specificity and sensitivity for differentiating the aqueous and non-aqueous deficient dry eyes were 83% and 86% respectively.
Chiu et al. (2000) used the SP-CTT and the PRT Test on 47 subjects to predict success in contact lens wear. The specificity and sensitivity for the SP-CTT value (cut-off value: 15 mm) were 52.4% and 88.5% respectively and those for PRT value (cut-off value: 18 mm) were 47.6% and 76.9% respectively. Chiu et al. concluded that the SP-CTT gave better prediction of successful contact lens wear than the PRT Test.
Tomlinson et al. (2001) performed the PRT Test and measured the tear volume by TMH test and fluorophotometry on 20 normal subjects. The wetted length of PRT Test was not correlated with the tear volume. They suggested that the PRT Test was unlikely to measure the tear volume and probably measured the uptake of fluid from the lower conjunctival sac. However, in their experiment, the order of the tests may have affect their results — the TMH measurement
may be affected as it was performed after the PRT Test, and the authors did not state the rest interval between each test.

3.2.6 Statistical Considerations

Some of the reported statistical results in previous studies (Hamano et al. 1983, Kurihashi 1986, Sakamoto et al. 1993) were questionable. The investigators treated the data of the left and right eyes of a subject as individual data points (see Section 3.2.2 (i), (iv-vii)). Therefore, the sample size was doubled. Since the pooled data are not independent, such analyses result in spuriously low p values (Rosner 1982, Newcombe and Duff 1987). Although this is only an issue if the null hypothesis has been rejected, if the null hypothesis has been accepted, then the question of statistical power arises. It is then only valid to conclude that two measures are not different, if the power to show some previously defined difference is stated.

The correlation coefficient measures the strength of a relation between two variables but not the agreement between them (Bland and Altman 1986). Thus, the correlation coefficient on its own is not an appropriate measure of the repeatability of a test. A t-test or a repeated measures analysis of variance do not provide any clinically useful information about agreement. Therefore, it is not ideal to analyse the repeatability of a test using correlation coefficient or a t-test or repeated measures analysis of variance.

A better expression of agreement can be obtained using the 95% limits of agreement between the two measures (Bland and Altman 1986). A judgement is then required as to whether these represent acceptable repeatability.
Table 3.2. Tear meniscus heights reported by previous investigators.

<table>
<thead>
<tr>
<th>Investigator(s) (Year)</th>
<th>No. of subjects (eyes) *</th>
<th>Position of eyes</th>
<th>Measuring methods</th>
<th>Mean (SD) (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holly &amp; Lemp (1977)</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>1.0</td>
</tr>
<tr>
<td>Lamberts et al. (1979)</td>
<td>43 (86)</td>
<td>?</td>
<td>SLO (eyepiece graticule)</td>
<td>0.23 (0.09)</td>
</tr>
<tr>
<td>Port &amp; Asaria (1990)</td>
<td>10 (20)</td>
<td>P1, P2, P3</td>
<td>SLO (pachometer)</td>
<td>RE: 0.42 (0.09), 0.66 (0.11), 0.44 (0.08) LE: 0.51 (0.08), 0.73 (0.09), 0.46 (0.08) 0.18 (0.03), 0.25 (0.05) 0.19 (0.04), 0.27 (0.04)</td>
</tr>
<tr>
<td></td>
<td>66 (132)</td>
<td>P1, P2</td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>age: 16-25 years</td>
<td></td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (42)</td>
<td>P1, P2</td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>age: 46-55 years</td>
<td></td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td>Patel &amp; Port (1991)</td>
<td>5 (10) VDU users [2F, 3M]</td>
<td>?</td>
<td>SLO (pachometer)</td>
<td>0.249 (0.053)</td>
</tr>
<tr>
<td></td>
<td>age: 25-46 years</td>
<td></td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (10) non-VDU users [3F, 2M]</td>
<td>?</td>
<td>SLO (pachometer)</td>
<td>0.163 (0.074)</td>
</tr>
<tr>
<td></td>
<td>age: 21-43 years</td>
<td></td>
<td>SLO (pachometer)</td>
<td></td>
</tr>
<tr>
<td>Lim &amp; Lee (1994)**</td>
<td>21 Normal</td>
<td>P1</td>
<td>SLO with a McIntyre lens</td>
<td>0.19 (0.05)</td>
</tr>
<tr>
<td></td>
<td>21 Dry</td>
<td></td>
<td></td>
<td>0.10 (0.04)</td>
</tr>
<tr>
<td>Guillot et al. (1996)</td>
<td>?</td>
<td>?</td>
<td>SLO (eyepiece graticule)</td>
<td>0.25-0.3</td>
</tr>
<tr>
<td>Mainstone et al. (1996) #</td>
<td>15 Normal [13F, 2M]</td>
<td>?</td>
<td>PCA</td>
<td>0.46 (0.173)</td>
</tr>
<tr>
<td></td>
<td>15 Dry [10F, 5M]</td>
<td></td>
<td>PCA</td>
<td>0.244 (0.089)</td>
</tr>
<tr>
<td>Guillot et al. (1997)</td>
<td>184 (368) CLW</td>
<td>?</td>
<td>SLO (graduated slits)</td>
<td>0.31 (0.11)</td>
</tr>
<tr>
<td></td>
<td>55 (110) non-CLW</td>
<td></td>
<td>SLO (graduated slits)</td>
<td>0.32 (0.11)</td>
</tr>
<tr>
<td>Oguz et al. (2000)</td>
<td>24 Dry</td>
<td>P1</td>
<td>SLO with a micrometer</td>
<td>0.19 (0.09)</td>
</tr>
<tr>
<td></td>
<td>29 Dry</td>
<td></td>
<td>SLO with a micrometer</td>
<td>0.21 (0.14)  #</td>
</tr>
<tr>
<td></td>
<td>29 Dry</td>
<td></td>
<td>SLO with a micrometer</td>
<td>0.24 (0.09)  #</td>
</tr>
<tr>
<td>Doughty et al. (2001)</td>
<td>56 Normal</td>
<td>P1</td>
<td>VRSM</td>
<td>0.172 (0.047)</td>
</tr>
<tr>
<td>Tomlinson et al. (2001)</td>
<td>20 Normal [10F, 10M]</td>
<td>?</td>
<td>SLO (pachometer)</td>
<td>0.35 (0.11)</td>
</tr>
</tbody>
</table>

Key:
- SD - standard deviation
- SLO - slit lamp observation
- VDU - visual display unit
- PCA - photographic and computer analyses
- VRSM - videography and rule scale measurement
- CLW - contact lens (soft, PMMA or RGP) wearers
- * Presumed to be Caucasian subjects unless specified
- ** - presumably Korean
- # - fluorescein added
- M, F - male, female subjects respectively
- P1, P2, P3 - eyes at primary position, 15° elevated, 15° depressed respectively
- - not specified or not clear
3.2.7 Comments

The CTT is a tear volume test. The performances of the SP-CTT and PRT Test have been shown to be good for normal HK-Chinese subjects compared to the ST. However, their performances on dry eye subjects have not been evaluated. In a recent study, the PRT Test as a tear volume test was queried (see Section 3.2.5). Therefore, further investigation of the SP-CTT and PRT Test in diagnosing dry eye patients have been conducted and are reported in this thesis (see Chapter 7 and 9).

3.3 Tear Meniscus Height (TMH)

Tear deficient dry eye is the largest category of dry eye (see Section 2.3.1). As an absent or decreased TM is one of the clinical signs in tear deficient dry eye (see Section 2.5.2), TMH measurement can be used as a diagnostic tool for dry eye.

3.3.1 Methods for Assessing Tear Meniscus Height (TMH)

In previously reported studies, three main methods of measuring TMH were used: direct observation using a slit lamp (Lamberts et al. 1979, Port and Asaria 1990, Patel and Port 1991, Lim and Lee 1991, Oguz et al. 2000, Tomlinson et al. 2001), computer analysis of photographic images (Mainstone et al. 1996, Golding et al. 1997) and scale measurement after video recording (Doughty et al. 2001). Table 3.2 shows a summary of the results reported by previous investigators.
3.3.1 (i) Slit Lamp Observation (SLO)

Lamberts et al. (1979) inserted a reticule into the eyepiece of a slit lamp. The reticule was calibrated (in 0.1 mm increments) and measurements of TMH were read directly from it. They reported a mean (SD) TMH of 0.23 (0.09) mm in 86 normal eyes (n=43) with six (7%) having a TMH of ≤ 0.1 mm.

Port and Asaria (1990) used a modified pachometer mounted on a slit lamp, and measured the TMH from the vertical doubling of the image. They found a mean (SD) TMH of 0.18 (0.03) mm with the eyes in the primary position in 66 normal subjects. The mean right TMH was significantly less than the mean left TMH. They explained that bilateral reflex tearing was stimulated as all measurements were performed on the right eyes first. The TMH of both eyes increased slowly after measurement of the TMH in the right eye. So, when the left eye was assessed, the TMH was already a little higher than normal.

Patel and Port (1991) used the same method as Port and Asaria (1990) to compare the TMH between Visual Display Unit (VDU) operators and non-VDU operators. The mean (SD) TMH for VDU and non-VDU operators were found to be 0.249 (0.053) mm and 0.163 (0.074) mm respectively. They suggested that reduced blinking rate for the VDU operators might have caused reflex tearing so that they had greater TMH.

Lim and Lee (1991) measured TMH with a Haag-Streit slit lamp and a McIntyre lens. They reported mean (SD) TMH of 0.19 (0.05) mm and 0.10 (0.04) mm for normal and dry subjects respectively.

Oguz et al. (2000) used a slit lamp equipped with a micrometer (Type 1 Zeiss micrometer scale) to measure the left central inferior TMH on 29 dry eye subjects without fluorescein. Then fluorescein was applied on the test eye.
After 5 minutes, the left central inferior TMH was re-measured. The observation system was set in the same horizontal plane with the illumination system at 90 deg, and tangential to the inferior TM. The inferior TM of five subjects were not visible without the aid of fluorescein, so only 24 dry eye subjects was measured, and their mean (SD) TMH was 0.19 (0.09) mm. With the aid of fluorescein, the mean (SD) TMH for 29 dry eye subjects was 0.21 (0.14) mm. No statistically significant difference in mean TMH value was found between with and without the aid of fluorescein. They also used photographic and computer analyses method to measure the TMH for the dry eye subjects (see next section).

Tomlinson et al. (2001) reported a mean (SD) TMH value of 0.35 (0.11) mm for their 20 asymptomatic subjects using the method reported by Port and Asaria (1990).

Figure 3.1. The tear meniscus parameter measurements – radius of curvature, height and width (adapted from Mainstone et al. 1996).
3.3.1 (ii) Photographic and Computer Analyses (PCA)

Mainstone et al. (1996) used a Nikon FS-3 photo slit lamp fitted with a non-contact endothelial attachment to photograph an optic section of the inferior TM at x120 magnification. Fluorescein was instilled into the inferior TM to enhance the photographic recording. The observation system was set tangentially to the central inferior TM and at 90 deg to the illumination system. They used a 0.2x5 mm beam at moderate illumination. Using a Nikon Coolscan 35 mm film scanner, the developed photographic images were digitalised and then downloaded onto a Macintosh Quadra 605 computer. The TMH was measured using the National Institutes of Health Image software. They investigated the potential of this method as a diagnostic test of dry eye (see Section 3.3.3).

Golding et al. (1997) used the same method (Mainstone et al. 1996) to measure TMH from 15 aqueous-deficient and 15 age-matched control subjects and used the National Institutes of Health Image tool to assess the tear meniscus curvature (TMC) from the dimensions of a circle fitted to the inner surface of the meniscus image. Golding et al. found a statistically significant correlation between the TMH and TMC (see Figure 3.1). They found that small TMC could be observed in eyes with low tear volume. However, the separate mean TMH for dry eye and normal subjects were not reported in this study. The mean (SD) TMH for 30 normal and dry eye subjects was reported to be 0.419 (0.157) mm (Golding et al. 1997).

Oguz et al. (2000) used a similar method to measure TMH of 29 dry eye subjects, and reported a mean (SD) TMH of 0.24 (0.09) mm.
3.3.1 (iii) Videography and Rule Scale Measurement

Doughty et al. (2001) obtained images of the right lower TM of 56 elderly subjects (over 60 years) by videography. The TMH was measured relative to a rule scale at high magnification from the stopped video frames. A total of five measurements at different positions were obtained (one at the centre and two 1 mm apart at either side from the centre. The mean (SD) TMH was 0.172 (0.047) mm.

3.3.2 Factors Affecting TMH Measurement

Factors that may affect TMH include fixation position of the eye during measurement, age and gender, and the ocular condition.

3.3.2 (i) Fixation Position of the Eye

Port and Asaria (1990) investigated the effect of fixation on TMH measurements. Using a modified pachometer, they measured the TMH of both eyes of 10 subjects with the subjects looking straight ahead (primary gaze), 15 deg up and 15 deg down. The mean TMH for the elevated position was found to be about 50% greater than those for primary and depressed positions. In another experiment on 87 subjects, the mean TMH for elevated positions was again found to be significantly higher than that for the primary position. They suggested that the difference might be due to (a) an increased surface tension and hydrostatic pressure difference between the preocular tear film and the tear meniscus, (b) better wetting characteristics of the bulbar conjunctiva and (c) the increase in peripheral flattening of the globe away from the limbus.
3.3.2 (ii) Age and Gender

To our knowledge, there is only one study reporting the effect of age and gender on TMH. Port and Asaria (1990) measured TMH (see Section 3.3.1 (i)) on two groups of subjects (young and presbyopic) who were non-contact lens wearers and without either on-going ocular treatment or previous medical ocular history. The 66 young subjects (34 females, 32 males) were of age 16-25 years. There was no difference in mean TMH between genders. They also measured the TMH of 21 presbyopic subjects of age ranging from 46-55 years, and no significant difference in the mean TMH was found between the younger subjects and presbyopic subjects.

3.3.2 (iii) Ocular Conditions

External eye inflammation can lead to excessive tearing which will increase the TMH. The conjunctival folds also affect the TMH measurement, and TMH decreases when the lid is not in good contact with the globe (Lamberts 1987). Blockage of the lacrimal drainage will also increase the TMH. Hence, when assessing TMH, it is necessary to ensure that there is no co-existing condition which might affect the measurement.

3.3.3 Reliability of TMH Assessment

Golding et al. (1997) measured TMH in 20 subjects on two visits, using a photographic method. The results were said to show high reliability* (r=0.79,

---

* The statistical analysis of their data is queried (see Section 3.2.6).
p=0.0001) and the TMH did not differ significantly between the visits (paired t-test, p>0.1).

3.3.4 Validity of TMH Assessment

Scherz *et al.* (1974) measured the tear volume of a subject (right eye - normal, left eye - KCS after dacrcoadenectomy) using the fluorescein dilution method and observed the TMH of this subject by direct slit lamp observation. Closure of the puncta, the tear volume of the right normal eye increased greatly and that of the left dry eye increased slightly. By direct slit lamp observation, the right TMH was significantly higher than the left TMH. They concluded that there was a direct correlation between tear volume and the TMH. They measured the tear volumes of 17 normal subjects and eight KCS subjects using the fluorescein dilution method. The mean tear volume of the normal subjects was found to be significantly higher than that of the KCS subjects. Therefore, tear volume was correlated with TMH.

Lim and Lee (1991) measured the TMH of 21 normal eyes and 21 dry eyes by direct slit lamp observation (see Section 3.3.1 (i)). The mean (SD) TMH for the normal eyes and dry eyes were 0.19 (0.05) mm and 0.10 (0.04) mm respectively. The TMH of normal subjects was significantly higher than that of dry eye subjects. They commented that ectropion would affect TMH measurement as the lid was not in contact with the globe.

Mainstone *et al.* (1996) measured the TMH after instillation of fluorescein (see Section 3.3.1 (ii)) in 15 normal and 15 dry eye subjects. The mean (SD) TMH for the normal and dry eye subjects were 0.46 (0.173) mm and 0.244 (0.089) mm respectively. With cut-off value of 0.35 mm, the specificity and sensitivity
of TMH for the diagnosis of dry eye were 66.7% and 93.3%. Fluorescein may induce reflex tearing and the instillation of fluorescein also increases the tear volume, and this probably explains why Mainstone et al. (1996) found a higher TMH for normal and dry eye subjects compared to the findings of other investigators. In a recent study (Greiner et al. 2000), the instillation of fluorescein altered the tear film lipid layer by an amount dependent on the volume instilled.

### 3.3.5 Comments

There are various methods used for measuring TMH, none without shortcomings. Eye movements may cause an error in graticule assessment with a slit lamp. The TMH may be underestimated by the pachometer method due to the difficulty in focusing the reflex. Exposure to light in photographic methods may lead to reflex tearing. Tear volume is increased by the instillation of fluorescein. The number of readings and the location of measurements may also affect the readings.

Although some investigators have reported TMH measurement to be useful in the diagnosis of tear deficient dry eye, the sample sizes of studies reported were usually too small to allow firm conclusions to be drawn. The tear volume and tear stability of the HK-Chinese have been found to be smaller and shorter respectively than those of Caucasian. The use of TMH value in the diagnosis of dry eye in Chinese requires normative values and further investigations are needed.
3.4 Dry Eye Questionnaire(s) (DEQ)

Patient symptoms, patient history and clinical signs (see Section 2.5) make important contributions to the diagnosis of dry eye. A DEQ is useful for gathering information regarding a patient’s symptoms and history. The practitioner can ask the patient the questions set in the DEQ (observer administered) or allow the patient to fill in the DEQ (patient-completed). Therefore, a validated DEQ of symptoms is one of the global tests for dry eye (Lemp 1995).

For marginal dry eye conditions, both the patient’s history and the results of the biomicroscopy examination are inadequate when used alone (McMonnies and Ho 1986). When the patient’s history via DEQ and biomicroscopy examination are used together, established dry eye conditions can be identified (McMonnies and Ho 1986). However, when completing a DEQ, some patients may misunderstand the meaning of the questions, and McMonnies and Ho have suggested that the DEQ should be completed by appropriately trained ancillary staff (i.e. observer-administered). This can save the practitioner’s time and a wider range of questions can be asked, and according to McMonnies and Ho, the responses have a high reliability and greater validity than those from patient-completed questionnaires. Significant correlation between the dry eye conditions and the total score of the DEQ used had been reported by various investigators (McMonnies and Ho (1987) and Lowther (1988)).
3.4.1 Types of DEQ

Different DEQ have been used by different investigators in different parts of the world. They can be divided into two types: simple and complex. The simple ones mainly consist of questions about primary symptoms and their frequencies (Anderson et al. 1972, Sargent et al. 1988, Schein et al. 1997). The complex ones contain questions not only about primary symptoms but also concerning secondary symptoms, medications and previous treatment etc. (McMonnies 1986, Doughty et al. 1997). Some are observer-administered while others are patient-completed.

The McMonnies’ DEQ (Mc-DEQ) has been widely used in previous studies (McMonnies and Ho 1987, McMonnies and Ho 1987, Snyder and Fullard 1991, DeCarlo et al. 1995, Charlton et al. 1996, McMonnies et al. 1998, Schiffman et al. 2000, Mitchell et al. 2000, Begley et al. 2001). Therefore, it will be discussed in detail in this chapter (see Section 3.4.1 (i)).

3.4.1 (i) Simple DEQ

The diagnosis of a disease can be based on the presence or absence of various symptoms or signs (Anderson et al. 1972). Anderson et al. (1972) evaluated 40 patients with rheumatoid arthritis and KCS to determine the prevalence of ocular symptoms and signs. Ten symptoms (see Appendix I) and seven signs were used in their study. The frequencies of the top five symptoms reported were found to be foreign body sensation - 80%, burning - 75%, dry feeling - 70%, tiredness - 65%, redness - 47.5%, and the frequencies of the top five observed signs were found to be sign of photophobia - 77.5%, irregularity of the corneal image - 52.5%, conjunctival hyperaemia - 27.5%, discharge -
27.5% and dull conjunctiva or cornea - 27.5%. From these observations, an equation was formed to calculate the final score for each patient (see Appendix I). Any patient with a score less than –2 would be classified as suffering from KCS. They found that the results based on the ten symptoms were "more repeatable and stable" than those based on the ten symptoms and seven signs. However, since the symptoms and signs were selected from dry eye subjects with rheumatoid arthritis, it is unclear if the same ten symptoms and seven signs would be appropriate for dry eye due to other causes.

3.4.1 (ii) Complex DEQ

McMonnies (1986) designed a 12 multiple choice DEQ (Mc-DE Appendix IIa). The questions included primary symptoms and their frequencies, previous treatment for dry eye, secondary symptoms that occur in circumstances that provoke a response in susceptible individuals, ocular and systemic factors that may be associated with dry eye symptoms, and drug usage that may provoke or exacerbate dry eye conditions. A scoring system using arbitrarily weighted scales derived from present understanding of symptoms and etiologies is presented in Appendix IIa. Mc-DEQ has been transcribed by the Author into Chinese (see Appendix IIb) and its used will be described in Chapter 9. The detail of the preparation of this Chinese version of Mc-DEQ is described in Section 5.2.4.

McMonnies and Ho (1986) examined 500 patients (323 contact lens wearers, 177 non-contact lens wearers) using the Mc-DEQ. Using the scoring system shown in Appendix IIa, the range of the total scores for these 500 patients was from zero to thirty-two and 95% of the scores were under 18. According to
their ages, 500 patients were divided into three age groups: under 25 years, 25-45 years and over 45 years. Contact lens wearers were found to have primary symptoms of dry eye more frequently than non-contact lens wearers. Soreness was the most frequently reported symptom for all subjects of 25-45 years but those under 45 years old reported burning as the most frequently symptoms. The frequencies of reported primary symptoms for the non-contact lens wearers were found to be soreness - 36%, scratchiness - 20%, grittiness - 15%, burning - 14% and dryness - 12%, however dryness was the most common primary symptom reported by the contact lens wearers. For subjects over 45 years old, females reported symptoms more frequently than males.

3.4.2 Symptoms of Dry Eye

The instability of the tear film causes ocular irritations in dry eye patients. As there are no specific sensors for dryness in the ocular surface, the subjective sensations caused by dry eye may be diversified (Murillo-lopez and Pflugfelder 1997). Patients with dry eye are likely to use descriptors such as ‘sensitive to light’, ‘dry’, ‘red’, ‘sticky discharge’, ‘burning’, ‘itching’, ‘scratching’, ‘hard to open’, ‘tiredness’ and ‘soreness’ (De Roeth 1950, Henderson 1950, De Roeth 1952, Whitcher 1987). These symptoms, however, are not specific for dry eye (Mathers 2000), and many are common to other ocular problems such as blepharitis, chronic conjunctivitis, foreign bodies in the conjunctiva or cornea and asthenopia associated with uncorrected refractive error (Henderson 1950). The symptoms of dry eye vary from mild eye awareness to extreme pain that patients cannot keep their eyes open. The symptoms are typically disproportionate to the signs (Farris 1997). Bjerrum (Bjerrum 1996) also
reported that ocular symptoms in KCS subjects had poor correlation with the clinical test results. Symptoms of dry eye were found to be more common in women and increased with age (Khurana et al. 1991, Bandeen-Roche et al. 1997, Schein et al. 1997, McCarty et al. 1998, Shimmura et al. 1999, Schaumberg et al. 2000).

The most common symptom of dry eye is foreign body sensation (Whitcher 1987, Jaanus 1990, Nelson 1994, Michelson 1997). McMonnies and Ho (1987) carried out the Mc-DEQ on 500 normal subjects and 68 KCS subjects. Patients with KCS reported symptoms of dryness, grittiness and burning significantly more often than the normal patients.

Toda et al. (1993) used a DEQ of 12 symptoms to record the ocular complaints of 534 patients. They classified patients with ocular fatigue as dry eye patients if there was no other cause identified. They found that 71.3% of dry eye patients with symptoms complained of ocular fatigue and concluded that ocular fatigue was the major symptom of dry eye. Twenty patients who complained of ocular fatigue were asked to define ocular fatigue more precisely. However, some of the descriptions of ocular fatigue from their patients were questionable, such as "I want to take eye drops".

Schein et al. (1997) examined the distribution and association of dry eye symptoms, ST results and rose bengal scores in 2,420 subjects (of age between 65 and 84 years). A simple DEQ (Sch-DEQ) was administered by a trained technician, and they found no correlation between symptoms, ST results and rose bengal scores. The authors explained that the symptoms were not specific enough to strengthen their associations with the tests performed. The ST and rose bengal staining measured different processes so that no, or only a weak
association was found between symptoms and test results. Their results showed that dry eye symptoms were not associated with age in people over 65 years old, or with gender.

Doughty et al. (1997) mailed a questionnaire to all optometrical practices in Canada in October 1994. The optometrists were asked to give the questionnaires to 30 successive and non-selected patients who presented themselves in their practices for eye care. A total of 13,517 questionnaires were returned. About 29% of the participants reported dry eye symptoms which were rated from occasional but mild to severe. The proportions of patients reporting any levels of symptoms of dry eyes and reporting severe symptoms were estimated to be 1 in 4 and 1 in 225 respectively. However these results may underestimate the problem, because ophthalmological practices, which may have more patients with severe symptoms, were not included.

Patient symptoms are most helpful in the diagnosis of the early dry eye (Jaanus 1990). Dryness and soreness of the eye were the most frequently reported symptoms in mild-to-moderate dry eye patients (Nichols et al. 1999). Nichols et al. (1999) concluded that diagnosing patients with frequent or severe complaints of dryness and soreness as dry eye would have high validity. A DEQ was sent by facsimile to 598 persons in Japan (Shimmura et al. 1999). They were asked to perform a self-diagnosis for dry eye according to the DEQ. The most common symptoms for the dry eye were found to be ocular fatigue, dryness and blurred vision. However, the result may be questionable as the ‘dry eye patients’ were based purely on self-diagnosis and the participants may have had other conditions with similar symptoms.
It should be noted that in previous studies the dry eye symptoms were reported from all types of dry eye patients. Most reports did not make any attempt to differentiate or classify the dry eye condition found in their subjects. Classification of the types of dry eye cannot be solely based on the dry eye symptoms.

3.4.3 Reliability

Fair to moderate repeatability of DEQ was found in several studies (Kinney 1999, Nichols and Zadnik 2000). Kinney (1999) evaluated the repeatability of the Mc-DEQ on 75 dry eye patients and concluded that the Mc-DEQ showed fair repeatability. However, Kinney did not mention the analysis method in the article. Nichols and Zadnik (2000) performed Mc-DEQ and the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) on 75 dry eye patients on two occasions by a single examiner. They reported that the Mc-DEQ and NEI VFQ-25 had only moderate repeatability. However, the statistic analysis method of repeatability was not clearly stated.

3.4.4 Validity

Several studies have shown that the Mc-DEQ has good validity for diagnosing dry eye (McMonnies and Ho 1987, Robboy and Orsborn 1989, Golding and Brennan 1993, McMonnies et al. 1998). McMonnies and Ho (1987) applied the Mc-DEQ to 500 patients without any dry eye symptoms (normal subjects) and 68 dry eye patients without
supervision (i.e. patient-administered). They further considered a sub-sample of 37 normal females and 63 dry eye females patients over 45 years of age from 568 subjects. Using discriminant analysis, the discriminant score was determined by the region of the overlap of the two distributions. The specificity and sensitivity in classifying the dry eye patients were 97% and 98% respectively by applying the discriminant score (generated from the subgroup) to all 568 subjects. However, the high specificity and sensitivity were questionable since the classification procedure was generated from a selected sub-group of normal and dry eye subjects within the large group (Oden et al. 1998).

Robboy and Orsborn (1989) investigated the responses of marginal dry eye contact lens wearers with the Mc-DEQ. Each subject who completed the Mc-DEQ was also asked, “Do you attribute reduced lens wearing time to dry eye symptoms?” Robboy and Orsborn then compared the test scores of Mc-DEQ and the positive responses to the question, and concluded that their findings proved the validity of the Mc-DEQ as a tool in identifying marginal dry eye soft contact lens wearers.

Golding and Brennan (1993) performed Mc-DEQ on 15 normal and 15 dry eye subjects. The specificity and sensitivity of Mc-DEQ were found to be 87% when using the cut-off score of 14. They concluded that Mc-DEQ was a useful clinical test for the diagnosis of dry eye.

McMonnies et al. (1998) analysed questionnaire responses from 50 patients suffering from Sjögren syndrome and 124 normal subjects using logistic regression to calculate the coefficients of each separate predictor variables (each question in the questionnaire) in a predictive equation to achieve the
initial classification from 75% of each sample. By applying the coefficients derived from this initial analysis on the remaining 25% of each sample, the specificity and sensitivity in classifying the dry eye patients were 88% and 85% respectively.

3.4.5 Comments

Although dry eye questionnaires have shown to have value, there is scope for improvement in some cases. For example, in the DEQ by Lacrimedics Inc., only a single box is provided to give a positive or negative answer. There are no questions about the severity or frequency of the symptoms. A subject who does not suffer from a particular symptom when completing the DEQ may have suffered from the symptom a few days ago and may not know whether to give a positive or negative answer under the symptom specified. One of the questions asked in the Mc-DEQ is “Do you regard your eye as being unusually sensitive to cigarette smoke, smog, air conditioning, central heating? Yes No Sometimes” and it is uncertain if the patient should answer ‘yes’ only if s/he is sensitive to any one or to all of the conditions specified. Some questions may not be applicable to Chinese living in HK, such those asking about central heating. Therefore, a Chinese version of Mc-DEQ (Mc-DEQC) was used in the current study for Chinese subjects to avoid misunderstanding.

A new DEQ was self-designed by the author and is described, under the name the SD-DEQ (in English) and SD-DEQC (in Chinese), in the following chapters. Details of the preparation of SD-DEQC will be described in Section 5.2.4. The SD-DEQC includes questions concerning the primary symptoms and their frequency, the use of medications that may exacerbate dry eye
symptoms, arthritis and mucous membrane dryness. As Mc-DEQ is widely used in other studies, we also compared our SD-DEQC results with the results obtained with the Mc-DEQC. For presentation in this thesis, the questions of DEQ were discussed in English (see Appendix IIa and IIIa).

The presence of dry eye or the potential risk of dry eye can be indicated by the total score of the Mc-DEQ for the individual patient or by using a predictive equation for dry eye based on the observation of the presence or absence of various symptoms or signs. However, the coefficients of the predictive equation (generated from discriminant analysis) for dry eye reported by McMonnies and Ho (1987) were based on findings for Caucasians. It is uncertain whether the predictive equation is applicable to Chinese. The values of the predictive equation and the Mc-DEQ in the diagnosis of dry eye in Chinese subjects were investigated and are discussed in Chapter 6 and Chapter 9 respectively.
Chapter 4

Introduction to Experimental Studies and Research Aims

4.1 Introduction

Most reports on the prevalence of dry eye are from Caucasian populations and these findings vary with different criteria of definition of dry eye (see Section 2.4). However, findings of the prevalence of dry eye on the Chinese population are scarce.

Anderson (1972) developed a predictive equation for dry eye based on the presence or absence of various symptoms. However, those symptoms were selected from dry eye subjects with rheumatoid arthritis. It is uncertain if those symptoms would be appropriate for all types of dry eye patients, and to our knowledge, there are no reports on the predictive equation for Chinese dry eye.

Dry eye is diagnosed by a combination of dry eye assessments, however reports of dry eye assessments in Chinese patients are scarce. Both the SP-CTT and the PRT test have been claimed to produce repeatable results on HK-Chinese although the treatment of data may not be most appropriate. However, these tests were only performed on normal subjects; it is uncertain how these tests would perform on dry eye subjects.
The TM represents more than 70% of the exposed tear volume (see Section 3.3). A diminished TMH indicates a decreased tear volume, a marked reduction in the aqueous portion of the tears. There have been a number of studies investigating TMH measurement as a diagnostic tool for dry eye patients (see Section 3.3.4), however varying results have been reported, probably due to the different methods used. HK-Chinese have less stable tears (see Section 2.6.1 (iii)) and smaller tear volume (see Section 3.2.2 (vii)) compared to Caucasian, but to our knowledge, there are no reports of TMH of Chinese eyes, normal or otherwise.

Various DEQ have been used in screening dry eye patients (see Section 3.4). McMonnies (1986) derived a DEQ which included questions designed to explore aspects such as primary and secondary dry eye symptoms, medications in use, systemic and ocular factors. The Mc-DEQ has been widely used as a standard test in other studies and is reported to be reliable. *All these DEQ are in English and none of them have been used on Chinese subjects. It is uncertain whether they are applicable to Chinese.* Therefore, the author prepared a self-designed DEQ in Chinese (SD-DEQC) to compare the results with those of Mc-DEQ in Chinese (Mc-DEQC).

### 4.2 Research Aims

Clinical tests for the diagnosis of dry eye must be valid and reliable, and ideally should be convenient in use and inexpensive. In the light of the uncertainties highlighted above, our aims were to determine in Chinese subjects
(i) the prevalence of dry eye in an eye clinic population in HK,
(ii) a model to predict whether a patient with particular symptoms has dry eye or not,
(iii) the effectiveness of the SP-CTT, PRT Test and the Mc-DEQC in discriminating between the normal and dry eye,
(iv) the specificities and sensitivities of the tests mentioned above,
(v) the effect of the different criteria used to define dry eye on the specificities and sensitivities of the SP-CTT, PRT Test and Mc-DEQC,
(vi) the repeatability of TMH measurement using the Topcon IMAGEnet system,
(vii) the mean TMH values in normal and dry eye,
(viii) the effectiveness of Mc-DEQC and SD-DEQC for diagnosis of dry eye.
Chapter 5

Investigation Techniques

5.1 Tests Used

Our aims involved use of the following tests:

(i) The self-prepared cotton thread test (SP-CTT)

(ii) The phenol red thread (PRT) Test (Showa Yakuhin Kako Company Limited, Japan)

(iii) Measurement of tear meniscus height (TMH) using the TOPCON IMAGEnet System

(iv) Two dry eye questionnaires (DEQ) (a) the Chinese Mc-DEQ and (b) a self-designed DEQ

(v) Ocular examination using a slit lamp biomicroscope.

5.2 Materials Used and Procedures of Each Test

5.2.1 SP-CTT

Materials: Self-prepared cotton threads, millimetre rule, stopwatch.

Preparation of the cotton threads (Cho 1993)

A commercially available orange-red cotton sewing thread (0.3 mm, brand ‘555’, cotton thread made in China) was selected for preparing the SP-CTT.
Determination of the wetted portion of the thread was based on measurement of the length of thread which had darkened in colour (i.e. because it was wet). The method for preparing the SP-CTT has been described in detail (Cho 1993). Briefly, a length of the thread was boiled for 30 min to remove the wax on the sewing thread and loosen the thread to improve its capillary action. After boiling, the thread was dried for about 1 hour. The thread was then cut into 70 mm lengths, and sterilised by soaking in 90% alcohol for 3 hours. The sterile threads were then dried overnight in a room of relatively constant humidity and temperature (68% humidity and temperature of 28°C) and then stored in sterile plastic bags.

Figure 5.1. The self-prepared cotton thread test (SP-CTT) (the blue arrow indicates the border between the wet and dry portions of the thread).
**Procedure for SP-CTT**

The procedure was explained carefully to the subject. A 70 mm length of treated thread was removed from the plastic bag and bent 3 mm from one end. The subject was asked to relax, and to look left and up when the right eye was tested (and to look right and up when the left eye was tested). The temporal part of the lower eyelid was gently pulled down, and 3 mm of one end of the thread was hooked over the lower lid. A stopwatch was started immediately and the subject was instructed to keep his/her eyes open and blink normally while maintaining the same position of gaze. After 15 s, the thread was removed, and the end of the wetted length of the thread was immediately marked by making a notch in the thread with a finger nail. The wetted length, which was darker in colour (see Figure 5.1), was measured from the tip with a millimetre (mm) rule. This value was recorded as the SP-CTT value in mm/15 s.

![Figure 5.2. The phenol red thread (PRT) Test (the red arrow indicates the border between the wet and dry portions of the thread).](image-url)
5.2.2 PRT Test

Materials: ‘Zone-Quick’ Phenol red thread test (Showa Yakuhin Kako Company Limited, Japan), millimetre rule, stop watch

Procedure (for PRT Test)

The testing procedure for the PRT Test was the same as for the SP-CTT. The wetted length of the PRT changed colour from yellow to red (see Figure 5.2). The testing period and the unit of the value recorded were as for the SP-CTT.

Figure 5.3. CCD camera with IMAGEnet System.
Figure 5.4. The captured image in the Topcon IMAGEnet system (the red arrow indicates the actual length of the green line drawn by the examiner to represent the tear meniscus height).

5.2.3 TMH Measurement with Topcon IMAGEnet System

Materials: Topcon SL-2F slit lamp biomicroscope and computer with the Topcon IMAGEnet System.

Procedure

A colour video camera (Model: SSC-DC50P, Sony Corp, Japan) with a C-mount attached to a TOPCON SL-2F slit lamp and an IBM computer installed with the TOPCON IMAGEnet System (see Figure 5.3) were used to capture and analyze images of the tear meniscus.
Before the experiment, we tried different settings of the slit lamp and different C-mount aperture sizes to determine the optimum setting for taking the clearest images. The optimal settings of the slit lamp were: 3x6 mm vertical slit, 16x magnification, and illumination level set at Normal. Images of the temporal tear meniscus, measured within 5 mm of the middle of the lower lid margin, were captured and stored. The aperture size of the C-mount was set at 22, which allowed clearest observation of the image. To avoid reflex tearing, a short light beam was used to prevent direct light shining across the pupil during image capture.

The procedure was explained carefully to the subject, who was then positioned comfortably in front of the slit lamp biomicroscope. The subject was asked to look straight with his or her eyes open, but not to consciously widen his or her eyes. For the repeatability experiment (Chapter 8), 2 sets of images were taken with the illumination system set at angles 20 deg and then 30 deg off the observation system for each eye. The measurement was always performed on the right eye first. For the main experiment (Chapter 9), only 1 set of images, at angle 20 deg, was taken. Up to 4 images were taken for each eye at each angle setting. The images were then stored in the computer. The examiner accessed the images taken in order to measure the TMH on a 15" computer monitor (see Figure 5.4) a few days later, after a collection of images from a number of subjects, so that she was masked as to the ocular condition of the subjects. The clearest image from each eye was chosen for the measurement of TMH, and the mean of 3 readings was recorded as the representative TMH (in mm) for that eye.
To allow the author to become experienced in using the IMAGEnet for the measurement of TMH, in the repeatability experiment (Chapter 8), the first set of TMH determined was discarded. The measurement of the TMH of each selected image was repeated and only this second set of measurements was used for analysis.

5.2.4 Dry Eye Questionnaire (DEQ)

Materials: McMonnies’ DEQ in Chinese version (Mc-DEQC) (see Appendix IIb) and a self-designed DEQ in Chinese version (SD-DEQC) (see Appendix IIIb).

Preparation of Mc-DEQC and SD-DEQC

As Mc-DEQ was in English, the SD-DEQ was also designed in English. The SD-DEQ was therefore based on the Mc-DEQ but with amendments made for local requirements and with some open-ended questions in order to collect more information. The two DEQ were translated into Chinese by the author. The Chinese version of the two DEQ (the Mc-DEQC and the SD-DEQC) were then translated back to English independently by two optometrists (who were unfamiliar with this study) in order to identify inaccurate translation or ambiguity. Amendments were made as necessary at this stage.

The Mc-DEQ includes questions on previous treatment, primary ocular symptoms, secondary symptoms, medications, arthritis and dry mucosa. Some terms or questions may not be applicable to Chinese. For example, central heating in Mc-DEQ (Question 7) is not applicable as there is no central heating in HK. From a pilot study (see Chapter 7), we found that ophthalmologists in
HK used very variable criteria for diagnosing dry eye and therefore for treating dry eye. Responses on question concerning previous treatment may therefore be of little value. Therefore, the SD-DEQ includes four questions concerning: (i) medication; (ii) primary ocular symptoms; (iii) arthritis and (iv) dry mucosa. The Mc-DEQC includes five primary ocular symptoms only, and a further five ocular symptoms were included in the SD-DEQC. In order to collect more information of the ocular symptoms and medications from the Chinese subjects, the patients were asked to specify what other symptoms they had and medications they were taking.

Procedure

The procedure was explained carefully to the subject by an assistant. After signing the consent form, the assistant went through each question in the first DEQ verbally with each subject. This was necessary as some elderly subjects were illiterate. After the tear tests, the author (using the standard wording) went through each question in the second DEQ verbally with each subject. Since two DEQ were used, and were performed by different persons, the order of DEQ to be completed was as follows:

Subjects No. 1-50 Mc-DEQC (Assistant) → SD-DEQC (Author)
Subjects No. 51-100 SD-DEQC (Assistant) → Mc-DEQC (Author)
Subjects No. 101-118 Mc-DEQC (Assistant) → SD-DEQC (Author)

Analysis Methods of the Mc-DEQ

The total score and the classification score from Discriminant Analysis were the two methods used to indicate the presence of dry eye or the potential risk
for dry eye. Both analysis methods were used for the Mc-DEQC and the SD-DEQC in Chapter 9 to allow comparison of the results obtained.

(i) Scoring System of Mc-DEQ and SD-DEQ

The system of scoring responses (according to Mc-Monnies and Ho (1986)) for Mc-DEQ is shown in Appendix Ila. The possible maximum total score was fifty-four. However, Mc-Monnies did not suggest any cut-off score values for dry eye in his previous studies. Therefore, a cut-off score value of 14, which was used in previous study by Golding and Brennan in 1993, was used in this current study.

(ii) Classification Score from Discriminant Analysis

According to Mc-Monnies and Ho (1987), the results were analyzed by using the Discriminant Analysis from the Statistical Package for the Social Science. All the responses to each question of Mc-DEQ were re-coded from 0 (no) to 3 (constantly) (see Appendix IIc). Subjects with discriminant score >-0.4 was classified as dry eye.

5.2.5 Ocular Examination Using Slit-lamp Biomicroscope


Procedure

After taking the images and performing the tear tests, a slit lamp examination was performed to check the corneal integrity and the blinking pattern. Any
staining (corneal staining with fluorescein dye) or abnormalities noted were recorded, and the data were excluded if our subject criteria were not satisfied. The severity of the corneal staining was classified into three types: mild, moderate and severe (adapted from Lowther and Malinovsky 1988) (see Section 2.6.1 (i) and Figure 2.3).

5.3 Subject Criteria

All subjects were Chinese and were recruited from the General Eye and Low Vision Centre, operated by the Hong Kong Society for the Blind. The author screened the patients’ clinical files and contacted them by phone. Patients were told that a lack of interest in participating would not in any way affect their treatment from the Centre. Unless otherwise stated, all subjects

1. were aged from 18 to 95 years,
2. reported good general health, and
3. had no history of ocular inflammation or anterior segment surgery.

Subjects were requested to come for the tests between 1 pm and 6 pm, and to avoid using eye drops or eye ointment on the test day to ensure that no eye medications were applied at least 12 hours before the test.

5.4 Ethical Approval and Subject Consent

All the experiments and procedures reported in this thesis were approved by the Human Subjects Ethics Sub-committee of The Hong Kong Polytechnic University. All subjects gave informed consent before participating in any
experiments, and all procedures complied with the Declaration of Helsinki, as revised in 2000.
Chapter 6

Prevalence of Dry Eye in an Eye Clinic
Population in Hong Kong

6.1 Introduction

The prevalence of dry eye reported in previous studies has varied from less than 1% to 25% (see Section 2.4). These figures were obtained using different criteria to define dry eye and many reports were related to Caucasian clinical populations. As far as we know there has been no report of the prevalence of dry eye in Chinese, and while the results of the study described below cannot be generalized to the whole population, they can, nevertheless, be compared with results from a number of other studies of Caucasian clinical population.

The objectives of this experiment were to determine, in a Chinese population:

(i) the prevalence of dry eye in a clinical sample in both the dry and humid seasons of the year,

(ii) the symptoms most frequently reported by dry eye subjects, and

(iii) a model (predictive equation) to predict whether a patient with particular ocular symptoms has dry eye or not,

(iv) the specificity and sensitivity of the above model for classification of normal and dry cases.
Table 6.1. The frequency of the ocular symptoms and clinical signs recorded in 741 files in the dry season and 857 files in the humid season.

<table>
<thead>
<tr>
<th>Ocular symptom or clinical sign</th>
<th>November (dry season)</th>
<th>March (humid season)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% in 25 dry eye cases (%)</td>
<td>% in 716 non-dry eye cases (%)</td>
</tr>
<tr>
<td>Dryness</td>
<td>24</td>
<td>2.5</td>
</tr>
<tr>
<td>Itchy</td>
<td>20</td>
<td>7.5</td>
</tr>
<tr>
<td>Tearing</td>
<td>20</td>
<td>11.5</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>32</td>
<td>9.8</td>
</tr>
<tr>
<td>Red</td>
<td>8</td>
<td>4.1</td>
</tr>
<tr>
<td>Pain</td>
<td>24</td>
<td>5.2</td>
</tr>
<tr>
<td>Discharge</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Ocular fatigue</td>
<td>8</td>
<td>5.7</td>
</tr>
<tr>
<td>Photophobia</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Burning</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Short TBUT</td>
<td>44</td>
<td>0.7</td>
</tr>
<tr>
<td>Fluorescein corneal staining</td>
<td>16</td>
<td>0.6</td>
</tr>
<tr>
<td>Partial blinker</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

6.2 Procedure

The prevalence of dry eye was determined from the General Eye and Low Vision Centre, operated by the Hong Kong Society for the Blind. Twelve visiting ophthalmologists and seven optometrists work in this eye centre. Clinical records in a two-week period in November (the dry season in HK) were surveyed. For patients who visited the Centre twice within the two weeks, only the first visit was included. Only the files of patients with Chinese names were used (we assumed that these patients were of Chinese origin from their names only). All patients were at least 18 years old. The ocular symptoms,
clinical signs and the diagnosis of each patient were retrieved from their files for analysis. This study was repeated in March (the humid season in HK). The ocular symptoms in the clinical records were self-reported by patients, typically when they were asked ‘how do your eyes feel?’ In this study, the results were gross estimates only as the data were records by different clinicians and ophthalmologists who probably have different criteria for the diagnosis of dry eye. Some used ocular symptoms and corneal staining while others used clinical signs such as reduced TMH, abnormal TBUT, and increase in tear debris and these were usually recorded with no specific grading of the severity of the condition.

6.3 Results

The mean humidity value in November recorded at the HK Observatory was 60% and that in March was 72%. A total of 741 and 857 clinical files were surveyed in November and March respectively. Ten ocular symptoms and three clinical signs were recorded from the clinical files (see Table 6.1). Foreign body sensation (32%) was the most frequently reported ocular symptoms from the dry eye cases in November (dry season) and foreign body sensation (34.6%) and dryness (34.6%) were the most frequently reported ocular symptoms from the dry eye cases in March (humid season). However, tearing (10.2%) was the most frequently reported ocular symptoms from the non-dry eye cases in both dry and humid seasons. Common symptoms in both seasons were dryness, itchy, tearing, foreign body sensation, red, pain,
discharge, ocular fatigue and photophobia. Burning was not commonly reported in either season.

Only 16% and 26.9% of the dry eye cases in the dry and humid season respectively had fluorescein corneal staining. Foreign body sensation was the most frequently reported ocular symptom in dry eye females over the age of 45 years in both the dry and humid seasons.

November (Dry Season)
There were 573 patients seen by ophthalmologists and 168 seen by optometrists during November. The mean (SD) age of these patients (515 females and 226 males) was 51.6 (16.3) years. A total of 25 dry eye cases (24 ophthalmological cases and one optometrical case) were diagnosed. The prevalence of dry eye in the private eye centre was 3.4%. The dry eye cases (21 females and 4 males) were of age 25 to 77 years. Eleven of the 21 female dry eye cases were more than 45 years old.

March (Humid Season)
There were 647 patients seen by ophthalmologists and 210 seen by optometrists during March. The mean (SD) age of these patients (583 females and 274 males) was 52.5 (16.7) years. A total of 26 dry eye cases (24 ophthalmological cases and 2 optometrical cases) were diagnosed by the ophthalmologists and optometrists using individually determined criteria. The prevalence of dry eye in the private eye centre was found to be 3.0%. The dry eye cases (24 females and 2 males) were of age 32 to 69 years. Sixteen of the 24 female dry eye cases were above 45 years old.
Table 6.2. The coefficients for each symptom in the predictive equation in dry and humid seasons.

<table>
<thead>
<tr>
<th>Ocular symptoms</th>
<th>Coefficients in Dry Season ($X_i$)</th>
<th>Coefficients in Humid Season ($X_i$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryness</td>
<td>+4.082</td>
<td>+4.524</td>
</tr>
<tr>
<td>Itchy</td>
<td>+0.56</td>
<td>+0.176</td>
</tr>
<tr>
<td>Tearing</td>
<td>+0.471</td>
<td>+0.47</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>+1.316</td>
<td>+0.942</td>
</tr>
<tr>
<td>Red</td>
<td>+0.359</td>
<td>−0.851</td>
</tr>
<tr>
<td>Pain</td>
<td>+1.828</td>
<td>+1.586</td>
</tr>
<tr>
<td>Discharge</td>
<td>−0.141</td>
<td>−0.094</td>
</tr>
<tr>
<td>Ocular fatigue</td>
<td>+0.284</td>
<td>+0.366</td>
</tr>
<tr>
<td>Photophobia</td>
<td>−0.321</td>
<td>−1.353</td>
</tr>
<tr>
<td>Burning</td>
<td>−0.181</td>
<td>0</td>
</tr>
<tr>
<td>Constant ‘a’</td>
<td>−0.501</td>
<td>−0.365</td>
</tr>
</tbody>
</table>

An outcome can be predicted by a linear combination of various predictor variables (Dawson-Saunders and Trapp 1994). The coefficients of the various predictor variables (i.e. ten symptoms) in the predictive equation were calculated by using discriminant analysis sub-programme from the Statistical Package for the Social Sciences (see Table 6.2). A discriminant score ($S$) was calculated by the predictive equation.

(i) Dry Season: Equation D

\[
S = 4.082(\text{dryness}) + 0.56(\text{itchy}) + 0.471(\text{tearing}) + 1.316(\text{foreign body sensation}) + 0.359(\text{red}) + 1.828(\text{pain}) - 0.141(\text{discharge}) + 0.284(\text{ocular fatigue}) - 0.321(\text{photophobia}) - 1.81(\text{burning}) - 0.501
\]
Equation D is the predictive equation for dry season. The ranges of discriminant score for classified normal and dry eye cases were from −0.823 to +0.673 and from +0.814 to +5.409 respectively using this model. According to the practitioners’ diagnoses, 83.1% of the cases (600 non-dry and 16 dry cases) were classified correctly using this equation when the cut-off discriminant score +0.81 was used. The specificity and sensitivity of this classification were found to be 83.8% and 64.0% respectively.

(ii) Humid Season: Equation H

\[ S = 4.524(\text{dryness}) + 0.176(\text{itchy}) + 0.47(\text{tearing}) + 0.942(\text{foreign body sensation}) - 0.851(\text{red}) + 1.586(\text{pain}) - 0.094(\text{discharge}) + 0.366(\text{ocular fatigue}) - 1.353(\text{photophobia}) + 0(\text{Burning}) - 0.365 \]

Equation H is the predictive equation for humid season. The ranges of discriminant score for classified normal and dry eye cases were found to be from −1.718 to +0.953 and from +1.047 to +6.686 respectively. According to the practitioners’ diagnoses, over 91.1% of the cases (766 non-dry and 15 dry cases) were classified correctly when the cut-off discriminant score +1.04 was used. The specificity and sensitivity of this classification were found to be 92.2% and 57.7% respectively.

6.4 Discussion

Our results showed that the prevalence of dry eye in an eye clinic population in HK was about 3% in both dry and humid seasons (humidity difference of 12% only). The humidity in HK is generally low in autumn and winter (from
September to February) and high in spring and summer (from March to August). However, the figures from the HK Observatory indicated a difference of only 12% in humidity between these two seasons during the study period, and our results were not affected by this narrow range of humidity difference (60% to 72%). As the specificities and sensitivities of the classifications from the two predictive equations were similar between the dry and humid seasons, only data from November (dry season) are discussed below.

The prevalence of dry eye from this study was found to be relatively low compared to previously reported studies (Schein et al. 1997, Caffery et al. 1998, Moss et al. 2000). This may be due to the following factors. When dry eye patients visited the eye clinics for assessment, the condition was generally moderate to severe with intolerable symptoms. Patients with marginal dry eye patients may not visit the eye clinics as they can tolerate the condition. This may be because medical services provided in this clinic are not free of charge. According to Chinese culture, visiting a doctor should be avoided whenever possible because it is considered bad luck.

Eye care practitioners have difficulties in diagnosing dry eye (see Section 1.1) and mild dry eye cases require a battery of diagnostic tests to confirm the diagnosis. In this experiment, the ophthalmologists and optometrists defined dry eye using a combination of TBUT, and observation of certain clinical signs and ocular symptoms. Not all ophthalmologists and optometrists used fluorescein on every patient and this could explain why the percentage of dry eye cases with fluorescein corneal staining was relatively low in this study. Dry eye cases without any obvious clinical signs may be overlooked or
misdiagnosed as allergic or infectious conjunctivitis (Norn 1992). Therefore, dry eye cases may be underdiagnosed in this study.

The use of different criteria to define dry eye would lead to different determinations of prevalence of dry eye. The prevalence of dry eye in the current experiment was found to be 3.4% whereas those reported in other studies ranged from 14.4% to 28.7% (Schein et al. 1997, Caffery et al. 1998, Moss et al. 2000), and the differences may be due to the use of different diagnostic criteria or to real racial differences. In this experiment, the prevalence of dry eye in the dry season was found to be 37.5% (28.1% in humid season) when the criteria for dry eye was based on dry eye symptoms alone. It was further reduced to 2.3% when the definition was based on any dry eye symptoms plus either short TBUT or fluorescein corneal staining. The low prevalence of dry eye found in this study is similar to the finding of Schein et al. (1997), who reported that the prevalence of dry eye was reduced to 3.5% when the definition was based on the presence of symptoms with one or more clinical signs.

Schein et al. (1997) reported that the prevalence of dry eye among the elderly aged 65 to 84 years was 18.1%. In their study, dry eye was defined based on the presence of three or more dry eye symptoms, collected via questionnaire which included six questions. As some dry eye symptoms are common with other eye diseases, therefore, the prevalence of dry eye based on dry eye symptoms alone in their study may not reflect the true prevalence.

We found that the most commonly reported symptom of dry eye was foreign body sensation, and this is in agreement with previous reports (Whitcher 1987, Jaanus 1990, Nelson 1994, Michelson 1997, Versura et al. 2001). In humid
season, dryness was also one of the common reported symptoms. Contrary to previous report (Toda et al. 1993), ocular fatigue was not the major symptom of dry eye in this study. A model for predicting dry eye (Equation D) was obtained from 716 non-dry eye cases and 25 dry eye cases, however only 16 out of 25 dry eye cases were classified correctly. Application of the model resulted in high specificity (83.8%) but poor sensitivity (64%). Each misclassified normal case reduced specificity by 0.14% but each misclassified dry eye case reduced the sensitivity by 4%. The poor sensitivity was probably due to the relatively small number of the dry eye cases. The coefficient of “foreign body sensation” in the predictive equation was smaller than that of “dryness”. This is because “foreign body sensation” was also commonly reported in the non-dry eye cases. It is possible that these cases, are actually marginal dry eye cases rather than normal or non-dry eye cases. This would then explain why poor sensitivity was obtained from the predictive equation.

In this study, history taking for all the patients whose files were surveyed was not always performed by the same personnel and this probably affect the results obtained to some extent as different personnel may have different procedures for history taking. Open-ended questions were used in this study and the validity of the results depended on the history taking technique (e.g. with or without probing) by the clinicians. In order to confirm the usefulness of this model, a larger group of dry eye cases should be included force-choice questions.
6.5 Conclusions

Our results show a relatively low prevalence of dry eye adults (3%) in a private eye centre in HK and the prevalence was not affected by mean humidity within the range of 60% to 72%. High specificity (83.8%) and poor sensitivity (64%) of the model for predicting dry eye was obtained. Foreign body sensation and dryness were the most common ocular symptoms among Chinese dry eye.

Prevalence determined may be affected by the criteria used for defining dry eye and ideally standardised diagnostic criteria must be agreed, and carefully adhered to, by participating clinicians. The validity of the model should be reconfirmed by using a larger group of dry eye subjects, force-choice questions and consistent history-taking technique.
Chapter 7

A Study of the specificity and sensitivity of a Self-prepared Cotton Thread Test and the Phenol Red Thread Test in the diagnosis of dry eye

7.1 Introduction

The Schirmer test (ST) has been criticized by many investigators as being a crude and unreliable test and three cotton thread tests (CTT) have been introduced as possible alternatives. The SP-CTT and the PRT Test have been reported to be reliable in normal subjects, however as mean PRT value of HK-Chinese has been shown to be significantly lower than those reported for Caucasian subjects (Cho and Kwong 1996), it is uncertain how these tests would perform on dry eye subjects in HK.

Reports on the specificity and sensitivity of the CTT are scarce. Golding and Brennan (1993) reported “low” specificity (67%) and sensitivity (67%) for the PRT Test in the diagnosis of KCS. Using a SP-PRT and a cut off value of 20 mm for differentiating the aqueous and non-aqueous deficient dry eyes, Patel et al. (1998) reported a specificity and sensitivity of 83% and 86% respectively. Chiu et al. (2000) used the SP-CTT and the PRT Test on 47 contact lens wearers and reported specificities and sensitivities of 52.4% and 88.5%
respectively for SP-CTT values (cut-off value: 15 mm), and 47.6% and 76.9% respectively for PRT values (cut-off value: 18 mm).

The aim of this present study was to investigate the specificity and sensitivity of a SP-CTT and the PRT Test for the diagnosis of dry eye in Chinese diagnosed by ophthalmologists in a private eye centre.

7.2 Subjects

Eighty-three Chinese subjects, 46 dry eye and 37 normal, were recruited in the General Eye and Low Vision Centre. All subjects were diagnosed by ophthalmologists in the centre. Asymptomatic patients were recruited as normal subjects. The dry eye group, all of whom were using artificial tears, comprised 40 females and 6 males (mean (SD) age: 53.5 (10.0) years). Patients who had undergone anterior segment surgery or who had ocular inflammation were excluded. The normal group comprised 32 females and 5 males (mean (SD) age: 55.7 (9.1) years). All subjects were requested to come for the tests after 1 p.m., and to avoid using eye drops or eye ointment on the test day.

Note: In this study, the criteria used for the diagnosis of dry eye by each ophthalmologist varied. For the diagnosis of dry eye, some used ocular symptoms and corneal staining while others used clinical signs such as reduced TMH, increase in tear debris and corneal staining.

7.3 Procedure

The subject was seated in the examination room and the purpose of the study and the testing procedure were explained by the author. One eye was tested with the SP-CTT and the other eye was tested with the PRT Test, one after the
other. We used the 'random' function of Microsoft Excel to assign which eye was measured first and which test was performed first. All thread tests were performed by the author and she was masked as to the ocular condition of the subjects as described in Section 5.2. After the thread tests, an ocular slit lamp examination was performed to confirm the corneal integrity. The procedure for conducting this examination was as described in Section 5.2.5. The temperature and humidity of the examination room were recorded each day before the tests were performed.

Figure 7.1. Mean SP-CTT and PRT values for the dry eye and normal groups. (Each error bar shows 1 SD of the mean)
7.4 Results

The temperature and humidity of the examination room were consistent throughout the study. Figure 7.1 shows a summary of the mean SP-CTT and PRT values for the dry eye and normal subjects. There was a statistically significant difference in the mean SP-CTT values between the dry eye and normal group (t-test for independent samples: p=0.03); but no difference was found in the mean PRT values between the two groups (t-test for independent samples: p=0.485).

The specificity and sensitivity of the SP-CTT for the diagnosis of dry eye were 78.4% and 45.7% respectively when a cut-off value of ≤4 mm was used. The specificity of the SP-CTT decreased to 56.8% and sensitivity increased to 65.2% when a cut-off value of ≤6.5 mm was used. Although there was no statistically significant difference in the mean PRT values between the normal and dry eye subjects, we calculated the specificity and sensitivity of the PRT Test for comparison purposes. The specificity of the PRT Test was 62.2% and its sensitivity was 45.7% when a cut-off value of ≤9 mm was used.

Thirteen out of 46 dry subjects (28%) were found to have mild-moderate punctate staining. No staining was found in the remaining subjects. Six out of 37 normal subjects (16%) also had mild staining. There was no statistically significant difference in the SP-CTT or PRT values between the subjects with staining and the subjects without staining in both groups (t-tests for independent samples: p>0.05). No other abnormality was noted.
7.5 Discussion

Our results showed a statistically significant difference in mean SP-CTT value between dry eye and normal subjects, but no significant difference was found in the mean PRT value between the two groups. The specificities and sensitivities of both the SP-CTT and the PRT Test were poor. The SP-CTT therefore appears to be a better diagnostic tool than the PRT Test for HK-Chinese dry eye patients although both tests have been reported to be reliable on normal HK-Chinese subjects (Cho 1993, Cho and Kwong 1996). In a recent study, Chui et al. (2000) found that the SP-CTT was a better test for predicting successful contact lens wear than the PRT Test (see Section 3.2.5). The difference in the performance of the two tests may be due to the different absorbencies of the type of threads used. In view of the short testing period, it has been suggested that the PRT Test measures residual tears in the lower lacrimal fornix (Hamano et al. 1990, Sakamoto et al. 1993). Presumably, tear volumes in the lower lacrimal fornices of the dry eye group were lower than those in the normal group. It is possible that as the volume of the lacrimal lake decreases during measurement, tear production is stimulated to some extent. As the PRT has higher absorbency, it may therefore be a larger stimulation for tear production than the SP-CTT thread. As a result, in the dry eye group, the PRT Test may be measuring not only the residual tears in the lower fornix but also some reflex tears. Blades and Patel (1996) also suggested that the absorption of tears by a PRT may stimulate an increase in lacrimal secretion. However, their experiment involved normal subjects only. Further investigations into this area will be necessary before firm conclusions can be drawn.
In the current study, we used different cut-off values based on different results reported by previous investigators. Golding and Brennan (1993) performed the PRT Test on 15 dry eye and 15 normal Caucasian subjects. The mean (SD) PRT values for dry eye and normal subjects were 20 (10) mm/15 s and 22 (7) mm/15 s respectively, and these two means were not significantly different. Using a cut-off value of <20.5 mm, they reported "low" specificity (67%) and sensitivity (67%) for the PRT Test. Our results are not comparable with those reported by Golding and Brennan (1993) since the mean PRT values reported for their subjects were significantly different from our findings (Welch's alternate t-tests: normal subjects, p=0.0001; dry eye subjects, p=0.0033). Also, 97.8% and 100% of our dry eye and normal subjects respectively had PRT values less than 20.5 mm. We earlier reported (Cho and Kwong 1996), significant differences between the mean PRT value of HK-Chinese and values published for Caucasian subjects (Sakamoto et al. 1993, Little and Bruce 1994); but no significant difference between the mean PRT value of HK-Chinese and those reported for Japanese subjects (Sakamoto et al. 1993) (see Section 3.2.2 (vii)). Hamano et al. (1990) found a high correlation between corneal complications and PRT values in contact lens wearers with PRT values under ≤9 mm. Assuming no significant difference in the PRT values between Japanese and HK-Chinese, we chose ≤9 mm as the cut-off value for the PRT Test in the current study.

Since there were no previous reports on the use of the SP-CTT as a diagnostic tool for dry eye problems, we used two different ways of determining the cut-off value for the calculation of specificity and sensitivity of this test in this study:
(a) Since ≤9 mm (cut-off value chosen for the PRT Test) is about half the mean PRT value (18.8 mm/15 s) for the Japanese subjects (Sakamoto et al. 1993), we chose half the mean SP-CTT value of the normal group (that is, ≤4 mm) as the first cut-off value;

(b) In a previous study (Cho and Kwong 1996), we performed some trials to observe the different absorbencies of the SP-CTT thread and the PRT. We found that 1 µl of saline wetted 25 mm and 33 mm of a SP-CTT thread and a PRT respectively, that is, 1 mm wet length of a PRT was approximately equivalent to 0.76 mm wet length of a SP-CTT thread. Also, in the current study, for the normal subjects, the ratio of the mean SP-CTT value to the mean PRT value was about 0.73. Hence, using this ratio (i.e. 0.73) as a guideline, 9 mm PRT value is approximately equivalent to 6.5 mm SP-CTT value, and this was the second cut-off value we chose for the calculation of the specificity and sensitivity of the SP-CTT.

Using a cut-off value of ≤4 mm for the SP-CTT and ≤9 mm for the PRT Test, the SP-CTT was the more specific test, though both tests show poor sensitivity (SP-CTT: specificity 78.4%, sensitivity 45.7%; PRT Test: specificity 62.2%, sensitivity 45.7%). However, when we used ≤6.5 mm as the SP-CTT cut-off value, the SP-CTT became less specific (56.8%) but more sensitive (65.2%). In this study, only 9 and 4 out of 46 dry eye subjects (28%) had mild and moderate staining respectively. Six of the 37 normal subjects (16%) also had mild staining. However, it is not unusual to find corneal staining in normal corneas (Schwallie et al. 1997). Our results show no significant difference in the SP-CTT and PRT values between the subjects with staining and subjects without staining in both groups.
Our results seem to indicate that neither the SP-CTT nor the PRT Test is very specific or sensitive for diagnosing Chinese dry eye patients (assuming the dry eye diagnoses made by the ophthalmologists were valid), a finding in agreement with those of Golding and Brennan (1993). We were unable to distinguish between normal and dry eye subjects using the PRT Test; either the PRT Test is not a useful test for the diagnosis of dry eye, or not all the dry eye subjects diagnosed were really suffering from dry eye. On the other hand, we found a significant difference in the SP-CTT results between our two groups of subjects. We suggest that our results should be used with caution as we are not sure, at this stage, if the tests we are using are valid or if our dry eye subjects were all truly suffering from dry eye. In HK, patients with ocular problems (non-contact lens wearers) will usually consult ophthalmologists rather than optometrists. Hence, in the current study, we recruited our dry eye subjects based on the diagnoses of ophthalmologists. Optometrists in HK usually do not question an ophthalmological diagnosis, however, the results of this study suggest that perhaps we should do so, at least where the diagnosis of dry eye is concerned (although there is no guarantee that optometrists would do a better job). We do not know the situation in other countries.

In order to confirm our results on the specificities and sensitivities of these two tests, this study should be repeated on dry eye subjects recruited using consistent and validated diagnostic criteria.

Lemp (1995) classified dry eye into two major categories: tear deficient dry eye and evaporative dry eye. Tear deficient dry eye involves a reduction of the lacrimal production leading to a fall in the tear volume in the conjunctival sac. Evaporative dry eye involves tear evaporation with a normal lacrimal function.
Since both tests used in the current study assessed the quantity of the tears, they would have poor specificity and sensitivity for evaporative dry eye subjects. Therefore, for the calculations of specificities and sensitivities of the tests, the type of dry eye subjects we really needed to recruit would be those who are tear deficient. The most common symptoms of dry eye are foreign body sensation, grittiness, itching, burning, redness and ocular fatigue etc (see Section 3.4.2). The most typical dry eye symptom for any type of dry eye is foreign body sensation (see Section 3.4.2). The clinical signs for all types of dry eye patients are fluorescein staining, and high tear osmolarity, and those only for tear deficient dry eye patients are diminished TM and low tear lactoferrin (Lemp 1995). Presumably, a dry eye patient who has diminished tear menisci could be classified as tear deficient dry eye. Fluorescein staining, conjunctival hyperemia and TMH can be easily assessed without high-technology equipment. We could recruit dry eye subjects who satisfy all the following criteria for further investigation into the specificity and sensitivity of the thread tests:

(a) diminished tear meniscus,

(b) presence of corneal staining which involved more than 1/3 of the inferior cornea (see Section 2.6.1 (i) and Figure 2.3),

(c) ocular symptoms either foreign body sensation or dryness when they were not using any eye drops.

The PRT Test is standardized, easy to use and is available commercially. However, our results raised the question of its validity in view of the poor specificity and sensitivity. Further investigation is required in this area.
7.6 Conclusions

Our results show a statistically significant difference in mean SP-CTT value between dry eye and normal subjects, but no difference in the mean PRT value was found between the two groups. The specificities and sensitivities of both the SP-CTT and PRT Tests were poor (56.8% and 65.2% for SP-CTT, 62.2% and 45.7% for PRT Test respectively) when applied to patients diagnosed by ophthalmologists in a private clinic. However, our results may be affected by the way we recruited our subjects and the choice of cut-off value and/or by the diagnostic criteria applied by the ophthalmologist. Further investigation should be carried out with stringent criteria for the subjects recruited before firm conclusion could be made about the validity of these CTT.

Paper published

Chapter 8

Tear meniscus height in normal and dry eyes

8.1 Introduction

Previous studies have shown that the tear menisci represent more than 70% of the pre-ocular tear volume (Holly 1981, Guillon and Guillon 1988). Due to gravity, the lower marginal tear strip represents the greatest part of the exposed tear volume (Port and Asaria 1990, Mainstone et al. 1996). It has been suggested that a diminished TMH indicates a marked reduction in the aqueous portion of the tears (Whitcher 1987). The tear volume determined using the fluorescein dilution method was found to have a correlation with the TMH (Scherz et al. 1974) and Mainstone et al. (1996) have suggested that TMH measurement is a useful alternative test for dry eye. The use of TMH values as a diagnostic tool for dry eye patients has been investigated previously (see Section 3.2), however different results have been reported from study to study. TMH is usually measured through direct observation, using a graticule eyepiece or pachometer in conjunction with a slit lamp, but some investigators used photography or videography (see Section 3.3.1). Since there is no standard method of measuring TMH, it is not surprising that different results have been reported by different investigators. The mean TMH reported for normal subjects ranged from 0.163 mm (Patel and Port 1991) to 0.46 mm (Mainstone et al. 1996). A number of investigators have reported or suggested
TMH of \( \leq 0.1 \) mm to be an appropriate cut-off value between normal and dry eye subjects (Lamberts \textit{et al.} 1979, Lamberts 1987, Port and Asaria 1990). It has been shown that HK-Chinese have less stable tears (Cho \textit{et al.} 1992, Cho and Brown 1993) and smaller tear volumes (Cho and Kwong 1996) compared with Caucasians, and there are no reports of TMH in Chinese eyes, normal or otherwise.

The aims of this study were to:

1. investigate the repeatability of TMH determination (of the lower lid) of normal and dry eye Chinese subjects using the TOPCON IMAGEnet system;

2. determine the specificity, sensitivity, the positive predictive value and the negative predictive value when TMH determination is used as a diagnostic tool for dry eye.

### 8.2 Subjects

Thirty-one Chinese were recruited from the General Eye and Low Vision Centre, operated by the Hong Kong Society for the Blind. The control group (Group 1) comprised 9 male and 11 female normal subjects of mean age 34.2 (SD 8.2) years. The test group (Group 2) comprised 11 dry eye female subjects of mean age 45.5 (SD 14.2) years. All subjects satisfied the criteria stated in Section 5.3. All normal subjects recruited were asymptomatic and were not taking any medication. All dry eye subjects satisfied the following criteria:

1. ocular symptoms, either foreign body sensation or dryness, when not using any eye drops (see Section 6.5),
2. presence of inferior corneal staining which involved more than 1/3 of the inferior cornea (see Section 2.6.1(i) and Figure 2.3),

3. no other ocular disease.

Before the commencement of the study, all subjects gave informed consent.

8.3 Procedure

The procedures for TMH measurement were as described in Section 5.2.3.

Two sets of images were taken with the illumination system offset at 20 deg and 30 deg from the observation system for each eye of Group 1 subjects. The TMH measurement was performed at 20 deg on the right eye first and then at 30 deg on the same eye. The same order of measurement was applied to the left eye. For Group 2 subjects, the images were only taken with the illumination system set at 20 deg off the observation system for each eye. Up to 4 images were taken for each eye at each angle setting. After taking the images, slit lamp examination was performed to check the corneal integrity. Any staining or abnormalities noted were recorded and the data excluded if our subject criteria were not satisfied. Corneal staining (with fluorescein) of the dry eye subjects was recorded. The staining criterion for our dry eyes was the inferior cornea with stained area greater than 1/3 of the whole cornea (see Section 2.6.1(i) and Figure 2.3). All subjects were required to return for another image capture session within one week of the first visit, at which time the same procedures were repeated. The temperature and humidity of the

* The capture of full images requires the observation system to be offset by at least 20 deg.
examination room were recorded each day when image captures were performed.

Calibration of the measuring scale of the TOPCON IMAGEnet system was performed before taking TM images and using the software. The author accessed the images taken to measure the TMH on a 15” computer monitor (see Figure 5.4) a few days later so that she was masked as to the ocular condition of the subjects. The clearest image from each eye was chosen for the measurement of TMH, and the average of 3 readings was recorded as the representative TMH (in mm) for that eye. After completion of TMH measurements for all the selected images, the author was considered experienced in the use of the IMAGEnet for measurement of TMH, and the TMH was measured again for each selected image and used for the following analysis. The first set of data was discarded.

**Treatment of data**

Distributions of the TMH values obtained were not significantly different from Normal (One Sample Kolmogorov-Smirnov D Tests, $p>0.05$). Therefore, Repeated Measures Analysis of Variance and t-test for independent samples, as appropriate, were used to test for differences between measurements. Statistical analysis was first performed to test for any significant difference between measurements. When no difference was found, repeatability of the data obtained was determined as follows: the 95% limits of agreement (mean difference±1.96SD) (Bland and Altman 1986) and the intraclass correlation coefficient (ICC) (Portney and Watkins 2000). In general, an ICC value above 0.75 indicates good reliability but, for most clinical measurements, to ensure
reasonable validity, it has been suggested that the ICC value should not be less than 0.9 (Portney and Watkins 2000).

Table 8.1. The mean TMH values for 11 dry eye and 20 normal subjects at different visits.

<table>
<thead>
<tr>
<th>Light Angle</th>
<th>Mean (SD) TMH (mm)</th>
<th>Mean (SD) TMH (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visit 1</td>
<td>Visit 2</td>
</tr>
<tr>
<td></td>
<td>RE</td>
<td>LE</td>
</tr>
<tr>
<td>20° (Dry)</td>
<td>0.17 (0.045)</td>
<td>0.15 (0.039)</td>
</tr>
<tr>
<td>20° (Normal)</td>
<td>0.24 (0.070)</td>
<td>0.24 (0.083)</td>
</tr>
<tr>
<td>30° (Normal)</td>
<td>0.26 (0.074)</td>
<td>0.25 (0.094)</td>
</tr>
</tbody>
</table>

**8.4 Results**

Table 8.1 shows a summary of the mean findings. The temperature and humidity of the examination room were consistent throughout the study. There were no significant differences between the mean TMH values measured using different light angles, between visits or between eyes for the normal subjects (Repeated measures ANOVA: $F=0.92$, $p>0.05$). For the dry eye subjects, there were no significant differences between visits or between eyes ($F=4.27$, $p>0.05$). Therefore, the following results relate to data from right eyes only. The mean TMH values for the dry eye subjects were significantly reduced compared to those of the normal subjects (t-tests for independent samples: $p<0.05$) at both visit 1 and visit 2. The TMH values measured with the TOPCON IMAGEnet System for the normal subjects at light angles 20 deg were only moderately repeatable for the normal and dry eye subjects, with ICC values of 0.70 and 0.76 respectively. The ICC for the normal subjects at light angle of 30 deg was 0.91. Figures 8.1 (a-c) show plots of the between-visit differences in TMH values against their means.
Figure 8.1. Between-visit differences in TMH values (right eye) as a function of their mean: (a) TMH at 20 deg for normal subjects (NR20) (b) TMH at 30 deg for normal subjects (NR30) (c) TMH at 20 deg for dry eye subjects (DR20).
The specificity and sensitivity of different values of TMH (0.01 steps), in the diagnosis of dry eyes are shown in Figure 8.2. At the cut-off value of 0.21 mm for visit 1, the specificity and sensitivity were optimal at 70.0% and 81.8% respectively. The predictive values of a positive test (PPV) and a negative test (NPV) at this cut-off value were found to be 60.0% and 87.5% respectively.

8.5 Discussion

Our result shows that, if we follow the guidelines given by Portney and Watkins (Portney and Watkins 2000), the repeatability values for of TMH values measured using the TOPCON IMAGEnet System at light angle of 20 deg for normal and dry eye subjects were only moderately good as the ICC values were 0.70 and 0.76 respectively. The repeatability was much better
with light angle of 30 deg — the ICC value was 0.91. To measure the TMH accurately, the light angle should be theoretically set normal to the TM but there is a limitation with the set up of the slit lamp with the TOPCON IMAGEnet System. The images were captured through the right eyepiece of the observation system. When the illumination system is set in the same direction as the observation system the image will be blocked by the illumination system. Before the commencement of the study, we tried a number of settings, 0, 5, 10, 15 and 20 deg off the observation system — and capture of a full image was possible only at light angles of 20 deg or more off the observation system. For Group 1, we decided to compare the TMH measurements at two different light angles 20 deg and 30 deg. We found that it was easier to observe the top line of the TMH with the light angle of 20 deg than of 30 deg. Although the variability of TMH values was less when a light angle of 30 deg was used, we thought the TMH was more accurately determined with the minimum deviation from normal incidence. Therefore, in view of our results, perhaps a study on the specificity and sensitivity of TMH assessment using light angle of 30 deg would be useful.

Figures 8.1(a-c) show the distributions of between-visit TMH differences against their means for the normal and dry eye subjects. The 95% limits of agreement for normal and dry eye subjects were −0.099 to +0.141 mm (see Figure 8.1a) and −0.062 to +0.082 mm respectively (see Figure 8.1c). Thus, the TMH of normal subjects measured a second time could be up to 0.099 mm less or 0.141 mm more than the first measurement, with a probability of 0.95. For our dry eye subjects, the TMH could be up to 0.062 mm less or 0.082 mm more than the first measurement. These variations, for both normal and dry eye
subjects, were nearly half of the TMH value for normal and dry eye subjects, and were in agreement with the ICC values, which, as mentioned before, were relatively low for both normal and dry eye subjects. In their study, where TMH values obtained on two separate visits were compared, Port and Asaria (1990) reported TMH differences of ±0.03 mm in 66 normal subjects. In the current study, the mean between-visit differences were ≤0.02 mm for both normal and dry eye subjects. However, our findings are limited by our relatively small sample size. Further investigation using larger sample size is required to confirm the findings of this study.

Lambert et al. (1979) found a mean (SD) TMH of 0.23 (0.09) mm on 86 normal eyes (n=43) and their value was close to our findings for normal subjects in the current study. Port and Asaria (1990) found a mean (SD) TMH of 0.18 (0.03) mm for their 66 normal subjects. When a cut-off value of ≤0.1 mm was used for the findings of these two studies, where subjects ranged from teenagers to the elderly, the specificity of TMH assessment was over 90% and the sensitivity was not reported. For the current study, if we used 0.1 mm as the cut-off value, the specificity would be 100% but the sensitivity would be 0%!

In an unpublished study, cited by Lamberts (1987), Lamberts reported that the TMH was 0.1 mm for 7 out of 9 dry eye subjects. In their study, Lim and Lee (1991) reported mean (SD) TMH values of 0.19 (0.05) and 0.10 (0.04) mm for their 21 normal and 21 dry eye subjects respectively. In a later study, Mainstone et al. (1996) found mean (SD) values for TMH of 0.46 (0.173) mm and 0.244 (0.089) mm for 15 normal and 15 dry eye subjects respectively (see Table 3.2). The differences in TMH between their normal and dry eye subjects were statistically significant. They reported that TMH assessment was a useful
diagnostic tool for aqueous deficient dry eye with a specificity of 66.7% and a sensitivity of 93.3% when a cut-off value of 0.35 mm was used. Mainstone et al. (1996) suggested that previously reported TMH values were smaller because they were underestimated, this being a reflection of the nature of the methods used by previous investigators for evaluating TMH. It is difficult to see the top of the meniscus using an optical pachometer, and high menisci might be missed in this situation. The precision of the graticule would also affect the measurements.

There are few other reports on TMH measurement, and there is little agreement in the normative values of TMH reported so far (see Table 3.2). Values for normal eyes ranged from 0.17 mm (Doughty et al. 2001) to 1.0 mm (Holly and Lemp 1977). The reasons for the lack of agreement between investigators may be the different methods used for measuring TMH. Slit lamp observation using an eyepiece graticule or a pachometry is a popular method (Jordan and Baum 1980, Port and Asaria 1990), however, Mainstone et al. (1996) suggested that when an eyepiece graticule is used, eye movements would lead to measurement errors, underestimating the TMH. In their study, Mainstone et al. (1996) measured the tear meniscus parameters using computer analysis of photographs of the lower tear meniscus lightly stained with fluorescein (see Section 3.3.1 (ii)). Lim and Lee (1991) measured TMH with a slit-lamp before and after instillation of fluorescein (see Section 3.3.1 (i)). They found that it was easier to measure TMH after fluorescein instillation but the TMH was higher than that before the instillation of fluorescein. They reported that TMH had returned to baseline after fluorescein instillation in 21 normal and 14 dry eyes within 4 minutes of fluorescein
instillation. Apart from the fact that the TMH of aqueous deficiency dry eye patient is scanty and a small amount of instilled fluorescein might affect the results greatly (Norn 1986), reflex tears induced by the flashlight of the camera when taking the photographs of the tear meniscus could also lead to an overestimation of TMH. In a recent study, Doughty et al. (2001) measured TMH by videography of 56 normal elderly subjects. The mean (SD) TMH was found to be 0.172 (0.047) mm. The vertical height of the magnified TM images was measured without the instillation of fluorescein. This seems to be another good method of TMH measurement, however further investigation of the repeatability and validity of this method of TMH measurement is needed.

In the current study, no fluorescein was added and the images were captured by the computer, so that eye movements and flashlight photography were avoided. The slit height of the illumination light source was set at 6 mm and the slit was always located across the lower eye lid without direct shining of light into the pupil of the eye, so that stimulation of reflex tearing, if any, was minimal.

The TMH is also subject to the influence of various other factors such as the blink rate, the length of the lower lid, the location of the punctum, lid-globe apposition, and the distance of the meibomian glands from the edge of the lid (Lamberts 1987). The palpebral aperture should perhaps also be considered when measuring the TMH (Doughty et al. 2001). The ocular condition of the eye may also affect the TMH measurement (see Section 3.3.2 (iii)). Chinese, in general, have smaller, less deep-set eyes, and tear volume has been reported to be lower in HK-Chinese when compared to findings reported for Caucasian subjects (Cho and Kwong 1996). These factors presumably would lead to a
reduced TMH in Chinese. It would be interesting to investigate the difference in normative TMH values between Chinese and Caucasians using the TOPCON IMAGEnet System.

From their study, Mainstone et al. (1996) concluded that TMH assessment is a useful test for the diagnosis of dry eyes. However, in the current study, the sensitivity of the TMH measurement was over 80% at a cut-off value 0.21 mm, but the repeatability was not good. The low ICC values also indicated that this test should perhaps be used with caution. In view of the small (but statistically significant) difference in the TMH between normal and dry eyes, we are not sure if TMH assessment through the eyepiece graticule of a slit lamp would be useful.

8.6 Conclusions

The repeatability of TMH determination (of the lower lid) of normal and dry eye Chinese subjects using the TOPCON IMAGEnet system is not good (ICC values: 0.70 and 0.76 respectively). The difference in TMH value between normal and dry eyes was found to be statistically significant. The specificity and sensitivity of TMH value as a diagnostic tool for dry eye were 70% and 82% respectively at a cut-off value 0.21 mm for Chinese, however the repeatability of measures is such that one measure could indicate normal and a repeated measure on the same eye could indicate dry eye. This however could be due to the small sample used in this study. The results need to be confirmed with a larger sample.
Paper published

Chapter 9

Performance of the Mc-Monnies Dry Eye Questionnaire, a Self-designed Dry Eye Questionnaire, and Cotton Thread Tests

9.1 Introduction

A single clinical test result has little significance in the diagnosis of dry eye (Taylor and Louis 1980) and a combination of clinical tests is necessary. Recent studies have shown that the tear volume and tear stability of HK-Chinese are significantly different from those of Caucasians (see Section 1.1) and the optimum cut-off values for the clinical diagnostic tests for dry eyes are therefore likely to be different for Chinese dry eye patients. We conducted a study (Chapter 7) to investigate the specificity and sensitivity of the SP-CTT and the PRT Test on normal and dry eye subjects, and poor specificities and sensitivities were found for both tests. As the dry eye subjects in the study were defined by different ophthalmologists using their own criteria, the results are somewhat equivocal. We used standardized criteria in recruiting the subjects for the study now described.

The Mc-DEQ was developed based on findings in Caucasian subjects, and its validity when applied to Chinese patients is uncertain as, to our knowledge, there is no report of the use of the Mc-DEQ on Chinese subjects/patients. A
SD-DEQC may be more appropriate for Chinese patients (see Section 5.2.4) and this will also be evaluated in this study. In addition, the Mc-DEQ was translated into Chinese (Mc-DEQC) for this study.

The main aim of the study reported in the current chapter was therefore to compare SP-CTT, PRT test and Mc-DEQC results between normal and dry eye subjects of Chinese origin, using a number of different sets of criteria for classifying normal and dry eyes. The specificity and sensitivity of each test were also determined, where appropriate. The other aims of this study were to compare results of the Mc-DEQC and the SD-DEQC from normal and dry eye Chinese subjects.

9.2 Subjects

All subjects satisfied the general criteria given in Section 5.3. One hundred and eighteen Chinese subjects (94 females and 24 males) were recruited from the General Eye and Low Vision Centre, operated by the Hong Kong Society for the Blind. The mean (SD) age of the subjects was 48.4 (10.7) years. Patients with a history of anterior segment surgery were excluded.

The TMH was used as one of the diagnostic criteria since we found a statistically significant difference in TMH (as measured in this study) between normal and dry eye subjects. We recognise, however, that at present the repeatability of TMH measures is not sufficiently good enough to distinguish clinically between normal and dry eyes. We therefore use TMH in an exploratory way.

The subjects were classified in two ways, as follows:
Figure 9.1. A summary of the grouping of subjects for this study.
Set 1 (less stringent criteria):

(a) Dry eye group 1D: subjects with no other ocular disease and who satisfied any two of the following criteria:

(i) presence of inferior corneal staining involving more than 1/3 of the cornea (see Section 2.6.1 (i) and Figure 2.3),

(ii) TMH ≤0.21 mm (see Section 8.6),

(iii) complaint of either dryness or foreign body sensation (see Section 6.5).

(b) Dry eye group 1TD: Group 1D subjects with TMH ≤0.21 mm (i.e. excluding subjects in group 1D who met criteria (i) and (iii) above only).

(c) Normal group 1N: subjects who did not satisfy the criteria set for Group 1D. Such subjects could have met (iii) above, and so only those who were not using any eyedrops were recruited.

Set 2 (more stringent criteria for both normal and dry eye subjects):

(a) Dry eye group 2D: subjects with no other ocular disease and who satisfied any two of the following criteria:

(i) presence of inferior corneal staining involving more than 1/3 of the cornea (see Section 2.6.1 (i) and Figure 2.3),

(ii) TMH ≤0.19 mm (see Section 9.5.1),

(iii) complaint of either dryness or foreign body sensation (see Section 6.5).

(b) Dry eye group 2TD: Group 2D subjects with TMH ≤0.19 mm (i.e. excluding subjects in group 2D who met criteria (i) and (iii) above only).
(c) Normal group 2N: Group 1N who had no symptoms of either foreign body sensation or dryness and no corneal staining.

Table 9.1. A summary of gender distribution and mean age of different groups of subjects.

<table>
<thead>
<tr>
<th>Subject Groups</th>
<th>Female</th>
<th>Male</th>
<th>Mean Age (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1D</td>
<td>40</td>
<td>8</td>
<td>46.8 (11.6)</td>
</tr>
<tr>
<td>Group 1TD</td>
<td>35</td>
<td>7</td>
<td>47.6 (11.8)</td>
</tr>
<tr>
<td>Group 1N</td>
<td>34</td>
<td>10</td>
<td>48.7 (10.3)</td>
</tr>
<tr>
<td>Group 2D</td>
<td>25</td>
<td>5</td>
<td>47.0 (13.2)</td>
</tr>
<tr>
<td>Group 2TD</td>
<td>17</td>
<td>4</td>
<td>49.2 (14.5)</td>
</tr>
<tr>
<td>Group 2N</td>
<td>9</td>
<td>7</td>
<td>48.2 (11.2)</td>
</tr>
</tbody>
</table>

Figure 9.1 summarises the grouping of subjects recruited for this study. A summary of the gender distribution and mean age of different groups of subjects is showed in Table 9.1.

9.3 Procedure

All subjects were asked to complete a Mc-DEQC and a SD-DEQC under supervision. The procedures for the completion of DEQ were as described in Section 5.2.4. After filling in the first DEQ (either the Mc-DEQC or the SD-DEQ), the TMH of each eye was measured by an assistant. One set of images was taken with the illumination system of the slit lamp set at angle 20 deg off the observation system for each eye using the procedures described in Section 5.2.3. After measuring the TMH, two thread tests were performed on all subjects by the author. One eye was tested with the SP-CTT and the other eye
was tested with the PRT Test, one after the other. We used the ‘random’ function of the spreadsheet to assign the eye and test order. The procedures for the thread tests were as described in Sections 5.2.1 and 5.2.2. After the thread tests, the subject was asked to fill in the other DEQ and was supervised by the author. The scoring systems were as described in Section 5.2.4.

A slit lamp examination was then performed to check the corneal integrity, the procedure being as described in Section 5.2.5. The temperature and humidity of the examination room were recorded each day before testing commenced.

The author accessed the images a few days later and measured the TMH of each subject (see Section 5.2.3).

![Graph showing data for SP-CTT and PRT for Sets 1 and 2.](image)

**Figure 9.2.** Mean SP-CTT and PRT values for Sets 1 and 2. (Each error bar shows 1 SD from the mean value)

(Groups 1D, 1TD, 1N – classified using less stringent sets of criteria, Groups 2D, 2TD, 2N – classified using more stringent sets of criteria)

### 9.4 Results

The temperature and humidity of the examination room were consistent throughout the study. The subjects were classified into the two sets defined
earlier. No significant difference was found in the mean age between the dry eye and normal groups (t-tests for independent samples: p>0.4).

9.4.1 Evaluation of the tests used

9.4.1 (i) SP-CTT and the PRT Test

Figure 9.2 shows the mean SP-CTT and PRT values obtained for all groups of subjects. There were no statistically significant differences in the mean SP-CTT or PRT values between the dry eye groups and the normal groups (Groups 1D vs 1N, Groups 1TD vs 1N, Groups 2D vs 2N and Groups 2TD 2N) (t-tests for independent samples: p>0.09).

Table 9.2. Median and range of Mc-DEQC, SD-DEQC (using the McMonnies’ scoring system) and SD-DEQC (NS - scores using the new scoring system) for Groups 1D, 1N, 2D and 2N.

<table>
<thead>
<tr>
<th>Test</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mc-DEQC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1D</td>
<td>18</td>
<td>2 – 34</td>
</tr>
<tr>
<td>Group 1N</td>
<td>14</td>
<td>4 – 35</td>
</tr>
<tr>
<td>Group 2D</td>
<td>18</td>
<td>2 – 34</td>
</tr>
<tr>
<td>Group 2N</td>
<td>11</td>
<td>4 – 24</td>
</tr>
<tr>
<td><strong>SD-DEQC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1D</td>
<td>12.5</td>
<td>3 – 56</td>
</tr>
<tr>
<td>Group 1N</td>
<td>9.5</td>
<td>0 – 42</td>
</tr>
<tr>
<td>Group 2D</td>
<td>12.5</td>
<td>3 – 56</td>
</tr>
<tr>
<td>Group 2N</td>
<td>4.5</td>
<td>0 – 29</td>
</tr>
<tr>
<td><strong>SD-DEQC (NS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1D</td>
<td>9</td>
<td>3 – 28</td>
</tr>
<tr>
<td>Group 1N</td>
<td>8.5</td>
<td>0 – 21</td>
</tr>
<tr>
<td>Group 2D</td>
<td>9</td>
<td>3 – 28</td>
</tr>
<tr>
<td>Group 2N</td>
<td>4</td>
<td>0 – 18</td>
</tr>
</tbody>
</table>

(Groups 1D, 1N – classified using less stringent sets of criteria, Groups 2D, 2N – classified using more stringent sets of criteria)
9.4.1 (ii) Mc-DEQC and SD-DEQC

The responses to the Mc-DEQC and the SD-DEQC were analysed by applying McMonnies’ scoring system and discriminant analysis. The total score and the discriminant score indicated the likelihood or degree of dry eye. The responses to each question were analysed using the chi-square test.

Table 9.2 shows the median and range of the Mc-DEQC scores and SD-DEQC scores (using the McMonnies’ scoring system and a new scoring system (see Section 9.5.3)) obtained for all groups of subjects. No statistically significant differences were found in the Mc-DEQC or the SD-DEQC scores using the same scoring system between Groups in Set 1 (Groups 1D vs 1N, Groups 1TD vs 1N) (Mann-Whitney test, p>0.3). However, the scores of both the Mc-DEQC and the SD-DEQC using the same scoring system for dry eye groups in Set 2 were found to be significantly higher from normal group in Set 2 (Groups 2D vs 2N, Groups 2TD vs 2N) (Mann-Whitney test, p<0.02).

Table 9.3. The specificities and sensitivities of the Mc-DEQC and the SD-DEQC in discriminating normal and dry eye subjects from different groups of subjects using discriminant analysis.

<table>
<thead>
<tr>
<th>Tests for Sets 1 and 2</th>
<th>Specificities</th>
<th>Sensitivities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Mc-DEQC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>56.8%</td>
<td>81.3%</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>100%</td>
<td>86.7%</td>
</tr>
<tr>
<td><strong>2. SD-DEQC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>65.9%</td>
<td>81.3%</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>100%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>

(Groups 1D, 1N – classified using less stringent sets of criteria, Groups 2D, 2N – classified using more stringent sets of criteria)
When the new scoring system (Appendix IIIa) was used, SD-DEQC could only discriminate between the normal and dry eye subjects in Set 2 (Groups 2D vs 2N, Groups 2TD vs 2N) (Mann-Whitney test, p<0.01).

Table 9.3 shows the specificities and sensitivities of the Mc-DEQC and the SD-DEQC in discriminating normal and dry eye subjects from different groups of subjects using discriminant analysis.

### 9.4.2 The change in optimum cut-off values when more stringent criteria for dry eye and normal groups were used

![Graph](image)

*Figure 9.3. Specificities and sensitivities of the SP-CTT for the diagnosis of dry eye, at different cut-off values for (a) Groups 1D and 1N, (b) Groups 2D and 2N.*

There was no statistically significant difference in the frequencies of answers between Groups 1D and 1N for any of the questions in the Mc-DEQC or in the SD-DEQC, except the question concerned with symptom of dryness (chi-square test, p<0.05). For Mc-DEQC, the frequencies of answers for the three questions concerning symptoms of dryness, grittiness and irritation upon
waking were found to be significantly different between Groups 2D and 2N (chi-square test, \( p \leq 0.007 \)). For SD-DEQC, only frequencies of answers of the questions concerning symptoms of dryness and grittiness were found to be significantly different between Groups 2D and 2N (chi-square test, \( p \leq 0.002 \)).

![Graphs showing sensitivity and specificity](image)

**Figure 9.4.** Specificities and sensitivities of the PRT for the diagnosis of dry eye, at different cut-off values for (a) Groups 1D and 1N, (b) Groups 2D and 2N.

<table>
<thead>
<tr>
<th>Tests for</th>
<th>Cut-off Values</th>
<th>Optimal Specificities (%)</th>
<th>Optimal Sensitivities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sets 1 and 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. SP-CTT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>5.5</td>
<td>52.3</td>
<td>54.2</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>4.5</td>
<td>62.5</td>
<td>56.7</td>
</tr>
<tr>
<td>2. PRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>12</td>
<td>54.5</td>
<td>60.4</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>10.5</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>3. Mc-DEQC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>16</td>
<td>59.1</td>
<td>58.3</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>13</td>
<td>68.8</td>
<td>76.7</td>
</tr>
<tr>
<td>4. SD-DEQC*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Set 1 (Groups 1D vs 1N)</td>
<td>9</td>
<td>50</td>
<td>56.3</td>
</tr>
<tr>
<td>Set 2 (Groups 2D vs 2N)</td>
<td>7</td>
<td>62.5</td>
<td>73.3</td>
</tr>
</tbody>
</table>

* using new scoring system

(Table 9.4. Optimal specificities and sensitivities of the SP-CTT, the PRT Test, the Mc-DEQC and the SD-DEQC (i) for Groups 1D and 1N and (ii) for Groups 2D and 2N.)

(Groups 1N, 1D – classified using less stringent sets of criteria, Groups 2N, 2D – classified using more stringent sets of criteria)
Although the SP-CTT, the PRT Test and MC-DEQC results were not able to discriminate between Groups 1D & 1TD and Group 1N statistically, we still determined the optimal specificities and sensitivities of SP-CTT and the PRT Test by using different cut-off values (0.5 steps) to compare the change in the cut-off values when more stringent subject criteria were used. The optimal specificities and sensitivities for the SP-CTT and the PRT Test obtained from Groups 1D and 1N, and from Groups 2D and 2N (see Figure 9.3 and Figure 9.4) are shown in Table 9.4.

![Graphs showing specificities and sensitivities](image)

**Figure 9.5.** Specificities and sensitivities of the Mc-DEQC at different cut-off values for (a) Groups 1D and 1N, (b) Groups 2D and 2N.

The specificities and sensitivities of the Mc-DEQC were determined by using different cut-off values (1.0 steps) to determine the cut-off value that would give the best specificity and sensitivity in diagnosing dry eye from Group 1D and 1N, and Groups 2D and 2N (see Figure 9.5). The optimal specificity and sensitivity for the Mc-DEQC obtained from Groups 1D and 1N, and Groups 2D and 2N are shown in Table 9.4.
Figure 9.6. Specificities and sensitivities of the SD-DEQC (new scoring system) at different cut-off values for (a) Groups 1D and 1N, (b) Groups 2D and 2N.

Using a new scoring system, the specificities and sensitivities of the SD-DEQC were determined by using different cut-off values (1.0 steps) to determine the cut-off value that would give the best specificity and sensitivity in diagnosing dry eye from Groups 1D and 1N, and Groups 2D and 2N. The optimal specificity and sensitivity for SD-DEQC obtained from Groups 1D and 1N, and Groups 2D and 2N (see Figure 9.6) are shown in Table 9.4. When more stringent subject criteria were used, the cut-off values of each test were reduced (see Table 9.4). The SP-CTT and the PRT Test showed poor specificity and sensitivity, but for the Mc-DEQC and SD-DEQC (using new scoring system), the specificity and sensitivity were improved from poor to moderate.
9.4.3 Correlation of the TMH and CTT results

There was no statistically significant correlation between the SP-CTT values and the TMH (Pearson’s $r = 0.002$, $p = 0.983$), or between the PRT values and the TMH (Pearson $r = 0.179$, $p = 0.052$).

9.5 Discussion

9.5.1 Classification of Subjects

Dry eye is a symptomatic condition (Whitcher 1987). Subjective and clinical findings in dry eye patients are poorly correlated and the reason for this is unclear (Lemp 1995). Under different diagnostic criteria, different values of prevalence of dry eye were obtained (see Section 2.4). In this study, we classify the dry eye subjects as having any two of the following: corneal staining, ocular symptoms (dryness or foreign body sensation) or low TMH. The specificity and sensitivity of TMH for the diagnosis of dry eye in Chinese population were 70% and 81.8% respectively at a TMH cut-off value 0.21 mm (see Section 8.4) and we used 0.21 mm as the cut-off value of TMH in this study. Absence or diminution of the TMH is the most helpful clinical sign in tear deficient dry eye (see Section 2.5.2). The smaller the cut-off value of TMH the higher the percentage of tear deficient dry eyes. However, as mentioned before, the TMH as measured in this study, was not sufficiently repeatable, although it was able to distinguish between normal and dry eye subjects.
Table 9.5. The number of dry eye subjects from Group 1D at different cut-off values of TMH.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>&gt;0.21 mm</th>
<th>≤0.21 mm</th>
<th>≤0.20 mm</th>
<th>≤0.19 mm</th>
<th>≤0.18 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of dry eye subjects in Group 1D</td>
<td>6</td>
<td>42</td>
<td>26</td>
<td>21</td>
<td>14</td>
</tr>
</tbody>
</table>

There were 42 subjects in Group 1TD having TMH ≤0.21 mm. The optimum cut-off TMH value for the diagnosis of tear deficient dry eye was determined by using different TMH values (0.1 steps) (see Table 9.5). The number of dry eye subjects dropped from 21 (50% of 42) to 14 (30% of 42) when the cut-off value of TMH decreased from 0.19 mm to 0.18 mm. We chose 0.19 mm as the cut-off value of TMH for Group 2 which contained at least 50% of the original dry eye subjects. Therefore, the number of subjects in the dry eye groups 1D, 1TD, 2D, 2TD were 48, 42, 30 and 21, respectively, and those in the normal Groups 1N and 2N were 44 and 16 respectively. The subjects in Groups 1TD and 2TD who were classified as having tear deficient dry eye formed the majority of the dry eye subjects, agreeing with the findings of Lemp (1995) (see Section 2.3.1 (i)).

In Chapter 6, the prevalence of dry eye was found to be reduced when more stringent diagnostic criteria were used. As expected, the number of dry eye subjects in this study was reduced as we used more stringent criteria to define the dry eye.
9.5.2 Evaluation of CTT

Cho and her co-worker studied the SP-CTT and PRT Test on HK-Chinese (see Section 3.1). The majority of their subjects were <45 years old. The wetted length of the SP-CTT and PRT Test decreased with age (see Section 3.1.1(iv)). Since our subjects were mostly >45 years old, as expected, our mean SP-CTT and mean PRT values were less than the values reported in previous studies on Chinese subjects (Cho and Douthwaite 1994, Cho et al. 1996, Cho and Kwong 1996, Chui et al. 2000).

Since the SP-CTT and the PRT Test are supposed to be measuring the tear volume, the type of dry eye subjects we really needed to recruit would be those who are tear deficient. These tests should have better performance on tear deficient dry eye than on evaporative dry eye, with probably poor specificity and sensitivity for evaporative dry eye subjects. As TMH has been claimed to be related to tear volume, we recruited tear deficient dry eye by using smaller TMH (i.e. from 0.21 mm to 0.19 mm) as a criterion. However, our results showed that neither the SP-CTT nor the PRT Test could discriminate between normal and dry eye subjects. The specificities and sensitivities of SP-CTT and the PRT Test did not improve even when more stringent subject criteria (i.e. TMH ≤0.19 mm) were used. Therefore, we concluded that the SP-CTT and the PRT Test are not good diagnostic tests for Chinese dry eye.

Our results also showed that the wet length of SP-CTT and the PRT Test were not correlated with the TMH. This result was in agreement with the findings of Tomlinson et al. (2001).
9.5.3 Evaluation of the Mc-DEQC and the SD-DEQC

In the McMonnies’ scoring system, the scores representing the frequency of each ocular symptom (question 2) were 4 (often) or 8 (constant) (see Appendix IIa). As the ocular symptoms for dry eye may also be common in other eye diseases, such weighting in the Mc-DEQ may yield poor specificity in screening dry eye subjects. Therefore, a new scoring system for the SD-DEQ was designed (see Appendix IIIa). For each question, the range of the score for each answer was from 0 (none) to 3 (daily/constantly).

Our results showed that most of the responses of the questions could not discriminate between the dry eye and the normal subjects. This may be because of variations in the diagnostic criteria used by the ophthalmologist. It would be worthwhile to repeat this work using standardized diagnostic criteria. Some medications, such as antihistamines, antidepressants, oral contraceptives and antispasmodics can cause dry eye (Terry 2001). Lacrimal gland secretion may also decrease due to the intake of systemic medications such as antihistamines, antihypertensives, antiparkinsonian agents, antitussives, belladonna alkaloids and psychotropics (Nelson 1994). However, over 83% of our subjects did not use any medications. Hence, the question concerning the use of these medications was probably not applicable to Chinese.

Over 80% of all responses for the questions concerning circumstances that provoke secondary symptoms were “not applicable” or “no”. That means these questions were not useful to discriminate dry eye from normal subjects.

A properly functioning blink keeps the anterior surface of the epithelium moist to maintain a clear and healthy cornea. Abelson and Holly (1977), using video recording, observed the different types of blinking in normal Caucasian
subjects – the percentage of different types of blinks were complete – 80.4%, incomplete – 17.3%, and twitch – 2.4%. A previous report (Sindt 1999) suggested that incomplete blinking was a cause of dry eye. However, in the current study, over 50% of both Group 1D and Group 1N subjects had incomplete blinks, when assessed behind the slit lamp (with the illumination system on). It is unclear if the different blinking pattern noted in the current study, compared to the report of Abelson and Holly, was due to racial differences or due to different methods used in determining the blinking patterns. Therefore, incomplete blinking did not seem to be a clinical sign for Chinese dry eye.

Dryness or foreign body sensation (grittiness) was selected as one of the criteria for our dry eye subjects. This may explain why only the frequencies of the responses to the questions concerning ocular symptoms of dryness and grittiness were found to be significantly different between the dry eye groups and normal groups. As other questions could not discriminate the dry eye subjects, neither the Mc-DEQC nor the SD-DEQC seems to be an effective screening tool for Chinese dry eye. This might be due to the scoring system used. As mentioned before, in the McMonnies’ scoring system, the scores representing the frequency of the ocular symptoms were 4 (often) or 8 (constant) (see Appendix IIa). As subjects in Group 2N were recruited only if they had neither dryness nor foreign body sensation, the scores of subjects in Group 2N would be expected to be significantly low when compared to those of subjects in Groups 2D and 2TD (see Section 9.4.1(ii)). Hence, a significant difference in the score of Mc-DEQC and SD-DEQC in Set 2 was expected. The weighting for the ocular symptoms in Mc-DEQC was relatively high. As
the ocular symptoms for dry eye are common in other eye diseases, such weighing in Mc-DEQC might yield poor specificity and sensitivity in screening dry eye subjects. SD-DEQC could not discriminate the normal and dry eye using both McMonnies’ scoring system and the new scoring system. With more stringent criteria, the specificities and sensitivities of both Mc-DEQC and SD-DEQC improved somewhat. When we used discriminant analysis to classify our subjects, poor specificities but high sensitivities were obtained with the Mc-DEQC and the SD-DEQC from subjects in Set 1. These results were not in agreement with the findings of Mc-Monnies and Ho (1987) who reported high specificity and high sensitivity. Since we found some questions in the Mc-DEQC not applicable to our Chinese subjects, it is possible that there may be a racial difference. However, high specificities and sensitivities were obtained with the Mc-DEQC and SD-DEQC with subjects in Set 2. As subjects in Group 2N had fewer symptoms than subjects in Group 1N, this could explain why high specificities in the Mc-DEQC and SD-DEQC were obtained from these subjects. The high sensitivities obtained when using discriminant scores instead of the total scoring system indicated that the former is a better method for analysing the results of the Mc-DEQC and SD-DEQC, however, poor specificities indicated that both DEQs were poor screening tests for dry eye. Neither Mc-DEQC nor SD-DEQC could effectively discriminate between the normal and dry eye subjects. The main reason for the poor performance of the DEQ was that the normal subjects also had similar ocular symptoms as the dry eye subjects. Golding and Brennan (1988) pointed out that the Mc-DEQ had not been tested on patients with other ocular disease such as bacterial, viral or allergic
conjunctivitis. The reported symptoms from these patients might mimic those with dry eye subjects. Hence, the validity of diagnosis of dry eye based on results from the Mc-DEQ may be queried (Golding and Brennan 1988). We therefore suggest trying the Mc-DEQC on patients with other ocular disease to confirm its validity as a diagnostic tool for dry eye.

In the current study, when subjects were classified using less stringent diagnostic criteria, the optimum cut-off score of the Mc-DEQC was found to be 16, but the specificity and sensitivity were poor. The cut-off score was reduced to 13 when the subjects were classified under more stringent criteria, and moderate specificity and sensitivity were found at 68.8% and 76.7% respectively. Our results did not agree with the findings for Caucasians subjects reported by Golding and Brennan (1993) who found high specificity (87%) and sensitivity (87%) of MC-DEQ using a cut-off score of 14. This may be due to different diagnostic criteria used to define dry eye between our study and theirs, or may be due to racial differences.

When we used the new scoring system, the cut-off score for the SD-DEQC in Groups 1D and 1N was found to be 9 with optimal specificity and sensitivity of 50.0% and 56.3% respectively. The cut-off score of the SD-DEQC for Groups 2D and 2N was reduced to 7 with high optimal specificity and sensitivity of 62.5% and 73.3% respectively. Therefore, the SD-DEQC with new scoring system seemed not to be a better screening tool than the Mc-DEQC.
9.6 Conclusions

The SP-CTT and the PRT Test are not good diagnostic/screening tests for Chinese dry eye. Results from these tests did not correlate well with the tear volume, as measured with the TMH, and so these do not appear to be tear volume tests. Discriminant analysis is a better method than the scoring system to analyse the results of the Mc-DEQC and the SD-DEQC, but as they are and on their own, the Mc-DEQC and SD-DEQC are poor screening tests for Chinese dry eye.
Chapter 10

Conclusions

10.1 Summary of current study

*What is the prevalence of dry eye in an eye clinic population in HK?*

The prevalence of Chinese dry eye was determined by a retrospective survey of patient files (dry season 741 subjects, humid season 857 subjects) from a private eye centre in HK. The prevalence of dry eye was about 3% and was not affected by mean humidity within the range of 60% to 72%.

*What is the best model to predict whether a patient with particular symptoms has dry eye?*

In agreement with findings from Caucasian eyes, foreign body sensation was the most common ocular symptom, and dryness was also commonly reported. Based on ten ocular symptoms, the following equations were derived to predict dry eye cases in the dry and the humid seasons. The discriminant score (S) indicates the likelihood or the degree of dryness when it is greater than a specified value.

(i) Dry Season

\[
S = 4.082(\text{dryness}) + 0.56(\text{itchy}) + 0.471(\text{tearing}) + 1.316(\text{foreign body sensation}) + 0.359(\text{red}) + 1.828(\text{pain}) - 0.141(\text{discharge}) + 0.284(\text{ocular fatigue}) - 0.321(\text{photophobia}) - 1.81(\text{burning}) - 0.501
\]
(ii) Humid Season

\[ S = 4.524(\text{dryness}) + 0.176(\text{itchy}) + 0.47(\text{tearing}) + 0.942(\text{foreign body sensation}) - 0.851(\text{red}) + 1.586(\text{pain}) - 0.094(\text{discharge}) + 0.366(\text{ocular fatigue}) - 1.353(\text{photophobia}) + 0(\text{Burning}) - 0.365 \]

*What are the specificity and sensitivity of the above models for classification of normal and dry cases?*

High specificities (>83%) but poor sensitivities (<65%) were obtained from both equations. The specificities and sensitivities of the predictive equations were 83.8% and 64% respectively in the dry season and 92.2% and 57.7% in the humid season. The poor sensitivity was influenced by the relatively small number of dry eye subjects (n=25).

*How effective are the SP-CTT, the PRT test and the Mc-DEQ in discriminating between the normal and dry eye?*

The SP-CTT initially appeared to be a better diagnostic tool than the PRT Test for diagnosing dry eye, although our results may have been affected by the choice of cut-off values, the diagnostic criteria used or the way in which we recruited our subjects. Using more stringent diagnostic criteria, however, we found that neither the SP-CTT nor the PRT Test was able to discriminate between normal and dry eye subjects. We found no statistically significant relationship between the results of the SP-CTT and the TMH, or between the findings of the PRT Test and the TMH.

Our results showed that most responses to the questions in the Mc-DEQC could not discriminate between normal and dry eye subjects. The total scores of the Mc-DEQC were not able to discriminate between normal and dry eye
but the discriminant scores seemed to be a better method in analysing the results.

*What are the specificities and sensitivities of the above tests in the diagnosis of dry eye?*

The SP-CTT, the PRT Test and the Mc-DEQC were unable to discriminate between normal and dry eye subjects and had poor specificities and sensitivities.

*How are the specificities and sensitivities of the above tests affected by the criteria used to define dry eye?*

When more stringent diagnostic criteria were applied, the specificities and sensitivities of the SP-CTT and the PRT Test did not improve, however the specificity and sensitivity of the Mc-DEQC did somewhat.

*How repeatable is TMH determination, using the TOPCON IMAGEnet system, in normal and dry eye subjects?*

The TMH of 20 normal and 11 dry eye patients (subjects with fluorescein corneal staining plus symptoms of either foreign body sensation or dryness) were measured using the Topcon IMAGEnet system on two occasions. The 95% limits of agreement of between-visit TMH differences for normal and dry eye subjects were $-0.099$ to $+0.141$ mm and $-0.062$ to $+0.082$ mm respectively.
What is the average TMH value in normal and dry eye subjects?

The mean (SD) TMH values for normal and dry eye subjects were 0.24 (0.045) and 0.17 (0.07) mm respectively. The sensitivity of the TMH as a diagnostic tool for dry eye was found to be over 80% at a cut-off value 0.21 mm, however the repeatability of measures is such that one measure could indicate normal and a repeated measure on the same eye could indicate dry eye.

How effective is the self-designed DEQ for the diagnosis of dry eye?

The SD-DEQC did not seem to be a better screening test for Chinese dry eye than the Mc-DEQC. The SD-DEQC using a new scoring system (similar results as the Mc-DEQC) had poor specificity and sensitivity when we used less stringent diagnostic criteria. When more stringent criteria were used, both the specificity and sensitivity of the SD-DEQC were improved somewhat.

10.2 Implication of the results

The prevalence of dry eye in the private eye clinic was about 3%. The predictive equations developed show potential for the diagnosis of dry eye, however, further studies are required to confirm the coefficients in the equations using a larger number of dry eye cases.

The SP-CTT and the PRT Test were unable to discriminate between normal and dry eyes, even when more stringent diagnostic criteria were applied. Results from these tests are not related to tear volume.

TMH measurement using a photo-slit lamp in conjunction with the IMAGEnet System was not sufficiently repeatable, however, it is a potentially useful test.
for the diagnosis of dry eye as it is the only test that we used which can
discriminate between normal and dry eye.

Based on the scoring system, neither the Mc-DEQC nor the SD-DEQC is a
good screening tool for Chinese dry eye, however the discriminant analysis
may be a better method than the scoring system to analyse their results
Clinically, in the absence of better tests, we therefore recommend use of the
fluorescein inferior corneal staining and the presence of ocular symptoms for
the diagnosis of dry eye. Local clinicians should agree and adopt uniform
diagnostic criteria for dry eye.

The tests described here are in common use around the world and used
universally for dry eye assessment. Our work indicates that the value of these
tests is extremely limited in a Chinese population.

10.3 Further investigations

Before the confirmation of the two dry eye predictive equations, further studies
are required to recalculate the coefficients of the equations from a larger
number of dry eye cases using force-choice questions and consistent history-
taking technique.

The repeatability of TMH measurements using the IMAGEnet System needs to
be confirmed with larger samples. There is also a need to evaluate and
compare results from other clinical methods of measuring TMH (e.g. using the
slit lamp with an eyepiece graticule).
The Mc-DEQ includes questions concerning primary ocular symptoms, secondary symptoms, previous dry eye treatment and medications that may evoke dry eye conditions. Previous studies have reported that the Mc-DEQ was a good screening test for dry eye. However, this questionnaire has not been used for patients having other ocular diseases with dry eye symptoms. As they are and on their own, both the Mc-DEQC and the SD-DEQC were poor screening tool for Chinese dry eye. Modified versions of the DEQ with special method of data analysis may be useful when used in conjunction with other tests, but this requires further investigation. The diagnosis of dry eye is complicated due to poor or lack of correlation between symptoms and results of clinical tests. Proper diagnosis is necessary for appropriate treatment. The world’s population, in general, is growing older and it is envisaged that there will be more and more patients complaining of dry eye problems. Therefore, further investigation on dry eye assessments is necessary.
References


47. Golding, T.R. and Brennan, N.A. “Diagnostic accuracy and inter-
34, pp.823 (1993)

test as a replacement for the Schirmer test”. Clin Exp Optom, Vol. 76,
pp.182 (1993)

49. Greiner, J., Finnemore, V., Exford, J., Herman, J., Glonek, T., Bueno, E.
and Korb, D. “Effects of fluorescein instillation methods on the tear film

50. Guillon, J. and Guillon, M. “Tear film examination of the contact lens

51. Hamano, H., Hori, M., Hamano, T., Mistunaga, S., Maeshima, J.,
Kojima, S., Kawabe, H. and Hamano, T. “A new method for measuring

52. Hamano, T., Mitsunaga, S., Kotani, S., Hamano, T., Hamano, K.,
Hamano, H., Sakamoto, R. and Tamura, H. “Tear volume in relation to

212, 5559 pp.16 (1996)

54. Henderson, J. “Keratoconjunctivitis sicca. A review with a survey of

55. Henderson, J.W. and Prough, W.A. “Influence of age and sex on flow of


120. Sargent, C., Ludlow, M., McCredie, M., Brooks, P. and Webb, J.


122. Schein, O., Munoz, B., Tielsch, J., Bandeen-Roche, K. and West, S.

123. Schein, O., Munoz, B., Tielsch, J., Bandeen-Roche, K. and West, S.

124. Schein, O., Tielsch, J., Munoz, B., Bandeen-Roche, K. and West, S.


126. Schiffman, R., Christianson, M., Jacobsen, G., Hirsch, J. and Reis, B.


Appendices

Appendix I

Dry Eye Questionnaire by Anderson et al. (1972) and their scoring system.

DEQ:

Place [Y] = Yes or [N] = No in each box

Symptoms:

1. Foreign body sensation [   ]
2. Burning [   ]
3. Tireness with or without difficulty in opening the eyes [   ]
4. Dry feeling with or without a poor response to physical or chemical irritants and emotions [   ]
5. Redness [   ]
6. Difficulty in seeing [   ]
7. Itchiness [   ]
8. Aches [   ]
9. Soreness or pain [   ]
10. Photosensitivity and excess of secretion which may appear to be watery, ropey, or as a film over the eye [   ]

Scoring Equation:

\[ S = 4.7 - 5.2x_1 - 3.0x_2 - 1.3x_3 - 5.4x_4 - 4.0x_5 + 1.1x_6 + 0.8x_7 - 1.9x_8 + 2.1x_9 - 2.0x_{10} \]

(where \( x_1 \) to \( x_{10} \) are the above numbered questions and \( x_i = 1 \) for a “yes” response and \( x_i = 0 \) for a “no” response)

A final score of \( S \) less than \(-2\) indicates KCS.
Appendix IIa

Dry Eye Questionnaire by Mc-Monnies (1986) and the Scoring System by Mc-Monnies and Ho (1986)

D/E Survey: Please answer the following by underlining the response most appropriate to you: Female Male

Age:
- Under 25 Years
- 25-45 Years
- Over 45 Years

F0 M0
F3 M1
F6 M2

Currently Wearing:

No Contact Lenses, Hard Contact Lenses, Soft Contact Lenses

1. Do you ever experience any of the following eye symptoms? (Please underline those that apply to you:)

Soreness Scratchiness Dryness Grittiness Burning

2. How often do your eyes have these symptoms? (Underline)

never 0 sometimes 1
often 4 constantly 8

3. Have you ever had drops prescribed or other treatment for dry eyes?

yes 6 no 0 uncertain 0

4. Do you suffer from arthritis?

yes 2 no 0 uncertain 0

5. Do you suffer from thyroid abnormality?

yes 2 no 0 uncertain 0

6. Do you experience dryness of the nose, mouth, throat, chest or vagina?

never 0 sometimes 1
often 2 constantly 4
7. Do you regard your eyes as being unusually sensitive to cigarette smoke, smog, air conditioning, central heating?

   yes 4  no 0  sometimes 2

8. Do your eyes easily become very red and irritated when swimming in chlorinated fresh water?

   not applicable 0  no 0  
   sometimes 1  yes 2

9. Do you take (please underline) antihistamine tablets or use antihistamine eyedrops, diuretics (fluid tablets), sleeping tablets, tranquilizers, oral contraceptives, medication for duodenal ulcer or digestive problems or for high blood pressure? or ___________________________ (write)

   none 0
   antihistamine/diuretics 2
   sleeping tablets/tranquilizers/oral contraceptives/
   duodenal ulcer/digestive/high blood pressure 1

10. Are your eyes dry and irritated the day after drinking alcohol?

    not applicable 0  no 0
    sometimes 2  yes 4

11. Are you known to sleep with your eyes partly open?

    not applicable 0  no 0
    sometimes 1  yes 2

12. Do you have eye irritation as you wake from sleep?

    yes 2  no 0  sometimes 1
乾眼的問卷：請圈出以下最貼切的答案。

性別：
a. 男 b. 女

年紀：
a. 25 歲以下 b. 25-45 歲 c. 45 歲以上

1. 閣下是否配戴眼鏡使用者？
a. 是（請圈出：硬鏡／軟鏡） b. 否

2. 閣下是否曾經因爲眼乾而使用藥物或接受其它治療？
a. 是 b. 否 c. 不肯定

3. 閣下曾否感受以下任何眼部不適（請圈出適合的感覺）？
a. 眼睛疼痛 b. 搞癢感 c. 乾燥感 d. 砂礫感 e. 灼熱感

4. 閣下的眼睛是否經常有以上症狀？
a. 從來沒有 b. 間歇性 c. 時常 d. 一定有

5. 閣下是否認爲自己的眼睛對於二手煙、霧霾、空氣調節、中央暖氣等非常敏感？
a. 是 b. 否 c. 間歇性

6. 當閣下於含氨氣的水中游泳時，閣下的眼睛是否容易變紅和不適？
a. 不適用 b. 是 c. 否 d. 間歇性

7. 當閣下飲酒後的一天，會否感覺到眼睛乾澀或眼部不適？
a. 不適用 b. 是 c. 否 d. 間歇性

8. 閣下有否服用或使用以下的藥物，請圈出
a. 抗敏藥丸 b. 抗敏眼藥水 c. 利尿藥丸 d. 安眠藥丸 e. 鎮靜藥物 f. 口服避孕丸
g. 十二指腸藥物 h. 消化系統藥物 i. 高血壓藥物 j. 其他，請說明：

9. 閣下是否患上關節炎？
a. 是 b. 否 c. 不肯定

10. 閣下是否曾感覺鼻乾、口乾、喉乾、胸乾及陰道乾燥？
a. 從來沒有 b. 間歇性 c. 時常 d. 一定有

11. 閣下是否患上甲狀腺的毛病？
a. 是 b. 否 c. 不肯定

12. 是否有別人告訴閣下在睡覺時眼瞼不能完全閉合？
a. 是 b. 否 c. 不肯定

13. 閣下從睡中驚醒時，會否感覺到眼睛有不適？
a. 是 b. 否 c. 不肯定
Appendix IIc

Dry Eye Questionnaire by Mc-Monnies and Ho (1987) with Re-coded

Values for Discriminant Analysis

D/E Survey: Please answer the following by underlining the response most appropriate to you: Female Male
Age: Under 25 Years, 25-45 Years, Over 45 Years
Currently Wearing: No Contact Lenses, Hard Contact Lenses, Soft Contact Lenses

1. Do you ever experience any of the following eye symptoms? (Please underline those that apply to you):
   Soreness (1) Scratchiness (1) Dryness (1)
   Grittiness (1) Burning (1)

2. How often do your eyes have these symptoms? (Underline)
   never (0) sometimes (1) often (2) constantly (3)

3. Have you ever had drops prescribed or other treatment for dry eyes?
   yes (2) no (0) uncertain (1)

4. Do you suffer from arthritis?
   yes (2) no (0) uncertain (1)

5. Do you suffer from thyroid abnormality?
   yes (2) no (0) uncertain (1)

6. Do you experience dryness of the nose, mouth, throat, chest or vagina?
   never (0) sometimes (1) often (2) constantly (3)
7. Do you regard your eyes as being unusually sensitive to cigarette smoke, smog, air conditioning, central heating?

   yes (2) no (0) sometimes (1)

8. Do your eyes easily become very red and irritated when swimming in chlorinated fresh water?

   not applicable no (0) sometimes (1) yes (2)

9. Do you take (please underline) antihistamine tablets (1), use antihistamine eyedrops (1), diuretics (fluid tablets) (1), sleeping tablets (1), tranquilizers (1), oral contraceptives (1), medication for duodenal ulcer (1) or digestive problems (1) or for high blood pressure (1)? or

   ____________________________ (write)

10. Are your eyes dry and irritated the day after drinking alcohol?

    not applicable no (0) sometimes (1) yes (2)

11. Are you known to sleep with your eyes partly open?

    not applicable no (0) sometimes (1) yes (2)

12. Do you have eye irritation as you wake from sleep?

    yes (2) no (0) sometimes (1)
Self-designed Dry Eye Questionnaire (SD-DEQ) and the New Scoring System

**Dry eye questionnaire:** Please ‘✓’ where appropriate.

**Sex / Age**: __________

1. Are you taking any medications? (Please ‘✓’ where appropriate)

**Sometimes (S):** less than two days a week; **Often (O):** between two and six days a week; **Daily (D):**

<table>
<thead>
<tr>
<th>Medications</th>
<th>“✓” where Appropriate</th>
<th>How Long? (months)</th>
<th>How Often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth control</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Menopause/hormones</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>high blood pressure</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Allergies</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Thyroid problems</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Diabetics</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Kidney problems (diuretics)</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Stomach/intestinal problems</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Antihistamine eye drops</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>eye drops or eye ointments</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
<tr>
<td>Others: (please specify: )</td>
<td></td>
<td></td>
<td>S/O/D</td>
</tr>
</tbody>
</table>
2. Do you have the following symptoms when not using any eye medications? (please ‘√’ where appropriate)

**Sometimes (S):** less than two days a week; **Often (O):** between two and six days a week; **Constantly (C):** Daily

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>‘√’ where Appropriate</th>
<th>Onset for How Long? (months)</th>
<th>How Often?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foreign body sensation</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Dryness</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Itchy</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Mucous discharge</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>Tearing</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>light sensitivity</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>tired eyes/ocular fatigue</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>eye pain/soreness</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
<tr>
<td>others: (please specify:)</td>
<td>RE, LE</td>
<td>S / O / C</td>
<td></td>
</tr>
</tbody>
</table>

3. Do you suffer from arthritis?

   Yes / No / Uncertain

4. Do you have dry mouth, nose, throat or vagina?

   Never / Sometimes / Often / Constantly
**New Scoring System for SD-DFQ**

<table>
<thead>
<tr>
<th>Question 1:</th>
<th>no 0</th>
<th>Sometimes 1</th>
<th>Often 2</th>
<th>Daily 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question 2:</td>
<td>no 0</td>
<td>Sometimes 1</td>
<td>Often 2</td>
<td>Daily 3</td>
</tr>
<tr>
<td>Question 3:</td>
<td>Yes 2</td>
<td>Uncertain 0</td>
<td>No 0</td>
<td></td>
</tr>
<tr>
<td>Question 4:</td>
<td>Never 0</td>
<td>Sometimes 1</td>
<td>Often 2</td>
<td>Constantly 3</td>
</tr>
</tbody>
</table>
Appendix IIIb

The Self-designed Dry Eye Questionnaire in Chinese Version (SD-DEQOC)

乾眼的問卷：請\(\checkmark\)出以下最貼切的答案。

性別 / 年齡：

1. 闆下近來是否服用或使用以下的藥物？（請\(\checkmark\)出最適當的答案）

<table>
<thead>
<tr>
<th>藥物</th>
<th>服用多久？(月)</th>
<th>什麼時間服用？</th>
</tr>
</thead>
<tbody>
<tr>
<td>口腔消炎丸</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>體質療程惡</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>炎血壓藥物</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>抗酸藥物</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>頸載藥物</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>消化系統藥物</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>抗酸藥用眼藥水</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>用眼藥水或眼藥膏</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
<tr>
<td>其他，請說明：</td>
<td>間歇性 / 時常 / 每日</td>
<td></td>
</tr>
</tbody>
</table>

2. 閔下的眼睛在不使用任何眼科藥物時，是否有以下症狀？（請\(\checkmark\)出適當的答案）

<table>
<thead>
<tr>
<th>症狀</th>
<th>什麼時候感到症狀？</th>
</tr>
</thead>
<tbody>
<tr>
<td>明確感</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>乾燥感</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>炎熱感</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>接觸感</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>紅眼</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>眼睛分泌物</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>流淚水</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>對光敏感</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>眼睛疲倦</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>眼睛疼痛</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
<tr>
<td>其他，請說明：</td>
<td>間歇性 / 時常 / 一定</td>
</tr>
</tbody>
</table>

3. 閩下是否患上乾眼症？
   a. 是 b. 否 c. 不肯定

4. 閩下是否曾感覺鼻乾、口乾、喉乾、或陰道乾燥？
   a. 從來沒有 b. 間歇性 c. 時常 d. 一定有
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTT</td>
<td>Cotton Thread Test</td>
</tr>
<tr>
<td>DEQ</td>
<td>Dry Eye Questionnaire</td>
</tr>
<tr>
<td>HK</td>
<td>Hong Kong</td>
</tr>
<tr>
<td>ICC</td>
<td>Intraclass Correlation Coefficient</td>
</tr>
<tr>
<td>KCS</td>
<td>Keratoconjunctivitis Sicca</td>
</tr>
<tr>
<td>M1</td>
<td>Method 1</td>
</tr>
<tr>
<td>M2</td>
<td>Method 2</td>
</tr>
<tr>
<td>M3</td>
<td>Method 3</td>
</tr>
<tr>
<td>Mc-DEQ(C)</td>
<td>Mc-Monnies’ Dry Eye Questionnaire (in Chinese)</td>
</tr>
<tr>
<td>NEI VFQ-25</td>
<td>National Eye Institute Visual Function Questionnaire</td>
</tr>
<tr>
<td>NSTD</td>
<td>Non-Sjögren Syndrome Tear Deficiency</td>
</tr>
<tr>
<td>PRT</td>
<td>Phenol Red Thread</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SD-DEQ(C)</td>
<td>Self-designed Dry Eye Questionnaire (in Chinese)</td>
</tr>
<tr>
<td>SP-CTT</td>
<td>Self-prepared Cotton Thread Test</td>
</tr>
<tr>
<td>SP-PRT</td>
<td>Self-prepared Phenol Red Thread</td>
</tr>
<tr>
<td>SSTD</td>
<td>Sjögren Syndrome Tear Deficiency</td>
</tr>
<tr>
<td>ST</td>
<td>Schirmer Test</td>
</tr>
<tr>
<td>TBUT</td>
<td>Tear Break Up Time</td>
</tr>
<tr>
<td>TM</td>
<td>Tear Meniscus</td>
</tr>
<tr>
<td>TMC</td>
<td>Tear Meniscus Curvature</td>
</tr>
<tr>
<td>TMH</td>
<td>Tear Meniscus Height</td>
</tr>
<tr>
<td>WCTT</td>
<td>White Cotton Thread Test</td>
</tr>
</tbody>
</table>