Serial Evaluation of Corneal Transplants.

A Thesis

submitted by

Graham Osborne Macalister.

for the degree of

Doctor of Philosophy.

to

City University, London.

Department of Optometry and
Visual Science.

Moorfields Eye Hospital

December 1995

To Eva who made this possible

CONTENTS.

List of Tables 7

List of Figures 9

Acknowledgements 13

Declaration 14

Abstract 15

Abbreviations 16

1. INTRODUCTION. PENETRATING KERATOPLASTY. 17

1.1 Development of Penetrating Keratoplasty 17
1.1.1 Early history 17
1.1.2 Experimental Keratoplasty 18
1.1.3 Development of modern techniques 19
1.1.4 1950 onwards. PK becomes routine surgery 23
1.1.5 The Changing Indications for Penetrating Keratoplasty 26

1.2 Studies on the outcome of penetrating keratoplasty **29**
1.2.1 Corneal topography consideration 29
1.2.2 The use of photokeratoscopes, and computerised topographical analysis. 30
1.2.3 Sequential evaluation 31

1.3 The effects of irregular post keratoplasty topography. **31**
1.3.1 Contrast sensitivity 31
1.3.2 Need for contact lenses 32
1.3.3 Need for refractive surgery 33

1.4 Aetiology and control of post keratoplasty astigmatism and topographical irregularity. **38**
1.4.1 Pre-surgical Factors 40
1.4.2 Surgical factors 46
1.4.3 Post- operative factors 93
1.4.4 Summary 95

1.5 Corneal transplant resensitisation 99
1.5.1 Innervation of the normal cornea 99
1.5.2 Transplant resensitisation 100

2. INTRODUCTION. MEASUREMENT OF CORNEAL TOPOGRAPHY. 109

2.1 Keratometry versus Keratoscopy. 109

2.2 Review of keratoscopes. 109
2.2.1 Target. 111

2.2.2 Optical System. 115

2.3 Choice of instrument **116**

3. INTRODUCTION. MEASUREMENT OF CORNEAL SENSITIVITY. **117**
3.1.1 Review of aesthesiometers 117
3.1.2 Choice of instrument 120

4. METHODS AND MATERIALS **122**

4.1 Follow up Schedule **122**

4.2 Patients **124**
4.2.1 Selection, exclusions 124
4.2.2 Patient characteristics 124

4.3 Surgical technique, and clinical management. **132**
4.3.1 Surgical technique 132
4.3.2 Long term care. 137

4.4 Measurement. Corneal topography **140**
4.4.1 PEK photokeratoscope. 140
4.4.2 Measurement of keratographs 143
4.4.3 Conversion of keratograph measurements to local radius of curvature 145
4.4.4 Repeatability 146
4.4.5 Conversion to corneal topography components 149
4.4.6 Number of semi-meridians measured 152
4.4.7 Statistical analysis 153

4.5 Measurement Touch Sensitivity **154**
4.5.1 Instrument mounting 154
4.5.2 Procedure 155
4.5.3 Reproducibility 155
4.5.4 Presentation of Data 156

5. RESULTS **157**

5.1 Topography **157**
5.1.1 Comparison between keratograph components and refraction 157
5.1.3 Changes in Astigmatism and Irregularity 165
5.1.4 Results of the Univariate analysis of Astigmatism and Irregularity. 168
5.1.5 Multivariate analysis of Astigmatism and Irregularity 178
5.1.6 Irregularity for other rings 187

5.2 Sensitivity **190**
5.2.1 Patients 190
5.2.2 Central sensitivity 190
5.2.3 Peripheral sensitivity 192
5.2.4 Effect of contact lens wear 195

6. DISCUSSION **197**

6.1 Topography **197**
6.1.1 Comparison between refraction and keratograph result 197

6.1.2 Application of topography components 210
6.1.3 Sequential follow-up 210
6.1.4 Other influences on topography 212
6.1.5 Results 213

6.2 Sensitivity **217**
6.2.1 Sequential follow up 217
6.2.2 Other influences on sensitivity 217
6.2.3 Results 219
6.2.4 Further research 220

7. SUMMARY AND CONCLUSIONS **222**

REFERENCES **225**

Appendix A Derivation of formulae for corneal curvature.

Appendix B Patient details.

Appendix C Derivation of Asymmetry Component.

Appendix D Optimum number of semi-meridians to be measured.

Appendix E 40 measurements of the same transplant at a single session.

Appendix F 10 repeat measurements (12 meridians).

Appendix G Radius of curvature values reduced to Components.

Appendix H Statistical methods.

Appendix I Sensitivity data.

List of Tables

TABLE 1.1 CHANGING INDICATIONS FOR PENETRATING KERATOPLASTY

TABLE 1.2 SELECTED PENETRATING KERATOPLASTY SERIES

TABLE 1.3 STUDIES SHOWING THE EFFECT OF DONOR/RECIPIENT DISPARITY ON POST-OPERATIVE ASTIGMATISM

TABLE 1.4 STUDIES INVESTIGATING SELECTIVE INTERRUPTED SUTURE REMOVAL

TABLE 1.5 STUDIES INVESTIGATING ADJUSTMENT OF A CONTINUOUS SUTURE

TABLE 1.6 A SELECTION OF SURGICAL KERATOMETERS

TABLE 1.7 FACTORS ASSOCIATED WITH HIGH POST-KERATOPLASTY ASTIGMATISM IN 29 EYES

TABLE 1.8 POST-OPERATIVE FOLLOW UP KERATOMETRIC ASTIGMATISM IN 2 CASES WITH KERATOCONUS

TABLE 4.1 VISIT SCHEDULE. TIME SINCE KERATOPLASTY.

TABLE 4.2 INDICATION FOR PENETRATING KERATOPLASTY

TABLE 4.3 THE PRIMARY INDICATION FOR THE INITIAL PENETRATING KERATOPLASTY IN THE REMAINING 17 PATIENTS

TABLE 4.4 PREVIOUS PENETRATING KERATOPLASTY

TABLE 4.5 INDICATIONS FOR THE OPERATIONS INVOLVED IN THIS STUDY

TABLE 4.6 APHAKIC PATIENTS

TABLE 4.7 DONOR CAUSE OF DEATH

TABLE 4.8 TREPHINE DIAMETER.

TABLE 4.9 DONOR /HOST DISPARITY

TABLE 4.10 STANDARD DEVIATIONS FOR 40 MEASUREMENTS OF THE SAME TRANSPLANT AT THE SAME SESSION.

TABLE 4.11 COMPARISONS MADE BETWEEN KERATOGRAPH COMPONENTS AND REFRACTION.

TABLE 5.1 ASTIGMATISM, PRE SUTURE REMOVAL; UNIVARIATE EFFECT ON THE INTERCEPT.

TABLE 5.2 ASTIGMATISM, PRE SUTURE REMOVAL; UNIVARIATE EFFECT ON THE SLOPE.

TABLE 5.3 IRREGULARITY, PRE SUTURE REMOVAL; UNIVARIATE EFFECT ON THE INTERCEPT.

TABLE 5.4 IRREGULARITY, PRE SUTURE REMOVAL; UNIVARIATE EFFECT ON THE SLOPE.

TABLE 5.5 ASTIGMATISM, AFTER SUTURE REMOVAL; UNIVARIATE EFFECT ON THE INTERCEPT.

TABLE 5.6 ASTIGMATISM, AFTER SUTURE REMOVAL; UNIVARIATE EFFECT ON THE SLOPE

TABLE 5.7 IRREGULARITY, AFTER SUTURE REMOVAL; UNIVARIATE EFFECT ON THE INTERCEPT.

TABLE 5.8 IRREGULARITY AFTER SUTURE REMOVAL; UNIVARIATE EFFECT ON THE SLOPE

TABLE 5.9 MULTIVARIATE MODEL FOR LOG-ASTIGMATISM

TABLE 5.10 MULTIVARIATE MODEL FOR LOG-IRREGULARITY

TABLE 6.1 THE TEN CASES WHICH SHOWED THE MOST DISPARITY BETWEEN AXIS OF ASTIGMATISM BY REFRACTION AND BY KERATOGRAPH ANALYSIS.

TABLE 6.2 THE TEN CASES WHICH SHOWED THE MOST DISPARITY BETWEEN ASTIGMATISM BY REFRACTION AND BY KERATOGRAPH ANALYSIS.

TABLE B.1 PATIENT DETAILS

TABLE D.1.CURVATURE MEASURED IN 72 SEMI-MERIDIANS. KERATOGRAPH # 1. (RING 3)

TABLE D.2. DIFFERENCE FROM THE VALUE OBTAINED WITH 72 SEMI-MERIDIANS. KERATOGRAPH # 1.

TABLE D.3. CURVATURE MEASURED IN 72 SEMI-MERIDIANS. KERATOGRAPH # 2. (RING 3)

TABLE D.4. DIFFERENCE FROM THE VALUE OBTAINED WITH 72 SEMI-MERIDIANS. KERATOGRAPH # 2.

TABLE E.1 40 MEASUREMENTS OF THE SAME TRANSPLANT (#27) AT A SINGLE SESSION.

TABLE F.1 10 MEASUREMENTS OF THE SAME TRANSPLANT AT A SINGLE SESSION.

TABLE G.1 EXAMPLE TO SHOW OBSERVED DATA AND THE CORRESPONDING REGULAR COMPONENT DATA.

List of Figures

FIGURE 1.1 CHANGING INDICATIONS FOR PENETRATING KERATOPLASTY (USA)

FIGURE 1.2 CHANGING INDICATIONS FOR PENETRATING KERATOPLASTY (EXCLUDING USA)

FIGURE 4.1 NUMBER OF PATIENTS CONTRIBUTING DATA AT EACH STAGE.

FIGURE 4.2 PEK INSTRUMENT OPTICS.

FIGURE 4.3 PHOTO ELECTRONIC KERATOSCOPE (PEK)

FIGURE 4.4 PHOTO ELECTRONIC KERATOSCOPE (PEK). OBLIQUE VIEW.

FIGURE 4.5 MICROFILM READER.

FIGURE 4.6 SHOWS A KERATOGRAPH PROJECTED ONTO THE MEASURING SCALE.

FIGURE 4.7 MOUNTING USED TO ATTACH THE COCHET-BONNET AESTHESIOMETER TO THE SLIT LAMP.

FIGURE 4.8 AESTHESIOMETER MOUNTED ON A HAAG-STREIT SLIT LAMP.

FIGURE 4.9 AESTHESIOMETER MOUNTED ON A HAAG-STREIT SLIT LAMP. CLOSE UP VIEW.

FIGURE 5.1 AXIS OF ASTIGMATISM. REFRACTION VERSUS KERATOGRAPH COMPONENT ANALYSIS

FIGURE 5.2 KERATOGRAPH REGULAR ASTIGMATISM COMPONENT (DIOPTRES)

FIGURE 5.3 KERATOGRAPH REGULAR ASTIGMATISM COMPONENT (INTERCEPT THROUGH ZERO)

FIGURE 5.4 RELATIONSHIP BETWEEN ASYMMETRY AND VISUAL ACUITY

FIGURE 5.5 RELATIONSHIP BETWEEN IRREGULARITY AND VISUAL ACUITY

FIGURE 5.6 CHANGES IN ASYMMETRY WITH TIME

FIGURE 5.7 CHANGES IN ASYMMETRY, COMPARISON BETWEEN RING 1 AND RING 2

FIGURE 5.8 ALL THE INDIVIDUAL PATIENT PROFILES SHOWING CHANGES IN ASTIGMATISM WITH TIME

FIGURE 5.9 THE PROFILES IN FIGURE 5.8 WERE SIMPLIFIED TO A LINEAR MODEL

FIGURE 5.10 ALL THE INDIVIDUAL PATIENT PROFILES SHOWING CHANGES IN IRREGULARITY WITH TIME

FIGURE 5.11 THE PROFILES IN FIGURE 5.10 WERE SIMPLIFIED TO A LINEAR MODEL

FIGURE 5.12 MULTIVARIATE RESULTS FOR ASTIGMATISM BEFORE SUTURE REMOVAL

FIGURE 5.13 CHANGES IN ASTIGMATISM OVER THE FULL POST-OPERATIVE PERIOD. QUADRATIC MODEL

FIGURE 5.14 MULTIVARIATE RESULTS FOR IRREGULARITY BEFORE SUTURE REMOVAL

FIGURE 5.15 CHANGES IN IRREGULARITY OVER THE FULL POST-OPERATIVE PERIOD. QUADRATIC MODEL

FIGURE 5.16 IRREGULARITY FOR RINGS 1, 2, 3, AND 4

FIGURE 5.17 THE EFFECT OF REPEAT KERATOPLASTY ON IRREGULARITY IN RINGS 1, AND 2

FIGURE 5.18 TIME FROM DEATH TO OPERATION FOR K-SOL AND FOR MK MEDIUM

FIGURE 5.19 NUMBER OF EYES CONTRIBUTING DATA AT EACH STAGE

FIGURE 5.20 CHANGE OF CENTRAL SENSITIVITY WITH TIME, MEAN VALUES

FIGURE 5.21 PROGRESSION OF CENTRAL SENSITIVITY

FIGURE 5.22 COMPARISON BETWEEN TRANSPLANT CENTRE AND PERIPHERY, MEAN SENSITIVITY AT EACH STAGE

FIGURE 5.23 DIFFERENCE BETWEEN TRANSPLANT CENTRE AND PERIPHERY FOR NON CONTACT LENS WEARERS

FIGURE 5.24 DIFFERENCE BETWEEN TRANSPLANT CENTRE AND PERIPHERY FOR CONTACT LENS WEARERS

FIGURE 5.25 TRANSPLANT CENTRE. COMPARISON BETWEEN CONTACT LENS WEARERS AND NON WEARERS

FIGURE 5.26 TRANSPLANT PERIPHERY. COMPARISON BETWEEN CONTACT LENS WEARERS AND NON WEARERS

FIGURE 6.1 PUPILLARY AXIS

FIGURE 6.2 LINE OF SIGHT

FIGURE 6.3 ILLUSTRATES THE DIFFERENCE BETWEEN THE LINE OF SIGHT AND THE VISUAL AXIS.

FIGURE 6.4 SHOWS THE DIFFERENCE BETWEEN THE LINE OF SIGHT AND THE KERATOSCOPE AXIS.

FIGURE A.1.RAY DIAGRAM FOR CONVEX MIRROR

FIGURE A.2 GEOMETRY FOR REFLECTION FROM SPHERICAL SURFACE.

FIGURE A.3 TWO CONSECUTIVE ARC ELEMENTS JOINED AT A REFLECTION POINT.

FIGURE A.4 CALCULATING X VALUES OF REFLECTION POINTS FROM CURVE ELEMENTS.

FIGURE C.1 CENTRE OF SPHERICAL POLAR DIAGRAM OFF-SET FROM THE ORIGIN

FIGURE C.2 TOPOGRAPHY COMPONENTS EXAMPLE 1

FIGURE C.3 TOPOGRAPHY COMPONENTS EXAMPLE 2

FIGURE C.4 TOPOGRAPHY COMPONENTS EXAMPLE 3

FIGURE C.5 TOPOGRAPHY COMPONENTS EXAMPLE 4

FIGURE C.6 TOPOGRAPHY COMPONENTS EXAMPLE 5

FIGURE C.7 TOPOGRAPHY COMPONENTS EXAMPLE 6

FIGURE C.8 TOPOGRAPHY COMPONENTS EXAMPLE 7

FIGURE C.9 TOPOGRAPHY COMPONENTS EXAMPLE 8

FIGURE C.10 TOPOGRAPHY COMPONENTS EXAMPLE 9

FIGURE C.11 TOPOGRAPHY COMPONENTS EXAMPLE 10

FIGURE C.12 TOPOGRAPHY COMPONENTS EXAMPLE 11

FIGURE C.13 TOPOGRAPHY COMPONENTS EXAMPLE 12

FIGURE C.14 TOPOGRAPHY COMPONENTS EXAMPLE 13

FIGURE C.15 TOPOGRAPHY COMPONENTS EXAMPLE 14

FIGURE C.16 TOPOGRAPHY COMPONENTS EXAMPLE 15

FIGURE C.17 TOPOGRAPHY COMPONENTS EXAMPLE 16

FIGURE C.18 TOPOGRAPHY COMPONENTS EXAMPLE 17

FIGURE D.1 CURVATURE PLOT FOR 72 SEMI-MERIDIANS. KERATOGRAPH # 1. (RING 3)

FIGURE D.2 CURVATURE PLOT FOR 72 SEMI-MERIDIANS. KERATOGRAPH # 2. (RING 3)

FIGURE D.3 VARIATION IN THE COMPONENT VALUE WHEN DIFFERENT NUMBERS OF SEMI-MERIDIANS ARE MEASURED.

FIGURE D.4 VARIATION IN THE COMPONENT VALUE WHEN DIFFERENT NUMBERS OF SEMI-MERIDIANS ARE MEASURED.

FIGURE E.1 THE 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT AT A SINGLE SESSION)

FIGURE E.2 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING1

FIGURE E.3 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 2

FIGURE E.4 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 3

FIGURE E.5 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 4

FIGURE E.6 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 5

FIGURE E.7 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 6

FIGURE E.8 0 DEGREE SEMI-MERIDIAN CURVATURES (40 MEASUREMENTS OF THE SAME TRANSPLANT) RING 7

FIGURE F.1 EFFECT OF DECENTRATION

FIGURE F.2 KERATOGRAPH 1 DEVIATION FROM THE MEAN

FIGURE F.3 KERATOGRAPH 2 DEVIATION FROM THE MEAN

FIGURE F.4 KERATOGRAPH 3 DEVIATION FROM THE MEAN

FIGURE F.5 KERATOGRAPH 4 DEVIATION FROM THE MEAN

FIGURE F.6 KERATOGRAPH 5 DEVIATION FROM THE MEAN

FIGURE F.7 KERATOGRAPH 6 DEVIATION FROM THE MEAN

FIGURE F.8 KERATOGRAPH 7 DEVIATION FROM THE MEAN

FIGURE F.9 KERATOGRAPH 8 DEVIATION FROM THE MEAN

FIGURE F.10 KERATOGRAPH 9 DEVIATION FROM THE MEAN

FIGURE F.11 KERATOGRAPH 10 DEVIATION FROM THE MEAN

FIGURE F.12 TEN KERATOGRAPHS OF THE SAME TRANSPLANT TAKEN ON THE SAME OCCASION.

FIGURE G.1 POLAR DIAGRAM

FIGURE G.2 POLAR DIAGRAM REPRESENTING A SPHERE

FIGURE G.3 POLAR DIAGRAM WITH PLOT REPRESENTING ASYMMETRY

FIGURE G.4 POLAR DIAGRAM WITH PLOT REPRESENTING REGULAR ASTIGMATISM

FIGURE G.5 ASYMMETRY VECTOR APPLIED TO EACH DATA POINT

FIGURE G.6 CHART SHOWING OBSERVED DATA AND THE CORRESPONDING REGULAR COMPONENT DATA. PX # 6

FIGURE G.7 REGULAR COMPONENT PLOT. PX # 6 (SIX MONTH STAGE, RING 1).

FIGURE I.1 SENSITIVITY DATA FOR ALL EYES

Acknowledgments

I would like to express sincere thanks to the following people:

Professor Geoff Woodward for his advice, encouragement, and patience over the years of this study.

Mr Roger Buckley for his guidance, and support, in allowing me to complete this longitudinal study, and providing access to his patients. Also for his assistance in arranging for the support of the Godfrey Research Fund.

Dr Bianca de Stavola for her invaluable assistance in the statistical analysis of the topography data.

Dr Daryl de Cunha for writing the programme which converted keratograph measurements into radius of curvature data.

Dr Ian Grant for help on the mathematics involved in the derivation of topography components.

Dr Sybil Ritten for her advice and allowing access to the records of Moorfields Eye Hospital Eye Bank.

I acknowledge the contribution of Miss F. N. Chin who collected the early data.

I would also like to express my gratitude to the patients who continued to return year after year.

I am particularly grateful to my wife Eva for the many hours spent at the microfilm reader, the keyboard, and so much more.

Declaration

I grant powers of discretion to the University Librarian to allow this thesis to be copied in whole or in part without further reference to me. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

Abstract

A prospective longitudinal trial, involving 108 eyes with transplanted corneas was carried out. The object was to use sequential observations taken from the same eye to investigate changes over time. The two variables studied were corneal topography and corneal touch sensitivity. Keratographs were obtained using the Photo Electronic Keratograph (PEK). An analysis technique was developed which enabled clinically meaningful topographical components to be derived from measurements of the keratograph. These components were; spherical equivalent, asymmetry, axis of asymmetry, regular astigmatism and its axis, and an irregularity component. The changes in astigmatism and irregularity were analysed using Multilevel Modelling. The principal results were that MK storage medium produced higher starting values for astigmatism, and that equal donor and host diameters gave a more rapid reduction of astigmatism in the period up to suture removal. No single factor determined astigmatism after suture removal.

The starting value for irregularity was significantly higher in repeat transplants, but no single factor appeared to determine the rate of reduction of irregularity.

Corneal touch sensitivity was measured with a Cochet Bonnet aesthesiometer, and revealed a slow but progressive resensitisation. There was a very large inter-subject variation. The central sensitivity was zero in more than 60% of the eyes at the five year stage. By ten years this proportion had reduced to just over 20%.

Abbreviations

ABK	Aphakic Bullous Keratopathy
AIDS	Acquired Immunodeficiency Syndrome
Ca	Carcinoma
CL	Contact Lens
cm	Centimetre
CMS	Corneal Modelling System
CON	Continuous Suture
D	Dioptre
DC	Dioptres of Cylinder
df	Degrees of Freedom
ENF	Epithelial Neuronotropic Factor
g	Gram
GTS	Guided Trephine System
HLA	Human Leukocyte Antigens
HPMC	Hydroxypropylmethyl Cellulose
INT	Interrupted Suture
IOL	Intraocular Lens
LED	Light Emitting diodes
LRT	Likelihood Ratio Test
M	Month
M-K	McCarey-Kaufman Medium
mm	Millimetre
mm Hg	Millimetres of mercury
N	Number of Subjects
NS	Not Statistically Significant

p	Probability
PAED	Paediatric
PBK	Pseudophakic Bullous Keratopathy
PEK	Photo Electronic Keratoscope
PK	Penetrating Keratoplasty
Px	Patient
ROGS	Removal of Graft Sutures
SAI	Surface Asymmetry Index
SD	Standard Deviation
SE	Standard Error
SRI	Surface Regularity Index
TSPCL	Transclerally Sutured Posterior Chamber Lens
UKTSS	United Kingdom Transplant Support Service
VA	Visual Acuity
W	Week
Y	Year

1. Introduction. Penetrating keratoplasty.

1.1 Development of Penetrating Keratoplasty

1.1.1 Early history

The problem of blindness caused by corneal opacities is as old as mankind. Ry Andersen [1] has collated the historical evidence on attempts made by ancient civilisations to treat eye conditions. He cites as documentary evidence a series of laws drawn up by the Babylonian king who reigned from 1728 to 1686 BC. While some relate to the payment for ophthalmic treatment, others give an insight into the type of treatment performed. Rule 218 states "If the doctor has opened a spot (nakkaptum) in a man's eye with the instrument of bronze, but destroyed the man's eye, his hands are to be cut off". This is interesting both as an early attempt to regulate the medical profession, and as an example of early eye surgery. It is tempting to imagine that this was an attempt to remove corneal scaring, but unfortunately the translation of the word "nakkaptum" is far from certain. Although there is evidence of rudimentary corneal surgery in ancient civilisations [1] treatment of opacities was probably limited to crude attempts at superficial keratectomy. This remained the state of affairs for many centuries, and in 1761 the Englishman Chevalier Taylor, an itinerant quack, writes about the use of a small curved knife, and also a small brush, to be used for this purpose. Although such keratectomies were widely performed in Europe, there was never any suggestion of replacement of corneal tissue, and the idea of an ocular transplant was confined to myth and folklore. The Grimm brothers developed this idea in their tale of the army surgeon whose eyes were transplanted with those of a cat. It was not until the nineteenth century that the subject of corneal transplantation was approached scientifically.

1.1.2 Experimental Keratoplasty

The first documented evidence of the concept of replacement of corneal tissue was in 1789. The Frenchman De Quengsy suggested the use of glass with a silver rim as a replacement cornea. Fortunately it appears that this was never carried out, and it was not until 1813 that we find the first discussion of the actual transplantation of corneal tissue. This was by Himly [2], but it was his pupil Reisinger[2], who, having witnessed the first skin graft at Guy's Hospital, was encouraged to experiment with corneal transplants in animals. He was followed by other experimenters in Germany during the 1830`s, but the lack of control of infection; anaesthesia; and adequate instrumentation; meant universal failure which led to despondency. The first successful transplant was by the Irish surgeon Samuel Biggar [2], who after a visit to Germany, transplanted the cornea of one gazelle to another while he was in Egypt. His report was published in 1837, and led to renewed interest and further attempts, including the transplantation of a pig's cornea to a human by Kissam [2] in New York. These experiments again met with failure. This was partially because it was not recognised that Biggar's success was in part due to the fact that he had transplanted between the same species (homoplasty). It was not until the work of Power [2] in 1872 that it was suspected that homoplasty was necessary. He was followed by Wolfe, a Scotsman working in Glasgow, who in 1879, concluded that success could be improved by using donor material from a freshly enucleated eye; by keeping all corneal incisions clean and exactly measured; and by protecting subjacent structures.

By this time ophthalmic surgery in general had taken great strides forward. This was due to the introduction of better instrumentation , and better dissemination of information through the work of Von Graefe. Also to the introduction of anaesthesia (Ether by Bigelow in Boston in 1846, and Chloroform by Simpson in Edinburgh in 1847), and antisepsis by Lister in 1867. Although anatomically successful transplants were now possible a truly transparent human corneal transplant was still illusive. The first true success is credited to von Hippel [2] in 1886. Interestingly this was in fact a hetereoplasty rather than a homoplasty, and was lamellar rather than full thickness. In later years von Hippel was influenced by Leber(1911) [2] who believed that the endothelium should remain undisturbed, and continued to develop the technique of lamellar grafting, inventing a clockwork trephine to aid the efficient removal of the superficial layers. The first successful full thickness transplants was not until the beginning of the twentieth century.

1.1.3 Development of modern techniques

The first surgeon to attain the goal of a full thickness corneal transplant which remained clear, was Edward Zirm [2]. He reported, in 1906, an eighteen month follow up of a homotransplant in a man with lime burns. It is rather ironic that the first success was for a condition which was, until relatively recent years, considered amongst the least favourable indications for keratoplasty. This was in fact an isolated success, and it was not until 1914 that Elschnig [3] reported the second successful full thickness transplant. However, the major contribution by Zirm, was not this one famous case, but the seven principles which he drew up.

- The donor material must be human, from a young healthy eye.
- The use of good trephine (von Hippel`s trephine).
- Adequate anaesthesia (ether).
- Strict asepsis (iodoform).
- The avoidance of direct contact with antiseptics.
- Protection of the donor material (between layers of gauze).
- Adequate retention of the graft (overlay sutures).

These principles formed the basis upon which those working in the field were able to carry forward the practice of full thickness keratoplasty. It was not until 1919 that Ascher [2] suggested the nomenclature, “penetrating” and “lamellar”, and in fact most transplants in the early decades of the twentieth century were lamellar. This was due to the work of von Hippel [2], and also of Fuchs` [2], who had reported a substantial series of 30 lamellar transplants as early as 1894, with some successes.

Elschnig [3] was one of the major proponents of penetrating keratoplasty, and his work, along with that of colleagues in Prague, extends over the first three decades of the twentieth century. In 1923 he reported a series of 92 penetrating transplants, nine of which remained clear. Improvement was slow but steady, and by 1930 [3] he was able to report 34 clear grafts out of a total of 174. He used either an enucleated fresh eye or a cadaver eye. Filatov [4] was working at roughly the same time in Odessa, and he also found most success with partial penetrating keratoplasty. This term was used to distinguish his 4mm diameter transplants from entire cornea transplants, which were also attempted. In 1935 Filatov [4] published results of 96 penetrating keratoplasties performed between 1923 and 1932, fourteen of which resulted in a permanent transparent union with the host. Filatov used cadaver eyes, and the main change he made from the technique of Elschnig was the introduction of a spatula into the anterior chamber in order to protect the iris and crystalline lens from the trephine, and also to prevent the prolapse of the vitreous. In Britain interest in keratoplasty was dormant, and opinion was summarised by Sir John Parsons in his text book, Diseases of the Eye, in 1924 in the following words:- " Keratoplasty, or the excision of a small disc of scarred cornea, and its replacement by a disc of rabbit or human cornea, is practically never successful; the transplanted tissue rapidly becomes opaque". It was against this background that Tudor Thomas [5] commenced a long series of animal experiments in 1922. By 1930 he was ready to perform his first transplant on man. The technique [5] which he had developed, included the use of grafts in the region of 5mm diameter, with the donor cut with a trephine slightly smaller than that used for the recipient cornea. The margins of the graft and host were to be cut on a slope, i.e. with shelving. In 1937 he was able to report success in 21 out of 36 transplants. The criteria for success was that any post operative opacity should be of a lesser degree than in the original condition. Other developments in Europe included the work of Vannas [6] who was the first to suggest punching the donor button from the endothelial side, and Franceschetti [2] of Switzerland, who developed a new corneal trephine with minute adjustments and a positive guard.

The impetus for further improvements in technique then moved to America with the work of Castroviejo [7]. He helped to popularise the use of direct sutures, as a more reliable method of securing the graft in place, rather than the radiating overlying sutures used by Tudor Thomas, or egg membrane which was advocated by Filatov. He also designed small precise instruments such as a new double-bladed knife. Castroviejo [7] initially used square grafts in the 1930`s, when it was difficult to obtain sharp trephines. The use of a double bladed instrument incorporating razor blade material gave the sharp cutting edges required for this type of surgery. It also made possible the dissection of grafts of varying sizes with the same instrument. Once trephines were improved, square grafts became less popular, and Castroviejo [8] eventually confirmed that there were very few distinct indications for square grafts, and that the surgeon`s choice was often largely a matter of personal preference, and familiarity with the technique. Castroviejo is also credited with the introduction of a technique using diathermy or cautery to flatten the cone in keratoconus prior to trephining the recipient, in order that the angle of cut is more regular. This technique was extensively used in the late 1960`s [9]. In 1938 Castroviejo [7] discussing a series of over 100 corneal transplants performed between 1933 and 1937, reported clear grafts in over 40% of unselected cases. By 1946 [10] he stated that clear grafts could be expected in 90% of suitable cases.

In contrast to this, European reports were less optimistic. For example the report by Francesschetti [11] who included all the visual results, good and bad. Castroviejo cited no exact figures, but gave only approximate numbers of cases and approximate percentages of successful results. All the major figures of this period, Eschnig, Filatov, Tudor Thomas, and Castroviejo, made important contributions to the improvement of penetrating keratoplasty technique, and published results of substantial series of transplants. However, the interpretation of these results is often difficult because of the omission of important data. For example, both Elschnig and Filatov did not mention the standard of improved vision, and Tudor Thomas concentrated purely on graft clarity, and paid little attention to visual results. Data on follow up period, an important factor on transplant evaluation, was often omitted by the authors of this period.

1.1.4 1950 onwards. PK becomes routine surgery

This is the period of most rapid development in penetrating keratoplasty. The earlier pioneers had improved technique considerably, and as early as 1939 Castroviejo [12] had felt able to state that " the results already obtained are sufficiently encouraging to justify its inclusion among the routine surgical procedures of ophthalmology ". Lamellar transplants continued to be used, and were particularly developed in France by Paufique. However, they now formed a small and decreasing proportion of the corneal transplants performed as follows-

Paton [13]	1953	14.8%	USA
Arensten et al [14]	1976	12.0%	USA
Morris & Bates [15] (Moorfields)	1989	5.6%	UK
Australian Graft Registry [16]	1993	4.0%	Australia

However in recent years there has been some renewed interest in lamellar keratoplasty. Benson et al [17] reported on lamellar keratoplasty for keratoconus, focusing on the visual recovery, which was prospectively studied and compared favourably with penetrating keratoplasty reports.

The improvements in penetrating keratoplasty during this period can be attributed to improvements in:-

Instrumentation and Techniques

Understanding of corneal physiology

Understanding of immunology

Preservation techniques

Drugs

1.1.4.(i) Instrumentation and Techniques

The introduction of ultrafine needles permitted more sophisticated suturing techniques. The advantages of the surgical microscope were promoted by Richard Troutman, whose techniques made a considerable contribution towards the reduction of postkeratoplasty astigmatism.

1.1.4.(ii) Understanding of corneal physiology

The role of the endothelium in the maintenance of corneal transparency was better appreciated. The importance of this layer to the transplant surgeon had been suspected as long ago as 1911 [2] , but it was only with the development of endothelial specular microscopes and the work of Maurice*, that the effect of surgery could be investigated. Bron and Brown were the first to quantify the post-operative endothelial cell loss.

[Bron AJ, Brown NA. Endothelium of the corneal graft. *Trans Ophthalmol Soc UK* 1974 **94** 863-873]

1.1.4.(iii) Immunology

The work of Maumenee* allowed the clinical signs of graft rejection to be recognised, and Khodadoust* provided the scientific explanation of those observations. Better understanding of the immunological bases of corneal rejection permitted the use of HLA tissue matched transplants. However, there is contradictory evidence from different studies as to the benefits of this. A more recent discovery [18] is that the immune privilege enjoyed by the cornea is related to its relative acellularity, rather than its avascularity, as had previously been supposed.

1.1.4.(iv) Supply of donor tissue

The rapid expansion in the number of transplants performed in America would not have been possible without a regular supply of viable material. This required organisations capable of integrating the supply of donor tissue with the demands of the surgeon. It was through the work of Townley Paton* that Eye Banks were instituted. The development of techniques for long term storage made Eye Banking easier, by simplifying transportation, improving the quality of material, and allowing tissue matching. One example of this is McCarey-Kaufman* tissue culture media. The need to screen donors for the AIDS and other viruses, put an extra responsibility on the Eye Banks [19, 20, 21] .

* cited by Casey TA. *Corneal grafting. Principles and practice.*(p14-15). 1984 Saunders Philidelphia

1.1.4.(v) Pharmacology

Improvements in therapeutics have been of great assistance to the transplant surgeon, particularly in the field of immunosuppression and antibiotics.

1.1.5 The Changing Indications for Penetrating Keratoplasty

The improvements instituted since 1950 have allowed corneal conditions which were previously considered to be a poor risk, to become treatable with penetrating keratoplasty. This results in changes to the range, and relative proportion of conditions, for which penetrating keratoplasty is performed. There are many reports detailing the indications over a certain period of time, and these have been brought together in Table 1.1. It is easier to see the trends when the data is presented in graphical form, and Figures 1.1 and 1.2 are derived from the data in Table 1.1 for the major indications. The data from the U.S.A. is separated from that of other countries for convenience of interpretation. It should be noted that not all authors used exactly the same categories in their classification system. This meant that some data had to be placed in the section for other indications, which might have been indicated elsewhere, had a more common classification system been adopted.

One of the improvements in keratoplasty technique which is illustrated in Figure 1.1 is the steady increase in keratoplasties for scarring due to Herpes Simplex, which originally had a poor prognosis. This increase is then followed by a decrease, which presumably relates to the increased success of non surgical management of the condition, i.e. the use of anti-viral drugs.

Period	N	Centre		Country	Regraft	Kerato conus	Fuchs	PBK	ABK	Herpes Simplex	Interstitial	Bacterial	Dystrophy Non Fuchs	Trauma	Chemical	Other
1941-45	*	Wilmer	14	USA		21	5.3			4	21		5.3	15.8	10.4	17.2
1946-50	*	Wilmer	14	USA	16	28	8				12	4	8	12		12
1951-55	*	Wilmer	14	USA	16.9	15.6	2.6		0.6	9.7	6.5	6.5	0.6	6.5	7.1	27.4
1947-55	17	Doheny	31	USA		29.4	5.8				5.8			11.7		47.3
1953-59	100	Moorfields	34	UK		6				19	35	20	3	2		15
1956-60	*	Wilmer	14	USA	19.7	11.2	5.9		0.7	19.7	4.6	9.2	5.9		10.5	12.6
1956-61	35	Doheny	31	USA	11.4	14.2	8.5			25.7	8.5	2.8			8.5	20.4
1961-65	*	Wilmer	14	USA	19.1	11.6	12.1		7	13.6	4	8.1	3	4.5	7.6	9.4
1962-67	99	Doheny	31	USA	21.2	15.1	10.1		7	15.1	7	3	5	4	4	8.5
1966-70	*	Wilmer	14	USA	27	13.7	15.2		15.6	4.7	5.1	2	5.9	3.1	3.5	4.2
1968-73	220	Doheny	31	USA	19.5	11.8	12.2		10.4	8.6	3.6	5.9	9	5	3.1	10.9
1971-73	**	Wilmer	14	USA	28.9	20.2	7.1		18.6	7.5	3.6	1.6	4.7	2	2	3.8
1970-74	100	Moorfields	33	UK		27	7		5	15	7	9	6		8	16
1971-75	747	E. Grinstead	36	UK	30.1	18.8	4.8		4	19.6	9.6	0.4	5.2	4.8	2	0.7
1974-78	339	Doheny	31	USA	12.3	11.5	8.5	15	14.7	7.6	3.2	5.8	2.6	5	2.6	11.2
1976-80	876	E.Grinstead	36	UK	35.6	19.1	1.5		11.6	10.2	4.7	0.3	4.4	2	1.3	9.3
1979-83	497	Doheny	30	USA	15.1	6.4	9.1	17.5	10.9	5	2	7.3	3.4	9.3	0.6	13.4
1981-85	1044	E.Grinstead	36	UK	51	11.2	4.5	1.1	4	11	3.4		4.8	3.7	0.5	4.8
1978-87	659	Vancouver	39	Canada	12.1	17.1	8.3	10.5	7.6	9	2.3	3.5	3.8	6.2		35.4
1982-86	511	Melbourne	38	Australia	16	37.2	3.3	7.9	4.3	12.3	0.4	3.8	1.8	4.9		8.1
1985-87	500	Moorfields **	15	UK	17.2	34.2	6.2	5	5.6	3.2	4	3	8.6	2		11
1980-88	1594	Seatle	29	USA	8.1	24	12.5	17.1	4.6	5.3	1.8	6.2	1.4	1.5	0.5	17
1983-88	2299	Wills	28	USA	10.1	15.1	16.3	22.9	14.4	4.4	3.8	2.5	1.7	2.5	0.5	5.8
1984-88	1019	Doheny	27	USA	18.2	7	4.4	28.2	8.6	4.5	0.1	2.8	1.6	0.5	1	23.1
1980-88	175	Belfast	35	UK	9.1	28.6	9.7	1.7		23.5	7.4		4.6	5.1		10.3
1985-88	3941	TBI Inc.	26	USA	17		13	23	10							37
1981-90	999	Utah	25	USA	13.1	24.2	5.8	23	5.6	3		5.7	2.4	0.8	1.3	15.1
1986-90	888	E.Grinstead	36	UK	42.5	19.2	4.7	6.7	4	6.4	3.3		6.7	1.3	1.3	3.9
1987-91	3184	UKTSSA ***	32	UK	18	18.5	11	12.7	5.8	8.2	9.1	2.9	3.7	2.2	1	6.9
1980-91	2962	Paris	37	France	8.6	27.2	8.3	4.5	5	12.4	3.4	1.5		2.7		26.4
1988-92	416	Jerusalem	24	Isreal	7	37.5	0.5		1.9	10.6		14.2	4.8	4.8	0.7	18
1990-92	3466	Australian Graft Registry	16	Australia	14	31	5	17	5	3	0.9	4.1	2			18
1989-93	1104	Doheny	22	USA	21.3	7.1	4.8	24.8	6.4	2.3	0.6	5.8	2.2	2.4	1	21.3

Table 1.1 Changing indications for penetrating keratoplasty (% for each indication). * Wilmer Institute study [14]. Numbers for each 5 year interval not given. Whole series had 1057 eyes (12% were lamellar grafts). ** Moorfields study [15] .5.6% were lamellar grafts. *** United Kingdom Transplant Support Services Authority.

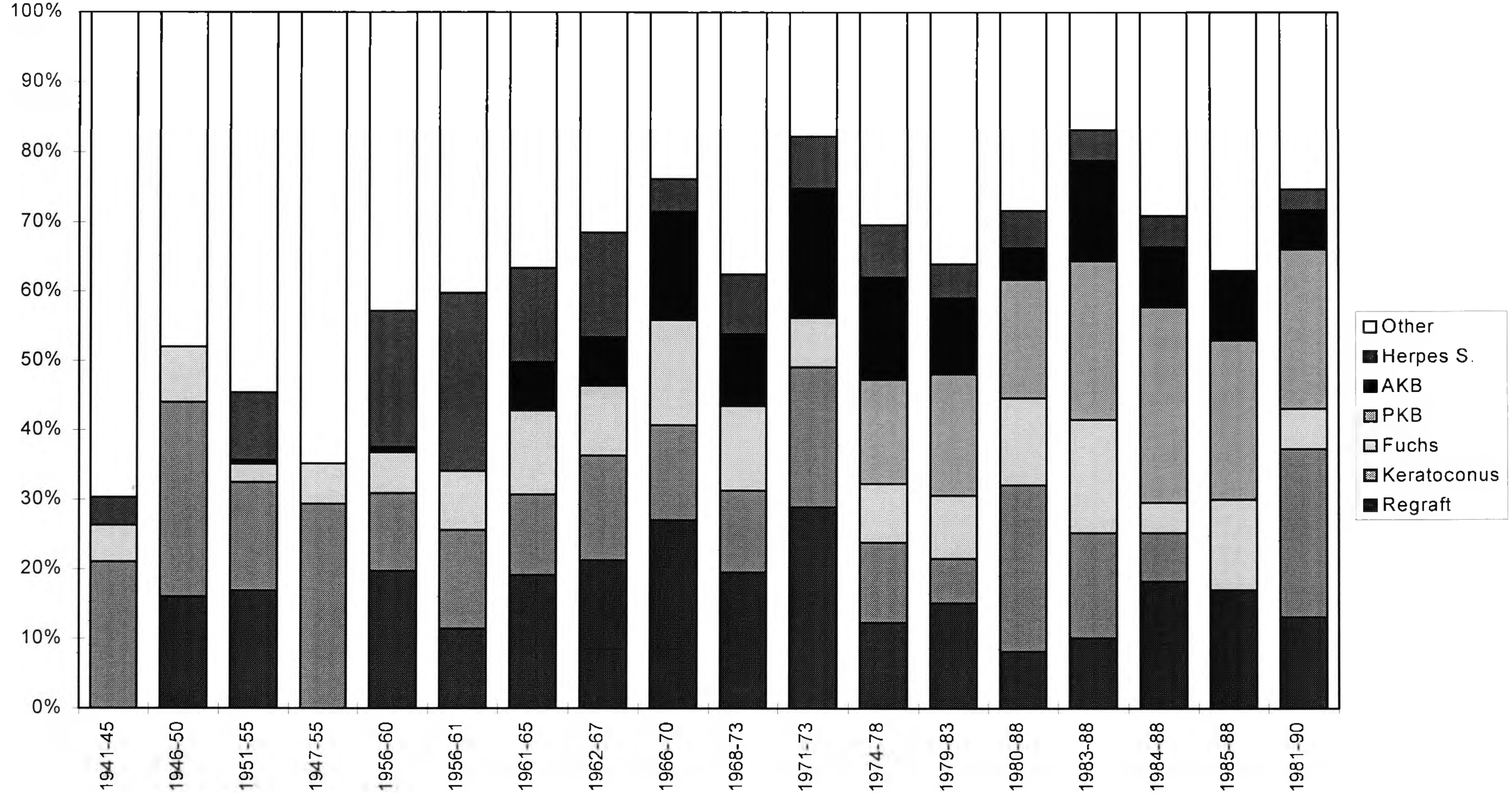


Figure 1.1 Changing indications for Penetrating Keratoplasty. USA. 1941-1990.

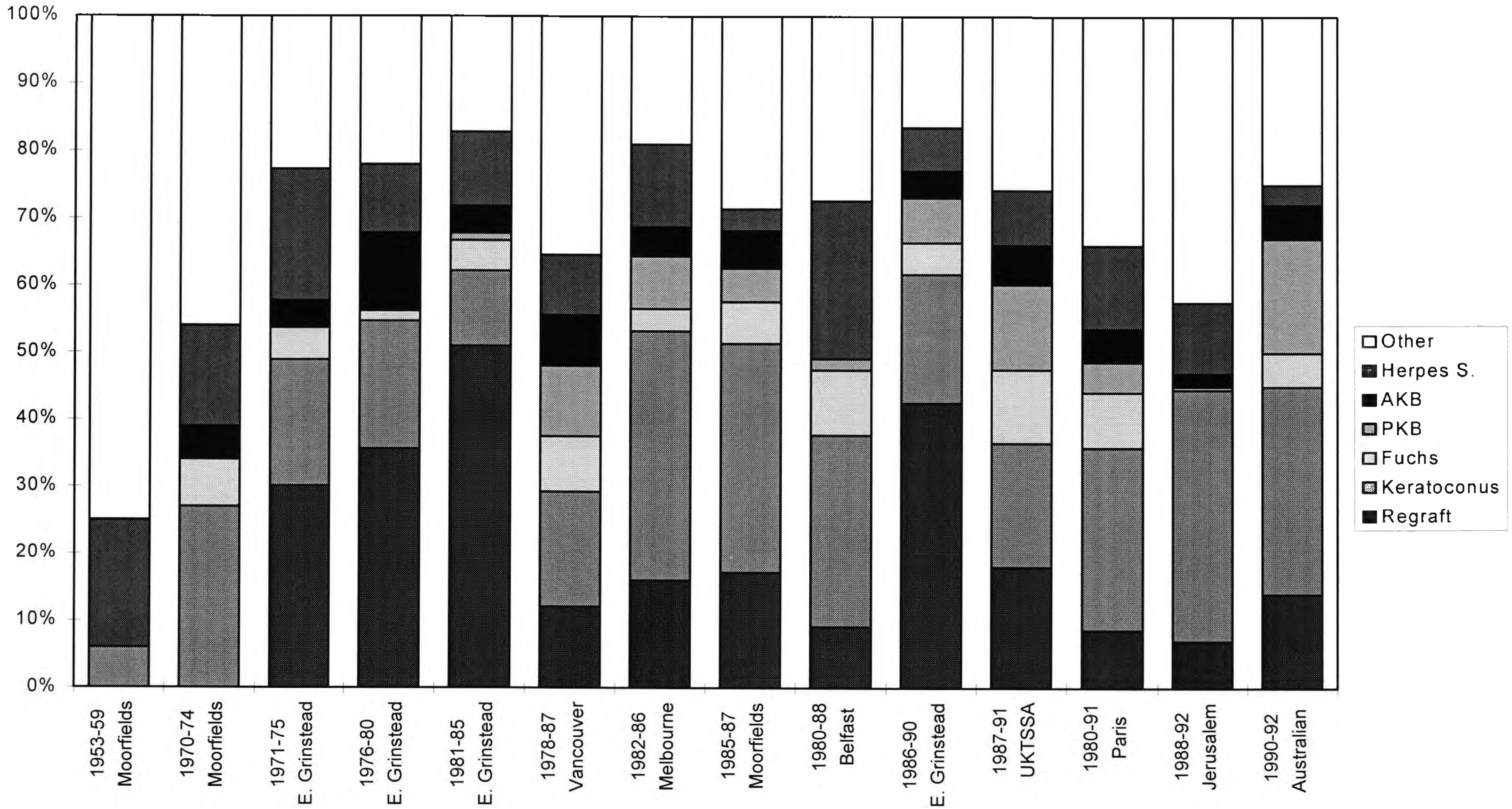


Figure 1.2 Changing indications for Penetrating Keratoplasty. Excluding USA. 1953-1992.

Bullous keratopathy with aphakia was also considered to be a poor risk at the beginning of this period. Success rates for this condition did improve, but another contributory factor could have been an increase in the number of cases presenting with aphakic bullous keratopathy (ABK) due to changes in cataract extraction techniques. This is certainly the case with the rise in penetrating keratoplasties for pseudophakic bullous keratopathy (PBK). The majority of the early intraocular lenses were either anterior chamber or iris-fixed. Despite improvements in techniques PBK remained the leading indication at one American centre [22] in the five year period 1989-1993.

Penetrating keratoplasty is now performed on patients of all ages. One report [23] describes corneal transplant operations that were performed on two infants who had unilateral congenital corneal opacification. Keratoplasty was performed within the first three weeks of life, and after a period of three years both transplants remained thin and clear.

As well as changes over time in the range of conditions treated with penetrating keratoplasty, there are also variations between different countries. These differences reflect varying endemic diseases, differences in the effectiveness of non surgical management, and a diversity of approaches to cataract surgery. This is well illustrated by the study by De Cock [24] of keratoplasty performed at one hospital in Jerusalem, where only 1.9% of the transplants were secondary to cataract surgery, in marked contrast to the more recent (after1970) American studies [25, 26, 27, 28, 29, 30, 31, 14] which range from 18.6% to 37.3% (the contrast with European [32, 33, 34, 35, 36, 37,] Australian [38] and Canadian [39] studies is slightly less marked). He also reports a higher proportion of transplants for keratoconus, which he attributes to difficulties in wearing contact lenses due to a high preponderance of allergic eye disease, and also to the dry dusty conditions.(Climatic conditions were also cited by Mamalis et al [25] for the high percentage of keratoconus in their series in Utah). The difference in locally endemic diseases is highlighted in the Jerusalem study which had microbial keratitis (14.2%) and trachomatous corneal scarring (10.8%) , as the second and third most frequent indications, after keratoconus(37.5%).

Two reports from Pakistan [40, 41] also highlight differences from the western world. In both these studies, scarring due to bacterial infection was the principal indication for keratoplasty.

In addition to differing needs for keratoplasty, non western countries often lack the resources to meet those needs. The resources lacking are equipment, training, and a lack of donor material due to the lack of Eye Banks, and to prejudice against organ donation [42, 43]. The diversity between east and west is highlighted by comparison of the annual number of corneal transplants. The Eye Bank Association of America [44] gives a total of 40,361 for 1990, whereas it is estimated that only a hundred transplants are performed each year in China [43], a country where there is an estimated 0.36 million patients who could potentially benefit from keratoplasty. However, eastern countries did sometimes show similar trends to those found in the west. Surgeons in Korea [45] reported fewer grafts for Herpes Simplex between 1967 and 1989, whereas keratoconus and bullous keratopathy increased.

Differences between individual hospitals within a country can also be seen. For example, the East Grinstead studies show a high proportion of regrafts because they are a tertiary referral centre. Claoue et al [46] have looked at the differences in keratoplasty practice between a teaching hospital, and a district general hospital, which were geographically very close.

1.2 Studies on the outcome of penetrating keratoplasty

1.2.1 Corneal topography consideration

Table 1.2 lists a number of reports on the outcome of a particular series of transplants. It can be seen that in the earlier reports the major criteria for success are graft clarity and improved vision compared with the pre-operative status. As recently as the early 1960`s two papers [7, 47] on the status of corneal transplantations made no mention of post-operative astigmatism, and in 1971 a discussion on the same topic by a panel of experts [8] it was also ignored. However, it can be seen from Table 1.2, that as the years advance, and improvements in technique bring higher proportions of clear grafts, other measures of outcome appear in the type of data collected. Notably measures of astigmatism, either from refraction or keratometry. By 1980 it was becoming recognised that transplant clarity was not sufficient, and consideration of corneal topography became more important. In that year a paper entitled " The principal problems of penetrating keratoplasty: graft failure and graft astigmatism ", was read by David Paton, at a symposium [48] . He commented on the results of a series of 133 of his own patients, but a more detailed account can be found in a paper by his colleague Dr. Perlman [49] .

One of the problems encountered in interpreting the results of the earlier series of transplant operations, is that in some of the studies, the length of time since

Author		#	Date	N	Follow up Min. or Range	Clarity %	Visual improve-ment %	VA	Refraction Cyl.(D) Mean or (Range)	Kerato-metry Cyl.(D) Mean or (Range)	Kerato-scopy
Elschnig		3	1930	139			22				
Filatov		4	1935	96	1-6y	15					
Tudor Thomas		274	1937	36	3M-5Y	58					
Castroviejo		275	1938	100			40				
Owens et al		276	1948	381	4m	36.5	*	*			
Scheie		277	1948	22		50	65				
Cavara & Bietti		278	1948	61	6m		60				
Stansbbury		279	1949	165	6m	45.5	22	*	*		
Franceschetti		11	1949	129		54					
Roberts		280	1950	100	4m	55					
Townley Paton		13	1953	299	2m	64.5	72				
Tudor Thomas		5	1955	100	4m	37					
Fine	A	281	1964	42		55	74				
Rycroft		282	1965	200		59.5					
Anseth	K	283	1967	50	9M-8Y				4.00		
Paton D		284	1970	40	3m			*	*		
Anseth & Palm		285	1971	159			80				
Keates & Falkenstein	K	286	1972	27	1-6y	100	100	*	1-5.5	*	
Troutman & Metzler	K	287	1972	82					4.3		
Pouliquen et al	K	288	1972	50			88				
Jensen & Maumenee		122	1974	99					*		
Witmer et al		289	1974			66			*		
Schwobel		124	1975	141						*	
Pouliquen	K	56	1976	21	1y				*	*	*

Table 1.2 . Selected penetrating keratoplasty series. Where the entire series is for one indication this is indicated: K=Keratoconus; A=Aphakic bullous keratopathy; P=Psuedophakic bullous keratopathy; T= Triple proceedure; R=Repeat keratoplasty. * = data collected

Author		#	Date	N	Follow up Min. or Range	Clarity %	Visual improve-ment %	VA	Refraction Cyl.(D) Mean or (Range)	Kerato-metry Cyl.(D) Mean or (Range)	Kerato-scopy
Moore & Aronson	K	251	1978	64	1y	92					
Richard et al	K	252	1978	50	6m-4y			*	*	*	
Farge		253	1978	330	1y	58		*			
Foulkes et al	A&F	152	1979	64	6-34M				5.30	5.10	
Olson et al	A	147	1979	46	post ROGS				3.22 (0-7)		
Cherry et al		121	1979	153						*	
Ruben & Colebrook	K	57	1979	53	7m-10y					5.0	*
Pallikaris	K	58	1980	105						*	*
Troutman & Gaster	K	112	1980	82	6m	98		*	*	4.0	
De Molfetta et al		254	1980	100	6m				*	4.2	
Olson et al	A	255	1980	59	1y	88		*	*		
Perl et al		146	1981	36†	1 M post ROGS				(†same size)	4.17	
Perl et al		146	1981	47‡	1 M post ROGS				(‡ 0.50oversize)	6.44	
Perlman		49	1981	113					4.87	2.53(SD)	
Bourne		256	1981	84		89		*			
Bourne et al	A&F	143	1982	41	13M					4.4	
Payne	K	257	1982	390	6m	93		*			
Paglen et al	K	258	1982	326	5y	90		*			
Chen	PAED	133	1993	30	14.8					2.84	
Waring et al	A	259	1983	123	18m	84	*				
Ehlers & Olson	K	260	1983	45	3y	98		*			
Kozarsky et al	P	261	1984	26	11m	80		*	4.6		
Heidemann et al		142	1985	99	1M				interrupted sutures	6.38I	
Heidemann et al		142	1985	53	1M				double running sut.	3.75	
Samples et al	P	51	1985	76	2-76m	83		*		4.0	*

Table 1.2 (continued) . Selected penetrating keratoplasty series. Where the entire series is for one indication this is indicated: K=Keratoconus; A=Aphakic bullous keratopathy; P=Psuedophakic bullous keratopathy; T= Triple proceedure; R=Repeat keratoplasty. * = data collected

Author		#	Date	N	Follow up Min. or Range	Clarity %	Visual improve-ment %	VA	Refraction Cyl.(D) Mean or (Range)	Kerato-metry Cyl.(D) Mean or (Range)	Kerato-scopy
Binder	T	262	1985	43	5-60m	100		*		2.75	
de Lavalette et al	K	263	1985	67	5-146m	100			4.7		
Binder	T	264	1986	68					*	3.06	
Crawford et al	T	265	1986	66		90		*	3.2	*	
Puchkowskaya	K	266	1986	266		93.5					
Feldman & Brown		215	1987	25		100		*	1.5	1.4	
Perry & Foulkes	K	151	1987	34	2-6Y					5.00	
Troutman & Lawless	K	52	1987	86	7-39m	100		*		5.4	
Treumer & Dunker		267	1987	81						*	
Meyer & Musch	T	268	1987	166	2-52m			*		5.0	
Girard et al	K	150	1988	72					3.66		
Koenig & Shultz	P	269	1988	17	2-32m	94		*	3.0		
Sayegh et al	K	270	1988	104	6m-9y		96	*	2.6		
Steinert et al	K	271	1988	10	3-81m			2.8	2.6	*	
Wilson & Bourne	K	123	1989	57	1M post ROGS				4.3 2.4	4.4 2.7	
Wilson & Bourne	F	123	1989	19	1M post ROGS				3.7 2.2	5.0 3.5	
Rapuano et al	R	272	1990	150	6m	74	*	*			
Kirkness et al	K	115	1990	201	1Y	97		*	5.6		
Price et al		50	1991	721	1Y			*			
Sharif & Casey	K	114	1991	100	4-16Y	93		*			
Girard et al	K	141	1992	15	5M-4Y				3.78 (1.75 - 6.00)	5.98 (0.87 - 13.62)	
Tuft et al	K	148	1992	60	6-7Y				4.24	0.77mm	
Javadi et al	K	153	1993	38	2M post ROGS				4.55	4.75	
Goble et al	K	113	1994	49					3.8 (0.50-14.00)		
Vail et al		273	1994	2385	1Y	98					

Table 1.2 (continued) . Selected penetrating keratoplasty series. Where the entire series is for one indication this is indicated: K=Keratoconus; A=Aphakic bullous keratopathy; P=Psuedophakic bullous keratopathy; T= Triple proceedure; R=Repeat keratoplasty. * = data collected

keratoplasty is not properly taken into account. For example, data from patients with a follow up of three months may be combined with data from three years. One study by Price et al [50] did look at the effect of time, and was able to show progression of acuity, and that this was most rapid in patients suffering from keratoconus, compared to those with Fuchs` dystrophy, and bullous keratopathy. Unfortunately, this study is flawed by the use of contact lens acuities in some cases. This tends to mask the topographical irregularities that are probably the cause of reduced visual acuity. The use of best corrected acuity measures after selective suture removal [51, 52], also makes the true comparison with other studies difficult.

1.2.2 The use of photokeratoscopes, and computerised topographical analysis.

Even though photokeratoscopes and computer analysis can give much more data, especially about the transplant periphery, they do not feature much in Table 1.2 in studies on graft outcome. Amsler [53, 54] working in the late 1940`s, was one of the first to see the opportunities offered by the photokeratoscope in the study of corneal transplants. Rycroft in his book (1955) [55] commented on Amslers` work:- " Thus it is seen that it is very instructive to follow up cases of corneal grafts by means of successive keratography. This is an objective standard which is convenient to study in parallel with the subjective criterion of the visual acuity in assessing the final operative result."

The idea of successive assessments of graft topography does not appear to have been taken up. In 1976 Pouliquen et al [56] used a photokeratoscope to document the irregularities of graft contour, as did Ruben and Colebrook [57] in 1979. The following year Pallikaris [58] used a photokeratoscope to compare pre-operative to post-operative topography. However, he appears to have limited its use to identifying the axis of astigmatism. In recent years there has been more use [59, 60, 61] of photokeratoscopes and computerised topography analysis on transplants, in order to plan refractive surgery, or selective suture removal.

1.2.3 Sequential evaluation

A truely sequential assessment of transplant topography was carried out by Khong [62] and her co-workers. This was a small study of 8 subjects with a limited follow up time of six months, and some of the data at six months may have been confounded by selective suture removal. However, this study does demonstrate the rate of change in topography in the early months of the transplant history. In particular, there appears to be a relationship between the improving measures of topographical regularity,(Surface Asymmetry Index and Surface Regularity Index), and the improvements in visual acuity.

1.3 The effects of irregular post keratoplasty topography.

1.3.1 Contrast sensitivity

Carney and Jacobs [63] used contrast sensitivity tests to demonstrate subtle visual decrements when comparing control subjects to those who had undergone penetrating keratoplasty for keratoconus. This effect was enhanced in the presence of a glare source. Wicker [64] and her co-workers found a difference between contact lens and spectacle contrast sensitivity, particularly in the mid to high spatial frequencies.

Mannis et al [65] also found a contrast sensitivity deficit when they compared 29 successful transplants to matched controls, where traditional Snellen acuity showed no difference. This is in contrast to a smaller study [66] of 7 eyes, published by the same authors, three years earlier. These 7 eyes all fell within the 95% confidence limits of the normal contrast sensitivity curve. Two papers [67, 68] have pointed out the difficulties in refracting eyes with corneal transplants, and suggested that information on corneal topography from either keratometer, or preferably photokeratoscope, can be used in the process of refraction. Rowsey et al [67] showed how graft asymmetry along one meridian can affect the retinoscopy reflex, and how graft tilt or dehiscence, can affect the photokeratoscope image. Mannis and Zadnick [68] pointed out that the photokeratoscope image can often explain why a clear transplant, with regular central keratometry, has poor acuity.

1.3.2 Need for contact lenses

Several studies have examined the proportion of patients who require to wear contact lenses to get optimal vision. Smiddy et al have written two papers on this subject, based at the same institution. In the earlier study [69] 60% wore contact lenses, while a later report [70] found only 27%. A large multi-centre centre study [71] gave a figure of 56% contact lens wearers.

Many papers have addressed the problems of fitting contact lenses on corneal transplants [72, 73, 74, 75, 76, 77, 78, 79, 80, 81].

William's et al [82] used a questionnaire to elicit the patients perceptions of the success of their transplant. One of the major reasons for dissatisfaction, was problems with contact lens wear. Coster [83] has discussed the results of this study, and advocated that the needs and lifestyle of the patient, need to be taken into account when considering criteria for success.

1.3.3 Need for refractive surgery

In cases of high astigmatism where spectacle correction fails to provide adequate visual rehabilitation, and where contact lens fitting is also unsuccessful, the patient is left with an eye that is essentially non functioning. These patients must then undergo further surgical intervention in an attempt to reduce the astigmatism.

A number of surgical methods have been proposed to correct post surgical astigmatism. As long ago as 1894 Bates [84] observed that a circumferential corneal incision lengthens the radius of curvature of that corneal meridian which is at right angles to the line of incision. He observed further that “the amount of astigmatism produced is greater the nearer the incision is to the centre of the cornea; and the amount of correction can be regulated by the number, depth, and location of the incisions”. In 1976 Barner [85] reviewed the different approaches to corneal section, thermal cautery and corneal resection, that were available at that time. He concluded that the only procedure which had a future was the crescent wedge resection. This was first described by Troutman in 1970, with quantification of results in a subsequent report in 1973 [86] . In this procedure the flat meridian is steepened by excision of a wedge of tissue following the line of the keratoplasty wound, and the gap closed by tight sutures. It is associated with a coupling effect, a simultaneous steepening of the flat meridian, and flattening of the steep meridian. The amount of steepening is approximately twice as much as the accompanying flattening. This technique has continued to be used in modified forms [87], and with specially designed knives [88, 89]. Van Rij and Waring [90] attempted to clarify the mechanisms by which incisions and sutures alter corneal astigmatism, by studying their effects on human eye bank eyes. A review [91] of 14 wedge resections carried out at one hospital over a period of six years, concluded that it remained an effective and moderately predictable technique.

Troutman [92] further advanced microsurgical techniques for the correction of post keratoplasty astigmatism by describing, in 1977, relaxing incisions placed in the steep meridian. These induced flattening of the steep meridian, and a corresponding steepening of the flat meridian, by a roughly equal amount. He found that the relaxing incision procedure had advantages over wedge resection in that it can be performed at the slit lamp, gives no initial overcorrection, and has a much shorter post operative course. This was confirmed by Krachmer and Fenze [93], who compared relaxing incisions to wedge resection. They found that the average reduction in corneal astigmatism was greater for the wedge resection, 6.50D as compared to 4.25D. However, the relaxing incision operation was successful in 75% of cases, with stabilisation of curvature in an average of three weeks, unlike wedge resection which usually took months. Various modifications have been made to the procedure in an effort to improve predictability, and also allow the surgeon to titrate the effect towards a particular goal. The effect can be augmented by the use of compression sutures placed on each side of the donor/host interface, 90 degrees away from the relaxing incision. [94, 95, 96, 97, 98,]. Satisfactory results [99] have also been reported with compression sutures employed without relaxing incisions. Some surgeons incise the original keratoplasty wound [94, 95, 96], while others place the incision within the donor tissue 0.5mm from the original wound. Generally the host tissue is left undisturbed in case regrafting becomes necessary. The number and distance of the incisions from the optic centre can be varied according to the effect desired [100]. This follows a study [101] on cadaver eyes which showed a direct linear relationship between corneal astigmatic change and decreasing optic zone size, and also to increasing incision length (when measured in degrees). Other surgeons [102] varied the number of incisions, then added compression sutures or semi-radial incisions if the initial incisions did not achieve the desired results. The inclusion of the semi-radial incisions effectively changed the procedure to trapezoidal astigmatic (Ruiz) keratotomy. This procedure has been shown to lack predictability [103], and Lindstrom [104] states that it has largely been abandoned in treating post keratoplasty refractive error. Another variation [105] of the standard relaxing incision procedure involved the planned spreading and recutting of the initial relaxing incision at one to three week intervals following the initial incisions. The wound was deepened and lengthened if more effect was required. Computerised videokeratoscopy has been used to study the effects of relaxing incisions on eye bank eyes [106]. It was also used in a retrospective analysis of six patients who underwent relaxing incisions [61], and it was used prospectively to plan the procedure [107]. The colour coded videokeratograph was used to identify the steep and flat semi- meridians, which were generally not orthogonal. The location of the incisions and the compression sutures, and also the incision length, was determined on the basis of individual topography.

Although these refractive surgery techniques can initiate large changes in postkeratoplasty astigmatism, the lack of predictability has remained a problem, despite the modifications which have been introduced over the years. Price and Whitson [108] reviewed 111 consecutive patients who received relaxing incisions between 1982 and 1989. Their analysis revealed a highly variable result, and although other authors reported similar average amounts of correction, they found a large variability between the results in individual patients. One of the earliest series of patients commenced in 1976, and consisted of 16 patients [109]. The surgical technique was the same in each case, yet the net decrease in astigmatism varied from a maximum of 8.88D, to as little as 0.75D. Critical analysis of the results of more recent studies reveals that the problem of predictability still remains. This can be seen in the study which had the benefit of computerised videokeratoscopy to plan the incisions [107]. This was published in 1991, and the amount of astigmatism reduced varies from 97% to 29%.

In addition to the lack of predictability, there is also the risk of complications. This is generally not thought to be high, but one study [102] on relaxing incisions proved to be an exception. There were only six patients involved, yet the complications included perforations in two cases, and graft reaction in two cases.

Despite these limitations, both relaxing incisions and wedge resection, have become part of the routine armamentarium of the surgeon faced with high degrees of post keratoplasty astigmatism.

The following protocol for astigmatism management was drawn up for one American hospital [110].

Astigmatism(D)	Surgical Approach
0 - 4	Observation or relaxing incisions
4 - 8.5	Relaxing incisions only
8.5 - 16	Relaxing incisions with compression sutures
16 - 20	Wedge resection, double wedge resection, or repeat penetrating keratoplasty
>20	Repeat penetrating keratoplasty

This agrees with the opinion of Troutman [111], who considered the relaxing incision to be the operation of choice for astigmatism less than 15D. Troutman [112] estimated that 27% of a series of keratoconics had "excessive" post operative astigmatism. In a study [86] quantifying the results of his wedge resection, he reported that 8% of a group with various indications for keratoplasty, had astigmatism greater than 9D. This was similar to the proportion of keratoconics requiring refractive surgery at various British centres.

St. Thomas'[113]	6%
East Grinstead [114]	8%

Moorfields [115] 18%

It can be seen that although these techniques are available, they are by no means a panacea. The fact that new solutions are being sought, confirms this. For example trials [116, 117] have been conducted to assess the suitability of Excimer Laser photorefractive keratectomy for irregular post keratoplasty astigmatism.

The seemingly intractable problem of post keratoplasty astigmatism means that many patients will only recover visual function with the accompanying side effects, such as the distortion and differential meridional magnification inherent in astigmatic spectacle correction. Alternatively they will be forced to wear contact lenses. For a significant proportion the only option will be further surgery which is uncertain in outcome, and not entirely without complications.

1.4 Aetiology and control of post keratoplasty astigmatism and topographical irregularity.

Many factors are thought to be associated with irregularity of corneal curvature after transplantation. The following list was drawn up by Binder in 1987, and it will be used as the outline structure for discussing the aetiology of post keratoplasty astigmatism.

Factors associated with post-keratoplasty astigmatism and topographical irregularity:

[Binder PS. Refractive errors encountered with the triple procedure. *Trans New Orleans Acad Ophthalmol* 1987 111-120]

Pre-surgical Factors

- Donor astigmatism, scars

- Donor age (paediatric cornea)
- Recipient corneal condition (thickness, oedema, vascularisation)
- Recipient astigmatism
- Previous keratoplasty

Surgical Factors

- Trephination error
- Eccentric trephination (donor and/or recipient)
- Trephine nicking, “walking”
- Trephine tilt
- Trephine with/without obturator

Suture Technique

- Suture form
- Combinations
- Donor/recipient disparity

Post Surgical Factors

- Focal wound vascularisation
- Donor/recipient melting

- Suture erosion, compression, torque
- Timing of suture removal and technique
- Wound dehiscence, override
- Wound healing

1.4.1 Pre-surgical Factors

1.4.1.(i) Recipient:Phakic/Aphakic

Perlman [49] used retrospective data to study which factors seemed to be most significant in creating excessive post-operative astigmatism.. All the patients who underwent penetrating keratoplasty by an individual surgeon in the period 1976-77, and whose best corrected VA was 6/18 or better, were included, giving a total of 113 eyes. Unfortunately, the time since keratoplasty was not included. This means that comparisons may have been made between transplants that were at a different point in the healing or topographical adjustment process. Furthermore, Perlman used a mixture of keratometry astigmatism and refractive astigmatism. These two measures of astigmatism are not equivalent, (Judge [118], Lugo et al [91]). One finding in the Perlman study was that patients who were aphakic prior to keratoplasty showed significantly higher astigmatism. On the other hand, when lens extraction was performed at the same time as keratoplasty, the astigmatism was not significantly higher than for phakic patients. Perlman attributed these findings to the absence of the lens-zonule diaphragm which might make the corneal ring less stable, and therefore more likely that there could be distortion and ballooning of the recipient aperture at the time of trephination.

Another study, by Samples and Binder [51], made a similar comparison between patients who had cataract extraction prior to keratoplasty and those who had extraction at the same time as keratoplasty. In this case the comparison was between patients who received corneal transplants because of psuedophakic bullous keratopathy (PBK), and those who underwent a triple procedure (penetrating keratoplasty, lens extraction and intraocular lens implant). It was found that significantly greater astigmatism was found in the PBK group (4.00 D compared to 2.93D), and this was attributed to prior treatment with corticosteroids and stromal oedema.

Van Rij and Waring [119] found that buttons trephined from aphakic eye bank eyes, were 0.11mm larger than those obtained from phakic eyes, under the same trephine conditions. However, there were only five eyes in each group, and the difference was not statistically significant.

Hartden et al [120] showed that transsclerally sutured posterior chamber lens (TSPCL) placement distorted the recipient bed shape at the time of keratoplasty. A retrospective study of 73 patients with bullous keratopathy who underwent penetrating keratoplasty, and placement of TSPCL, was carried out. This showed a bimodal distribution of the axis astigmatism. which showed that the axis was related to the positioning of the TSPCL. A study of cadaver eyes was then carried out. It showed that if suture fixation of the haptics of the TSPCL was within 0.75mm of the limbus, the recipient bed was widened by 0.3mm along the meridian of the haptics. Whereas this meridian was narrowed by 0.2mm if fixation was 3mm posterior to the limbus. It is interesting to note that in the retrospective study, the relationship between the axis of astigmatism, and TSPCL placement, was only statistically significant in the early post-operative period (4.4 ± 3.2 months). At the final visit, mean post-operative period 26.2 ± 10.9 months, the axis of astigmatism was random. This may have been due to the influence of selective suture removal.

1.4.1.(ii) Host Disease.

Perlman [49] found no significant difference in astigmatism between the different host diseases requiring keratoplasty. Cherry et al [121] also found similar results for astigmatism amongst the different diagnostic groups in their study of 153 patients. However, the point in the graft history when astigmatism was assessed was not standardised. This ranged from less than five months to over 24 months. Although no sequential measurements of astigmatism were made, the authors felt able to quote a mean rate of reduction in astigmatism of 0.036 Diopters per month of follow-up. Jensen & Maumenee [122] also found no difference for astigmatism between different diagnostic groups (follow-up period not reported). Part of the study by Wilson & Bourne [123] compared the post suture removal astigmatism of a group of 64 keratoconics to 19 patients suffering from Fuchs` dystrophy. Both groups underwent the same surgical technique (0.25mm oversize donor, and double running suture), and there was no difference in either keratometric or refractive astigmatism. These findings contrast with those of Schwobel [124] who found higher astigmatism in patients with keratoconus. Bigar [125] on the other hand, found exactly the opposite. He reported the results of 425 penetrating keratoplasty operations performed between 1980 and

1985. Two diagnostic groups were compared, one with keratoconus (N=220), and the other with "degenerations" (N=105). The latter also included herpes simplex, trauma, aphakia, psuedophakia, and congenital glaucoma. The final astigmatism was significantly lower in the keratoconus group (4.6D versus 5.3D). A study by Insler et al [126] of 31 patients who were aphakic or psuedophakic found that those with Fuchs` dystrophy showed the least astigmatism (2.09D), while scarred corneas demonstrated the greatest astigmatism (6.20D). The difference was statistically significant (p=0.005). Binder [127], in a study on selective suture removal, found that keratoconics demonstrated more astigmatism than other diagnostic groups, but this difference was not statistically significant.

However, it is thought that recipient tissue weakness may be one cause of astigmatism following penetrating keratoplasty. This theory was tested by Au et al [128] who investigated the effect of controlled surgical thinning of one area of the host cornea following penetrating keratoplasty. This was done by a lamellar keratectomy (6x3x0.25mm) in a rabbit model. The corneal topography was monitored with a 12 ring corneascope, before keratectomy and then at 5 days and 28 days post-keratectomy. The change in astigmatism was calculated by using vector analysis, to convert the pre and post keratectomy astigmatism into x and y components. The y component lay along the meridian containing the keratectomy, and was found to flatten by 5.07 D at day 28, confirming that tissue weakness can induce astigmatism. However it should be noted that this was the mean change for all 10 eyes, and the standard deviation was high (5.53 D), with four eyes showing little or no change due to the keratectomy.

1.4.1.(iii) Previous keratoplasty

The study by Perlman [49] found significantly less astigmatism in repeat transplants.

1.4.1.(iv) Recipient Corneal Curvature.

Katz & Forster [129] conducted an investigation into the factors affecting calculations of intraocular lens power in triple procedures. They looked for any effect of recipient curvature on the outcome, but they could find no correlation between the pre-operative and post-operative keratometry readings. This is in contrast to the findings of Pallikaris [58] who compared the pre-operative and post-operative topography of 105 patients who underwent penetrating keratoplasty for keratoconus. He used a Placido disc based analysis system, and he found that in 64% of the cases the post operative axis of astigmatism correlated well (within 30 degrees) with the pre- operative axis. Binder [130] used multiple regression analysis on the results of 108 penetrating keratoplasty operations. He found that the pre-operative astigmatism did not predict post-operative astigmatism.

1.4.1.(v) Donor corneal curvature

A small study by Abdel-Hakim[262] has indicated that there may a relationship between donor corneal power and post-operative transplant power. Dave [131] developed a keratometer which can conveniently be used to measure cadaver eyes, and found similar results. However this was also a very small study (N=5), and it appears that only mean keratometry readings were taken with no reference to astigmatism.

Van Rij and Waring [119] investigated the influence of high astigmatism on the shape of the button obtained by trephination. They found comparable shapes to that achieved in spherical corneas. Although the mean astigmatism was high, 16.2 D, this was induced by an anterior radial suture across the limbus, which may have been neutralised simply by the pressure of the trephine.

1.4.1.(vi) Donor age

Studies of adult transplant recipients receiving infant donor tissue (younger than two years of age), have reported very steep transplant curvatures [258-260] and a myopic shift [258 259], as well as normal transplant curvatures [259 260], and no myopic shift [259 270]. The probability that steep high powered transplants will result, has encouraged some surgeons [132, 133] to use paediatric donor material to correct large ametropias in aphakic patients undergoing penetrating keratoplasty. However, in the opinion of Koenig [134] the inability to predict the post-operative refractive error and the difficulty with contact lens correction (should that be necessary) make this an unsuitable form of refractive keratoplasty. He also states that infant donor corneas are more flexible, making manipulation during surgery more difficult. There is no evidence that this flexibility, or the steepness of the donor disc compared to the host, are responsible for increased astigmatism or topographical irregularity. In fact one study [133] using donors from new-borns aged 1-28 days, in 30 cases with an average follow-up of 14.8 months, found the mean keratometric astigmatism was only 2.84D.

It might be reasonable to assume that patients younger than two years of age who required a transplant might achieve best refractive results with tissue from a donor of the same age. However, Gloor et al [135] have shown that younger recipients will encounter myopic shift similar to adults who receive material from younger donors.

1.4.2 Surgical factors

1.4.2.(i) Donor Diameter

(a) Astigmatism and irregularity

Smaller transplants , less than 6.5 mm create larger amounts of astigmatism, whereas larger, greater than 8.5 mm, closer to the limbal vascularisation, have a higher risk of rejection [136]. This clinical observation is born out by theoretical calculations published by Olson [137]. His mathematical model predicted that disparity of size between donor disc and recipient opening has more effect on the final curvature if smaller trephines are used. For instance he has shown that a donor disc of 4mm combined with a recipient bed diameter of 5mm, would effect the final curvature twice as much as a combination of 7mm donor and 8mm recipient, even though the disparity is 1mm in each case. However, Olson also points out that at about the 7 to 8mm trephine size, improvement with increased donor size is relatively minimal. In fact Jensen & Maumenee [122] found a tendency towards higher astigmatism with increasing transplant size in this range. The mean values for the keratoconic group (N=39) changed from 3.35 DC with a 7.00 mm disc, to 4.62 DC with a 8.00 mm disc. A similar trend was found for the non keratoconus group, but no differences were statistically significant.

1.4.2.(ii) Donor / host disparity

A number of studies have looked at the effect of difference in diameter between the donor button and the host aperture into which it is placed. Olson and Kaufman have shown that high intraocular pressure is related to crowding of the chamber angle in aphakic keratoplasties [138, 139]. However the effect of varying the donor size on glaucoma does not appear to be an important issue in phakic keratoplasty [140,141,142], and surgeons have experimented with the effect of differing graft/host disparities on the resulting corneal topography. The results are generally given as either the refractive error expressed as the spherical equivalent; or as astigmatism expressed in terms of refractive cylinder, or keratometry astigmatism.

(a) Spherical equivalent

The difference in diameter between the donor button and the host aperture has a direct influence on the post-operative corneal curvature. An oversized graft will result in steeper curvature than one that that has been matched to the host. Several studies have investigated the difference between matched and 0.5 mm oversized grafts. (Bourne [143], Duran [144], Heidemann [142]). They show an average difference of three Diopters or more. Troutman [145] gave a more precise quantification of the effect. He stated that for every 0.1mm increase in donor button diameter over the recipient bed diameter there will be a corresponding increase in average keratometry of 0.67 D. Other studies [146, 147] found no difference in spherical equivalent. Keratoplasty for keratoconus often results in undesirable amounts of myopia, and has been the subject of several studies. Goble et al [113] advocated the use of same size transplants, and Girard et al [141] recommended the use of transplants 0.25mm smaller than the recipient bed. Studies of keratoconic keratoplasty by Tuft et al [148] and Lanier et al [149] have shown that corneal curvature is not the only determinant of the spherical equivalent refractive error, and that axial length must also be considered.

(b) Astigmatism and irregularity

Perl et al [146] compared a group of 36 with same size grafts, to a group of 47 with 0.5 mm oversize grafts, and although they found no difference between the means of each group in terms of final refractive error (spherical equivalent), they did find that the over size grafts produced significantly more keratometric astigmatism (6.44 D against 4.17 D). A similar study by Olson et al [147] found no difference in spherical equivalent or refractive astigmatism, (patients were either aphakic prior to keratoplasty or underwent a combined keratoplasty and lens extraction). Girard et al [150] compared the post suture removal refractive astigmatism (under cycloplegia) for three groups of transplants for keratoconus, (Graft = Host, N=55, 4.19 D; Graft<Host, N=6, 2.82 D; Graft>Host, N=11, 3.66 D). The grafts which were smaller than the recipient opening had less refractive astigmatism (P<.01). It should be noted that the surgical technique employed in this study involved the cauterisation of the cone prior to trephining the host cornea. This effectively enlarges the aperture due to shrinkage of the central area. In contrast to this Heidemann et al [142], in a large randomised prospective trial comparing 93 over sized grafts to 80 same sized grafts, found no difference in post-operative keratometric astigmatism.

Perry & Foulks [151] conducted a study on 34 keratoconus patients. In all cases the removal of the host button was initiated with a 7.5mm trephine, and half of the group received a similar size donor button, while the remaining 17 patients received a donor cut with a trephine 0.5mm larger. The post suture removal keratometric astigmatism was significantly larger for the oversize group (5.97 D compared to 4.02 D $p < 0.05$).

This is in contrast to an earlier study carried out by the same authors [152] in 1979. This reviewed the cases of 64 patients suffering from either Fuchs` dystrophy or aphakic bullous keratopathy. No significant difference in refractive or keratometric astigmatism was found between the same size and the 0.5mm oversize groups. However, variation in the actual size of donor disc could have occurred because some were cut from the posterior surface against a teflon block, while others were obtained by trephination from the anterior surface in fresh, moist chamber-stored eyes. Also it is not clear whether astigmatism was assessed before or after suture removal.

Bourne et al [143] performed a similar study (41 aphakic patients suffering from either Fuchs` dystrophy or aphakic bullous keratopathy, who received either same sized or 0.5mm oversized transplants). At no time in the 13 month follow-up, including after suture removal, was there any significant difference in keratometric astigmatism.

In 1993 Javadi et al [153] published the results of a study which compared two groups of keratoconic patients, one with a donor trephine 0.25mm larger than that used for the recipient bed (N=18), and the other group with a trephine 0.50mm larger (N=20). They found no significant difference in refractive or keratometric astigmatism.

Wilson and Bourne [123] also studied keratoconus patients. They compared 13 eyes transplanted with a donor button cut to the same size as the recipient bed, to 57 transplants which were 0.25mm over size. No significant difference in refractive or keratometric astigmatism was found.

Goble et al [113] reported the results of a retrospective analysis of 49 transplants for keratoconus. All had the same size trephine for both host and donor corneas. The mean post operative refractive astigmatism was 3.8D (range 0.50 to 14.00). Unfortunately there was no control group for comparison, but the authors were of the opinion that the use of same size transplants in keratoconus might lead to post operative astigmatism. This was because the tension in the continuous suture needs to be greater when the same size host and donor trephines are used, in comparison with the tension in an equivalent suture used to secure an oversized button. The tight suture tends to compress those areas of the host which are thinner, more elastic or ectatic, whereas more normal areas of the host are less compressed. This may have the effect of reducing irregular astigmatism.

The mathematical model developed by Olson [137] considers the effect donor/host size disparity has on the chord length from donor margin to donor margin. Changes in this chord length are then assumed to be solely responsible for changes in the transplant curvature. Olson points out that the major factor determining the induced curvature change is the amount of disparity taken up by the recipient cornea. For example, if the recipient corneal tissue bends, stretches or compresses such that the chord length across the recipient opening exactly matches that of the donor disc, there will be no change of curvature induced in the donor. This ideal situation is unlikely, and Olson has shown mathematically the induced curvature change has a linear relationship with the proportion of wound disparity taken up by the recipient cornea. This may not seem a particularly helpful finding, since this is not a factor that can be measured. However, it does show how much this unpredictable variable can effect the curvature change induced by tissue disparity. This may account for the variation reported in the literature, with a range of zero to four diopters resulting from each 0.1mm of wound disparity [137].

Table 1.3 summarises the results of the studies which have investigated the effects of donor/host disparity on post operative astigmatism. Only three studies show a statistically significant difference, and it is difficult to draw any firm conclusions because different studies involved varying patient diagnoses and surgical techniques. The larger figure for astigmatism has been highlighted on Table 1.3, and it is interesting to note that generally the trend was for the same size transplants to have more astigmatism than the 0.5mm oversize transplants. Curiously it was only those studies which did have a significant difference that showed the opposite trend.

1.4.2.(iii) Trephination

(a) Introduction

Although studies involving the intentional oversizing or undersizing the donor button relative to the recipient bed have failed to demonstrate a systematic effect on post-operative astigmatism, many corneal surgeons believe that the actual trephine technique (for both donor and recipient) plays a major role in the aetiology of post-operative astigmatism. The work of various researchers indicates that a small disparity

Author	#	Date	Retro/Pro-spective	Same surgeon	Diagn-osis	Interupted or running suture	Follow up	Under size donor	N	Astigm-atism D	Equal size donor	N	Astigm-atism D	Over size donor	N	Astigm-atism D	Method	Sig. diff.
Perl et al	146	1981	R	Yes	M	Mix	min 1.5 M Post ROGS				=	36	4.17	+0.50	47	**6.44**	Ker	Yes
Girard et al	150	1988	R	Yes	K	Int	post ROGS	-0.25	6	2.82	=	55	**4.19**	+0.50 & +0.25	11	**3.66**	Ref	Yes
Perry & Foulks	151	1987	P	2 Surgeons	K	Run	min 1.5M post ROGS				=	17	4.02	+0.50	17	**5.97**	Ker	Yes
Olson et al	147	1979	P	No	A	Run	post ROGS				=	25	**3.33**	+0.50	21	2.93	Ref	No
Heidem-ann et al	142	1985	P	2 Surgeons	M	Mix	1M post ROGS				=	66	**5.80**	+0.50	86	5.21	Ker	No
Foulks et al	152	1979	R	No	ABK Fuchs	94%Run 6% Int	6-9M post op				=	32	**4.10**	+0.50	32	3.60	Ref	No
Bourne et al	143	1982	R	Yes	ABK Fuchs	Run (double)	1M post ROGS				=	**15**	**4.50**	+0.50	5	3.8	Ker	No
Javadi et al	153	1993	P	Yes	K	Run	2M post ROGS				* +0.25	18	**4.6** (R) 4.6 (K)	+0.50	20	4.5 (R) **4.9** (K)	Ref Ker	No
Wilson & Bourne	123	1989	R	Yes	K	Run (double)	Min 1M post ROGS				=	13	**5.4** (R) **5.7** (K)	+0.25	57	4.3 (R) 4.3 (K)	Ref Ker	No

Table 1.3 Studies showing the effect of donor/recipient disparity on post-operative astigmatism

* This study compared +0.25mm oversize to +0.50mm oversize

** Astigmatism with undersize was significantly less than either same size or oversize

R = Retrospective P = Prospective M = Mixed K = Keratoconus A = Aphakic ABK = Aphakic Bullous Keratopathy

Ker = Keratometer Ref = Refraction Sig. diff. = Significant difference in one meridian versus another could create significant astigmatism. Studies in which the disparity was intended to be equal in all meridians gave the following keratometric power changes for a 0.05mm disparity: Heidemann [142] 2.7D; Duran [144] 3.3D; Bourne [143] 2.7D. Troutman quoted his results as 0.67D per 0.1mm disparity. However, when the disparity is intentionally created in only one meridian, as in refractive surgery to reduce post keratoplasty astigmatism, the figures are slightly different. When Troutman [86] first quantified the effects of his wedge resection operation on 10 patients, he found a mean reduction of astigmatism of 8.7D for a wedge which was 1.5mm at its greatest width. It should be noted that in this case both the steep and flat meridians were changed. The principal effect is to steepen the flat meridian by removing tissue along that meridian, but flattening of the steep meridian also occurs.

(b) Tissue excess or deficiency

Cohen et al [154] tested the hypothesis that the meridian with the relatively greatest amount of tissue at the wound would become the direction of the flattest meridian, and the meridian with the relatively least amount of tissue at the wound would become the direction of the steepest post operative meridian. They performed penetrating keratoplasty on 8 cats, and measured photographically the shape and size of the donor button, and host bed, prior to suturing. This information on the inaccuracies of each trephine cut was fed into a computer programme which identified the meridian of most overlap between donor and host, and the meridian of most tissue deficiency. The resultant steep and flat meridians were sufficiently closely aligned with the meridians of tissue deficiency, and overlap, to indicate that the hypothesis was correct. They used photokeratoscopy combined with their own Photogrammetric Index Method of keratograph analysis, but they were unable to quantify the relationship between tissue disparity, and topography. Measurements were taken at 42, 161, and 289 days, and it is interesting to note that the relationship between meridian of tissue disparity, and topography became less evident as time went on. There was also a tendency for the topography to become more symmetrical with time. The authors believed that corneal elasticity allowed the topography to change towards its pre- operative symmetrical shape.

Mahjoub and Au [155] set out to quantify the relationship between tissue shape disparity and the resultant astigmatism. They investigated the effects of creating an oval donor or an oval host bed by a block resection of a crescent of tissue 0.5mm x 6.0mm. Rabbits were used; 18 with oval donor. 15 with oval recipient, and 14 as a control group with round host and donor. They used a 12 ring photokeratoscope to assess the topography at 75 days after transplantation. Their analysis consisted of the amount of astigmatism and its axis, so it appears that the photokeratoscope was being used as a convenient way of obtaining keratometry readings on animals. The axis of astigmatism was then referred to the meridian of tissue disparity, by using vector analysis to determine the net change. They found 4.4D of astigmatism induced by the oval recipient, and 7.2D when the tissue crescent was removed from the donor. They believed the higher figure was due to the site of tissue removal being closer to the optical centre. The average spherical keratometry measurements (i.e. the mean of the two keratometry readings) remained the same for all three groups, including the control group. This implies that steepening of the axis of tissue deficiency must have been accompanied by a similar amount of flattening of the other principal meridian.

Troutman [156] looked at this problem from the standpoint of the clinician trying to reduce post-keratoplasty astigmatism. The study by Cohen at al [154] measured the location and amount of tissue excess or deficiency in the match between donor and host bed, and then tried to relate that to the axis and amount of astigmatism. Troutman and his co-workers Swinger and Belmont [156] took another approach. They assumed that if they rotated the donor disc in the recipient bed until the inaccuracies of the two trephine cuts complemented each other to give a minimum tissue discrepancy, then astigmatism would be reduced. Cohen et al [154] had used photographic methods to determine the exact button shape, but Troutman et al [156] did not attempt any measurements. They merely rotated the donor disc until a spherical appearance was observed with a qualitative surgical keratometer. They claimed that this rotation sometimes caused striking changes in the apparent astigmatism. However, when the results of the 40 keratoconic patients in the study were compared with those of a control group, (35 keratoconic patients with no donor rotation), there was no significant difference in astigmatism, either before, or after suture removal. It should be noted that in both groups, once the donor had been secured, the continuous suture tension was adjusted using the surgical keratometer as a guide. While the sutures remained in place this procedure would tend to mask any reduction in astigmatism achieved by donor rotation. Although this cannot be said of the situation after suture removal. It is possible that the use of a qualitative surgical keratometer is not the best means of judging the degree of rotation to minimise shape discrepancy. It should also be noted that no measurements of shape disparity were made, so it is possible that a round donor was being rotated in an irregularly shaped wound, which would not be expected to reduce tissue disparity. Clearly the authors were surprised that donor rotation did not offer a significant improvement, and nine years later two of the original authors were involved in a repeat of the original study. The surgical procedure was exactly the same, except that the fixation ring for scleral support was omitted, and fewer patients were involved. On this occasion, the rotated transplants did show significantly less post suture removal astigmatism ($p< 0.01$), even although fewer subjects were involved. Rotation group (N=29) 2.27D; control group (N=21) 4.64D. Belmont [157] and her co-workers Troutman and Buzard, attributed this change in results to greater experience with the technique of rotating the donor disc within the recipient bed.

Van Rij et al [158] used photographic measurements of donor button shape in an experiment to test the hypothesis that an eccentric trephine incision creates an oval opening that contributes to astigmatism. They had found that markedly eccentric grafts tended to produce high degrees of astigmatism, an observation which had been made earlier by Hallerman [159]. In order to substantiate this anecdotal observation they recorded the post suture removal astigmatism in six eccentric transplants, where the widest portion of the host corneal rim was at least twice the width of the narrowest portion, as measured with the slit-beam ruler. Various diagnosis were represented in this group (1 Fuchs`, 1 keratoconus, 2 aphakic bullous keratopathy, and 2 herpes simplex), so the control group was arranged by selecting for each patient with an eccentric transplant, four to six consecutive patients with central transplants done for the same corneal disease, by the same surgeon, at approximately the same time. This control group consisted of 34 eyes, and gave a mean post suture removal keratometric astigmatism of 4.66D. This was in marked contrast to the mean for the six eccentric transplants, which was 10.38D. In four cases the direction of transplant displacement lay within 23 degrees of the flat meridian of the resulting astigmatic topography. However, in the remaining two transplants, the flat meridian, and direction of displacement, were 130 and 112 degrees apart. It has been suggested by Perlman [49], that corneal tissue balloons into the trephine opening as the circular incision is made .Van Rij et al [158] postulated that if this is the case then eccentric trephination would cause different amounts of tissue to balloon into the trephine in different axes. Thus, an oval host wound results, with the long axis in the direction of displacement toward the limbus. This is because the trephine touches and depresses the cornea along this axis first, drawing more tissue into the trephine opening in this direction, than in the direction 90 degrees away. Because more tissue is excised in this direction, an oval incision results, with the long axis in the direction of displacement. Unfortunately, the laboratory experiments on 10 fresh donor eyes failed to confirm this theory. Five donor buttons were trephined eccentrically and the axis of displacement marked with a suture. Measurement of the diameter along this axis and the axis at 90 degrees, was done from photographs of the edge profile. The diameter along both the endothelial and epithelial surfaces was measured. These two measurements were averaged to obtain the diameter of the button in one axis. (It might have been interesting to record the difference between these figures, since the slope of the button edge may influence how well the donor and host margins coapt to permit good wound healing). The five eccentrically trephined buttons were found to be slightly oval. The mean difference between the major and minor axes was 0.11mm, with the long axis lying in the direction of eccentric displacement. However, the remaining five eyes, which were trephined centrally, were oval to a similar degree, (0.13mm). The only difference between the two groups was that the longer axis consistently lay in the direction of decentration, whereas in the centrally trephined eyes, the long axis was oriented randomly. The authors were unable to elucidate how the astigmatism related to eccentric transplants came about. They surmised that wound healing may have been affected by difficulty in accurately apposing the donor and host margins. This could be due to variations in the slope from the endothelium to the epithelium, or it could be due to differences in tissue thickness. Also, an eccentric transplant will be surrounded by more donor tissue at some points than others. This is important because it is the host tissue which must flex, compress, or stretch, in order to accommodate tissue disparity, if the host is to be free from forces acting on its topography.

(c) Trephine tilt

Olson [160] believed that trephine tilt would cause the donor button to be oval, and he developed a formula to predict the long axis diameter of the button, when a trephine of a given size was used at a given angle. This was simply based on two parallel lines intercepting an inclined plane, and did not take into account the compression of tissue, or the ballooning of tissue into the trephine opening.

Krumeich et al [161] also produced mathematical models to demonstrate the effect of trephine tilt. One model considered the cornea to be a flat surface similar to the Olson [160] model. The other was more realistic, and considered the cornea as a curved surface. However, when calculations were performed, both models gave very similar results, predicting astigmatism of 1.58D, 5.90D, and 11.99D for trephine tilt angles 0f 5, 10, and 15 degrees respectively.

Cohen et al [162] attempted to quantify the relationship between trephine tilt, and wound size and shape. Eyebank eyes were hand trephined at 0. 5, 10, 15, 20, and 25 degrees of tilt. The button endothelial edges were measured from photographs. They did not find the increased ovality that was predicted by the Olson [160] model. In fact there was no real difference between the results for 0, 5, 10, and 15 degrees of tilt. Only when angles of 20 and 25 degrees were used was there an appreciable increase in ovality. The authors of this study and Olson [160] comment that it is extremely difficult to ensure hand held trephination without some tilt, and that even when this was attempted, some disparity of shape always occurred. Cohen et al [162] also found that the major and minor axes of the oval discs lay roughly 90 degrees away from the angle predicted by the simple Olson [160] model. They postulated that rotation of the trephine in the cutting process, occurs about a fulcrum which is located at the point where the trephine first touches the cornea. However, they considered that compression did not occur here where the first cutting of tissue takes place, but that it did occur ahead of the cutting edge. This meant that compression was situated at two points on either side of the trephine approximately 90 degrees further round the circumference than the fulcrum point. Since compression is associated with ballooning of tissue, the maximum button diameter would occur along this axis, and not along the axis in which the tilt took place. Cohen et al [162] used a manometric system to maintain a constant intraocular pressure of the donor globes which were being trephined in their laboratory study. (They actually state that it was adjusted to 40mm Hg, but a figure of 40cm of water seems more likely). This system has been criticised because it requires more tissue deformation before tissue is cut. In the normal clinical situation, with a closed fluid system, intraocular pressure increases as pressure is exerted by the trephine.

(d) Button Shape

The shape and quality of edge cut of the donor material can influence the quality of the final topography. The donor button is trephined from the endothelial surface with the donor corneo-scleral disc lying on a suitably shaped firm surface. Not only does this protect the endothelium from damage, but it is also said to give a cleaner cut (Brightbill et al [215]).

Studies on the trephination of the recipient have generally measured parameters of the excised button, on the assumption that these are exactly matched in the shape and edge contour of the recipient bed [49].

Perlman [49] measured the diameter of 20 buttons obtained by trephination of whole globes, on a specially designed grid consisting of concentric circles. He found that the epithelial diameters tended to be larger than intended, and the endothelial diameters smaller, in other words, overcutting. The buttons were not exactly circular, and it is not known if the figure given by this grid accurately represents the mean diameter that would have been derived if the diameter had been sampled at various points around the circumference.

In 1979 Olson [163] investigated the relationship between button size and trephine technique. His principal findings were that the button size was larger:-

1. If the epithelial surface was trephined rather than the endothelial surface.

2. For higher intraocular pressure

3. For higher obturator settings.

4. For duller trephines

However, there were only one or two eyes in each group, and a double fixation ring was used. It was Olson [160] himself who concluded, in a paper written two years later, that such rings can considerably distort corneal shape.

Van Rij and Waring [119] undertook a larger investigation of the configuration of the donor buttons cut from human eye bank eyes, under controlled intraocular pressure. They used 5 different trephine types, and varied the conditions under which they were used, giving a total of 12 different techniques. Each technique was used on 5 eyes. Six cross-sectional photographs being taken of the button edge profile at 30 degrees around the circumference. Measurements from these photographs produced the following variables:-

1. Chord length diameter, anterior (epithelial) surface.

2. Chord length diameter, posterior (endothelial) surface.

3. Undercut (average epithelial - average endothelial diameter).

4. Ovality, epithelial surface (longest diameter - shortest diameter).

5. Ovality endothelial surface (longest diameter - shortest diameter).

6. Variation around the circumference of the angle of the button edge (largest deviation from the vertical - smallest deviation).

They produced a rank order of the ability of each of the five trephines to cut a round regular anteroposterior button, based on the scores for the last three variables above:-

1. Hanna trephine (suction ring adheres to limbus).

2. Free-standing disposable Franceschetti type trephine blade.

3. Motorised rotating trephine (Micro Keraton System Hans Gueder Ltd), providing rotation commences prior to contact.

4. Hessburg-Barron vacuum trephine (suction ring adheres to the cornea 0.5mm out from the trephine).

5. Disposable trephine with handle.

A number of other findings were deduced from the data. (Where there was statistical significance this is indicated.) The authors related their findings to several basic factors in the trephination process:-

Variable stromal resistance

The endothelial diameter was always higher than the epithelial diameter, which is referred to as undercutting. This is thought to be related to the fact that the cornea consists of layers of tissue which vary in their resistance to cutting. A trephine blade that approaches the curved corneal surface axially, and not radially, will encounter asymmetric lateral resistance, and the incision will deviate outward.

Tissue protrusion into the trephine opening

This was used to explain the following observations:-

- Both the epithelial and endothelial diameters were larger than the trephine which cut them.

- The effect of intraocular pressure. The only eyes which did not show undercutting were those trephined at very low intraocular pressure, 5mm Hg In this case the trephine was thought to indent the cornea, causing it to take a completely different course. The protrusion into the trephine was thought to increase the anterior diameter at the expense of the posterior diameter. Thus, protrusion was thought to reduce the undercutting, which occurred through the asymmetric lateral resistance of the stromal layers.

- Increased force (60g weight) led to larger diameters on both surfaces. The extra weight was also found to reduce undercutting ($p< 0.005$) . This could also be explained in terms of increased protrusion, although the authors did not make this point.

- The authors also noted that the only trephine with an obturator caused less undercutting. Unfortunately, they then reversed their protrusion theory, and postulated that the reduction in protrusion caused by the obturator, would cause a reduction in undercutting by a decrease in the endothelial diameter. They had previously suggested that reduction of protrusion as intraocular pressure increased, resulted in a smaller anterior diameter, and therefore more undercutting.

It is tempting to try to use the findings of this study to justify a simple theory such as tissue protrusion, but the causes may well be more complex, and in any case, not all the findings were statistically significant.

Other findings which were significant include:-

- The variation in diameter (ovality) was always greater on the endothelial surface ($p<0.001$).
- The two trephines which were held perpendicular to the corneal surface (Hessburg-Barron vacuum trephine; Hanna suction trephine), showed most consistency in the angle of the button edge. When the disposable trephine was hand held, and not mounted on a handle, it gave a similar consistency.

These results are in broad agreement with those from an earlier study by Tilanus and Van Rij [164]. Similar measurement techniques were used to compare three trephines: free-standing trephine, trephine with handle,and Gueder motorised trephine (no suction or vacuum trephines were studied). The other major difference between the two studies was that fresh pig eyes were used, (17 for each trephine type), and the intraocular pressure was not maintained by a manometric system. The intraocular pressure was adjusted 10 to 15mm Hg by tightening a gauze band around the equator of the eye. Unfortunately, the corneas of these eyes were very soft, making it almost impossible to measure the correct epithelial and endothelial diameters, and angles of the corneal button edges after trephination. Greater firmness was achieved by submerging the eyes in a 2% formaldehyde solution for 2 hours. The major difference in results from those of theVan Rij and Waring [119] study, was that there was no undercutting. In the buttons cut with the motor trephine, the mean epithelial and endothelial diameters were equal, and the disposable trephine, both with and without handle, produced overcutting, i.e. epithelial diameter larger than endothelial. This may have been due to the difference in the nature of the tissue being cut. The results for diameter difference (ovality), and variation of edge angle, were similar to those of the Van Rij and Waring [119] study. The endothelial surface was more oval than the epithelial surface. The handle mounted trephine performed worse than either of the other two trephines in terms of both endothelial surface ovality, and variation of edge angle. The differences were statistically significant, and were attributed to the position in which the handle must be held in order to see the incision process. It was thought necessary to be able to view through a hollow trephine with the operating microscope.

(e) The Donor Button Techniques

The donor button can be trephined from a whole eye, but as long ago as 1939 Vannas [6] advocated punching corneo-scleral discs from the endothelial side. The improved quality of cut, and the widespread use of corneas preserved in tissue culture media, have meant that this is now a frequently used technique.

Michaelson [165] demonstrated that a more vertical cut was obtained with posterior trephination. This was confirmed by Brightbill et al [166] who compared partial anterior trephination completed with scissors, to posterior punching. Not only were the button sides more vertical, but endothelial cell integrity was better preserved. Duffin and Olson [167] stated that the results they found with a vertical guided trephine (Lieberman Corneal Punch) were superior in terms of ovality, when compared to results from free hand techniques. Troutman [168] showed that endothelial surface trephination yielded buttons which were smaller by 0.2 mm, than those obtained by epithelial trephination. Olson [163] found the difference ranged from 0.25 to 0.50mm. However, this difference could be minimised if the anterior trephination was done with an obturator raised to 0.2mm. Olson [169] also demonstrated with electron microscopy the differences in sharpness that can occur between trephines, and he was able to show [163] that blunt trephines produced larger buttons. Olson [170] also commented that irregularity will result if the trephine does not approach the tissue perpendicularly, or if the tissue, or the block upon which it rests, are not centred. He advocated the use of a piston guided trephine. Such instruments have been designed by Pollack and Capella [171] and Bourne [172]. These early instruments punched the donor tissue against a paraffin block. This was subsequently replaced by a teflon block [173] cut with a depression suitable for supporting the donor in the correct shape. Tanne [174] proposed the use of a polycarbonate block cut with an arrangement of curvatures over specific diameters, to best approximate the shape of the anterior surface of the cornea and para-sclera. Vrabec et al [175] described the Iowa PK press. The major modifications of the Bourne press include a spring activated piston without lateral sway, a centring device for the Teflon cutting pad, and the ability to accommodate a wider range of trephine sizes. However, a photographic study [175] of outer dimensions did not reveal any significant improvement in the quality of cut. Pflugfelder et al [176] added a further refinement to the cutting block. The donor disc is accurately positioned on the cutting block, using a centration mark as advocated by Brightbill [166]. The corneal tissue is then held in place by suction. This is applied through four radial cuts, resulting in four radial marks on the epithelium. These are then aligned with similar radial marks applied to the host, prior to trephination, with a four incision radial keratotomy marker. This allows proper alignment of the circumferences of the donor and host corneas, despite any host scleral infolding that may occur. These markers allow accurate placement of the initial four cardinal sutures, which is a critical factor in minimising post operative astigmatism. Pflugelder et al [176] have shown mathematically, that if the second cardinal suture is passed through an 8mm button, 175 degrees rather than 180 degrees from the first suture, then a tissue discrepancy of 0.17mm will result in the perpendicular meridian. If the second suture is misaligned by 10 degrees rather than 5 degrees, the tissue disparity increases to 0.35mm. (There will also be a lesser tissue disparity of 0.03mm in the same meridian as the sutures.) Gorovoy and Stern [177] also reported on the use of a cornea marking device to aid the accurate placement of the initial cardinal sutures, and Dunker and Nolle [178] described one designed to give perfect spacing of a double running torque-antitorque suture. Neither of these two papers produced data to substantiate the claims that these marking devices can reduce post-keratoplasty astigmatism. A number of scientific papers [179, 180, 181] on other aspects of penetrating keratoplasty, record the use of a corneal marker, as a standard part of their operating technique.

(f) Recipient Bed Techniques

Numerous devices have been introduced in an attempt to make the recipient opening more circular and vertical. Most of these attempt to eliminate excessive or unbalanced pressure between the cutting edge and the cornea. Some also attempt to maintain the trephine blade parallel to the axis of the eye.

One approach was the use of motorised trephines. Early models included those devised by Arato [182] and Kadesky [183]. These were not universally accepted, and one of the criticisms was that they tended to produce a corkscrew type edge profile. However, a more recent model. the Micro-Keraton, manufactured by Hans Gueder, has been shown by Schanzlin and co-workers [184] to produce less stromal lamellar disruption and a smoother interface, than manual trephines. This design also permits the surgeon to view the cutting process through the hollow trephine from above, with the benefit of the operating microscope.

Single point cutters are supported on the limbus or sclera, which is thought to reduce the problem of corneal distortion. Crock et al [185] described a trephine with a single angle cutting blade, with a rotating glass obturator to support the cornea inside the blade, a metal support outside the blade, and a friction plate with serrated edges for limbal fixation. The Lieberman [186, 187] single point cam guided trephine is secured to the globe by suction at the limbus, but without an inner obturator, or outer support surface for the cornea. It has the advantage that the angle of cut can be adjusted, and the cam can be changed so that any diameter, or any shape (including oval) can be cut. It should be borne in mind that neither of these instruments can be used to match the vertical edges of a punched donor.

Another approach was to use conventional circular cutters but with suction to support the area of cornea being cut. The Caldwell trephine adheres to the central host cornea utilising the operating theatre`s suction unit. A retrospective study by Insler, Cooper, and Caldwell [126] of 31 patients whose operations included this technique, gave a mean post suture removal astigmatism of 3.9D. This compares well with other studies, but cannot be considered to be an outstanding improvement, especially since the range extended to 10D of astigmatism. Hessburg and Barron [188] described a disposable trephine, with fixation to the cornea maintained by a suction ring immediately outside the circular trephine blade. There was no obturator or outer corneal support surface. Duffin and co-workers [189] reported accurate spherical cuts in the anterior stroma but with a tendency towards outward bevelling in the posterior layers. Krumeich and colleagues [161] describe their Guided Trephine System (GTS). The instrument is fixed to the limbus of the recipient eye with a suction ring. There is a glass obturator which serves to applanate the central cornea. The authors claim that this prevents undercutting and produces vertical cuts. The system can be adapted to cut donor buttons from the anterior surface, with similar applanation. An artificial anterior chamber is also incorporated, which allows the fluid pressure on the inner surface of the donor tissue to equal that of the recipient eye. This is intended to ensure that the conditions for donor and recipient trephination are as similar as possible. Belmont and her co-workers [190] conducted a clinical trial to evaluate the Krumeich guided trephine system (GTS). Twenty six eyes underwent penetrating keratoplasty for keratoconus. Eleven were performed with manual trephination of both donor and host, while in a further ten patients the donor was cut manually, but the GTS used for the host. The remaining five eyes had guided trephination of both donor and host. The two groups with the guided trephine system demonstrated significantly less post suture removal astigmatism, than the manual trephine. The results were statistically significant for the three different measures of astigmatism; refractive, keratometric, and videokeratography (Corneal Modelling System, CMS). Bull et al [191] described a double guided trephine. Suction is applied at the limbus and in the centre of the cornea. Cutting is performed by a motor trephine which rotates between the inner and outer suction. The Hanna [192, 193] trephine system combines some of the best features of previous instruments. A limbal suction ring fixates the trephine perpendicular to the cornea. There are also support surfaces on either side of the circular trephine blade to enhance the verticality of the cut. Laser non contact trephination has the potential to eliminate corneal topography distortion. Serdarevic et al [194] compared trephination with a 193nm excimer laser, to free hand and suction trephination. The laser trephined rabbit and human cadaver eyes more regularly, and precisely without distortion of corneal topography, and with less damage to adjacent tissues. They also found that in an animal autograft model, the morphology of wound healing was not adversely affected by the laser. Naumann et al [195] reported on the use of excimer laser trephination of 70 patients who underwent penetrating keratoplasty for a variety of conditions. They were able to cut non circular buttons, and used elliptical metal mask with, and without orientation teeth. The elliptical outline facilitated fitting of the donor into the recipient bed, and the orientation teeth made fitting even easier. No unexpected complications such as disturbances of wound healing were seen. Data on astigmatism after suture removal was available for some patients, and the mean value was 4.6D. If no dramatic improvement in terms of astigmatism can be demonstrated for laser trephination, the cost may limit its acceptance.

(g) Discussion

Lieberman and Troutman [196] discussed some of the simplifications and assumptions made in models used in the analysis of topography following penetrating keratoplasty:-

- Donor and recipient are perfectly spherical. In a more sophisticated model they would be regularly aspheric, implying that the rate of peripheral flattening is the same in all meridians.
- Donor and recipient are equal thickness in all meridians.
- Each stromal bundle is identical to its neighbour.
- The central optical zones are at the geometric centre
- The central optical zones are equal in size and curvature
- Astigmatism is solely a function of the central corneal zone, and is not related to the peripheral zone.
- There is perfect wound healing.
- The surface area and the total volume of donor tissue is equal to the surface area and volume removed from the recipient.

They point out some of the deficiencies in these assumptions.

- Videokeratography has shown that the rate of flattening can vary between semi meridians only 10 degrees apart.

- Pachymetry studies have shown that the cornea thickens towards the periphery, but the rate of thickening can vary from meridian to meridian. For example, at the same distance from the centre, the inferior nasal cornea is typically thicker than the opposite superior temporal area.

- The arrangement of collagen bundles in the stroma appears to vary as you move from anterior, to the posterior stroma, and also from the periphery towards the centre. The deeper layers appear to contribute most to the structural strength of the cornea.

- The optical centre is rarely at the geometric centre, and donor and recipient are not likely to have the same curvature.

Lieberman and Troutman [196] consider that surgeons ought to be able to take these factors into account. They believe that in the future oval grafts will be used to correct astigmatism present in the host. The accurate cutting of these non circular shapes could be achieved either by the Lieberman [186] single point cam guided trephine, or by excision with an eximer laser [197, 194]. They envisage that in the future, topographical and pachymetric data will be analysed by a computer programme, which will suggest a cutting path that is custom designed for that pair of tissues. This will be calculated to ensure that the tissue on either side of the wound is matched for curvature and thickness, and also to incorporate tissue disparity in the correct area, in order to correct and pre- existing astigmatism. They suggest that this would require orientating the donor disc in the host, to match the orientation it had in the donor eye; e.g. right eye inferior nasal quadrant from a right donor eye, would be rotated to the corresponding position in a right eye host. Lieberman and Troutman [196] also suggest that there would be advantages in cutting both donor and host from the anterior surface, at an angle more perpendicular to the stroma. For example at an angle of 20 degrees to the vertical, instead of vertical to the axis of the eye as at present. This paper is included in this review as an indication of some of the factors involved in the trephination process that could influence the quality of the post- operative topography. The authors themselves describe their paper as speculative.

1.4.2.(iv) Scleral ring

The use of a scleral ring to support the globe during surgery has been advocated by McNeill et al [198]. This was based on an earlier report by Flieringa, on the use of a thin circular steel ring, sutured to the sclera, concentric with the limbus. These rings are sutured to the superficial sclera, and uneven tension in these sutures may lead to distortions of the globe. This particularly important when the recipient bed is being trephined, since it can lead to a distorted wound shape and ultimately to astigmatism. [160]. A recent report by Stevens and Steele [199] described the use of two straight, 150 micrometer diameter, 16mm length suture needles passed through clear cornea, to act as anterior segment splint supports. They recommended this as an alternative to a suture-fixated ring support, but did not investigate the effect on post-operative astigmatism.

1.4.2.(v) Sutures

Suture Material

Before the 1970's, absorbable suture materials, or silk sutures were commonly employed for post- keratoplasty closure. Since that time they have been completely abandoned in favour of non absorbable monofilament materials. The 10-0 nylon has become the most popular material. The monofilament construction permits smooth passage through corneal tissue, and the level of tissue reaction is greatly reduced. Over the years, improvements in manufacturing techniques have produced stronger and more consistent threads. Rennie et al [200] were able to show that the Alcon 10-0 suture is a mechanically consistent material in terms of its stress/strain characteristics, and therefore, variations between one suture and the next cannot be the cause of variable amounts of post- operative astigmatism. The authors used a test ring that enabled the sutures to be loaded with a gradually increasing force, and the resultant extension in their length to be measured. This meant that all tests were carried out in air (at a temperature of 22^{o} C), which differs from the conditions under which the sutures will be used. Another characteristic of nylon is that it is subject to an additional deformation known as creep, i.e. the stress on the material, instead of remaining constant for a fixed extension, slowly reduces as its structure modifies with time. Rennie et al [200] also investigated creep. They showed that the greater the initial forces on the suture, the faster the load induced in the suture reduces. This has a beneficial effect for the surgeon in that a suture which is inserted too tightly will tend to relax more quickly than one which is at the correct tension, thereby helping to achieve a uniform surgical result.

Alternative monofilament materials.

Polypropylene (Prolene) suture is a truly non absorbable material, not subject to the hydrolysis of nylon, and possessing high tensile strength. However, it has the practical disadvantage of being a stiff material, suffering from the elasticity of nylon, but lacking its ease of handling. It is rarely used in keratoplasty.

Polyester (Mersilene) suture was developed as another alternative material that would not be biodegraded, and thus allow for permanent tension to be maintained. Mersilene is stronger than nylon, and is also much less elastic. The benefits of Mersilene were confirmed in two reports by Frueh and her co-workers [201, 202] involving combined interrupted and running suture technique with selective suture removal. One study [201] involved 25 patients with 11-0 nylon running sutures. Nine of the running sutures broke spontaneously, causing a significant increase in astigmatism. In the other study [203] Mersilene running sutures were used, and spontaneous suture dissolution did not occur throughout the follow up period (mean 27.2 months, range 10 to 46 months).

A study by Ramselaar et al [204] found no difference in keratometric astigmatism at 6 months, when nylon and Mersilene were compared. They also found minimal tissue response to the Mersilene sutures, in rabbit corneas. Tissue reaction was monitored at regular intervals with the slit lamp, and then by histology, and scanning electron microscopy.

This is in direct contrast to the findings of two prospective trials by Bertram et al [205]. One was a randomised comparison between nylon and Mersilene in a combined interrupted/running technique. The Mersilene was 5.5 times more likely to have handling related complications, and 3 times more likely to have tissue related complications. (Handling related complications:- tight suture; loose suture; cheesewiring; wound leak; dehiscence; exposed knot.) (Tissue related complications:- infiltration; infection; broken suture; epithelial defect; neovascularisation; allograft reaction; graft failure.) The second trial involved 23 eyes, each with a single running Mersilene suture with post- operative adjustment of suture tension to reduce astigmatism. There was a high complication rate of 69%, and the mean astigmatism at 6 months was 4.03D. Although they were able to reduce post- operative astigmatism with the adjustment of a single running Mersilene suture, the level of success was below that of other surgeons [206, 207], who employed suture adjustment. It is interesting to note that the incidence of suture related problems appeared to have a direct influence over the final astigmatism. Bertram et al 292 found eyes with significant suture related complications were 2.85 times more likely to have greater than 4.00D of refractive astigmatism.

Suture Technique

In 1979 Troutman [208] wrote that sutures did not determine post-keratoplasty astigmatism. In other words the use of interrupted or continuous suture techniques, in and of themselves, had no effect on the final astigmatism. At that time he felt that tissue factors such as trephine errors, were much more important, and that the primary role of sutures was to maintain wound apposition. Van Rij and Waring [209] investigated the influence of sutures on astigmatism. To do this they devised an experiment on adult rhesus monkeys. They attempted to isolate the effect of wound irregularities by replacing the homolateral button without rotating it. Suture related astigmatism was induced in three eyes by the use of unequal suture lengths. Eight 10-0 sutures with large bites (3/8 circle needle, suture length 1.5mm) were placed in the vertical axis, while eight small bites (bicurve needle, suture length 1.0mm) were placed in the horizontal axis. Interrupted sutures of equal length and tightness were used in the four control eyes. The mean astigmatism which resulted was 10.55D which contrasted greatly with the control group of four eyes which had sutures of equal length (1.64D keratometric astigmatism). However, when all the sutures were removed at 11 weeks, the astigmatism in the experimental group reduced to 2.73D, which was not statistically different from the control group (1.01D). The authors suggested that it was unlikely that sutures induce permanent astigmatism.

Although the permanency of suture induced astigmatism is in doubt, many surgeons have attempted to minimise it. intra-operative keratometry has been used as a guide to suture adjustment, to minimise astigmatism at the time of keratoplasty. Since the introduction of monofilament sutures in penetrating keratoplasty a number of strategies have been devised to modify suture technique and reduce astigmatism.

The first strategy was to use a single running suture that was intended to distribute the tension around the keratoplasty wound, diminish selective tension in one meridian, and therefore diminish the astigmatism. The drawback was that if high astigmatism was present, there was no clinically useful way to adjust the suture, and the patient had to tolerate the astigmatism for 12 to 18 months until suture removal. When the running suture was removed, the astigmatism could increase or decrease.

The second approach was to use a double running suture. The tightly tied 10-0 nylon suture held the wound closed during the first few months of healing and then it was removed, allowing a more loosely placed, 11-0 nylon suture to retain wound apposition with less tension and presumably less astigmatism. This allowed earlier visual rehabilitation in many cases, but did not allow the surgeon to control the astigmatism.

The third approach was to combine running and interrupted sutures. The surgeon could selectively remove tight sutures that compressed the tissue and created a steep axis of astigmatism, while the running suture maintained good wound apposition.

The fourth approach was to use a double running suture, but instead of simply removing the 10-0 suture, it was adjusted so as to redistribute tension away from the steep meridian towards the flat meridian, thus reducing astigmatism.

(a) Selective Suture Removal

Selective suture removal to reduce post-operative astigmatism was first proposed by Cottingham [210] at the American Academy of Ophthalmology meeting in 1980. He selectively removed interrupted sutures between two and eight weeks after keratoplasty. He either removed three equally spaced at each of two separate visits, or six sutures at one visit. This resulted in a mean of 1.5 D of astigmatism for a group of 67 transplants, which compared very favourably with astigmatism reported in other series. However, it should be noted that these results were taken when the continuous suture, and six of the interrupted sutures, were still in place.

A number of studies followed the report by Cottingham [210], and these are summarised in Table 1.4 [211, 212, 213, 214, 127, 215, 216, 217, 60].

Selection

Selection of the appropriate suture to remove can be achieved through a combination of keratometry, retinoscopy, refraction and detection of stress lines by inspection with the slit lamp. These tools are limited to describing one steep and one flat corneal meridian, a situation that may be particularly misleading in patients undergoing keratoplasty in whom irregular or complex astigmatism is common. Photokeratoscopy and computer-assisted videokeratography provide a much more powerful tool, which allows detection of hemimeridians of steepness or flatness, and localisation of more subtle contour abnormalities. The keratometer locates tight sutures in a cataract wound because the steep keratometric axis intersects the incision at only one point. In contrast, any given keratometric axis intersects a keratoplasty wound twice, once on each side of the transplant. Thus identifying the steep or flat keratometric axis does not identify which of the two sides of the wound accounts for most of the astigmatism.

Binder [127] commented that tight sutures produced flattening around the suture but steepening within the suture meridian. If the distortion lay in two quadrants 180° apart, then the two opposing sutures were removed. If only one quadrant was affected, then single or adjacent pairs of sutures were removed. Harris et al [212] examined all the readable keratographs obtained from 29 eyes which had undergone penetrating

Author	#	Date	Retro/ Pro-spective	Group	N	Selection	Timing	Results			
Stainer, Perl, Binder	214	1982	Retro		50	Keratometry & Corneascope	As early as 1M	Mean reduction 3.40D	Range 0-10D	Most when 2 cut simultan-iously	
Binder	127	1985	Pro	Group I begun 6-8W	56	"	1or2 removed, repeated 1M later as required. Most out by 1Y.	1M pre-adj 7.4	2M 5.4	8-10M 4.3	14-16M 3.6
				Group II begun 3W	148	"	"	7.5 NS	4.2 $p < 0.05$	3.2 $p < 0.01$	2.2 $p < 0.01$
				Groups I&II	204	"		7.5	4.4	3.3	3.0
Feldman & Brown	215	1987	Retro		25	Keratometry	Begun at 12W, continued weekly until keratometry stable on 2 separate occasions.	Mean Astigmatism 1.37D	(Follow up 3-21M)		

Table 1.4 Studies investigating selective interrupted suture removal.

Unless stated otherwise the suture technique was a combination of 12 or 16 interrupted 10-0 sutures, with a running 11-0 suture.
All studies gave values for astigmatism while some sutures remained in situ.

Author	#	Date	Retro/ Pro- spective	Group	N	Selection	Timing	Results			
Burk Waring Radjee Stulting	211	1988	Retro	I	68	Keratometry, refraction, slit lamp, and keratoscope.	3W-50W, one to four removed ar each visit	Wide range of change	2 to 3 D change per visit	Only 54% had a reduction	
				1A	30	"	3W-50W, subset of group I : only one removed per visit.	2.3 D Mean change per visit	No vatiation with post- op time		
Harris Waring Burk	212	1989	Retro		29	Keratoscope (Nidek: 9 ring)	Only one removed per visit. Start at 6W, continuing at 2W intervals until < 3D or no further change.	Keratograph Symmetric oval D-shape Focally indented	N 9 14 6	Keratometer reduction 0.44 D 2.07 D 6.60 D	Vector change 3.60 D 4.81 D 7.65 D
Pradera Ibrahim Waring	213	1989	Retro	combined transplant & IOL	44	Keratoscope (Nidek: 9 ring), refraction, keratometer	Begun at 1M. One or two at each visit. Repeated for approx. 6M, till astigmatism < 3.0 D, or change between visits < 1.0 D.	Pre-removal 1 to 3W 5.11 D (Refractive astigmatism)	after removal 2 to 11 M 2.50 D	Final visit 6 to 30 M 2.84 D	

Table 1.4 (continued). Studies investigating selective interrupted suture removal.

Unless stated otherwise the suture technique was a combination of 12 or 16 interrupted 10-0 sutures, with a running 11-0 suture.
All studies gave values for astigmatism while some sutures remained in situ.

Author	#	Date	Retro/ Pro-spective	Group	N	Selection	Timing	Results			
Musch Meyer Sugar Soong	216	1989	Pro	Double running 10-0/11-0	60	Keratometer, Keratoscope (12 ring)	10-0 removed at 3M if broken or astigmatism >3D. 11-0 removed at 1Y if warrented.	Keratometer astigmatism Median	3M 3.5	6M 3.0	1Y 4.0
				12 int 10-0 running 11-0	60		Begun at 1M. Repeated at 1M intervals untill <3D or all removed. (Average 2 per visit)		4.0	3.0	2.5 p=0.06
Burk Waring Harris	217	1990	Retro	Single visit, multiple suture removal	29		Sutures removed at one visit untill astigmatism < 3 D	At 1 Year 3.1 D			
				Multiple visit, single suture removal	24		One suture removed at successive visits 2 W apart untill astigmatism < 3 D	1.9 D			
Strelow Cohen Leavitt Laibson	60	1991	Retro	Selected cases with high astigmatism precluding spectacles	29	EyeSys topographic map	One removal session from 4 to 49 M. One or two removed.	3 to 5 W (after removal). Net decrease in 21 out of 29 cases.	Refraction 1.4 D	Keratometry 0.9 D	EyeSys 1.0D

Table 1.4 (continued). Studies investigating selective interrupted suture removal.

Unless stated otherwise the suture technique was a combination of 12 or 16 interrupted 10-0 sutures, with a running 11-0 suture.
All studies gave values for astigmatism while some sutures remained in situ.

keratoplasty with selective suture removal. There was a total of 81 keratographs, and they were classified into the following groups :-

Symmetrically oval	38%
D- shape	30%
Focally indented	9%
Minimally disrupted	6%
Incomplete	13%
Uninterpretable	4%
	100%

Harris et al [212] used this classification system in their analysis of the change in astigmatism resulting from single suture removal. The transplants with focally indented keratograph patterns had most change in astigmatism.

Binder [127] found that suture removal had no effect on corneal curvature in some patients. He observed that these were patients who demonstrated regular corneal astigmatism in rings 7, 8, or 9 of the corneascope, and no irregular astigmatism surrounding individual sutures. In his opinion these cases most likely represented oval donor buttons and/or oval recipient beds.

Kozarsky and Waring [218] came to similar conclusions. They used a similar classification system to Harris et al, and found that grafts with symmetrical oval mires showed less reduction of astigmatism after removal of one or two sutures, while those with asymmetrical focal wound compression show a greater reduction. If excess tightness of the suture was the main reason for astigmatism, then selective suture removal would have a pronounced effect, but if other factors such as an oval host opening, an asymmetrically bevelled donor or host wound, or an eccentrically placed transplant were present, selective suture removal may be less effective.

Rowsey et al [219] discussed the use of keratoscopy, slit lamp biomicroscopy, and retinoscopy in the selection of tight sutures. Keratoscopy observations indicating tight sutures include peripheral indentation of the keratoscope rings, decentration of the corneal apex away from the tight suture, and individual circular images reflected from the hillocks between tight sutures. Slit lamp observations indicative of tight sutures include a doughnut of tissue compression, Kaye's epithelial white dots, and epithelial or endothelial stress lines, which radiate towards the entrance point of the tight suture. In retinoscopy the narrowest side of the beam points towards the tightest suture.

Strelow [60] and his co-workers set up a study to evaluate the usefulness of computer assisted corneal topography in selective suture removal. They found that the preliminary choice of sutures to be removed, made on the basis of refraction, keratometry, and inspection; was changed in 20 out of 29 cases, when information added by the EyeSys topographic map was considered.

Vector analysis

Table 1.4 presents the mean change in astigmatism for a particular group of patients. This does not show the range of individual responses to selective suture removal.

Burk [211] and her co-workers pointed out that there was a wide range of responses. In fact although there was a mean reduction in astigmatism of 2 to 3 D per removal, only 54% of the cases showed a reduction. They also pointed out that vector analysis, which takes change of axis into account, would report a much higher apparent change of astigmatism. (A computer program to calculate vector change was published by Calossi et al [220]). Harris et al [212] presented their results as both net keratometric change and induced astigmatism determined by vector analysis. It can be seen from their results on Table 1.4 that keratographs with a symmetric oval pattern showed little net keratometric change, but more vector change. This may mean that the effect of selective suture removal in these cases was to leave the amount of astigmatism relatively unchanged, but with a change of axis. In contrast, the keratographs with focal indentation showed the most change of all, with little change of axis.

Effect of the remaining sutures

The premise behind the use of combined interrupted and running sutures is that the flexibility of selected suture removal allows the surgeon to reduce astigmatism after penetrating keratoplasty more rapidly, increasing the rate of visual rehabilitation. This is in contrast to the effects of running nylon sutures that must usually be left in place 12 to 18 months before the wound is healed. The theory of selective suture removal is based on the assumption, that, if the corneal curvature can be modified in the early post-operative period, it will remain in that configuration on a permenant basis. It is unknown whether the early reduction of astigmatism by suture manipulation can set the cornea on a more spherical configuration during wound healing. Although Binder [130] has demonstrated a greater reduction in astigmatism when sutures are selectively removed less than 1 year after surgery as compared to more than 1 year after surgery, there is no statistical proof that holding the cornea in an ideal configuration will ultimately lower astigmatism. The reports on selective suture removal tend to concentrate on the immediate effects, and because some sutures remained in place when the results were obtained, it is not possible to take them as the ultimate astigmatism that the technique can obtain. Two studies have shown that curvature cannot be considered to be stabilised until all the sutures have been removed [211,221]. They point out that suture removal can influence corneal curvature in an unpredictable manner, even when it is performed several years after surgery. Musch and Mayer [222] believe that that the inability to accurately predict the final corneal curvature is partially attributable to the lack of studies documenting post-suture removal topography in a large patient series.

In fact, Stainer et al [214] did record the change that occurred when they removed the 11-0 running suture, after twelve months, in 10 out of the 50 patients in their study. They described the changes as unpredictable, the mean astigmatism increased by 1.5 D in seven patients, and decreased by 1.5 D in the remaining three. Binder [127] also reported the change when the running suture was removed in 75 patients, who had considerable astigmatism despite selective removal of the individual sutures. The mean value did not change, and 23 eyes obtained less astigmatism (0.5-7.0 D), 24 eyes developed more astigmatism (0.12-7.87 D), and three eyes had no change. Binder [127] concluded that all but six corneas were “fixed” in topography by the selective suture removal. These six corneas developed changes of 3.75 to 7 D after all sutures were removed.

Timing

Burk [211] and her co-workers investigated the effect of time on the change achieved by removing a single suture. They believed that there would be a greater change when removal was early in the post-operative period. But the average change was 2.3 D per suture regardless of the point within the first post-operative year.

Optimum number to remove per visit.

Burk [217] and her colleagues compared two separate groups of consecutive penetrating keratoplasties in avascular corneas, with different timing of selective suture removal. The post- operative schedule which included a series of visits at which only one suture was removed, appeared to offer better control over the final amount of astigmatism than attempting to remove all the tight sutures required to achieve 3D or less of astigmatism at a single visit. The major drawback in attempting to remove all the tight sutures at a single visit was the large change in astigmatism that occurred between the end of that visit, and the following visit.

Disadvantages

The disadvantages [212] of selective removal of interrupted sutures include, more frequent visits, and more time per visit. Also there are long term disadvantages associated with leaving the remaining sutures in place indefinitely. These include possible increased sub-epithelial fibrosis, and periodic loosening or breaking of sutures, with eruption through the epithelium, and creation of inflammation, vascularisation, and sometimes infection [223, 224].

(b) Adjustment

Techniques of adjustment, or selective suture removal during the post-operative period are based on the premise that if the cornea is made as spherical as possible during the healing period, it will remain that way after all the sutures are removed. McNeill and Wessels [206] were one of the first to publish results of adjusting a continuous suture in the early post- operative period. They first adjusted a continuous suture as a temporary first aid measure in an eye with a persistent wound leak. Tightening the suture in that quadrant caused steepening. The induced astigmatism persisted, but was later totally reversed when the tight quadrant was loosened.

A technique was developed which involved rotating the suture from the area of the flat meridian (tightening effect), to the area of the steep meridian (loosening effect), thereby steepening the flat meridian, and flattening the steep meridian. The slack from each loop that was tightened was passed to the next suture, which was tightened, and the slack passed on in the direction towards the steep meridian. Alternating between the slit lamp microscope (adjustment), and the keratometer (measurement) was needed to achieve the desired end point.

It appeared that holding the transplant in a given degree of astigmatism while healing takes place does affect the final outcome after suture removal. McNeill and Wessels

[206] claimed that selective removal of interrupted sutures had several disadvantages when compared to their technique of running suture adjustment.

- Limited attempts. Only a limited number of interrupted sutures can be removed.
- Relaxation only. The only possible effect of removing sutures is to release tension in a specific meridian, allowing surgeon to reverse an overcorrection, and to repeat the procedure to increase the effect.
- Irreversibility. If the wrong suture is cut, reversal is generally not possible.
- Unpleasant surprises. It is impossible to predict the magnitude of the effect of removing a suture [180 179].
- No fine control. However, with suture adjustment it is possible to finely adjust the zone of increased or decreased tension backward and forward.

The work of McNeill and Wessels [206] has been followed by several papers reporting on the success of this technique. The results are summarised in Table 1.5. In some instances [225, 181] the technique was modified to include revision of the wound in the steep meridian, by separating the anterior two thirds of the stroma. Others [225, 202] reported that they opened the epithelium around the entire circumference of the wound. One paper by Clinch et al [181] retrospectively analysed data for a group of 30 consecutive cases in which a double running 10-0/11-0 suture was used, They used forceps to partially open the stromal wound in the steep meridian. If the 10-0 suture could not be adequately adjusted (or if it broke), it was removed leaving the 11-0

Author	#	Date	Retro/ Pro-spective	Group	N	Suture	Bites	Selection	Timing	Wound Revision	Results	Results	Results	Results
McNeill & Wessels	206	1989	Retro	Adjust	205	Single 10-0	17-26 mean 21	Round keratometer mire	As early as first day, repeated as necessary towards goal of 3.00D	No	pre-adj (<3M) 5.30D	post- adj (3-6M) 2.87D	post- adj (>6M) 3.23D	post- ROGS 3.58D
				Control	136	Single 10-0	17-26 mean 21				5.50D NS	4.80D $p<0.0001$	4.71D $p<0.0001$	5.25D $p<0.0001$
Lin et al	180	1990	Pro	Adjust	8	Single 10-0	16	CMS colour coded map	1W to 1M , sucessive visits till astigm <2.50D	No	pre-adj 1M 6.70D	post- adj 2M 1.90D	post- adj 3M (as 2M)	post- adj 4M (as 2M)
				Control	10	Double 10-0 11-0	16				5.90D NS	5.50D $p<0.005$	(as 2M) $p<0.005$	(as 2M) $p<0.005$

Table 1.5 Studies investigating adjustment of a continuous suture.

Author	#	Date	Retro/ Pro-spective	Group	N	Suture	Bites	Selection	Timing	Wound Revision	Results	Results	Results	Results
Nabors et al	225	1991	Selected group	Group Selection criteria >4.50D	52	Single 10-0		Keratometer	Single adjustment session. Mean 9.4W. Range 1W to 47W	Yes	pre-adi 9.97D	post- adi 1.89D		
Temnycky et al	202	1991	Pro	Adjust	33	Single 10-0	24	CMS Video-keratography	3W to 6W, further sessions untill <3.00D	Yes	pre-adi 8.41D	post- adi (3 to 4M) 2.22D		
				Control	72	Single 10-0 & 4 int.	16				4 to 6W 6.20D	3 to 4M as at 4 to 6W		
Hope-Ross et al	179	1993	Selected group	Group Selection criteria >4.00D	20	Single 10-0	16	Refraction Keratometry Keratoscopy	5 to 32W, further sessions untill <4.00D	No	pre-adi 6.33D	post- adi 2.66D		

Table 1.5 (continued) . Studies investigating adjustment of a continuous suture.

suture to provide wound stabilisation. Unfortunately, they reported results for the whole group including the six patients who had less than 3.00D of astigmatism, and did not require any suture adjustment. This report has been omitted from Table 1.5 because it is difficult to establish the amount of astigmatism reduction which can be attributed to the adjustment. The final astigmatism (minimum follow up of 6 months) was 2.66D.

In all the studies except one [225] the continuous suture was readjusted at subsequent visits if the previous adjustment had not reduced the astigmatism to the goal set down in the protocol. Nabors et al [225] performed adjustment at one single visit. The timing of this visit varied between 1 and 47 weeks after keratoplasty, and the authors were able to show that the reduction in astigmatism was not related to the time elapsed since keratoplasty. In other words the amount of healing that had already taken place did not appear to effect the amount of astigmatism change that could be achieved by running suture tension adjustment. This is contrary to the view held by McNeill and Wessels [206] who commented that the progressive healing of the donor/host interface by scar tissue, makes it more difficult to achieve a meaningful change by suture adjustment later than six months after surgery, although some modification can be obtained. Nabors et al [225] also found that there was no relationship between pre-adjustment astigmatism and post- adjustment astigmatism. In this study 2 patients developed transplant rejections within one month of suture adjustment. Regression of astigmatism can be seen in the results of the McNeill and Wessels [206] study (Table 1.5), and this was confirmed by Nabors et al [225] who quoted a figure of 0.92D mean increase in astigmatism from the immediate post- adjustment value.

Comparison between running suture adjustment and selective interrupted suture removal

Van Meter et al [207] carried out a retrospective study which compared two groups of patients. One group (N = 31) received a combination of continuous 11-0 nylon suture and 12 or 16 interrupted 10-0 nylon sutures which were selectively removed. The second group (N = 26) received a single continuous 10-0 nylon suture that was adjusted. The latter technique gave significantly less astigmatism (1.5 D against 3.2 D, $p < 0.01$). Filatov et al [226] confirmed this result with a prospective randomised study (2.7 D against 3.9 D, $p < 0.02$).

Long term results of suture adjustment

Frueh and her co-workers [201] attempted to evaluate whether the low degrees of astigmatism achieved early in the post-keratoplasty period with the combined interrupted/running suturing technique, were maintained for long periods of time. For 13 to 70 months (mean, 30.2 months), they monitored a group of patients (25 eyes) who had previously undergone the combined interrupted/running suture technique with selective removal (12 interrupted 10-0 nylon sutures and one running 11-0 nylon suture). Nine running sutures broke spontaneously, causing a significant increase of the keratometric astigmatism of the entire population from 1.7 (± 1.6) to 3.4 (± 2.6) diopters. The mean vector corrected change in astigmatism after suture breakage was 4.9 (± 2.6) diopters. These results indicate that the selective suture technique can maintain low degrees of astigmatism only if the sutures remain intact. The authors concluded that the effect of keratoplasty suturing techniques on astigmatism should probably include follow up that is sufficiently long to indicate its long term value to the patient.

1.4.2.(vi) Intra-operative keratometry

Surgical keratometers were conceived as an aid that would help minimise post-operative astigmatism. They allow the surgeon to measure and modify corneal curvature during suturing. In 1977 Troutman [227] introduced the first commercially available intra-operative keratometer. This is attached to the operating microscope, and projects a series of twelve fibre optic point sources of light arranged in a circle onto the surface of the cornea. This device permits simultaneous intra-operative evaluation of surgical manipulation and its effects on topography. Troutman [227, 112] compared results with and without intra-operative adjustment of suture tension on the basis of his instrument. There was no statistically significant difference in post-operative astigmatism, either before or after suture removal. He also used his intra-operative keratometer to rotate the donor disc relative to the recipient bed, again with no reduction in post- operative astigmatism. The lack of evidence supporting the benefits of surgical keratometers in penetrating keratoplasty, did not alter their development, and a selection are shown in Table 1.6

Instrument	Type	Mount-ing	Comments
Karickhoff Keratometer [228]	Single ring	Hand	Qualitative

Instrument	Type	Mount -ing	Comments
Van Loehnan Keratoscope [228]	7 concentric rings	Hand	Qualitative
Maloney Surgical Keratoscope [228]	7 concentric rings	Hand	Qualitative
Astigmatism Control Enforcer (ACE) [228]	5 concentric rings	Hand	Qualitative
Astigmatic Ruler [229]	5 single rings, ranging from circular to an ellipse corresponding to 8 D of astigmatism	Hand	Semi-quantitative
Troutman Keratometer [227]	12 points	Micro-scope	Qualitative
Amoils operative keratometer [228]	Single ring, 20 points	Micro-scope	Quantitative
OV-1 keratometer [228]	Single ring. Image diameter compared to a series of reference circles	Micro-scope	Quantitative
Terry keratometer [228]	Single ring, prism doubling	Micro-scope	Quantitative
Keratoring modified by Igarashi et al [230]	Single ring, with on-line image analysis	Micro-scope	Quantitative
Varidot Keratometer [228]	Single ring, 24 diamond shape points	Micro-scope	Quantitative
Zeiss surgical keratometer [228]	Single ring, prism doubling	Micro-scope	Quantitative
Nidek keratometer [228]	Electronic digitisation of the image of 8 LED's	Micro-scope	Quantitative
SK-1 Canon Automated Keratometer [231]	Electronic digitisation of the image of a single ring	Micro-scope	Quantitative
PAR Corneal Topography System [232]	Raster photogrammetry.	Micro-scope	Quantitative
ACT-1 (Visionary Systems Inc.) [233]	Raster photogrammetry	Micro-scope	Quantitative

Table 1.6. A selection of surgical keratometers.

All qualitative methods of estimating corneal astigmatism are subject to the same limitations. Interpretation of keratoscopic images is dependant upon experience and skill of the observer. Even the most experienced observer has difficulty in reliably detecting astigmatism less than two to three dioptres [234]. Hand held devices are also prone to positional error [234]. In addition, these devices prevent simultaneous surgical manipulations while evaluating the keratoscopic image.

Despite the limitations of qualitative intra-operative keratometers, a study by Serdarevic and her co-workers [235] has shown them to be effective in reducing post-operative astigmatism. This is in contrast to the findings of Troutman [227, 112] who also used a microscope mounted circular target. The Serdarevic [235] study was a prospective, randomised clinical trial, using a single running suture. Twelve patients underwent surgery with intra-operative adjustment of the suture tension, and their results were compared with those of a control group of 13 patients. At one month the mean topographic astigmatism (computerised videokeratoscope) was significantly higher in the control group 4.89D, versus 1.50D for the intra-operative group. At 6 months there was still a significant difference, even although 77% of the control patients had undergone post- operative suture adjustment, in an attempt to reduce their astigmatism. None of the group that had intra-operative adjustment, based on the qualitative keratometer, required post- operative adjustment.

Most of the quantitative keratometers use the classic optical principles of the von Helmholtz keratometer, and depend on the subjective localisation of the axis of astigmatism. Their accuracy is based upon the measurement of a sphero-cylindrical surface. Because the cornea is not a perfect sphero-cylindrical surface the precision of the device has inherent limitations.

The SK-1 Canon automated keratometer [231] makes use of non parallel electronic image digitisation. However, this is limited to the use of a single ring.

It is not practical to mount a Placido type target around an operating microscope which comprises sufficient rings to image a substantial area of the cornea. However, in 1988, Warnicki et al [236], introduced corneal imaging systems which use close range raster photogrammetry. They produce a true topographical map of the entire cornea by calculating corneal elevation rather than the angle of reflection used by Placido disc based videokeratoscopes. A regular pattern of known geometry is projected onto the cornea. The pattern is then viewed and imaged from an offset angle. Using the image of the projected pattern and information about its geometry, elevation values for each discrete point in the projected pattern can be completed. These systems require neither a smooth reflective surface, nor precise spatial alignment for accurate imaging, unlike Placido disc based videokeratoscopes which must be coaxial, and at a defined working distance. Because raster stereogrammetry systems use two non coaxial optical paths, they can easily be integrated around an operating microscope, thus permitting topographic imaging during surgical manipulation. One disadvantage is that the cornea in a transparent, non diffusing surface, and additional means must be used to visualise the projected pattern on the corneal surface. In the prototype intra-operative instrument using the PAR corneal topography system [232], this is accomplished by staining the tear film with topical fluorescein and illuminating the pattern with a cobalt blue light. Another prototype instrument the ACT-1, described by Thall and Lange [233], requires a less convenient means of rendering the cornea a diffusely reflecting surface. This is done by draping the cornea with a thin (about 12μm) membrane. It is claimed to have mechanical properties that enable it to conform to the cornea. Despite this drawback, the description of this instrument is interesting because of a refinement. The accuracy can be enhanced by making several measurements and displacing the projector slide a fraction of the grid interval between each measurement. This technique is known as phase shifting, and permits the measurement of 14,000 data points. Other improvements in the mathematical analysis of raster images have been put forward by de Cunha and Woodward [237]. Instruments of this type probably hold the best promise for the measurement of corneal transplant topography.

1.4.2.(vii) Surgeon

It is not known how much the variations in technique that occur between different individual surgeons, can effect post-operative astigmatism. However, research on formulae for intraocular lens calculations in triple procedures, stresses that each surgeon should individualise his or her formula by noting the average keratometer readings for a series of patients. One study [238] has investigated the effect lack of experience in performing keratoplasty has on post-operative astigmatism. They found that, in a retrospective series of 63 consecutive cases performed by residents, in a well supervised setting, the results were comparable with those reported in the literature (mean astigmatism 4.15D).

1.4.3 Post- operative factors

1.4.3.(i) Wound Healing

It is thought that the differences in focal wound healing around the circumference of the graft host interface may give rise to astigmatism. A study by Tripoli, Cohen and Proia [239] set out to evaluate any possible relationship between wound healing and astigmatism. Thirteen cats had successful penetrating keratoplasties after intentionally misshapen donor corneas were misaligned in misshapen corneal beds. All trephines were tilted at an angle of 20^{0} in order to induce a non circular cut. At six months after transplantation photokeratoscopy was performed with the corneascope (9 rings), and the directions of the longest and shortest chords across the second ring were considered to represent the flat and steep meridians. Four histologic sections were then prepared, one at each end of the meridians. Seven histological features of the graft/host interface were quantitatively analysed. These were epithelial thickness, stromal thickness, area of lamellar alteration, and four features relating to Descemet`s membrane. The results showed that when these morphometric features of wound healing were aggregated for all four positions, there was a relationship with astigmatism. However, when each meridian was considered separately there was no significant difference in morphometry that might explain why one meridian had become steep, and the other flat. The authors admit that although all four sections of the same wound had similar histopathology, a different histopathologic appearance of the wound at locations other than the steep and flat meridians could not be ruled out. The means used to identify the flat and steep meridians, that is to say the longest and shortest chord on a single ring of the keratograph, offers no real advantage over keratometry. Indeed the concept that corneal shape can be described by the central curvature in two principle meridians ninety degrees apart, has been entrenched in the minds of researchers and clinicians because of the many years of dependence on the keratometer. Many factors may act to distort the topography of corneal transplants and they may come to differ from the normal corneal shape i.e. two orthogonal principal meridians, in a complex way. Thus thinking in terms of two principle meridians even though it is realised that they may not be ninety degrees apart, may not be an appropriate approach. It is possible that sampling at regular intervals around the graft/host interface might have yielded some differences in healing morphology. The authors acknowledged that the use of a cat model restricts the application of the results to human corneas which are smaller, thinner, and steeper. They also have a Bowman`s layer which is absent in cats.

Several authors have examined the histology of human keratoplasty wounds [240, 241, 242, 243, 244, 245, 246, 247, 248]. Melles et al [247] found that epithelial ingrowth and incarceration of Bowman`s layer and/or Descement`s membrane in unsutured wounds appeared to disrupt wound healing. However, only one study [248] related histopathalogic wound morphology specifically to the amount of corneal astigmatism after penetrating keratoplasty. They found that incarceration of Bowman`s layer into the stroma was more frequently found in corneas with greater than 5.00 diopters of astigmatism than in corneas with less than 3.00 D of astigmatism.

The importance of good wound apposition is highlighted by the work of Melles and Binder [247] who investigated the morphology of corneal wound healing in 25 penetrating keratoplasty specimens. This was contrasted with the morphology of 25 specimens of corneas that had undergone various keratotomy procedures that did not involve wound suturing. The sutured wounds were characterised by sub-epithelial fibroplasia, recovery of collagen fibre continuity. This was in contrast to the unsutured wounds which had no sub-epithelial fibroplasia, but had fibroblasts and collagen fibre orientation parallel to the wound.

1.4.3.(ii) Transplant Rejection

Troutman [249] stated that late graft reaction can markedly alter transplant astigmatism. (This appears to be an anecdotal clinical observation.)

1.4.4 Summary

In 1988 Pflugfelder [176] wrote " Factors that contribute to the development of astigmatism after keratoplasty may be divided into (1) differences between the shapes of the donor button and recipient opening, (2) misalignment of the donor button within the host bed, (3) distortions induced by sutures, and (4) curvature changes resulting from corneal healing. The multifactoral nature of the problem makes determination of the relative contribution of individual factors difficult. It is generally felt, however, that the relative shapes and alignment of donor and host corneas are of greatest significance in the development of astigmatism."

Hoppenreijs et al [250] retrospectively evaluated the factors which were associated with excessive post- keratoplasty astigmatism, in 29 eyes in which surgical correction of astigmatism was indicated. The results are summarised in Table 1.7

Factors	High astigmatism (>5 D), before suture removal	Astigmatism that gradually increased after suture removal	Astigmatism that increased immediately after suture removal	Total
Graft elevation	3	2	10	15
Wound dehiscence	3	-	-	3
Thin recipient	2	-	-	2
Oval graft/recipient or overcut	8	-	-	8
Suture tension	-	-	9	9
Unknown	2	1	-	3

Table 1.7. Factors associated with high post-keratoplasty astigmatism in 29 eyes.

In the group where astigmatism increased after all sutures were removed, the average increase was 8.8D (range 5 to 16.5D). Ten of these nineteen patients showed graft elevation, despite the fact that sutures were only removed after an average 22.9 months (range 5 to 71 months).

In three other patients the astigmatism increased gradually over the years. Suture removal did not seem to be of importance here.

Two cases, both keratoconics, showed an extraordinary course of astigmatism, as shown below. (Table 1.8). These are not typical results and may relate to instability of the host tissue.

Case (A) Post- op. follow-up	Astigmatism (D)	Steepest Meridian	Case (B) Post- op. follow-up	Astigmatism (D)	Steepest Meridian
1 Year	5	104°	1 Year	3	120°
2 Year	2	115°	3 Year	4	110°
3 Year	1	84°	5 Year	5	120°
4 Year	3	62°	10 Year	6	115°
5 Year	3	67°	15 Year	11	115°
6 Year	5	45°	16 Year	11.2	120°
7 Year	6	48°			
8 Year	7	52°			
9 Year	9	55°			

Table 1.8 Post-operative follow up of keratometric astigmatism in two cases with keratoconus.

The authors concluded that the factors that produce post-operative astigmatism are not well defined, but the four main ones are:-

1. wound healing
2. suture loosening and suture configuration and tension
3. wound configuration
4. the pre- operative state of the cornea

This study also demonstrates the possible instability of keratoplasty wounds, and the late, apparently spontaneous changes in astigmatism after penetrating keratoplasty in some eyes. These results further highlight the need for a long term serial evaluation of changes in transplant topography.

1.5 Corneal transplant resensitisation

1.5.1 Innervation of the normal cornea

The normal cornea is particularly well supplied with sensory nerves. Rozsa and Beuerman [290] give a figure of 6000 terminals per mm^2 in the cornea of rabbits, a density many times greater than that reported for any other tissue. Human corneal nerves derive from the ophthalmic division of the trigeminal epithelium, and enter the eye via the ciliary nerves. There are two routes into the cornea. One route runs direct from the sclera into the middle and anterior stromal layers, coursing centrally in radial fashion and moving anteriorly [291]. Once in the anterior layers of the stroma, the nerves form a network, the sub-epithelial plexus. A few of the nerves penetrate Bowman`s membrane to form a plexus in the basal layers of the epithelium [292, 293]. Udea et al [294] estimate that this occurs at approximately 400 sites. Lim and Ruskell [295] demonstrated a second route, in which epithelial innervation derives from a sub-conjunctival plexus and passes directly into the basal layers of the epithelium. On entering the epithelium, the axons divide and continue in leashes, which may run for several hundred microns. Nerves move anteriorly from the basal epithelial plexus, along an approximately vertical route [293], before terminating in the superficial layers of the epithelium. The epithelial nerves have varicosities, which have been identified as both efferent and afferent (sensory) terminals [294, 292]. Sensitivity is much greater in the central cornea, and the distribution of sensitivity between the centre and periphery has been investigated by Millodot and Larson [296].

As well as the protective function afforded by this high degree of sensitivity, corneal nerves also appear to have a trophic function. This has been shown by Beuerman and Schimmelpfennig [297], who found that the absence of functioning corneal nerves had a deleterious effect on epithelial metabolism and healing. They produced lesions in the trigeminal ganglion by radiofrequency thermocoagulation; subsequent experiments indicated that the denervated cornea was approximately 2.5 times more permeable to fluorescein, and showed decreased cell proliferation and a delayed healing response to abrasions. One possible explanation is that denervated epithelium, when injured, cannot benefit from antidromic stimulation, for example, by Substance P which is transmitted to peripheral nerve endings by axoplasmic flow, and is released following painful stimulation.

1.5.2 Transplant resensitisation

1.5.2.(i) Psychophysical studies

A number of studies have been carried out on the resensitisation of corneal transplants, and most of these show that it occurs in a slow manner, and is sometimes incomplete even after many years. There is, however considerable disagreement between these studies.

Early research on the touch sensitivity of corneal transplants were limited to instruments which were basically only modifications of the von Frey hairs. Escapini [298] found a rapid return in cases of keratoconus and Fuch`s dystrophy, and was able to show that recovery of sensation was independent of the clarity of the graft. This was contrary to the conclusions of Franceschetti and Badel [299] who believed that reinnervation was essential if a graft were to remain clear.

The instrument devised by Boberg-Ans in 1955 was the forerunner of the Cochet Bonnet aesthesiometer, and gave researchers the opportunity of more precise testing. Despite this, there continued to be considerable disagreement between different studies. Skriver [309] reported that sensitivity tended to be normal about twelve months after transplantation, and Sedan et al [300] found recovery as early as four months. Whereas Ruben and Colebrook [301] could detect normal levels in only one third of their patients at the three year stage. They believed that the return of sensitivity was progressive. However, a later study by Rao et al [302] came to the opposite conclusion. Those workers found that only a few eyes showed any recovery of sensitivity in the transplant centre, and that this was not related to the length of post-operative period. A more recent study by Tugal-Tutkun et al [303] reported that only one transplant had normal central sensitivity at 2 years, and that half of their sample of 71 eyes were completely anaesthetic at the time of testing. Unfortunately the time from keratoplasty to sensitivity testing varied from 2 weeks to 15 years. However, they were able to demonstrate a progressive return of sensitivity which did not appear to be related to patient age or the pre-operative diagnosis. A larger study of 210 eyes conducted in China [304] showed that in the period 5 to 6 years after keratoplasty, 40% of transplants achieved normal sensitivity. However, extending the post- operative period to 7 - 22 years only gave a marginal increase to give a total of 50% achieving normal sensitivity.

A further complication in reviewing the literature on resensitisation is differences in the equipment used. Although most of the research was carried out with the Cochet Bonnet aesthesiometer, other instruments have also been used.

The Corneal Micro Aesthesiometer [305] is a non-contact device which uses a jet of air to convey force to the cornea. It was used to compare [306] the sensitivity of two groups of patients who had undergone keratoplasty. The younger group (mean age 35) had a significantly lower threshold than the older patients (mean age 75). However since the post-operative period was not taken into account, these results have little value.

Draeger and his colleagues used an electro-mechanical instrument of their own design. This gives a reading in terms of force (Newtons x 10^{-5}). In other words the threshold is given as the minimum amount of force exerted at the tip of the probe that will elicit a response. A report of a retrospective study is given by Draeger [307]. Measurements were obtained at 6 months, 15 months, three years and eight years. The mean threshold for the transplant centre at six months was very high, effectively representing anaesthesia. There was a gradual increase in sensitivity up to three years, with no apparent improvement in the period to eight years. Unfortunately there is no mention in this report of the number of patients involved and there are no error bars on the charts, so it is difficult to assess the significance of these results. Though there seems little doubt that the sensitivity profiles shown do represent a complete reversal of the profile found in normal corneas, which are most sensitive in the centre. By contrast the centre of the transplanted corneas was always least sensitive. Four peripheral points were measured on the donor tissue 1mm in from the scar, and these were always more sensitive than the centre, even at the eight year stage.

In another study, more conclusive results regarding the centripetal progression of sensitivity was reached by the adoption of a different approach. Mathers et al [308] measured the nearest point to the transplant centre that could detect an aesthesiometer filament set at 2 cm. In this way, it was possible to demonstrate and quantify the progression of sensitivity from the periphery towards the centre, in terms of distance per month.

There is some evidence that different diagnostic groups have a different prognosis in terms of resensitisation. In the Chinese study [304] those who underwent keratoplasty for Herpes Simplex Keratitis showed much slower recovery, with only 17% achieving normal sensitivity at the 7 to 22 year stage, compared to a figure of 50% for the other diagnostic groups. This pattern has been found by other authors [307, 309, 298], and it is generally expected [310] that recovery of sensation will be more pronounced after keratoplasty for keratoconus or Fuch's dystrophy, than following herpetic keratitis or alkali burns. Stamer et al [311] studied 56 patients. They were split into nine different groups according to the reason for keratoplasty. Those who suffered from keratoconus showed a faster recovery, compared to the endothelial dystrophies and other groups. This was particularly marked when considering the transplant periphery, where 50% of the keratoconics had " normal to slightly reduced " sensitivity at four months and all had normal sensitivity at two years.

Most of the studies mentioned above took a group of transplants that had each reached a different stage in their history, and measured sensitivity in each eye on only one occasion. There are several exceptions. In the study by Tugal-Tutkun et al [303] 21 out of 71 eyes were tested on two occasions, and in the Mathers [308] study 8 out of 91 eyes had repeat measurements. There appears to have been one early attempt to perform a truly sequential follow up, this was by Zorab [312] a surgeon working in Southampton during the 1950's. He followed 68 corneal grafts, some of which were lamellar. Forty-four of these never regained any sensation. He also found that sensation seldom recovers in less than a year, but many still recover after an interval as long as six years. Unfortunately, this study is flawed by its use of a wisp of cotton wool as the stimulus, and a somewhat anecdotal approach to reporting the results. Another more recent attempt at a sequential study was by Stamer et al [311], who had a post-operative follow up schedule of 1 month, 4 months, 1 year, 2 years and 3 years. The number of patients who were reported to be involved was 189. However the authors admit that attendance for all assessments was rare and there appears to be only one section in the results that makes use of sequential measurements in the same patient. This is the comparison between 4 month and 1 year data and only 36 patients are represented.

1.5.2.(ii) Histological studies

The histological evidence on the nature of corneal nerve regeneration is almost entirely confined to animal studies. Caution should therefore be applied if these results are to be extrapolated to the human situation. It should also be noted that a variety of different methods have been used to cut or destroy the nerves whose regeneration is being studied. For example removal of the epithelium using heptanol [313] will have little effect on stromal nerves, and is completely different to a penetrating keratoplasty.

Studies carried out on animals in the 1950`s, such as those by Rexed and Rexed [314] showed that by one week there was complete degeneration of the nerves within the area affected by an incision. Earlier studies by Escarpini [298] had shown that the host nerves degenerate not only in the area of the incision, but up to 2mm peripheral from it. However, the Rexed [314] study found this retrograde degeneration in very few nerves, and then only for a maximum distance of 0.5mm. They found that the severed ends of the host nerves show regeneration activity as early as 3 days. Single neurites send out filaments towards the scar, often running parallel for some distance before penetrating it. By three weeks a network of new fibres is seen within the area bounded by the scar. This study involved rabbits with arcuate incisions down to the level of Descemet`s membrane, varying in circumference from 90° to 360°. The authors used von Frey hairs to test sensitivity, but commented on the difficulty in distinguishing a true positive response.

More recent work has involved a broadly similar approach. Rozsa, Guss, and Beuerman [315] also used rabbits, and part of their study involved 180° penetrating perilimbal incisions. They found that neural growth from the unaffected portion provided only a minor contribution to reinnervation. The primary source was nerves that had penetrated the scar. They were able to show that this had occurred by 90 days, and was accompanied by a sub-epithelial plexus with some intraepithelial terminals. This work, with 180° perilimbal incisions, was repeated by Chang-Ling et al [316], who extended the follow up period to 30 months, and included psychophysical assessment of sensitivity with the Cochet Bonnet aesthesiometer. They found that sensitivity was significantly reduced in the superior cornea (2 to 3 mm from the limbus) throughout the 30 months. Histochemical examination showed a reduced number of stromal nerve trunks in the affected portion. Also, each trunk contained fewer axons. The basal epithelial plexus was also deficient. These authors concluded that the observed reduction in sensitivity was ultimately related to stromal innervation. They believed that although extensive stromal reinnervation had occurred, the extent and quality of the stromal nerves was inadequate to restore a normal epithelial plexus.

Confirmation that touch sensitivity is related to the status of the stromal nerves is to be found in a paper by Chan-Ling et al [317]. They performed 8 mm circular keratotomies on cat corneas. The depth of the main incision varied between 49% and 91% of corneal thickness, with some full thickness incisions (i.e. penetrating autografts). They found a statistically significant correlation between the disruption of stromal nerves (as indicated by the depth of the incision), and reduction in touch sensitivity (Cochet Bonnet aesthesiometer). The 360° incision used here is much more relevant to the question of corneal transplant resensitisation. It had been thought that the limited reinnervation after penetrating keratoplasty was due to the fact that nerves which managed to penetrate the scar, were further hampered in their journey by the lack of an endoneurial tube within the stroma. However, this study shows that reinnervation is limited even when nerves emerge from the scar tissue immediately opposite a ready made pathway. This is the route taken by the nerve before its` distal portion became degenerated following the incision.

A study by Rao et al [318] used a surgical technique that is closer to the corneal transplant situation. They performed rotated autografts in the right eyes of 23 rabbits. At nine months after surgery no corneal nerves could be detected by histochemical means in the graft centre, which correlated well with results from the Cochet Bonnet aesthesiometer. Histological examination of the graft periphery revealed changes in nerve density over time. The first week showed a marked decline. This was followed by a proliferation which resulted in higher densities than the control eyes. The period from one to four months revealed minimal changes, but there was then a further increase in density from four months to the end of the study at nine months. It should be remembered that these were autografts, which are different from corneal transplantations, where reinnervation must occur in foreign tissue.

It is interesting to note that regeneration of stromal nerves is more rapid in the absence of scar tissue, and complications derived from mechanical incision. This was shown in a study by Chan et al [319], which used a transcorneal freezing technique to produce a 2mm circular, central wound in a rabbit cornea. All the cornea cells, nerves, and associated Schwann cells were dead inside the wound, but the extra cellular matrix components remained intact. Paradoxically the faster regeneration of the stromal nerves and sub-epithelial plexus, was not matched by an equally rapid epithelial reinnervation, which remained as incomplete as in the other models.

Heptanol has been used to produce a well defined corneal wound, deprived of epithelium, and intraepithelial nerves. Partial regeneration of rabbit epithelial nerves was found by one month [320] (35 to 47% less than the control), with no further improvement up to 10 weeks [313]. This was confirmed by partial restoration of touch sensitivity [313] (Cochet Bonnet aesthesiometer). The results [320] also suggest that Epithelial neuronotropic factor (ENF) which is secreted by epithelial cells may mediate nerve regeneration.

All of the above studies involve the use of animal corneas. One study, by Tervo et al [321], did examine human corneas following penetrating keratoplasty. Only three corneas were assessed, and since they were obtained after retransplantation, they are not representative of successful transplants which are in the majority. However, since it is known that reinnervation is not affected by corneal transparency, the fact that the study relies on failed transplants may be less important. Histochemical examination demonstrated that neural regeneration was limited to the basal epithelial plexus, with only a few stromal nerve trunks forming, despite a post- operative period of 29 years in one case. This tends to support the work of Lim and Ruskell [295] which showed that in monkeys, nerves to the epithelium do not transverse Bowman`s membrane, but enter the epithelium at the limbus. Tervo et al [321] found incomplete recovery of sensitivity even when the epithelial nerve supply appeared to be established. They concluded that stromal nerves were important to sensory recovery, and that it was the lack of stromal nerves which accounts for the differences in observed sensitivity between the human and animal studies.

2. Introduction. Measurement of corneal topography.

2.1 Keratometry versus Keratoscopy.

Keratoscopy is a qualitative or quantitative method of assessing the anterior corneal contour. This is generally achieved by observation of the virtual image (First Purkinje image) of a target object reflected by the corneal surface. The nature of the target is such that assessment can be made simultaneously in more than one meridian, unlike simple keratometry where the mires define the ends of a simple linear object, allowing measurement in only one meridian at a time. Keratometry depends on two assumptions. Firstly, that the two principal meridians containing the maximum and minimum curvatures, are orthogonal. Secondly, that in any given meridian, curvature is symmetrically disposed on either side of a central point. Neither of these assumptions is applicable to the topography of corneal transplants. Therefore some form of keratoscope is required.

2.2 Review of keratoscopes.

The first person to investigate corneal curvature was Scheiner, who in 1619 compared the corneal image size, to that produced by glass spheres of known diameter, held close to the cornea. In this instance the target was the bars over a distant window. Brewster, in 1827, suggested examining the image of a candle, and Senff did further work in 1846, but it was not until 1847 that the first instrument that might be considered a keratoscope was invented. This was devised by Henry Goode during an endeavor to determine whether the cause of ocular astigmatism in a subject was corneal. The target consisted of a small luminous square. This was held a few inches from the eye, which meant that a much larger area of the cornea could be assessed than with the distant window bars used by Scheiner. Although distortion is more readily observed on a square than a circle, keratoscopes were now developed with circular targets. The first to use this form was Antonio Placido, a Portuguese ophthalmologist ,who in 1880 designed a flat circular disc with alternate black and white concentric rings, with a small central hole through which the examiner could observe the images. A central tube was also incorporated as an aid to alignment. The Placido disc permits qualitative assessment of corneal topography, but quantitative assessment requires measurement of the image size. The advantage of this target was that it was composed of many parts which act as separate objects whose images may be used to obtain curvature values over a relatively large area of the cornea. Ideally these measurements should be made simultaneously, meaning that a method of image capture for subsequent measurement was required.. The incorporation of photography is credited by Levene to both Placido , and to Javal, who were working independently. Javal applied this to the qualitative analysis of pathological irregularity, but Gullstrand [322] in 1896, was the first to apply photokeratoscopy to the systematic measurement of corneal topography.

Gullstrand [322] used a flat target consisting of four rings concentric with the camera objective. Each white ring had a thin black centre which made location easier when the negative was viewed with a measuring microscope. The area of cornea covered was not very large. The design was such that the normal to the cornea at the reflection point for the outermost ring subtended an angle of 17^0 6` 30" with the optic axis of the instrument. For a cornea of 7.8mm radius this corresponds to a chord length of 4.6mm.

In order to increase the area of cornea covered, Gullstrand [322] took 6 exposures of each eye, two with central fixation, and one each for fixation superiorly, inferiorly, left and right along the principal meridians. These secondary fixation points were chosen on the basis of calculations derived from the central keratograph. This effectively increased the meridional chord length to 9.8mm, but at the expense of the introduction of further errors. One of these was inaccuracy in the location of the centre of rotation of the eye (Wittenberg [323]). This confirmed that simultaneous acquisition of all the image points is preferable. Despite its limitations the Gullstrand [322] instrument does possess all the major elements of modern keratoscopes:- a target; an optical system capable of capturing the reflected image created by the cornea, and focusing it on a recording plane; and a recording system which creates a permanent record capable of measurement.

Progress in the development of photokeratoscopy techniques can be considered by looking at the improvements in two aspects of instrument design; the target, and the optical system.

2.2.1 Target.

(a) Target type.

Circular targets continued to be used because they permitted analysis along any semi meridian, which is particularly important in the assessment of distorted corneas which do not have two principal meridians 90 degrees apart. Line, bar or point targets were used on several photokeratoscopes. These were mounted on two perpendicular arms, which could be rotated along the principal corneal meridians, providing these had already been determined by keratometry. Line or bar targets have not been used on any modern instruments. (The Rasterstereography technique developed in the late 1980`s do make use of a grid target, but since it is not the reflected image that is analysed, this technique is not considered as keratoscopy. The advantages of these instruments, which were developed after the commencement of the study reported in this thesis, are discussed in chapter 6.)

The number of rings used has varied with different instruments as photokeratoscopy has developed. Generally more rings with less separation between them means more data points, which is important when trying to fit a mathematical curve to a given meridional section. However, this must be set against the extra effort involved in analysis, and generally the number of rings was restricted until the advent of computer assisted keratoscopes. Another consideration on the optimal separation of individual target rings is that in distorted corneas the image rings can become blurred, or even be missing in places, making it difficult to distinguish one ring from the other if they are too close together.

Another possible target improvement is the radius of the innermost ring, which should be as small as possible so that curvature near the centre of the cornea can be assessed. This is a drawback of this particular design of instrument, and in practice the area of unknown central curvature is often determined by the diameter of the camera objective which must be placed at the centre of the target.

(b) Target Locus.

This refers to the shape of the three dimensional surface upon which the target is drawn.

- Plane Targets.

The Gullstrand photokeratoscope used a flat target, and despite its limitation, this design continued to be used in experimental photokeratoscopes, and even in some commercially available instruments. The Fincham [324] photokeratoscope designed in 1953 was one of the best to use a plane target. It consisted of six concentric rings designed so that when they were reflected from a spherical surface, the rings in the reflected image would appear equal in width and equally spaced. When this 20cm diameter target was placed 6cm from the eye, it covered a corneal diameter of 7mm according to Fincham. This represents one of the major drawbacks of plane targets: limited corneal coverage. The other is curvature of the image field, making it impossible to focus the entire image on a flat film plane.

- Hemispherical Targets.

Targets drawn on the inner surface of a hollow hemisphere offered improvements in both coverage and field curvature (Donaldson [325]).

- Cylindrical Targets.

In 1930 Dekking, a Dutch ophthalmologist, found that the inner surface of a hollow cylinder also, proved successful in reducing field curvature, and also allowed potential observation of a 12mm region, though this was reduced by vignetting by the subjects nose, brows and lids. He also noted that "bending out" the sides of his cylindrical target surface produced an even flatter virtual image. This was later developed by Knoll in 1961, and eventually commercially produced by Bausch and Lomb in 1963. Ludlam and Wittenberg [326, 327] modified the Knoll cylindrical photokeratoscope for their work. They concluded that the optimum object locus to provide a flat reflected image from a spherical surface, was an elliptical target. However, as the cornea is aspheric, they concluded that an exactly flat reflected image was impossible, and that their cylindrical target afforded a good compromise. A modified cylindrical target was later used by El Hage [328].

- Ellipsoidal target

Several instruments were developed using an ellipsoidal target. These included the Photo Electronic Keratoscope (PEK) [329]. This instrument was originally a plane target keratoscope designed by Reynolds in 1959. It was subsequently modified by Townsley, who claimed that his ellipsoidal target would produce a flat image when reflected by a cornea which was itself ellipsoidal. This was only strictly true for a corneal ellipsoid with an apical radius of 7.67 mm (44.0 D), and any deviation from this curvature, or any astigmatism or corneal distortion would result in some loss of focus in the recording plane. The experimental instrument designed by Holden [330] also used an ellipsoid target. A cardioid target surface, which closely resembles an ellipsoid, was used by Amiard [331].

(c) Target Illumination.

In the majority of keratoscopes the target is illuminated in such a way that the light emanates from any given point on the target as though it was a secondary source propagating rays in all directions. It is only the light which is reflected back from the cornea, such that it passes through the nodal point of the camera system, that is of interest in the calculation. The angle of this incident ray is dependent on the position of the target ring, and the point of reflection at the corneal surface. However, the calculation of corneal curvature can be considerably simplified with no need for differentiation or integration, if the angle of incidence is known (El Hage [332]). This is known as directional illumination. El Hage [332] proposed the use of reflective target surfaces which could be angled relative to the light source in order to produce a certain angle of incidence. Collimated targets were incorporated into the instruments by Amiard [331], Fuji [333], and Westheimer [334], also used projected targets. However, none of these designs has been adopted in any recent photokeratoscopes.

2.2.2 Optical System.

The requirements of the optical system are that it should bring the image of the target reflected by the cornea into focus at the recording plane. Two aspects of the optical system are involved in this task, Firstly the viewing system which allows the operator to accurately focus the instrument on the corneal image. Secondly the optical system which accurately transfers the corneal image to the recording plane. Design changes in order to facilitate focussing include the use of ametropia correction in the eyepiece, a magnifying eyepiece, split prism, ground glass focusing screen and alignment cross. This part of the optical system must have a narrow depth of focus in order to permit accurate focusing. This means the use of a wide aperture.

Conversely, the camera system requires a small aperture in order to maximise the depth of field at the recording plane. This is important because it is unlikely that the image in the cornea will be located exactly on a flat plane. Improvements in the quality of the image at the film plane can also be made by designing the optical components to minimise off-axis aberrations such as field curvature, astigmatism, distortion, and coma. Amiard and Cochet [335] have discussed the control of these aberrations. They have also shown how they can affect magnification for the off-axis rays from the more peripheral target rings, and have proposed appropriate calibration procedures.

Another modification of the optical system was used to reduce the effect of errors to focus. This was the use of a telecentric stop, which is placed at the second focal plane of the optical system. This has the effect of reducing the rays that emerge onto the film plane to only those that have passed nearly parallel to the optic axis. This means that the height of the reflection point (from the optic axis) is independent of the distance from the cornea to the image reflected by the cornea. Thus focusing errors have less effect on the calculations. Telecentric systems were used by Westheimer [334], Amiard and Cochet [335], and by El Hage [328] with his EHP model.

2.3 Choice of instrument

The PEK instrument was chosen from those available at the commencement of this study, for the following reasons. Focus errors are reduced by the use of an ellipsoidal target, and a shallow depth of field in the optical system. Centration errors are reduced by an alignment system which permits accurate relocation for repeat measurements on subsequent occasions. The raw data is produced in a hard copy format (polaroid photograph), which can then be analysed by any method thought to be appropriate, rather than being restricted to a proprietary analysis system. Several computerised video keratoscopes have become available since the start of this study, and their advantages and disadvantages are discussed in chapter 6.

3. Introduction. Measurement of corneal sensitivity.

3.1.1 Review of aesthesiometers

The first attempt to measure corneal sensitivity precisely was by Von Frey [336]. He used different length hairs attached with wax at the tip of small glass rods to provoke a sensation. Each hair was calibrated and the force it exerted on the cornea known. No significant improvements were made until Boberg-Ans [337] substituted a single nylon filament of constant cross-section for the series of hairs. The length of the filament projecting from the metal holder was indicated on a centimeter scale in the handle, and could be simply altered by a milled wheel, to produce all the test forces.

Some improvements were recommended by Cochet and Bonnet, including the use of two alternative filament thicknesses (0.08mm and 0.12mm), and their instrument was first commercially produced in 1960 by Luneau and Cofignon in Paris. Since then the majority of work done on corneal sensitivity has been carried out on this instrument. When used as a hand held instrument it does , however, have a number of drawbacks:-

1. Apprehension on the part of the subject when the instrument is brought towards the eye can induce a premature blink reflex, and also give a lower touch threshold. This was demonstrated by Bonnet and Millodot [338] by testing in the dark using infra red illumination.

2. Difficulty in observing when the filament has just touched the cornea, and in observing the bend induced in the filament. The instrument has been calibrated by Cochet and Bonnet to show the force transmitted to the cornea for each filament length

when the filament is bent by 5 degrees. Milladot and Larson [339] have shown how much the force applied changes when the angle is not exactly 5 degrees.

3. The nylon filament bends under its own weight taking up the form of a curve. This makes it difficult to ensure that the tip is placed at right angles to the corneal surface. Larson [340] showed how the angle at which the filament is applied to the cornea was found to have an important influence on the force applied.

4. Changes in humidity and temperature beyond a certain range have been shown to affect the characteristics of the nylon filament (Millodot and Larson [339]).

5. The shape of the nylon tip is not reproducible, meaning that the pressure distribution is not known. However, the usual practice of converting the force applied into terms of pressure, implies that equal pressures would have an equal chance of eliciting a response. In other words a force of 50g applied to the tip of cross-sectional area $0.0113mm^2$ (0.12mm diameter filament) would have the same effect as 500g applied to a tip ten times larger in area. It is by no means certain that this is the case (Draeger [341]).

6. The relationship between filament length and force applied is non linear, such that changes in length of filament cause less effect on force when the filament is fully extended.

The use of a specially designed holder to attach the Cochet Bonnet aesthesiometer to the observation arm of a slit lamp makes the approach of the filament towards the subject slightly less apparent than it is when the instrument is hand held. More importantly, the system permits the contact between the filament and the cornea to be viewed under magnification. It is also easier to arrange for the tip of the filament to be kept perpendicular to the corneal surface, and the speed of approach can easily be controlled by the joy stick of the slit lamp.

Although this mounting system does offer considerable improvement, problems still remain, and other instruments have been developed in order to further reduce errors in the force applied. These include those of Hamano [342] (1960), Schirmer [343] (1963), Larson and Millodot [340] (1970), Gotz [344] (1972), Beuerman and McCully [344] (1978), and Draeger [341] (1979). The most notable are the Larson - Millodot design [340], and the design by Draeger [341]. Unfortunately, neither instrument is produced commercially. These two instruments share the same basic principles, in that the force applied is controlled by electro-mechanical mechanical means. They avoid the changes in nylon with humidity, and problems of tip reproducibility, by using a platinum wire.

The dependence on the skill of the operator to apply the correct force is avoided by using a spring mechanism which has a wide range, and can be finely set to produce any desired force. Immediately the probe makes contact with the cornea, a light beam incident on a photoelectric cell is broken, causing the probe to retract. This allows the measurement to be taken within the period of physiological blink. The Dragger instrument also permits "dynamic" aesthesiometry with a continuous increase in force while the probe remains in contact with the cornea. This gives a higher threshold than that obtained by the more usual method of constant stimulii in which the force is increased by steps until a 50% response is obtained.

A new device for corneal aesthesiometry was reported in an ARVO abstract in 1988. It employs a controlled jet of air as the stimulus, and was fully described in 1992 [305]. The manufacturers claim that the diameter of the stimulus area is limited to 2mm, but this would not have given sufficient resolution in terms of stimulus position for it to be useful in this study. Another air pulse aesthesiometer is being developed by Murphy and Patel [345], which has been used to investigate sensitivity following Photo Refractive Keratectomy.

Carbon dioxide lasers have been used as the stimulus in some experiments. This has the advantage that the small parcel of energy applied to the cornea can be highly controlled in terms of intensity, size, and duration. However, it should be born in mind that this instrument assesses the detection of heat and not touch.

3.1.2 Choice of instrument

Although some of the more recent instruments described in section 3.1.1 may appear to be more accurate than the slit lamp mounted Cochet Bonnet instrument, accuracy is not directly proportional to the sophistication of the instrument according to Millodot [346]. He believes that the response is more dependent on the subjects attitude and apprehension.

The problem of the remaining inaccuracies of the Cochet Bonnet aesthesiometer assume less importance when one considers the situation of this particular research:-

1. Firstly all the measurements are to be taken in the same air conditioned basement room, with little variation in humidity. A previous study conducted in the same circumstances by Bleshoy [347], measured humidity and temperature over a period of time as 58.3% (SD= ± 8.0), and 21.7 degrees C (SD = ± 1.8).

2. There is the non -linearity which means that a given change in length of the filament has less effect on the force applied in the low threshold end of the range. However, this is not a problem since most grafts will have touch sensitivities at the opposite end of the range.

3. Only one experienced observer who has acquired the necessary skills will be used.

4. The subjects themselves have the opportunity to become adept at making the necessary judgments, because the readings are repeated over a long period of time. They are introduced to the technique at approximately the six months stage when there is no sensitivity, and confidence can be built up.

Taking all these factors into account it was decided that a mechanically simple instrument such as the Cochet Bonnet, which could be relied upon to function well over the number of years the study was to take, would be preferable to a more sophisticated one which might be prone to break down.

The Cochet Bonnet also has the advantage that its results can be directly compared with much of the other work done in this field.

4. Methods and materials

4.1 Follow up Schedule

This study was commenced in September 1983 by another researcher, Miss FN Chin, who collected the data for the first two years. The original protocol called for measurements of corneal thickness, endothelial morphology, corneal sensitivity and corneal topography. A total of 142 patients were enrolled in this study. The schedule of visits was drawn up on the basis of the expected changes in these variables over time. This schedule was continued throughout the study. Only the data derived from photokeratoscopy and aesthesiometry is presented in this thesis.

Post-operative
1 month
3 month
6 month
9 month
1 year
18 month
2 year
Annually thereafter

Table 4.1 Visit schedule. Time since keratoplasty.

It was not always possible for patients to conform exactly to the schedule of appointments and a tolerance was accepted in the timing of data collection. Appointment (1) within two weeks of surgery; appointment (2) ± one week; appointments (3-6) ± one month; appointment (7) ± two months and ± three months for the remaining appointments. The schedule was based on a four week month and a twelve month year. No measurements were within the first month after suture removal, in order to allow the corneal topography to equilibrate to a steady state.

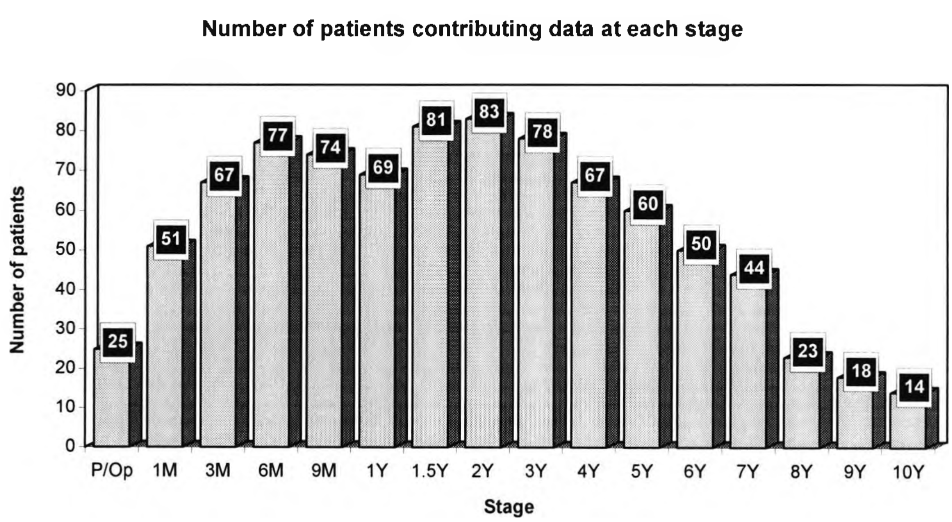


Figure 4.1 Number of patients contributing data at each stage.

4.2 Patients

4.2.1 Selection, exclusions

It was not possible to obtain a satisfactory sequential series of PEK keratographs from all the patients enrolled in the main study. This was due to several factors. The main reasons were a poor record of attendance, and gross corneal distortion resulting in a poor quality keratograph image not capable of analysis. Photographic problems were also responsible in some cases.

This prospective longitudinal study was set up to obtain a series of sequential measurements from each patient, rather than single observations from individual patients, each at a different point in the post-operative period. Therefore, those patients who did not have a satisfactory sequence of PEK keratographs were excluded. leaving a total of 108 patients available for analysis in the topography section of this study.

4.2.2 Patient characteristics

4.2.2.(i) Indication for penetrating keratoplasty

The majority of the patients in the study suffered from keratoconus.

Keratoconus	91	84%
Other diagnoses	17	16%

Table 4.2 Indication for penetrating keratoplasty

The primary indication for the initial penetrating keratoplasty in the remaining 17 patients is shown below.

Interstitial keratitis			1
Fuchs' dystrophy			3
Lattice dystrophy			3
Scarring	Herpes Simplex	3	
		1	
			4
Bullous keratopathy secondary to :-			
	Anterior chamber intraocular lens	3	
	Glaucoma	1	
	Buphthalmos	1	
	Ulcer in lamellar graft	1	
			6
Total			17

Table 4.3 The primary indication for the initial penetrating keratoplasty in the remaining 17 patients

4.2.2.(ii) Previous penetrating keratoplasty

For nine eyes, 8% of the total in the study, this was a repeat keratoplasty.

Second transplant	6 eyes
Third transplant	2 eyes
Fourth transplant	1 eye

Table 4.4 Previous penetrating keratoplasty

4.2.2.(iii) Indications for the operations involved in this study

Indication		
Keratoconus		87
Interstitial keratitis		1
Fuchs' dystrophy		3
Lattice dystrophy		3
Herpes Simplex		2
Bullous keratopathy	Glaucoma	1
	Buphthalmos	1
	Ulcer in lamellar graft	1
Failed transplant	Keratoconus (2nd transplant)	4
	Herpes Simplex (2nd transplant)	1
	Smallpox Scarring (3rd transplant)	1
	Anterior chamber i.o.l. (2nd transplant)	1
	Anterior chamber i.o.l (3rd transplant)	1
	Anterior chamber i.o.l (4th transplant)	1
	Total	108

Table 4.5 Indications for the operations involved in this study

4.2.2.(iv) Aphakia

Twelve patients (11%) were either aphakic prior to the operation, or had combined cataract extraction and penetrating keratoplasty.

Aphakic prior to keratoplasty.	5
Double procedure. Penetrating keratoplasty and extracapsular cataract extraction.	5
Triple procedure. Penetrating keratoplasty, extracapsular cataract extraction, and intraocular lens implantation.	2

Table 4.6 Aphakic patients

4.2.2.(v) Age

The mean age of the patients at the time of surgery was 37 years (SD 13, range 14 to 74). The ages of the keratoconus patients tended to be clustered in the third or fourth decade of life, reflecting the natural history of the disease [348], whereas the remaining patients tended to have their operations later. The mean age of the keratoconic patients was 34 years (SD 10, range 14 to 74). This is in contrast to the mean age of the patients with other diagnoses, which was 56 years (SD 10, range 25 to 71).

4.2.2.(vi) Sex

Male 70 (65%)

Female 38 (35%)

When the keratoconics are analysed separately the preponderance of males becomes even more pronounced, (Male 63, Female 28). This gives a ratio of 2.25 to 1, which is slightly higher than the ratio of 1.92 to 1, derived by Tuft et al [348] from a large sample of 2498 keratoconic patients.

4.2.2.(vii) Right or Left

62 Right (57%)

46 Left (43%)

Tuft et al [348] also found a slightly higher proportion of right eyes. 51.7% of 757 eyes transplanted for keratoconus were right.

4.2.2.(viii) Atopy

30% of the patients had a history suggestive of atopic disease. This is lower than would be expected from a group with a high proportion of keratoconics. Tuft et al [348] found an incidence of 52.8% in their large sample of keratoconics.

4.2.2.(ix) Hydrops

5 patients suffered an acute hydrops prior to keratoplasty, (5.5% of the keratoconics). This agrees with the findings of Tuft et al [348]. They found that corneal hydrops was the primary indication for penetrating keratoplasty in 4.3% of a group of 575 keratoconics.

4.2.2.(x) Donor age

The age of the donor was available in 95% of the cases. The mean age was 52 years (SD 22, range 11 weeks to 95 years).

4.2.2.(xi) Donor cause of death

The cause of death, as noted in the Eye Bank records, is shown below.

Donor cause of death

Brain tumour	1
Ca	1
Ca Bladder	3
Ca Breast	3
Ca Bronchius	1
Ca Kidney	1
Ca Lung	2
Ca Ovary	1
Ca Pelvis / carcinomatosis	1
Ca Rectum	1
Ca Stomach	1
Cancer tongue	1
Carcinoma	1
Carcinomatosis	4
Cerebral meningioma	1
Chondrosarcoma	1
Disseminated adenocarcinoma	1
Glioma	1
Malignant glioma	1
Malignant histiocytosis	1
Neoplastic disease. Total	**28**

Brain haemorrhage	1
Cerebral haemorrhage	1
Cerebro vascular accident	3
Sub-dural haemorrhage	1
Sub-arachnoid haemorrhage	11
Cerebro vascular accident. Total	**17**

Cardiac arrest	4
Cardiac failure	1
Cardiogenic shock	1
Coronary	1
Coronary thrombosis	1
Heart attack	1
Heart/pacemaker failure	1
Left ventricular failure	1
Myocardial infarct	5
Cardiovascular disease. Total	**16**

Adult respiratory distress	1
Asphyxia	1
Bronchi pneumonia	2
Chronic obstructive airways disease	3
Cystic fibrosis	1
Pneumonia	1
Pulmonary embolism	1
Respiratory failure	2
Pulmonary disease. Total	**12**

"Old age"	1
Chronic renal failure Diabetes	1
Cot death	1
Drug overdose	2
Insulin overdose	1
Acute lymphatic leukaemia Pneumonia	1
Chronic lymphatic leukaemia	1
Leukaemia Heart attack	1
Other total	**9**
Head injury	2
RTA	8
Trauma total	**10**
Brain stem dead	1
Collapsed	1
Brought in dead	1
Unrecorded	12
Unknown or unrecorded total	**15**
Live donor: Malignant Melanoma	1

Table 4.7 Donor cause of death

Unfortunately the recorded cause of death is sometimes the end stage pathology, and does not always directly relate to the primary cause. Thus it is not possible, from the data available, to detect donors suffering from a collagen deficiency, which could have affected the qualities of the donor material. The only items in the list of causes, which might relate to collagen deficiency, are "cardiac failure" and "left ventricular failure", which could have been caused by mitral valve prolapse.

4.2.2.(xii) Donor storage

Fresh whole eye 62 cases (57.4%)

M-K medium 23 cases (21.3%). (McCarey-Kaufman medium. Tissue culture medium with 5% Dextran, HEPES buffer, and gentamicin sulphate)

K-Sol 22 cases (20.4%). (Tissue culture medium with 2.5% Chondroitin sulphate, HEPES buffer, gentamicin sulphate, and sodium bicarbonate)

Organ culture 1 case (0.9%). (Tissue typed donor button obtained from UKTSS, Bristol)

4.2.2.(xiii) Contact lens wear

Exactly half of the patients (54), wore a contact lens for a significant period of time following keratoplasty. These were all rigid gas permeable lenses prescribed for visual reasons, and do not include the soft therapeutic lenses which were worn for short periods by several patients.

With one exception contact lens fitting was always undertaken after the final removal of all sutures. The mean number of months between the final removal of all sutures and commencement of wear was 13 (SD 17, range 2 to 93 months).

4.2.2.(xiv) Suture configuration

89 cases (82%) had a single continuous 10/0 nylon suture.

15 cases (14%) had 16 interrupted 10/0 nylon sutures.

4 cases (4%) had a combination of an eight bite single continuous 10/0 nylon suture and eight interrupted 10/0 nylon sutures.

4.2.2.(xv) Suture removal timing

The mean interval between keratoplasty and the final removal of all sutures was 22 months (SD 12, range 5 to 78).

4.2.2.(xvi) Rejection episodes

28 patients (26%) experienced one or more episodes which were treated as a rejection with increased dosage of steroids.

4.2.2.(xvii) Refractive surgery

Ten patients (9%) underwent refractive surgery in order to correct unacceptable astigmatism or irregular corneal topography. In all cases relaxing incisions were performed. One of these patients suffered from Fuchs' dystrophy and the remainder were keratoconics.

4.3 Surgical technique, and clinical management.

4.3.1 Surgical technique

The majority of the operations were carried out by two surgeons. A third surgeon performed some of the keratoplasties in the first year of the study.

Surgeon X 55 operations (51%)

Surgeon Y 40 operations (37%)

Surgeon Z 13 operations (12%)

All patients were operated under general anaesthesia. Globe fixation was achieved by sutures to the superior and inferior rectus. In aphakic cases and the cases where a cataract extraction was to be performed, a single ring (Fleiringa ring or broad titanium ring) was secured to the sclera with (6/0) silk sutures, in order to support the anterior segment during surgery.

In some cases two double overlay sutures of 7/0 silk were inserted and then loosened and laid flat on the bulbar conjunctiva. A paracentesis at the limbus was also performed in most cases. This could be used to insert either air or liquids into the anterior chamber. A number of different substances were used throughout the period of the study. These included various solutions (balanced salt solution, Ringers, Hartmans) and viscoelastic materials such as hydroxypropylmethyl cellulose (HPMC) and Healon (Sodium hyaluronate 10mg/ml), used to protect the corneal endothelium from mechanical trauma.

Excision of the host disc was achieved primarily through the use of a blade and scissors. The depth of the trephine cut was minimal and was used as a guide for the blade. The majority of the corneal thickness was cut with the blade which was held perpendicular to a tangent to the corneal surface. The anterior chamber was entered with the blade and the excision completed with scissors, which were sloped backwards to result in a perpendicular cut. This is necessary because the shearing action of scissors would result in an undercut if the scissors were held perpendicular. In two cases a Draeger motorised trephine was used.

In cases where the donor material had been stored it was in the form of a corneo-scleral disc and this was punched from the endothelial side. A freehand punch and a silicone rubber cutting block with a curved indentation intended to match the corneal shape, were used. When the donor material was in the form of a whole eye the excision technique was similar to that applied to the host, except that the majority of the excision was achieved with the freehand trephine. The intra-ocular pressure of the donor eye was increased by injection through a paracentesis at the limbus, in order to reduce distortion during trephination.

The donor disc was placed in the recipient bed and the preplaced overlay sutures then tied giving temporary fixation to the transplant. The anterior chamber was then reformed by injection through the previously prepared paracentesis.

The donor disc was initially secured in position by four interrupted stay sutures (10/0 nylon) placed at the four cardinal points. The first suture was placed at 12 o'clock followed by a suture at 6 o'clock. Additional sutures were then placed at 3 and 9 o'clock. Subsequent suturing also used 10/0 nylon and in the majority of the transplants consisted of the placement of a single continuous suture. Once this was complete the four cardinal stay sutures were removed. Alternatively a further 12 interrupted sutures were inserted, giving a total of 16. In four cases a combination of an eight point continuous suture with eight interrupted sutures was employed.

An eight point marker was used as a guide for the positioning of sutures, in a small number of cases. Quantitative intra-operative keratometry was not used, but small hand held keratoscopes were employed in some cases for qualitative observation through the operating microscope. One consisted of a small cylinder with a series of seven concentric rings applied to the internal surface (Van Loehnan keratoscope), while the other was a reduced size Placido disc (Haneda). The surgeon attempted to tie all sutures with equal tension, and those that were judged to be too loose or too tight by visual inspection were replaced during surgery. All knots were buried in the recipient cornea.

All patients received sub-conjunctival injection of corticosteroid and antibiotic at the conclusion of surgery.

4.3.1.(i) Trephine diameter

In cases of keratoconus, the diameter of the host trephine was chosen so as to encompass the diseased tissue, as revealed by the Fleischer's ring. Though in some cases it was necessary to decentre the host excision.

The donor disc was trephined from the endothelial side. The diameter of the donor trephine ranged from 6 mm to 9.5 mm.

Donor trephine (mm)	Number used
6	1
7	3
7.5	18
7.75*	1
8	42
8.25*	2
8.5	30
8.75*	3
9	4
9.25	1
9.5	1
unrecorded	2
	108

Table 4.8 Trephine diameter.

* These three trephines were specially made for one of the surgeons and were introduced later in the study.

4.3.1.(ii) Donor/host disparity

In 35 cases the donor and host trephines were recorded as being equal in diameter. One involved donor storage in K-sol and the remaining 34 cases involved fresh whole donor eyes. In 12 patients the disparity was not recorded. These patients all underwent surgery in the early part of the study when all donor material was trephined from fresh whole eyes. It was the usual practice to use the same trephine for both donor and host excision, except in aphakia when the donor button was cut larger than the host bed, in order to reduce the risk of glaucoma. In the 12 early cases where the trephine disparity was not recorded, it was assumed that the 10 phakic patients had equal diameter trephines, and the 2 aphakic patients had a disparity of 0.5mm. A table summarising the trephine diameter disparity for all the patients is shown below.

Disparity (mm)	Number of patients
0 (equal diam.)	45
0.25	2
0.50	55
0.75	5
1.00	1
total	108

Table 4.9 Donor /host disparity

4.3.1.(iii) Immediate post-operative care. Medication.

The follow-up visits were dictated by each individual course, but routinely occurred at about one week post-operatively and about three to four week intervals thereafter during the first six months. Topical corticosteroids and antibiotics were prescribed in tapering dosages after surgery.

4.3.2 Long term care.

4.3.2.(i) Steroids.

Topical steroids were used for variable periods, usually up to one year.

4.3.2.(ii) Rejection episodes.

Rejection episodes were managed by intensive topical steroid therapy, usually on an in-patient basis so that application could be as frequent as half hourly during the night.

4.3.2.(iii) Resuturing.

Resuturing was done for wound dehiscence.

Five patients required resuturing following surgery.

#6. Initially secured with an eight point star continuous suture with eight interrupted sutures. A step developed at the edge of the transplant in sectors corresponding to the continuous suture peaks and the patient was admitted for resuturing. This procedure was carried out 15 weeks after the original surgery and entailed the removal of the continuous suture and the insertion of a further eight interrupted sutures.

#44. Initially secured with a continuous suture, but dehisced so was resutured one month after the original surgery. The continuous suture was removed and 18 interrupted sutures were inserted.

#83. Two months after keratoplasty the transplant dehisced and required resuturing.

#103. One bite of the continuous suture loosened due to inflammation and the transplant margin became rather proud superotemporally. As a result, this quadrant was resutured.

#108. As a result of trauma, the majority of donor/host junction was ruptured. The patient was admitted and underwent emergency surgery the same day. A vitreolensectomy was performed and the original donor cornea secured with 16 interrupted sutures.

Four patients required resuturing in the period following suture removal.

#48. One year seven months after keratoplasty the 16 interrupted sutures were removed in two stages. Initially four sutures were selectively removed, one at 45° and one at 60° and the corresponding sutures 180° opposite. When the remainder were removed the inferior portion dehisced, so six sutures were inserted inferiorly. However the superior portion then dehisced, so the remaining ten sutures were reinserted. These were left in situ for a further two years four months, with the result that the final removal of all sutures was delayed until almost four years after the original operation.

#65. The transplant dehisced shortly after the removal of the continuous suture. It was replaced and remained in situ for the remainder of the study.

#60. The transplant dehisced shortly after the removal of the continuous suture, and two weeks later it was replaced with 16 interrupted sutures. These were subsequently removed selectively.

#91. When the continuous suture was removed a step developed between the host and donor in the superotemporal quadrant. Three interrupted sutures were inserted one month later. This did not result in any improvement, so these were removed and replaced by a further four interrupted sutures.

4.3.2.(iv) Suture removal. Timing.

The timing of suture removal varied from case to case. Wound healing takes longer when closure is accomplished with a continuous suture. When interrupted sutures were used they could be removed earlier, and were sometimes removed selectively in an attempt to modify post-operative astigmatism.

The earliest that suture removal was undertaken for a patient on this study was five months after keratoplasty. This was unusual, especially since this was a continuous suture. Removal was necessary at this early stage because the nasal loops had become loose and blood vessels were encroaching along the suture tracks.

4.4 Measurement. Corneal topography

4.4.1 PEK photokeratoscope.

(a) Focus

It is important that a well focused image reaches the photographic plane. Not only does this ensure that the keratograph can be accurately measured, it also ensures the target is at the appropriate distance from the cornea. The PEK instrument reduces focusing errors in two ways. Firstly by employing a shallow depth of field, 0.01mm, and secondly in the design of the target.

Target

PEK instrument employs a target consisting of seven concentric rings. These are formed by passing light from a diffuse source through ring shaped apertures in a mask. The central portion of each bright ring consists of a thin black line, which aids accurate measurement of the keratograph. The ring target is housed inside what appears to be a hollow cone, but the locus of the target is in fact ellipsoidal. This ensures that the virtual image reflected from the cornea lies in a flat plane just behind the cornea. Strictly speaking this holds true for a cornea with a particular apical radius of curvature and shape factor. Any deviation from this will result in a curved image plane and variations in focus between different rings on the keratograph. The target was designed for a model cornea of 7.63mm (44.00D) apical radius. The manufacturers did not give the shape factor of the model cornea, but it was most likely to be close to .2, which was the mean value found for a population of normal subjects.

The target differs from that employed by more modern video keratoscopes, in that the ring which will be reflected from the outermost areas of the cornea has the smallest diameter, and is positioned very close to the cornea. This means that it is less likely that the nose or brows will obscure part of the cornea, but the proximity of the target causes difficulty in holding the top lid up with a finger, when that is necessary.

The target is designed so that the central ring creates a virtual image 3mm in diameter. The image of each successive ring is 1mm wider, so that the seventh ring has a diameter of 9mm in the image plane. This means that the fifth and sixth rings are likely to correspond to the graft host junction, and it is only the first four ring that will always represent the topography of the transplant itself.

(b) Relocation

This study involves sequential assessments of corneal topography. It was therefore important to choose an instrument which had a system which enabled the operator to direct the instrument towards the same point on the cornea on each occasion.

The PEK instrument achieves this in two ways. Firstly. the patients visual axis is aligned with the optic axis of the instrument. This is done by asking the patient to fix on a target which is located on the optic axis of the instrument at the principal point of the system. To the patient this appears at infinity.

Secondly the instrument position is adjusted by means of a joystick, until its axis is normal to the corneal surface. When this alignment is achieved, a light beam directed down the instrument axis towards the cornea will be reflected back along the axis towards the observer. This system is illustrated in Figure 4.2. Light is directed down a small tube A. The light reflects off a mirror B, through a small hole in another mirror C, and reflects off a third mirror D. The thin beam of light next traverses the length of the instrument along the instrument axis, and strikes the corneal surface. If, and only if, the incident light is normal to the corneal surface, the light beam will be reflected back along its original path, and much of it returns through the small hole in mirror C. However, there is sufficient divergence in the light beam that the returning light beam is wider than the pinhole in the second mirror C, and thus, is reflected through the eyepiece E, into the eye of the observer. When this unique condition is met, the observer will see a dark centre spot, the pinhole, surrounded by a light background. When the shutter is released mirror D is raised and the film F is exposed.

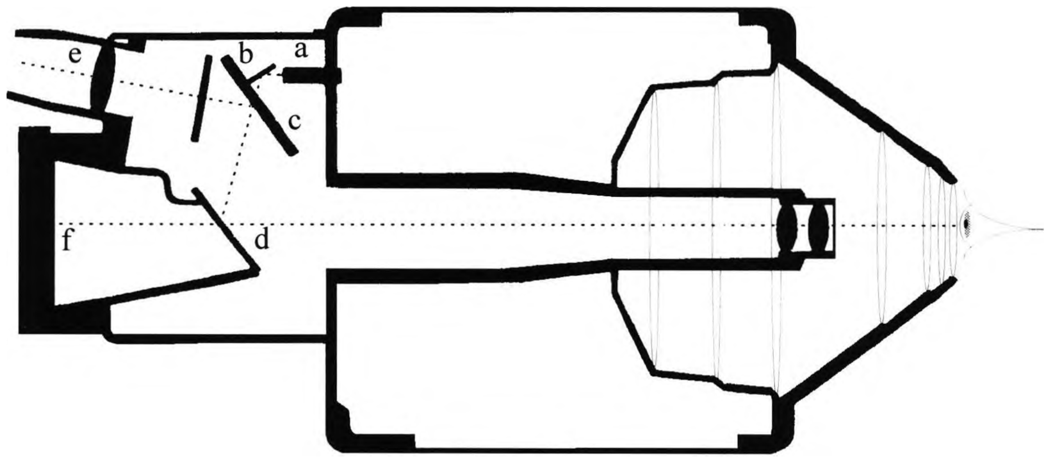


Figure 4.2 PEK instrument optics.

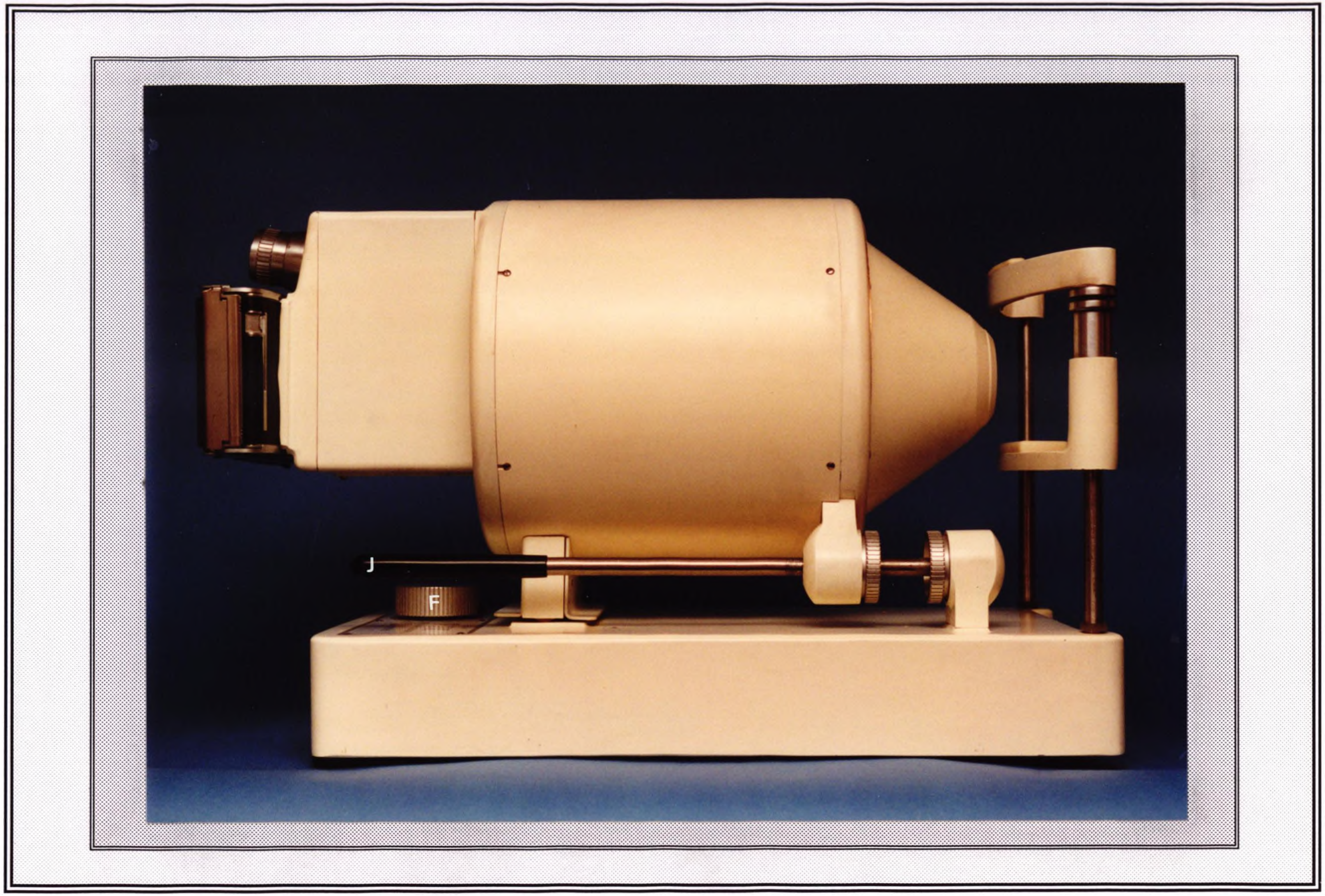


Figure 4.3 Photo Electronic Keratoscope (PEK) Joystick **J** and Focusing knob **F** are used to correctly position and focus the instrument relative to the subject's eye.

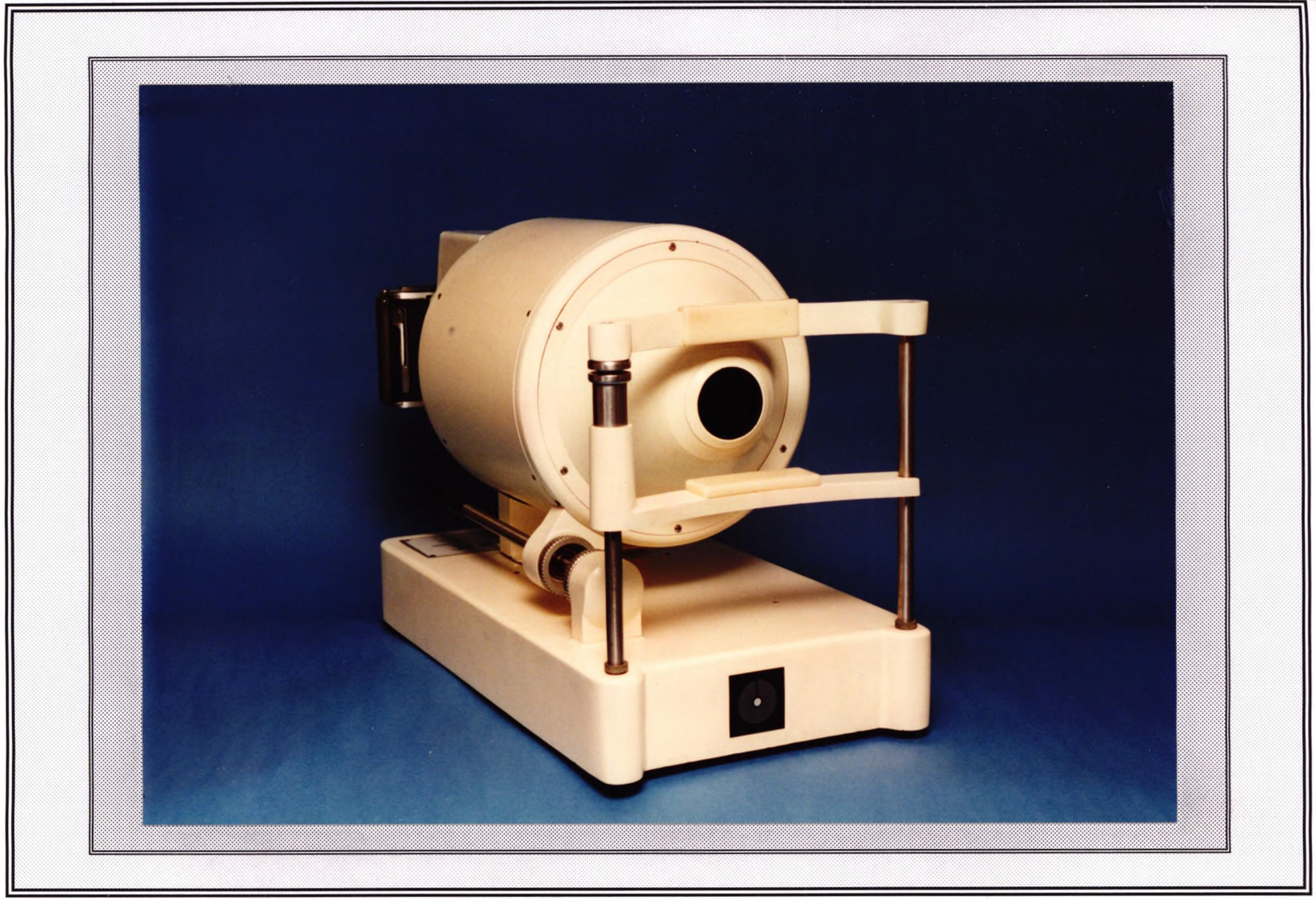


Figure 4.4 Photo Electronic Keratoscope (PEK) Oblique view showing the chin and head supports used to maintain the subject's eye in position in front of the aperture in the cone, which houses the internally illuminated target, consisting of 7 concentric rings.

The pencil of light which is directed down the axis of the instrument appears as a spot in the middle of the ring images on the keratograph. The topography analysis adopted in this study, measures the distribution of curvature relative to this point. Unfortunately this does not correspond to any particular cornea feature such as the apex (the region of greatest curvature), geometric centre, pupil centre, or even the highest point on the cornea (i.e. the point closest to the fixation target). Its only significance is that it represents the point on the cornea that is perpendicular to the keratoscope axis, when the patient fixates an on axis point. Maloney [349] has proposed that point should be known as the corneal vertex.

4.4.2 Measurement of keratographs

Microfilm reader

The analysis system developed by the manufacturers of the PEK, involved a projection system which produced an enlarged image of the keratograph. The location of the two principal meridians was identified, and the diameter of each ring measured along these meridians. This system assumes that there is regular astigmatism, with two principal meridians separated by 90°. It also assumes that for a given meridian, corneal curvature is symmetrically disposed on either side of the corneal apex. Neither of these assumptions is valid in the case of corneal transplants. Therefore a new measuring system had to be devised.

The ideal equipment for measuring the keratographs should be inexpensive and compact. In addition there is a fundamental requirement that there should be absolute certainty that the magnification of the projection system remains stable, over the

Figure 4.5 Microfilm reader showing the scale used to measure the keratograph in 12 semi-meridians.

Figure 4.6 shows a keratograph (from eye # 27) projected onto the measuring scale.

entire period that the keratographs were measured. This excludes any system where the projection optics are not physically attached to the screen. Another important requirement is that it should be ergonomically sound, allowing the operator reasonable comfort. It was decided that a microfilm reader would meet all these requirements.

Scale

A measuring scale was printed and placed over the microfilm reader screen. This consisted of a central point, with a millimetre scale radiating outwards along each of the twelve semi-meridians to be measured. A straight edged piece of plastic was attached to the glass platform upon which the keratographs were placed. The edge of the keratograph was butted up against this straight edge so that the horizontal axis of the keratograph was always parallel to the 180° axis of the measuring scale. The keratograph was then held flat, and in this position by a thin glass plate (free from optical distortions) and a heavy metal ring.

The platform was free to move in the vertical and horizontal, but not to rotate. It was moved until the central dot on the keratograph image was positioned directly over the centre of the measuring scale. The distance of each ring from the central reference point could be read directly off each of the twelve semi-meridian scales.

Criteria for Measurement

The locus of the keratoscope target was chosen carefully so that all 7 rings would be in focus at the photographic film plane. However, this can only be strictly true for a spherical cornea with a particular apical radius, and shape factor. In the case of highly irregular corneas the image of the keratoscope ring may be extremely out of focus, and some parts of the circumference may be missing altogether. This means that some degree of subjectivity comes into the measurement. This occurs in the judgement of the central point of a blurred section of ring. Subjectivity is also involved when it is decided that part of a keratograph image is so poor that reliable information cannot be obtained from it. It was decided that these judgements would be made more consistently if a single operator was responsible for measuring the keratographs. The vast majority of measurements were carried out by one operator (EM), with a few of the earlier measurements by the author.

Although subjectivity can be undesirable in a scientific study, attempts to remove human judgement from the process by automation can also lead to problems. Antalis et al [350] compared the ability of two video keratoscopes to describe the topography of abnormal corneas. They commented that both systems were capable of producing erroneous topography maps when faced with high degrees of irregularity. They also said that the smaller more closely packed mires of the 22 ring TMS-1 instrument, were more likely to become confluent and unreadable, than the eight rings of the Corneal Analysis System. Thus the seven ring target of the PEK may be the best choice for this study.

4.4.3 Conversion of keratograph measurements to local radius of curvature

The distance from the centre point on the keratograph to the ring was measured along each of the twelve semi-meridians. These distances were converted to local radii of curvature. The derivation of the calculations involved in this procedure is given in Appendix A.

4.4.4 Repeatability

Two trials were set up to estimate the ability of this system to obtain repeatable measurements of curvature on a corneal transplant.

4.4.4.(i) Repeatability under optimal conditions

Forty PEK pictures were taken of the same transplant on the same occasion. The subject (# 27) was highly motivated, was not photophobic, and had no difficulty in fixating the keratoscope target. Keratoplasty had been performed six years earlier, and there was now relatively little distortion, giving good quality keratographs. This was in effect an assessment of the system under ideal conditions. (One of these 40 keratographs can be seen in Figure 4.6)

Confounding variables - Fatigue.

The first two keratographs were regarded as a practice session, and the subsequent 40 keratographs were used in the analysis of repeatability. Suitable breaks were taken to avoid tiring the subject, and the whole process lasted just under two hours. It was thought that the ability of the operator to accurately focus the instrument, might have diminished over this period, adding an extra source of error. A note was made of the time at which each keratograph was taken, and it can be seen from the charts in

Appendix E that variability from the mean value did not appear to increase with time and fatigue was not an influence. Therefore it appears that this estimate of the repeatability taken from many readings at a single session, will give a good indication of the repeatability of readings taken on different occasions.

Confounding variables - Operator bias in keratograph measurement.

The 7 rings were measured along the 0° semi-meridian, giving seven readings per keratograph. Thus the operator measuring the 40 keratographs would very soon have an idea of what the seven readings were expected to be, which could influence the subjective judgement of the exact position of the ring. To avoid this, the operator was forced to make a judgement of the ring position without being able to view the scale. This was done by covering the relevant part of the scale with a piece of paper. A cross engraved on a perspex sheet was then used to mark the position of the ring. This was held still while the paper was removed, revealing the scale underneath.

Results

The forty curvature readings, along the 0° semi-meridian, were obtained for each of the seven rings. These are plotted in the first chart in Appendix E. The peaks and troughs are created when the curvature derived from one keratograph differs markedly from the next in the series. Often the pattern of peaks and troughs is repeated in the plot for each ring, indicating that some factor is causing the reading for all seven rings to be shifted in the same direction. It is most likely that this is an error in focusing the instrument, but it could also be a centration error. Appendix E also contains separate plots for each ring. These are represented as deviations from the mean value. The standard deviations of the forty readings are shown in Table 4.2 below.

Ring	Standard deviation
1	0.058
2	0.047
3	0.041
4	0.050
5	0.073
6	0.062
7	0.088

Table 4.10 Standard deviations for 40 measurements of the same transplant at the same session.

Thus under ideal conditions the variability of this measuring system is in the region of 0.05mm radius of curvature for the central four rings.

4.4.4.(ii) Repeatability with poorer quality keratographs

The forty keratographs mentioned above give an indication of the potential repeatability when the reflected image from the corneal transplant produces a well defined keratograph. Unfortunately, this is rarely the case, so another transplant was chosen in order to investigate how much repeatability is reduced when the keratographs are difficult to measure. Ten PEK pictures were taken of this eye at the same session. Copies of these ten keratographs are included in Appendix F. The image quality varies between different rings and different quadrants, therefore all 12 semi-meridians were measured for all 7 rings. The resulting local radius of curvature readings for rings 1 to 7 are given in Appendix F. These tables show that the standard deviation of 10 readings varied according to the clarity at the point being measured. The standard deviation ranged from 0.05mm radius of curvature at best, to 0.31mm at worst. The blank spaces in the tables indicate that the operator (EM) considered those points to be too indistinct to be measured. Examination of the corresponding areas on each keratograph can give an indication of the criteria used in these judgements. It can be seen that it was possible to measure the majority of the points on the central four rings, but rings 5, 6, and 7 are poorly represented. This pattern was found in many of the keratographs measured, and in some cases, especially the more distorted transplants, it was not possible to obtain a full set of 12 measurements for each of the central four rings.

4.4.5 Conversion to corneal topography components

A method was devised which enabled the twelve radius of curvature readings for each ring to be converted into components which gave clinically meaningful descriptions of corneal topography.

These were:-

1. The mean radius of curvature for the whole ring (i.e. spherical equivalent)

2. Asymmetry.

If, in any given meridian, the corresponding points on either side of the cornea vertex have equal curvature, the asymmetry component would be zero.

3. The angle of asymmetry is the direction in which the asymmetry lies.

4. Regular Astigmatism. The difference in radius of curvature between the two principal meridians which are at right angles.

5. Axis of astigmatism. The angle of the flattest meridian.

6. Irregularity. This is a measure of the deviations from a perfect sphere which cannot be accounted for by the regular components: Asymmetry and Astigmatism.

A full explanation of these components is to be found in Appendix G. The mathematical derivation of these components is included in Appendix C, along with a number of examples showing radius of curvature plots, and the topography components which can be derived from them.

A comparison was made between the astigmatism component derived from keratograph analysis, and the astigmatism results obtained by refraction. Both the magnitude and the axis of astigmatism were compared.

The visual acuity achieved at each refraction was also recorded. This was used to investigate whether asymmetry or irregularity had any influence on the best corrected visual acuity.

The following Comparisons were made:-

Keratograph components		Refraction
Astigmatism	versus	Astigmatism
Axis of Astigmatism	versus	Axis of Astigmatism
Asymmetry	versus	Visual Acuity
Irregularity	versus	Visual Acuity

Table 4.11 Comparisons made between keratograph components and refraction.

A search was made of the clinical notes of the patients involved in this study. Fifty eight of those that were available had at least one refraction which coincided with, or was sufficiently close to, a keratoscopy assessment.

In this thesis, corneal topography is described in terms of radius of curvature rather than converting to corneal power. Mandell [354] has discussed the various ways of making this conversion, and the assumptions involved. Comparison with refractive results necessitated conversion of the keratograph results, and the formula used was

$$\text{Astigmatism(D)} = \frac{(n-1)}{(r_1 - r_2)}$$ where r is in mm, and n is taken as 1.3375.

The refractions were done by a number of different optometrists, including the author, in the setting of a busy out patients clinic. There was, therefore, no standardisation of visual acuity measurement. This was done on conventional high contrast Snellen charts, with no control of the exact illumination or test distance. The Snellen acuities were converted to the LogMAR format (Log of minimum angle of resolution). The point on the LogMAR scale corresponding to acuities such as “6/6 part” or “6/9-2” was gauged by interpolation. The results are shown in Chapter 5.

4.4.6 Number of semi-meridians measured

Although manual measurement of keratographs has certain advantages over automated measurement (see above), it is very time consuming. Since a total of 881 keratographs were analysed, it was necessary to limit the number of measurements made on each ring of the keratograph, without excessively affecting the variables which were derived from those measurements.

A trial was conducted to determine the effect that a reduction of the number of semi-meridians has on the variables derived from each ring (Spherical Equivalent, Asymmetry, Angle of Asymmetry, Axis of Astigmatism, and Irregularity). Two keratographs were measured at 5° intervals, giving a total of 72 readings of radius of curvature around the ring. The third ring was measured in each case. Keratograph #1 represented a transplant which had high astigmatism (0.76mm) but low irregularity (0.06mm). Keratograph #2 represented a transplant with a relatively low amount of regular astigmatism (0.37mm), but high irregularity (0.33mm).

The 72 data points were analysed in order to describe the curvature in terms of the regular components, and the irregularity component. The effect on the component values, caused by reducing the number of data points, was assessed. The details are given in Appendix D. They show that little gain in precision was to be made by using

18 semi-meridians rather than 12. Since this would cause a 50% increase in the workload of keratograph measurement, it was decided that each ring of the keratograph would be measured along 12 semi-meridians, separated by 30°.

4.4.7 Statistical analysis

Each keratograph ring can be described in terms of the six topography components mentioned above. The object of this research was to study changes in topography over time. Astigmatism and Irregularity were thought to be the most clinically relevant components, so they were modelled against time. A technique known as multi-level modelling was used. It was possible with this technique to determine the relative effects of each of the patient variables, and treatment variables. A detailed description is contained in Appendix H.

4.5 Measurement. Touch sensitivity

4.5.1 Instrument mounting

The Cochet-Bonnet aesthesiometer with a filament of 0.12mm diameter was used. The barrel of the aesthesiometer is placed in a holder, and held tight by a screw. This holder is mounted on a bracket which is attached to the arm bearing the observation system of the slit lamp. The holder can be rotated, and raised or lowered, so that when the filament is adjusted to the desired length, the tip can be fixed in position to be in focus in the centre of the field of view of the observation system. The holder can also be tilted so that the filament tip is parallel to the horizontal lines in the eyepiece graticule. This is necessary to ensure that the filament approaches at right angles to the corneal surface. The aesthesiometer projected through a hole in the centre of a black disc, which housed fixation lights at 3, 6, 9 and 12 o'clock . These were positioned to ensure that the subjects eye moved in such a way as to bring the peripheral area of the cornea to be tested at right angles to the filament. They also served as an aid to relocation of these points at subsequent visits. The joy stick was used to bring the aesthesiometer and observation system, which were locked together, at a slow and controlled speed towards the cornea. The angle and speed of approach could be checked by observing the approach of the filament top and its mirror image in the cornea. The aesthesiometer barrel and the observation system were fixed at an angle of approximately 50 degrees so that a magnified side view of the filament touching the cornea was possible.

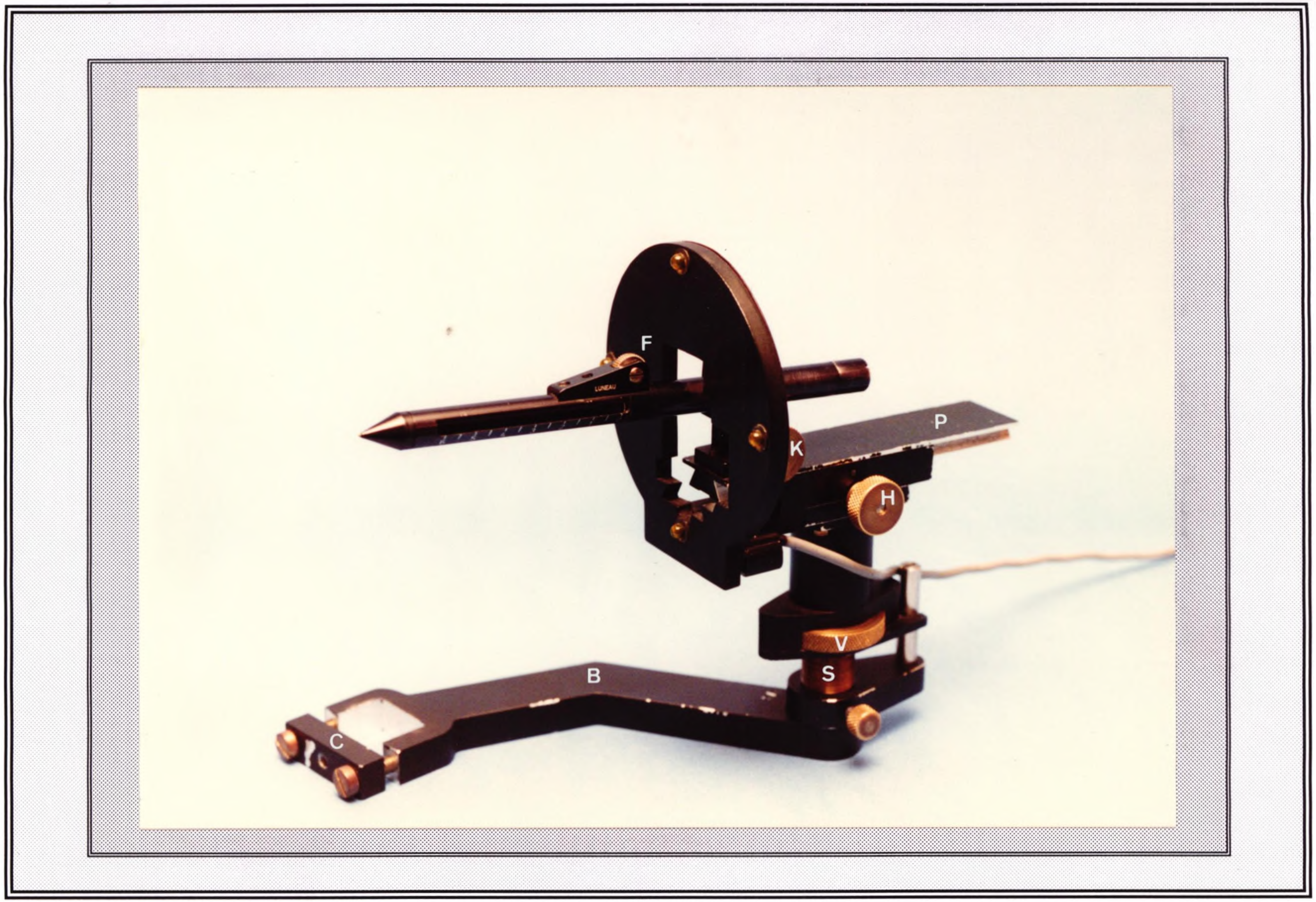


Figure 4.7 Mounting used to attach the Cochet-Bonnet aesthesiometer to the slit lamp. Bar **B** is clamped **C** to the support for the slit lamp observation system. Platform **P** can be moved in the x,y,and z directions. It rotates about spindle **S**, and knobs **V** and **H** control vertical and horizontal movement respectively. The aesthesiometer is attached to platform **P** and the angle of inclination in the vertical plane is adjusted using knob **K**.Knob **F** adjusts the length of filament extending from the aesthesiometer barrel, which is directly read off the scale.

Figure 4.8 Aesthesiometer mounted on a Haag-Streit slit lamp.

Figure 4.9 Shows how the slit lamp observation system **O** can be used to get a magnified side view of the aesthesiometer filament. The round black screen **S** supports the light emitting diodes **L** at each of the four cardinal points. These were used as fixation targets while testing the corneal periphery.

4.5.2 Procedure

Each assessment was started with a filament length beyond the subject's threshold. The filament was then shortened successively until the subject responded to more than 50% of the presentations. This filament length was then recorded as the sensitivity. Five presentations were made at each filament setting. Thus the criterion for a positive response was the detection of touch at three or more of the five presentations of a given filament length.

In practice, measurements are taken on the basis of approach till a minimum angle of bend is observed, rather than trying to estimate an angle of 5 degrees (Millodot [351]). Control of the speed and angle of approach can be assisted by observing the filament and its mirror image as they approach each other and eventually touch when contact is made.

Sensitivity was assessed at the transplant centre and at four cardinal points approximately 1mm in from the host-donor boundary. The majority of the donor buttons were either 7.5mm, 8.0mm, or 8.5mm in diameter, making these peripheral points approximately 3mm from the transplant centre.

4.5.3 Reproducibility

The precision of measurement is said to be high with this instrument. Hirji [352] found that repeated sequential measurement on the same subject gave a repeatability of 40%. Millodot and O'Leary [353] found good reproducibility on the same subjects ($r = +0.99$), and variations from one occasion to another did not usually exceed 5%. Bleshoy [347] confirmed this repeatability of 5% on a group of three normal subjects tested on three separate occasions. He did, however, find more variation (20%) when he tested peripheral rather than central areas. It should be borne in mind that repeatability for normal subjects may be very different to that found in grafted corneas with little or no sensitivity.

4.5.4 Presentation of Data .

The Cochet-Bonnet model is one of the most widely used aesthesiometers. Some researchers have presented their data in terms of pressure, using the table supplied by the manufacturer to convert the filament length into force exerted at the tip, and then divide the result by the known area of the tip (0.01131mm^2 cross-section area for a 0.12mm diameter filament). Other instruments, such as the one devised by Draeger [307] give a digital reading of the force exerted. The use of pressure units implies that if the force applied was doubled but spread over double the area the resultant stimulus to touch sensitivity would be unchanged. It is by no means certain that this is the case, and some authors have just reported the force and the diameter of filament used. Alternatively, some authors quote only the length of filament. Most previous studies on corneal transplants have used the Cochet-Bonnet instrument with a 0.12mm diameter filament, and have expressed their sensitivity results as filament lengths. This study adopted the latter convention.

5. Results

5.1 Topography

5.1.1 Comparison between keratograph components and refraction

The results are shown as a scatter plot of the refractive value against the keratograph component value. A linear regression line is plotted on each chart, along with the correlation coefficient R^2.

In Figure 5.1, the chart comparing the axis from refraction to the axis from keratograph analysis, the axes are extended beyond 180°. This was done because it was necessary to add 180° to some values in order to make valid comparisons. For instance 5° and 175° are very close in terms of astigmatism axis, but algebraically they differ by 170°. The solution adopted was to add 180° to the smaller value, i.e. 5° becomes 185°, thus making comparison between 185° and 175°.

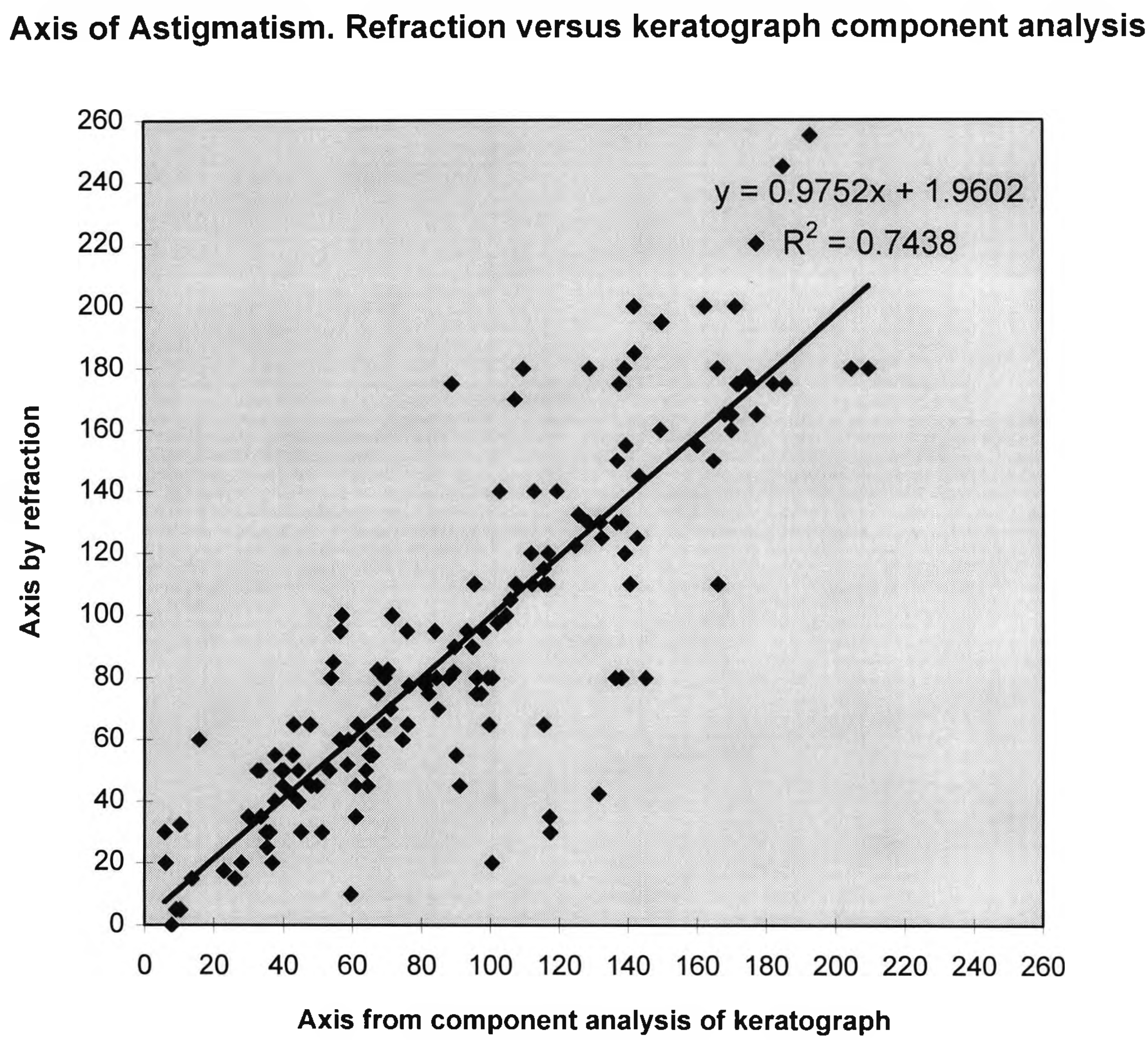


Figure 5.1 Axis of Astigmatism. Refraction versus keratograph component analysis.

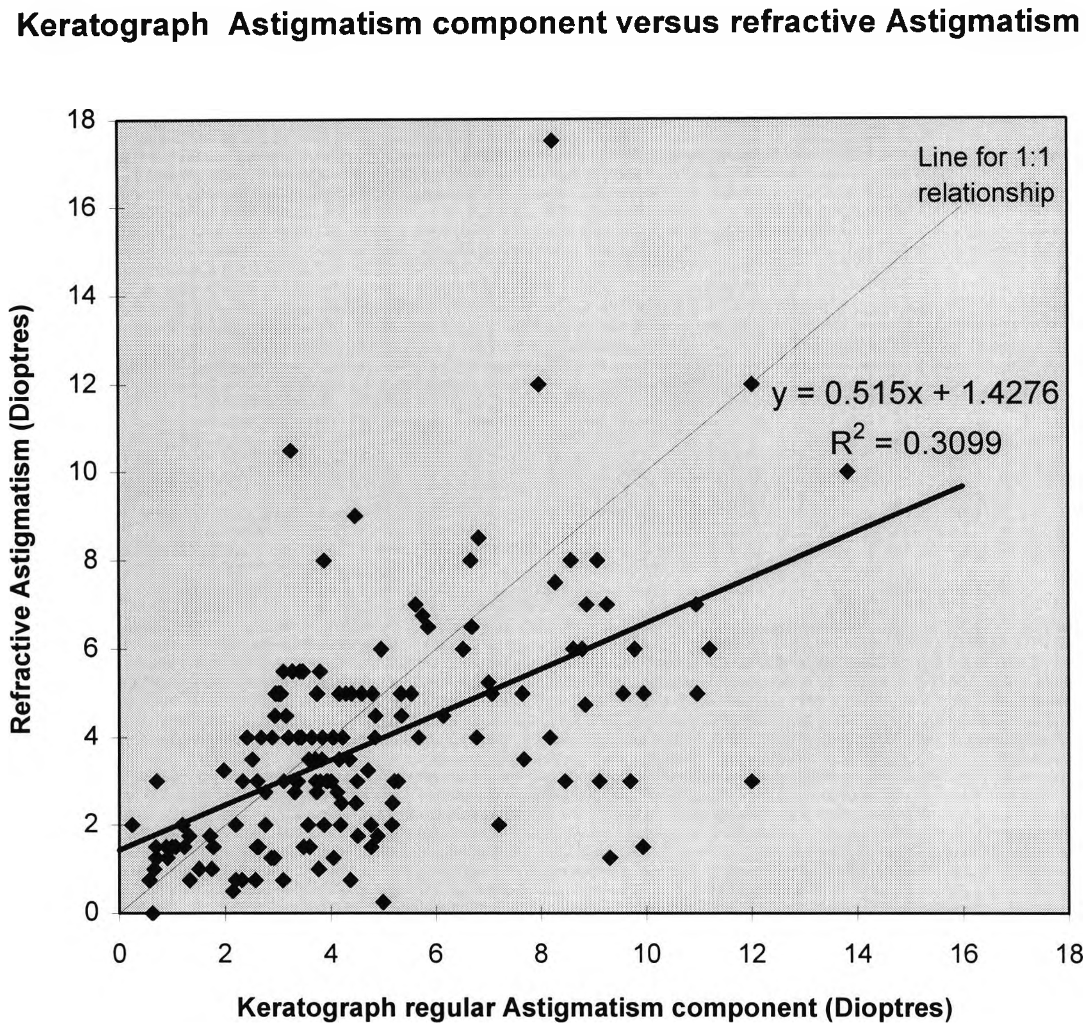


Figure 5.2 Keratograph regular Astigmatism component (Dioptres).

Figure5.2 shows the relationship between keratograph astigmatism and refractive astigmatism. The regression line (y = 0.52x + 1.43) indicates that refraction generally gives a lower value for astigmatism than the keratograph analysis. However, the regression line passes above the line for a one to one relationship in the region near the origin. Thus keratograph astigmatism under 3.00D, would be expected to yield a higher amount when assessed by refraction, with a value of zero on the keratograph scale corresponding to 1.43 on the refraction axis. This anomaly can be avoided if the regression line is made to pass through the origin (see Figure 5.3).

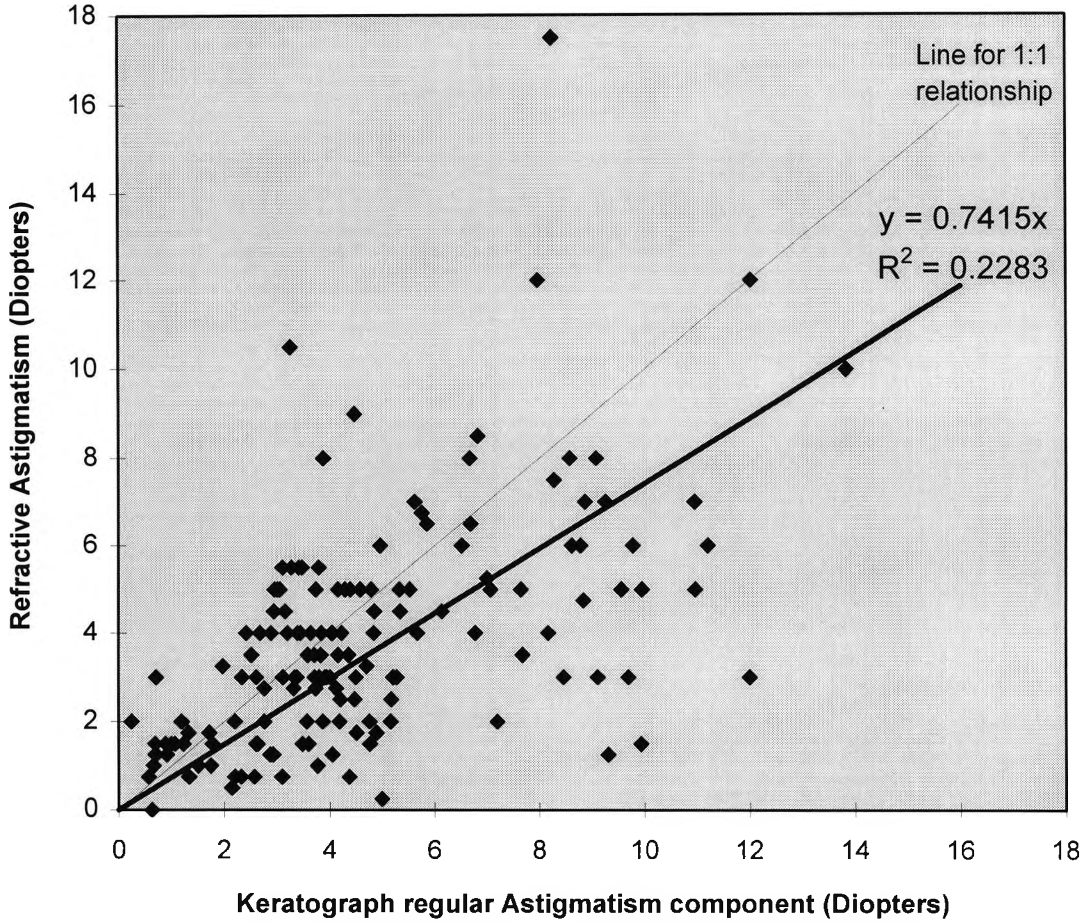


Figure 5.3 Keratograph Astigmatism component versus refractive Astigmatism. In this plot the regression line is made to pass through the origin. When this restriction is applied the regression line changes to y = 0.74x , and the regression coefficient R^2 is reduced from 0.31 to 0.23.

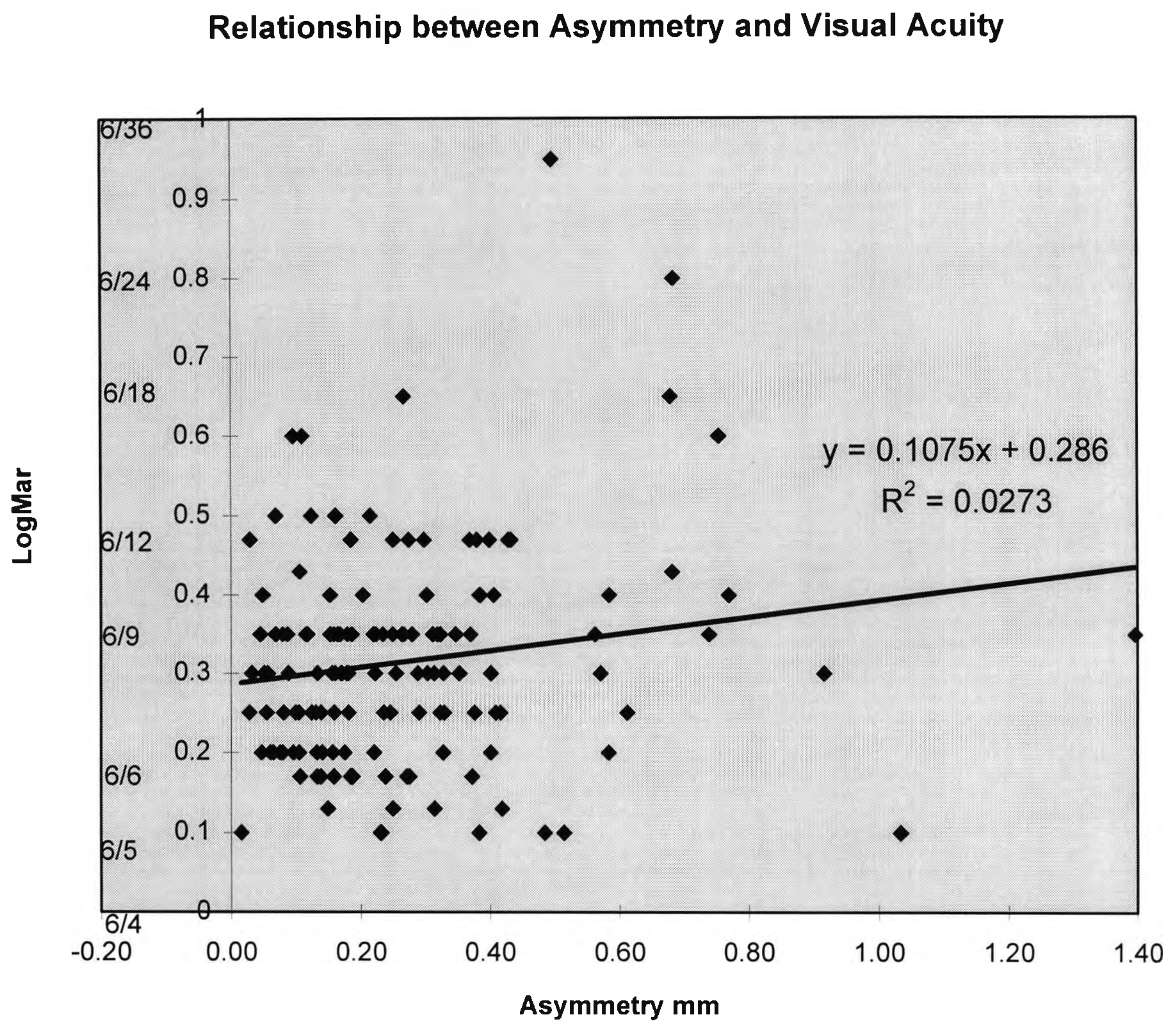


Figure 5.4 Relationship between Asymmetry and Visual Acuity.

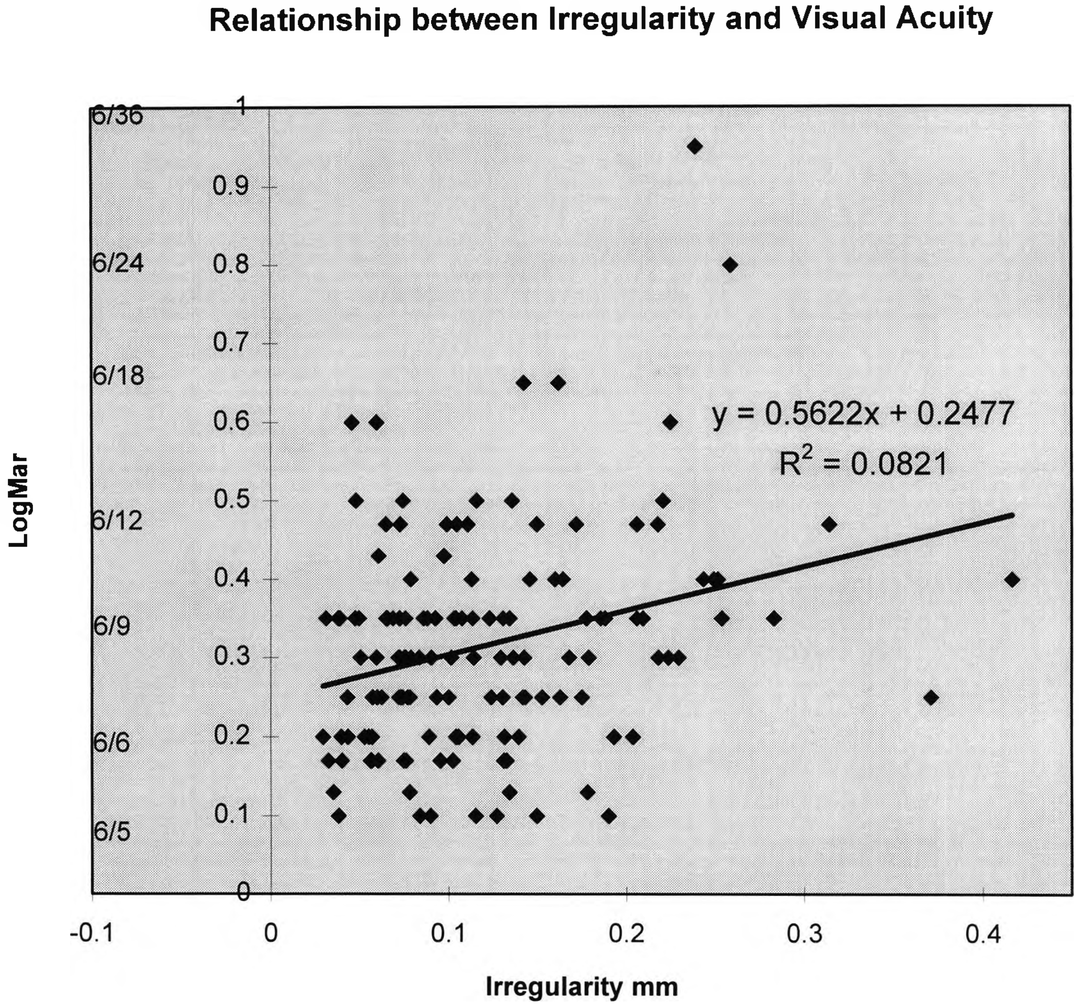


Figure 5.5 Relationship between Irregularity and Visual Acuity.

5.1.2 Changes in Asymmetry with time

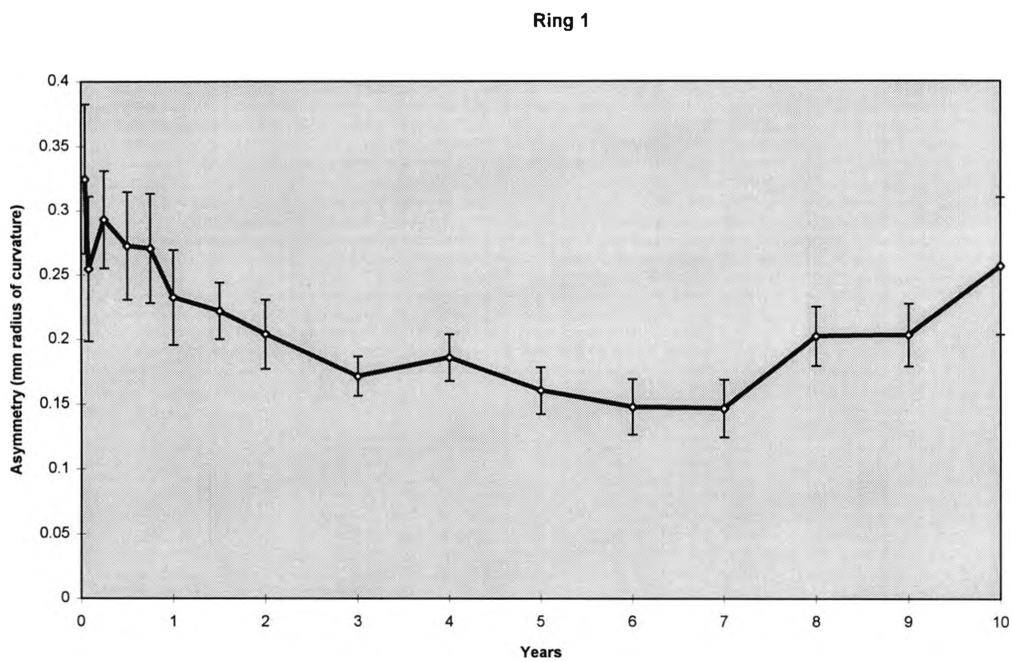


Figure 5.6 Changes in Asymmetry with time

Figure 5.6 shows a gradual reduction in the Asymmetry component over the first seven years of the post-operative period. There is then an apparent increase in asymmetry during years eight, nine, and ten.

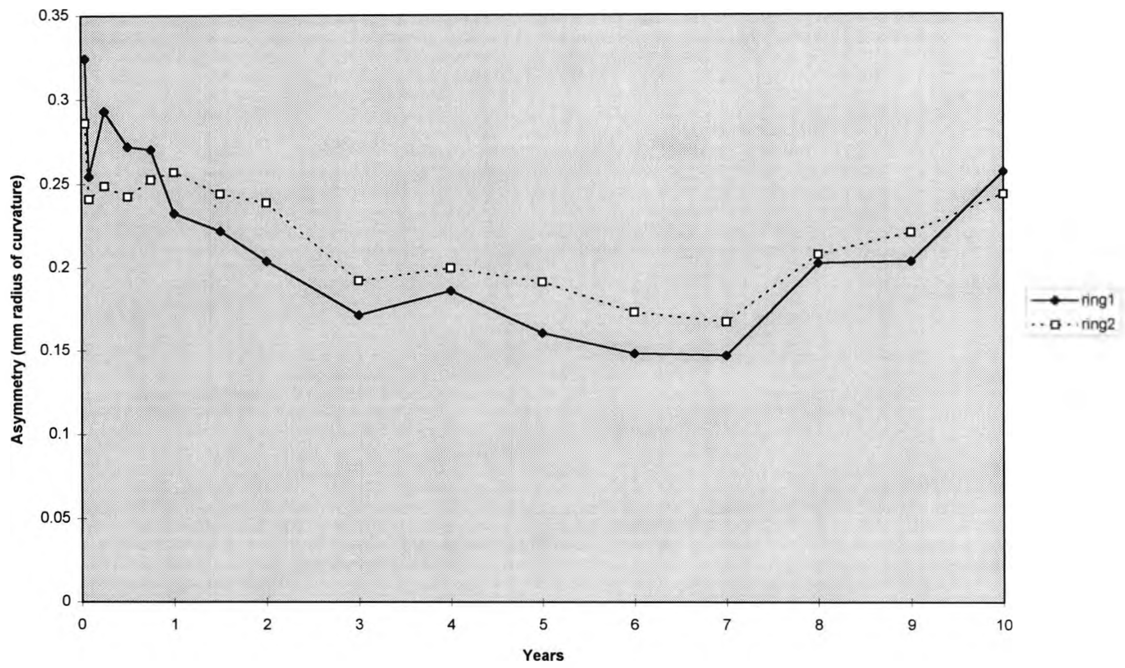


Figure 5.7 Changes in Asymmetry, comparison between ring 1 and ring 2

There appeared to be a small but insignificant trend for the more peripheral rings of the keratograph to exhibit more asymmetry than the central ones. It can be seen in Figure 5.7 that ring 1 showed less asymmetry than ring 2. However, this was not the case during the first nine months following surgery, the period when most changes in topography are taking place.

5.1.3 Changes in Astigmatism and Irregularity

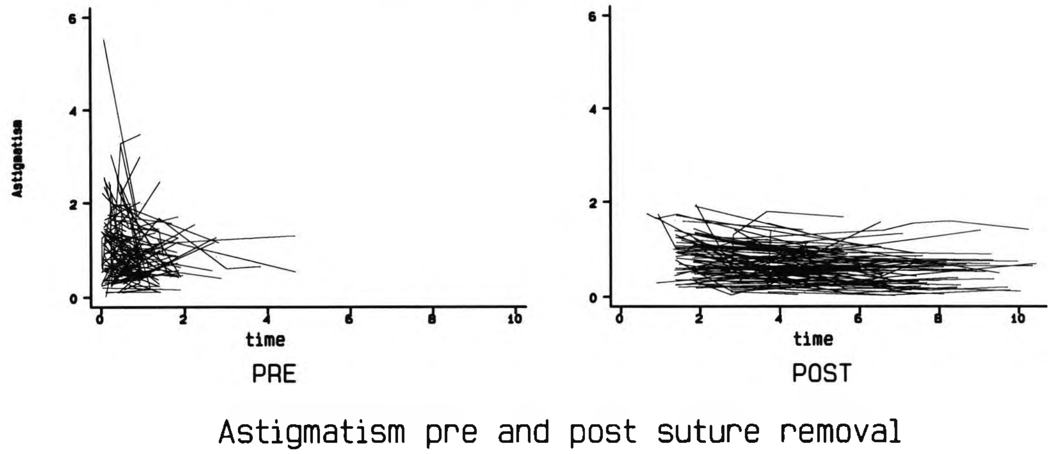


Figure 5.8 All the observed individual patient profiles showing changes in astigmatism with time

Figure 5.8 shows all the individual patient profiles on the same chart. This conveys little information in itself, except a general trend which is different after suture removal. However, it is obvious that there is considerable inter-subject variation. The ordinary least squares regression line for log astigmatism was derived for each patient. The technique of Multilevel modelling [356] was then applied to these log linear regression lines. An example of the result of this technique is given in Figure 5.9 which shows the models derived from the data illustrated in Figure 5.8. These are, therefore, models for all the patients.

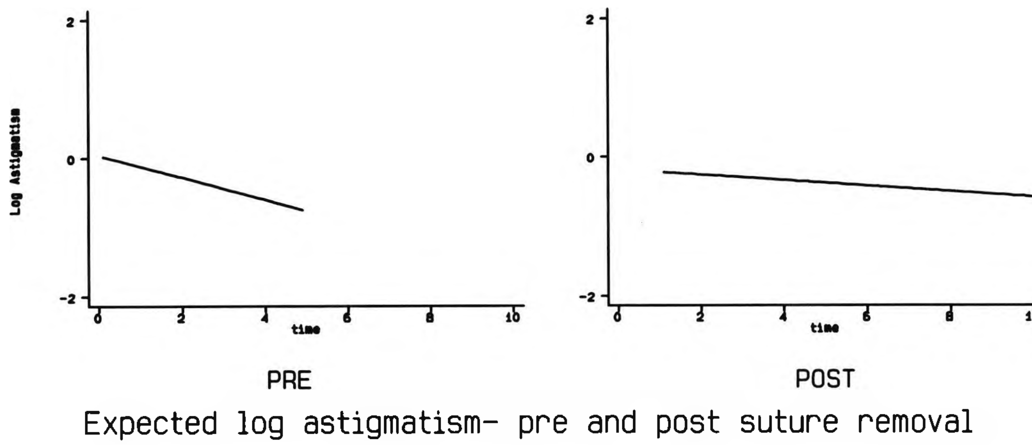
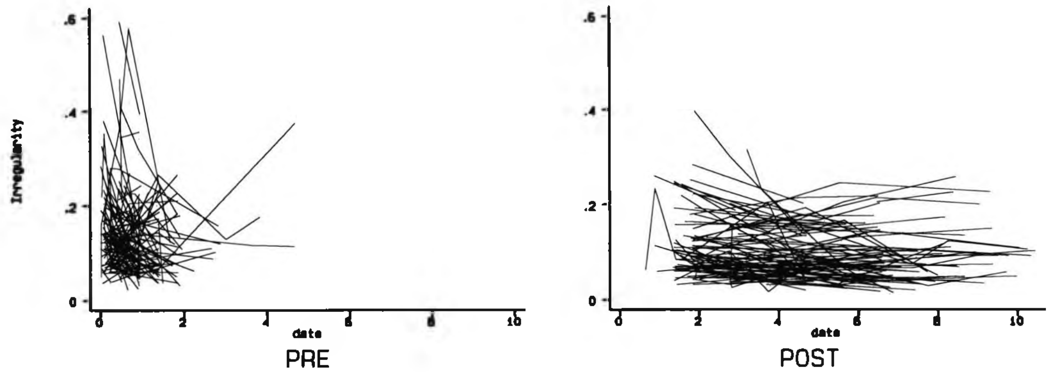


Figure 5.9 The profiles in figure 5.8 were simplified to a linear model

Figures 5.10 and 5.11 Illustrate the result of applying this Multilevel modelling technique to the Irregularity data for all the patients.

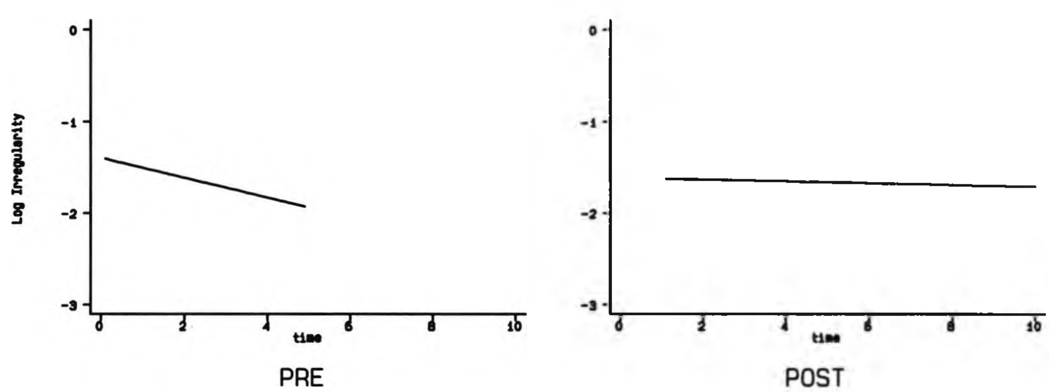
The derivation of a model which can condense the changes observed in each patient into a single linear equation is not an end in itself, it is a tool which enables comparisons to be made. The object of the analysis is to explain the inter-subject variability observed. For example, what factors determine a higher starting value for Astigmatism or Irregularity, and more importantly what determines the rate of reduction.

Thirteen variables were examined to determine their influence on the outcome. Each was taken in turn, and the patients were grouped according to the categories of the variable. For example, the variable age has three categories (<30, 31-40, >40). A model was derived for each category, and the slopes of these models were then compared. If little difference was found then it was unlikely that the variable had an influence on the outcome. Similar comparisons were made for the intercepts. At this stage only one variable is considered at a time, and it is therefore, considered as univariate analysis. The results are presented in the next section.



Irregularity pre and post suture removal

Figure 5.10 All the observed individual patient profiles showing changes in Irregularity with time



Expected log irregularity- pre and post suture removal

Figure 5.11 The profiles in figure 5.10 were simplified to a linear model

A weak association was found between improvement in Astigmatism, and improvement in Irregularity. The correlation coefficient was + 0.35.

5.1.4 Results of the Univariate analysis of Astigmatism and Irregularity.

Notes for Univariate Tables

The "estimated parameter" can be thought of as the coefficient in the equation of the regression line (i.e. the model) for that particular group of patients. Taking the first line of Table 5.1 as an example; the variable is patient age, and in this table it is being tested for its effect on the intercept coefficient for astigmatism, (i.e. $b_0 + b_1 t_i e_i$). The age variable has been divided into categories. The category containing the largest number of patients has been chosen as baseline, and the remaining two categories are then compared to it. Thus the intercept coefficient (b_0) for the age <=30 model is 0.08, and the intercept coefficient for the age 31-40 category is 0.07 lower (i.e. 0.08 - 0.07 = 0.01). Whereas the model for the age >40 category has an intercept on the log astigmatism axis which is 0.02 higher than the baseline intercept.

These figures are difficult to interpret clinically because they relate to Astigmatism on a log scale. The fourth column of the table contains more useful information. This is the percentage change relative to the baseline intercept, based on the original scale, before the log transformation was carried out. The question then arises, are the differences shown here statistically significant? For this example, is the intercept, or starting astigmatism for 31-40 year old patients, really 7% lower? In statistical terms this is a test of hetereogeneity of the three categories. Is the difference between them zero or not? The simplest form of test for significance examines the ratio between the estimate, and the precision of the estimate, given by the Standard Error (SE). The t-test takes this form, and the result is regarded as significant if the ratio is above a certain level. The

Likelihood Ratio Test (LRT) [357] is a more sophisticated version, which also examines a ratio, but gives an overall appreciation of how important the variable is.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	0.08	(0.10)				
Age: **31- 40**	-0.07	(0.13)	-7%			
Age: > **40**	0.02	(0.14)	+2%	0.4	2	0.80
Sex: **Male** (baseline)	-0.05	(0.09)				
Sex: **Female**	0.21	(0.12)	+23%	2.9	1	0.09
Side: **Right** (baseline)	0.06	(0.04)				
Side: **Left**	-0.06	(0.12)	-6%	0.3	1	0.58
Diagnosis: **Keratoconus** (baseline)	0.02	(0.08)				
Diagnosis: **Other**	0.14	(0.19)	+15%	0.5	1	0.48
Suture: **Continuous** (baseline)	-0.01	(0.08)				
Suture: **Interrupted**	0.23	(0.15)	+26%	2.4	1	0.12
Disparity: = **0 mm** (baseline)	0.09	(0.08)				
Disparity: > **0 mm**	0.19	(0.13)	+21%	2.3	1	0.13
Surgeon: **X** (baseline)	0.08	(0.10)				
Surgeon: **Y**	-0.04	(0.13)	-4%			
Surgeon: **Z**	-0.36		+30%	2.5	2	0.20
Graft diam: < **8 mm** (baseline)	0.05	(0.09)				
Graft diam: **8 - 8.5 mm**	-0.02	(0.13)	-2%			
Graft diam: > **8.5 mm**	-0.06	(0.21)	-6%	0.1	2	0.95
Donor's age: <= **55**(baseline)	0.12	(0.09)				
Donor's age: > **55**	-0.15	(0.11)	-14%	1.8	1	0.18
Storage: **Fresh** (baseline)	-0.01	(0.09)				
Storage: **K Sol**	-0.05	(0.14)	-5%			
Storage: **MK**	0.29	(0.13)	+34%	5.9	2	0.05
Phakic (baseline)	0.03	(0.08)				
Aphakic	0.23	(0.19)	+26%	1.6	1	0.21
First keratoplasty (baseline)	0.03	(0.08)				
Repeat keratoplasty	0.26	(0.18)	+30%	2.1	1	0.15
Death to Op. hours: < **36** (baseline)	0.03	(0.08)				
Death to Op. hours: **36-72**	0.02	(0.12)	+2%			
Death to Op. hours: > **72**	0.32	(0.23)	+38%	2.0	2	0.37

Table 5.1 Astigmatism, PRE suture removal; Univariate effect on the intercept.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-0.22	(0.08)				
Age: **31- 40**	0.11	(0.10)	+12%			
Age: > **40**	0.11	(0.11)	+12%	1.3	2	0.51
Sex: **Male** (baseline)	-0.19	(0.07)				
Sex: **Female**	0.08	(0.10)	+8%	0.6	1	0.44
Side: **Right** (baseline)	-0.14	(0.07)				
Side: **Left**	-0.08	(0.10)	-8%	0.7	1	0.40
Diagnosis: **Keratoconus** (baseline)	-0.18	(0.06)				
Diagnosis: **Other**	0.13	(0.16)	+14%	0.7	1	0.40
Suture: **Continuous** (baseline)	-0.20	(0.06)				
Suture: **Interrupted**	0.16	(0.11)	+17%	2.2	1	0.14
Disparity: = **0 mm** (baseline)	-0.28	(0.09)				
Disparity: > **0 mm**	0.17	(0.10)	+19%	3.1	1	0.08
Surgeon: **X** (baseline)	-0.09	(0.08)				
Surgeon: **Y**	-0.09	(0.10)	-8%			
Surgeon: **Z**	-0.40	(0.18)	-30%	5.2	2	0.07
Graft diam: < **8 mm** (baseline)	-0.17	(0.07)				
Graft diam: **8 - 8.5 mm**	0.03	(0.10)	+3%			
Graft diam: > **8.5 mm**	-0.01	(0.16)	-1%	0.1	2	0.95
Donor's age: <= **55**(baseline)	-0.16	(0.07)				
Donor's age: > **55**	-0.002	(0.09)	-0.2%	0.03	1	0.86
Storage: **Fresh** (baseline)	-0.19	(0.07)				
Storage: **K Sol**	-0.01	(0.11)	-1%			
Storage: **MK**	0.16	(0.11)	+17%	2.2	2	0.33
Phakic (baseline)	0.06	(0.07)				
Aphakic	0.20	(0.18)	+22%	1.2	1	0.27
First keratoplasty (baseline)	0.06	(0.07)				
Repeat keratoplasty	0.22	(0.17)	+25%	1.6	1	0.21
Death to Op. hours: < **36** (baseline)	-0.05	(0.07)				
Death to Op. hours: **36-72**	0.05	(0.13)	+5%			
Death to Op. hours: > **72**	-0.23	(0.29)	-20%	0.8	2	0.67

Table 5.2 Astigmatism, PRE suture removal; Univariate effect on the slope.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-1.37	(0.05)				
Age: **31- 40**	-0.07	(0.07)	-7%			
Age: > **40**	0.03	(0.07)	+3%	1.8	2	0.42
Sex: **Male** (baseline)	-1.41	(0.04)				
Sex: **Female**	0.03	(0.06)	+3%	0.3	1	0.58
Side: **Right** (baseline)	-1.42	(0.04)				
Side: **Left**	0.06	(0.06)	+6%	1.0	1	0.32
Diagnosis: **Keratoconus** (baseline)	-1.41	(0.04)				
Diagnosis: **Other**	0.16	(0.10)	+17%	2.6	1	0.11
Suture: **Continuous** (baseline)	-1.41	(0.04)				
Suture: **Interrupted**	0.12	(0.08)	+13%	2.3	1	0.13
Disparity: = **0 mm** (baseline)	-1.38	(0.05)				
Disparity: > **0 mm**	-0.02	(0.06)	-2%	0.1	1	0.75
Surgeon: **X** (baseline)	-1.37	(0.05)				
Surgeon: **Y**	-0.06	(0.06)	-6%			
Surgeon: **Z**	-0.03	(0.12)	-3%	0.8	2	0.67
Graft diam: < **8 mm** (baseline)	-1.35	(0.04)				
Graft diam: **8 - 8.5 mm**	-0.08	(0.06)	-8%			
Graft diam: > **8.5 mm**	-0.15	(0.11)	-12%	2.6	2	0.27
Donor's age: <= **55**(baseline)	-1.37	(0.04)				
Donor's age: > **55**	-0.05	(0.06)	-5%	0.6	1	0.44
Storage: **Fresh** (baseline)	-1.38	(0.05)				
Storage: **K Sol**	-0.04	(0.08)	-4%			
Storage: **MK**	0.02	(0.07)	+2%	0.5	2	0.77
Phakic (baseline)	-1.41	(0.04)				
Aphakic	0.20	(0.10)	+22%	3.1	1	0.08
First keratoplasty (baseline)	-1.42	(0.04)				
Repeat keratoplasty	0.36	(0.09)	+43%	14.1	1	<0.001
Death to Op. hours: < **36** (baseline)	-1.38	(0.04)				
Death to Op. hours: **36-72**	-0.04	(0.07)	-4%			
Death to Op. hours: > **72**	0.02	(0.12)	+2%	0.3	2	0.86

Table 5.3 Irregularity, PRE suture removal; Univariate effect on the intercept.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-0.14	(0.04)				
Age: **31- 40**	0.01	(0.06)	+1%			
Age: > **40**	0.09	(0.06)	+9%	2.3	2	0.32
Sex: **Male** (baseline)	-0.13	(0.03)				
Sex: **Female**	0.05	(0.06)	+5%	0.6	1	0.44
Side: **Right** (baseline)	-0.12	(0.03)				
Side: **Left**	0.01	(0.06)	+1%	0.01	1	0.92
Diagnosis: **Keratoconus** (baseline)	-0.13	(0.03)				
Diagnosis: **Other**	0.17	(0.09)	+19%	4.0	1	0.05
Suture: **Continuous** (baseline)	-0.14	(0.03)				
Suture: **Interrupted**	0.10	(0.05)	+11%	3.4	1	0.07
Disparity: = **0 mm** (baseline)	-0.12	(0.03)				
Disparity: > **0 mm**	0.02	(0.06)	+2%	0.1	1	0.75
Surgeon: **X** (baseline)	-0.10	(0.04)				
Surgeon: **Y**	-0.03	(0.06)	-3%			
Surgeon: **Z**	-0.05	(0.10)	-5%	0.3	2	0.86
Graft diam: < **8 mm** (baseline)	-0.08	(0.04)				
Graft diam: **8 - 8.5 mm**	-0.04	(0.06)	-4%			
Graft diam: > **8.5 mm**	-0.15	(0.08)	-14%	3.2	2	0.20
Donor's age: <= **55**(baseline)	-0.11	(0.04)				
Donor's age: > **55**	-0.0003	(0.05)	0%	0.0001	1	0.99
Storage: **Fresh** (baseline)	-0.10	(0.04)				
Storage: **K Sol**	-0.05	(0.06)	-5%			
Storage: **MK**	0.04	(0.06)	-4%	1.8	2	0.41
Phakic (baseline)	-1.39	(0.03)				
Aphakic	0.04	(0.08)	+4%	0.2	1	0.66
First keratoplasty (baseline)	-1.38	(0.04)				
Repeat keratoplasty	0.03	(0.08)	+3%	0.1	1	0.75
Death to Op. hours: < **36** (baseline)	-1.39	(0.04)				
Death to Op. hours: **36-72**	0.06	(0.06)	+6%			
Death to Op. hours: > **72**	-0.02	(0.15)	-2%	1.0	2	0.61

Table 5.4 Irregularity, PRE suture removal; Univariate effect on the slope.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-0.06	(0.09)				
Age: **31- 40**	-0.21	(0.12)	-19%			
Age: > **40**	-0.10	(0.13)	-9%	3.1	2	0.22
Sex: **Male** (baseline)	-0.19	(0.08)				
Sex: **Female**	0.002	(0.11)	+0.2%	0.001	1	0.99
Side: **Right** (baseline)	-0.13	(0.09)				
Side: **Left**	-0.13	(0.11)	-12%	0.5	1	0.48
Diagnosis: **Keratoconus** (baseline)	-0.21	(0.08)				
Diagnosis: **Other**	0.19	(0.14)	+21%	1.8	1	0.18
Suture: **Continuous** (baseline)	-0.21	(0.08)				
Suture: **Interrupted**	0.21	(0.15)	+23%	2.0	1	0.16
Disparity: = **0 mm** (baseline)	-0.20	(0.10)				
Disparity: > **0 mm**	0.02	(0.11)	+2%	0.02	1	0.89
Surgeon: **X** (baseline)	-0.14	(0.09)				
Surgeon: **Y**	-0.06	(0.11)	-6%			
Surgeon: **Z**	-0.17	(0.17)	-16%	1.1	2	0.59
Graft diam: < **8 mm** (baseline)	-0.15	(0.12)				
Graft diam: **8 - 8.5 mm**	-0.03	(0.14)	-3%			
Graft diam: > **8.5 mm**	-0.07	(0.14)	-7%	0.2	2	0.91
Donor's age: <= **55**(baseline)	-0.12	(0.08)				
Donor's age: > **55**	-0.09	(0.10)	-9%	0.8	1	0.37
Storage: **Fresh** (baseline)	-0.19	(0.08)				
Storage: **MK**	-0.01	(0.13)	-1%			
Storage: **K Sol**	0.14	(0.13)	+15%	1.4	2	0.50
Phakic (baseline)	-0.16	(0.06)				
Aphakic	+0.20	(0.16)	+22%	1.5	1	0.22
First keratoplasty (baseline)	-0.14	(0.06)				
Repeat keratoplasty	0.05	(0.21)	+5%	0.1	1	0.82
Death to Op. hours: < **36** (baseline)	-0.15	(0.07)				
Death to Op. hours: **36-72**	-0.01	(0.11)	-1%			
Death to Op. hours: > **72**	0.15	(0.21)	+16%	0.5	2	0.78

Table 5.5 Astigmatism, AFTER suture removal; Univariate effect on the intercept.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-0.03	(0.02)				
Age: **31- 40**	-0.01	(0.02)	-1%			
Age: > **40**	-0.01	(0.02)	-1%	0.4	2	0.84
Sex: **Male** (baseline)	-0.04	(0.01)				
Sex: **Female**	-0.001	(0.02)	-0.1%	0.001	1	0.99
Side: **Right** (baseline)	-0.03	(0.02)				
Side: **Left**	-0.02	(0.02)	-2%	0.8	1	0.37
Diagnosis: **Keratoconus** (baseline)	-0.04	(0.01)				
Diagnosis: **Other**	0.01	(0.02)	+1%	0.3	1	0.60
Suture: **Continuous** (baseline)	-0.04	(0.01)				
Suture: **Interrupted**	0.04	(0.03)	+4%	1.9	1	0.17
Disparity: = **0 mm** (baseline)	-0.05	(0.02)				
Disparity: > **0 mm**	0.02	(0.02)	+2%	1.1	1	0.30
Surgeon: **X** (baseline)	-0.04	(0.01)				
Surgeon: **Y**	-0.001	(0.02)	-0.1%			
Surgeon: **Z**	-0.03	(0.03)	-3%	1.1	2	0.58
Graft diam: < **8 mm** (baseline)	-0.04	(0.02)				
Graft diam: **8 - 8.5 mm**	0.01	(0.02)	+1%			
Graft diam: > **8.5 mm**	0.01	(0.02)	+1%	0.02	2	0.99
Donor's age: <= **55**(baseline)	-0.04	(0.01)				
Donor's age: > **55**	-0.0001	(0.02)	0%	0.0001	1	0.99
Storage: **Fresh** (baseline)	-0.04	(0.01)				
Storage: **MK**	0.01	(0.02)	+1%			
Storage: **K Sol**	0.003	(0.02)	+0.3%	1.4	2	0.50
Phakic (baseline)	-0.04	(0.01)				
Aphakic	0.02	(0.03)	+2%	0.7	1	0.42
First keratoplasty (baseline)	-0.04	(0.01)				
Repeat keratoplasty	-0.003	(0.04)	-3%	0.001	1	0.99
Death to Op. hours: < **36** (baseline)	-0.04	(0.01)				
Death to Op. hours: **36-72**	-0.001	(0.02)	-0.1%			
Death to Op. hours: > **72**	-0.02	(0.04)	-2%	0.1	2	0.95

Table 5.6 Astigmatism, AFTER suture removal; Univariate effect on the slope
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-1.60	(0.03)				
Age: **31- 40**	-0.003	(0.06)	-0.3%			
Age: > **40**	0.01	(0.06)	+1%	0.001	2	0.99
Sex: **Male** (baseline)	-1.62	(0.04)				
Sex: **Female**	0.04	(0.05)	+4%	0.7	1	0.42
Side: **Right** (baseline)	-1.60	(0.04)				
Side: **Left**	-0.01	(0.05)	-1%	0.03	1	0.86
Diagnosis: **Keratoconus** (baseline)	-1.63	(0.03)				
Diagnosis: **Other**	0.15	(0.07)	+16%	5.1	1	0.03
Suture: **Continuous** (baseline)	-1.62	(0.03)				
Suture: **Interrupted**	0.09	(0.07)	+9%	1.5	1	0.23
Disparity: = **0 mm** (baseline)	-1.61	(0.05)				
Disparity: > **0 mm**	-0.01	(0.05)	-1%	0.02	1	0.89
Surgeon: **X** (baseline)	-1.61	(0.04)				
Surgeon: **Y**	0.01	(0.06)	+1%			
Surgeon: **Z**	0.02	(0.08)	+2%	0.02	2	0.99
Graft diam: < **8 mm** (baseline)	-1.48	(0.05)				
Graft diam: **8 - 8.5 mm**	-0.17	(0.06)	-16%			
Graft diam: > **8.5 mm**	-0.17	(0.06)	-16%	9.0	2	0.01
Donor's age: <= **55**(baseline)	-1.61	(0.04)				
Donor's age: > **55**	0.03	(0.05)	+3%	0.2	1	0.66
Storage: **Fresh** (baseline)	-1.60	(0.04)				
Storage: **MK**	-0.01	(0.06)	-1%			
Storage: **K Sol**	0.04	(0.06)	+4%	0.5	2	0.77
Phakic (baseline)	-1.61	(0.03)				
Aphakic	0.10	(0.08)	+11%	1.4	1	0.24
First keratoplasty (baseline)	-1.61	(0.03)				
Repeat keratoplasty	0.28	(0.10)	+32%	6.8	1	0.01
Death to Op. hours: < **36** (baseline)	-1.61	(0.03)				
Death to Op. hours: **36-72**	0.01	(0.06)	+1%			
Death to Op. hours: > **72**	0.18	(0.11)	+20%	2.8	2	0.25

Table 5.7 Irregularity, AFTER suture removal; Univariate effect on the intercept.
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

Variable	Estimated parameter	(s.e.)	Estimated % change	LRT	d.f.	P value
Age: <= **30** (baseline)	-0.02	(0.01)				
Age: **31- 40**	0.01	(0.01)	+1%			
Age: > **40**	0.02	(0.01)	+2%	3.9	2	0.14
Sex: **Male** (baseline)	-0.02	(0.01)				
Sex: **Female**	0.01	(0.01)	+1%	1.3	1	0.25
Side: **Right** (baseline)	-0.02	(0.01)				
Side: **Left**	0.01	(0.01)	+1%	0.9	1	0.35
Diagnosis: **Keratoconus** (baseline)	-0.02	(0.01)				
Diagnosis: **Other**	0.02	(0.01)	+2%	3.5	1	0.06
Suture: **Continuous** (baseline)	-0.01	(0.01)				
Suture: **Interrupted**	0.01	(0.01)	+2%	1.1	1	0.29
Disparity: = **0 mm** (baseline)	-0.01	(0.01)				
Disparity: > **0 mm**	-0.01	(0.01)	-1%	1.1	1	0.29
Surgeon: **X** (baseline)	-0.02	(0.01)				
Surgeon: **Y**	0.01	(0.01)	+1%			
Surgeon: **Z**	0.01	(0.01)	+1%	1.1	2	0.57
Graft diam: < **8 mm** (baseline)	0.01	(0.01)				
Graft diam: **8 - 8.5 mm**	-0.02	(0.01)	-2%			
Graft diam: > **8.5 mm**	-0.03	(0.01)	-3%	8.4	2	0.02
Donor's age: <= **55**(baseline)	-0.02	(0.01)				
Donor's age: > **55**	0.01	(0.01)	+1%	2.3	1	0.13
Storage: **Fresh** (baseline)	-0.01	(0.01)				
Storage: **MK**	-0.02	(0.01)	-2%			
Storage: **K Sol**	-0.01	(0.01)	-1%	2.1	2	0.35
Phakic (baseline)	-0.02	(0.01)				
Aphakic	0.02	(0.01)	+2%	2.8	1	0.09
First keratoplasty (baseline)	-0.01	(0.01)				
Repeat keratoplasty	0.04	(0.02)	+4%	4.6	1	0.03
Death to Op. hours: < **36** (baseline)	-0.01	(0.01)				
Death to Op. hours: **36-72**	-0.01	(0.01)	-1%			
Death to Op. hours: > **72**	-0.01	(0.02)	-1%	0.9	2	0.64

Table 5.8 Irregularity AFTER suture removal; Univariate effect on the slope
Estimated % change is based on the original scale not the log scale. *LRT* = likelihood ratio test.

5.1.5 Multivariate analysis of Astigmatism and Irregularity

The object of the analysis is to determine the reasons for the variation between patients in the pattern of change over time. It is necessary to refine the results obtained in the univariate analysis. It is necessary to test the possibility that a particular category in a given variable appears to have a significant effect only because the patients which it encompasses have other characteristics which are the true determinants. In other words, we wish to exclude results which can be explained by a combination of variables. An example of this can be found in Table 5.2, by looking at the effect of the variable: Surgeon. A negative slope indicates a reduction in astigmatism with time, and a change towards a more negative figure indicates a faster decline. It appears that the patients operated on by Surgeon Z had a 30% faster reduction in astigmatism, when compared to the baseline (Surgeon X). The significance level was p=0.07. The group of patients operated on by Surgeon Z was relatively small in number, and was not in fact a homogeneous group. It contained a higher proportion of the categories which appear to have a beneficial influence on the rate of astigmatism decline. This group had a similar proportion of patients with keratoconus compared to the other diagnoses, but there were no repeat keratoplasties. Also, only continuous sutures were used, and there were much fewer of the largest transplant diameter category, (8% versus 49%, and 35% for the other two surgeons). Another positive factor, was that all the donor corneas were fresh, with none stored in MK medium.

Multivariate analysis was used to distinguish the effects that were due to a combination of variables, and the effects due to the principal determinants of the observed changes. This was done by taking all the thirteen variables examined in univariate analysis, and sequentially including them in the model.

In the case of changes in Astigmatism in the pre-suture removal period, the multivariate analysis eventually led to the conclusion that the treatment of the donor material prior to surgery was a major determinant of the intercept. The donor material stored in MK medium had a higher starting value for astigmatism compared to those that were fresh, or were stored in K-sol.

The slope was primarily determined by the disparity between the donor and host diameters. Those trephined with the same size of trephine for the donor and host, showed a faster reduction of astigmatism, than those where the donor button was cut larger than the recipient opening. These results are summarised in Table 5.9 and Figure 5.12.

No single variable was found to affect either the slope or intercept of log-astigmatism after suture removal. The lower part of Table 5.9 shows the variance of individual profiles. This is in fact the residual variance which remains once the effect of the main determinant variables, Storage, and Disparity, is removed.

		PRE removal	POST removal
		Estimated parameter (s.e.)	Estimated parameter (s.e.)
Intercept			
Storage			
	Baseline (Fresh)	-0.002 (0.08)	-0.14 (0.06)
	Effect of MK	0.24 (0.13)	no effect
Slope			
Disparity			
	Baseline (Disparity = 0)	-0.28 (0.08)	-0.04 (0.01)
	Effect of disparity (per mm)	0.34 (0.17)	no effect
Variance of individual profiles			
Within Subjects		0.08	0.06
Between Subjects			
	For Intercept	0.37	0.23
	For Slope	0.14	0.003

Table 5.9 Multivariate model for log-astigmatism

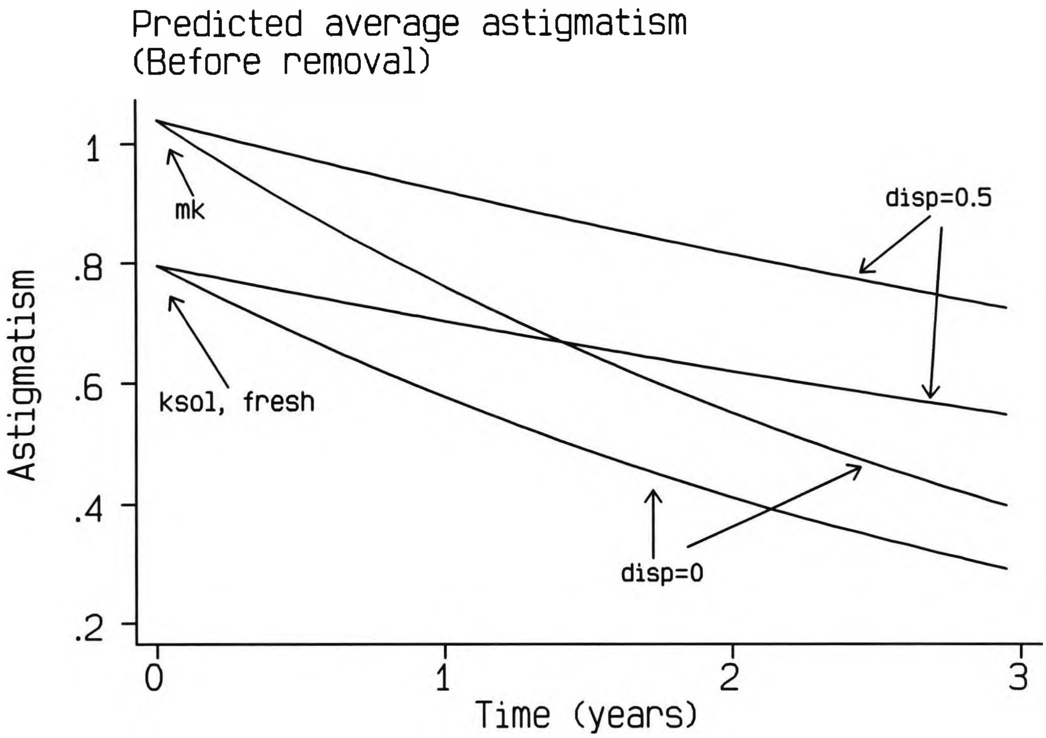


Figure 5.12 Multivariate results for Astigmatism before suture removal

In statistical terms a model of the kind derived here from multivariate analysis is thought to be more robust if it is *parsimonious*, that is to say it contains as few variables as possible. If an attempt is made to include too many variables the power of the model is weakened. It should be noted that although previous surgery is not included in the final model, repeat keratoplasties were found to have a slower decline in astigmatism prior to suture removal (p=0.09).

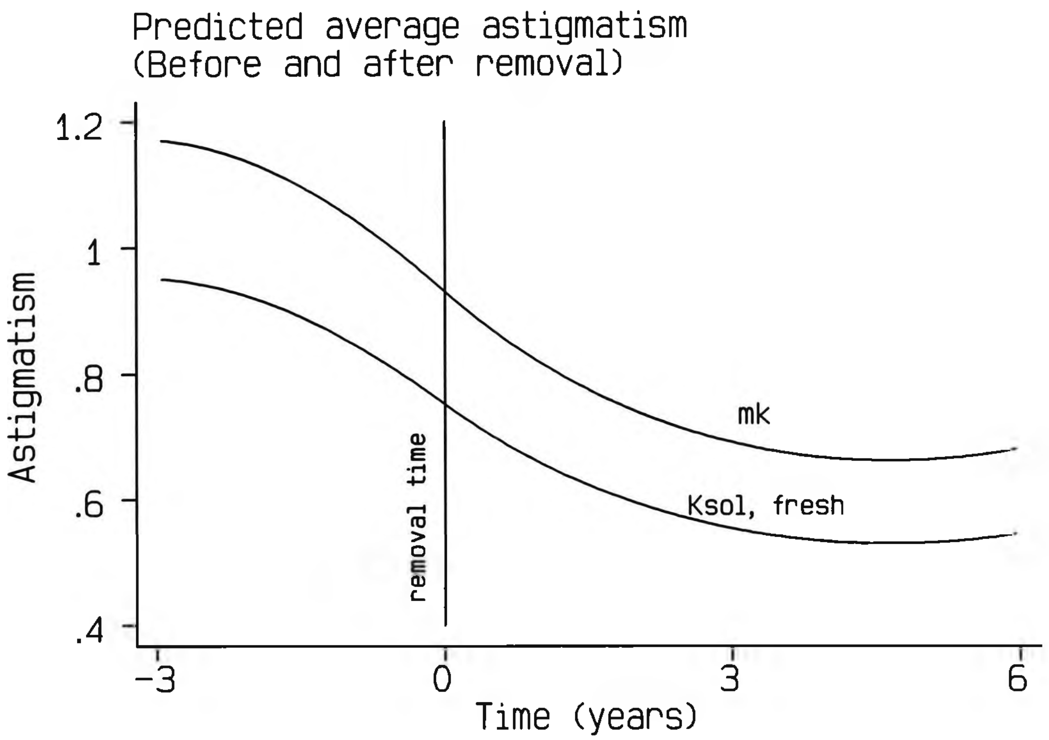


Figure 5.13 Changes in Astigmatism over the full post-operative period. Quadratic model

Figure 5.13 shows a model for changes in Astigmatism which covers the period before, and after suture removal. This has been done by taking the date of suture removal as time - zero. This means that for each patient the point in the profile corresponding to suture removal is aligned over the zero point. When this was done, there did not appear to be any particular trend to the changes immediately post-suture removal. When the individual profiles were amalgamated using the multilevel modelling techniques, no abrupt change appeared to take place at the time of suture removal.

The log linear model was appropriate for the time span involved in the pre-suture removal analysis, and also for the post-suture removal period. However, when the time span was expanded to take in the entire post-operative period, it became apparent that a quadratic model would be a better match for the pattern of changes taking place.

($x = \alpha + \beta t + \beta_2 t^2$ is the general quadratic equation. The shape is determined by the sign of the coefficients β and β_2)

The effect of storage technique continues to play the same role as it did in the multivariate model, i.e. a higher intercept with MK medium. However, no single variable appeared to affect the slope. Disparity, which affected the slope in the pre-removal period, was not important post-removal, and did not affect the overall model. Variables which appeared to show a slower decline of astigmatism included repeat surgery, and disparity > 0, but their effect was not significant.

Irregularity

The results in Table 5.10 show that repeat surgery had an effect on the intercept for log-irregularity, in both periods. However, multivariate analysis revealed that no single variable determined the rate of change of irregularity, either before or after suture removal. Although no variable emerged as significant, some trends were observed in the pre-removal period. Larger transplant diameters appeared to have a decreasing effect on the intercept, and a diagnosis other than keratoconus appeared to cause a slower decline in irregularity. However, a large proportion of patients with a repeat keratoplasty had a diagnosis other than keratoconus (56%), and smaller transplant diameters (44% were in the category with the smallest diameter, less than 7.5mm). These proportions are much higher than the corresponding figures for patients with no previous surgery, (12% with diagnosis “other”, and 20% with diameter less than 7.5mm). Thus these variables were not significant in the multivariate model. Similar trends were found after removal, but again they were not significant.

		PRE removal	POST removal
		Estimated parameter (s.e.)	Estimated parameter (s.e.)
Intercept			
Repeat surgery			
	Baseline (First keratoplasty)	-1.42 (0.03)	-1.61 (0.03)
	Effect of Repeat keratoplasty	0.36 (0.09)	0.28 (0.10)
Slope			
	All eyes	-0.11 (0.03)	-0.01 (0.005)
	No single parameter determined the slope		

Variance of individual profiles			
Within Subjects		0.04	0.02
Between Subjects			
	For Intercept	0.07	0.05
	For Slope	0.02	0.001

Table 5.10 Multivariate model for log-irregularity

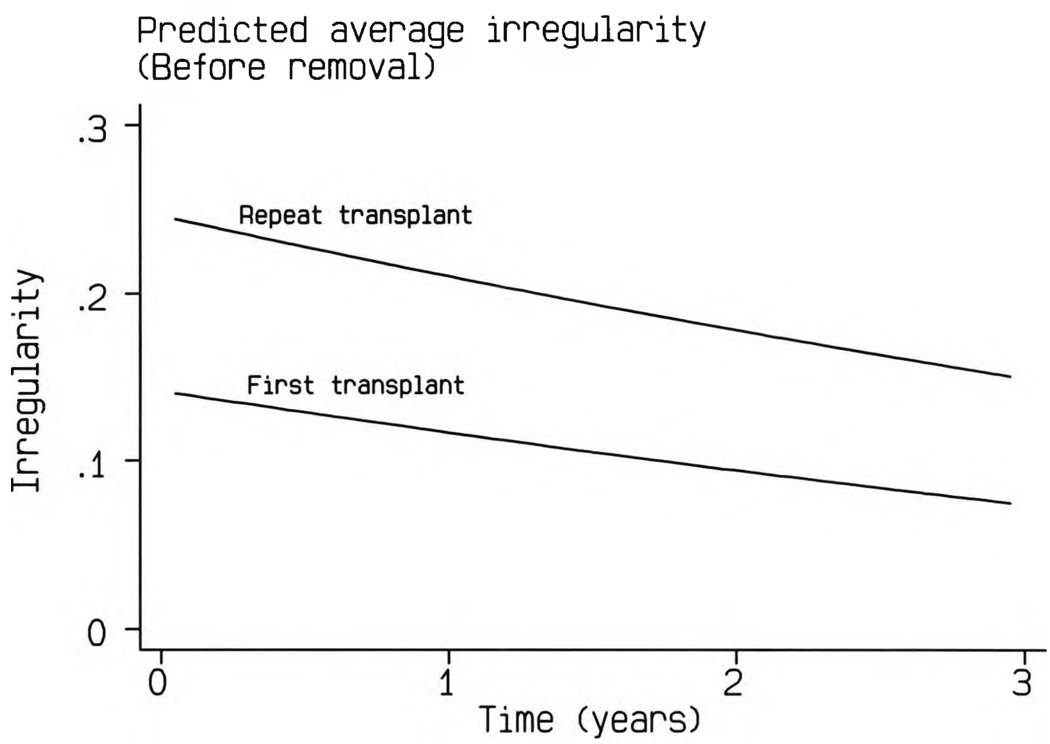


Figure 5.14 Multivariate results for Irregularity before suture removal

Figure 5.15 shows the model for changes in irregularity over the entire post-operative period. It was derived in the same way as the model for astigmatism in Figure 5.13. It is also a quadratic, but the differences in coefficients give it a different shape. It is obvious from Figure 5.15 that having a repeat keratoplasty gives a higher intercept, but this also has a subtle effect on the slope. In fact, two nearly equivalent multivariate models could be fitted. The one shown in Figure 5.15, and one in which transplant diameter explained differential intercepts, and previous surgery explained differential slopes. Smaller diameters gave a higher intercept, and previous keratoplasty gave a slower decline.

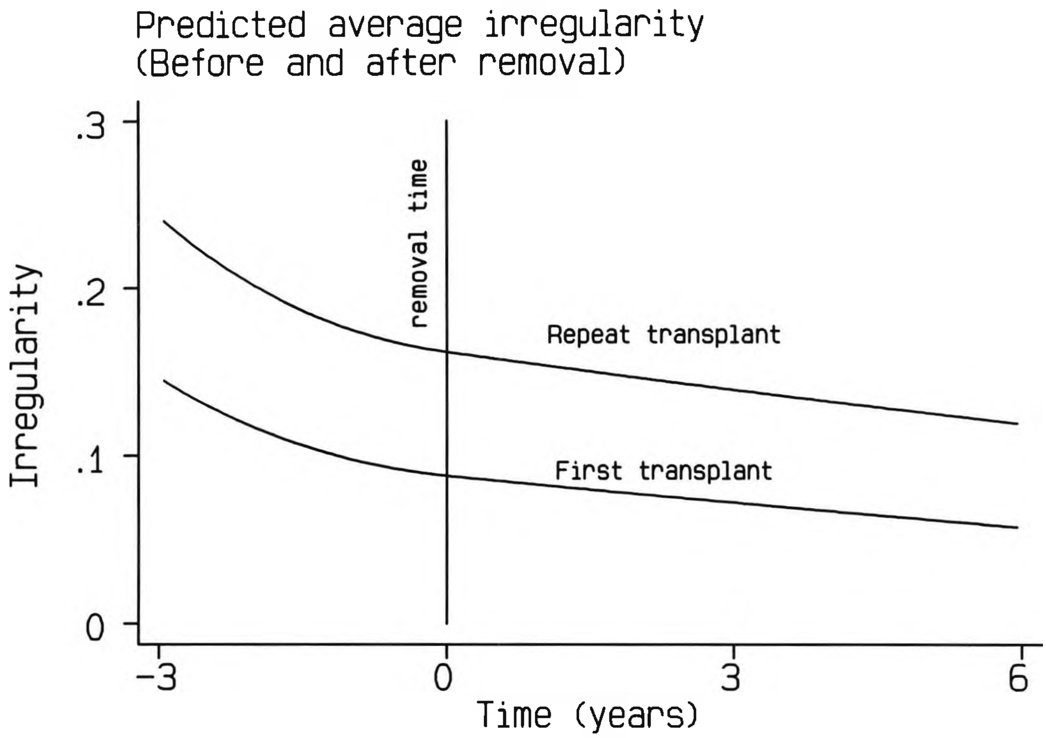


Figure 5.15 Changes in Irregularity over the full post-operative period. Quadratic model

5.1.6 Irregularity for other rings

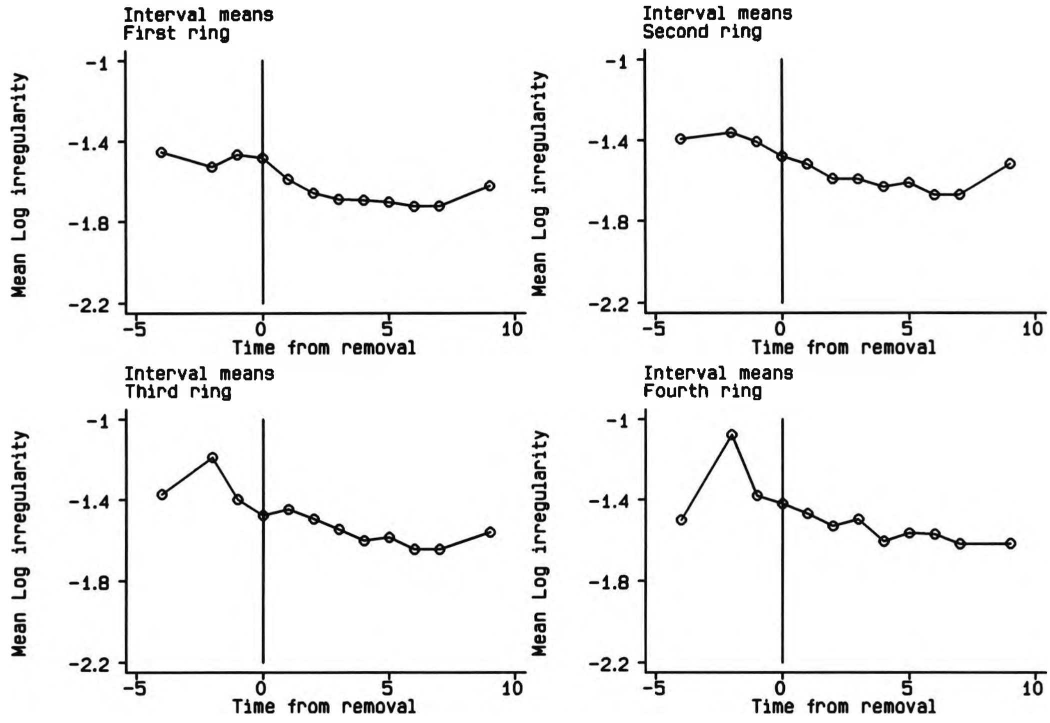


Figure 5.16 Irregularity for rings 1, 2, 3, and 4

Figure 5.16 shows plots describing the mean irregularity (on a log scale), for the first four rings. These are the mean values for each time interval. The profiles are very similar.

Analysis showed that the individual profiles for rings 2, and 3, are affected by repeat keratoplasty, diagnosis, and transplant diameter, at a rate very similar to that found for ring 1. For example, the effect on the Irregularity intercept, for the whole post-operative period, was very similar for all four rings. Ring 1 0.32 (0.10), Ring 2 0.33 (0.10), Ring 3 0.33 (0.13), Ring 4 0.34 (0.15). (The figures in brackets are the standard errors).

This is illustrated in Figure 5.17 which shows how the mean values for log-irregularity vary with the time interval. The left hand plot includes all patients, and the right hand plot those with a repeat transplant.

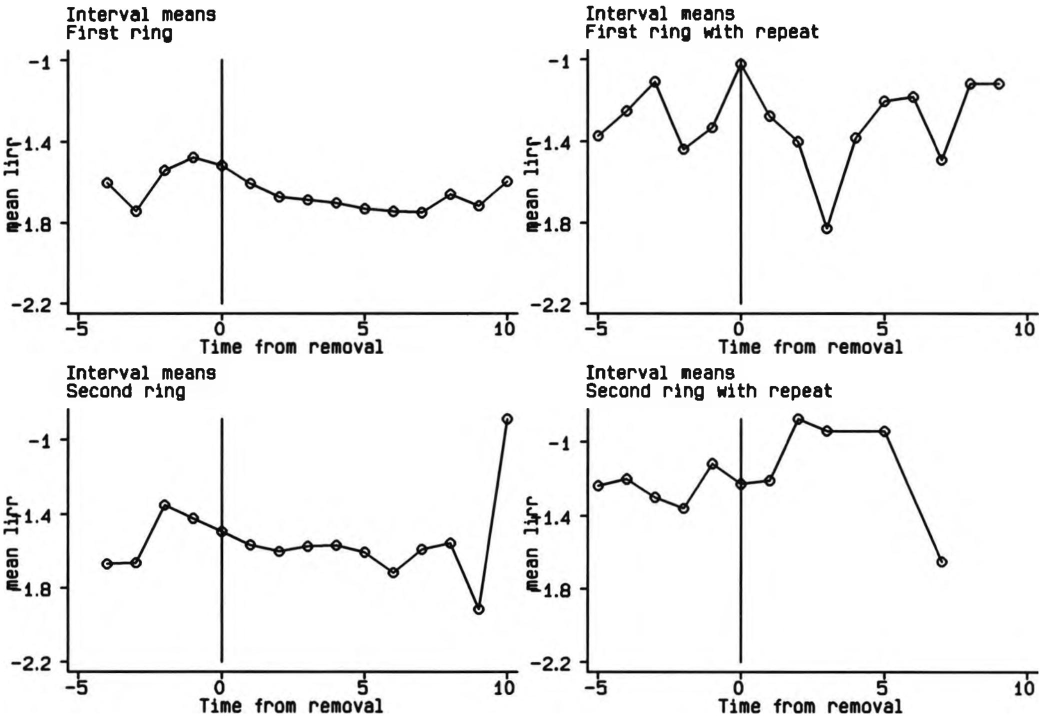


Figure 5.17 The effect of repeat keratoplasty on Irregularity in rings 1, and 2

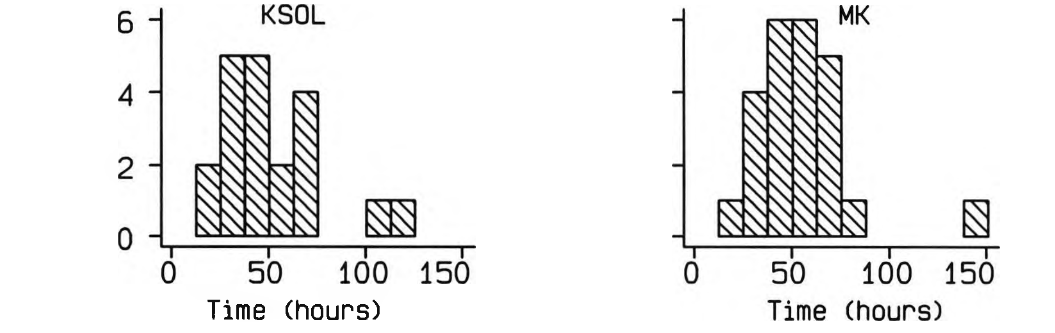


Figure 5.18 Time from death to operation for K-Sol and for MK medium

Figure 5.18 shows that MK medium was associated with longer times elapsed between the death of the donor, and the operation. It is therefore possible that the higher intercept for astigmatism is related to storage time rather than the storage medium itself.

5.2 Sensitivity

5.2.1 Patients

Sixty six subjects met the criteria for inclusion in the sensitivity analysis. The remainder were considered to have had insufficient sequential follow-up.

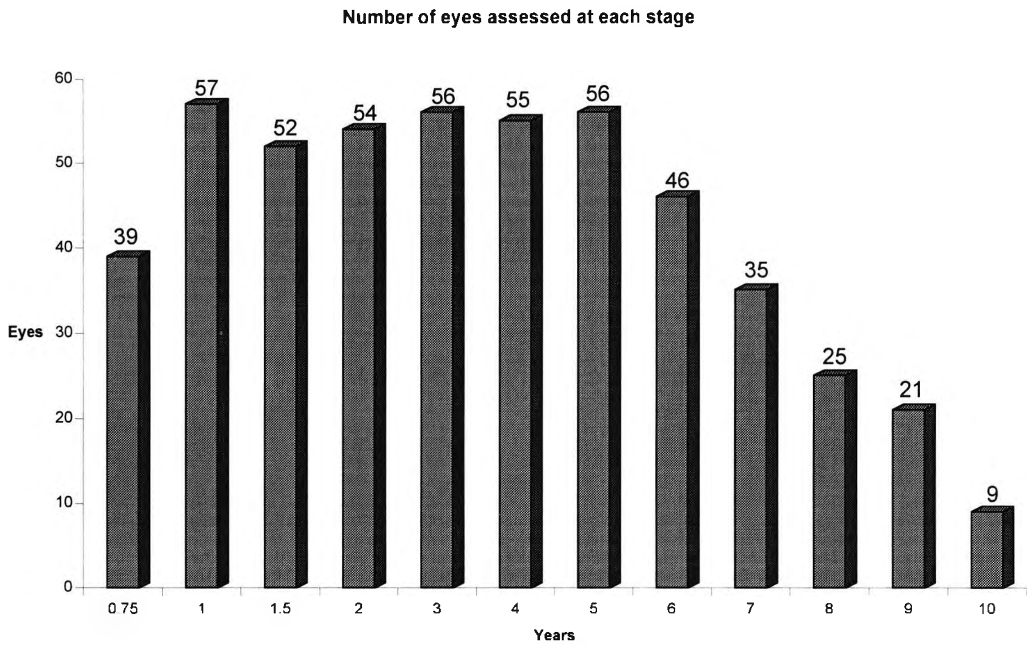


Figure 5.19 Number of eyes contributing data at each stage

5.2.2 Central sensitivity

The results are shown in graphical, and tabular form in Appendix I. They show a very considerable inter-subject variation in the return of touch sensitivity. When the mean values for all the subjects at each stage are plotted (see Figure 5.20), a very gradual increase in central sensitivity is revealed.

The earliest time following surgery at which any central sensitivity could be reliably detected was at one year. Some readings of 1cm were recorded earlier, but since subsequent assessments showed no sensitivity, it was considered that these might have been artefactual, and perhaps initiated by apprehension.

It was decided to amalgamate the seven possible sensitivity readings into three groups, rather than use all 7 points on the 0 to 6 scale. This was because of the variability already mentioned, and because analysis on the basis of a 7 point scale would have resulted in very small numbers at the higher sensitivity end of the scale. Four bands were used: "no sensitivity"; 1 or 2cm; 3 or 4cm; and 5 or 6cm. Figure 5.21 shows that when this approach is taken for all 66 subjects, a clear pattern of slow but progressive resensitisation is revealed.

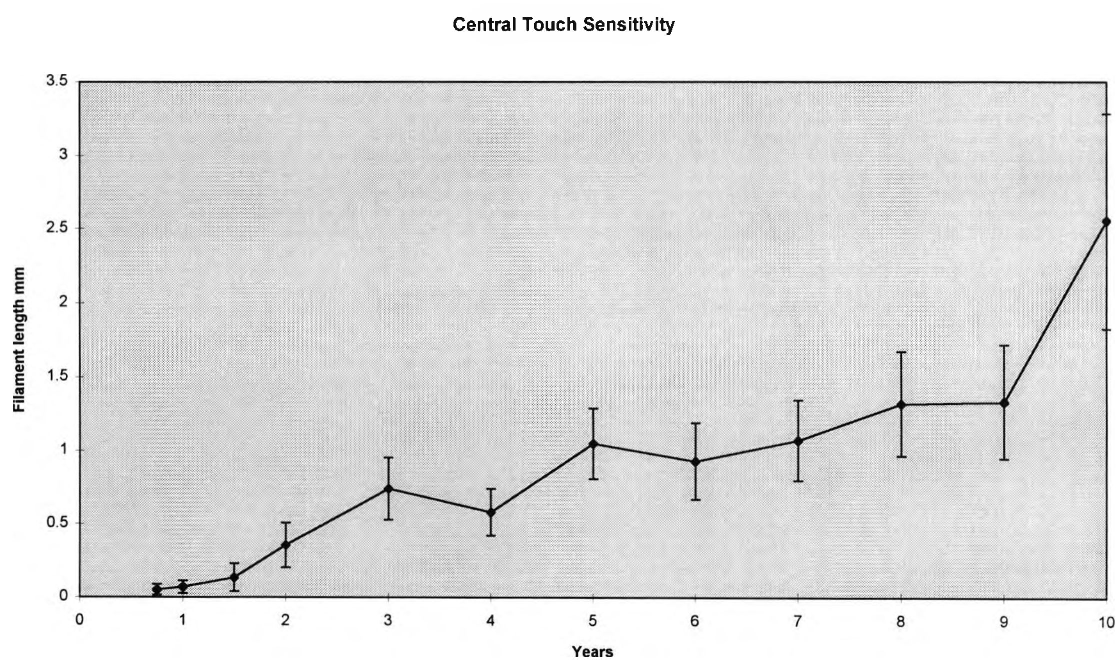


Figure 5.20 Change of central sensitivity with time, mean values

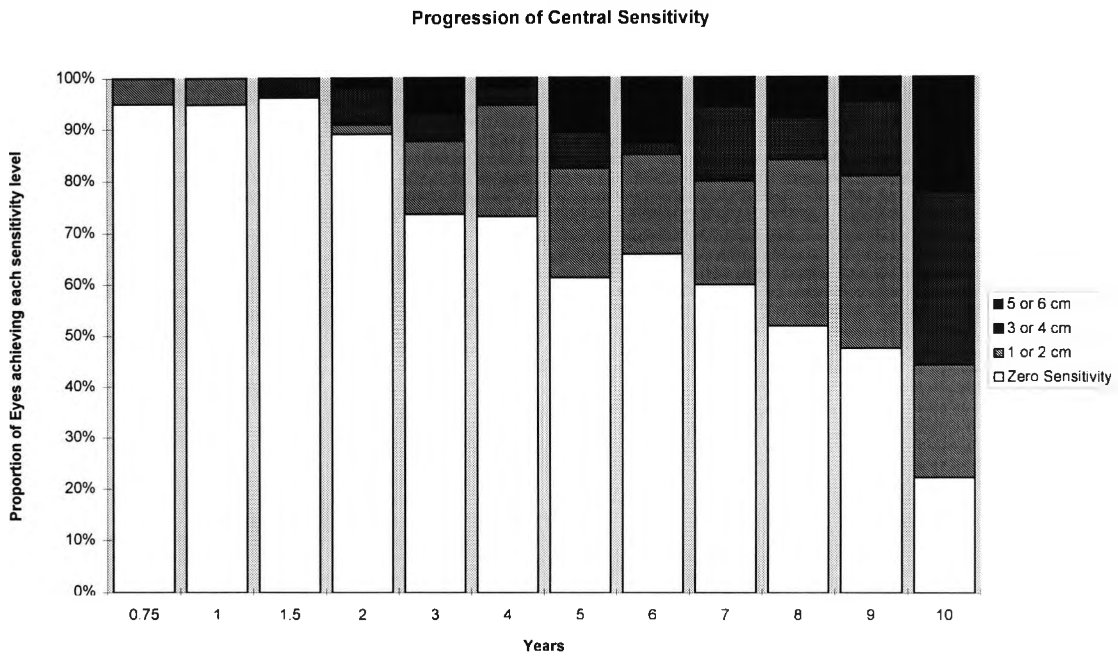


Figure 5.21 Progression of central sensitivity

5.2.3 Peripheral sensitivity

It was expected that sensitivity would progress from the periphery of the transplant towards the centre. However, when the mean of the four peripheral points was compared to the central sensitivity. it was not always found to be more sensitive. Figure 5.22 shows the transplant periphery was generally more sensitive, but that this difference was not always significant.

The reason for this may lie in the effect of contact lens wear on corneal sensitivity. Figure 5.23 shows higher sensitivity in the transplant periphery for non wearers. However, Figure 5.24 reveals that when contact lenses are worn there is virtually no difference in sensitivity between the transplant periphery, and the centre.

Examination of Figure 5.25 shows that for central sensitivity, contact lens wearers, and non wearers have broadly similar results. This is in contrast to the periphery of the transplant, where it appears that the contact lens wearers have depressed sensitivity compared to their non wearing counterparts.

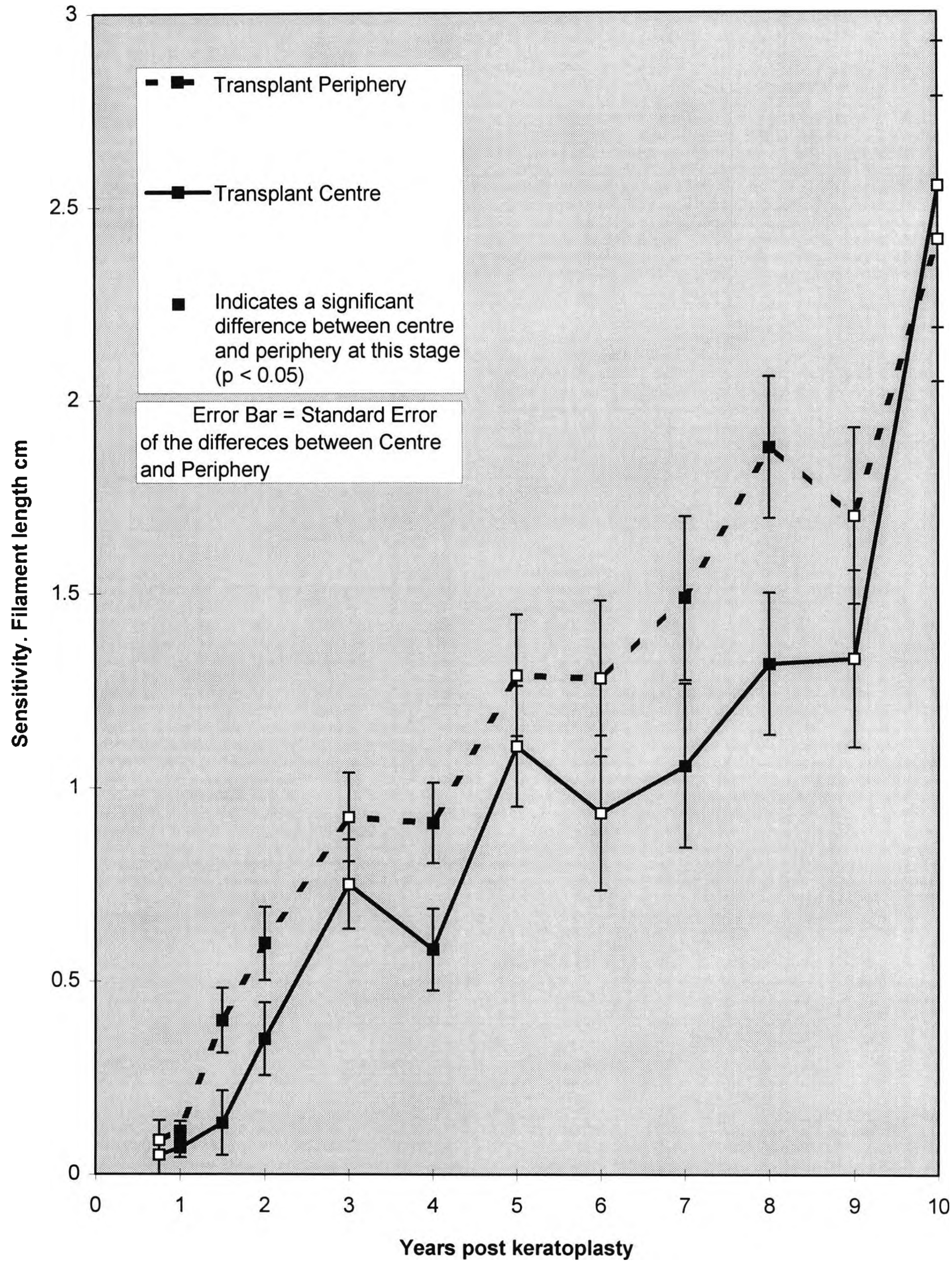


Figure 5.22 Comparison between transplant centre and periphery, mean sensitivity at each stage

5.2.4 Effect of contact lens wear

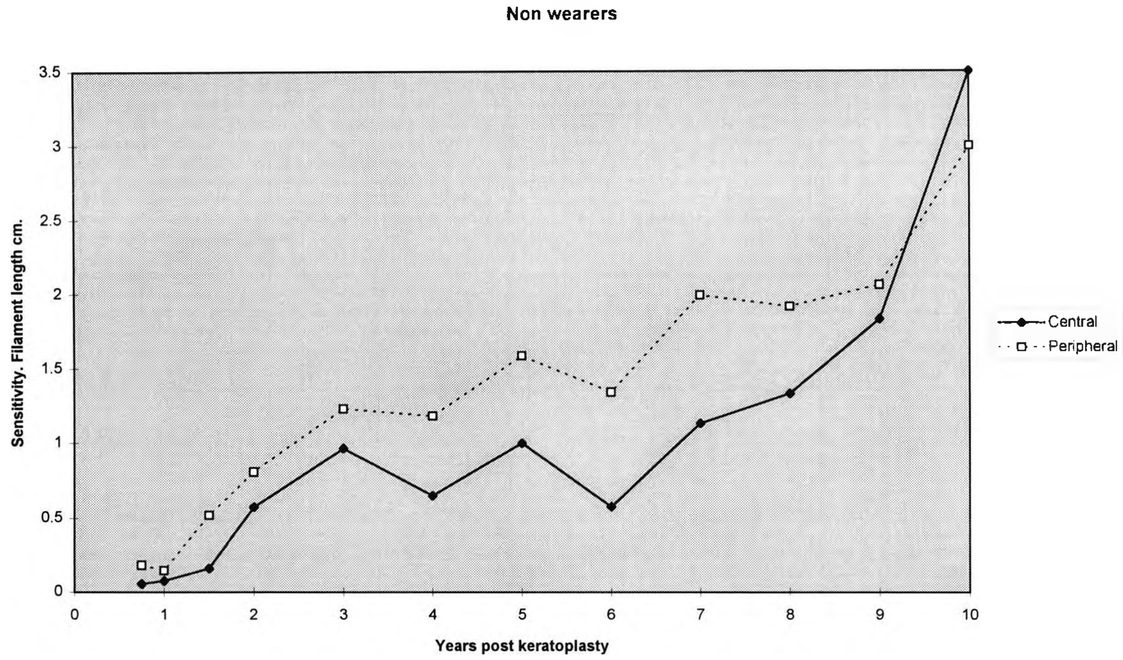


Figure 5.23 Difference between transplant centre and periphery for non contact lens wearers

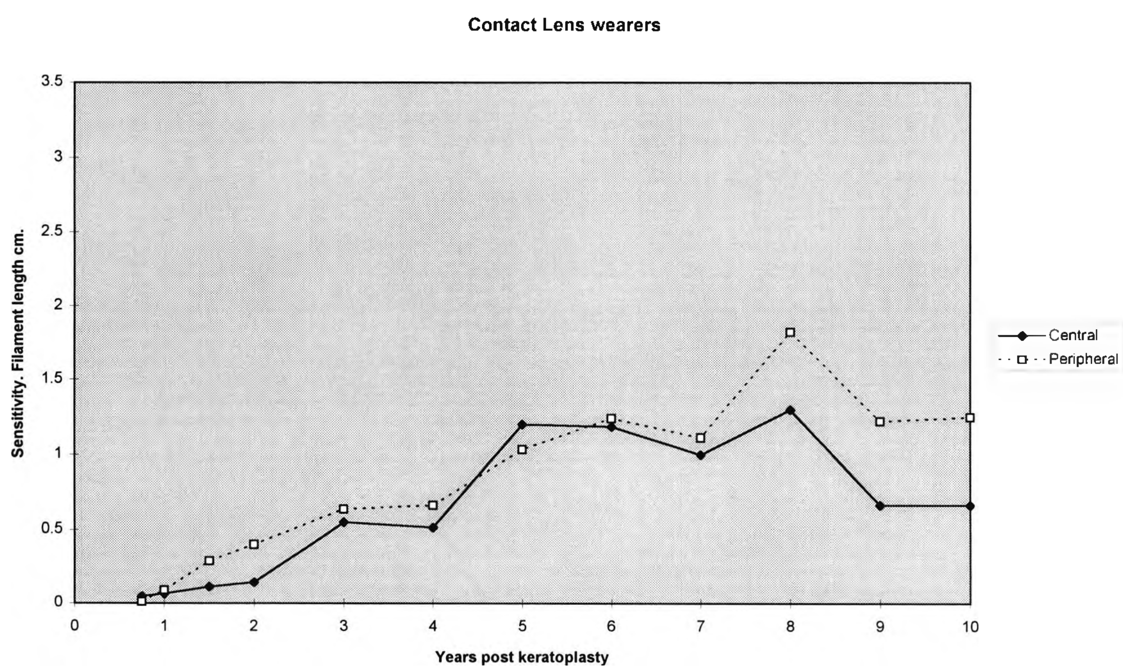


Figure 5.24 Difference between transplant centre and periphery for contact lens wearers

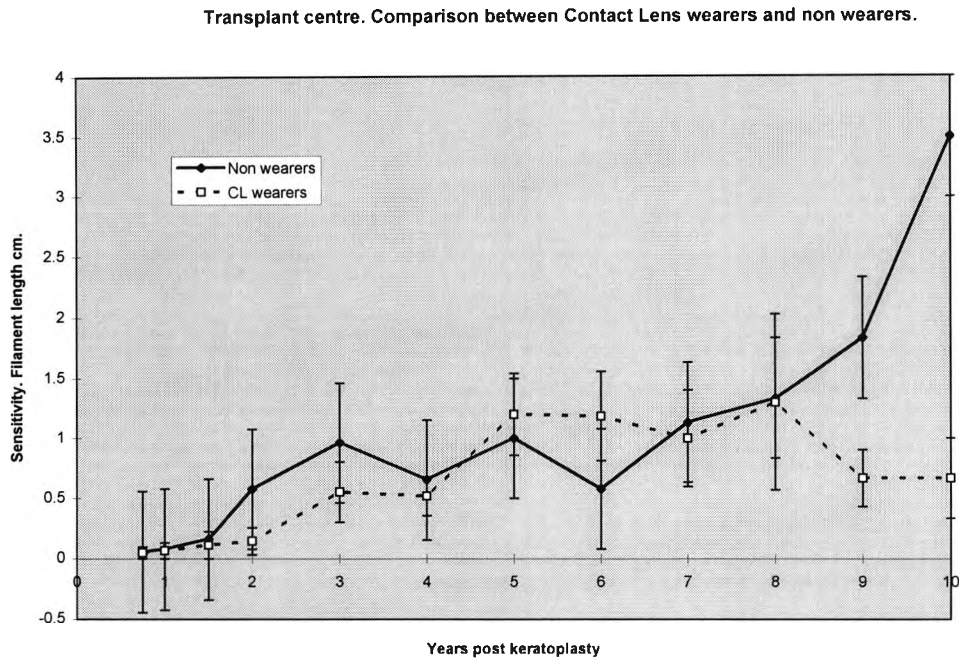


Figure 5.25 Transplant centre. Comparison between contact lens wearers and non wearers

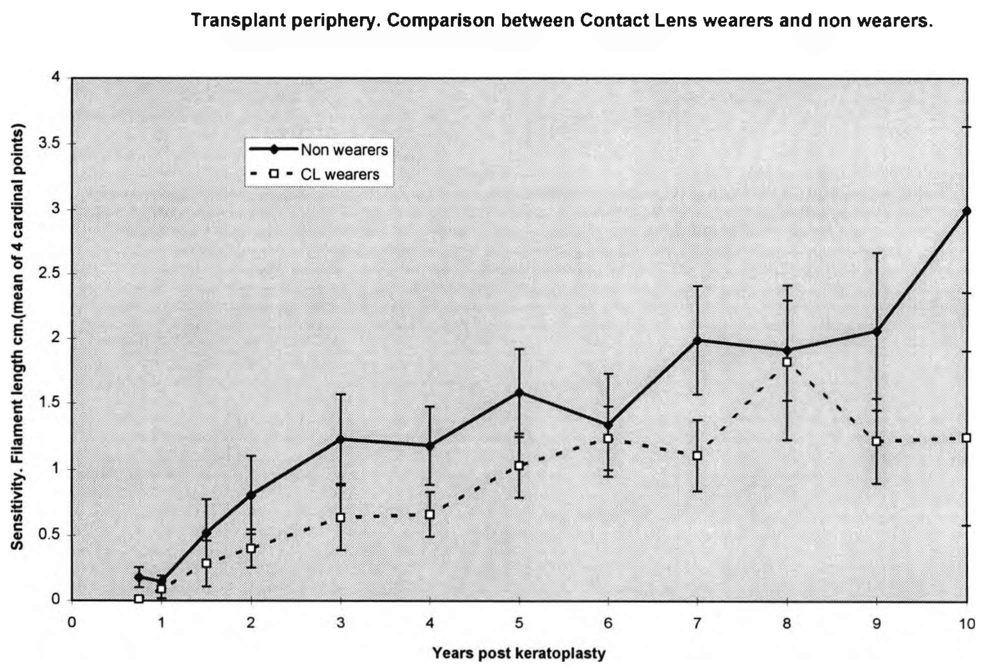


Figure 5.26 Transplant periphery. Comparison between contact lens wearers and non wearers

6. Discussion

6.1 Topography

6.1.1 Comparison between refraction and keratograph result

6.1.1.(i) Axis of Astigmatism

The linear regression line shows that overall there is good agreement between the axis obtained by refraction and that derived from the keratograph component. The equation of the regression line is $y = 0.97x + 1.96$ indicating that there is almost a 1:1 relationship (1:0.97), with an intercept of very close to zero (1.96 degrees).

In Figure 5.1 the majority of the points are clustered around the regression line, but there are also a number which indicate considerable difference in the axis obtained by the two methods. These cases of disparity reduce the correlation coefficient to its value of 0.74. An attempt was made to discover the characteristics which were responsible for these disparities. The ten cases which showed the most disparity were identified, and the keratograph components are shown alongside the refraction results in Table 6.1.

	Px	Stage	Refraction Astigmatism	Refraction Axis	Keratograph Astigmatism		Keratograph Axis	Irregularity	Asymmetry	ring
			D		mm	D				
a	7	1.5Y	1.75	80	.25	1.32	145	.11	.14	1
b	29	1.5Y	2.00	20	.24	1.20	101	.07	.74	1
					.33		98	.07	.94	2
					.13		15	.10	.81	3
c	33	9M	1.50	180	.12	0.69	110	.09	.25	1
					.06		157	.12	.28	2
d	35	3M	1.50	175	.20	1.22	89	.14	.27	1
					.14		134	.48	.25	2
e	38	1M	3.25	170	.31	1.97	107	.22	.29	1
					.34		116	.13	.21	2
f	57	6M	1.50	30	.69	2.63	117	.10	1.40	1
g	58	5Y	1.50	75	.30	1.78	13	.14	.17	1
					.36		173	.26	.27	2
					.32		15	.21	.38	3
					.31		20	.21	.41	4
h	60	5Y	1.50	35	.17	1.00	117	.09	.08	1
					.10		116	.09	.10	2
i	71	7Y	1.50	42.5	.87	4.76	132	.14	.33	1
					.70		134	.16	.35	2
					.52		135	.15	.36	3
					.38		149	.13	.46	4
j	73	1.5Y	2.00	65	.38	2.20	5	.10	.38	1
					.47		167	.09	.45	2

Table 6.1 The ten cases which showed the most disparity between Axis of Astigmatism by Refraction and by Keratograph analysis.

Only one of these ten cases had refractive astigmatism greater than 2.00D. Therefore these are relatively low amounts of astigmatism, and when combined with the irregularity and asymmetry shown in Table 6.1, it is not surprising that there is difficulty in assessing the axis of astigmatism. It is interesting to note that in cases (b), (c), and (d), the axis of astigmatism differs markedly between rings, as well as between keratograph analysis and refraction. It is difficult to tell whether this represents a failure to accurately measure the axis under certain circumstances, or whether there is a general change of axis as you move from the centre towards the periphery. It is possible that a torsion effect induced by sutures could be responsible for this shift in axis between centre and periphery. All three of the examples cited are of assessments done before the suture removal.

In most of these cases it was not possible to derive keratograph components for each of the four central rings. This was because part of the keratograph ring was too indistinct to obtain the required 12 radius of curvature values. The lack of keratograph components for some rings is therefore an indirect indicator of irregularity.

6.1.1.(ii) Astigmatism

Figure 5.2 shows the relationship between keratograph astigmatism and refractive astigmatism. The regression line ($y = 0.52x + 1.43$) indicates that refraction generally gives a lower value for astigmatism than the keratograph analysis. A similar result is found when the regression line is set to go through zero (Figure 5.3), and the regression coefficient R^2 is reduced from 0.31 to 0.23.

The reason for the relatively low correlation coefficient was investigated by the method used for the axis of astigmatism. The 10 cases which showed the most disparity between astigmatism assessed by refraction, and by keratograph analysis, were identified, and can be seen in Table 6.2.

	Px	Stage	Refraction Astigmatism D	Refraction Axis	Keratograph Astigmatism mm	Keratograph Astigmatism D	Axis	Irregularity	Asymmetry	ring
a	28	1.5Y	3.00	45	1.32	8.46	64	.25	.15	1
					1.12	7.21	63	.26	.22	2
					0.82	5.34	62	.23	.18	3
					0.62	4.08	58	.21	.22	4
b	52	3M	5.00	110	1.76	10.97	108	.12	.16	1
					1.79	10.92	105	.14	.23	2
					1.68	9.83	105	.12	.30	3
					1.59	9.08	104	.08	.38	4
c	55	9M	10.50	150	0.58	3.25	165	.03	.42	1
d	59	1.5Y	17.50	32.5	1.42	8.24	10	.15	.41	1
e	64	5Y	3.00	115	1.42	12.00	116	.14	.50	1
					1.53	12.93	120	.07	.97	3
f	64	6Y	3.00	15	1.04	9.70	150	.09	.51	1
					0.90	8.30	138	.08	.65	2
g	79	3Y	2.00	65	1.23	7.20	100	.09	.05	1
					1.01	6.01	100	.07	.02	2
					0.64	3.94	106	.09	.14	3
h	83	1.5Y	3.00	50	1.42	9.11	33	.17	.06	1
					1.33	8.60	31	.24	.07	2
					1.15	7.54	34	.27	.12	3
i	86	1.5Y	1.50	180	1.69	9.94	25	.27	.33	1
					1.16	6.99	17	.25	.07	2
j	94	1Y	1.25	110	1.67	9.31	112	.26	.68	1
					1.01	5.48	154	.44	1.28	2

Table 6.2 The ten cases which showed the most disparity between Astigmatism by Refraction and by Keratograph analysis.

In eight out of the ten cases the astigmatism was lower when assessed by refraction. The remaining two cases (c) and (d) had high amounts of refractive astigmatism, 10.50D and 17.50D. These were presumed to be accurate refractions since they produced good acuities, ($6/5_{-2}$ and $6/9_{-2}$ respectively).

It was only possible to analyse the first ring which showed considerable asymmetry in both cases. The astigmatic component from subsequent rings might have yielded a result nearer to that found by refraction. Indeed cases (a), (g), (h), (i), and (j) all show a trend for the astigmatism to reduce towards the periphery, although the astigmatism in the outermost ring available is always considerably more than the refractive result.

The mean astigmatism for the 150 refractions was 3.81D, which was significantly lower than 4.63D, the mean of the values obtained by keratograph analysis (paired t-Test, $p<0.001$). This result is similar to that found by Judge et al [118] who found refractive astigmatism to be less than astigmatism found by keratometry. This difference was statistically significant (2.95D : 5.43D), for the 65 eyes examined prior to suture removal, but was not significant for the 50 eyes examined after suture removal (3.70D : 4.27D).

6.1.1.(iii) Asymmetry

Figure 5.4 shows that there appears to be little correlation between asymmetry and visual acuity. However, it must be remembered that asymmetry does not imply irregularity. In asymmetry the spherical and regular astigmatic components are not symmetrically disposed around the corneal vertex (the point on the cornea that is perpendicular to the keratoscope axis when the patient fixates a point on the axis).

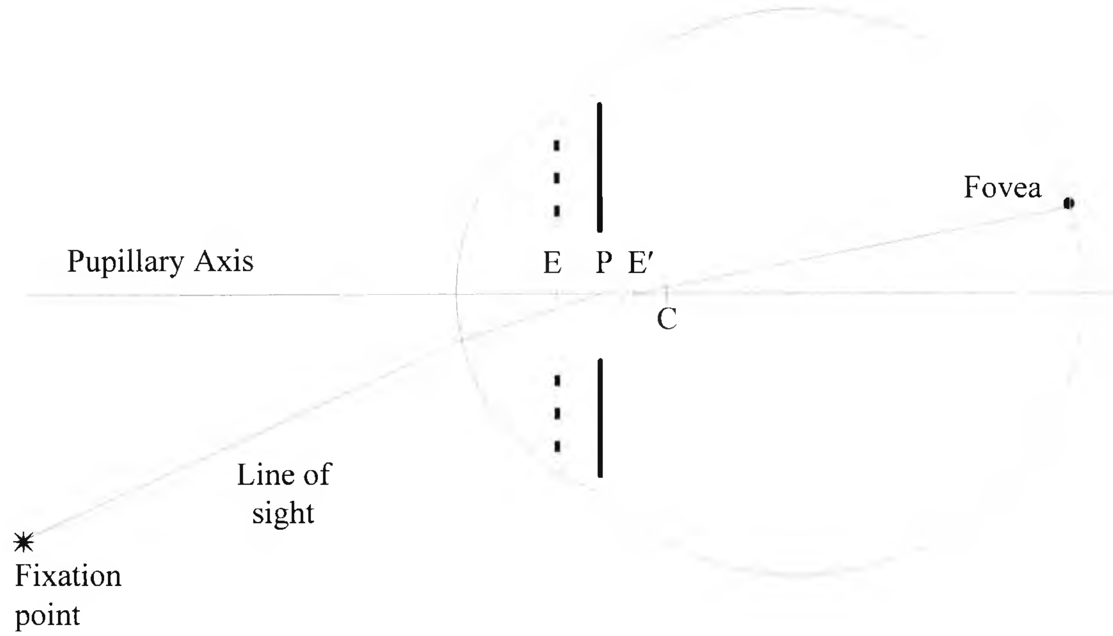
When considering asymmetry in relation to visual acuity it is important to distinguish the axes which relate to keratoscopy and the axes which relate to the image forming properties of the eye.

A number of theoretical points and reference lines are used to describe the optical properties of an eye.

1. The geometric centre of the cornea is the point equidistant from the limbus. It is generally eccentric to the optic and visual axes, and has no particular relevance to corneal topography alignment or image formation.

2. Optic axis is the theoretical line that joins the centre of curvature of the cornea and the centres of curvature of the crystalline lens. Unfortunately the eye is not an optically co-axial system, so that even if these three centres of curvature were exactly aligned, they would not coincide with the visual axis, because the fovea is not located exactly at the posterior pole. It is usually in a temporal and inferior position.

3. The pupillary axis. The pupillary axis is a more useful reference line, since it can be located using clinical test methods, and even in extremely asymmetric eyes is found to be reproducible[355].



Schematic diagram.

Figure 6.1 Pupillary axis

Pupillary axis is the line from the centre of the entrance pupil E that is perpendicular to the cornea. All lines that are perpendicular to the cornea must pass through its centre of curvature. Therefore the pupillary axis can also be defined as the line that passes through the centre of the entrance pupil E, and the centre of curvature C.

4. Line of sight. This reference line can also be located clinically, and is the most relevant when considering the image forming qualities of the cornea.

Light travelling along the Line of Sight is directed from the fixation point towards the centre of the entrance pupil. It is refracted at the cornea, and passes through the centre of the real pupil P, emerging from the crystalline lens as though coming from the centre of the exit pupil E′. It must eventually strike the fovea because by definition the subject is looking at the fixation point.

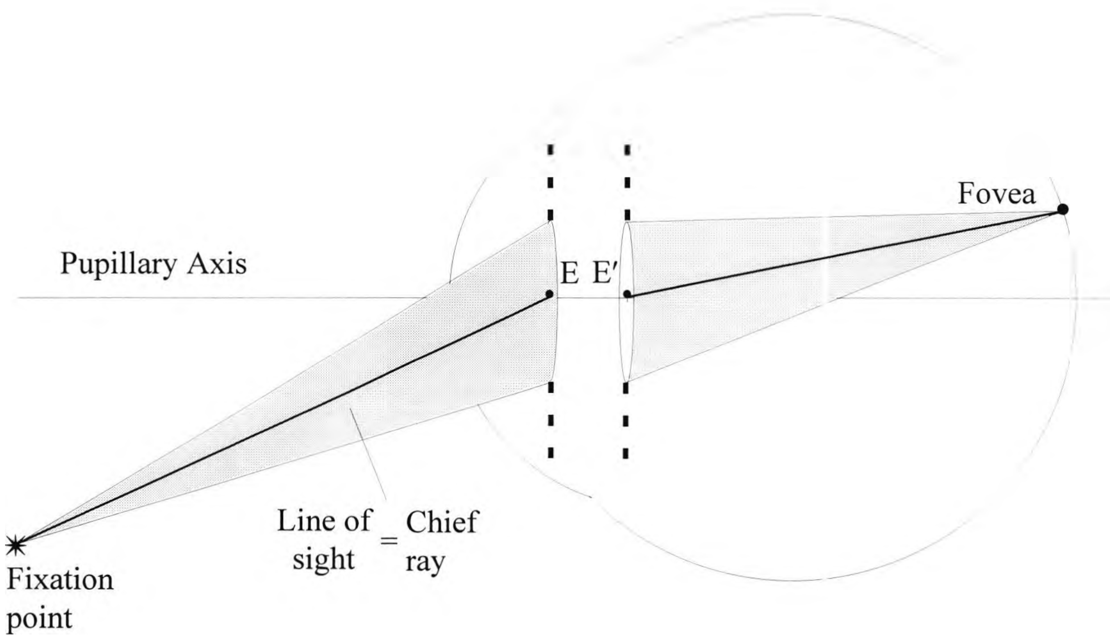


Figure 6.2 Line of sight

The line of sight represents the central or chief ray of the bundle of light rays passing from the fixation point through the actual optics of the eye to the fovea.

5. The visual axis.

This is a theoretical line which cannot be located clinically, because the nodal points cannot be found in a real eye without measuring every ocular component.

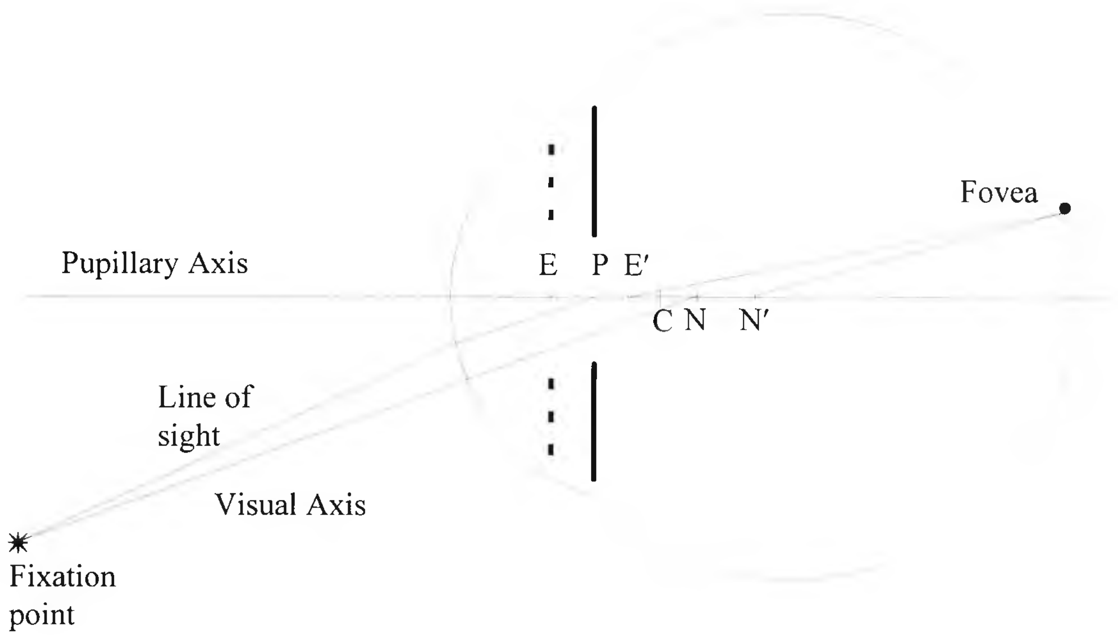


Figure 6.3 Illustrates the difference between the line of sight and the visual axis.

The visual axis passes from the fixation point through the nodal points to the fovea. It is useful in calculating object and image sizes, but it does not represent the actual path of light passing through the eye.

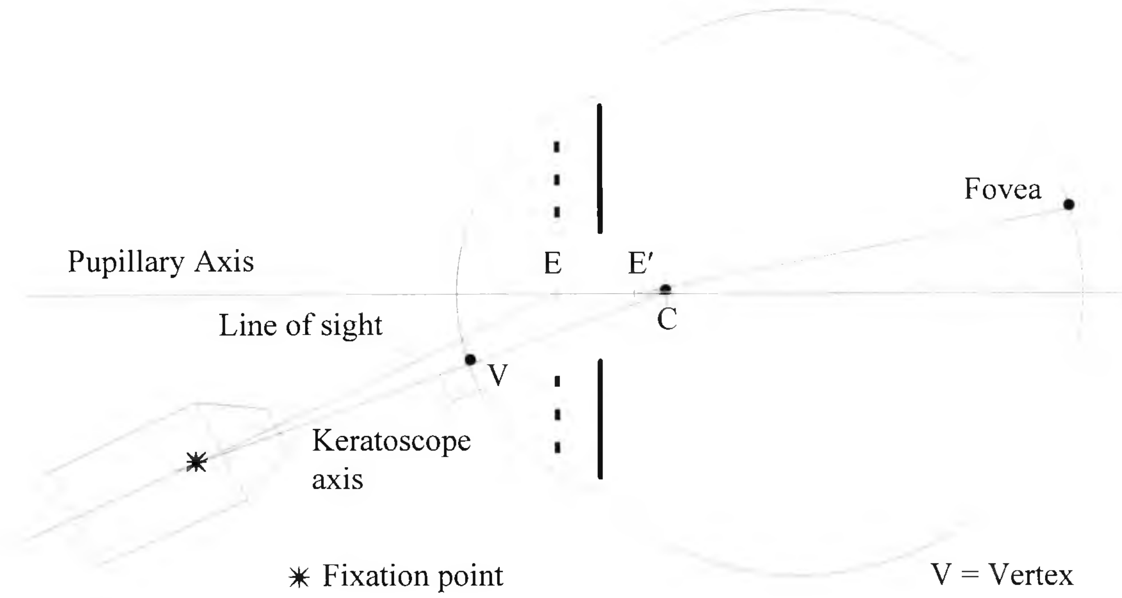


Figure 6.4 Shows the difference between the line of sight and the keratoscope axis.

The alignment system of the keratoscope ensures that the keratoscope axis is normal to the cornea (i.e. directed towards the centre of curvature), whereas the line of sight passes from the fixation point towards the centre of the entrance pupil.

Figure 6.4 shows that the keratoscope axis does not coincide with the line of sight and is therefore not aligned with the chief ray of the image forming bundle.

Maloney [349] defines the vertex normal as the line from the fixation point that intersects the corneal surface at right angles. The intersection point is known as the corneal vertex, and is shown in Figure 6.4 as V. This point does not necessarily correspond to the region of greatest curvature which is usually referred to as the corneal apex. Providing the cornea is convex the vertex will be the point on the cornea that is closest to the fixation point. Maloney [349] points out that if the cornea is not convex, it is possible for it to produce more than one line that satisfies the condition for a vertex normal. For example a very ectatic cone surrounded by a concave gutter might produce two Purkinje images, which would have to be distinguished by reference to the pupil, and, or, slit lamp inspection.

It is a drawback of Placido disc based systems that radius of curvature readings must be referred to the corneal vertex, which does not coincide with the line of sight. It is possible that the asymmetry found in the polar diagram plots of radius of curvature is merely an artefact of this particular measurement system. However, this seems unlikely because there does appear to be a trend for higher asymmetry values in the immediate post operative period which then reduces in subsequent months (see Table 5.6).

6.1.1.(iv) Irregularity

Figure 5.5 shows that there is very little correlation between the Irregularity component and visual acuity.

Wilson and Klyce [358] have investigated the relationship between visual acuity and quantitative measures of corneal shape anomaly. They examined two indices derived from computerised video keratoscope images taken from 31 patients. This group contained a wide variety of normal, diseased, and surgically altered corneas. Best spectacle corrected visual acuity was assessed with a Bailey-Lovie Acuity Chart, and the computerised topographic analysis was performed using the Corneal Modelling System (CMS). The surface asymmetry index (SAI) was determined by an algorithm developed by Dingledein et al [359]. It is a measure of central corneal asymmetry, and although the correlation coefficient was relatively low (0.632), it was concluded that asymmetry was a determinant of the optical performance of the anterior corneal surface. In contrast to this the surface regularity index (SRI) showed a higher correlation (0.80).

In this thesis there was no strong correlation between acuity and the topography components, Asymmetry and Irregularity. This may have been due to lack of control over the conditions of the refraction , and in particular visual acuity testing. It is possible that the use of standardised testing with low contrast charts might have produced closer correlations. There are no reports on the repeatability of subjective refraction in corneal transplants. Following penetrating keratoplasty the cornea does not necessarily conform to a sphero-cylindrical shape format, and since the cornea is the major refractive element in the eye, it is reasonable to assume that repeatability of refraction would be much less than in normals. The repeatability for refraction in normals has been assessed by Rosenfield and Chiu [360] under masked conditions where the examiner was unaware of the previous findings. They found 95% confidence limits of ± 0.27D, and recommended that at least ± 0.50D should be adopted as the minimum significant change in refraction. Another trial by Zadnik et al [361] gave a higher value, ± 0.75D. This was despite the fact that her trial was not masked, which might have been expected to cause a bias towards better agreement between results on separate occasions. Khong and her associates [62] claim to have found that both the SAI and SRI correlated well with log visual acuity and log contrast sensitivity. No correlation coefficient was quoted, and this longitudinal trial was of limited duration, and limited numbers. Eight corneal transplants were examined, over a period of six months.

Camp et al [362] developed a computer model for the effect of topography on optical performance. They found that both log visual acuity, and log contrast sensitivity were correlated with the SAI and SRI.

It should be borne in mind that the irregularity component derived from the topography data in this thesis differs from the SRI. The SRI is a measure of the deviation from a regular change in curvature as you progress radially from the centre to the periphery along a given semi-meridian. This is not very practical if there are as few as four readings in each semi-meridian measured, which was often the case when the PEK keratoscope was used on corneal transplants. The irregularity component avoids this problem by examining deviations from a regular change in curvature as you progress through 360° around a given keratoscope ring. In fact, it is a measure of the deviation from the best fit sphero-cyl, but excluding asymmetry which is derived separately. This approach enabled a clinically useful component, describing irregularity, to be derived from the limited number of data points available in this study. It does have one drawback. It requires symmetrically arranged data. This means that if one data point out of the twelve on the keratograph ring is too indistinct to be measured, the topography components cannot be calculated. (This was mentioned earlier in relation to table 6.1).

6.1.2 Application of topography components

The extraction of astigmatism measurements by considering the changes in curvature that occur as you move round a reflected ring through 360°, was described by Maloney et al [363]. This is useful in finding the sphero-cyl model that best fits the observed cornea.

In the case of a healing corneal transplant it is particularly important to be able to describe how much the cornea deviates from the ideal sphero-cylindrical form. A straight forward root mean square averaging of the deviations of the observed data, from the best fit sphero-cyl, can be done. In this approach, a perfectly sphero-cylindrical cornea which was not centred around the corneal vertex, would appear to have irregularity. It is much better to be able to consider asymmetry, and irregularity separately. A paper by Hjortdal et al [364] described the use of Fourier analysis to extract an asymmetry component, and a component for regular astigmatism.

This was done by using the first and second harmonics of the Fourier series. The formula for the second harmonic was the same as the formula derived by Maloney et al [363]. However, there was no real justification that the formula for the first harmonic truly represented asymmetry. It was therefore thought necessary to check the formula for asymmetry, by deriving it mathematically. This derivation is included in Appendix C.

6.1.3 Sequential follow-up

This study is prospective, and involves the sequential assessment of repeated measurements for a substantial number of patients over a period of up to 10 years, with 50 eyes contributing data at 6 years. Most studies have a much shorter follow-up period. The prospective study by Khong and her associates [62] was limited to 6 months. A recent paper by Tuft et al [365] included 184 patients who had received a corneal transplant for keratoconus. This was a retrospective examination of sequential assessments in the three years after suture removal. Unfortunately, measurements were limited to refraction and keratometry. It is interesting to note that Tuft [365] also found a wide inter-subject variation in the profile of change during this 3 year period.

One advantage of the long follow-up period employed for this thesis is that many of the operations date back to a period when selective suture removal was less common. The pressure for earlier visual rehabilitation, led to the introduction of these techniques, which make it difficult to chart the natural course of improvements in topography. Fortunately, very little data had to be discarded because it was influenced by these interventions. One problem of the long follow-up period is a high proportion of missing data, and lost to follow-up. This was in part due to death, and patients moving to other parts of the country. Keratoconics are thought to be particularly mobile in this respect. A study is open to question if it shows a gradual improvement in a parameter which is associated with a gradual diminution of the pool of subjects. There is always the suspicion that it is the subjects with the poorest response who drop out, causing the apparent improvement. In this study it was difficult to encourage patients to attend for regular measurements if they had been discharged from their out-patients clinic. It was thought that contact lens wearers might be over represented because they had to return on a regular basis for aftercare. Fortunately this was not the case. This can be seen by examining the group of patients who had the best record of attendance for the sequential assessments. That is to say the 65 who met the criteria for inclusion in the study. Almost exactly half of these were contact lens wearers, which is lower than the proportion given in two papers (60% [281] and 56% [71]).

Another potential bias is the fact that 10 patients had both eyes included in the study. However, a study by Woodward et al [366] on the likelihood of penetrating keratoplasty in keratoconics, has shown that there is no real association between the two eyes of the same subject. It is for this reason that terms such as inter-eye variation have been discarded, and inter-subject used in preference.

6.1.4 Other influences on topography

There are a number of factors which could also influence the observed changes in topography. In general these are not significant when compared to the gross irregularities to be found in corneal transplants. Clark [367] has detailed the potential sources of variation in topography, and Kwitko et al [368] have used a computerised videokeratoscope to demonstrate a diurnal variation in transplant topography. The observed changes are much higher than would be expected from the normal changes [369] in corneal curvature during adult life.

One factor which does have an influence on the observed topography, is contact lens wear. A number of authors [370, 371, 372, 373] have used computerised videokeratoscopes to document corneal topography changes induced by the rigid gas permeable contact lenses. Other studies have been carried out specifically to determine the effect on corneal transplants. Woodward et al [374] retrospectively analysed refractive and keratometric astigmatism, and found that the contact lens wearing group had a significantly greater reduction in astigmatism. Wilson et al [375] reported the results of a preliminary retrospective study. Results from the Corneal Modelling System, showed a reduction in astigmatism and an improved Surface Regularity Index, after a six month period of contact lens wear. However, only five patients were involved, and there was no control group. A slightly larger study was carried out by Sperber et al [376] who fitted contact lenses much later in the post-operative period, and found only 0.75D reduction in astigmatism.

The absence of a control group, in each of these two studies, serves to illustrate the need for model to show what changes could be expected, if contact lenses were not worn.

Unfortunately, it is not practical to ask corneal transplant patients to cease to wear their contact lenses for 48 hours prior to the assessment appointment in order to allow the effects of contact lens wear to settle. Often these patients are visually dependant on contact lens wear.

6.1.5 Results

6.1.5.(i) Asymmetry

Figure 5.6 shows a gradual reduction in the Asymmetry component over the whole post-operative period. Years eight, nine, and ten are an exception. The asymmetry appears to rise again during this period. However, it should be remembered that the number of eyes involved at this stage was reduced. The error bar for the ten year stage is understandably large. It is also possible that the group of subjects involved in the final part of the study may have been less homogeneous, and had higher representation of significant factors. For example repeat surgery, which is a determinant of slower reduction in irregularity.

Univariate Analysis

Some variables appear to be exhibiting a strong trend, yet they do not appear in the Multi-variate result. For instance interrupted sutures appear to have a deleterious effect in all of the pre-removal period. That is to say a higher starting value (intercept), and a slower decline, for both Astigmatism and Irregularity. These differences were never significant at the 5% level, and they do not appear in the multivariate model because there is a high correlation, between interrupted sutures, and a disparity >0. The >0 disparity group contains approximately 80% of the interrupted suture group.

Another variable which appeared to be having some effect was Aphakia. However it transpired that aphakia was correlated to the diagnosis group.

Multivariate model for Astigmatism

Storage

Transplants stored in MK medium had higher starting astigmatism compared to fresh transplants or those stored in K-Sol. This is a new finding. Many studies have compared different storage media, but generally this has been in terms of the ability to maintain the viability of material. The effect on the outcome, in terms of topography, has received little attention. It must be remembered that the MK group had a longer interval from donor death to the operation, and that this could also be a determining factor.

Disparity

Donor buttons which were cut larger than the recipient opening resulted in a slower decline in astigmatism. The literature on this subject is rather contradictory, with some studies favouring no disparity, while others produced less astigmatism with all over-size donor buttons (see table 1.3). It must be remembered that these studies are not sequential, they are not looking at the rate of improvement in astigmatism.

Previous Transplant

Repeat keratoplasty was found to influence the irregularity intercept, both before and after suture removal. No single factor affected the rate of reduction of Irregularity.

Perlman [49] found significantly less astigmatism with repeat keratoplasties. However, this was a retrospective study, and it did not take into account the time elapsed since surgery. There appeared to be a correlation between repeat surgery, and larger transplant diameters. Therefore, it seems likely that in most cases the surgeon chose to cut further out than the original transplant, thus removing the ring of scar tissue at the previous graft/host interface. If this is the case, then it is difficult to say why repeat keratoplasty should be a determinant of the slope of Irregularity.

Transplant Diameter

This variable was a strong contender for the major determinant of the Irregularity intercept. The effect of transplant diameter has been studied. One author [136] considered that smaller transplants (<6.5mm) create larger amounts of astigmatism. This was contradicted by Jensen and Maumenee [122] who found greater astigmatism for an eight mm diameter, compared to a seven mm diameter.

Diagnosis other than Keratoconus

If the graft diameter had been included in the final multivariate model, it would have been accompanied by diagnosis “other”, as the determinant of the slope, giving a slower decline of irregularity. A number of studies have investigated the effect of diagnosis on astigmatism. The majority [49, 121, 122, 123], of studies found no difference, while one [124] found higher astigmatism in keratoconics. Bigar [125] found the opposite.

Multivariate models for the combined pre- and post-suture removal period.

These models appear to indicate that suture removal is nothing more than a temporary perturbation in the time course of astigmatism or irregularity.

A number of papers [379, 59, 378] have described the topographical changes that occur when all the sutures are removed. Although corneal astigmatism changed unpredictably, and sometimes by large amounts when all the sutures were removed, the mean value for all the patients was unchanged in two of the studies [377, 327], and only changed by 0.52D in the third [378]. It should be born in mind that the model summarises the changes for all the subjects, even though there may be a very considerable inter-subject variation.

Further Research

A randomised study should be carried out in order to determine any relationship between topography and storage method, or storage time.

A study of changes in transplant curvature should be carried out using a true topography system, which gives heights rather than local radius of curvature. This would avoid the problem inherent in the Placido disc based systems; the fact that all readings must be related to corneal vertex. The raster stereography systems [511, 510, 273] might prove suitable.

6.2 Sensitivity

6.2.1 Sequential follow up

Most of the previous studies on corneal transplant resensitisation did not take sequential repeat measurements from the same eye. They examined a series of patients who had each reached a different point in the post-operative period. A single assessment of sensitivity was made of each eye. Some studies [303, 308] did make a few repeat measurements of the same eye, but they cannot be considered as truly sequential. Stamer et al [311] appear to have set out to perform a longitudinal study, including measurements up to the three year stage, but very little sequential data was reported. This thesis reports a prospective study which is truly sequential, and reports data for a substantial number of patients (66). The longest follow-up period was ten years, with the majority of patients (56) contributing data at the five year stage. Some previous studies reported results from longer post-operative periods, but these were generally isolated, non-sequential assessments. Stamer et al [311] recruited a larger number of patients (189), but only 36 of these gave data which showed changes over time in an individual patient.

6.2.2 Other influences on sensitivity

Millodot [346] has reviewed the factors which influence sensitivity in normal corneas. These include age, eye colour, time of day, and menstruation. These factors probably had relatively little effect, when considered against the changes following penetrating keratoplasty.

Local anaesthetics have an intentional, but short term effect on sensitivity. The duration of the effect of Benoxinate 0.4% has been reported [381] to be 30 minutes. A study by Polse et al [382] investigated the effects of dosage using a modified Cochet Bonnet aesthesiometer. They found a mean recovery time for 0.4% Benoxinate to be 52 minutes with a range of 30 - 60 minutes. Whereas Draeger [307] cites a study which found a recovery period of 15 minutes.

When patients in this study attended for research assessment, and for a clinic appointment on the same day, the sensitivity measurements were generally taken before tonometry was performed. If tonometry had been performed, the patient was asked to wait until a minimum of one hour had elapsed from the time of tonometry.

Contact lens wear also has a significant effect on corneal sensitivity [383, 384, 385, 386]. Half of the patients in this study were prescribed contact lenses at some point following suture removal. It was not practical to ask them to remove their lenses for 48 hours prior to a research assessment of sensitivity. The effects of contact lens wear can be seen in Figures 5.23, 5.24, and 5.25. These figures present a comparison between contact lens wearers, and non wearers. They show that contact lens wear appeared to depress sensitivity in the periphery of the transplant, but had little influence on the central area. This finding is difficult to explain. Initial experiments by Polse [387] indicated that the loss of sensitivity could be explained by trauma from the contact lens, which might allow the difference between the effect on the centre and periphery to be explained in terms of contact lens fit. However, subsequent experiments by Millodot and O`Leary [353] confirmed that contact lens induced loss of sensitivity was related to hypoxia, and not to trauma.

This differential effect on the transplant periphery had an effect on the assessment of the centripetal resensitisation, making it less obvious that sensitivity was progressing from the periphery towards the centre. Another possible reason for this, is the influence of apprehension on the subjective response [338]. When central sensitivity was assessed, the patients were often aware of the approach of the nylon filament towards their eye. This was less obvious when the four peripheral points were being assessed.

6.2.3 Results

The results of this prospective longitudinal study are in general agreement with earlier work. They show a slow but progressive recovery of touch sensitivity. The level of sensitivity is sometimes lower than in other reports. It is interesting to note that at the three year stage, Ruben and Colebrook [301] found that a third of their subjects had achieved normal sensitivity, whereas in this study the corresponding figure is 8%, with 74% having no measurable sensitivity. However, the difference in criteria for determining the threshold should be born in mind. Ruben and Colebrook [301] recorded the filament length that first elicited any response, whereas this study used a 50% response criteria, which is far more rigorous and tends to produce lower sensitivity readings.

The return of a small degree of sensitivity only at the six year stage, exhibited by one subject in this study, contradicts the view held by Ruben and Colebrook [301] that little or no resensitisation occurs after 4 years.

However, the most important finding which has arisen from the sequential data taken from the same patient, is the very large intra-subject variability. This is evident from the charts in Appendix I. This variability has implications for those studies which have sought to infer the trend of resensitisation by analysing data at only one point in the graft history.

The work of Beuerman and Schimmelpfennig [297] on corneal desensitisation suggests that the high incidence of hypoaesthesia or anaesthesia among transplants should have effects on the metabolism and healing properties of the epithelium. A number of authors [388, 389, 390, 391, 392, 393] have described abnormalities of the epithelium following keratoplasty, which are generally most evident in the first year. However, these abnormalities are neither permanent nor as severe as the clinical picture seen in neuroparalytic keratitis. The reasons for this are uncertain, but it is possible that the presence of functioning corneal nerves in the host periphery, or low levels of donor resensitisation, are sufficient to promote a more normal epithelial metabolism.

6.2.4 Further research

Our understanding of the resensitisation of corneal transplants would benefit from further histological studies of human corneal transplant material. The difficulty with this approach is that there are very few circumstances which lead to such tissue becoming available. Also there is no possibility of monitoring changes in innervation over a period of time. A non-invasive technique in vivo is required. Work by Auran et al [394] suggests that the Scanning Slit Confocal Microscope can be used to observe the basal epithelial nerve plexus, and also nerves as deep as the sub-epithelial plexus. It therefore appears that this instrument could be useful in the study of transplant reinnervation.

7. Summary and Conclusions

A prospective longitudinal study was carried out in order to investigate the changes which take place in corneal topography following penetrating keratoplasty. Changes in corneal touch sensitivity were also monitored.

Improvements in techniques have brought about higher success rates for penetrating keratoplasty. Originally, success was measured in terms of clarity, but much more attention is now paid to the quality of the visual outcome. High amounts of regular astigmatism, combined with some irregular astigmatism, can limit the potential of an otherwise technically successful transplant. This often leads to the necessity for contact lens wear, or in extreme cases, to refractive surgery.

Many studies have been carried out in order to determine how post-operative astigmatism can be reduced. These generally investigated how one particular factor influences the outcome. In some cases the results of these trials were contradictory. For example, the trials investigating the effect of disparity between donor and host diameters. Post-keratoplasty astigmatism has multiple origins, and the subjects in these trials may have differed in aspects other than disparity.

Some of these factors may have had an unknown effect on the outcome.
The analysis of the data in this thesis was carried out with multilevel modelling. This technique allowed the various factors to be analysed together, in order to determine their relative importance as determinants of astigmatism.

This study is also unique in that it uses sequential measurements of corneal topography. These permit analysis of the rate of change of topography.

The instrument used was a simple 7 ring photokeratoscope. An analysis system was developed which allowed keratograph measurements to be converted into topography components, which are meaningful in the clinical sense. The Regular Astigmatism and the Irregularity components were chosen for full multivariate analysis using multilevel modelling.

The factor which was most important in determining the starting astigmatism was the method of donor storage. MK medium gave higher starting values than K-sol or corneas which were fresh. The rate of change in the period up to suture removal was determined by the disparity between donor and host diameters. Donor buttons cut with the same trephine showed a more rapid reduction in astigmatism. No single factor determined the changes in astigmatism in the period following suture removal.

In the case of the Irregularity component, the most important factor determining the starting value, was whether there had been a previous penetrating keratoplasty operation in that eye. Repeat keratoplasties showed a higher starting value. No single factor determined the rate of change of Irregularity either before or after suture removal, and repeat keratoplasty continued to have a significantly higher starting value for the period after suture removal.

The surgeon faces many choices in deciding how to proceed, and these choices may sometimes be conflicting. It is hoped that the results of this analysis, giving the relative importance of the factors involved, will allow the compromise decisions to be made on a rational basis.

The results of the sensitivity trial indicate a slow but progressive return of corneal touch sensitivity. However there was a very wide inter-subject and intra-subject variation in resensitisation, which must be born in mind when interpreting any sensitivity data which was not obtained on a sequential basis.

1 Ry Andersen S. The eye and its diseases in antiquity. *Acta Ophthalmol* 1994 **72** (suppl 213)

2 cited by Rycroft BW. *Corneal Grafts.* Butterworths: London. 1955.

3 Elschnig A. Keratoplasty. *Arch Ophthalmol* 1930 **4** 165 - 173

4 Filatov VP. Transplantation of the cornea. *Arch Ophthalmol* 1935 **13** 321 - 347

5 Tudor Thomas JW. Considerations affecting technique and results in keratoplasty. *Trans Ophthal Soc UK* 1955 **75** 473 - 512

6 Vannas M. Some suggestions for improved operating technique in corneal transplantation. *Albrecht v Graefes Arch Ophthalmol* 1939 **140** 709 - 794

7 Castroviejo A. Results of corneal transplantation. *Arch Ophthalmol* 1938 **19** 834 - 835

8 Iliff CE, Castroviejo R, Hughes WF, King JH, Zimmerman LE. Present status of corneal transplant surgery. *Trans Am Acad Ophthal Oto-lar* 1963 **67** 292 - 319

9 Paton D. Advances in keratoplasty, 1971. *Ophthalmic Surg* 1971 **2** (6) 236 - 242

10 Castroviejo R. Indications and contraindications for keratoplasty and keratectomies. *Am J Ophthalmol* 1946 **29** 1081 - 1089

11 Franceschetti A. Corneal grafting. *Trans Ophthal Soc UK* 1949 **69** 17 - 35

12 Castroviejo R. Present status of keratoplasty. *Arch Ophthalmol* 1939 **22** 114 - 126

13 Paton RT. Corneal transplantation: A review of 365 operations. *Trans Am Ophthalmol Soc* 1953 **51** 581 - 609

14 Arentsen JJ, Morgan B, Green WR. Changing indications for keratoplasty. *Am J Ophthalmol* 1976 **81** (3) 313 - 318

15 Morris RJ, Bates AK. Changing indications for keratoplasty. *Eye* 1989 **3** 455 - 459

16 Australian Corneal Graft Registry. *Aust NZ J Ophthalmol* 1993 **21** (2 suppl) 1 - 48

17 Benson WH, Goosey CB, Prager TC, Goosey JD. Visual improvement as a function of time after lamellar keratoplasty for keratoconus. *Am J Ophthalmol* 1993 **116** 207 - 211

18 Williams KA, White MA, Ash JK, Coster DJ. Leukocytes in the graft bed are associated with corneal graft failure: analysis by immunohistology and actuarial graft survival. *Ophthalmology* 1989 **96** 38 - 44

19 Danneffel MB, Sugar A. Incidence of HIV antibody-positive eye/cornea donors in hospital versus medical examiner cases. *Cornea* 1990 **9** (3) 271 - 272

20 Centers for Disease Control. USPHS. Draft guidelines for prevention of transmission of HIV through transplantation of human tissue and organs. Nov 1993. 1993

21 Caron MJ, Wilson R. Review of the risk of HIV infection through corneal transplantation in the United States. *J Am Optom Assoc* 1994 **65** (3) 173 - 178

22 Flowers CW, McLeod SD, McDonnell PJ, Smith RE. Changing indications for penetrating keratoplasty. *Cornea* 1995 **14** (6) 583 - 588

23 Orlin SE, Hertle R, Raber IM. Neonatal penetrating keratoplasty.(Castroviejo Cornea Society abstracts) *Cornea* 1994 **13** (1) 98

24 De Cock R. Penetrating keratoplasty in the West Bank and Gaza. *Eye* 1994 **8** 29 - 34

25 Mamalis N, Anderson CW, Kreisler KR, Lundergan MK, Olson RJ. Changing trends in the indications for penetrating keratoplasty. *Arch Ophthalmol* 1992 **110** 1409 - 1411

26 Hyman L, Yang C, Wittpenn J, Stark W. Indications and techniques of penetrating keratoplasty: 1985-1988. *Invest Ophthalmol Vis Sci (supp.)* 1990 **30** 269

27 Mohamadi P, McDonnel JM, Irvine JA. Changing indications for penetrating keratoplasty. 1984-1988. *Am J Ophthalmol* 1989 **107** 550 - 552

28 Brady SE. Clinical indications and procedures associated with penetrating keratoplasty. 1983-1988. *Am J Ophthalmol* 1989 **108** 118 - 122

29 Lindquist TD, McGlothan JS, Rotkis WM, Chandler JW, Indications for penetrating keratoplasty: 1980-1988. *Cornea* 1991 **10** (3) 210 - 216

30 Robin JB, Gindi JJ, Koh K, Schanzlin DJ, Rao NA, York KK, Smith RE. An update of the indications for penetrating keratoplasty. *Arch Ophthalmol* 1986 **104** 87 - 89

31 Smith RE, McDonald HR, Nesburn AB, Minckler DS. Penetrating keratoplasty. Changing indications, 1947 to 1978. *Arch Ophthalmol* 1980 **98** 1226 - 1229

32 Vail A, Gore SM, Bradley BA, Easty DL, Rogers CA. Corneal transplantation in the United Kingdom and Republic of Ireland. *Br J Ophthalmol* 1993 **77** 650 - 656

33 Ainslie D. Corneal grafting: a comparison between then and now. *Trans Ophthal Soc UK* 1974 **94** 137 - 143

34 Ainslie D. A survey of 100 penetrating corneal grafts. *Trans Ophthal Soc UK* 1959 **79** 209 - 220

35 Kervick GN, Shepherd WFI. Changing indications for penetrating keratoplasty. *Ophthalmic Surg* 1990 **21** (3) 227

36 Sharif KW, Casey TA. Changing indications for penetrating keratoplasty, 1971-1990. *Eye* 1993 **7** 485 - 488

37 Legeais JM, Labetoulle M, Renard G, Gaillot D, Pouliquen Y. Indications for penetrating keratoplasty. An eleven years retrospective study of 2962 cases. *J Fr Ophtalmol* 1993 **16** (10) 516 - 522

38 Brooks AM, Weiner JM. Indications fot penetrating keratoplasty: a clinicopathological review of 511 corneal specimens. *Aust NZ J Ophthalmol* 1987 **15** (4) 277 - 281

39 Damji KF, Rootman J, White VA, Dubord PJ, Richards JS. Changing indications for penetrating keratoplasty in Vancouver, 1978-87. *Can J Ophthalmol* 1990 **25** (5) 243 - 248

40 Saeed N, Khan MD. A 4-year review of keratoplasty in Pakistan. *Pakistan J Ophthalmol* 1989 **5** (4) 99 - 102

41 Moghal KI. Corneal transplant surgery in Rawalpindi. *Pakistan J Ophthalmol* 1989 **5** (4) 115 - 117

42 Tahija SG, Sukardi I, GondhowiarjoTD, Humurwono GB. Penetrating keratoplasty in Indonesia. *Refract Corneal Surg* 1991 **7** 466

43 Xiu An Zhu, Feng Ming Li. A survey of penetrating keratoplasty in China. *Refract Corneal Surg* 1991 **7** 466 - 467

44 Nenno C, Abel R. Corneal transplant statistics in the United States. *Refract Corneal Surg* 1991 **7** 467 - 468

45 Uhm SL, Chung SK, Myung YW, Rhee SW. Clinical analysis of keratoplasty over 23 year time span. *J Korean Ophthalmol Soc* 1991 **32** 421 - 429

46 Claoue C, Falcon M, Shilling J. Penetrating keratoplasty in South East London 1981-1986: epidemiological aspects and demands on medical resources. *J R Soc Med* 1990 **83** 245 - 248

47 Kaplan M. Results in corneal transplant surgery. *Ann Ophthalmol* 1971 **3** 490 - 493

48 Paton D. The principal problems of penetrating keratopolasty: graft failure and graft astigmatism. *Trans New Orleans Acad Ophthalmol: Symposium on medical and surgical disease of the cornea.* 1980 248 - 283

49 Perlman EM. An analysis and interpretation of refractive errors after penetrating keratoplasty. *Ophthalmology* 1981 **88** 39 - 45

50 Price FW, Whitson WE, Marks RG. Progression of visual acuity after penetrating keratoplasty. *Ophthalmology* 1991 **98** 1177 - 1185

51 Samples JR, Binder PS. Visual acuity, refractive error, and astigmatism following corneal transplantation for pseudophakic bullous keratopathy. *Ophthalmology* 1985 **92** 1554 - 1560

52 Troutman RC, Lawless MA. Penetrating keratoplasty for keratoconus. *Cornea* 1987 **6** (4) 298 - 305

53 Amsler M. Keratographic observations on grafts. *Ann Oculist* 1947 **180** 746 - 748

54 Amsler M. The tectonic nature of perforating corneal grafts. *Arch Ophthalmol Paris* 1950 **10** 589 - 592

55 cited by Rycroft BW. *Corneal Grafts.* Butterworths: London. 1955.

56 Pouliquen Y, Drilevitch J, Giraud J-P. Etude de l'astigmatisme residuel apres keratoplasties trasfixiantes dans le keratocone. *Archs Ophtal, Paris* 1976 **36** 555 - 564

57 Ruben M, Colebrook E. Keratoconus keratoplasty curvatures and contact lens wear. *Br J Ophthalmol* 1979 **63** (4) 268 - 273

58 Pallikaris I. Die praoperative placidophotographie bei keratokonus und ihre bedeutung im zusammenhang mit dem postoperativen astigmatismus. *Albrecht v Graefes Arch Klin exp Ophthal* 1980 **213** 87 - 99

59 Lin DT, Wilson SE, Reidy JJ, Klyce SD, Mcdonald MB, Insler MS, Kaufman HE. Topographic changes that occur with 10-0 running suture removal following penetrating keratoplasty. *Refract Corneal Surg* 1990 **6** 21 - 25

60 Strelow S, Cohen EJ, Leavitt KG, Laibson PR. Corneal topography for selective suture removal after penetrating keratoplasty. *Am J Ophthalmol* 1991 **112** 657 - 665

61 Maguire LJ, Bourne WM. Corneal topography of transverse keratotomies for astigmatism after penetrating keratoplasty. *Am J Ophthalmol* 1989 **107** (4) 323 - 330

62 Khong AM, Mannis MJ, Plotnick RD, Johnson CA. Computerized topographical analysis of the healing graft after penetrating keratoplasty for keratoconus. *Am J Ophthalmol* 1993 **115** 209 - 215

63 Carney LG, Jacobs RJ. Problems remaining after successful keratoplasty for keratoconus. *Clin Exp Optom* 1989 **72** (1) 22 - 25

64 Wicker D, Sanislo S, Green DG. Effect of contact lens correction on sine wave contrast sensitivity in keratoconus patients after penetrating keratoplasty. *Optom Vision Sci* 1992 **69** (5) 342 - 346

65 Mannis MJ, Zadnik K, Johnson CA, Adams C. Contrast sensitivity after penetrating keratoplasty. *Arch Ophthalmol* 1987 **105** 1220 - 1223

66 Mannis MJ, Zadnik K, Johnson CA. The effect of penetrating keratoplasty on contrast sensitivity in keratoconus. *Arch Ophthalmol* 1984 **102** 1513 - 1516

67 Rowsey JJ, Rubin ML. Refraction problems aftrer refractive surgery. *Surv Ophthalmol* 1988 **32** (6) 414 - 420

68 Mannis MJ, Zadnik K. Refracting the corneal graft. *Surv Ophthalmol* 1990 **34** (6) 436 - 440

69 Smiddy WE, Hamburg TR, Kracher GP, Stark WJ. Keratoconus. Contact lens or keratoplasty? *Ophthalmology* 1988 **95** 487 - 492

70 Smiddy WE, Hamburg TR, Kracher GP, Stark WJ. Visual correction following penetrating keratoplasty. *Ophthalmic Surg* 1992 **23** (2) 90 - 93

71 Lass JH, Lembach RG, Park SB, Hom DL, Fritz ME, Svilar GM, Nuamah IF, Reinhart WJ, Stocker EG, Keates RH, Moran CT, Cobo LM, Foulks GN. Clinical management of keratoconus. *Ophthalmology* 1990 **97** 433 - 445

72 Woodward EG. Contact lens fitting after keratoplasty *J Br Contact Lens Assoc* 1981 **4** (2) 42 - 49

73 Lopatynsky M, Cohen EJ, Leavitt KG, Laibson PR. Corneal topography for rigid gas permeable lens fitting after penetrating keratoplasty. *CLAO J* 1993 **19** (1) 41 - 44

74 Beekhuis WH, van Rij G, Eggink FA, Vreugdenhil W, Schoevaart CE. Contact lenses following keratoplasty. *CLAO J* 1991 **17** (1) 27 - 29

75 Mannis MJ, Zadnik K, Deutch D. Rigid contact lens wear in the corneal transplant patient. *CLAO J* 1986 **12** (1) 39 - 42

76 Astin CL. Fitting corneal grafts - some unusual cases. *J Br Contact Lens Assoc* 1990 **13** (1) 88 - 90

77 Daniel R. Fitting contact lenses after keratoplasty. *Br J Ophthalmol* 1976 **60** 263 - 265

78 Yu DD, Kletzky DL, Lemp MA. Corneal graft dehiscence secondary to suction-cup device use for contact lens removal. *Arch Ophthalmol* 1992 **110** 1050 - 1051

79 Davis LJ. Rigid gas permeable extended wear (RGPEW) for the postoperative patient: a review and clinical observations. *J Am Optom Assoc* 1994 **65** (3) 179 - 186

80 Zadnik K. Contact lenses in the geriatric patient. *J Am Optom Assoc* 1994 **65** (3) 193 - 197

81 Woodward EG. The role of rigid contact lenses in the management of keratoconus. *J Br Contact Lens Assoc* 1991 **14** (4) 211 - 217

82 Williams KA, Ash JK, Pararajasegaram P, Harris S, Costner DJ. Long-term outcome after corneal transplantation. Visual result and patient perception of success. *Ophthalmology* 1991 **98** (5) 651 - 657

83 Coster DJ. Some factors which affect the visual outcome of corneal transplantation. *Eye* 1991 **5** 265 - 278

84 Bates WH. A suggestion of an operation to correct astigmatism. *Arch Ophthalmol* 1894 **23** 9 - 13

85 Barner SS. Surgical treatment of corneal astigmatism. *Ophthalmic Surg* 1976 **7** (1) 43 - 48

86 Troutman RC. Microsurgical control of corneal astigmatism in cataract and keratoplasty. *Trans Am Acad Ophthal Oto-lar* 1973 **77** 563 - 572

87 Frucht-Pery J. Wedge resection for postkeratoplasty astigmatism. *Ophthalmic Surg* 1993 **24** (8) 516 - 518

88 van Rij G, Vijfvinkel G. Correction of postkeratoplasty astigmatism by razor blade and V-shaped knife wedge resection. *Ophthalmic Surg* 1983 **14** (5) 406 - 410

89 Jensen RP, Jensen AC. Surgical correction of astigmatism by microwedge resection of the limbus. *Ophthalmology* 1978 **85** 1288 - 1298

90 van Rij G, Waring GO. Changes in corneal curvature induced by sutures and incisions. *Am J Ophthalmol* 1984 **98** 773 - 783

91 Lugo M, Donnenfeld ED, Arensten JJ. Corneal wedge resection for high astigmatism following penetrating keratoplasty. *Ophthalmic Surg* 1987 **18** (9) 650 - 653

92 Troutman RC. *Microsurgery of the anterior segment of the eye: the cornea, optics and surgery.* Mosby. St. Louis. 1977 p 286.

93 Krachmer JH, Fenzl RE. Surgical correction of high postkeratoplasty astigmatism. Relaxing incision vs wedge resection. *Arch Ophthalmol* 1980 **98** 1400 - 1402

94 Price NC, Steele ADMcD. The correction of post-keratoplasty astigmatism. *Eye* 1987 **1** 562 - 566

95 Mandel MR, Shapiro MB, Krachmer JH. Relaxing incisions with augmentation sutures for the correction of postkeratoplasty astigmatism. *Am J Ophthalmol* 1987 **103** 441 - 447

96 Fronterre A, Portesani GP. Relazing incisions for postkeratoplasty asigmatism. *Cornea* 1991 **10** (4) 305 - 311

97 Lustbader JM, Lemp MA. The effect of relaxing incisions with multiple compression sutures on post-keratoplasty astigmatism. *Ophthalmic Surg* 1990 **21** (6) 416 - 419

98 McCartney DL, Whitney CL, Stark WJ, Wong SK, Bernitsky DA. Refractive keratoplasty for disabling astigmatism after penetrating keratoplasty. *Arch Ophthalmol* 1987 **105** 954 - 957

99 Limberg MB. Dingeldein SA, Green MT, Klyce SD, Insler MS, Kauffman HE. Corneal compression sutures for the reduction of astigmatism after penetrating keratoplasty. *Am J Ophthalmol* 1989 **108** 36 - 42

100 Saragoussi JJ, Abenhaim A, Waked N, Koster HR, Pouliquen YJ. Results of transverse keratotomies for astigmatism after penetrating keratoplasty: A retrospective study of 48 consecutive cases. *Refract Corneal Surg* 1992 **8** 33 - 38

101 Duffey RJ, Jain VN, Tchah H, Hoffmann RF, Lindstrom RL. Paired arcuate keratotomy. A surgical approach to mixed and myopic astigmatism. *Arch Ophthalmol* 1988 **106** 1130 - 1135

102 Arffa RC. Results of a graded relaxing incision technique for post keratoplasty astigmatism. *Ophthalmic Surg* 1988 **19** (9) 624 - 628

103 Merck MP, Williams PA, Lindstrom RL. Trapezoidal keratotomy. A vector analysis. *Ophthalmology* 1986 **93** 719 - 726

104 Lindstrom RL. Surgical correction of refractive errors after penetrating keratoplasty. *Int Ophthalmol Clin* 1994 **34** 35 - 53

105 Forstot SL. Modified relaxing incision technique for postkeratoplasty astigmatism. *Cornea* 1988 **7** (2) 133 - 137

106 Lundergan MK, Rowsey JJ. Relaxing incisions. Corneal topography. *Ophthalmology* 1985 **92** 1226 - 1236

107 Frangieh GT, Kwitko S, McDonnell PJ. Prospective corneal topographic analysis in surgery for postkeratoplasty astigmatism. *Arch Ophthalmol* 1991 **109** 506 - 510

108 Price FW, Whitson WE. The art of surgical correction for postkeratoplasty astigmatism. *Int Ophthalmol Clin* 1991 **31** (1) 59 - 67

109 Krachmer JH, Ching SS. Relaxing corneal incisions for postkeratoplasty astigmatism. *Int Ophthalmol Clin* 1983 **23** 153 - 159

110 Vrabec MP, Florakis GF, Krachmer JH. Corrective surgery for astigmatism. *Int Ophthalmol Clin* 1988 **28** (2) 145 - 149

111 Troutman RC. Corneal wedge resections and relaxing incisions for postkeratoplasty Astigmatism. *Int Ophthalmol Clin* 1983 **23** 161 - 168

112 Troutman RC, Gaster RN. Surgical advances and results of keratoconus. *Am J Ophthalmol* 1980 **90** 131 - 136

113 Goble RR, Hardman Lea SJ, Falcon MG. The use of the same size host and donor trephine in penetrating keratoplasty for keratoconus. *Eye* 1994 **8** 311 - 314

114 Sharif KW, Casey TA. Penetrating keratoplasty for keratoconus: complications and long-term success. *Br J Ophthalmol* 1991 **75** 142 - 146

115 Kirkness CM, Ficker LA, Steele AD, Rice NS. The success of penetrating keratoplasty for keratoconus. *Eye* 1990 **4** 673 - 688

116 Gibralter R, Trokel SL. Correction of irregular astigmatism with the excimer laser. *Ophthalmology* 1994 **101** 1310 - 1315

117 Campos M, Hertzog L, Garbus J, Lee M, McDonnell PJ. Photorefractive keratectomy for severe postkeratoplasty astigmatism. *Am J Ophthalmol* 1992 **114** 429 - 436

118 Judge D, Gordon L, Vander-Zwaag, Wood TO. Refractive versus keratometric astigmatism postkeratoplasty. *Refract Corneal Surg* 1990 **6** (3) 174 - 178

119 van Rij G, Waring GO. Configuration of corneal trephine opening using five different trephines in human donor eyes. *Arch Ophthalmol* 1988 **106** 1228 - 1233

120 Hardten DR, Holland EJ, Doughman DJ, Nelson JD, Evangelista AW, Ketchman JM. Clinical and anatomical study of the effect of transscleral fixation of posterior chamber lenses on early postkeratoplasty astigmatism. *Cornea* 1993 **12** (4) 282 - 288

121 Cherry PM, Pashby RC, Tadros ML, Wolf A, Chipman ML, Basu PK, Dixon WS, Hunter WS, Thompson GA. An analysis of corneal transplantation:II Postoperative astigmatism. *Ann Ophthalmol* 1979 **11** 669 - 672

122 Jensen AD, Maumenee AE. Refractive errors following keratoplasty. *Trans Am Ophthalmol Soc* 1974 **72** 123 - 131

123 Wilson SE, Bourne WM. Effect of recipient-donor trephine size disparity on refractive error in keraoconus. *Ophthalmology* 1989 **96** 299 - 305

124 Schwobel M. Der postoperative astigmatismus nach perforierenden keratoplastiken. *Albrecht v Graefes Arch klin exp Ophthal* 1975 **196** 61 - 69

125 Bigar F. Die perforierende Keratoplastik - ein keratorefraktiver Eingriff. *Klin Mbl Augenheilk* 1987 **190** 268 - 269

126 Insler MS, Cooper HD, Caldwell DR. Final surgical results with a suction trephine. *Ophthalmic Surg* 1987 **18** (1) 23 - 27

127 Binder PS. Selective suture removal can reduce postkeratoplasty astigmatism. *Ophthalmology* 1985 **92** 1412 - 1416

128 Au YK, Mahjoub SB, Reynolds MD, Hart JC. Effect of recipient lamellar keratectomy on corneal topography in penetrating keratoplasty. *CLAO J* 1990 **16** (4) 306 - 307

129 Katz HR, Forster RK. Intraocular lens calculation in combined penetrating keratoplasty, cataract extraction and intraocular lens implantation. *Ophthalmology* 1985 **92** 1203 - 1207

130 Binder PS. The effect of suture removal on postkeratoplasty astigmatism. *Am J Ophthalmol* 1988 **105** 637 - 645

131 Dave AS, McCulley JP. Demonstration of feasability of application of a portable keratometer to cadaveric donor corneas. *Cornea* 1994 **13** (5) 379 - 382

132 Pfister RR, Breaud S. Aphakic refractive penetrating keratoplasty using newborn donor corneas. A preliminary report on an alternative approach to refractive correction. *Ophthalmology* 1983 **90** 1207 - 1212

133 Chen JQ. Refractive evaluation of donor corneas from the newborn in aphakic penetrating keratoplasty. *Chung-Hua-Yen-Ko-Tsa-Chih* 1993 **29** (4) 224 - 226

134 Koenig SB. Donor age.In Chapt 43(Donor selection) in *Corneal surgery. Theory, technique and tissue. 2nd ed. Edited by Brightbill FS.* 1993

135 Gloor P, Keech RV, Krachmer JH. Factors associated with high postoperative myopia after penetrating keratoplasties in infants. *Ophthalmology* 1992 **99** 775 - 779

136 Buxton NJ, Buxton DF, Westphalen JA. Indications and contraindications. Chapt 8 in *Corneal surgery. Theory, technique and tissue. 2nd ed. Edited by Brightbill FS.* 1993

137 Olson RJ. Corneal curvature changes associated with penetrating keratoplasty: A mathematical model. *Ophthalmic Surg* 1980 **11** (12) 838 - 842

138 Olson RJ, Kaufman HE. A mathematical description of causative factors and prevention of elevated intraocular pressure after keratoplasty. *Invest Ophthalmol Vis Sci* 1977 **16** 1085 - 1092

139 Olson RJ. Aphakic keratoplasty:Determining donor size to avoid elevated intraocular pressure. *Arch Ophthalmol* 1978 **96** 2274 - 2276

140 Sugar J. Phakic keratoplasty. Chapt. 11 in *Corneal surgery. Theory, technique and tissue. 2nd ed. Edited by Brightbill FS.* 1993

141 Girard LJ, Esnaola N, Rao R, Barnett L, Rand WJ. Use of grafts smaller than the opening for keratonic myopia and astigmatism. A prospective study. *J Cataract Refract Surg* 1992 **18** 380 - 384

142 Heideman DG, Sugar A, Meyer RF, Musch DC. Oversized donor grafts in penetrating keratoplasty. A randomized trial. *Arch Ophthalmol* 1985 **103** 1807 - 1811

143 Bourne WM, Davison JA, O'Fallon WM. The effects of oversize donor buttons on postoperative intraocular pressure and corneal curvature in aphakic penetrating keratioplasty. *Ophthalmology* 1982 **89** 242 - 246

144 Duran JA, Malvar A, Diez E. Corneal dioptric power after penetrating keratoplasty. *Br J Ophthalmol* 1989 **73** 657 - 660

145 Troutman RC. *Microsurgery of the anterior segment of the eye: the cornea, optics and surgery.* Mosby, St. Louis. 1977

146 Perl T, Charlon KH, Binder PS. Disparate diameter grafting. Astigmatism, intraocular pressure. and visual acuity. *Ophthalmology* 1981 **88** 774 - 781

147 Olson RJ, Mattingly TP, Waltman SR, Kaufman HE. Refractive variation and donor tissue size in aphakic keratopkasty. A prospective randomized study. *Arch Ophthalmol* 1979 **97** 1480 - 1481

148 Tuft SJ, Fitzke FW, Buckley RJ. Myopia following penetrating keratoplasty for keratoconus. *Br J Ophthalmol* 1992 **76** 642 - 645

149 Lanier JD, Bullington RH, Prager TC. Axial length in keratoconus. *Cornea* 1992 **11** (3) 250 - 254

150 Girard LJ, Eguez I, Esnaola N, Barnett L, Maghraby A. Effect of penetrating keratoplasty using grafts of various sizes on keratoconic myopia and astigmatism. *J Cataract Refract Surg* 1988 **14** 541 - 547

151 Perry HD, Foulks GN. Oversize donor buttons in corneal transplantation surgery for keratoconus. *Ophthalmic Surg* 1987 **18** (10) 751 - 752

152 Foulks GN, Perry HD, Dohlman CH. Oversize corneal grafts in penetrating keratoplasty. *Ophthalmology* 1979 **86** 490 - 494

153 Javadi MA, Mohammadi MJ, Mirdehghan SA, Sajjadi SH. A comparison between donor-recipient corneal size and its effect on the ultimate refractive error induced in keratoconus. *Cornea* 1993 **12** (3) 401 - 405

154 Cohen KL, Tripoli NK, Pellom AC, Kupper LA, Fryczkowski AW. Effect of tissue fit on corneal shape after transplantation. *Invest Ophthalmol Vis Sci* 1984 **25** 1226 - 1231

155 Mahjoub SB, Au Y. Astigmatism and tissue-shape disparity in penetrating keratoplasty. *Ophthalmic Surg* 1990 **21** (3) 187 - 190

156 Troutman RC, Swinger CA, Belmont S. Selective positing of the donor cornea in penetrating keratoplasty for keratoconus: postoperative astigmatism. *Cornea* 1984 **3** 135 - 139

157 Belmont SC, Troutman RC, Buzard KA. Control of astigmatism aided by intraoperative keratometry. *Cornea* 1993 **12** (5) 397 - 400

158 van Rij G, Cornell FM, Waring GO, Wilson LA, Beekhuis WH. Postoperative astigmatism after central vs eccentric penetrating keratoplasties. *Am J Ophthalmol* 1985 **99** 317 - 320

159 Hallerman W. Keratoplastik und keratoprothesen. Probleme der keratoplastik. *Ber Dtsch Ophthalmol Ges* 1972 **71** 279 - 289

160 Olson RJ. The effect of scleral fixation ring placement and trephine tilting on keratoplasty wound size and donor shape. *Ophthalmic Surg* 1981 **12** 23 - 26

161 Krumeich J, Binder PS, Knulle A. The theoretical effect of trephine tilt on postkeratoplasty astigmatism. *CLAO J* 1988 **14** (4) 213 - 219

162 Cohen KL, Holman RE, Tripoli NK, Kupper LL. Effect of trephine tilt on corneal button dimensions. *Am J Ophthalmol* 1986 **101** 722 - 725

163 Olson RJ. Variation in corneal graft size related to trephine technique. *Arch Ophthalmol* 1979 **97** 1323 - 1325

164 Tilanus M, van Rij G. An experimental comparison of three methods for trephination of the cornea and the consequent variations in the configurations of the trephine openings. *Graefes Arch Clin Exp Ophthalmol* 1987 **225** 50 - 52

165 Michaelson IC. Slope of sides of corneal grafts and recipient beds. *Br J Ophthalmol* 1954 **38** (19) 19 - 21

166 Brightbill FS, Polack FM, Slappey T. A comparison of two methods for cutting donor corneal buttons. *Am J Ophthalmol* 1973 **75** (3) 500 - 506

167 Duffin RM, Olson RJ. Laboratory analysis of the Lieberman corneal punch. *Ophthalmic Surg* 1983 **14** (2) 153 - 155

168 Troutman RC. *Microsurgery of the anterior segment of the eye: the cornea, optics and surgery.* Mosby, St. Louis. 1977

169 Olson RJ. Variation in disposable corneal trephine sharpness. *Ophthalmic Surg* 1984 **15** (7) 590 - 591

170 Olson RJ. Modulation of postkeratoplasty astigmatism by surgical and suturing techniques. *Int Ophthalmol Clin* 1983 **23** 137 - 151

171 Polack FM, Capella J. A corneal punch. *Am J Ophthalmol* 1969 **67** 966 - 967

172 Bourne WM. A corneal trephine press. *Trans Am Acad Ophthal Oto-lar* 1973 **77** 479 - 480

173 Brightbill FS, Calkins B. New forceps and cutting block for donor corneas. *Am J Ophthalmol* 1980 **89** (5) 744 - 745

174 Tanne E. A new donor cutting block for penetrating keratoplasty. *Ophthalmic Surg* 1981 **12** (5) 371 - 372

175 Vrabec MP, Krachmer JH, Florakis GJ. Iowa PK press for donor corneas - a comparative study of donor corneal shape. *Refract Corneal Surg* 1992 **8** 475 - 477

176 Pflugfelder SC, Parel JM, Denham D, Mandelbaum S. A suction trephine block for marking donor corneal buttons. *Arch Ophthalmol* 1988 **106** 276 - 281

177 Gorovoy MS, Stern GA. A new technique for insuring proper suture alignment in penetrating keratoplasty. *Cornea* 1982 **1** 263 - 267

178 Ducker GI, Nolle B. A new cornea marking device for penetrating keratoplasty and refractive corneal procedures. *Ophthalmologica* 1995 **209** 25 - 26

179 Hope-Ross MW, McDonnell PJ, Corridan PG, Naylor G, Tan-Yee A. The management of post-keratoplasty astigmatism by post-operative adjustment of a single continuous suture. *Eye* 1993 **7** 625 - 628

180 Lin DT, Wilson SE, Reidy JJ, Klyce SD, McDonald MB, Kaufman HE, McNeill JI. An adjustable single running suture technique to reduce postkeratoplasty astigmatism. A preliminary report. *Ophthalmology* 1990 **97** 934 - 938

181 Clinch TE, Thompson HW, Gardner BP, Kaufman SC, Kaufman HE. An adjustable double running suture technique for keratoplasty. *Am J Ophthalmol* 1993 **116** 201 - 206

182 Arato S. A new electro-motor cornea- trephine for keratoplasty. *Ophthalmologica* 1951 **121** 38 - 40

183 Kadesky D. An electric automatic trephine. *Am J Ophthalmol* 1951 **34** 1038

184 Schanzlin DJ, Robin JB, Spence DJ. Clinical and ultrastructure analysis of variable speed corneal trephination. *Ophthalmic Surg* 1983 **14** 755 - 758

185 Crock GW, Pericic L, Rajendran B, Chapman-Smith JS, Carroll N, Maclean H, Scrimgeour J. A new system of microsurgery for human and experimental corneal grafting. *Br J Ophthalmol* 1978 **62** 81 - 85

186 Lieberman DM. The single point cam guided trephine: An interim report. *Ophthalmic Surg* 1981 **12** (3) 185 - 189

187 Lieberman DM. A new corneal trephine. *Am J Ophthalmol* 1976 **81** (5) 684 - 685

188 Hessburg PC, Barron M. A disposable corneal trephine. *Ophthalmic Surg* 1980 **11** (10) 730 - 733

189 Duffin RM, Olson RJ, Ohrloff C. Analysis of the Hessburg.Barron vacuum trephine. *Ophthalmic Surg* 1984 **15** (1) 51 - 54

190 Belmont SC, Zimm JL, Storch RL, Draga A, Troutman RC. Astigmatism after penetrating keratoplasty using the Krumeich guided trephine system. *Refract Corneal Surg* 1993 **9** 250 - 254

191 Bull H, Deutschmann S, Schlote H-W. Doppelt gefuhrtes vakuumtrepansystem,, asmotom " *Fortschr Ophthalmol* 1991 **88** 574 - 576

192 Waring GO, Hanna KD. The Hanna suction punch block and trephine system for penetrating keratoplasty *Arch Ophthalmol* 1989 **107** 1536 - 1539

193 Pouliquen Y, Ganem J, Hanna K, Saragoussi JJ. New trephine for keratoplasty (Hanna trephine). *Dev Ophthalmol* 1985 **11** 99 - 102

194 Serdarevic ON, Hanna K, Gribomont AC, Savoldelli M, Renard G, Pouliquen Y. Excimer laser trephination in penetrating keratoplasty. *Ophthalmology* 1988 **95** 493 - 505

195 Naumann GO, Seitz B, Lang GK, Langenbucher A, Kus MM. 193 nm excimer laser trephination in perforating keratoplasty. Report of 70 patients. *Klin Monatsbl Augenheilkd* 1993 **203** (4) 252 - 61

196 Lieberman DM, Troutman RC. The theory of " other than round " corneal transplantation. *Refract Corneal Surg* 1992 **8** 97 - 100

197 Lang GK, Naumann G, Koch J. A new elliptical incision for corneal transplantation using an excimer laser. *Arch Ophthalmol* 1990 **108** 914 - 915

198 McNeill JI, Goldman KN, Kaufman HE. Combined scleral ring and blepharostat. *Am J Ophthalmol* 1977 **83** 592 - 593

199 Stevens JD, Steele AD. Straight needle corneal splinting for anterior segment surgery. *Ophthalmic Surg* 1994 **25** (4) 259 - 261

200 Rennie L, Fleming W, Clark D, Ellerton C, Bosanquet R. Some mechanical properties of 10/0 monofilament nylon sutures. *Eye* 1994 **8** 343 - 345

201 Frueh BE, Feldman ST, Feldman RM, Sossi NP, Frucht-Pery J, Brown SI. Running nylon suture dissolution after penetrating keratoplasty. *Am J Ophthalmol* 1992 **113** 406 - 411

202 Temnycky GO, Lindahl KJ, Aquavella JV, Erdey RA. Early visual rehabilitation following keratoplasty usingle a single continuous adjustable suture technique. *Ophthalmic Surg* 1991 **22** (4) 208 - 212

203 Frueh BE, Brown SI, Feldman ST. 11-0 Mersilene as running suture for penetrating keratoplasty. *Am J Ophthalmol* 1992 **114** 675 - 679

204 Ramselaar JA, Beekhuis WH, Rijneveld WJ, van Andel MV, Dijk F. Mersilene (polyester), a new suture for penetrating keratoplasty. *Doc Ophthalmol* 1992 **82** 89 - 101

205 Bertram BA, Drews-Botsch C, Gemmill M, Gueli J, Murad M, Waring GO. Complications of mersilene sutures in penetrating keratoplasty. *Refract Corneal Surg* 1992 **8** 296 - 305

206 McNeill JI, Wessels IF. Adjustment of single continuous suture to control astigmatism after penetrating keratoplasty. *Refract Corneal Surg* 1989 **5** 216 - 223

207 van Meter WS, Gussler JR, Soloman KD, Wood TO. Postkeratoplasty astigmatism control. Single continuous suture adjustment versus selective interrupted suture removal. *Ophthalmology* 1991 **98** 177 - 183

208 Troutman RC. Astigmatic considerations in corneal graft. *Ophthalmic Surg* 1979 **10** (5) 21 - 26

209 van Rij G, Waring GO. Suture-induced astigmatism after a circular wound in the Rhesus monkey. *Cornea* 1986 **5** (1) 25 - 28

210 Cottingham AJ. Residual astigmatism following keratoplasty. *Ophthalmology* 1980 **87** Suppl. 113 - 114

211 Burk LL, Waring GO, Radjee B, Stulting RD. The effect of selective suture removal on astigmatism following penetrating keratoplasty. *Ophthalmic Surg* 1988 **19** (12) 849 - 854

212 Harris DJ, Waring GO, Burk LL. Keratography as a guide to selective suture removal for the reduction of astigmatism after penetrating keratoplasty. *Ophthalmology* 1989 **96** 1597 - 1607

213 Pradera I, Ibrahim O, Waring GO. Refractive results of successful penetrating keratoplasty, intraocular lens implantation with selective suture removal. *Refract Corneal Surg* 1989 **5** 231 - 239

214 Stainer GA, Perl T, Binder PS. Controlled reduction of postkeratoplasty astigmatism. *Ophthalmology* 1982 **89** 668 - 676

215 Feldman ST, Brown SI. Reduction of astigmatism after keratoplasty. *Am J Ophthalmol* 1987 **103** (3) 477 - 478

216 Musch DC, Meyer RF, Sugar A, Soong HK. Corneal astigmatism after penetrating keratoplasty. The role of suture technique. *Ophthalmology* 1989 **96** 698 - 703

217 Burk LL, Waring GO, Harris DJ. Simultaneous and sequential selective suture removal to reduce astigmatism after penetrating keratoplasty. *Refract Corneal Surg* 1990 **6** (3) 179 - 187

218 Kozarsky AM, Waring GO. Photokeratoscopy in the management of astigmatism following keratoplasty. *Dev Ophthalmol* 1985 **11** 91 - 98

219 Rowsey JJ, Fowler WC, Terry MA, Scoper SV. Use of keratoscopy, slit-lamp biomicroscopy, and retinoscopy in the management of astigmatism after penetrating keratoplasty. *Refract Corneal Surg* 1990 **7** 33 - 41

220 Calossi A, Verzella F, Penso A. Computer program to calculate vectorial change of refraction induced by refractive surgery. *Refract Corneal Surg* 1993 **9** 276 - 282

221 Musch DC, Meyer RF, Sugar A. The effect of removing running sutures on astigmatism after penetrating keratoplasty. *Arch Ophthalmol* 1988 **106** 488 - 492

222 Musch DC, Meyer RF. Preoperative measurements. Chapt. 10 in *Corneal surgery. Theory, technique and tissue. 2nd ed. Edited by Brightbill FS.* 1993

223 Tavakkoli H, Sugar J. Microbial keratitis follwing penetrating keratoplasty. *Ophthalmic Surg* 1994 **25** (6) 356 - 360

224 Harris DJ, Stulting RD, Waring GO, Wilson LA. Late bacterial and fungal keratitis after corneal transplantation. *Ophthalmology* 1988 **95** 1450 - 1457

225 Nabors G, Vander Zwaag R, Van Meter WS, Wood TO. Suture adjustment for postkeratoplasty astigmatism. *J Cataract Refract Surg* 1991 **17** (5) 547 - 550

226 Filatov V, Steinert RF, Talamo JH. Postkeratoplasty astigmatism with single running suture or interrupted sutures. *Am J Ophthalmol* 1993 **115** 715 - 721

227 Troutman RC, Kelly S, Kaye D, Clahane AC. The use and preliminary results of the Troutman surgical keratometer in cataract and corneal surgery. *Trans Am Acad Ophthal Oto-lar* 1977 **83** 232 - 238

228 Frantz JM, Reidy JJ, McDonald MB. A comparison of surgical keratometers. *Refract Corneal Surg* 1989 **5** 409 - 413

229 Hyde LL. The surgical astigmatic ruler. *Am Intra-ocular Impant Soc J.* 1984 **10** 84 - 86

230 Igarashi S, Yoshida A, Igarashi H, Kojima M. Measurement of the radius of corneal curvature with the Maloney surgical keratometer and an on-line keratometer imagery processing system. *J Jpn Ophthalmol Soc* 1993 **97** 58 - 64

231 Simon G, Parel J-M, Nose I, Lee W. Modification, calibration, and comparative testing of an automated surgical keratometer. *Refract Corneal Surg* 1991 **7** 151 - 160

232 Belin MW. Intraoperative raster photogrammetry - the PAR corneal topography system. *J Cataract Refract Surg* 1993 **19** Supplement 188 - 192

233 Thall EH, Lange SR. Preliminary results of a new intraoperative corneal topography technique. *J Cataract Refract Surg* 1993 **19** Supplement 193 - 197

234 Levene JR. An evaluation of the hand keratoscope as a diagnostic instrument for corneal astigmatism. *Br J Physiol Optics* 1962 **19** 237 - 251

235 Serdarevic ON, Renard GJ, Pouliquen Y. Randomized clinical trial comparing astigmatism and visual rehabilitation after penetrating keratoplasty with and without intraoperative suture adjustment. *Ophthalmology* 1994 **101** 990 - 999

236 Warnicki JW, Rehkopf PG, Curtin SA. Corneal topography using computer analysed rasterstereographic images. *Appl Opt* 1988 **27** 1135 - 1140

237 de Cunha DA, Woodward EG. Measurement of corneal topography in keratoconus. *Ophthalmic Physiol Opt* 1993 **13** 377 - 382

238 Wiggins RE, Cobo M, Foulks GN. Results of penetrating keratoplasty by residents. *Arch Ophthalmol* 1990 **108** 851 - 853

239 Tripoli NK, Cohen KL, Proia AD. Cat keratoplasty wound healing and corneal astigmatism. *Refract Corneal Surg* 1992 **8** 196 - 203

240 Filatov VP. Transplantation of the cornea *Arch Ophthalmol* 1935 **13** 321 - 347

241 Thomas JW. The clinical record and histology of two successful corneal grafts in man. *Trans Ophthal Soc UK* 1935 **55** 114 - 136

242 Morpurgo F, Ferrata L. Histopathalogic observations on keratoplasty in man. *Am J Ophthalmol* 1951 **34** 786 - 787

243 Vejdovsky PV, Mazanec K. Examen histologique d`un greffon de cornee transparent apres la keratoplastie. *Ophthalmologica* 1955 **130** 344 - 353

244 Henderson JW, Reimer WJ. Separation of Descement`s membrane in keratoplasty. *Am J Ophthalmol* 1968 **65** 375 - 378

245 Morrison JC, Swan KC. Bowman`s layer in penetrating keratoplasties of the human eye. *Arch Ophthalmol* 1982 **100** 1835 - 1838

246 Morrison JC, Swan KC. Descement`s membrane in penetrating keratoplasties of the human eye. *Arch Ophthalmol* 1983 **101** 1927 - 1929

247 Melles GR, Binder PS. A comparison of wound healing in sutured and unsutured corneal wounds. *Arch Ophthalmol* 1990 **108** 1460 - 1469

248 Lang GK, Green WR, Maumenee AE. Clinicopathologic studies of keratoplasty eyes obtained post mortem. *Am J Ophthalmol* 1986 **101** 28 - 40

249 Troutman RC. Surgical correction of high corneal astigmatic errors after successful keratoplasty. *Adv Ophthalmol* 1972 **27** 170 - 179

250 Hoppenreijs VP, Van Rij G, Beekhuis WH, Rijneveld WJ, Rinkel Van Driel E. The causes of high astigmatism after penetrating keratoplasty. *Doc Ophthalmol* 1993 **85** (1) 21 - 34

251 Moore TE, Aronson SB. Results of penetrating keratoplasty in keratoconus. *Adv Ophthalmol* 1978 **37** 106 - 108

252 Richard JM, Paton D, Gasset AR. A comparison of penetrating keratoplasty and lamellar keratoplasty in the surgical management of keratoconus. *Am J Ophthalmol* 1978 **86** 807 - 811

253 Farge EJ. Results of penetrating keratoplasty over a four- year period. *Ophthalmology* 1978 **85** 650 - 654

254 De Molfetta V, Brambilla M, De Casa N, Arpa P, Riva M. Residual corneal astigmatism after perforating keratoplasty. *Ophthalmologica* 1980 **179** 316 - 321

255 Olson RJ, Mattingly TP, Waltman SR, Kaufman HE. Aphakic keratoplasty. Visual acuity and optical errors. *Ophthalmology* 1980 **87** 680 - 686

256 Bourne W. Current techniques for improved visual results. *Ophthalmic Surg* 1981 **12** 321 - 327

257 Payne JW. Primary penetrating keratoplasty for keratoconus: A long term follow-up. *Cornea* 1982 **1** 21 - 27

258 Paglen PG, Fine M, Abbott RL, Webster RG. The prognosis for keratoplasty in keratoconus. *Ophthalmology* 1982 **89** 651 - 654

259 Waring GO, Welch SN, Cavanagh HD, Wilson LA. Results of penetrating keratoplasty in 123 eyes with pseudophakic or aphakic corneal edema. *Ophthalmology* 1983 **90** 25 - 33

260 Ehlers N, Olsen T. Long term results of corneal grafting in keratoconus. *Acta Ophthalmol* 1983 **61** 918 - 926

261 Kozarsky AM, Stopak S, Waring GO, Stilting RD, Wilson LA, Cavanagh HD, Cornell FM. Results of penetrating keratoplasty for pseudophakic corneal edema with retention of intraocular lens. *Ophthalmology* 1984 **91** 1141 - 1146

262 Perry PS. Intraocular lens powers used in the triple procedure. *Ophthalmology* 1985 **92** 1561 - 1566

263 Renardel de Lavalette JG, Renardel de Lavalette A, Van Rij G, Beekhuis WH, De Beijer-Dominicus JA. Long term results of corneal transplantations in keratoconus patients. *Doc Ophthalmol* 1985 **59** 93 - 97

264 Binder PS. The triple procedure. Refractive results. 1985 update. *Ophthalmology* 1986 **93** 1482 - 1488

265 Crawford GJ, Stulting RD, Waring GO, Van Meter WS, Wilson LA. The triple procedure. Analysis of outcome, refraction, and intraocular lens power calculation. *Ophthalmology* 1986 **93** 817 - 824

266 Puchkowskaya NA, Titarenko SD. Neues in der behandlung des keratokonus. *Klin Mbl Augenheilk* 1986 **189** 11 - 14

267 Treumer H, Duncker G. Refraktion des auges nach perforierender keratoplastik *Fortschr Ophthalmol* 1987 **84** 503 - 505

268 Meyer RF, Musch DC. Assessment of success and complications of triple procedure surgery. *Am J Ophthalmol* 1987 **104** 233 - 240

269 Koenig SB, Schultz RO. Penetrating keratoplasty for pseudophakic bullous keratopathy after extracapsular cataract extraction. *Am J Ophthalmol* 1988 **105** 348 - 353

270 Sayegh FD, Ehlers N, Farah I. Evaluation of penetrating keratoplasty in keratoconus. *Acta Ophthalmol* 1988 **66** 400 - 403

271 Steinert RF, Wagoner MD. Long-term comparison of epikeratoplasty and penetrating keratoplasty for keratoconus. *Arch Ophthalmol* 1988 **106** 493 - 496

272 Rapuano CA, Cohen EJ, Brady SE, Arentsen JJ, Laibson PR. Indications for and outcomes of repeat penetrating keratoplasty. *Am J Ophthalmol* 1990 **109** 689 - 695

273 Vail A, Gore SM, Bradley BA, Easty DL, Rogers CA. Corneal graft survival and visual outcome. *Ophthalmology* 1994 **101** 120 - 127

274 Tudor Thomas JW. Results of corneal transplantation. *Brit Med J* 1937 114 - 116

275 Castroviejo R. Results of corneal transplantation. *Arch Ophthalmol* 1938 **19** 834 - 835

276 Owens WC, Frank JJ, Leahey B, Messier PE, Scheie HG, Vincent BR, Wadsworth JA, Stansbury FC. Symposium: Corneal transplantation. V. Results. *Am J Ophthalmol* 1948 **31** 1394 - 1399

277 Scheie HG. Indications and results in keratoplasty. *Arch Ophthalmol* 1950 **43** 785 - 788

278 Cavara V, Bietti GB. Nos results dans les greffes de la cornee. *Bulletins et memoires de la Societe Francaise D'Ophtalmologie* 1948 **61** 9 - 22

279 Stansbury FC. Corneal transplantarion. 1. Visual and cosmetic results. *Arch Ophthalmol* 1949 **42** 813 - 844

280 Roberts JE. Statistics on results of keratoplasty. *Am J Ophthalmol* 1950 **33** (2) 21 - 23

281 Fine M. Penetrating keratoplasty in aphakia. *Arch Ophthalmol* 1964 **72** 50 - 56

282 Rycroft B. The corneal graft-past, present, and future. *Trans Ophthal Soc UK* 1965 **85** 459 - 517

283 Anseth A. Keratoplasty for keratoconus. A report of 50 operated eyes. *Acta Ophthalmol* 1967 **45** 684 - 687

284 Paton D. Results of penetrating keratoplasty with microsurgical technique. A review of 40 consecutive cases. *Int Ophthalmol Clin* 1970 **10** 347 - 377

285 Anseth A, Palm E. Surgical treatment of corneal disorders. *Acta Ophthalmol* 1971 **49** 552 - 564

286 Keates RH, Falkenstein S. Keratoplasty in keratoconus. *Am J Ophthalmol* 1972 **74** (3) 442 - 444

287 Troutman RC, Metzler M. Astigmatism and myopia in keratoconus. *Trans Am Ophthalmol Soc* 1972 **70** 266 - 277

288 Pouliquen Y, Bellivet J, Lecoq PJ, Clay C. Keratoplastic transfixiante dans le traitement du keratocone. *Arch Ophthalmol (Paris)* 1972 **32** (11) 735 - 744

289 Witmer R, Bigar F, Schwobel M. Der postoperative astigmatismus nach perforierender keratoplastik. *Ophthalmologica* 1976 **172** 101 - 105

290 Rozsa AJ, Beuerman RW. Density and organisation of free nerve endings in the corneal epithelium of the rabbit. *Pain* 1982 **14** 105 - 120

291 Zander E, Weddell G. Observations on the innervation of the cornea. *J Anat* 1951 **85** (1) 68 - 99

292 Matsuda H. Electron microscopic study of the corneal nerve with special reference to its endings. *Jpn J Ophthalmol* 1968 **12** 163 - 173

293 Schimmelpfennig B. Nerve structures in the human central corneal epithelium. *Albrecht Von Graefes Arch Clin Exp Ophthalmol* 1982 **218** 14 - 20

294 Ueda S, del Corro M, LoCascio JA, Aquavella JV. Peptidergic and catecholaminergic fibres in the human corneal corneal epithelium. An immunohistochemical and electron microscopic study. *Acta Ophthalmol (suppl)* 1989 **192** 80 - 90

295 Lim CH, Ruskell GL. Corneal nerve access in monkeys. *Albrecht Von Graefes Arch Clin Exp Ophthalmol* 1978 **208** 15 - 23

296 Millodot M, Larson W. New measurement of corneal sensitivity: a preliminary report. *Am J Optom* 1969 **46** 261 - 265

297 Beuerman RW, Schimmelpfennig B. Sensory denervation of the rabbit cornea affects epithelial properties. *Exp Neurol* 1980 **69** 196

298 Escarpini H. Degeneration and regeneration of nerves in the corneal transplant. *Arch Ophthalmol* 1948 **39** 135 - 161

299 Franceschetti A, Babel J. Examen histologique d'une greffe corneene transparente: le comportement des nerfs. *Ann Oculist (Paris)* 1947 **180** 142 - 145

300 Sedan J, Payrau P, Martin J. La recuperation esthesique des greffons de keratoplastie. *Societe Francaise d'Ophthalmologie* 1960 **73** 24 - 36

301 Ruben M, Colebrook E. Keratoplasty sensitivity. *Br J Ophthalmol* 1979 **63** 265-267

302 Rao GN, John T, Ishida N, Aquavella J. Recovery of corneal sensitivity in grafts following penetrating keratoplasty. *Ophthalmology* 1985 **92** 1408 - 1411

303 Tugal-Tutkun I, Akarcay K, Kozer-Bilgin L, Sansoy N, Urgancioglu M. Corneal sensitivity after penetrating keratoplasty. *Eur J Ophthalmol* 1993 **3** (2) 66 - 70

304 Gong XM. Recovery of corneal sensitivity following keratoplasty and corneal diseases. *Chinese J Ophthalmol* 1992 **28** (3) 150 - 152

305 Weinstein S, Drozdenko R, Weinstein C. A new device for corneal esthesiometry: clinical significance and application. *Clin Eye Vision Care* 1992 **4** (3) 123 - 128

306 Davidian M, Zaidman GW, Bainnson D, Weinstein C, Weinstein S, Drozdenko R. Measurement and mapping of corneal sensation in normal and diseased corneas. *Invest Ophthalmol Vis Sci* 1994 **30** 577 - 1990

307 Draeger J. *Corneal sensitivity. Measurement and clinical importance.* 1984 Springer-Verlag. New York -Wien. ISBN 0-387-81794-8.

308 Mathers WD, Jester JV, Lemp MA. Return of human corneal sensitivity after penetrating keratoplasty. *Arch Ophthalmol* 1988 **106** 210 - 211

309 Skriver K. Reinnervation of the corneal graft. *Acta Ophthalmol* 1978 **56** 1013 - 1015

310 Martin XY, Safran AB. Corneal hypoesthesia. *Surv Ophthalmol* 1988 **33** (1) 28 - 40

311 Stamer L, Bohnke M, Draeger J. Entwicklung der Hornhautsensibilitat nach Keratoplastik. *Fortschr Ophthalmol* 1994 **84** 432 - 435

312 Zorab EC. Corneal sensitivity after grafting. *Proc Roy Soc Med* 1971 **64** 117 - 118

313 de Leeuw AM, Chan KY. Corneal nerve regeneration. *Invest Ophthalmol Vis Sci* 1989 **30** (9) 1980 - 1990

314 Rexed B, Rexed U. Degeneration and regeneration of corneal nerves. *Br J Ophthalmol* 1950 **35** 38 - 49

315 Rozsa AJ, Guss RB, Beuerman RW. Neural remodeling following experimental surgery of the rabbit cornea. *Invest Ophthalmol Vis Sci* 1983 **24** 1033 - 1051

316 Chan-Ling T, Tervo K, Tervo T, Vannas A, Holden BA, Eranko L. Long term neural regeneration in the rabbit following 180 degree limbal incision. *Invest Ophthalmol Vis Sci* 1987 **28** 2083 - 2088

317 Chan-Ling T, Vannas A, Holden BA, O`Leary DJ. Incision depth affects the recovery of corneal and neural regeneration in the cat. *Invest Ophthalmol Vis Sci* 1990 **31** 1533 - 1541

318 Rao GN, John T, del Cerro M, Aquavella JV. Corneal innervation following experimental penetrating keratoplasty. *Invest Ophthalmol Vis Sci (Suppl)* 1986 91

319 Chan KY, Jarvelainen M, Chang JH, Edenfield MJ. A cryodamage model for studying corneal nerve regeneration. *Invest Ophthalmol Vis Sci* 1990 **31** (10) 2008 - 2021

320 Chan KY, Jones RR, Bark DH, Swift J, Parker JA, Haschke RH. Release of Neuronotrophic factor from rabbit corneal epithelium during wound healing and nerve regeneration. *Exp Eye Res* 1987 **45** 633 - 646

321 Tervo T, Vannas A, Tervo K, Holden BA. Histochemical evidence of limited reinnervation of human corneal grafts. *Acta Ophthalmol* 1985 **63** 207 - 214

322 Ludlam WM. Translation of:- Gullstrand A. Photographic-ophthalmometric and clinical investigation of corneal refraction.1896 *Am J Optom Arch Am Acad Optom* 1966 **43** 143 - 214

323 Wittenberg S, Ludlam WM. Derivation of a system for analysing the corneal surface from photokeratoscopic data. *J Opt Soc Am* 1966 **56** (11) 1612 - 1615

324 Fincham EF. The photokeratoscope. *Med Biol Illustration* 1953 **3** 87 - 93

325 Donaldson DD. A new camera for medical stereophotography with special reference to the eye. *Arch Ophthalmol* 1972 **52** 564 - 570

326 Ludlam WM, Wittenberg S, Rosenthal J, Harris G. Photographic analysis of the ocular dioptric components. Part III. The acquisition, storage, retrieval, and utilization of primary data in photokeratoscopy. *Am J Optom* 1967 **44** 276 - 296

327 Ludlam WM, Wittenberg S. Measurements of the ocular dioptric elements utilizing photographic methods. part II. Cornea- theoretical considerations. *Am J Optom* 1966 **43** 249 - 267

328 El Hage SG. A new photokeratoscopic technique. *Optical Engineering* 1976 **15** (4) 308 - 311

329 Townsley MG, Ridge P. New equipment and methods for determining the contour of the human cornea. *Contacto* 1967 **11** (4) 72 - 81

330 Holden BA. A study of the development and control of myopia and the effects of contact lenses on corneal topography. *PhD Thesis The City University London* 1970

331 Amiard H. Pratique de la photokeratometrie. *Le Contact* 1972 **29** 1 - 15 Paris, Laboratoires Ysoptic

332 El Hage SG. Suggested new methods for photokeratoscopy a comparison for their validities. Part 1. *Am J Optom Arch Acad Optom* 1971 **48** 897 - 912

333 Fujii T, Maruyama S, Ikeda M. Determination of corneal configuration by the measurement of its derivatives. *Optica Acta* 1972 **19** 425 - 430

334 Westheimer G. A method of photoelectric keratoscopy. *Am J Optom Arch Am Acad Optom* 1965 **42** (5) 315 - 320

335 Amiard H, Cochet P. Photokeratometrie. *Le Contact* 1972 **25** 1 - 16 Paris, Laboratoires Ysoptic.

336 Frey M von. Berichte uber die Verhaindlungen der Koniglich Sachsichen. *Ges Wiss* 1894 **46** 185 - 196

337 Boberg-Ans J. Experience in clinical examination of corneal sensitivity. *Br J Ophthalmol* 1955 **39** 709 - 726

338 Bonnet R, Millodot M. Corneal aesthesiometry, its measurement in the dark. *Am J Optom* 1966 **43** 238 - 243

339 Millodot M, Larson W. Effect of bending of the nylon thread of the Cochet-Bonnet aesthesiometer upon recorded pressure. *The contact lens* 1967 **1** (3) 5 - 28

340 Larson WL. Electro-mechanical corneal aesthesiometer. *Br J Ophthalmol* 1970 **54** 342 - 347

341 Draeger J. Klinische ergebnisse der aesthesiometrie der hornhaut. *Ber Dtsch Ophthal Ges* 1979 **76** 389 - 395

342 Hamano H. Topical and systemic influences of wearing contact lenses. *Contacto* 1960 **4** 41 - 48

343 Schirmer KE. Corneal sensitivity and contact lenses. *Br J Ophthalmol* 1963 **47** 493 - 495

344 Beuerman RW, McCulley JP. Comparative clinical assessment of corneal sensation with a new aesthesiometer. *Am J Ophthalmol* 1978 **86** 812 - 815

345 Murphy PJ, Patel S. A review of corneal touch sensitivity. *Optometry Today* 1995 **35** 20 - 23

346 Millodot M. A review of research on the sensitivity of the cornea. *Ophthalmic Physiol Opt* 1984 **4** (4) 305 - 318

347 Bleshoy H. Neuropathology and sensitivity in the keratoconic cornea. *Doctoral thesis.* 1990 City University. London.

348 Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. *Ophthalmology* 1994 **101** 439 - 447

349 Maloney RK. Corneal topography and optical zone location in photorefractive keratectomy. *Refract Corneal Surg* 1990 **6** 363 - 371

350 Antalis JJ, Lembach RG, Carney LG. A comparison of the TMS-1 and the corneal analysis system for the evaluation of abnormal corneas. *CLAO J* 1993 **19** (1) 58 - 63

351 Millodot M. Studies on the sensitivity of the cornea. *Optician* 1969 **14** 267 - 271

352 Hirji NK. Some aspects of the design and ocular response to synthetic hydrogel contact lenses intended for continuous usage. *Doctoral thesis.* 1978 University of Aston, Birmingham, England.

353 Millodot M, O'Leary DJ. Corneal fragility and its relationship to sensitivity. *Acta Ophthalmol* 1981 **59** 820 - 826

354 Mandell RB. The enigma of the corneal contour. *CLAO J* 1992 **18** (4) 267 - 273

355 Mandell RB, Horner D. Alignment of videokeratoscopes. 1993
Chapter 10 in *An atlas of Corneal Topography* Sanders DR, Koch DD. Slack. Thorofare. NJ. USA. ISBN. 1-55642-218-0 200

356 Goldstein H. *Multilevel statistical models* 1995 second editon. Edward Arnold. London.

357 Dwyer JH, Manning F, Lippert P, Hoffmeister H. *Statistical Models for Longitudinal Studies of Health.* 1992 Oxford University Press. ISBN O-19-505473 -3 p.137

358 Wilson SE, Klyce SD. Quantitative descriptors of corneal topography. *Arch Ophthalmol* 1991 **109** 349 - 353

359 Dingeldein SA, Klyce SD, Wilson SE. Quantitative descriptors of corneal shape derived from computer-assisted analysis of photokeratographs. *Refract Corneal Surg* 1989 **5** 372 - 378

360 Rosenfield M, Chui NN. Repeatability of subjective and objective refraction. *Optom Vision Sci* 1995 **72** (6) 577 - 579

361 Zadnik K, Mutti DO, Adams AJ. The repeatability of measurement of the ocular components. *Invest Ophthalmol Vis Sci* 1992 **33** (7) 2325 - 2333

362 Camp JJ, Maguire LJ, Cameron BM, Robb RA. A computer model for the evaluation of the effect of corneal topography on optical performance. *Am J Ophthalmol* 1990 **109** 379 - 386

363 Maloney RK, Bogan SJ, Waring GO. Determination of corneal image-forming properties from corneal topography. *Am J Ophthalmol* 1993 **115** 31 - 41

364 Hjortdal OJ, Erdmann L, Bek T. Fourier analysis of video keratographic data. *Ophthalmic Physiol Opt* 1995 **15** (3) 171 - 185

365 Tuft SJ, Gregory W. Long term refraction and keratometry after penetrating keratoplasty for keratoconus. *Cornea* 1995 **14** (6) 614 - 617

366 Woodward EG, Moodaley LC, O'Hagan A. Predictors for likelyhood of corneal transplantation in keratoconus. *Eye* 1990 **4** (3) 493 - 496

367 Clark BAJ. Variations in corneal topography. *Aust J Optom* 1973 **56** 399 - 413

368 Kwitko S, Garbus JJ, Hwang DG, Gauderman WJ, McDonnell PJ. Computer-assisted study of diurnal variation in corneal topography after penetrating keratoplasty. *Ophthalmic Surg* 1992 **23** (1) 10 - 16

369 Fledelius HC, Stubgaard M. Changes in refraction and corneal curvature during growth and adult life. A cross-sectional study. *Acta Ophthalmol* 1986 **64** 487 - 491

370 Ruiz-Montenegro J, Mafra CH, Wilson SE, Jumper JM, Klyce SD, Mendelson EN. Corneal topographic alterations in normal contact lens wearers. *Ophthalmology* 1993 **100** 128 - 134

371 Maeda N, Klyce SD, Hamano H. Alteration of corneal asphericity in rigid gas permeable contact lens induced warpage. *CLAO J* 1994 **20** (1) 27 - 31

372 Wilson SE, Lin DT, Klyce SD, Reidy JJ, Insler MS. Topographic changes in contact lens induced corneal warpage. *Ophthalmology* 1990 **97** 734 - 744

373 Wilson SE, Lin DT, Klyce SD, Reidy JJ, Insler MS. Rigid contact lens decentration: A risk factor for corneal warpage. *CLAO J* 1990 **16** (3) 177 - 182

374 Woodward EG, Moodaley LC, Lyons C, Davison C, Buckley RJ, Barbur VA. Post keratoplasty dimensional and refractive change in contact lens and spectacle corrected cases. *Eye* 1990 **4** 689 - 692

375 Wilson SE, Friedman RS, Klyce SD. Contact lens manipulation of corneal topography after penetrating keratoplasty: A preliminary study. *CLAO J* 1992 **18** (3) 177 - 182

376 Sperber LT, Lopatynsky MO, Cohen EJ. Corneal topography in contact lens wearers following penetrating keratoplasty. *CLAO J* 1995 **21** (3) 183 - 190

377 Mathers WD, Gold JB, Kattan H, Lemp MA. Corneal steepening with final suture removal after penetrating keratoplasty. *Cornea* 1991 **10** (3) 221 - 223

378 Mader TH, Yuan R, Lynn MJ, Stulting RD, Wilson LA, Waring GO. Changes in keratometric astigmatism after suture removal more than one year after penetrating keratoplasty. *Ophthalmology* 1993 **100** 119 - 127

379 Belin MW, Litoff D, Strods SJ, Winn SS, Smith RS. The PAR Technology corneal topography system. *Refract Corneal Surg* 1992 **8** 88 - 96

380 Belin MW, Zloty P. Accuracy of the PAR corneal topography system with spatial misalignment *CLAO J* 1993 **19** (1) 64 - 68

381 Bryant JA. Local and topical anesthetics in ophthalmology. *Surv Ophthalmol* 1969 **13** (5) 263 - 283

382 Polse KA, Keener RJ, Jauregui MJ. Dose-response effects of corneal anaesthetics. *Am J Optom Physiol Opt* 1978 **55** (1) 8 - 14

383 Millodot M, Henson DB, O'Leary DJ. Measurement of corneal sensitivity and thickness with PMMA and gas-permeable contact lenses. *Am J Optom Physiol Opt* 1979 **56** (10) 628 - 632

384 Millodot M. Effect of hard contact lenses on corneal sensitivity and thickness. *Acta Ophthalmol* 1975 **53** 576 - 584

385 Millodot M. Effect of long-term wear of hard contact lenses on corneal sensitivity. *Arch Ophthalmol* 1978 **96** 1225 - 1227

386 Douthwaite WA, Connelly AT. The effect of hard gas permeable contact lenses on refractive error, corneal curvature, thickness and sensitivity. *J Br Contact Lens Assoc* 1986 **9** (1) 14 - 20

387 Polse KA. Etiology of corneal sensitivity accompanying contact lens wear. *Invest Ophthalmol Vis Sci* 1978 **17** 1202 - 1206

388 Kaye DB. Epithelial response in penetrating keratoplasty. *Am J Ophthalmol* 1980 **89** 381 - 387

389 Lohman IE, Rao GN, Aquavella JV. In vivo microscopic observations of human corneal epithelial abnormalities. *Am J Ophthalmol* 1982 **93** 210 - 217

390 Marechal-Courtois C, Delcourt JC. Wide field specular microscopy of corneal epithelium. *CLAO J* 1986 **12** 165 - 172

391 Lemp MA. The surface of the corneal graft: in vivo colour specular microscopic study in the human. *Trans Am Ophthalmol Soc* 1990 **87** 619 - 657

392 Tsubota K, Mashima Y, Murata H, Yamada M. Specular microscopic observation of corneal epithelium following penetrating keratoplasty. *Jpn J Clin Ophthalmol* 1990 **44** 131 - 134

393 Tsubota K, Yamada M, Naoi S. Specular microscopic observations of human corneal epithelial abnormalities. *Ophthalmology* 1991 **98** 184 - 191

394 Auran JD, Koester CJ, Kleiman NJ, Rapaport R, Bomann JS, Wirotsko BM, Florakis GJ, Koniarek JP. Scanning slit confocal microscopic observation of cell morphology and movement within the normal human anterior cornea. *Ophthalmology* 1995 **102** 33 - 41

395 Townsley MG. New knowledge of the corneal contour. *Contacto* 1970 **14** (3) 38 - 43

396 Sampson PD. Fitting conic sections to "very scattered" data: an iterative refinement of the Bookstein alogorithm. *Comp Graph and Image Proc.* 1982 **18** 97 - 108

397 Porril J. Fitting ellipses and predicting confidence envelopes using a bias corrected Kalman filter. *Image and Vision Computing.* 1990 **8** 37 - 41

398 Bibby MM. Computer assisted photokeratoscopy and contact lens design. *Optician* 1976 **171** (4423) 37-44; (4424) 11-17; (4426) 15-17.

399 Yuen HK, Illingworth J, Kittler J. Detecting partially occluded ellipses using the Hough transform. *Image and Vis Comp.* 1989 7 31 - 37

400 Rabash J, Woodhouse G. *MLn command reference.* 1995 Institute of Education. London.

Appendix A . Derivation of formulae for corneal curvature.

The information in this appendix is taken from "Measurement of corneal topography and transparency" by DA de Cunha, doctoral thesis, City University, 1995, with kind permission of the author.

If the cornea is treated as a convex mirror, topographical information can be derived by measuring the image size of an object reflected from the corneal surface. Applying standard paraxial ray equations to the image and object sizes, the radius of curvature of the equivalent spherical mirror is calculated. Figure A.1 shows the ray diagram for a convex mirror.

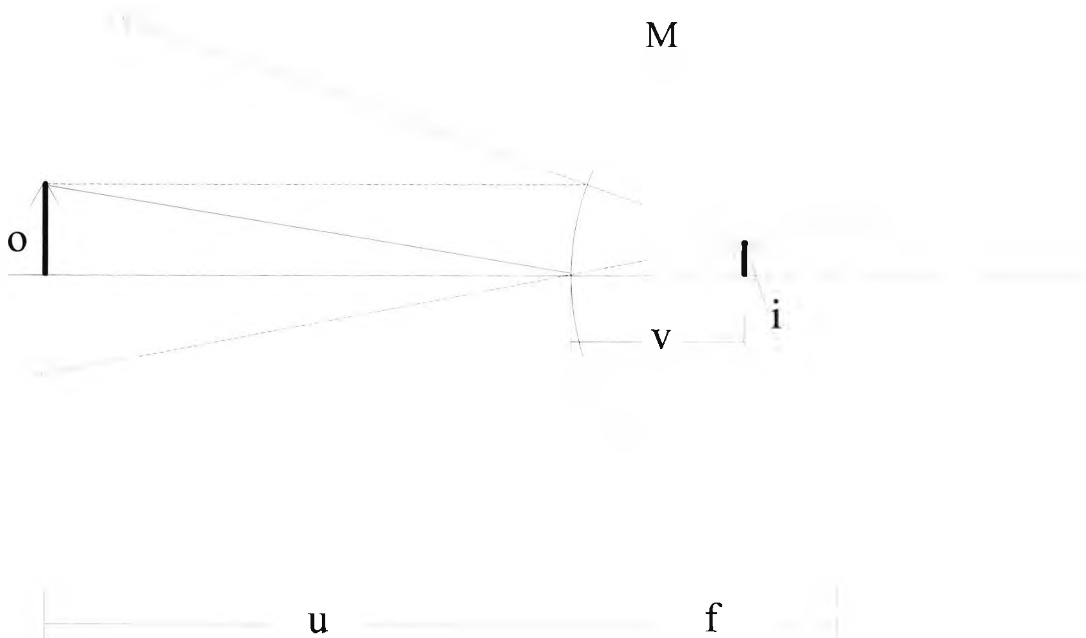


Figure A.1.Ray diagram for convex mirror

Ray from an object ***O*** is reflected from a spherical convex mirror ***M***, forming an image at ***v*** of height ***i***. The object distance is ***u*** and the focal length of the mirror is *f*.

Considering the image magnification we have

(A.1) $$\frac{i}{o} = \frac{v}{u}$$

Further the image distance is assumed to coincide with the focal point of the mirror.

Then, if ***r*** is the mirror radius of curvature

(A.2) $$v = \frac{r}{2}$$

combining equation (A.1) with (A.2) and solving for ***r***

(A.3) $$r = \frac{2ui}{o}$$

Equation (A.3) is the basic equation of keratometry and produces one radius of curvature value for an image height along a given meridian.

To generate a profile for a given meridian, a reflection point on the surface must be calculated for each object ring. This is done using the geometry shown in Figure A.2 (Townsley [329]).

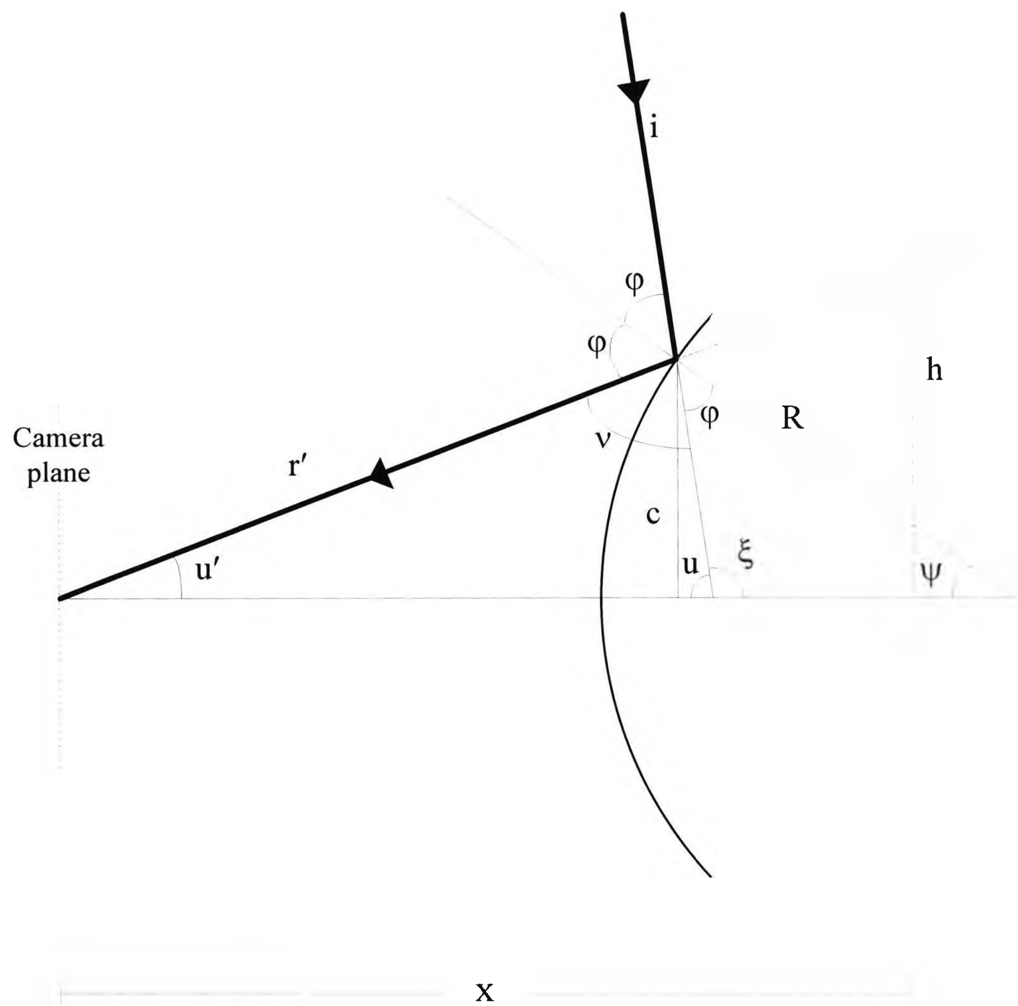


Figure A.2 Geometry for reflection from spherical surface.

i = incident ray from target, r′ = reflected ray to camera,

h = image height of ring, R = Radius of curvature of reflecting surface,

x = focusing distance of camera, c = semichord.

To find the incident ray intersection point with the surface, R and ψ must be calculated. For a known image size, R can be found from equation (A .3) and ψ is derived from Figure A.2 as follows

(A.4) $$u' + u + \vartheta = 180^{\circ}$$

(A.5) $$\vartheta + 2\varphi = 180^{\circ}$$

(A.6) $\therefore u' + u = 2\varphi$

and

(A.7) $\varphi + \xi + \psi = 180°$

(A.8) $u + \xi = 180°$

(A.9) $\therefore \varphi + \psi = u$

Substitute φ into equation (A.6)

(A.10) $u' + u = 2(\psi + u)$

(A.11) $\psi = (u - u')/2$

where $\tan u' = h/2$

and $\tan u \cong o/x$ where o = object ring height.

To build up the profile, the cornea is assumed to have a smooth shape with no abrupt changes in radius of curvature. Consecutive arc elements can then be joined together at the reflection points.

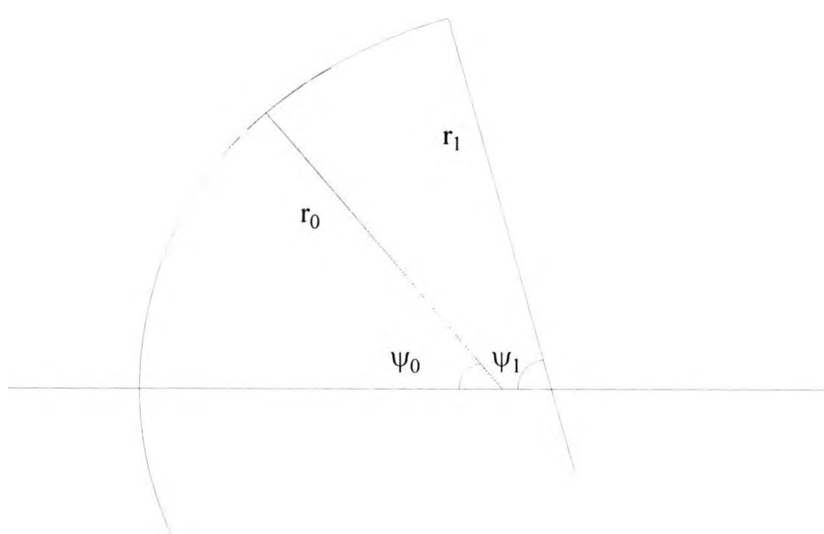


Figure A.3 Two consecutive arc elements joined at a reflection point.

Figure A.3 shows the situation for 2 circular sections and also shows the movement of the centre of curvature. Points on the surface in x,y must be found and an ellipse fitted to them to complete the description of the profile. The semichord c in Figure A.2 gives the y value and is found at each reflection point by

(A.12) $$y = R \sin \psi$$

The x value of each reflection point is calculated by summing the sagittal distance of successive curve elements from the vertex x_0. This is shown in Figure A.4

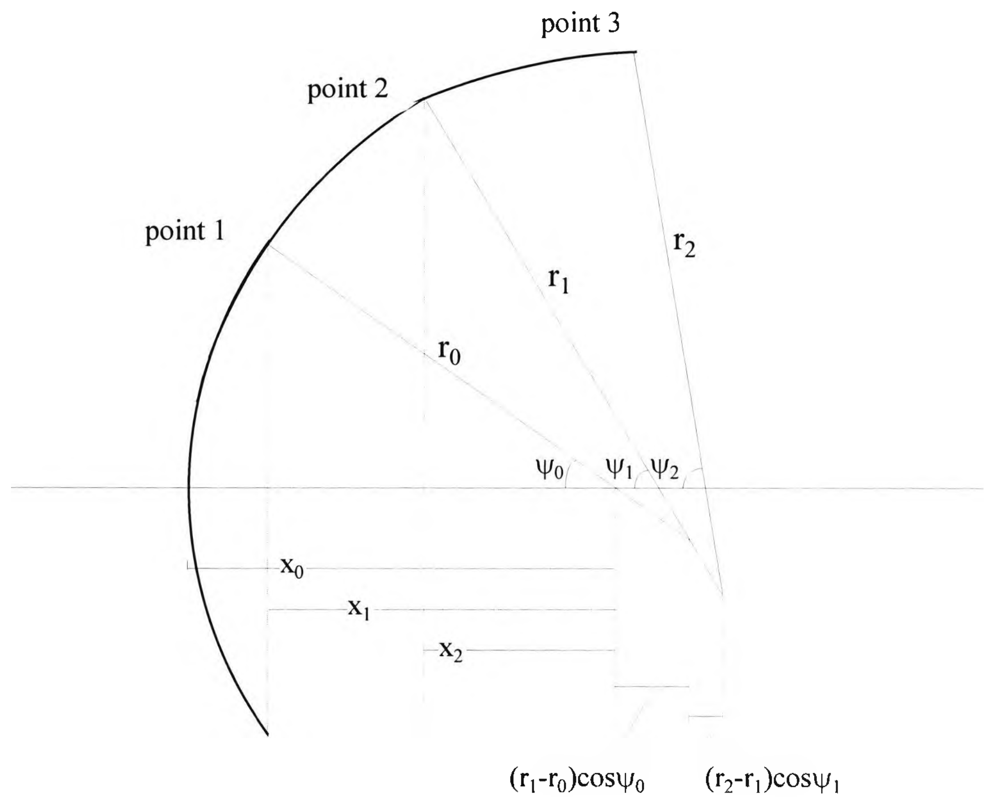


Figure A.4 Calculating x values of reflection points from curve elements.

In Figure A.4 x_0 = radius of curvature of central arc r_0 .

For the first point

(A.13) $$x_1 = r_0 \cos\psi_0$$

The first sag value is then

(A.14) $sag0 = x_0 - x_1$

For the next point, x_2 is given by

(A.15) $x_2 = r_1\cos\psi_1 - [(r_1 - r_0)\cos\psi_0]$

and the sag value (sag1) is

(A.16) $sag1 = x_1 - x_2$

For the third point, x_3 is given by

(A.17) $x_3 = r_2\cos\psi_2 - [(r_2-r_1)\cos\psi_1 + (r_1-r_0)\cos\psi_0]$

and the sag value (sag2) is

(A.18) $sag2 = x_2 - x_3$

Hence for successive points the sag distances are calculated and summed from the vertex position to give successive x, y points on the cornea relative to the vertex.

After points on the surface have been calculated, an ellipse or other conic section must be fitted to them to give a description of the surface. Unfortunately the usual ellipse or conic section equations are unworkable when applied to a least squares method of data fitting (Townsley [395]). The equations must ,therefore, be fitted using an iterative method giving results within some error bound chosen by the operator (Sampson [396], Porril [397]). Because points on the ellipse are only known around the central curvature area, a large number of ellipses possessing identical central curvatures but different shape factors can be fitted to the data (Bibby [398]).

Therefore, in fitting an ellipse, the establishment of the ellipse centre is probably the most important step in achieving acceptable results (Yuen [399]). The first assumption to be made is to place the major axis of the fitted ellipse along the axis of the instrument. Further, the locus of the centres of curvature (evolute) of the curve elements has the minor axis as its asymptote. If the position of the minor axis can be estimated by extrapolating the evolute, then the semi-major axis of the ellipse can be established. This fixes the position of the origin along the x axis.

The equation of the ellipse centred about the origin is given by

(A.19) $$\frac{x^2}{a^2} + \frac{y^2}{b^2} = 1$$

a = semi-major axis

b = semi-minor axis

with shape factor is given by

(A.20) $$s = 1 - \frac{b^2}{a^2}$$

Appendix B

Patient Details

Table B.1 overleaf shows details for each patient

KEY

Eye	Right (***R***.) or Left (***L***.)
Sex	Male (***M***.) or Female (***F***.)
Age	In years at the time of keratoplasty
Diagnosis	Reason for transplant
	K = Keratoconus
	Interstitial = Interstitial keratitis
	***Fuchs`*** = Fuchs` dystrophy
	HSK = Herpes Simplex Keratitis
	Bullous iol = Bullous keratopathy secondary to anterior chamber intraocular lens (for myopia in one eye, for aphakia in two eyes)
	Bullous G = Bullous keratopathy secondary to glaucoma
	Bullous B = Bullous keratopathy secondary to buphthalmos
	Bullous L = Bullous keratopathy secondary to ulcer in lamellar graft
	Lattice = Lattice dystrophy
	Scar S/px = Scaring secondary to smallpox
Hydrops	***H*** = Patients who suffered corneal hydrops prior to keratoplasty
Aphakic	***Prior*** = Patients who were aphakic prior to keratoplasty
	Double = Patients who underwent a double procedure, i.e. combined penetrating keratoplasty and extracapsular cataract extraction
	Triple = Patients who underwent a triple procedure, i.e. combined penetrating keratoplasty, extracapsular cataract extraction and intraocular lens implantation

Regraft For the majority of patients this was the first penetrating keratoplasty in that eye

2 = This was the second transplant in that eye

3 = This was the third transplant in that eye

4 = This was the fourth transplant in that eye

Atopy *A* = Patients who had a history suggestive of atopic disease

Age of Donor The donor age is shown in years. There was one paediatric donor under one year old, and this is shown as "*3M*", meaning 3 months.

Storage The donor material was either "***fresh***" whole eye, or stored in "***MK***" M-K medium, or "***K-sol***".

Sutures ***Con*** = continuous

Int = 16 interrupted

Mix = a combination of an eight bite continuous suture and eight interrupted sutures

Op. to final ROGS = the interval (in months) between the operation and the final removal of all sutures

Final ROGS to CL fit

= the interval (in months) between the final removal of all sutures and the issue of a rigid gas permeable contact lens. One patient commenced wear before the final removal of all sutures, and this is denoted by a negative figure. A blank space denotes no post-operative contact lens wear

Rejection Episode(s)

R = patient who experienced one or more rejection episodes

Refractive surgery

Y = patient who underwent relaxing incisions

** = data not recorded at the time of surgery

* = trephine disparity not recorded at the time of surgery, data reckoned from the normal practice at that time.

	Eye	Sex	Age	Diagnosis	Hydrops	Aphakic	Regraft	Atopy	Age donor	Storage	Surgeon	Graft Diam. mm	Host diam. mm	disparity	Suture	Op to final ROGS (M)	Final ROGS to CL fit (M)	Rejection episode(s)	Refractive Surgery
1	R	M	32	K					54	MK	Y	7.5	7	0.5	con	22			
2	R	M	28	K					75	K sol	X	8.5	8	0.5	con	38	8	R	
3	R	M	27	K				A	**	Fresh	Y	8	8	0	con	20			
4	L	F	29	K				A	74	K sol	Y	8	7.5	0.5	con	16	7		
5	R	F	45	K					35	MK	X	8.5	8	0.5	con	15	6		
6	R	F	42	K				A	67	K sol	Y	8	7.5	0.5	int	34	-17		
7	L	F	54	K					57	Fresh	Y	7.5	7.5	0	con	14			
8	R	M	36	K					52	MK	Y	8.5	8	0.5	con	18	8		
9	L	M	24	K					9	K sol	X	9.25	8.5	0.75	con	30	7	R	
10	L	M	33	K					12	Fresh	Z	8	8	0	con	12			
11	L	M	31	K					53	Fresh	Z	7.5	7.5	0	con	13			
12	R	M	34	K					20	MK	X	8	7.5	0.5	con	13			
13	L	F	35	K				A	57	Fresh	Y	8	8	0	con	14			Y
14	R	F	38	K				A	37	K sol	X	8.5	8	0.5	con	21			Y
15	R	F	26	K					50	Fresh	Y	8.5	8	0.5	con	26	16		
16	L	M	35	K					86	MK	Y	8.5	8	0.5	con	35	4	R	
17	R	F	37	K				A	63	MK	X	8.5	8	0.5	con	12	11		
18	L	F	33	K				A	58	Fresh	Y	8	8	0	con	20	5		
19	R	F	50	K					47	K sol	Y	8.5	8	0.5	con	31	3		
20	L	M	29	K					34	Fresh	Y	8	8	0	con	5	15		
21	R	M	53	K				A	**	Fresh	Y	8.5	8.5	0	con	39			
22	R	F	32	K	H				26	MK	X	8.25	7.5	0.75	con	29			
23	L	M	28	K				A	67	Fresh	X	8.5	7.5	1	con	17	13	R	
24	L	M	43	K					28	Fresh	Z	7.5	7.5	0	con	12	5		
25	L	M	28	K					34	Fresh	Y	7.5	7.5	0	con	17		R	

	Eye	Sex	Age	Diagnosis	Hydrops	Aphakic	Regraft	Atopy	Age donor	Storage	Surgeon	Graft Diam. mm	Host diam. mm	disparity	Suture	Op to final ROGS (M)	Final ROGS to CL fit (M)	Rejection episode(s)	Refractive Surgery
26	R	M	37	K					86	Fresh	X	8	7.5	0.5	con	44	31		Y
27	L	M	31	K					41	K sol	X	7.5	7	0.5	con	24	5	R	Y
28	R	M	30	K					38	MK	Y	8	7.5	0.5	con	12	12		
29	L	M	30	K					43	MK	Y	9.5	9	0.5	con	26	54		
30	R	M	55	Interstitial					84	Fresh	X	*6.5	6.5	*0	con	53			
31	L	M	65	Fuchs'		Triple			72	Fresh	Y	7.5	7.5	0	con	26			
32	L	M	59	HSK			2		39	Fresh	X	8.5	8.5	0	int	19		R	
33	R	M	36	K					57	Fresh	X	8.5	8.5	0	con	35		R	
34	R	M	26	K					67	Fresh	Y	8	8	0	con	15	9		
35	R	M	34	K					78	K sol	X	8.5	8.25	0.25	con	23	3		
36	R	M	41	K					22	Fresh	X	8	7.5	0.5	con	34			Y
37	L	F	36	K					61	K sol	Y	8.5	8	0.5	con	20			
38	R	F	34	K	H				59	Fresh	Y	7.5	7.5	0	con	18			
39	L	F	57	Fuchs'		Prior			62	MK	X	7.5	7	0.5	con	12			Y
40	R	M	62	K		Prior	2		80	MK	Y	8.75	8	0.75	int	78		R	
41	L	F	66	Bullous iol		Prior	3		66	Fresh	X	7.5	*7	*0.5	int	18		R	
42	R	F	71	Bullous iol		Prior	4		27	MK	X	7.5	7	0.5	int	17		R	
43	L	F	56	Lattice				A	47	Fresh	Y	8	8	0	con	19			
44	R	F	59	Lattice				A	3M	MK	X	8.5	8	0.5	int	63		R	
45	R	F	24	K					59	MK	X	7.75	7.5	0.25	con	18			
46	L	M	55	K					62	Fresh	Z	8	8	0	con	29			
47	R	F	29	K				A	**	Fresh	X	7.5	*7.5	*0	con	16	7		Y
48	L	F	48	K				A	61	K sol	X	8	8	0	int	18	39		
49	L	M	32	K					35	Fresh	Z	8	8	0	con	13	3		
50	L	F	46	K	H			A	**	Fresh	Z	8	8	0	con	11			

	Eye	Sex	Age	Diagnosis	Hydrops	Aphakic	Regraft	Atopy	Age donor	Storage	Surgeon	Graft Diam. mm	Host diam. mm	disparity	Suture	Op to final ROGS (M)	Final ROGS to CL fit (M)	Rejection episode(s)	Refractive Surgery
51	R	F	47	K				A	68	Fresh	X	8	8	0	con	16			
52	R	F	27	K				A	32	MK	X	8.5	8	0.5	con	12	6		
53	R	M	24	K				A	25	Fresh	X	8	7.5	0.5	int	24	9		
54	L	M	50	K				A	76	Fresh	X	9	8.5	0.5	con	21	6		
55	R	M	38	K					56	Fresh	Y	8	8	0	con	13	5		
56	R	M	29	K					7	K sol	X	8	7.5	0.5	con	18	2		
57	L	F	59	Fuchs'		Double			19	Fresh	X	8	7.5	0.5	con	13			
58	R	F	33	K					72	Fresh	Y	8	8	0	con	27		R	
59	L	M	39	K					67	Fresh	X	8	8	0	con	13	9		Y
60	L	F	38	K					65	Fresh	X	8.5	8	0.5	con	12	8	R	
61	R	F	40	K					75	K sol	X	8	7.5	0.5	con	35	2	R	
62	R	M	29	K				A	75	Fresh	X	7.5	*7.5	*0	con	13	3	R	
63	L	M	24	K					77	Fresh	Z	8	8	0	con	13			Y
64	L	F	58	Lattice					75	Fresh	X	7	7	0	con	17		R	
65	L	F	53	Bullous iol		Double	2		71	Fresh	X	7.5	*7	*0.5	con	13			
66	L	M	49	HSK					87	Fresh	Z	7	7	0	con	14	4	R	
67	R	M	74	K		Triple	2	A	74	MK	Y	8.5	8	0.5	mix	42			
68	R	M	24	K				A	37	Fresh	Z	9	9	0	con	13	10	R	
69	R	F	17	K			2		73	Fresh	X	8	8	0	int	57		R	
70	R	M	30	K					27	K sol	X	8.5	8	0.5	con	8	5	R	
71	R	M	25	K					48	Fresh	Y	*7.5	7.5	*0	con	12			
72	R	M	28	K				A	21	MK	Y	8	7.5	0.5	mix	59	5		
73	R	M	24	K				A	64	K sol	Y	7.5	7	0.5	int	23			
74	R	M	20	K					80	Fresh	Y	8	8	0	con	31			
75	R	F	22	K					52	MK	Y	8.5	8	0.5	con	17	16		

	Eye	Sex	Age	Diagnosis	Hydrops	Aphakic	Regraft	Atopy	Age donor	Storage	Surgeon	Graft Diam. mm	Host diam. mm	disparity	Suture	Op to final ROGS (M)	Final ROGS to CL fit (M)	Rejection episode(s)	Refractive Surgery
76	L	M	22	K					17	Fresh	Z	8	*8	*0	con	22	5	R	
77	L	M	36	K					50	K sol	X	8.25	7.5	0.75	int	24	7		
78	R	F	69	Bullous G		Double			69	Fresh	X	8.5	8	0.5	con	24			
79	R	M	38	K					95	Fresh	X	7.5	*7.5	*0	con	23	93		
80	R	M	31	K					81	Fresh	X	8	*8	*0	con	16	2		
81	L	M	28	K				A	70	Fresh	Y	8	8	0	con	15			
82	R	M	31	K				A	30	Fresh	X	8	7.5	0.5	int	9			
83	L	M	58	Bullous L		Prior			82	MK	Y	8.5	8	0.5	con	24			
84	R	F	29	K				A	72	Fresh	X	9	8.5	0.5	con	19	8		
85	R	M	14	K				A	**	Fresh	X	8.5	*8.5	*0	con	19	12	R	Y
86	R	M	48	Scar s/px		Double	3		78	Fresh	Y	8	7.5	0.5	int	58			
87	R	M	28	K	H				80	Fresh	X	8	7.5	0.5	con	12			
88	R	M	40	K					34	Fresh	Y	8	7.5	0.5	con	20	3	R	
89	L	M	34	K					42	K sol	Y	8	7.5	0.5	mix	18	7	R	
90	L	M	47	K				A	62	MK	Y	8.5	8	0.5	con	12	2	R	
91	R	F	36	K					35	K sol	X	8.5	8	0.5	con	17	55		
92	R	M	35	K				A	68	Fresh	Z	7.5	*7.5	*0	con	7			
93	R	M	23	K			2		30	Fresh	X	7	7	0	int				
94	L	M	25	HSK					89	Fresh	Z	6	6	0	con	9			
95	L	M	25	K					54	MK	Y	8.5	8	0.5	mix	22	6		
96	R	M	15	K					39	K sol	X	8.75	8.25	0.5	con	15			
97	L	M	31	K					36	MK	Y	8	7.5	0.5	con	18			
98	R	M	16	K				A	6	K sol	X	8.5	8	0.5	con	23			
99	L	M	26	K					55	MK	X	8.5	8	0.5	con	15			
100	L	F	48	Bullous B		Double			18	MK	X	9	8.5	0.5	int	13		R	

	Eye	*Sex*	*Age*	*Diagnosis*	*Hydrops*	*Aphakic*	*Regraft*	*Atopy*	*Age donor*	*Storage*	*Surgeon*	*Graft Diam. mm*	*Host diam. mm*	*disparity*	*Suture*	*Op to final ROGS (M)*	*Final ROGS to CL fit (M)*	*Rejection episode(s)*	*Refractive Surgery*
101	L	F	32	K					14	Fresh	X	7.5	7.5	0	con	13	3		
102	R	M	35	K				A	54	Fresh	X	8	*8	*0	con	24			
103	L	M	18	K					70	K sol	Y	8.5	8	0.5	con	29	8		
104	L	M	34	K				A	38	Fresh	Z	8	8	0	con	19	52		
105	R	M	36	K				A	50	Fresh	Y	8	7.5	0.5	con	16	31		
106	R	F	44	K	H				44	Fresh	X	8	7.5	0.5	con	27	2	R	
107	R	M	35	K					19	K sol	X	8.75	8	0.75	con	17			
108	R	M	32	K					28	MK	X	8.5	8	0.5	con	10	19		

Appendix C

Derivation of Asymmetry Component.

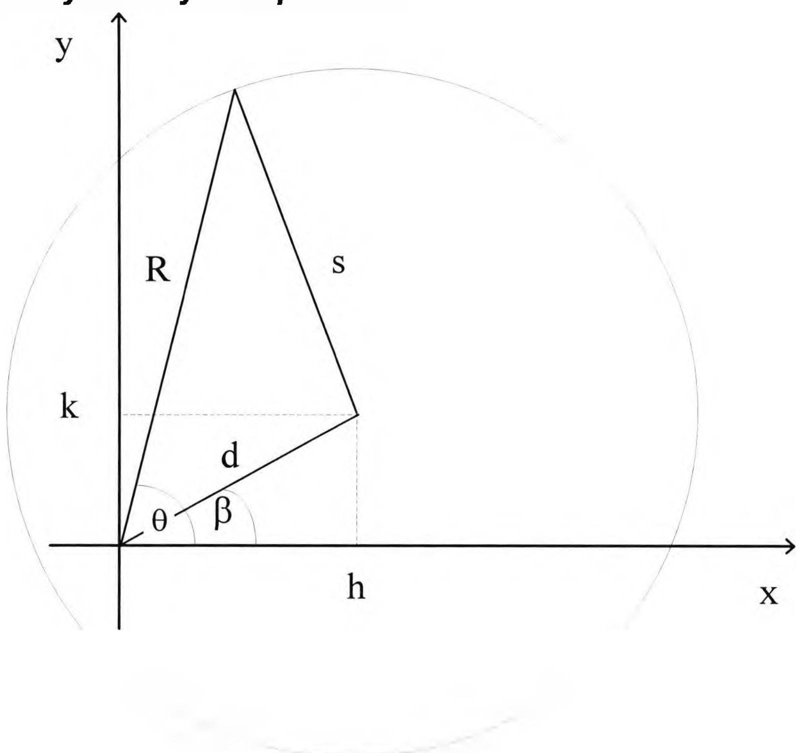


Figure C.1 Centre of spherical polar diagram off-set from the origin

s = radius of circle

d = off-set distance of centre from origin

R = distance from origin to any point on the curve

h = x-component of the off-set distance d

k = y-component of the off-set distance d

β= angle of off-set

θ = angle at which R is measured

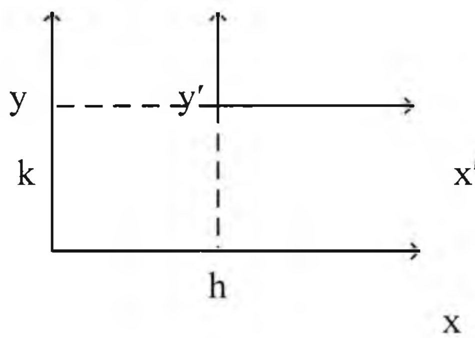
$$\sin\beta = \frac{k}{d} \therefore k = d\sin\beta$$

$$\cos\beta = \frac{h}{d} \therefore h = d\cos\beta$$

also x co-ordinate = R cos θ = x

y co-ordinate = $R \sin\theta = y$

The origin in x-y is shifted from an origin at the centre of the circle by (h , k)



$\therefore$ x - co-ordinate $\quad x = x' + h \quad x' = x - h$

y - co-ordinate $\quad y = y' + k \quad y' = y - k$

This relates co-ordinates in (x , y) to co-ordinates based on the centre of circle

The equation of the circle in co-ordinates (x' , y') (i.e. origin at centre) is :-

$x'^2 + y'^2 = s^2$

$\therefore (x - h)^2 + (y - k)^2 = s^2$

$\therefore (R\cos\theta - h)^2 + (R\sin\theta - k)^2 = s^2$

$\therefore R^2\cos^2\theta - 2hR\cos\theta + h^2 + R^2\sin^2\theta - 2kR\sin\theta + k^2 = s^2$

$\therefore R^2\cos^2\theta + R^2\sin^2\theta - 2hR\cos\theta - 2kR\sin\theta + h^2 + k^2 - s^2 = 0$

$\therefore R^2(\cos^2\theta + \sin^2\theta) - 2R(h\cos\theta + k\sin\theta) + h^2 + k^2 - s^2 = 0$

$\therefore R^2 - 2R(h\cos\theta + k\sin\theta) + h^2 + k^2 - s^2 = 0$

This is a quadratic of the form $aR^2 + bR + c = 0$

where $a = 1$

$b = -2(h\cos\theta + k\sin\theta)$

$c = h^2 + k^2 - s^2$

Solution is $$x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

$$\therefore R = \frac{+2(h\cos\theta + k\sin\theta) \pm \{(2(h\cos\theta + k\sin\theta))^2 - 4(h^2 + k^2 - s^2)\}^{1/2}}{2}$$

$$= \frac{2(h\cos\theta + k\sin\theta) \pm \{4(h\cos\theta + k\sin\theta)^2 - 4(h^2 + k^2 - s^2)\}^{1/2}}{2}$$

$$= \frac{2(h\cos\theta + k\sin\theta) \pm \{4[(h\cos\theta + k\sin\theta)^2 - (h^2 + k^2 - s^2)]\}^{1/2}}{2}$$

$= h \cos \theta + k \sin \theta \pm \{ (d \cos \beta \cos \theta + d \sin \beta \sin \theta)^2 - (d^2 - s^2) \}^{1/2}$

$= h \cos \theta + k \sin \theta \pm \{ d^2 (\cos \beta \cos \theta + \sin \beta \sin \theta)^2 - d^2 + s^2 \}^{1/2}$

$= h \cos \theta + k \sin \theta \pm \{ d^2 (\cos (\theta - \beta)^2 - d^2 + s^2 \}^{1/2}$

$= h \cos \theta + k \sin \theta \pm \{ d^2 (\cos^2 (\theta - \beta) - 1) + s^2 \}^{1/2}$

$= h \cos \theta + k \sin \theta \pm \{ d^2 (- \sin^2 (\theta - \beta)) + s^2 \}^{1/2}$

$R (\theta) = h \cos \theta + k \sin \theta \pm \{ s^2 - d^2 \sin^2(\theta - \beta) \}^{1/2}$

$\sin^2 (\theta - \beta)$ has max value of 1. $\therefore$ If $d \ll s$, then

$s^2 - d^2 \sin^2 (\theta - \beta) \rightarrow s^2$

$\therefore R (\theta) = h \cos \theta + k \sin \theta + s$ (for positive root)

$\therefore R (\theta) = s + h \cos \theta + k \sin \theta$

$[h = d \cos \beta]$

$[k = d \sin \beta]$

$\therefore R(\theta) = s + d \cos \beta \cos \theta + d \sin \beta \sin \theta$

$= s + d (\cos \beta \cos \theta + \sin \beta \sin \theta)$

$R(\theta) = s + d \cos (\theta - \beta)$

To determine values of s, d and β

Value of s

The average of any function over an interval is

e.g. $$\bar{R}(\theta) = \frac{\int_{\theta_1}^{\theta_2} R(\theta)d\theta}{\int_{\theta_1}^{\theta_2} d\theta}$$

In this case we want to determine averages over the range where $\theta_1 = 0$ and $\theta_2 = 2\pi$

i.e. the average around the whole circle.

$$\bar{R}(\theta) = \frac{\int_0^{2\pi}(s + h\cos\theta + k\sin\theta)d\theta}{\int_0^{2\pi} d\theta}$$

$$= \frac{\int_0^{2\pi} d\theta + h\int_0^{2\pi}\cos\theta d\theta + k\int_0^{2\pi}\sin d\theta}{[\theta]_0^{2\pi}}$$

$$= \frac{[s\theta]_0^{2\pi} + h[\sin\theta]_0^{2\pi} + k[-\cos\theta]_0^{2\pi}}{[2\pi - 0]}$$

$$= \frac{1}{2\pi}\{ s . 2\pi - 0 + h(\sin 2\pi - \sin 0) + k(-\cos 2\pi + \cos 0)\}$$

$$= \frac{1}{2\pi}\{ s . 2\pi + h(0 - 0) + k(-1 + 1)\}$$

$$= \frac{1}{2\pi} . 2\pi s$$

$$= s$$

∴ The average of all the measured distances from the origin is the radius of the circle. If the average is estimated from the 12 readings then

$$\frac{\sum_{i=1}^{12} R_i(\theta)}{\sum_{i=1}^{12}} = \frac{1}{12}\{\sum_{i=1}^{12} R_i(\theta)\} = s$$

Values of d and β

In order to find the values of d and β, we must first find the values of h and k. From these we can calculate the magnitude and angle of the asymmetry.

Firstly we must determine the relationship between the average y component of the measured points and k.

The average y component of the measured points is

$$\bar{y} = \frac{\int_0^{2\pi} y\,d\theta}{\int_0^{2\pi} d\theta} = \frac{\int_0^{2\pi} R\sin\theta\,d\theta}{\int_0^{2\pi} d\theta} \qquad (y = R\sin\theta)$$

$R = s + h\cos\theta + k\sin\theta$

$$\therefore\ \bar{y} = \frac{\int_0^{2\pi} \sin\theta(s + h\cos\theta + k\sin\theta)d\theta}{\int_0^{2\pi} d\theta}$$

$$= \frac{\int_0^{2\pi} (s\sin\theta + h\sin\theta\cos\theta + k\sin^2\theta)d\theta}{[\theta]_0^{2\pi}}$$

$$= \frac{1}{2\pi}\ \{\int_0^{2\pi}(s\sin\theta d\theta + h\int_0^{2\pi}\sin\theta\cos\theta d\theta + k\int_0^{2\pi}\sin^2\theta d\theta\}$$

$$= \frac{1}{2\pi}\ \{ s\,[-\cos\theta\,]_0^{2\pi}\ + h\int_0^{2\pi} \tfrac{1}{2}\sin 2\theta d\theta + k[\frac{\theta}{2} - \sin\frac{\theta}{2}]_0^{2\pi}\}$$

$$= \frac{1}{2\pi}\ \{ s\,[-1 + 1\,] + \frac{h}{2}[-\tfrac{1}{2}\cos 2\,\theta\,]_0^{2\pi}\ + k\,[\,\frac{2\pi}{2} - \sin\frac{2\pi}{2} - 0 + \sin 0]\}$$

$$= \frac{1}{2\pi}\ \{ s\,[\,0\,] + \frac{h}{2}[-\tfrac{1}{2}\cos 4\pi + \tfrac{1}{2}\cos 0] + k(\frac{2\pi}{2} - 0 - 0 + 0)\}$$

$$= \frac{1}{2\pi}\ (\,0 + \frac{h}{2}(0) + \frac{k}{2}.2\pi)$$

$$= \frac{1}{2\pi} . \frac{k}{2} 2\pi$$

$$= \frac{k}{2}$$

Average over 12 values is $\frac{1}{12}\sum_{i=1}^{12} R_i(\theta_i)\sin\theta_i = \frac{k}{2}$

A similar process must be performed in order to determine the relationship between the average x component of the measured points and h.

The average x component of the measured points is

$$\bar{x} = \frac{\int_0^{2\pi} x d\theta}{\int_0^{2\pi} d\theta} = \frac{\int_0^{2\pi} R\cos\theta d\theta}{\int_0^{2\pi} d\theta} \qquad (x = R\cos\theta)$$

R = s + h cos θ + k sin θ

$$\therefore \quad \bar{x} = \frac{\int_0^{2\pi} \cos\theta(s + h\cos\theta + k\sin\theta)d\theta}{\int_0^{2\pi} d\theta}$$

$$= \frac{\int_0^{2\pi} (s\cos\theta + h\cos^2\theta + k\sin\theta\cos\theta)d\theta}{[\theta]_0^{2\pi}}$$

$$= \frac{1}{2\pi} \{ \int_0^{2\pi} (s\cos\theta d\theta + h\int_0^{2\pi} \cos^2\theta d\theta + k\int_0^{2\pi} \sin^2\theta\cos\theta d\theta\}$$

$$= \frac{1}{2\pi} \{ s[\sin\theta]_0^{2\pi} + h[\frac{\theta}{2} + \sin\frac{\theta}{2}]_0^{2\pi} + k\int_0^{2\pi} \tfrac{1}{2}\sin 2\theta d\theta\}$$

$$= \frac{1}{2\pi} \{ s[\sin 2\pi - \sin 0] + h[\frac{2\pi}{2} + \sin\frac{2\pi}{2} - 0 - \sin 0] + k[-\tfrac{1}{2}\cos 2\theta]_0^{2\pi}$$

$$= \frac{1}{2\pi} \{ s[0 - 0] + \frac{h}{2}[2\pi + 0 - 0 - 0] + \frac{k}{2}[-\tfrac{1}{2}\cos 4\pi + \tfrac{1}{2}\cos o]\}$$

$$= \frac{1}{2\pi} \{ \frac{h}{2}.2\pi + \frac{k}{2}(-\tfrac{1}{2} + \tfrac{1}{2})\}$$

$$= \frac{1}{2\pi} \cdot 2\pi \cdot \frac{h}{2}$$

$$\bar{x} = \frac{h}{2}$$

Average over 12 values is $\frac{1}{12}\sum_{i=1}^{12} R_i(\theta_i)\cos\theta_i = \frac{h}{2}$

We can now deduce h from the average x component of the measured points

$$h = \frac{1}{6}\sum_{i=1}^{12} R_i(\theta_i)\cos\theta_i$$

and can deduce k from the average y component of the measured points

$$k = \frac{1}{6}\sum_{i=1}^{12} R_i(\theta_i)\sin\theta_i$$

The components for the magnitude and the angle of asymmetry, d and β, can now be calculated :-

$$d = \sqrt{h^2 + k^2}$$

$$\beta = \arctan(k/h)$$

Astigmatism Component

In this thesis the formula used to describe the curvature changes in a given ring is :-

(1) $$R_\theta = s + d\cos(\theta - \beta) + c/2\cos 2(\theta - \phi)$$

The asymmetry component was derived above. The astigmatic component has been published in a refereed journal by Maloney, Bogan and Waring [652]. A rigorous mathematical derivation is therefore not included in this thesis, but a brief resume is included below.

The equation for an ellipsoid centred at the origin of an x,y,z co-ordinate system is :-

$$\frac{x^2}{a^2} + \frac{y^2}{b^2} + \frac{z^2}{c^2} = 1 \qquad \text{with semi axes a, b, and c.}$$

The apex of an ellipsoid is a close approximation to a perfect sphero-cylindrical surface. The formula can be reduced to :-

$$z^2 + \frac{D_x}{\alpha} x^2 + \frac{D_y}{\alpha} y^2 = 1$$

x and y define a position on the iris plane and the z -axis is the vertex normal to the cornea. D_x is the power at the apex along the 180° meridian and D_y the power in the 90° meridian. α is the constant 337.5 which relates corneal power in diopters to radius of curvature in mm.

Converting to cylindrical co-ordinates with x = s cos θ and y = s sin θ (where r is the radius from the centre of the keratograph), and rearranging :-

$$z^2 + \frac{r^2}{\alpha}\left(\frac{D_x + D_y}{2} + \frac{D_x - D_y}{2}\cos 2\theta\right) = 1$$

This equation can differentiated, with a θ fixed to give dz/dr and d^2z/dr^2. These quantities are then substituted into the standard formula for radius of curvature of a section of a curved surface, with two principal sections, such as a rotation ellipse. If the second order and higher terms are discarded, then the dioptric power of this ellipsoid at any point near its apex is :-

$$D_{(r,\theta)} = \frac{D_x + D_y}{2} + \left(\frac{D_x - D_y}{2}\right)\cos 2\theta$$

This ellipsoid is oriented along the x- and y- axes. If it is oriented along the meridian ϕ, its equation is given by:

$$D_{(r,\theta)} = \frac{D_x + D_y}{2} + \left(\frac{D_x - D_y}{2}\right)\cos 2(\theta - \phi) \quad (2)$$

The term $\frac{D_x + D_y}{2}$ represents the average power of the two principal meridians, which for a perfect sphero-cylindrical surface, equals the average in all the meridians. This is represented by the term s in the main equation (1).

Astigmatism has been defined as the difference between the two principal meridians. Therefore the term $\frac{D_x - D_y}{2}$ represents half the astigmatism or c/2.

Formula (2) was used, but in this thesis the values were input as radius of curvature.

The constants for the astigmatic component, c and ϕ, were derived from the twelve observed data points in the same manner as the constants d and β, except that cos of twice the angle θ and sin of twice the angle θ are used.

$$h_{astig} = \frac{1}{6}\sum_{i=1}^{12} R_i(\theta_i)\cos 2\theta_i$$

$$k_{astig} = \frac{1}{6}\sum_{i=1}^{12} R_i(\theta_i)\sin 2\theta_i$$

The constants c and ϕ, the magnitude and axis of astigmatism, were then calculated in the same manner as for asymmetry :-

$$c = \sqrt{h_{astig}^2 + k_{astig}^2}$$

$$\phi = \arctan\left(\frac{k_{astig}}{h_{astig}}\right)$$

Examples of Components derived from individual keratograph rings.

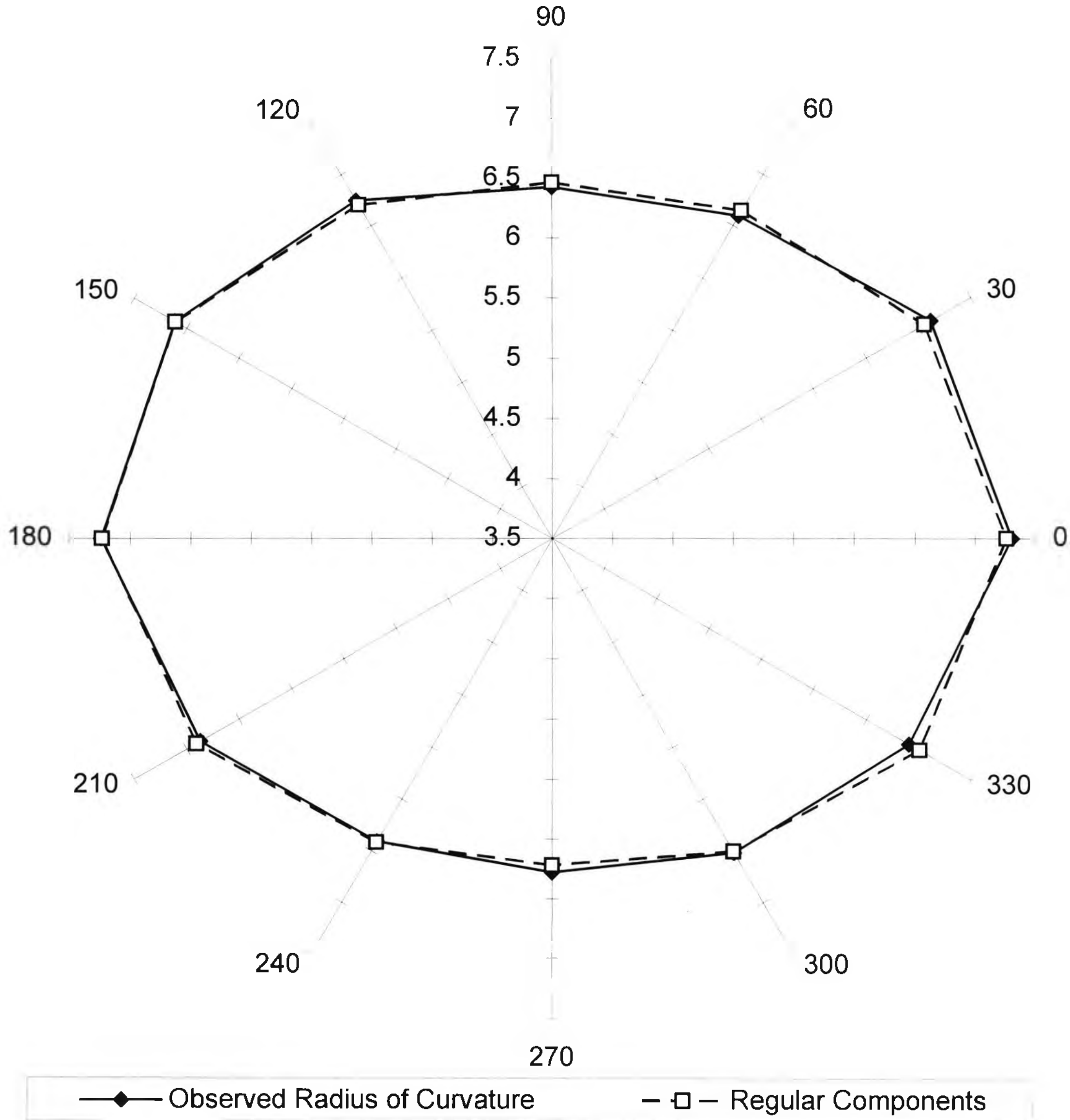
Figures C.2. to C.7 show regular astigmatism at various axes ranging from 0 to 180 degrees.

Figure C.9 shows a rare example of a transplant that is almost spherical.

The remaining figures have higher amounts of Irregularity.

Figure C.17 shows an example with particularly high Asymmetry. In this case the scale of the axis of the polar diagram had to be changed in order to accommodate all the data. In all the previous examples the scale was kept constant in order to facilitate comparison. The distance from the centre to the edge represented a range of 4 mm of radius of curvature.

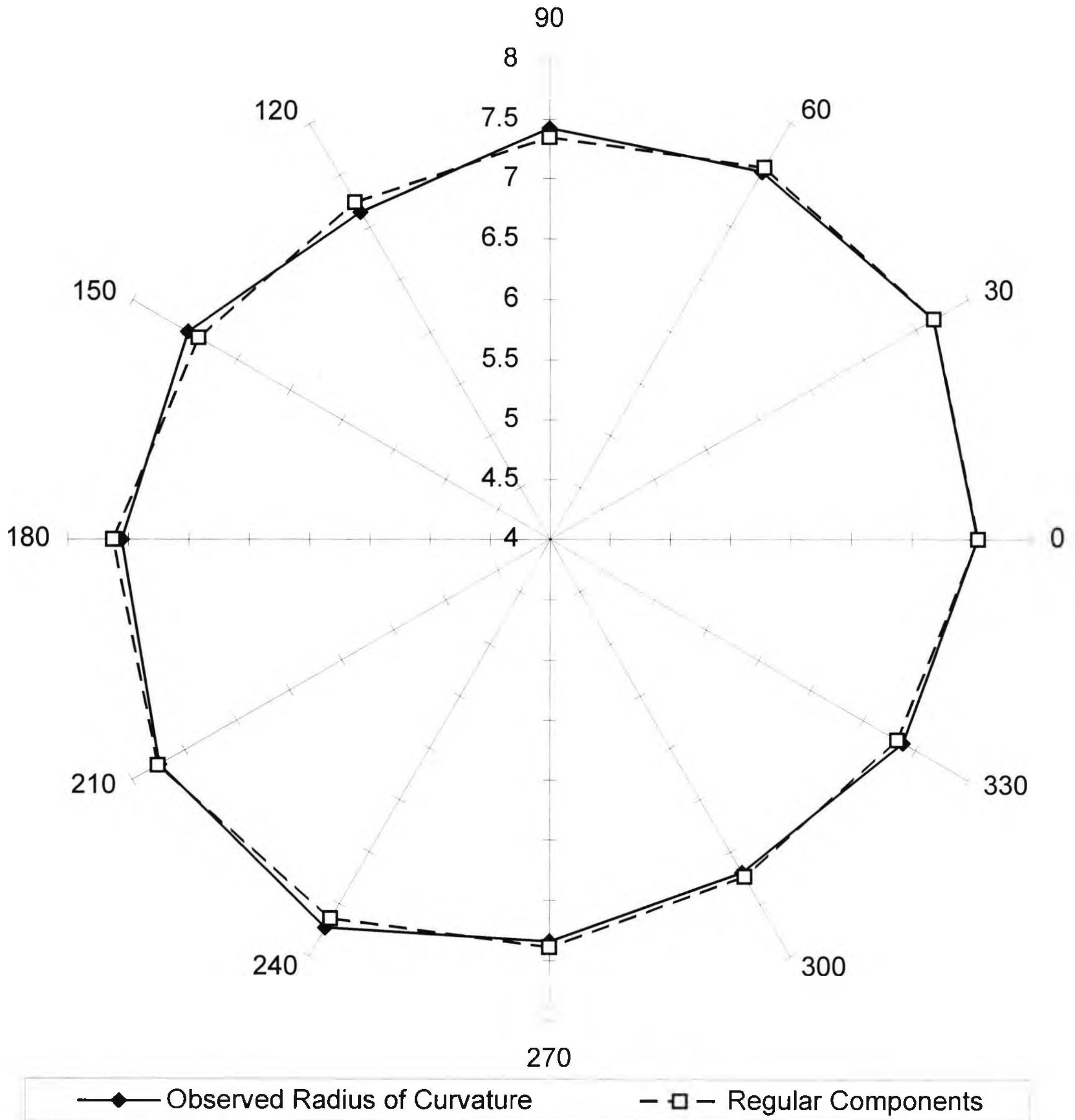
Figure C.18 describes the same data as in Figure C.17 except that the asymmetry component has been omitted from the calculations. The result is that the Astigmatic component is centred on the origin and the deviation from the observed data points is much greater, resulting in an artificially high Irregularity component.



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.31	7.12	6.59	6.43	6.75	7.11	7.24	6.87	6.41	6.28	6.52	6.91
Regular Components	7.26	7.06	6.64	6.46	6.70	7.11	7.23	6.91	6.42	6.22	6.51	7.01
Deviation	0.05	0.06	-0.05	-0.04	0.05	0.01	0.00	-0.04	-0.01	0.06	0.01	-0.10

Patient #	Stage	ring #		s	d	β	c	ϕ	I
8	1Y	1		6.79	0.12	84	0.91	177	0.05

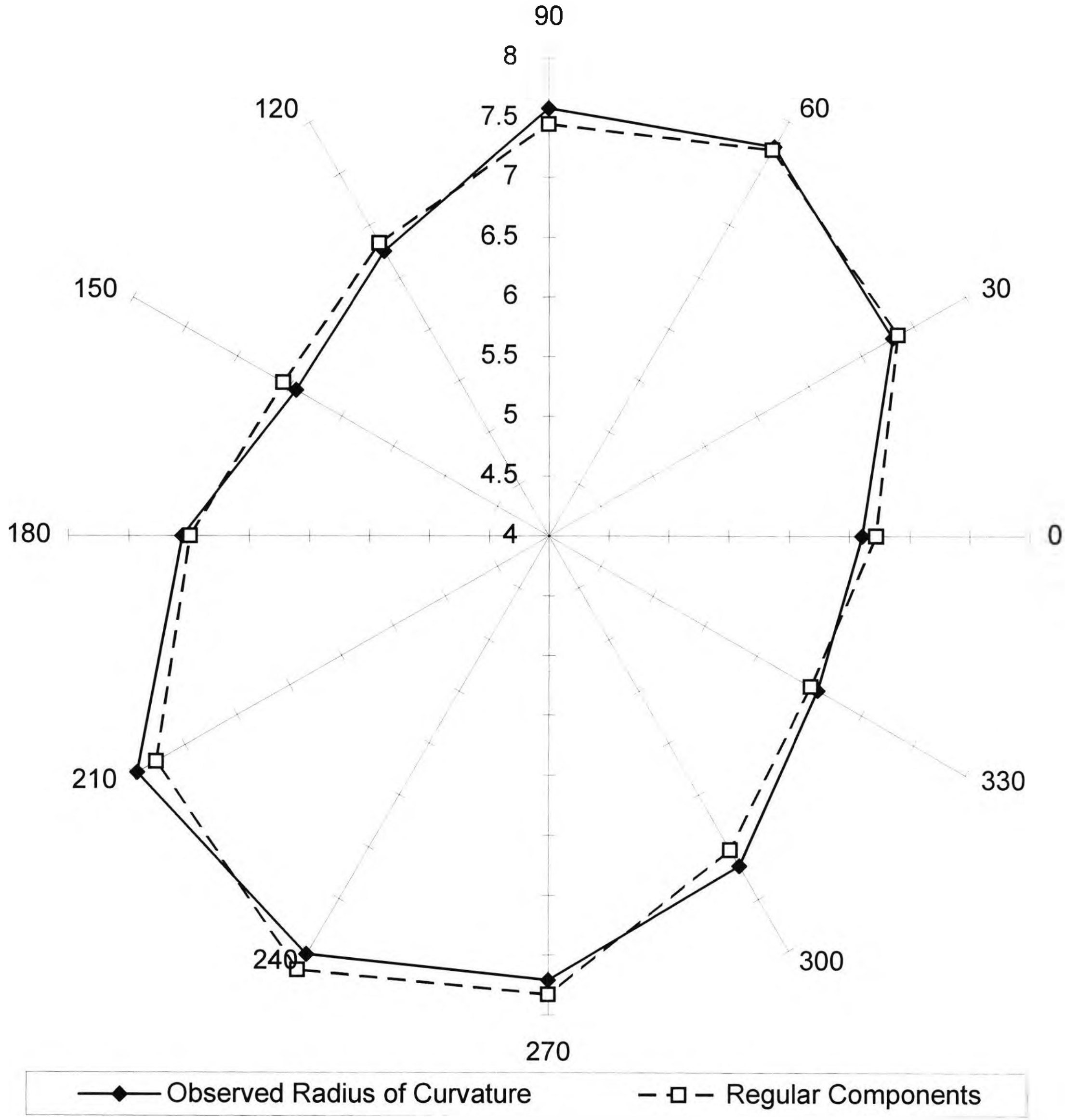
Figure C.2



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.54	7.67	7.52	7.42	7.15	7.47	7.55	7.74	7.73	7.34	7.20	7.38
Regular Components	7.55	7.67	7.56	7.34	7.24	7.37	7.62	7.76	7.64	7.39	7.24	7.33
Deviation	-0.01	0.00	-0.04	0.08	-0.09	0.10	-0.07	-0.02	0.09	-0.05	-0.04	0.05

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
23	3M	1		7.48	0.04	210	0.48	31	0.06

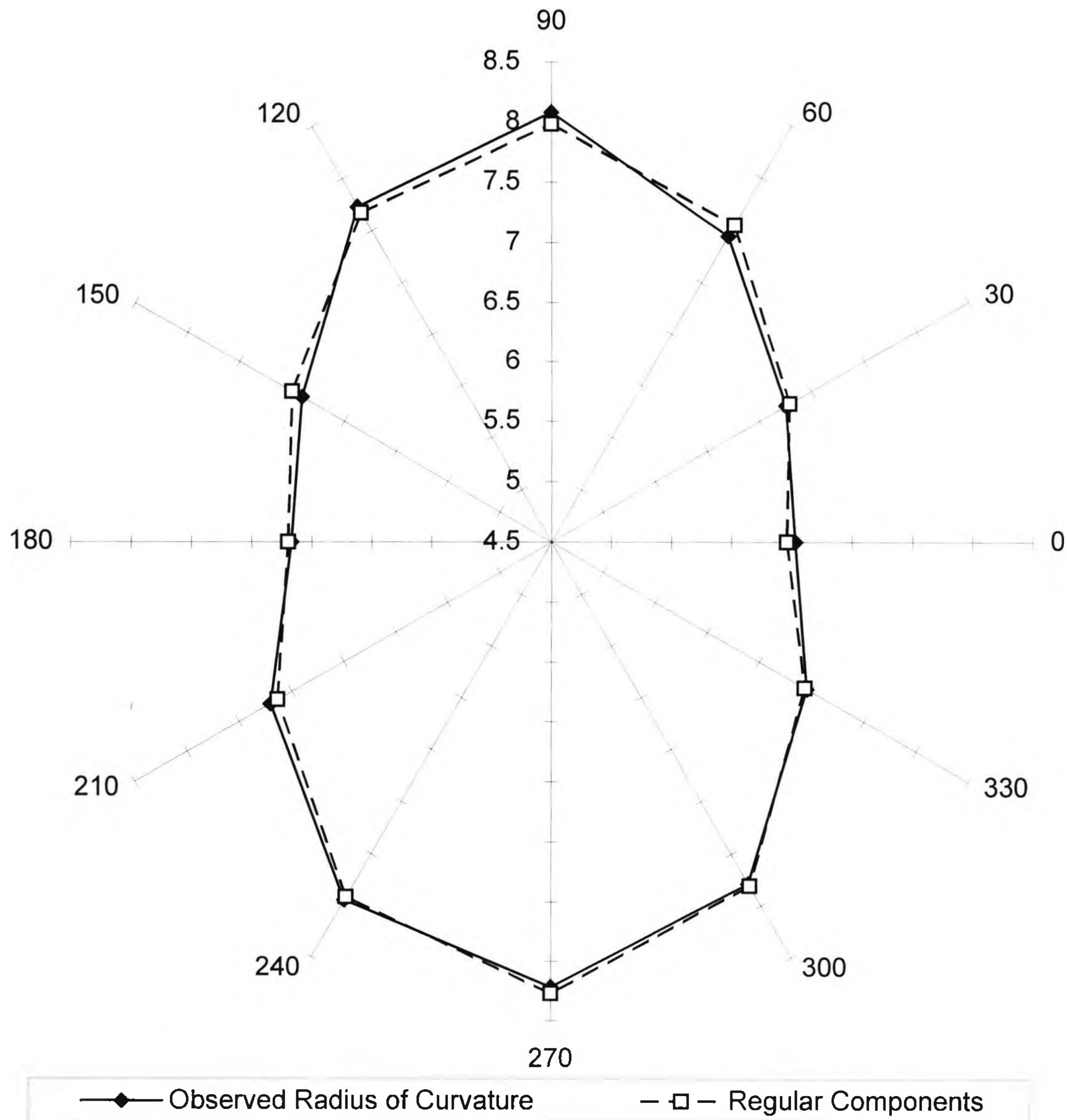
Figure C.3



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	6.61	7.30	7.75	7.58	6.75	6.44	7.05	7.96	8.04	7.71	7.18	6.59
Regular Components	6.72	7.35	7.72	7.45	6.83	6.56	6.99	7.78	8.19	7.83	7.03	6.52
Deviation	-0.11	-0.05	0.03	0.13	-0.08	-0.12	0.06	0.18	-0.15	-0.12	0.15	0.07

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
6	3Y	1		7.25	0.24	235	1.42	62	0.11

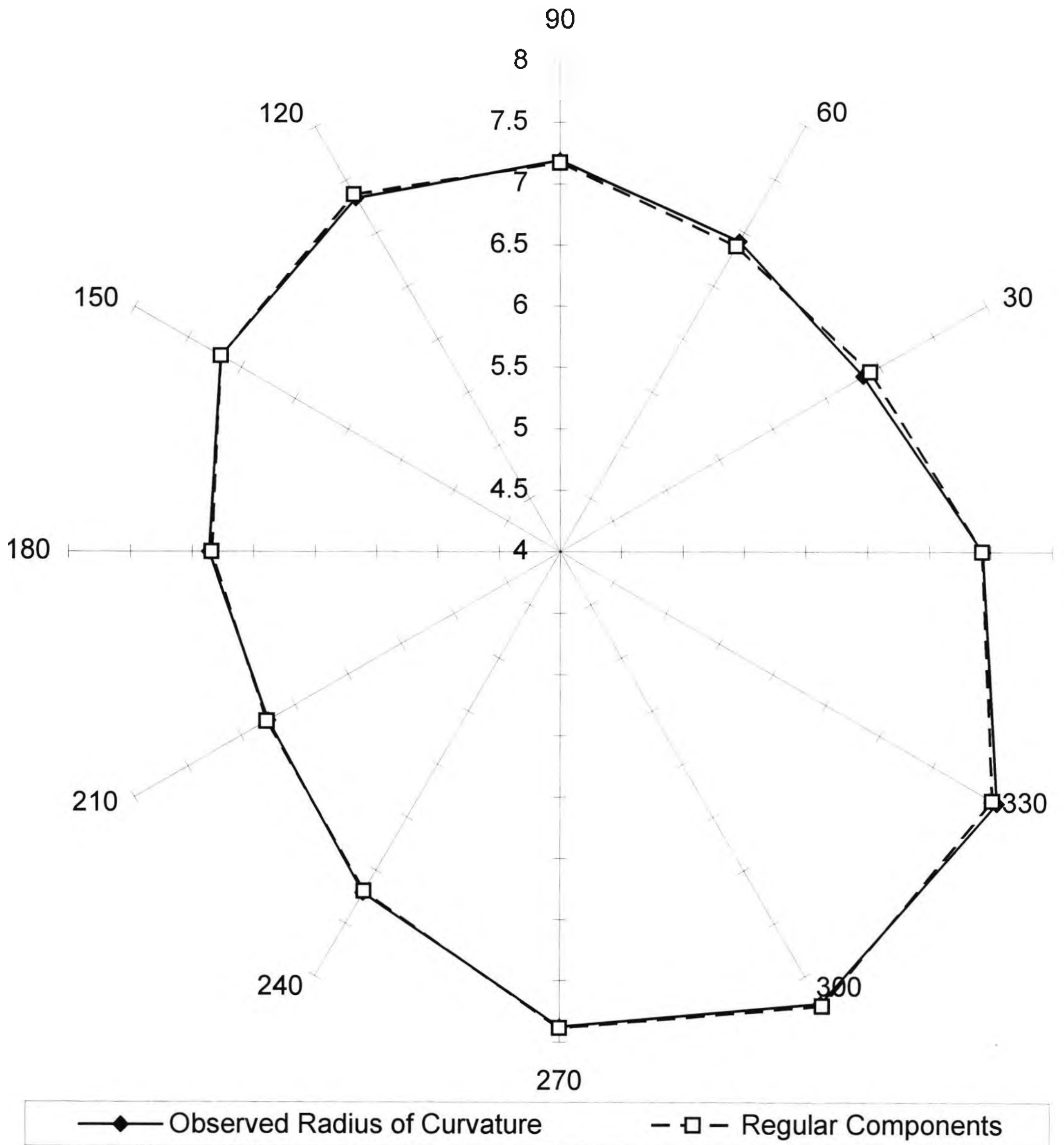
Figure C.4



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	6.53	6.75	7.45	8.08	7.73	6.90	6.67	7.20	7.95	8.21	7.78	6.96
Regular Components	6.46	6.79	7.55	7.98	7.68	7.00	6.70	7.13	7.92	8.27	7.81	6.94
Deviation	0.07	-0.03	-0.11	0.10	0.06	-0.10	-0.03	0.07	0.03	-0.05	-0.02	0.02

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
9	2Y	1		7.35	0.19	231	1.55	90	0.06

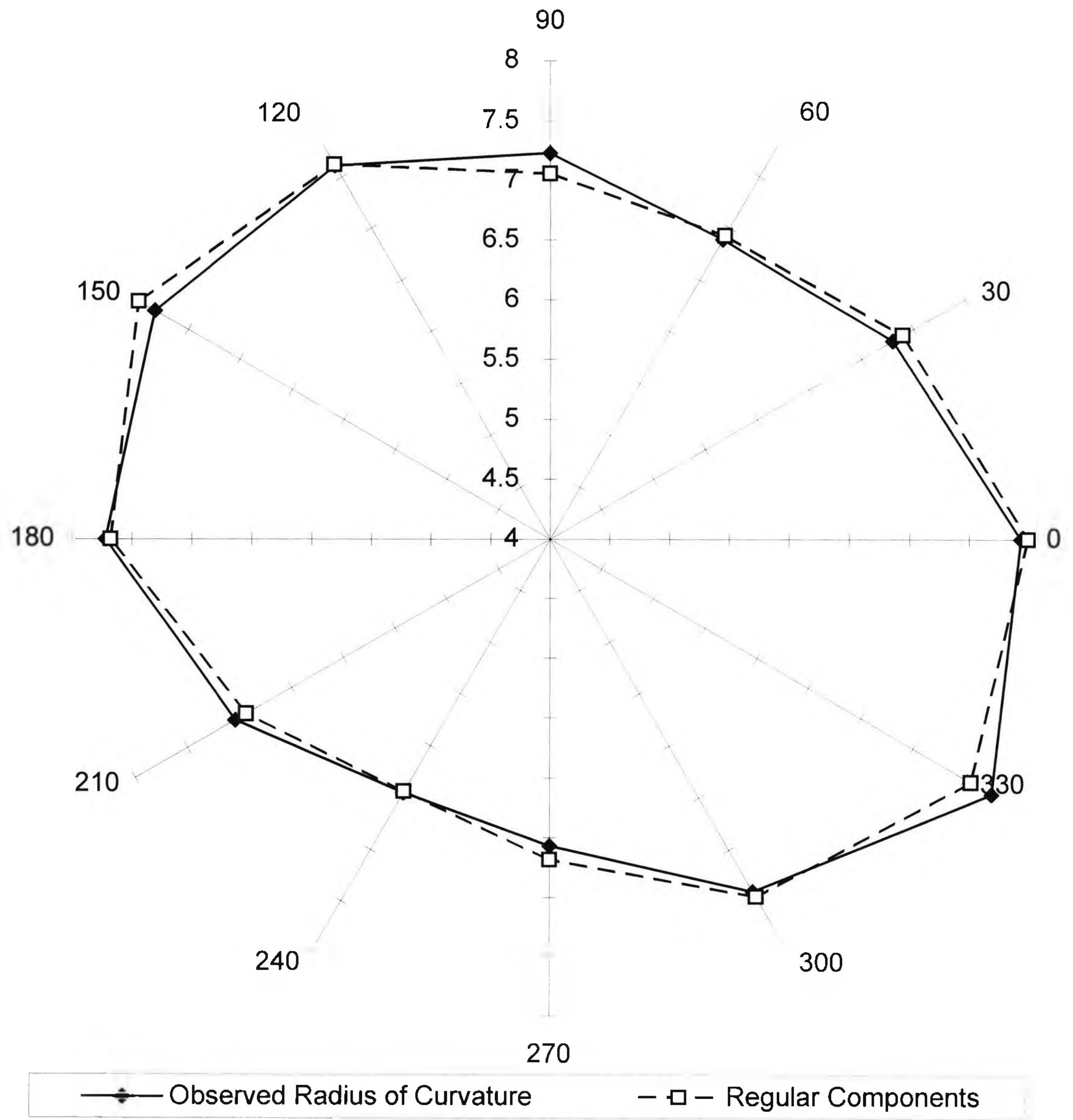
Figure C.5



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.43	6.85	6.92	7.19	7.33	7.19	6.86	6.75	7.21	7.87	8.25	8.10
Regular Components	7.43	6.91	6.87	7.17	7.37	7.19	6.84	6.76	7.20	7.89	8.28	8.06
Deviation	0.01	-0.06	0.05	0.02	-0.04	0.00	0.02	-0.02	0.02	-0.01	-0.03	0.04

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
16	5Y	1		7.33	0.46	309	0.99	123	0.03

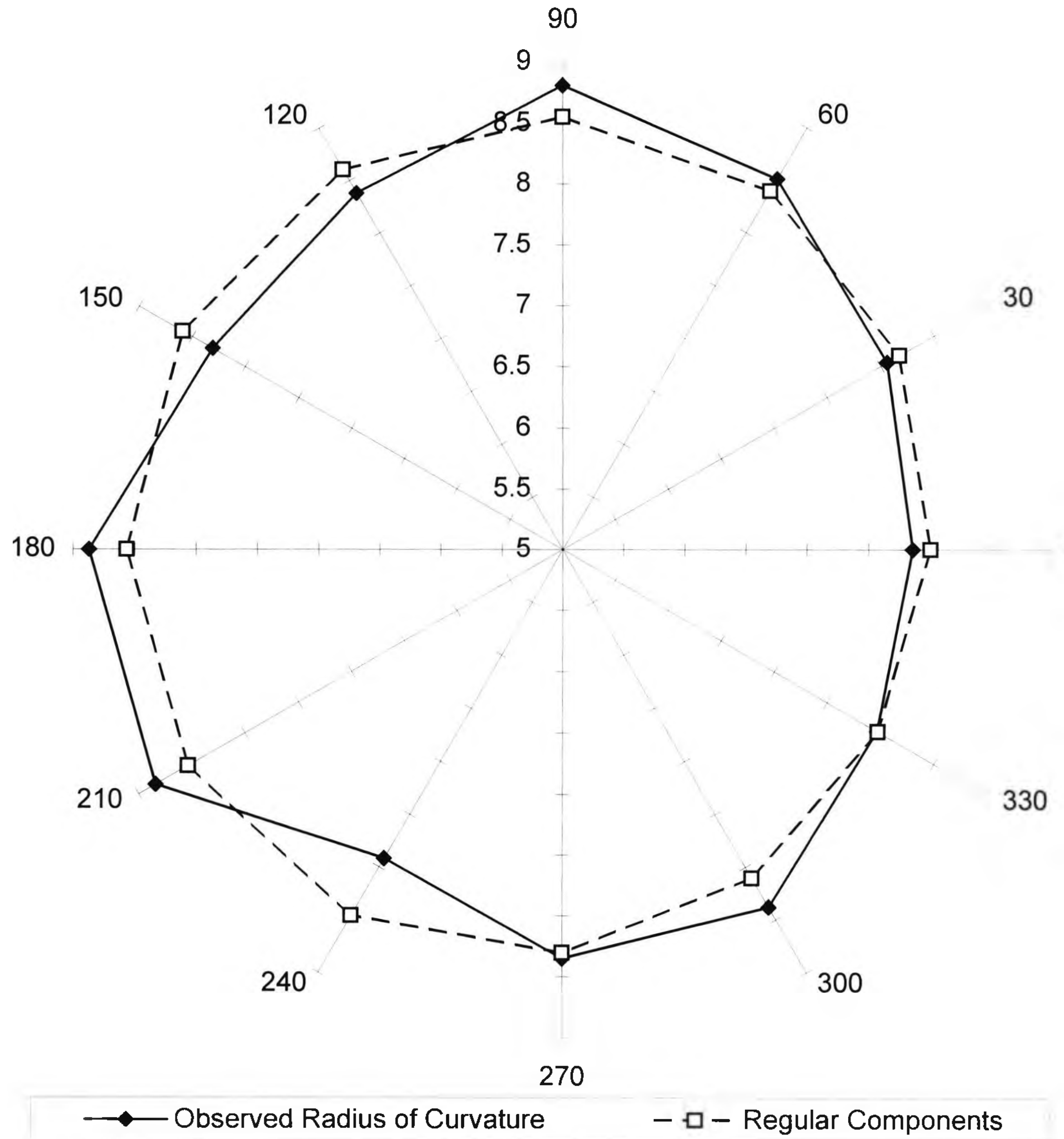
Figure C.6



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.94	7.30	6.89	7.23	7.61	7.82	7.72	7.04	6.45	6.57	7.41	8.26
Regular Components	7.99	7.40	6.93	7.06	7.62	7.98	7.67	6.93	6.44	6.68	7.45	8.06
Deviation	-0.06	-0.10	-0.04	0.17	-0.01	-0.16	0.04	0.10	0.01	-0.12	-0.05	0.20

Patient #	Stage	Ring #		s	d	β	c	ϕ	l
6	6M	1		7.35	0.25	50	1.38	157	0.11

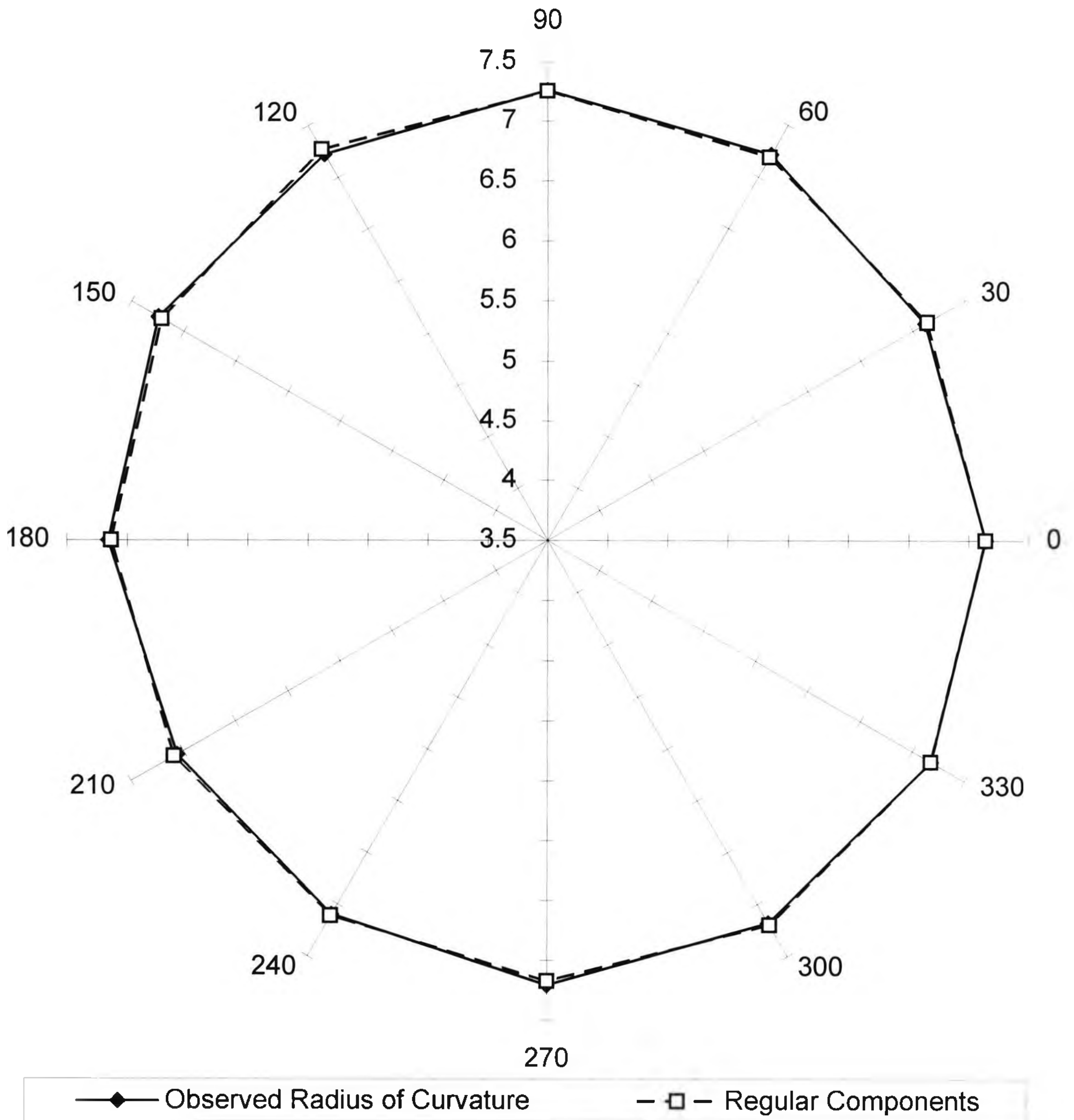
Figure C.7



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.86	8.06	8.51	8.81	8.38	8.31	8.87	8.84	7.92	8.35	8.38	7.97
Regular Components	8.00	8.17	8.40	8.55	8.60	8.59	8.56	8.54	8.46	8.30	8.11	7.98
Deviation	-0.14	-0.11	0.11	0.26	-0.22	-0.28	0.31	0.30	-0.54	0.05	0.27	-0.01

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
7	9Y	1		8.36	0.31	156	0.17	75	0.26

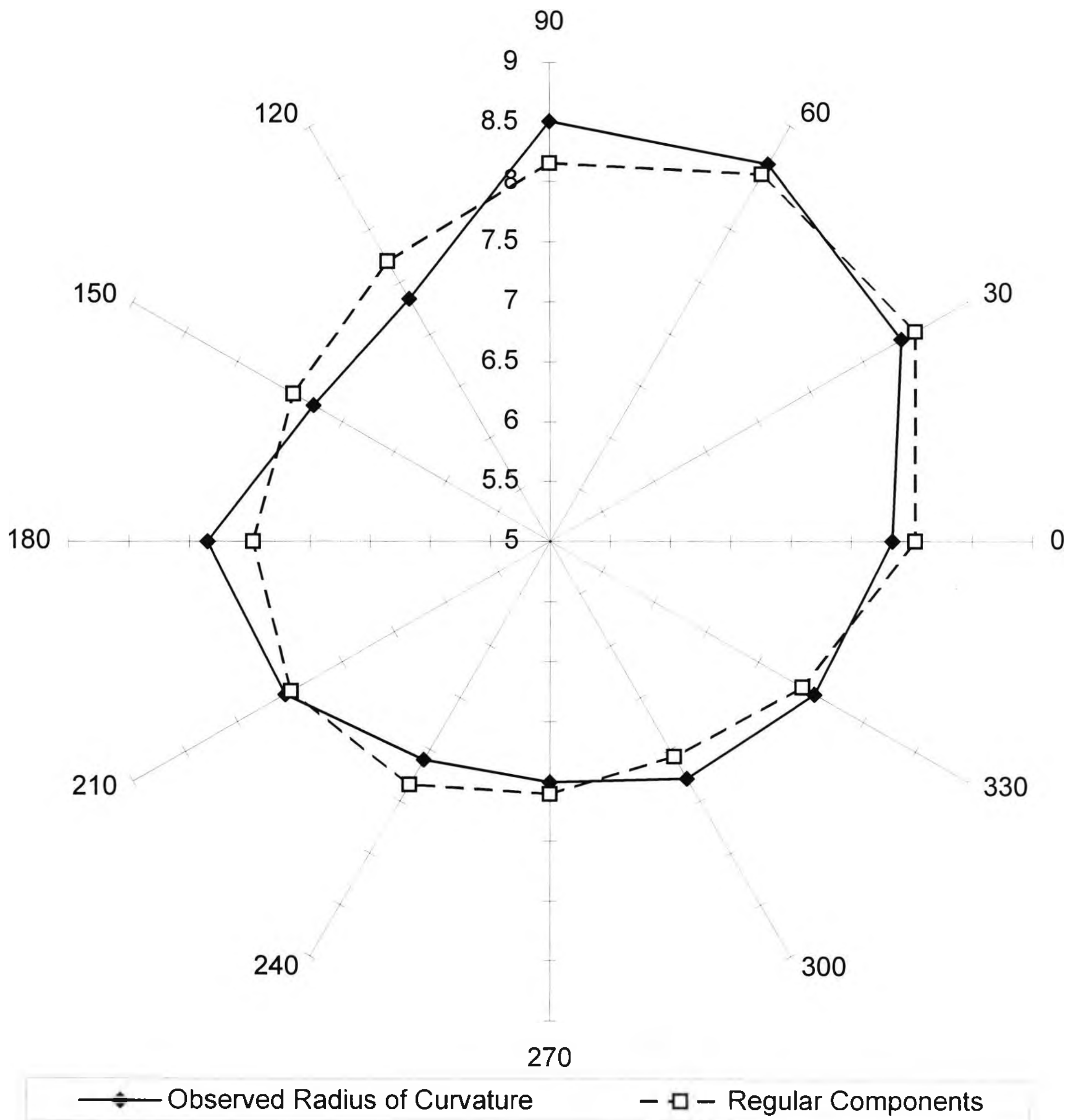
Figure C.8



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.14	7.12	7.22	7.26	7.22	7.24	7.16	7.06	7.10	7.20	7.18	7.18
Regular Components	7.14	7.14	7.19	7.25	7.27	7.21	7.13	7.09	7.11	7.17	7.20	7.18
Deviation	0.00	-0.02	0.03	0.00	-0.04	0.03	0.02	-0.03	-0.01	0.04	-0.02	0.00

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
9	7Y	1		7.17	0.04	86	0.12	116	0.02

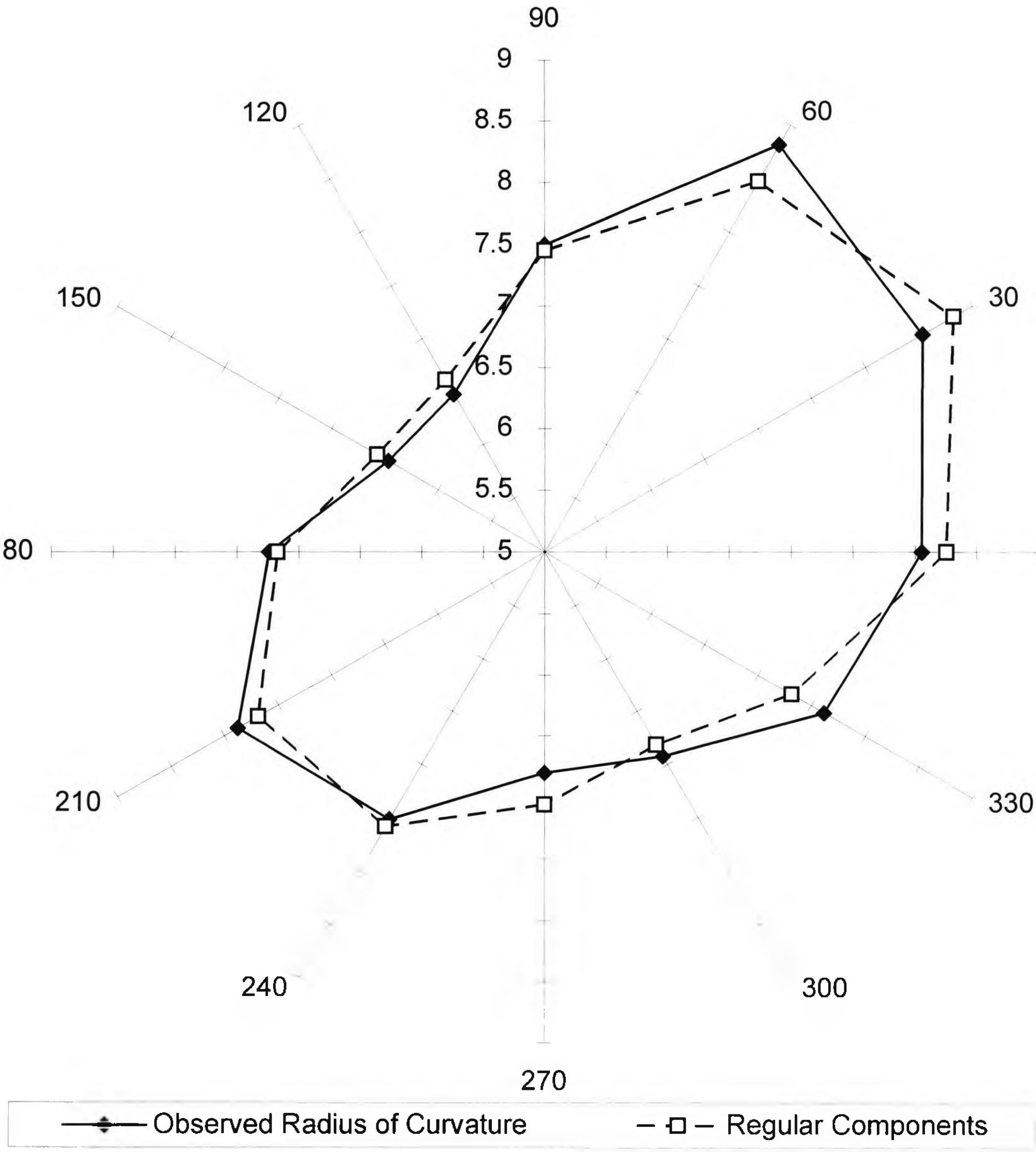
Figure C.9



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.84	8.37	8.63	8.51	7.34	7.27	7.85	7.54	7.10	7.01	7.28	7.54
Regular Components	8.03	8.50	8.53	8.16	7.70	7.46	7.47	7.49	7.34	7.11	7.07	7.42
Deviation	-0.19	-0.13	0.10	0.35	-0.36	-0.19	0.38	0.05	-0.24	-0.10	0.21	0.12

Patient #	Stage	Ring #		s	d	β	c	ϕ	l
29	6M	1		7.69	0.59	62	0.65	40	0.23

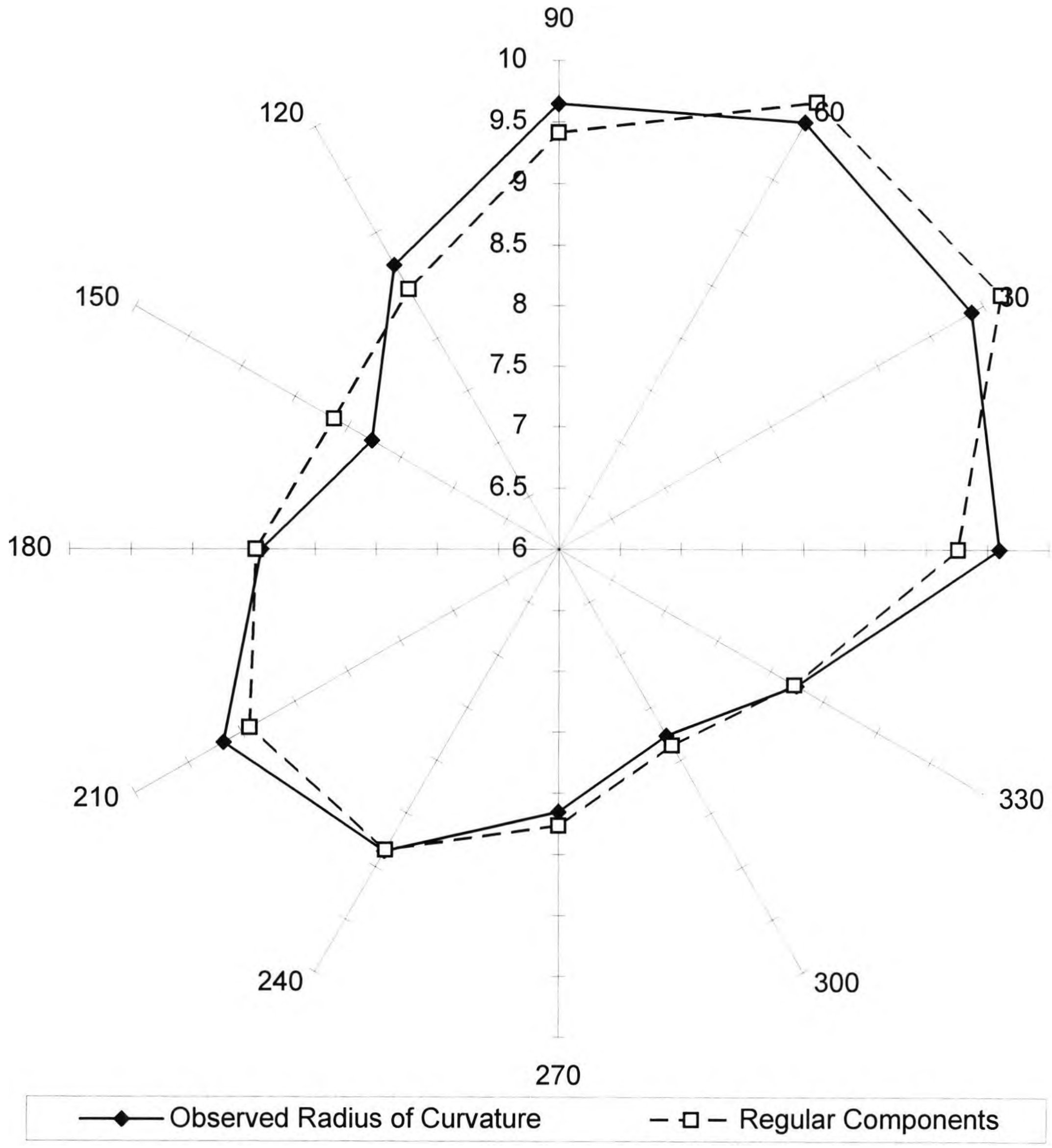
Figure C.10



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	8.05	8.53	8.81	7.50	6.48	6.47	7.24	7.87	7.52	6.80	6.92	7.62
Regular Components	8.26	8.82	8.47	7.45	6.61	6.57	7.17	7.69	7.58	7.06	6.82	7.31
Deviation	-0.20	-0.29	0.34	0.05	-0.14	-0.11	0.07	0.19	-0.07	-0.26	0.11	0.31

Patient #	Stage	Ring #		s	d	β	c	ϕ	l
29	7Y	1		7.48	0.58	20	1.58	37	0.20

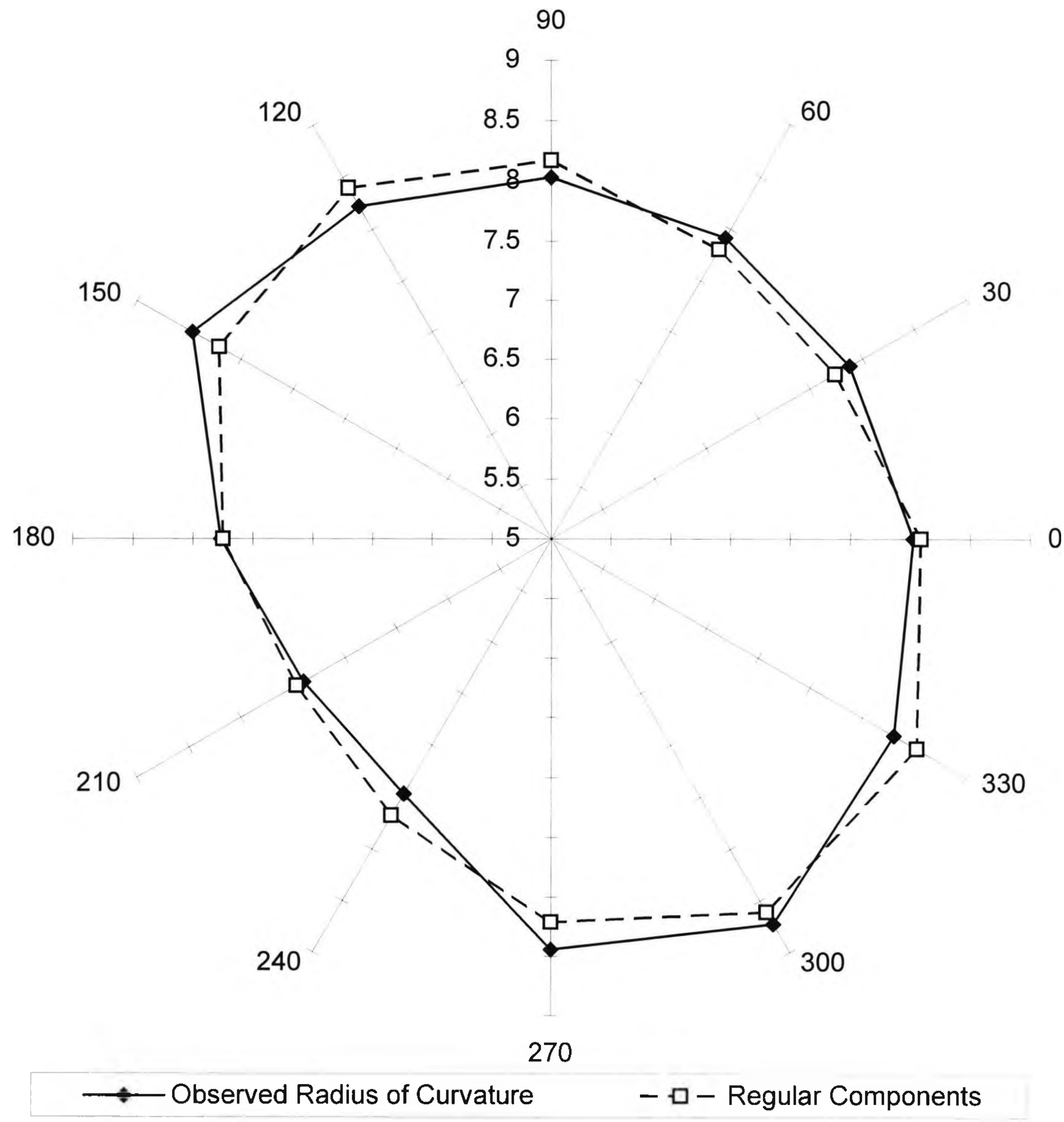
Figure C.11



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	9.60	9.89	10.03	9.65	8.70	7.77	8.44	9.17	8.85	8.15	7.76	8.24
Regular Components	9.26	10.17	10.22	9.41	8.47	8.13	8.48	8.92	8.84	8.26	7.86	8.23
Deviation	0.34	-0.28	-0.19	0.24	0.23	-0.36	-0.05	0.24	0.01	-0.11	-0.09	0.02

Patient #	Stage	Ring #		s	d	β	c	ϕ	l
53	1.5Y	1		8.85	0.69	56	1.58	44	0.21

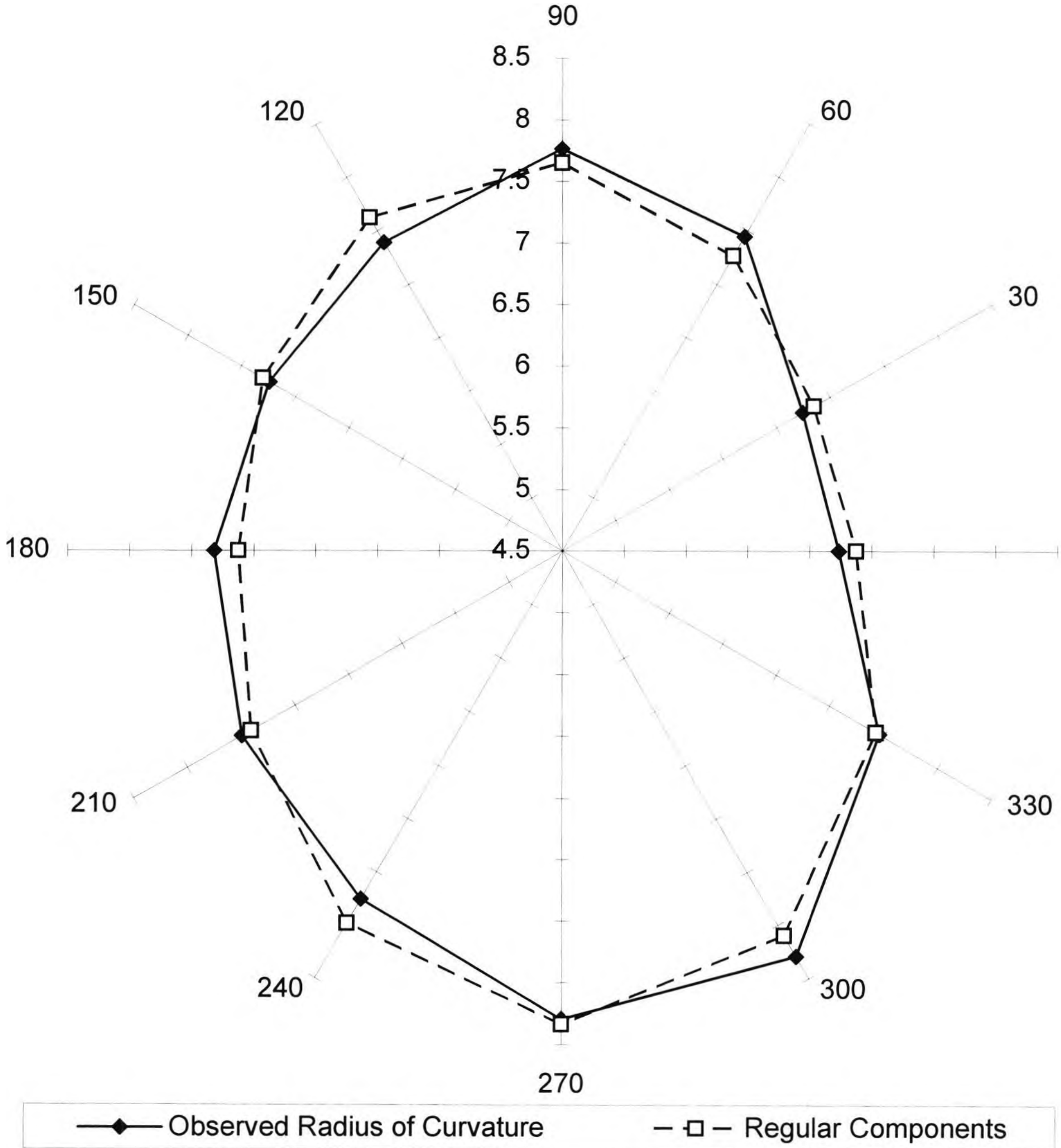
Figure C.12



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	8.02	7.88	7.92	8.03	8.22	8.47	7.77	7.40	7.46	8.44	8.72	8.30
Regular Components	8.08	7.74	7.81	8.17	8.40	8.21	7.75	7.47	7.67	8.21	8.61	8.52
Deviation	-0.06	0.14	0.11	-0.14	-0.18	0.25	0.02	-0.07	-0.21	0.23	0.12	-0.22

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
49	7Y	1		8.05	0.17	353	0.92	126	0.16

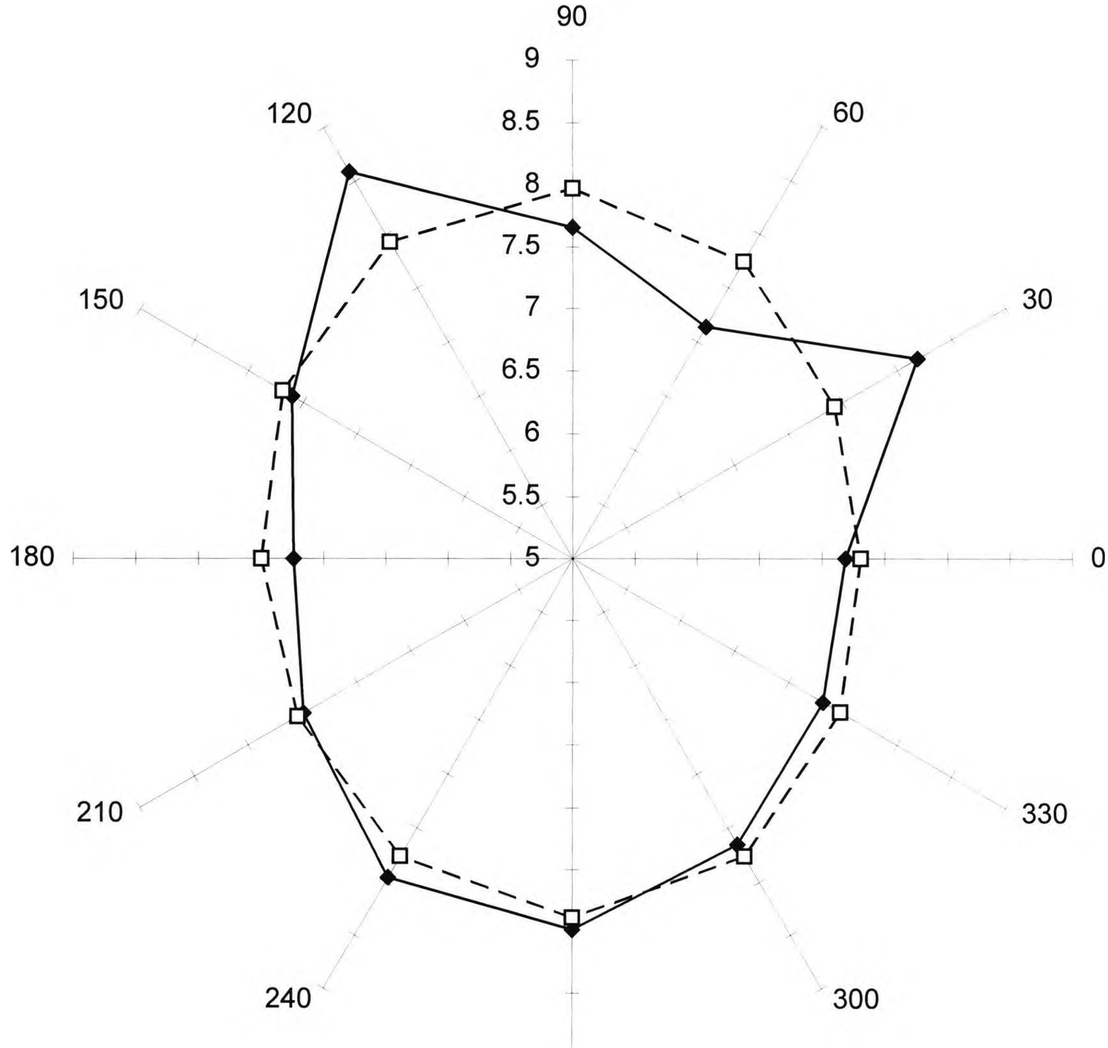
Figure C.13



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	6.74	6.74	7.45	7.76	7.39	7.24	7.32	7.49	7.76	8.30	8.29	7.46
Regular Components	6.87	6.85	7.26	7.65	7.62	7.30	7.12	7.41	7.99	8.34	8.10	7.43
Deviation	-0.14	-0.10	0.18	0.11	-0.23	-0.06	0.20	0.08	-0.23	-0.04	0.20	0.03

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
73	5Y	1		7.49	0.37	250	1.03	98	0.15

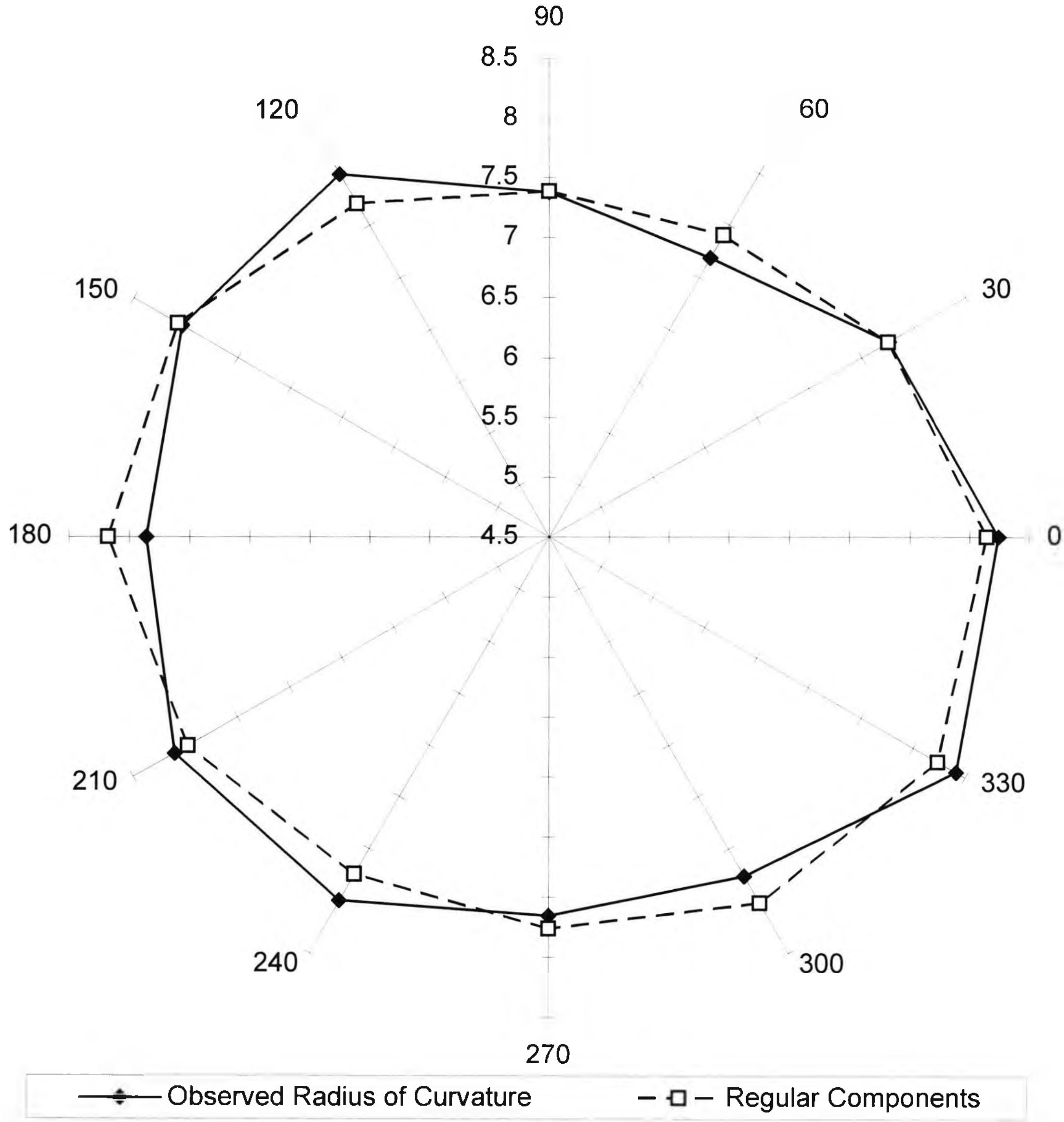
Figure C.14



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	7.19	8.19	7.14	7.65	8.59	7.60	7.24	7.49	7.96	7.99	7.65	7.32
Regular Components	7.31	7.43	7.74	7.97	7.93	7.69	7.50	7.55	7.76	7.89	7.76	7.48
Deviation	-0.12	0.76	-0.60	-0.32	0.66	-0.09	-0.26	-0.05	0.20	0.10	-0.11	-0.16

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
72	5Y	1		7.67	0.10	156	0.54	96	0.37

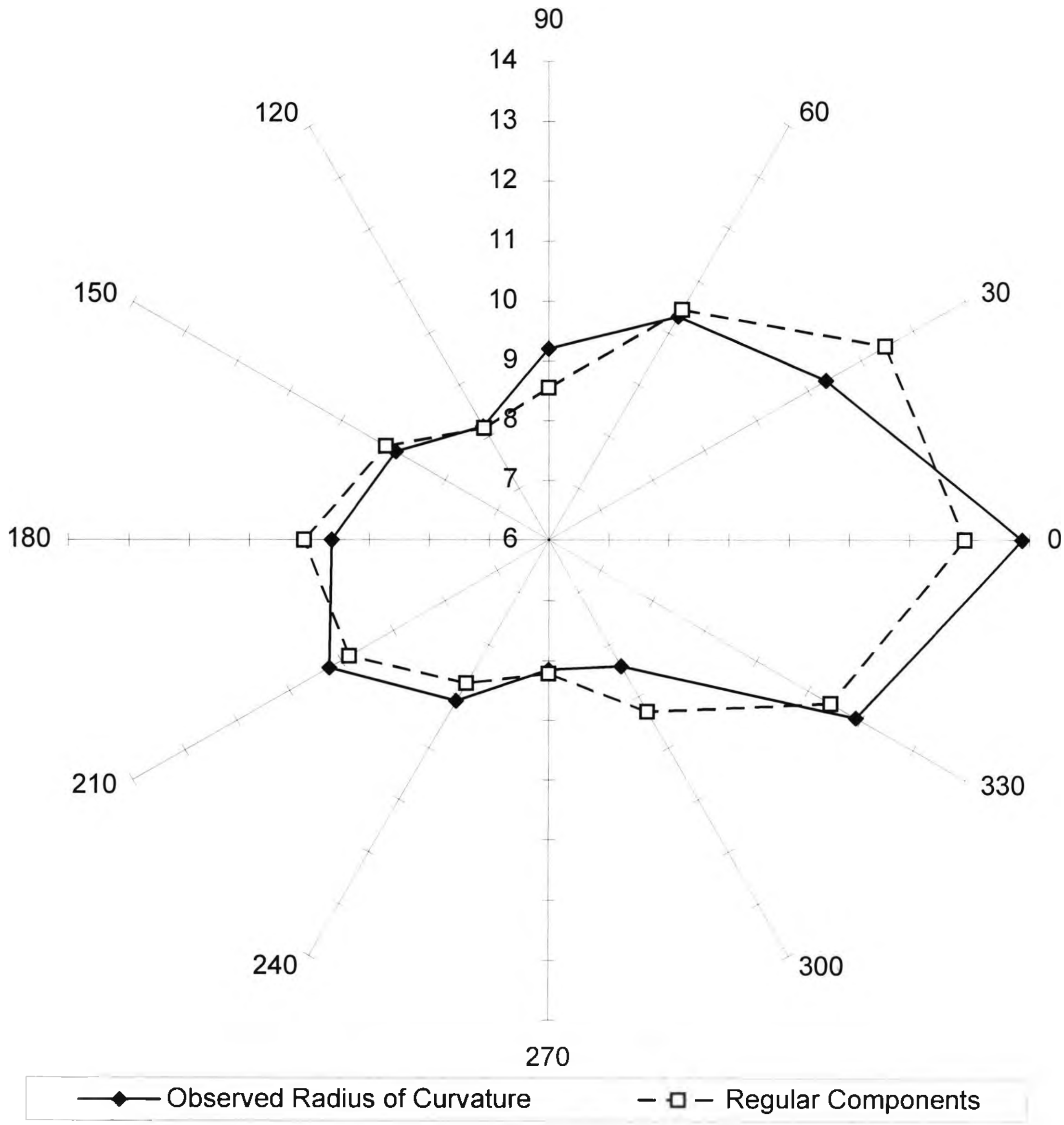
Figure C.15



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	8.24	7.76	7.19	7.37	8.00	8.04	7.86	8.10	8.00	7.66	7.76	8.41
Regular Components	8.14	7.76	7.40	7.38	7.71	8.08	8.18	7.98	7.75	7.76	8.02	8.24
Deviation	0.10	0.01	-0.21	-0.01	0.29	-0.04	-0.32	0.13	0.25	-0.11	-0.26	0.18

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
96	2Y	1		7.87	0.19	265	0.67	165	0.19

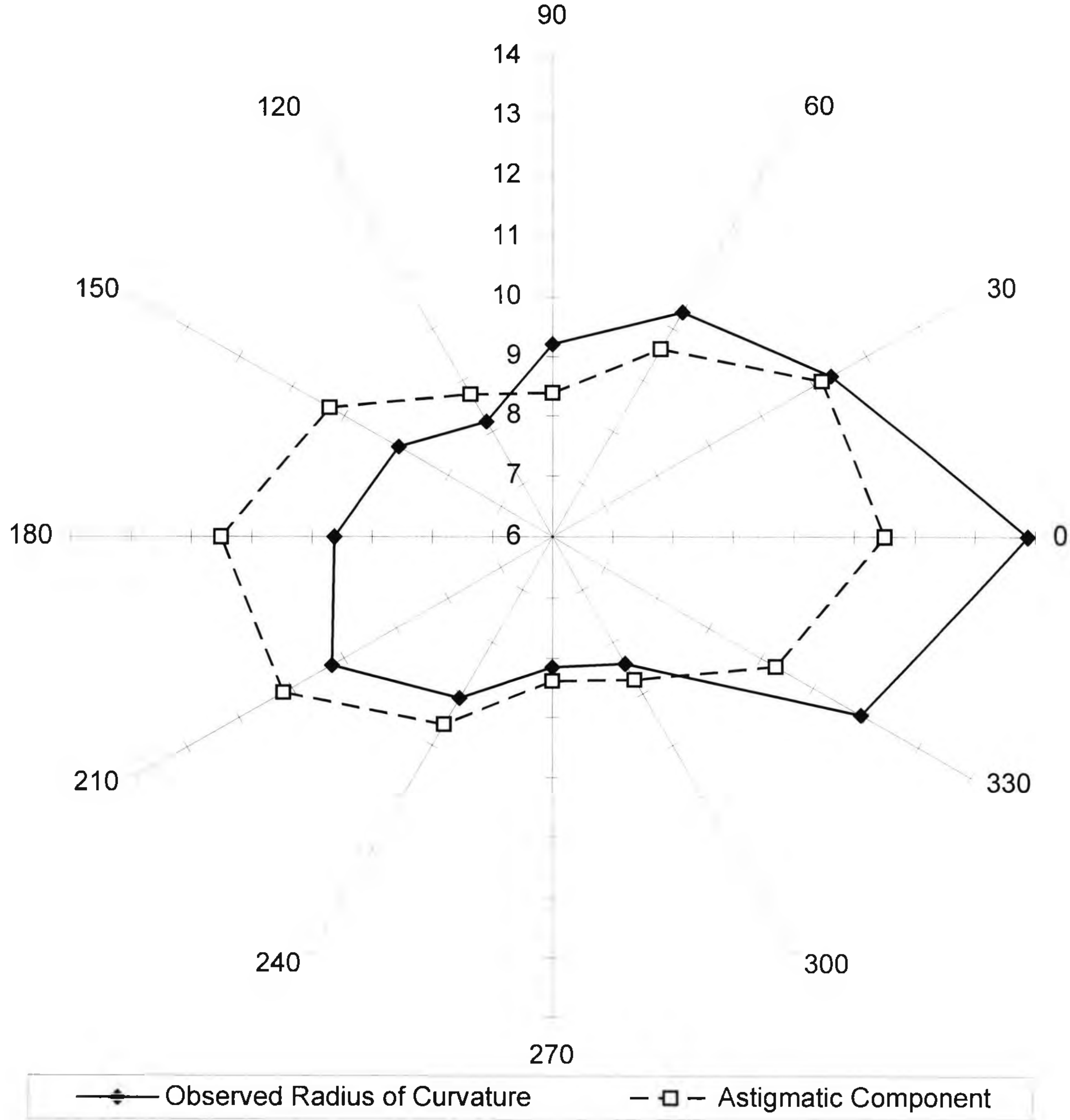
Figure C.16



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	13.87	11.33	10.32	9.20	8.20	8.95	9.63	10.23	9.08	8.15	8.42	11.91
Regular Components	12.91	12.47	10.45	8.55	8.16	9.14	10.09	9.85	8.75	8.22	9.29	11.43
Deviation	0.96	-1.13	-0.13	0.65	0.03	-0.19	-0.46	0.39	0.34	-0.06	-0.87	0.48

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
94	6M	1		9.94	1.42	7	3.28	9	0.59

Figure C.17



Semi-meridians	0	30	60	90	120	150	180	210	240	270	300	330
Observed Radius of Curvature	13.87	11.33	10.32	9.20	8.20	8.95	9.63	10.23	9.08	8.15	8.42	11.91
Astigmatic Component	11.50	11.16	9.60	8.38	8.73	10.28	11.50	11.16	9.60	8.38	8.73	10.28
Deviation	2.37	0.17	0.72	0.82	-0.53	-1.33	-1.87	-0.92	-0.52	-0.23	-0.31	1.62

Patient #	Stage	Ring #		s	d	β	c	ϕ	I
94	6M	1		9.94			3.28	9	1.17

Figure C.18 Irregularity markedly increases in the absence of the Asymmetry component

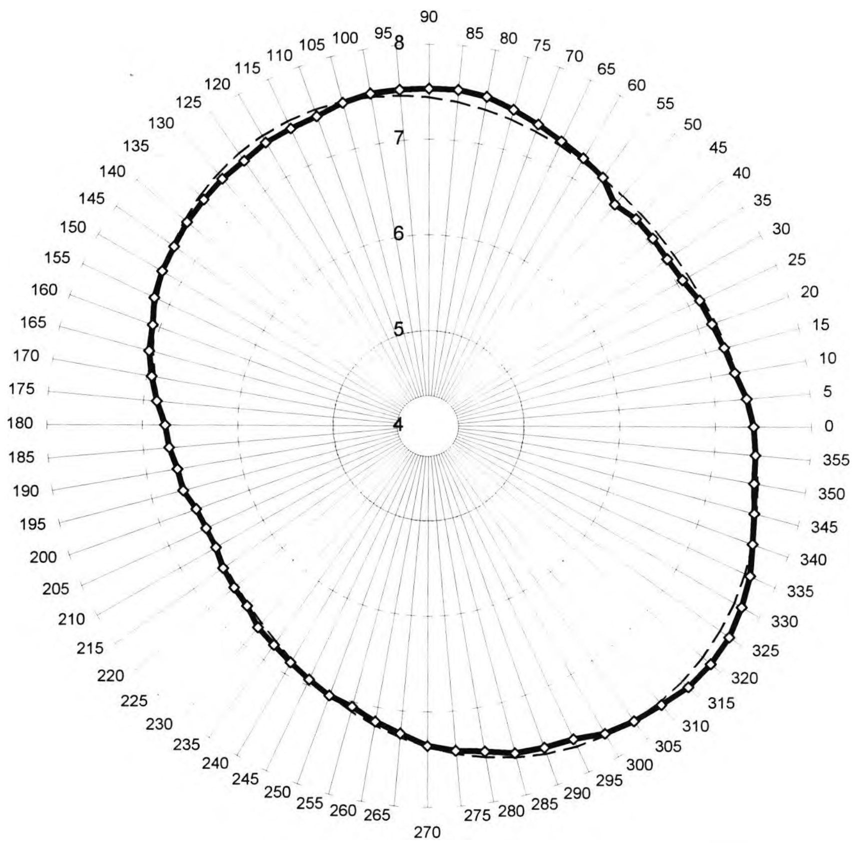
Appendix D

Trial to determine the optimum number of semi-meridians to be measured. Details of the two keratographs measured at 5° intervals. Keratograph # 1 had a high amount of regular astigmatism and Keratograph # 2 had relatively low astigmatism but high Irregularity.

The 72 data points were analysed in order to describe the curvature in terms of regular components, and the irregularity. The results are shown in Figure D.1 and Figure D.2. This process was then repeated six times, firstly using every second reading (36 semi-meridians), then using every third reading (24 semi-meridians), every fourth reading (18 semi-meridians), every sixth reading (12 semi-meridians), every eighth reading (9 semi-meridians),and lastly every twelfth reading (6 semi-meridians). The components derived from measurements in 72 semi-meridians were regarded as the best description of the keratograph ring. These were taken as a base line, to which subsequent results derived from fewer data points could be compared. The absolute difference (regardless of sign) from the baseline (72 semi-meridians) value was calculated, and these are shown in Table D.2 and Table D.4. These differences are presented graphically for each of the six components in Figure D.4 and Figure D.5.

semi-meridian	0	5	10	15	20	25	30	35	40	45	50	55
curvature mm	7.4	7.34	7.25	7.2	7.15	7.13	7.07	7.05	7.06	7.07	7.03	7.18
semi-meridian	60	65	70	75	80	85	90	95	100	105	110	115
curvature mm	7.24	7.29	7.36	7.43	7.5	7.53	7.53	7.53	7.53	7.5	7.45	7.43
semi-meridian	120	125	130	135	140	145	150	155	160	165	170	175
curvature mm	7.42	7.38	7.37	7.34	7.31	7.26	7.23	7.17	7.08	7.03	6.95	6.86
semi-meridian	180	185	190	195	200	205	210	215	220	225	230	235
curvature mm	6.76	6.73	6.67	6.66	6.59	6.57	6.57	6.62	6.65	6.68	6.77	6.81
semi-meridian	240	245	250	255	260	265	270	275	280	285	290	295
curvature mm	6.87	6.94	7.01	7.05	7.15	7.24	7.36	7.42	7.47	7.55	7.59	7.62
semi-meridian	300	305	310	315	320	325	330	335	340	345	350	355
curvature mm	7.72	7.77	7.81	7.86	7.87	7.85	7.79	7.72	7.61	7.53	7.46	7.43

Table D.1.Curvature measured in 72 semi-meridians. Keratograph # 1. (ring 3)



Observed curvature ------------- Regular components

Components	Spherical equivalent 7.24 mm	Asymmetry 0.30 mm	Angle of Asymmetry 6 degrees	Astigmatism 0.76 mm	Axis of Astigmatism 122 degrees	Irregularity 0.06 mm

Figure D.1 Curvature plot for 72 semi-meridians. Keratograph # 1. (ring 3)

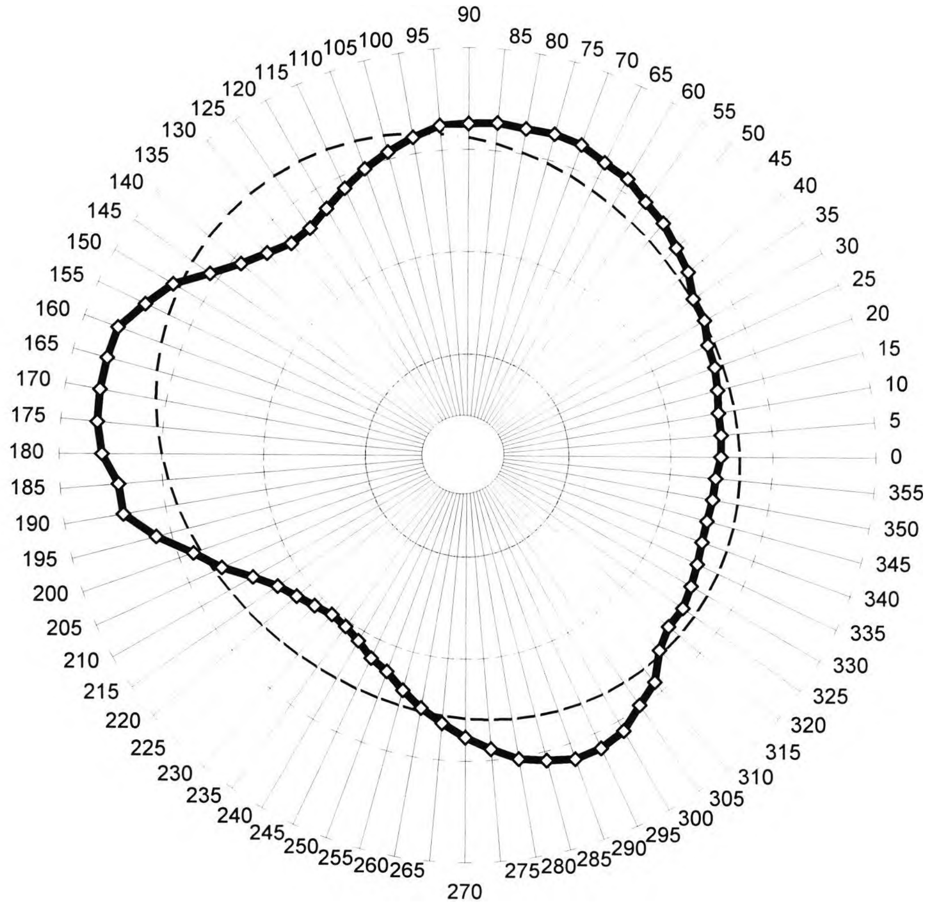
semi-meridians	Spherical equivalent	Asymmetry	Angle of Asymmetry	Astigmatism	Axis of Astigmatism	Irregularity
72	0	0	0	0	0	0
36	-0.00167	-0.00179	-0.43993	0.008224	-0.23138	0.000656
24	0.002222	0.002875	0.16379	0.00928	0.027716	-0.00427
18	0.001389	0.009468	1.041384	0.001554	-0.49968	-0.00241
12	0.004722	0.013602	-0.62176	0.014217	-0.321	-0.00765
9	0.009167	0.01945	-0.63981	0.01553	0.083978	0.012914
6	-0.00694	0.021964	-3.11385	-0.09023	-1.0095	-0.05181

Table D.2. Difference from the value obtained with 72 semi-meridians. Keratograph # 1.

Keratograph # 2

semi-meridian	0	5	10	15	20	25	30	35	40	45	50	55
curvature mm	7.99	8	8	8.04	8.08	8.1	8.18	8.2	8.32	8.39	8.48	8.54
semi-meridian	60	65	70	75	80	85	90	95	100	105	110	115
curvature mm	8.63	8.67	8.74	8.76	8.75	8.77	8.75	8.74	8.66	8.57	8.48	8.38
semi-meridian	120	125	130	135	140	145	150	155	160	165	170	175
curvature mm	8.28	8.21	8.2	8.29	8.41	8.59	8.84	8.99	9.15	9.16	9.16	9.14
semi-meridian	180	185	190	195	200	205	210	215	220	225	230	235
curvature mm	9.08	8.93	8.92	8.65	8.35	8.15	7.92	7.76	7.67	7.6	7.55	7.56
semi-meridian	240	245	250	255	260	265	270	275	280	285	290	295
curvature mm	7.61	7.7	7.76	7.89	8.02	8.14	8.27	8.39	8.52	8.59	8.66	8.66
semi-meridian	300	305	310	315	320	325	330	335	340	345	350	355
curvature mm	8.61	8.48	8.39	8.19	8.1	8.1	8.05	8	7.96	7.94	7.95	7.95

Table D.3. Curvature measured in 72 semi-meridians. Keratograph # 2. (ring 3)



Observed curvature ---------- Regular components

Components	Spherical equivalent 8.24 mm	Asymmetry 0.31 mm	Angle of Asymmetry1 21 degrees	Astigmatism 0.37 mm	Axis of Astigmatism 134 degrees	Irregularity 0.33 mm

Figure D.2 Curvature plot for 72 semi-meridians. Keratograph # 2. (ring 3)

semi-meridians	Spherical equivalent	Asymmetry	Angle of Asymmetry	Astigmatism	Axis of Astigmatism	Irregularity
72	0	0	0	0	0	0
36	0.00375	0.000202	-0.09002	0.001345	0.650535	0.005328
24	0.001806	0.003479	-0.20118	-0.00627	0.523844	-0.00253
18	0.000694	0.000324	-0.29496	-0.00507	-0.04442	0.001187
12	0.007639	-0.00419	-2.51751	0.04324	0.55123	-0.00745
9	-0.00208	0.018845	2.816703	-0.01582	3.641036	-0.0064
6	0.023472	-0.06591	3.655424	0.131659	21.95827	0.07561

Table D.4. Difference from the value otained with 72 semi-meridians. Keratograph # 2.

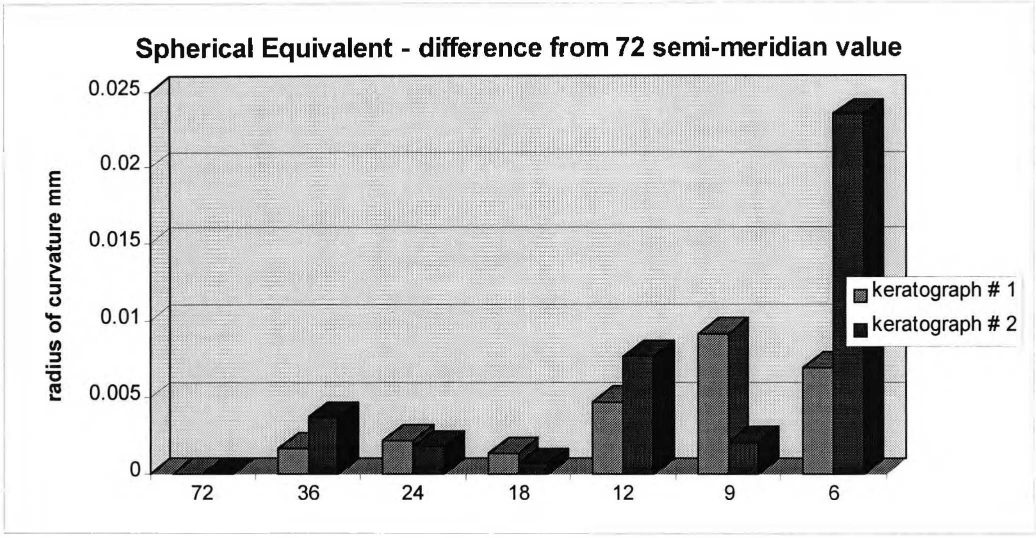
Initial inspection of Figures D.3 and D.4 shows that it is only when the number of data points is reduced to six or nine that a marked variation occurs from the component value derived from 72 points. Thus 12 semi-meridians may represent the best compromise between time spent on measurement, and precision of results. In the case of the spherical equivalent (mean radius of curvature), the variation begins to increase at 12 semi-meridians, but this is a small increase, and it is in the component which is least important in the final analysis. The variation in Asymmetry gradually increases with fewer data points, but it is at an acceptable level at 12 semi-meridians. Interestingly the result here was much better for the keratograph with marked irregularity (keratograph 2). The opposite was the case when the angle of the asymmetry was measured. The results were worse for the irregular keratograph, but at 12 semi-meridians the variation was only 2.5 degrees, and this component also does not figure particularly prominently in subsequent analysis.

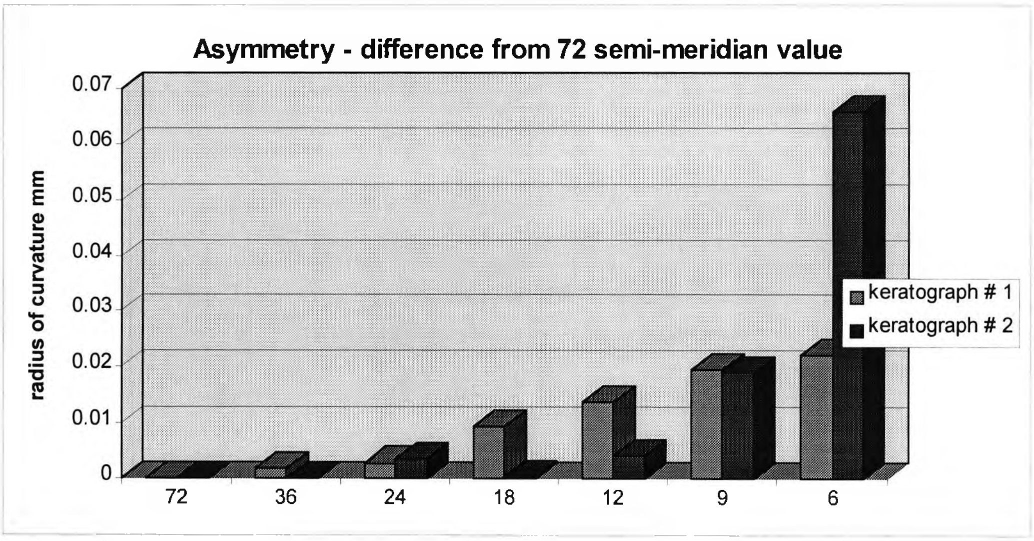
The most important components are Regular Astigmatism and Irregularity. In the case of astigmatism there was little variation until six semi-meridians, except for keratograph

2 which showed more variation at 12 semi-meridians than at nine. This probably indicates that for an irregular keratograph there will be certain key meridians which will accurately determine the astigmatism. In this case it may be that the nine semi-meridians were better positioned to assess this particular astigmatism than the 12 semi-meridians.

The axis of astigmatism remained remarkably stable when the semi-meridians were reduced as far as 12, even with keratograph 2, which had relatively little astigmatism, and a lot of irregularity. Irregularity was also relatively stable when the data points were reduced to twelve, and it is interesting to note that the variation in the irregularity value was similar for regular and irregular keratographs.

Taking all six charts together it did not appear that any great gain in precision was to be made by using 18 semi-meridians rather than 12, but there would be a 50% increase in the workload of keratograph measurement. It was therefore decided that each ring of the keratograph would be measured along 12 semi-meridians, separated by 30°.





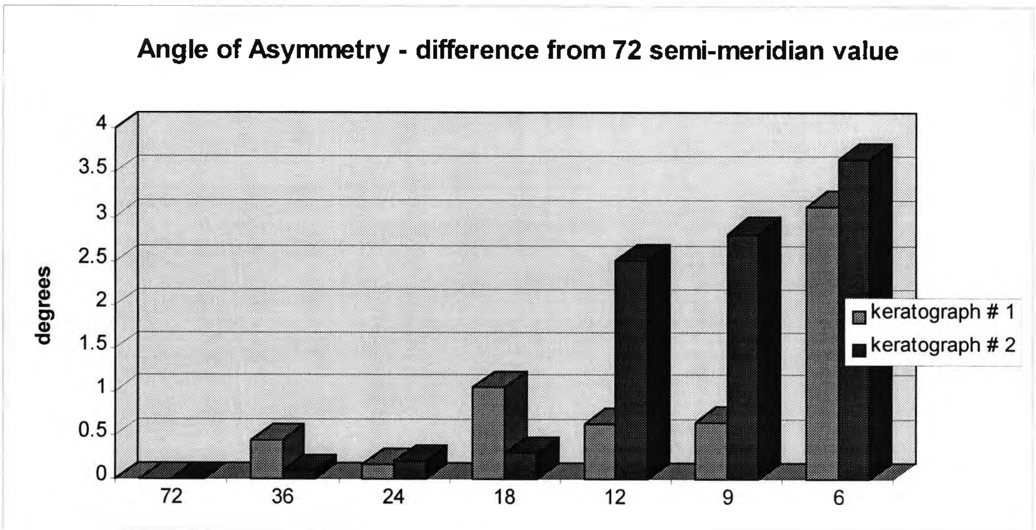
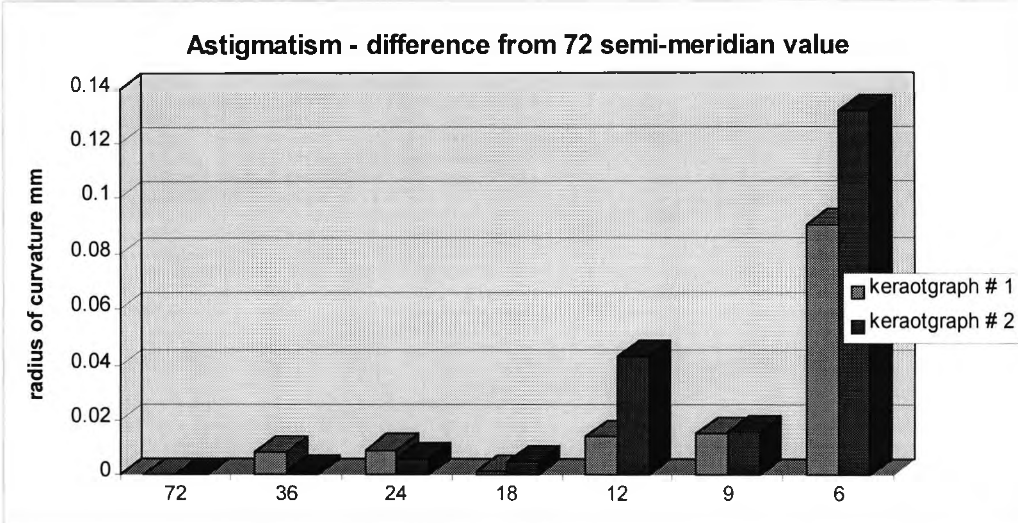
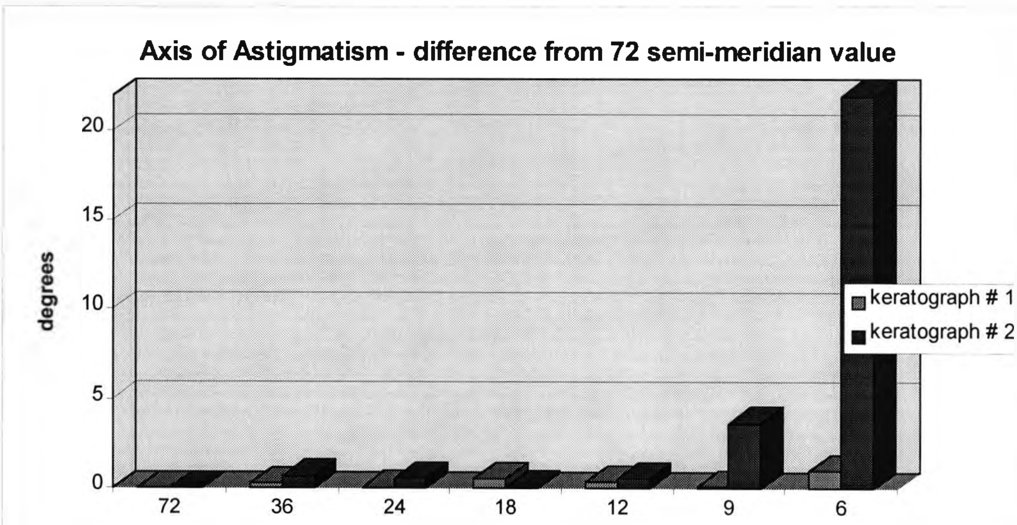


Figure D.3 Variation in the component value when different numbers of semi-meridians are measured. The charts show the difference from the value obtained with 72 semi-meridians. (Absolute difference regardless of sign).





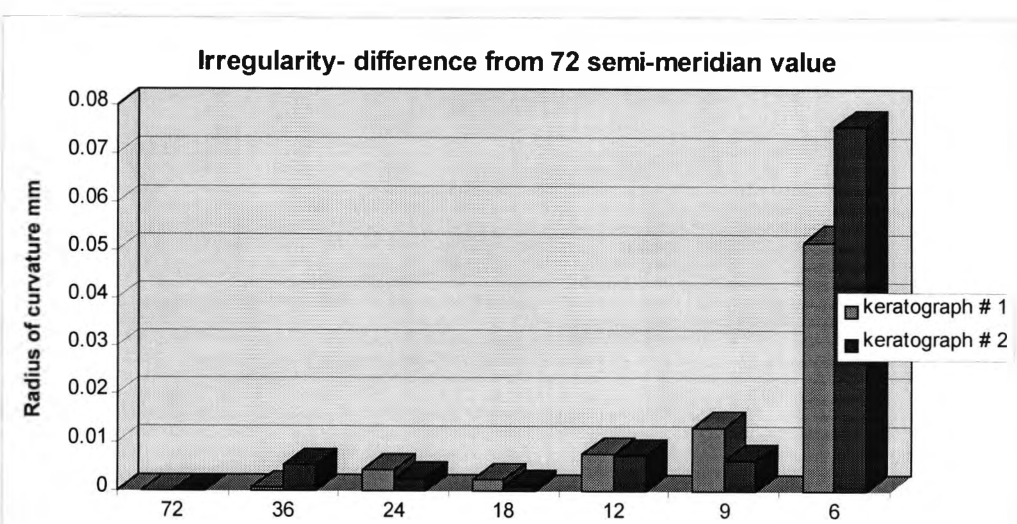


Figure D.4 Variation in the component value when different numbers of semi-meridians are measured. The charts show the difference from the value obtained with 72 semi-meridians. (Absolute difference regardless of sign).

Appendix E

Keratograph	Ring 1	Ring 2	Ring 3	Ring 4	Ring 5	Ring 6	Ring 7
1	7.91	7.92	7.89	7.78	7.7	7.59	7.58
2	7.91	7.87	7.83	7.69	7.57	7.51	7.43
3	7.89	7.85	7.83	7.66	7.5	7.45	7.37
4	7.92	7.88	7.84	7.74	7.62	7.57	7.49
5	7.88	7.93	7.89	7.72	7.52	7.46	7.4
6	8.04	7.99	7.92	7.79	7.68	7.64	7.56
7	7.92	7.94	7.84	7.71	7.6	7.53	7.46
8	7.96	7.96	7.89	7.74	7.61	7.57	7.69
9	7.92	7.96	7.91	7.74	7.59	7.55	7.46
10	8.07	8.05	7.98	7.82	7.72	7.62	7.57
11	7.91	7.9	7.9	7.75	7.65	7.56	7.5
12	8.08	8.02	7.97	7.84	7.76	7.69	7.64
13	8	7.98	7.94	7.82	7.71	7.65	7.61
14	7.99	7.94	7.91	7.77	7.66	7.59	7.54
15	7.94	7.94	7.9	7.77	7.66	7.6	7.57
16	7.99	7.99	7.93	7.73	7.61	7.57	7.49
17	7.96	7.96	7.92	7.78	7.66	7.59	7.54
18	8	7.97	7.92	7.81	7.67	7.59	7.59
19	8.04	7.98	7.94	7.84	7.73	7.68	7.61
20	7.96	7.93	7.88	7.74	7.63	7.57	7.49
21	8.02	7.99	7.93	7.82	7.71	7.64	7.6
22	7.88	7.86	7.83	7.68	7.56	7.52	7.43
23	7.96	7.97	7.92	7.82	7.72	7.62	7.6
24	8.04	7.98	7.94	7.82	7.72	7.67	7.6
25	7.99	7.98	7.95	7.82	7.71	7.64	7.65
26	7.96	7.97	7.91	7.76	7.62	7.55	7.49
27	7.94	7.94	7.89	7.7	7.57	7.49	7.42
28	7.96	7.99	7.95	7.82	7.73	7.64	7.6
29	7.91	7.91	7.86	7.74	7.58	7.51	7.39
30	7.96	7.91	7.86	7.74	7.57	7.53	7.42
31	7.91	7.92	7.88	7.74	7.64	7.54	7.5
32	7.92	7.88	7.83	7.68	7.55	7.51	7.49
33	7.94	7.87	7.88	7.74	7.57	7.51	7.43
34	7.99	7.98	7.88	7.74	7.57	7.52	7.43
35	7.8	7.85	7.81	7.66	7.47	7.45	7.33
36	7.88	7.92	7.86	7.73	7.49	7.51	7.36
37	7.92	7.94	7.87	7.71	7.58	7.52	7.45
38	8.04	7.97	7.92	7.79	7.66	7.59	7.54
39	7.91	7.96	7.88	7.7	7.56	7.48	7.42
40	7.94	7.97	7.9	7.74	7.59	7.54	7.43
Mean	7.95	7.94	7.89	7.75	7.63	7.56	7.50
Standard Deviation	0.058	0.047	0.041	0.050	0.073	0.062	0.088

Table E.1 40 measurements of the same transplant (#27) at a single session.

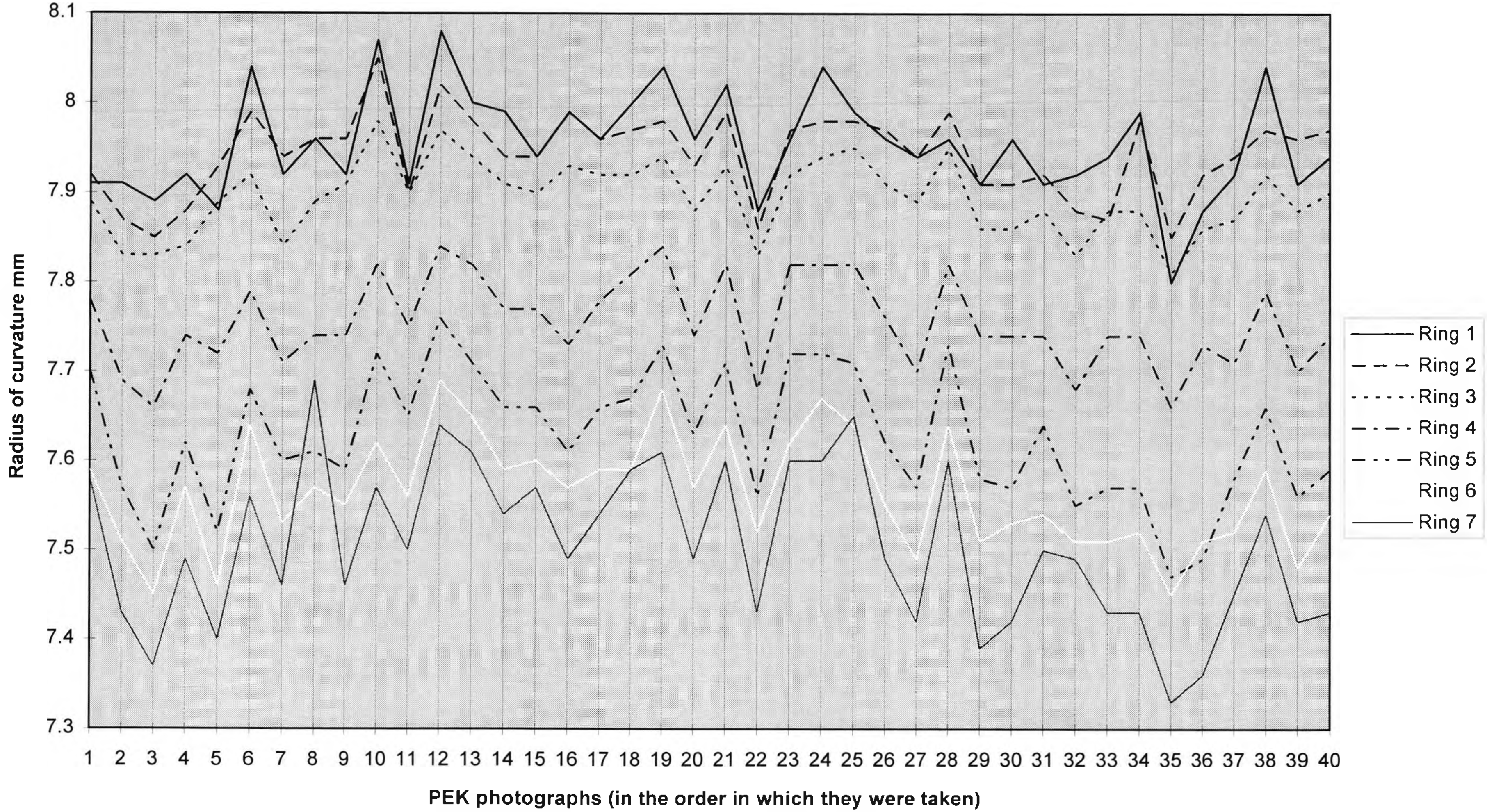


Figure E.1 The 0 degree semi-meridian curvatures (40 measurements of the same transplant at a single session)

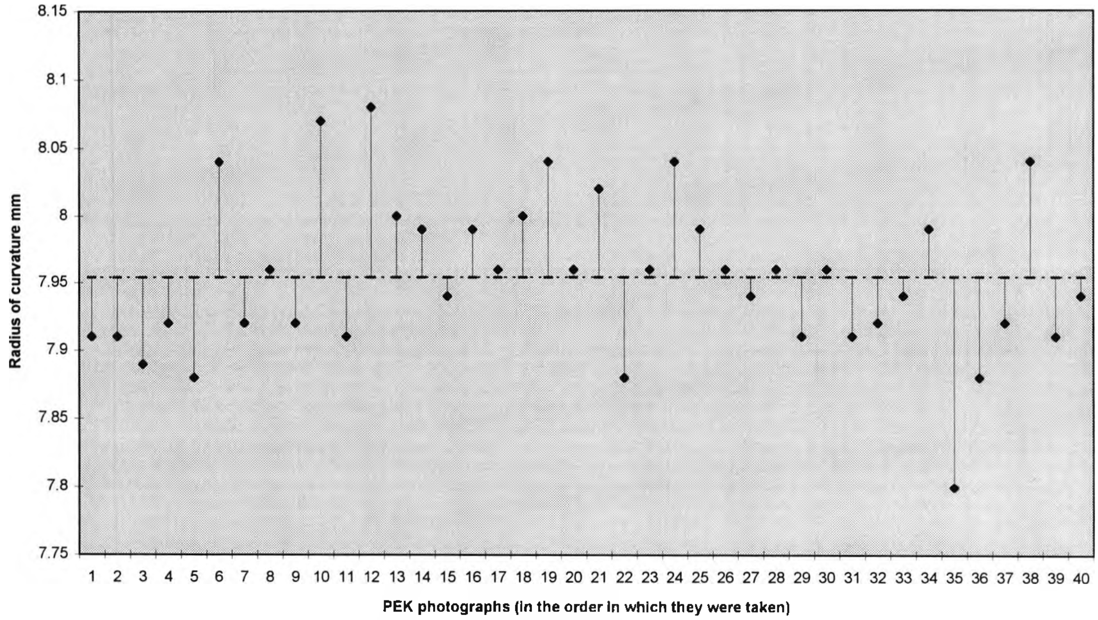


Figure E.2 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring1 - Standard Deviation of 40 measurements = 0.058 (mean 7.95)

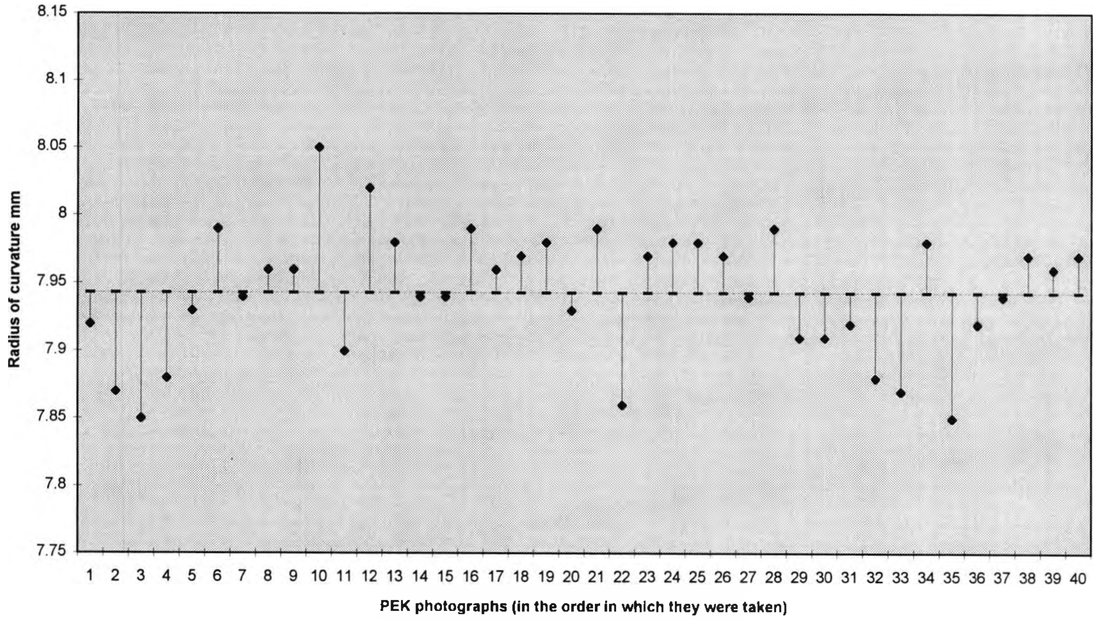


Figure E.3 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring 2 - Standard Deviation of 40 measurements = 0.047 (mean 7.94)

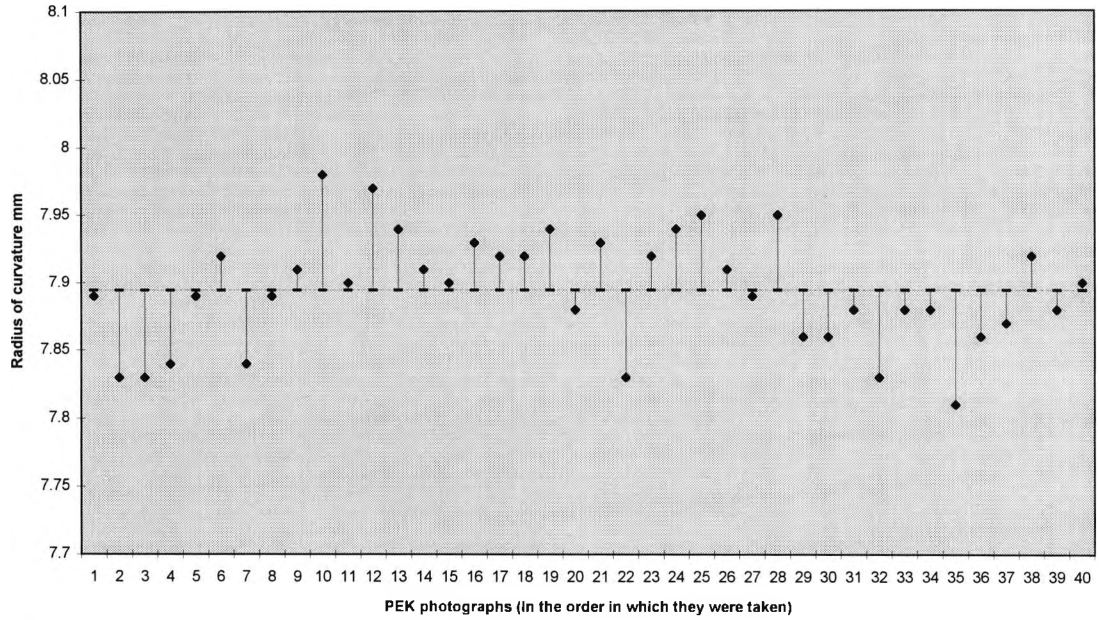


Figure E.4 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring 3 - Standard Deviation of 40 measurements = 0.041 (mean 7.89)

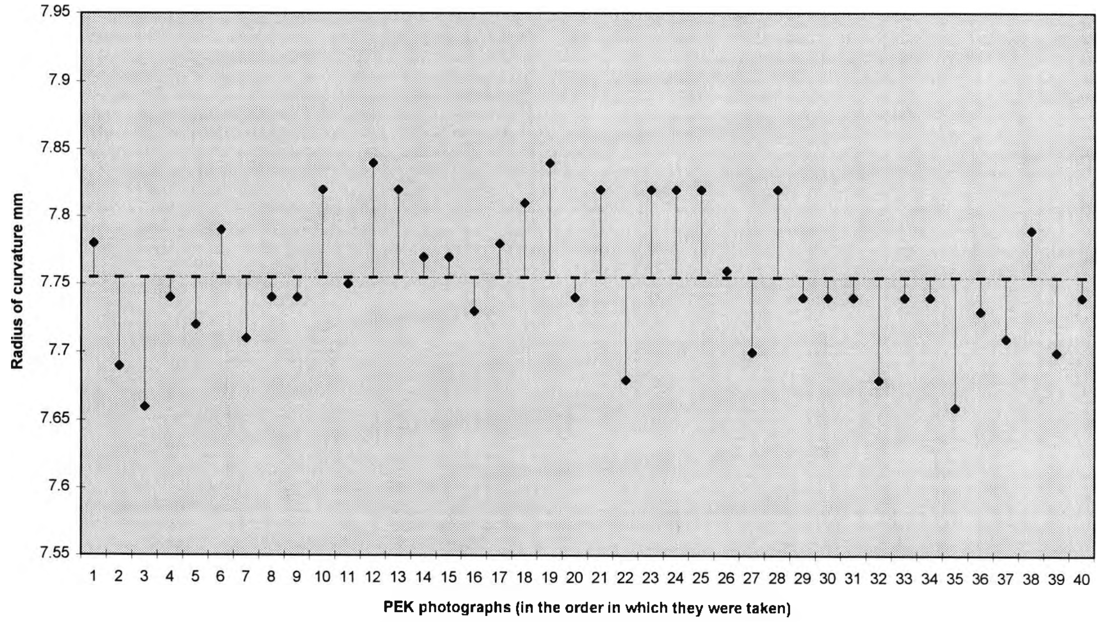


Figure E.5 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring 4 - Standard Deviation of 40 measurements = 0.050 (mean 7.75)

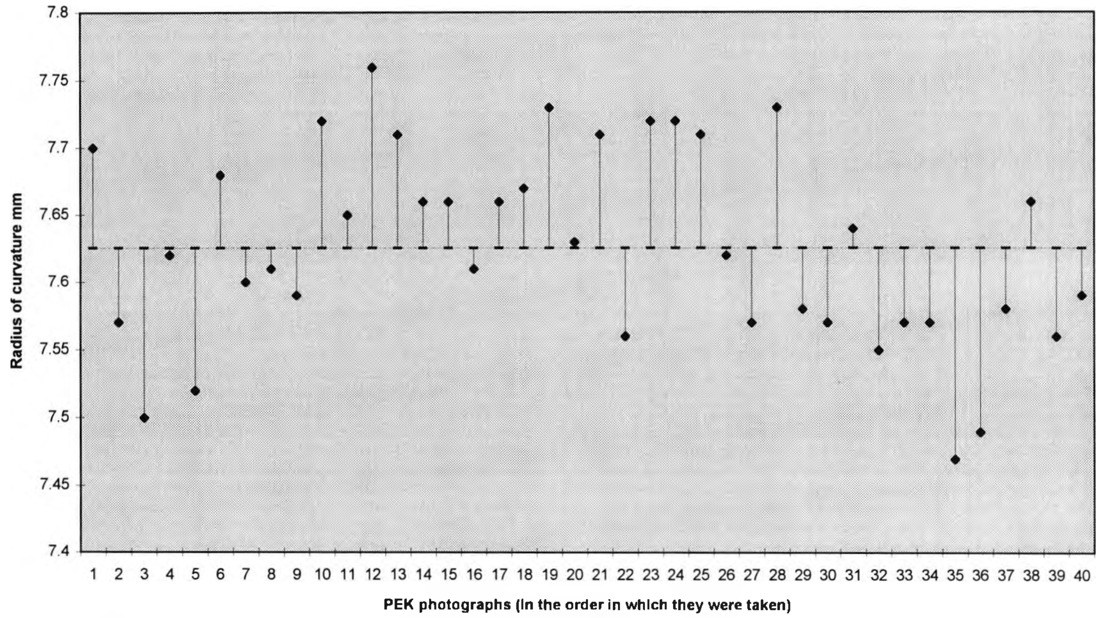


Figure E.6 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring 5 - Standard Deviation of 40 measurements = 0.073 (mean 7.63)

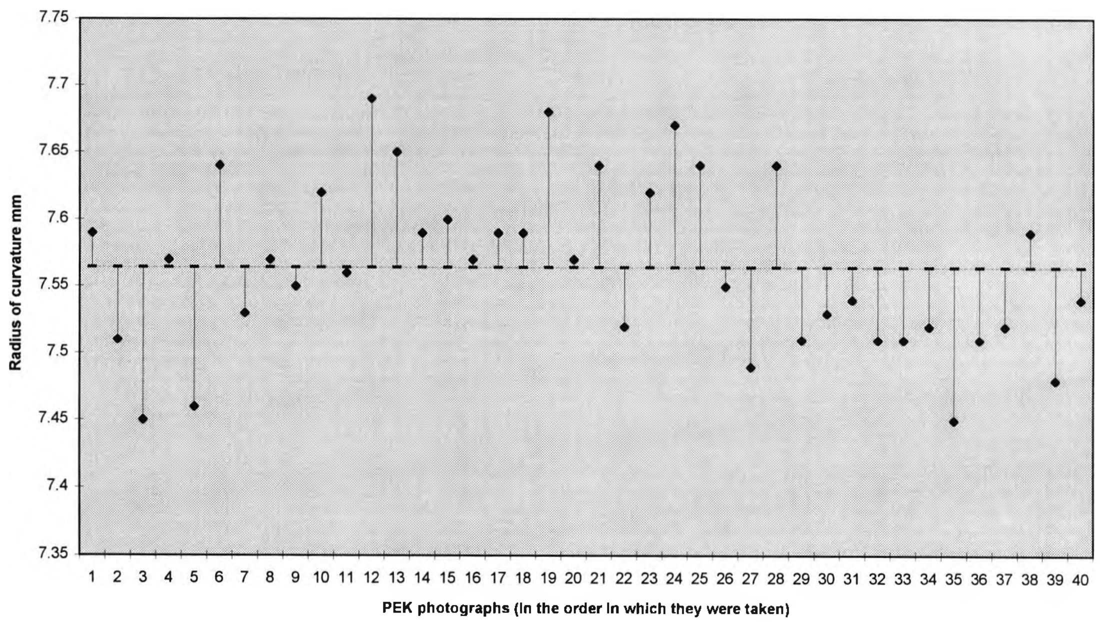


Figure E.7 0 degree semi-meridian curvatures (40 measurements of the same transplant) Ring 6 - Standard Deviation of 40 measurements = 0.062 (mean 7.56)

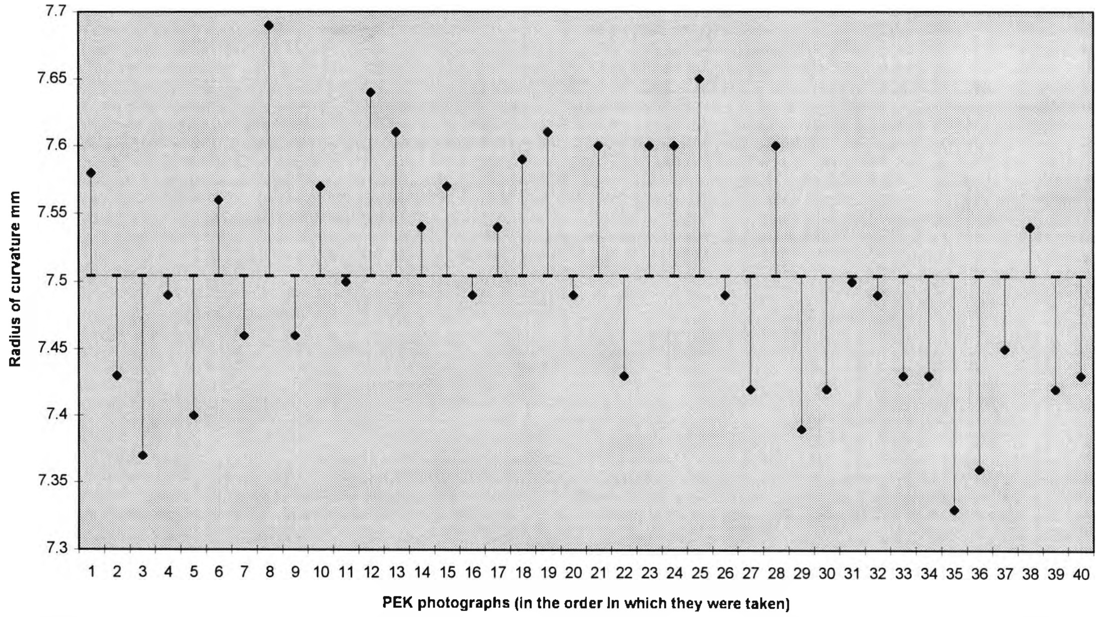


Figure E.8 0 degree semi-meridian curvatures (40 measurements of the same transplant)
Ring 7 - Standard Deviation of 40 measurements = 0.088 (mean 7.50)

Appendix F

10 measurements of the same transplant at a single session.

Local radius of curvature mm

	Ring 1											
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1	9.65	10.28	9.65	8.32	7.73	8.1	8.98	9.49	8.7	8.15	7.99	8.43
2	9.65	10.14	9.49	8.38	7.83	8.18	9.1	9.49	8.67	8.08	7.78	8.37
3	9.81	10.28	9.33	8.1	7.8	8.23	9.21	9.57	8.68	8.18	8.38	8.59
4	9.65	10.12	9.46	8.45	7.73	7.99	8.78	9.35	8.7	8.37	7.97	8.45
5	9.7	10.2	9.46	8.3	7.72	8.07	9.06	9.49	8.67	8.19	7.99	8.51
6	9.66	10.2	9.36	8.27	7.77	8.18	9.08	9.41	8.59	8.1	7.99	8.49
7	9.7	10.36	9.68	8.46	7.77	8.07	8.84	9.57	8.75	8.23	7.99	8.4
8	9.59	10.15	9.51	8.38	7.75	8.07	8.94	9.38	8.57	8.07	7.88	8.4
9	9.7	10.39	9.65	8.37	7.75	8.1	8.94	9.49	8.78	8.19	7.96	8.53
10	9.81	10.76	9.95	8.42	7.99	8.21	9	9.51	8.75	8.24	8.86	8.54
std.dev.	0.07	0.19	0.18	0.11	0.08	0.08	0.13	0.07	0.07	0.09	0.31	0.07

	Ring 2											
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1	9.43	10.29	9.49	8.5	7.91	8.1	9.17	10.09	9.04	8.72	8.33	8.92
2	9.37	10.17	9.45	8.54	7.93	8.19	9.63	10.17	9.16	8.71	8.23	8.9
3	9.51	10.29	9.45	8.3	7.83	8.31	9.76	10.24	9.04	8.81	8.56	9.12
4	9.36	10.18	9.57	8.62	7.86	7.98	9.15	9.98	9.16	8.72	8.29	8.98
5	9.49	10.23	9.45	8.44	7.85	8.11	9.51	10.14	9.12	8.74	8.34	9
6	9.43	10.13	9.4	8.41	7.85	8.18	9.54	10.11	9.01	8.62	8.31	8.92
7	9.55	10.35	9.66	8.63	7.91	8.03	9.37	10.23	9.25	8.86	8.48	8.94
8	9.48	10.11	9.45	8.48	7.86	8.09	9.4	10.04	8.86	8.6	8.31	8.92
9	9.57	10.3	9.57	8.54	7.85	8.11	9.57	10.16	8.96	8.66	8.33	8.93
10	9.99	10.37	9.66	8.6	7.97	8.23	9.38	10.11	9.05	8.74	8.44	8.9
std.dev.	0.18	0.09	0.09	0.10	0.05	0.10	0.19	0.08	0.11	0.08	0.10	0.07

	Ring 3											
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1	9.42	9.81	9.34	8.56	8.06	8.16	9.32	10.03	9.43	8.81	8.47	8.96
2	9.37	9.81	9.27	8.57	8.08	8.24	9.67	9.91	9.34	8.77	8.43	8.88
3	9.43	9.76	9.15		7.91	8.29	9.41	10.05	9.25	8.77	8.43	9.12
4	9.41	9.96	9.38	8.67	8	8.02	9.12	9.9	9.36	8.77	8.41	9.14
5	9.43	9.81	9.29	8.52	8	8.03	9.32	10.11	9.34	8.77	8.46	8.96
6	9.41	9.8	9.22	8.49	8	8.25	9.34	10	9.36	8.74	8.44	8.96
7	9.45	9.9	9.43	8.6	8.06	8.11	9.22	10.14	9.51	8.96	8.51	9
8	9.39	9.86	9.29	8.55	8.02	8.19	9.2	9.93	9.34	8.81	8.46	8.78
9	9.48	9.92	9.36	8.58	8.05	8.17	9.32	10.04	9.34	8.77	8.47	9.05
10	9.53	9.94	9.41	8.67	8.13	8.3	9.55	10.17	9.49	8.96	8.58	9.15
std.dev.	0.05	0.07	0.09	0.06	0.06	0.10	0.16	0.09	0.08	0.08	0.05	0.12

Table F.1 10 measurements of the same transplant at a single session.

Ring 4												
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1	9.25	9.72	9.29	8.73	8.25	8.37	9.26	9.55	9.37		8.46	9.09
2	9.27	9.7	9.27	8.7	8.28	8.41	9.27	9.61		8.47	8.3	8.9
3	9.34	9.66				8.41	9.23	9.57	9.01			9.13
4	9.17	9.67	9.31	8.52	8.13	8.14	9.1	9.48	9.36		8.41	8.92
5	9.25	9.67	9.19	8.59	8.16	8.15	9.25	9.59	9.29			9.06
6	9.25	9.65	9.21	8.61	8.21	8.41	9.25	9.58	9.21	8.77	8.45	9.05
7	9.34	9.82	9.35	8.65	8.27	8.28	9.19	9.59	9.49	8.81	8.53	9.13
8	9.25	9.67	9.27	8.63	8.24	8.29	9.21	9.57	9.26	8.68	8.37	8.94
9	9.27	9.81	9.35	8.73	8.25	8.33	9.22	9.55				9.1
10	9.49	9.89	9.43	8.84	8.37	8.53	9.37	9.69		8.77	8.57	9.19
std.dev.	0.09	0.08	0.07	0.09	0.07	0.12	0.07	0.05	0.15	0.14	0.09	0.10

Ring 5												
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1	9.28	9.54	9.34				9.12	9.34				9.07
2	9.31	9.51	9.21			8.64	9.13	9.34				
3		9.51						9.34				
4		9.48						9.2				8.92
5		9.51	9.31				9.09	9.34				
6		9.49			8.33			9.33				8.97
7		9.68	9.39		8.44		9.06	9.4				
8		9.52	9.27			8.4	9.06	9.27				8.92
9		9.56	9.36			8.54	9.12	9.3				9.05
10		9.83	9.51		8.58	8.71	9.38					9.2
std.dev.	0.02	0.11	0.10		0.13	0.13	0.11	0.06				0.11

Ring 6												
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1		9.61	9.29			8.82	9.11	9.18				9.03
2		9.56				8.85	9.14	9.17				
3							9.16	9.09				
4		9.53	9.12				8.87	9.05				8.94
5		9.44	9.13				9.1	9.16				9.03
6		9.52				8.75	9.13	9.14				9
7		9.75	9.31			8.72	9.08	9.24				9.09
8		9.56	9.19				9.01	9.09				9
9		9.69				8.75	9.09	9.13				9.09
10		9.93				9.02						9.32
std.dev.		0.15	0.09			0.11	0.09	0.06				0.12

Ring 7												
Photo #	0	30	60	90	120	150	180	210	240	270	300	330
1								9.05				
2								9				
3								8.95				
4								8.91				
5								9				
6								8.99				
7								9.11				
8								8.98				
9								9.05				
10												
std.dev.								0.06				

Table F.1 continued. 10 measurements of the same transplant at a single session.

F.

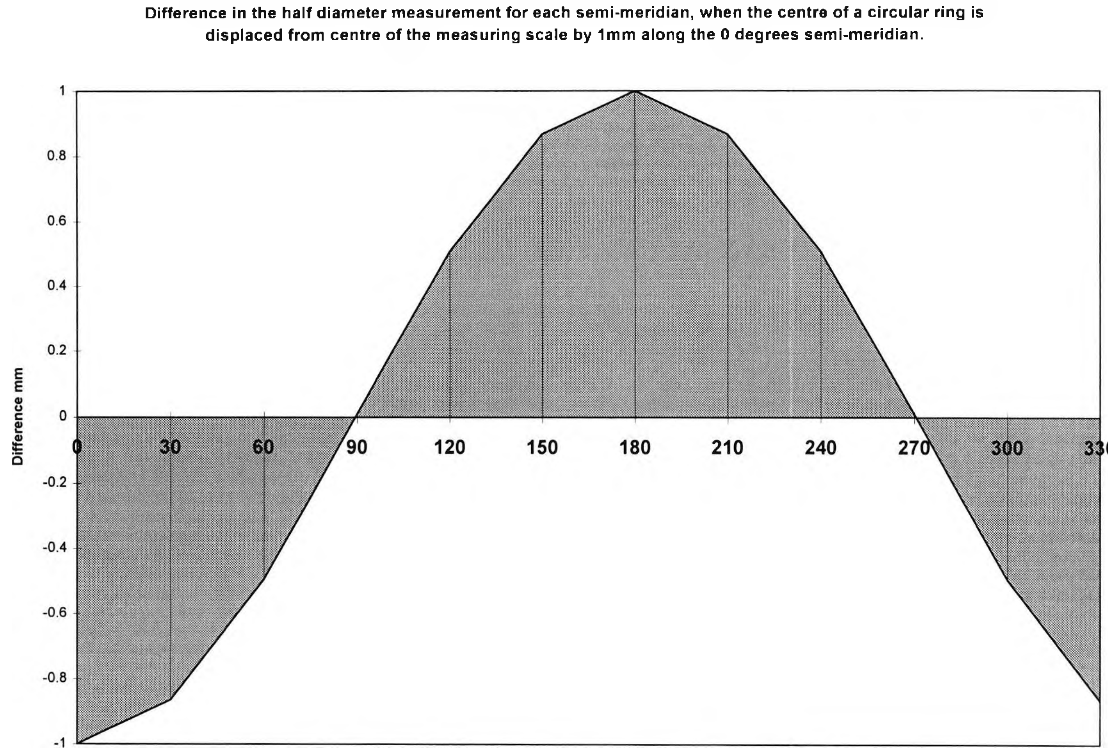


Figure F.1 Effect of decentration

Chart showing how a decentration along the 0 degree semi-meridian would cause deviations from the correct value, for the radius of curvature measurements in the other semi-meridians.

The plots below show the deviation from the mean value obtained from all 10 keratographs. The units are therefore mm radius of curvature.

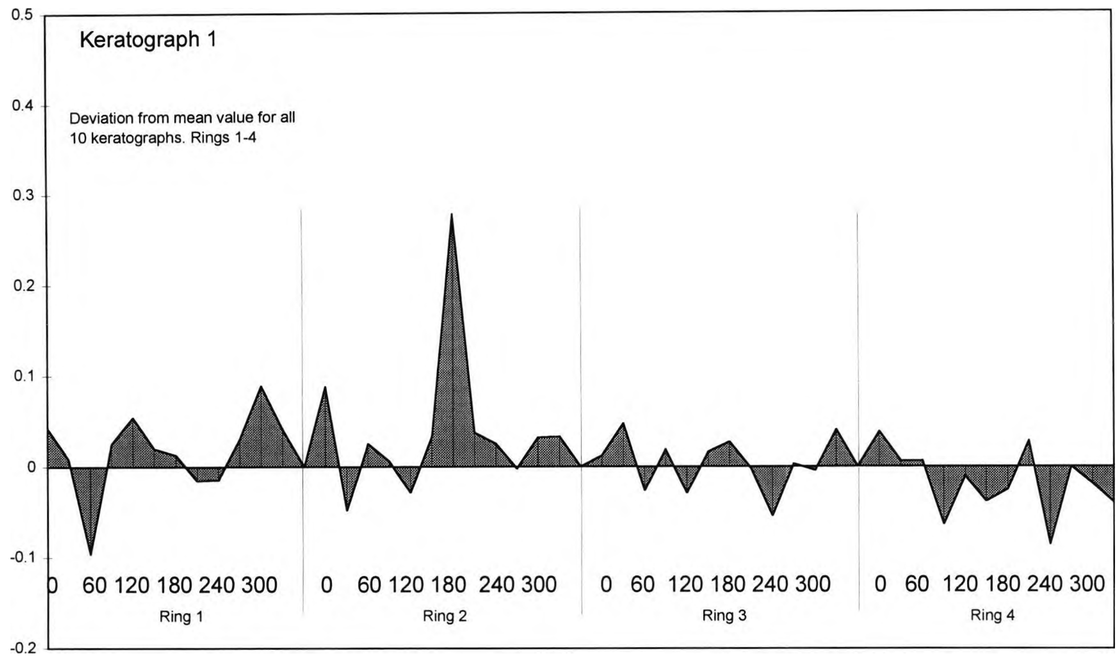


Figure F.2 Keratograph 1 deviation from the mean

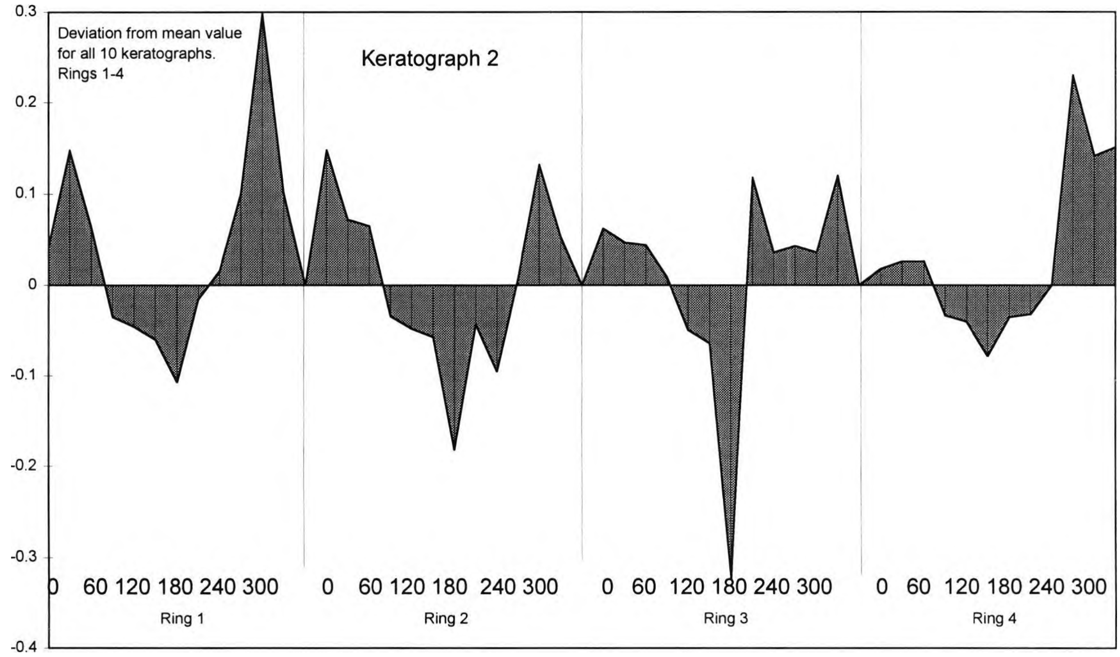


Figure F.3 Keratograph 2 deviation from the mean

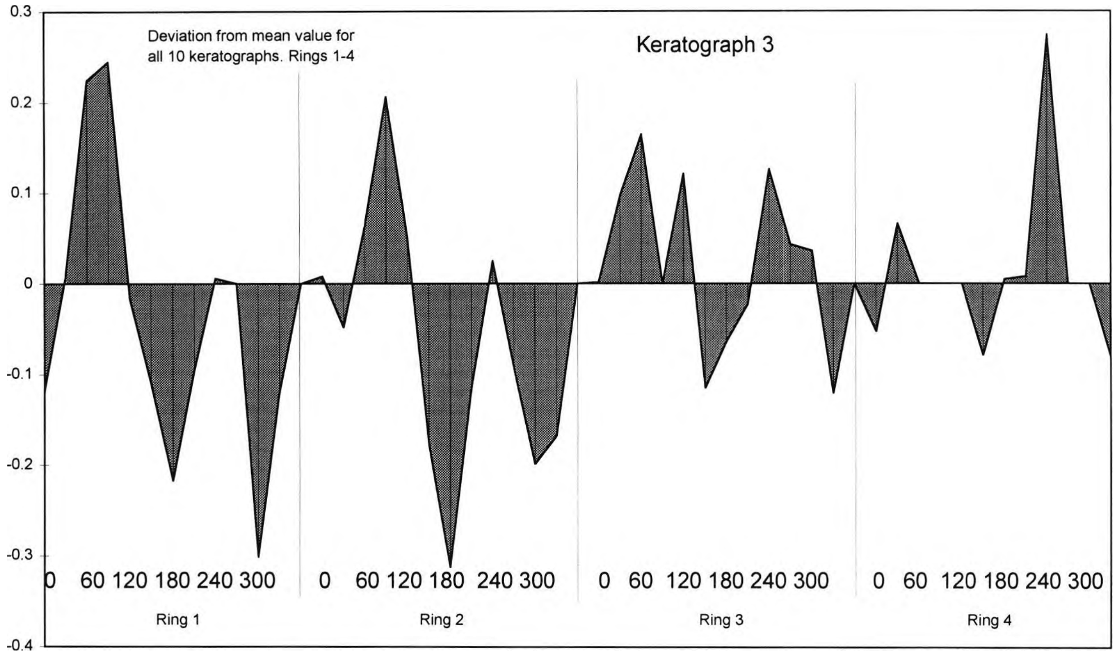


Figure F.4 Keratograph 3 deviation from the mean

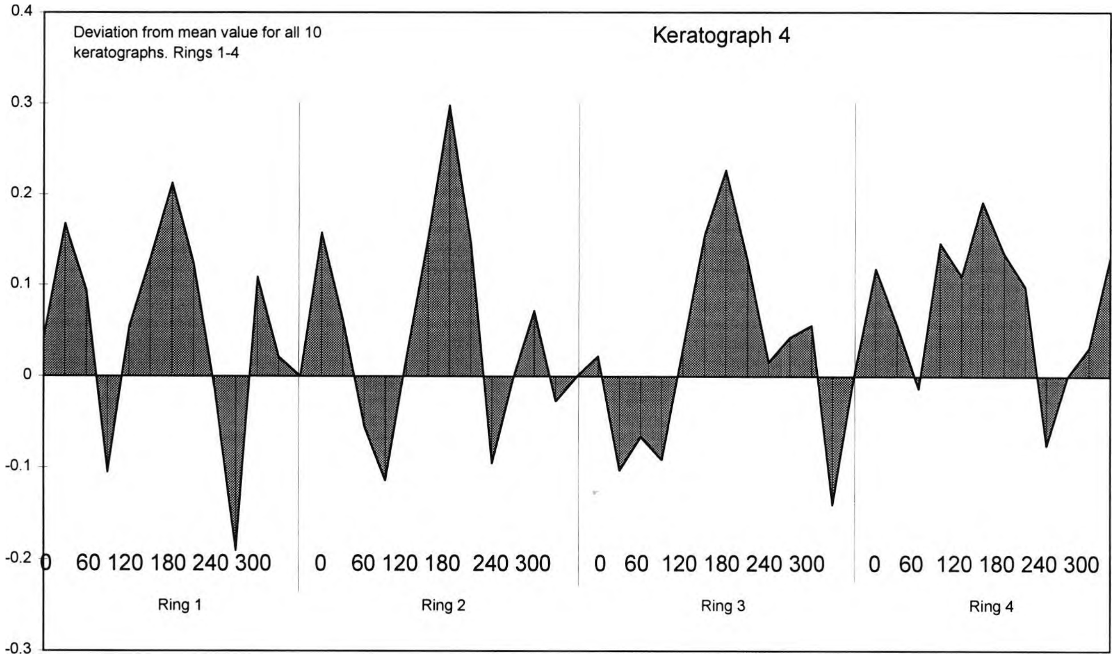


Figure F.5 Keratograph 4 deviation from the mean

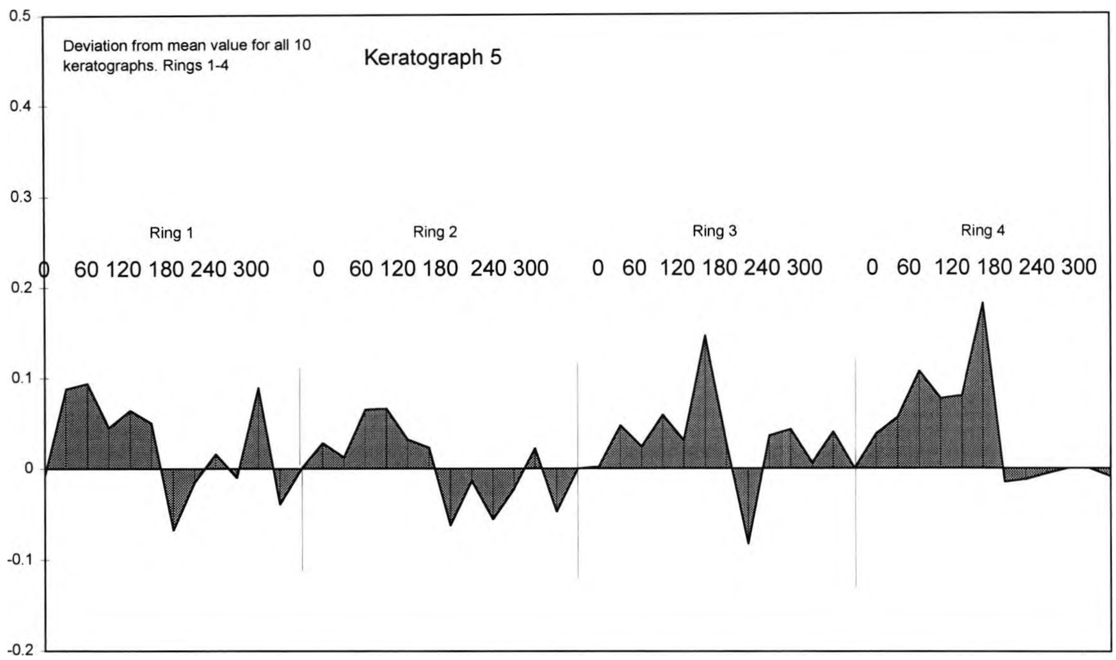


Figure F.6 Keratograph 5 deviation from the mean

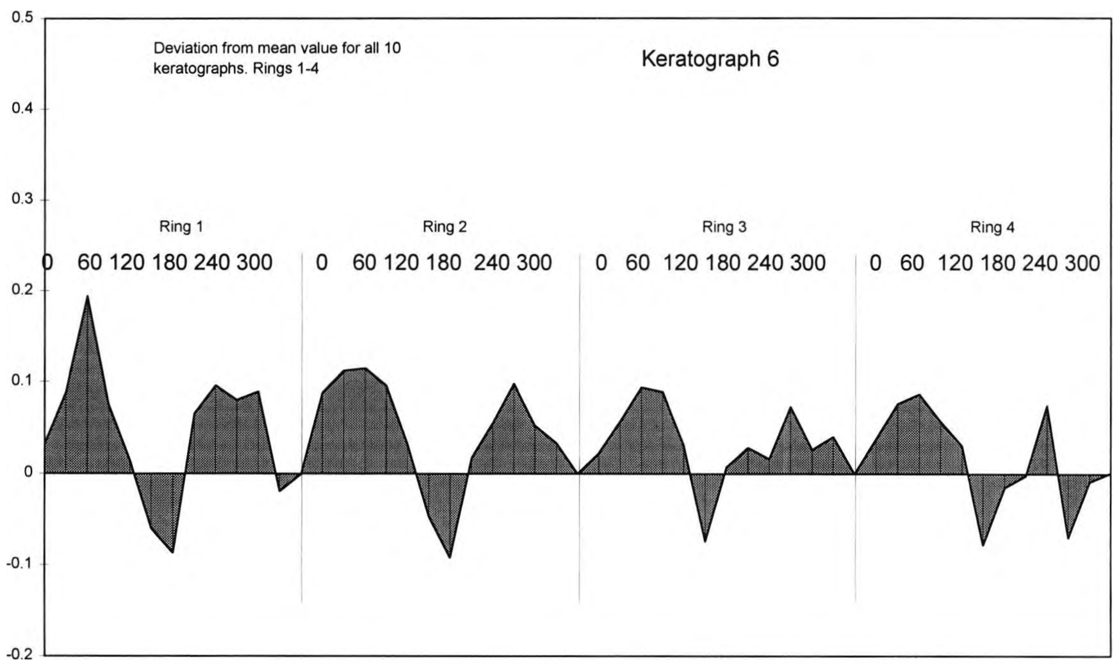


Figure F.7 Keratograph 6 deviation from the mean

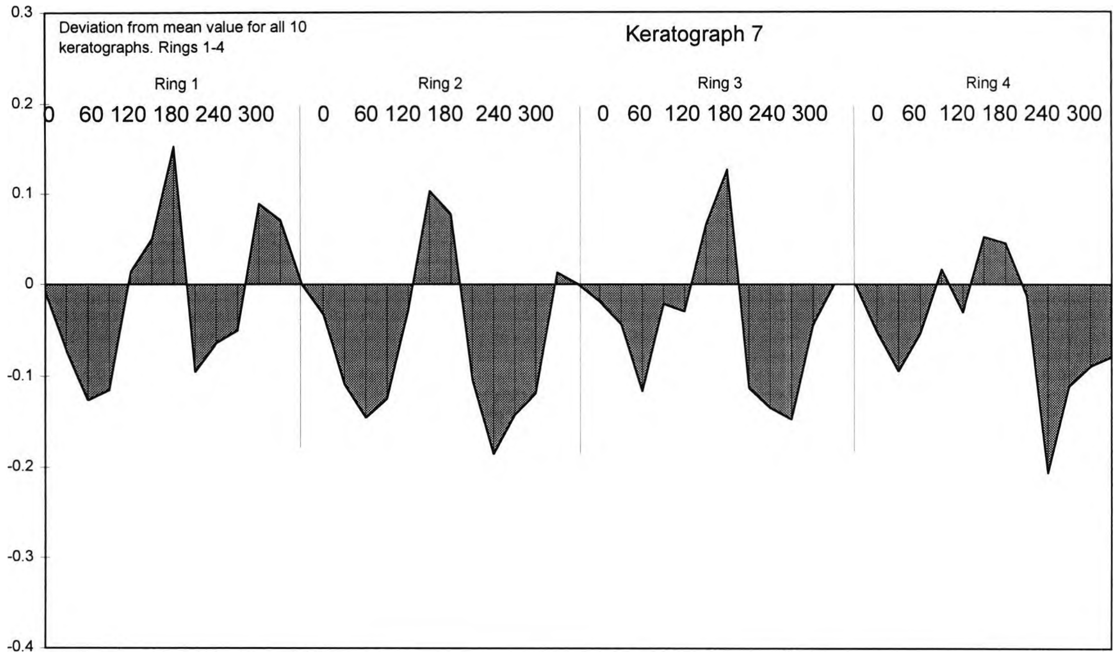


Figure F.8 Keratograph 7 deviation from the mean

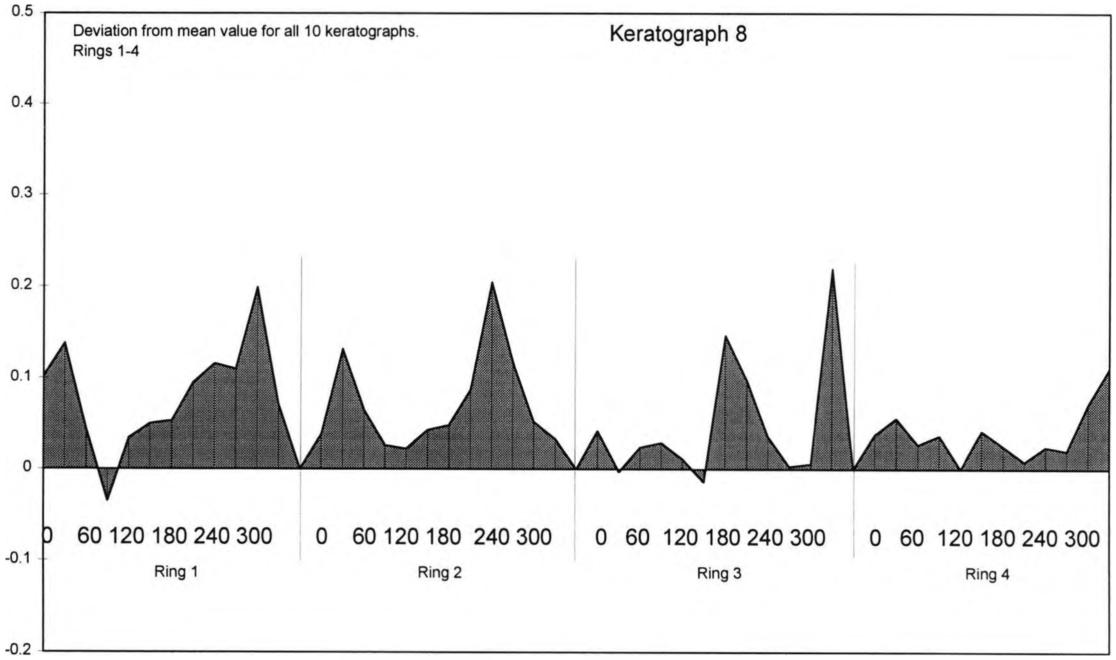


Figure F.9 Keratograph 8 deviation from the mean

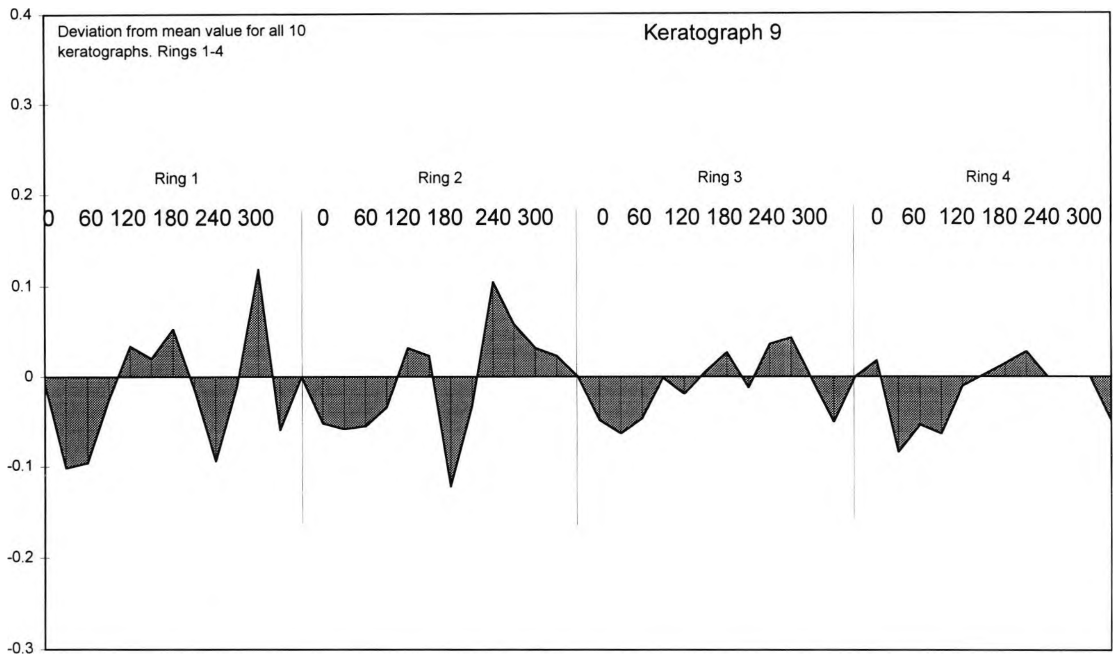


Figure F.10 Keratograph 9 deviation from the mean

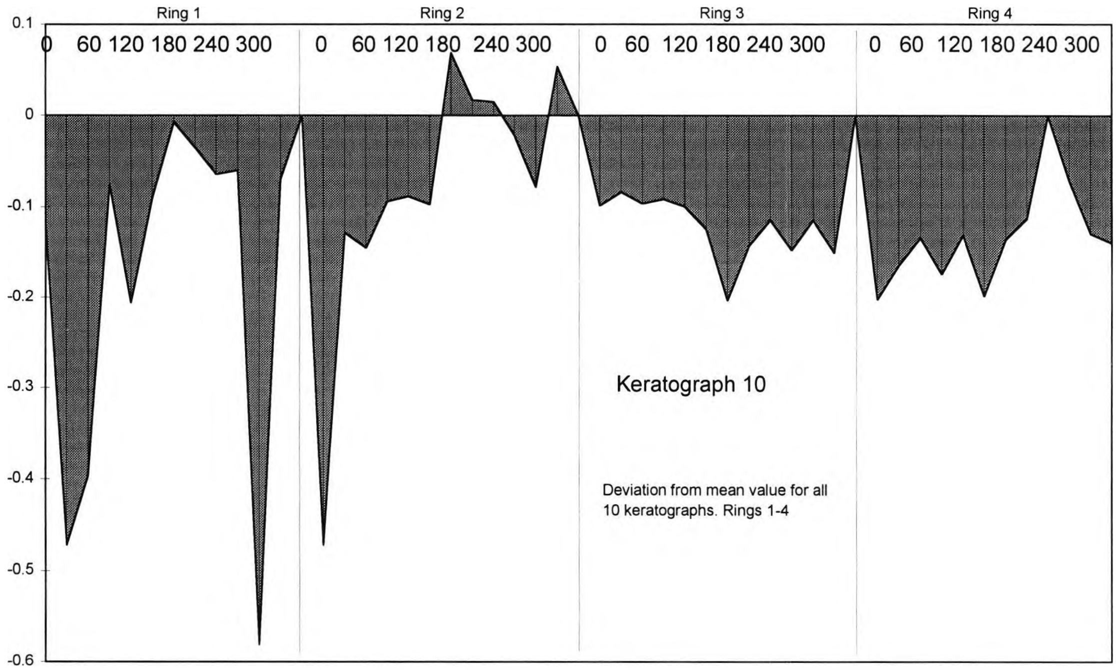
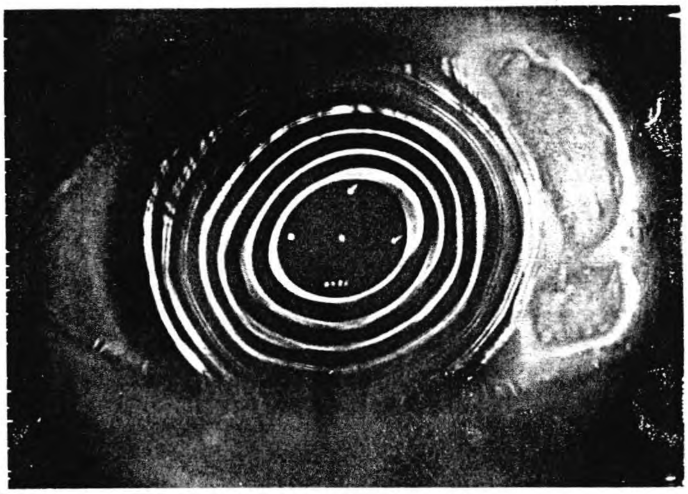
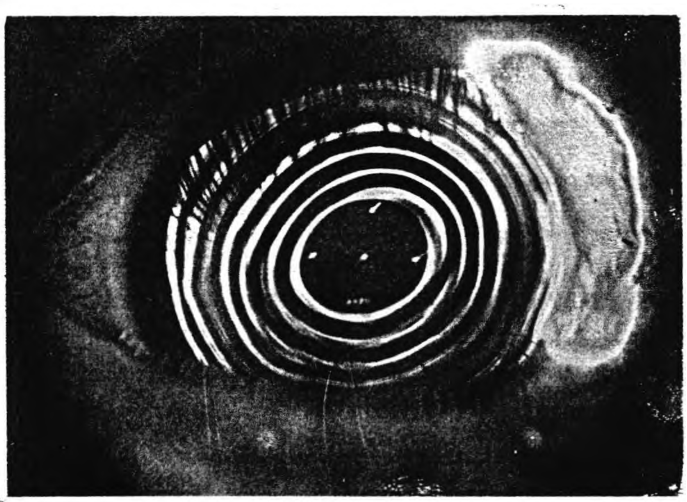


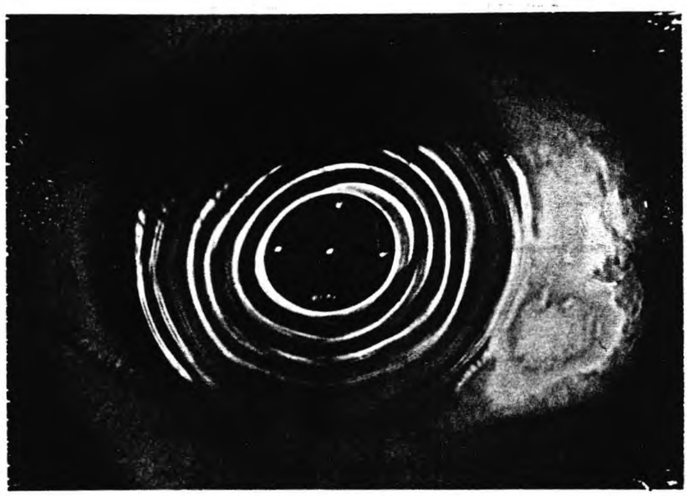
Figure F.11 Keratograph 10 deviation from the mean



Keratograph 1

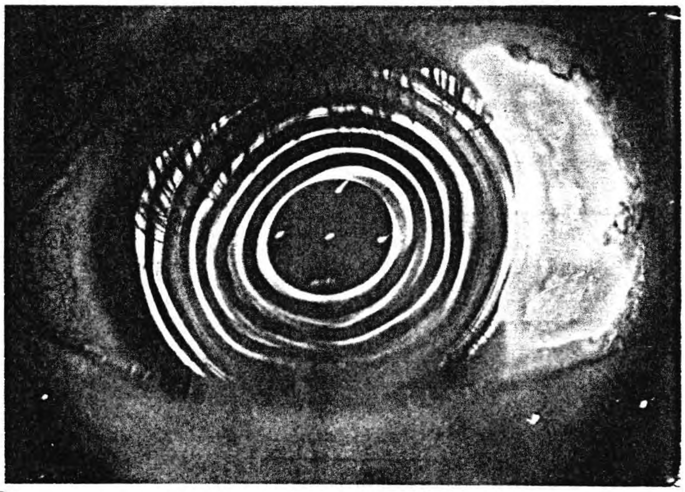


Keratograph 2

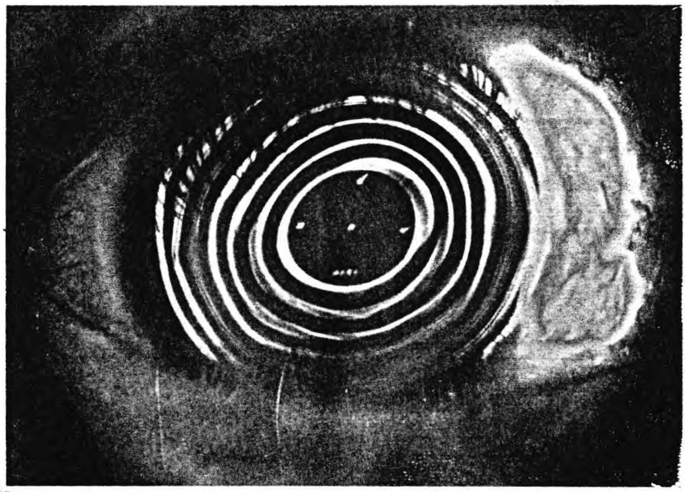


Keratograph 3

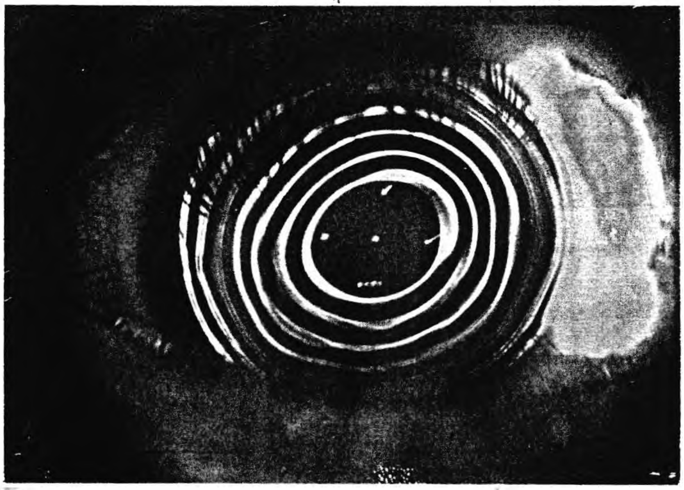
Figure F.12 Ten keratographs of the same transplant taken on the same occasion.



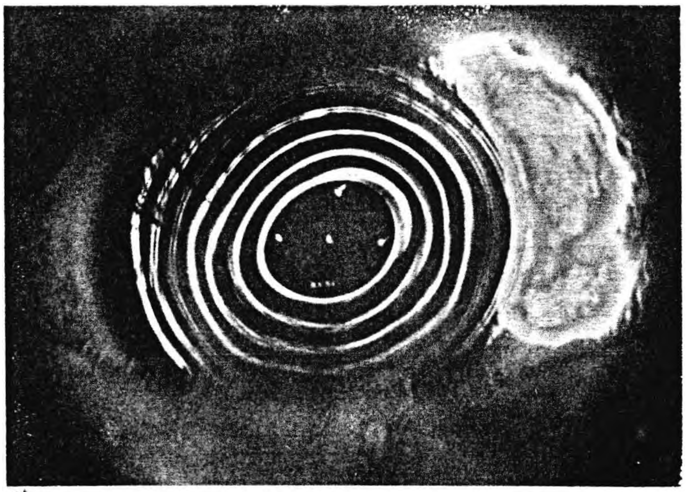
Keratograph 4



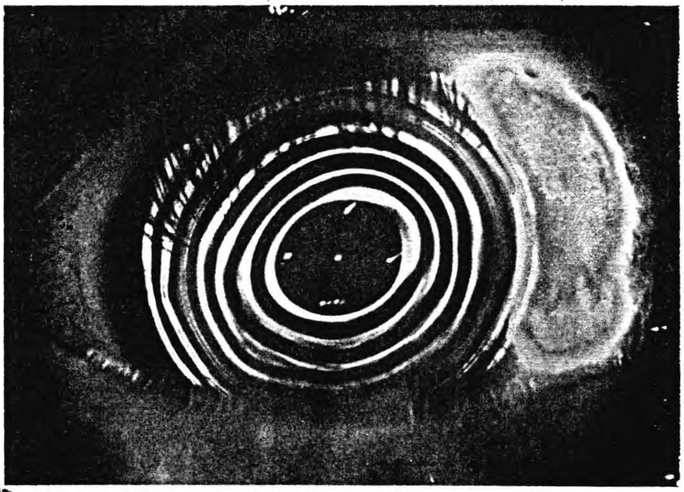
Keratograph 5



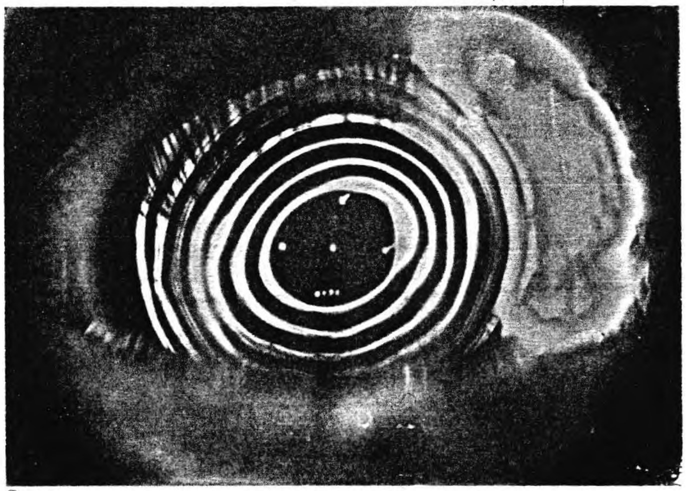
Keratograph 6



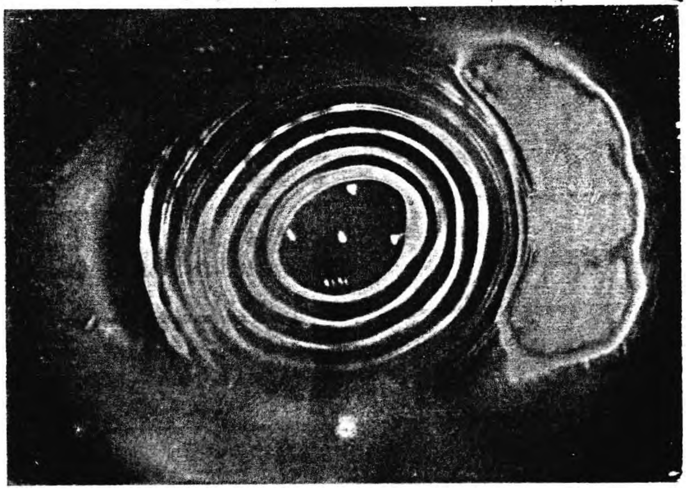
Keratograph 7



Keratograph 8



Keratograph 9



Keratograph 10

Appendix G . Radius of curvature values reduced to Components

The radius of curvature values (R) derived from a given ring of a keratograph can be plotted in a polar diagram to represent how they vary in different meridians.

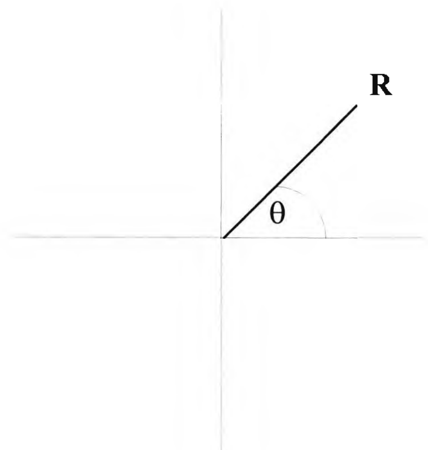


Figure G.1 Polar diagram

This is a two dimensional representation of how the curvature changes. It only relates to one ring, so it is describing how curvature on the cornea varies as you move through 360°, at a particular fixed distance from the corneal vertex (the point where the keratoscope axis meets the cornea).

The simplest situation to describe is a sphere. In this case the radius of curvature would be the same for all angles θ and the polar diagram would be a circle centred on the origin.

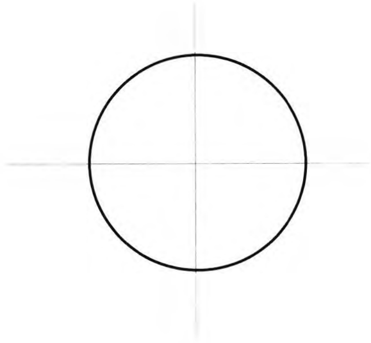


Figure G.2 Polar diagram representing a sphere

It would also be possible to have a polar diagram plot which consisted of a circle which is not centred on the origin. For example:-

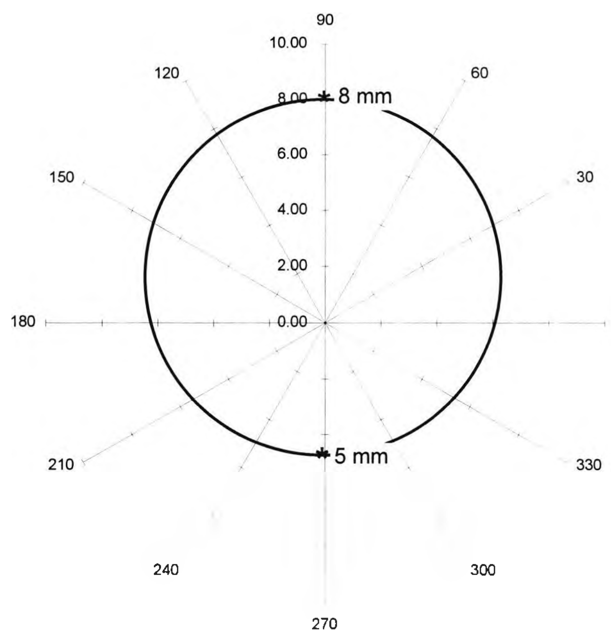


Figure G.3 Polar diagram with plot representing asymmetry

It must be borne in mind that the plot derived from a single target ring represents the radius of curvature at corneal locations which lie on a circle centred on the corneal vertex. In other words the locations where the curvature is being measured are symmetrically arranged around the corneal vertex. The decentred plot above indicates that the two points (*) in the vertical meridian (which are at equal distances from the vertex) do not have equal curvatures. In other words the curvature is asymmetrically disposed around the corneal vertex.

This form of asymmetry, where the inferior cornea is steeper than the superior cornea, is to be found in keratoconus, and it is probable that some form of asymmetry is present in other situations where the cornea is subject to distortion.

In both asymmetry and astigmatism the radius of curvature varies as you pass round the circle on the corneal surface where curvature is being measured. However, the type of variation is different in each case.

In the case of asymmetry there will be one maximum and one minimum, and these will be separated by 180°. The maxima and minima therefore lie on the same meridian.

In astigmatism there are two maxima and two minima. The radius of curvature reaches a maximum, then passes through a minimum before reaching another maximum and a final minimum. The maxima and minima are separated by 90°, and do not lie on the same meridian, as in asymmetry.

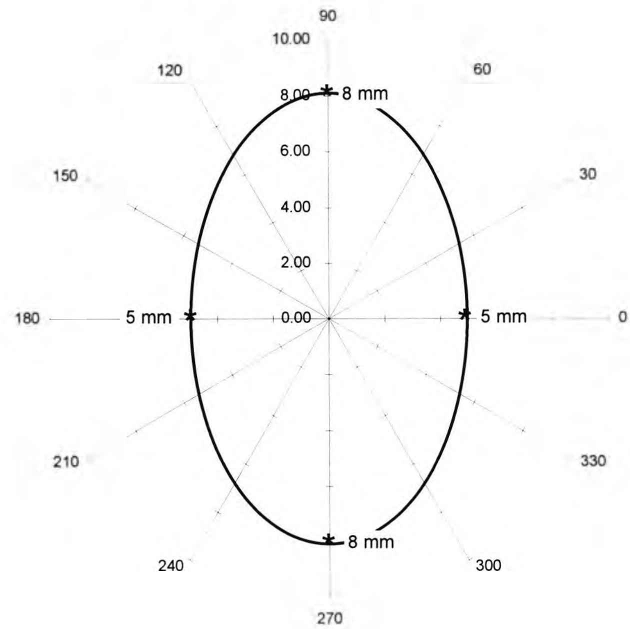


Figure G.4 Polar diagram with plot representing Regular Astigmatism

When the astigmatism is considered to be regular the two principal meridians are separated by exactly 90°. In addition there is no asymmetry. That is to say, for any given meridian the corresponding points on either side of the vertex have equal curvature.

We have seen that when corneal curvature is plotted in two dimensions as a polar diagram, the simplest result is a circle centred on the origin. This describes a sphere. The circle may be decentred from the origin. This represents asymmetry of curvature on the cornea. In addition, the shape of the circle on the two dimensional plot may become oval, which represents corneal astigmatism.

The amount the plot is decentred from the origin can be taken as a measure of the asymmetry. The angle at which the decentration is greatest can be taken as the direction of asymmetry, and can be any angle between 0 and 360°. Thus asymmetry can be thought of as a vector with magnitude and direction. This can also be expressed in terms of the x and y co-ordinates of the polar diagram. If the asymmetry co-ordinates were subtracted from the co-ordinates of each of the observed data points, the plot would become symmetrically arranged around the origin.

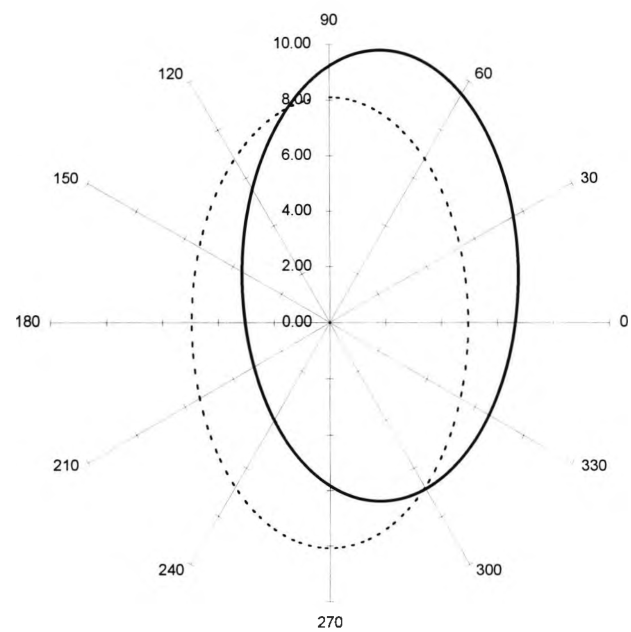


Figure G.5 Asymmetry vector applied to each data point

The plot represents variations in radius of curvature, therefore the units of asymmetry must also be mm of radius of curvature. It should be noted that the only decentration involved is on the plot, the two dimensional representation of corneal curvature. This should not be thought to represent any form of decentration of the cornea itself. The fact that asymmetry is measured in mm might suggest that it represents the distance the corneal apex is decentred from the corneal vertex. This is not the case.

Astigmatism is also measured in terms of mm of radius of curvature. Like asymmetry, it is described in terms of magnitude and an angle. The angle can vary through 180°, and in this thesis it is taken as the axis containing the maximum radius of curvature. In other words the flattest meridian.

A cornea which deviates from a true sphere in terms of asymmetry and astigmatism can be described mathematically:-

(1) $R_\theta = [s] + [\ d \cos(\theta - \beta)] + [c/2 \cos 2 (\theta - \phi)]$

This shows how the radius of curvature, for a given ring, changes with the angle θ, when there is asymmetry and astigmatism present.

R_θ is the radius of curvature at angle θ and s, d, β, c and ϕ are constants

s is the mean radius of curvature for the whole ring (or spherical equivalent)

d is the asymmetry

β is the angle of asymmetry

c is the astigmatism (the difference in radius of curvature between the two principal meridians

ϕ is the axis of astigmatism (angle of the flattest meridian)

These are all parameters which have some physical meaning, and can readily be related to the three dimensional structure of the cornea. In this thesis they will be used to monitor changes as a function of time, treatment etc.

Thinking in terms of the two dimensional polar diagram the constant s represents the radius of the circle centred on the origin. If there is asymmetry present you have to add a component [d cos (θ - β)] to the formula, which uses the constants d and β to alter how the curvature changes as θ changes. If there is astigmatism you have to add a second component [c/2 cos 2 (θ - ϕ)], which uses constants c and ϕ to further alter how the curvature varies with θ.

These can be considered as the components that describe corneal curvature when it has been deformed in a regular way by asymmetry and astigmatism. Appendix C describes how formula (1) is derived and how the parameters for the regular components can be calculated from the radius of curvature values measured from one ring on a keratograph.

An example is shown below.

Semi-meridian	0	30	60	90	120	150	180	210	240	270	300	330
Observed radius of curvature	7.94	7.30	6.89	7.23	7.61	7.82	7.72	7.04	6.45	6.57	7.41	8.26
Regular Components	7.99	7.40	6.93	7.06	7.62	7.98	7.67	6.93	6.44	6.68	7.45	8.06
Deviation	-.05	-.10	-.04	.17	-.01	-.16	.05	.11	.01	-.11	-.04	.20

Table G.1 Example to show observed data and the corresponding regular component data. Px # 6 (six month stage, Ring 1) **Irregularity = root mean square of deviations = 0.107.**

These twelve observed radius of curvature values can be reduced to the constants which determine the regular components:-

$s = 7.35$

$d = 0.25$

$\beta = 50°$

$c = 1.38$

$\phi = 157°$

If these constants are then substituted into equation (1) a radius of curvature value can be derived for each of the twelve semi-meridians. This data represents the regular components of the observed data, and they can be plotted alongside the observed data.

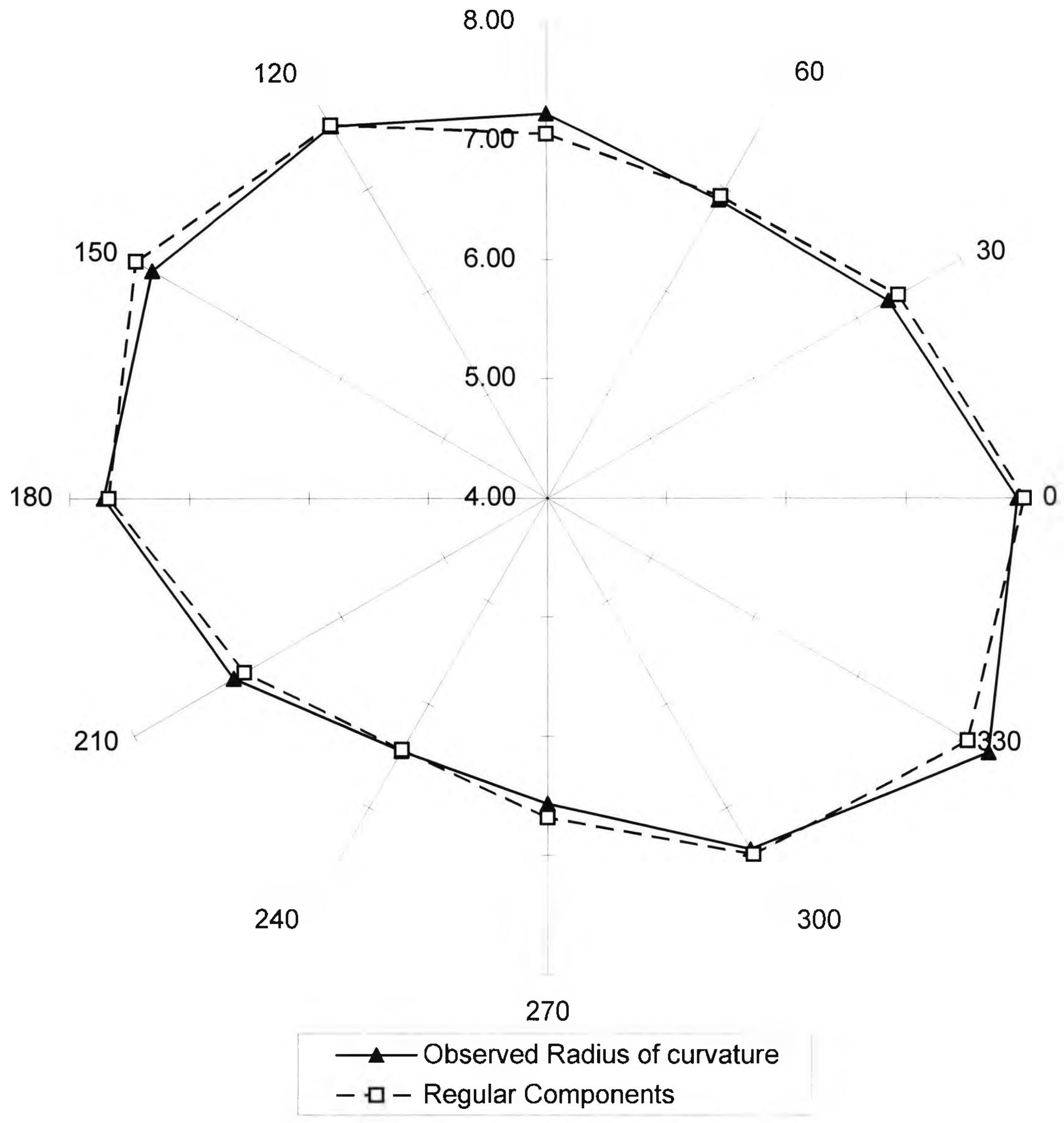


Figure G.6 Chart showing observed data and the corresponding regular component data. Px # 6 (six month stage, Ring 1)

It can be seen that there is not an exact match between the observed data and the regular component data. This indicates that in addition to the regular deformations, asymmetry and astigmatism, there is also irregular deformations. The difference between the regular component data, and the observed data can be taken as a measure of this irregularity. In this thesis the irregularity component is defined as the root mean square of the individual deviations of the observed data from the regular component data. In this example the irregularity was 0.107.

The plot of the regular component data can be seen more easily if it is shown without the observed data.

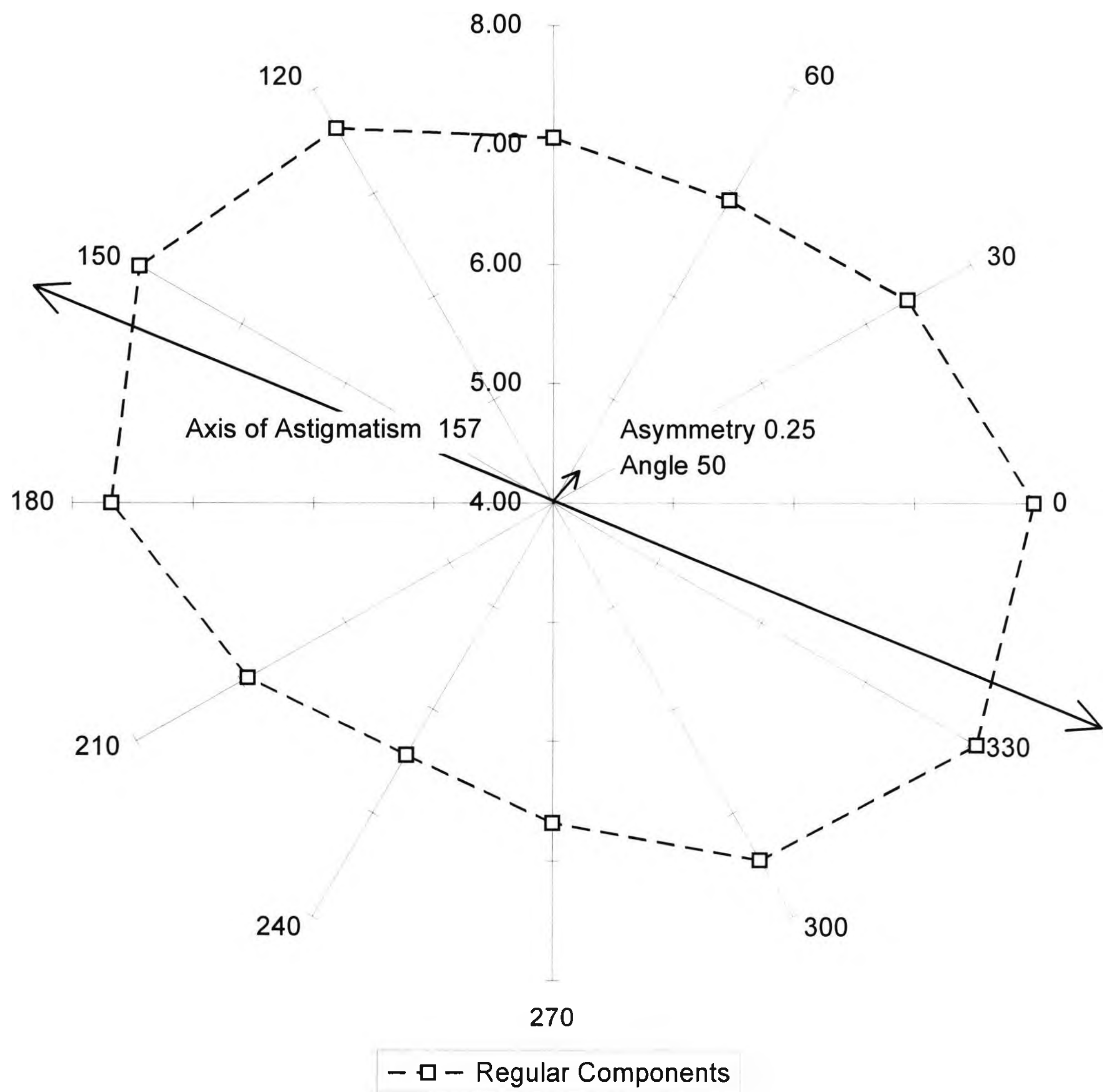


Figure G.7 Regular component plot. Px # 6 (six month stage, Ring 1).

The plot is decentred in the direction of 50°, by an amount corresponding to 0.25mm radius of curvature.

Appendix C contains further examples of data from individual keratographs, with the corresponding regular component constants (s, d, β, c, and ϕ), and the irregularity component (I). The examples were chosen to include different amounts and angles of asymmetry and astigmatism, and different degrees of irregular distortion.

Appendix H Statistical Methods

Introduction

The analysis of repeated measurements of astigmatism and irregularity on the same subjects at different points in time requires careful considerations.

Simple comparisons of individual values at different times would be inappropriate, firstly because their observation times may not coincide and secondly, because such comparisons would ignore the additional information available on every subject. An alternative approach would be to produce estimates of the individual linear regressions of astigmatism and irregularity over time. This would be useful as a first assessment of the data.

More complex modelling techniques are required, however, to investigate the effect of some potential prognostic variables - such as age at operation or diagnosis - on the observed changes over time of the two variables of interest, astigmatism and irregularity.

A statistical model is a mathematical relationship between two or more variables that gives an approximate description of the observed data. It does not necessarily describe the underlying mechanism of the relationship between the variables, but it is a simplification which is compatible with the data.

The simplification process, i.e. creating a model, necessitates that certain assumptions are made. For instance that all the transplants change over time in approximately the same fashion. A review of the data in this thesis revealed that it was reasonable to assume (for the purposes of creating a model) that log astigmatism and log irregularity varied linearly with time. Therefore, it was possible to use a simple linear model rather than a more complex mathematical relationship such as a quadratic. Other assumptions may also be required, such as normal distribution of the data. An additional benefit of conversion to a log scale is that 1 unit on the linear scale becomes zero on a log scale. This means that the data is conveniently distributed either side of zero.

Statistical models are often used to predict an outcome given certain values for the input variables. Therefore, the output from models can be thought of as the *predicted* values to distinguish it from the original data. In the case of the models used in this analysis, the output values are the parameters to describe a straight line (i.e. intercept and slope), which can be referred to as the predicted profile.

Examination of the individual regression lines reveals a high inter subject variation. This makes a simple predictive model impractical. The objective of this analysis is to be able to explain the variability. Why does the post operative change in astigmatism and irregularity vary so much in different patients? Can the variation be explained in terms of patient characteristics, such as age, or condition requiring keratoplasty, or in terms of their treatment, e.g. donor/host disparity or suture technique.

The class of multilevel regression (ML) models [356] is used here. These models are a direct generalisation of linear regression models. The starting point is the result obtained from fitting individual regression lines to the data from each subject. These are based on the assumption that astigmatism or irregularity (both on a log scale) vary with time *t* according to a linear function (note that a linear relationship with time seems adequate for this data, but non-linear functions could be fitted if necessary).

Let X denote either log-astigmatism or log-irregularity for a subject j. Then the linear regression model is specified as,

$$X_i = b_0 + b_1 t_i + e_i$$

where $X_i = X(t_i)$ is the value that X takes for subject j at the i-th observation time t_i and the errors e_i are normally distributed with mean 0 and variance σ^2_e. The coefficients (b_0, b_1) and the variance σ^2_e are specific to each subject j, and are estimated separately on each individual data.

Multilevel models.

In order to investigate the reasons why the individual lines differ, a more complex model is required, where the information from all the subjects can be pooled together and compared in terms of other characteristics of these subjects (e.g. gender or age).

To specify an ML model suitable for this type of data the linear model [356] is generalised as follows,

$$X_{ij} = b_{0j} + b_{1j} t_{ij} + e_{ij}$$

where $X_{ij} = X(t_{ij})$ is the value that X takes for subject j at the i-th observation time t_{ij} and the errors e_{ij} are normally distributed with mean 0 and variance σ^2_e and $\mathrm{cov}(e_{ij}, e_{ij'}) = 0$

for $j \neq j'$. The random coefficients (b_{oj} , b_{lj}) are specific to each subject j and are assumed to be jointly normally distributed with mean (β_0 ,β_1) and convariance matrix Σ (with elements (σ^2_{u0} , σ^2_{u1} , σ_{u01})).

The random coefficients (b_{oj} , b_{1j}) may be expressed as functions of other variables such as age or treatment. For example, they could be expressed as,

$$b_{0j} = \beta_0 + \delta_{01}\text{age} + \delta_{02}\text{treat} + u_{0j}$$

$$b_{1j} = \beta_1 + \delta_{11}\text{age} + \delta_{12}\text{treat} + u_{ij}$$

where the errors (u_{0j} , u_{1j}) are specific to each individual j and are assumed to be normally distributed with mean zero and covariance matrix Σ ([356] Chapter 6).

Note that in this hierarchical model the terms e_{ij} are known as level I errors, since they capture the variation over time of the observations within each subject, and the u_j are known as level II errors as they capture the variation of the observations between subjects ([356] Chapter 2).

Restricted maximum likelihood procedures are used to estimate (β_0 , β_1), (δ_{01} , δ_{02} , δ_{11} , δ_{12}), σ^2_e and Σ. The statistical software Mln [400] can be used to fit these models.

Fitting the simplest specification of an ML model (i.e. including only an intercept and a slope, no covariates) leads to individual estimates of the regression lines which are very close to those shown in figures 5.8 and 5.9 . The main differences between these results and those obtained from the linear regression method are that the ML estimated regression lines are available also for the subjects with few observations, and that the regression lines of those patients with fewer observations are less extreme because they are “moderated” by the information available from the subjects with more follow-up data.

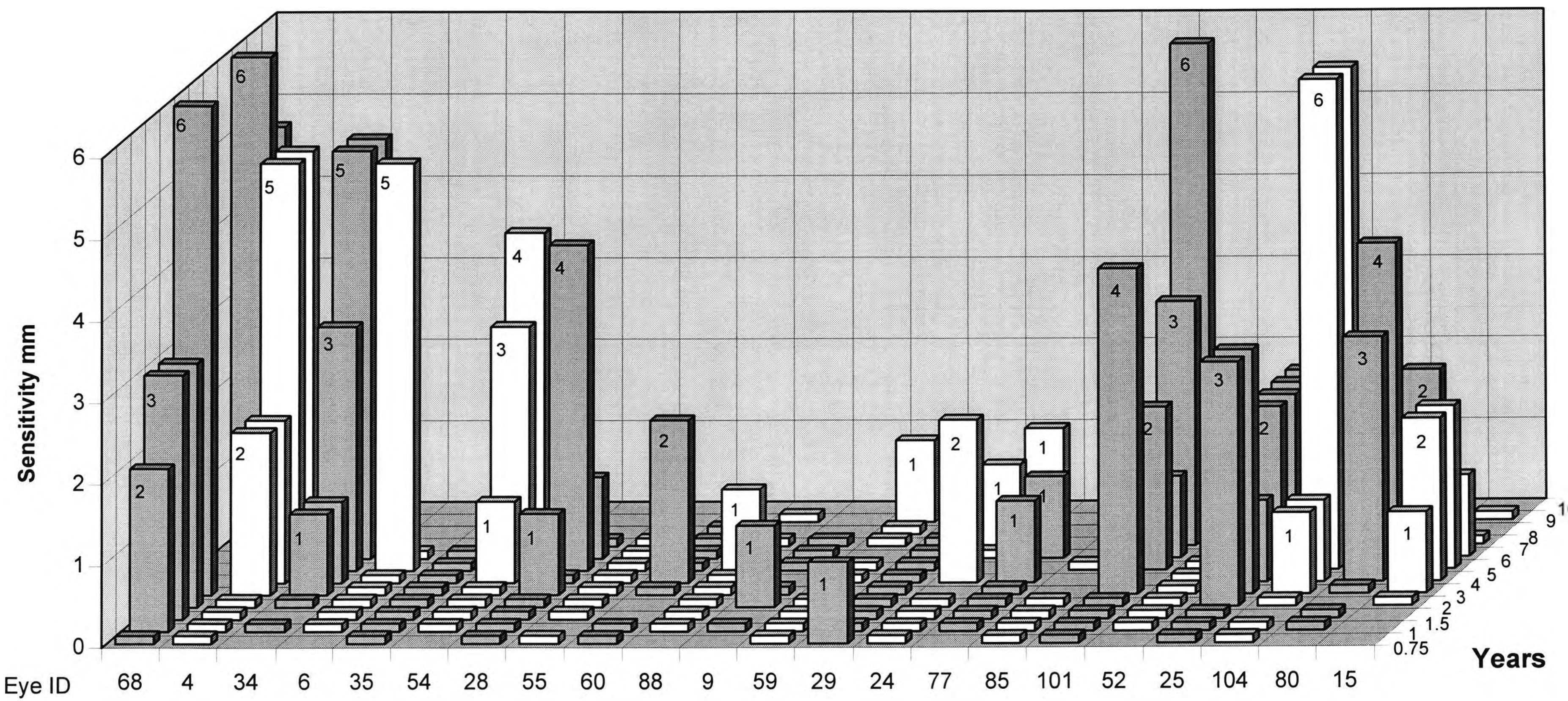
There are two further advantages in using ML models. The first consists of the ability of ML models to formally include other variables in the specification of intercept and slope. In other words these variables can be investigated to assess whether they explain the differences in these two individual specific parameters.

The second advantage lies in the estimates of the amount of variation in the data that is due to the spread of values over time within each subject and that due to differences between the subjects. Investigation of these components of variation is used to improve the model specification. Furthermore, the relative sizes of these two components can be considered when the results are generalised to a larger population.

Appendix I Sensitivity data

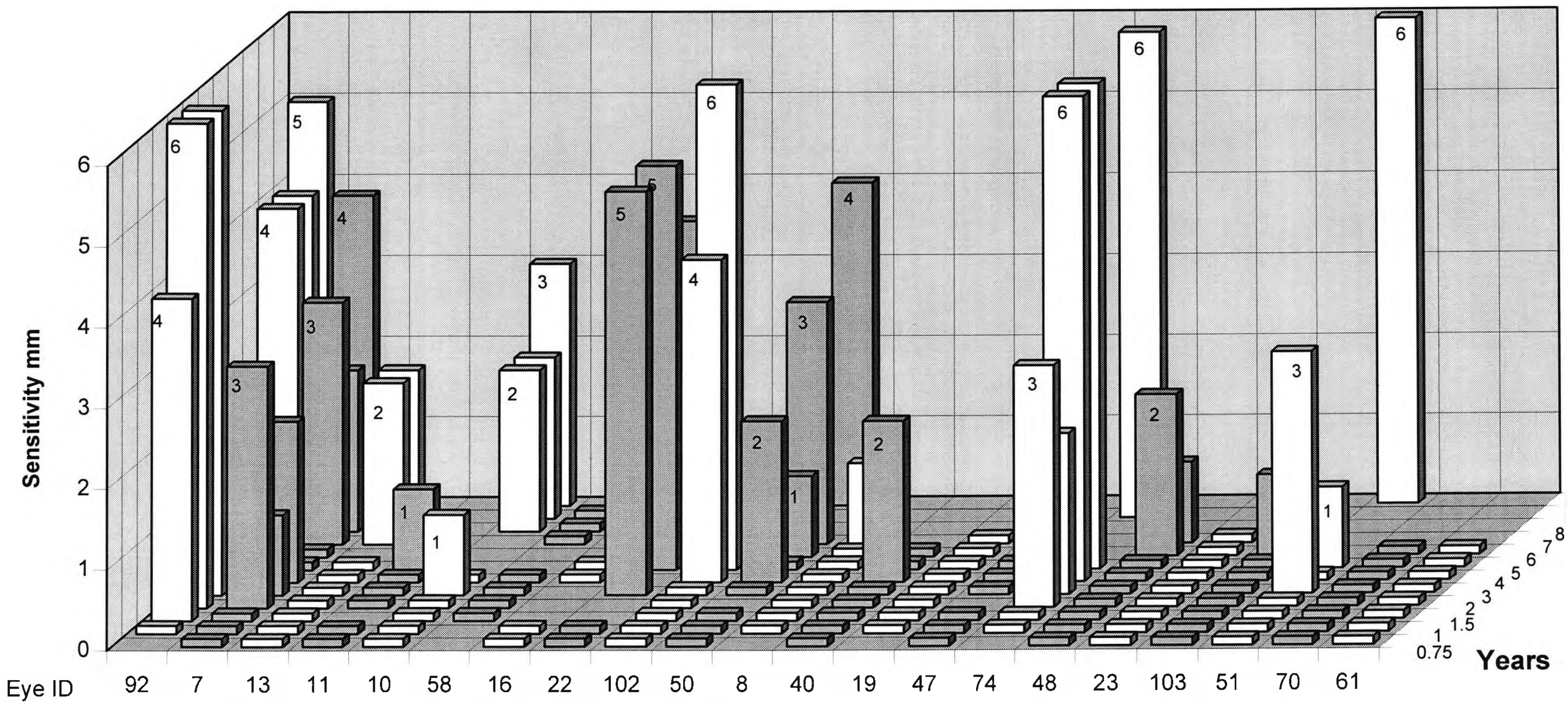
Sensitivity data is illustrated in Figure I.1 overleaf. The 65 patients have been split into three groups for convenience. The order in which they are presented is random.

Note that sensitivity readings taken after relaxing incision refractive surgery, were excluded from the analysis.



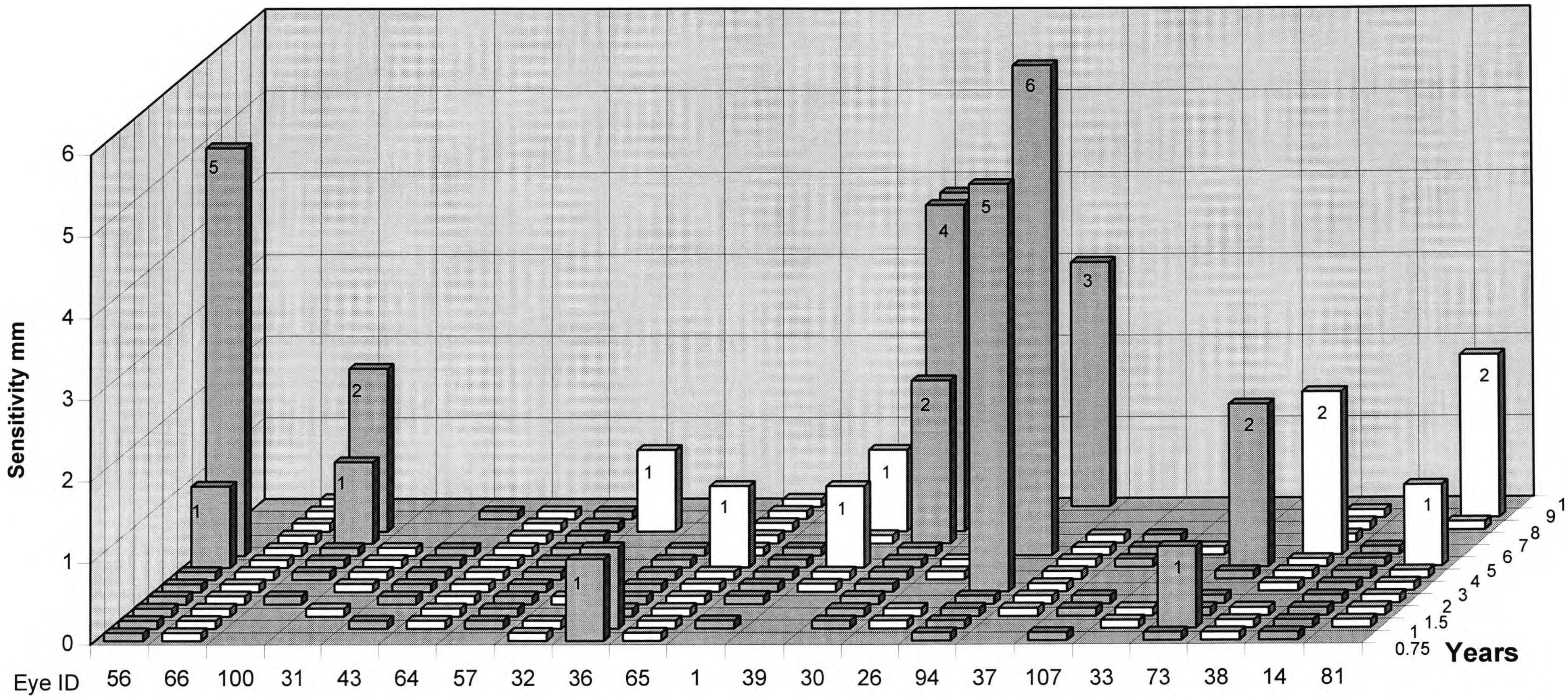
Years	68	4	34	6	35	54	28	55	60	88	9	59	29	24	77	85	101	52	25	104	80	15
10														1			1					
9										0		1		0			2	1		1	1	0
8	5								0			0		0			6	0	2	0	2	
7	6		5				0	0	0	0	0	0	0	1			3	0	2	3	0	0
6		5	5	0	0	4	1	0	0	0	0		0	0	1		1	0	2	6	0	1
5		5	3	5	0	3	4	0	0	1	0	0	0			0	2	0	2	6	4	2
4		2	1	0	0	1	0	0	2	0		0	0	2	1			0	1	1	3	2
3	6	2	1	0	0	0	1	0	0	0	0	0	0		0		4	0	3	1	0	1
2	3	0	0	0	0	0	0	0		0	1	0	0	0	0	0	0	0	3	0		0
1.5	3	0		0	0	0	0	0		0		0	0	0	0	0	0	0	0		0	
1	2	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	
0.75	0	0			0		0	0	0			0	1	0		0	0		0	0		

Figure I.1 Changes in **central** touch sensitivity in the years following keratoplasty. The data is presented in three sections. Section 1 is above.



Years	92	7	13	11	10	58	16	22	102	50	8	40	19	47	74	48	23	103	51	70	61
10	5				3					4									6		
9	4	4			2	0									6						
8	4	2	2		2	0					0										
7		3	2			0		4		3	1		0			1	0				
6		0								1	0	0	0			2	0	1		0	0
5		0	0	1			0	5	6	0	0	0	0	0	6	0	0	0	1	0	0
4		2	0	0	0	0	0		4	2	0	2	0	0	6	0	0	0	0	0	0
3	6	1	0	0	1	0		5	0	0	0	0	0	0	2	0	0	0	3	0	0
2	6	3	0	0	0	0			0		0	0	0		3	0	0	0	0	0	0
1.5	4	0	0		0	0			0	0	0	0	0	0	0	0	0	0	0	0	0
1	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.75		0	0	0	0		0	0	0	0		0		0		0	0	0	0	0	0

Figure I.1 Changes in **central** touch sensitivity in the years following keratoplasty. The data is presented in three sections. Section 2 is above.



56	66	100	31	43	64	57	32	36	65	1	39	30	26	94	37	107	33	73	38	14	81	Years
	0								0					3								10
	0			0	0	0			0			4							0		2	9
	0	2			0	0	1		0		1	4							0		0	8
	0	1			0	0			0		0	2			0	0			0			7
5	0	0	0	0	0	0		0	0	0		0		6	0	0	0		2	0		6
1	0	0	0	0	0	0		0	1	0	1	0	0		0	0		2	0	0	1	5 Years
0	0	0	0	0	0	0		0	0	0	0	0	0		0			0	0	0	0	4
0	0		0	0	0	0		0	0	0	0	0		5	0				0	0	0	3
0	0	0		0	0	0	0	0	0	0		0		0	0	0		0		0	0	2
0	0		0		0	0		0	0			0	0	0	0	0	0	0	0	0	0	1.5
0	0			0	0	0	0	1	0	0		0	0	0			0	1	0	0	0	1
0	0						0	1	0					0		0		0	0	0		0.75

Figure I.1 Changes in **central** touch sensitivity in the years following keratoplasty. The data is presented in three sections. Section 3 is above.