BINDING SERVICES
Tel +44 (0)29 2087 4949
Fax +44 (0)29 20371921
e-mail bindery@cardiff.ac.uk

Ocular morphology in people with Down's syndrome

Ping Ji

Submitted for the degree of Doctor of Philosophy

School of Optometry & Vision Sciences

Cardiff University

2006

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Acknowledgements

I wish I could express my thanks in Chinese to all the people who have been helping and supporting me during my studies at Cardiff University.

First of all, my thanks go to my supervisor, Dr. Maggie Woodhouse who has patiently guided me through my studies. Without her expertise and knowledge, I could not have gained the confidence or kept the work going. She was always approachable, thoughtful and positive, which made my studies enjoyable and go smoothly.

I am grateful to a number of people who have involved in my study. Within the school, Mr. S John, Mr. JE Morgan, Mr. ME Johnson, Mr. R Rattan, Dr. M Trego helped with the evaluation of the equipments and those generous colleagues as being volunteers sitting for me. My thanks also should go to Moorfield Eye hospital for the loan of the model eye. Mr. M Deacon took some measures as part of clinical evaluation of children with Down's syndrome.

Dr. SA Naroo, from Aston University, did corneal image analysis and kindly answered many relevant questions. Dr. AL Jones and Dr. PO Watts, from University of Wales College of Medicine, performed the analysis of fundus photographs. Dr. F Ennis offered invaluable advice for data analysis. Mr. Paul McGeoghan advised on statistics. My thanks also go to some lovely people for constantly supporting my work, especially Sue, Ioanna, Hening, Yadan, Liu and Jun.

I am most grateful to Mrs. Peggy Spencer and her son, Paul, who have been welcoming me into their homes and looking after me, which helped me settle here and made my life much easier. I could not have completed this work without the emotional and financial support of my dear family. My lovely husband, Changling, has waited patiently for my return home. My parents, brothers and sister have shown me love and understanding and have always been there to encourage and support me.

I have also been so lucky in having pleasant housemates who have supported me during my time here.

My thanks must go to all the child and adult subjects who took part in the project. Without their continued support, and generous funding from the Welsh Assembly the study would not have been possible.

My thanks to you all!

Cardiff University

Ocular morphology in people with Down's syndrome

Ping Ji

Doctor of Philosophy

2006

Summary

The study describes the morphology of eyes in children and adults with Down's syndrome (DS) including ocular biometric parameters (axial length, cornea, anterior chamber, lens and pupil size) and retinal features. It is important to understand any links between ocular structures and visual function.

Children with DS and adults with DS have significantly thinner corneas both in the centre and periphery, smaller corneal radius, higher corneal power, higher corneal aberration and lower lens power compared to their respective control children and adults. Further, there was a significant difference in the correlation of axial length and refraction between DS children (n=46) and controls (n=50). Therefore, refraction in people with DS appeared to be determined by those abnormal refractive components.

A larger disc and rim were found in children with DS compared to controls. An increased number of vessels were found in periphery of the retina in children with DS. However, there was a similar distribution of retinal vessels in DS children and controls. The presence of the peripapillary atrophy in children with DS (67%) was much higher than that of controls (28%). No significant correlation was found between the total number of vessels and visual function such as refraction, visual acuity and accommodation among children with DS.

Keratoconus was present in 8 adults with DS, however, no keratoconus was found in children with DS but abnormal corneal topography was more common in children with DS compared to that in controls. No significant difference was found in measured intraocular pressure between DS adults and the controls.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Angle-closure glaucoma (ACG)
Anterior chamber depth (ACD)
Anterior chamber angle (ACA)
Anterior chamber volume (ACV)
Axial length (AL)
Best-fit sphere (BFS)
Central corneal thickness (CCT)
Corneal radius (CR)
Central lens density (CLD)
Down's syndrome (DS)
Intraocular Pressure (IOP)
Maximum lens density (MLD)
Minimum corneal thickness (MCT)
Nasal-Superior (NS)
Nasal-Inferior (NI)
Normal Tension Glaucoma (NTG)
Ocular Hypertension (OHT)
Open angle glaucoma (OAG)
Optic nerve head (ONH)
Partial coherence interferometer (PCI)
Peripapillary atrophy (PPA)
Periphery corneal thickness (PCT)
Quality Specification (QS)
Quality Factor (QF)
Refractive index (RI)
Signal-to-noise ratio (SNR)
Standard deviation (SD)
Success rate (SR)
Temporal-Superior (TS)
Temporal-Inferior (TI)
Visual acuity (VA)

LIST OF CONFERENCE ABSTRACTS

1. Properties of the cornea and optic disc in people with DS
   Ping Ji, J. Margaret Woodhouse
   (Oral presentation, UK Down's Syndrome Research Forum 2004, Portsmouth, UK)

2. Properties of the fundus and optic disc in children with DS
   Ping Ji[1], J. Margaret Woodhouse[1], Patrick O. Watts[2], James E. Morgan[2]
   Optometry & Vision Sciences, Cardiff University[1],
   Department of Ophthalmology, University of Wales College of Medicine[2]
   (Poster presentation, ARVO 2005, USA)

3. Properties of the optic disc in children with DS
   Ping Ji, J. Margaret Woodhouse, Patrick O. Watts, James E. Morgan
   (Oral presentation, International Down's Syndrome Conference 2005, Portsmouth, UK)

4. Children with DS have lower lens power, does it explain their under-accommodation?
   Ping Ji[1], J Margaret Woodhouse[1], Fergal A Ennis[1], Shehzad A Naroo[2], Patrick O Watts[3].
   Optometry & Vision Sciences, Cardiff University[1],
   School of Life & Health Sciences, Aston University[2],
   University Hospital of Wales, University of Wales College of Medicine[3].
   (Oral presentation, Nottingham Eye Symposium 2006, UK)

5. Retinal feature in children with DS
   Ping Ji, J. Margaret Woodhouse, Adrian L. Jones, James E. Morgan
   Patrick O. Watts.
   (Poster presentation, Nottingham Eye Symposium 2006, UK)
   Winner of the prize for best poster

6. Retinal feature in children with DS
   Ping Ji, J. Margaret Woodhouse, Adrian L. Jones, James E. Morgan
   Patrick O. Watts.
   (Oral presentation, the 6th International Congress of Ophthalmology & Optometry, 2006, China)

7. The ocular biometry in children with DS by the Oculus Pentacam system and IOL-Master
   Ping Ji, J Margaret Woodhouse, Fergal A Ennis, Shehzad A Naroo, Patrick O Watts.
   (Poster presentation, ARVO 2006, USA)

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

Chapter 1

Introduction

1.1 The structure of the thesis

This thesis describes a study of the morphology of eyes in children and adults with Down's syndrome (DS) since it is recognised that visual and refractive defects are common in people with DS. It is important to understand the contribution that ocular structures make to such defects. Two aspects are of particular interest, keratoconus (common in people with DS) and glaucoma (of which little is known in people with DS).

The first part of the thesis includes this introductory chapter 1, which is a review of the general health and ocular features in people with DS. It is also specifically related to keratoconus and glaucoma. The later section of this chapter outlines the aims of the project and its procedures.

The second part of the thesis includes chapter 2, 3, 4 and 5. Chapter 2 describes the options of the equipment and evaluation procedures. Chapter 3 presents the ocular biometry measurement and the analysis procedures including axial length, properties of the cornea, lens, anterior chamber and pupil size. Additionally, corneal topography was assessed to detect keratoconus. Chapter 4 concerns the quantitative features of the optic disc and retinal vessels. Chapter 5 considers detecting glaucoma in people with DS. Again, in the final part of each chapter, the findings and its implications are presented and discussed.

Finally, Chapter 6 summarizes the main findings and discusses their implications. The possible limitations of the whole study are considered and future research is suggested.

1.2 General features in people with DS

1.2.1 Epidemiology

Down's syndrome (DS) is the most frequent cause of severe learning disability and also the most common chromosomal anomaly in live births. The incidence of DS is approximately 10 per 10,000 live births, which is universal and appears to occur with equal frequency across the world (Bishop et al. 1997; Cornel et al. 1993; Dolk et al. 2005; Forrester and Merz 2002; Johnson et al. 1996; Metneki and Czeizel 2005; Olsen et al. 1996; Siffel et al. 2004). In the UK, around 1000 babies are born with DS every year (Nicholson and Alberman 1992).

Maternal serum screening (multiple-marker screening) are most widely used to screen for DS in younger women (Cuckle et al. 1987; DiMaio et al. 1987; Iliyasu et al. 2002; Wald et al. 1992; Wald et al. 1999). The diagnosis of DS is typically made at birth by characteristic physical features or within the first 2 years of life by cytogenetic analysis (Kenue et al. 1995; Mutton et al. 1991). Despite increasing termination of DS pregnancies (resulting from the greater availability of antenatal screening and diagnosis), there has been no significant reduction in live birth prevalence (Bell et al. 2003; Stratford and Steele 1985). It may be due to the improved survival rate in all infants with DS.

1.2.2 Genetics

After the pioneering description of DS by a physician, JL Down (Down 1866), almost one century was needed to find the aetiology of the syndrome. An extra chromosome 21 in people with DS was first discovered in France (Lejeune et al. 1959). The partial 21 trisomy was found later (Poissonnier et al. 1976). Three types of DS were discovered:

i. Trisomy 21 is present in 95 percent of persons with DS, which means the presence of a whole extra chromosome 21 in each cell.
ii. In 3-4 precent of cases, DS is caused by a translocation, which means that only a part of a supernumeral chromosome 21 has attached itself to another chromosome (most often 14, 21 or 22). Thus there exists an extra part of chromosome 21 in each cell. Most chromosome-21 translocations are sporadic.

iii. Mosaicism, occurs in 2 percent of cases, which means an individual with DS having cells of two types: abnormal cells in the body which contain three chromosomes 21; normal cells which have the normal number of two chromosomes 21.

The chromosomes are holders of the genes that direct the production of a wide range of materials which the body needs. The chromosome 21 has been fully sequenced (Hattori et al. 2000; Sakaki et al. 2000), and has about 1% of a human's genetic material on it (Deloukas et al. 1998). As more is learned about the genes contained on chromosome 21, it is likely that the origins of additional clinical manifestations of DS will be better understood. For instance, a gene for amyloid (an abnormal protein found in the brain of individuals with Alzheimer's disease), is located on chromosome 21, which may explain why people with DS are at an increased risk for developing Alzheimer's disease and ageing early (Frangione et al. 1996).

It has been suggested that DS is a gene dosage disease (Amstad and Cerutti 1990; Epstein 1988; Epstein et al. 1982; Sinha 2005). In other words, due to trisomy, there is an over expression or overproduction of certain proteins, encoded by normal genes on the extra chromosome, which imbalances some of the biochemical and physiological pathways, important for the development and function of the organs and tissues affected in people with DS.

1.2.3 Physical characteristics and facial morphometry

Patients with DS have physical features that distinguish them. The tongue is usually too large for the oral cavity, causing the individual to habitually hold the mouth open. The hand and feet are short and stubby, with multiple dermatoglyphic irregularities. Abdominal protuberance is often seen and most likely is the result of hypotonic muscles. Short stature and overweight are common signs in people with DS (Cronk et al. 1988; Fonseca et al. 2005; Melville et al. 2005; Myrelid et al. 2002; Styles et al. 2002). Growth hormone deficiency may aggravate their growth retardation and lead to a reduced pubertal growth spurt (Anneren et al. 1999). Hence, the individuals with DS reach their final height at relatively young ages (Myrelid et al. 2002).

In addition, the prevalence of upward slanting of the palpebral fissure (range from 43% to 97%) and epicanthal folds (range from 38% to 64%) are highly common in people with DS (da Cunha and Moreira 1996; Fierson 1990; Kim et al. 2002; Liza-Sharmini et al. 2006; Lyle et al. 1972; Shapiro and France 1985). It may caused by malformation of the sphenoid bone or an angle orientation of the orbits (Lyle et al. 1972). Woodhouse et al. carried out the study on facial morphometry, in respect of spectacle wear, showed that children with DS differ from control children (Woodhouse 1998; Woodhouse et al. 1994):

i. smaller interpupillary distance in older children (age of 9-12);
ii. lower crest height;
iii. shorter front-to-bend.

1.2.4 Common health problems

The most commonly reported health problems are vision, hearing and minor respiratory problems (Selikowitz 1992; Turner et al. 1990). The higher prevalence of ocular anamolies in people with DS is reviewed in a later section. Hearing loss occurs in approximately two thirds of children with DS (Harigai 1994; Roizen et al. 1993). These children may also develop sleep apnoea (brief periods of arrested respiration during sleep) as a consequence of upper airway obstruction from enlarged tonsils and adenoids (Dahlqvist et al. 2003; Stebbens et al. 1991).

Congenital heart abnormalities are present in 28%-67% of children with DS, and is one of the leading causes of death in individuals with DS (Kallen et al. 1996; Marino 1996; Satge et al. 1998; Selikowitz 1992; Stoll et al. 1998).

Life expectancy for people with DS has improved to more than 50 years (Baird and Sadovnick 1987; Eyman and Call 1991; Roizen and Patterson 2003), resulting from improvements in medical care, early identification and treatment with support. The process of physical ageing seems to be accelerated in individuals with DS (Brown 1979; Devenny et al. 1996; Fromage and Anglade 2002).

Individuals with DS are also more likely to suffer from thyroid dysfunction (Karlsson et al. 1998; Prasher 1999), leukaemia (Satge et al. 1998), diabetes

(Milunsky and Neurath 1968; Ohyama et al. 2000; Van Goor et al. 1997) and several skin conditions (Pueschel et al. 1992).

1.2.5 Development and cognitive aspects

People with DS have intelligence disability of varying degrees. The reduced cognitive processes of people with DS have been well documented (Connolly 1978; Rohr and Burr 1978; Sloper et al. 1990), including intelligence quotient score ranging from 30 to 70 and averaging around 50 (Chapman and Hesketh 2000), difficulties with spatial memory, poor long-term memory performances and difficulties acquiring new skills (Chabert et al. 2004).

In general, infants with DS show relatively normal abilities in prelanguage behaviour, learning and memory (Oller and Seibert 1988; Steffens et al. 1992). The learning and memory problems become considerably more noticeable as the infant grows to childhood and adolescence. Children with DS are especially poor at language performance compared to non-related children of the same cognitive level (Hodapp and Zigler 1990), but there are also cases in which language capacity is within normal range. It is also commonly accepted that their language comprehension skills are more advanced than their expressive language (Kumin 1996). Although these children generally have poor verbal short-term memory skills, their visual-motor skills are relatively strong (Wong and Ho 1997). Concerning academic skills, their reading ability is better than arithmetic (Carr 1995).

One major point to be stressed is that this has less to do with the inability of children with DS to acquire words or linguistic constructions and more to do with their inability to 'stabilize' the information that they do manage to acquire (Wishart 1993; Wishart and Duffy 1990). Test-retest reliability is very low because successes gained in one test might not appear upon retest and new skills show up, only to disappear shortly thereafter. A paper reviewed the neural and cognitive features of DS (Nadel 2003). The author stated "I will suggest that difficulties in both the acquisition of information (learning), and the long-term storage and retrieval of information (memory) are a part of the phenotype of DS." This view

was supported that chromosomal regions may be involved in specific cognitive functions (Chabert et al. 2004).

The motivational difficulties and developmental instabilities were observed by Wishart (1993). However, it has been reported that children with DS were just as persistent as the typically developing children with the challenging tasks (Gilmore et al. 2003). The studies of maternal directive and supportive behaviour have concluded mothers of children with DS exerted greater control in most of the aspects of directiveness, while mothers of children without DS were more likely to silently watch their children (Mahoney et al. 1990; Tannock 1988).

Studies indicate that children with translocation DS do not differ cognitively or medically from those with trisomy 21 (Johnson and Abelson 1969). However, children with mosaic DS, (perhaps because their trisomic cells are interspersed with normal cells) have typically higher scores on intelligence quotient tests and have fewer medical complications than children with translocation or trisomy 21 (Fishler and Koch 1991).

1.3 Ocular features in people with DS

1.3.1 The cornea

The cornea is a transparent tissue at the front of the eye, which is one of the principal refractive elements of the eye. The majority of corneal growth occurs pre-natally with nearly all post-natal growth being found to occur within first few years of life (Sorsby et al. 1961). Paediatric central corneal thickness (CCT) increases slowly over time and reach adult thickness at 5 to 9 years of age (Hussein et al. 2004). There is a less than 10-micron change per decade as the cornea becomes thinner with age (Foster et al. 1998).

Shape of the cornea

Generally, the cornea is smaller in the vertical diameter than in the horizontal diameter. Advances in corneal mapping technology have allowed for more accurate and complete descriptions of the corneal shape. The contour of the human cornea is closely modelled by a conic section, which is described by asphericity and apical radius of curvature. The profile of a cornea along any

meridian can be considered as part of an ellipse, meaning that it becomes flatter from the centre to the periphery.

The aspheric shape of the cornea has been the focus of numerous studies, which quantifies the rate of curvature change from apex to periphery (Eghbali et al. 1995; Gatinel et al. 2002; Wang et al. 1989). It was assumed that the cornea could be described by the conic section (Bennett and Rabbetts 1991; Douthwaite and Sheridan 1989; Guillon et al. 1986; Kiely et al. 1982; Kiely et al. 1984). Three commonly used parameters in the optometric literature to quantitatively describe corneal shape are: the '*Q*' value, the shape factor '*p*' and the eccentricity '*e*' (Cheung et al. 2000; Douthwaite 2003; Dubbelman et al. 2006; Gatinel et al. 2002; Holladay 1997; Lam et al. 1999; Lindsay et al. 1998; Pardhan and Beesley 1999; Wang et al. 1989). These parameters are related to each other by the following equations:

$p = 1+Q$ or $e^2 = -Q$

Kiely et al. (1982) first attempted to provide a mean value of Q = -0.26. Guillon (1986) found a mean value of Q = -0.18. Bennett et al.(1991) described the asphericity by p-value. Douthwaite et al. (2003) reported that the range of normality for the p-value was from 0.56 to 1.08. Davids et al. (2005) reported the mean value of Q= -0.35. All in all, the typical shape of the human cornea is that of a prolate ellipse, flattening from corneal apex to periphery (Fig. 1-1).

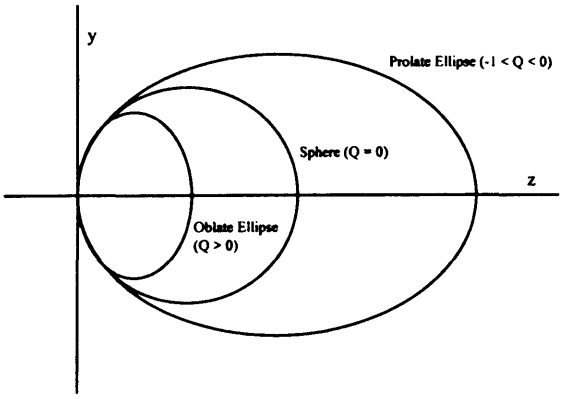


Fig. 1-1: Conic sections of asphericity, *Q (Davis et al. 2005)*
***Q* > 0, oblate ellipsoid**
***Q* = 0, sphere**
–1 < *Q* < 0, prolate ellipsoid with the major axis in the *z* direction

It was reported that hyperopic eyes tended to have less negative Q, more prolate than those of emmetropes and myopes (Davis et al. 2005; Llorente et al. 2004). Most recently, Dubbelman (2006) stated "The asphericity of both corneal surfaces is independent of gender and radius. However, with age, the asphericity changes significantly, which results in a slight peripheral thinning of the cornea."

Aberration of the cornea

Aberration of the cornea indicates the extent to which the distribution differs from that of a perfect optical system. It has been found that the corneal wavefront aberrations varied widely from subject to subject for each Zernike term (Wang et al. 2003). Despite a large inter-subject variability, the average amount of aberration in the human cornea tends to increase moderately with age (Amano et al. 2004; Jahnke et al. 2006; Oshika et al. 1999). In other words, there is a tendency of the cornea to become more spherical with age, increasing spherical aberration, more irregular and other high-order asymmetric aberrations.

Corneal aberration may contribute to degradation of the retinal image quality and therefore to visual performance (Gobbe and Guillon 2005; He et al. 2002). It has been suggested that high levels of axial aberration play a role in myopia development (Charman 2005; He et al. 2002; Llorente et al. 2004). In contrast, some studies find no differences in the aberration characteristics of myopes, emmetropes and hyperopes (Cheng et al. 2003; Porter et al. 2001).

Properties of the cornea in people with DS

Corneal abnormalities in people with DS have been reported such as reduced corneal thickness, reduced corneal radius and higher corneal power (Doyle et al. 1998; Evereklioglu et al. 2002; Haugen et al. 2001a) (Table 1-1).

Computerized corneal topography are used to observe properties of cornea in children and adults with DS (Doyle et al. 1998; Haugen et al. 2001a; Liza-Sharmini et al. 2006; Vincent et al. 2005). Doyle et al. described:" Corneal topography was generally of a regular "bow tie" pattern, 2% had overt keratoconus and 6% had corneal topography with inferior steepening." Vincent et al. (2005) reported that difference in corneal power between the two eyes and steepness of the inferior

cornea versus the superior cornea of each individual with DS was significantly different from the control population.

Table 1-1: Summary of corneal measurements in people with DS

	Doyle	Haugen	Everklioglu	Vincent
Year	1998	2001	2002	2005
Age (years)	15 - 22	14 – 26	5 – 15	10mons–18years
No. subjects	50	46	28	21
Methods	Corneal topography	Corneal topography	Ultrasound pachymetry	Corneal topography
CCT (mm)	n/a	0.48±0.04	0.49 ±0.39	n/a
Corneal power (D)	n/a	46.39 ±1.95	n/a	46.66 ± 1.64
Corneal topography	6% abnormal changes	25% abnormal changes	n/a	39% abnormal changes

It was reported that the conical corneas seen in keratoconus patients with DS who present for corneal grafting are thinner than those from keratoconus patients without DS (Haugen et al. 2001b). Moreover, acute swelling of the conical cornea is far more common in keratoconus patients with DS than those without DS (Pierse and Eustace 1971; Tuft et al. 1994). Therefore, it appears that DS people have inherent corneal thinning. It can be speculated that there might be a connection between chromosome 21 and the thinning of the cornea. The gene encoding the a-1 chain of type VI collagen, a major constituent of the corneal stroma, is on chromosome 21 (Hattori et al. 2000; Rabinowitz 1998). The stroma of cornea is derived from the neural crest cells. Hence, it has been suggested that the common defect in the migration or differentiation of neural crest cell may lead to this thinning (Bertelsen and Seim 1974).

In addition, it was speculated that the increased curvature may be due to the reduced mechanical rigidity as a result of the thinning of the corneal stroma (Haugen et al. 2001b).

1.3.2 The anterior chamber

The anterior chamber is the space in the eye that is behind the cornea and in front of the iris, which is filled with the aqueous humour. Anterior chamber has normally reached its maximum depth by about 15 years of age (Sorsby et al. 1961). The aqueous passes first into the posterior chamber and then flows forward through the pupil into the anterior chamber. The aqueous drains out of the eye via the trabecular meshwork into the aqueous veins. The production and drainage of aqueous fluid determines intraocular pressure. Therefore, the configuration of anterior chamber is relevant to the pathogenesis of glaucoma (Ashaye 2003; Caprioli et al. 1986; Congdon et al. 1999; Devereux et al. 2000; Sakai et al. 1996).

To our knowledge, only Haugen performed ACD measurement and reported that the mean ACD in individuals with DS was 3.45±0.34 mm, which was very similar to that of normal individuals (3.40±0.23mm) (Haugen et al 2001a).

1.3.3 The lens

The normal lens

The lens is a flexible transparent structure with two convex surfaces, which is suspended radially from the ciliary body. The lens itself is surrounded by a thick lens capsule which is the basement membrane of the lens epithelial cells. The bulk of the lens consists of lens fibres. The newest lens fibres are found in the outermost layer of the fibres in the cortex. The mature fibres are gradually buried deeper in the nucleus. The lens increases in size and cell numbers throughout life (Smith and Pierscionek 1998). An increase in thickness with age has been confirmed (Brown 1974; Cook et al. 1994). However, no change with age was reported in the study of lens thickness using the Magnetic resonance imaging (MRI) techniques (Strenk et al. 2004).

Properties of the lens in people with DS

The prevalence of the lens opacities ranges from 0% to 50% in people with DS (Doyle et al. 1998; Fierson 1990; Haugen et al. 2001a; Hestnes et al. 1991; Igersheimer and Mautner 1951; Jaeger 1980; Kim et al. 2002; Robb and Marchevsky 1978; Wong and Ho 1997) (Table 1-2).

The majority of lens opacities were small and located in the periphery. Among young adults with DS the frequency of small "flake" opacities in the lens is high (range from 20-49%) and the number of opacities tends to increase with age. Differences in the age would therefore be a main factor, which are in line with the previous reports that lens opacities began to appear in DS people between 6 -10 years of old and were almost universally present after the age of 16 years (Igersheimer and Mautner 1951; Robb and Marchevsky 1978). In addition, different technique used for checking the presence of lens opacities may influence the prevalence of lens opacities.

Table 1-2: Summary of lens opacities in people with DS

Author	Year	No. subjects	Age	Lens opacity
Igershimer et al.	1951	125	6-10years	2%
Fierson et al.	1990	150	2months-20years	42%
Hestness et al.	1991	30	20-72years	50%
Berk et al.	1996	55	2months-25years	20%
Doyle et al.	1998	50	15-22years	38%
Haugen et al.	2001	47	14-26years	28%
Kim et al.	2002	123	6months-14years	3%
Liza-sharmini et al.	2006	60	1month-17years	0%

With the more advanced technology, it has been stated that individuals with DS had reduced lens thickness and increased density of the lens compared to the age-matched controls (Haugen et al. 2001a).

Although abnormalities of the lens capsule do not appear to be characteristic of DS, there might be some link with the pathology of cataract. Reports of the prevalence of cataract in people with DS are varied from 0%-47% (Berk et al. 1996; Hestnes et al. 1991; Kim et al. 2002; Rosenfield et al. 1996; Woodhouse et al. 1997). The age range of the studies population undoubtedly had effect on the

reported prevalence of cataract. The method of examining the eye also had an effect on the possible detection of cataract, for example, whether the pupil is dilated or not. The prevalence of congenital cataract is frequent in DS people (range from 1-6%) (Liza-Sharmini et al. 2006; Merin and Crawford 1971; Tsiaras et al. 1999). It has been suggested that impairment in the antioxidant system may be a possible mechanism for early cataract formation in people with DS (Cengiz et al. 2002).

1.3.4 The retina and optic disc

The normal retina and optic disc

The retina lines the inside of the eyeball. The retina includes both the sensory neurons that response to light and intricate neural circuits that can convert the information from the external environment into neural impulses. The optic nerve head (ONH) is situated in the nasal side of the retina. The fovea is located 3.5mm temporal to the ONH. A circular field of approximately 6mm around the fovea is the central retina while beyond this point is the peripheral retina, extending up to 21mm from the centre of the optic disc. The central retina close to the fovea is considered thicker than the peripheral retina. This is due to the increased packing density of photoreceptors and their associated bipolar and ganglion cells in central retina compared with peripheral retina.

The terms optic disc or ONH can be used interchangeably; this is the place where retinal ganglion cells exit the eye through an opening called the scleral canal. The optic disc also refers to the tissues composed of millions of nerve fibres that originate in the ganglion cell layer of the retina and converge on the nerve head from all points in the fundus. The optic disc comprises the neuroretinal rim and the optic cup. It is usually surrounded by the Elschnig scleral ring, which may or may not be accompanied by other peripapillary atrophy (PPA) (Jonas et al. 1988a; Jonas et al. 1988b, c). The Elschnig scleral ring is a thin, cream coloured border, which marks the termination of the retinal pigment epithelium. Its appearance may be confused with the margin of the disc. The cup is the central depression of the disc and does not contain any nerve fibres, hence its pale appearance. The rim is formed by the ganglion cell axons that extend over, and turn sharply into the

scleral canal and normally appears a healthy pink as the nerve fibres have a rich vascular supply.

The cup and rim size positively correlates with the size of the disc (Bengtsson 1976; Budde et al. 2000; Caprioli and Miller 1987; Hellstrom and Svensson 1998; Jonas et al. 1988b). The number of nerve fibres is directly related to the area of the disc (Jonas et al. 1992; Panda-Jonas et al. 1994). It was found that the number of axons per optic nerve has a high degree of variability. The nerve fibres density per unit area was higher in eyes with small optic disc than those with large optic discs (Jonas et al. 1992). Age related loss of ganglion cells and the thinning of retinal nerve fibre layer have been reported (Jonas and Dichtl 1996; Jonas et al. 1992) .

The disc area ranges from 1.87 mm^2 to 3.22 mm^2 according to different studies (Hellstrom et al. 1997; Hellstrom and Svensson 1998; Jonas et al. 1988b; Mansour 1992; Rimmer et al. 1993; Varma et al. 1994). The size of the optic disc is influenced by high refractive errors (Jonas 2005b; Jonas et al. 1999), the methods of correcting the magnification of the images (Bengtsson and Krakau 1977, 1992; Bennett et al. 1994; Garway-Heath et al. 1998; Langenbucher et al. 2003; Littmann 1982; Quigley and Dube 2003; Rudnicka et al. 1998) and the race (Varma et al. 1994).

Table 1-3: Summary of planimetry evaluation of the disc in normal people

Author	Year	No. subjects	Age (years)	Methods	Disc size (mm^2)
Jonas et. al	1988	319	43	Planimetry	2.89±0.44
Mansour et. al	1991	121	21-54	Mannual Planimetry	2.66-3.02
	1992	66	2-10		2.66-3.22
Rimmer et. al	1993	17	2-10	Post-morterm	1.87±0.44
		31	>10		2.19±0.54
Varma et. al	1994	3387	>40	Planimetry	2.63-2.94
Hellstrom et. al	1997	100	3-20	Planimetry	2.69±0.44

PPA

The feature of the PPA has been described as the result of misalignment between the boundaries of the three tissues that form the scleral canal: the epithelium, the choroid and the sclera (Nevarez et al. 1988). PPA has been subdivided into the peripheral Zone α and central Zone β, which reflects the severity of atrophy. Zone α refers to the area that exhibits irregular pigmentation and may appear more marked. Zone β refers to the area where the pigmentation is completely absent, which is the zone most adjacent to the optic disc margins and allows visibility of the choroidal vessels and the sclera. The inter-individual variability that characterises the development of the two zones is congenital and influenced by gender and race. This latter aspect particularly applies to Zone α which is frequently observed in heavily pigmented eyes and is therefore more prevalent in dark skin races.

High myopic eyes usually demonstrate a PPA area expanding concentrically around the optic disc margins (Jonas et al. 1989). In addition, the extent of PPA is associated with progressive optic disc damage and progressive visual field defects in glaucoma and may be useful for monitoring progressive glaucomatous damage (Jonas 2005a; Jonas and Konigsreuther 1994; Park et al. 1996; Uchida et al. 1998). It has been also reported that position of the central retinal vessel trunk influences the location of PPA in glaucoma (Jonas et al. 2001). The author stated: "The longer the distance to the central retinal vessel trunk exit, the more enlarged is PPA and the smaller is the neuroretinal rim."

In addition, it has been observed that the prevalence of both zones increases with age (Jonas and Fernandez 1994). Therefore, PPA can also be considered as a feature of the normal ageing retina.

Blood supply to the retina and optic disc

The retina is situated between two sets of arteries and veins: the ciliary vessels of the choroid, branches of the central retina artery and the central retinal vein. The central retinal vein is always situated temporally to the retinal artery, which is usually at the upper nasal quadrant of the disc in normal eyes (Jonas and Fernandez 1994).

ONH is the site of entry and exit of the retinal vascular system. The main source of blood supply to the ONH itself is via the posterior ciliary artery. There is an additional lesser supply via the central retina artery and the choroidal circulation. The surface nerve fibre layer is supplied by the retinal circulation (Bathija 2000). Blood supply to the ONH is sectorial in distribution, and there is a significant variation between individuals. The ONH venous drainage is via the central retinal vein.

The retina is supplied by the central retina artery, which enters the eye via ONH. It then branches into four major vessels each supplying its own quadrant of the retina. Each branch passes deeper into the retina and may penetrate as far as the inner nuclear layer, from which the venules return to the larger superficial retinal veins. As the vessels branch into small capillaries across the retina and the ONH, the retina vessels show a monotonic decrease in diameter, which becomes more prominent with increase in the distance from the ONH.

The retinal vessel diameter may reflect the need of the vascular supply in the corresponding superficial retinal area. It has been reported that the retinal arteries crossing ONH have wider diameters at the TI (Temporal-Inferior) followed by TS (Temporal-Superior), NS (Nasal-Superior) and NI (Nasal-Inferior) (Jonas and Schiro 1993), which complies with the density distribution of retinal nerve fibres layer. It has also been reported that the regional blood flow is higher in temporal than nasal but the same blood flow in superior and inferior (Feke et al. 1989; Rassam et al. 1996; Riva et al. 1985). After all, the temporal contains the highly metabolic area of the macula. Similarly, the vessel diameters are larger in the temporal than in the nasal retina, but similar between the superior and inferior retina (Jean-Louis et al. 2005), which therefore are in agreement with earlier blood flow studies.

Since retinal and ONH vasculature have no autonomic nerve supply, retina blood flow is auto-regulated, that is, responsive to the local metabolic activity (Johnson 1986). Therefore, in various conditions, auto-regulation protects the retinal circulation and provides a constant blood flow (Delaey and Van De Voorde 2000). It has been reported that a decrease of the retinal blood flow with a rate of 8% per

decade (Boehm et al. 2005; Groh et al. 1996). Failure of auto-regulation commonly occurs very early in many retinal vascular diseases such as diabetes mellitus and hypertension.

Properties of the retina and optic disc in people with DS

A few studies have described retinal abnormalities in people with DS (Ahmad and Pruett 1976; Berk et al. 1996; da Cunha and Moreira 1996; Sherk and Williams 1979; Williams et al. 1973).

Lowe first reported that the disc appeared pinker in people with DS (Lowe 1949). Later, by using the hand-held fundus camera, William (1973) described that there was an increased number of retinal vessels crossing the optic disc margin (n=50, age 10-25 years), suggesting this sign may be useful in the clinical diagnosis of DS in newborns. Ahmad et al. (1976), by using indirect ophthalmoscope, stated that the disc appeared 'more rosy than normal' (n=32, age 18-62 years). Sherk et al. (1979) counted the number of arterioles, venules and large vessels crossing the disc margin (n=100, age 14-50 years) and showed a similar results to William's study. In Berk's study (1996), an increased number of retinal vessels crossing the optic disc was detected in 38.1% cases.

Hypoplasia is recognized as a congenital anomaly which may affect one or both nerves. Optic nerve hypoplasia was described in two post-mortem retina, along with the diminution of retinal ganglion cell and the nerve fibre layers (Fierson 1990; Ginsberg et al. 1980). Fierson (1990) reported optic nerve hypoplasia in 10% of a group of 150 children and young adults with DS aged 2 months to 20 years who were examined by using an ophthalmoscope. However, the criteria for identifying hypoplasia were not described.

Children with DS are believed to be more susceptible to retinoblastoma (Brichard et al. 2003; Moll et al. 2002; Satge et al. 2001; Satge et al. 2005). Retinal detachment was reported (Berk et al. 1996; Liza-Sharmini et al. 2006). Although diabetes appears to be associated with DS (Milunsky and Neurath 1968; Ohyama et al. 2000; Van Goor et al. 1997), there is a low prevalence of diabetic retinopathy in people with DS and explained that there are some inherent protective factors

against the development of diabetic retinopathy such as the relatively low pressure, myopia and growth hormone deficiencies (Fulcher et al. 1998).

1.3.5 Axial length

Axial length (AL) refers to the distance from the cornea to the retina epithelium. Growth of the AL is mainly caused by increasing length of vitreous cavity. A minor role in human eye growth is also played by increasing depth of the anterior chamber (Katuzny and Koszewska-Kolodziejczak 2005).

The role of AL in emmetropisation is evident from the significant correlation between AL and refraction. Moreover, the AL/CR (corneal radius) ratio has been used to give a better correlation with refraction than is obtained with AL (Garner et al. 2004; Osuobeni 1999). A "high ratio" (i.e. > 3.0) has been suggested to be a predictor or correlation of myopia, which may indicate the extent to which an imbalance between AL and CR contributes to progression toward myopia (Ojaimi et al. 2005). Interestingly, a strong association between body height, body weight and AL was found (Ojaimi et al. 2005; Selovic et al. 2005), suggesting physiological of the body growth are correlated with the development of eye.

AL in people with DS was only measured by ultrasound pachymetry in two studies (Doyle et al. 1998; Haugen et al. 2001a). Both studies reported that there is a similar range of values for AL and an association between refraction and AL in people with DS as in their controls.

1.3.6 Other ocular features in people with DS

Iris

There are two typical features of the iris in DS people: peripheral white spots (Brushfield's spots) or "speckling", and a thinning of the iris stroma. The peripheral spots were first described in the majority of individuals with DS people by Brushfield (1924). Thinning of the iris stroma in DS subjects was first pointed out by Lowe (1949), and has later been described by several authors (Berk et al. 1996; Fierson 1990; Jaeger 1980). The cause of these iris changes is not known. Fierson (1990) described Brushfield's spots as consisting of condensation of the normal iris stromal connective tissue and hypothesised that the decrease in iris

pigmentation often seen in DS may reflect thinning of this iris stroma in which the pigment melanin is located.

Blepharitis

Blepharitis has long been described as an ocular feature of people with DS. The prevalence reported in the literature is 6% to 47% (Berk et al. 1996; da Cunha and Moreira 1996; Liza-Sharmini et al. 2006; Lyle et al. 1972). The variation may be explained by different examination techniques, for example, general observation versus a detailed slit lamp examination. It is probably due to impaired lachrymal drainage coupled with eye rubbing (Berk et al. 1996). One author postulated that the high frequency of blepharitis in people with DS was related to an impaired immune response (Catalano 1990).

Lacrimal obstruction

The prevalence of lacrimal obstruction is significant higher, ranging from 17% to 30% in people with DS (Berk, 1996; Da Cunha 1996; Kim et al. 2002).

1.4 Reduced visual function in people with DS

1.4.1 Higher refraction

Refraction development in normal people

At birth, newborns commonly demonstrate high levels of hyperopia and astigmatism that reduce towards emmetropia rapidly during the first year of life. This process is known as emmetropisation (Ehrlich et al. 1997; Gwiazda et al. 1984; Ingram and Barr 1979). Emmetropisation may be described as the development of the AL of the eye matching the power of the cornea and lens. Gilmartin summarized the eye growth as follows: "Eye growth has shown to consist of a rapid infantile phase whereby, in the first 3 years of life, the cornea and the lens had to compensate 20 D or so for an increase in AL of 5 mm. Between 3-13 years, the compensation of lens and cornea has only to be approximately 3 D for around a 1mm increase in AL."(Gilmartin 2004). The normal growth patterns are eye lengthens, and the lens flattens, thins and loses optical power.

Change in distribution of refractive error with age in normal children was shown in Fig. 1-2. The mean spherical equivalent refraction drops from hypermetropic values towards emmetropia, and the distribution of spherical equivalent refractive values becomes narrow (Gwiazda et al. 1993a). The presence of refractive error can be considered to represent a failure of the emmetropisation (Gwiazda and Thorn 1999). Table 1-4a summarize the studies on refractive error prevalence reported across nations (Dandona et al. 2002; Goh et al. 2005; Junghans et al. 2002; Saw et al. 2002; Villarreal et al. 2000).

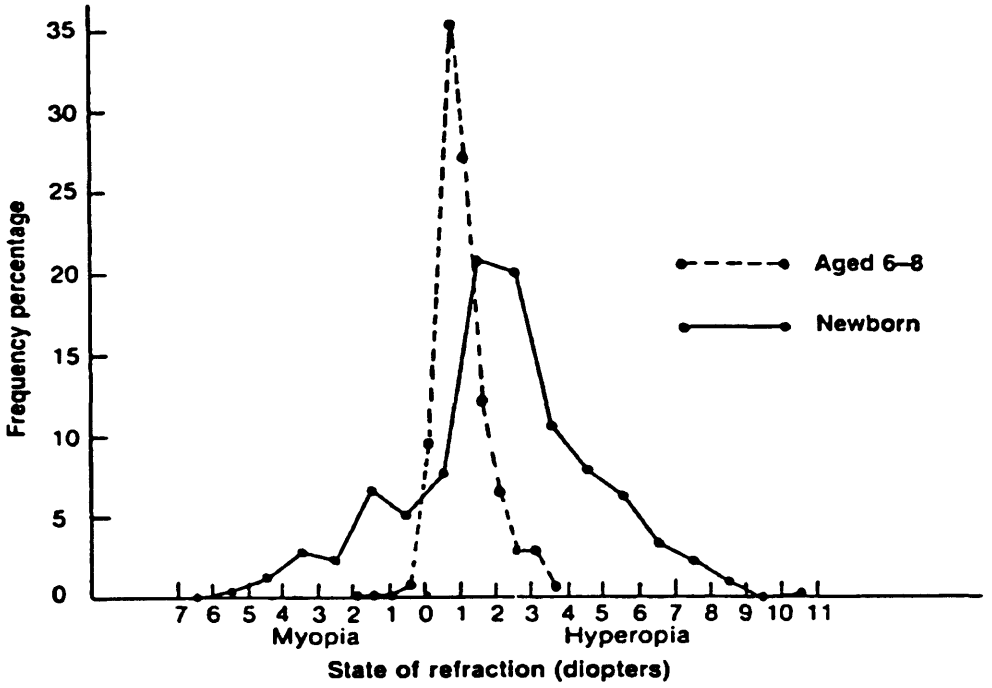


Fig. 1-2: Change in distribution of refractive error with age in normal children

Table 1-4a: Summary of the prevalence of refraction in general population

Author	Year	No. Subjects	Age (Years)	Myopia	Hyperopia
Villarreal et al.	2000	1045	12-13	45.0%≤-0.5D	8.4%>+1.0D
Saw et al.	2002	1453	7	29.0%≤-0.5D	n/a
			8	34.7≤-0.5 D	
			9	53.1% ≤-0.5D	
Junghans et al.	2002	2571	5	2.8%≤-0.5D	46.1%≥+0.5D
			12	8.7%≤-0.5D	24.1%≥+0.5D
Dandona et al.	2002	4074	7-15	4.1%≤-0.5D	0.8%≥+2.0D
Goh et al.	2005	2571	7	9.8%≤-0.5D	3.8%≥+2.0D
			15	34.4%≤-0.5D	1.0%≥+2.0D

An individual's refractive state could be influenced by a number of factors including genetic, environmental and nutritional factors (Grosvenor and Scott 1991; McBrien and Barnes 1984; Mutti et al. 2002; Mutti and Zadnik 1996; Mutti et al. 1996; Rosenfield and Gilmartin 1999; Wallman and Winawer 2004). Theoretically aberrations must interfere with blur interpretation and accommodation and may also disrupt emmetropisation in the developing myope. Eyes with high amounts of aberration should be insensitive to blur. In fact, it has been demonstrated that myopic patients are less sensitive to blur than emmetropic patients (Rosenfield and Abraham-Cohen 1999). Moreover, growth hormone may play a role in ocular development and the physiological process of emmetropisation (Parentin et al. 2004). It has been reported that there are many similarities in the growth patterns for both the emmetropising and persistent hyperopes, whereas the differences in growth lie mainly between the emmetropes and myopes (Jones et al. 2005).

Refraction in people with DS

All the studies agree that individuals with DS seem to become either significantly hypermetropic or myopic (Berk et al. 1996; da Cunha and Moreira 1996; Fierson 1990; Haugen et al. 2001a; Hestnes et al. 1991; Jaeger 1980; Kim et al. 2002; Liza-Sharmini et al. 2006; Lowe 1949; Lyle et al. 1972; Perez-Carpinell et al. 1994;

Shapiro and France 1985; Wong and Ho 1997; Woodhouse et al. 1997; Woodhouse et al. 1996) (Table 1-4b). The majority of papers reported hypermetropia to be most common. However, the degree of myopia in DS individuals can be extremely high (da Cunha and Moreira 1996; Fierson 1990; Woodhouse et al. 1997). The astigmatic part of refraction has not been studied as extensively as the spherical part in patients with DS.

Table 1-4b: Summary of the refraction in DS people: previous literature

Author	Year	Age	No. Subjects	Hyperopia	Myopia	Astigmatism
Shapiro et al.	1985	8months-28years	54	27%>+5.0D	10%<-1.0D	25%>3.0D
Fierson et al.	1990	2months-20years	150	18%>+3.0D	12%<-2.0D	35% >+2.0D
Hestnes et al.	1991	20-72years	30	29%>+1.0D	59%<-1.0D	47%>0.75D
Perez-Carpinesll et al.	1994	7-20years	72	41%>+1.0D	25%<-1.0D	64%>1.0D
Woodhouse et al.	1997	3months-1year	93	21%>+3.0D	9%<-0.75D	26%>+2.0D
		1-4years		42%>+3.0D	9%<-0.75D	22%>+2.0D
		4-12years		42%>+3.0D	13%<-0.75D	38%>+2.0D
Haugen et al.	2001	3months-11yearr	40	40%>+2.0D	8%<-1.5D	53%>+1.0D
Kim et al.	2002	6months-14years	123	12%>+3.0D	26%<-0.75D	31%>+0.75D
Liza-Sharmini et al.	2006	1month-17years	60	29%>+0.5D	25%<-0.5D	8.3%>+0.75D

The significant variations may be due to the following reasons:

i. Different ways of reporting refraction;
ii. Different criteria being used to classify refraction;
iii. Different age ranges of the subjects;
iv. Different regions and races.

Different refraction techniques being used by different authors, e.g. cycloplegic vs. noncycloplegic refraction. It was noted that mean refraction and the range of errors in early infant do not differ between normal children and children with DS (Woodhouse et al. 1997). However, she stated: "The refraction distribution does not narrow in the majority of children with DS, but rather gets wider compared to age-matched controls." In other words, refraction and the variance of range of refraction in people with DS increased with age. Cregg et al. (2003) offered a good explanation for no difference in the change of mean refraction in children with DS: "Although some children showed an increase in hyperopia, others showed a negative shift in spherical power to emmtropia and even myopia, and thus the mean remained constant".

The causes of refractive error in people with DS were studied (Berk et al. 1996; Bromham et al. 2002; Cregg et al. 2001; Cregg et al. 2003; da Cunha and Moreira 1996; Ferak and Cernay 1984; Haugen et al. 2001c; Woodruff et al. 1980). Woodruff et al. (1980) stated that: "Prematurity and dismaturity predispose to learning disability, and it is suggested that these causes tend to retard or distort development of ocular structures and induce refractive errors." Berk et al. (1996) stated that: "We believe that hypermetropia is compatible with the nature of DS, which is basically a generalized inhabitation of growth." Moreover, it was reported that DS children with congenital cardiopathy had proportionally more myopia or myopic astigmatism than DS children without these cardiac malformations (Bromham et al. 2002). The study of Cregg et al. (2003) showed no association between refraction and strabismus in children with DS and suggested that children with DS may be destined not to undergo emmetropisation. It was also postulated that the failure of emmetropisation process in children with DS may be part of a general dysfunction, as is the failure of accurate accommodation (Haugen et al. 2001c). Thus, to some extent, abnormal refraction development in people with DS may mainly result from the general abnormal physiological features.

Haugen et. al also stated "Reduced accommodation in early childhood, carrying a blurred retinal image for near objects may be an aetiological factor for abnormal refraction development." In addition, a strong right-left specificity of the axes encountered in DS people with oblique astigmatism. It was explained that the

thinner cornea and higher curvature might be more likely influenced by the anatomy of the surrounding structures, that is, the eyelid pressure and the palpebral fissure. Therefore, if eyelid pressure is regarded as a main cause of astigmatism, it may explain why oblique astigmatism is more prevalent in DS than in the normal population (Haugen et al. 2001c).

1.4.2 Reduced accommodation

Accommodation refers to the ability of the eye to see distant objects or close objects by focusing an image on the retina (Maddock et al. 1981). Contraction of the ring-shaped ciliary muscle reduces the length of the muscle and relaxes the zonules of the lens, which allows the lens to move forwards, and inward. This increases the curvature of the lens and the refractive power. In the general population, many factors have been found to influence accommodation including retinal defocus (Gwiazda et al. 1993b; Kruger and Pola 1987), refractive error (Goss and Zhai 1994), visual acuity (Charman 1986; White and Wick 1995), cognitive demand and mental effort (Bullimore and Gilmartin 1987, 1988; Iwasaki 1993; Winn et al. 1991). Lindstedt (1983) first reported that there was a failing accommodative function in people with DS. Since then, it was researched comprehensively by later studies (Cregg et al. 2001; Haugen et al. 2001c; Woodhouse et al. 2000; Woodhouse et al. 1993; Woodhouse et al. 1996) (Table 1-5).

Table 1-5: Summary of accommodation ability in people with DS:

Author	Year	No. subjects	Age	Reduced accommodation
Lindstedt	1983	18	Children	73%
Woodhouse et al.	1993	26	6 - 14years	92%
Woodhouse et al.	1996	53	3- 57months	92%
Woodhouse et al.	2000	77	4.7-84.7months	68%
Haugen et al.	2001	60	2 - 12years	55%
Haugen et al.	2001	36	14- 26years	39%

The causes of under-accommodation in children in DS have remained inexplicable. It has been linked to visual acuity, hypermetropia, strabismus and cognitive level (Cregg et al. 2001; Haugen et al. 2001c; Woodhouse et al. 2000;

Woodhouse et al. 1996).Woodhouse (1996) has suggested that reduced visual acuity in DS may affect their ability to identify the blur and refine their accommodation response. Cregg et al. (2001) reported findings from the same cohort of Woodhouse that there was a greater lag of accommodation in hyperopes than myopes and emmetropes. Haugen et al. (2001) found no significant association between 'poor accommodation' and the presence of strabismus. He suggested that the poor accommodation in children with DS may be also due to reduced elasticity of the lens or abnormalities in the ciliary muscle, or a combination of these different factors (Haugen et al. 2001a; Haugen et al. 2001c; Haugen et al. 2004).

In addition, increased cognitive demand can increase the amount of accommodation. Hence, a possible explanation may be the poorer level of concentration. However, no significant association between cognitive development and the accommodation ability was found in Woodhouse's later study (Woodhouse et al. 2000). A recent study from the same cohort showed that bifocals aid near focusing for children with DS (Stewart et al. 2005). In other words, children with DS wearing bifocals 'learn' to accommodate accurately. Thus, children with DS appeared to have quite large amounts of accommodation available.

Cholinergic deficiency in the brains of DS infants has been found (Florez et al. 1990). Reduced cholinergic transmission may also affect the structures of the eye involved in accommodation.

1.4.3 Reduced Visual acuity

Visual acuity (VA) refers to the spatial limit of visual discrimination, and is a description of the finest detail that a person can perceive. Reduced VA is reported in people with DS by a number of studies (Berk et al. 1996; Courage et al. 1994; da Cunha and Moreira 1996; Doyle et al. 1998; Haugen et al. 1995; Haugen et al. 2001a; Haugen et al. 2001c; Hestnes et al. 1991; Jaeger 1980; Liza-Sharmini et al. 2006; Lyle et al. 1972; Perez-Carpinell et al. 1994; Shapiro and France 1985; Tsiaras et al. 1999; Wong and Ho 1997; Woodhouse et al. 1996) (Table1-6).

The variation is most likely explained by the different methods to measure acuity and the method chosen depends on the child's age, level of attention, comprehension and communication. Thus, the results obtained with the various tests are not directly comparable. In many cases, the prevalence might be accounted for by the relatively high incidence of ocular abnormalities (including refractive error and strabismus).

Table 1-6: Summary of Binocular VA in people with DS

Author	Year	No. Subjects	Age	Binocular VA
Lyle et al.	1972	44	5-29years	32% (6/15-6/30)
Hestnes et al.	1991	30	20-72years	57% acuity somewhat reduced 23% marked visual problem
Courage et al.	1994	51	2months-18years	Reduced acuity compared to controls of same age
Woodhouse et al.	1996	53	3-57months	No improvement in BVA compared to controls
Haugen et al.	2001	43	14-26years	Reduced VA
Liza-sharmini et al.	2006	60	1month-17years	60% <6/12

It has been suggested that under-accommodation may play a role in the defective visual development of acuity and contrast sensitivity in children with DS (Cregg et al. 2001; Haugen et al. 2001c; Woodhouse et al. 1996). The VA value of younger infants with DS (before 6 months of age) is within normal range (Courage et al. 1994). The development of VA was found behind their typically developing peers, which is not explained either by refraction or by the effect of poor accommodation. A sudden change in VA maybe associated with physiological changes in the visual cortex (Woodhouse et al. 1996). There is evidence of reduction in the number and density of neurons and a delay in cortical maturation (Buxhoeveden et al. 2002; Wisniewski 1990), which could contribute to the VA process. Moreover, abnormal spatial vision persists in children with DS in the absence of ocular abnormality. This would suggest that abnormal retino-cortical visual processing may lead to a reduced visual function (John et al. 2004; Suttle and Turner 2004).

1.4.4 Other visual function defects

Reduced contrast sensitivity

Reduced contrast sensitivity has been reported in people with DS (Courage et al. 1997; Perez-Carpinell et al. 1994). One recent study considered that contrast sensitivity tested with conventional behavioural techniques may reflect sensory deficits of optical or neural origin or a loss of performance (John et al. 2004). They compared objective acuity and contrast sensitivity measurements recorded with visual-evoked potentials. The DS group had reduced acuity and contrast sensitivity when compared with the control subjects. Therefore, reduced contrast sensitivity in children with DS supports the idea of an underlying sensory deficit in the visual system.

Strabismus

Strabismus is a deficit in the muscular control of the eyes, causing the eyes to look in different directions. It is present in approximately 2-4% of the general population (Abrahamsson et al. 1999). The prevalence varies from 9% to 69% in people with DS (Cregg et al. 2003; Haugen and Hovding 2001; Hestnes et al. 1991; Kim et al. 2002; Liza-Sharmini et al. 2006; Lyle et al. 1972; Shapiro and France 1985; Wagner et al. 1990; Woodhouse et al. 1997; Yurdakul et al. 2006). All studies show that the most frequent pattern of strabismus was esotropia (Table 1-7). There are various hypotheses regarding the causes of strabismus in children with DS such as uncorrected high refractive error (Jaeger 1980; Lowe 1949), and brain damage (Schiavi 1997).

nystagmus

The other feature is the presence of nystagmus might be 3%-33% in people with DS (Awan 1977; Berk et al. 1996; Castane et al. 2004; da Cunha and Moreira 1996; Hestnes et al. 1991; Kim et al. 2002; Liza-Sharmini et al. 2006; Perez-Carpinell et al. 1994; Shapiro and France 1985; Wagner et al. 1990; Wong and Ho 1997).

Table 1-7: The frequency of nystagmus and strabismus in people with DS

Author	Year	No. Subjects	Age	Nystagmus	Strabismus
Lyle et al.	1972	44	5-29 years	15%	n/a
Shapiro & France et al.	1985	53	7-36 years	9%	43% (42% esotropia)
Wagner et al.	1990	188	2months-24years	30%	n/a
Hestnes et al.	1991	30	20-72years	13%	69% (65% esotropia)
Woodhouse et al.	1997	93	3months-12years	3%	19% (all esotropia)
Kim et al.	2002	123	6months-14 years	22%	25%
Liza-Sharmini et al.	2006	60	1month-17years	33%	27%

1.5 Keratoconus

1.5.1 Clinical features of keratoconus

Keratoconus is a noninflammatory condition in which the cornea assumes a conical shape because of the progressive thinning of the corneal stroma. In most cases the area of conical protrusion is surrounded by Vogt's striae (vertical stress lines visible in the deep stroma), and Fleischer's ring (epithelial iron deposition line) around the base of the cone and may result in high irregular astigmatism. The corneal thinning affects its optical function. Therefore, patients often present a history of progressive myopia, oblique astigmatism, and a reduction of spectacle-corrected VA. In most cases, it tends to progress gradually over many years, but in some cases it may advance rapidly (Tuft et al. 1994). The condition is almost always bilateral, but can be very asymmetric (Behrens-Baumann 1994; Holland et al. 1997; Hustead 1993; Rabinowitz et al. 1993). Keratoconus occurs in about 0.1% of the general population (Rabinowitz 1998). There is no male or female preponderance. It is usually sporadic, although 6-8% of cases have a family history, often with all autosomal dominant mode of inheritance with variable expressivity (Gonzalez and McDonnell 1992; Rabinowitz et al. 1990; Rabinowitz et al. 1992).

1.5.2 Etiology of keratoconus

A review article by Rabinowiz (1998) showed that the cause of keratoconus has not been confirmed in spite of a number of studies being done. However, a number of local and systemic conditions have been implicated in its etiology such as atrophy, connective tissue disorders and evidence from histopathological studies. The changes in corneal structure that occur in keratoconus, which probably are under direct genetic control.

All the studies suggest that genes play an important role in the etiology of keratoconus. Recent linkage analysis has suggested a gene locus for keratoconus on chromosome 21 (Rabinowitz YS ZUL 1999). Moreover, two genes encoding the subunits a-1 and a -2 in collagen type VI (which is mostly found in the deep layers of the corneal stroma) are also located on chromosome 21. In comparison with normal cornea, the expression of 471 of the 5600 genes on the microarrays was changed in the keratoconus samples. These genes are believed to be involved in

keratoconus. In the past few years, different research groups have gathered considerable information on the genetics of corneal dystrophies. In autosomal dominant keratoconus, chromosomal localization to chromosome 21 has been found by genetic mapping studies and the VSX1 gene has been implicated in the pathogenesis of the disease (Bisceglia et al. 2005; Heon et al. 2002).

It has been shown that irregularities in the apotosis system may be responsible for the thinning in keratoconus (Wilson et al. 1996). The biomechanical properties of keratoconus and normal corneas have been compared (Andreassen et al. 1980). It was found that the mechanical strength of the cornea was reduced in keratoconus. The relatively small load values for keratoconic corneas were only partially explained by corneal thinning. Qualitative differences in the keratoconus cornea were a significant factor in explaining their relatively reduced strength (Krachmer et al. 1984). Collagen is the predominant protein in the cornea, accounting for 71% of its dry weight. Many reports in the literature suggest an abnormality in collagen metabolism in patients with keratoconus. An x-ray diffraction study comparing normal and keratoconic human corneas revealed no difference in collagen interfibrillar spacing, demonstrating that the stromal thinning in keratoconus is not due to a closer packing of collagen fibrils but it is due to a loss of collagen (Fullwood et al. 1990).

Environmental factors such as eye rubbing and contact lens wear may cause progression of this disorder in genetically predisposed individuals. The induced corneal trauma by eye rubbing is considered as a significant etiological factor in the development of keratoconus. Keratoconus patients do rub their eyes more often than normal controls. But a cause-and-effect relationship is difficult to prove (Krachmer 1984).

1.5.3 Diagnosis of keratoconus

In the past the diagnosis of keratoconus has relied upon the history and the subjective assessment of clinical signs. The clinical approach to keratoconus is looking for classical signs. Moreover, in milder cases the typical features are not obvious and the clinicians have to rely on more subtle signs.

With corneal topography becoming more widely available, the possibility of screening a higher risk group for keratoconus becomes more feasible. Corneal topography is a computer assisted diagnostic tool that creates three-dimensional maps of the cornea and produces a detailed visual description of the shape and power of the cornea. In other words, corneal topography provides both a qualitative and quantitative evaluation of corneal curvature (see more in chapter 3, section 3.1.3). Also, it has become apparent that some corneas can have the topographic features of mild keratoconus in the absence of the other clinical signs (Harrison and Maguire 1995; Maguire and Bourne 1989; Maguire and Lowry 1991). Therefore, it is a useful tool in the study of the true incidence of keratoconus (see more in chapter 3, section 3.1.3).

1.5.4 Association between keratoconus and DS

Prevalence in people with DS

The prevalence of keratoconus in people with DS varies widely with a range of 0% to 30% (Haugen et al. 2001a; Haugen et al. 2001b; Liza-Sharmini et al. 2006; Lyle et al. 1972; Tsiaras et al. 1999) (Table 1-8), mainly due to the difficulties in diagnosing subtle cases of keratoconus, different methods and different age groups. For instance, keratoconus typically presents in the late teens or early adulthood between the ages of 15 and 25 years, so has not been found in several studies of children and young adults with DS (Liza-Sharmini et al. 2006; Shapiro and France 1985; Woodhouse et al. 1997). The highest reported prevalence of keratoconus was amongst the two studies who have the oldest subjects (Haugen et al. 2001b; Hestnes et al. 1991) (Table 1-8).

Table 1-8: Summary of the prevalence of the keratoconus in people with DS

Author	Year	No. Subjects	Age	Prevalence of keratoconus
Lyle et al.	1972	44	5-29years	5%
Shapiro & France et al.	1985	53	2.2-8.4years	0%
Fierson et al.	1990	150	7-36years	15%
Hestnes et al.	1991	30	20-72years	30%
Haugen et al.	1992	30	15-90years	20%
Woodhouse et al.	1997	93	3months-12years	0%
Doyle et al.	1998	50	15-22years	2%
Tsiara et al.	1999	68	5-19years	1.5%
Haugen et al.	2001	47	14-26years	13%
Vincent et al.	2005	21	10months-18years	9.5%
Liza-Sharmini et al.	2006	60	1month-17years	0%

Etiology in people with DS

The cause of the increased prevalence of keratoconus in DS is also not known. The most frequent chromosomal abnormality occurring in association with keratoconus is DS due to trisomy 21. Genetic alterations leading to structural or biochemical changes in the cornea, and extensive eye rubbing are the two main hypotheses.

The inherent corneal thinning is probably an important aspect of the development of keratoconus in people with DS. The gene encoding type VI collagen, a major constituent of the corneal stroma, is on chromosome 21 (Hattori et al. 2000; Rabinowitz 1998). Therefore, as people with DS have a trisomy 21, there might be a connection between this gene with the alteration of corneal thickness, altered

elements of corneal stroma and higher incidence of keratoconus in people with DS. Pierse and Eustace (1971) cited many reports of corneal hydrops occurring in patients with DS and stated that acute hydrops occurs with increased frequency in keratoconus patients with mental deficiency. They also suggested that ruptures in Descemet's membrane occur in these patients because of eye rubbing in response to chronic blepharitis or a basic defect in the corneal collagen matrix (Pierse and Eustace, 1971).

Diagnosis in people with DS

In the past, diagnosis of keratoconus was based on clinical examination (Haugen 1992; Shapiro and France 1985; Wong and Ho 1997). Only resent studies have been based on more sensitive diagnostic tests such as corneal topography in people with DS (Doyle et al. 1998; Haugen et al. 2001a; Liza-Sharmini et al. 2006; Vincent et al. 2005). The variability in the frequencies of keratoconus also reflects the subjective diagnosis criteria. It appeared that the older age group may have a higher frequency of keratoconus .

1.6 Glaucoma

1.6.1 Classification of glaucoma

Glaucoma is described as a syndrome of progressive optic neuropathy with optic nerve damage and retinal nerve fibre changes, which leads to a loss of visual function. According to the mechanism of damage to the optic nerve, glaucoma is now divided into open angle glaucoma (OAG) and angle-closure glaucoma (ACG). OAG is a slowly progressive atrophy of the optic nerve, characterized by the loss of peripheral visual function, an excavated appearance of the optic disc and the presence of an open anterior chamber angle. ACG is a condition in which the outflow of aqueous from the eye is blocked due to the closure of the anterior chamber angle, which causes a rapid rise in IOP. This type of glaucoma is also known as acute glaucoma or narrow angle glaucoma. It is very different from OAG in that blindness from ACG can be both painful and rapid.

Glaucoma is further divided according to whether the cause is primary or secondary. Primary glaucoma is more common as there are no apparent associated factors causing the disease. Secondary glaucoma develops because of other disease(s). Primary open angle glaucoma is the commonest type of glaucoma in the UK (Crick 1994).

1.6.2 Prevalence of glaucoma

Glaucoma is the second major cause of blindness in the normal population (Quigley 1996; Thylefors et al. 1995). Recent studies have recorded prevalence of 1% to 3% (Weih et al. 2001b). Different populations tend to suffer from different types of glaucoma. In a review of a number of studies including European, African and Asian people, OAG is more common in African and European population. However, ACG is more prevalent in Asia (Quigley 1996). In addition, the age adjusted prevalence for white and black adult populations over 40 is 1.6% and 4.6% respectively (Tielsch et al. 1991b).

1.6.3 Etiology of glaucoma

The mechanism of damage in glaucoma is not yet clear, and may be multifactorial. It is assumed that increased IOP damages the optic nerve if it is not compensated for by a sufficient auto-regulation. Most of the theories on the pathogenesis of glaucoma can be grouped into either mechanical or vascular categories.

The mechanical theory suggests that optic nerve damage can be caused by increased IOP through biochemical or structural factors. There is histological and experimental evidence that damage to the neural optic nerve by IOP occurs at the lamina cribrosa level (Parrow et al. 1992; Sogano et al. 1993). Since many researchers have demonstrated structural changes induces in the ONH by IOP elevation (Burgoyne et al. 2005; Caprioli and Spaeth 1984; Quigley et al. 1991). The mechanical theory is more prevalent in patients with a higher IOP. Anatomical changes in the ONH are not only associated with the loss of the ganglion cells axons but also with the rearrangement of the extracellular matrix in the ONH (Morgan 2000). The tissue remodelling leading to excavation is specific for glaucoma (Hernandez 2000).

The vascular theory considers that the optic nerve damage is a consequence of insufficient blood supply due to either increased IOP or by other factors reducing ocular blood flow. Research supports the view that ocular blood flow is indeed reduced in the majority of glaucoma patients (Flammer et al. 2002; Hafez et al. 2003; Tielsch et al. 1991a). Therefore, the microvasculature may fail to nourish the axons of the ONH, which also may interfere with the delivery of nutrients or removal of metabolic waste by the capillaries. Glaucoma damage may also be specially associated with the disturbance of the choroidal circulation (Spraul et al. 2002). The concurrence of haemorrhages, retinal vein occlusions and the sectoral damage pattern of the disc in certain glaucoma patients are considered as supportive evidence for the role of localised vascular impairment in glaucoma (Sonnsjo and Krakau 1993). The vascular theory may be the predominant factor in patients who develop glaucoma with a low IOP.

Two genes have been identified as factors that contribute to OAG, defects in the myocilin gene primarily causes elevated pressure (Stone et al. 1997) and the optineurin gene, appears to contribute to disease in familial low-tension glaucoma (Rezaie et al. 2002). In addition to these genes, some studies have identified chromosomal regions likely to contain OAG susceptibility genes (Pang et al. 2006; Richards et al. 1996; Wiggs et al. 2000).

With the advances in genetic technology and molecular biology it may turn out that all of those factors are involved to some degree.

1.6.4 Risk factors in the development of glaucoma

Glaucoma carries many risk factors. It is crucial to understand them in order to properly diagnose and manage this condition.

IOP

The most potential risk factor for the development of glaucoma is elevated IOP. IOP represents the pressure of aqueous humour within the eye. A number of reports have demonstrated that the incidence of glaucoma rises as IOP increases (Hollows and Graham 1966; Kass et al. 1980; Pohjanpelto and Palva 1974; Sommer et al. 1991). Also, the incidence of OAG is five times greater in patients whose IOP is higher than 21mmHg than those with IOP lower than 21mmHg (Armaly 1980; Morris et al. 1994). An IOP level of 21mmHg was chosen because the mean value of IOP measurement from a number of studies was found to be 15.5mmHg (Armaly 1965; Hollows and Graham 1966). Therefore, 21mmHg was higher by twice the standard deviation than the mean value of 15.5mmHg (as the IOP value was assumed to be normally distributed).

a) Normal Tension Glaucoma

Normal Tension Glaucoma (NTG) patients have IOP within the statistical normal levels but they suffer from progressive visual field loss (Anderson et al. 2003). Therefore, it is now recognized that what is a normal IOP for one person may cause damage in another. In population studies, up to 50% of white patients with glaucoma have IOP of less than 21 mmHg (Weih et al. 2001b). In the Baltimore Eye Study, half of all POAG patients were found to have IOP less than 21 mm Hg

at the time of study (Tielsch et al. 1991a). Findings from a larger trial have indicated that NTG patients require IOP reductions of approximately 30% to prevent progression of functional visual field loss (Poinoosawmy et al. 1998).

b) Ocular Hypertension

Ocular Hypertension (OHT) patients have an IOP of more than 21 mmHg but have no sign of glaucoma. However, the level of tolerance of IOP is likely to be very low once the laminar structures have exceeded their threshold of elasticity after prolonged exposure to high IOP levels. Therefore, IOP treatment might need to be tailored at levels that are much lower than normal (Burgoyne et al. 2005).

Age

The risk of glaucoma increases with age. The incidence of glaucoma in older people over 60 is greater than those under 40 (Armaly 1980; Coleman and Brigatti 2001; Klein et al. 1992). The Baltimore Eye Survey found that the prevalence of glaucoma was 3.5 times higher for white persons of 70 to 79 years as compared with persons of 40 to 49 years (Tielsch et al. 1991b).

Family history

Family history is a strong risk factor of developing glaucoma. It has been estimated that first-degree relatives of patients with glaucoma are more likely to develop glaucoma (Hulsman et al. 2002; Miller 1978; Tielsch et al. 1994; Wolfs et al. 1998).

Refractive error

It is generally accepted that there is an increased prevalence of glaucoma amongst people with myopia. Two recent population studies demonstrated that myopic eyes had a 1.6 - 3.3 times increased risk of glaucoma (Mitchell et al. 1999; Wong et al. 2003). One of the reasons as to why glaucoma should be more frequent in myopic eyes is that IOP in moderate myopia was significantly higher than that in emmetropia (Nomura et al. 2004). It also has been suggested that myopic eyes are more susceptible to the effects of elevated IOP (Perkins and Phelps 1982). In addition, myopic eyes might have abnormal connective tissue that could predispose to glaucoma (Fong et al. 1990). It was reported that the

lamina cribrosa is significantly thinner in highly myopic eyes, which decreases the distance between the intraocular space and the cerebrospinal fluid spacet, which may explain the increased susceptibility to glaucoma in highly myopic eyes (Jonas et al. 2004a).

Diabetes mellitus

Several studies have demonstrated a statistical association between diabetes and OAG (Tielsch et al. 1995; Weih et al. 2001a; Wilson et al. 1987). Diabetes decreases microvascular perfusion of the small vessels around the ONH, which leads to increasing susceptibility to increase IOP.

Anatomical risk factors to glaucoma

a. Corneal thickness

There is an increased susceptibility to glaucoma severity in patients with thinner corneas (Brandt et al. 2001; Gordon et al. 2002; Herndon et al. 2004; Hewitt and Cooper 2005; Medeiros et al. 2003; Shimmyo et al. 2003). It may be that patients with thinner cornea also have thinner sclera, which makes them more susceptible to glaucoma damage.

b. Blood pressure

Blood pressure and vascular dysfunction should be considered. Raised blood pressure has been found to be positively related to IOP (McLeod et al. 1990). But the relationship between blood pressure and glaucoma seems more complex (Hayreh et al. 1999; Meyer et al. 1996). Generally speaking, perfusion pressure is defined as blood pressure minus IOP in the eye (Sommer 1996). There is a link between the perfusion pressure of the optic nerve (which is, in essence, its blood supply) and glaucoma (Leske et al. 1996; Mitschischek 1991; Tielsch et al. 1995). The lower this perfusion pressure is, the higher the risk of glaucoma seems to be. As blood pressure is a factor in calculating the perfusion pressure, it might have some effect.

c. Retinal vessels

Retinal vessels are thought to influence the susceptibility of the retinal nerve fibres to glaucoma damage. They provide them with nutritional support and possibly act

as an element of additional anatomical support within the ONH structure. It is speculated that the vessels may protect the nerve fibres (Chihara and Honda 1992). Baring of the vessels is common feature of the glaucoma retina. The vessels are hanging unsupported over the disc area. They are increasingly apparent in correlation to the degree of thinning of the underlying rim area. It is controversial whether the prevalence of cilioretinal arteries could be an additional protective parameter against the progression of damage especially in the temporal ONH region (Lee and Schwartz 1992). Or they have a rather insignificant influence in glaucoma progression (Budde and Jonas 2003).

d. The size of the optic disc

There is conflicting evidence as to whether the size of the optic disc is a risk factor in glaucoma. A study suggested that large optic discs may be susceptible to glaucomatous visual field damage at statistically normal IOP readings (Burk 1992). However, several studies stated that glaucoma is independent of the disc size (Jonas 2005b; Jonas et al. 1988c; Jonas and Papastathopoulos 1996; Quigley et al. 1999). It was reported that with the exclusion of highly myopic eyes, the shape of the optic disc is not markedly important for pathogenesis, early diagnosis and differential diagnosis of glaucoma (Jonas 2005; Jonas et al. 1988c; Jonas and Papastathopoulos 1996).

1.6.5 Diagnosis of glaucoma

There are many clinical manifestations of glaucoma. Classically, visual field evaluation, the ONH appearance, IOP reading and anterior chamber angle assessment are the main reliable indicators. A sensitivity and specificity of over 90% has been reported using a combination of tests for glaucoma detection in normal people (Harper and Reeves 1999). The best combination was visual field analysis, optic disc cupping and IOP (leong et al. 2003). Recently, CCT is considered as an important measurement in the accurate diagnosis of patients with glaucoma and those suspected patients.

Visual field evaluation in glaucoma

Visual field represents the extent of space an eye views when directed in a fixed, straight-ahead position, which enables a direct measurement of the functional capacity of the retina. Visual field measurement can determine the stage of the disease by assessing the extent of the field loss. Modern visual field testing employs automated computer-generated light detection measurements at multiple locations throughout the field of vision. However, in early glaucoma, progression of the visual field may occur in the presence of little change in the appearance of the ONH. Therefore, visual field is not sensitive enough to detect structural change as by the time a visual field defect can be detected, substantial damage to the nerve fibres has already occurred (Harwerth et al. 1999; Harwerth et al. 2004; Quigley et al. 1982; Quigley et al. 1989).

Changes of the ONH in glaucoma

Since it is the optic nerve fibres that are damaged in glaucoma, the assessment of the optic disc should provide key information about the integrity of the optic nerve. All the following signs of the ONH are suggestive of glaucoma: an enlarged cup size, acquired pit of the optic nerve, thinning of the rim, increased pallor, a shift in the position of the blood vessels, notches or haemorrhages (Broadway et al. 1999; Jonas and Schiro 1993). Progression of glaucomatous ONH changes are small rim area and large beta zone of PPA but independent of the size of the optic disc and alpha zone of PPA and retinal vessel diameter (Jonas et al. 2004b). Many studies have confirmed that PPA can increase in glaucoma optic neuropathy (Uchida et al. 1998). Even in experimental glaucoma, the development of PPA has been described (Hayreh et al. 1998). PPA simply reflects neuronal atrophy, connective tissue alterations and unveiling pre-existing atrophy of the retinal pigment epithelium in glaucoma.

The development of glaucomatous ONH leads to changes in ganglion cells layers. The retinal nerve fiber layer thickness is significantly decreased in glaucoma (Matsumoto et al. 2003; Matsuno et al. 2001). These changes precede visual field loss (Armaly 1980; Johnson et al. 2003; Quigley et al. 1999; Sogano et al. 1993). Early detection of ONH structural anomalies may lead to alternative forms of treatment thus delaying the progression of OAG. Therefore, observation of the

ONH is a very useful tool in the diagnosis of glaucoma, the identification of progressive damage and the consequent therapeutic management.

IOP variations in glaucoma

For many years, glaucoma has had raised IOP as part of its definition but this has increasingly been shown to be misleading. IOP is often inadequate for predicting those at risk of the development and progression of glaucoma as some glaucoma patients have normal IOP. Since there can be a variety of responses to different pressures, it is difficult to define a safe range of IOP, even it is widely accepted that a healthy IOP is between 11-22mmHg. For instance, according to the Beaver Dam Study, 2.1% of the population above 40 years has glaucoma, and only half of these individuals are aware that they have the disease. One third to one half of patients with glaucoma exhibit normal IOP at the initial examination. In population studies, 50% of subjects with glaucoma have IOP under 21mmHg and 10% of OHT could go on to sustain glaucomatous damage.

Glaucoma with normal IOP or with elevated IOP differs in predictive factors for the eventual progression of glaucomatous optic nerve damage. For patients with an elevated IOP, significantly predictive factors for eventual progression of glaucoma were older age, advanced perimetric damage, smaller rim, and larger area of PPA. In contrast, in the normal IOP group, a significant predictive factor was the presence of disk haemorrhages at baseline (Martus et al. 2005).

However, IOP readings have always suffered from multiple source errors. Most importantly, there are extensive data in the literature demonstrating how properties of the cornea influence IOP measurement such as CCT readings (Graf 1991; Matsumoto et al. 2000; Recep et al. 2001; Whitacre et al. 1993), corneal curvature (Cennamo et al. 1997; Chatterjee et al. 1997; Chihara et al. 2005; Gimeno et al. 2000; Orssengo and Pye 1999; Shimmyo et al. 2003; Svedberg et al. 2005) and corneal elasticity (Harada and Naoi 2004; Svedberg et al. 2005). The apparent effect of corneal thickness on clinical IOP measures has been observed with combinations of optical pachymetry, contact tonometry, ultrasound pachymetry and non-contact tonometry (Graf 1991; Matsumoto et al. 2000; Recep et al. 2001). To date, there are many different studies researching the appropriate correction

factors (Ehlers et al. 1975; Shah et al. 1999; Wolfs et al. 1997). Overall, the magnitude of the effect in apparently normal corneas is rather small, i.e. around a 1.5 mmHg difference in IOP for a 10% difference in CCT (Doughty et al. 2002) (it will discussed more in chapter 5).

CCT measurement

The role of CCT in glaucoma is basically divided into two parts. The first part involves recalculating IOP by using an algorithm since it is well documented that CCT affects the estimation of IOP. Thin corneas produced underestimations of the IOP, whereas thick corneas produced the opposite (Whitacre et al. 1993). The second more complicated part of CCT is an independent risk factor for the development of glaucoma from previous studies (Brandt et al. 2001; Gordon et al. 2002; Herndon et al. 2004; Hewitt and Cooper 2005; Medeiros et al. 2003; Shimmyo et al. 2003).

CCT is a dynamic parameter that may changed by a number of ocular and systemic factors, including race, age, gender, corneal curvature and time of the day (Alsbirk 1978; Doughty and Zaman 2000; Foster et al. 2003; Herndon et al. 1997). A recent study suggested that more than one reading on separate occasions may be required to assess the risk of progression of glaucoma in clinical practice. Readings may also vary due to the variability of corneal thickness, limitations of the equipment and the experience of the operator (Wickham et al. 2005). However, another study has not shown statistically significant CCT variations during the day in suspected and glaucomatous patients, therefore, suggesting that only one CCT measurement is sufficient (Cronemberger et al. 2005).

Anterior chamber assessment

Gonioscopy is a mandatory test for anterior chamber assessment in ACG patients (Bonomi et al. 2000). It is critical to observe the anterior chamber configuration in ACG patients. The methods used for evaluating anterior chamber configuration include ultrasound biomicroscopy, A-mode ultrasonography and Scheimpflug principle imaging (Friedman et al. 2003; Olbert and Kehrhahn 1992; Richards et al. 1988).

1.6.6 Glaucoma in people with DS

Occurrence of glaucoma in people with DS is apparently rare. Infantile glaucoma has been reported in children with DS (Traboulsi et al. 1988; Wong and Ho 1997). Two case reports have described the development of a flat anterior chamber and raised IOP following acute corneal hydrops (Jacoby et al. 1990; McClellan and Billson 1988). A recent study reported four cases of glaucoma in children with DS (Liza-Sharmini et al. 2006): Two cases of infantile glaucoma, one case of glaucoma suspect and one case of secondary glaucoma. The secondary glaucoma was due to bilateral chronic uveitis. Several investigators who have studied large numbers of DS patients did not report glaucoma, possibly due to the difficulties in the detection (it will be discussed in Chapter 5, section 5.1.1).

However, people with DS may carry risk factors of the development of glaucoma the same as in the general population such as thinner cornea, higher refractive error and ageing earlier.

1.7 Outline of the project

1.7.1 Aims of the project

It is well documented that people with DS have ocular defects (da Cunha and Moreira 1996; Fierson 1990; Woodhouse et al. 1997). Our study aimed to understand the contribution that ocular structures make to such defects. The first part of our study (chapter 3) aimed to measure ocular biometric parameters among our subjects including axial length, corneal shape, anterior chamber parameters, lens density and lens thickness. In addition, the inter-relationship between refractive components was investigated and compared in child subjects. Further, the relationship between visual function and ocular biometry in children with DS was investigated. Additionally, keratoconus was detected by corneal topography, giving an indication of the prevalence among our children and adults with DS.

The unique retinal features in people with DS has been observed and reported (Ahmad and Pruett 1976; Berk et al. 1996; da Cunha and Moreira 1996; Sherk and Williams 1979; Williams et al. 1973). However, there is very little information available about their quantitative features of the retina. Therefore, the second part of the study (chapter 4) aimed to investigate the dimensions of the optic disc and the retinal vasculature in children with DS. It was concerned with an assessment of the number of arteries and veins crossing the disc, their distribution and width of vessels.

To extend our work, the detection of glaucoma in people with DS was considered (chapter 5). In order to identify suspect glaucoma among our adults with DS, we aimed to measure IOP, investigate the relationship between corneal parameters and IOP, and evaluate the appearance of the optic disc in fundus photographs.

Thus, our study aimed to provide important information about the ocular biometric features and the unusual appearance of the retina and disc in people with DS. Detection of keratoconus and glaucoma were of particular interest.

1.7.2 Procedures of the project

Selection and evaluation of equipment

At the beginning of the study, several pilot studies were performed in order to select the most suitable equipment (chapter 2). There were three vital points to be considered in order to gain the full co-operation of the subjects: a) a speedy examination; b) comfortable. i.e. no use of eyedrops which might distress the subjects; c) non-contact equipment.

The IOL-Master, the Oculus Pentacam system, a Topcon non-mydriatic fundus camera and I-care tonometer were chosen and used in our study. The magnification of the fundus camera was worked out.

Recruitment of subjects

a. Child subjects

The cohort of the Cardiff DS Vision Research Unit was founded in 1992/3, and covers the ages of children between 3 months to 16 years. The population is from South and West Wales. Despite no longer actively recruiting children to the cohort, it is continually increasing due to parent and professional recommendation, and referrals from local Health Authorities.

Prior to commencement of the present study, more than one hundred families from the cohort (with children aged 4 years and older) were invited to take part in our study through our Information Day. Information sheets and consent forms were then sent to our cohort family (appendix 2a). Forty six consent letters were signed and returned by the parents and, when appropriate, by the child with DS.

For the period of study from September 2004 to Sep 2005, control children were recruited. In order to minimize the effect of various factors on the measures of size of the optic disc, our intention was to recruit a control group who were matched with children with DS for refractive error. This was because the magnification of the fundus will be dependent not only on the optical system of the camera, but also on the subject's refractive error and eye-size. Moreover, the size of the optic disc is influenced by the method of measurement and race (Caprioli and Miller 1987; Meyer et al. 2001).

All the records of child patients within the School clinic between 2001 and 2005 were reviewed. Eighty local children who matched the following criteria were selected.

i. Ages of 4 to 16 years;
ii. That they had visited our clinic within the last eighteen months and lived in South Wales, concentrating especially on children of Cardiff University staff members. That is, it was convenient for them to participate.
iii. They had refractive errors similar to those children with DS who were taking part.
iv. They had no ocular abnormalities.

Eighty letters with information sheets and consent forms were then sent out to the parents of those local children (appendix 2a). Forty-eight children's parents signed and returned the consent form to enrol their children in our study. A week later a follow up phone call was made to acknowledge their support and confirm when they could visit our clinic. Finally, forty-four children kept their appointment for our study. Four additional children were recruited when they visited our Special Assessment Clinic. Two more children were siblings of children with DS who came together to our clinic and were delighted to be receiving a share of the attention. Therefore, fifty control children participated in our study.

After completion of the measurements, an acknowledgement letter (appendix 2b) and one fundus photograph ('photograph of the back of the eye') were posted to each child as a reward.

In order to recruit child subjects for the Pentacam image (which took place after the 'retinal' study), ninety-six letters with up-to-date information about our research were sent off to our cohort and control children who took part in the 'retinal' study (appendix 3). Twenty five children with DS and twenty eight control children's parents signed and returned the consent form to enrol their children in this study. Twelve children with DS and six control children gave their consent for cycloplegia to be used for lens thickness measurement.

b. Adult subjects

All the records of adults DS patients who had visited our Special Assessment Clinic and were co-operative for the last eye test within the last three years between 2001 and 2005 were reviewed. Sixty-seven adults with DS (17 years and over) were selected and invited by letter to participate in our study. Eleven of the subjects were known to have keratoconus, from clinical record. The information sheets about the study were enclosed and sent to the family or care home for the adults with DS (appendix 5). Twenty-two consent letters for participation were signed and returned. However, four subjects later dropped out because of illness and two withdrew their permission. In addition, the seven Community Learning Disability Teams in South Wales were contacted by phone calls. Only one team nurse was willing to pass the information to thirty DS patients in her area. Four DS patients were recruited in this way. Each consent form returned was acknowledged by telephone, the family or carer of the subjects were then given the opportunity to ask any questions about the study, and an appointment was then made. As a result, 20 adults with DS were recruited.

Sixteen control subjects volunteered for the Pentacam images via friends, staff and students in the school. Oral consent was given in each case. The control adults were chosen individually to match the refraction with all the co-operative subjects with DS as closely as possible. Twenty control subjects volunteered for IOP and CCT measurements via friends, staff and students in the school and signed the consent form (appendix 7).

Table 1-9: Characteristics of all the subjects

	DS Children	**Control Children**	**DS Adults**	**Control Adults**
No. subjects	46	50	19	16
Gender	28 males 18 females	29 male 21 female	10 males 9 females	7 males 9 females
Age (years) Mean±SD (Range)	10.5±3.3 (4-16)	11.0±3.2 (5-16)	33.6±14.2 (19-58)	36.5±9.8 (19-59)
Resource	From South and North Wales			

Ethical issues

Since all of the subjects were recruited by virtue of being part of the research cohort, or were patients of the School clinic, or were members or friends of members of the School, the appropriate committee was the School of Optometry & Vision Sciences Human Science Ethical Committee. The application was submitted and all recruitment procedures and experimental protocols were approved prior to any data collection.

Parents and carers of the subjects were contacted for initial consent for participation in the study. All control subjects were able to read the information leaflet and sign the consent form. However, 'informed' consent cannot be assumed in subjects with DS. Therefore, during the study every care was taken to explain to the subjects what was happening and coercion was not used. If subjects appeared to be willingly took part (by placing their chin on the chin rest for example), gentle verbal encouragement was used. However, if a subject clearly did not want to participate, or became uncooperative part way through procedures, the examination was halted. All recruitment procedures and experimental protocols were approved by a local Ethical Research Committee.

Data collection procedures

The testing procedures were undertaken in the clinic of the School where a parent or guardian was present at all times. Although the corneal topography study is described first in this thesis, the 'retinal' study took place first.

a. Child subjects

Full descriptions of protocols are given in Chapter 3 and 4. In most cases, a fundus photograph was first taken. The subjects were then asked to sit for the AL measurement. Afterwards, the children were taken to the consulting rooms for further eye examinations including refraction, visual acuity and accommodation. On the second visit, those children who were co-operative in the first visit sat only for the Pentacam images. In the cases of those children who did not fully co-operate on their first visit, they were asked to repeat the failed examination if possible. In addition, for those who were agreeable, 0.5% Tropicamide was used and the Pentacam images were then taken for lens thickness measurement.

b. Adult subjects

Full descriptions of protocols are given in Chapter 3, 4 and 5. In most cases of DS adults, the following steps were taken in the following order:

i. Fundus photograph
ii. AL measurement
iii. Pentacam images
iv. IOP measurement
v. Refractive error measurement
vi. VA measurement

Lastly, family history of keratoconus and glaucoma, the frequency of rubbing eyes per day were recorded when the subjects visited our clinic.

1.7.3 Data analysis procedures

Corneal topography analysis

All the reliable images were viewed by Dr. Shehzad Naroo (Lecturer, University of Aston), who has considerable expertise in corneal topography and detection of keratoconus. Objective analysis of the images by the Pentacam system was also used (see chapter 3, section 3.3.1).

Fundus photograph analysis

a. Retinal features

Those good quality images of fundus were measured with the use of the ImageNet software 2000 by one experienced observer Dr. Adrian Jones (Optometrist, University Hospital of Wales), which images matched for AL in DS children and controls (for more details, see 4.2.4). Those good quality images of the fundus were corrected for refraction and corneal radius, and planimetry measurement was performed with the use of custom software (for more details, see 4.2.4) by the same observer ALJ. The author (PJ) counted the number of retinal vessels in fundus photographs and measured their width (see 4.2.5).

b. Glaucomatous changes in the fundus photography

All the good quality images of the fundus were viewed seperately by ALJ and an ophthalmologist (Patrick O. Watts, University Hospital of Wales) for glaucomatous

changes (see 5.2.3). Afterwards, a second ophthalmologist (James E. Morgan, University Hospital of Wales and the School of Optometry & Vision Sciences) reviewed the suspect photographs from a clinical perspective.

Statistical methods

The measures of the right eye of each subject were chosen for data analysis. The measures of the left eye were only accepted if that of the right eye was not available, or not reliable. Prior to data analysis, the data was checked for outliers and their possible effects on the interpretation of the analysis. There is no widely accepted method to decide whether to exclude or include extreme values (Armstrong et al. 2005; Tabachnick 1996). In our study, if it was a genuine score, outliers were included in the data analysis. Distribution for all the data was tested for normality with histograms, boxplot, Kolmogorov-Smirnov test or Shapiro-Wilk test. It was considered as a significant difference from normal value when $p \leq 0.05$. Values are presented as mean ± Standard Deviation (SD), which are generally most informative statistics for distribution.

Association between two variables was presented by Pearson or Spearman correlation co efficient. ANOVA was then performed in order to determine the strength and direction between two variables. Pearson correlation (R), the coefficient of determination (R^2), the significant level and the regression equation were presented when there was a statistically significant association between two variables. The difference was tested in order to compare the correlation (see Appendix 1). The significant difference was reported when observed z score (z_{obs}) is out range of the value from –1.96 to 1.96 (Pallant 2001). The difference in linear regression was tested between two groups. ANOVA was performed to test whether the two lines differ in slope or constant. To determine whether the residual variances are different, the ratio of the two variances was to be tested by a two-tailed variance ratio F-test after dividing the larger variance by the smaller (Armstrong et al. 2005).

All the statistical techniques used in each chapter are summarized and presented as an appendix 1.

Chapter 2

Pilot studies
Selection and evaluation of procedures for equipment

2.1 Axial length measurement

2.1.1 Choice of equipment for axial length measurement

In the past, conventional ultrasound measuring devices have played a decisive role in the measurement of axial length. Ultrasound is transmitted to the eye from a transducer and sound is reflected back to the transducer from tissue interfaces. However, the technique has been confounded by potential misalignments, corneal indentation during measurement and large measurement variability (Binkhorst 1981; Kurtz et al. 2004; Steele et al. 1992).

Currently, IOL-Master provides a non-contact technique with no risk of infection or corneal abrasion. The reproducible and precise AL measurements achieved with IOL-Master were shown to be better than that of ultrasound in earlier studies (Findl et al. 2001; Goyal et al. 2003; Haigis et al. 2000; Kielhorn et al. 2003; Lam et al. 2001; Rose and Moshegov 2003; Rudnicka et al. 1992; Santodomingo-Rubido et al. 2002; Sheng et al. 2004). Two recent studies have also shown that it is considered particularly appropriate for AL measurement in children (Carkeet et al. 2004; Quinn et al. 2003). Moreover, it is possible to achieve consistent readings with little variation with IOL-Master (Olsen and Thorwest 2005). Additionally, it is less time consuming and has the advantages of improved precision and patient acceptability when compared to conventional applanation ultrasound biometry. Therefore, IOL-Master (Zeiss, Germany) was selected in our study.

2.1.2 Principles of how the IOL-Master works

The Zeiss IOL-Master is based on partial coherence laser interferometry (PCI) to measure AL. It is a combined biometry instrument which measures parameters of the human eye needed for intraocular lens calculation (see Fig. 2-1). The IOL-Master measures the ocular AL between the corneal vertex and retinal epithelium along the visual axis using a red fixation beam, with a resolution of 12 µm and a precision of 5 µm (Drexler et al., 1996). It utilises PCI technique, which generates interference patterns from the

combination of a reference beam with a second beam reflected from the ocular components.

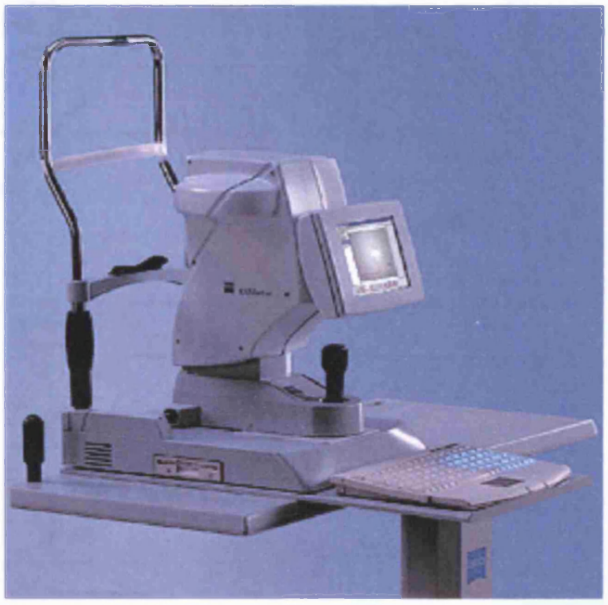


Fig. 2-1: A picture of IOL Master (Zeiss, Germany)

The basic principle of optical biometry is depicted schematically in Fig.2-2. A dual beam of infrared light is emitted by a semiconductor diode laser (λ= 780 nm) of high spatial coherence and short coherence length (160 μm). The eye to be measured and the photodetector are situated at the interferometer. Both partial beams are reflected at the corneal surface and the retina. Interference occurs if the path difference between the beams is smaller than the coherence length. The interference signal received by the photodetector is measured, dependent on the position of the interferometer mirror, which can be measured precisely. The optical distance is used to derive geometric intraocular distances by incorporating the group refractive indices of the respective ocular media (cornea, lens, aqueous and vitreous humour).

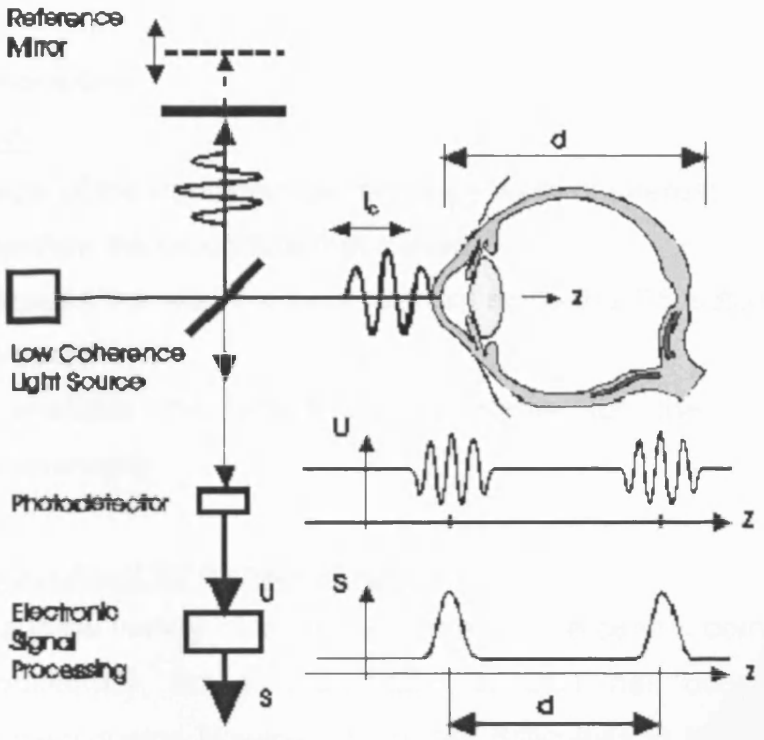


Fig. 2-2: A diagram showing principle of a dual beam partial coherence interferometer

It also measures quickly and precisely the ocular parameters in separate measurements such as corneal radius, corneal power and anterior chamber depth. These additional measures are not performed in our study.

2.2 Pilot study (1): Validation of the Pentacam system

2.2.1 Introduction

Aims of study

Three aspects of the Pentacam performance were of interest:

i. To confirm the procedure that it used;
ii. To assess the effect of poor fixation; since the DS subjects might not fix properly.
iii. To evaluate the effect of cycloplegia for the lens thickness measurement;

Choice of equipment for corneal assessment

There are a large variety of techniques to measure central corneal thickness (CCT). Traditionally, the gold standard for CCT has been provided by ultrasound pachymetry. However, there are difficulties in alignment (Gordon et al. 1990; Higgins et al. 1993). That is to say, it is difficult to locate accurately the same points of measurements in a serial measurement. This may result in falsely large variations in corneal thickness as the thickness increases from the centre to the periphery of the cornea. What is more, it needs anaesthesia and contact of the probe.

A novel apparatus capable of taking CCT measurement is the Oculus Pentacam system (Fig. 2-3) (principle of it is described in a later section). The CCT values obtained with the use of the Pentacam system tend to be closer to ultrasound pachymetry and with less variability compared with Orbscan in many recent studies (Barkana et al. 2005; Buehl et al. 2006; O'Donnell and Maldonado-Codina 2005; Rufer et al. 2005).

The main advantage of the Pentacam system is that the eye screening system does not rely on placido-based technology for corneal topography. With more advanced technology, it also defines the optical properties of the cornea such as radius and asphericity. Polynomial decomposition has been used to determine corneal aberrations. Noticeably, the true corneal power is

provided by the Pentacam which takes posterior corneal surface and corneal thickness into account. As an anterior segment analysis system, it also provides information for anterior chamber parameters (Buehl et al. 2006; Meinhardt et al. 2005) and lens properties. The effect of tear film fluctuations on corneal topography measurements was minor. More importantly, it is suitable for our subjects with learning disability since it is a non-contact technique whereby the anterior surface, the thickness profile, and the posterior surface are determined in one step. This eliminates alignment errors that may occur and accelerates the measurement procedure.
Therefore, the Pentacam system was chosen as the most suitable for the current study.

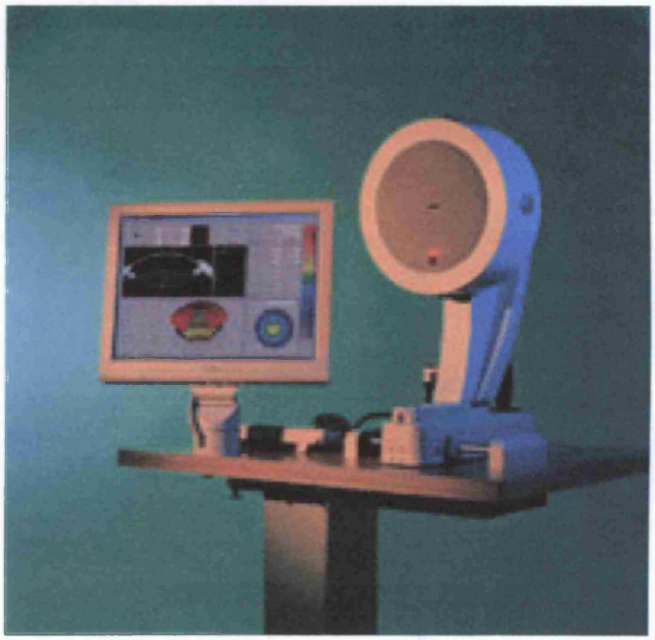


Fig. 2-3: A picture of the Pentacam system (Oculus, Germany, 1.11 version software)

Principles of how the Pentacam system works

The Pentacam system uses a rotating Scheimpflug camera and a visible slit light source (blue at 474 nm). The camera on the rotating wheel takes a

complete picture around the optical axis of the eye from the anterior surface of the cornea up to the posterior surface of the lens (Fig. 2-4).

The overview image from the Pentacam system gives several evaluations of the eye being measured (Fig. 2-4). The system shows the camera position (Fig. 2-4a) and analyzes the Scheimpflug pictures (Fig. 2-4b) automatically by recognizing the central curvature and constructs the centre line through the cornea, the anterior chamber and the lens accordingly. It then calculates and projects a model of the anterior eye segment (Fig. 2-4c). The corneal topography is shown as well (Fig. 2-4d).

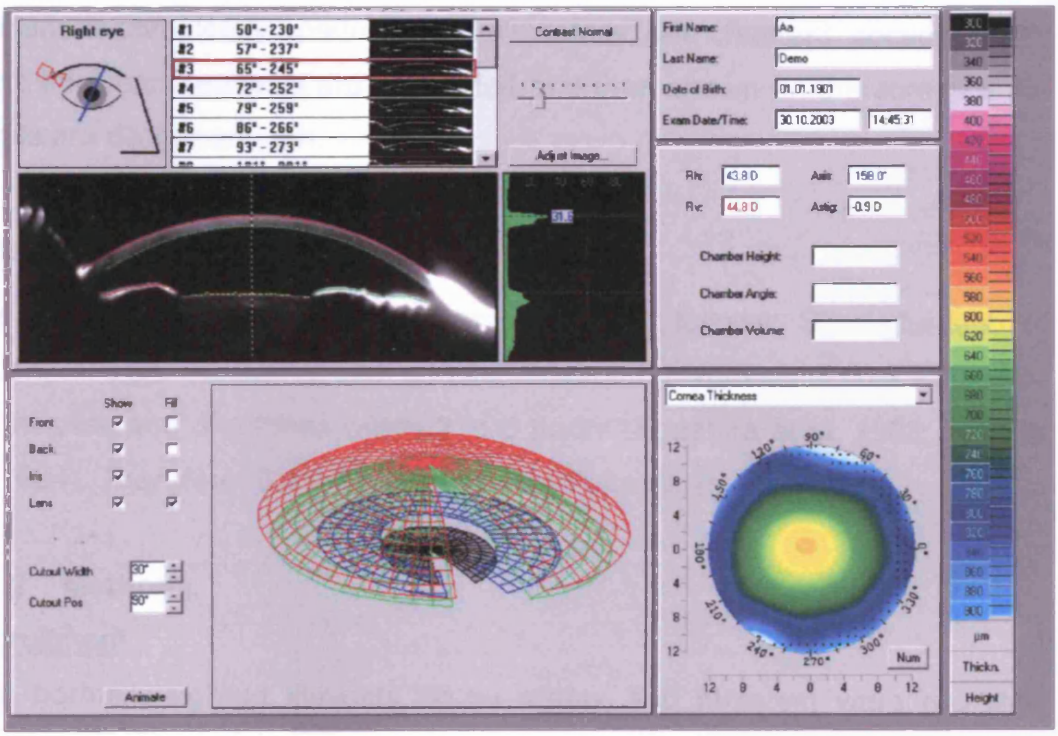


Fig. 2-4: The overview image from the Pentacam system

a) Upper left: Camera/slit lamp position and the cross-section of the eye;

b) Left center: Scheimpflug image and densitometry of the lens;

c) Lower left half: Virtual eye

d) Lower right : Corneal topography

Within 2 seconds, the Pentacam system rotates and acquires 25 images that contain 5000 measurement points on the corneal surface. It provides a topography map of the anterior and posterior surface of the cornea. It also provides a number of keratoconus indices on the keratoconus map as an objective method of detection of keratoconus (for more details, see chapter 3, section 3.3.1). Additionally, anterior chamber parameters including anterior chamber volume (ACV), anterior chamber angle (ACA) and anterior chamber depth (ACD) are calculated from the three-dimensional model (for more details, see chapter 3, section 3.2.7). The density of the lens is standardized from 0 to 100. Therefore, 0 means the lens shows no clouding, 100 means the lens is completely opaque (for more details, see chapter3, section 3.3.2). Lens thickness readings are calculated and then shown on the screen if the pupils are dilated enough.

The choice of mydriatic of the agent

The advantages of use of Tropicamide are as follows: Short duration of action, minimal number of side effects, maximum mydriasis occurs within 15-40 minutes and dissipates within 2 to 6 hours (Egashira et al. 1993; Mutti et al. 1994). Therefore, 0.5% Tropicamide was chosen in our study.

2.2.2 Methods

Recruitment

Five normally-sighted subjects (three males, two females) were recruited from our university. Mean age of the subjects is 35.6 ± 9.9 years. Three subjects' pupils were dilated for lens thickness measurement. Oral consent was given by all the subjects.

Examination procedures

The examiner (PJ) took all the measurements by the Pentacam system (the details about how to use it are in the next section). The procedures of the measurements were as follows:

First of all, one drop of 0.5% Tropicamide was put in the right eye of the subjects for the lens thickness measurement. Images for the right eye were

then taken every 1-2 minutes until the pupil size and the lens thickness values were kept at a relative stable level. It took 40- 50 minutes and about 30 images were taken.

Aiming to assess the effects of poor fixation, the following five additional measurements were then taken of the left eye of all the subjects: One was taken when the subject was looking at the fixation light; One was taken when the subject was looking to the right approximately 2.5 cm away from the centre; One was taken when the subject was looking to the right again, and tilting her or his head; One was taken when the subject was looking above the fixation light; One was taken without the blue fixation light when the subject was looking at the centre of the black circle. The above procedure took a further 10 minutes. Therefore, the whole procedure took 60 to 70 minutes for each subject.

Use of the Pentacam system

The Pentacam system was used in a darkened room. The subject's chin was placed on the chin rest and the forehead rested against the forehead strap. The subject was instructed to look at the blue fixation light.

Firstly, the examiner adjusted the Pentacam so that the subject's pupil came into view by moving the joystick. The apex of the cornea was marked by the yellow circle and the pupil was marked by the big blue circle. The pupil image showed the position of the measuring head in vertical or horizontal direction (Fig. 2-5a: upper centre). Secondly, the live Scheimpflug image and alignment red dot were visible by adjusting the joystick forward and backward. The apex of the cornea was marked by the red dot (Fig. 2-5b: lower left). Then the examiner made the final adjustment to reach the best position by following the red arrows (Fig. 2-5c: lower centre). During this time, the subject was asked to keep looking at the blue fixation light and open his/her eyes widely. The image capture was then taken automatically when the red dot was on the red line and yellow circle was in the cross.

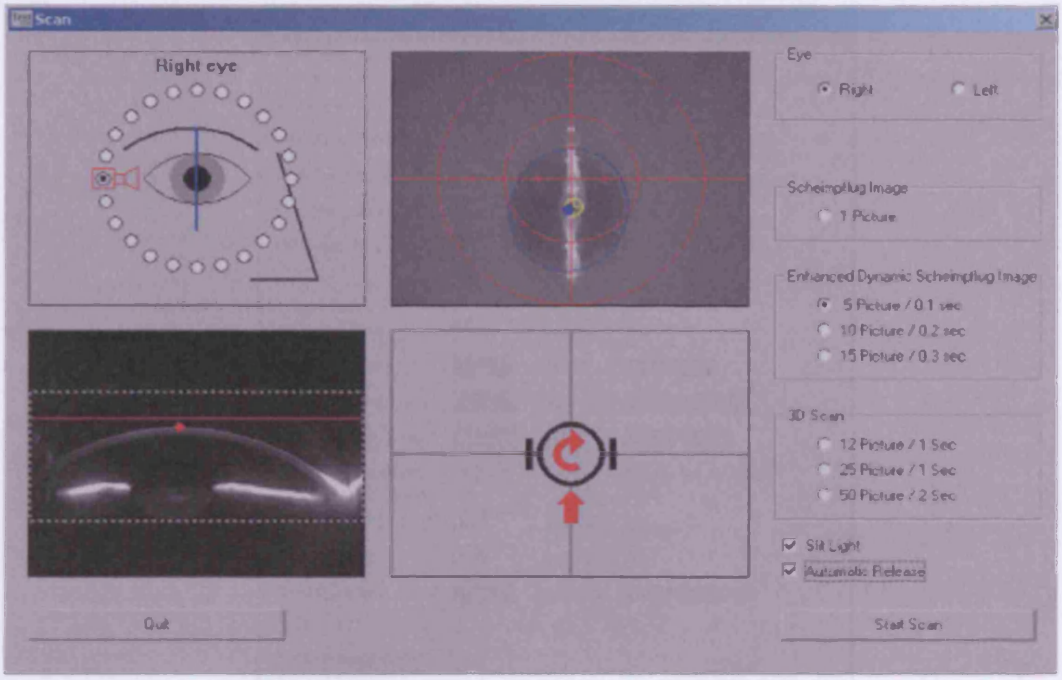


Fig. 2-5: The Image on the Pentacam screen before starting scan

a) The **upper centre** is "the image of pupil", which is for preadjustment.

b) The **lower left** is the "live Scheimpflug image"

c) The **lower centre** shows information for the fine alignment

QS (Quality specification) was shown on the screen (Fig. 2-6). The system, therefore, indicates the reason if the image is of poor quality. It also provides detailed information about over which area the front and back of cornea have been measured, the alignment level, eye movement condition and a value of QF (Quality Factor). QF gives the degree to which the image was disturbed by patient's blinking or extraneous light influences. According to the manual, the data were regarded as valid:

i. The analyzed area was higher than 50%;
ii. QF > 95%;
iii. Lost segments were lower than 3;
iv. The value of eye movement was lower than 150.

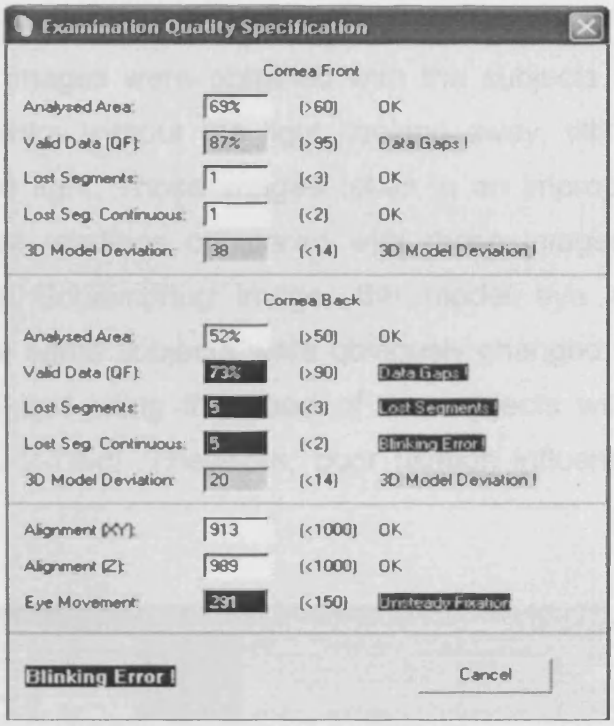


Fig. 2-6: Examination quality specification table (QS Table)

2.2.3 Results and discussions

Should the blue slit light be kept on or off when taking images?

Following the manual, the blue fixation light is used for screening purposes in order to get an impression of the condition of the lens without dilating the pupil, thus enhancing the patient's comfort. The subsequent results from our pilot study proved that there is no big difference between the measurement with the lights on or off if the subjects were instructed to look at the centre of the black circle (Table 2-1). However, it was shown that it may be better to put the blue light on in order to complete the examination more quickly and successfully. Firstly, it provides information for the fine alignment on the alignment screen, which is helpful for the examiner to take good images in a short space of time. Secondly, it is much easier for the subjects to fixate a light rather than looking at a whole black circle. Subjects with DS are more likely to lose interest or look away due to poor co-operation and lack of comprehension. Therefore, it could reduce the chance of the subject looking away from the centre of the black circle.

To assess the effects of poor fixation

The readings of images were obtained with the subjects fixating the light, looking at the centre without the light, looking away, tilting the head and looking above the light. Those images taken in an improper position gave obviously different readings compared with those images taken properly (Table 2-1). The Scheimpflug image, the model eye and the corneal topography of the same subjects were obviously changed by misalignment, improper fixation and tilting the head of the subjects with the Pentacam system (see Fig. 2-7a-c). Therefore, poor fixation influenced the readings greatly.

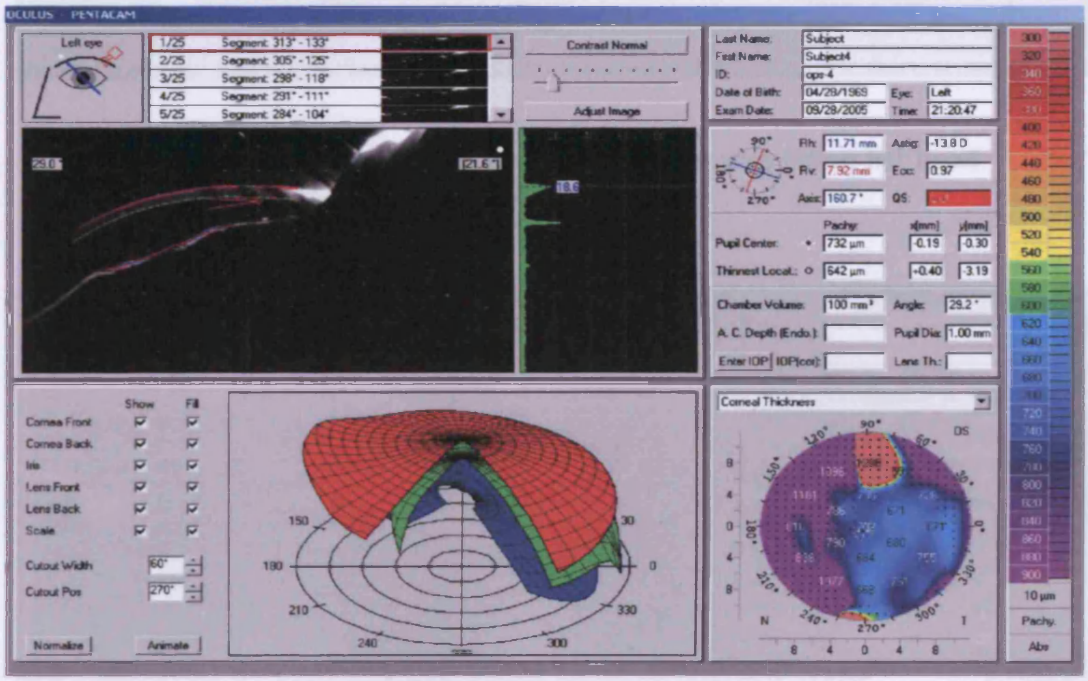


Fig. 2-7a: The image taken when the subject was looking away

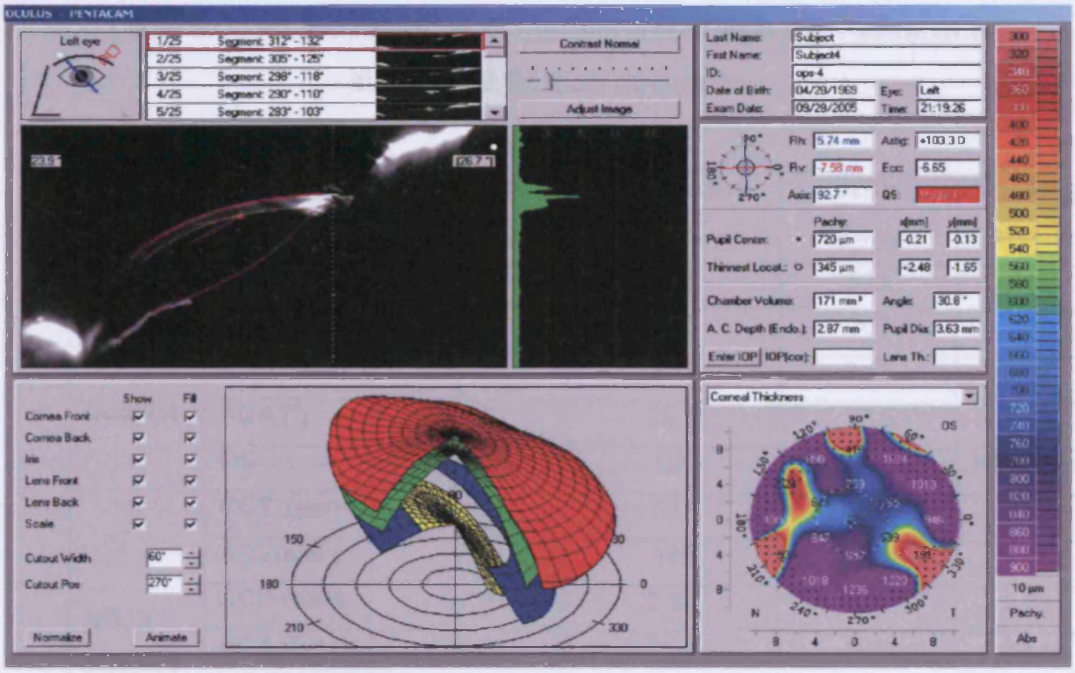


Fig. 2-7b: The image taken when the subject was tilting her head

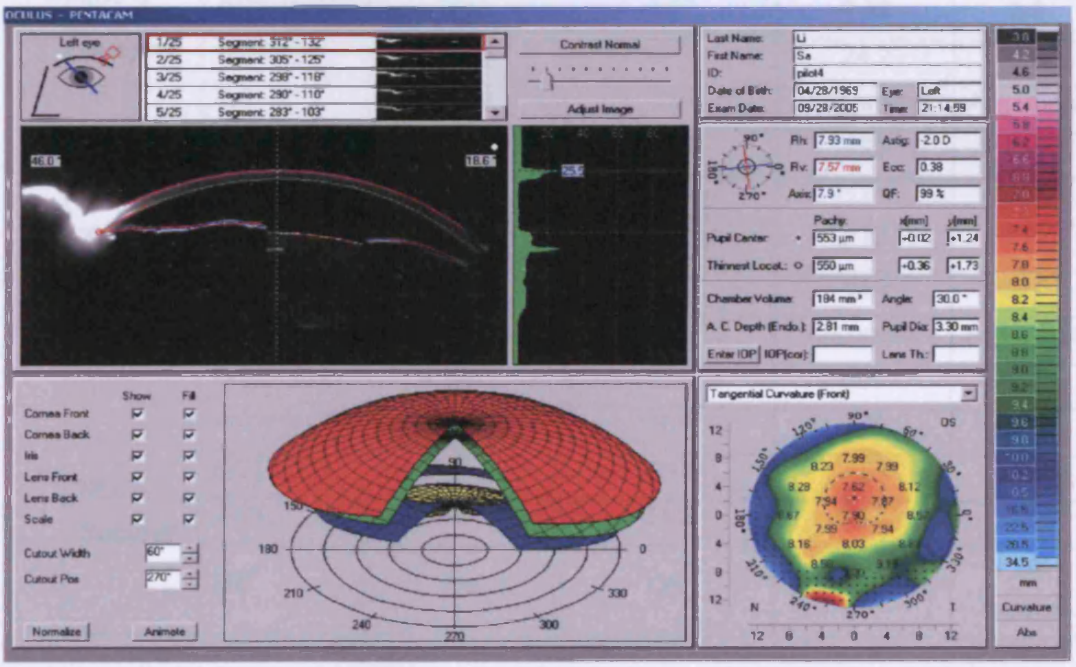


Fig. 2-7c: The image taken when the subject was looking above the light

Table 2-1: All the readings of measurement with the Pentacam at different fixation direction

		Fixating the light	Without the light	Looking away	Looking above
NO. 1 Subject	CCT (μm)	606	593	613	615
	ACV(mm^2)	198	196	203	204
	ACD (mm)	3.15	3.14	3.15	3.16
	ACA (^{0})	29.2	29.7	17.5	29.1
	QS	OK	OK	Poor fixation	Alignment
NO. 2 Subject	CCT (μm)	542	547	444	562
	ACV(mm^2)	166	148	169	154
	ACD (mm)	3.16	2.94	N/A	2.83
	ACA (^{0})	33.5	31.0	N/A	33.4
	QS	OK	OK	Alignment	Poor fixation
NO. 3 Subject	CCT (μm)	528	526	497	670
	ACV(mm^2)	223	203	268	252
	ACD (mm)	3.63	3.57	3.12	2.8
	ACA (^{0})	45.2	44.7	24.2	21.5
	QS	OK	OK	Alignment	Alignment
NO. 4 Subject	CCT (μm)	573	566	720	553
	ACV(mm^2)	188	147	171	184
	ACD (mm)	3.06	2.87	2.87	2.81
	ACA (^{0})	32.5	27.6	-11.6	30.0
	QS	OK	OK	Alignment	Alignment
NO. 5 Subject	CCT (μm)	541	558	601	558
	ACV(mm^2)	168	167	176	167
	ACD (mm)	3.32	3.13	3.01	3.13
	ACA (^{0})	38.7	34.2	34.8	34.2
	QS	OK	OK	Poor fixation	Poor fixation

To evaluate the effects of cycloplegia for the lens thickness measurement

The effect of cycloplegia on lens thickness, pupil diameter during the test in three subjects is presented Fig 2-8. As expected, the pupil size was highly associated with the action time of the cycloplegia in the subjects (Pearson correlation: 0.831, 0.959, 0.970, $p < 0.01$) (Fig. 2-8a). The lens thickness measurement was highly associated with the action time of the cycloplegia as well (Pearson correlation: 0.338, 0.674, 0.256, $p < 0.01$) as well (Fig. 2-8b). A statistically significant positive association was found between the lens thickness and pupil size in No.1 and No. 2 subjects (Pearson correlation: 0.635, 0.649 respectively, $p < 0.01$) (Fig. 2-8c).

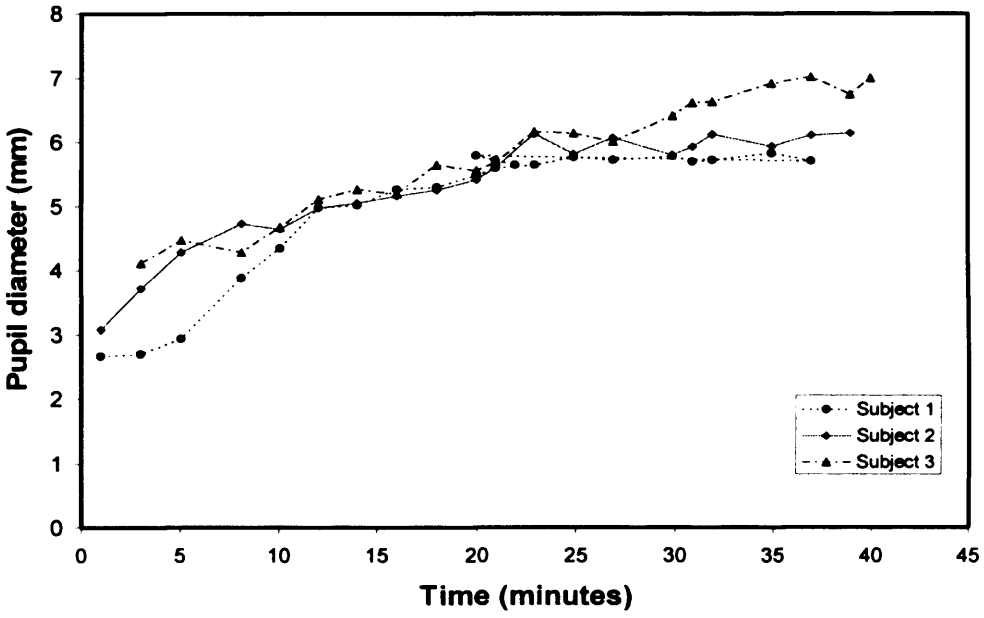


Fig. 2-8a: The effect of cycloplegia on pupil diameter during the test

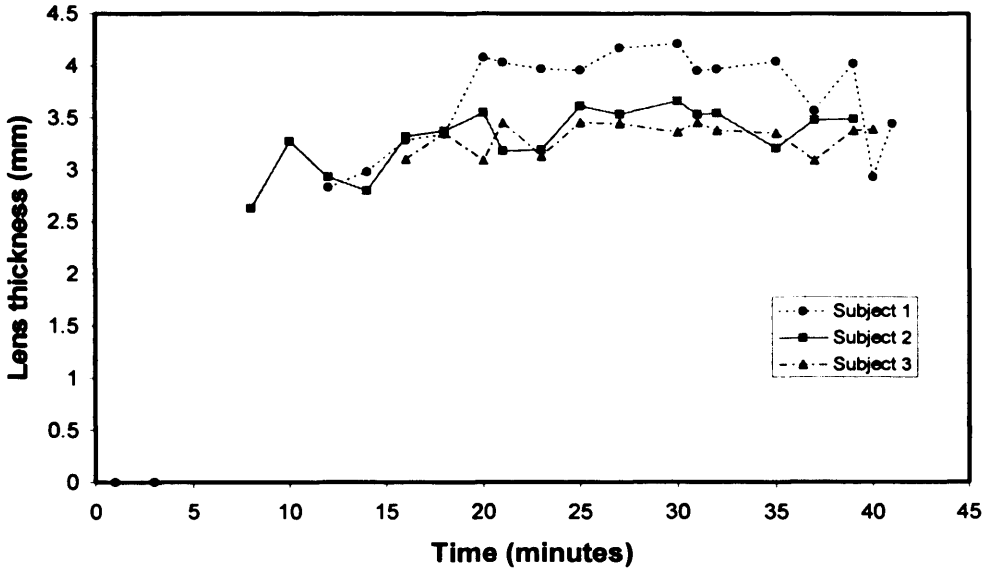


Fig. 2-8b: The effect of cycloplegia on lens thickness during the test

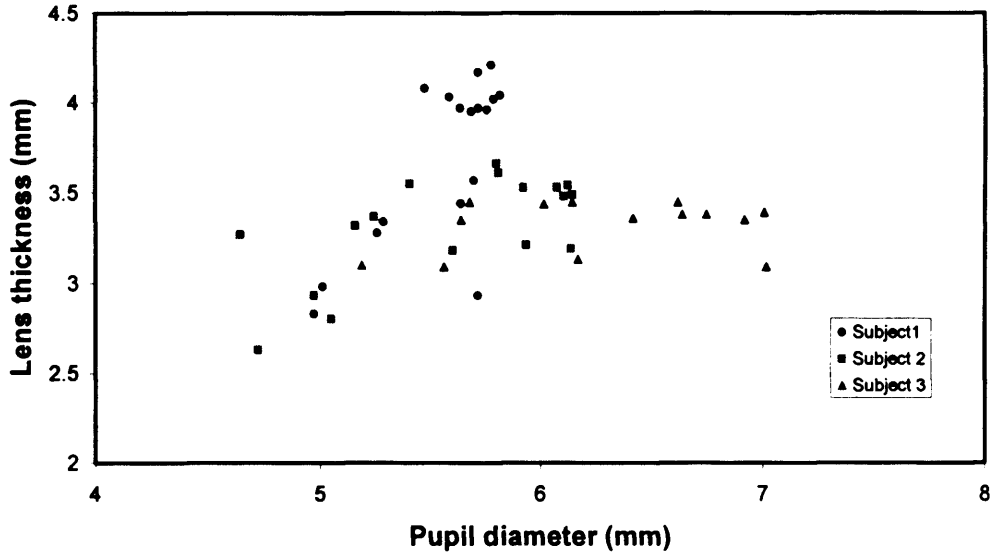


Fig. 2-8c: The effect of pupil diameter on lens thickness

If the size of the pupil was not big enough (below 4.5 to 5 mm, see Fig. 2-8c), no lens thickness reading was shown by the Pentacam system. Lens thickness was shown automatically on the screen when the pupil size was big enough. Moreover, the readings of lens thickness increased with the action time of the cycloplegia and the size of the pupil (Fig. 2-8b, c). It then fluctuated with a small range after the size of the pupil was above 5.5 mm or when the cycloplegia had worked for at least 20 minutes.

The variability of the lens thickness could be due to the variability of the measurement with the Pentacam system. In addition, different levels of cycloplegia can result in different estimates of lens thickness because the lens is not adequately stabilized by a cycloplegia. Thus, it is reasonable to assume that the variability of the lens thickness obtained with the Pentacam system might be due to the fluctuations of accommodation by incomplete cycloplegia.

2.2.4 Conclusions

The blue fixation light should be kept on in order to complete the examination quickly and successfully in our main study. Poor fixation greatly influences the readings compared to those values from the images taken in a proper position. It is, therefore, important to give the subject appropriate instructions and try to maintain their fixation. It is also essential to check the quality of the images and select those reliable images for the further analysis. Cycloplegia has significant effect on the pupil diameter and lens thickness during the test. The lens thickness reading should be measured after 20 minutes using cycloplegia and when the pupil size is above 5.5 mm.

2.3 Pilot study (2):
Selection of procedures for refraction and fundus photography

2.3.1 Introduction

Aims of the study

The first aim was to test the compliance of the DS subjects with the fundus camera. The second aim was to assess whether an autorefractor could be used for measuring refractive error in our main study.

Choice of equipment for fundus photography

Fundus photography is routinely performed to observe changes to the retina and the optic disc in practice. It has benefited from the development of digital imaging devices.

Over the past decade, Heiderberg Retina Tomography (HRT), a confocal scanning laser microscope for vivo 3-dimension imaging, has been considered as the gold standard for evaluation of the optic disc for glaucoma. However, the acquisition of retinal photography skills is likely to be very individual-specific and patients need to co-operate well during the examination.

A non-mydriatic fundus camera is also a valuable and reliable screening tool for the observation and morphometric analysis of the retina (Detry-Morel et al. 2004; Lamoureux et al. 2006; Massin et al. 2003; Murgatroyd et al. 2004; Shiba et al. 1999). Excellent repeatability and agreement between the HRT and non-mydriatic fundus camera has been reported (Lamoureux et al. 2006). Moreover, fundus image quality taken with a non-mydriatic fundus camera by non-professionals can be as accurate as those taken by a fully trained professional photographer (Maberley et al. 2004). Even HRT is available in our school; however, the author considered that the level of co-operation needed was too demanding for the subjects of this study. Therefore, a non-mydriatic fundus camera was chosen for our study.

Principles of how the Topcon fundus camera works

Our study used a Topcon non-mydriatic TRC_NW6S fundus camera, which is connected with a SONY DXC-950MD video camera (see Fig. 2-9). The camera uses Gullstrand's reflex free principle. The illumination and viewing systems are imaged in separate regions of the pupil preventing the corneal and lens reflexes being viewed. Fundus cameras contain two light sources—a tungsten filament illuminating system and a second light, which is flashed when the photograph is taken. This increases the illumination of the fundus. Non-mydriatic fundus cameras use infrared light (which does not induce miosis). The image can be focused using the infrared light. The speed of the flash units used for taking the photograph is so fast that the pupil cannot constrict before the photograph is taken. However, the technique is not suitable for patients with small pupils.

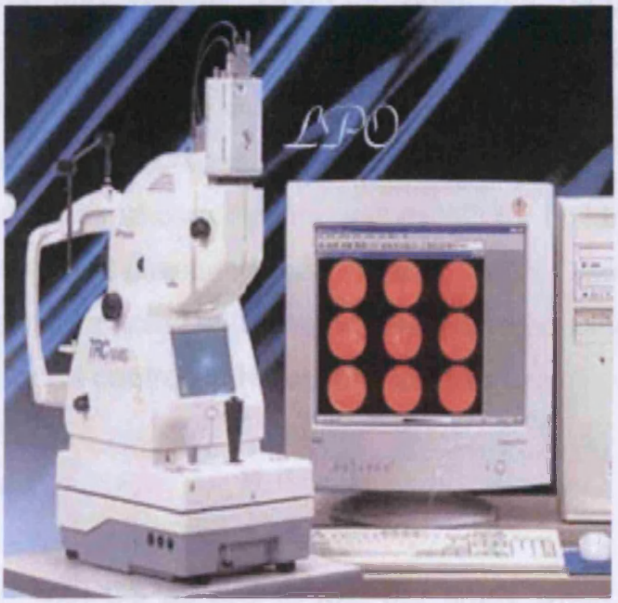


Fig. 2-9: A picture of a Topcon TRC_NW6S fundus camera

Choice of measuring refractive error

Objective testing is the choice for establishing the amount of refractive error for our subjects with learning disability. There are several available methods of measuring objective refractive error in our school: autorefraction,

cycloplegic retinoscopy and Mohindra retinoscopy. Since autorefraction is a much faster procedure and does not necessarily require a clinician, autorefraction was considered.

a. Autorefraction

Autorefraction is an established method (Isenberg et al. 2001; Iuorno et al. 2004; Logan et al. 2005; Pesudovs 2004). The Topcon KR-7500 autorefractor was used in our study. The device has an auto-fogging mechanism to relax accommodation. Measurements were taken using the auto-tracking and auto-shoot functions (from the manual).

b. Mohindra retinoscopy

Studies have shown the use of Mohindra technique as an accurate alternative to cycloplegic retinoscopy for children (Mohindra and Molinari 1979; Saunders and Westall 1992). It does not require the use of a cycloplegic. It makes two assumptions: 1. that the retinoscope light does not stimulate accommodation; 2. that as a result the eye assumes its resting level of accommodation (Owens et al. 1980). A correction factor of 1.25D for adults, 1D for children above 2 years and 0.75D for children younger than 2 years is recommended (Saunders and Westall 1992). Disadvantages are that it requires a certain amount of skill and experience on the part of examiner and the lack of exact control of the accommodation.

2.3.2 Methods

Recruitment

Twelve children with DS agreed to join our study when they came to the University clinic for their regular eye tests. Four control children who are the siblings of children with DS were also recruited at the same visit. Six additional control children were willing to join when they attended their appointment for an eye test. Oral consent was given by both parents and children.

Examination procedures

During all the subject's eye tests, near retinoscopy was carried out by JMW for measuring refraction (as described in detail in chapter 3, section 3.2.4.). Afterwards, fundus photographs of both eyes were taken by the author (PJ). Lastly, refractive error was measured again with the use of autorefractor by the author (PJ). All refraction measures were carried out without cycloplegia. These measurements took about 8 minutes for control children. It took much longer for children with DS, depending on their co-operation.

Use of the Topcon fundus camera

The examiner (PJ) used the fundus camera in a dimly lit room. She set the picture angle to 30° first and aligned the subject's eye in the centre of the screen by moving the joystick. In the meantime, the subject was instructed to look at the internal fixation target—a green light. The examiner brought the instrument slowly closer to the subject until the retinal image appeared on the video monitor. The fixation target helped to achieve consistent photographs. When properly aligned, the photographic field was centered between the optic disc and the macula. It provided photographic documentation of the optic disc, the macular and about two disc diameters of retina temporal to the optic disc (Fig. 2-10). The captured image was sent to the external recording device and displayed on the colour video monitor. The examiner viewed each digital image immediately. If it was not good enough, a second one was taken at the same sitting. However, the risk involved in increasing the number of photographs is that their quality may decline, due to the pupillary construction induced by repetitive flashes.

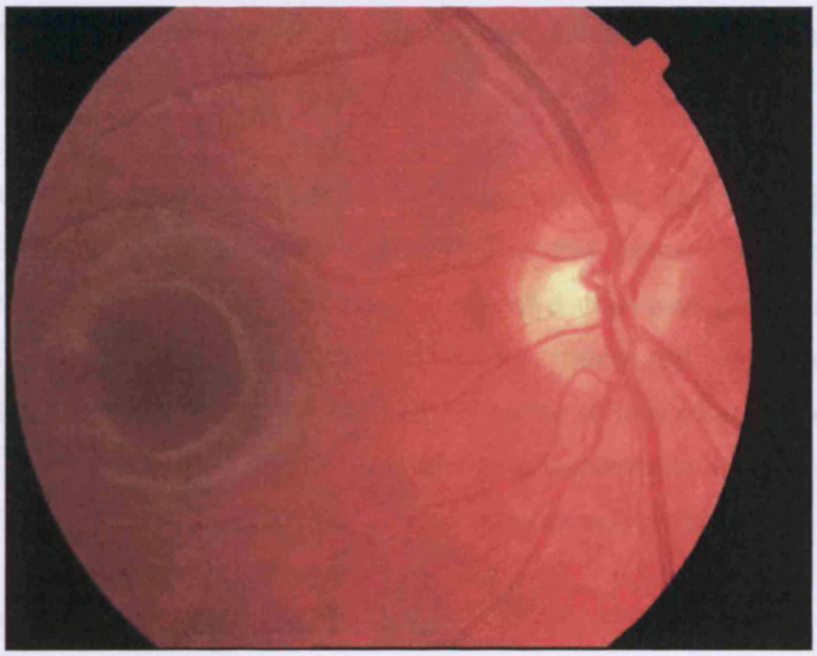


Fig. 2-10: A fundus photograph of the right eye, one subject with DS

2.3.3 Results and discussions

Measuring refractive error

All the child subjects were measured successfully during the eye examination by near retinoscopy. All control children co-operated well with the auto-refractor. However, only six of twelve children with DS were able to co-operate with the auto-refractor.

It showed that auto-refraction was a less successful procedure with the children with DS. This was possibly due to the children being tired as they already had had a complete time-consuming eye test and fundus photography taken. It was difficult to keep their further attention at one visit. However, using near retinoscopy, the children were encouraged by the examiner (JMW) by asking them to follow the light in the dark as if playing a game. This held their attention better while refraction was measured. Moreover, all the children with DS in the cohort were used to Mohindra retinoscopy and it was shown to be successful in previous studies (Cregg et al. 2001; Woodhouse et al. 1997). It is an established technique that has been shown to give equivalent results to cycloplegic retinoscopy in children

with DS and in control children (Saunders and Westall 1992; Woodhouse et al. 1997).

Taking the whole examination procedure into account, all our subjects need to sit still for axial length measurement and the other ocular biometrical parameters. Autorefraction requires the use of a chin and hest rest as well. However, accommodation is needed to be measured with the use of retinoscopy by JMW. Therefore, it seemed better to use near retinoscopy by JMW during the eye test rather than using auto-refractor in order to retain their attention and complete all the measurements successfully.

Fundus photography

Fundus photographs of both eyes from twelve children with DS and ten control children were taken. Two children with DS could not keep still and look at the fixation light at all. Taking the future planimetric evaluation into consideration, the quality of each photograph was scored by the following:

Grade 1 - Good: focus very well, the whole optic disc visible;

Grade 2 - Moderate, the whole optic disc visible, assessable but limited;

Grade 3 - Poor, not the whole optic disc visible;

The photographs scored as Grade 1 and 2 can be accepted in the planimetric evaluation and photographs scored as Grade 3 were rejected. Quality of the fundus photography is shown in Table 2-2. The success rate of fundus photography was 83% and 100% in DS children and control children respectively.

Table 2-2: Quality of fundus photography in 22 children

Image quality	**DS Children**		**Control children**		**evaluation**
	Right	Left	Right	Left	
1 Good	2	1	8	7	Accepted
2 Moderate	8	9	2	3	Accepted
3 Poor	2	2	0	0	Rejected

2.3.4 Conclusions

The procedures for fundus photography and retinoscopy were adequately successful. Therefore, the Topcon fundus camera and Mohindra retinoscopy were chosen for the main study.

2.4 Pilot study (3): To obtain the camera magnification

2.4.1 Aim of the study

This pilot study aimed to work out the magnification of the Topcon fundus camera in order to correct the magnification of the camera for the planimetry evaluation. All the procedures followed previous studies (Garway-Heath et al. 1998; Rudnicka et al. 1998).

2.4.2 Methods

The conversion factor from pixels to microns

The conversion factor from pixels to microns was calculated based on the chip type of the SONY DXC-950MD video camera which was connected with the Topcon fundus camera. The chip features are as follows: Sensing area (mm): 6.4*4.8; Picture elements (pixels): 752*582. So, the conversion factor for the chip (mm/pixel) is 6.4/752=0.0085 or 4.8/582=0.0085 mm/pixel.

Procedures of experiment

One Moorfields model eye was used to investigate the relationship between the actual size of a fundus feature and its photographic image as in a previous study (Rudnicka et al. 1992). The model eye has a micrometer head and a vernier scale to adjust the axial length for the required refractive error. Prior to the commencement of the experiment, the value of the micrometer setting to produce a required refractive error (on retinoscopy) from +11 to -14 D was recorded by an optometrist (SJ). However, the reading on the micrometer is not the true axial length.

The following steps were carried out for the camera scaling experiments. Firstly, a square target of 2 mm was printed with a laser printer and then laminated. The true size of the target was measured with a travelling microscope.

Secondly, the square target was applied to the fundus surface of the model eye. Distilled water was used to fill the anterior and posterior chambers. The fundus surface was attached to the micrometer head and vernier scale.

Thirdly, images were taken with the Topcon camera at the 30^0 field setting with the model eye set at different values, corresponding to a range of ocular refractions from +11.0 D to -14.0 D by rotating the micrometer. Between +/- 6D, images were recorded every 1D and thereafter every 2D. In all cases, the square object was centred in the camera field (Fig. 2-11).

Lastly, the pixels of each side length of the square target (s) in the photo was measured by 2000 ImageNet software. It was noted that the target rotated at the same time as the micrometer was rotated to adjust the required refractive error. It was very important that the same side length of the target was measured. Therefore, the longest side length was recorded each time.

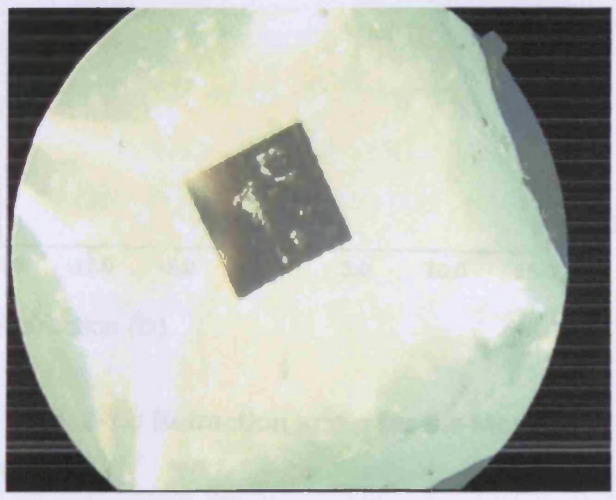


Fig. 2-11: A photo for the square target taken by fundus camera

Camera scaling calculations

Eye factor (q) and camera factor (p) were worked out by the different formulae which were provided by Garway-Heath (1998). The "q" factor for the Moorfield eye was calculated by the formula:

$$q=-0.0051\times Ref + 0.2962$$

for the range of ametropia settings of the model eye. The true size of the target (t), the photo size of the target (s) and eye factor (q) had been worked out, therefore, the "P" factor for the eye was calculated by the formula:

$$p= t/qs.$$

The Rudnicka paper stated "with telecentric instruments, the value of p is constant over an acceptable range of ametropia, provided the instrument is aligned and focused correctly." (Rudnicka et al. 1998). Refractive error against p for the model eye was plotted (Fig. 2-12). The slope is close to zero and the Topcon camera can be considered telecentric: $Y = - 0.0019X + 1.67$.

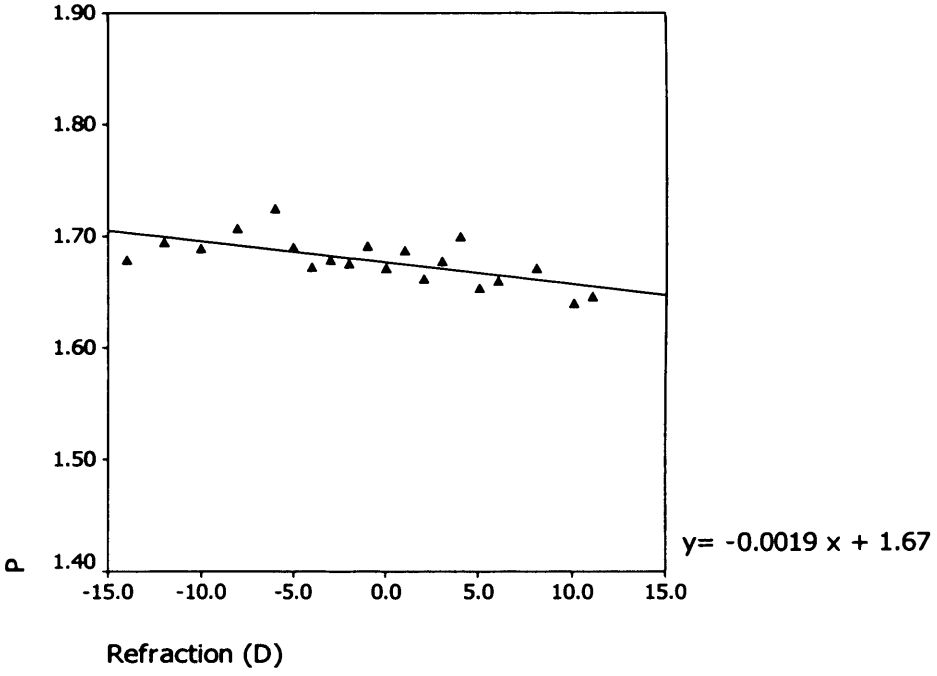


Fig. 2-12: Refraction and p for the Model eye

2.4.3 Conclusion

The Topcon non-mydriatic TRC_NW6S fundus camera was telecentric. The scaling code was written in the software by JEM (Appendix 8).

2.5 Pilot study (4): Validation of the Impact tonometer

2.5.1 Introduction

Aims of the study

A recent update in calibration of the I-care tonometer has made a validation study necessary. We aimed to test the accuracy of the I-care tonometer by comparing it with Goldmann tonometer. Additionally, the impact of CCT on IOP reading by both tonometers was compared.

Choice of tonometers

Tonometers are instruments designed to evaluate the IOP. Most devices rely on the principles of applanation, which means deforming an area of the cornea with a small amount of force that is used to calculate the IOP. Goldmann tonometer has been the gold standard for 40 years because it is accurate and reproducible (Dielemans et al. 1994; Gilchrist 1996; Moses 1961).

The non-contact Pulsair tonometer has many advantages over the contact tonometer and has also shown high accuracy when compared with Goldmann tonometer (Atkinson et al. 1992; Bricker et al. 1990; Lawson-Kopp et al. 2002; Lin et al. 2003; Mackie et al. 1996; Vernon 1995; Yucel et al. 1990). In addition, local anaesthetic is not required, it is easier to use, However, it has been reported that the non-contact tonometry is influenced more than conventional applanation tonometry by the corneal thickness (Cennamo et al. 1997; Graf 1991). In addition, The Pulsair was reported uncomfortable by some subjects (Kontiola and Puska 2004).

The I-care rebound tonometer has a simple construction and has the possibility of measuring IOP without a local anaesthetic (Fernandes et al. 2005; Garcia-Resua et al. 2006; Kontiola and Puska 2004; Leiva et al. 2006). The round tip minimizes the risk of corneal injury from the probe's impact (Kontiola 2000). It is also easy to perform and the measurement is barely noticed by the patient since the tonometer is intended for use by general

practitioners, optometrists and for the home monitoring of intraocular pressure (Kontiola and Puska 2004). Therefore, compliance would be expected better for subjects with DS.

The evaluation studies have been done by the inventor, which were mostly on animals (Danias et al. 2003; Goldblum et al. 2002; Kontiola et al. 2001). A comparison with the Pulsair 3000 in an elderly population proved that there was a similar result and it was better tolerated by patients (Kontiola and Puska 2004). It has been recently reported that measurement of IOP in normal, healthy subjects using the I-Care tonometer produced a small, statistically insignificant, positive bias when compared with the Goldmann tonometer (Davies et al. 2006). However, two other studies concluded that the I-care tonometer significantly overestimates IOP when compared with the measurement of Goldmann tonometry (Fernandes et al. 2005; Garcia-Resua et al. 2006). Fernandes at al. suggested: "I-care would be clinically acceptable for a screening method; however, IOP with a suspicious range (values above 21 mmHg) must be reassessed or be referred for a Goldman tonometer evaluation."

Principles of how the Goldmann tonometer works

The Goldmann applanation tonometer is a biprism mounted on a standard slit-lamp, which is used to applanate (flatten) the anaesthetised fluorescein stained cornea. The IOP calculation is based on the Imbert - Fick principle, whereby an external force (exerted by the tonometer) against a sphere (the eye) equals the pressure within the sphere times the area flattened by the force. The higher the IOP, the greater the force required.

Principles of how the I-care tonometer works

The I-care tonometer is also called a rebound tonometer (Fig. 2-13). It is based on making a moving object collide with an eye rather than applanation. The motion parameters of the object are monitored. The device is made by Tiolat (Helsinki, Finland). The disposable probes consist of a magnetic steel wire shaft covered with a round plastic tip at the end. The probe is 40 mm

long, 0.3 mm in diameter with a 1.7-mm diameter plastic end-tip and 23.8–24.0 mg weights. The probe speed, before hitting the eye, is adjusted to 0.25–0.4 m/s (Kontiola and Puska 2004; Kontiola 2000).

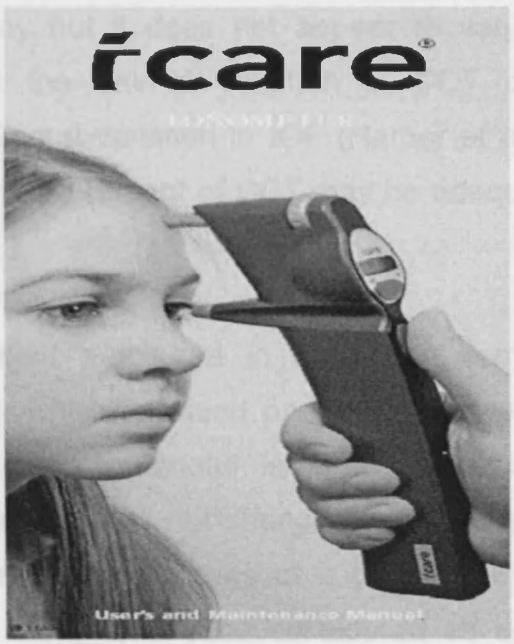


Fig. 2-13: The Impact tonometer (Helsinki, Finland)

2.5.2 Methods

Recruitment

According to the International Standardisation of Tonometers (ISO/TR 8612:1997), at least 40 eyes should be observed. In our study, twenty adult subjects (9 males, 11 females) were selected from friends, staff and students in the School according to the following exclusion criteria:

i. High corneal astigmatism (≥1D), that is, those eyes displaying an oval contact image with the Goldmann tonometer;
ii. Corneal scarring or corneal surgery including corneal laser surgery;
iii. Contact lens wearers.

Consent forms for participation were signed after showing the information sheets to the subjects (appendix 7).

Examination procedures

The subjects were first asked to sit in front of the Pentacam system for CCT measurement (Use of the Pentacam system is presented in section 2.2). The procedure took 2–3 minutes for both eyes. The CCT for an individual eye varies during the day but it does not appear to vary significantly during working hours and the diurnal variation in CCT does not contribute significantly to the diurnal variation in IOP (Harper et al. 1996; Mills 2000). Therefore, a single measurement of CCT may be adequate as a guide to its effect on IOP.

The IOP measurement procedure in our study complied with the ISO (ISO/TR 8612:1997), which is based on three observers for 40 eyes: Two Goldmann and one Impact tonometer. In addition, there are two prerequisites in the test: a) the patient shall not change his/her body posture throughout the IOP measurement; b) both eyes of a patient can be included in the measuring process. They should be considered as being independent of each other. Therefore, the subjects sat in the same chair during the whole test and both eyes were measured. Goldmann was carried out by two experienced optometrists (MET for the first time, RR for the second time). Impact tonometer was carried out by the author (PJ).

Following topical anaesthesia and instillation of fluorescein, the subject was positioned for the first Goldmann measurement by the examiner (MET). After 6 minutes interval, the Impact tonometer was used by the second examiner, the author (PJ). It took 3 minutes for both eyes. After a further 5 minutes, the Goldmann was carried out for the second time by another examiner (RR), with additional anaesthesia and fluorescein instillation.

The delay between measures was to ensure sufficient time for the eye to regain its preapplanation IOP, as it has been reported that the repeated measurement of IOP by applanation tonometry could lower the IOP by 0.1 - 0.7 mm Hg (Sudesh et al. 1993). A 2-10 minutes interval between successive IOP measurements is adequate to allow the eye to regain its preapplanation level (Recep et al. 1998). Only one Goldmann reading is taken by each

observer to avoid the tendency for IOP to decrease on multiple testing (Wilke 1972). The tips of the probe of the tonometers were changed between subjects.
During the three measurements, the subjects didn't change their position. The three examiners recorded their readings separately, and did not confer.

Use of the I-care tonometer

The subject was seated in front of the examiner, with the eyes of the examiner at the same level as those of the subject. The I-care tonometer was held in front of the eyes of the patient at an estimated distance of about 3-10 mm. The subject was asked to look in a distance in order to keep their eyes still and divert their attention away from the tonometer. The examiner adjusted the distance and position of the tonometer first and then pressed the button when it was ready. The tip of the probe hit the central cornea. Measurements were carried out by carefully operating the measurement button, to avoid shaking the tonometer. The probe moved freely about 3-7 mm, impacted to the eye and bounced back. The IOP reading was shown on the screen automatically. A disposable probe was used for each subject. Six measurements were taken consecutively.

The software shows "Error" in the following circumstances: a) The probe hit the eyelid rather than the central cornea; b) The tonometer was tilted upwards too much or too far away from the eye. Only valid reading were accepted and recorded.

Use of the Goldmann tonometer

Following topical anaesthesia and instillation of fluorescein, the subject was positioned at the slit lamp and the tonometer was swung into place. After aligning the tonometer in front of the cornea, the examiner looked through the slit lamp ocular just as the tip contacted the cornea. Upon contact, the tonometer tip flattened the central cornea and produced a thin circular outline of fluorescein. A prism in the tip visually split this circle into two semicircles that appeared green while viewed through the slit lamp oculars (Fig. 2-14).

The tonometer force was adjusted manually until the two semicircles just overlapped. The amount of force required to do this was translated by the scale into a pressure reading in mm Hg.

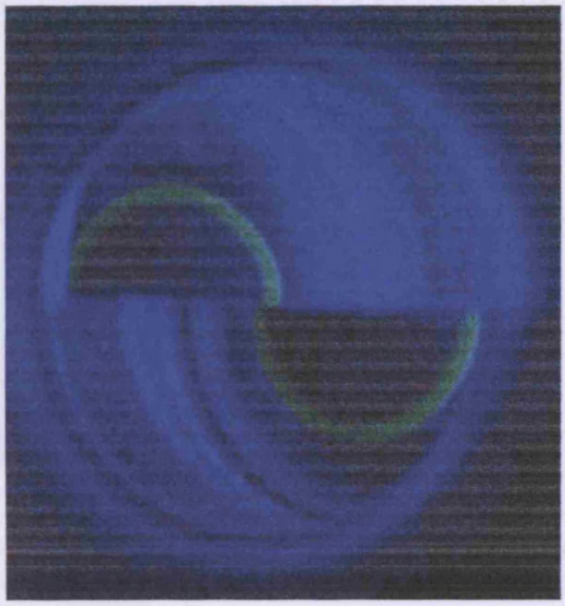


Fig. 2-14: Using the Goldmann tonometer

2.5.3 Results and discussions

Twenty subjects (9 males and 11 females) were recruited and forty eyes were analysed. Mean age of subjects was 27.75 years (range 22-43 years). Mean IOP measured using the Goldmann tonometer head (mean of the two Goldmann readings) and the I-care tonometer was 13.2±2.2mm Hg; 13.3±2.6mm Hg respectively. A paired t-test showed no significant difference between Goldmann and Impact tonometer ($p = 0.753$).

The 'Bland-Altman' analysis has been shown to be the better statistical method to use, specific for assessing the correlation between two methods of clinical measurement (Bland and Altman 1986). A plot of the difference between the methods against their mean is more informative (Fig. 2-15). The slope of the regression line for this plot was not significantly different from zero ($y=-1.993+0.16x$, $p=0.301$), indicating that the difference between the two instruments does not vary with absolute IOP.

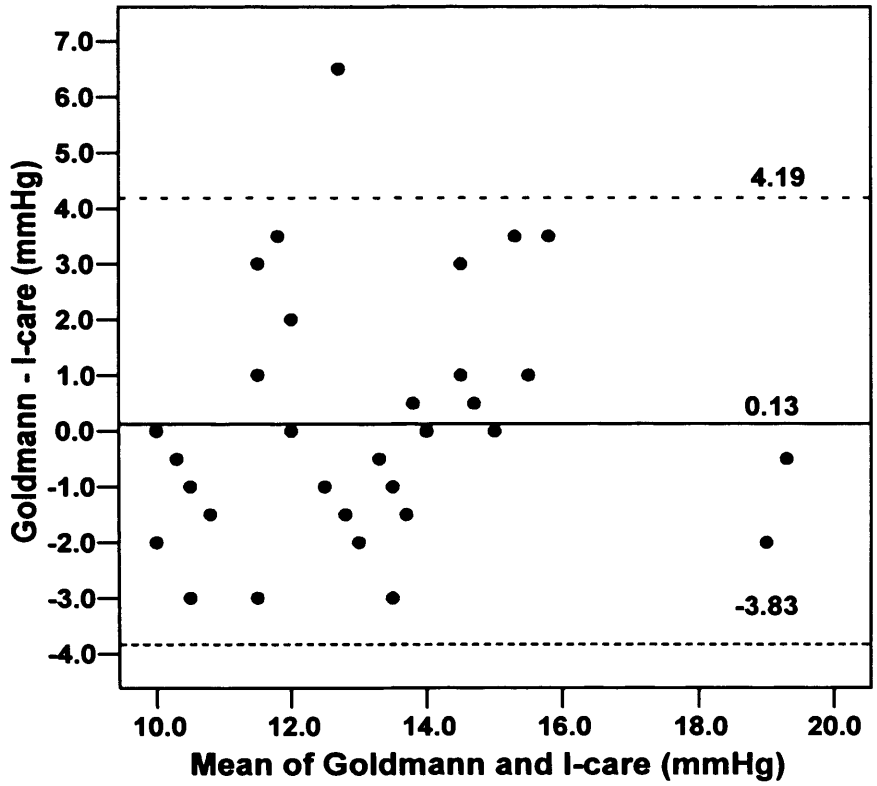


Fig. 2-15: Bland-Altman analysis

The mean difference was 0.13mmHg and SD was +2.03mmHg. The mean difference plus or minus 2 SD of the differences was -3.83 to 4.19 mmHg. It shows that 95% of the differences between Impact and Goldmann results fall between these two values.

Pearson correlation between CCT and IOP was 0.486 by Impact tonometer and 0.426 by Goldmann (p= 0.001) (see Fig 2-16a-b). There is no statistically significant difference in the strength of correlation between CCT for IOP measured by Impact and Goldmann tonometer (Z_{obs} = 0.328).

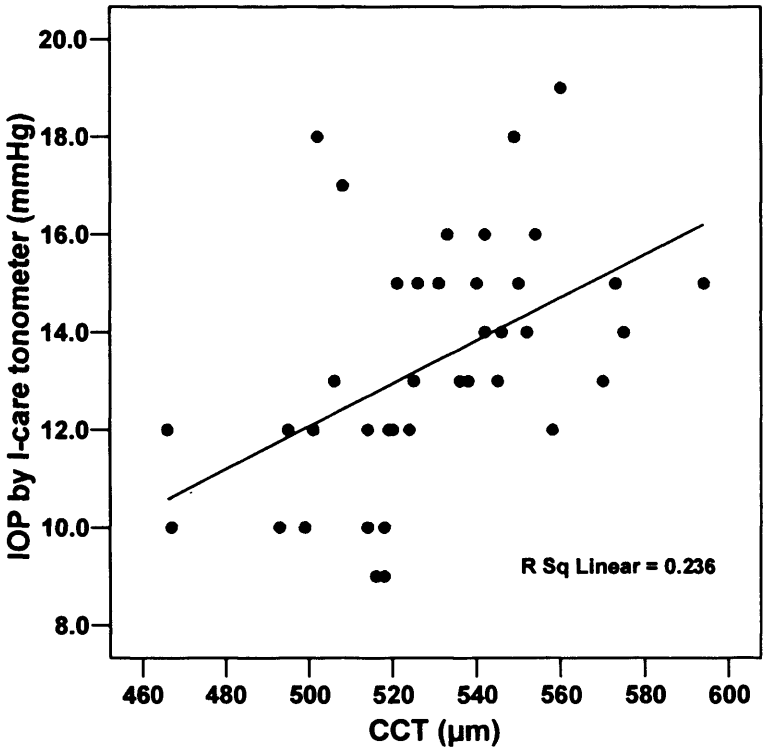


Fig. 2-16a: CCT and IOP by the Impact Tonometer

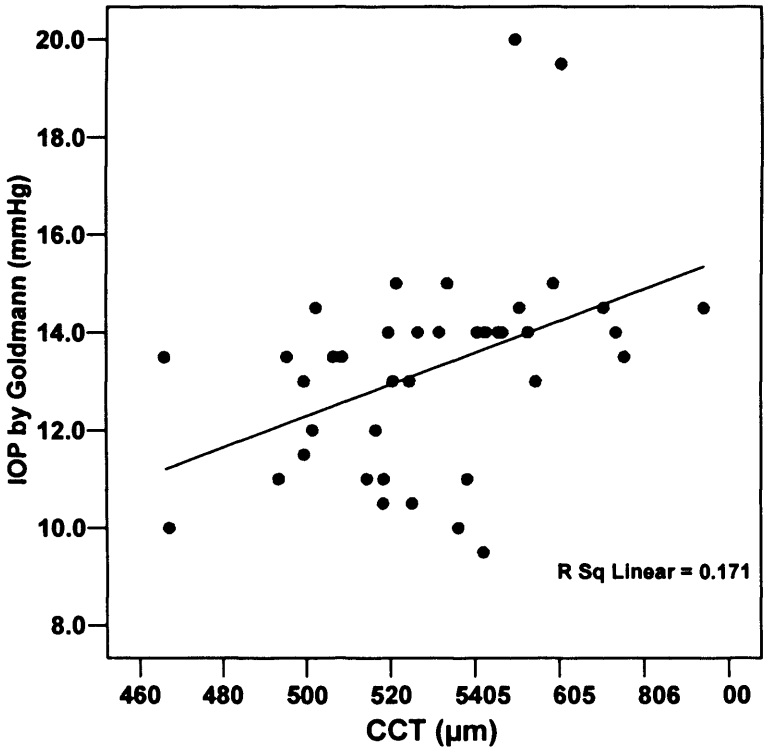


Fig. 2-16b: CCT and IOP by the Goldmann tonometer

The Goldmann yielded the expected relationship between IOP and CCT: a 10% change in CCT gave rise to a change in IOP of 1.56 mmHg. The I-care showed a slightly greater effect of CCT: a 10% change in CCT gave rise to a change in IOP of 2.2mmHg.

2.5.4 Conclusions

The combination of a high correlation coefficient and the Bland-Altmann approach showed that the two instruments are in good agreement. Both instruments showed a similar relationship between IOP and CCT. Thus, the I-care tonometer gives acceptable readings on comparison with Goldmann tonometer, and given its obvious advantages for subjects with learning disabilities is a valid choice for this study.

2.6 Overall conclusions

In conclusion, the above pilot studies have selected the appropriate instrumentation for the main study. The sophisticated Pentacam system, I-care tonometer and retinoscopy were selected. The Topcon TRC-NW6S fundus camera was suitable and the magnification of the camera was worked out. These pilot studies also improved the author's operational skills for the equipment.

Chapter 3

Ocular biometry and corneal topography in people with DS

3.1 Introduction

3.1.1 Ocular biometry in people with DS

As reviewed in chapter 1, there is a similar range of values for AL and an association between refraction and AL in people with DS as in their controls (Doyle et al. 1998; Haugen et al. 2001a). However, thinner CCT and higher corneal power was reported in DS subjects compared to controls in previous studies (Doyle et al. 1998; Evereklioglu et al. 2002; Haugen et al. 2001a). Moreover, a number of studies have described the presence of flake lens opacity in people with DS (Doyle et al. 1998; Fierson 1990; Haugen et al. 2001a; Hestnes et al. 1991; Igersheimer and Mautner 1951; Jaeger 1980; Kim et al. 2002; Robb and Marchevsky 1978; Wong and Ho 1997). Finally, parameters such as the anterior chamber depth, lens thickness and lens density have only been measured in Haugen's study, showing similar anterior chamber depth, relatively reduced lens thickness and increased lens density for 40 subjects with DS, aged 19 to 26 years (Haugen et al. 2001a).

The hypothesis was that the poor visual performance in people with DS may be explained by the abnormal ocular biometry or abnormal correlation between refractive components. For instance, refractive error is the result of mismatched association among the ocular components; correlations between the total refraction of the eye and the individual optical elements may explain the failure of emmetropisation in children with DS. Inaccurate accommodation (which is common in children with DS) may be influenced by properties of the lens. In addition, reduced acuity (which is a common finding in DS) and small pupil size will increase the depth of focus of the eye. The small pupil size would be needed to account for the reduced accommodation in DS. Therefore, the first aim was to measure visual function (including refraction, VA and accommodation) and ocular biometric parameters (including AL, cornea, lens, anterior chamber parameters and pupil size) among our subjects. Additionally, the inter-relationship between ocular parameters was calculated and compared between DS children and control children. The relationship between visual function and ocular biometry in children with DS was then investigated as well.

To our knowledge, this is the first study measuring periphery corneal thickness, posterior corneal power, corneal asphericity, corneal aberration, pupil diameter, anterior chamber volume and angle in people with DS. It is also the first study to use IOL-master in patients with DS

3.1.2 Corneal topography and keratoconus in people with DS

As reviewed in chapter 1, corneal topography has been used as a screening tool for keratoconus detection in people with DS (Doyle et al. 1998; Haugen et al. 2001a; Liza-Sharmini et al. 2006; Vincent et al. 2005). In addition, keratoconus typically presents in the late teens or adults with DS (Haugen et al. 2001b; Hestnes et al. 1991), and has not been reported in studies of children with DS (Liza-Sharmini et al. 2006; Vincent et al. 2005).

The second aim of this part of study was to detect keratoconus by corneal topography, giving an indication of the prevalence among our subjects with DS.

3.1.3 Corneal topography and detection of keratoconus

Corneal topography provides a tool for detection of keratoconus. It also defines the optical properties of the normal and abnormal cornea. Corneal topography appears to have taken two separate forms to describe the cornea:

a. Coloured topographic maps; Popular and practical topographic maps tend to include curvature maps, elevation and pachymetry maps (Fig. 3-1).

b. Quantitative descriptors to describe corneal shape such as corneal radius and asphericity.

Corneal map: meridian, scale and the colour spectrum

It is essential to check the meridian, the label on the scale and the colour spectrum before studying a corneal map. A meridian is a line that spans the diameter of the cornea from one point on the limbus to a point on the opposing limbus. The label on the scale in the corneal topography map gives the type of measurement which is being displayed: elevation in μm, curvature in mm and power in D (diopters). The topography map is colour-coded in

order to quantify the shape of the cornea. For instance, in an elevation map, the values lower than the reference plane are shown by cooler colours such as blue and green and the values higher than the reference plane are shown by warmer colours such as red, orange and yellow. On curvature maps, warmer colours represent the steeper area whereas cooler colours mark the flatter area (see Fig. 3-1). Therefore, it is extremely important to check the type of scale on the map being studied.

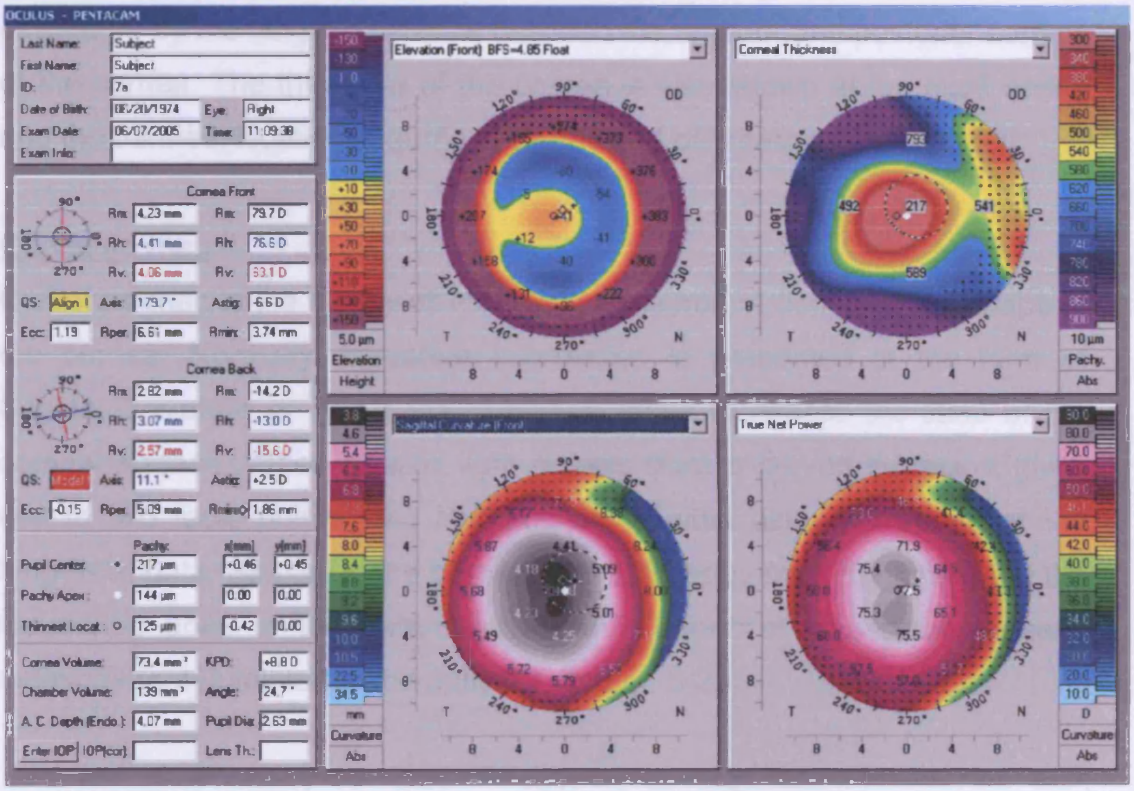


Fig. 3-1: Corneal topography of one DS adult with keratoconus using the Pentacam (Elevation, Pachymetry, Sagittal curvature and True net power map)

Elevation Map

The Pentacam system generates relative height data from the selectable reference bodies. It has a set default to a BFS (best-fit sphere) reference plane, which consists of a sphere fitted as accurately as possible to the true shape of the cornea. Subtraction of the highest data from a BFS shows actual location of corneal surface features and its irregularities. Positive values mean measurements above the reference body and negative values

mean measurements below the reference body. The true elevation map locates the position of the apex of the cone for keratoconus (Schwiegerling and Greivenkamp 1996).

Pachymetry map

The Pentacam system evaluates corneal thickness across the entire corneal surface (usually about 9 mm of information is represented from the anterior cornea) and shows the thickness of every single location of the cornea. It is calculated by the height difference between the anterior and posterior surface of the cornea. The thickness of the cornea is also shown at the pupil centre and the thinnest location in terms of values and orientation (see Fig. 3-1).

Curvature map

Curvature map is the most well-established method of depicting the shape of the cornea. Normally, curvature information is presented in the form of Sagittal curvature or Tangential curvature maps to assess the state of the corneal surface. When off-axis light reflects from a curved surface it gives rise to two focal points, one contains the sagittal data and the other the tangential data. Sagittal is the perpendicular distance from the tangent at the measuring point to the axis, which has a spherical bias because each measurement is related to the optical axis (Fig. 3-2a).

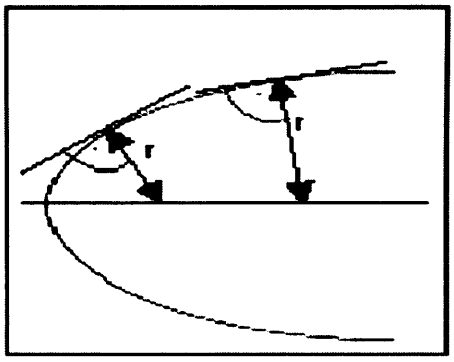


Fig. 3-2a: A diagram showing Sagittal curvature (from the Pentacam manual)

Tangential is the curvature of the measuring point, which applies to the

sphere that best fits the shape of a small area surrounding each point (see Fig. 3-2b). It has less spherical bias because the curvature is calculated for an individual without reference to the visual axis (Klein and Barsky 1995; Roberts 1994).

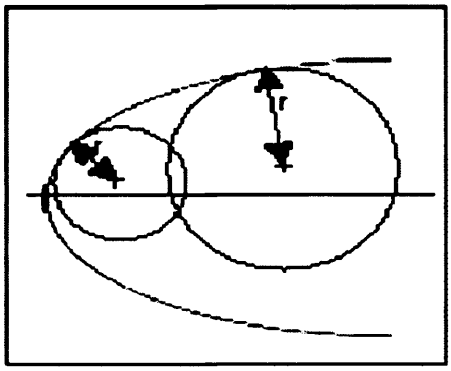


Fig. 3-2b: A diagram showing Tangential curvature (from the Pentacam manual)

Keratoconus detection by corneal topography

Corneal topography has enhanced the ability to detect keratoconus in a quantifiable and reproducible manner. In order to remove the subjectivity of the assessment and the need for experience, specific corneal indices have been developed by numerous studies with the development of sophisticated equipment and technology. The determination of quantitative indices from corneal topography has been suggested as a means of detecting keratoconus (Arntz et al. 2003; Auffarth et al. 2000; Cairns and McGhee 2005; Dastjerdi and Hashemi 1998; Holland et al. 1997; Klyce et al. 2000; Liu et al. 1999; Maeda et al. 1995; Maeda et al. 1994; Maguire and Bourne 1989; Rabinowitz 1993; Rabinowitz and McDonnell 1989; Rabinowitz and Rasheed 1999; Smolek and Klyce 1997; Wang et al. 1989; Wilson and Klyce 1991; Wilson et al. 1991).

Auffarth (2000) emphasized that elevation map is essential for the detection of keratoconus. Arntz (2003) suggested that placement of the apex, anterior and posterior corneal elevation, minimum corneal thickness, anterior chamber depth and corneal diameter should be considered in the detection of patients with an increased risk for developing keratoconus. Although

several of the corneal irregularity indices were generated from the Orbscan system, sensitivity, specificity and accuracy do not improve from the combination of a larger number of indices (Hainline, Kollbaum and Springs, 2006). However, it was stated that the detailed knowledge of the posterior surface seems beneficial in detecting keratoconus (Hainline et al. 2006). Even though much progress has been made in corneal topography systems, it is still difficult to detect subclinical keratoconus.

Table 3-1: Summary of keratoconus detection index

Author	**Year**	**Keratoconus detection index**
Rabinowitz et al.	1989	Inferior-Superior Value (I-S) Central corneal power (K)
Wilson et al.	1991	Surface regularity index (SRI) Surface asymmetry index (SAI)
Maeda et al.	1994, 1995	Keratoconus predictability index (KPI)
Rabinowitz et al. Klyce et al.	1999 2000	KISA index (K, I-S, AST, Srax) AST quantifies the degree of regular cornea astigmatism; Srax means the screwed radial axis index; which quantifies irregular corneal astigmatism

A valuable review about corneal topography by Cairns (2005) pointed out that some maps differ by reference location. For instance, if the whole peripheral cornea was not captured in the map, the reference body may have an increased radius of curvature to best fit the steeper more central region. Further, it may return deceptive values. Therefore, special care should be taken if a complete map is not provided.

3.2 Methods (Descriptions of clinical techniques)

3.2.1 Subjects

The procedures of recruitment were described in chapter 1, section 1.7.2. Forty six DS children, fifty control children, nineteen DS adults took part in the measurement of refraction, visual acuity, accommodation and axial length. Twenty-five children with DS and twenty-eight control children participated in Pentacam images. Twelve children with DS and six control children gave their consent for cycloplegia to be used for lens thickness measurement. Sixteen control adults were measured for refraction and the Pentacam system. The measures of the right eye of each subject were chosen for data analysis. The measures of the left eye were only accepted if that of the right eye was not available, or not reliable.

All the children attended the whole tests accompanied by their parents. Amongst nineteen adults with DS, eight were accompanied by the family member; seven were accompanied by their carers whilst four were accompanied by both.

For each adult with DS, the frequency of eye rubbing per day (0=Once or less, 1=Twice –Six times, 2= More than seven times) and family history of keratoconus were elicited from the carers or family members.

3.2.2 Examination procedures

All the adult subjects took part in the whole test at one visit. The child subjects were tested on more than one occasion. At the first visit, the subjects sat for the AL measurement first. Afterwards, the subjects were taken to the consulting rooms for measuring refraction, VA and accommodation (only for child subjects). It was approximately 30 minutes in total for each subject. At the second visit, those children who completed the above test in the first visit only sat for the Pentacam images. In the cases of those children who failed to co-operate, they were asked to repeat the failed examination if possible. In addition, for those who were agreeable, 0.5% Tropicamide was used and the Pentacam images were taken again for lens thickness measurement. It lasted 30 minutes more.

All the reliable images of corneal topography were viewed by an experienced observer (SAN) in order to detect keratoconus. Objective analysis of the images by the Pentacam system was also used (see section 3.3.1). The author measured the lens density in the Pentacam image (see section 3.3.2).

3.2.3 Use of the IOL-Master

The selection of IOL-Master for AL measurement and the principles of how it works were described in chapter 2, section 2.1.

The subject was seated in front of the IOL-Master. The seat and table height were adjusted so that his/her eyes were level with the two ring marks on the side rails of the headrest. In some cases, small children were asked to kneel on the seat, or it was necessary for a child to sit on their parent's lap, or with parents's hand held under their chin, if the child's face was quite small.

The first step was to focus the machine. The subject was instructed to fixate the yellow light first. For children, the examiner (PJ) asked them to keep looking at the yellow light and persuaded them to sit as still as possible by saying: "What is the colour of the light? Or does the light move?" The examiner focused the machine by means of the six light spots arranged in a circle. The focusing was complete when they were centrally aligned with the subjects' pupil. In order to keep the subject's attention and fixation, this step should be done quickly.

The next step was to activate "ALM mode (Axial length measurement)". In order to maintain their interest, the subjects were asked to tell the examiner when they noticed the yellow light change and what colour they saw (a red light should be seen when the machine is ready to start the ALM mode). The magnification of the view was changed so that only a small section of the eye was visible to the examiner. The bright reflection of the alignment light was seen, with a green cross hair with a circle in the middle of the display. The examiner then saw a thin vertical line by adjusting the joystick. It was then aligned so that the reflection was in the cross hair circle. Before taking measurements, the subject was reminded to look at the light again. This was to ensure a good result the first time round and prevent avoidable repetition. In the case of co-operative children, this procedure was relatively quick (10-

15 seconds per eye). However, if the examiner or child's parents could not persuade the child to maintain good fixation, it took much longer.

The signal-to-noise ratio (SNR) is a measure of the quality of the data obtained. According to the manual, SNR >2.0 is the acceptable level for data. In our study, the AL was accepted when SNR was more than 2.0. If SNR< 2.0 and if it was caused by a restless child or a poor alignment, the examiner repeated the measurements. In some cases of subjects with DS, no acceptable data were obtained. A maximum of 20 measurements are permitted per eye per day (from the manual). This is to ensure patient comfort and safety, also to relieve the boredom of the examination. A second appointment and visit to the clinic was arranged if possible.

3.2.4 Measuring refractive error

Refraction was carried out with Mohindra retinoscopy for all the children and for adults with DS in the same clinic room by an experienced optometrist (JMW) (The choice of methods of measuring refraction was discussed in chapter 2, section 2.3). It was performed in total darkness at a near distance of 50 cm. The only light was the examiner's dim retinoscope beam. The subject was required to face the examiner and fixate the light. The examiner held a trial lens in front of the fixating eye and retinoscopy was performed (see Fig. 3-3). A working distance correction of 1.00D was applied for children 1.25D for young adults and 2.00D for presbyopic adults (Cregg et al. 2003; Saunders and Westall 1992). Control adults were measured by the Topcon KR-7500 autorefractor, according to the manufacturer's instructions.

Mean spherical refractive error was used to describe the refraction of each subject. Refraction was divided into three types: myopia was ≤ -0.5 D; emmetropia was between -0.5 D and +0.5 D; hyperopia was ≥ +0.5 D.

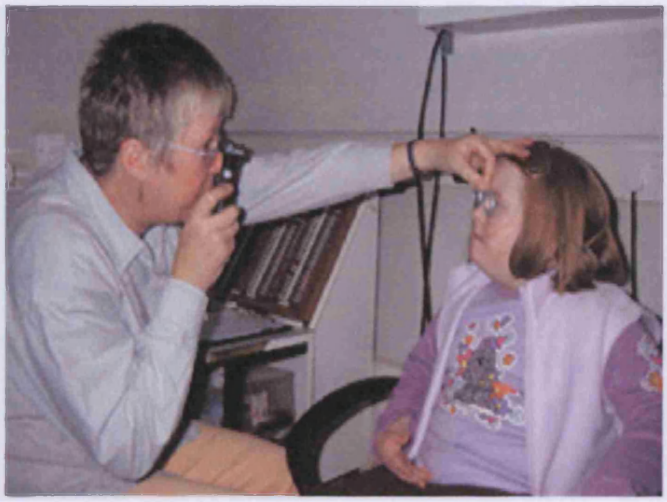


Fig. 3-3: A picture showing measurement of refraction

3.2.5 Measuring VA

There are many methods for evaluating VA in young children. Recognition acuities (this refers to the capacity to identify a form or its orientation) are more sensitive to pathological and physiological degradation than resolution acuities (this refers to the smallest angular separation between neighbouring targets that can be resolved) (Leat et al. 1999). Therefore, all subjects participating in our study were measured monocularly with recognition acuity. The Keeler Crowded Test or the Kay Picture Test was used. Both tests employ crowded optotypes and LogMAR sequencing. Children with DS may not be able to perform letter tests, whereas a control child of the same age may be capable of this. A recent study (Jones et al. 2003) has shown that the two tests produce equivalent results in children. Testing was either by the author (PJ), by an optometrist (JMW) or by an orthoptist (MD).

The Keeler Crowded Test requires a child to name or match letters, presented in the form of a flip chart book. Each line contains the same number of letters (four). The test also contains two booklets so that the individual does not memorize the letter order (Fig. 3-4).

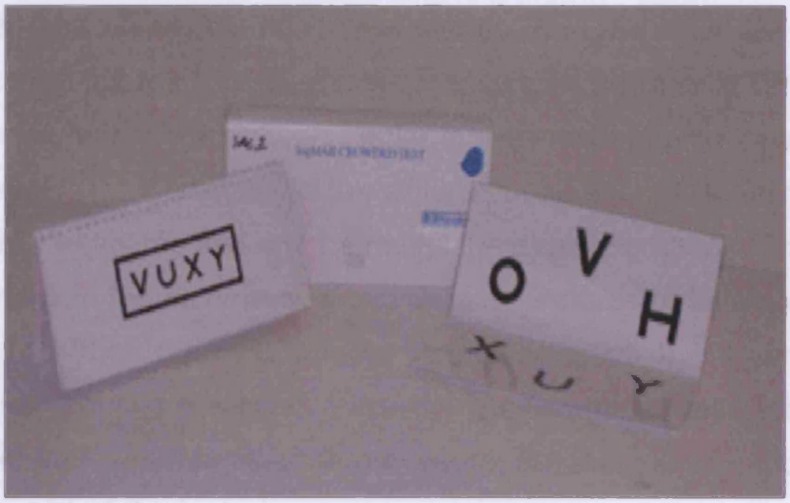


Fig. 3-4: A picture of the Keeler Crowded Test Card

The Kay Picture Test is designed for younger children and people who cannot identify letters. It uses familiar pictures as targets rather than letters aimed being interesting for children and therefore maintain their attention. It contains eight different pictures in a flip chart format. Eight pictures are used in groups of four throughout the test (except sizes 1.0 and 0.9 where there are two per line) (Fig. 3-5). A criticism of this test is that it only offers a limited range of possible pictures (eight in all) and so a child may be able to guess the answers. Therefore, a child must identify 2 pictures correctly before they can proceed to the next level.

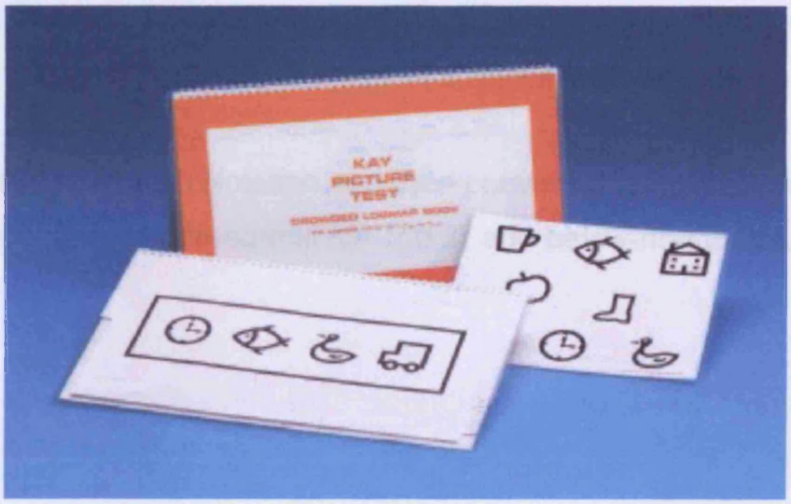


Fig. 3-5: A picture of the Kay Picture Test Card

The examiner took up her/his position 3 metres from the child and opened the test book from the front, beginning with the largest pictures or letters. The examiner started at the first picture or letter in the row of four by pointing to it and asked the child to identify it. As the pictures or letters got smaller and the child could not identify the first one correctly, the examiner checked the other pictures or letters in the same row. If two or more pictures or letters could be seen in that row, then the next smaller size was tested. If only one or no picture or letter could be named correctly, the examiner returned to the previous larger size and repeated the procedure, checking all four pictures or letters. At the end of the test, the examiner brought the charter closer to let the subject see the unidentified letter or picture clearly in order to keep their confidence. Rather than allowing the subject to decide when the letters become indistinguishable, the subjects were encouraged to guess the identity of each letter or picture. Several studies have shown that subjects may achieve different acuity scores because of differences in responding to questions when they are not confident about the answers rather than because of variations in visual function (Higgins et al. 1984; Sokol et al. 1980). In our methods the testing methods were kept consistent to avoid this discrepancy as far as possible.

In our study, the Kay Picture Test was more often used with children with DS. It kept the children's attention far better than the letter test as it was easier to recognize and more interesting. In some cases, the matching card was used, which allowed the children to match the picture rather than name it.

VA was recorded in Snellen Notation and then converted to LogMar acuity in our study. It was divided into normal VA (≤0.3) and below-normal VA (>0.3) (Hall 1996).

3.2.6 Measuring accommodation

The modified Nott technique was used to measure accommodation by the same optometrist (JMW). This technique is considered to be a repeatable and valid objective technique compared to the subjective 'push-up' method or auotorefractor (McClelland and Saunders 2003; Rosenfield et al. 1996). It has been used successfully in children with DS (Cregg et al. 2001; Haugen et al. 2001c; Woodhouse et al. 2000; Woodhouse et al. 1993; Woodhouse et al. 1996). However, it has been reported that there is an increase in standard deviation with an increase in accommodative demand (Leat and Gargon 1996).

A near cube target was mounted on a metre ruler at a set distance from the child's eye: 10 cm and 16.7 cm, equivalent to 10 D and 6 D respectively. The cube (an internally illuminated translucent cube of 4.0*4.0*4.3 cm) had different black on white pictures and could be rotated in order to maintain the child's interest. As the examiner held the ruler by one hand, the retinoscope was held by the other hand. One end of the ruler was gently placed on the child's cheeks. To ensure that the child was attending to the cube, the examiner asked the child to fixate the target by asking questions about the picture, for instance, "Can you count for me how many rain drops in the picture?" The examiner assessed the accommodative state by moving the retinoscopy toward or away from the child in order to find the neutral point. If accommodation was accurate at the distance being tested then a 'neutral' reflex was observed. If the child was under-accommodating, then a 'with' movement was seen and the examiner moved away from the child until the neutral point was found (Fig. 3-6). The position was then recorded. The distance between the neutral point and the target was used to calculate the lag of accommodation. All children wore their spectacles to correct a distance refractive error, if these had been prescribed. Some children had bifocals. Accommodation was measured both through the bifocal segment and through the distance portion.

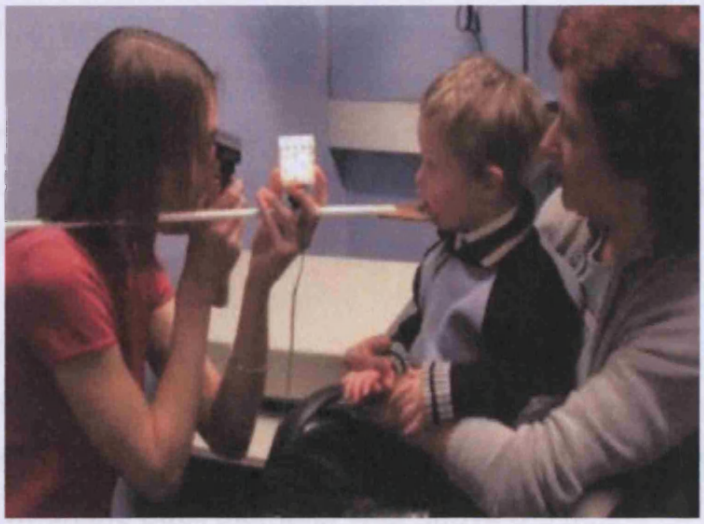


Fig. 3-6: A picture showing testing accommodation

Accurate accommodation was defined a lag ≤0.75 D at either (or both) 10.00 cm (10 D) or 16.7 cm (6 D) (The relationship between dioptres and distances is D=100/n, where "n" is the response/demand in cm) (Leat and Gargon 1996). It was used to define a significant lag of accommodation in previous study (Leat and Gargon 1996; Rouse et al. 1984; Stewart et al. 2005; Woodhouse et al. 2000; Woodhouse et al. 1996):

Accommodation lag (D) = Accommodative response - Accommodative demand

Accommodation was divided into three types: accurate, inaccurate and becoming accurate. Becoming accurate was defined as the group of children who could accommodate after wearing bifocals (the benefit of the previous study with our cohort).

3.2.7 Taking the Pentacam images

The selection of the Pentacam system, the principles of how it works and how to use it were described in chapter 2, section 2.2.

The subject was instructed to fixate the blue light while the examiner was adjusting the Pentacam. The image capture was taken automatically when the adjustment was done. However, in some cases with DS subjects, the examiner had to disable the "Automatic release" and take the image manually at the point when all the alignment cues were deemed to be

correct. However, if the QS (Quality Specification) was shown as "Blink" , "Align" or "Fix " rather than "OK", the image was taken again. It took 2 minutes for both eyes of control subjects to be examined. The whole procedure lasted much longer with most of DS subjects depending on their degree of co-operation.

For those children who agreed to pupil dilation for lens thickness measurement, one drop of 0.5% Tropicamide was then put in both eyes after completion of the other tests. After 20 minutes or so, the second Pentacam image was taken when the pupil diameter was above 5.5 mm.

The terms used to describe the corneal pachymetry and corneal keratometry, anterior chamber and lens parameters are explained as below:

- Central corneal thickness (CCT) is the thickness of the cornea in the centre of the pupil in μm. Minimum corneal thickness (MCT) is depicted as the thinnest corneal thickness in μm. Peripheral corneal thickness (PCT) is the mean thickness of the corneal zones 6 mm around the thinnest point in μm.

- Corneal radius (CR) is the mean central radius in mm, of the two major meridians in the 3 mm ring of the cornea. The Rmin value is the steepest point of the cornea, which is the minimum radius of the cornea. The Rper value is the flattest radius in the zone between 7mm and 9mm ring of the cornea. Both surfaces of the corneal power are calculated by using the formula below:
  Anterior corneal power = $(n_2 - n_1)/CR$;
  Posterior corneal power = $(n_3 - n_2)/CR$;
  Total corneal power = anterior corneal power + posterior corneal power
  n_1= 1.000 (RI of air), n_2= 1.376 (RI of corneal tissue),
  n_3 = 1.336 (RI of the aqueous)

- Eccentricity of the cornea is calculated as 'e' by the Pentacam. According to $Q = -e^2$, Q is calculated as well, which describes the asphericity of the

cornea. Aberration of the cornea was calculated by Zernike coefficient. If there is no abnormal Zernike coefficient, the aberration coefficient will be equal to 0.0. Values exceeding 1.0 are indicating that the corneal surface contains untypical wave components.

- The anterior chamber is defined as the distance between the posterior surface of the cornea and the anterior surface of the lens. ACV (Anterior chamber volume) is calculated in mm^2, from the distance between the back surface of the cornea and the front surface of the lens integrated in a 12 mm diameter around the corneal apex. Anterior chamber angle (ACA) is the smaller of the two chamber angles in the horizontal section. Anterior chamber depth (ACD) is the distance in mm, from the back surface of the cornea to the front surface of the lens.

- Pupil diameter is depicted as an average value in mm, over the measurement period.

3.2.8 Lens power calculation

In those cases in which spherical equivalent (SE), keratometry (K), anterior chamber depth (ACD) and axial length (AL) were measured successfully, the contribution of the lens was calculated by using the formula (Haugen et al. 2001a):

$$\text{LENS POWER} = n\left(\frac{1}{AL - ACD} - \frac{1}{\frac{n}{CR + MSE} - ACD}\right)$$

where LP is the lens power in diopter, n is the RI of the aqueous and the vitreous (n=1.336). AL and ACD are given in meters. This formula calculates the lens power, provided that the refraction of the whole lens takes place at the anterior lens surface (anterior vertex). Therefore, the total lens power is approximately 3 D more than it (Haugen et al. 2001a).

3.3 Pentacam image analysis

3.3.1 Corneal topography

The quality of corneal topography

Prior to assessing the corneal topography, both the QS (Quality Specification) of the images and the judgment of the author (PJ) were taken into account in deciding whether the values should be accepted. The system indicates the reason if the image is of poor quality or not (for more, see chapter 2, section 2.2). With the information from the QS table, the examiner, therefore, was able to observe the quality of the image as a whole and then discard those images which were considered not good enough for further image analysis.

Objective assessment of the corneal topography by the Pentacam

A keratoconus level map from the Pentacam system gives an early identification of a wide variety of corneal abnormalities. The classification is based on various indices which were calculated from relevant curvature data, height and Zernike analysis (Fig. 3-7). The Pentacam compares the measured values with the mean values and SD of a normal population. When the measured value is >mean+2.5SD, it is regarded as abnormal. The classification of keratoconus of each image was recorded by the author. Noticeably, the analysis is entirely based on the topography of the anterior cornea surface data. In those cases with moderate or severe keratoconus, an abnormal cornea was often noted by the author on the Scheimpflug image (Fig. 3-8).

ISV: (Index of Surface Variance) Value of curvature variation from the mean curvature.

IVA: (Index of Vertical Asymmetry) Value of curvature symmetry comparison of the upper and lower area.

KI: (Keratoconus Index) Increases with severity of keratoconus.

CKI: (Center Keratoconus Index) Increases with severity of central keratoconus.

IHA: (Index of Height Asymmetry) Value of height data symmetry comparison of the upper and lower area.

IHD: (Index of Height Decentration) Value of the decentration of height data in vertical direction.

RMin: (Minimum Sagittal Curvature) Smallest sagittal curvature in the 8mm-zone.

ABR: (Aberration coefficient) Value of the aberrations of the cornea front calculated with Zernike Analysis.

Fig. 3-7: Keratoconus indices table from the Pentacam system

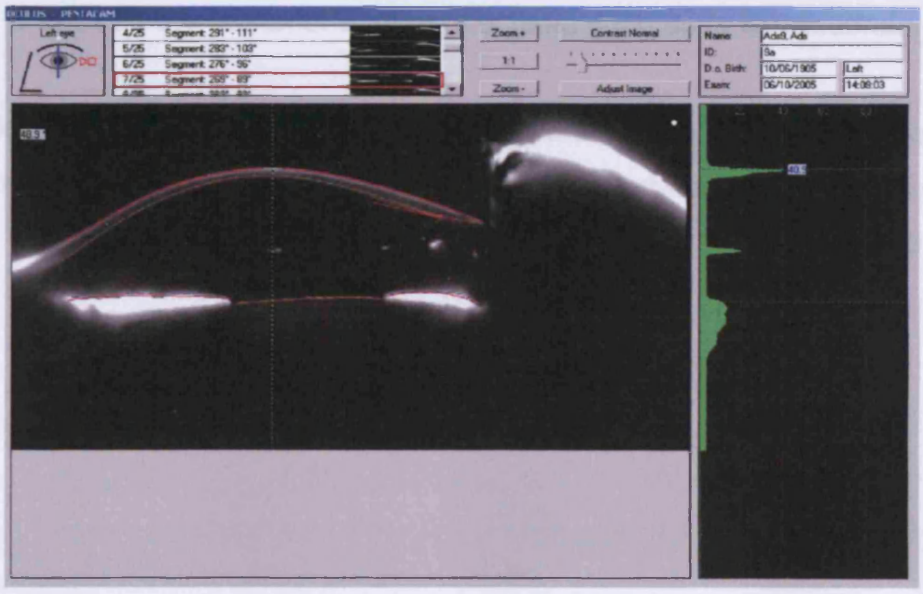


Fig. 3-8: A Scheimpflug image of one DS subject with keratoconus

Subjective assessment of the corneal topography

The observer (SN) viewed all the recorded images and formed his own opinion of the keratoconus status by corneal topography without knowing the results of the Pentacam system or to which subject group each image belonged. The following are the principles which the observer used for the assessment of the corneal topography and provided to the author:

1. Using a curvature picture of the front or back of the cornea: look at the steepest and flattest meridians. If the steepest and flattest lines are not perpendicular to each other then this indicates irregularity. If the axes are less than 70 degrees apart, keratoconus will be suspected. On a normal cornea they will be perpendicular (even in patients with higher levels of regular astigmatism) (Naroo and Morgan 1997).
2. The Rmin value is the minimum radius of the cornea. The Rper value is the flattest radius in the zone between the 7mm and 9mm ring of the cornea. A lower Rmin value than average value may indicate steepness as in keratoconus. A higher Rper value indicates that there is a degree of flattening, which is usually in the opposite quadrant to the Rmin.
3. Typically the keratoconus eye will have greater values for "e".
4. Looking at the posterior curvature maps, increased steepening as shown on the posterior suggests ectasia such as in keratoconus.

Once keratoconus was diagnosed, it was graded on a 0-4 scale as follows KK Possible, KK1= Slight/Trace, KK2=Mild, KK3=Moderate, KK4=Severe. This is according to Efron scales used in contact lenses (Efron et al. 2001).

3.3.2 Lens densitometry

Prior to measuring lens density, the Scheimpflug image was opened and then checked in the image which the camera was in the horizontal position (Image 7 of 25, Segment 89°-269°) (Fig. 3-9). The lens density reading was not available if the lens was not visible in the image (Fig. 3-9).

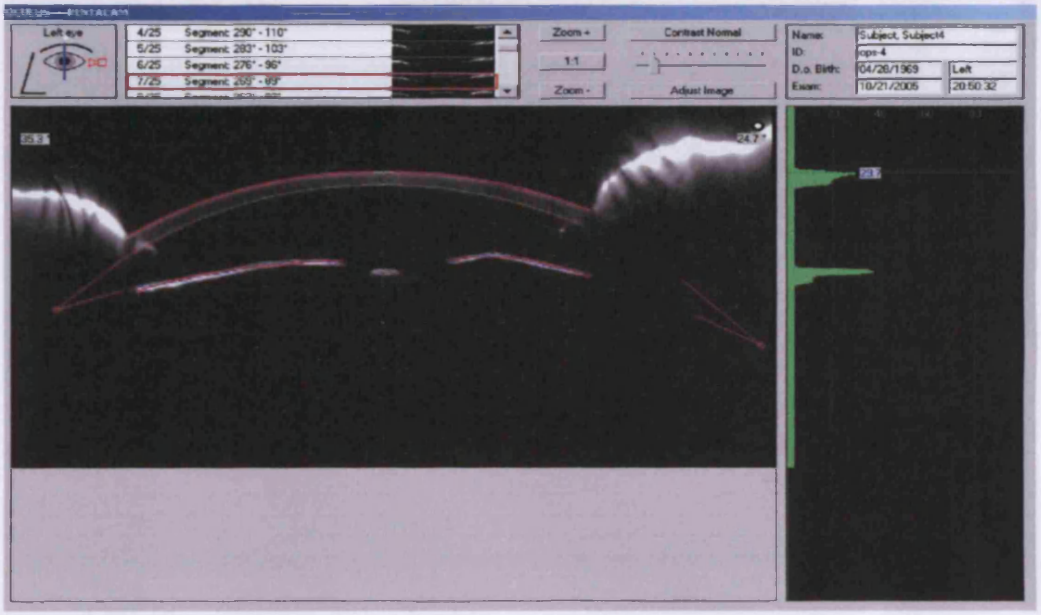


Fig. 3-9: A Scheimplug image showing that the lens is not visible, (probably due to a smaller pupil)

An axis line of the anterior eye segment is automatically constructed from the apex of the cornea. A cross marker is then automatically placed by the system at the intersecting points between the axis and the anterior surface of the cornea. The yellow dotted line marks the anterior surface of the lens. The horizontal marker "----" shows the position of the cursor. In the densitogram at the right hand side (green colours), the yellow line indicates the beginning of the lens (Fig. 3-10).

The densitometer measures the amount of density and variation within lens. Central lens density (CLD) and maximum lens density (MLD) were measured at the cursor point, with the cursor placed manually. The density of the lens is standardized from 0 to 100. i.e. 0 means the lens shows no clouding, however, 100 means the lens is completely opaque. The horizontal marker

was placed at the centre of the lens (Fig. 3-10). It shows the densitometry reading over the pupil centre at the right hand scale (green colours). The lens centre was judged by eye and the readings were recorded as CLD.

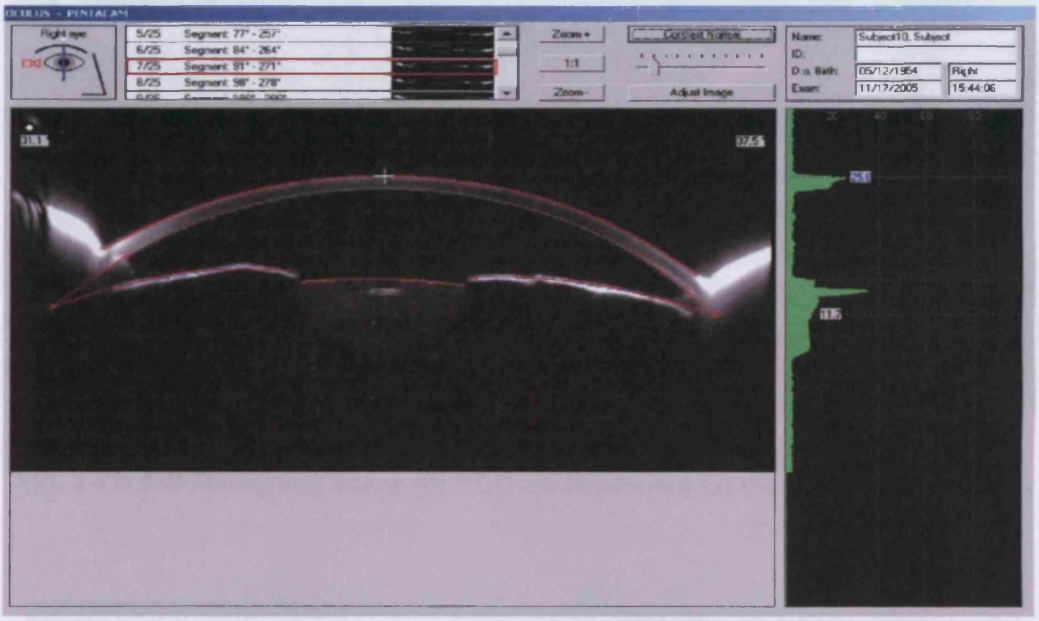


Fig. 3-10: A Scheimpflug image when the marker is in the centre of the lens

The peak of lens density was shown in solid green at the right hand scale. The horizontal marker was then moved around to the different points within the lens and placed at the point where the MLD was shown. In each case, the maximum reading occurred at different points and layers of the lens. For instance, MLD may be shown when the marker was placed at the anterior of the lens (Fig. 3-11) or at the centre of the lens (Fig. 3-12).

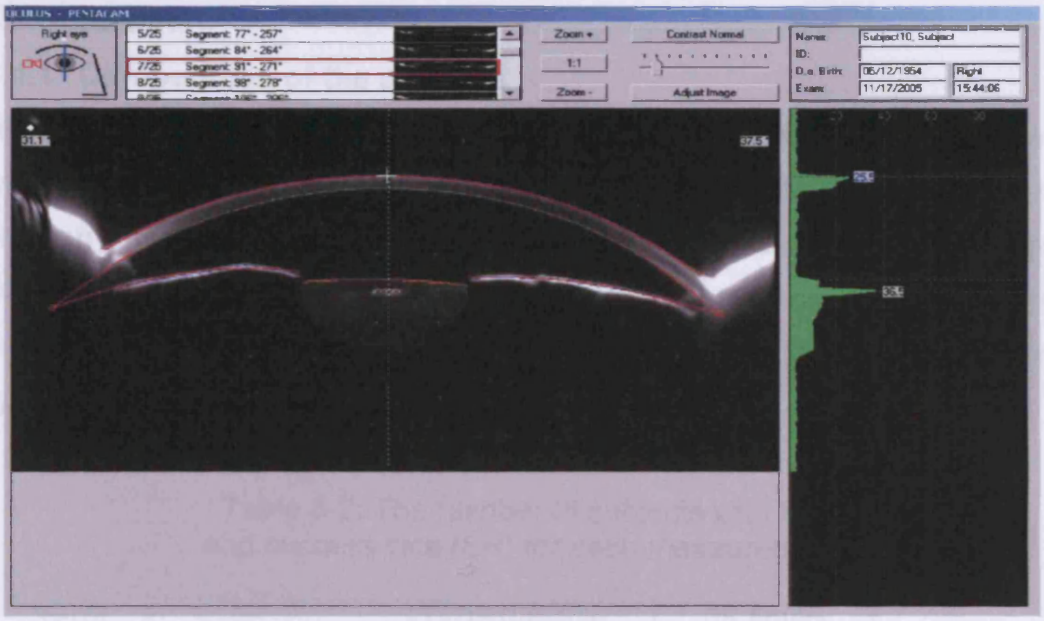


Fig. 3-11: A Scheimpflug image for MLD measurement (at the anterior of the lens)

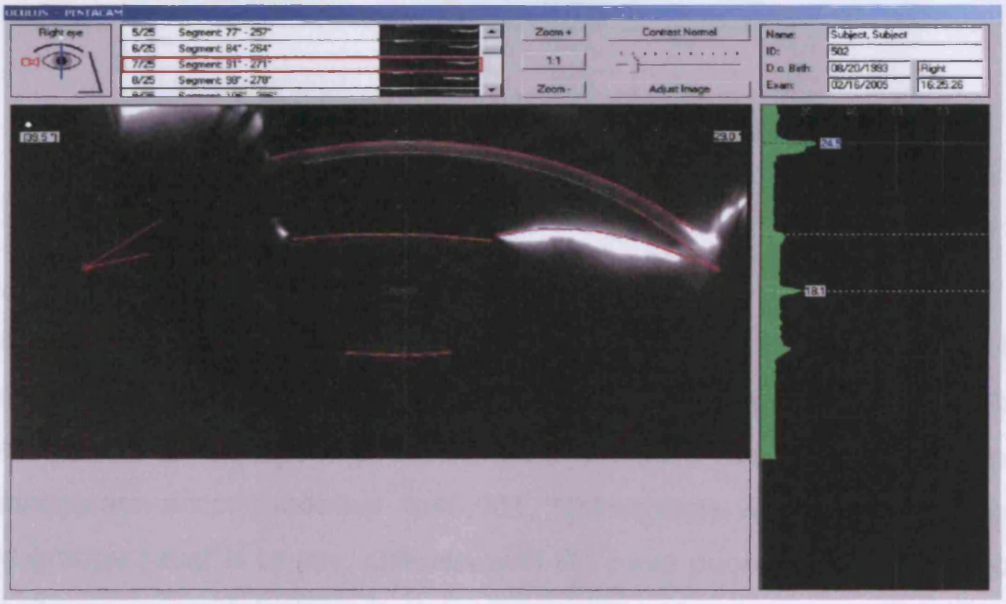


Fig. 3-12: A Scheimpflug image for MLD measurement (at the centre of the lens)

3.4 Results

3.4.1 Co-operation of the subjects

All the control children and adults successfully completed all of the tests which they attended. Twenty-five DS children and twenty-eight control children who were approached and agreed to take Pentacam images. Twelve DS children and five control children gave consent for lens thickness measurement. Table 3-2 shows the number of the subjects with DS who co-operated for each measurement.

Table 3-2: The number of subjects with DS and success rate (SR) for each measurement

	DS Children		DS Adults	
	No.	SR (%)	No.	SR (%)
Refraction	46	100.0	14	74.7
VA	46	100.0	14	74.7
Accommodation	46	100.0	n/a	
AL	43	93.4	13	68.4
Pentacam image	18	72.0	14	74.7
Lens thickness	9	75.0	n/a	

3.4.2 Ocular function

Findings of the ocular function of all the subjects are shown in Table 3-3. No significant difference in refraction ($p=0.835$, Independent t-test), but significant difference in VA ($p<0.001$, Mann-Whitney Test) and the presence of inaccurate accommodation ($p<0.001$, Chi-square) were found between child groups (that is to say, children with DS have poorer VA and are more likely to accommodate inaccurately compared with those controls.). There was no significant difference in refraction in DS adults without keratoconus and control adults ($p>0.05$, Independent t-test). As expected, DS adults with keratoconus have higher refraction (-8.50±6.96 D) and poorer VA (0.4±0.12) compared to those DS adults without keratoconus ($p<0.001$, Mann-Whitney Test).

Table 3-3: Findings of the ocular function

	DS Children	Control Children	DS Adults without KC	Control adults
Meansph (D)	+2.20 ± 3.49	+2.35 ±3.46	-2.83 ± 6.30	-2.03 ± 3.47
Range	-6.75 - +9.38	-4.50 - +11.38	-16.80 - +3.88	-7.25 - +2.63
VA (LogMar)	0.19 ± 0.16	0.02± 0.14	0.20±0.20	N/A
Range	0.00-0.50	-0.20-0.50	-0.10-0.40	
Presence of under-accommodation	52% (n=24)	12% (n=6)	N/A	

More hyperopia was found in both child groups (Fig. 3-13a). However, both myopia and hyperopia were found in adult subjects. There were 82.2% children with DS and 98% control children seeing 0.3 (6/12) or better (Fig. 3-13b).

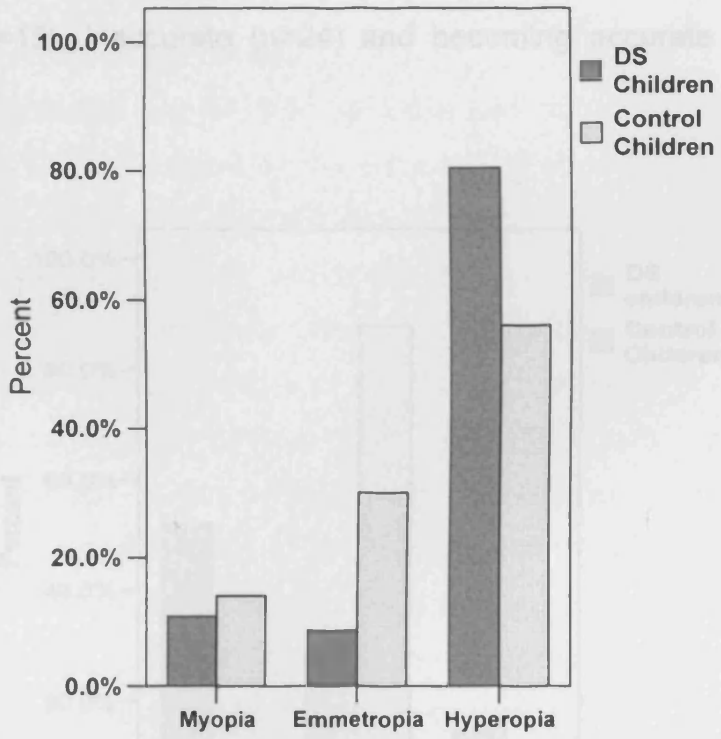


Fig. 3-13a: Refraction in child subjects

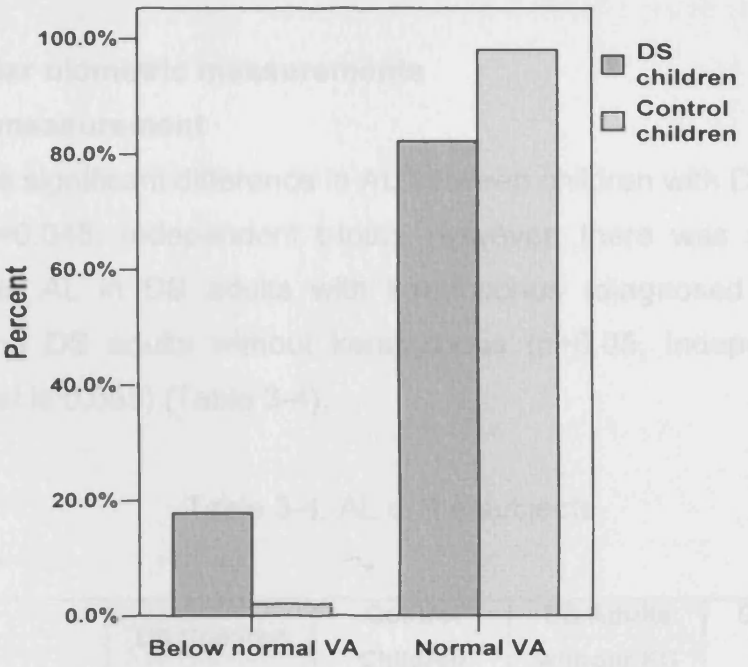


Fig. 3-13b: VA in child subjects

In children with DS, the accommodation was divided into three groups: accurate (n=15), inaccurate (n=24) and becoming accurate (n=7) (Fig. 3-13c).

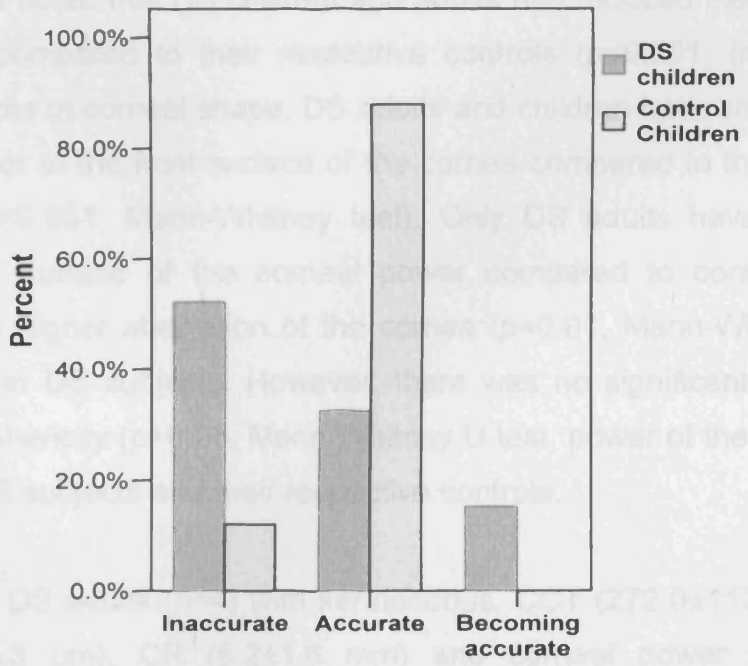


Fig. 3-13c: Accommodation ability in child subjects

3.4.3 Ocular biometric measurements

3.4.3.1 AL measurement

There was a significant difference in AL between children with DS and control children ($p=0.048$, Independent t-test). However, there was no significant difference in AL in DS adults with keratoconus (diagnosed from clinical records) and DS adults without keratoconus ($p>0.05$, Independent t-test, power of test is 0.053) (Table 3-4).

Table 3-4: AL of the subjects

	DS Children	Control Children	DS Adults without KC	DS Adults with KC
AL Mean±SD (mm)	22.06 ± 1.31	22.65 ± 1.51	23.56 ± 1.97	23.59 ± 2.08
Range	19.28 - 25.37	19.39 - 26.01	21.35 - 28.16	22.06 - 28.47

3.4.3.2 Properties of the cornea

Corneal parameters for all the subjects are shown in Table 3-5a, b. Distribution of CCT and CR in all the subjects are shown in Fig. 3-14 and Fig. 3-15. It was noted that DS children and adults had reduced mean CCT, PCT and MCT compared to their respective controls ($p<0.001$, Independent t-test). In terms of corneal shape, DS adults and children have smaller CR and higher power of the front surface of the cornea compared to their respective controls ($p<0.001$, Mann-Whitney test). Only DS adults have significantly lower back surface of the corneal power compared to control adults. A significantly higher aberration of the cornea ($p<0.01$, Mann-Whitney U test) was found in DS subjects. However, there was no significant difference in corneal asphericity ($p>0.05$, Mann-Whitney U test, power of the test is 0.419) between DS subjects and their respective controls.

In terms of DS adults (n=4) with keratoconus, CCT (272.0±117.2 μm), MCT (229.5±150.3 μm), CR (5.2±1.6 mm) and corneal power (68.8±18.5D), asphericity of the cornea (e: 0.58±0.43; Q: -0.48±0.58) and aberration

(4.43±2.61) were obviously different from DS adults without keratoconus (n=10) ($p<0.001$, Mann-Whitney U test).

Table 3-5a: Findings of the corneal parameters in child subjects

	DS children	**Control children**	**P-value**
No. subject	**18**	**28**	
CCT (μm) Mean±SD	**475.7±35.8**	**540.7±38.4**	**<0.001**
MCT (μm) Mean±SD	451.8±59.0	533.9±46.8	<0.001
PCT (μm) Mean±SD	**555.4±38.8**	**617.4±46.1**	**<0.001**
Front surface of the corneal Power (D) Mean±SD	51.0±2.1	47.6±1.3	<0.001
Back surface of the corneal Power (D) Mean±SD	**-6.3±0.5**	**-6.1±0.2**	**0.070**
Total corneal Power (D) Mean±SD	44.5±1.8	41.5±1.6	<0.001
Asphericity			
e Mean±SD	**0.34±0.39**	**0.47±0.19**	**0.131**
Q Mean±SD	-0.26±0.23	-0.26±0.17	0.994
Aberration Mean±SD	**2.3±1.6**	**1.3±1.3**	**0.004**

(Independent t-test or Mann-Whitney U test, DS children vs. Control children)

Table 3-5b: Findings of the corneal parameters in adult subjects

	DS adults without KC	Control adults	P value
No. subject	**10**	**16**	
CCT (μm) Mean±SD	475.4±33.3	544.7±31.3	<0.001
MCT (μm) Mean±SD	**461.4±43.0**	**541.5±32.8**	**<0.001**
PCT (μm) Mean±SD	566.9±51.8	624.0±30.1	<0.001
Front surface of the corneal Power (D) Mean±SD	**51.3±2.8**	**48.1±1.7**	**0.001**
Back surface of the corneal Power (D) Mean±SD	-5.7±0.6	-6.3±0.2	0.001
Total corneal Power (D) Mean±SD	**44.9±2.4**	**41.8±1.5**	**<0.001**
Asphericity			
e Mean±SD	0.15±0.15	0.19±0.19	0.679
Q Mean±SD	-0.15±0.15	-0.07±0.06	0.152
Aberration Mean±SD	**2.5±1.5**	**1.2±1.0**	**0.001**

(Independent t-test or Mann-Whitney U test, DS adults vs. Control adults)

CCT and PCT were significantly associated in DS children ($r=0.596$, $p<0.001$) and control children ($r=0.943$, $p<0.001$). Noticeably, the correlation between CCT and PCT were significantly different between DS children and controls ($Z_{obs}=-3.296$). No other corneal parameters, refraction or VA was significantly related to asphericity and aberration of the cornea in DS child subjects.

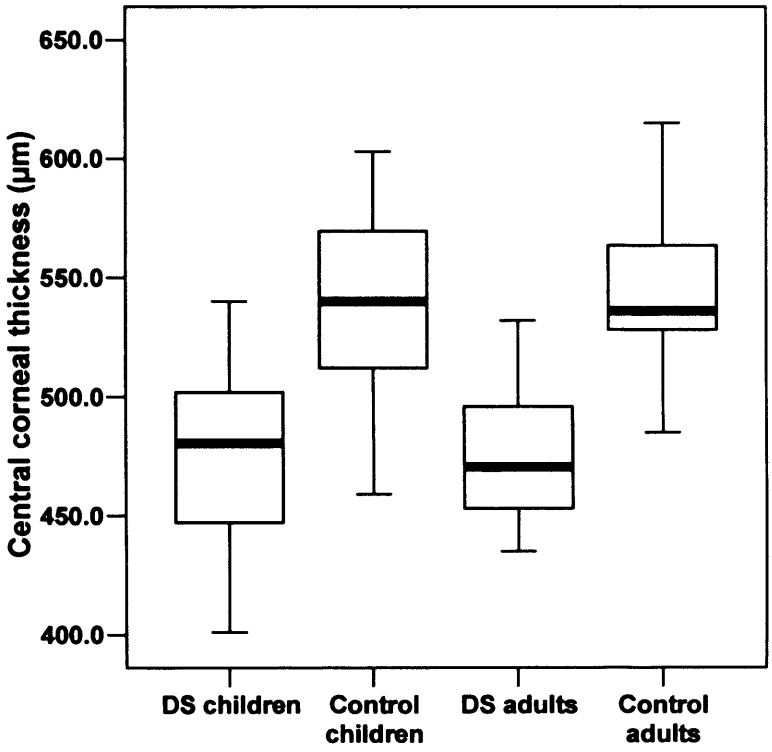


Fig. 3-14: CCT in all the subjects

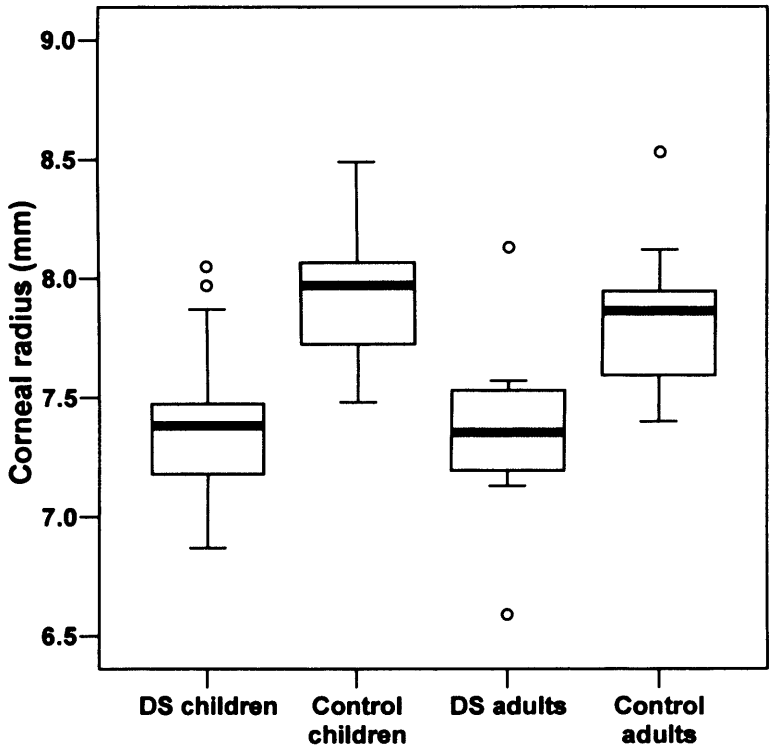


Fig. 3-15: CR in all the subjects

3.4.3.3 Properties of the lens

Lens density

Four adults with DS had cataract which were visible with non-dilated pupils. There was no visible lens opacity in any of the child subjects during the eye examination which was checked by JMW. No significant difference in the mean CLD and MLD was found between DS subjects and their controls ($p > 0.05$, Mann-Whitney U test). However, DS and control adults have significant higher CLD compared to that of both children groups (Table 3-6).

Table 3-6: The MLD, CLD of all the subjects

	DS children	DS adults	P-value	Control children	Control adults	P-value
No. subjects	18	10		27	16	
CLD Mean ±SD	**7.0±1.9**	**9.9±2.6**	**0.026**	**7.9±2.5**	**10.6±3.4**	**0.001**
MLD Mean ±SD	19.7±8.6	18.0±6.5	0.892	18.6±5.3	23.4±9.7	0.167

(Mann-Whitney test, DS children Vs. DS adults; Control children Vs. Control adults)

CLD was correlated with age in control adults (Spearman correlation $r=0.506$, $p<0.05$) and also in adults with DS ($r=0.776$, $p<0.05$). CLD and MLD were associated with each other only in children and adults with DS (Spearman correlation $r=0.511$, $p<0.05$; $r=0.652$, $p<0.05$ respectively).

Calculated lens power

Lower calculated lens power was found in children with DS (21.37±1.35D) than that of control children (23.54±1.87D) ($p<0.001$, Mann-Whitney U test). Since lens power might influence a child's accommodative ability, comparison of calculated lens power for children with DS who accommodate inaccurately (n=6), and those accurately (n=7) and those becoming accurately (n=4) were made. However, no significant difference was found between those children ($p=0.709$, Kruskal-Wallis test).

Lens thickness

It appeared that the lens thickness was slightly lower in children with DS (n=9) (3.34±0.36mm) compared to that of control children (n=5) (3.56±0.11mm), but this was not statistically significantly (p=0.204, Independent t-test, the test power is 0.665).

3.4.3.4 Properties of the anterior chamber

No significant difference was found between subjects with DS and their respective controls in ACA, ACV and ACD (p>0.05, Independent t-test) (Table 3-7).

Table 3-7: The ACA, ACV and ACD of all the subjects

	DS Children	Control Children	P-value	DS Adults without KC	Control Adults	P-value
ACD (mm) Mean ±SD	3.2±0.4	3.4±0.3	0.196	3.2±0.3	3.1±0.5	0.593
ACV (mm^2) Mean ±SD	204.1±40.0	207.8±38.6	0.751	190.0±45.4	188.9±51.1	0.999
ACA (^{0}) Mean ±SD	38.0±7.9	37.7±9.6	0.939	36.9±3.9	38.6±8.0	0.286

3.4.3.5 Pupil diameter

No significant difference in pupil diameter was noted between DS children (3.27±0.52mm) and control children (3.45±0.83mm) (p=0.406, Independent t-test, power of test is 0.222); DS adults and control adults (2.84±0.58mm vs. 3.00±0.51mm) (p=0.445, Independent t-test, power of test is 0.169).

3.4.3.6 Correlation between optical components

No significant difference was found in the AL/CR ratio between our DS children and controls (3.00±0.16 vs. 2.88±0.20) (p=0.055, Independent t-test, power of test is 0.707). However, DS adults have a much higher AL/CR ratio 3.50±0.71).

Calculated lens power was significantly associated with AL (r=-0.799, p<0.001), AL/CR (r=-0.795, p<0.001), refraction (r=0.581, p=0.001) and ACD (r=0.677, p<0.001) only in control children. Additionally, significant negative association between ACD and refraction was only found in control children (r=0.656, p<0.001).

Significant negative association between AL and refraction, AL/CR and refraction were found both in DS subjects and controls (see Table 3-8; Fig. 3-16; Fig. 3-17). Noticeably, there was a significant difference in the correlation of AL and refraction between DS children and controls (Z_{obs}=2.647). However, no significant difference in the correlation of AL/CR and refraction was found between DS children and controls (Z_{obs}=0.799). Comparing the linear regression of AL and refraction in both groups, the slope was the same (p=0.468); the elevation (p=0.002) and the residual variance were significantly different at 0.05 level of probability (F=2.465, df1=41, df2=48). "In terms of the linear regression of AL/CR and refraction, the slope (p=0.058) and the residual variance did not reach the significance at 0.05 level of probability (F=1.313, df1=15, df2=26), however, the elevation (p=0.001) were significantly different."

Table 3-8: Correlation between AL and refraction; AL/CR and refraction

		R	R^2	Equation	p-value
AL - Refraction	DS children	0.680	0.462	Y=41.66-1.79X	<0.001
	Control children	0.885	0.783	Y=48.24-2.03X	<0.001
AL/CR - Refraction	DS children	0.889	0.789	Y=51.95-16.70X	<0.001
	Control children	0.933	0.870	Y=37.68-12.52X	<0.001

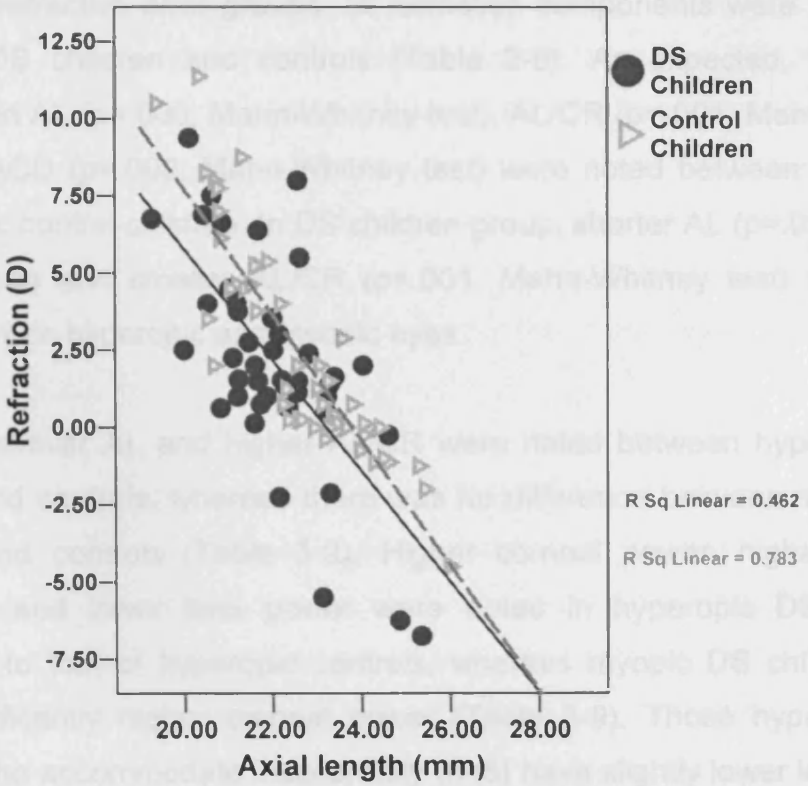


Fig. 3-16: AL and Refraction in child subjects

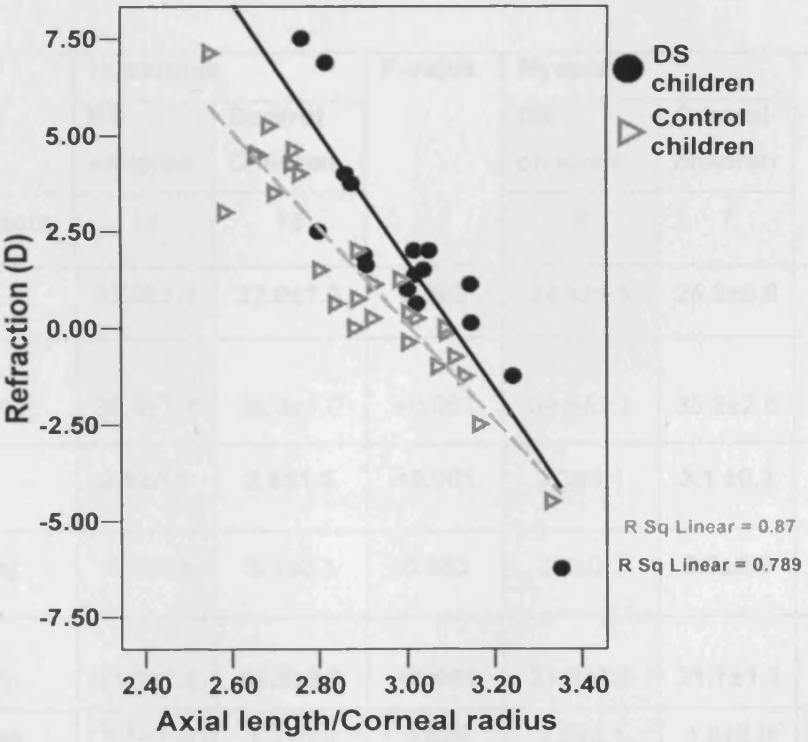


Fig. 3-17: AL/CR and Refraction in child subjects

Based on refractive error groups, all refraction components were compared between DS children and controls (Table 3-9). As expected, significant difference in AL (p=.000, Mann-Whitney test), AL/CR (p=.001, Mann-Whitney test) and ACD (p=.000, Mann-Whitney test) were noted between hyperopic and myopic control children. In DS children group, shorter AL (p=.016, Mann-Whitney test) and smaller AL/CR (p=.001, Mann-Whitney test) were also noted between hyperopic and myopic eyes.

However, similar AL and higher AL/CR were noted between hyperopic DS children and controls, whereas there was no difference between myopic DS children and controls (Table 3-9). Higher corneal power, higher corneal aberration and lower lens power were noted in hyperopic DS children compared to that of hyperopic controls, whereas myopic DS children only have significantly higher corneal power (Table 3-9). Those hyperopic DS children who accommodate inaccurately (n=5) have slightly lower lens power than those accurately (n=7) but not significantly.

Table 3-9: Refraction components of refractive error groups

	Hyperopia		**P-value**	**Myopia**		**P-value**
	DS children	**Control Children**		**DS children**	**Control children**	
No. subjects	14	15		6	7	
AL (mm)	**22.0±1.1**	**22.0±1.0**	**0.983**	**24.1±1.1**	**25.0±0.8**	**0.429**
Corneal Power (D)	38.9±1.7	36.3±1.0	<0.001	39.5±1.3	35.2±2.6	0.020
AL/CR	**2.9±0.1**	**2.8±1.3**	**<0.001**	**3.3±0.1**	**3.1 ±0.3**	**0.260**
ACD (mm)	3.1±0.4	3.1±0.3	0.863	3.3±0.3	3.6±0.2	0.147
Lens Power (D)	**21.3±1.4**	**24.5±1.7**	**<0.001**	**21.5±1.5**	**21.7±1.3**	**0.905**
Aberration	2.5±1.8	1.3±0.9	0.028	1.5±0.1	1.6±2.0	0.945

(Independent t-test or Mann-Whitney U test, DS children vs. controls)

3.4.4 Detection of keratoconus

According to the previous clinical records, there were five DS adults with keratoconus. Two more adults with DS who had not been seen previously in the clinic were detected with keratoconus clinically during the course of this study by JMW. All child subjects were examined with retinoscopy by JMW and no suspicions of keratoconus arose. 26 images from DS children, 41 from control children and 18 from DS adults were examined by the observer and the Pentacam system.

According to the observer's judgment, most of DS children (n=13) were considered as having trace keratoconus, whereas with the Pentacam most of DS children were considered to have a normal cornea (n=14) (Fig. 3-18a). Noticeably, there were twice as many DS children with suspicious keratoconus by the observer (n=20), compared to that of the Pentacam (n=9).

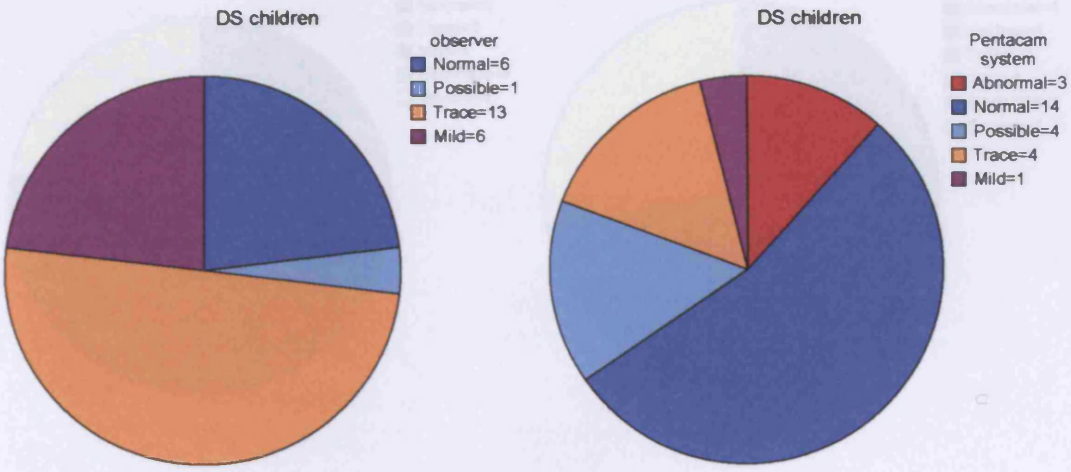


Fig. 3-18a: Pie chart for the detection of keratoconus in DS children

With regard to the control children and adults with DS, the same number of control children (n=7) and adults with DS (n=12) were detected as having keratoconus by both methods of detecting the keratoconus (see Fig. 3-18b-c).

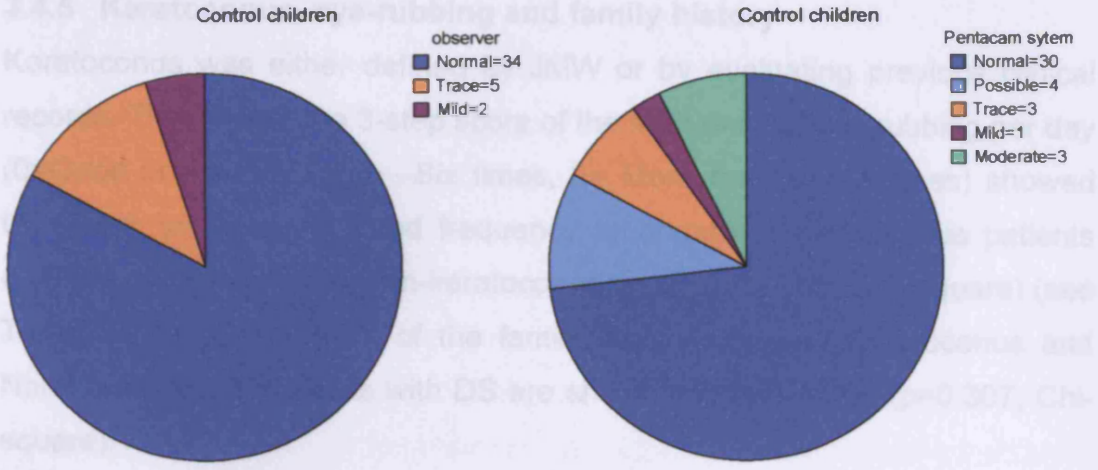


Fig. 3-18b: Pie chart for the detection of keratoconus in control children

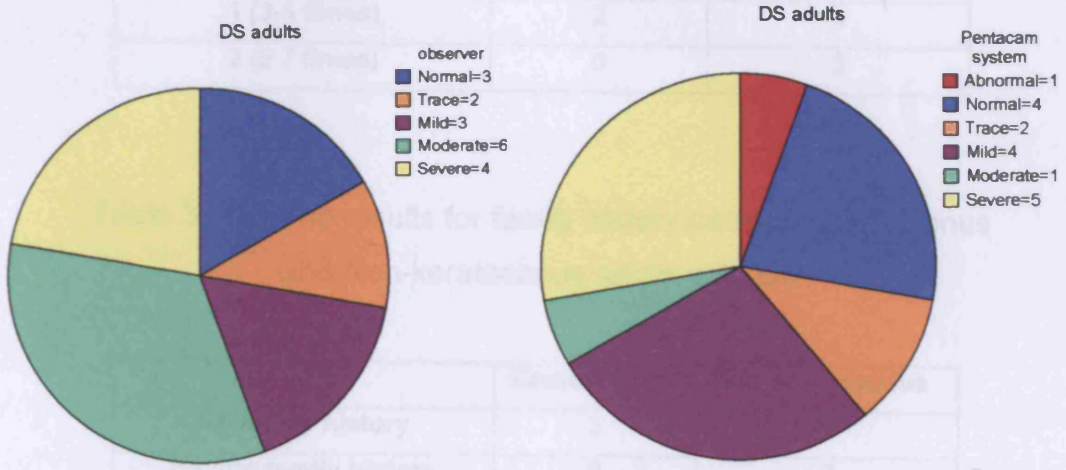


Fig. 3-18c: Pie chart for the detection of keratoconus in DS adults

3.4.5 Keratoconus, eye-rubbing and family history

Keratoconus was either defined by JMW or by evaluating previous clinical records. The results of a 3-step score of the frequency of eye rubbing per day (0=Once or less, 1=Twice –Six times, 2= More than seven times) showed that there was no increased frequency amongst the keratoconus patients compared to those of the non-keratoconus group (p=0.055, Chi- square) (see Table 3-10a). The results of the family history between Keratoconus and Non-keratoconus in adults with DS are shown in Table 3-10b (p=0.307, Chi-square).

Table 3-10a: The result for frequency of eye rubbing per day between keratoconus and Non-keratoconus subjects

Frequency of eye rubbing	Keratoconus	Non-keratoconus
0 (≤ once)	3	7
1 (3-6 times)	2	4
2 (≥ 7 times)	0	3

Table 3-10b: The results for family history between keratoconus and Non-keratoconus adults with DS

	Keratoconus	Non-keratoconus
No family history	5	6
Having family history	0	0
Don't know	2	6

3.5 Discussion

3.5.1 Co-operation of the subjects

Measuring Refraction, VA, Accommodation and AL

All control children completed all the measurements successfully. All children with DS co-operated well with refraction, VA and accommodation measurements. The level of compliance was noted to be higher than that as reported in other studies in children with DS (Haugen et al. 2001c; Liza-Sharmini et al. 2006). The advantage of our study was that many of the children with DS from our longitudinal cohort had received regular visual tests by the same experienced optometrist (JMW). It appeared that they may be familiar with the surroundings and remembered the testing procedure, which may increase their motivation. In fact, the level of motivation of children with DS can strongly influence the results of cognitive tests (Wishart and Duffy 1990). Therefore, it is likely to be the explanation of the good co-operation for the ocular function. However, the author failed to obtain reliable AL with 7% children with DS. This might be due to the IOL-Master relying on adequate foveal fixation to obtain measures. Their lack of comprehension of fixing the light may result in failure of this test. Success rates for the adults with DS for refractive error, VA and AL measurements were lower than that of shown in Haugen's study (Haugen et al. 2001a).

Taking the Pentacam image

With regard to the Pentacam image, 75% children with DS and 74% adults with DS were able to co-operate, which was lower than that reported by Haugen (83%) and Doyle (98%) for the corneal topography (Doyle et al. 1998; Haugen et al. 2001a). This difference may be due to the different age groups and different testing methods utilised in these studies. The Pentacam system takes 1-2 seconds to obtain a measurement. The main reasons for failure were tilting their head, blinking, fidgeting or lack of comprehension of the test in those subjects with DS. In addition, the camera rotated twice around the border of the black circle just in front of the subject, may distract their attention and result in them looking away from the fixation light.

It is noted that not many DS children (n=12) and control children (n=5) were involved in the lens thickness measurement. The main reason was the

difficulty in persuading child subjects to pay a return visit, while the additional use of eye drops further discouraging attendance. Unlike control children, the parents of children with DS from our longitudinal cohort were shown to be more supportive and were more likely to attend a second visit.

3.5.2 Visual function

High refractive error was found in the majority of our subjects with DS. Compared to controls, DS children have poorer VA and higher prevalence of under accommodation, which is consistent with the previous studies (reviewed in Chapter 1).

Surprisingly, there were 82% children with DS seeing 0.3 (6/12) or better in our cohort, which is higher (i.e. better VA) than the other studies (Courage et al. 1994; Doyle et al. 1998; Evereklioglu et al. 2002; Haugen et al. 2001a; Liza-Sharmini et al. 2006; Tsiaras et al. 1999). Different age groups used in various studies may be a contributing factor. In addition, another possible explanation may be applicable to our study, which was stated by Doyle (1998) "Visual performance has been maximised by early refraction and appropriate glasses, with good follow up in the cohort".

3.5.3 Ocular biometric features

3.5.3.1 Properties of the AL

The mean AL of DS children is smaller than that of our controls, which is not in line with Haugen's study who reported that the AL of young adults with DS was similar to that of controls (Haugen et al 2001a). However, the similar AL value was found between hyperopic DS children and controls. Further, both hyperopic DS children and controls have shorter AL and smaller AL/CR compared to that of myopic eyes.

No significant difference was found in the AL/CR ratio between our DS children and controls, which is in accordance with the results of Haugen. In our study, DS adults have a much higher AL/CR ratio compared to our child subjects, which may be due to the more myopic mean refraction in DS adults (-2.83±6.30 D) compared to DS children and controls (2.20±3.49 D vs. 2.35±3.46 D).

There was no significant difference in the mean AL of DS adults with keratoconus and those without keratoconus in our study, which is contrary to the report that keratoconus eye has greater AL (Li et al. 2005; Touzeau et al. 2004).

3.5.3.2 Properties of the cornea and its implications

Thinner central cornea and higher corneal power in DS subjects compared to that of controls were in agreement with the previous studies (Doyle et al. 1998; Evereklioglu et al. 2002; Haugen et al. 2001a). No significant difference was found in asphericity between subjects with DS and controls even though corneal thickness and radius are significantly different, which is in line with the statement by Dubbelman et al. (2006) "A steep cornea is not likely to be more or less aspheric than a flat cornea. The asphericity of both corneal surfaces is independent of gender and radius." It appears that the cornea of people with DS was prolate shape similar to controls. However, corneal aberration was significantly more positive in people with DS and it is interesting in view of the poorer VA in people with DS. However, no significant correlation between aberration and VA was found in our study.

Hyperopic DS children have significantly higher corneal power and aberration than that of hyperopic controls, whereas myopic DS children have significantly higher corneal power but not significantly different aberration. Since the participants in both child groups were mostly hyperopic (Fig. 3-13a), we have to bear in mind that the overall difference mainly lies in hyperopic eyes.

What causes the abnormality?

The biometric parameters of the cornea in people with DS were different from the normal. The conical corneas seen in keratoconus patients with DS who present for corneal grafting are thinner than those from keratoconus patients without DS (Haugen et al. 2001b). Moreover, acute swelling of the conical cornea is far more common in keratoconus patients with DS than those without DS (Pierse and Eustace 1971; Tuft et al. 1994). The inherent corneal thinning may result from the gene disorders in people with DS. The gene encoding the a-1 chain of type VI collagen, a major constituent of the corneal stroma, is on chromosome 21 at Locus 21q22.3 (Hattori et al. 2000; Rabinowitz 1998). Therefore, as people with DS have a trisomy 21, there might be a connection between this gene and the thinning of the cornea.

The thinning of stroma of both the iris and the cornea is present in people with DS (Bertelsen and Seim 1974). Moreover, these tissues are both derived from the neural crest cells. Hence, it has been suggested that the common defect in the migration or differentiation of neural crest cells may lead to this thinning (Bertelsen and Seim 1974).

Thus, it was speculated that the increased curvature may be due to the reduced mechanical rigidity as a result of the thinning of the corneal stroma (Haugen et al. 2001b). That is to say, the central region of the cornea is likely to become weak due to tissue thinning, which in turn causes the tissue to bulge and consequently changes the shape of the cornea. However, CCT and CR were not correlated in our DS subjects. Therefore, it may not be the whole explanation for the reduced curvature in people with DS.

Its implications

Thinner corneal thickness and higher corneal power in people with DS may be associated with abnormalities in collagen. Therefore, it is more likely that corneal rigidity differs from that of ordinary people. Firstly, the inherent corneal thinning is probably an important aspect of the development of keratoconus in DS. In other words, the thin cornea may predispose for the development of keratoconus. Secondly, this difference could give rise to a

false reading of the IOP. Many studies have pointed out that properties of the cornea other than the thickness and curvature, such as corneal elasticity may affect IOP measurement (Harada and Naoi 2004; Svedberg et al. 2005), which was discussed in chapter 5. The corneal aberration was higher, which may influence the balance of the aberration of the eye. Thus, it may lead to refractive error in people with DS. Moreover, higher corneal aberration may lead to degradation of the retinal image quality and therefore to visual performance (Gobbe and Guillon 2005; He et al. 2002) and explain, in part, the poor VA in children with DS.

3.5.3.3 Properties of the lens

'Flake' lens opacity has been reported in people with DS in a number of studies, as reviewed in Chapter 1. However, no lens opacity of visual significance was found in this study of child subjects. Pupils were not dilated for clinical examination, so very peripheral lens opacities may have been missed. Four adults with DS (29%) had cataract visible with non-dilated pupils.

Our finding of a thinner lens in our nine child subjects with DS compared to that of the five controls (3.34±0.36mm vs. 3.56±0.11mm – not significant) was similar to the results of Haugen (3.27±0.29mm vs.3.49±0.20mm) (Haugen et al 2001a). Haugen's study had much larger subject numbers (40 with DS), and the difference was statistically significant. He also reported higher lens density in people with DS (age range from 19-26 years). However, in our study, no significant difference in lens density was found between DS subjects and controls. Both studies utilise arbitrary units to measure lens density so that the direct comparisons are not possible. It may be due to the different methods and different age groups. Our calculated lens power was 2.1D weaker than control subjects, which is close to the 1.8D difference reported by Haugen et al (Haugen et al 2001a).

However, there was no significant difference in lens power between children who accommodate accurately and those who do not. Further, when the different refraction groups are considered separately, hyperopes with accurate accommodation have higher lens power, although the difference is non-significant. Whether this is a real trend remains to be seen when larger numbers of subjects can be assessed. There could be factors other than just lens power coming into play to influence whether an individual child with DS accommodates accurately, even with a low lens power. It is discussed more in chapter 6, section 6.2.3.

3.5.3.4 Properties of the anterior chamber

Mean ACD of young adults with DS (3.45±0.34 mm) was first reported by Haugen (Haugen et al. 2001a), which was deeper than our results (DS children 3.11±0.36 mm, DS adults 3.29±0.46 mm), but neither study showed a significant difference between DS and respective controls.

3.5.3.5 Pupil diameter

To our knowledge, pupil diameter of people with DS was first examined in our study. Subjects with DS have similar pupil size to our controls. Therefore, poor accommodation in children with DS cannot be explained by reduced pupil size resulting in increased depth of focus of the eye.

3.5.3.6 Correlation between optical components

Since refractive error is the result of mismatched association among the refractive components, correlations between the total refraction of the eye and the individual optical elements may explain the failure of emmetropisation in children with DS. Linear correlation between AL and refraction in people with DS was noted in our study, which is in accordance with previous studies (Doyle et al. 1998; Haugen et al. 2001a).

Our correlation equation was

$y = 44.71 - 1.92x$, where y is mean sphere and x is axial length.

Doyle et al. (1998) and Haugen et al. (2001) found the following equations respectively:

$y = 37.98 - 1.63x$ and $y = 38.20 - 1.67x$.

There is no statistically significant difference between the three equations. However, in our study, the relationship between refraction and AL was not similar in children with DS and controls. There was also a significant difference in the association between AL/CR with refraction in both child groups. Moreover, refractive components were correlated well as expected in control child but not in DS children. The fact that they are not correlated suggests that the lack of coordination between the components may result in refractive error.

The difference between children with DS and control children seems to lie with hyperopes. With only 6 myopes in the DS group, numbers are too small to draw any firm conclusions.

3.5.4 Detection of keratoconus

No clinical signs of keratoconus (0%) were detected in the examination of our children with DS, which is consistent with the other two studies for children with DS (Liza-Sharmini et al. 2006; Vincent et al. 2005). 2% was reported with keratoconus and 6% had an abnormal corneal topography in Doyle's study (within the age range of 15 to 22 years). In terms of the prevalence of keratoconus in adults with DS, 13% and 20% were reported in Haugen's two studies (within the age range of 19 to 26 years and from 15 to 90 years) (Haugen 1992; Haugen et al. 2001a). In our study, 47% of adults with DS have keratoconus (within the age range of 19 to 58 years), from a biased sample as our subjects were mainly selected, being a clinical population and are very likely to be biased towards those with visual problems. It appeared that the older age group may have a higher frequency of keratoconus.

On assessing corneal topography to detect keratoconus, it can be seen that objective and subjective methods gave similar results in control children and adults with DS. Seven adults with DS with keratoconus by clinical examination were picked up by both methods. Seven control children by subjective method and eleven by objective method were detected as having suspect corneas but all had normal corneas on clinical examination. This raises the possibility that the criteria adopted by both methods are too lenient to be clinically useful. In most situations only clinically suspect corneas would be examined by corneal topography. JMW made the decision not to follow up the study diagnosis with control children, but to place a note in the subject's records as a reminder to examine the cornea thoroughly at their next visit.

3.5.5 Keratoconus, eye rubbing frequency and family history (adults with DS)

No association between eye rubbing frequency and keratoconus was found in our study, which is in contrast to the study by Haugen (Haugen 1992). However, it is consistent with Vincent (Vincent et al. 2005). No association between family history and keratoconus was found. However, Vincent reported that there was a greater incidence of abnormal topographic changes

in the parents of children with DS, suggesting a genetic basis for corneal structural abnormality (Vincent et al. 2005).

3.6 Conclusions

The majority of our subjects with DS have refractive error and under-accommodation. Poorer VA was confirmed compared to our control children. With regard to the ocular biometry measurements, thinner CCT and PCT, smaller CR and higher corneal power were confirmed in people with DS. Higher aberration of the cornea was noted in people with DS. The shape of the cornea was prolate in people with DS similar to the controls. Calculated lens power was lower in children with DS compared to controls. Adults with DS and with keratoconus have deeper ACD compared to those adults with DS but without keratoconus. No other significant difference was found in anterior chamber parameters and pupil size between subjects with DS and controls.

It was confirmed that there was significant correlation between AL and refraction, the AL/CR and refraction in both child groups. However, it was noted that the correlation between AL and refraction was significantly different between children with DS and controls. Thus, it appeared that refraction is determined by AL and CR in the different way as in the general population.

Clinically, keratoconus was present in 40% (n=8) adults with DS, however, no keratoconus was found in children with DS. Abnormal corneal topography was more common in children with DS compared to those controls. Hence, more children with DS were detected with suspicious keratoconus. There was no association of the eye-rubbing, family history and frequency in DS adults with keratoconus compared to those of the non-keratoconus group.

Chapter 4

Retinal features in people with DS

4.1 Introduction

4.1.1 Retinal features in people with DS

As reviewed in chapter 1, retinal abnormalities were described in people with DS, but these studies have been limited to the description of the blood vessels (Ahmad and Pruett 1976; Berk et al. 1996; da Cunha and Moreira 1996; Sherk and Williams 1979; Williams et al. 1973). To our knowledge, no studies have documented the quantitative characteristics of the disc itself in people with DS. It may be due to the difficulty of determining objectively the optic disc area by traditional technique.

Therefore, the first aim of this part of study was to quantify the optic disc by planimetric evaluation. The hypothesis was that optic disc was smaller in DS children due to the following considerations. First of all, hypermetropia, often of considerable degree is very common in DS. Hyperopic eyes are smaller and hence, may be expected to have smaller optic discs (Lempert 2003). Secondly, disc relates directly to the number of nerve fibres in the optic nerve. A decreased number of neurons (Wisniewski 1990) and dendritic atrophy (Becker et al. 1991) in the visual cortical area in people with DS have been reported, both of which might be associated with fewer optic nerve fibres and therefore a smaller optic disc. Thirdly, a scarcity of nerve fibres may be a factor in the explanation for reduced visual functions (Hellstrom and Svensson 1998). VA is below-normal in children with DS, and a recent study from our group has shown that the deficit persists even when motivational and concentration factors are excluded by the use of objective electrophysiological techniques (John et al. 2004), suggesting that there is a neural basis for the deficit.

In addition, the distribution, the diameter and the structural integrity of the vessels are aspects defining the general health of the vasculature. It has been reported that the abnormalities of the vascular pattern are associated with various ocular diseases (Klein et al. 2004a; Klein et al. 2004b; Mitchell et al. 2005) and they also provide unique information applicable to the study of various systemic vascular disorders such as stroke, coronary heart diseases and diabetes (Klein et al. 2004b; Wang et al. 2003; Wong et al. 2002; Wong and McIntosh 2005; Wong et al. 2005).

Therefore, the second aim of this part of study was to observe the features of retinal vessels in our subjects. The functional significance of children with DS having more retinal vessels is not straightforward. However, it was hoped that further information about the arteries and veins, their direction, distribution and width may imply the real blood supply situation in children with DS to some extent. If retinal blood flow is abnormal in DS, there may be an influence on eye growth and visual function. Thus, any possible association between the distribution of the vessels and visual performance such as refraction, VA and accommodation was investigated.

4.1.2 Planimetric evaluation

Planimetry refers to the methods that use fundus photography to produce measurements of the ONH structure. It has been widely used in research for the observation and morphometric analysis of the ONH and for the diagnosis and assessment of glaucoma (Bartz-Schmidt et al. 1995; Garway-Heath and Hitchings 1998; Garway-Heath et al. 1997; Hatch et al. 1999; Jonas et al. 1989a; Morgan et al. 2005a; Morgan et al. 2005b; Nguyen et al. 2001; Rudnicka et al. 2001; Sanchez Perez et al. 2001). The true measurements of the optic disc size or the diameters of the retinal vessels from a fundus photograph are dependent on obtaining the camera magnification and the magnification of the eye.

Magnification of the fundus photograph

Various methods to correct the camera and eye magnification have been published and all make assumptions about the optics of the eye to a greater or lesser extent (Bengtsson and Krakau 1977, 1992; Bennett et al. 1994; Garway-Heath et al. 1998; Langenbucher et al. 2003; Littmann 1982; Quigley and Dube 2003; Rudnicka et al. 1998).

For the first time, Bengtsson and Krakau (1977) described the nature of the camera and its magnification for measuring the size of the optic disc from a photographic image. In this paper, they also presented the formulae for calculating image magnification based on the refractive error of the eye.

Since then other authors have presented different methods based on:

i. ametropia and keratometry (Littmann 1982);
ii. AL only (Bengtsson and Krakau 1992; Bennett et al. 1994)
iii. AL, ACD, lens thickness, keratometry and ametropia (Bennett et al. 1994).
iv. Bennett and Littmann's methods were compared (Garway-Heath et al. 1998). The AL method differs little from more detailed calculations, suggesting that the AL method is most accurate.

Camera magnification was discussed and presented in Rudnicka's study (Rudnicka et al. 1998). They compared and presented the magnification properties of different fundus cameras. More importantly, they first demonstrated the appropriate magnification formula for cameras in image size calculations. Noticeably, two novel methods were described later. Quigley et al. (2003) stated "The focusing knob position of the camera reflects the spectacle refraction of the eye being photographed; therefore, it can be used in retinal photographic screening programs." Langenbucher (2003) presented a numerical calculation scheme which was based on ametropia, keratometry, AL, ACD and LT in order to determine the total magnification of the camera and an individual eye using paraxial raytracing. It was proved to be related to the respective values of the classical Littmann formula as well as to enhanced methods described by Bennett et al. (1994) and Garway-Heath et al. (1998).

Planimetric evaluation software

The custom digital planimetry software was initially written by JEM and was developed with the work of a computer expert (GP). The algorithms used for the magnification correction of the images were derived from the work of Garway-Heath et al. (1998), namely, based on the keratometry and refraction settings of the examined eye. This magnification formula is sufficient for ocular refraction of less than 7 diopters. The initial version proved to be a good technique for planimetric evaluation of stereoscopic images in previous studies in the school (Morgan et al. 2005a; Morgan et al. 2005b; Sheen et al. 2004). The current version was modified by incorporating the scaling factor of the Topcon fundus camera, which was worked out with the use of a Moorfield model eye (For more detail, see

chapter 2. section 2.4).

The digital software enables an observer to view stereoscopic or monoscopic images. It involves the demarcation of the ONH properties including the area of the disc, the rim and the cup. Digital stereoscopic optic disc assessment provides a better estimation of the cup and a higher level of interobserver agreement compared with monoscopic assessments (Morgan et al. 2005a). However, in the current study, the stereoscopic camera was not considered sufficiently user-friendly to use with subjects with DS and so only monoscopic images were available. In addition, the software also provides a new function for vessel width measurement.

Before the custom digital software was ready, the ImageNet 2000 software which was installed in the Topcon camera was initially used for planimetry measurement. Since we could not have the ImageNet software scaled for magnification of the fundus photograph, only those fundus photographs matched in AL within 0.05mm were evaluated. Because the corneal power is higher in children with DS (see chapter 3, section 3.4.3), magnification would be expected to differ between the two groups. The average corneal power for each group was also used to correct the difference in magnification; therefore, relative planimetric measurements were obtained.

Both software had been used in previous studies, to perform subjectively evaluation of the disc. But the custom software would be expected to be more precise than the ImageNet software as the following advantages:

i. The magnification of eye was corrected individually and the magnification of the camera was considered;
ii. More details of drawing of planimetry, i.e. the area of cup, the maximum and minimum diameter of the disc ;
iii. It provided the vessels measurement;

The limitation was that it had a range of certain set refractive error and corneal radius, which is narrower than our groups. In other words, some good images may not be able to be assessed with it.

In fact, we initially aimed to correct the magnification of the eye by AL since it was proved that AL is more accurate to correct the magnification of the eye than the methods which use keratometry and ametropia alone (Garway-Heath et al. 1998). In addition, AL was found to be the most important predictor of size for most of the optic disc parameters (Rudnicka et al. 2001). However, it is time-consuming and tedious to modify the custom software, and required the services of the specialist programmer. Thus, the custom software still only took ametropia and keratometry into account in order to correct the magnification of the eye to obtain absolute planimetric measurements.

Additionally, it has been a concern that there is considerable variation in the definition of the optic disc and cup borders among observers, which arises because the observer is required to judge the inner circumference of the scleral ring of Elschnig and distinguish this from the presence of PPA. This variability can be reduced by using trained and experienced observers (Garway-Heath et al. 1999; Hatch et al. 1999; Miglior et al. 2002; Sheen et al. 2004; Varma et al. 1988). Since it was important that the observer was masked to subject group (DS or controls) when evaluating the images, it was not possible for the author to evaluate the images herself. Therefore, one experienced observer (ALJ) was involved in the current study for planimetry evaluation.

4.1.3 Assessing the retinal vessels

Several investigations developed more quantitative approaches in order to measure the diameter of all arteries and veins for the identification of the earliest changes associated with diseases of vascular aetiology. Established methods of measuring vessel width are based on:

i. Manual methods from photographic or digitized film images (Hodge et al. 1969; Hubbard et al. 1999; Newsom et al. 1992); However, observers varied their interpretation of a vessel's edge, and might have overestimated the true width of the retinal vessel widths from the images shown (Jonas et al. 1988b; Jonas et al. 1989b; Stromland et al. 1995).

ii. Computer-assisted methods from digitized fundus photographs (Sherry et al. 2002; Wong et al. 2004); The observer selected a segment of the vessel and

the software calculated its width (Stromland et al. 1995).

iii. Semi-automated methods, which adopt a linear densitometry technique to automate the measurement of vessel calibre based on edge detection and boundary tracing (Arend et al. 2002; Chapman et al. 2001; Chen et al. 1994; Suzuki 1995; Wu et al. 1995).

The relevant literature showed that measurements have been combined in a variety of ways such as the sum of widths for arterioles and veins, the ratio of the sums, the totaling of their squares. Moreover, it was demonstrated that there was marked variability in the branching pattern among individuals (both size and number of branches). This prevented direct comparison of arteriolar measurement between individuals (Stokoe and Turner 1966). Consequently, some techniques attempted to summarize the arteriolar calibre or vein calibre by using formulae (Hubbard et al. 1999; Parr and Spears 1974).

The distribution of the retinal vessels may reflect the need of vascular supply in the corresponding superficial retinal area. The following four questions were of interest in our study:

a. Do children with DS have more retinal vessels crossing the disc or beyond the disc compared to control children?
b. Do the retinal vessels of children with DS distribute in a similar pattern compared to control children? That is, in which segment do they have more vessels, in Superior or Inferior, Temporal or Nasal?
c. Do children with DS have more arteries, veins or both compared to control children?
d. Do the sizes of the vessels of children with DS differ from control children?

4.2 Methods

4.2.1 Subjects

The procedures of recruitment were described in chapter 1, section 1.7.2. Fundus photographs were taken in those same forty-six children with DS, fifty control children and nineteen adults with DS at their first visit.

4.2.2 Procedures

The author (PJ) performed fundus photography binocularly on all children with DS and controls, adult subjects with DS (see section 4.2.3). The good quality fundus photograph from children with DS was matched for the AL of the eye, within 0.05 mm accuracy, with one photograph from the controls. The photographs from each pair (n=14) were corrected for the corneal power and subsequently were evaluated with the Imagenet 2000 planimetry software by the observer ALJ (see section 4.2.4.2). When the scaling of the custom software was completed, the magnification for those fundus photographs were corrected according to the corneal radius and refraction and then evaluated with the use of custom digital planimetry software by the same observer ALJ. The planimetry procedures are described in detail in a later section (4.2.4.2).

The last part of the investigation of retinal vessels included the good fundus images from each eye of 31 children with DS and 46 control children and 4 adults with DS. The author viewed these images with the custom software, recording the number of the retinal vessels present at the disc margin and retinal periphery (section 4.2.5). Vessel width, after correction for corneal radius and refraction, was measured in each child with DS (n=17), control children (n=28) and adults with DS (n=4).

4.2.3 Taking fundus photograph

The study used a Topcon non-mydriatic TRC_NW6S fundus camera. The principles of how it works and how to use it were described in chapter 2, section 2.3. The right eye was always photographed first. The captured image was displayed on the colour video monitor. The examiner (PJ) showed the photograph of his/her eye to the subject with DS by saying: "Look, this is the back of your eye.

Do you want one for your left eye as well?" The subject was often interested and another photograph of the eye was done as quickly as possible. The examiner viewed each digital image immediately. If it was not good enough, a second one was taken at the same sitting. Otherwise, a second visit was arranged if necessary and possible for the subject.

4.2.4 Planimetric evaluation

Assessing the quality of the fundus photograph

Image quality was determined on the basis of illumination and the photographic field, which should include both the optic disc and the macula. The fundus images were excluded as a consequence of one or more of the following conditions:

i. The photograph was of poor quality, namely too dark, not uniformly illuminated or overexposed;
ii. Corneal radius was not available or was ranked out of the range of values the software was set for i.e. corneal radius below 7.0mm; refraction less than -7.0D;
iii. The peripheral retinal area named Zone A (see section 4.2.5, Fig. 4-2) was not visible overall;

The clearer image of the eyes of one subject was used for the monoscopic planimetry evaluation and retinal vessel assessment. All selected monoscopic images were then coded by the author. Thus only one eye of each subject was included in the further analysis.

Planimetric evaluation

Planimetry evaluation was performed by the experienced observer (ALJ) masked to whether the individual was from the DS group or the controls. The image was magnified in order to make a precise measurement but was not subjected to any software enhancement.

a. ImageNet software

ImageNet 2000 software was available for the Topcon camera, but this did not correct for magnification as was discussed earlier. Instead, fundus photographs

were analysed only for eyes matched for AL (within 0.05mm). That is, for each photograph of a child with DS, a photograph of a control child with the same AL was identified. 14 paired subjects who were matched for AL and corneal power was available. The observer (ALJ) performed the planimetry evaluation with those images by using the ImageNet 2000 software. The disc margin was marked. Additionally, the observer drew a line from the centre of the disc to the centre of the fovea (judged by eye) in order to measure Fovea-Disc distance. The values of disc size and Fovea-Disc distance were presented and recorded in mm^2 and mm. A formula was used to correct the difference in magnification of those fundus photographs, using the average corneal power for each child.

b. Custom digital software

The observer evaluated the fundus photography with the use of the custom digital software in the following steps:

Firstly, refractive error and radius of cornea of the examined eye were entered into the software in order to correct the magnification of the fundus photograph.

Secondly, by using a cursor, the observer outlined the margin of the optic disc, which is defined as the inner border of the scleral canal (Fig. 4-1). The optic disc is surrounded by the scleral ring of Elschnig, and may be accompanied by PPA. In some cases, its appearance may be confused with the margin of the disc. In addition, the margins are not clear in cases with small discs due to the overcrowding of the nerve fibres when they exit from the eye. Therefore, care was taken when marking the border of the disc. Disc shape is denoted by an index, defined as the ratio of the minimum and maximum of the optic disc axis.

Thirdly, the optic cup border (inner circumference of the rim) was marked (Fig. 4-1). This can be achieved by following the course of the blood supply and contour of the ONH.

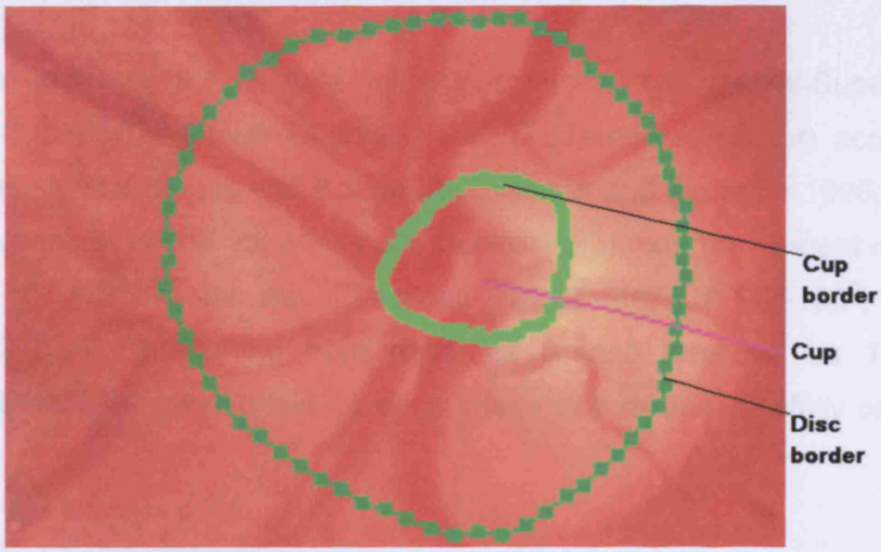


Fig. 4-1: A fundus photograph of the left eye, one subject with DS, showing the planimetric evaluation

Areas of interest were outlined as points by the observer and then interconnected by colour coded lines for the area of the disc and cup respectively (Fig. 4-1). The observer could revise the measurement by altering the points. Once these adjustments had been made, the software calculated and provided each parameter in pixels and mm^2. The maximum and minimum diameter of the disc was automatically measured by the software.

4.2.5 Assessing the retinal vessels

Setting up the images

In order to analyze the images in four sections: NS (Nasal-Superior), TS (Temporal-Superior), NI (Nasal-Inferior) and TI (Temporal-Inferior) according to the previous studies (Jonas and Budde 2002; Jonas and Grundler 1998; Jonas et al. 1988b; Jonas et al. 1989b; Jonas and Schiro 1993), one transparent mask was drawn and divided into four equal sections (NS: 0^0-90^0; TS: 90^0-180^0; NI: 180^0-270^0; TI: 270^0-360^0), starting from nasal as 0^0 and temporal as 180^0. The transparent masks were overlaid on each image in turn and carefully centred on the disc.

Prior to counting and measuring retinal vessels, the border of the optic disc and cup was marked by the observer (PJ) in order to automatically obtain the Zone A, which is the area between the first and second circles (Fig. 4-2). These were centered at the geometric centre of the disc, and were 2mm and 4mm away from the disc margin (Fig. 4-2). Vessels were evaluated within the rim area and Zone A (for number and width).

The retinal vessels in all fundus photographs with good quality were counted and measured in the four sections of the disc and then the four sections of Zone A. Images were magnified in order to improve the view of the course and edge of the vessels. Only those images corrected for corneal radius were measured for width. The measuring procedure took about 20 minutes for each photograph.

Identifying the retinal vessel

The arteries and veins were counted separately in the disc and Zone A. The observer identified each vessel to be measured as an artery or a vein. It was suggested from previous studies (Stromland et al. 1995)

i. Arterioles are shown in a lighter orange-red colour, with a strong central light reflex, straighter and smoother in outline;
ii. Veins are shown in a darker purple-red colour, with little or no central light reflex, tortuous, more irregular in outline;

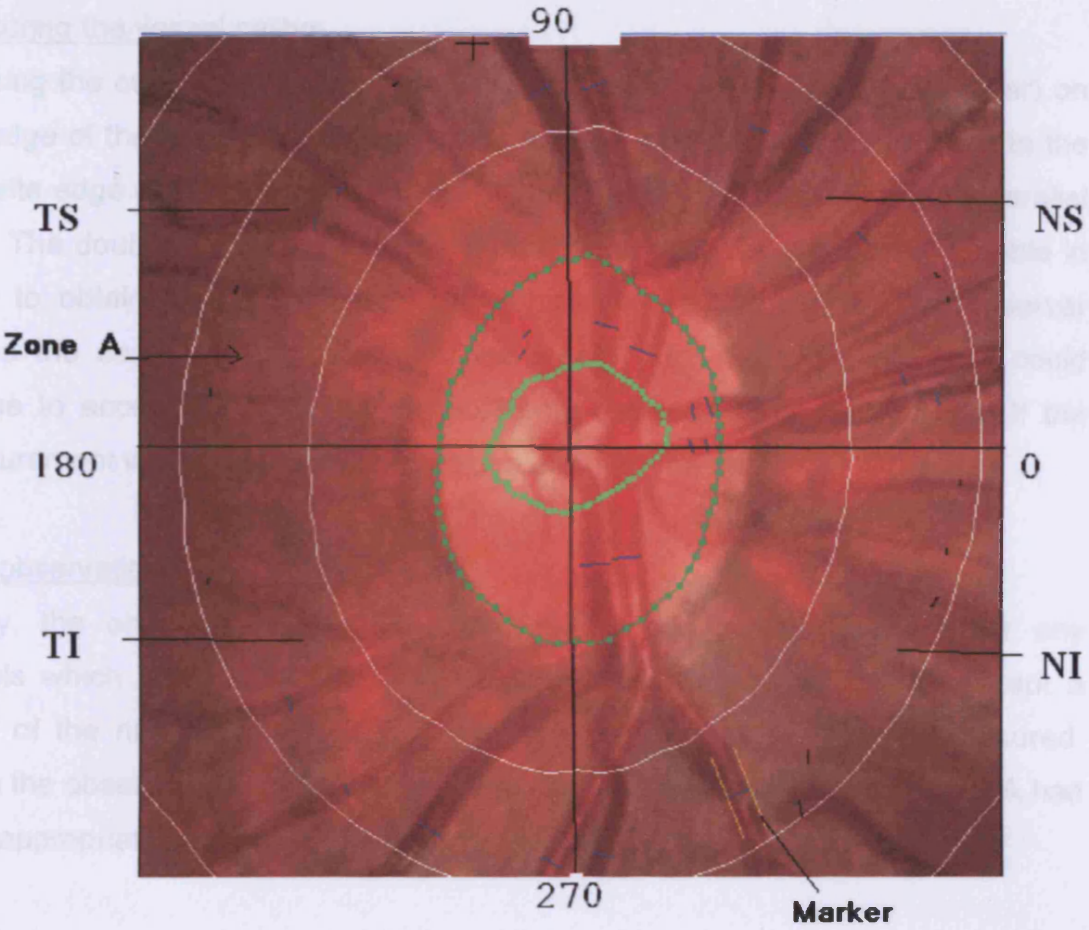


Fig. 4-2: A fundus photograph of the right eye of one subject showing the vessel assessment. It demonstrates the optic disc, zone A and the four sections (NS: 0^0-90^0; TS: 90^0-180^0; TI: 180^0-270^0; NI: 270^0-360^0), starting from nasal as 0^0 and temporal as 180^0).

Selecting the region of interest

The observer selected the region of interest for that vessel, using the following rules:

i. Choosing a vessel segment in the outer third of the rim or Zone A;

ii. If a vessel bifurcates within the disc or zone A, the branches after the bifurcation were measured;

iii. Choosing a stretch of vessel in order to minimize any effect of that branching or crossing; a relatively straight vessel segment rather than curved.

Measuring the vessel calibre

By using the cursor, the observer put one of the double parallel lines (Marker) on one edge of the vessel (Fig. 4-2). The second parallel line was then moved to the opposite edge of the vessel by enlarging the distance between the double parallel lines. The double lines were kept parallel with the vessel as much as possible in order to obtain the shortest distance across the retinal vessel. The observer clicked the cursor and finalized the line length (Fig. 4-2). The observer could choose to accept or reject the measurement depending on its precision. If the measurement was rejected, the observer measured the vessel again.

Final observation

Finally, the observer reviewed the digitized fundus image, checking for any vessels which were not marked with a blue marker. The observer also kept a count of the number of arteries and veins which had already been measured. When the observer was satisfied that all retinal vessels in the disc and Zone A had been appropriately measured, the data were recorded.

The vessels were then divided into three groups that were relatively easy to identify visually. They were grouped as large (>0.035units), medium (0.020-0.035units) and small (<0.020units) according to the measured diameter.

4.3 Results

4.3.1 Co-operation of the subjects

The number and success rate (SR) of the subjects for the fundus photograph is shown in Table 4-1.

Table 4-1: The number of subjects and SR for the fundus photograph

Fundus Photography	DS Children		Control Children		DS Adults	
	No.	SR	No.	SR	No.	SR
	38	83%	50	100%	8	37%

Table 4-2 summarizes the number of images analyzed for the purpose of measurement of the disc size, vessel diameter and vessel count respectively by the custom software.

Table 4-2: The number of fundus images for evaluation by custom software

Measurements	DS Children No.	Control Children No.	DS Adults No.
Disc size	17	30	4
Width of vessel	17	28	4
No. vessels	31	46	4

4.3.2 Planimetric evaluation of the optic disc

ImageNet software

The 2000 ImageNet software were performed in the subjects matched for AL. When only AL was matched, significantly larger disc (Independent t-test, p=0.010) and longer Fovea-Disc distance (Independent t-test, p=0.016) were found in children with DS than that of controls. The results are shown in Table 4-3. However, after the magnification of the corneal power was corrected in those cases with matched AL, only the disc size was significantly larger (Mann-Whitney

U test, p=0.044, power of test is 0.805). The longer Fovea-Disc distance was not significant in children with DS (Mann-Whitney, U test, p=0.352, power of test is 0.187).

Table 4-3: Comparison of the results by the ImageNet software

	DS children	DS children	Control children	P value
No. subjects	**14 •**	**14 • •**	**14**	
AL (mm) Mean±SD	22.20±1.27		22.21±1.26	0.980
Meansph (D) Mean±SD	1.59±3.02		2.63±2.65	0.338
Corneal power (D) Mean±SD	45.36±2.20		42.49±1.81	0.001
Disc size (mm) Mean±SD	4.97±0.92	4.59±0.44	4.06±0.63	0.044
Fovea-Disc Distance (mm) Mean±SD	7.01±0.68	6.45±0.63	6.29±0.44	0.352

(Independent t test or Mann-Whitney DS children Vs. Controls)

• Subjects matched for AL but with uncorrected magnification of the cornea

• • Subjects matched for AL but with corrected magnification of the cornea

The custom digital software

Results of the planimetric evaluation by the custom digital software are shown in Table 4-4. It revealed that the mean disc size and rim size in children with DS were significantly larger than that of the controls (Independent t-test, $p<0.05$). However, there is no significant difference in mean cup size or C/D ratio. The shape index is similar in both groups, indicating that the disc in children with DS has a similar shape to that in the control children.

Table 4-4: Findings of the planimetric evaluation by the Custom software

	DS Children	Control Children	P value
No. subjects	17	31	
Disc size (mm) Mean±SD	2.40±0.52	2.10±0.36	0.024
Cup size (mm) Mean±SD	0.71±0.30	0.61±1.33	0.872
C/D ratio Mean±SD	0.29±0.09	0.29±0.10	0.890
Rim size (mm) Mean±SD	1.69±0.40	1.47±0.27	0.031
Shape Index Mean±SD	0.88±0.06	0.90±0.06	0.361

(Independent t-test or Mann-Whitney test DS children vs. controls)

Significant correlation between disc size and cup size ($r=0.622$, $p<0.001$ vs. $r=0.652$, $p<0.001$), disc size and rim size ($r=0.833$, $p<0.001$ vs. $r=0.649$, $p<0.001$) were noted in DS children and control children. Moreover, there was no significant difference in these correlations between DS children and control children ($z_{obs}=1.305$; $z_{obs}=-0.152$). A larger disc size with a larger rim was noted in both groups by linear regression (Table 4-5, Fig. 4-3). Comparing the linear regression of disc size and rim size in both groups, the slope ($p=0.361$); the elevation ($p=0.341$) and the residual variance were not significantly different at 0.05 level of probability ($F=1.646$, $df1=15$, $df2=29$). However, no significant correlation was found between disc size and VA or between rim size and VA in both groups.

Table 4-5: Correlation of disc parameters in child subjects

Correlation		R	R^2	Equation	p-value
Disc size –Cup size	DS children	0.622	0.387	Y=0.164+1.081X	0.008
	Controls	0.652	0.427	Y=0.157+0.847X	< 0.001
Disc size - Rim size	DS children	0.833	0.693	Y=0.057+1.087X	< 0.001
	Controls	0.649	0.422	Y=0.086+0.847X	< 0.001

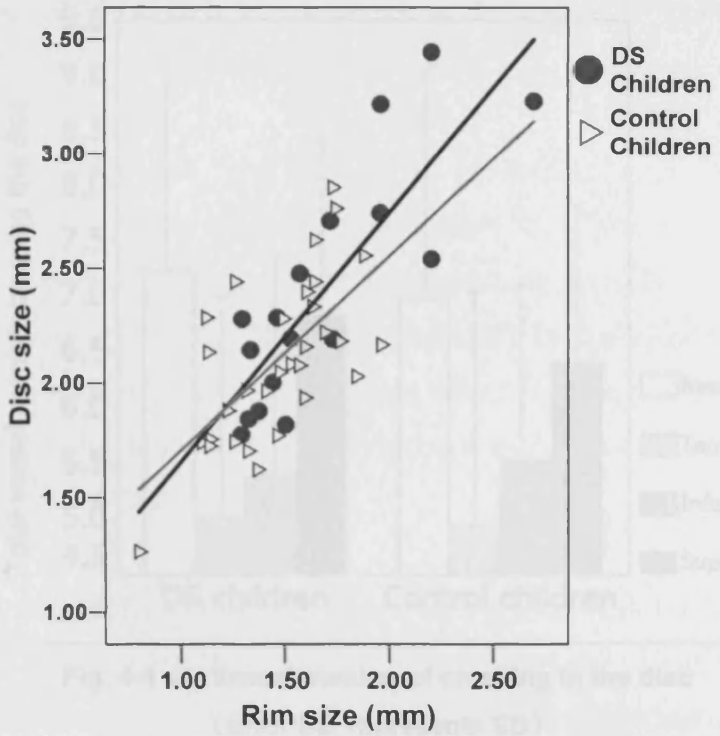


Fig. 4-3: Disc size and rim size

4.3.3 Assessing the retinal vessels

Distribution of the retinal vessels

Children with DS had significantly both more veins (13.1±3.7) and more arteries (7.8±2.4) in Zone A than control children (10.5±3.1; 6.3±2.0) (Independent t-test, $p<0.01$), but not for those crossing the disc, suggesting that retinal vessels of children with DS bifurcate more after leaving the disc margin (Fig. 4-4a1-2). Further, in Zone A, it was noted that more retinal vessels distributed nasally (NS+NI) than temporally (TS+TI) (Paired t-test, $p=0.017$), superiorly (NS+TS) than inferiorly (NI+TI) (Paired t-test, $p<0.01$) in both child groups.

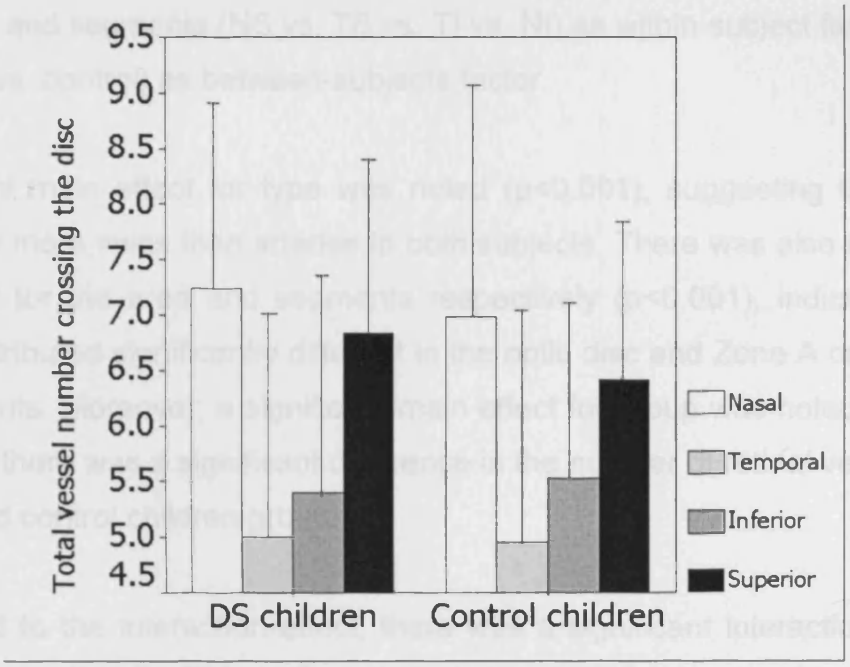


Fig. 4-4 a1: Vessel number of crossing in the disc

（Error bar represents SD）

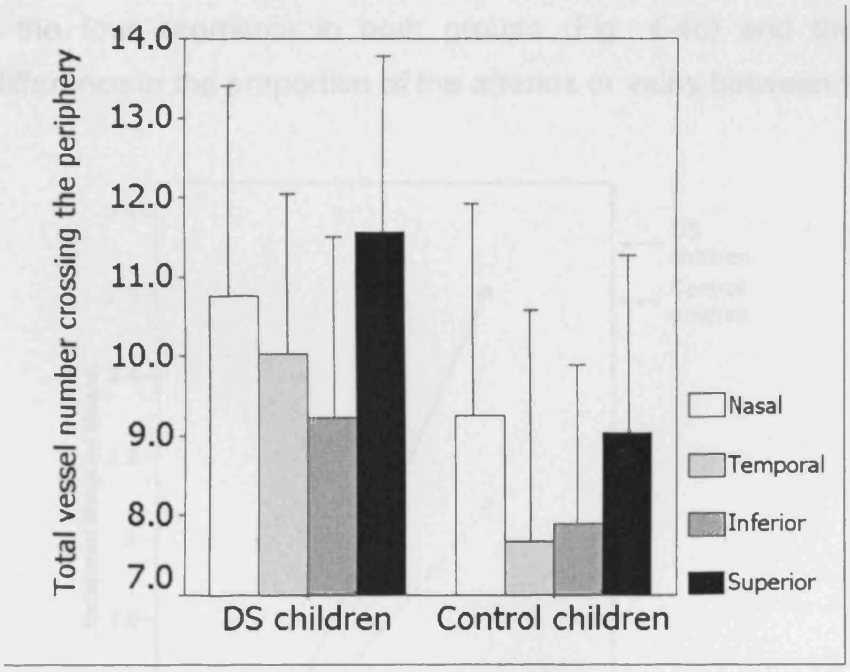


Fig. 4-4 a2: Vessel number of crossing in Zone A

（Error bar represents the SD）

Repeated measures ANOVA was conducted to explore the impact on the number of retinal vessels of the type of vessel (artery vs. vein), the distribution in area (disc

vs. zone A) and segments (NS vs. TS vs. TI vs. NI) as within-subject factors and group (DS vs. control) as between-subjects factor.

A significant main effect for type was noted ($p<0.001$), suggesting there was a significantly more veins than arteries in both subjects. There was also a significant main effect for the area and segments respectively ($p<0.001$), indicating retinal vessels distributed significantly different in the optic disc and Zone A or across the four segments. Moreover, a significant main effect for group was noted ($p<0.001$), suggesting there was a significant difference in the number of retinal vessels in DS children and control children group.

With regard to the interaction effect, there was a significant interaction effect for area*group ($p<0.001$). This indicated that the number of retinal vessels were significantly different between disc and Zone A for DS and control children (Fig. 4-4b). However, the interaction effects for segments*group and type*group did not reach statistical significance ($p=0.120$), suggesting that the vessels distributed similarly in the four segments in both groups (Fig. 4-4c) and there was no significant difference in the proportion of the arteries or veins between two groups.

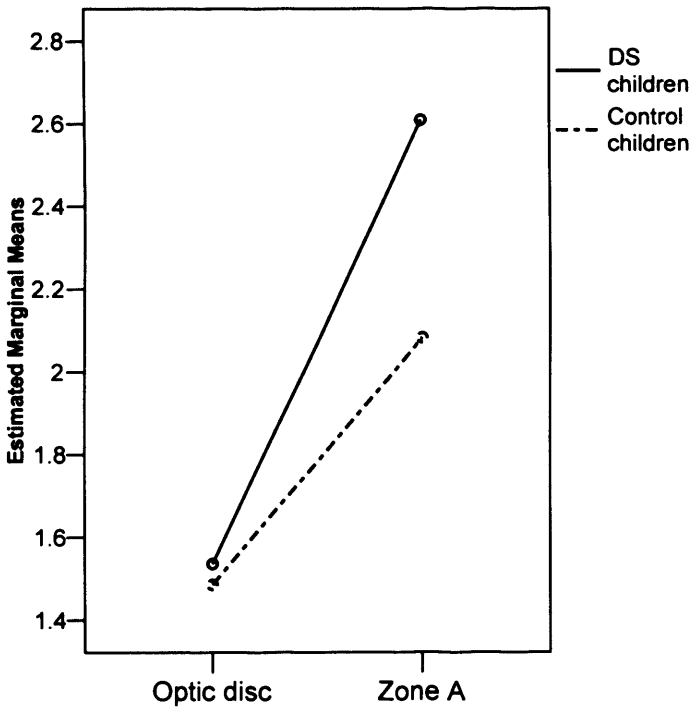


Fig. 4-4b: Plot of interaction effect of area*group

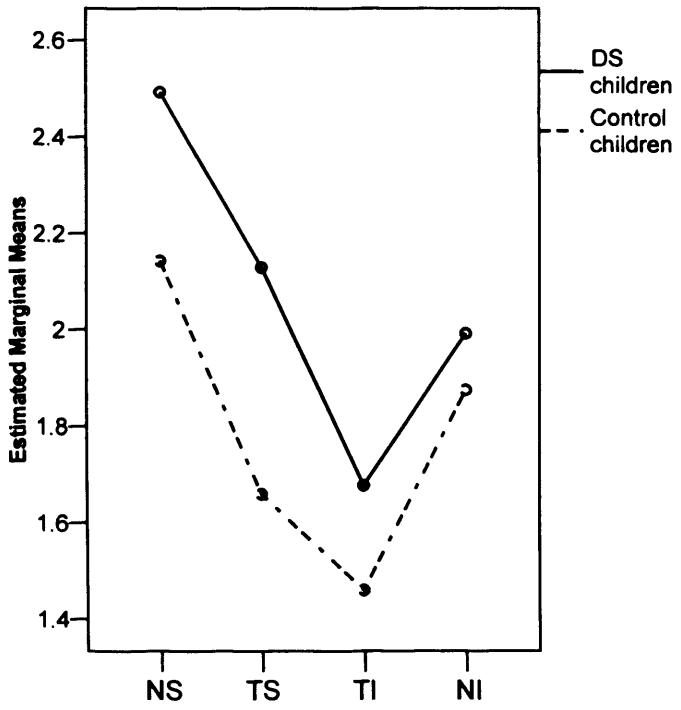


Fig. 4-4c: Plot of interaction effect of segments*group

Width of retinal vessels

The width of retinal vessels is shown in Table 4-6. The mean width of arteries in children with DS was significantly larger than that of controls crossing the disc (Mann-Whitney U test, $p<0.05$). In terms of the vessels extending to Zone A, no significant difference in the mean width of arteries and veins was found between children with DS and control children (Mann-Whitney U test, $p>0.05$).

Table 4-6: Width of retinal vessels (in arbitrary units) in both groups

	DS Children		Control Children	
Area	Disc	Zone A	Disc	Zone A
No. subjects	17		31	
Width of arteries	0.029±0.005	0.021±0.007	0.026±0.005	0.022±0.004
Width of veins	0.029±0.006	0.025±0.009	0.031±0.006	0.028±0.009

Large, medium and small vessels

Fig 4-5a shows the number of vessel width group in Zone A. It is clear that most vessels crossing Zone A were medium vessels in both groups.

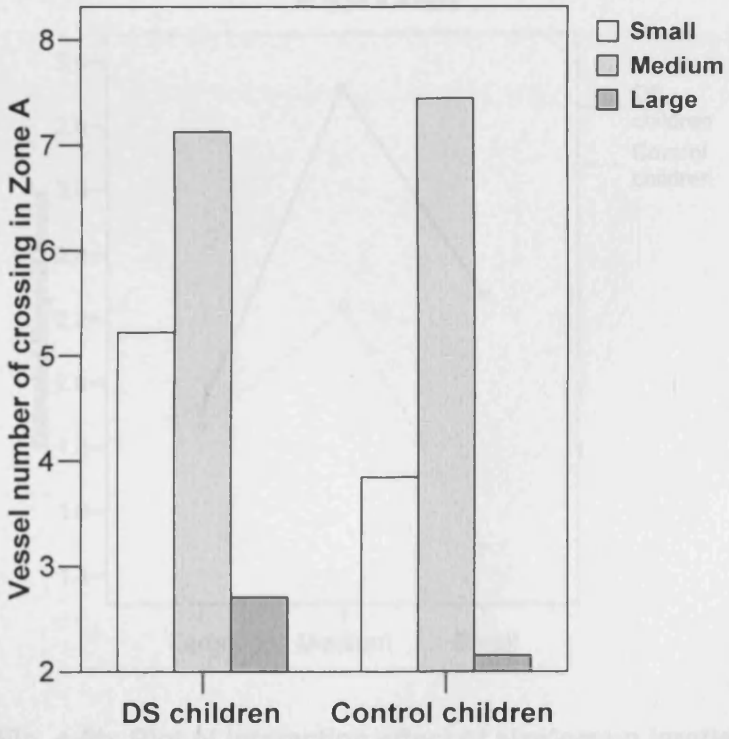


Fig. 4-5a: Vessel numbers of crossing in Zone A (vessel width group)

Repeated measures ANOVA was conducted to quantify the distribution of the vessel when size of vessel (large vs. middle vs. small, type (artery vs. vein) and area (the disc vs. zone A) as within-subject factor and group (DS vs. control) as between-subjects factor.

There was a significant main effect for size of the vessel ($p<0.001$), suggesting there was a significant difference in the number of retinal vessels in terms of large, middle or small vessels.

There was a significant interaction effect for type*size ($p<0.001$). This indicated that the number of arteries and veins were significantly different in terms of the size of vessels. Most vessels are middle arteries and veins in the two child groups (Fig. 4-5b-c). In conclusion, there were significantly more small arteries and veins in children with DS than controls crossing Zone A (Fig. 4-5b-c). However, the interaction of size*group did not reach the significant level ($p=0.089$). This suggested that there was no significant difference in the proportion of small, medium and large vessels between two groups.

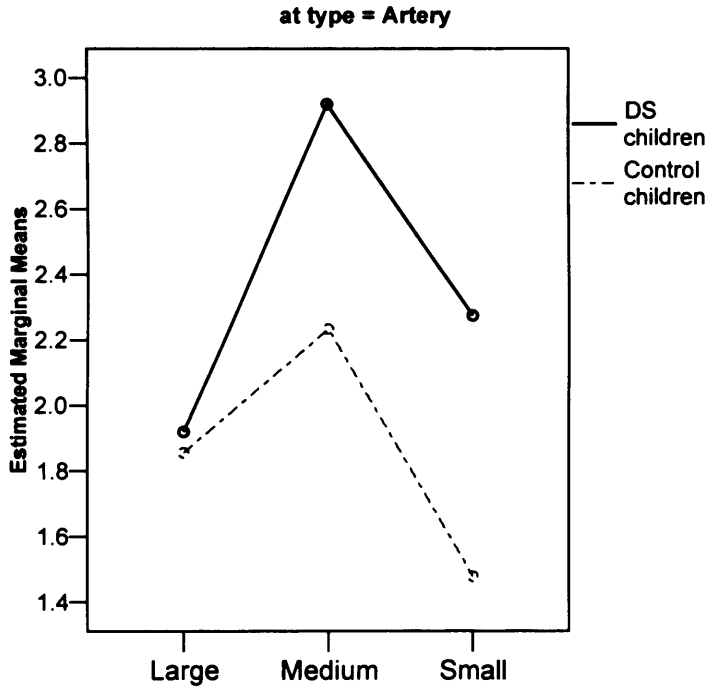


Fig. 4-5b: Plot of interaction effect of size*group (areties)

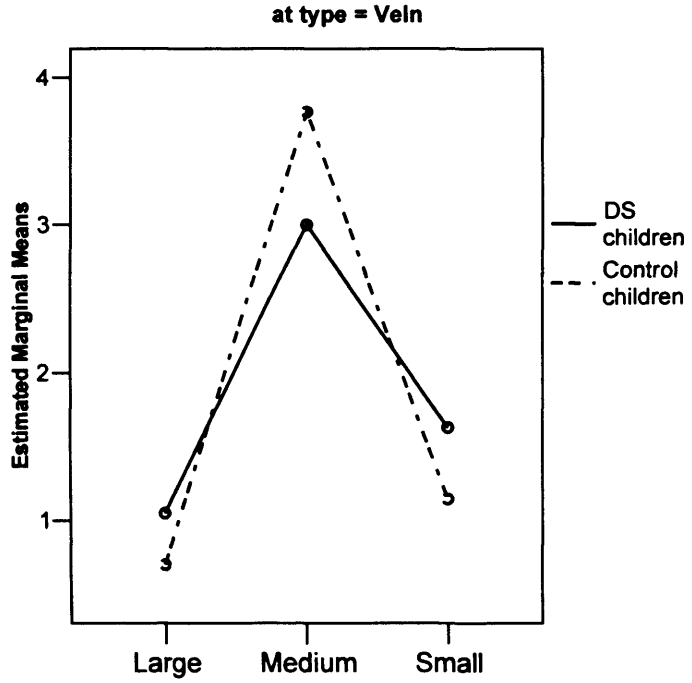


Fig. 4-5c: Plot of interaction effect of size*group (veins)

The distribution of retinal vessels and visual function

No significant correlation was found between the total number of vessels and refraction, the total number of vessels and VA among children with DS. Our study found no significant difference in the total number of retinal vessels between those children with DS who accommodate accurately and those who do not (Mann-Whitney U test, $p>0.05$).

4.4 Discussion

4.4.1 Co-operation of the subjects

Most cases of poor photographs were caused by children with DS being unable to fixate the target or perhaps blinking or fidgeting. The parents were often asked to help the child keep still during the exam. In some cases with DS adults, the poor quality of the photographs was due to media opacities, higher corneal astigmatism, refractive error and keratoconus.

4.4.2 Planimetric evaluation of the optic disc

Unexpectedly, the optic disc and rim areas were found to be significantly larger in children with DS than controls but they remained within the range of values estimated in the general population (Hellstrom et al. 1997a; Hellstrom and Svensson 1998; Jonas et al. 1988a; Mansour 1992; Rimmer et al. 1993; Varma et al. 1994). A larger disc associated with a larger rim was also found in both groups. . It was reported that a larger disc may indicate a larger retinal surface (Papastathopoulos et al. 1995). However, Fovea-Disc distance is not significant longer in children with DS compared to controls in our study.

It can be speculated that this finding has a genetic basis or it could even be attributed to the influence of growth factors before the eye is fully developed, known to alter the genetically predetermined disc size (Hellstrom and Svensson 1998). In addition, it was reported that the disc is larger in highly myopic eyes (Jonas 2005; Jonas et al. 1999). It corresponds to histomorphometric studies in which globes with an AL above 26 mm exhibited an ONH enlargement (Jonas et al. 2004). Increased axial elongation in myopias may lead to mechanical stretching and thinning of the choroids and retinal pigment epithelium with concomitant vascular and degenerative changes (Pierro et al. 1992). It was described that myopic eyes become larger in all three dimensions, but more in length than height, and more so in height than width (Atchison et al. 2004). People with DS may become highly myopic when getting older. But since there were only 6 myopes in our study, myopia cannot account for large discs.

Considering the previous studies, it can be inferred that the optic disc area, the

count of the retinal photoreceptors and ganglion cells axons and the retinal surface are all correlated with each other. Eyes with larger discs compared with eyes with small discs may indicate the following:

- Higher number of nerve fibres (Panda-Jonas et al. 1994) but lower density (Jonas et al. 1992).
- A higher count of retinal photoreceptors (Panda-Jonas et al. 1994) and more retinal pigment epithelium cells (Panda-Jonas et al. 1996). Taking into account a loss of photoreceptors in glaucoma, it may point toward a higher anatomic reserve capacity in glaucomatous eyes with large discs than in eyes with small discs. Eyes with large optic discs and more photoreceptors may be able to lose more cells before visual deficits occur than eyes with small discs and fewer photoreceptors.
- It may be combined with a larger retinal surface (Jonas et al. 1992), presumably more retinal ganglion cells (Papastathopoulos et al. 1995).
- More cilioretinal arteries, which are those vessels that show no obvious connection to the central retinal artery or its branches, that emerges at or close to the disc border. It was reported that there are more cilioretinal arteries in large optic disc (Jonas et al. 1988b). Jonas (1988) explained: "The larger the disc, the longer its circumference. Therefore, the larger the interface between the optic nerve scleral canal and the choroids. Hence, a ciliary artery may be more likely to find its way through the separating tissue into the optic nerve scleral canal and onto the retinal surface."

The cilioretinal arteries are associated with larger disc size but are generally a rare finding so, their presence would not have facilitated a more detailed comparison between the vasculature of subjects with DS and controls. Thus, the analysis of the fundus photography data was not extended to investigate the contribution of the cilioretinal arteries in the DS retinas.

4.4.3 Assessing the retinal vessels

Retinal vessel features

Our study confirmed an increased number of retinal vessels in children with DS, which is in line with the previous studies (Ahmad and Pruett 1976; Berk et al. 1996; Sherk and Williams 1979; Williams et al. 1973). In our study, children with DS have more arteries and veins beyond the discs, due to increased branching, but not those crossing the disc compared to controls. It implies that vessels bifurcate more after leaving the disc margin, which is contrary to William's (1973) explanation: "The spoked pattern of vessels appears to be the result of early bifurcation of vessels before they cross the disc margin."

However, there was no significant difference in the distribution of the retinal vessels between children with DS and controls. More retinal vessels distributed nasally than temporally; superiorly than inferiorly in both groups.

It is unknown why retinal vessels branch more in people with DS. It was reported that changes in disc morphology are often associated with abnormal retinal vascular pattern (Hellstrom et al. 1997b). Retinal vessels may possibly act as an element of anatomical support within the ONH structure.

In addition, people with DS are at a high risk of congenital heart defects. It has been shown that there was a strong correlation between the retinal vascular tortuosity and low arterial oxygen saturation (Mansour et al. 2005). Therefore, it was postulated that patients with congenital heart defects have a low arterial oxygen saturation (Mansour et al. 2005), which may lead to a hypervascularization process, that is the development of more blood vessels. However, it was reported that there was no significant difference in the number of retinal vessels for those with DS who either do or don't have heart defects (Sherk and Williams 1979). As far as we know, there is no report about more blood vessels in the other parts of the body in people with DS.

In the general population, studies focus on vessels width changes for special diseases such as diabetes, hypertension rather than vessel numbers. When the

total number, distribution and size of the retinal vessels were analyzed in our study, it appeared that children with DS do not have significant difference in retinal vessels patterns compared to that of controls. Our observations provide information on the normal physiological variations of the retina in people with DS.

Further, if retinal blood flow is abnormal in DS, there may be an influence on eye growth and visual function. Our study found no association between poor visual performance (refraction, VA and accommodation) and the distribution of the vessels in children with DS. Thus, this might support that children with DS do not have abnormal retinal blood supply.

4.5 Conclusions

This study was undertaken to evaluate the optic disc and the retinal vessel properties in children with DS compared to controls. In conclusion: firstly, a larger disc and rim were found in children with DS compared to that of our controls. Similarly positive correlation between the disc size and rim size was also found in both groups. Secondly, in terms of the distribution of the retinal vessels, our current study showed that the increased number of arterials and veins was due to branching once they leave the optic disc in children with DS. However, there was no significant difference in distribution of the retinal vessels between DS children and controls. Noticeably, more retinal vessels distributed nasally than temporally; superiorly than inferiorly in both groups. Thirdly, with regard to the size of the vessels, the width of the arteries of children with DS was larger than that of controls crossing the disc. Additionally, children with DS have significantly more small and middle size of arteries and more small size of veins compared to controls.

Chapter 5

To consider the detection of glaucoma in people with DS

5.1 Introduction

5.1.1 To consider the detection of glaucoma in people with DS

Apart from reported infantile glaucoma in people with DS (Traboulsi et al. 1988), few studies have reported the prevalence of glaucoma in people with DS (Liza-Sharmini et al. 2006). However, people with DS may carry risk factors for the development of glaucoma. Firstly, people with DS have a thinner cornea (Doyle et al., 1998; Haugen et al., 2001a; Everekliogłu et al., 2002). There is an increased susceptibility to glaucoma severity in patients with thinner corneas (Brandt et al., 2001; Gordon et al., 2002; Medeiros et al., 2003; Shimmyo et al., 2003; Herndon et al., 2004; Hewitt and Cooper, 2005). Secondly, vascular risk factors were significantly more common in patients with thin corneas (Doyle, Bensaid and Lachkar, 2005). People with DS have abnormal retinal vessels (Ahmad and Pruett 1976; Berk et al. 1996), which are described more in Chapter 4. Therefore, they may have significant risks of glaucoma at an early age. Thirdly, high refractive error has been associated with an increased risk of developing glaucoma. People with DS have a higher refractive error (RF, 1949; Shapiro and France, 1985; Hestnes et al., 1991; Perez-Carpinell et al., 1994; Woodhouse et al., 1996; Woodhouse et al., 1997; Haugen et al., 2001a; Kim et al., 2002; Liza-Sharmini et al., 2006). Lastly, the risk of glaucoma increases with age. People with DS are ageing earlier in many respects (Brown, 1979; Devenny et al., 1996; Fromage and Anglade, 2002). In addition, the risk of glaucoma in diabetes mellitus is high. People with DS are more likely to have diabetes mellitus (Milunsky and Neurath, 1968; Van Goor et al., 1997; Ohyama et al., 2000).

Glaucoma was not reported in those studies with a large numbers of DS patients (Shapiro and France 1985), probably due to the difficulties in detection. Unique retinal appearance of people with DS may tend to mask glaucomatous signs. Additionally, the low corneal rigidity in people with DS may give artificially low IOP readings. Therefore, our hypothesis was that glaucoma goes undetected in people with DS.

Clinically, as was described in chapter 1, section 1.6.5, in the general population, the best traditional combination of three variables for detecting glaucoma was visual field analysis, optic disc cupping and IOP measurement (Harper and Reeves 1999; leong et al. 2003). In recent years, it has been widely suggested that CCT should be routinely measured because of its impact on the estimation of IOP and as an independent risk factor for the development of glaucoma (Brandt et al. 2001; Gordon et al. 2002; Herndon et al. 2004; Hewitt and Cooper 2005; Medeiros et al. 2003; Shimmyo et al. 2003).

However, there are limitations of detecting glaucoma in people with DS. First, visual fields are very difficult to evaluate in people with learning disabilities, the procedure being limited by anxiety, lack of comprehension, poor attention and long reaction times. To our knowledge, there are no reports about visual field testing in people with DS.

Secondly, identifying structural changes to the disc is important for the diagnosis of glaucoma. A number of signs of the optic disc are suggestive of glaucoma such as an enlarged cup size, smaller rim area and a shift in the position of the blood vessels or haemorrhages (Broadway et al. 1999; Jonas and Schiro 1993). Thus, morphologic features of the optic disc are predictive factors for the development of glaucoma that may be useful signs of glaucoma in people with DS. However, people with DS have abnormal retinal features such as larger disc and rim, more branching retinal vessels (see chapter 4), which could make it more difficult to judge, particularly for practitioners unfamiliar with the retinal appearance of people with DS. The assessment of the C/D ratio is also a critical criterion with suspected glaucoma (Garway-Heath et al. 1998; Harwerth et al. 1999; Quigley et al. 1989; Zeyen and Caprioli 1993). In addition, many studies have confirmed that PPA can increase in glaucoma optic neuropathy (Jonas 2005; Uchida et al. 1998). Even in experimental glaucoma, the development of PPA has been described (Hayreh et al. 1998).
The first aim of the study was therefore to evaluate the appearance of the optic disc, the C/D ratio and whether PPA was present or absent in fundus photographs for all the subjects.

IOP measurement is the other key indicator in detecting glaucoma. As far as we are aware, lower IOP in children with DS was reported only in one study (subjects with the age of 5-15 yrs) (Everklioglu 2002). However, IOP readings were influenced by corneal properties, which are discussed below. Moreover, the importance of CCT as an independent risk factor in the accurate diagnosis of patients with glaucoma and patients in whom glaucoma is suspected has been highlighted. CCT is therefore an important measurement that may be helpful in the detection of glaucoma. The second aim of the current study was to measure IOP and investigate the relationship between corneal parameters and IOP in order to identify suspect glaucoma among our adults with DS.

5.1.2 Relationship between IOP and properties of the cornea

There is plenty of evidence in the literature showing that IOP is influenced by corneal parameters. Assessment of corneal thickness is important in comparing the IOP of eyes of different patients since it has been reported that thinner corneas result in artificially lower IOP readings (Graf 1991; Matsumoto et al. 2000; Recep et al. 2001; Whitacre et al. 1993). The original reports on the calibration and validation of the Goldmann applanation tonometer indicated that cornea thickness might have an impact on the outcome of tonometry measures and that the instrument was suitable only for "normal" human corneas (Goldmann and Schmidt 1957, 1961).

To date, there are many different studies researching the appropriate correction factors. Three studies (Ehlers et al. 1975; Shah et al. 1999; Wolfs et al. 1997) have suggested that the average error of tonometry for a 10 μm deviation from the normal CCT is 0.71 mmHg, 0.19 mmHg and 0.50mmHg respectively). Overall, the magnitude of the effect in apparently normal corneas is rather small, i.e. around a 1.5 mmHg difference in IOP for a 10% difference in CCT (Doughty et al. 2002). However, no single formula has been universally accepted. With regard to the true IOP and corneal parameters, another possibility was stated by Brandt (2003): "CCT may be a component of corneal elasticity, but it is likely not the only component. The mix of collagen types, packing density of collagen fibrils and the extra-cellular matrix may dwarf the effect of CCT on the accuracy of IOP estimation."

The advent of refractive surgery, in which the cornea is thinned to correct myopia, has give further information on the effect of corneal properties. That is, along with corneal thickness, corneal radius may have some effects on IOP estimations (Cennamo et al. 1997; Chatterjee et al. 1997; Chihara et al. 2005; Gimeno et al. 2000; Orssengo and Pye 1999; Shimmyo et al. 2003; Svedberg et al. 2005). It was agreed by previous studies that there was a positive correlation between IOP and corneal curvature. Interestingly, it has also been pointed out that a property of the cornea other than the thickness and curvature, such as corneal elasticity may affect IOP measurement (Harada and Naoi 2004; Svedberg et al. 2005). It was thus speculated that the level of corneal elasticity might be negatively related to IOP in that more elastic corneas might be associated with normal or lower IOP and conversely that a decrease in the elasticity of the cornea might be associated with elevated IOP (Harada and Naoi 2004).

Table 5-1: The formula for the corrected IOP

Author	Year	Formula
Ehlers et al.	1975	IOP=0.07*(535-CCT)+ measured IOP
Wolfs et al.	1997	IOP=0.02*(535-CCT)+measured IOP
Shah et al.	1999	IOP=0.05*(535-CCT)+measured IOP
Orssengo and Pye et al.	1999	IOP=measured IOP/K IOP=measured IOP/ {(520-CCT)/1000} * 2.87 +1 Based on corneal radius =7.8mm

A detailed exploration of the mechanical characteristics of the cornea and the role of CCT in IOP error were done by Orssengo and Pye (1999). However, one recent study tended to investigate the efficacy of currently available correction factors in correcting IOP and concluded: "both the Ehlers formula and the Orssengo and Pye model could be erroneous and lead to overcorrection of IOP, thus resulting in erroneously low corrected IOP eyes with thicker cornea and erroneously high corrected IOP in eyes with thinner cornea."(Gunvant et al. 2005). Thus, it is still very difficult to determine the extent to which these corneal parameters influenced the IOP estimations

5.2 Methods

5.2.1 Subjects

The procedure of recruitment was described in chapter 1, section 1.7.1. Those good fundus images of all the subjects including children and adults were selected and coded. Both eyes were included since the study aimed to investigate the abnormal changes in the retina. In total, there were 74 fundus images from DS children, 100 from control children and 7 from DS adults.

Only the same twenty DS adults who had attended the previous study took part in the IOP measurement. Twenty control adults were those who joined the pilot study for validating the accuracy of I-care tonometer (see chapter 2, section 2.5).

5.2.2 Procedures

All the coded fundus images of all the subjects were assessed if glaucomatous signs were present or not by two observers separately (ALJ and POW) (see 5.2.3). The author (PJ) measured IOP for all the DS adult subjects (see 5.2.4). Family history of glaucoma in each subject was elicited from the carers or family members during their visits. Afterwards, three formulae were used to adjust measured IOP separately:

Corrected IOP=0.02*(535-CCT)+measured IOP by Wolfs;

Corrected IOP=0.07*(535-CCT)+ measured IOP by Shah;

Corrected IOP=0.05*(535-CCT)+measured IOP by Ehlers

5.2.3 Assessing glaucomatous changes in the optic disc

Two observers (POW and ALJ) separately viewed and assessed the ONH for glaucomatous changes in the fundus photograph, masked as to the subject group and to the age of the subjects. Both observers judged whether PPA was present or not. PPA was then divided into a central Zone (α) and a peripheral zone (β). All images were classified in two groups: images with normal appearance and images with suspicious glaucoma. POW judged the C/D ratio, which was based on standard clinical criteria. ALJ measured C/D ratio by the custom digital software (see section 4.3.3).

5.2.4 Measuring IOP

The I-care tonometer was chosen and tested for accuracy compared with Goldmann tonometer (chapter 2, section 2.3). IOP Measurements were carried out by carefully operating the measurement button, to avoid shaking the tonometer. Six measurements were taken consecutively. According to the manual, the highest and the lowest readings are discarded by the pre-programmed software and then the average IOP value is calculated from the rest. Only valid readings were accepted and recorded.

5.3 Results

5.3.1 Co-operation of the subjects

The co-operation of fundus photograph for all the subjects was discussed in chapter 4, section 4.3.1 and section 4.4.1. Fourteen DS adults and all control adults completed IOP measurement successfully. Among them, eleven DS adults co-operated with CCT measurement.

5.3.2 Glaucomatous ONH changes

In the adult subjects with DS (n=8), two had PPA but no suspicious glaucoma was noted by two observers. In child subjects, two observers found no significant difference in the C/D ratio between children with DS and controls. The presence of the PPA (Zone α and Zone β) and suspicious glaucoma in child subjects by two observers are shown in Table 5-2. The presence of Zone α and Zone β were significantly higher in children with DS compared to that of controls ($p<0.05$ Chi-square). More children with DS were detected with suspicious glaucoma by both observers. A glaucoma specialist (JEM) reviewed the suspect photographs from a clinical perspective. No glaucoma was detected on the basis of the fundus photographs and JEM was satisfied that no clinical follow-up was needed.

Table 5-2: The result of ONH changes by two observers

	Observer 1 (ALJ)		Observer 2 (POW)	
	DS children	Control children	DS children	Control children
No. images	78	100	78	100
PPA - Zone α	15 (19%)	8 (8%)	14 (18%)	4 (4%)
PPA - Zone β	47 (60%)	27 (27%)	20 (36%)	13 (13%)
Suspicious glaucoma	8 (17%)	3 (3%)	7 (10%)	5 (5%)

5.3.3 Measured IOP and corrected IOP

Measured IOP was lower in DS adults (12.3±2.7 mmHg) compared to that of the controls (13.8±2.5 mmHg) but not significant (p=0.1 Independent t-test). A huge difference among DS subjects was noted in the corrected IOP when different formulas were used while similar corrected IOP appear in control adults (Table 5-3, Fig. 5-1).

Table 5-3: Corrected IOP by three formulae

Corrected IOP (mmHg)	DS adults	Control adults
By Wolfs	13.4±2.6	13.9±2.3
By Shah	15.1±2.5	14.1±2.1
By Ehlers	16.1±2.7	14.1±2.3

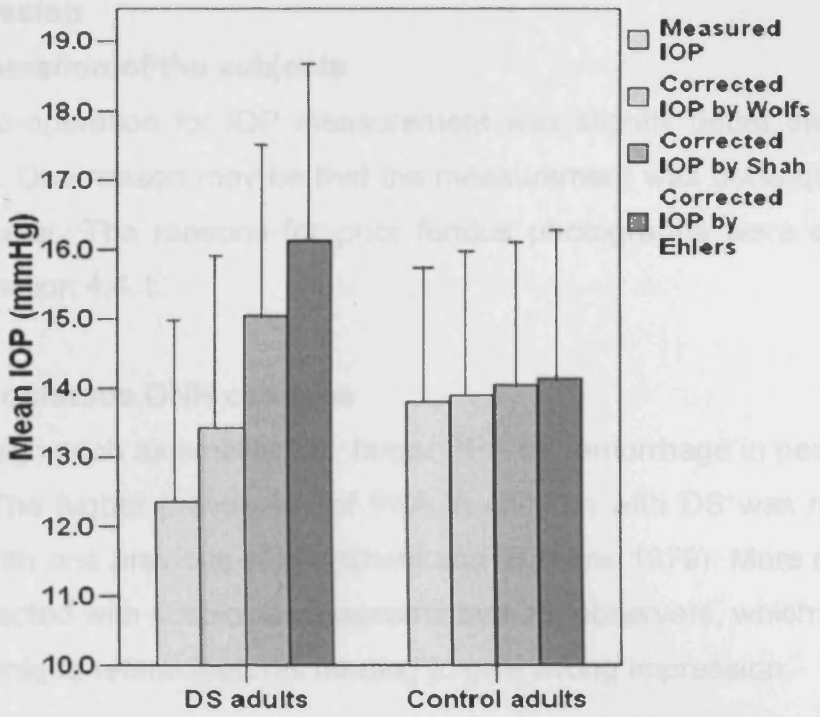


Fig. 5-1: Measured IOP and corrected IOP (Error bars represents SD)

IOP and CCT were only associated highly in control adults (r=0.528, p=0.017). No significant correlation was found for IOP- CCT and IOP-CR in adult subjects with DS.

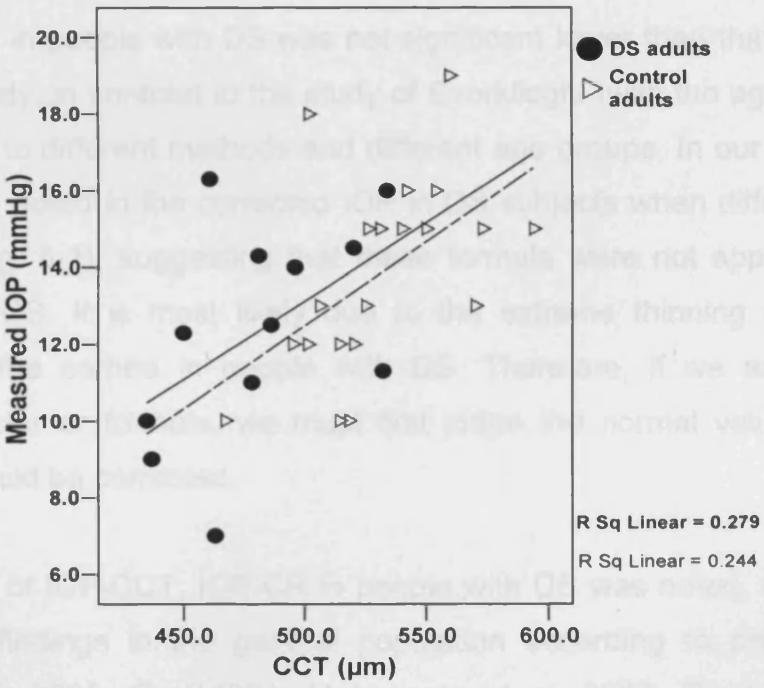


Fig. 5-2: CCT and measured IOP

5.4 Discussion

5.4.1 Co-operation of the subjects

DS adult's co-operation for IOP measurement was slightly better than the other part of study. One reason may be that the measurement was done quickly by the I-care tonometer. The reasons for poor fundus photographs were discussed in Chapter 4, section 4.4.1.

5.4.2 Glaucomatous ONH changes

No obvious sign such as smaller rim, larger PPA or hemorrhage in people with DS was noted. The higher prevalence of PPA in children with DS was noted, which was in line with one previous study (Sherk and Williams 1979). More children with DS were detected with suspicious glaucoma by both observers, which may be due to that their unique retinal features tending to give wrong impression.

In all the subjects, PPA occurred more often in β zone than α zone. It was reported that β zone PPA occurs more often in glaucomatous eyes than in normal eyes (Jonas 2005). Additionally, frequency of β zone of PPA are significantly correlated with variables indicating the severity of the glaucomatous ONH (Jonas 2005).

5.4.3 Measured IOP and corrected IOP in the subjects

Measured IOP in people with DS was not significant lower than that of controls in the current study, in contrast to the study of Everklioglu (with the age of 5-15 yrs). It may be due to different methods and different age groups. In our study, a huge difference was noted in the corrected IOP in DS subjects when different formulas were used (Fig. 5-1), suggesting that these formula were not applicable among subjects with DS. It is most likely due to the extreme thinning and abnormal properties of the cornea in people with DS. Therefore, if we are to adopt a conversion factor or formula, we must first judge the normal value from which deviations should be corrected.

No correlation of IOP-CCT, IOP-CR in people with DS was noted, which is not in line with the findings in the general population according to previous studies (Chihara et al. 2005; Graf 1991; Matsumoto et al. 2000; Recep et al. 2001; Svedberg et al. 2005; Whitacre et al. 1993).

5.5 Conclusion

I-care tonometer was a successful technique for measuring IOP in adults with glaucoma. Contrary to our expectations, subjects with DS do not appear to have significantly lower recorded IOP than normal controls. The correction for CCT remains a problem, but a clinical recommendation could now be made that IOP is routinely assessed in adults with DS using the I-care tonometer.

There were no obvious signs such as smaller rim or disc hemorrhages by assessing the fundus photograph in our subjects with DS, which were predictive factor for glaucoma patients. However, this was a small scale study. If the prevalence of glaucoma were the same in DS as in the general population, we would not expect to see it in nineteen adults of this age range. Considering the fact that there were more suspect glaucoma cases in children with DS than control children, their unique retinal features may lead to the wrong diagnosis rather than mask the glaucomatous changes in the disc.

The observation in this study may further aid our understanding of the detection of glaucoma in people with DS. However, the question still remains - do people with DS develop glaucoma or not?

Chapter 6

Discussion

6.1 Summary of the results

The major results of our study are as follows:

Visual functions (Chapter 3)

The majority of children with DS has refractive errors (especially hyperopic) and accommodate inaccurately. It was confirmed that poorer VA in our subjects with DS compared to that in controls.

Ocular biometric parameters (Chapter 3)

- There was a significant correlation between AL and refraction, AL/CR and refraction in both groups. A significant difference was noted in the correlation of AL and refraction but not in the correlation of AL/CR and refraction between children with DS and controls.
- People with DS have thinner corneas both in the centre and periphery, smaller CR, higher corneal power of the front cornea and higher corneal aberration compared to controls. No significant difference in asphericity of the cornea, corneal power of the back cornea and pupil size was noted between people with DS and controls.
- Calculated lens power was lower in children with DS compared to controls. No significant difference in lens density and lens thickness was noted between DS subjects and controls. Cataract was present in four adults with DS.
- No significant difference was found in anterior chamber parameters between subjects with DS and controls. However, adults with DS and with keratoconus have deeper ACD compared to those adults with DS but without keratoconus.

Corneal topography and keratoconus detection (Chapter 3)

- Clinically, keratoconus was present in 40% adults with DS (n=8) from a possibly biased sample, however, no keratoconus was found in children with DS.
- More children with DS were detected with suspicious keratoconus by corneal topography both objectively and subjectively.
- There was no difference in the eye-rubbing frequency in DS adults with keratoconus group compared to those of the non-keratoconus group.

Features of the retinal and optic disc (Chapter 4)

- A larger disc and rim were found in children with DS compared to that of our controls. Similar positive correlation between the size of disc and rim was also found in both groups.
- Children with DS have more arteries and veins beyond the discs, due to increased branching, but not those crossing the disc compared to controls. However, the distribution of retinal vessels in four segments was not significantly different between DS children and controls.
- Further, the mean width of arteries crossing the disc in children with DS was significantly smaller than that of controls. In terms of the vessels extending to periphery, however, no significant difference in the mean width of arteries and veins was found between children with DS and control children.
- Lastly, children with DS have significantly more small and middle size arteries and more small size of veins compared to our controls.

Glaucoma detection (Chapter 5)

- The presence of the PPA (both Zone α and Zone β) in children and adults with DS was much higher than that of controls.
- No significant difference was found in measured IOP between DS adults and the controls. It was shown that the traditional correction formula taking CCT into account may not be applicable to correct the measured IOP in people with DS.
- No glaucoma was detected among our subjects with DS.

6.2 General discussion and conclusions

6.2.1 Recruitment and co-operation

There was a good response to letters sent to the Cardiff cohort and clinical local patients in the current study, which may be due to the two factors: one is that there is a regular visit to the clinic for those children with DS from our cohort. Another reason is that the test time was often arranged during the half–term when it was convenient for the families to come.

The co-operation of people with DS was better than expected in each part of the study. Motivation and concentration might be strongly influenced by the child's emotion. E.g. level of tiredness at the visiting time, which is likely to change the co-operation. It also seemed to the author that children with DS were encouraged and persuaded more by their parents to participate in the study (rather than giving their own unprompted consent), which was in line with studies of maternal directive and supportive behavior (Mahoney et al. 1990; Tannock 1988), concluding that mothers of children with DS exerted greater control in most of the aspects of directiveness, while mothers of children without DS were more likely to silently watch their children. It was proved that it would be very difficult to get precise measurement without help from parents in our study. Overall, it appeared that children with DS were just as persistent as the typically developing children with the challenging tasks (Gilmore et al. 2003).

6.2.2 Refraction development in people with DS

As reviewed in chapter 1, it has been shown that failure of emmetropisation is a characteristic of many children with DS (Haugen et al. 2001; Woodhouse et al. 1997). Thus, in most children with DS, significant refractive errors are maintained or develop beyond infancy. What may lead to the failure of emmertropisation in children with DS? A number of previous studies have speculated that the failure of emmetropisation process in children with DS may be part of a general dysfunction. Thus, to some extent, abnormal refraction development in people with DS may mainly result from the general abnormal physiological features.

The abnormal values of refractive components may lead to abnormal refraction development such as shorter axial length, higher corneal power and lower lens power. Moreover, the higher aberration of the cornea in DS subjects may be another factor resulting in failure of emmtropisation. In addition, since refractive error is the result of mismatched association among the ocular components, correlations between the total refraction of the eye and the individual optical elements may explain the failure of emmetropisation in children with DS. If the hypothesis above were upheld, the parameters would not show good correlation. The fact that they are not correlated in the same way as in controls suggests that there is lack of coordination between the components that results in refractive error. Thus, it is reasonable to assume that refraction in people with DS appeared to be determined by those abnormal ocular parameters and abnormal correlation between those parameters.

Children with DS are more likely to have growth hormone deficiency (Anneren et al. 1999). Noticeably, it was reported that growth hormone deficiency may lead to hyperopia (Parentin et al. 2004). Therefore, this may be the explanation of the higher frequency of hyperopia in children with DS. Typical children with hyperopia (> +1.5D) are more likely to remain hyperopic (Hirsch 1964; Pointer 2001). This may account for the fact that hyperopic children with DS show little change.

The inherent thinning of the cornea and the presence of keratoconus may explain the myopia shift in adults with DS. In addition, it has been recently hypothesized that myopia shifts may have occurred as a consequence of cataract development. In other words, the progression of opacity in the lens nucleus may initiate the development of myopia (Saw et al. 2005). Since there is a high prevalence of cataract in people with DS, this may also be the case in those DS people with high myopia.

6.2.3 What causes accommodation deficit in people with DS?

As reviewed in chapter1, the causes of under-accommodation in children with DS have been linked to visual acuity, hypermetropia, strabismus and cognitive level (Cregg et al. 2001; Haugen et al. 2001; Woodhouse et al. 2000; Woodhouse et al. 1996).

Knowledge about the properties of the lens is essential for understanding the accommodation system in people with DS. In our study, calculated lens power was lower in children with DS compared to controls, which seemed to support our hypothesis that the high presence of inaccurate accommodation in children with DS is mainly influenced by a weaker lens. An increased change in lens curvature is needed for each dioptre of power change in accommodation. If this were the case, then a child with DS would need greater ciliary muscle contraction per dioptre change in accommodation. In other words, they would need to put a greater effort to accommodate compared to a control child. In most cases, perhaps the child chooses to put up with a lower accommodative response (and a slightly out-of-focus image) simply because of the demanding effort he or she would need to accommodate accurately. Therefore, we expected that children who accommodate accurately would have more powerful lenses than those who are inaccurate.

However, no significant difference in calculated lens power was found between those children with DS who can accommodate accurately and those who did not. The low power of the test may fail to find the significant difference if there really is since sample numbers in this analysis are small. Further, hypermetropes with accurate accommodation do indeed have higher lens power, although the difference is very small and non-significant. Whether this is a real trend remains to be seen when larger numbers of subjects can be assessed.

There could be factors other than just lens power coming into play to influence whether an individual child with DS accommodates accurately, even with a low lens power.

Reduced visual acuity and small pupil size will increase the depth of focus of the eye. The small pupil size would be needed to account for the reduced accommodation in DS subjects. However, pupil diameter of subjects with DS was not significantly different to that of our controls. Therefore, poor accommodation in children with DS cannot be explained by reduced pupil size resulting in increased depth of focus of the eye.

It has been reported that neurologically handicapped children are likely to be less capable of compensating for the visual defect than normal children (Bader and Woodruff 1980). The weak accommodation in DS may be part of a general dysfunction of the central nervous system. The nervous impulses to ciliary muscle may need to be taken into account as well. However, nothing as yet is known of nervous control of accommodation in children with DS.

6.2.4 Retinal and optic disc features in people with DS

Contrary to our hypothesis, the optic disc in children with DS was unexpectedly larger than that of control children (see chapter 4). The cause is unknown. It can be speculated that this finding has a genetic basis or it could even be attributed to the influence of growth factors before the eye is fully developed, known to alter the genetically predetermined disc size (Hellstrom and Svensson 1998). No significant correlation between VA and disc size was found in either groups.

When the total number, distribution and size of the retinal vessels were analyzed in our study, it appeared that children with DS do not have significant difference in retinal vessels patterns compared to controls. Further, our study found no association between poor visual performance (refraction, VA and accommodation) and the distribution of the vessels in children with DS. Thus, this might support the fact that children with DS do not have abnormal retinal blood supply.

It is important clinically because discs can be very difficult to evaluate in people with DS with an unique optic disc. Our observations provided information on the normal physiological variations of the retina in people with DS.

6.2.5 Non-ocular influence on the biometric parameters

The growth of the eye and those structures may follow the general growth pattern since it is well-known that race, age and gender have impacted on ocular parameters such as AL, lens thickness and disc size (Bowd et al. 2002; Hyman et al. 2005; Kashiwagi et al. 2000; Mutti et al. 2000; Varma et al. 1994; Zadnik et al. 2003).

Many aspects of human vision deteriorate with age. It has been suggested that a rapid form of ageing occurs in the brains of children with DS (Buxhoeveden et al. 2002). Moreover, the process of physical ageing seems to be accelerated in individuals with DS (Brown 1979; Devenny et al. 1996; Fromage and Anglade 2002). So, are the abnormal ocular parameters premature ageing? For instance, the PPA is very common in children with DS, which is also a sign of retina ageing in normal population.

A recent population study among the general population showed that CCT values are independent of refraction, gender, age, height and body mass index. However, there was a positive significant correlation between CCT and body weight (Rufer et al. 2005). In contrary, people with DS have thinner cornea although overweight is common in people with DS (Cronk et al. 1988; Fonseca et al. 2005; Melville et al. 2005; Myrelid et al. 2002; Styles et al. 2002). The inherent corneal thinning in people with DS may result from overexpression of genes and so that it may be responsible for some abnormal features of the eye. The abnormality in corneal collagen may lead to abnormal strength, elasticity and form of the cornea. Therefore, as people with DS have a trisomy 21, there might be a connection between this gene and the thinning of the cornea.

AL may be influenced by low height in people with DS. There is evidence that axial eye length responds to adolescent growth acceleration, which means that the greater increase of axial eye length results from pubescent body growth (Selovic et al. 2005). However, growth hormone deficiency in people with DS may aggravate their growth retardation and lead to a reduced pubertal growth spurt. As a result, it may hinder the increase of the AL. Interestingly, it was reported that AL is positively related to body weight and height (Ojaimi et al. 2005; Selovic et al. 2005). High prevalence of being overweight in people with DS have been demonstrated in many studies (Cronk et al. 1988; Fonseca et al. 2005; Melville et al. 2005; Myrelid et al. 2002; Styles et al. 2002). However, people with DS don't have longer AL in ours and the previous studies.

6.2.6 Detection of keratoconus

The prevalence of keratoconus in our DS subjects is consistent with previous studies (see chapter 3, section 3.5.4). As reviewed in chapter 3, section 3.1.3, even though much progress has been made in corneal topography systems, an exact diagnosis of suspect keratoconus is still difficult.

In our study, amongst children with DS the difference between the two techniques was marked, with the observer detecting twice as many cases of suspected keratoconus as the Pentacam system. The difference may arise because detection by the Pentacam system was only based on the anterior surface of the cornea, whereas the observer considered both surfaces of the cornea. Additionally, the observer did not know which images were from subjects with DS and which were controls, but was, nevertheless, aware that some of the images were of subjects with DS, and was also aware of the purpose of this part of the study.

The high detection rate of keratoconus (in children for whom keratoconus was not suspected clinically) suggests that suspected keratoconus is more difficult to detect than either a normal cornea or severe keratoconus (However, we need to bear in mind the possible over-detection of keratoconus in control children).

The difficulty in evaluating corneas in children with DS may be due to the following reasons:

i. Children with DS have abnormal corneas such as thinner cornea, higher curvature, abnormal asphericity and aberration, which are also the signs for the development and progression of keratoconus. This might result in difficulties for both assessments for suspected keratoconus.
ii. The subjective diagnosis criteria may be influenced by the known high prevalence of keratoconus in DS, especially for suspected keratoconus and trace keratoconus.

The findings suggested children with DS have abnormalities of corneal shape even in the absence of clinical evidence of keratoconus, which are in line with the study by Vincent (2005). Clearly, there are questions about the difficulties of diagnosing keratoconus in its early stages, in young subjects with DS. More importantly, the abnormal results in the corneal topography may predict the development of keratoconus later.

6.2.7 To consider the detection of glaucoma in people with DS

People with DS may carry risk factors including ageing earlier, higher refraction and thinner cornea, as discussed in chapter 5. However, glaucoma was not detected among our DS subjects, which was in line with previous studies (chapter 5).

We have argued that the unique retinal features may mask glaucomatous signs of the disc. However, it turned out that unusual features in retina may mislead suspicious glaucoma in our studies. Measured IOP in people with DS was not significantly lower than that of controls. IOP readings may be false because of the abnormal corneal properties (extreme thinning and abnormal properties of the cornea). In contrast, certain factors may be protective including low blood pressure and more branching of retinal vessels in people with DS. Thus, they may have true low IOP. However, the questions still remain: Is glaucoma missed in people with DS and do people with DS develop glaucoma or not? However, the measured IOP in DS subjects was low. If people with DS have 'true' low IOP, they may not develop glaucoma.

6.3 Possible limitations of the study

6.3.1 Subject recruitment

All efforts were made to recruit a valid representative sample of children with DS. People with DS comprise a small special population. Therefore, there are inherent limitations in recruiting large numbers of subjects with DS. However, Cardiff Down's syndrome Vision Research Unit that is the main source of recruitment for the children with DS in the study has one of the largest available datasets. The sample size was limited in adults with DS (n=14) with a wide range of age (19-58 years).

Bias may be present in the study because our subjects with DS who attend the clinic for eye test may be more likely in have ocular problems. However, just half of our completed longitudinal study cohort participated in our study, which is a fair representation of children with DS in general. Bias is less likely to the children who are part of a study cohort, but more likely for adult subjects. So, the conclusions by comparison of normal children and DS children should be representative.

6.3.2 Data collection

The co-operation of subjects is an important parameter to be considered, as it is compromised in DS. It can not be subjectively evaluated and it is likely to introduce uncontrolled variability in the results. When the examination procedure was affected by low co-operation of the subjects, repeated test had to be performed. Images were rejected on the basis of co-operation and quality of image. The examiner excluded the data before analysis. This resulted in reducing the number of subject in each measurement. However, in this way, the variability of the examination would not influence the outcome of study. In addition, the examiner was masked to the actual values of the measurements, thus, not influencing the true discrepancies noted between normal and DS subjects.

Most sophisticated equipment is designed for able, alert and co-operative young adults and their equipment design cannot be fully adjusted to meet the special needs of people with physical limitations and learning disabilities. For instance, for some children with DS who had small faces, even when the necessary adjustment was made, the distance of the chin rest and head rest remained too large. In such cases, their mother/father's hand was placed on the chin rest to increase the height.

However, such adjustment could not overcome the difficulties and even for an experienced operator, the precision of measurement could be influenced.

Equipment that was able to perform automated procedures was specifically selected for the purposes of this study considering the special needs of our subjects with DS. However, they were still under software development. This was mostly occurring with the Pentacam system, with the result that the data had to be exported several times based on the most updated version of the software. Moreover, unlike the traditional methods, the performance of more modern techniques is not well-documented such as Pentacam system and I-care tonometer. At the earliest stages of the study pilot studies had to be performed to validate the methodology of the main study.

Another limitation of the data collection may be that the information from the subject's day carer about family history of keratoconus and glaucoma may not be accurate.

6.3.3 Planimetry evaluation

Quantitative analysis provides a more sensitive means of assessment of the optic disc by software. However, the exact determination of magnification factors was a most difficult issue, as we discussed earlier in section 4.1.2. The true size of the disc is influenced by several factors, including the AL, CR, refractive error and optical aberrations of the individual. Therefore, correcting the magnification and an objective assessment of the fundus photograph were the most important aspect of our study. Different ONH values were obtained by the same observer between the Novel digital software and the ImageNet 2000 software, even for the same images of the same subjects. The obvious difference in the ONH parameters between the two methods showed the fact that ONH parameters in fundus photographs were influenced greatly by the different methods to correct the magnification of the examined eye.

In addition, planimetry is subjected to measurement errors due to observer variability in the assessment. The technique is limited by its reliance upon the observer to identify the boundary of the optic disc as this is still subject to human

decision as to how the boundaries are defined in the programming of the software. In order to minimize it, an experienced observer performed the evaluation. A comparison of the two groups has been performed with similar technique limitations in our study.

6.4 Future work

6.4.1 Aberration of the cornea and keratoconus detection

In a future study, the aberration of the cornea in people with DS can be studied further. More recently, it has been reported that the ocular aberration may provide a sensitive and reliable tool to detect keratoconus (Gobbe and Guillon 2005). Moreover, corneal aberration may contribute to degradation of the retinal image quality and therefore to visual performance (Gobbe and Guillon 2005; He et al. 2002) and explain, in part, the poorer VA that children with DS exhibit

The abnormal changes in the corneal topography of our child subjects may predict the development of keratoconus later. Thus, a follow-up study of the corneal topography in our cohort is necessary.

6.4.2 Ocular components development in people with DS

The visual development of DS subjects has been followed since 1992 in Cardiff DS Vision Research Unit and the present study provided a detailed account of the ocular features of children in our cohort. It would be advisable that a longitudinal study is conducted in the future to evaluate their refractive errors over time and observe the accompanying changes in ocular biometry. For example, high myopia occurs in people with DS (Berk et al. 1996; da Cunha and Moreira 1996). So far, very few of our cohorts have myopia and so we expect some of the present cohort to become myopic in the future. Monitoring the growth of the various components of the eye in detail may help to explain the development of refractive errors not only in people with DS but also in the general population.

6.4.3 Lens thickness and lens curvature

The lens power is lower in children with DS than controls in our study. However, it is unknown whether this difference results from a flattening of the surface, a difference in lens thickness or a change of the equivalent index of the lens.

Moreover, knowledge about the change in the internal structure of the lens is necessary for optical and mechanical modelling of the eye and accommodation system in DS. Refractive error is related to anatomic and functional difference in the lens thickness, curvature and opacities. Therefore, in future studies, it will be worthwhile to measure the lens thickness and lens curvature in people with DS.

6.4.4 Retinal shape

It has been reported that as myopia increases, all dimensions increase with the axial dimension increasing more than the vertical dimension, which in turn increases more than the horizontal dimension. However, the retina stretches more in width and height than length (Atchison et al. 2005). The relative difference in the increase of these dimensions means that as the degree of myopia increases the retinal shape decreases in oblateness. Therefore, to some extent, retinal shape is important in understanding the development of refraction in people with DS. Magnetic resonance imaging (MRI) has been used to provide pictorial representations of sections through the living eye at multiple positions, from which a detailed investigation of ocular dimensions can be made (Atchison et al. 2004; Singh et al. 2006). Examining children with poor concentration and comprehension by MRI will represent a challenge.

6.4.5 IOP measurement

It was shown that the correction formula may not be applicable to correct the measured IOP in people with DS, which support the explanation that CCT and IOP may be dependent on corneal pathology. There is evidence in the literature showing how difficult it is to determine the extent to which these corneal parameters influenced the IOP estimations (Cennamo et al. 1997; Chatterjee et al. 1997; Chihara et al. 2005; Gimeno et al. 2000; Orssengo and Pye 1999; Shimmyo et al. 2003; Svedberg et al. 2005). However, it has been suggested that IOP measurement using the ocular blood flow machine is not affected by changes in CCT (Shah, 1998). If the IOP may be the only reliable indicator for the detection of glaucoma in people with DS, the true IOP in people with DS should be measured in a future study.

Statistical methods

Parametric methods are mathematical procedures for statistical hypothesis testing which assume that the distributions of the variables being assessed are normally distributed and that the variances of the distributions being compared are similar. Non-parametric methods are for statistical hypothesis testing which make no assumption about the frequency distributions of the variables being assessed. Non-Parametric tests may be, and often are, more powerful in detecting population differences when certain assumptions are not satisfied. In our study, with regard to the normally distributed continuous data, parametric tests were used. For non-normally distributed data, non-parametric tests were used (Mann-Whitney test, Kruskal Wallis test). The categorical data were tested by Chi-square.

a) Comparing the correlation

The following procedure was used to test whether the correlations for the two groups are significantly different (Pallant, 2001). First, the R value was converted into z scores; Secondly, the below equation was used to calculat the Z_{obs} value. The significant difference was reported when observed z score (z_{obs}) is out range of the value from –1.96 to 1.96 (Pallant, 2001).

$$Z_{obs} = \frac{Z_1 - Z_2}{\sqrt{\frac{1}{N_1 - 3} + \frac{1}{N_2 - 3}}}$$

b) Bland-Altman analysis

Bland-Altman analysis for comparison of two methods of clinical measurement is frequently used in scientific publications. The difference between the two methods of measurement is plotted against the average obtained with each of the two techniques. 95% of the differenced in the population is lie between mean+/-2SD. The upper and lower limits of this interval are called the limits of agreement. The agreement limits provide the variation of the values of the technique compared to the other (Petrie and Csabin, 2005).

Appendices

Appendix 1

Purpose (Chapter 2)	Test
Compare the readings of I-care tonometer and Goldmann tonometer	
Is there a difference in IOP readings by 2 tonometers?	Paired t-test and Bland-Altman analysis
What is the relationship between IOP and CCT by 2 tonometer?	Peasrson correlation Compare correlation
Purpose (Chapter 3)	**Test**
Comparing 2 groups: DS children and control children	
Is there a difference in Meansph, VA, AL between 2 groups?	Independent t-test, Mann-Whitney test
Is there a difference in the presence of inaccurate accommodation between 2 groups?	Chi-square test
Is there a difference in those ocular biometric parameters (cornea, lens, ACD and pupil size)?	Independent t-test, Mann-Whitney test
Exploring relationships	
What is the relationship between CCT and PCT; CCT and MCT; CCT and CR for child groups?	Regression Line or Spearman correlation
What is the relationship between AL and refraction, AL/CR and refraction?	Regression Line
Is there a difference in the above relationship between groups?	Comparison of regression lines
What is the relationship between corneal power, ACD, lens power and refraction for 2 child groups?	Correlation
Is there difference in the refractive components between child subjects among refractive error groups?	Independent t-test, Mann-Whitney test

Appendix 1

Purpose (Chapter 4)	Test
Comparing 2 groups: DS children and control children	
Is there a difference in relative disc size and F-D distance between 2 child groups by ImageNet software?	Independent t-test, Mann-Whitney test
Is there a difference in absolute disc size, rim size, cup size and C/D ratio between 2 child groups?	Independent t-test, Mann-Whitney test
In terms of the total vessel numbers, its there a difference between two children groups for arteries and veins in four segments?	Repeated Measurements (ANOVA)
Is there a difference in mean width of vessels (arteries and veins) between 2 child groups?	Mann-Whitney test Wilconxon Signed test
Exploring relationships	
What is the relationship between disc size and rim size; disc size and cup size in 2 groups?	Correlation or regression line
Is there a difference in the above relationship between groups?	Comparison of regression lines

Purpose (Chapter 5)	Test
Comparing 2 groups: DS adults and control adults	
Do DS adults have lower IOP than that of controls?	Independent t-test
Is there a difference in the presence of PPA, Zone a, Zone b and suspicious glaucoma for 2 child groups by 2 observers?	Chi-square
Exploring relationships	
What is the relationship between CCT and IOP in DS adults?	Pearson correlation
What is the relationship between CR and IOP in DS adults?	Pearson correlation

Invitation letter – parent of children with Downs' syndrome

School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Dear parent

I am writing to introduce myself.
My name is Ping ,Ji, and I am a new research student in the Down's Syndrome Vision Research team. If you were at our information day before Christmas, you may remember that I explained the nature of my research.

For those of who didn't meet me then, here is a summary: My subject is "The retinal appearance in children with Down's syndrome; association with visual function".

Our program will investigate the dimensions of the optic disc and the retinal vessels (at the back of the eye) of children, in order to determine any associations between retinal features and visual development. (You may know that visual development is different in children with Down's syndrome from 'ordinary' children).

There are two measurements I will do:
--Take a picture of the back of your child's eyes, using the fundus (retinal) camera. This is used in exactly the same way as a normal camera with a short flash, and will cause no discomfort at all.
-- I will measure eye-size with an instrument that shines light into the eye and assesses the reflections. This instrument provides non-contact recording – that is, we don't need to use drops.

If you agree to take part, I will take the pictures during your next routine visit to the eye clinic here in the university, and we will post on a copy of the photo if you wish.

I would like to thank you in anticipation for your co-operation. If you have any questions or queries regarding this study, please do not hesitate to contact me on
029 2087-6163.

I look forward to seeing you soon,

Your sincerely,

Ping Ji

Appendix 2

Invitation letter – parent of children with Downs' syndrome
School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

CONSENT FORM

THE RETINAL APPEARANCE IN CHILDREN WITH DOWN'S SYNDROME; ASSOCIATION WITH VISUAL FUNCTION

Researchers: Ping Ji, Dr Maggie Woodhouse

I agree to take part in the follow-up study. ☐

I understand that my participation is voluntary and that I am free to withdraw at any time.

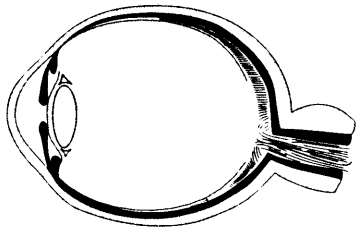
☐

Parents Name_____ Signature _____

Child's Name_____ Signature _____

Contact Address: _____
_____
_____

Thank you very much for continued support!



i

Appendix 2b

School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

With my compliments

Parents of XX

Dear parents of XX

I want to express my sincere thanks to you for allowing your child joining my research project. I am enclosing a photograph of the back of her eye which she might be interested in seeing and perhaps keep it as a souvenir of her visit to our eye clinic.

Thank you once again for your help,

Yours sincerely,

Ping Ji

Postgraduate
Cardiff School of Optometry and Vision Sciences
Cardiff University
Redwood Building
King Edward VII Avenue
Cardiff CF10 3NB

Appendix 3

School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

Dear Parents/Guardians of XX

I am Ji Ping, who is doing eye research with Dr Margaret Woodhouse in the eye clinic of Cardiff university as I mentioned in the previous letters. I hope you don't mind I contact you again as we are really keen to recruit normal children in our further research project which is related with the properties of the optic disc in children with Down's syndrome recently.

You will remember that I asked to take photos of the back of their eyes before. Now that I have analysed photos of 92 children's eyes (both with and without Down's syndrome), the results are exciting and completely unexpected. It appears that the structures at the back of the eyes, such as the optic nerve, are *bigger* in children with Down's syndrome. This would usually make children shortsighted, but, of course, most of the children are not shortsighted. The only way we can explain this at the moment is to assume that the children's eyes are a *different shape* to the eyes of other children.

In order to follow this up, we now need to take photos of the front of the children's eyes to look at the shape and size there. We would really like to be able to photograph the lens in the eye, and the only way we can do this is to use drops to widen the pupil. I am writing now to ask you if you are willing to bring Jordon to the clinic for it during the coming half term (from 9:00 AM to 4:00 PM on 2nd, 3rd of Jun). We will, of course, pay the travel expenses. We know that some children don't like drops, so we are only going to use drops if Jordon says that it is okay. We still can get a useful photo without eyedrops.

If you are willing to help again, please choose the suitable time and sign the consent letter and post back by the enclosed stamped- addressed envelope.
Any help you could give us would be really appreciated.
We are looking forward to getting reply from you,

Yours truly,

Ping Ji
School of Optometry & Vision Sciences
Cardiff University

Appendix 3

School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

The retinal appearance in children with Down's syndrome; association with visual function

Researchers: Ping Ji, Dr Maggie Woodhouse

CONSENT FORM

Please tick

I have read and understood the Information Sheet and have been given the opportunity to ask questions. _____

I understand that my participation is voluntary and that I am free to withdraw at any time. _____

I agree to take part in the study. _____

Parents Name_____ Signature _____

Child's Name_____ Signature _____

Child's D.O.B_____ Date _____

Contact details:

Address_____ Telephone number_____

_____ E-mail address _____

_____

Most suitable day / time: _____

Thank you!

RECORD OF CHILDREN ---MAIN STUDY

NAME D.O.B AGE: GENDER:		SUBJECT/ CONTROL GROUP VISIT TIMES: DATE: TESTED BY:
	R	L
RETINOSCOPE:		
VISUAL ACUITY		
ACCOMMODATION	10CM	16.7CM
FUNDUS CAMERA: (IMAGE CODE)		
IOL MASTER ----AXIAL LENGTH		

Appendix 5

INFORMATION SHEET

Dear XX

We are members of the Down's syndrome Vision Research Team and the Ocular Genetics Research Team of Optometry School at Cardiff University. Together we are planning two studies involving adults with Down's syndrome.

We are writing to invite you to attend our clinic to join the studies: 'Optic disc and corneal properties in people with Down's syndrome; their impact on the detection of glaucoma.' and 'Genetic causes of keratoconus in Down's syndrome'. We are keen to recruit people to ensure that the studies are a success. We enclose our information sheet in details and consent form.

Any help you could give us would be really appreciated.
We are looking forward to getting reply from you,
Yours truly,

Ping Ji & Jack Sheppard
Research Students
School of Optometry and Vision Science
Cardiff University

Who we are

I am Ping Ji and my supervisor is Maggie Woodhouse. We are members of the Down's Syndrome Vision Research Team.

I am Jack Sheppard and my supervisor is Marcela Votruba. We are members of the Ocular Genetics Research Team.

Together we are planning two studies involving adults with Down's syndrome.
We are keen to recruit people to ensure that the studies are a success. We are inviting you to attend our clinic to join the studies.

Ping's study is

'Optic disc and corneal properties in people with Down's syndrome; their impact on the detection of glaucoma'.

Glaucoma is an eye disease that becomes more likely as we get older. Because it doesn't cause any discomfort, a person who has glaucoma in the early stages doesn't usually know it. At the moment we have no idea of how common glaucoma is in people with Down's syndrome. Because people with Down's syndrome have eyes that are often 'different' to other people's eyes, it may be difficult to detect glaucoma. For example, the cornea in people with Down's syndrome possesses a number of abnormal properties. Intra-ocular pressure is measured by instruments that temporarily distort the shape of the cornea, and the instruments are calibrated for the average cornea. Thinner corneas, such as most people with Down's syndrome have will give inaccurate readings, and it is possible that glaucoma is missed.
Damage due to glaucoma is apparent in changes to the optic disc. However, the optic disc often looks different in people with Down's syndrome, and changes may be difficult to interpret.

So we intend to study the optic disc appearance and corneal properties along with intra-ocular pressure in people with Down's syndrome to determine two things:

- Firstly whether glaucoma ever arises in people with Down's syndrome
- Secondly, if it does arise, how we might best detect it in the early stages.

Once you have agreed to join the study and come along to our clinic, we will carry out a normal eye examination including measuring detail vision and refractive error (long or short-sight). In addition, there are **four measurements** that we also want to do:

The size of the eye
This is done with an instrument that shines a light into your eye and measures the reflections.

A photo of the back of your eye
The photo will be taken with a retinal or fundus camera.

Corneal topography
This means a very accurate measure of the shape of your cornea.

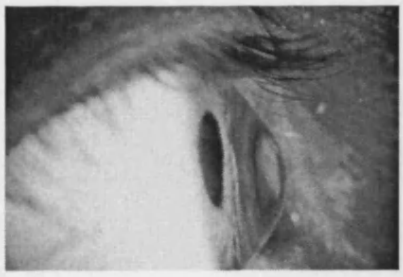
The above three measurements mean that all you have to do is to put his/her chin onto a rest and keep still for a few seconds. We will not use eye-drops.

Intra-ocular pressure
For this we need to touch your eye with a small probe. The measurement is made in a fraction of a second, and you will probably not be able to feel it. Once again, no eye-drops.

Jack's study is

Genetic causes of keratoconus in Down's Syndrome.

Keratoconus
Keratoconus (KC) is a condition in which the cornea becomes conical in shape because of the thinning of the cornea. This impairs the vision at both near and distance. It usually starts in late childhood. It can be corrected up to a point with contact lenses, although when KC is more advanced only a corneal graft will restore sight.



Up to 15% of people with Down's syndrome have KC, which is far more than the general population, but we do not know why this is so. One hypothesis is that environmental factors, such as eye rubbing, may contribute, whilst other hypotheses involve the role of key genes that may be involved together with environmental factors.

The genetic causes of KC are being investigated internationally, but so far only a small number of genes have been directly implicated. One of these genes is called VSX1. So far it has only been studied and been found to be abnormal in some people with KC who do not have Down's syndrome. So we would like to look for the gene in people with Down's syndrome, including those without keratoconus as well as those with it.

Study procedure
When you come to the clinic, we will ask you for a sample for DNA analysis. This sample may be a mouth wash, buccal scrape (from the inside of your cheek) or a blood sample (up to 20 ml max). You can choose which you prefer.

At the end of the study we will destroy all samples, and they will not be used for any other study.

Expected outcomes

If it turns out that the same gene VSX1 is associated with keratoconus in Down's syndrome, then it will be useful to identify children with Down's syndrome who may go on to develop KC, at an early stage. Then we will be able to provide help for their eyesight as early as possible.

What we offer you if you join our study

- We will offer support and advice regarding your eyes and vision.
- We will post on a copy of the retinal photo if you wish.
- We will pay travel expenses for you (and your friend or family member) to come to the clinic

What you need to do now

If you are willing to join one or both of our studies, please fill in the form overleaf. Simply tick the boxes and sign your name. Your friend or family member can sign for you, or as well as you.
We will then contact you by post or telephone to arrange your visit to us.

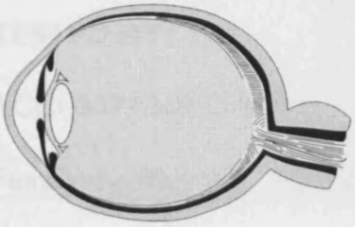
Where we are

The clinic is situated in the School of Optometry &Vision Science, in the Redwood Building, King Edward VIIth Avenue, which is in the centre of Cardiff.

Consent form

Ping

Ping would like to measure your eye in three different ways and take a photo of it. She will send you a copy of your photo if you wish.



I am happy to join Ping's study ☐

Jack

Jack would like to take a sample and look at your DNA.

I am happy to join Jack's study ☐

I would prefer mouthwash ☐ cheek swab ☐ blood sample ☐

My name .....

My signature.....

Carer's name..... Relationship.....

Signature.....

Contact address.....

.....

Telephone no.....

RECORD OF ADULTS ---MAIN STUDY

NAME D.O.B AGE: GENDER:		SUBJECT/ CONTROL GROUP VISITING DATE: TESTED BY: ACCOMPANIED BY: Family member or Staff carer
	R	L
Pentacam image		
CCT		
IOP		
ALM		
Refractive Error		
VA		
Fundus photograph		
Question 1	Do you have a close family history (parents, brother or sister) of glaucoma? Yes No Don't know	
Question 2	Do you have a close family history (parents, brother or sister) of keratoconus? Yes No Don't know	
Question 3	How often do you rub your eyes? once or less/per day 3-6 times/per day 7 times or more/per day	
Co-operation		

Information sheet for adults
School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

"Comparison of the Impact tonometer with Goldmann applanation tonometry"

Aim

To confirm the accuracy of the Impact tonometer before introducing it into our project

Proceures

Once you have agreed to join the study, we will carry out two measurements:

1. Intraocular pressure(IOP), which will be measured three times in one of your eyes

A. by Goldmann tonometer

This instrument (the 'gold standard' for IOP measures) involves placing a small probe against your eye. We will first instil a drop of local anaesthetic, so that you will not feel the procedure at all.

B. by Impact tonometer

For this we need to touch your eye again with a small probe. The measurement is made in a fraction of a second, and you will probably not be able to feel it. This instrument does not need anaesthetic, but the effect of the initial drop will probably still be there.

C .by Goldmann tonometer a second time

We may need to instil a second drop of anaesthetic, if the first has worn off.

2. Central Corneal Thickness(CCT) *by the Oculus Pentacam*

You will be asked to sit in front of the camera with your forehead against a rest. The computer then takes photos to measure the thickness of your cornea and the corneal topography. It is a non-invasive procedure, easy to perform.

If you agree to take part, please sign the consent form, and if you have any questions or queries regarding joining this study, please do not hesitate to contact me on 029 2087-6471 or e-mail me : jip1@cf.ac.uk.

You can change your mind at any time and decide not to take part.

We would like to thank you in anticipation for your co-operation !

Appendix 7

Information sheet for adults

School of Optometry & Vision Sciences, Cardiff University
Tel: 029 2087 6163

Comparison of the Impact tonometer with Goldmann applanation tonometry

Researchers: Ping Ji, Dr Maggie Woodhouse

CONSENT FORM

Please tick

I have read and understood the Information Sheet and have been given the opportunity to ask questions. _____

I understand that my participation is voluntary and that I am free to withdraw at any time. _____

I agree to take part in the study. _____

Full Name _____ D.O.B _____

Signature _____

Visiting Date _____

Thank you !

Scaling code for the Topcon camera

```
// receive the scale variables back to main form

procedure
TStereo_window.ReceiveScaleVariables(Scale:ScaleRecord);
var
  radcurve:real;
  refraction:real;
  rad1:real;
  rad2:real;
  sphere:real;
  cyl:real;
  p:real;
  //s:real;
  q:real;
begin
  ScaleVariables := Scale;

  rad1 := ScaleVariables.k1; // convert to old nomenclature
  rad2 := ScaleVariables.k2;
  sphere := ScaleVariables.Sphere;
  cyl := ScaleVariables.Cylinder;

  // work out S
  if ImageSingle then
    S := ((ScaleVariables.Vert / ImageHeight) +
(ScaleVariables.Horiz / ImageWidth)) / 2
  else if ImagePair then
    S := ((ScaleVariables.Vert / ImageHeight) +
(ScaleVariables.Horiz / ImageWidth)) / 2
  else
    MessageDlg('Stereo Error: S.', mtInformation, [mbOK], 0);

  //writeln(Imagewidth);
  //writeln(Imageheight);
  //writeln('S ', S);
 // James' scaling code......
//calculate the magnification factor
  radcurve := (rad1+rad2)/2;
  refraction := sphere + (cyl/2);//mean speherical refractive
error
```

```
{
 calculate the conversion factor for pixels to microns based on
the camera type
 true image size = p.q.s where              NB all units in
metres...1/metres = D
 p = camera factor
 s = size of object on photographic film or in this case in
terms of pixels on screen
 (Rudnicka et al Ophthalmology 1998: 105: 2186-2192)
}
     Else if (ScaleVariables.Camera =3)then //'TOPCON NW6S Non
myd 30 deg'- the text is go in the status bar
     begin      //inserted by JEM 4.11.05
      p := 1.62;; //telecentric
     s := 0.024; //mm per pixel based on the TOPCON
camera SONY DXC 950P
        GL_Status('s = 0.024);
    End



//q = eye factor(calculated using Ted Garway heath's method
(BJO 1998: 82: 352-361)
    refraction := refraction/(1-(0.014*refraction)); // JEM
from page 645 of above paper refraction = Fsp and is taken
direct off the autorefractor
   q := 1/((17.21/radcurve)+1.247 + (refraction/17.455));
// conversion factor (KTrue) for pixels := P*q*s
  ScaleVariables.Ktrue := p*(q*S);// multiply the number of
pixels by this value to get the linear dimension in mm
  ScaleVariables.KArea := sqr(ScaleVariables.KTrue);
//sqr(p*q)*(sqr(s));//from Rudnicka et al Ophthalmology 1998
105: 2186-2192 p2191
  GL_Status('T:' + floattostrF(ScaleVariables.KTrue, fffixed,
7, 5) + '  mm/pixel at retina   S:' + floattostrF(S, fffixed,
7, 5) + ' mm/pixel on film');
  Paint;
end;
```

Bibliography

Abrahamsson M, Magnusson G, and Sjostrand J (1999) Inheritance of strabismus and the gain of using heredity to determine populations at risk of developing strabismus. *Acta Ophthalmol Scand* 77: 653-657.

Ahmad A, and Pruett R C (1976) The fundus in mongolism. *Arch Ophthalmol* 94: 772-776.

Alsbirk P H (1978) Corneal thickness. I. Age variation, sex difference and oculometric correlations. *Acta Ophthalmol (Copenh)* 56: 95-104.

Amano S, Amano Y, Yamagami S, Miyai T, Miyata K, Samejima T, and Oshika T (2004) Age-related changes in corneal and ocular higher-order wavefront aberrations. *Am J Ophthalmol* 137: 988-992.

Amstad P, and Cerutti P (1990) Genetic modulation of the cellular antioxidant defense capacity. *Environ Health Perspect* 88: 77-82.

Anderson D R, Graham S, and Pillunat L (2003) Normal-tension glaucoma. *J Glaucoma* 12: 164-166.

Andreassen T T, Simonsen A H, and Oxlund H (1980) Biomechanical properties of keratoconus and normal corneas. *Exp Eye Res* 31: 435-441.

Anneren G, Tuvemo T, Carlsson-Skwirut C, Lonnerholm T, Bang P, Sara V R, and Gustafsson J (1999) Growth hormone treatment in young children with Down's syndrome: effects on growth and psychomotor development. *Arch Dis Child* 80: 334-338.

Arend O, Remky A, Plange N, Martin B J, and Harris A (2002) Capillary density and retinal diameter measurements and their impact on altered retinal circulation in glaucoma: a digital fluorescein angiographic study. *Br J Ophthalmol* 86: 429-433.

Armaly M F (1965) On the Distribution of Applanation Pressure. I. Statistical Features and the Effect of Age, Sex, and Family History of Glaucoma. *Arch Ophthalmol* 73: 11-18.

Armaly M F (1980) Lessons to be learned from the Collaborative Glaucoma Study. *Surv Ophthalmol* 25: 139-144.

Armstrong R A, Eperjesi F, and Gilmartin B (2005) The use of correlation and regression methods in optometry. *Clin Exp Optom* 88: 81-88.

Arntz A, Duran J A, and Pijoan J I (2003) [Subclinical keratoconus diagnosis by elevation topography]. *Arch Soc Esp Oftalmol* 78: 659-664.

Ashaye A O (2003) The anterior chamber angles in Nigerians. *Afr J Med Med Sci* 32: 315-320.

Atchison D A, Jones C E, Schmid K L, Pritchard N, Pope J M, Strugnell W E, and Riley R A (2004) Eye shape in emmetropia and myopia. *Invest Ophthalmol Vis Sci* 45: 3380-3386.

Atchison D A, Pritchard N, Schmid K L, Scott D H, Jones C E, and Pope J M (2005) Shape of the retinal surface in emmetropia and myopia. *Invest Ophthalmol Vis Sci* 46: 2698-2707.

Atkinson P L, Wishart P K, James J N, Vernon S A, and Reid F (1992) Deterioration in the accuracy of the pulsair non-contact tonometer with use: need for regular calibration. *Eye* 6 (Pt 5): 530-534.

Auffarth G U, Wang L, and Volcker H E (2000) Keratoconus evaluation using the Orbscan Topography System. *J Cataract Refract Surg* 26: 222-228.

Awan K J (1977) Uncommon ocular changes in Down's syndrome (mongolism). *J Pediatr Ophthalmol* 14: 215-216.

Bader D, and Woodruff M E (1980) The effects of corrective lenses on various behaviors of mentally retarded persons. *Am J Optom Physiol Opt* 57: 447-459.

Baird P A, and Sadovnick A D (1987) Life expectancy in Down syndrome. *J Pediatr* 110: 849-854.

Barkana Y, Gerber Y, Elbaz U, Schwartz S, Ken-Dror G, Avni I, and Zadok D (2005) Central corneal thickness measurement with the Pentacam Scheimpflug system, optical low-coherence reflectometry pachymeter, and ultrasound pachymetry. *J Cataract Refract Surg* 31: 1729-1735.

Bartz-Schmidt K U, Sundtgen M, Widder R A, Weber J, and Krieglstein G K (1995) Limits of two-dimensional planimetry in the follow-up of glaucomatous optic discs. *Graefes Arch Clin Exp Ophthalmol* 233: 284-290.

Bathija R (2000) Optic nerve blood flow in glaucoma. *Clin Exp Optom* 83: 180-184.

Becker L, Mito T, Takashima S, and Onodera K (1991) Growth and development of the brain in Down syndrome. *Prog Clin Biol Res* 373: 133-152.

Behrens-Baumann W (1994) Detection of keratoconus before refractive surgery. *Ophthalmology* 101: 794-795.

Bell R, Rankin J, and Donaldson L J (2003) Down's syndrome: occurrence and outcome in the north of England, 1985-99. *Paediatr Perinat Epidemiol* 17: 33-39.

Bengtsson B (1976) The variation and covariation of cup and disc diameters. *Acta Ophthalmol (Copenh)* 54: 804-818.

Bengtsson B, and Krakau C E (1977) Some essential optical features of the Zeiss fundus camera. *Acta Ophthalmol (Copenh)* 55: 123-131.

Bengtsson B, and Krakau C E (1992) Correction of optic disc measurements on fundus photographs. *Graefes Arch Clin Exp Ophthalmol* 230: 24-28.

Bennett A G, and Rabbetts R B (1991) What radius does the conventional keratometer measure? *Ophthalmic Physiol Opt* 11: 239-247.

Bennett A G, Rudnicka A R, and Edgar D F (1994) Improvements on Littmann's method of determining the size of retinal features by fundus photography. *Graefes Arch Clin Exp Ophthalmol* 232: 361-367.

Berk A T, Saatci A O, Ercal M D, Tunc M, and Ergin M (1996) Ocular findings in 55 patients with Down's syndrome. *Ophthalmic Genet* 17: 15-19.

Bertelsen T I, and Seim V (1974) The cause of irreversible mydriasis following keratoplasty in keratoconus: a preliminary report. *Ophthalmic Surg* 5: 56-58.

Binkhorst R D (1981) The accuracy of ultrasonic measurement of the axial length of the eye. *Ophthalmic Surg* 12: 363-365.

Bisceglia L, Ciaschetti M, De Bonis P, Campo P A, Pizzicoli C, Scala C, Grifa M et al. (2005) VSX1 Mutational Analysis in a Series of Italian Patients Affected by Keratoconus: Detection of a Novel Mutation. *Invest Ophthalmol Vis Sci* 46: 39-45.

Bishop J, Huether C A, Torfs C, Lorey F, and Deddens J (1997) Epidemiologic study of Down syndrome in a racially diverse California population, 1989-1991. *Am J Epidemiol* 145: 134-147.

Bland JM, Altman DG (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lance*:i:307-310.

Boehm A G, Koeller A U, and Pillunat L E (2005) The effect of age on optic nerve head blood flow. *Invest Ophthalmol Vis Sci* 46: 1291-1295.

Bonomi L, Marchini G, Marraffa M, Bernardi P, De Franco I, Perfetti S, and Varotto A (2000) Epidemiology of angle-closure glaucoma: prevalence, clinical types, and association with peripheral anterior chamber depth in the Egna-Neumarket Glaucoma Study. *Ophthalmology* 107: 998-1003.

Bowd C, Zangwill L M, Blumenthal E Z, Vasile C, Boehm A G, Gokhale P A, Mohammadi K et al. (2002) Imaging of the optic disc and retinal nerve fiber layer: the effects of age, optic disc area, refractive error, and gender. *J Opt Soc Am A Opt Image Sci Vis* 19: 197-207.

Brandt J D, Beiser J A, Kass M A, and Gordon M O (2001) Central corneal thickness in the Ocular Hypertension Treatment Study (OHTS). *Ophthalmology* 108: 1779-1788.

Brichard B, Vermylen C, De Potter P, and Casteels I (2003) Down syndrome: possible predisposition to retinoblastoma. *Med Pediatr Oncol* 41: 73-74.

Bricker S R, McGalliard J N, and Mostafa S M (1990) The Keeler Pulsair air impulse tonometer. Comparison with the Perkins hand-held applanation tonometer for peri-operative measurement of intra-ocular pressure. *Anaesthesia* 45: 36-39.

Broadway D C, Nicolela M T, and Drance S M (1999) Optic disk appearances in primary open-angle glaucoma. *Surv Ophthalmol* 43 Suppl 1: S223-243.

Bromham N R, Woodhouse J M, Cregg M, Webb E, and Fraser W I (2002) Heart defects and ocular anomalies in children with Down's syndrome. *Br J Ophthalmol* 86: 1367-1368.

Brown N (1974) The shape of the lens equator. *Exp Eye Res* 19: 571-576.

Brown W T (1979) Human mutations affecting aging--a review. *Mech Ageing Dev* 9: 325-336.

Budde W M, and Jonas J B (2003) [Influence of ciliary-retinal arteries on functional damage in open-angle glaucoma]. *Ophthalmologe* 100: 1067-1070.

Budde W M, Jonas J B, Martus P, and Grundler A E (2000) Influence of optic disc size on neuroretinal rim shape in healthy eyes. *J Glaucoma* 9: 357-362.

Buehl W, Stojanac D, Sacu S, Drexler W, and Findl O (2006) Comparison of three methods of measuring corneal thickness and anterior chamber depth. *Am J Ophthalmol* 141: 7-12.

Bullimore M A, and Gilmartin B (1987) Tonic accommodation, cognitive demand, and ciliary muscle innervation. *Am J Optom Physiol Opt* 64: 45-50.

Bullimore M A, and Gilmartin B (1988) The accommodative response, refractive error and mental effort: 1. The sympathetic nervous system. *Doc Ophthalmol* 69: 385-397.

Burgoyne C F, Downs J C, Bellezza A J, Suh J K, and Hart R T (2005) The optic nerve head as a biomechanical structure: a new paradigm for understanding the role of IOP-related stress and strain in the pathophysiology of glaucomatous optic nerve head damage. *Prog Retin Eye Res* 24: 39-73.

Buxhoeveden D, Fobbs A, Roy E, and Casanova M (2002) Quantitative comparison of radial cell columns in children with Down's syndrome and controls. *J Intellect Disabil Res* 46: 76-81.

Cairns G, and McGhee C N (2005) Orbscan computerized topography: attributes, applications, and limitations. *J Cataract Refract Surg* 31: 205-220.

Caprioli J, and Miller J M (1987) Optic disc rim area is related to disc size in normal subjects. *Arch Ophthalmol* 105: 1683-1685.

Caprioli J, and Spaeth G L (1984) Comparison of visual field defects in the low-tension glaucomas with those in the high-tension glaucomas. *Am J Ophthalmol* 97: 730-737.

Caprioli J, Spaeth G L, and Wilson R P (1986) Anterior chamber depth in open angle glaucoma. *Br J Ophthalmol* 70: 831-836.

Carkeet A, Saw S M, Gazzard G, Tang W, and Tan D T (2004) Repeatability of IOLMaster biometry in children. *Optom Vis Sci* 81: 829-834.

Carr J (1995) *The developmental study--Down syndrome.* Cambridge: Cambridge University Press.

Castane M, Boada-Rovira M, and Hernandez-Ruiz I (2004) [Eye conditions as features of Down's syndrome in patients over 40 years of age]. *Rev Neurol* 39: 1017-1021.

Casteels I, Harris CM, Shawkat F, Taylor D (1992) Nystagmus in infancy. *Br J Ophthalmol.* Jul; 76 (7): 434-7.

Catalano R A (1990) Down syndrome. *Surv Ophthalmol* 34: 385-398.

Cengiz M, Seven M, and Suyugul N (2002) Antioxidant system in Down syndrome: a possible role in cataractogenesis. *Genet Couns* 13: 339-342.

Cennamo G, Rosa N, La Rana A, Bianco S, and Sebastiani A (1997) Non-contact tonometry in patients that underwent photorefractive keratectomy. *Ophthalmologica* 211: 341-343.

Chabert C, Jamon M, Cherfouh A, Duquenne V, Smith D J, Rubin E, and Roubertoux P L (2004) Functional analysis of genes implicated in Down syndrome: 1. Cognitive abilities in mice transpolygenic for Down Syndrome Chromosomal Region-1 (DCR-1). *Behav Genet* 34: 559-569.

Chapman N, Witt N, Gao X, Bharath A A, Stanton A V, Thom S A, and Hughes A D (2001) Computer algorithms for the automated measurement of retinal arteriolar diameters. *Br J Ophthalmol* 85: 74-79.

Chapman R S, and Hesketh L J (2000) Behavioral phenotype of individuals with Down syndrome. *Ment Retard Dev Disabil Res Rev* 6: 84-95.

Charman W N (1986) Static accommodation and the minimum angle of resolution. *Am J Optom Physiol Opt* 63: 915-921.

Charman W N (2005) Aberrations and myopia. *Ophthalmic Physiol Opt* 25: 285-301.

Chatterjee A, Shah S, Bessant D A, Naroo S A, and Doyle S J (1997) Reduction in intraocular pressure after excimer laser photorefractive keratectomy. Correlation with pretreatment myopia. *Ophthalmology* 104: 355-359.

Chen H C, Newsom R S, Patel V, Cassar J, Mather H, and Kohner E M (1994) Retinal blood flow changes during pregnancy in women with diabetes. *Invest Ophthalmol Vis Sci* 35: 3199-3208.

Cheng X, Bradley A, Hong X, and Thibos L N (2003) Relationship between refractive error and monochromatic aberrations of the eye. *Optom Vis Sci* 80: 43-49.

Cheung S W, Cho P, and Douthwaite W (2000) Corneal shape of Hong Kong-Chinese. *Ophthalmic Physiol Opt* 20: 119-125.

Chihara E, and Honda Y (1992) Preservation of nerve fiber layer by retinal vessels in glaucoma. *Ophthalmology* 99: 208-214.

Chihara E, Takahashi H, Okazaki K, Park M, and Tanito M (2005) The preoperative intraocular pressure level predicts the amount of underestimated intraocular pressure after LASIK for myopia. *Br J Ophthalmol* 89: 160-164.

Coleman A L, and Brigatti L (2001) The glaucomas. *Minerva Med* 92: 365-379.

Congdon N G, Spaeth G L, Augsburger J, Klancnik J, Jr., Patel K, and Hunter D G (1999) A proposed simple method for measurement in the anterior chamber angle: biometric gonioscopy. *Ophthalmology* 106: 2161-2167.

Connolly J A (1978) Intelligence levels of Down's syndrome children. *Am J Ment Defic* 83: 193-196.

Cook C A, Koretz J F, Pfahnl A, Hyun J, and Kaufman P L (1994) Aging of the human crystalline lens and anterior segment. *Vision Res* 34: 2945-2954.

Cornel M C, Breed A S, Beekhuis J R, te Meerman G J, and ten Kate L P (1993) Down syndrome: effects of demographic factors and prenatal diagnosis on the future livebirth prevalence. *Hum Genet* 92: 163-168.

Courage M L, Adams R J, and Hall E J (1997) Contrast sensitivity in infants and children with Down syndrome. *Vision Res* 37: 1545-1555.

Courage M L, Adams R J, Reyno S, and Kwa P G (1994) Visual acuity in infants and children with Down syndrome. *Dev Med Child Neurol* 36: 586-593.

Cregg M, Woodhouse J M, Pakeman V H, Saunders K J, Gunter H L, Parker M, Fraser W I et al. (2001) Accommodation and refractive error in children with Down syndrome: cross-sectional and longitudinal studies. *Invest Ophthalmol Vis Sci* 42: 55-63.

Cregg M, Woodhouse J M, Stewart R E, Pakeman V H, Bromham N R, Gunter H L, Trojanowska L et al. (2003) Development of refractive error and strabismus in children with Down syndrome. *Invest Ophthalmol Vis Sci* 44: 1023-1030.

Crick R P (1994) Epidemiology and screening of open-angle glaucoma. *Curr Opin Ophthalmol* 5: 3-9.

Cronemberger S, Calixto N, Costa L T, and Soares F M (2005) Corneal thickness and daily curve of intraocular pressure in suspected and glaucomatous patients. *Arq Bras Oftalmol* 68: 185-188.

Cronk C, Crocker A C, Pueschel S M, Shea A M, Zackai E, Pickens G, and Reed R B (1988) Growth charts for children with Down syndrome: 1 month to 18 years of age. *Pediatrics* 81: 102-110.

Cuckle H S, Wald N J, and Thompson S G (1987) Estimating a woman's risk of having a pregnancy associated with Down's syndrome using her age and serum alpha-fetoprotein level. *Br J Obstet Gynaecol* 94: 387-402.

da Cunha R P, and Moreira J B (1996) Ocular findings in Down's syndrome. *Am J Ophthalmol* 122: 236-244.

Dahlqvist A, Rask E, Rosenqvist C J, Sahlin C, and Franklin K A (2003) Sleep apnea and Down's syndrome. *Acta Otolaryngol* 123: 1094-1097.

Dandona R, Dandona L, Srinivas M, Sahare P, Narsaiah S, Munoz S R, Pokharel G P et al. (2002) Refractive error in children in a rural population in India. *Invest Ophthalmol Vis Sci* 43: 615-622.

Danias J, Kontiola A I, Filippopoulos T, and Mittag T (2003) Method for the noninvasive measurement of intraocular pressure in mice. *Invest Ophthalmol Vis Sci* 44: 1138-1141.

Dastjerdi M H, and Hashemi H (1998) A quantitative corneal topography index for detection of keratoconus. *J Refract Surg* 14: 427-436.

Davies L N, Bartlett H, Mallen E A, and Wolffsohn J S (2006) Clinical evaluation of rebound tonometer. *Acta Ophthalmol Scand* 84: 206-209.

Davis W R, Raasch T W, Mitchell G L, Mutti D O, and Zadnik K (2005) Corneal asphericity and apical curvature in children: a cross-sectional and longitudinal evaluation. *Invest Ophthalmol Vis Sci* 46: 1899-1906.

Delaey C, and Van De Voorde J (2000) Regulatory mechanisms in the retinal and choroidal circulation. *Ophthalmic Res* 32: 249-256.

Deloukas P, Schuler G D, Gyapay G, Beasley E M, Soderlund C, Rodriguez-Tome P, Hui L et al. (1998) A physical map of 30,000 human genes. *Science* 282: 744-746.

Detry-Morel M, Zeyen T, Kestelyn P, Collignon J, and Goethals M (2004) Screening for glaucoma in a general population with the non-mydriatic fundus camera and the frequency doubling perimeter. *Eur J Ophthalmol* 14: 387-393.

Devenny D A, Silverman W P, Hill A L, Jenkins E, Sersen E A, and Wisniewski K E (1996) Normal ageing in adults with Down's syndrome: a longitudinal study. *J Intellect Disabil Res* 40 (Pt 3): 208-221.

Devereux J G, Foster P J, Baasanhu J, Uranchimeg D, Lee P S, Erdenbeleig T, Machin D et al. (2000) Anterior chamber depth measurement as a screening tool for primary angle-closure glaucoma in an East Asian population. *Arch Ophthalmol* 118: 257-263.

Dielemans I, Vingerling J R, Hofman A, Grobbee D E, and de Jong P T (1994) Reliability of intraocular pressure measurement with the Goldmann applanation tonometer in epidemiological studies. *Graefes Arch Clin Exp Ophthalmol* 232: 141-144.

DiMaio M S, Baumgarten A, Greenstein R M, Saal H M, and Mahoney M J (1987) Screening for fetal Down's syndrome in pregnancy by measuring maternal serum alpha-fetoprotein levels. *N Engl J Med* 317: 342-346.

Dolk H, Loane M, Garne E, De Walle H, Queisser-Luft A, De Vigan C, Addor M C et al. (2005) Trends and geographic inequalities in the prevalence of Down syndrome in Europe, 1980-1999. *Rev Epidemiol Sante Publique* 53 Spec No 2: 2S87-95.

Doughty M J, Laiquzzaman M, Muller A, Oblak E, and Button N F (2002) Central corneal thickness in European (white) individuals, especially children and the elderly, and assessment of its possible importance in clinical measures of intra-ocular pressure. *Ophthalmic Physiol Opt* 22: 491-504.

Doughty M J, and Zaman M L (2000) Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. *Surv Ophthalmol* 44: 367-408.

Douthwaite W A (2003) The asphericity, curvature and tilt of the human cornea measured using a videokeratoscope. *Ophthalmic Physiol Opt* 23: 141-150.

Douthwaite W A, and Sheridan M (1989) The measurement of the corneal ellipse for the contact lens practitioner. *Ophthalmic Physiol Opt* 9: 239-242.

Down J (1866) Observations on an ethnic classification of idiots. *Clin Lect Report Med Surg Staff London Hosp*: 259-262.

Doyle S J, Bullock J, Gray C, Spencer A, and Cunningham C (1998) Emmetropisation, axial length, and corneal topography in teenagers with Down's syndrome. *Br J Ophthalmol* 82: 793-796.

Dubbelman M, Sicam V A, and Van der Heijde G L (2006) The shape of the anterior and posterior surface of the aging human cornea. *Vision Res* 46: 993-1001.

Efron N, Morgan P B, and Katsara S S (2001) Validation of grading scales for contact lens complications. *Ophthalmic Physiol Opt* 21: 17-29.

Egashira S M, Kish L L, Twelker J D, Mutti D O, Zadnik K, and Adams A J (1993) Comparison of cyclopentolate versus tropicamide cycloplegia in children. *Optom Vis Sci* 70: 1019-1026.

Eghbali F, Yeung K K, and Maloney R K (1995) Topographic determination of corneal asphericity and its lack of effect on the refractive outcome of radial keratotomy. *Am J Ophthalmol* 119: 275-280.

Ehlers N, Bramsen T, and Sperling S (1975) Applanation tonometry and central corneal thickness. *Acta Ophthalmol (Copenh)* 53: 34-43.

Ehrlich D L, Braddick O J, Atkinson J, Anker S, Weeks F, Hartley T, Wade J et al. (1997) Infant emmetropization: longitudinal changes in refraction components from nine to twenty months of age. *Optom Vis Sci* 74: 822-843.

Epstein C J (1988) Specificity versus nonspecificity in the pathogenesis of aneuploid phenotypes. *Am J Med Genet* 29: 161-165.

Epstein C J, Epstein L B, Weil J, and Cox D R (1982) Trisomy 21: mechanisms and models. *Ann N Y Acad Sci* 396: 107-118.

Evereklioglu C, Yilmaz K, and Bekir N A (2002) Decreased central corneal thickness in children with Down syndrome. *J Pediatr Ophthalmol Strabismus* 39: 274-277.

Eyman R K, and Call T L (1991) Life expectancy of persons with Down syndrome. *Am J Ment Retard* 95: 603-612.

Feke G T, Tagawa H, Deupree D M, Goger D G, Sebag J, and Weiter J J (1989) Blood flow in the normal human retina. *Invest Ophthalmol Vis Sci* 30: 58-65.

Ferak V, and Cernay J (1984) [Macroscopic structure of the iris in children with Down's syndrome and in their mothers]. *Bratisl Lek Listy* 81: 188-195.

Fernandes P, Diaz-Rey J A, Queiros A, Gonzalez-Meijome J M, and Jorge J (2005) Comparison of the ICare rebound tonometer with the Goldmann tonometer in a normal population. *Ophthalmic Physiol Opt* 25: 436-440.

Fierson W (1990) *Opthalmological aspects. In Clinical Perspectives in the Management of Down Syndrome.* New York: Springer-Verlag.

Findl O, Drexler W, Menapace R, Heinzl H, Hitzenberger C K, and Fercher A F (2001) Improved prediction of intraocular lens power using partial coherence interferometry. *J Cataract Refract Surg* 27: 861-867.

Fishler K, and Koch R (1991) Mental development in Down syndrome mosaicism. *Am J Ment Retard* 96: 345-351.

Flammer J, Orgul S, Costa V P, Orzalesi N, Krieglstein G K, Serra L M, Renard J P et al. (2002) The impact of ocular blood flow in glaucoma. *Prog Retin Eye Res* 21: 359-393.

Florez J, del Arco C, Gonzalez A, Pascual J, and Pazos A (1990) Autoradiographic studies of neurotransmitter receptors in the brain of newborn infants with Down syndrome. *Am J Med Genet Suppl* 7: 301-305.

Fong D S, Epstein D L, and Allingham R R (1990) Glaucoma and myopia: are they related? *Int Ophthalmol Clin* 30: 215-218.

Fonseca C T, Amaral D M, Ribeiro M G, Beserra I C, and Guimaraes M M (2005) Insulin resistance in adolescents with Down syndrome: a cross-sectional study. *BMC Endocr Disord* 5: 6.

Forrester M B, and Merz R D (2002) Epidemiology of Down syndrome (Trisomy 21), Hawaii, 1986-97. *Teratology* 65: 207-212.

Foster P J, Baasanhu J, Alsbirk P H, Munkhbayar D, Uranchimeg D, and Johnson G J (1998) Central corneal thickness and intraocular pressure in a Mongolian population. *Ophthalmology* 105: 969-973.

Foster P J, Machin D, Wong T Y, Ng T P, Kirwan J F, Johnson G J, Khaw P T et al. (2003) Determinants of intraocular pressure and its association with glaucomatous optic neuropathy in Chinese Singaporeans: the Tanjong Pagar Study. *Invest Ophthalmol Vis Sci* 44: 3885-3891.

Frangione B, Castano E M, Wisniewski T, Ghiso J, Prelli F, and Vidal R (1996) Apolipoprotein E and amyloidogenesis. *Ciba Found Symp* 199: 132-141; discussion 141-135.

Friedman D S, Gazzard G, Foster P, Devereux J, Broman A, Quigley H, Tielsch J et al. (2003) Ultrasonographic biomicroscopy, Scheimpflug photography, and novel provocative tests in contralateral eyes of Chinese patients initially seen with acute angle closure. *Arch Ophthalmol* 121: 633-642.

Fromage B, and Anglade P (2002) [The aging of Down's Syndrome subjects]. *Encephale* 28: 212-216.

Fulcher T, Griffin M, Crowley S, Firth R, Acheson R, and O'Meara N (1998) Diabetic retinopathy in Down's syndrome. *Br J Ophthalmol* 82: 407-409.

Fullwood N J, Meek K M, Malik N S, and Tuft S J (1990) A comparison of proteoglycan arrangement in normal and keratoconus human corneas. *Biochem Soc Trans* 18: 961-962.

Garcia-Resua C, Gonzalez-Meijome J M, Gilino J, and Yebra-Pimentel E (2006) Accuracy of the new ICare rebound tonometer vs. other portable tonometers in healthy eyes. *Optom Vis Sci* 83: 102-107.

Garner L F, Stewart A W, Kinnear R F, and Frith M J (2004) The Nepal longitudinal study: predicting myopia from the rate of increase in vitreous chamber depth. *Optom Vis Sci* 81: 44-48.

Garway-Heath D F, and Hitchings R A (1998) Quantitative evaluation of the optic nerve head in early glaucoma. *Br J Ophthalmol* 82: 352-361.

Garway-Heath D F, Poinoosawmy D, Wollstein G, Viswanathan A, Kamal D, Fontana L, and Hitchings R A (1999) Inter- and intraobserver variation in the analysis of optic disc images: comparison of the Heidelberg retina tomograph and computer assisted planimetry. *Br J Ophthalmol* 83: 664-669.

Garway-Heath D F, Ruben S T, Viswanathan A, and Hitchings R A (1998a) Vertical cup/disc ratio in relation to optic disc size: its value in the assessment of the glaucoma suspect. *Br J Ophthalmol* 82: 1118-1124.

Garway-Heath D F, Rudnicka A R, Lowe T, Foster P J, Fitzke F W, and Hitchings R A (1998b) Measurement of optic disc size: equivalence of methods to correct for ocular magnification. *Br J Ophthalmol* 82: 643-649.

Garway-Heath D F, Wollstein G, and Hitchings R A (1997) Aging changes of the optic nerve head in relation to open angle glaucoma. *Br J Ophthalmol* 81: 840-845.

Gatinel D, Haouat M, and Hoang-Xuan T (2002) [A review of mathematical descriptors of corneal asphericity]. *J Fr Ophtalmol* 25: 81-90.

Gilchrist J M (1996) On the precision and reliability of IOP measurements. *Br J Ophthalmol* 80: 586-587.

Gilmartin B (2004) Myopia: precedents for research in the twenty-first century. *Clin Experiment Ophthalmol* 32: 305-324.

Gilmore L, Cuskelly M, and Hayes A (2003) A comparative study of mastery motivation in young children with Down's syndrome: similar outcomes, different processes? *J Intellect Disabil Res* 47: 181-190.

Gimeno J A, Munoz L A, Valenzuela L A, Molto F J, and Rahhal M S (2000) Influence of refraction on tonometric readings after photorefractive keratectomy and laser assisted in situ keratomileusis. *Cornea* 19: 512-516.

Ginsberg J, Ballard E T, Buchino J J, and Kinkler A K (1980) Further observations of ocular pathology in Down's syndrome. *J Pediatr Ophthalmol Strabismus* 17: 166-171.

Gobbe M, and Guillon M (2005) Corneal wavefront aberration measurements to detect keratoconus patients. *Cont Lens Anterior Eye* 28: 57-66.

Goh P-P, Abqariyah Y, Pokharel G P, and Ellwein L B (2005) Refractive Error and Visual Impairment in School-Age Children in Gombak District, Malaysia. *Ophthalmology* 112: 678-685.

Goldblum D, Kontiola A I, Mittag T, Chen B, and Danias J (2002) Non-invasive determination of intraocular pressure in the rat eye. Comparison of an electronic tonometer (TonoPen), and a rebound (impact probe) tonometer. *Graefes Arch Clin Exp Ophthalmol* 240: 942-946.

Goldmann H, and Schmidt T (1957) [Applanation tonometry.]. *Ophthalmologica* 134: 221-242.

Goldmann H, and Schmidt T (1961) [Further contribution to applanation tonometry]. *Ophthalmologica* 141: 441-456.

Gonzalez V, and McDonnell P J (1992) Computer-assisted corneal topography in parents of patients with keratoconus. *Arch Ophthalmol* 110: 1413-1414.

Gordon A, Boggess E A, and Molinari J F (1990) Variability of ultrasonic pachometry. *Optom Vis Sci* 67: 162-165.

Gordon M O, Beiser J A, Brandt J D, Heuer D K, Higginbotham E J, Johnson C A, Keltner J L et al. (2002) The Ocular Hypertension Treatment Study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 120: 714-720; discussion 829-730.

Goss D A, and Zhai H (1994) Clinical and laboratory investigations of the relationship of accommodation and convergence function with refractive error. A literature review. *Doc Ophthalmol* 86: 349-380.

Goyal R, North R V, and Morgan J E (2003) Comparison of laser interferometry and ultrasound A-scan in the measurement of axial length. *Acta Ophthalmol Scand* 81: 331-335.

Graf M (1991) [Significance of the corneal thickness in non-contact tonometry]. *Klin Monatsbl Augenheilkd* 199: 183-186.

Groh M J, Michelson G, Langhans M J, and Harazny J (1996) Influence of age on retinal and optic nerve head blood circulation. *Ophthalmology* 103: 529-534.

Grosvenor T, and Scott R (1991) Comparison of refractive components in youth-onset and early adult-onset myopia. *Optom Vis Sci* 68: 204-209.

Guillon M, Lydon D P, and Wilson C (1986) Corneal topography: a clinical model. *Ophthalmic Physiol Opt* 6: 47-56.

Gunvant P, O'Leary D J, Baskaran M, Broadway D C, Watkins R J, and Vijaya L (2005) Evaluation of tonometric correction factors. *J Glaucoma* 14: 337-343.

Gwiazda J, Scheiman M, Mohindra I, and Held R (1984) Astigmatism in children: changes in axis and amount from birth to six years. *Invest Ophthalmol Vis Sci* 25: 88-92.

Gwiazda J, and Thorn F (1999) Development of refraction and strabismus. *Curr Opin Ophthalmol.* 10 293-299.

Gwiazda J, Thorn F, Bauer J, and Held R (1993a) Emmetropization and the progression of manifest refraction in children followed from infancy to puberty. *Clin Vis Sci* 8: 337-344

Gwiazda J, Thorn F, Bauer J, and Held R (1993b) Myopic children show insufficient accommodative response to blur. *Invest Ophthalmol Vis Sci* 34: 690-694.

Hafez A S, Bizzarro R L, and Lesk M R (2003) Evaluation of optic nerve head and peripapillary retinal blood flow in glaucoma patients, ocular hypertensives, and normal subjects. *Am J Ophthalmol* 136: 1022-1031.

Haigis W, Lege B, Miller N, and Schneider B (2000) Comparison of immersion ultrasound biometry and partial coherence interferometry for intraocular lens calculation according to Haigis. *Graefes Arch Clin Exp Ophthalmol* 238: 765-773.

Hainline B C, Kollbaum P, and Springs K (2006) Evaluation Of The Orbscan Detection Indices For Keratoconus. Program 572.

Hall D M B (1996) *Health for all children.* Third ed. Oxford, New York, Tokyo: Oxford University Press.

Harada Y, and Naoi N (2004) Corneal elasticity as a measure of intra-ocular pressure: a controlled clinical examination. *Kobe J Med Sci* 50: 141-152.

Harigai S (1994) [Longitudinal studies in hearing-impaired children with Down's syndrome]. *Nippon Jibiinkoka Gakkai Kaiho* 97: 2208-2218.

Harper C L, Boulton M E, Bennett D, Marcyniuk B, Jarvis-Evans J H, Tullo A B, and Ridgway A E (1996) Diurnal variations in human corneal thickness. *Br J Ophthalmol* 80: 1068-1072.

Harper R A, and Reeves B C (1999) Glaucoma screening: the importance of combining test data. *Optom Vis Sci* 76: 537-543.

Harrison D A, and Maguire L J (1995) Biomicroscopic evidence of keratoconus with an apex power of 45.5 diopters by videokeratoscopy. *Am J Ophthalmol* 119: 366-367.

Harwerth R S, Carter-Dawson L, Shen F, Smith E L, 3rd, and Crawford M L (1999) Ganglion cell losses underlying visual field defects from experimental glaucoma. *Invest Ophthalmol Vis Sci* 40: 2242-2250.

Harwerth R S, Carter-Dawson L, Smith E L, 3rd, Barnes G, Holt W F, and Crawford M L (2004) Neural losses correlated with visual losses in clinical perimetry. *Invest Ophthalmol Vis Sci* 45: 3152-3160.

Hatch W V, Trope G E, Buys Y M, Macken P, Etchells E E, and Flanagan J G (1999) Agreement in assessing glaucomatous discs in a clinical teaching setting with stereoscopic disc photographs, planimetry, and laser scanning tomography. *J Glaucoma* 8: 99-104.

Hattori M, Fujiyama A, Taylor T D, Watanabe H, Yada T, Park H S, Toyoda A et al. (2000) The DNA sequence of human chromosome 21. *Nature* 405: 311-319.

Haugen O H (1992) Keratoconus in the mentally retarded. *Acta Ophthalmol (Copenh)* 70: 111-114.

Haugen O H, Aasved H, and Bertelsen T (1995) Refractive state and correction of refractive errors among mentally retarded adults in a central institution. *Acta Ophthalmol Scand* 73: 129-132.

Haugen O H, and Hovding G (2001) Strabismus and binocular function in children with Down syndrome. A population-based, longitudinal study. *Acta Ophthalmol Scand* 79: 133-139.

Haugen O H, Hovding G, and Eide G E (2001a) Biometric measurements of the eyes in teenagers and young adults with Down syndrome. *Acta Ophthalmol Scand* 79: 616-625.

Haugen O H, Hovding G, Eide G E, and Bertelsen T (2001b) Corneal grafting for keratoconus in mentally retarded patients. *Acta Ophthalmol Scand* 79: 609-615.

Haugen O H, Hovding G, and Lundstrom I (2001c) Refractive development in children with Down's syndrome: a population based, longitudinal study. *Br J Ophthalmol* 85: 714-719.

Haugen O H, Hovding G, and Riise R (2004) [Ocular changes in Down syndrome]. *Tidsskr Nor Laegeforen* 124: 186-188.

Hayreh S S, Jonas J B, and Zimmerman M B (1998) Parapapillary chorioretinal atrophy in chronic high-pressure experimental glaucoma in rhesus monkeys. *Invest Ophthalmol Vis Sci* 39: 2296-2303.

Hayreh S S, Podhajsky P, and Zimmerman M B (1999) Role of nocturnal arterial hypotension in optic nerve head ischemic disorders. *Ophthalmologica* 213: 76-96.

He J C, Sun P, Held R, Thorn F, Sun X, and Gwiazda J E (2002) Wavefront aberrations in eyes of emmetropic and moderately myopic school children and young adults. *Vision Res* 42: 1063-1070.

Hellstrom A, Chen Y, and Stromland K (1997a) Fundus morphology assessed by digital image analysis in children with fetal alcohol syndrome. *J Pediatr Ophthalmol Strabismus* 34: 17-23.

Hellstrom A, Hard A L, Chen Y, Niklasson A, and Albertsson-Wikland K (1997b) Ocular fundus morphology in preterm children. Influence of gestational age, birth size, perinatal morbidity, and postnatal growth. *Invest Ophthalmol Vis Sci* 38: 1184-1192.

Hellstrom A, and Svensson E (1998) Optic disc size and retinal vessel characteristics in healthy children. *Acta Ophthalmol Scand* 76: 260-267.

Heon E, Greenberg A, Kopp K K, Rootman D, Vincent A L, Billingsley G, Priston M et al. (2002) VSX1: a gene for posterior polymorphous dystrophy and keratoconus. *Hum Mol Genet* 11: 1029-1036.

Hernandez M R (2000) The optic nerve head in glaucoma: role of astrocytes in tissue remodeling. *Prog Retin Eye Res* 19: 297-321.

Herndon L W, Choudhri S A, Cox T, Damji K F, Shields M B, and Allingham R R (1997) Central corneal thickness in normal, glaucomatous, and ocular hypertensive eyes. *Arch Ophthalmol* 115: 1137-1141.

Herndon L W, Weizer J S, and Stinnett S S (2004) Central corneal thickness as a risk factor for advanced glaucoma damage. *Arch Ophthalmol* 122: 17-21.

Hestnes A, Sand T, and Fostad K (1991) Ocular findings in Down's syndrome. *J Ment Defic Res* 35 (Pt 3): 194-203.

Hewitt A W, and Cooper R L (2005) Relationship between corneal thickness and optic disc damage in glaucoma. *Clin Experiment Ophthalmol* 33: 158-163.

Higgins K E, Jaffe M J, Coletta N J, Caruso R C, and de Monasterio F M (1984) Spatial contrast sensitivity. Importance of controlling the patient's visibility criterion. *Arch Ophthalmol* 102: 1035-1041.

Higgins S E, Fishbaugh J A, Strike D J, and Rapuano C J (1993) Reproducibility and variation of corneal thickness in different locations in the cornea as measured by an ultrasonic pachymeter. *Insight* 18: 14-18.

Hirsch M J (1964) Predictability of Refraction at Age 14 on the Basis of Testing at Age 6--Interim Report from the Ojai Longitudinal Study of Refraction. *Am J Optom Arch Am Acad Optom* 41: 567-573.

Hodapp R, and Zigler E (1990) Applying the developmental perspective to individuals with Down Syndrome. *Children with Down Syndrome: a developmental perspective*. Cambridge: Cambridge University Press. pp. 1-28

Hodge J V, Parr J C, and Spears G F (1969) Comparison of methods of measuring vessel widths on retinal photographs and the effect of fluorescein injection on apparent retinal vessel calibers. *Am J Ophthalmol* 68: 1060-1068.

Holladay J T (1997) Corneal topography using the Holladay Diagnostic Summary. *J Cataract Refract Surg* 23: 209-221.

Holland D R, Maeda N, Hannush S B, Riveroll L H, Green M T, Klyce S D, and Wilson S E (1997) Unilateral keratoconus. Incidence and quantitative topographic analysis. *Ophthalmology* 104: 1409-1413.

Hollows F C, and Graham P A (1966) Intra-ocular pressure, glaucoma, and glaucoma suspects in a defined population. *Br J Ophthalmol* 50: 570-586.

Hubbard L D, Brothers R J, King W N, Clegg L X, Klein R, Cooper L S, Sharrett A R et al. (1999) Methods for evaluation of retinal microvascular abnormalities associated with hypertension/sclerosis in the Atherosclerosis Risk in Communities Study. *Ophthalmology* 106: 2269-2280.

Hulsman C A, Houwing-Duistermaat J J, Van Duijn C M, Wolfs R, Borger P H, Hofman A, and De Jong P T (2002) Family score as an indicator of genetic risk of primary open-angle glaucoma. *Arch Ophthalmol* 120: 1726-1731.

Hussein M A, Paysse E A, Bell N P, Coats D K, Brady McCreery K M, Koch D D, Orengo-Nania S et al. (2004) Corneal thickness in children. *Am J Ophthalmol* 138: 744-748.

Hustead J D (1993) Detection of keratoconus before keratorefractive surgery. *Ophthalmology* 100: 975.

Hyman L, Gwiazda J, Hussein M, Norton T T, Wang Y, Marsh-Tootle W, and Everett D (2005) Relationship of age, sex, and ethnicity with myopia progression

and axial elongation in the correction of myopia evaluation trial. *Arch Ophthalmol* 123: 977-987.

Ieong A, Murdoch I, Cousens S, Healey P, and Theodossiades J (2003) Sensitivity and specificity of two glaucoma case-finding strategies for optometrists. *Ophthalmic Physiol Opt* 23: 341-346.

Igersheimer J, and Mautner H (1951) About changes of the crystalline lens in mongoloids. *Am J Ment Defic* 55: 370-376.

Iliyasu Z, Gilmour W H, and Stone D H (2002) Prevalence of Down syndrome in Glasgow, 1980-96--the growing impact of prenatal diagnosis on younger mothers. *Health Bull (Edinb)* 60: 20-26.

Ingram R M, and Barr A (1979) Changes in refraction between the ages of 1 and 3 1/2 years. *Br J Ophthalmol* 63: 339-342.

Isenberg S J, Del Signore M, and Madani-Becker G (2001) Use of the HARK autorefractor in children. *Am J Ophthalmol* 131: 438-441.

Iuorno J D, Grant W D, and Noel L P (2004) Clinical comparison of the Welch Allyn SureSight handheld autorefractor versus cycloplegic autorefraction and retinoscopic refraction. *J Aapos* 8: 123-127.

Iwasaki T (1993) Effects of a visual task with cognitive demand on dynamic and steady-state accommodation. *Ophthalmic Physiol Opt* 13: 285-290.

Jacoby B, Reed J W, and Cashwell L F (1990) Malignant glaucoma in a patient with Down's syndrome and corneal hydrops. *Am J Ophthalmol* 110: 434-435.

Jaeger E A (1980) Ocular findings in Down's syndrome. *Trans Am Ophthalmol Soc* 78: 808-845.

Jahnke M, Wirbelauer C, and Pham D T (2006) [Influence of age on optical aberrations of the human eye.]. *Ophthalmologe.*

Jean-Louis S, Lovasik J V, and Kergoat H (2005) Systemic hyperoxia and retinal vasomotor responses. *Invest Ophthalmol Vis Sci* 46: 1714-1720.

John F M, Bromham N R, Woodhouse J M, and Candy T R (2004) Spatial vision deficits in infants and children with Down syndrome. *Invest Ophthalmol Vis Sci* 45: 1566-1572.

Johnson C A, Sample P A, Zangwill L M, Vasile C G, Cioffi G A, Liebmann J R, and Weinreb R N (2003) Structure and function evaluation (SAFE): II. Comparison of optic disk and visual field characteristics. *Am J Ophthalmol* 135: 148-154.

Johnson P C (1986) Autoregulation of blood flow. *Circ Res* 59: 483-495.

Johnson R C, and Abelson R B (1969) Intellectual, behavioral, and physical characteristics associated with trisomy, translocation, and mosaic types of Down's syndrome. *Am J Ment Defic* 73: 852-855.

Johnson Z, Lillis D, Delany V, Hayes C, and Dack P (1996) The epidemiology of Down syndrome in four counties in Ireland 1981-1990. *J Public Health Med* 18: 78-86.

Jonas J B (2005a) Clinical implications of peripapillary atrophy in glaucoma. *Curr Opin Ophthalmol* 16: 84-88.

Jonas J B (2005b) Optic disk size correlated with refractive error. *Am J Ophthalmol* 139: 346-348.

Jonas J B, Berenshtein E, and Holbach L (2004a) Lamina cribrosa thickness and spatial relationships between intraocular space and cerebrospinal fluid space in highly myopic eyes. *Invest Ophthalmol Vis Sci* 45: 2660-2665.

Jonas J B, and Budde W M (2002) Is the nasal optic disc sector important for morphometric glaucoma diagnosis? *Br J Ophthalmol* 86: 1232-1235.

Jonas J B, Budde W M, Nemeth J, Grundler A E, Mistlberger A, and Hayler J K (2001) Central retinal vessel trunk exit and location of glaucomatous parapapillary atrophy in glaucoma. *Ophthalmology* 108: 1059-1064.

Jonas J B, Budde W M, and Panda-Jonas S (1999) Ophthalmoscopic evaluation of the optic nerve head. *Surv Ophthalmol* 43: 293-320.

Jonas J B, and Dichtl A (1996) Evaluation of the retinal nerve fiber layer. *Surv Ophthalmol* 40: 369-378.

Jonas J B, and Fernandez M C (1994) Shape of the neuroretinal rim and position of the central retinal vessels in glaucoma. *Br J Ophthalmol* 78: 99-102.

Jonas J B, and Grundler A E (1998) Prevalence of diabetes mellitus and arterial hypertension in primary and secondary open-angle glaucomas. *Graefes Arch Clin Exp Ophthalmol* 236: 202-206.

Jonas J B, Gusek G C, Guggenmoos-Holzmann I, and Naumann G O (1988a) Size of the optic nerve scleral canal and comparison with intravital determination of optic disc dimensions. *Graefes Arch Clin Exp Ophthalmol* 226: 213-215.

Jonas J B, Gusek G C, and Naumann G O (1988b) Optic disc, cup and neuroretinal rim size, configuration and correlations in normal eyes. *Invest Ophthalmol Vis Sci* 29: 1151-1158.

Jonas J B, Gusek G C, and Naumann G O (1988) Optic disk morphometry in high myopia. *Graefes Arch Clin Exp Ophthalmol* 226: 587-590.

Jonas J B, Gusek G C, and Naumann G O (1988c) [Parapapillary diameter of retinal vessels. I. Estimating the size of the optic papilla (a papillometric study of over 264 normal eyes)]. *Klin Monatsbl Augenheilkd* 192: 325-328.

Jonas J B, Gusek G C, and Naumann G O (1989a) [Correlation of intra- and para-papillary glaucomatous changes--a planimetric study of 200 normal and 450 glaucoma eyes]. *Fortschr Ophthalmol* 86: 95-98.

Jonas J B, and Konigsreuther K A (1994) Optic disk appearance in ocular hypertensive eyes. *Am J Ophthalmol* 117: 732-740.

Jonas J B, Martus P, Horn F K, Junemann A, Korth M, and Budde W M (2004b) Predictive factors of the optic nerve head for development or progression of glaucomatous visual field loss. *Invest Ophthalmol Vis Sci* 45: 2613-2618.

Jonas J B, Nguyen N X, and Naumann G O (1989b) Optic disc morphometry in simple optic nerve atrophy. *Acta Ophthalmol (Copenh)* 67: 199-203.

Jonas J B, Nguyen X N, and Naumann G O (1989c) Parapapillary retinal vessel diameter in normal and glaucoma eyes. I. Morphometric data. *Invest Ophthalmol Vis Sci* 30: 1599-1603.

Jonas J B, and Papastathopoulos K I (1996) Optic disc shape in glaucoma. *Graefes Arch Clin Exp Ophthalmol* 234 Suppl 1: S167-173.

Jonas J B, and Schiro D (1993) Visibility of the normal retinal nerve fiber layer correlated with rim width and vessel caliber. *Graefes Arch Clin Exp Ophthalmol* 231: 207-211.

Jonas J B, Schmidt A M, Muller-Bergh J A, Schlotzer-Schrehardt U M, and Naumann G O (1992) Human optic nerve fiber count and optic disc size. *Invest Ophthalmol Vis Sci* 33: 2012-2018.

Jones D, Westall C, Averbeck K, and Abdolell M (2003) Visual acuity assessment: a comparison of two tests for measuring children's vision. *Ophthalmic Physiol Opt* 23: 541-546.

Jones L A, Mitchell G L, Mutti D O, Hayes J R, Moeschberger M L, and Zadnik K (2005) Comparison of ocular component growth curves among refractive error groups in children. *Invest Ophthalmol Vis Sci* 46: 2317-2327.

Junghans B, Kiely P M, Crewther D P, and Crewther S G (2002) Referral rates for a functional vision screening among a large cosmopolitan sample of Australian children. *Ophthalmic Physiol Opt* 22: 10-25.

Kallen B, Mastroiacovo P, and Robert E (1996) Major congenital malformations in Down syndrome. *Am J Med Genet* 65: 160-166.

Karlsson B, Gustafsson J, Hedov G, Ivarsson S A, and Anneren G (1998) Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. *Arch Dis Child* 79: 242-245.

Kashiwagi K, Tamura M, Abe K, Kogure S, and Tsukahara S (2000) The influence of age, gender, refractive error, and optic disc size on the optic disc configuration in Japanese normal eyes. *Acta Ophthalmol Scand* 78: 200-203.

Kass M A, Hart W M, Jr., Gordon M, and Miller J P (1980) Risk factors favoring the development of glaucomatous visual field loss in ocular hypertension. *Surv Ophthalmol* 25: 155-162.

Katuzny B J, and Koszewska-Kolodziejczak A (2005) [Changes of axial dimensions of the eye during growth in emmetropia, myopia and hyperopia]. *Klin Oczna* 107: 292-296.

Kenue R K, Raj A K, Harris P F, and el-Bualy M S (1995) Cytogenetic analysis of children suspected of chromosomal abnormalities. *J Trop Pediatr* 41: 77-80.

Kielhorn I, Rajan M S, Tesha P M, Subryan V R, and Bell J A (2003) Clinical assessment of the Zeiss IOLMaster. *J Cataract Refract Surg* 29: 518-522.

Kiely P M, Carney L G, and Smith G (1982) Diurnal variations of corneal topography and thickness. *Am J Optom Physiol Opt* 59: 976-982.

Kiely P M, Smith G, and Carney L G (1984) Meridional variations of corneal shape. *Am J Optom Physiol Opt* 61: 619-626.

Kim J H, Hwang J M, Kim H J, and Yu Y S (2002) Characteristic ocular findings in Asian children with Down syndrome. *Eye* 16: 710-714.

Klein B E, Klein R, Sponsel W E, Franke T, Cantor L B, Martone J, and Menage M J (1992) Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 99: 1499-1504.

Klein R, Klein B E, Moss S E, Wong T Y, Hubbard L, Cruickshanks K J, and Palta M (2004a) The relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy: XIX: the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *Arch Ophthalmol* 122: 76-83.

Klein R, Klein B E, Tomany S C, and Wong T Y (2004b) The relation of retinal microvascular characteristics to age-related eye disease: the Beaver Dam eye study. *Am J Ophthalmol* 137: 435-444.

Klein S A, and Barsky B A (1995) Method for generating the anterior surface of an aberration-free contact lens for an arbitrary posterior surface. *Optom Vis Sci* 72: 816-820.

Klyce S D, Smolek M K, and Maeda N (2000) Keratoconus detection with the KISA% method-another view. *J Cataract Refract Surg* 26: 472-474.

Kontiola A, and Puska P (2004) Measuring intraocular pressure with the Pulsair 3000 and Rebound tonometers in elderly patients without an anesthetic. *Graefes Arch Clin Exp Ophthalmol* 242: 3-7.

Kontiola A I (2000) A new induction-based impact method for measuring intraocular pressure. *Acta Ophthalmol Scand* 78: 142-145.

Kontiola A I, Goldblum D, Mittag T, and Danias J (2001) The induction/impact tonometer: a new instrument to measure intraocular pressure in the rat. *Exp Eye Res* 73: 781-785.

Krachmer J H, Feder R S, and Belin M W (1984) Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol* 28: 293-322.

Kruger P B, and Pola J (1987) Dioptric and non-dioptric stimuli for accommodation: Target size alone and with blur and chromatic aberration. *Vision Research* 27: 555-567.

Kumin L (1996) Speech and language skills in children with Down syndrome.*Mental Retardation and Developmental Disabilities Research Reviews*. pp. 109-115.

Kurtz D, Manny R, and Hussein M (2004) Variability of the ocular component measurements in children using A-scan ultrasonography. *Optom Vis Sci* 81: 35-43.

Lam A K, Chan C C, Lee M H, and Wong K M (1999) The aging effect on corneal curvature and the validity of Javal's rule in Hong Kong Chinese. *Curr Eye Res* 18: 83-90.

Lam A K, Chan R, and Pang P C (2001) The repeatability and accuracy of axial length and anterior chamber depth measurements from the IOLMaster. *Ophthalmic Physiol Opt* 21: 477-483.

Lamoureux E L, Lo K, Ferraro J G, Constantinou M, Keeffe J E, Muller A, and Taylor H R (2006) The Agreement between the Heidelberg Retina Tomograph and

a Digital Nonmydriatic Retinal Camera in Assessing Area Cup-to-Disc Ratio. *Invest Ophthalmol Vis Sci* 47: 93-98.

Langenbucher A, Seitz B, and Viestenz A (2003) Computerised calculation scheme for ocular magnification with the Zeiss telecentric fundus camera. *Ophthalmic Physiol Opt* 23: 449-455.

Lawson-Kopp W, DeJong A, Yudcovitch L, Williams S, Kohl P, and Yolton R L (2002) Clinical evaluation of the Keeler Pulsair 3000 non-contact tonometer. *Optometry* 73: 81-90.

Leat S J, and Gargon J L (1996) Accommodative response in children and young adults using dynamic retinoscopy. *Ophthalmic Physiol Opt* 16: 375-384.

Leat S J, Shute R, H., and Westall C, A. (1999) *Assessing children's vision - a handbook*. Oxford: Butterworth-heinemann:

Lee S S, and Schwartz B (1992) Role of the temporal cilioretinal artery in retaining central visual field in open-angle glaucoma. *Ophthalmology* 99: 696-699.

Leiva M, Naranjo C, and Pena M T (2006) Comparison of the rebound tonometer (ICare) to the applanation tonometer (Tonopen XL) in normotensive dogs. *Vet Ophthalmol* 9: 17-21.

Lejeune J, Turpin R, and Gautier M (1959) [Chromosomic diagnosis of mongolism.]. *Arch Fr Pediatr* 16: 962-963.

Lempert P (2003) Axial length-disc area ratio in esotropic amblyopia. *Arch Ophthalmol* 121: 821-824.

Leske M C, Warheit-Roberts L, and Wu S Y (1996) Open-angle glaucoma and ocular hypertension: the Long Island Glaucoma Case-control Study. *Ophthalmic Epidemiol* 3: 85-96.

Li S W, Li Z X, Shi W Y, Zeng Q Y, and Jin X M (2005) [Clinical features of 233 cases of keratoconus]. *Zhonghua Yan Ke Za Zhi* 41: 610-613.

Lin Z, Ye X, Chen X, Dai Z, and Guan Z (2003) [Refractive error and the intraocular pressure: findings in the Chinese eyes]. *Yan Ke Xue Bao* 19: 208-210, 220.

Lindsay R, Smith G, and Atchison D (1998) Descriptors of corneal shape. *Optom Vis Sci* 75: 156-158.

Littmann H (1982) [Determination of the real size of an object on the fundus of the living eye]. *Klin Monatsbl Augenheilkd* 180: 286-289.

Liu Z, Huang A J, and Pflugfelder S C (1999) Evaluation of corneal thickness and topography in normal eyes using the Orbscan corneal topography system. *Br J Ophthalmol* 83: 774-778.

Liza-Sharmini A T, Azlan Z N, and Zilfalil B A (2006) Ocular findings in Malaysian children with Down syndrome. *Singapore Med J* 47: 14-19.

Llorente L, Barbero S, Cano D, Dorronsoro C, and Marcos S (2004) Myopic versus hyperopic eyes: axial length, corneal shape and optical aberrations. *J Vis* 4: 288-298.

Logan N S, Davies L N, Mallen E A, and Gilmartin B (2005) Ametropia and ocular biometry in a U.K. university student population. *Optom Vis Sci* 82: 261-266.

Lowe R (1949) The eyes in mongolism. *Br J Ophthalmol*: 131-174.

Lyle W M, Woodruff M E, and Zuccaro V S (1972) A review of the literature on Down's syndrome and an optometrical survey of 44 patients with the syndrome. *Am J Optom Arch Am Acad Optom* 49: 715-727.

Maberley D, Morris A, Hay D, Chang A, Hall L, and Mandava N (2004) A comparison of digital retinal image quality among photographers with different levels of training using a non-mydriatic fundus camera. *Ophthalmic Epidemiol* 11: 191-197.

Mackie S W, Jay J L, Ackerley R, and Walsh G (1996) Clinical comparison of the Keeler Pulsair 2000, American Optical MkII and Goldmann applanation tonometers. *Ophthalmic Physiol Opt* 16: 171-177.

Maddock R J, Millodot M, Leat S, and Johnson C A (1981) Accommodation responses and refractive error. *Invest Ophthalmol Vis Sci* 20: 387-391.

Maeda N, Klyce S D, and Smolek M K (1995) Comparison of methods for detecting keratoconus using videokeratography. *Arch Ophthalmol* 113: 870-874.

Maeda N, Klyce S D, Smolek M K, and Thompson H W (1994) Automated keratoconus screening with corneal topography analysis. *Invest Ophthalmol Vis Sci* 35: 2749-2757.

Maguire L J, and Bourne W M (1989) Corneal topography of early keratoconus. *Am J Ophthalmol* 108: 107-112.

Maguire L J, and Lowry J C (1991) Identifying progression of subclinical keratoconus by serial topography analysis. *Am J Ophthalmol* 112: 41-45.

Mahoney G, Fors S, and Wood S (1990) Maternal directive behavior revisited. *Am J Ment Retard* 94: 398-406.

Mansour A M (1992) Racial variation of optic disc parameters in children. *Ophthalmic Surg* 23: 469-471.

Mansour A M, Bitar F F, Traboulsi E I, Kassak K M, Obeid M Y, Megarbane A, and Salti H I (2005) Ocular pathology in congenital heart disease. *Eye* 19: 29-34.

Marino B, & Pueschel,S.M (1996) *Heart diseases in person with Down syndrome.* Paul H. Brookers Publishing Co.

Martus P, Stroux A, Budde W M, Mardin C Y, Korth M, and Jonas J B (2005) Predictive factors for progressive optic nerve damage in various types of chronic open-angle glaucoma. *Am J Ophthalmol* 139: 999-1009.

Massin P, Erginay A, Ben Mehidi A, Vicaut E, Quentel G, Victor Z, Marre M et al. (2003) Evaluation of a new non-mydriatic digital camera for detection of diabetic retinopathy. *Diabet Med* 20: 635-641.

Matsumoto C, Shirato S, Haneda M, Yamashiro H, and Saito M (2003) Study of retinal nerve fiber layer thickness within normal hemivisual field in primary open-angle glaucoma and normal-tension glaucoma. *Jpn J Ophthalmol* 47: 22-27.

Matsumoto T, Makino H, Uozato H, Saishin M, and Miyamoto S (2000) The Influence of Corneal Thickness and Curvature on the Difference Between Intraocular Pressure Measurements Obtained with a Non-contact Tonometer and Those with a Goldmann Applanation Tonometer. *Jpn J Ophthalmol* 44: 691.

Matsuno K, Kurimoto Y, Umihira J, Hoya T, and Yoshimura N (2001) Comparative study of retinal nerve fiber layer loss in normal-tension glaucoma and chronic open-angle glaucoma. *Ophthalmologica* 215: 108-112.

McBrien N A, and Barnes D A (1984) A review and evaluation of theories of refractive error development. *Ophthalmic Physiol Opt* 4: 201-213.

McClellan K A, and Billson F A (1988) Spontaneous onset of ciliary block glaucoma in acute hydrops in Down's syndrome. *Aust N Z J Ophthalmol* 16: 325-327.

McClelland J F, and Saunders K J (2003) The repeatability and validity of dynamic retinoscopy in assessing the accommodative response. *Ophthalmic Physiol Opt* 23: 243-250.

McLeod S D, West S K, Quigley H A, and Fozard J L (1990) A longitudinal study of the relationship between intraocular and blood pressures. *Invest Ophthalmol Vis Sci* 31: 2361-2366.

Medeiros F A, Sample P A, and Weinreb R N (2003) Corneal thickness measurements and visual function abnormalities in ocular hypertensive patients. *Am J Ophthalmol* 135: 131-137.

Meinhardt B, Stachs O, Stave J, Beck R, and Guthoff R (2005) Evaluation of biometric methods for measuring the anterior chamber depth in the non-contact mode. *Graefes Arch Clin Exp Ophthalmol*: 1-6.

Melville C A, Cooper S A, McGrother C W, Thorp C F, and Collacott R (2005) Obesity in adults with Down syndrome: a case-control study. *J Intellect Disabil Res* 49: 125-133.

Merin S, and Crawford J S (1971) The etiology of congenital cataracts. A survey of 386 cases. *Can J Ophthalmol* 6: 178-182.

Metneki J, and Czeizel A E (2005) Increasing total prevalence rate of cases with Down syndrome in Hungary. *Eur J Epidemiol* 20: 525-535.

Meyer F, Renard J P, Roux L, Rigal-Sastourne J C, Tuil A, Dot C, May F et al. (2001) [Value of a new non-contact biometer for intraocular crystalline lens power calculation]. *J Fr Ophtalmol* 24: 1060-1066.

Meyer J H, Brandi-Dohrn J, and Funk J (1996) Twenty four hour blood pressure monitoring in normal tension glaucoma. *Br J Ophthalmol* 80: 864-867.

Miglior S, Albe E, Guareschi M, Rossetti L, and Orzalesi N (2002) Intraobserver and interobserver reproducibility in the evaluation of optic disc stereometric parameters by Heidelberg Retina Tomograph. *Ophthalmology* 109: 1072-1077.

Miller S J (1978) Genetics of glaucoma and family studies. *Trans Ophthalmol Soc U K* 98: 290-292.

Mills R P (2000) If intraocular pressure measurement is only an estimate-then what? *Ophthalmology* 107: 1807-1808.

Milunsky A, and Neurath P W (1968) Diabetes mellitus in Down's Syndrome. *Arch Environ Health* 17: 372-376.

Mitchell P, Cumming R G, and Mackey D A (1999) Inhaled corticosteroids, family history, and risk of glaucoma. *Ophthalmology* 106: 2301-2306.

Mitchell P, Leung H, Wang J J, Rochtchina E, Lee A J, Wong T Y, and Klein R (2005) Retinal vessel diameter and open-angle glaucoma: the Blue Mountains Eye Study. *Ophthalmology* 112: 245-250.

Mitschischek E (1991) [Ciliary perfusion pressure in primary open angle glaucoma]. *Klin Monatsbl Augenheilkd* 199: 264-266.

Mohindra I, and Molinari J F (1979) Near retinoscopy and cycloplegic retinoscopy in early primary grade schoolchildren. *Am J Optom Physiol Opt* 56: 34-38.

Moll A C, Imhof S M, Bouter L, den Otter W, and Koten J W (2002) An infant with Down syndrome and retinoblastoma. A possible non-fortuitous association. *Ophthalmic Genet* 23: 135-136.

Morgan J E (2000) Optic nerve head structure in glaucoma: astrocytes as mediators of axonal damage. *Eye* 14 (Pt 3B): 437-444.

Morgan J E, Sheen N J, North R V, Choong Y, and Ansari E (2005a) Digital imaging of the optic nerve head: monoscopic and stereoscopic analysis. *Br J Ophthalmol* 89: 879-884.

Morgan J E, Sheen N J, North R V, Goyal R, Morgan S, Ansari E, and Wild J M (2005b) Discrimination of glaucomatous optic neuropathy by digital stereoscopic analysis. *Ophthalmology* 112: 855-862.

Morris J K, Mutton D E, Ide R, Alberman E, and Bobrow M (1994) Monitoring trends in prenatal diagnosis of Down's syndrome in England and Wales, 1989-92. *J Med Screen* 1: 233-237.

Moses R A (1961) Repeated applanation tonometry. *Ophthalmologica* 142: 663-668.

Murgatroyd H, Ellingford A, Cox A, Binnie M, Ellis J D, MacEwen C J, and Leese G P (2004) Effect of mydriasis and different field strategies on digital image screening of diabetic eye disease. *Br J Ophthalmol* 88: 920-924.

Mutti D O, Jones L A, Moeschberger M L, and Zadnik K (2000) AC/A ratio, age, and refractive error in children. *Invest Ophthalmol Vis Sci* 41: 2469-2478.

Mutti D O, Mitchell G L, Moeschberger M L, Jones L A, and Zadnik K (2002) Parental myopia, near work, school achievement, and children's refractive error. *Invest Ophthalmol Vis Sci* 43: 3633-3640.

Mutti D O, and Zadnik K (1996) Is computer use a risk factor for myopia? *J Am Optom Assoc* 67: 521-530.

Mutti D O, Zadnik K, and Adams A J (1996) Myopia. The nature versus nurture debate goes on. *Invest Ophthalmol Vis Sci* 37: 952-957.

Mutti D O, Zadnik K, Egashira S, Kish L, Twelker J D, and Adams A J (1994) The effect of cycloplegia on measurement of the ocular components. *Invest Ophthalmol Vis Sci* 35: 515-527.

Mutton D E, Alberman E, Ide R, and Bobrow M (1991) Results of first year (1989) of a national register of Down's syndrome in England and Wales. *Bmj* 303: 1295-1297.

Myrelid A, Gustafsson J, Ollars B, and Anneren G (2002) Growth charts for Down's syndrome from birth to 18 years of age. *Arch Dis Child* 87: 97-103.

Nadel L (2003) Down's syndrome: a genetic disorder in biobehavioral perspective. *Genes Brain Behav* 2: 156-166.

Naroo S, and Morgan P (1997) Corneal topography of a family with known keratoconic patients. *Contact Lens and Anterior Eye* 20: 170.

Nevarez J, Rockwood E J, and Anderson D R (1988) The configuration of peripapillary tissue in unilateral glaucoma. *Arch Ophthalmol* 106: 901-903.

Newsom R S, Sullivan P M, Rassam S M, Jagoe R, and Kohner E M (1992) Retinal vessel measurement: comparison between observer and computer driven methods. *Graefes Arch Clin Exp Ophthalmol* 230: 221-225.

Nguyen N X, Horn F K, Langenbucher A, and Mardin C Y (2001) [Conventional versus digital planimetry of optic disc photograph: a clinical comparative study]. *Klin Monatsbl Augenheilkd* 218: 727-732.

Nicholson A, and Alberman E (1992) Prediction of the number of Down's syndrome infants to be born in England and Wales up to the year 2000 and their likely survival rates. *J Intellect Disabil Res* 36 (Pt 6): 505-517.

Nomura H, Ando F, Niino N, Shimokata H, and Miyake Y (2004) The relationship between intraocular pressure and refractive error adjusting for age and central corneal thickness. *Ophthalmic Physiol Opt* 24: 41-45.

O'Donnell C, and Maldonado-Codina C (2005) Agreement and repeatability of central thickness measurement in normal corneas using ultrasound pachymetry and the OCULUS Pentacam. *Cornea* 24: 920-924.

Ohyama Y, Utsugi T, Uchiyama T, Hanaoka T, Tomono S, and Kurabayashi M (2000) Prevalence of diabetes in adult patients with Down's syndrome living in a residential home. *Diabetes Care* 23: 705-706.

Ojaimi E, Morgan I G, Robaei D, Rose K A, Smith W, Rochtchina E, and Mitchell P (2005) Effect of stature and other anthropometric parameters on eye size and refraction in a population-based study of Australian children. *Invest Ophthalmol Vis Sci* 46: 4424-4429.

Olbert D, and Kehrhahn O H (1992) Biometric constancy of the anterior eye segment as demonstrated by slit image photography according to the Scheimpflug principle. *Ophthalmic Res* 24: 27-31.

Oller D K, and Seibert J M (1988) Babbling of prelinguistic mentally retarded children. *Am J Ment Retard* 92: 369-375.

Olsen C L, Cross P K, Gensburg L J, and Hughes J P (1996) The effects of prenatal diagnosis, population ageing, and changing fertility rates on the live birth prevalence of Down syndrome in New York State, 1983-1992. *Prenat Diagn* 16: 991-1002.

Olsen T, and Thorwest M (2005) Calibration of axial length measurements with the Zeiss IOLMaster. *J Cataract Refract Surg* 31: 1345-1350.

Orssengo G J, and Pye D C (1999) Determination of the true intraocular pressure and modulus of elasticity of the human cornea in vivo. *Bulletin of Mathematical Biology* 61: 551-572.

Oshika T, Klyce S D, Applegate R A, and Howland H C (1999) Changes in corneal wavefront aberrations with aging. *Investigative Ophthalmology & Visual Science* 40: 1351-1355.

Osuobeni E P (1999) Ocular components values and their intercorrelations in Saudi Arabians. *Ophthalmic Physiol Opt* 19: 489-497.

Owens D A, Mohindra I, and Held R (1980) The effectiveness of a retinoscope beam as an accommodative stimulus. *Invest Ophthalmol Vis Sci* 19: 942-949.

Pallant J (2001) *SPSS Survival Manual*. Buckingham: Open University Press.

Panda-Jonas S, Jonas J B, and Jakobczyk-Zmija M (1996) Retinal pigment epithelial cell count, distribution, and correlations in normal human eyes. *Am J Ophthalmol* 121: 181-189.

Panda-Jonas S, Jonas J B, Jakobczyk M, and Schneider U (1994) Retinal photoreceptor count, retinal surface area, and optic disc size in normal human eyes. *Ophthalmology* 101: 519-523.

Pang C P, Fan B J, Canlas O, Wang D Y, Dubois S, Tam P O, Lam D S et al. (2006) A genome-wide scan maps a novel juvenile-onset primary open angle glaucoma locus to chromosome 5q. *Mol Vis* 12: 85-92.

Papastathopoulos K I, Jonas J B, and Panda-Jonas S (1995) Large optic discs in large eyes, small optic discs in small eyes. *Exp Eye Res* 60: 459-461.

Pardhan S, and Beesley J (1999) Measurement of corneal curvature in young and older normal subjects. *J Refract Surg* 15: 469-474.

Parentin F, Tonini G, and Perissutti P (2004) Refractive evaluation in children with growth defect. *Curr Eye Res* 28: 11-15.

Park K H, Tomita G, Liou S Y, and Kitazawa Y (1996) Correlation between peripapillary atrophy and optic nerve damage in normal-tension glaucoma. *Ophthalmology* 103: 1899-1906.

Parr J C, and Spears G F (1974) General caliber of the retinal arteries expressed as the equivalent width of the central retinal artery. *Am J Ophthalmol* 77: 472-477.

Parrow K A, Shin D H, Tsai C S, Hong Y J, Juzych M S, and Shi D X (1992) Intraocular pressure-dependent dynamic changes of optic disc cupping in adult glaucoma patients. *Ophthalmology* 99: 36-40.

Perez-Carpinell J, de Fez M D, and Climent V (1994) Vision evaluation in people with Down's syndrome. *Ophthalmic Physiol Opt* 14: 115-121.

Perkins E S, and Phelps C D (1982) Open angle glaucoma, ocular hypertension, low-tension glaucoma, and refraction. *Arch Ophthalmol* 100: 1464-1467.

Pesudovs K (2004) Autorefraction as an outcome measure of laser in situ keratomileusis. *J Cataract Refract Surg* 30: 1921-1928.

Petrie A, and Csabin C (2005) *Medical statistical at a glance*. 2nd ed. Malden, Oxford, Carlton: Blackwell Publishing Ltd.

Pierro L, Camesasca F I, Mischi M, and Brancato R (1992) Peripheral retinal changes and axial myopia. *Retina* 12: 12-17.

Pierse D, and Eustace P (1971) Acute keratoconus in mongols. *Br J Ophthalmol* 55: 50-54.

Pohjanpelto P E, and Palva J (1974) Ocular hypertension and glaucomatous optic nerve damage. *Acta Ophthalmol (Copenh)* 52: 194-200.

Poinoosawmy D, Fontana L, Wu J X, Bunce C V, and Hitchings R A (1998) Frequency of asymmetric visual field defects in normal-tension and high-tension glaucoma. *Ophthalmology* 105: 988-991.

Pointer J S (2001) A 6-year longitudinal optometric study of the refractive trend in school-aged children. *Ophthalmic Physiol Opt* 21: 361-367.

Poissonnier M, Saint-Paul B, Dutrillaux B, Chassaigne M, Gruyer P, and de Blignieres-Strouk G (1976) [Partial trisomy 21 (21q21 - 21q22.2)]. *Ann Genet* 19: 69-73.

Porter J, Guirao A, Cox I G, and Williams D R (2001) Monochromatic aberrations of the human eye in a large population. *J Opt Soc Am A Opt Image Sci Vis* 18: 1793-1803.

Prasher V P (1999) Down syndrome and thyroid disorders: a review. *Downs Syndr Res Pract* 6: 25-42.

Pueschel S M, Scola F H, and Pezzullo J C (1992) A longitudinal study of atlanto-dens relationships in asymptomatic individuals with Down syndrome. *Pediatrics* 89: 1194-1198.

Quigley H A (1996) Number of people with glaucoma worldwide. *Br J Ophthalmol* 80: 389-393.

Quigley H A, Addicks E M, and Green W R (1982) Optic nerve damage in human glaucoma. III. Quantitative correlation of nerve fiber loss and visual field defect in glaucoma, ischemic neuropathy, papilledema, and toxic neuropathy. *Arch Ophthalmol* 100: 135-146.

Quigley H A, Brown A, and Dorman-Pease M E (1991) Alterations in elastin of the optic nerve head in human and experimental glaucoma. *Br J Ophthalmol* 75: 552-557.

Quigley H A, Dunkelberger G R, and Green W R (1989) Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. *Am J Ophthalmol* 107: 453-464.

Quigley H A, Varma R, Tielsch J M, Katz J, Sommer A, and Gilbert D L (1999) The relationship between optic disc area and open-angle glaucoma: the Baltimore Eye Survey. *J Glaucoma* 8: 347-352.

Quigley M G, and Dube P (2003) A new fundus camera technique to help calculate eye-camera magnification: a rapid means to measure disc size. *Arch Ophthalmol* 121: 707-709.

Quinn G E, Francis E L, Nipper K S, Flitcroft D I, Ying G S, Rees R C, Schmid G F et al. (2003) Highly precise eye length measurements in children aged 3 through 12 years. *Arch Ophthalmol* 121: 985-990.

Rabinowitz Y S (1993) Corneal topography. *Curr Opin Ophthalmol* 4: 68-74.

Rabinowitz Y S (1998) Keratoconus. *Surv Ophthalmol* 42: 297-319.

Rabinowitz Y S, Garbus J, and McDonnell P J (1990) Computer-assisted corneal topography in family members of patients with keratoconus. *Arch Ophthalmol* 108: 365-371.

Rabinowitz Y S, Maumenee I H, Lundergan M K, Puffenberger E, Zhu D, Antonarakis S, and Francomano C A (1992) Molecular genetic analysis in autosomal dominant keratoconus. *Cornea* 11: 302-308.

Rabinowitz Y S, and McDonnell P J (1989) Computer-assisted corneal topography in keratoconus. *Refract Corneal Surg* 5: 400-408.

Rabinowitz Y S, Nesburn A B, and McDonnell P J (1993) Videokeratography of the fellow eye in unilateral keratoconus. *Ophthalmology* 100: 181-186.

Rabinowitz Y S, and Rasheed K (1999) KISA% index: a quantitative videokeratography algorithm embodying minimal topographic criteria for diagnosing keratoconus. *J Cataract Refract Surg* 25: 1327-1335.

Rabinowitz YS ZUL Y H, Wang Y, Rotter J (1999) Keratoconus: non-parametric linkage analysis suggests a gene locus near the centromere of chromosome 21. *Invest Ophthalmol Vis Sci* 40: suppl564.

Rassam S M, Patel V, Chen H C, and Kohner E M (1996) Regional retinal blood flow and vascular autoregulation. *Eye* 10 (Pt 3): 331-337.

Recep O F, Hasiripi H, Cagil N, and Sarikatipoglu H (2001) Relation between corneal thickness and intraocular pressure measurement by noncontact and applanation tonometry. *J Cataract Refract Surg* 27: 1787-1791.

Recep O F, Hasiripi H, Vayisoglu E, Kalayci D, and Sarikatipoglu H (1998) Accurate time interval in repeated tonometry. *Acta Ophthalmol Scand* 76: 603-605.

Rezaie T, Child A, Hitchings R, Brice G, Miller L, Coca-Prados M, Heon E et al. (2002) Adult-onset primary open-angle glaucoma caused by mutations in optineurin. *Science* 295: 1077-1079.

Richards D W, Russell S R, and Anderson D R (1988) A method for improved biometry of the anterior chamber with a Scheimpflug technique. *Invest Ophthalmol Vis Sci* 29: 1826-1835.

Richards J E, Lichter P R, Herman S, Hauser E R, Hou Y C, Johnson A T, and Boehnke M (1996) Probable exclusion of GLC1A as a candidate glaucoma gene in a family with middle-age-onset primary open-angle glaucoma. *Ophthalmology* 103: 1035-1040.

Rimmer S, Keating C, Chou T, Farb M D, Christenson P D, Foos R Y, and Bateman J B (1993) Growth of the human optic disk and nerve during gestation, childhood, and early adulthood. *Am J Ophthalmol* 116: 748-753.

Riva C E, Grunwald J E, Sinclair S H, and Petrig B L (1985) Blood velocity and volumetric flow rate in human retinal vessels. *Invest Ophthalmol Vis Sci* 26: 1124-1132.

Robb R M, and Marchevsky A (1978) Pathology of the Lens in Down's syndrome. *Arch Ophthalmol* 96: 1039-1042.

Roberts C (1994) Characterization of the inherent error in a spherically-biased corneal topography system in mapping a radially aspheric surface. *J Refract Corneal Surg* 10: 103-111; discussion 112-106.

Rohr A, and Burr D B (1978) Etiological differences in patterns of psycholinguistic development of children of IQ 30 to 60. *Am J Ment Defic* 82: 549-553.

Roizen N J, and Patterson D (2003) Down's syndrome. *Lancet* 361: 1281-1289.

Roizen N J, Wolters C, Nicol T, and Blondis T A (1993) Hearing loss in children with Down syndrome. *J Pediatr* 123: S9-12.

Rose L T, and Moshegov C N (2003) Comparison of the Zeiss IOLMaster and applanation A-scan ultrasound: biometry for intraocular lens calculation. *Clin Experiment Ophthalmol* 31: 121-124.

Rosenfield M, and Abraham-Cohen J A (1999) Blur sensitivity in myopes. *Optom Vis Sci* 76: 303-307.

Rosenfield M, and Gilmartin B (1999) Accommodative error, adaptation and myopia. *Ophthalmic Physiol Opt* 19: 159-164.

Rosenfield M, Portello J K, Blustein G H, and Jang C (1996) Comparison of clinical techniques to assess the near accommodative response. *Optom Vis Sci* 73: 382-388.

Rouse M W, Hutter R F, and Shiftlett R (1984) A normative study of the accommodative lag in elementary school children. *Am J Optom Physiol Opt* 61: 693-697.

Rudnicka A R, Burk R O, Edgar D F, and Fitzke F W (1998) Magnification characteristics of fundus imaging systems. *Ophthalmology* 105: 2186-2192.

Rudnicka A R, Edgar D F, and Bennett A G (1992) Construction of a model eye and its applications. *Ophthalmic Physiol Opt* 12: 485-490.

Rudnicka A R, Frost C, Owen C G, and Edgar D F (2001) Nonlinear behavior of certain optic nerve head parameters and their determinants in normal subjects. *Ophthalmology* 108: 2358-2368.

Rufer F, Schroder A, Arvani M K, and Erb C (2005) [Central and peripheral corneal pachymetry--standard evaluation with the Pentacam system]. *Klin Monatsbl Augenheilkd* 222: 117-122.

Sakai H, Sato T, Koibuchi H, Hayakawa K, Yamakawa R, and Nagataki S (1996) [Anterior chamber dimensions in patients with angle-closure glaucoma measured by an anterior eye segment analysis system]. *Nippon Ganka Gakkai Zasshi* 100: 546-550.

Sakaki Y, Hattori M, Toyoda A, Watanabe H, Yada T, Taylor T, Park H S et al. (2000) [Determination of DNA sequence of the whole chromosome 21]. *Tanpakushitsu Kakusan Koso* 45: 2520-2527.

Sanchez Perez A, Honrubia Lopez F M, Larrosa Poves J M, Polo Llorens V, and Melcon Sanchez-Frieras B (2001) [The Autocad system for planimetric study of the optic disc in glaucoma: technique and reproducibility study]. *Arch Soc Esp Oftalmol* 76: 551-558.

Santodomingo-Rubido J, Mallen E A, Gilmartin B, and Wolffsohn J S (2002) A new non-contact optical device for ocular biometry. *Br J Ophthalmol* 86: 458-462.

Satge D, Gembara P, Sasco A J, Francannet C, Desjardins L, Vekemans M, and Demeocq F (2001) An infant with Down syndrome and retinoblastoma. A possible non-fortuitous association. *Ophthalmic Genet* 22: 117-123.

Satge D, Schorderet D F, Balmer A, Beck-Popovic M, Addor M C, Beckmann J S, and Munier F L (2005) Association Down syndrome-retinoblastoma: a new observation. *Ophthalmic Genet* 26: 151-152.

Satge D, Sommelet D, Geneix A, Nishi M, Malet P, and Vekemans M (1998) A tumor profile in Down syndrome. *Am J Med Genet* 78: 207-216.

Saunders K J, and Westall C A (1992) Comparison between near retinoscopy and cycloplegic retinoscopy in the refraction of infants and children. *Optom Vis Sci* 69: 615-622.

Saw S M, Carkeet A, Chia K S, Stone R A, and Tan D T (2002) Component dependent risk factors for ocular parameters in Singapore Chinese children. *Ophthalmology* 109: 2065-2071.

Saw S M, Gazzard G, Shih-Yen E C, and Chua W H (2005) Myopia and associated pathological complications. *Ophthalmic Physiol Opt* 25: 381-391.

Schiavi C (1997) Comitant strabismus. *Curr Opin Ophthalmol* 8: 17-21.

Schwiegerling J, and Greivenkamp J E (1996) Keratoconus detection based on videokeratoscopic height data. *Optom Vis Sci* 73: 721-728.

Selikowitz M (1992) Health problems and health checks in school-aged children with Down syndrome. *J Paediatr Child Health* 28: 383-386.

Selovic A, Juresa V, Ivankovic D, Malcic D, and Selovic Bobonj G (2005) Relationship between axial length of the emmetropic eye and the age, body height, and body weight of schoolchildren. *Am J Hum Biol* 17: 173-177.

Shah S, Chatterjee A, Mathai M, Kelly S P, Kwartz J, Henson D, and McLeod D (1999) Relationship between corneal thickness and measured intraocular pressure in a general ophthalmology clinic. *Ophthalmology* 106: 2154-2160.

Shapiro M B, and France T D (1985) The ocular features of Down's syndrome. *Am J Ophthalmol* 99: 659-663.

Sheen N J, Morgan J E, Poulsen J L, and North R V (2004) Digital stereoscopic analysis of the optic disc: evaluation of a teaching program. *Ophthalmology* 111: 1873-1879.

Sheng H, Bottjer C A, and Bullimore M A (2004) Ocular component measurement using the Zeiss IOLMaster. *Optom Vis Sci* 81: 27-34.

Sherk M C, and Williams T D (1979) Disc vascularity in Down's syndrome. *Am J Optom Physiol Opt* 56: 509-511.

Sherry L M, Wang J J, Rochtchina E, Wong T, Klein R, Hubbard L, and Mitchell P (2002) Reliability of computer-assisted retinal vessel measurementin a population. *Clin Experiment Ophthalmol* 30: 179-182.

Shiba T, Maruo K, and Akahoshi T (1999) Development of a multi-field fundus photographing system using a non-mydriatic camera for diabetic retinopathy. *Diabetes Res Clin Pract* 45: 1-8.

Shimmyo M, Ross A J, Moy A, and Mostafavi R (2003) Intraocular pressure, Goldmann applanation tension, corneal thickness, and corneal curvature in Caucasians, Asians, Hispanics, and African Americans. *Am J Ophthalmol* 136: 603-613.

Siffel C, Correa A, Cragan J, and Alverson C J (2004) Prenatal diagnosis, pregnancy terminations and prevalence of Down syndrome in Atlanta. *Birth Defects Res A Clin Mol Teratol* 70: 565-571.

Singh K, Logan N, and B. G (2006) Three-dimensional modeling of the human eye based on magnetic resonance imaging. *Invest Ophthalmol Vis Sci* 47: 2272-2279.

Sinha S (2005) Anti-oxidant gene expression imbalance, aging and Down syndrome. *Life Sci* 76: 1407-1426.

Sloper P, Cunningham C, Turner S, and Knussen C (1990) Factors related to the academic attainments of children with Down's syndrome. *Br J Educ Psychol* 60 (Pt 3): 284-298.

Smith G, and Pierscionek B K (1998) The optical structure of the lens and its contribution to the refractive status of the eye. *Ophthalmic Physiol Opt* 18: 21-29.

Smolek M K, and Klyce S D (1997) Current keratoconus detection methods compared with a neural network approach. *Invest Ophthalmol Vis Sci* 38: 2290-2299.

Sogano S, Tomita G, and Kitazawa Y (1993) Changes in retinal nerve fiber layer thickness after reduction of intraocular pressure in chronic open-angle glaucoma. *Ophthalmology* 100: 1253-1258.

Sokol S, Domar A, and Moskowitz A (1980) Utility of the Arden grating test in glaucoma screening: high false-positive rate in normals over 50 years of age. *Invest Ophthalmol Vis Sci* 19: 1529-1533.

Sommer A (1996) Glaucoma risk factors observed in the Baltimore Eye Survey. *Curr Opin Ophthalmol* 7: 93-98.

Sommer A, Tielsch J M, Katz J, Quigley H A, Gottsch J D, Javitt J, and Singh K (1991) Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch Ophthalmol* 109: 1090-1095.

Sonnsjo B, and Krakau C E (1993) Arguments for a vascular glaucoma etiology. *Acta Ophthalmol (Copenh)* 71: 433-444.

Sorsby A, Benjamin , B and Sheridan M (1961) Refraction and its components during growth of the eye from the age of three. *Med Res Coun Spec Report. No. 301.* HMSO London.

Spraul C W, Lang G E, Lang G K, and Grossniklaus H E (2002) Morphometric changes of the choriocapillaris and the choroidal vasculature in eyes with advanced glaucomatous changes. *Vision Res* 42: 923-932.

Stebbens V A, Dennis J, Samuels M P, Croft C B, and Southall D P (1991) Sleep related upper airway obstruction in a cohort with Down's syndrome. *Arch Dis Child* 66: 1333-1338.

Steele C F, Crabb D P, and Edgar D F (1992) Effects of different ocular fixation conditions on A-scan ultrasound biometry measurements. *Ophthalmic Physiol Opt* 12: 491-495.

Steffens M L, Oller D K, Lynch M, and Urbano R C (1992) Vocal development in infants with Down syndrome and infants who are developing normally. *Am J Ment Retard* 97: 235-246.

Stewart R E, Margaret Woodhouse J, and Trojanowska L D (2005) In focus: the use of bifocal spectacles with children with Down's syndrome. *Ophthalmic Physiol Opt* 25: 514-522.

Stokoe N L, and Turner R W (1966) Normal retinal vascular pattern. Arteriovenous ratio as a measure of arterial calibre. *Br J Ophthalmol* 50: 21-40.

Stoll C, Alembik Y, Dott B, and Roth M P (1998) Study of Down syndrome in 238,942 consecutive births. *Ann Genet* 41: 44-51.

Stone E M, Fingert J H, Alward W L, Nguyen T D, Polansky J R, Sunden S L, Nishimura D et al. (1997) Identification of a gene that causes primary open angle glaucoma. *Science* 275: 668-670.

Stratford B, and Steele J (1985) Incidence and prevalence of Down's syndrome--a discussion and report. *J Ment Defic Res* 29 (Pt 1): 95-107.

Strenk S A, Strenk L M, Semmlow J L, and DeMarco J K (2004) Magnetic resonance imaging study of the effects of age and accommodation on the human lens cross-sectional area. *Invest Ophthalmol Vis Sci* 45: 539-545.

Stromland K, Hellstrom A, and Gustavsson T (1995) Morphometry of the optic nerve and retinal vessels in children by computer-assisted image analysis of fundus photographs. *Graefes Arch Clin Exp Ophthalmol* 233: 150-153.

Styles M E, Cole T J, Dennis J, and Preece M A (2002) New cross sectional stature, weight, and head circumference references for Down's syndrome in the UK and Republic of Ireland. *Arch Dis Child* 87: 104-108.

Sudesh S, Moseley M J, and Thompson J R (1993) Accuracy of Goldmann tonometry in clinical practice. *Acta Ophthalmol (Copenh)* 71: 185-188.

Suttle C M, and Turner A M (2004) Transient pattern visual evoked potentials in children with Down's syndrome. *Ophthalmic Physiol Opt* 24: 91-99.

Suzuki Y (1995) Direct measurement of retinal vessel diameter: comparison with microdensitometric methods based on fundus photographs. *Surv Ophthalmol* 39 Suppl 1: S57-65.

Svedberg H, Chen E, and Hamberg-Nystrom H (2005) Changes in corneal thickness and curvature after different excimer laser photorefractive procedures and their impact on intraocular pressure measurements. *Graefes Arch Clin Exp Ophthalmol* 243: 1218-1220.

Tabachnick B G F, L. S. (1996) *Using multivariate statistics*. New York: HarperCollins.

Tannock R (1988) Mothers' directiveness in their interactions with their children with and without Down syndrome. *Am J Ment Retard* 93: 154-165.

Thylefors B, Negrel A D, Pararajasegaram R, and Dadzie K Y (1995) Global data on blindness. *Bull World Health Organ* 73: 115-121.

Tielsch J M, Katz J, Quigley H A, Javitt J C, and Sommer A (1995) Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology* 102: 48-53.

Tielsch J M, Katz J, Singh K, Quigley H A, Gottsch J D, Javitt J, and Sommer A (1991a) A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *Am J Epidemiol* 134: 1102-1110.

Tielsch J M, Katz J, Sommer A, Quigley H A, and Javitt J C (1994) Family history and risk of primary open angle glaucoma. The Baltimore Eye Survey. *Arch Ophthalmol* 112: 69-73.

Tielsch J M, Sommer A, Katz J, Royall R M, Quigley H A, and Javitt J (1991b) Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *Jama* 266: 369-374.

Touzeau O, Scheer S, Allouch C, Borderie V, and Laroche L (2004) [The relationship between keratoconus and axial myopia]. *J Fr Ophtalmol* 27: 765-771.

Traboulsi E I, Levine E, Mets M B, Parelhoff E S, O'Neill J F, and Gaasterland D E (1988) Infantile glaucoma in Down's syndrome (trisomy 21). *Am J Ophthalmol* 105: 389-394.

Tsiaras W G, Pueschel S, Keller C, Curran R, and Giesswein S (1999) Amblyopia and visual acuity in children with Down's syndrome. *Br J Ophthalmol* 83: 1112-1114.

Tuft S J, Gregory W M, and Buckley R J (1994) Acute corneal hydrops in keratoconus. *Ophthalmology* 101: 1738-1744.

Turner S, Sloper P, Cunningham C, and Knussen C (1990) Health problems in children with Down's syndrome. *Child Care Health Dev* 16: 83-97.

Uchida H, Ugurlu S, and Caprioli J (1998) Increasing peripapillary atrophy is associated with progressive glaucoma. *Ophthalmology* 105: 1541-1545.

Van Goor J C, Massa G G, and Hirasing R (1997) Increased incidence and prevalence of diabetes mellitus in Down's syndrome. *Arch Dis Child* 77: 186.

Varma R, Steinmann W C, Spaeth G L, and Wilson R P (1988) Variability in digital analysis of optic disc topography. *Graefes Arch Clin Exp Ophthalmol* 226: 435-442.

Varma R, Tielsch J M, Quigley H A, Hilton S C, Katz J, Spaeth G L, and Sommer A (1994) Race-, age-, gender-, and refractive error-related differences in the normal optic disc. *Arch Ophthalmol* 112: 1068-1076.

Vernon S A (1995) Reproducibility with the Keeler Pulsair 2000 non-contact tonometer. *Br J Ophthalmol* 79: 554-557.

Vickers, A (2005) Parametric versus non-parametric statistics in the analysis of randomized trials with non-normally distributed data. *BMC Medical Research Methodology.* 5: 35

Villarreal M G, Ohlsson J, Abrahamsson M, Sjostrom A, and Sjostrand J (2000) Myopisation: the refractive tendency in teenagers. Prevalence of myopia among young teenagers in Sweden. *Acta Ophthalmol Scand* 78: 177-181.

Vincent A L, Weiser B A, Cupryn M, Stein R M, Abdolell M, and Levin A V (2005) Computerized corneal topography in a paediatric population with Down syndrome. *Clin Experiment Ophthalmol* 33: 47-52.

Wagner R S, Caputo A R, and Reynolds R D (1990) Nystagmus in Down's syndrome. *Ophthalmology* 97: 1439-1444.

Wald N J, Cuckle H S, Densem J W, Kennard A, and Smith D (1992) Maternal serum screening for Down's syndrome: the effect of routine ultrasound scan determination of gestational age and adjustment for maternal weight. *Br J Obstet Gynaecol* 99: 144-149.

Wald N J, Watt H C, and Hackshaw A K (1999) Integrated screening for Down's syndrome on the basis of tests performed during the first and second trimesters. *N Engl J Med* 341: 461-467.

Wallman J, and Winawer J (2004) Homeostasis of eye growth and the question of myopia. *Neuron* 43: 447-468.

Wang J J, Mitchell P, Leung H, Rochtchina E, Wong T Y, and Klein R (2003a) Hypertensive retinal vessel wall signs in a general older population: the Blue Mountains Eye Study. *Hypertension* 42: 534-541.

Wang J Y, Rice D A, and Klyce S D (1989) A new reconstruction algorithm for improvement of corneal topographical analysis. *Refract Corneal Surg* 5: 379-387.

Wang L, Dai E, Koch D D, and Nathoo A (2003b) Optical aberrations of the human anterior cornea. *J Cataract Refract Surg* 29: 1514-1521.

Weih L M, Mukesh B N, McCarty C A, and Taylor H R (2001a) Association of demographic, familial, medical, and ocular factors with intraocular pressure. *Arch Ophthalmol* 119: 875-880.

Weih L M, Nanjan M, McCarty C A, and Taylor H R (2001b) Prevalence and predictors of open-angle glaucoma: results from the visual impairment project. *Ophthalmology* 108: 1966-1972.

Whitacre M M, Stein R A, and Hassanein K (1993) The effect of corneal thickness on applanation tonometry. *Am J Ophthalmol* 115: 592-596.

White J M, and Wick B (1995) Accommodation in humans with juvenile macular degeneration. *Vision Res* 35: 873-880.

Wickham L, Edmunds B, and Murdoch I E (2005) Central corneal thickness: will one measurement suffice? *Ophthalmology* 112: 225-228.

Wiggs J L, Allingham R R, Hossain A, Kern J, Auguste J, DelBono E A, Broomer B et al. (2000) Genome-wide scan for adult onset primary open angle glaucoma. *Hum Mol Genet* 9: 1109-1117.

Wilke K (1972) Effects of repeated tonometry. genuine and sham measurements. *Acta. Ophthalmol (Copenh)* 50: 574-582.

Williams E J, McCormick A Q, and Tischler B (1973) Retinal vessels in Down's syndrome. *Arch Ophthalmol* 89: 269-271.

Wilson M R, Hertzmark E, Walker A M, Childs-Shaw K, and Epstein D L (1987) A case-control study of risk factors in open angle glaucoma. *Arch Ophthalmol* 105: 1066-1071.

Wilson S, He Y, and Weng J (1996) Epithelial injury induces keratocyte apoptosis: hypothesized role for the interleukin-1 system in the modulation of corneal tissue organization and wound healing. *Exp Eye Res* 62: 325-337.

Wilson S E, and Klyce S D (1991) Advances in the analysis of corneal topography. *Surv Ophthalmol* 35: 269-277.

Wilson S E, Lin D T, and Klyce S D (1991) Corneal topography of keratoconus. *Cornea* 10: 2-8.

Winn B, Gilmartin B, Mortimer L C, and Edwards N R (1991) The effect of mental effort on open- and closed-loop accommodation. *Ophthalmic Physiol Opt* 11: 335-339.

Wishart J G (1993) The development of learning difficulties in children with Down's syndrome. *J Intellect Disabil Res* 37 (Pt 4): 389-403.

Wishart J G, and Duffy L (1990) Instability of performance on cognitive tests in infants and young children with Down's syndrome. *Br J Educ Psychol* 60 (Pt 1): 10-22.

Wisniewski K E (1990) Down syndrome children often have brain with maturation delay, retardation of growth, and cortical dysgenesis. *Am J Med Genet Suppl* 7: 274-281.

Wolfs R C, Klaver C C, Ramrattan R S, van Duijn C M, Hofman A, and de Jong P T (1998) Genetic risk of primary open-angle glaucoma. Population-based familial aggregation study. *Arch Ophthalmol* 116: 1640-1645.

Wolfs R C, Klaver C C, Vingerling J R, Grobbee D E, Hofman A, and de Jong P T (1997) Distribution of central corneal thickness and its association with intraocular pressure: The Rotterdam Study. *Am J Ophthalmol* 123: 767-772.

Wong T Y, Klein B E, Klein R, Knudtson M, and Lee K E (2003) Refractive errors, intraocular pressure, and glaucoma in a white population. *Ophthalmology* 110: 211-217.

Wong T Y, Klein R, Sharrett A R, Duncan B B, Couper D J, Tielsch J M, Klein B E et al. (2002) Retinal arteriolar narrowing and risk of coronary heart disease in men and women. The Atherosclerosis Risk in Communities Study. *Jama* 287: 1153-1159.

Wong T Y, Knudtson M D, Klein R, Klein B E, Meuer S M, and Hubbard L D (2004) Computer-assisted measurement of retinal vessel diameters in the Beaver Dam Eye Study: methodology, correlation between eyes, and effect of refractive errors. *Ophthalmology* 111: 1183-1190.

Wong T Y, and McIntosh R (2005) Systemic associations of retinal microvascular signs: a review of recent population-based studies. *Ophthalmic Physiol Opt* 25: 195-204.

Wong T Y, Shankar A, Klein R, Klein B E, and Hubbard L D (2005) Retinal arteriolar narrowing, hypertension, and subsequent risk of diabetes mellitus. *Arch Intern Med* 165: 1060-1065.

Wong V, and Ho D (1997) Ocular abnormalities in Down syndrome: an analysis of 140 Chinese children. *Pediatr Neurol* 16: 311-314.

Woodhouse J M (1998) Investigating and managing the child with special needs. *Ophthalmic Physiol Opt* 18: 147-152.

Woodhouse J M, Cregg M, Gunter H L, Sanders D P, Saunders K J, Pakeman V H, Parker M et al. (2000) The effect of age, size of target, and cognitive factors on accommodative responses of children with Down syndrome. *Invest Ophthalmol Vis Sci* 41: 2479-2485.

Woodhouse J M, Hodge S J, and Earlam R A (1994) Facial characteristics in children with Down's syndrome and spectacle fitting. *Ophthalmic Physiol Opt* 14: 25-31.

Woodhouse J M, Meades J S, Leat S J, and Saunders K J (1993) Reduced accommodation in children with Down syndrome. *Invest Ophthalmol Vis Sci* 34: 2382-2387.

Woodhouse J M, Pakeman V H, Cregg M, Saunders K J, Parker M, Fraser W I, Sastry P et al. (1997) Refractive errors in young children with Down syndrome. *Optom Vis Sci* 74: 844-851.

Woodhouse J M, Pakeman V H, Saunders K J, Parker M, Fraser W I, Lobo S, and Sastry P (1996) Visual acuity and accommodation in infants and young children with Down's syndrome. *J Intellect Disabil Res* 40 (Pt 1): 49-55.

Woodruff M E, Cleary T E, and Bader D (1980) The prevalence of refractive and ocular anomalies among 1242 institutionalized mentally retarded persons. *Am J Optom Physiol Opt* 57: 70-84.

Wu D C, Schwartz B, Schwoerer J, and Banwatt R (1995) Retinal blood vessel width measured on color fundus photographs by image analysis. *Acta Ophthalmol Scand Suppl*: 33-40.

Yucel A A, Sturmer J, and Gloor B (1990) [Comparison of tonometry with the Keeler air puff non-contact tonometer "Pulsair" and the Goldmann applanation tonometer]. *Klin Monatsbl Augenheilkd* 197: 329-334.

Yurdakul N S, Ugurlu S, and Maden A (2006) Strabismus in Down syndrome. *J Pediatr Ophthalmol Strabismus* 43: 27-30.

Zadnik K, Manny R E, Yu J A, Mitchell G L, Cotter S A, Quiralte J C, Shipp M et al. (2003) Ocular component data in schoolchildren as a function of age and gender. *Optom Vis Sci* 80: 226-236.

Zadnik K, Mitchell G L, Jones L A, Burr D, Moeschberger M L (2004) Normal eye growth in emmetropic schoolchildren. *Optom Vis Sci* 81: 819-828.

Zeyen T G, and Caprioli J (1993) Progression of disc and field damage in early glaucoma. *Arch Ophthalmol* 111: 62-65.