KERATOCONUS: THE DISEASE AND ITS PROGRESSION

A thesis submitted by

Edwin Geoffrey Woodward

for the Degree of Doctor of Philosophy

to

The City University, London

Department of Optometry and Visual Science
The City University
London EC1V OHB.

June 1980

[redacted]

KERATOCONUS: THE DISEASE AND ITS PROGRESSION.

List of Tables.

Tables (contd.)

Tables (contd.)

Illustrations.

Illustrations (contd.)

Fig.19 Modified Pachometer with digital read out.

Fig.20 Modified Pachometer. Eye Piece setting.

Fig.21 Modified Pachometer. Slit width setting.

Fig.22 Optical path of slit beam and reflected light.

Fig.23 Narrow slit beam in use. Note reflections of Donaldson lights.

Fig.24 Haag-Streit depth measuring attachment No.II.

Fig.25 Bausch and Lomb Keratometer Optical system.

Fig.26 Bausch and Lomb Keratometer mires.

Fig.27 Elongated endothelial cells in Keratoconus and in a graft. (From Laing et al 1979).

Acknowledgements.

I would like to thank my supervisors Professor C.M. Ruben for his invaluable advice on a subject in which he has a lifetimes experience, Professor G.M.Dunn for his constructive criticism and encouragement and for making available the facilities offered to me by the University and in particular the Department of Optometry and Visual Science.

I record my thanks to the Board of Governors of Moorfields Eye Hospital for permission to carry out the clinical work in the Department of Contact Lens and Prosthetics.

My task has been made much easier by the help given to me by [redacted] with the statistical analyses and [redacted] with literature searches.

I would like also to acknowledge the assistance of all my colleagues in the Department of Contact Lens and Prosthetics particularly those who have worked in the Keratoconus clinic.

Finally my thanks to [redacted] for her support and encouragement during the last five years.

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.

Although Keratoconus has been recognised as a clinical entity for more than two millenia, the documentation of the change it produces in corneal dimensions has been only sparsely investigated and reported upon. This thesis analyses the parametric changes in 100 Keratoconus corneae over a two year period and the concurrent changes in visual acuity.

Topographical pachometry with a specially modified pachometer allowed corneal thickness to be measured at nine distinct points on the cornea. Anterior chamber depth and corneal radii being measured with conventional instruments. The results show that corneal thinning always precedes corneal ectasia, so that early diagnosis would be aided by the use of instruments measuring corneal thickness rather than by those relying on reflections from the anterior corneal surface. The pattern of corneal thinning follows a fairly predictable path with time, the greatest amount of thinning occuring in the first two years from onset. The cornea tends eventually to stabilize at a corneal thickness 60% of normal. The greater rate of thinning always occurs at an eccentric but relatively central position. A positive correlation was found between visual acuity reduction and corneal thinning, irrespective of the mode of correction.

The patient sample was also analysed in terms of maternal age, social class and educational attainments. Here a significant new finding was that Keratoconus is a maternal age related condition. There is an inference that social class and educational attainments of the patients may also be a reflection of the generally older age of the mother. This also implies that some of the traits ascribed by clinicians to patients suffering from Keratoconus are to be anticipated and can be explained in socio-economic terms.

KERATOCONUS THE CONDITION

A) EARLY HISTORY

Although the condition of Keratoconus has been known from early times references to it have not been found in the medical literature of the Greeks and Romans. The earliest writings on the condition known today would seem to be those of the Arabian physicians of the 11th century.

Nottingham (1854) refers to a latin translation of the Dresden manuscript of the Arabic work on the anatomy, physiology and diseases of the eye of Alii Ben Isa, which was then in the course of translation. This mentions the condition and Nottingham comments that had the Arabians only learnt the art of printing they would have been much more famous in ophthalmology.

In the year 1748, Mauchart published, at Tubingen a dissertation on conical cornea, or "Staphyloma Diaphanum" as he terms it; and in 1766, Taylor in his "Nova Nosographia Ophthalmica", published at Ham burg and Leipzig, concisely described the same disease but using the name "Ochlodes".

Taylor, an itinerant ophthalmologist, described by Sorsby (1933) as a charlatan, described Keratoconus as had previously Benedict Duddell.

However, the writings of Mauchart or Taylor do not seem to have attracted much attention for the famous ophthalmologist Scarpa published at Pavia in 1801 an article "Staphyloma" which describes in a long note a case of Keratoconus in a female. He writes that he does not know where in classification to place this condition, makes no allusion to the descriptions of either Mauchart or Taylor and leads the reader to suppose that he had neither seen nor read of it before.

In the early 19th century the terms, conical cornea, Keratoconus and hyperkeratosis seem to have been interchangeable and all are used in one of the earliest and most complete monographs on the condition published in 1854 by Nottingham. (See Fig. 1) This was undoubtedly the first monograph which adequately described the condition and differentiated it from other abnormalities of the cornea.

PRACTICAL OBSERVATIONS

ON

CONICAL CORNEA,

AND ON THE

SHORT SIGHT,

AND

OTHER DEFECTS OF VISION CONNECTED WITH IT.

BY

J. NOTTINGHAM, M.D.,

FELLOW OF THE ROYAL COLLEGE OF SURGEONS OF ENGLAND, CORRESPONDING
MEMBER OF THE MEDICAL SOCIETY OF EMULATION OF PARIS, OF THE ROYAL
MEDICAL SOCIETY OF BERLIN, OF THE ACADEMIES OF MEDICINE AND
SURGERY OF MADRID AND BARCELONA, AND OF THE ACADEMY
OF NATURAL SCIENCES OF SPAIN; SURGEON TO
THE ST. ANNE'S EYE AND EAR INSTITUTION
LIVERPOOL.

LONDON:
JOHN CHURCHILL.
LIVERPOOL: DEIGHTON & LAUGHTON
1854.

Fig. 1. Title Page "Practical Observations on Conical Cornea"
Nottingham 1854.

Nottingham was a pupil of Dalrymple and after that he left London on a 'Grand Tour' of all the ophthalmological centres of Europe, learning as he went. He became a member of learned societies and academies in Paris, Madrid, Rome, Berlin and Barcelona, finally returning to become Surgeon to St. Anne's Eye and Ear Instititution, Liverpool. He did not confine his interests to the eye but wrote textbooks on urology and neurology in both man and domestic animals.

His book on conical cornea, dedicated to Dalrymple, (See Fig. 2) consists mainly of accurate and painstaking descriptions of patients, differentiating clearly between Keratoconus and other ectatic conditions. There are no separate chapters and he wanders between clinical descriptions, speculation on aetiology and comparative anatomy with gay abandon.

TO

THE MEMORY

OF

Dalrymple,

THESE PAGES ARE MOST RESPECTFULLY DEDICATED,

AS A TRIBUTE OF ADMIRATION FOR

DEPARTED GENIUS,

AND FOR EXCELLENCE ASSOCIATED WITH A NAME

WHICH IS ALREADY INSCRIBED UPON MONUMENTS

OF MORE DURABLE CHARACTER.

Fig. 2. Dedication by Nottingham 1854.

Virtually all he writes accords with modern ideas on the condition. However, one idea which might not be accepted now is that the eye may be affected by the condition before birth, even though it may occur very early in life. He also states that it is not known in other animals than man, except possibly goldfish.

He comments on regional variations in the incidence of the disease saying it is more common in Scotland, Northern England, Northern Germany and China. There is a considerable literature on Keratoconus from the Nordic countries so this may be the first reference to a racial incidence. Many of the patients he saw are described as scrofulous, so possibly in the light of modern ideas on the connection of Keratoconus with atopy these may have been forms of eczema. Also, a great number of the patients were suffering from tuberculosis, but, presumably, so were quite a high percentage of the working class population of Liverpool in the mid 19th century.

In terms of the present writers thesis, the most significant disclosure in the book is that Nottingham was probably the first ophthalmologist to appreciate that the cornea actually became thinner in Keratoconus as well as protruding. Jaeger had noted this on one patient at post mortem, but as the patient had died from tuberculosis he had ascribed the corneal thinning to this.

On page 147 of his work on Keratoconus Nottingham wrote: "In the story of the conical cornea, we should advance considerably if any means of accurately determing the thickness of the living cornea could be hit upon". It is hoped that this thesis based mainly on measurements of the thickness of the living cornea will advance the story a little.

In 1868 von Graefe ascribed the condition to a raised intraocular pressure and did not classify it as a separate entity. Pathological investigations by Bowman (1857) and Brailey (1875) did not go very far in explaining the condition.

Vertical striae in keratoconic cornae were first described by Elschnig (1894) and acute Keratoconus or corneal hydrops was first described by Terrien (1906).* In the same year Fleischer described his ring and in the following year Salzmann (1907) wrote of the corneal scarring which occurs corresponding to ruptures in Bowmans membrane.

Thus by the beginning of the twentieth century the condition was well described clinically and yet, as Duke Elder writes in volume VIII of his system ophthalmology in 1965: "A multitude of theories has

been put forward to account for its development, most of them relating to relatively few cases, none of them of general applicability, and all of them representing inadequate attempts to solve a problem which in our present state of ignorance is insoluble".

* The term corneal hydrops is a much older one. It was used by the Persians for advanced Keratoconus as the appearance was of a drop on the cornea.

KERATOCONUS

A) EARLY HISTORY

REFERENCES

BOWMAN (1857) — Roy. Lond. Ophthal. Hosp.Rep,2,154

BRAILEY (1875) — Roy. Lond. Ophthal. Hosp.Rep, 8,287

ELSCHNIG (1894) — Klin. Mbl. Augenheilk, 32,23

FLEISCHER (1906) — Munch. med. Wschr. 53, 625

von GRAEFE (1868) — Berl. Klin. Wschr., 5,241

MAUCHART (1748) — Staphyloma vaxatum nomen (Diss) Tübingen

NOTTINGHAM (1854) — Practical Observations on Conical Cornea Churchill London

SALZMANN (1907) — v. Graefes Arch. Ophthal, 67, 1

SCARPA — Referred to by Nottingham (see above)

SORSBY A. (1933) — A short History of Ophthalmology Staples Press London

TAYLOR (1766) — Nova nosographia ophthalmica Hamburg 21

TERRIEN (1906) — Arch. Ophthal (PARIS) 26, 9

B) INCIDENCE

Nottingham stated that in Liverpool where he practiced it was a rare disease and he saw only a few patients each year.

However, it is very difficult to obtain exact figures as to the frequency. Jonkers (1950) found the incidence in Holland to be 1 in 40,000 of the general population, Whereas other authors have given figures as low as 1 in 286, Catsch (Germany) (1938) and 1 in 703 Cambiaggi (Italy) (1955). Franceschetti and Carones (Italy) (1960) and Jaensch (Switzerland) (1929) consider the incidence to be approximately 1 in 3,000. Forest (England) (1929) 1 in 7,000. Ruben (1977) basing his figures upon the number of Keratoconus patients treated at Moorfields for a catchment area which is approximately 5 million arrived at a figure of 1 in 10,000 who must be affected by this condition. The variation in the figures may be partially explained by the variable diagnosis of the abortive forms of the condition. For example Kornerup and Lodin (1959) showed that there is a significantly higher incidence of "bi-oblique corneal astigmatism" amongst dermatitis cases that amongst controls and some authors would classify these cases as Keratoconus.

Amsler (1961) using a classification based on subjective impression of mire distortion found of 600 cases 52% were of the rudimentary type and might often not be diagnosed.

There is no agreement over sex ratio in the incidence of the disease. Bath (1948), Thomas (1955), Fox (1910), Nuel (1900), Hansell and Sweet (1903) and Wood and Woodruff (1907) all report a preponderance of women sufferers, particularly "females of a feeble or debilitated constitution" which may well represent their view of the condition at the time of writing. Whereas Amsler (1961), Karseras and Ruben (1976), Obrig and Salvatori (1958) and Arias (1962) found a preponderance of males in their groups. The sex distribution of the present study will be given in a later chapter.

Cullen and Butler (1963) in an examination of 143 patients suffering from Downs Syndrome found a high incidence of Keratoconus, 5.5%. The association of Keratoconus with Downs Syndrome has been reported by many authors including Hofman (1956), Zajacz (1963) and Stucchi and Erpelding (1960). An analysis of the maternal age of 150 cases of Keratoconus in the present study forms the subject of a late chapter in this thesis.

B) INCIDENCE

REFERENCES

ARIAS V.C. (1962) "El Queratacono su correcion per medio de Lentes de Contacto 4-41 Arch. Soc.Oftal Optom.

AMSLER M. (1961) "Quelques donnees du Probleme du Keratocone Bull. Soc.Belge.Ophthal 129, 331-334

BARTH J. (1948) "Statisk uber 300 Keratoconusfalle mit 557 befallenen Augen". Thesis Zurich.

CAMBIAGGI A. (1955) "Evidenza Statistica della Associozone della Degenenozione Pigmentoza della Retina con il Cheratocono" G. Ilal oftal 8, 13-17

CATSCH A. (1938) Korrelationspathalogische Untersuchunger I Albrecht v. Graefe Arch. Ophthal 138, 866-892

CULLEN J.F. & BUTLER H.J. (1963) "Mongolism (Down's Syndrome) and Keratoconus" Brit. J. Ophthal 47.6. 321-330.

FORREST J. (1929) "The Recognition of Ocular Disease" p.77 J. and H. Taylor, London

FRANCESCHETTI A. and CARONES H.V. (1960) G. ital oftal 13, 143-160

FOX L.W. (1910) "A Practical Treatise on Ophthamology" p.231 Appletons, London

HANSELL H.F. & SWEET W.M. (1903) "Diseases of the Eye" p.229 Rebman.

HOFMAN (1956) Klin.Mbl.Augenheilk 129, 756

JAENSCH P.A. (1929) "Keratoconus die Engebrisse de Forschung de Cetzen 20 Jahre". Zbl. ophth 21, 305-327

KARSERAS A.G. & RUBEN M. (1976) Brit. J. Ophthal. 60.522

JONKERS G.H. (1950) Keratoconus Ned. Tijdschu.Geneesk 2, 1313-1315

KORNERUP T. & LODIN A. (1959) "Ocular changes in 100 cases of Besniers Prurigo Atopic Dermatitis". Acta Ophthalmologica Kbh.Val. 37.508-521

NOTTINGHAM J. (1854) "Conical Cornea" Churchill London

NUEL J.P. (1900) (Liege) writing in Norris & Oliver "System of Diseases of the Eye" Vol. IV 249-253 Lewin London

OBRIG T.E. & SALVATORI P. (1958) "Contact Lenses" p.p. 145-146. The Chilton Co. New York.

RUBEN M. (1977) "Treatment of Keratoconus" Aust. Journ. Optom 644

STUCCHI & ERPELDING (1966) Confin. neurol. 20, 376

THOMAS C.I. (1955) "Keratoconus" in "The Cornea" pp 233-244 ed. CC Thomas Springfield Illinois

WOOD C.A. & WOODRUFF T.A. (1907) Commoner Diseases of the Eye p. 306-307 W.T. Keene

ZAJACZ (1963) Klin. Mbl. Augenheilk 143, 503

C) AETIOLOGY

Many theories have been advanced to account for the corneal changes found in Keratoconus but the precise nature of this condition still remains obscure. In 1854 Nottingham wrote:
"The etiology of the disease is not more advanced that its pathology, although many very interesting observations have been made respecting the time of life, constitutional pecularities, concomitant affections, general or local as well as the influences of exposure or occupation of the eyes, which seem to have been noticed in connection with the origin or aggravation of the malady; some however, of the conditions alluded to, may now and then be regarded as accidental, and, if so, must occasionally be viewed in the light of coincidence, rather than in that of cause".

One hundred and forty six years later we are not very much further forward.

One group of theories has suggested that the condition is developmental in origin. Salzmann (1907) described the condition as a primary anomaly of growth, Politzer (1952) as a lack of development of the corneal mesenchyme and Stahli (1918) considered it an extreme instance of the normal biological variation which found expression in refractive errors.

Another view is that it represents a degenerative condition. The exact site of the degenerative process is not the same in all theories. Some workers describe it as an mesenchymopathy (Sbordone and de Simone, 1957, Alajmo, 1957), while Teng (1963) considered the primary defect to be a degenerative fragmentation of the basal membrane of the epithelium associated with breaks in Bowmans membrance.

Capeman (1965) and Ridley (1966) suggested that Keratoconus might be initiated by eye rubbing in response to mental stress or emotional tension, but Karseras and Ruben (1976) found no significant psychoneurotic factors in Keratoconus patients compared with patients in the control group.

Many authors have suggested that it is secondary to some disease process or state of lowered nutrition. It has been associated with lymphogranuloma venereum (Vazquez-Barriere, 1942, Racha 1944) with spring catarrh (Bietti and Ferraboschi 1958) and with atopic eczema (Bereston and Baer 1942; Galin and Berger 1958; Kornerup and Lodin 1959; Spencer and Fisher 1959; Franceschetti and Carones 1960).

This well recognized association with atopic conditions and its relationship with allergic dermatitis, asthma and hay fever led a group of workers (Davies, Lobascher, Menon, Rahi and Ruben 1976) to study the immunological profile of Keratoconus patients in order to establish whether the ocular changes were similarly associated with an abnormal immunological pattern. Using a group of 100 Keratoconus patients with a control group of 100 matched invididuals who were attending eye clinics for non-inflammatory conditions they found the following results:

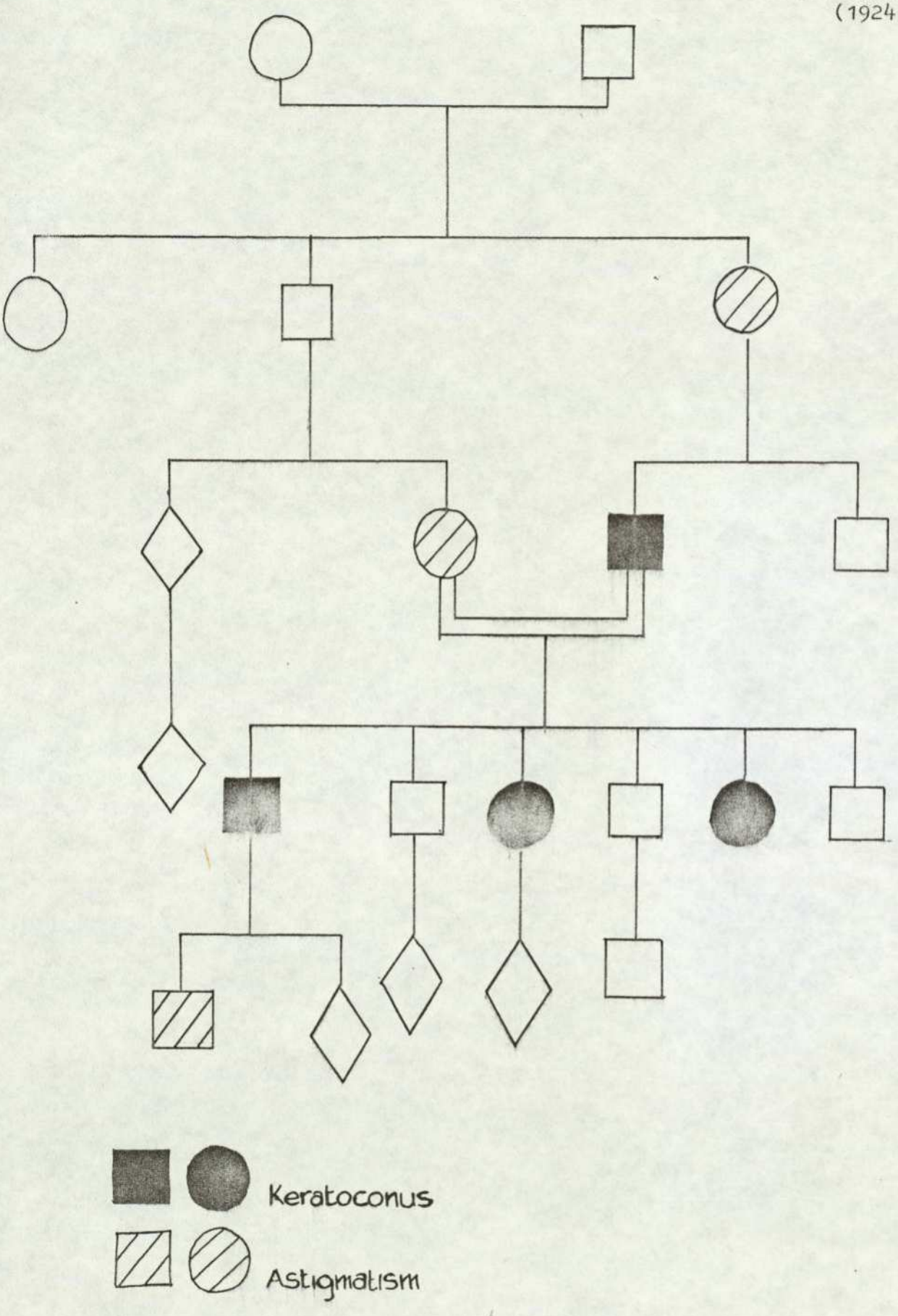
1) A definite history of atopy was found in 35% of cases of Keratoconus as against 12% in a control group.
2) Serum Ig E was significantly raised in the Keratoconus group but no such changes were noted in the tears.
3) Serum Immunoglobulins G & M were also raised, contrary to the findings of other observers, Ig A levels were normal.
4) A proportion of the cases of Keratoconus showed in their blood the presence of antinuclear and antinucleolar antibodies, rheumatoid factor, and antibodies to smooth muscle mitochondria, reticulin, gastric parietal cells and thyroglobulin.

The authors conclude that it is likely that for some unknown reason Keratoconus co-exists with immunological abnormalities of a generalized type and that Keratoconus is a forme fruste of a functionally abnormal mesenchymal system, manifesting itself only in the cornea. Biochemical and ultrastructural studies seem to support this notion. Keratocytes which are involved in the synthesis and secretion of collagens and proteoglycans (i.e. the ground substance) which exert molecular constraints for the regular organisation of the Corneal lamellae (Boercherding, Blocik, Sittig, Bizzell, Breen and Weinstein 1975), appear to malfunction in Keratoconus. The keratocytes show features of active synthesis as well as gradual degeneration and vaculoation (Pouliquen, Faure, Limon and Bisson, 1968). The synthesis of collagen takes place in various steps involving translation, hydroxylation, helix formation, glycoxylation, secretion, conversion of the precursor, aggregation and cross linking. These processes are not only dependent on various enzymes which are genetically controlled, but on several other factors in the micro-environment (e.g. ascorbic acid) which may affect the process of cross

linkage and the laying down of collagen in a regular pattern. A defect in any of these processes will affect fibrillogenesis in the cornea and may lead to the changes so commonly seen in Keratoconus. It has recently been found that in humans the chromosome 6 contains the genes for transplantation antigens and linked to this major histocompatibility region of the chromosomes are the immune response genes (i.e. IR Gene) which control the immunological responses of the individual (Fesenstein and Pena-Martinez 1975). It is not surprising therefore that a close relationship exists between atopy, raised IgE and several histo-compatibility antigens, particularly HLA-B7 (Good-friend, Lapkoff and Marsh 1973). Studies on serum IgE in monozygotic and dizygotic twins suggest an inherited genetic function in IgE production. (Hamburger and Bazaral 1972).

It has long been noted that there can be an hereditary occurrence of Keratoconus but the nature of its transmission is by no means clear, nor does it appear to be common; a circumstance perhaps due in part to a failure to recognise attenuated forms showing very slight anomalies in members of a pedigreee. A recessive transmission is suggested by quite a number of cases showing a familial incidence in which consanguinity has sometimes figured (van de Hoeve 1924) but occasionally a dominant form has been reported (Stahli 1925). (See Fig. 3.)

Fig. 3(a) Keratoconus inheritance. Recessive after van der Hoeve, (1924)



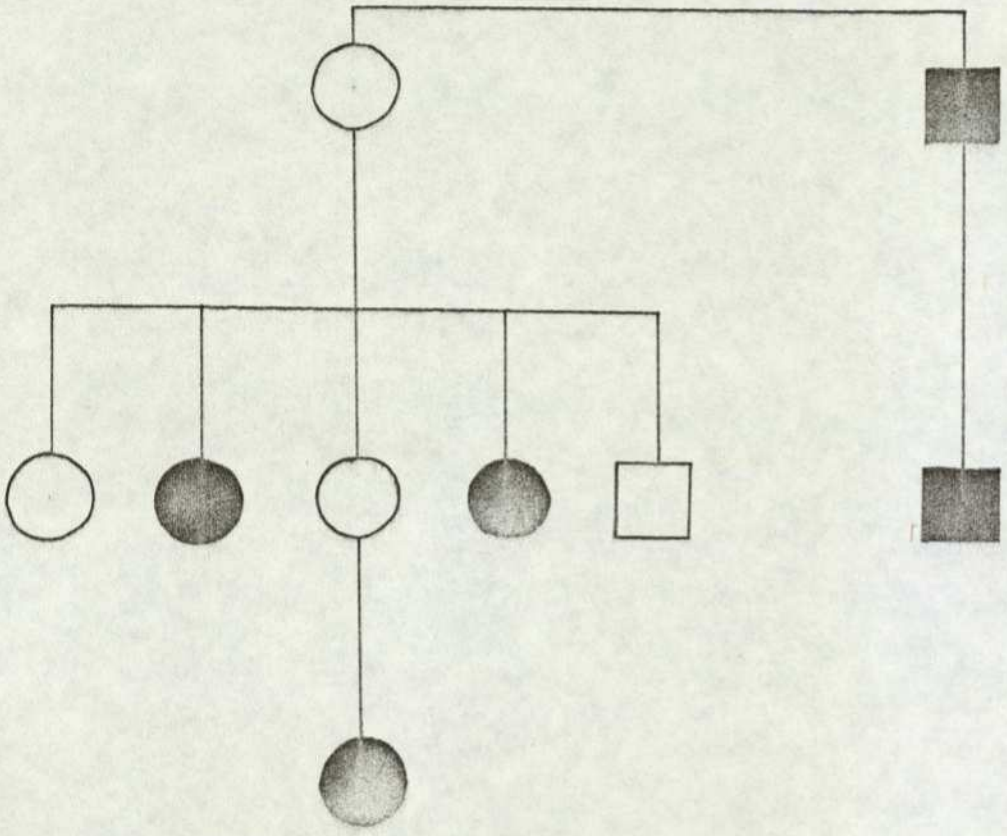


Fig. 3(b) Keratoconus inheritance. Dominant after Stahli, 1925.

Davies, P.D. Lobascher D Menon J.A. Rahi A.H.S. and Ruben M. (1976) end their paper by postulating that since the immunoglobulin producing lymphocytes and the keratocytes are of mesenchymal origin at least some of the genes controlling the synthesis of collagen and the ground substance proteoglycans are located somewhere near the genes that are concerned with the synthesis of serum immunglobulins and the antigenic recognition receptors on the surface of the lymphocytes. If this were true such metabolic disturbances would involve the entire connective tissue of the body wich is not the case in Keratoconus, though blue sclera is a congenital anomaly of connective tissue and hypermobility of joints in association with Keratoconus has been reported. In the absence of a generalized connective tissue disorder in Keratoconus the authors assume that structural genes concerned with collagen synthesis will express themselves differently in different tissues since it is an accepted fact that the function of a structural gene depends on the activity of the cellular microenvironment, intra-cytoplasmic metabolites and the operator and repressor genes.

The section of this thesis which is concerned with maternal age of patients (q.v.) lends support to a genetic aetiology of the condition in that the distribution of maternal age is similar to that of many other conditions knownto be caused by genetic abnormalities.

At the time of writing, this theory is probably the most widely accepted and research work is being concentrated in the immunological field. The other field of research is in the biochemistry of Keratoconus and reports show a reduction in the total collagen content of the keratoconoid cornea and therefore in the hydroxyproline concentration. (Buddecke and Wallensak 1966: Prous and Goldman 1971, Pouliquen, Graf, Frouin, Faure, Robert and Junqua 1972), Robert, Schillinger, Moczar, Junqua and Moczar give similar findings and add "many abnormal keratocytes can be seen showing morphological anomalies of the membrane, accumulation of lysozymes and a disintegration of the nucleus." This they interpret as a modification in the relative rates rates of the biosynthesis of collagen and of the structural glycoproteins in the dystrophic keratocytes. This "metabolic shift" they consider could be genetic in origin. A genetic basis is thus possible in the aetiology of the condition, and is proven in some instances, but its precise nature is still far from clear.

C) AETIOLOGY

REFERENCES

ALAJMO G. (1957) — ital.Oftal., 10, 275.

BARCHERDING M.S. (1975) — BLOCIK L.J. SITTIG. R.A., BIZZELL J.W., BREEN AND WEINSTEIN H.G. Exp.Eye Res. 21.59

BERESTON & BAER (1942) — Arch. Derm.Sypg (Chicago) 46,358.

BIETTI & FERRABOSCHI (1958) — Bull. Soc franc Ophtal., 71, 185

BUDDECKE E. & WOLLENSAK J. (1966) — v. Graefes Arch. Ophthal. 171, 105

COPEMAN P.D.M. (1965) — Brit. med.J., 2, 977

DAVIES P.D. LOBASCHER D., MENON J.A., RAHI A.H.S. & RUBEN M. (1976) — Trans. ophthal. Soc. U.K. 96.173

FESENSTEIN H. & PENA-MARTINEX J. (1975) — Ann. rheum. Dis 34, Suppl.No.187

FRANCESCHETTI & CARONES G. (1960) — ital Oftal 13, 143.

GALIN & BERGER (1958) — Amer. J. Ophthal. 45, 904

GOODFRIEND L., LAPKOFF C.B. & MARSH D.G. (1973) — J. Allergy 51.81

HAMBURGER R.N. & BAZARUL M. (1972) — J. Allergy 49.91

KORNERUP & LODIN (1959) — Acta Ophthal (Kbh) 37, 508

KARSERAS A.G. & RUBEN M. (1976) — Brit J. Ophthal 60, 522.

POLITZER (1952) — Anat. Anz. 98, 390

POULIQUEN Y., GRAF B., FROUIN M.A., FAURE J.P., ROBERT L., & JUNQUA S. (1972) — Ber. dtsch. ophthal Ges 71,52

POULIQUEN Y., FAURE J.P., LIMON A., & BISSON J. (1968) — Arch Ophthal 28, 283

PROUS R. & GOLDMAN J.N. (1971) — Ophthal Res. 2. 223.

RIDLEY F. (1966) — 'Contact Lenses-Symposium, Munich-Feldafing'. p.p. 163-173 Kanger, Basel and New York

ROBERT L., SCHILLINGER G., MOEZAR M., JUNQUA S., & MOEZAR E. (1970) — Arch. Ophtal. 30, 589

ROCHA (1944) — Rev.bres.Oftal 3, 123

SALZMANN (1907) — v. Graefe Arch. Ophthal 67 1

SBORDONE & DE SIMONE (1957) — Arch. Ottal 61, 497.

SPENCER & FISHER (1959) — Amer. J. Ophthal 47, 332.

STAHLI (1918) (1925) Klin. Mbl.Augenheilk 60, 721, 75, 465

TENG (1963) Amer. J. Ophthal 55, 18

VAN DE HEYT (1930) Trans. Amer. Ophthal. Soc.28, 352

VAZQUEZ-BARRIERE (1942) Ophthal ibero-amer. 4,223

VAN DER HOEVE (1924) Z.Augenheilk. 52, 321; 53, 342.

D) THE MANAGEMENT OF KERATOCONUS - HISTORICAL

The early literature describes many attempts to check the disease by surgical measures and as Duke-Elder writes, "many of them ingenious in their conception and heroic in their fulfilment".

Adams (1817) practiced extraction of the lens, whilst Tyrrell (1840) displaced the pupil by drawing the iris into a corneo-scleral section. Several other ophthalmologists attempted to improve vision by modifying the pupillary aperture Bowman (1857) by iridesis, whilst v. Graefe (1858) and Wells (1873) advocated iridectomy.

Attempts to control the progression of the condition by lowering the intra-ocular pressure were made by Desmarres (1847) and Bell (1875) who used repeated paracentesis.

However, the most successful approach seemed to be that of scarring the apex of the cornea in an attempt to strengthen it. Littell (1937) used silver nitrate and a full description of surgical techniques is given by Nottingham (1854). The techniques Nottingham used were all designed to produce, in a controlled manner, scarring of the cornea in order to reinforce it. Cauterization, using silver nitrate and mercury is described, and the passing of a seton through the cornea, but he concluded the most simple and least dangerous technique was a straightforward puncturing of the cornea. There is also a long discussion on keratoplasty. He describes how Nussbaum had "reglazed" rabbits' eyes by suturing in glass buttons. Hinley in 1840 had attempted keratoplasty unsuccessfully using heterografts. Nottingham also mentions using glass shells filled with gelatine, but the first report of a powered contact lens used in connection with Keratoconus was by Fick (1888). Fick, a Zurich ophthalmologist used the services of Muller, a glass blower, well known for his skill in blowing artificial eyes, to make a shell which was then optically powered.

In his bravura monograph Nottingham describes very clearly the optical correction of the condition, perhaps demonstrating that he learnt a great deal of optics on his continental tour, English ophthalmologists in general being less interested in this part of their work.

Amongst the methods of correction he suggested are high power negative cylindrical lenses with vertical axes, pin holes and stenopaic slits.

CURRENT THOUGHTS ON THE MANAGEMENT OF KERATOCONUS

In this thesis the word management is used advisedly in that the word treatment is eschewed. In most medical dictionairies treatment is defined as follows: "Therapeutics, therapy; the institution of measures or the giving of remedies designed to cure a disease". Using the word in this narrow sense the fitting of a contact lens is not a treatment of the condition.

Some writers such as Clifford Hall (1963) and Voss (1962) have suggested that scleral contact lenses can have a direct therapeutic effect in the keratoconic eye in that the progressive deterioration may be halted, but these views would not be supported today. Most writers agreeing with Ruben and Trodd (1976) that there is no recession of the rate of progress of Keratoconus with contact lens wear, irrespective of the fitting. Kemmetmuller (1962) had no doubt that large corneal lenses had a direct therapeutic effect in Keratoconus.

The indication for contact lenses in Keratoconus is now considered to be correction of vision and not to prevent progression, the results of this thesis do not indicate that there is a significant difference in the rates of progression between eyes wearing contact lenses and those not.

The most commonly fitted type of lens is that of a corneal diameter manufactured from a hard material. The most expediential philosophy has been the subject of some discussion. Some writers such as Clifford Hall (1963) have advocated large (10.00mm to 11.50mm) flat fitting lenses with the specific intention of compressing the cone whilst the lens is worn and for some time afterwards. However, this approach is now considered to hasten the rate of scarring in the sub Bowman's stroma; Ruben (1979). An alternative approach is to fit small thin lenses not much larger than the cone itself; Arias (1962). With this type of fitting philosophy the problems tend to be optical, the small thin lenses have an effective optic diameter not much greater than 4.00 mm. As they centre on the cone itself, which is rarely situated on or near the visual axis, monocular diplopia is a common patient complaint. In this country the most widely accepted approach is one where there is an apical contact area 2-3 mm, an intermediate clearance zone, a mid peripheral contact annulus, with conventional edge lift at the periphery. This may be achieved by specifically

designed tricurve lenses or by Offset conoid design, Ruben (1975).

At the time of writing the advent of new hard lens material, with significant gas transmission properties and wetting contact angles considerably lower than that of polymethylmethacrylate offers exciting prospects in hard corneal lens design and tolerance in keratoconus. One can surmise that lenses will be larger and with less edge lift thus affording better tolerance on hypersensitive patients.

The high incidence of atopy occurring concurrently with Keratoconus means that many patients who would benefit from contact lenses are found to be suffering from hay fever and vernal conjunctivitis, both of which conditions militate against a good tolerance to hard corneal lenses. It is thus not surprising that the use of hydrogel materials is considered particularly in the earlier development of the condition.

A hydrogel lens of appreciable thickness (0.35mm or greater) will neutralize a significant amount of the irregular astigmatism of the keratoconic cornea and the residual cylindrical error can often be corrected with supplementary spectacles. Lower water content hydrogels with a higher rigidity will correct more corneal astigmatism for a given thickness than ones with a higher water content. Ruben (1978) has described hydrogel lenses of trapezoid back surface configuration which by incompletely moulding to the cornea give a surprisingly good visual and tolerance result on advanced case of Keratoconus.

Although in general hydrogel lenses do not provide such a good visual acuity as hard lenses, many patients accept this in return for a better tolerance.

Westerhout (1973) suggested the use of combination hydrogel and hard corneal lenses in an attempt to obtain the acuity of a hard lens with the tolerance of hydrogel lens. Such a combination does provide a good acuity, but management can be difficult especially with regard to patient handling and few patients are known to be wearing such devices at the time of writing.

As reported earlier scleral lenses have been fitted in Keratoconus for nearly one hundred years and there are still many patients in whom this is the only form of contact lens correction that can be worn. Cross (1946) gives a success rate of 74% with scleral lenses but one must bear in mind that they were the only type of lenses available at that time. The marked irregularity of the cornea means that scleral

lenses are invariably fitted by the impression technique, the choice of back optic radius being determined by the method chosen to facilitate tear ingress, with minimum clearance fenestrated lenses the back central optic radius has to be approximately 0.5mm flatter than the mean keratometry, Marriott (1968). If channels are used a flatter back optic radius is chosen.

Where corneal sensitivity causes problems with contact lens tolerance Ruben (1976) has suggested a corneal desensitization operative procedure. This procedure involves a razor knife following a trephine marking and cutting down to half the corneal thickness thus severing superificial and some deeper non medullated nerves. The effect is said not to be permanent.

Cautery, Elschnig (1904), Knapp (1929) or diathermy, Carpenter (1915) to the cone has been advised for many years and more recently Gassett (1972) has reported that the application of controlled heat to the cone can shrink the collagen figres of the cornea thus producing a flattening of the cone area. However, doubts as to safety of this type of treatment have been voiced as there is a high risk of producing corneal necrosis and changes in the endothelium.

By far the most widely used surgical procedure in Keratoconus is keratoplasty, advocated by Castroviejo (1949) it has proved its value in the management of many cases of Keratoconus. In terms of a clear graft success rates are very high, Pouliquen et al (1972), Keates and Falkenstein (1972), Davies, Ruben and Woodward (1977). Ruben and Hegazy (1975) reported that 97% of their grafted patients had acuity of 6/24 or better.

The indications for grafting are obviously different for individual ophthalmologists, but a general consensus would seem to give indications as follows:

1) Visual acuity 6/18 or less
2) Intolerance to contact lenses
3) Unresolved corneal hydrops

Marechal-Courtois and Prijat (1972) claimed that 8% of Keratoconus cases justified keratoplasty.

Clifford Hall (1963) reported two cases in which Keratoconus had redeveloped after keratoplasty, but Ruben and Colebrook (1979) found no evidence of this in cases examined with the photoelectric keratograph. However, following keratoplasty in Keratoconus high

degrees of astigmatism may still remain and 90% need some form of optical correction, usually contact lenses. Ruben and Colebrook report a reduction in post graft astigmatism following the wearing of contact lenses.

The only complication of penetrating keratoplasty that seems to be peculiar to Keratoconus is the occurence of a paretic pupil. Urrets-Zavalia (1963) published this as an observation and suggested that the association of a fixed dilated pupil, iris atrophy and secondary glaucoma constituted a specific syndrome, which has since frequently been known by his name. Later Alberth and Schnitzler (1970) published a series of cases with paretic pupils but without glaucoma. Davies and Ruben (1975) found an incidence of 5% of paretic pupils after Keratoplasty for Keratoconus. They explained the paretic pupils on a basis of ischaemic atrophy of the sphincter pupillae muscle secondary to an iris strangulation phenomenon occurring during surgery. The relative frequency of a dilated pupil together with the common finding of focal iris atrophy after minimal surgical trauma to the iris in cases of Keratoconus made them conclude that the pathology in this condition is not confined to the cornea but probably extends to the iris and possibly to the scleral envelope as well.

The life of a graft is a matter for conjecture, grafts are known to have survived for up to 20 years, but the work of Ruben and Colebrook shows that most penetrating grafts are thicker than normal cornea and indicates that the water uptake is abnormal in the stroma. This is almost certainly due to endothelial dysfunction.

But there is no doubt that patients with advanced Keratoconus can expect good results after a major operative procedure. Ruben (1977) gives a failure rate of 7% in his own series over a 10 year period of follow up and his results are similar to those of other surgeons.

D) MANAGEMENT OF KERATOCONUS

REFERENCES

ADAMS (1817) — J. Sci Arts, 2, 403

ALBERTH B., & SCHNITZLER A. (1971) — Klin.Mbl. Augenheilk 159, 330

ARIAS V.C. (1962) — "El Queratocono Su Correccion por Medio de Lente de Contacto", p. 4-41. Arch Soc. Oftal Optom.

BELL (1875) — Principles of Surgery, London e, 325

BOWMAN (1857) — Roy.Lond.Ophthal.Hosp.Rep, 2, 154

CASTROVIEJO R. (1949) — Keratoplasty in treatment of Keratoconus, Arch. Ophth, 42 776-800

CARPENTER (1904) — Ophthal 21, 177

CLIFFORD HALL (1963) — Brit.Joun.Phys.Optcs. 20.4. 215

CROSS A.J. (1946) — Brit. J. Ophthal 33, 421-425

DAVIES P.D. & RUBEN M. (1975) — Brit.J. Ophthal. 59, 4 pp 223-238

DAVIES P.D., RUBEN M. & WOODWARD E.G. (1977) — Keratoconus: An analysis of the factors which influence the optical results of keratoplasty. Paper read at European Contact Lens Society of Ophthalmologist Symposium. Ghent March 1977 (in press)

DESMARRES (1847) — Traité de maladies des yeux, Paris 344

ELSCHNIG (1904) — Amer. J. Ophthal 21, 177

FICK (1888) — Arch. Augenheilk, 18, 279

GASSET A.R. (1972) Thermokeratoplasty. Address to the American Academy of Ophthalmalogist

KEATES R.H. & FALKENSTEIN A. (1972) Keratoplasty in Keratoconus. Amer J. Ophth. 74(3),442-444

KEMMETMULLER H. (1962) "Corneal Lenses and Keratoconus" Int. Society of Contact Lens Specialists 7th Congress Philadelphia (April 1962) in Contacto (July 1962)

KNAPP A. (1929) "Aetiology and Treatment of Keratoconus". Trans. Amer. Ophth. Soc. 27, 63

LITTELL (1837) Diseases of the Eye, Phila, 277

MARRIOTT P.J. (1968) L'adaptation des verres scleraux a partir du moulage de l'oeil. Cah.Verres Cont. 16,2

MARECHAL-COURTOIS C. & PROJAT E. (1972) Relative values of contact lenses and keratoplasty in the treatment of Keratoconus. The Contact Lens 3 (6) 36-37 Jan. 1972

NOTTINGHAM (1854) Practical Observations on Conical Cornea, London

POULIQUEN Y. (1972) et al.Keratoplastic transfixante dans le traitement du kerato-cone. A propos de 60 cas. Archs. Ophthal, Paris 30, 497

RUBEN M. (1975) Contact Lens Practice. 283. Bailliere Tindall London

RUBEN M. (1979) Soft Contact Lenses. 255. Bailliere Tindall London

RUBEN M. "Soft Contact Lenses". Second Int. Medical Symposium. ed. Mishima Tokyo. pp 50-56 (1976)

RUBEN M. & HEGAZY M.A. (1975) Contact Lens Acuity in Keratoconus, Keratoplasty. Int. Contact Lens Clinic Fall, 1975

RUBEN M. & TRODD C. (1976) 'Scleral Lens in Keratoconus'. Contact and Intra-ocular Medical Journal 2 (1) 18-20

RUBEN M. & COLEBROOK E. (1979) Brit. Journ. of Ophthal 63,4 pp 268-273

RUBEN M. (1979) Aust. Journ.Optom. 62,4 April

TYRRELL (1840) Diseases of the Eye, London, 1, 277

VAN GRAEFE (1858) V. Graefes Arch.Ophthal, 4(2) 271

URRETS-SAVALIA A. (1963) Amer.J. Ophthal 56, 257

VOSS E.H. & LIBERATORE J.C. (1962) Int. Soc. Contact Lens Specialists, Philadelphia. pub. Contacto, July.

WELLS (1873) Diseases of the Eye, 3rd ed. Phila. 149

WESTERHOUT D. (1973) The Contact Lens. Vol. 4 pp. 3-22

THE MEASUREMENT OF CORNEAL THICKNESS

A) HISTORICAL

Blix (1880) was the first to perfrom a direct optical measurement of the corneal thickness in a living eye. He was not an ophthalmologist but professor of physiology at Uppsala and was particularly interested in anthropometric measurements of many organs of the body.

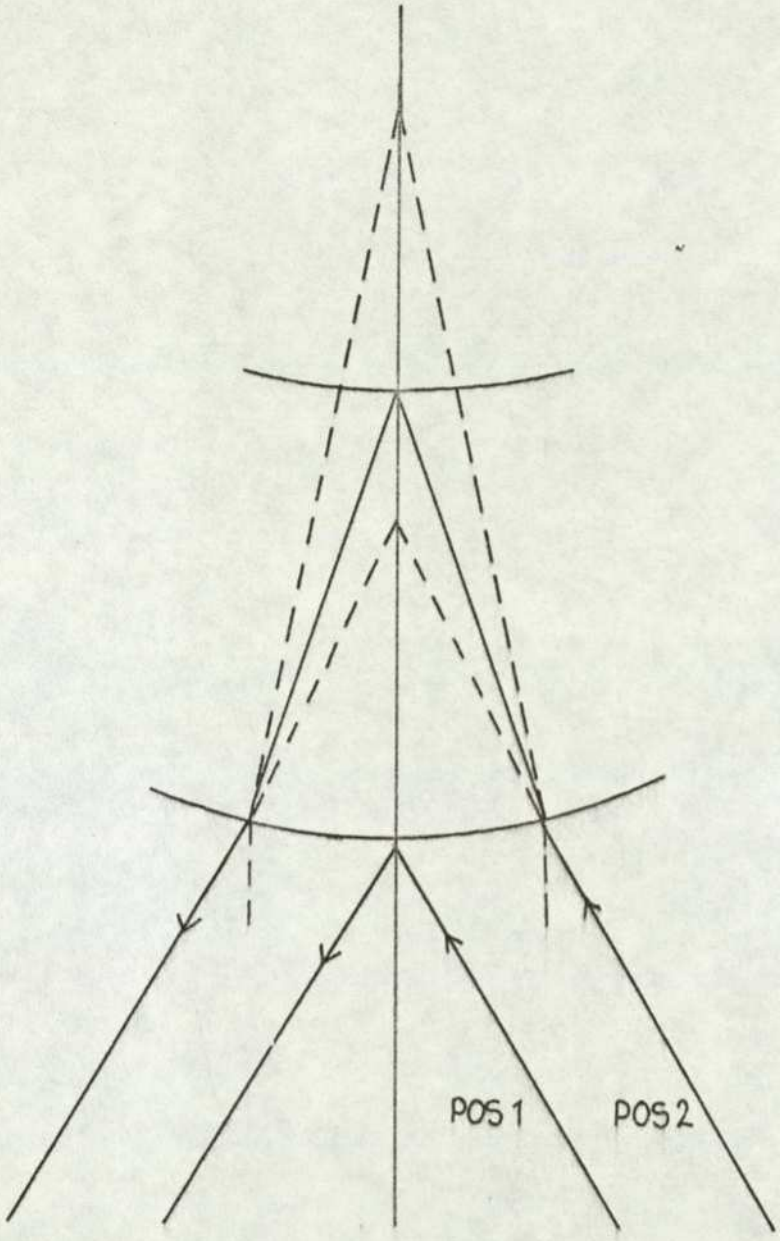


Fig. 4. Blix: corneal thickness measuring method (1880)

His method of measurement was successive focusing on the specular reflexes from the anterior and posterior corneal surfaces. (See Fig. 4.) Two microscope tubes with optical systems of equal power were used, converging at an angle of 39° towards a point in front of the tubes, the apparatus being movable along the line bisecting the angle between the tubes. An illuminated cross in one tube gave an image at the point of intersection of the microscope axis. The apparatus was first arranged so that this image was observed in the other microscope by reflection in the anterior corneal surface. By moving the apparatus forward along the line bisecting the angle between the two microscopes until the image is seen by reflection in the posterior surface, the distance moved is the apparent thickness of the cornea. From this the real thickness may be calculated if a value is assumed for the refractive index of the corea.

Thus when this thesis is presented it will be exactly 100 years since the first in vivo measurement of human corneal thickness.

A problem with this method was the large difference in the brightness of the reflected image from the anterior and posterior surfaces of the cornea. In an effort to overcome this Gullstrand (1909) used two different light sources - a weak one for the anterior surface and a bright one for the posterior corneal surface.

Von Bahr (1948) simplified the original method of Blix by using rotating parallel glass plates to superimpose the two reflections instead of a travelling microscope. The successive focusing technique was finally developed into a commercial instrument by Maurice and Giardini (1951)who considered their instrument to have an accuracy in the region of $\pm$ 0.01mm.

The alternative way of measuring the apparent corneal thickness is to measure the apparent thickness of the optical section. Dependant upon the angle of incidence of the light and the observation angle the real thickness may be calculated in different ways from the measured apparent thickness. (Juillerat & Korby) (1928). Using this principle Jaeger (1952) developed a commercially available instrument for use with the Haag-Streit Slit Lamp model 900. This instrument (considerably modified) was used in this study and a full description is given in a later section.

B) CURRENT METHODS

The two currently commercially available instruments use different optical principles the Maurice-Giardini pachometer by aligning the specular reflexes from the two corneal surfaces and the Jaegar designed attachment measuring the apparent thickness of the optical section. Honneger and Genee (1968) made a direct comparison between the two instruments and found the latter to show the smaller measuring error and the simpler to use. The instrument suffers from various errors due to the method of fixation used but this is discussed in a later section.

Another alternative method is to use ultrasound. However, the ultrasonic measuring system is only considered accurate to $\pm$0.05mm of tissue thickness and as valid measurement of variation is also subject to error through possible misalignment of the sound beam with the visual axis the magnitude of this error could be as great as 0.10mm, Coleman and Carlin (1967). Thus optical methods are very much superior in accuracy to ultrasonic ones at the time of writing unless, of course, the cornea suffers from a loss of transparency.

Sources of Error in Optical Methods

However, despite refinements to increase the accuracy of the instrument by Donaldson (1966), Mishima and Hedbys (1968) and Ehlers and Sperling (1977) in all cases a value has to be assumed for the refractive index of the cornea to obtain the real thickness from the apparent thickness. Arne and Rengstorff (1972) have pointed out that index changes cause apparent changes in thickness and errors occur when these new indices are not used in calculating actual corneal thickness. Consequently, in such cases, it is apparent thickness that is measured and it is incorrect to refer to those measurements as corneal thickness. They suggested that the term 'pachometer units' rather than corneal thickness is used in referring to observed changes in corneal thickness. In the same paper they calculate that variations in anterior corneal radius produce negligible changes in apparent corneal thickness which is comforting in terms of this thesis.

Fatt and Harris (1973) consider the changes in refractive index to be of less significance.

Most writers on the subject have written in terms of corneal oedema not of corneal thinning. If the refractive index of the cornea does change in Keratoconus an increase in the refractive index would

increase the apparent thinning and a decrease in refractive index would make it appear less.

C) TOPOGRAPHICAL PACHOMETRY

Martola and Baum (1968) were the first to measure peripheral corneal thickness in the living eye. Mandell and Polse (1969) took measurements away from the visual axis but only in the horizontal meridians.

Bailey and Carney (1972) also took corneal thickness measurements at 20° and 40° from the visual axis using a modified Haag-Streit pachometer on a Nikon photo slit lamp, but again only in the horizontal meridians. Tomlinson (1972) found that corneas with a greater central thickness had a greater peripheral thickness. Again measurements were only taken in the horizontal meridian and only in one direction 25° temporal. El Hage and Beaune (1973) did measure in other directions in their investigation into corneal thickness change with the menstrual cycle and noted that the thickness did vary but this was not the subject of the paper and little detail is given.

Peripheral thickness changes induced by contact lens wear have been investigated by El Hage and Leach (1975), Harris et al (1975), Sanders et al (1975) and Carney (1975).

The difficulty with all peripheral instruments is locating exactly where the measurement is being taken, the simplistic approach used by many investigators and the difficulty this engenders is discussed fully in a later chapter of this thesis.

D) NORMAL CORNEAL THICKNESS VARIATION

Values of central corneal thickness as given in the literature:

Authors	Corneal Thickness (mm ± S.D.)	No.of Eyes	Year
Von Bahr	0.565 ± 0.035	224	1948
Maurice & Giardini	0.507 ± 0.028	44	1951
Lavergne & Kelecom	0.510 ± 0.04	198	1962
Donaldson	0.522 ± 0.041	268	1966
Martola & Baum	0.523 ± 0.039	209	1968
Mishima & Hedbys	0.518 ± 0.02	40	1968
Lowe	0.517 ± 0.034	157	1969
Kruse Hansen	0.520 ± 0.018	76(rt.)	1971
Kruse Hansen	0.524 ± 0.02	74(lft)	1971

The systematic difference between right and left eyes noted by Kruse Hansen (1971) is fully discussed in the chapter on instrumentation. All the above values were obtained by optical methods.

Carney (1975) found central corneal thickness values very much lower than any other investigators figures 0.4634 ± 0.0279, no explanation is given for this.

Figures for peripheral values have been given by Martola and Baum (1968), Carney (1975) and Tomlinson (1972) but they are not directly comparable because of the problems of locating the measured position.

Most writers agree on the following points:-

1) Corneal thickness is independent of sex and age. Martola & Baum (1968), Lowe (1969) and Kruse Hansen (1971).
2) There is no correlation between refractive error and central thickness, Martola & Baum (1968), Kruse Hansen (1971).
3) There is no correlation between central corneal thickness and radius, nor to axial length of globe, Kruse Hansen (1971).
4) There are diurnal variations in corneal thickness. The cornea is thickest on awakening. Mandell & Fatt (1965), Schouer et al (1973) and Friedman (1973).

There is not an extensive literature on the measurement of corneal thickness in pathological conditions. Spaeth (1962) found a permanent increase of 0.06% in corneal thickness in a group of aphakic eyes, but this could be due to endothelial dysfunction or the fact that the group had worn contact lenses. Kruse Hansen (1971) was the first to demonstrate that central corneal thickness increases significantly with increasing intra-ocular pressure. In terms of the present thesis Mandell and Polse (1969)

proposed the use of a topographical pachometer as an aid to the diagnosis of Keratoconus.

In contrast there is a plethora of literature on corneal thickness changes induced by varying normal physiological conditions and by wearing contact lenses. The literature is great and only a few examples will be cited. Wilson & Fatt (1974) investigated the relationship between tear tonicity and corneal thickness. Several workers have investigated the effect on corneal thickness when oxygen tension is altered, showing gradual corneal swelling during the periods of oxygen deprivation, Carney (1975).

Contact Lens - induced corneal swelling has been investigated by Kinsey (1973), Miller (1968), Sanders et al (1975), El Hage et al (1975), Bailey & Carney (1972) and Harris (1975) amongst others.

All writers conclude that contact lens wearing produces corneal thickness changes. The amount of thickening varies with lens type and fitting philosophy. Typical figures are up to 11% scleral lenses, up to 7% with steeply fitted hard corneal lenses and some hydrogel lenses as low as 3% with flat fitting corneal lenses and thin hydrogel lenses. Most hard corneal lenses worn in Keratoconus would be considered to be flat fitting in the terms of reference of the writers, but it is accepted that the wearing pattern of those patients who wore contact lenses in the study must have had some effect on corneal thickness.

REFERENCES

ARNE R.S. & RENGSTORFF R.H. (1972) — Amer. J. of Optom.50 383-386

BAILEY I.L. & CARNEY L.G. (1972) — J.Am.Optom.Assoc.43(6) 669-672

BLIX M. (1879-80) — Oftalmometriska studier. Uppsala. Läkareförenigs Färhandiglingar 15:349-420

COLEMAN D.J. & CARLIN B. (1967) — Arch.Ophthal 77:124-127

CARNEY L.G. (1975) — "Effect of hypoxia on central and peripheral corneal thickness and corneal topography". Aust. J.Optom 58:61-65

CARNEY L.G. (1975) — Am.J. Optom & Physical Optics.52:521-533

DONALDSON D.D. (1966) — Arch.Ophthal, Chicago 76 25-31

EHLERS N. & SPERLING S. (1977) — Acta ophthal (Kbh) 55

EL HAGE S.C. & BEAULNE G.C. (1973) — "Changes in central and peripheral corneal thickness with menstrual cycle". Am.J.Optom. & Arch.Am.Aca. Optom. 50, 863-871

EL HAGE S.G. & LEACH N.E. (1975) — J. Amer.Acad.Optom. 46 (3) 296-302

EL HAGE S.G. & BEAULNE G.C. (1975) — "Relationship between changes in corneal configuration and thickness. Am.J. Optom & Physical Optics 52:823-833

FATT I. & HARRIS M.G. (1973) — Amer.J.Optom. 50 383-386

FRIEDMAN M.H. (1973) — "Unsteady aspects of corneal thickness control". Exp.Eye.Res. 15(5): 645-658

GULLSTRAND A. (1909) Die Dioptrik des Auges. In Handb.der Physiol. Optik (H.von Helmholtz) 3. Aufl.1 Bd.Voss Hamburg p.279-282

HARRIS M.G., SARVER M.D. & POLSE K.A. (1975) Am. J. Optom & physiol. Optics 52: 313-319

HONNEGER H. & GENEE E. (1968) Graefes Arch.Klin.exp.Ophthal 174 262-270

JAEGER W. (1952) Graefes Arch.Ophthal 153:120-131

JUILLERAT & KOBY F.E. (1928) Determination de l'epaisseur de la cornee sur le vivant au moyen de la lampe a fente. Rev.gen d'Ophthal. 153:120-131

KINSEY V.E. (1973) Am.J. Ophthal & Arch.Am.Aca Optom 50,863-871

KRUSE HANSEN F. (1971) "A Clinical study of the normal human central corneal thickness". Acta Ophthalmologic (Kbh) 49, 83-84

LOWE R.F. (1969) "Central Corneal Thickness"Brit. Journ.Ophthal 53:824-826

MANDELL R.B. & POLSE K.A. (1969) Keratoconus: Spatial Variation of Corneal Thickness as a Diagnostic test. Arch. Ophthal 82 182-188

MANDELL R.B. & FATT I. (1965) "Thinning of the human cornea on awakening" Nature, 208:292-293

MARTOLA D.M. & BAUM J.L. (1966) "Central and peripheral corneal thickness". Arch. Ophthal 76: 25-31

MAURICE D.M. & GIARDINI A.A. (1951) Brit.J.Ophthal 35, 169-177

MILLER D.M. (1968) Arch.Ophthal 80:430-432

MISHIMA S. & HEDBYS B.O. (1968) Arch.Ophthal Chicago 80, 710-713

SANDERS T.L., POLSE K.A., SARVER M.D. & HARRIS M.G. (1975) Amer. J. Optom & Physiol. Optics 52:393-397

SCHAUER K.R. HUGHES C.C. JARRELL J.R. (1973) Opto.Weekly 64(27): 664-661

SPAETH C. (1962) Trans.Am.Acad.Ophthal. & Otol. 294-302

TOMLINSON A. (1972) A clinical study of the central peripheral thickness variation of the human cornea. Acta Ophthalmologica 50(1):73-82

VAN BAHR G. (1948) Acta Ophthal,Kbh 26, 247-265

WILSON G. & FATT I. (1974) Am.J.Optom.Physiol Optics. 51:75-83

THE MEASUREMENT OF ANTERIOR CORNEAL SURFACE CURVATURE

A) HISTORICAL

The long standing method of measuring corneal radius of curvature is by use of the keratometer (or ophthalmometer) and its invention is usually credited to Helmholtz (1856). (See Figs. 5,6,7.)

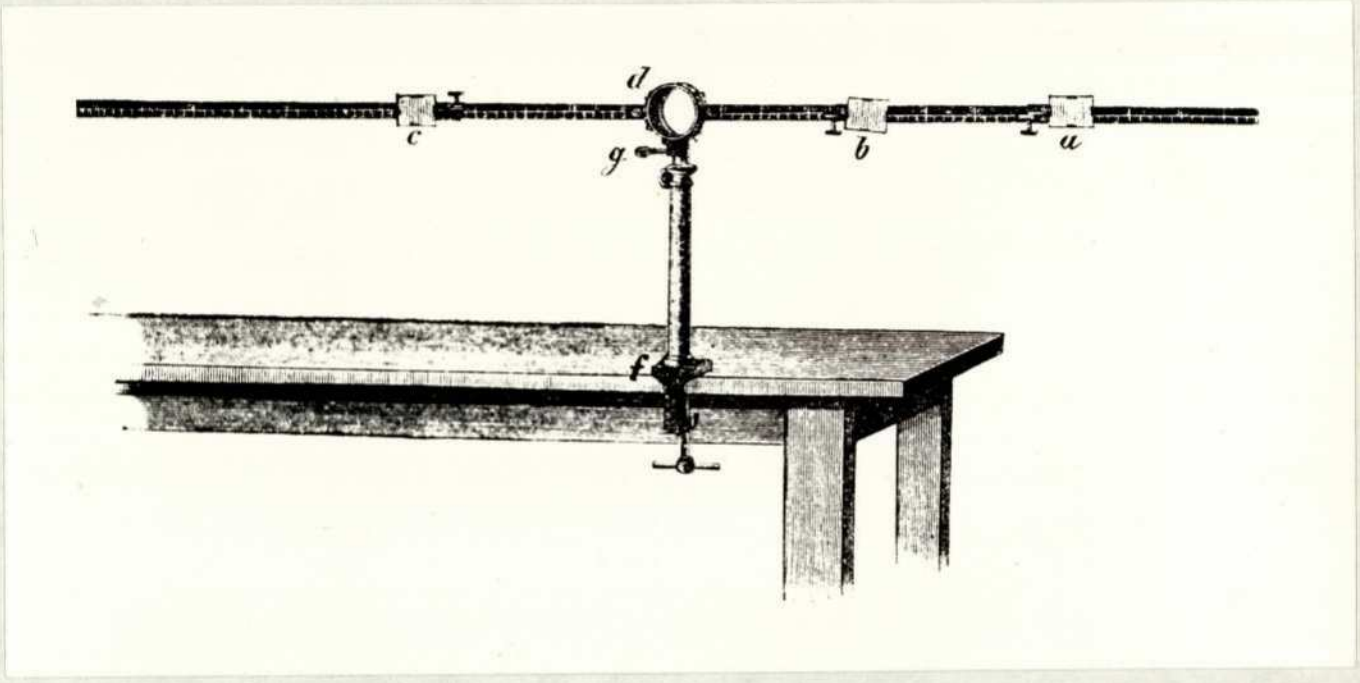


Fig. 5. Keratometer of Helmholtz (1856)

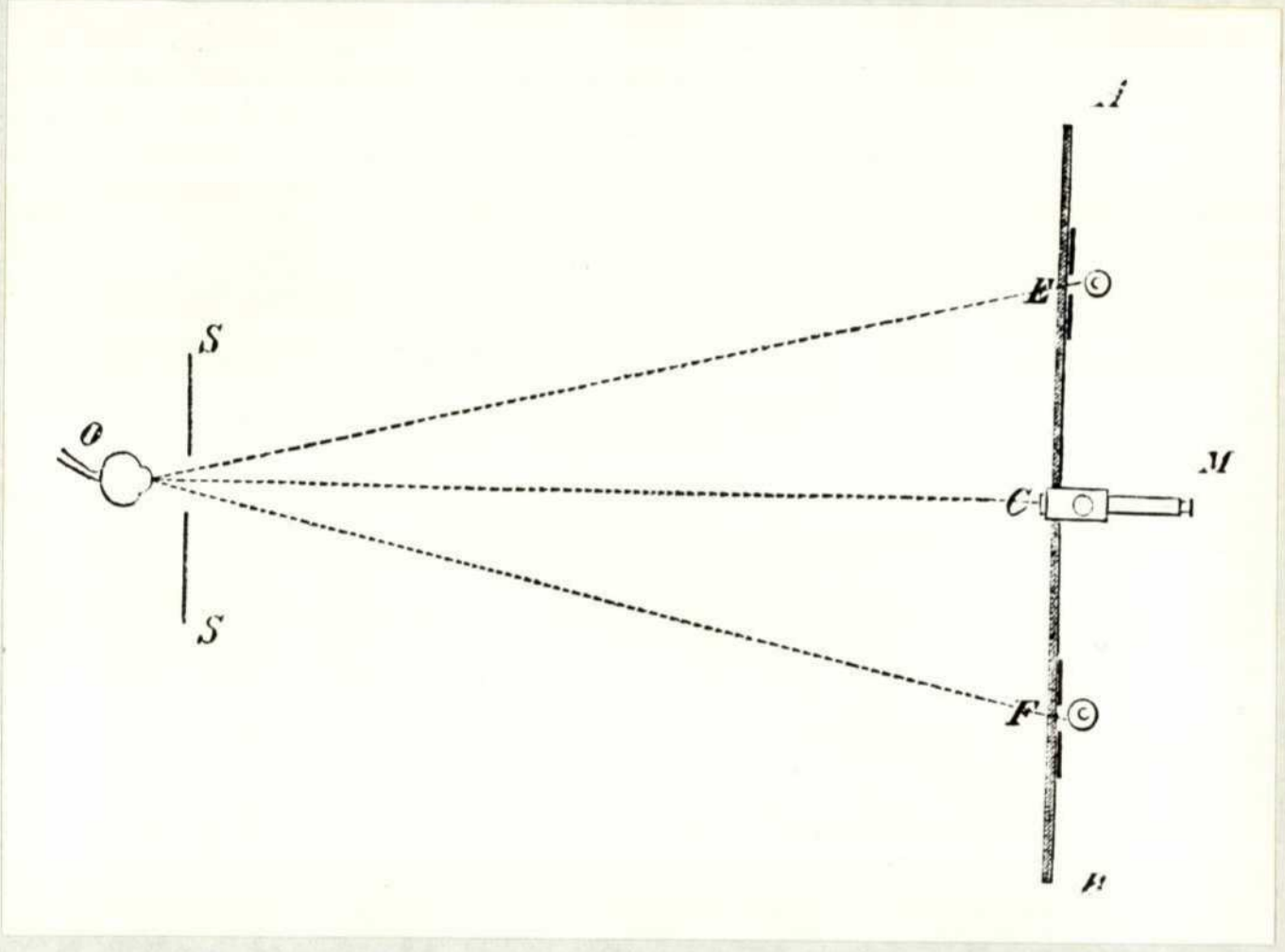


Fig. 6. Optical System. Helmholtz keratometer (1856).

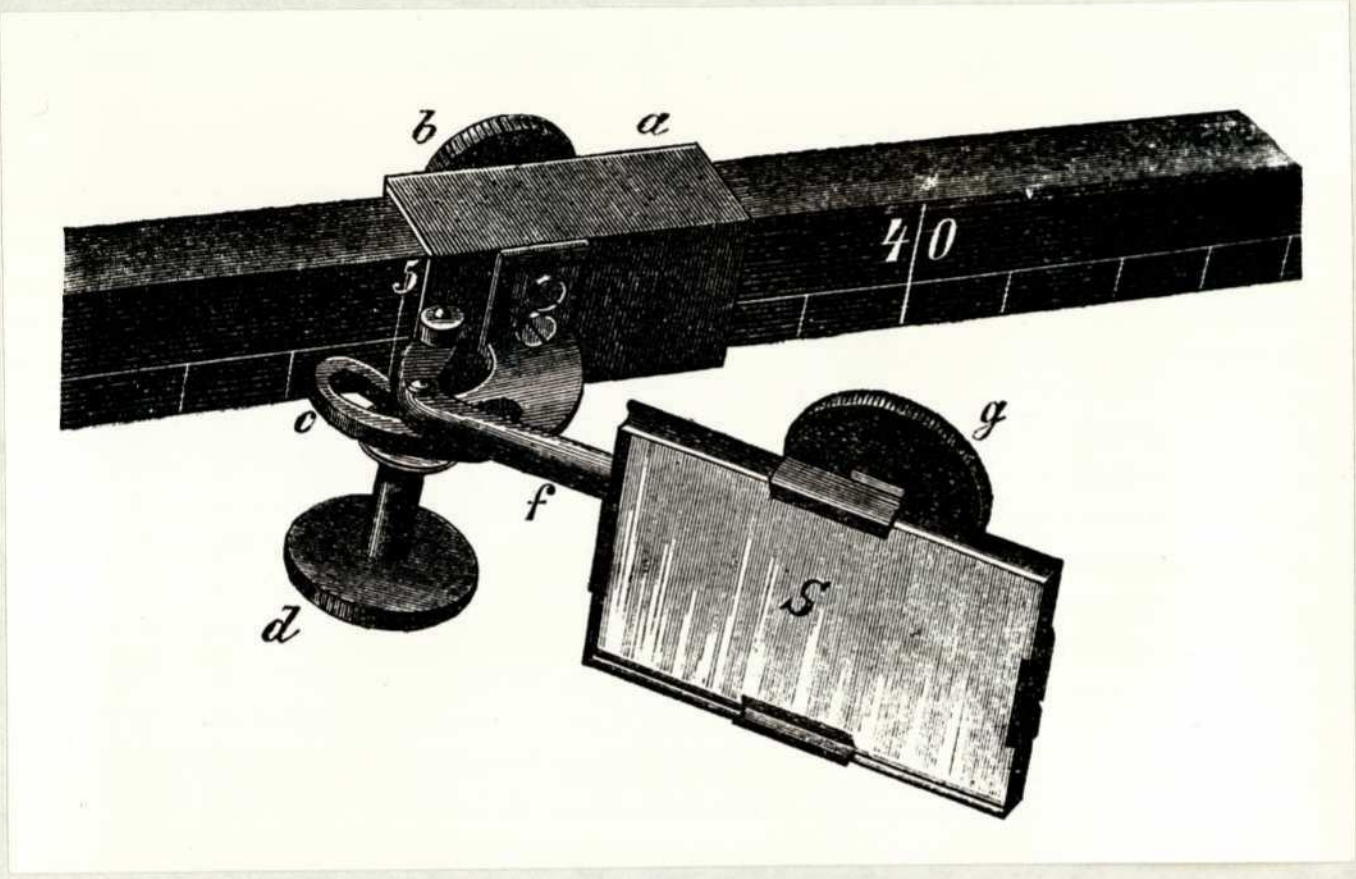


Fig. 7. Detail of mirror (mire) Helmholtz Keratometer (1856).

However, attempts to determine the central corneal radius by utilizing its relationship with the size of the image formed by reflection at its anterior surface go back much earlier. As pointed out by Levene (1977), Scheiner (1619) attempted this and Hare & Ramsden (1795) measured corneal radii in experimentation concerned with theories of accommodation in which they thought corneal radius possibly changed on accommodation. Krause (1832) measured the radius of corneal curvature in an excised eye and Kohlrausch (1840) took measurements on a living eye. Senff (1846) recognised the peripheral flattening of the cornea and also established that the apex of the cornea does not necessarily coincide with its intersection with the visual axis.

The apocryphal story is that Helmholtz first tried to determine corneal radii by standing a patient on the opposite side of a room to a square window. He than held by the eye a series of steel balls changing the radii until the reflected image of the window in the ball was the same size as the image in the cornea. This ball was then of the same radius as the cornea. True or not this illustrates very neatly the keratometry is simply the measurement of an image in a convex mirror.

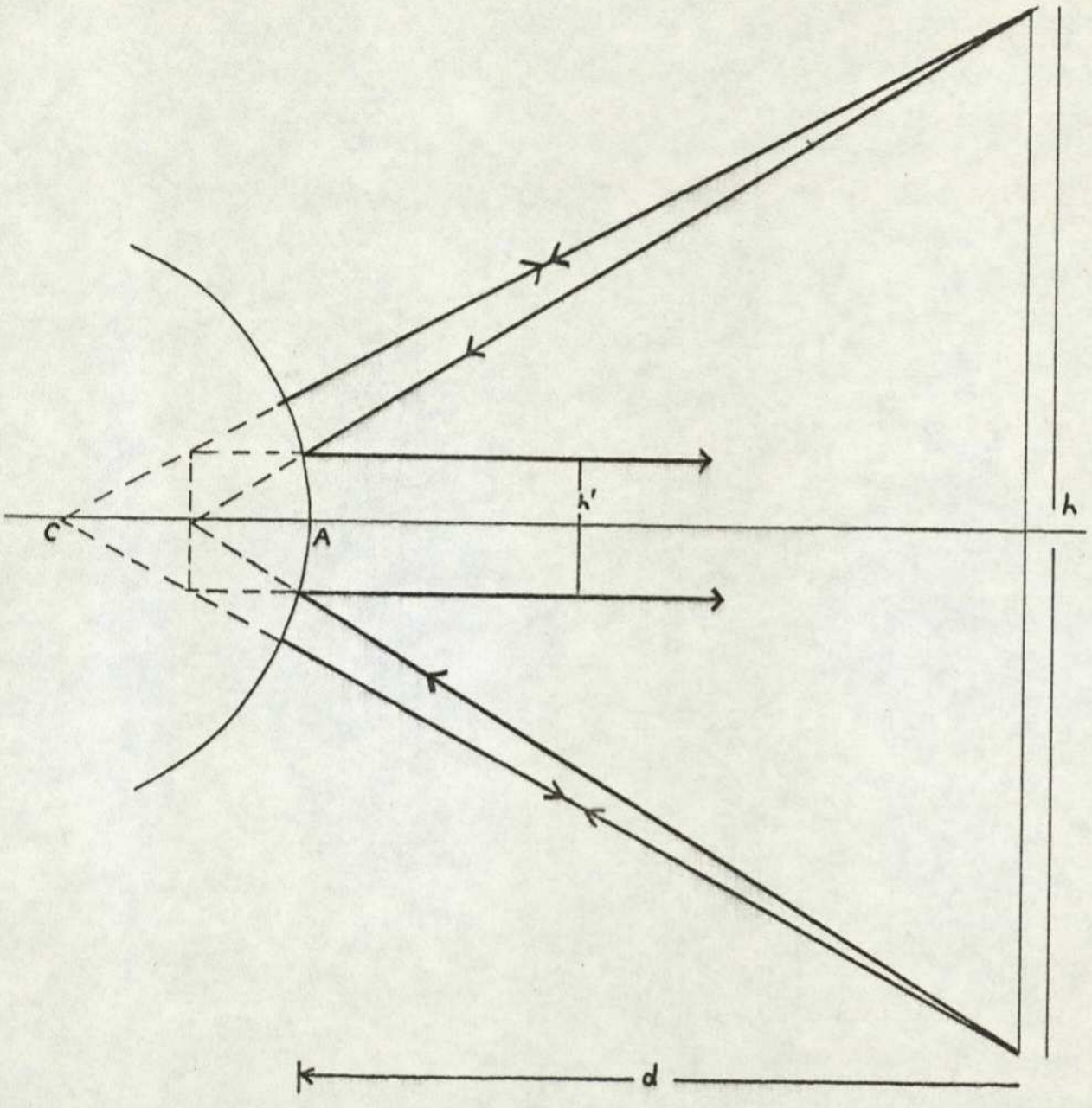


Fig. 8. Optical principle of Keratometry.

h = image size, i.e. mires or window

In this diagram the corneal radius is AC which geometrically is the same as $\frac{2\ dh'}{h}$

If the eye was quite stationary as is a steel ball the image size could be simply measured with a graticule in the eyepiece. However, because of eye movements, the use of a graticule is not easy so Helmholtz introduced the well known optical principle of doubling into the instrument. Now all that was required was the juxtaposing of two images which even if moving slightly will do so at the same speed and in the same direction.

The basic optics of a doubling system are:-

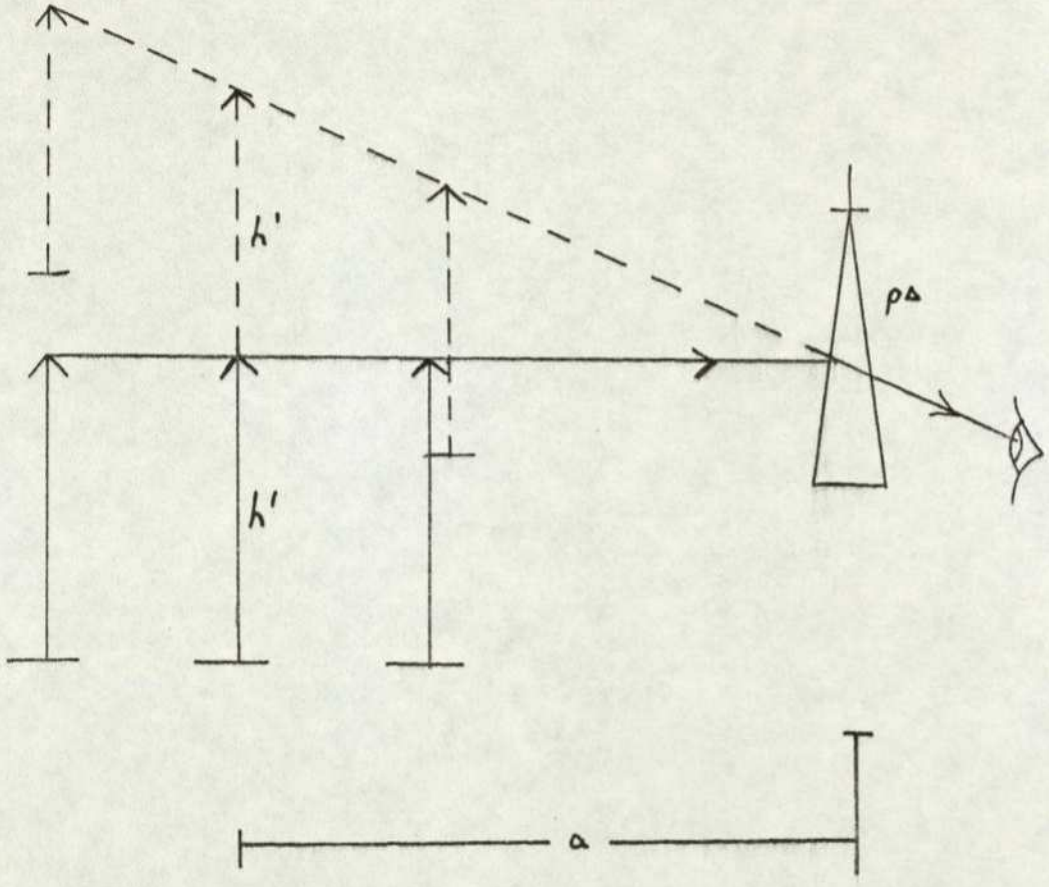


Fig. 9. The doubling principle.

If a prism of power P is interposed in half the observation aperture an image of size **h'** will be seen doubled. When the doubled image is seen exactly adjacent to each other it will be at distance 'a' so that $\frac{h'}{a} = \frac{P}{100}$

$$h' = \frac{aP}{100}$$

In the original Helmholtz instrument the doubling was actually produced by glass plates. A prism was first used for doubling by Landolt (1878), Javal & Schoitz (1881) used a Woolaston prism with specially shaped "mires" as test objects. Unlike Helmholtz's instrument no calculations were necessary by the user and the instrument was direct reading. This was the first practical clinical instrument and is essentially the same as several keratometers available today.

B) CURRENT METHODS

Three clinically feasible methods of measuring the curvature of the anterior corneal surface are available at the moment.

1) Keratometry
2) Photokeratoscopy
3) Interferometry

Keratometry

Keratometers in use today fall into two main groups:

1) Instruments where the power and positions of the doubling device are fixed and the mire separation variable. This is as in the original Javal-Schiotz design and will soon have been in use for 100 years.
2) Instruments where the image size (i.e. mire separation) is fixed but power of the doubling device variable. An example of this type is the Bausch and Lomb instrument used in this study and described fully in the chapter on instrumentation.

A comprehensive study of keratometers used clinically today does not fall within the scope of this thesis. However, consideration of the limitations of keratometry is relevant to the evaluation of results obtained in Keratoconus.

Firstly, in keratometry light from the mires is not reflected from the corneal pole at which the telescope is directed but from two small areas either side of it. There is no standardization of mire diameter or mire separation, therefore, different instruments use different zones of reflection. As the normal cornea is aspheric different instruments record different radii of curvature for the same area. In the case of Keratoconus where the area is more irregular readings taken with different instruments are even less comparable.

Secondly, keratometers are calibrated on the assumption that the two reflecting areas are of equal radius on a spherical surface and the resultant radius is ascribed to the keratometric pole. Even on a normal cornea this means that no true measurement is taken of areas within the annulus formed by the reflecting areas or outside it. In Keratoconus the two reflecting zones in any one meridian are nearly always of different curvature thus increasing this error. Thus in Keratoconus, keratometric measurements are less accurate than on

normal corneae and become increasingly so as the condition progresses. Clinically, this becomes quite obvious when one mire is extremely distorted and the other much less so. Here as the cone apex is always decentred from the visual axis one mire may be reflected from relatively normal cornea and the other from the cone itself.

Thirdly, a keratometer may be limited in its range so that it cannot take a reading on a steepened keratoconic cornea. However, if the reflected image is magnified by a low powered positive lens placed just in front of the keratometer objective, a reading may be taken. The interposing of this extra lens means that the instrument has to be recalibrated and a full description of this given in the instrumentation chapter of this thesis. **See Chapter 5.**

Thus keratometers have a somewhat limited value in the measurement of the progression of Keratoconus, as a diagnostic aid they are invaluable and in the early stages they do provide a sensitive measure of the corneal steeping but as the condition progresses they become less accurate and only record gross changes in curvature.

It might be thought that instruments adapted for peripheral corneal measurement would be useful in the monitoring of Keratoconus. Several instruments including the Zeiss, Guilbert-Routit, Bausch and Lomb and American Optical have "topographical attachments" whereby the patients fixation is diverted to points away from the keratometer axis so that the reflection zones fall on to more peripheral portions of the cornea.

With the Topogometer attachment for the Bausch and Lomb keratometer and the topographical attachment for the American Optical CLC Ophthalmometer, the device for varying the fixation is graduated in mm from the centre of the cornea. The designers of these instruments do not seem to have considered seriously the position of the centre of rotation of the eye. Their calibration is based on simple trigometry using the displacement of the fixation target and **the distances from keratometer objective to corneal vertex and corneal vertex to centre of rotation. (A fuller treatment of this will be given in the Instrumentation Chapter.) The writer corresponded with American Optical asking what value the designer had assumed for the distance of the corneal vertex to the centre of rotation. The reply was :**

"1. The assumed corneal vertex distance from centre of rotation was 11.3 mm"

"2. Although it is now thought the corneal vertex distance MAY be 14.45 mm in normal practice the difference is not significant."

It is the writers view that topographical attachments should only be calibrated in terms of degrees of displacement of fixation target from the visual axis. With normal corneae one can then say with confidence that subsequent measurement on the same eye will be taken at the same position. In the case of progressing Keratoconus this is not so, as the corneal vertex/centre of rotation distance is increasing. In view of this and the inherent errors of conventional keratometers used with peripheral fixation it was decided not to use these devices in the current study. The inherent errors are mainly due to the fact that keratometry theory assumes a common axis for the centre of curvature of all parts of the cornea whereas in practice the centres of curvature for the peripheral zones are offset from the central axis of symmetry. Mandell and Polse (1969) used small mire keratometry with peripheral fixation in their investigations of Keratoconus but found the procedure was very time consuming and the results insufficiently accurate and reliable.

Photokeratoscopy

Fundamentaly, the principle of photokeratoscopy is the same as the principle of keratometry - to determine the relationship between the size of the target and the size of its virtual image formed by the cornea, acting as a convex mirror. From this the relationship the radius of corneal curvature can be determined from known optical formulae.

Helmholtz (1909) described the first photokeratoscope which had a flat target of black and white concentric rings which was placed in front of the eye to be measured. A camera set in an aperture at the centre of the target was used to photograph the corneal image. The radius of curvature for a given part of the cornea was calculated from the target rings separation in the part of the corneal image that had been reflected from that corneal area.

This and many later instruments suffered from two deficiencies - inadequate target design and an inaccurate method of data analysis.

Ludlum and Wittenberg (1966) showed it is necessary to have a target shape which will have an image in a flat place so that all the rings in the image on the photographic negative will be sharp and the

cornea can be accurately focused. Some workers solved this problem by using targets of cylindrical and hemispherical shape Dekking (1930), Kroll (1961) and Stone (1962).

In contemporary photokeratoscopy data reduction is based on an analysis of the sagital depth from the vertex to any of the reflection points. Here again a full treatment of this is outside the scope of this present thesis but a detailed analysis is given by Townsley (1967).

Townsley is the designer of the Wesley-Jessen PEK 2000 instrument. In this instrument the targets lie in the place of an ellipse giving a sharp image in a flat plane. The resultant photograph is first analysed on an analog computer and the resultant data then computed on a digital computer.

The final print out present the data in the form of central corneal curvature and the deviation from it towards the periphery. A typical print out from a keratoconic eye is shown. (See Fig. 10.)

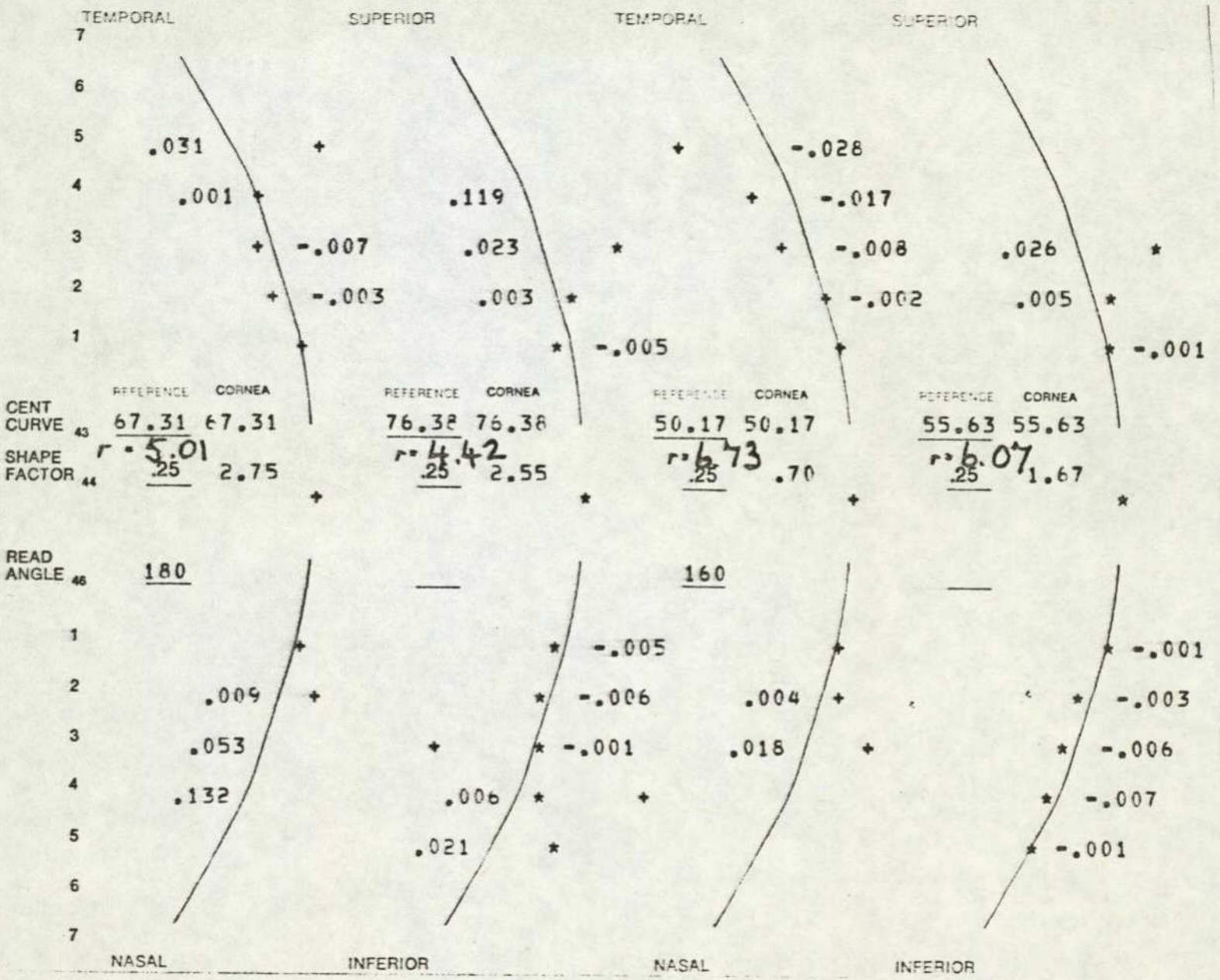


Fig. 10. P.E.K. print-out. Patient suffering from Keratoconus.

The corneal area which can be measured from a single photokeratogram is limited only when the target ring images formed by the cornea are blocked by the lid, nose or brow of the subject.

At the commencement of this study, photokeratoscopy was considered as a routine procedure on every patient at every visit. However, as all the photographs had at that time to be sent to the United States for computer analysis it was decided that this was not feasible. Furthermore in the more advanced cases of Keratoconus it is not possible to obtain a photograph with all the rings in focus as the targets are arranged to be sharp on more normal corneae. Perhaps more importantly in Keratoconus the corneal image is not plane and errors due to the curvature of the corneal image become significant. Mandell and St Helen (1971). Thus as with keratometry as the condition progresses the accuracy of the measurements becomes less and less. However, there is no doubt keratoscopy gives a more valid interpretation of changes in the peripheral area than does keratometry.

Interferometry

The use of Moiré fringes in the measurement of corneal contours was suggested by Poster et al (1968). Late the same year the same authors gave details of their corneal toposcope which was adapted to record photographically, they stated that artefacts were produced by variable tearing. A year later the same authors produced a final report. The conclusions were that the method was feasible and a long term study was advisable. No values for actual measurements obtained were presented in any of the three papers. The only indication given of results obtained were statements such as "there as toposcopic evidence of the regularity of the ectasia; which perhaps suggests that the photographic methods used were not sufficiently accurate for measurement purposes.

Mandell and Polse (1969) found interferometry methods not to be sufficiently accurate for the detection of early Keratoconus.

Other methods which have been used include stereophotogrametry, Bonnet (1959) and Le Grand (1961) and photography of the slit beam of the cornea. Martin (1959) and Stone (1962).

As to the future, photoelectric scanning using a laser beam would seem to have great potential. S.I.R.A. (Scientific Instrument Research Association) have developed an instrument which will accurately plot changes in aspheric reflecting surfaces. This was

originally designed for checking the surface of lenses for microscope, gun sights etc. but may well prove amenable to adaption for measuring the human eye.

C) NORMAL CORNEAL RADII VARIATION

Papers on the normal variation of corneal radii have been written by Reuss (1877-80), Awerbach (1900), Zeeman (1911) and Czellitzer (1927). But the two classical papers are by Tron (1934) and Stenstrom (1946). Both the authors conclude that the variation of the radius of the cornea follows the chance distribution of the regular binomial curve.

However, their results were slightly different:

Tron Arithmetic Mean 7.77 standard deviation $\pm$ 0.34

Stenstrom Arithmetic Mean 7.86 standard deviation $\pm$ 0.26

As the two workers also obtained slightly different values for other optical elements of the eye it may be that they were measuring on significantly different populations. As there is a considerable racial variation in refractive errors, Duke Elder (1949), there is almost certainly a racial variation in corneal curvature. Contact lens practitioners and manufacturers have found a different lens design necessary for the occidental and oriental eye.

It is interesting to note that the spread of the two workers' results gives very nearly the same figure for the flattest radii.

References

AWERBACH (1900) — Dioptrics of the Eye with varying Refraction. Moscow

BONNET R. (1959) — Review d'Optique 38,447

CZELLITZER (1927) — K.M. Aug. /xxix 301

DEKKING H.M. (1930) — Zur Photographie de Hanhautoherflaeche Albrechts von Graefe's 124,708

DUKE ELDER (1949) — Textbook of Ophthalmology Vol IV p.4247. Kimpton London

GREENWALD & PANNER POSTER M.G. GELFER (1968) — Optical Classification of Keratoconus Amer. J. Optom 45 pp 216 230

HELMHOLTZ (1856) — Physiol Opt. 1

HELMHOLTZ (1909) — Treatise on Physiological Optics (1909) from third German ed by J.P.C. Southall Vol 1 Rochester NY Optical Society of America (1924)

HOME E. (1795) — Phil Trans R Soc 85, 2

JAVAL & SCHIOTZ (1881) — An d'Oc /xxxvi 5

KOHLRAUSCH (1840) — (1840) quoted by Helmholtz in "Handbook des Physiologischer Optik (1909) Translated as Treatise on Physiological Optics ed Southall J.P.C. Dover publications. London 1962.

KROLL H.A. (1961) — "Corneal Contours in the General Population as revealed by the Photokeratoscope" Amer J Optom 38 389

KRAUSE (1832) — "Bemerkungwyn uber den Bau und die Diemensionon des menschlicken Augen" Meckesl Arch Anat. Physiol, 6, 86

LANDOLT (1878) — Internat Cong. Geneva "Traite Complet d'O iii"

LE GRAND Y. (1961) — Transactions Int. Oph. Congress p67 British Opt Assoc London

LEVENE J.R. (1977) "Clinical Refraction and visual science" 128-9 Butterworth London

LUDLUM W.M. & WITTENBERG S. (1966) "Deviation of a System for analysing the cornea from Photokeratoscopic data" Journal of the Opt Soc America 56 (11) 1612-1615

MANDELL R.B. POLSE K.A. (1969) Arch Ophthal 28 182-188

MANDELL R.B. ST HELEN R. (1971) Mathematical Model of the Corneal Contour. Brit. J. Physiol. Optics 26,3, 183-197

REUSS (1880) Wien med Presse 200, 234

SCHEINER (1619) "Occlusive Fundamentism Opticum" Innsbruck

SENFF R. (1909) Quoted by Helmholtz (1909) see KOHLRAUSCH

STONE J. (1912) "The validity of existing methods of measuring corneal contour compared with suggested New Methods. Brit.J. Physiol Opt 19 205

STENSTROM (1946) Acta Ophthal (Kbh) Supp

TOWNSLEY M. (1971) "New equipment and Methods for determining the contour of the human cornea" Contacto Vol 11 (4) p72-81

TRON (1934) V. Grafes. Arch Ophthal 132, 182

ZEEMAN (1911) AFO /xxviii 93

MEASUREMENT OF ANTERIOR CHAMBER DEPTH

A) HISTORICAL

Measurement of the depth of the anterior chamber has been attempted by many authors, employing various types of optical and photographic methods. Figures for the value in hypermetropia, emmotropia and myopia are given in the literature by Horstmann (1879), Plantenga (1898), Awerbach (1900), Sannte (1905) and Zeeman (1911). However, the first measurements of significant accuracy are usually attributed to Lindstedt (1916). Prior to this all other workers had used methods of successive focusing on the posterior surface of the cornea and the anterior surface of the lens. Lindstedt's ingenious method was, that one focal line of a variable astigmatic light beam was placed on the anterior surface of the cornea while the other was focused on to the anterior surface of the lens. A deduction must be made for the thickness of the cornea. The probable error of this method was $\pm$ 0.02mm. Lindstedts method was further refined by Rosengren (1930) and Stenstrom 1953). (See Fig. 11.) Photographic methods appear to have been first described by Friedenwald and Pierce (1932).

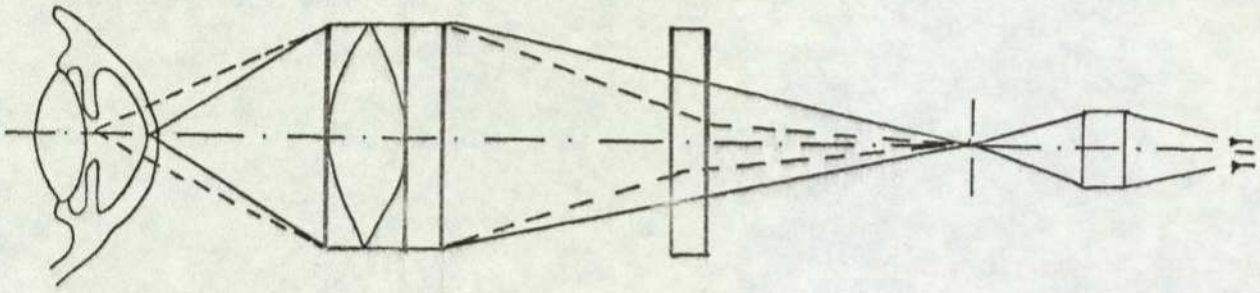


Fig. 11. The measurment of anterior chamber depth. Stenstrom (1946)

B) CURRENT METHODS

1. Photographic
2. Optical
3. Ultrasonic

Photographic

The procedure introduced by Goldmann (1940) and further developed by Hein (1941) is considered to be one of the most exact methods of measurements. However, it involves taking many photographs of successive layers of the anterior chamber, it is a time consuming and somewhat complicated procedure and is not applicable to a clinical instrument.

Optical

As with pachometry the depth of the anterior chamber may be measured optically in two ways:

i) By focusing differentially on the posterior surface of the cornea and the anterior surface of the lens four beams of light emitted from a point source. The increased divergence of the two beams focusing furthest back in the eye is brought about by interposing of a negative lens is calibrated against the apparent chamber depth which is recalculated to give the real chamber depth. This is the method used by Tornquist (1953) in his extensive study on 398 normal patients. With this method systematic errors arise from the following causes:

   a) The refraction at the posterior surface of the cornea is neglected in calculating the real chamber depth.
   b) The measurement is made along the visual axis instead of along the optic axis.
   c) There may be accommodation of the investigated eye.

   The systematic error of this method is in the region of $\pm$ 0.02mm.

ii) By measuring the apparent thickness of the optical section of the anterior chamber as first suggested by Jaeger (1952). Calmettes et al (1953) used this method to take measurements on 114 normal patients. When this method was used to produce a standard attachment for the Haag-Streit 900 Slit Lamp Weekers et al (1972) used it to take measurements on 2395 eyes.

In this study Weekers and his co-workers quote measurements taken on a Keratoconus patient, but only on one case and on one occasion.

A similar attachment was used in the present study.

The main error of this method is in the application of a correction factor for a varying corneal radius particularly when the corneal radius is grossly different from the median values for the normal eye. Tables of correction factors are readily available but they require keratometric readings and as explained in an earlier section these become unreliable with the steeper assymetric keratoconic cornea. Thus it has to be accepted that the accuracy of the anterior chamber depth measuring device declines on unusually shaped corneae. The systematic error of the method on relatively normal eyes is in the region of $\pm$ 0.03mm.

Ultrasonic

The measurement of the depth of the anterior chamber by using ultrasonic transducers is well documentated. A full description is given by Coleman and Carlin (1967).

However, as with corneal thickness the ultrasound technique is considered to be accurate to 0.05mm of tissue thickness. However, misalignment of the sound beam with the visual axis could double this error so only variations of more than 0.10mm are considered significant. Thus at the time of writing the method is not as accurate as optical ones.

C) NORMAL VARIATIONS

All writers in recent times agree that the anterior chamber depth varies with age increasing from birth until the late teens and thereafter steadily decreasing.

Valid comparisons between writers are difficult to make for two reasons. Firstly, because they have used differing age intervals; secondly, because some writers such as Calmette et al (1958) did not measure the corneal thickness and deduct it, so they are actually quoting anterior chamber depth plus corneal thickness. Typical figures for the two best known writers on the subject of variation with age are as follows:

Tornquist (1953)	19 to 21 - 3.18mm;	34 to 36 - - 2.98mm
	49 to 51 - 2.76mm;	64 to 66 - 2.69mm
Calmettes et al (1958)	12 to 15 - 3.65mm;	20 to 30 - 3.76mm
	30 to 50 - 3.46mm;	50 to 80 - 3.23mm

There is also a significant variation with the refractive state of the eye. In general the chamber is shallower in hyperopia and deeper in myopia than in **emmetropia.** Further considerations will be given to this in the chapter dealing with anterior depth measurements in the study.

REFERENCES

AWERBACH (1900) "Zur Dioptrik der Augen bei verschiedenen Refraktionen, Moscow.

CALMETTES, DEADATI, HURAN & BECHAC (1958) Arch. Ophthal (Paris) 18,513

COLEMAN D.J. & CARLIN B. (1967) "A new system for visual axis measurement in the human eye using ultrasound". Arch Ophthal 77 124-127

FRIEDENWALD J.S. & PIERCE H.F. (1932) Arch. Ophth. 7 583

GOLDMANN H. (1940) Ophthalmologica98, 257

HEIN M. (1941) Ophthalmologica 102, 193

HORSTMANN (1879) v. Graefes Arch. Ophthal, 25 (1) 79

Jaeger (1952) v. Graefe, Arch. Ophthal 153, 120-131

LINDSTEDT (1916) Arch. Augenheilk 80, 104

PLANTENGA (1898) Ned. T. Geneesk, 34, 360

ROSENGREN B. (1930) Acta Ophth.(Kbh) 8.99

SANNTE (1905) Linse maalinger, Copenhagen

STENSTROM S. (1953) Acta. Ophth.(Kbh) Suppl. 26

TORNQUIST R. (1953) Acta Ophthalmologica (Kbh) Suppl.39

WEEKERS R.
DELMARCELL Y.
COLLIGRAN J. &
LUYCKC J.
(1973) Documenta Ophthalmogica 34, 413-434

ZEEMAN
(1911) v. Graefes Arch. Ophthal 78,93

INSTRUMENTATION

The apparatus used in the preparation of this thesis was as follows:

1) Modified No. 1 Haag Streit Depth measuring attachment.

2) No. II Haag Streit Depth measuring attachment.

Both of these were used in conjunction with the B900 model Haag Streit Slit Lamp.

3) Bausch and Lomb Keratometer, Model No. GH4389. Supplementary positive power lenses were used in conjunction with this instrument to extend the range so that steeper then usual curvatures could be measured.

The Haag Streit Depth Measuring Attachment No.1.

There were two pachometers commercially available at the commencement of this study, the Maurice - Giardini pachometer which attaches to a slightly modified form of the Zeiss slit lamp and the attachment I to the Haag-Streit Slit Lamp model 900. Honneger and Genee (1968) made a direct comparison between the two instruments and the Haag-Streit model showed the smaller measuring error and appeared to be the most simple to use.

As already mentioned in the Historical section, the instrument is based on a principle first given by Jillerat and Koby (1928) (See Fig. 12.) but independently developed by Jaeger (1952).

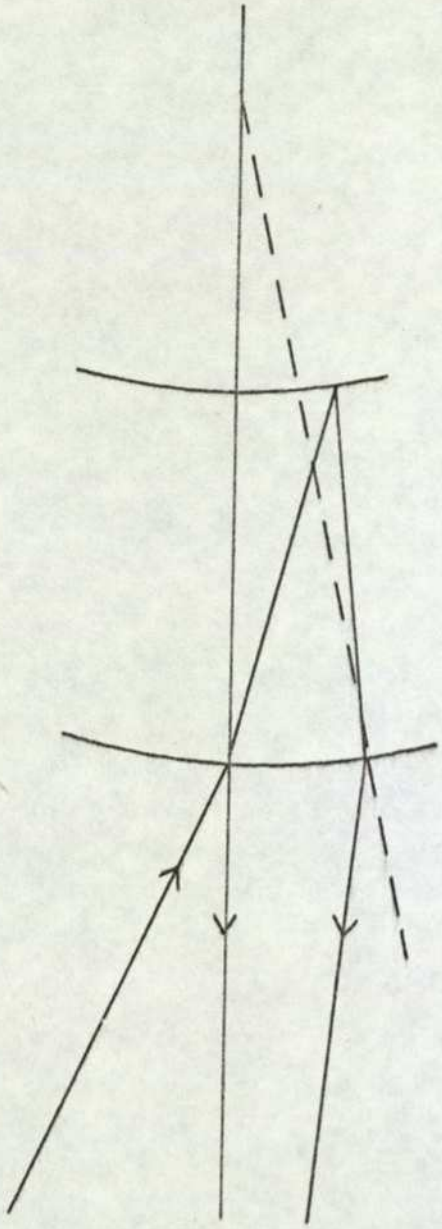


Fig. 12. Measurment of the apparent thickness of the optical section. The principle of Juillerat, Koby and Donaldson.

In its standard form the apparatus consists of an attachment to the Haag Streit Slit Lamp containing two glass plates in front of the right microscope, a lower fixed and an upper rotatable around a vertical axis. The incident light comes through a vertical aperture in a diaphragm extending from the attachment and securing an angle of 40° between the incident light beam and the axis of the right microscope. (See Fig. 13.) Some confusion was caused when it was found that when set up in this manner the protractor scale on the axis of symmetry of the instrument did not read 40° but this is in fact calibrated for a line which bisects the axes of the two microscopes, which accounts for the apparent discrepancy. The right ocular is replaced by a special split image ocular, dividing the visual field into lower and upper halves. (See Fig. 14.) The light passing through the upper rotatable and the lower fixed glass plates is seen in the upper and lower visual field respectively. (See Fig. 15.)

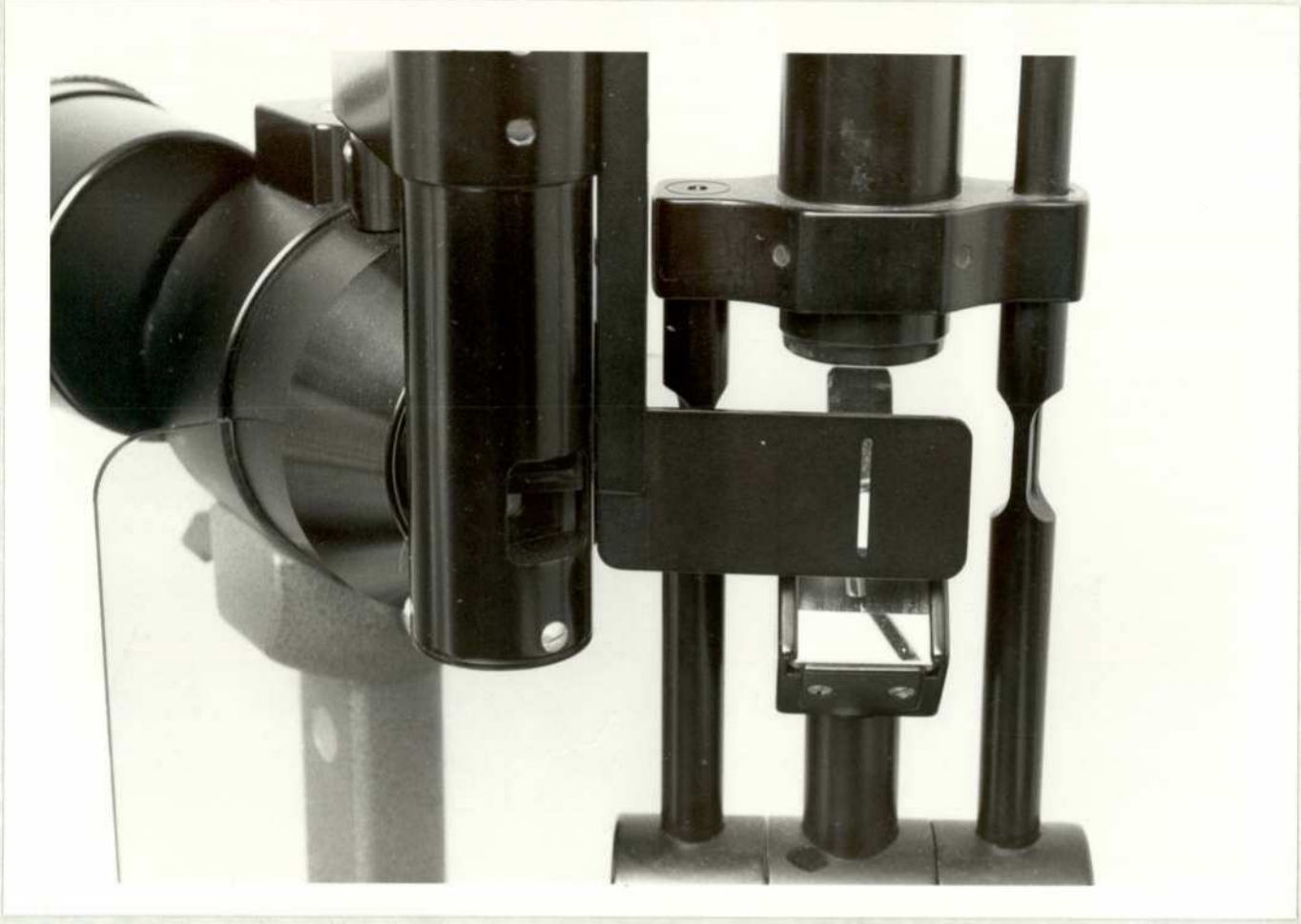


Fig. 13. Haag-Streit Pachometer. Patients view.

Fig. 14. Haag-Streit Pachometer. Split Image ocular.

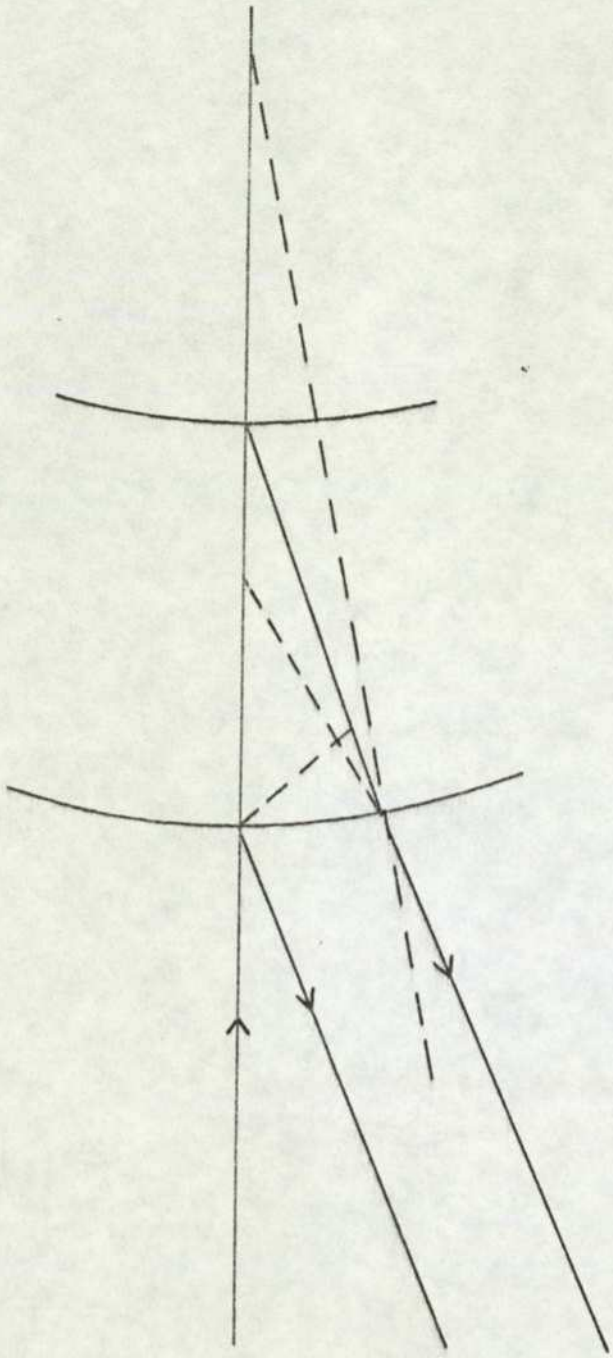


Fig. 15. Measurmentof the apparent thickness of the optical section. Light falls perpendicular on to the cornea. The apparent optical section is measured from the side.

Using this method the microscopic magnification does not influence the measurement (Jaeger 1952) and the high objective magnification (x 1.6) may be used and facilitates the taking of measurements. Goldman (1968) showed that the refractive status of the observer does not influence the measurement.

Haag Streit supply tables giving correction factors for non-linearity and correction in corneal curvature, but state this correction is not significant except in cases of megalocornea, keratoconus etc.

The instrument in its standard form has the patient fixating down the incident light beam. Not only does this introduce the limitation that only central thickness can be measured but also introduces the possibility of certain measuring errors.

According to the optical principle the incident light should fall perpendicular to the cornea but when the patient fixes the incident light the measurement is made along the line of sight and not along the perpendicular to the cornea. This introduces a measuring error and a systematic difference between right and left eyes.

There are may definitions of the axes in the eye and the angles between them, but it is generally accepted that the line of sight is the line in the optical system followed by the light ray to the fovea. The angle between the line of sight and a line perpendicular to the anterior corneal surface and passing through the apparent centre of the pupil is known as kappa.

Kruse Hansen (1971) has shown using this instrument that often corneal thickness was the greater in the left eye and that if corneal thickness difference between the right and left eyes is plotted against the sum of the angles kappa of the two eyes a significant correlation is found (P 0.001, R = 0.84).

The Modified Pachometer

In this investigation the Haag-Streit pachometer was modified after a manner first suggested by Donaldson (1966) and further modified by Mandell and Polse (1969).

In the present study a mounting was placed in front of the standard Haag-Streit instrument which contained two green and eight red light-emitting diodes all of which could be switched on and off independently. (See Fig. 16.)

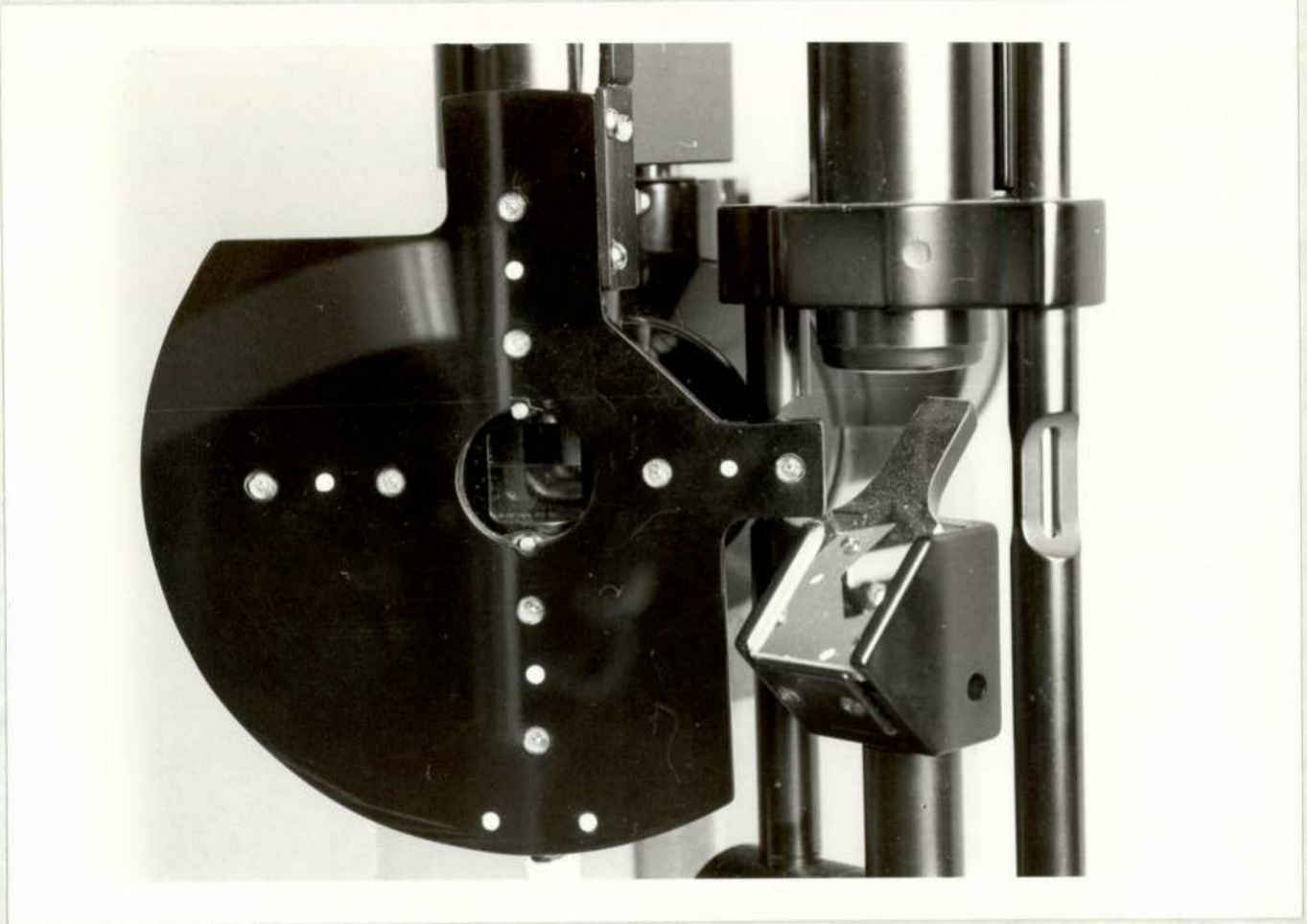


Fig. 16. Modified Pachometer. Patients view showing L.E.D's.

The two green L.E.D.'s were placed immediately above and below the right hand objective of the biomicroscope. The subjects were asked to fixate between the two green lights and the instrument then aligned so that the corneal images of the lights viewed through the microscope can be seen above and below the corneal section to be measured, thus ensuring that the microscope was perpendicular to the corneal surface at any measurement position. This is of course the reverse of the procedure with the standard instrument where the patient fixates into the vertical aperture diaphragm in front of the illuminating system.

The eight red L.E.D.'s were arranged in a cross on the axes of the concentric circles of diameter 40 mm and 20 mm and are used as fixation targets.

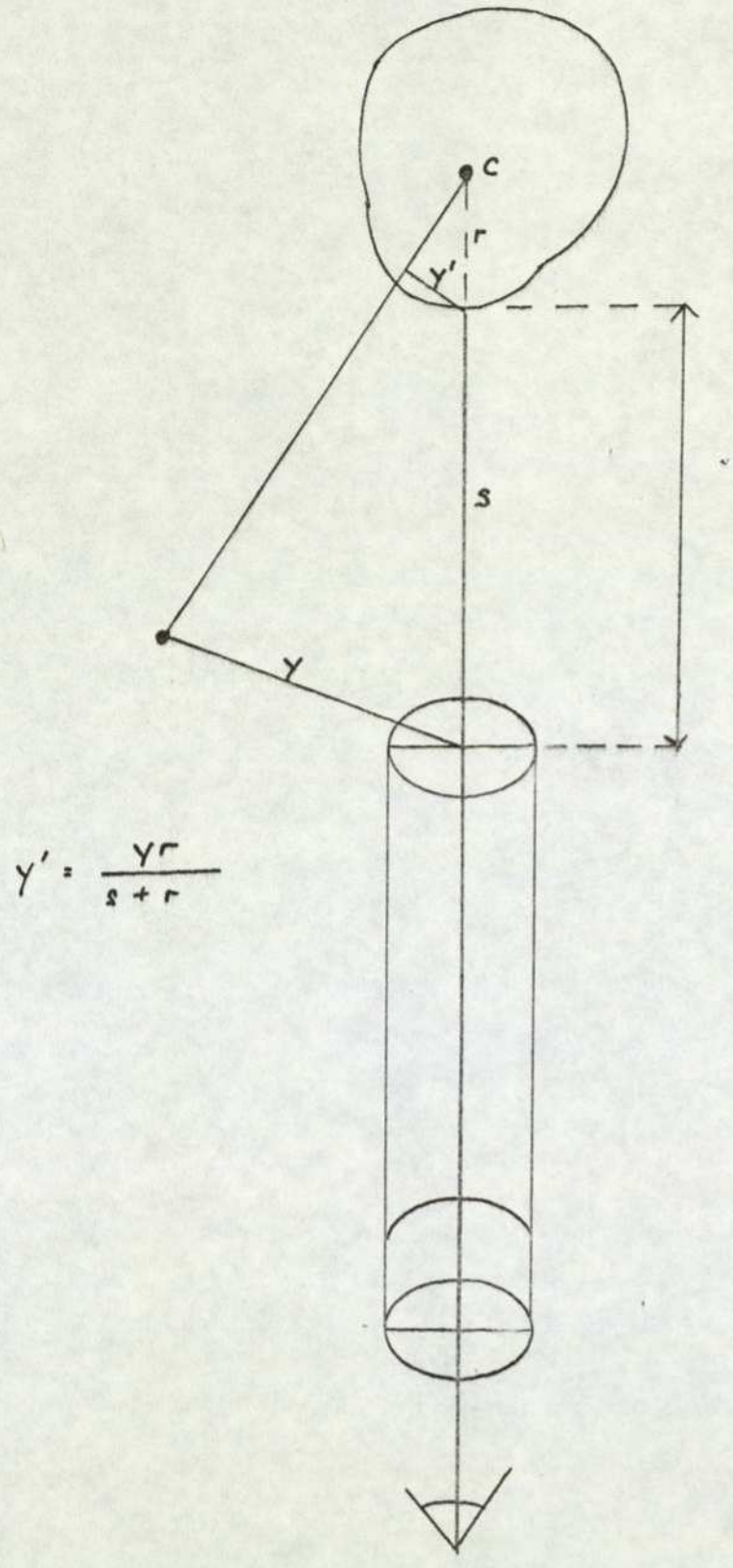


Fig. 17. Calculation of corneal position measured. from Mandell & Polse (1969).

Other researchers such as Mandell and Polse (1969) (See Fig. 17.) have attempted to apply simple trigonometry to this arrangement to determine the corneal position measured and have in fact published their findings in the form of graphs plotting corneal thickness (mm) against Distance from thinnest point (mm).

However attempts to use the same method as Mandell and Polse produced **anomalous** results, particularly with regard to the outermost targets. Mandell and Polse do not state what figure they assumed for the distance from the anterior surface of the cornea to the centre of rotation of the eye and various authors give figures between 13 and 15.4 mm. These figures are also assumed to apply to the normal eye so the variation must be even greater in Keratoconic eyes.

Assuming a distance of 15 mm. for the distance between the anterior surface of the cornea and the centre of rotation of the eye and a distance of 60 mm. from the corneal vertex to the plane of the targets, calculations gave the inner targets to be measuring at 7.00 mm. apart and the outer ones at 14 mm. The inner figures seemed reasonable but the outer ones were palpably absurd as this would be outside the limits of normal corneae and it was quite obvious when using the instrument with the patient fixating the outer targets that one was measuring in the cornea.

The explanation of this anomaly would appear to be that assumptions as to the centre of rotation of the eye are not valid with the ocular excursions involved in fixating the outer targets which amount to approximately 28^{o}in all directions.

Adler (1953) writes as follows:

"The centre of rotation is described as a fixed point when considering the eye as an optical instrument, but physiologic studies have shown this is not true. The centre of rotation is not fixed at all but moves along a curve at a variable distance from the visual axes, always in a line perpendicular to the axis when the eye is in the primary position. One must conclude that the centre of rotation is an ever changing one and that it is incorrect to speak of a fixed centre of rotation of the eye. The approximate centre of rotation lies 15.4 mm. back of the cornea and about 1.6 mm. to the nasal side of the geometric centre of the globe. This approximate centre holds fairly well for rotations of the globe in the horizontal - outwards 20^{o} and inwards 30^{o}.

Since this centre of rotation is eccentric, a slight translatory displacement of the eyeball must occur during such rotations. In inward rotation the globe protudes somewhat and in outward rotation it recedes slightly." "Unfortunately the notion of a fixed centre has been deeply ingrained in ophthalmologic thinking and has been made practical use of. For example, methods have been devised to locate foreign bodies inside the globe by X-ray. Photographs are taken in different positions of rotation of the globe and the shadow of the foreign body cast on a film at a fixed distance from the globe. The calculation made from these data assumes that the globe is rotated around a fixed centre of rotation. Spectacle lenses have been made which are supposed to give sharp images on the retina, not only when one looks through their geometric centre, but also when looking through the periphery of the lens. These lenses have been calculated on the assumption that the globe had a fixed centre of rotation or at least that the deviations from this position were so small as to be negligible. This assumption seems to be invalid."

Thus it can be seen that measurements taken away from the centre of the cornea will not be taken at exactly the same distance from the visual axis on different patients. The distance from the centre of rotation of the globe which is not fixed anyway will vary with total globe length. All that can be said with certainty is that the topographical fixation targets subtend angles of 14^{o} and 28^{o} at the cornea and that the instrument should measure corneal thickness at the same positions at each visit on a given patient.

The recording system of the instrument was modified by coupling the measurement shaft of the basic instrument to a digital read out in an electronic recording system by a potentiometer. (See Fig. 18 and 19).

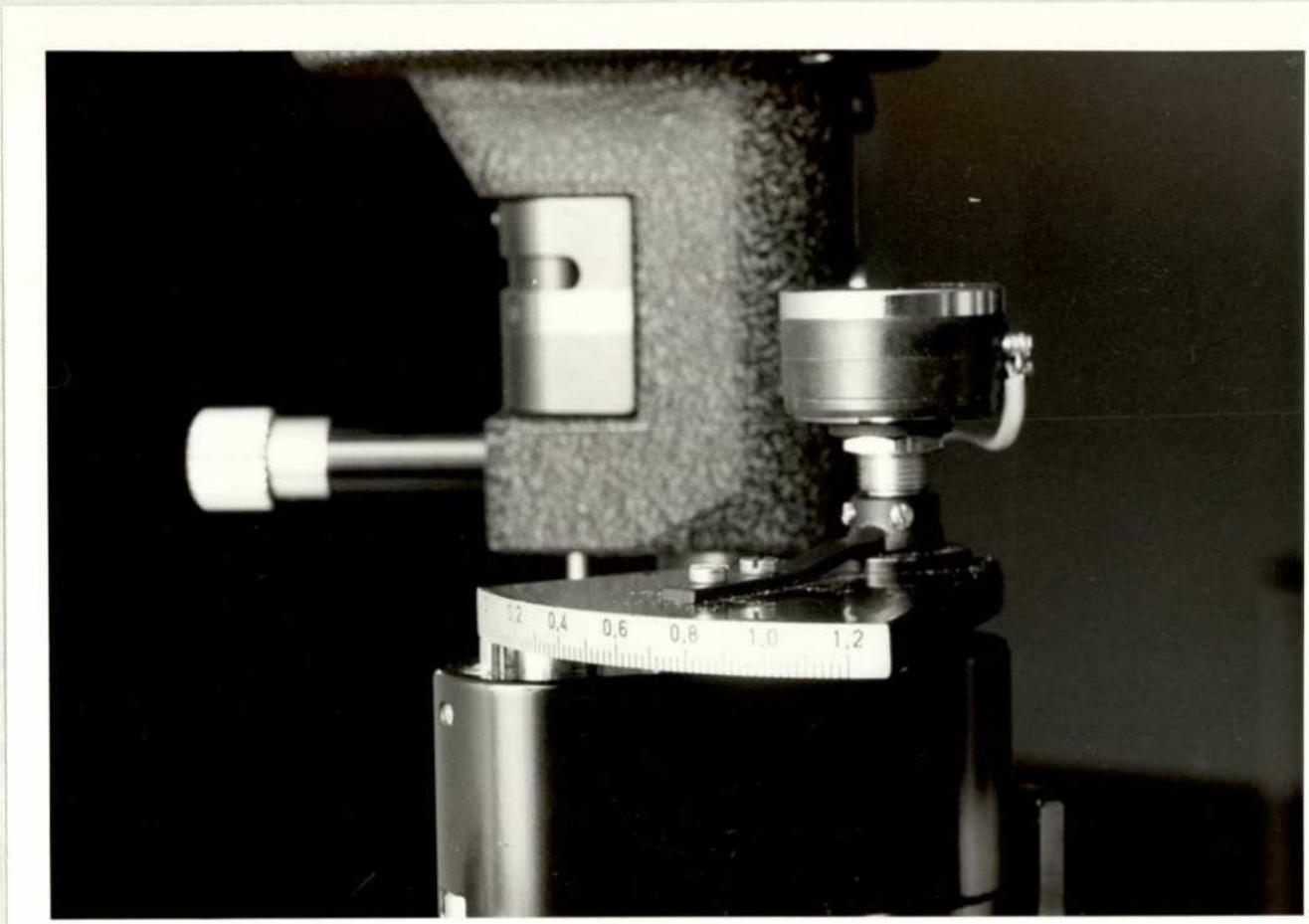


Fig. 18. Modified Pachometer. Patentiometer.

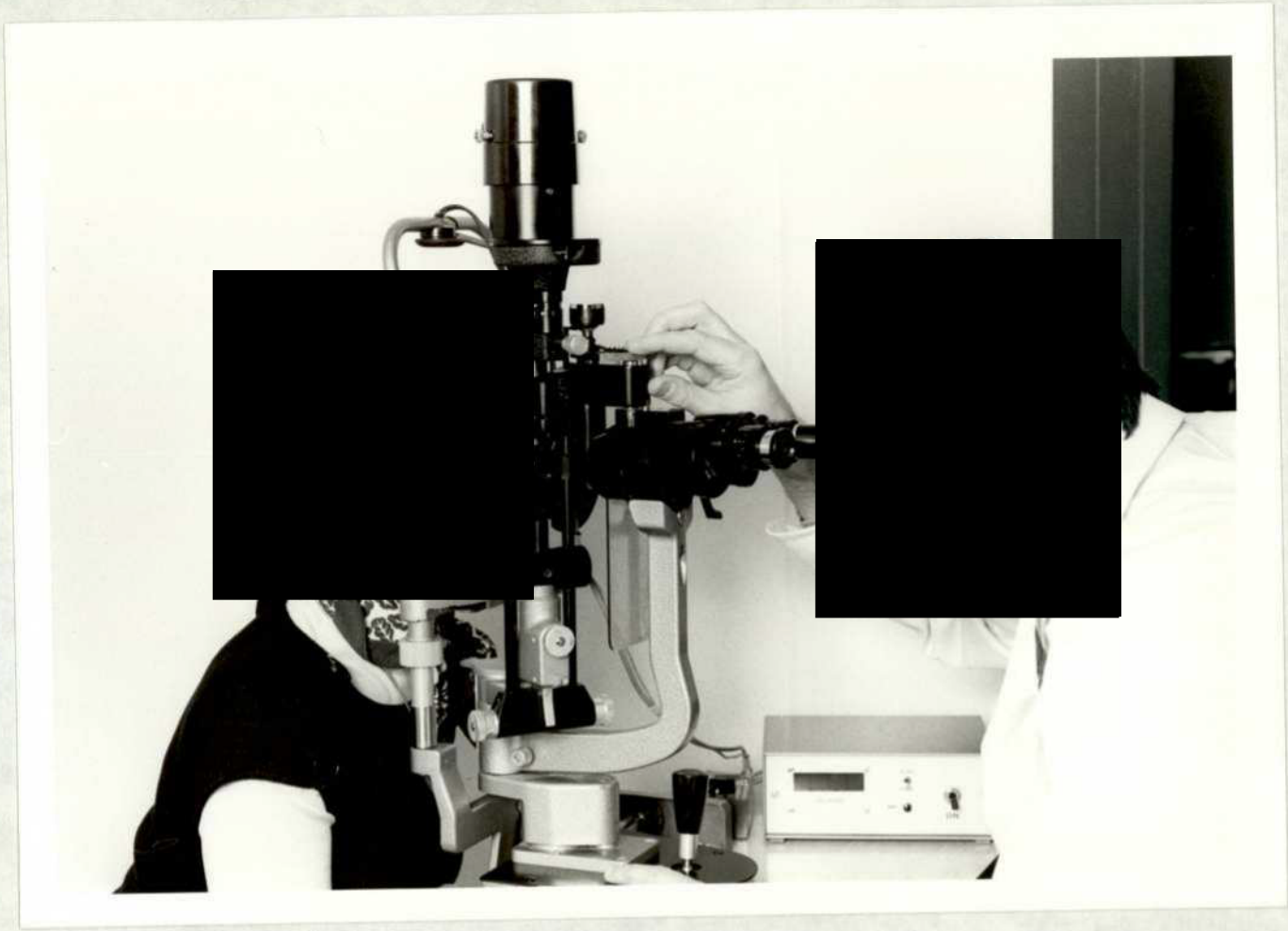


Fig. 19. Modified Pachometer with digital read out.

As the instrument now had the viewing system perpendicular to the corneal surface instead of the illumination system, the original calibrations no longer applied and recalibration was necessary. Furthermore the basic instrument was calibrated for a separation between the viewing and illuminating systems of 40° whereas in the modified version the problem of accommodating the plate carrying the L.E.D.'s made a separation of 35° more convenient and the protractor at the base of the instrument was always at this setting.

Fig. 20. Modified Pachometer. Eye Piece setting.

As the glass rotating plates of the pachometer were not modified in any way, the right x 10 eyepiece was set at + 2.50 D.S. as with the standard instrument. (See Fig. 20.) The slit width was standardised at the 7 setting thoughout the study; this was the narrowest setting which gave a bright enough image to see coincidence of the measurement points. (See Fig. 21.)

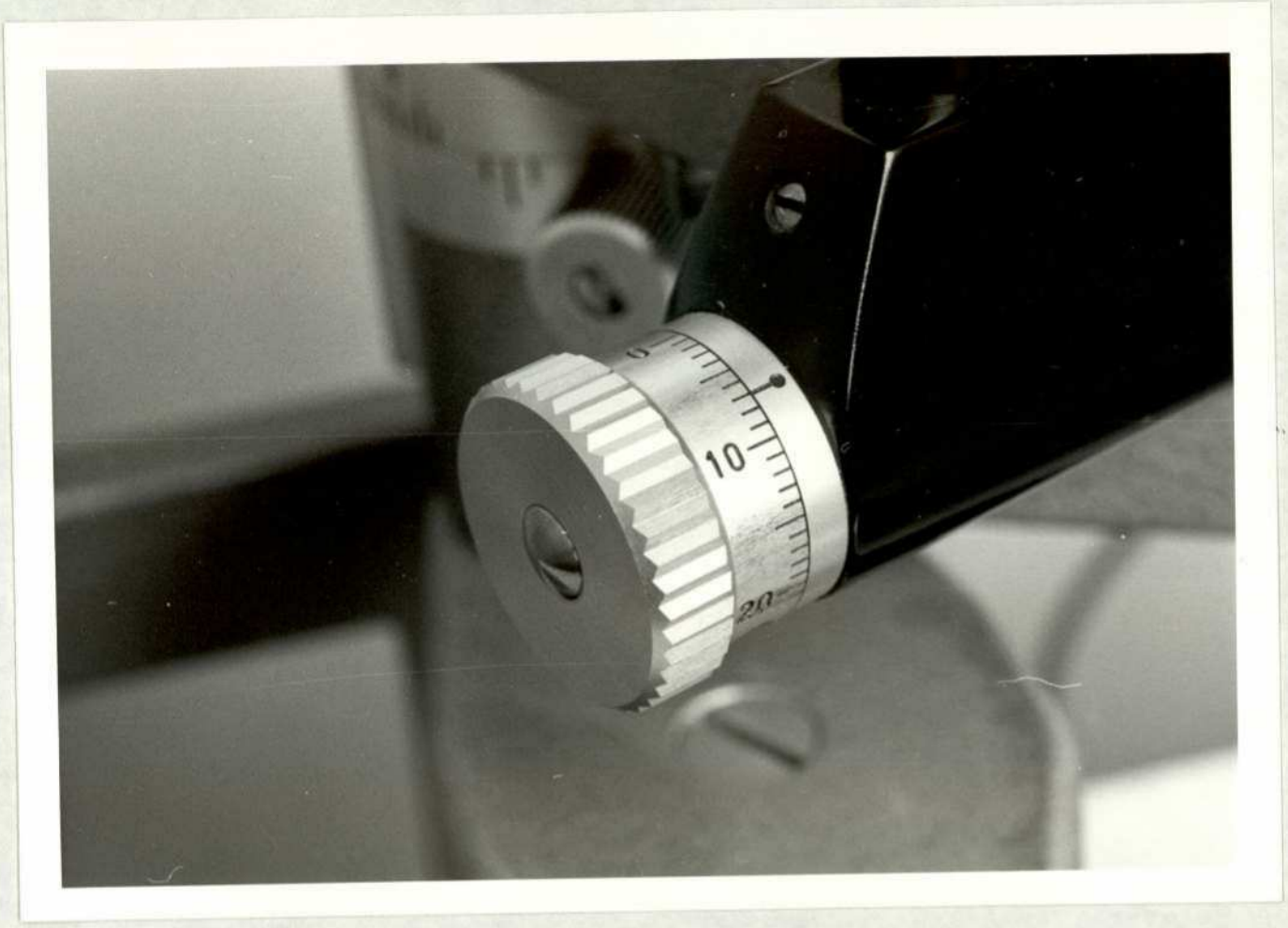


Fig. 21. Modified Pachometer. Slit Width Setting.

Calibration

As had been noted earlier, it was necessary to recalibrate the instrument for two reasons. Firstly, that the viewing system was now perpendicular to the corneal surface and not the illumination system and secondly, the separation between the two systems was now 35° instead of the original 40°. An interesting point that was noted is that when a Haag Streit Pachometer is set up in its original form with the illumination system passing light through the vertical aperature in the diaphragm, the protractor does not record a separation of 40° between the two systems as one would expect from the literature. The explanation of this apparent anomaly is that with the pachometer in place on the slit lamp only the right had eyepiece of the microscope is used whereas the protractor measures from a line which bisects the two converging axes of the binocular microscope.

The method chosen for calibration was that used by other workers of taking measurements of hard contact lenses of known thickness and making a correction for the different refractive indices of P.M.M.A. and cornea.

When using this technique Mandell and Polse used contact lenses of different thickness but having an average value of 8.00 mm. for the radius of the anterior surface. This seems very surprising unless the instrument was originally designed and calibrated for use on normal corneae and not keratoconoid ones. Even so it still appears a little strange that the 'artificial corneae' to be measured should have an anterior surface radius somewhat flatter than that of the average human cornea.

For the purposes of this study six afocal contact lenses were manufactured all having an anterior surface radius of 7.00 mm. as it was felt this would more approach the kind of values that would be encountered in a study on patients with Keratoconus.

The Afocal Contact Lenses were manufactured with the following thicknesses - 0.12, 0.21, 0.31, 0.41, 0.51, 0.60. This thickness was checked mechanically with a micrometer by the observers.

Apparent measurements were then taken with the viewing system at right angles to the lens. Results were as follows:-

Lens No. 6	Pachometer Read Out	
Thickness 0.60	0.736	
	0.760	
	0.746	
	0.746	Mean 0.745
	0.743	
	0.743	
	0.745	
	0.737	
Lens No. 5	Pachometer Read Out	
Thickness 0.51	0.684	
	0.660	
	0.653	
	0.652	Mean 0.663
	0.669	
	0.671	
	0.656	
	0.662	
Lens No. 4	Pachometer Read Out	
Thickness 0.42	0.573	
	0.576	
	0.564	
	0.579	Mean 0.574
	0.580	
	0.575	
	0.569	
	0.574	
Lens No. 3	Pachometer Read Out	
Thickness 0.31	0.437	
	0.451	
	0.438	
	0.436	Mean 0.445
	0.447	
	0.449	
	0.454	
	0.449	

Lens No. 2	Pachometer Read Out	
Thickness 0.21	0.321	
	0.320	
	0.327	
	0.327	Mean 0.328
	0.325	
	0.330	
	0.336	
	0.338	
Lens No. 1.	Pachometer Read Out	
Thickness 0.11	0.196	
	0.155	
	0.185	
	0.195	Mean 0.180
	0.179	
	0.194	
	0.165	
	0.168	

It is interesting to note that there was a greater 'spread' of measurements with the 'thinnest' artificial cornea.

It was now necessary to make correction for the differing refractive indices. (See Fig. 22.)

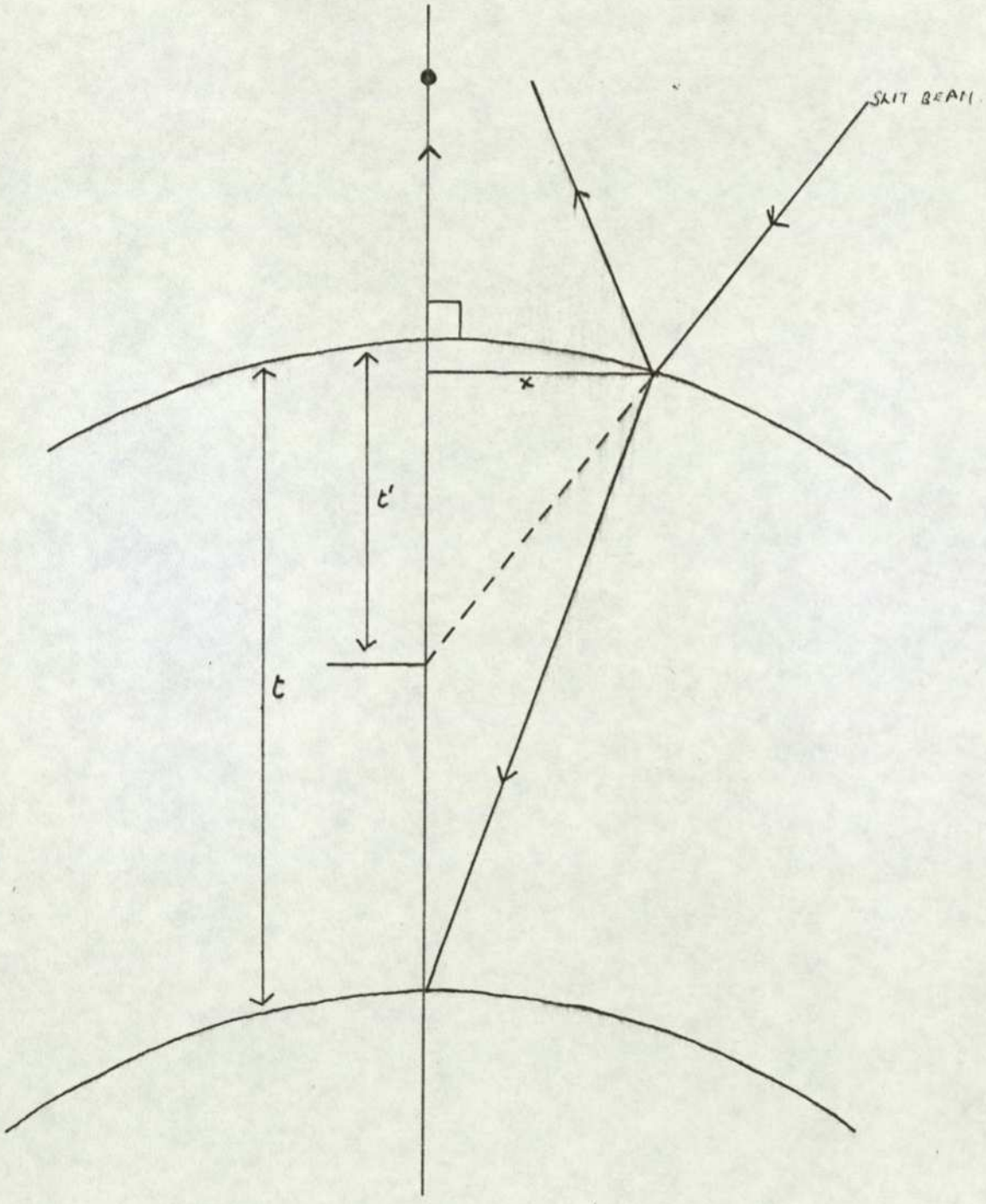


Fig. 22. Optical path of slit beam and reflected light.

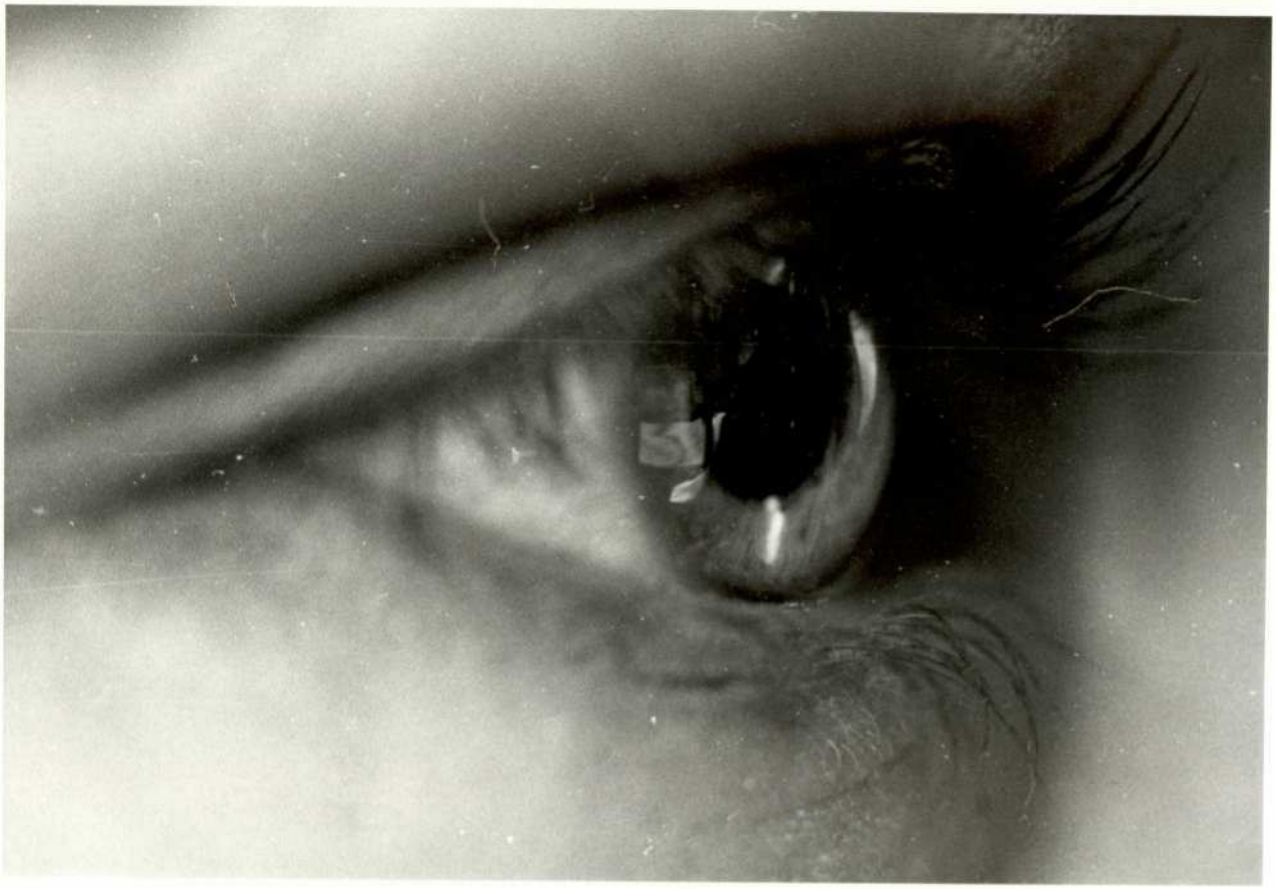


Fig. 23. Narrow slit beam in use. Note reflections of Donaldson lights.

r = radius of anterior surface.

Given t = true thickness

x = Apparent thickness of the slit lamp section

t' = Paraxial image of true thickness

Apparent corneal thickness x is proportional to the paraxial image t'.

$$\frac{1}{t'} - \frac{1.376}{t} = \frac{-0.376}{r}$$

$$\therefore t = \frac{1.376\ t'\ r}{0.376\ t' + r}$$

1·376 = refractive index of cornea

1.49 = refractive index perspex

Repeating the procedure to find the thickness for a contact lens of $\wedge$ = 1.49

$$t = \frac{1.49\ t'\ r}{0.49\ t' + r}$$

Thus the ratio of corneal thickness to contact lens thickness when the apparent thickness is equal is

$$\frac{t\ cor}{t\ lens} = \frac{1.376\ (0.49\ t' + r)}{1.49\ (0.376\ t' + r)}$$

Assuming an average value of r as 7.00 mm. as chosen earlier and an apparent thickness of t' of 0.45 being in the centre of a range of measurement.

$$\frac{t\ cor}{t\ lens} = \frac{1.376\ (0.49 \times 0.45 + 7)}{1.49\ (0.376 \times 0.45 + 7)}$$

$$= 0.930$$

Using similar methods Mandell and Polse obtained a figure of 0.925, the difference being accounted for by the different anterior surface radii chosen.

Using this factor a table was prepared converting the artificial plastic corneae to 'equivalent corneal thickness'.

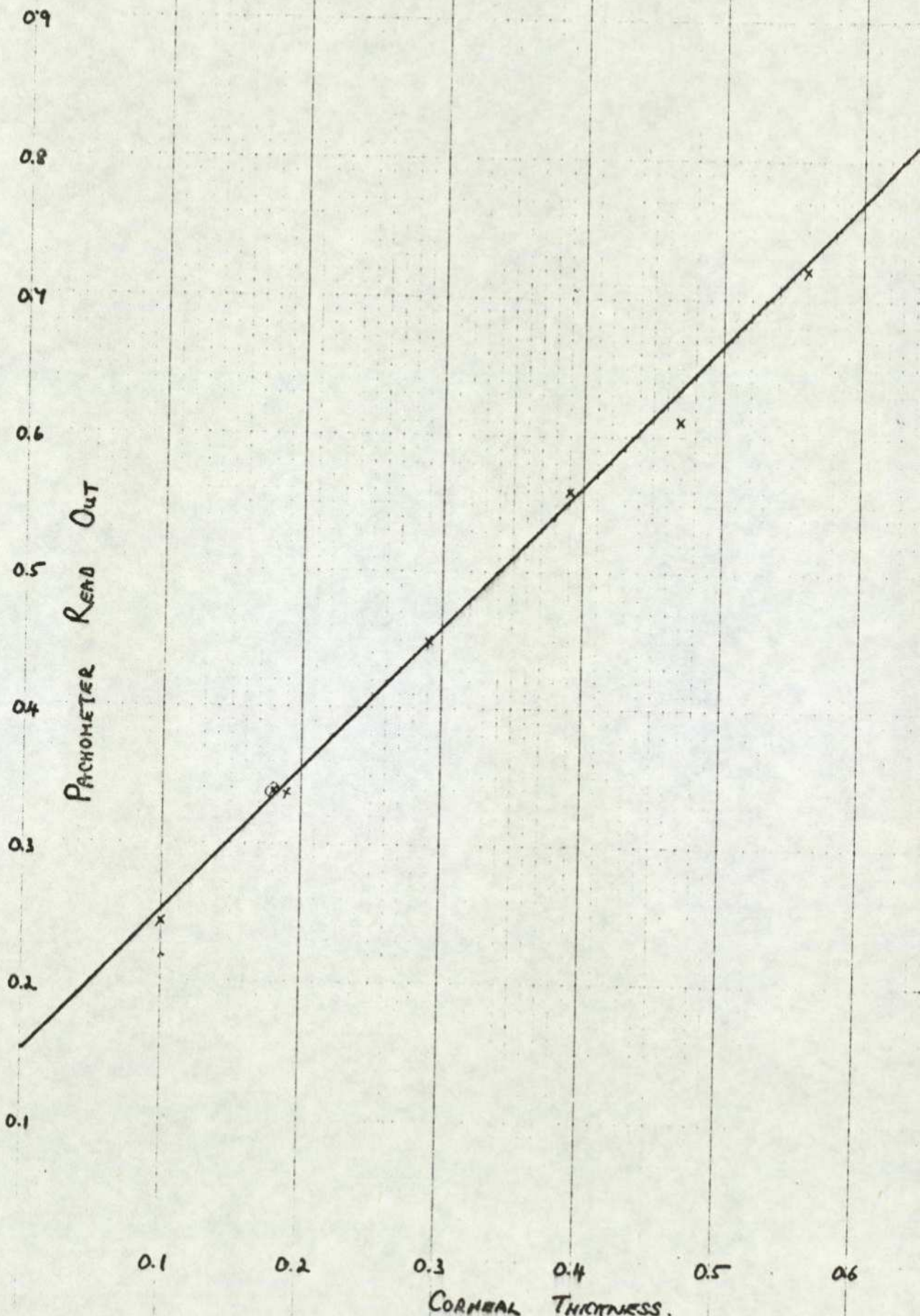
Lens No.	"Actual Thickness"	"Equivalent Corneal Thickness"
1	0.11	0.10
2	0.21	0.19
3	0.31	0.29
4	0.42	0.39
5	0.51	0.47
6	0.60	0.56

These values could then be plotted on a graph against the recorded read out.

"Equivalent Corneal Thickness"	Pachometer Read Out
0.10	0.24
0.19	0.34
0.29	0.45
0.39	0.57
0.47	0.61
0.56	0.72

The straight line graph produced was then used to convert directly the pachometer read out into true corneal thickness. See Graph 5.1.

Graph. 5.1.


0·9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
Pachometer Read Out
0.1
0.2
0.3
0.4
0.5
0.6
Corneal Thickness.

The Haag Streit Depth Measuring Attachment No. II

This instrument (See Fig. 23.) is used in exactly the same way as the modified No.I attachment with the exception that a + 6.00 D.S. addition is added to the right X 10 eye piece and the measuring points are the corneal epithelium and the anterior surface of the lens, consequently the corneal thickness is measured separately and deducted from the result.

Fig. 24. Haag-Streit depth measuring attachment No. II

Although not mentioned in the operating instructions for the instrument, it was considered that the state of the subject's accommodation must influence the depth of the anterior chamber, especially as the study involved subjects all of the pre-presbyopic age group.

A paper by D.J. Coleman Wachinich and Corlin showed conclusively that anterior chamber depth does decrease significantly in young adults on accommodation. Using young medical students as subjects they found that when accommodating 6 D. anterior chamber depth decreased by 0.26 to 0.30 mm.

As the basis for this paper was ultrasonography rather than optical methods, it was deemed advisable to confirm these findings using the Haag Streit instrument. Accordingly three subjects were chosen, all between the ages of 20 and 25, and their anterior chamber depth measured, 0.50% cyclopentolate was then instilled in the measured eye and the measurements repeated 30 minutes later.

Results:

Subject 1

Anterior chamber depth		Anterior Chamber depth after cycloplegia	
3.08		3.20	
3.10	Mean 3.09	3.20	Mean 3.19
3.10		3.18	

Subject 2

Anterior chamber depth		Anterior chamber depth after cycloplegia	
3.00		3.18	
3.00	Mean 3.00	3.17	Mean 3.17
3.01		3.17	

Subject 3

Anterior chamber depth		Anterior chamber depth after cycloplegia	
3.05		3.18	
3.07	Mean 3.06	3.16	Mean 3.17
3.06		3.15	

These results indicated that with young adult subjects some degree of accommodation invariably occurred when the instrument was used. Since the amount of accommodation in use was shown to have a

significant effect on the anterior chamber depth, it was decided throughout this study to instill 0.5% Cyclopentolate into subjects' eyes at least 30 minutes before taking measurements of the anterior chamber depth.

The Bausch and Lomb Keratometer

Although Helmholtz is usually credited with the invention of the keratometer, **Levene** (1977) throws doubt on this and suggests that Home and Ramsden (1795) were the first to check corneal radii in their measurements in connection with theories of accommodation. For the purposes of this study a commercially available instrument that was simple to use and readily amenable to have the range of measurement extended by the use of supplementary lenses was required. As the Bausch and Lomb instrument was already being used in the Keratoconus Clinic, it was decided to continue using this instrument. The circle in the mire target in this particular instrument had been found especially useful when looking for mire distortions of corneal contour in very early cases of Keratoconus.

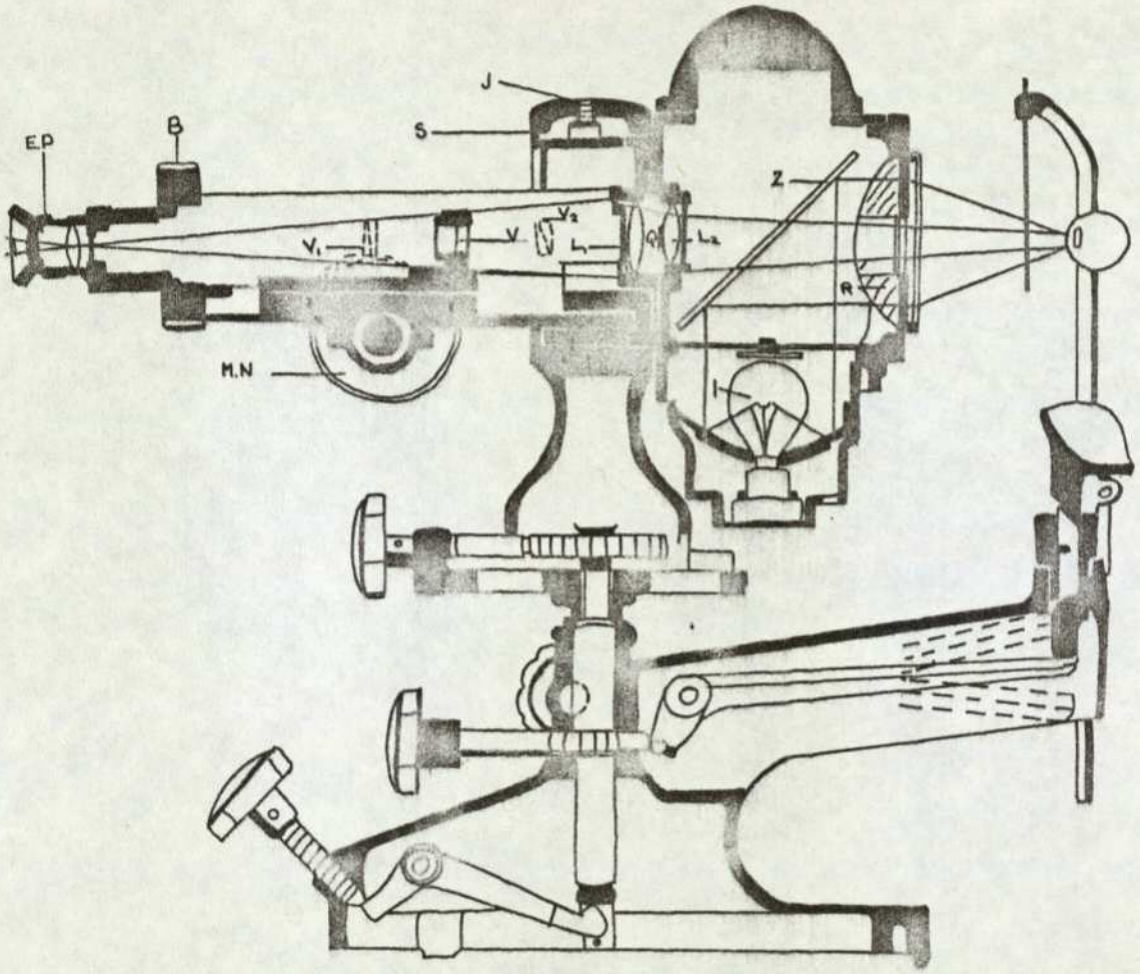


Fig. 25. Bausch and Lomb Keratometer. Optical system.

The optical system of the Bausch and Lomb keratometer is shown in the diagram above. (See Fig. 25.) The illumination system begins at Lamp I from which rays are reflected by an elliptical reflector to pass through a filter and diffusing screen. They are then reflected by a silvered mirror Z to a condensing lens R through which they pass to illuminate the mires, M. Rays leaving the mires are reflected from the cornea and produce a virtual image whose size may then be measured to determine the radius of curvature of the cornea.

The Bausch and Lomb instrument is of the variable doubling variety. That is to say that the mires have a constant separation and the virtual image size is measured by a variable doubling system.

This is achieved by the use of 4 apertures placed between the two objectives of the viewing telescope. Apertures C and D contain base in and base down prisms respectively. The mire image is viewed through all four apertures. Aperture C causes a doubled image in the horixontal plane and aperture D in the vertical plane. The doubling is varied by movements along the axis of the prisms in apertures C and D. Apertures A and B simply work on the Scheiner principle in that they do not contain prisms which would displace the image but give rise to two closely overlapped direct images unless the telescope is in sharp focus. (See Fig. 26.)

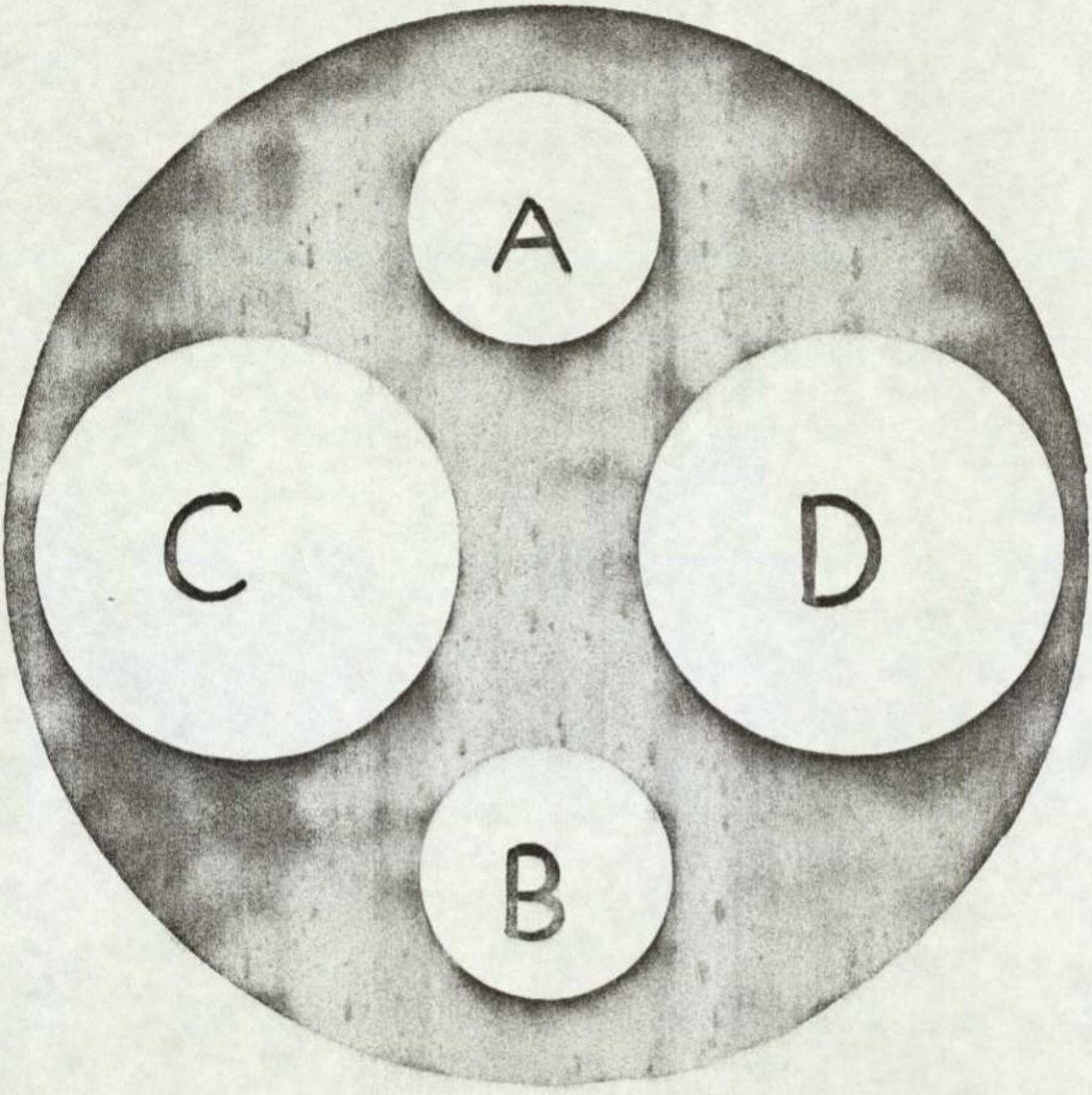


Fig.26(a). Bausch and Lomb Keratometer. Apertures.

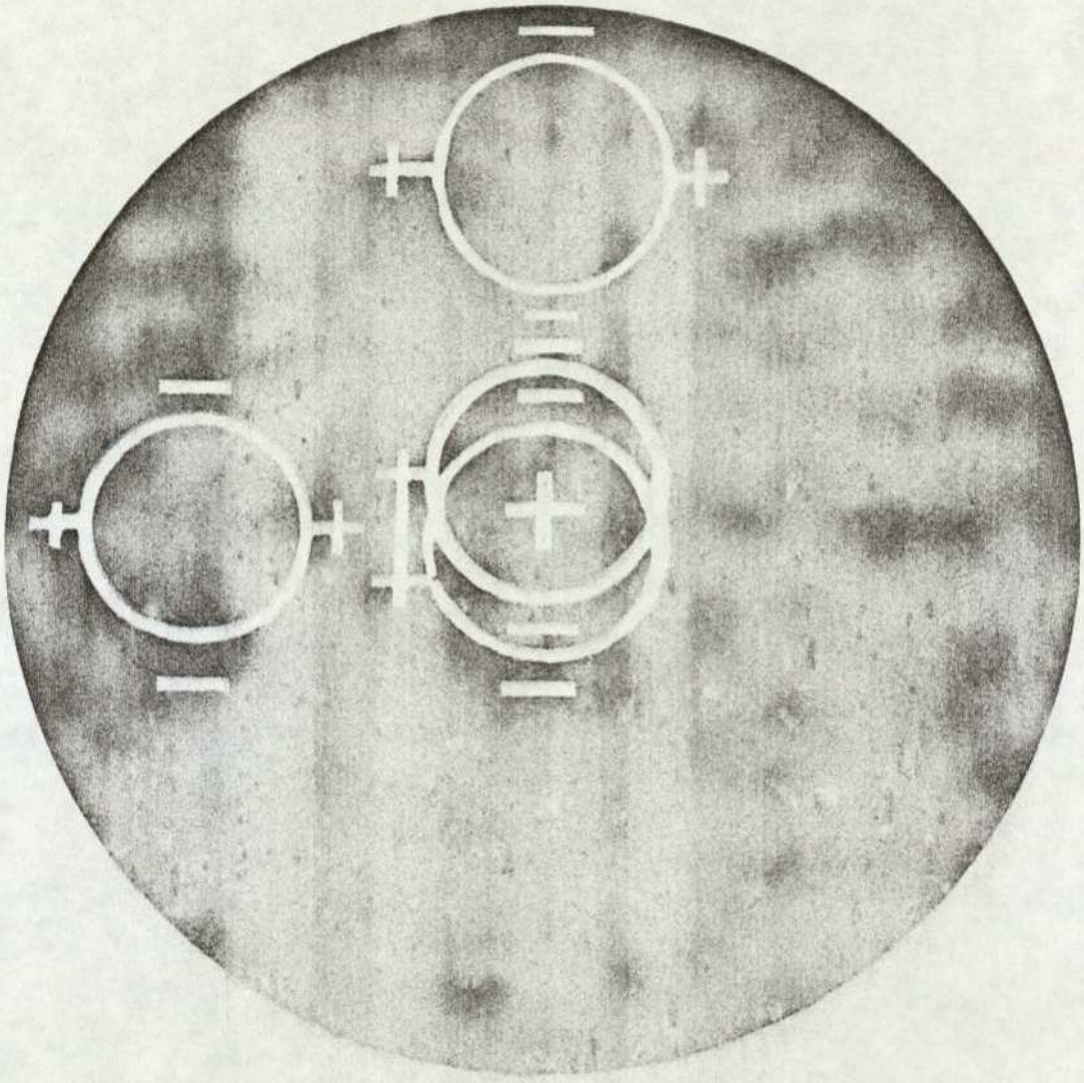


Fig.26(b). Bausch and Lomb Keratometer mires.

The area of the cornea actually measured has been studied by Mandell (1964) and Lehman (1967). They reported the width of the zones of reflection of the Bausch and Lomb instrument to be 0.1 mm. with a separation of about 2.9 mm. in the range of corneal curvature encountered in this study. This meant that corneal radii were measured inside the zone of movement represented by the first ring of topographical fixation targets of the modified pachometer.

In its standard form the instrument would not measure corneal radii steeper than 6.5 mm. which was by no means steep enough for this study. To recalibrate the instrument to measure steeper radii a + 2.00 D.S. trial case lens was placed just in front of the keratometer objective and a series of steep steel balls of known radii were observed. A graph was then plotted of recorded values against actual values. From this a conversion table was prepared which allowed corneal radii as steep as 4.95 to be measured.

B. & L. KERATOMETER

Conversion Tables +2.00 D.S. Add.

Apparent	True	Apparent	True
6.50	4.95	7.55	5.81
6.55	5.00	7.60	5.86
6.60	5.03	7.65	5.90
6.65	5.08	7.70	5.95
6.70	5.12	7.75	6.00
6,75	5.16	7.80	6.04
6.80	5.20	7.85	6.08
6.85	5.25	7.90	6.12
6.90	5.29	7.95	6.16
6.95	5.32	8.00	6.20
7.00	5.35		
7.05	5.42	8.05	6.24
7.10	5.46	8.10	6.27
7.15	5.50	8.15	6.31
7.20	5.53	8.20	6.35
7.25	5.57	8.25	6.39
7.30	5.61	8.30	6.43
7.35	5.66	8.35	6.47
7.40	5.70	8.40	6.50
7.45	5.74	8.45	6.55
7.50	5.78	8.50	6.60

The supplementary lens was held in a plastic disc specifically made for the Bausch and Lomb keratometer known as the "Inns Extension Disc."

Experimental Routine

When the project was originally conceived, it was envisaged that measurements could be taken during the weekly Keratoconus Clinics that are held in the Department of Contact Lens and Prosthetics. However when the apparatus was assembled and calibrated one was soon disabused of this idea.

Firstly, the combined group of measurements took at least half an hour to carry out, which made it impossible for this to be done during the usual busy clinic. Secondly, as mentioned earlier, to obtain a high degree of accuracy with the pachometer it was necessary to use the narrowest possible slit beam. When this was done it was found that observation of the juxtaposition of the split images was very much facilitated by having the room in total darkness. This again was obviously quite impractical in a busy clinic and would have meant my absence from the clinic for long periods of time.

The following routine was thus evolved after the first few weeks. Patients were made separate appointments for measurements to be taken and seen in a room which could be used in total darkness. Immediately on arrival cycloplegic drops were instilled in both eyes. This was done then so that adequate cycloplogia for the anterior chamber depth measurements had been obtained by the end of the allotted time. Topographical pachometry was then carried out before a significant degree of cycloplegia was effective. If it were delayed, then, because of accommodation power loss, the patients had great difficulty in fixating the L.E.D. fixation targets. It was also found that patients found fixation easier if the non measured eye was occluded with a patch. Keratometry was the next procedure and here fixation did not normally present a problem. It would have been desirable and no doubt much more accurate if patients wearing contact lenses who constituted the bulk of the sample, could have left their lenses out for some considerable period of time before measurement of corneal curvature. But as for most of these patients contact lenses are the only way of achieving anything like normal vision, it would have been quite unrealistic to ask them to leave their lenses out prior to their

appointment. The final procedure was the anterior chamber depth measurement.

In general co-operation from patients was extremely good. They were on the whole an intelligent and articulate group and understood the purpose of the project and became most interested in their own measurements.

ADLER, F.H. (1953) "Physiology of the Eye, Clinical Application" p.p. 308-309. Henry Kapton London.

COLEMAN D.J., WACHINICH & CORLIN B. (1968) Ophthalmic Ultrasound. Proceedings of the Fourth International Congress of Ultrasonography in Ophthalmalogy. Philadelphia 1968. The Mosby Co. 134-141 (1969)

DONALDSON D.D. (1966) "A new instrument for the measurement of corneal thickness". A.M.A. Archs. Ophthal. 76, 25-31

GOLDMAN H. (1968) Biomicroscopy of the eye. Ames. J. Ophthal. 66: 789-804

HOME E. (1795) Phil. Trans. R.Soc., 85, 2.

HONEGGER H. & GENEE E. (1968) Hornhautdickenmessung. Ein Vergleich verschiedener Gerate. Graefes Arch. Klin. exp. Ophthal. 174: 262-270

JAEGER W. (1952) Trefenmessung de menschlichen Vorderkammer mit plan parallen Platten (Zusatzgerat zur Spaltlampe). Graefes Arch. 153: 120-131.

JUILLERAT & KOBY F.E. (1928) Determination de l'epaisseur de la cornee sur le vivant au moyen de la lampe a fente. Rev.gen d'Ophthal. 42: 203-207

KRUSE HANSEN F. (1971) A clinical study of the normal human corneal thickness. Acta ophthal. Kbh 49: 82-89

LEHMAN S.P. (1967) Corneal areas utilized in keratometry. The Optician 154, 261.

LEVENE J.R. (1977) "Clinical Refraction and Visual Science p.p. 128-129. Butterworths, London 1977.

MANDELL R.B. (1964) Corneal area utilized in keratometry. Am.J. Optom. 41, 50.

MANDELL R.B. & POLSE KA. (1969) "Keratoconus: spatial variation of corneal thickness as a diagnostic test." A.M.A. Archs. Ophthol., 82 182 - 188.

THE PATIENT SAMPLE

The patients in this sample were all new referalls to the Keratoconus Clinic of the Department of Contact Lens and Prosthetics, Moorfields Eye Hospital, London E.C.1.

The Keratoconus Clinic was established in 1972 with its purpose described in the introductory document as follows:-

"The function of the Keratoconus Clinic is to bring together patients with keratoconus so that the natural history of the disease may be documented, the aetiology investigated and the management planned over a prolonged period."

The clinic brings together workers interested in investigating the ocular manifestations as well as the systemic associations of the disease.

Particular interest will be taken in the following:

A. Local Ocular Changes of Keratoconus

1. Changes in corneal curvature.
2. Changes in thickness and clarity of the cornea.
3. Evaluation of the corneal signs of keratoconus.

There then follows a further list of local ocular changes, associated ocular changes and systemic diseases associated with keratoconus.

In the clinic exact criteria for the diagnosis of keratoconus were laid down as follows:

Minimal Requirement (1) Irregular images of the keratometer mires in the presence of a clear cornea of normal biomicroscopic appearance.

Additional Features (2) Other clinical signs of keratoconus, e.g.

a) Fleischer's ring
b) Stromal striae
c) Conical shaped cornea visible. Positive Munson's sign.
d) Apical scarring of the cornea (Ruptures in Bowmann's Membrane, reticular scarring, Maltese Cross, Rupture in Descemet's membrane).
e) Apical thinning of the cornea
f) Visibility of corneal nerves.
g) Hydrops Corneae

Although the patients were new referrals they were not necessarily newly diagnosed. Many patients referred to this clinic had been diagnosed as keratoconus for some years particularly those from other hospitals. Often the case was referred when the management of the condition was becoming more difficult. For example when keratoplasty might be indicated or when a steepening cornea took the patient outside the range of contact lens fitting sets for more normal eyes. Patients moving into the area were another group falling in to this category. The new patients just diagnosed, came mainly from other clincs at Moorfields, eye departments at other London hospitals, or from ophthalmic opticians in the General Ophthalmic Service via General Practioners.

There was no special selection of patients, the clinic received two or three new patients each week and they were routinely asked if they were willing to make four extra visits to the hospital over the ensuing two years. They were not asked, if they lived a long way from Moorfields, or if they did not expect to be in the London area in two years time. This excluded many of the student population and possibly accounts for the slightly higher age group found in the study than anticipated.

The first patients entered the study on October 29th, 1976 and the last in August 1977. As it was intended to take measurements on 100 eyes, 55 patients were admitted to the study to allow for some wastage. Gratifyingly patient co-operation was extremely good 50 patients out of the original 55 completing all four visits. Many of the patients became intrigued by the study and spontaneously volunteered to come for extra visits if necessary.

The one patient who underwent keratoplasty at another London hospital took a great deal of trouble to contact the writer so that measurements could be taken before the graft procedure took place.

Of the patients approached approximately two thirds agreed to enter the study. The ones declining to do so usually had very good reasons such as the problem of looking after very young children or the fact that they worked unsocial hours.

In addition to the more obvious questions the patients were asked the age of their mother and father when they were born and also the standard of their education.

When analysis of this data was commenced it became apparent that

Page 116. *

Although the control group came from Moorfields Eye Hospital the Contact Lens Department was then situated at the High Holborn branch so the sample would not be exactly the same as in the present study.

the maternal age at birth was of particular interest. On the advice of a statistician (see acknowledgements) details of the maternal age of a further 95 patients of the keratoconus clinic were obtained to increase the statistical validity of the study. The results of this form a separate chapter of this thesis, as do the results obtained from an analysis of the patient's education.

Sex

Of the Initial Sample

32 Males (58.18%)

23 Females (41.82%)

With the Sample enlarged to 150, the figures became

91 Males (60.60%)

59 Females (39.40%)

Karseras and Ruben in a paper published in 1976 and using patients from the same hospital department found from a sample of 75 patients that 71% were male. In their control group of 231 randomly selected outpatients (one in five) from the same hospital 47% were male.* The question of sex ratio has already been discussed and references given in the introduction to this thesis in the section on incidence of the condition. A point of note is that all the writers who found a preponderance of females wrote between 1900 and 1955, whilst those finding a preponderance of males wrote between 1958 and 1976. This is not to say that the ratio between the sexes is changing because in the earlier writings the size of the sample is not usually given. Also the effect of two world wars on the male/female ratio must be remembered.

Table 6.1.

Age

Frequency Distribution

Age at first visit	Number of patients
14-15	3
16-17	7
18-19	6
20-21	6
22-23	7
24-25	4
26-27	9
28-29	2

Age at first visit	Number of patients
30-31	2
32-33	2
34-35	0
36-37	2
38-39	2
40-41	2
42	1
	55

Mean = 24.45

Standard Deviation = 7.29

See Graph No. 6.1.

Table 6.2.

Years since Diagnosis	Number of patients
0	21
1	12
2	8
3	4
4	4
5	1
7	1
9	1
13	1
18	2

See Graph No. 6.2.

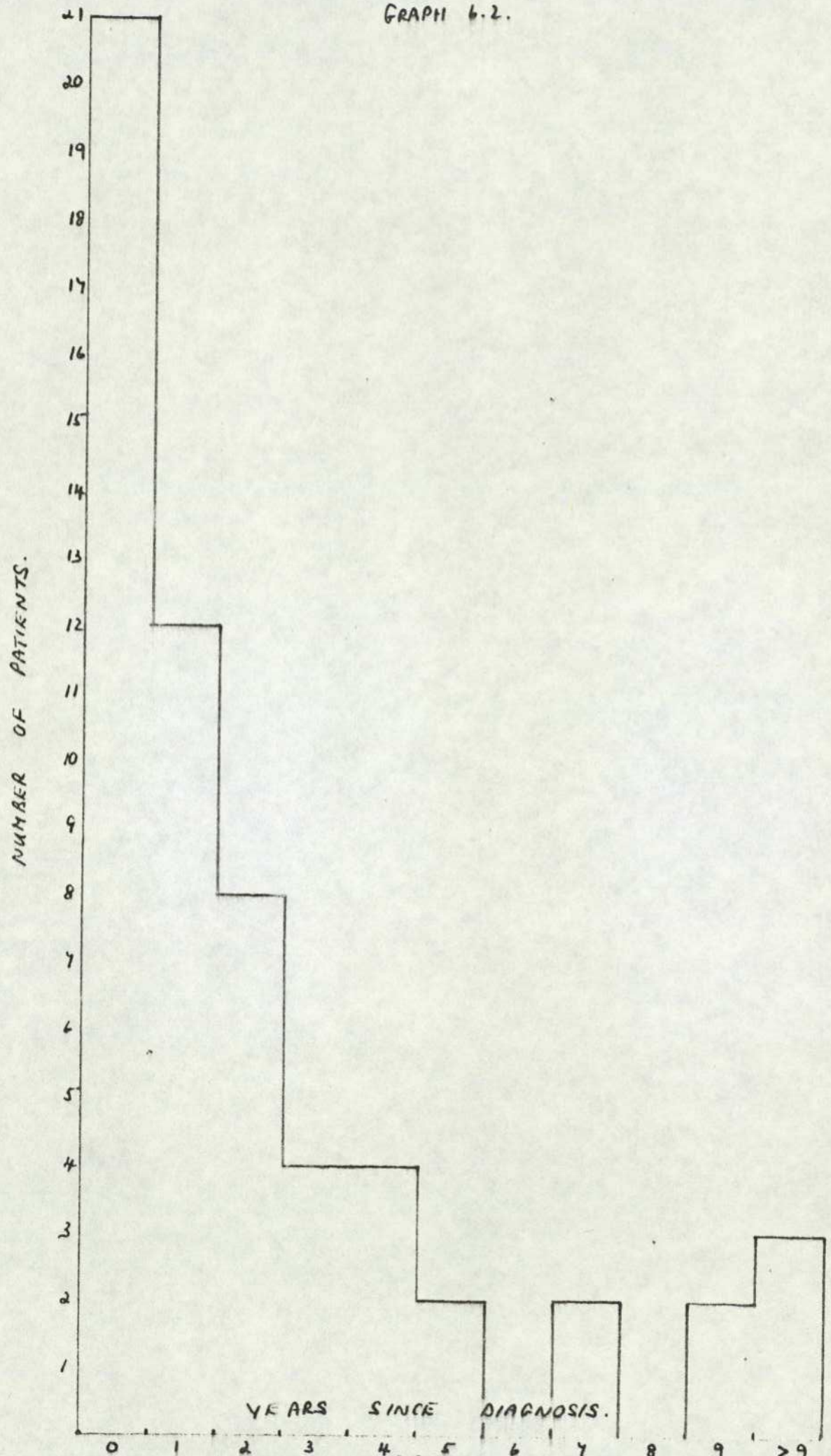
Table 6.3.

Age at Diagnosis	Number of patients
12-13	2
14-15	9
16-17	6
18-19	7
20-21	6
22-23	6
24-25	3
26-27	8
28-29	1
30-31	0
32-33	2

GRAPH 6.1.

NUMBER OF PATIENTS.
1
2
3
4
5
6
7
8
9
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
AGE AT FIRST VISIT.

GRAPH 6.2.


NUMBER OF PATIENTS.
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
YEARS SINCE DIAGNOSIS.
0
1
2
3
4
5
6
7
8
9
>9

GRAPH 4.3.

NUMBER OF PATIENTS.
1
2
3
4
5
6
7
8
9
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
AGE AT DIAGNOSIS

Age at Diagnosis	Number of patients
34-35	1
36-37	0
38-39	2
40-41	1
42	1
	55

Mean = 22.18

Standard Deviation = 7.31

See Graph No. 6.3.

At first sight these figures seem surprisingly high. Duke Elder (1965) in discussing keratoconus writes, "it usually manifests itself about puberty, becoming evident most commonly in girls between 10 and 16 years of age". This view of the condition is certainly not supported by the present study. It is possible that in former times only the more extreme forms of the condition were detected and **Several of the patients in the study had only a mild form of the condition.** Possibly better training and instrumentation of ophthalmic opticians who perform more then 80% of the refractions in the country is responsible for more of the milder degrees of the condition being detected.

An analysis of age at diagnosis in relation to degree of corneal thinning occurring is given later in this thesis.

Method of Optical Correction and Visual Acuity

At the first visit to the keratoconus clinic the 55 patients had optical corrections in the following forms:

Table 6.4.

No Optical Correction	31	56.36%
Spectacles	4	7.27%
Corneal Lenses	17	30.91%
Scleral Lenses	3	5.45%

When last seen the optical corrections were:

Table 6.5.

No Optical Correction	5	9.09%
Spectacles	5	9.09%
Corneal Lenses	41	74.55%
Scleral Lenses	3	5.45%
Hydrogel Lenses	1	1.82%

Where a patient was wearing contact lenses of two different types, the one quoted is the one with the longer wearing time.

The visual acuities of the 5 patients not wearing any optical correction at the end of the studies were:

Table 6.6.

1)	R 6/36	L 6/36
2)	R 6/12	L 6/5
3)	R 6/18	L 6/6 (had L. Keratoplasty)
4)	R 6/4	L 6/12
5)	R 6/60	L 6/6

As can be seen apart from the first case who was of low intelligence and did not really seem aware of her visual disability, all the others had a normal level of visual acuity in one eye. The figures would suggest a lack of motivation to wear a contact lens in one eye only, when the acuity remains good in the other eye.

The visual acuities of the 5 patients wearing spectacles at the end of the study were:

Table 6.7.

1)	R 6/12	L 6/9
2)	R 6/18	L 6/9
3)	R 6/9	L 6/9
4)	R 6/6	L 6/18
5)	R 6/6	L 6/6

Here again every patient had at least one eye with an acuity which could be considered within normal limits.

The frequency distribution of the visual acuity of the 82 eyes that wore corneal lenses at the end of the study was as follows:

Table 6.8.

Visual Acuity	No. of Eyes	%
6/4	2	2.44
6/5	20	24.39
6/6	18	21.95
6/9	36	65.45
6/12	4	4.88
6/18	2	2.44

The visual acuities of the 3 patients wearing scleral lenses at the end of the study were:

Table 6.9.

1)	R 6/9	L 6/6
2)	R 6/9	L 6/12
3)	R 6/6	L 6/9

As can be seen the visual acuities obtainable with scleral lenses were comparable to those with corneal lenses.

The solitary patient wearing hydrogel lenses which were of Toyo 29.6% water content had a visual acuity of

R 6/18 L 6/6

Occupation of Patients

The occupation of the patients was recorded with two possibilities in mind.

1) to establish if there were any environmental causation of the condition.

2) To determine the social class of the patient by using Registrar Generals classification based on occupation. Karseras and Ruben (1976) in their study at the same hospital found more than half the patients were from social class I and II, whereas in a random selection of ophthalmic outpatients the majority came from class III.

The occupations of the patients in the study were:

Table 6.10.

		Number
1.	Student	17
2.	Civil Servant	6
3.	Housewife	4
4.	Nurse	3
5.	Solicitor	2
6.	Social Worker	2
7.	Lecturer/Teacher	2
8.	Engineer	2
9.	Salesman	2
10.	Librarian	2
11.	Dentist	1
12.	Artist	1

	Occupation	Number
13.	Electrician	1
14.	Publisher	1
15.	Accountant	1
16.	Secretary	1
17.	Printer	1
18.	Computer Programmer	1
19.	Taxi Driver	1
20.	Plumber	1
21.	Telephonist	1
22.	Shop Assistant	1
23.	Musician	1

Since the census of 1911 it has been the Registrar General's practice to group the occupational units of the census into a small number of broad categories known as social class. The basis and rationale of this categorization is as follows:

The unit group included in each of the categories (i.e. social classes) has been selected so as to ensure that, so far as is possible, each category is **homogeneous** in relation to the basic criterion of the general standing within the community of the occupations concerned. This criterion is naturally correlated with, and its application conditioned by other factors such as education and economic environment, but it has no direct relationship to the average level of remuneration of particular occupations. Each occupational unit group has been assigned as a whole to a Social Class and is not a specific assignment of individuals based on the merits of a particular case.

In the 1971 census Social Class III was split, this class contained 49% of the occupations of economically active persons in Great Britain and was felt to be too non-specific.

Contemporary census material uses the following classification.

I Professional etc.

II Intermediate

III Skilled (N) Non-manual
(M) Manual

IV Partly skilled

V Unskilled

The patients in the study were classified using the Registrar Generals Classification of Occupations 1970 which has a list of more than 20,000 separate occupational titles which are grouped into 200 occupational units. The 4 housewives were classified on the basis of their previous educational attainments: the students on the subjects studied.

The figures obtained were compared with figures from the 1975 10% sample (Economic Activity Part 4).

The results from the sample were:

Table 6.11.

Social Class	Number	%
I	16	29.09
II	26	47.27
III N	8	14.55
III M	4	7.27
IV	1	1.82
V	0	0

Comparison with General Population (1975 10% Sample)

Table 6.12.

	I	II	III(N)	III(M)	IV	V	ALL
Keratoconus Group	29.09	47.27	14.55	7.27	1.82	0	100
General Population	4	18	21	28	21	8	100

These figures show the same tendency, but are even more skewed than the results of Karseras and Ruben in that 76% of the patients come from social class I and II. It is, of course, quite possible that people from these classes were more likely to offer to co-operate in a study of this nature. Also patients in social class V are often not paid if they are away from work, so are less likely to volunteer which may well explain the absence of any patient from this class in the study. It can be argued that people from the higher social classes are more likely to get to Moorfields in that they are more active in seeking advice if their vision deteriorates in one eye and persist until they are referred. Nevertheless, despite all these considerations it would appear that there could be reasons why keratoconus patients tend to be of a higher social class then the general population. One possible answer is the age at which different social classes tend to have their

children.

The Newsoms (1963) in a study of 700 families in Nottingham produced clear evidence that mothers are younger in the manual classes. This can be seen not only in terms of earlier marriage, but also in relation to the fact that the interval between marriage and the first birth (and to some extent between subsequent births) is shorter for manual mothers than for non- manual mothers (Woolf 1971).

Percentage of mothers under age of 21 at birth of first child by social class.

Table 6.13.

	Social Class (Registrar General AB definition 1960)					
	I	II	III(N.M)	III(M)	IV	V
Mothers under 21 %	4.78	7.97	13.29	21.27	24.46	28.19

(Derived from table 10 Newson & Newson 1963)

Comparing these with social class distribution in the Keratoconus sample

i.e.	29.07	47.27	14.55	7.27	1.82	0

See Graph 6.4

It would seem very likely that there is a causal relationship between the social class of keratoconus patients and the age of their mothers at birth. The relationship between maternal age and the incidence of keratoconus will be discussed in a later chapter. The educational attainments of the keratoconus group are also considered in a later chapter and their social class is almost certainly a summation of these 2 factors.

KERATOCONUS SAMPLE
MOTHERS UNDER AGE OF 21 AT BIRTH OF FIRST CHILD
50
40
30
20
10
% OF PATIENTS
I
II
III
III
IV
V
(NON MANUAL)
(MANUAL)
SOCIAL CLASS

GRAPH 6.4.

REFERENCES

DUKE ELDER (1965)	"System of Ophthalmology" Henry Kipton. London Vol. VIII p.964
KARSERAS & RUBEN (1976)	"Aetiology of Keratoconus" Brit.J.Ophthal. 60, 522.
NEWSON J. & NEWSON E. (1963)	"Infant Care in an Urban Community" Allen & Unwin, London.
WOOLF M. (1971)	"Family Intentions" H.M.S.O. London table 3.13

RESULTS: ANALYSIS OF.

A. Keratoconus Sample Maternal Age

After a considerable number of years working with patients suffering from Keratoconus the writer formed the impression that when first presenting for fitting with contact lenses patients were often accompanied by relatively ageing parents.

It is nowadays fashionable to decry the work of Sir Francis Galton particularly that dealing with eugenics, but his writings in connection with anthropometry seem applicable to the present study.

"General impressions are never to be trusted. Unfortunately when they are of long standing they become fixed rules of life and assume a prescriptive right not to be questioned. Consequently those who are not accustomed to original inquiry entertain a hatred and horror of statistics. They cannot endure the idea of submitting their sacred impressions to cold bloodedverification.

But it is the triumph of scientific man to rise superior to such superstitions, to devise tests by which the value of beliefs may be ascertained and to feel sufficiently masters of themselves to discard contemptuously whatever may be untrue."

Francis Galton

1822 - 1911

Although the impression that the writer had formed was possibly not a general one and probably not of long standing the verification or otherwise seemed a worthwhile exercise. Consequently when the original patients on the study first presented they were asked the age of their mother and father when they were born. Preliminary analysis of these findings strongly suggested there was a significantly different frequency distribution of the age of mother at birth as compared with the general population. On the advice of a statistician information on maternal age at birth was collected from a further 95 consecutive patients attending the Keratoconus clinic to give a total sample of 150.

The results obtained are given in Appendix 1.

The paternal age was not taken in these extra 95 patients because of the problem of comparison with the general population. Prior to 1961 Paternal age was not recorded and is not published in the Registrar General's Statistical Review.

The results for the initial sample are as follows:- (See following page.)

Table 7.1.

Frequency Distribution Maternal Age (Initial Sample)

Age of Mother	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	3	2	16	17	11	4	2	55
%	5.45	3.64	29	31	20	7.27	3.64	100

Table 7.2.

Frequency Distribution Paternal Age (Initial Sample)

Age of Father	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	0	10	19	18	3	2	1	53
%	0	18.87	35.85	33.96	5.66	3.77	1.88	100

In two cases the age of the patients father was not known by the patient. The age given in every case is of course that of the putative father which is an inherently less reliable figure than that of maternal age.

The years of births of the patients in the initial study were in the period 1935 - 1962.

Table 7.3.

The frequency distribution of the expanded sample was as follows:-

Age of Mother	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	5	18	37	47	33	8	2	150
%	3.33	12.00	24.67	31.33	22.00	5.33	1.33	

The years of births of the patients in the extended study were in the period 1909 - 1965.

This spread of years of birth presents an historiographic problem in that the pattern of child bearing had changed during that period.

The Frequency Distribution of the years of birth was:-

Table 7.4.

YEAR	NUMBER OF PATIENTS	YEAR	NUMBER OF PATIENTS	YEAR	NUMBER
1909	1	1939	4	1952	4
1913	1	1940	4	1953	6
1919	1	1941	5	1954	9
1927	1	1942	4	1955	5
1928	2	1943	3	1956	4
1929	1	1944	6	1957	6
1930	1	1945	2	1958	4
1932	1	1946	3	1959	9
1933	1	1947	5	1960	8
1935	2	1948	4	1961	9
1936	1	1949	9	1962	3
1937	3	1950	7	1963	2
1938	2	1951	5	1964	1
				1965	1

Total number of patients 150

Mean year of birth 1949

Standard Deviation 12.36

However there was by no means a normal distribution of patients 128 being born after 1939. As 112 of the sample of 150 were born in the period 1940 - 1960 it seemed reasonable to look at Births by Maternal Age for these years.

Source Registrar General Statistical Review

Office Population Census and Surveys. (See following page.)

Table 7.5.

MATERNAL AGE

1940	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	27043	144693	195863	136697	74264	23453	2016	604029
%	4.48	23.95	32.43	22.63	12.29	3.88	0.33	100

Table 7.6.

MATERNAL AGE

1950	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	31753	200406	244007	136767	87398	25796	1829	728556
%	4.36	27.51	33.57	18.77	12.00	3.54	0.25	100

Table 7.7.

MATERNAL AGE

1960	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number	46067	229064	233579	143475	77261	17736	1315	748498
%	6.15	30.50	31.21	19.17	10.32	2.37	0.18	100

Although not comparable with the sample the % figures for 1973 are as follows:-

Table 7.8.

MATERNAL AGE

1973	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
%	8.6	33.4	37.7	13.9	5.1	1.3	0.1	100

As can be seen for the whole of the period under consideration the tendency was for women to have their children earlier and earlier and the tendency continued for at least a further 13 years. However, although outside the scope of this thesis it is interesting to note that this trend has now been reversed (see Cartwright A, recent trends in family building and contraception, Studies in Medical and Population Subjects No. 34 H.M.S.O. 1978). It remains to be seen if this will have any effect on the incidence of conditions such as Keratoconus.

We can now tabulate births by maternal age for the general population against the Keratoconus sample.

Table 7.9.

MATERNAL AGE

	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL	
General Population 1940	4.48	23.95	32.43	22.63	12.29	3.88	0.33	100	%
General Population 1950	4.36	27.51	33.57	18.77	12.00	3.54	0.25	100	%
General Population	6.15	30.50	31.21	19.17	10.32	2.37	0.18	100	%
Keratoconus Sample	3.33	12.00	24.67	31.33	22.00	5.33	1.33	100	

Bearing in mind that the mean year of birth for the sample was 1949 but that the sample was skewed towards the later years it would seem that the most valid comparison would be with the 1950 figures.

Another way of presenting the figures would be to consider the percentage of births to women over 30 and over 35.

YEAR	Maternal Age 30+	Maternal Age 35+
GENERAL POPULATION 1940	39.13	16.50
GENERAL POPULATION 1950	34.58	15.79
GENERAL POPULATION 1960	32.04	12.87
1973	20.04	6.5
KERATOCONUS SAMPLE	59.99	28.66

The number of babies born to women over the age of 35 has been falling both in absolute terms and as a percentage since 1965 so if there is a connection between maternal age and the instance of Keratoconus there should be a fall in the number of cases presenting over the next few years.

Statistical Analysis

An appropriate analysis for this type of data is X^2 - Goodness of fit test. This test is used when data can be classified into a number of mutually exclusive categories and one wishes to test if the observed frequencies in each category differ significantly from those which could be expected if some hypothesis were true. If any of the "expected" frequencies are less than 5 in any category, that category should be combined with one or more of its neighbouring categories.

In this thesis, the hypothesis that maternal age distribution of Keratoconus patients does not differ significantly from the maternal age distribution of the general population is tested against the alternative hypothesis that it does differ.

The X^2 goodness of fit test compares the "observed" frequencies, in the Keratoconus sample with the "expected" frequencies, as derived from some model or base population. A large X^2 indicates significant differences between the distributions.

The choice of the model population might be questioned for appropriateness in that the Registrars Generals population census data describe a population at fixed points in time (1940, 1950 and 1960) whereas the sample of patients were born over a wider time period when the pattern might have been different or changing. Fortunately the

distribution of these three census years of maternal age is remarkably similar (see Graph No. 7.1). Since the arithmetic mean year of birth of the sample of 150 patients is 1949 and the median is 1951 it seems appropriate to take the 1950 data as the most useful predictor of "expected" frequencies.

Chi-square Goodness of Fit Tests — Small Sample (N = 55)

X^2 = (observed frequency - expected frequency)^2 /expected frequency

degrees of freedom = N - 1, where N = number of categories.

Note if expected frequency 5 in any category, that category must be combined with adjacent categories - as in the case of 20, (40 - 44) and (45 - 49) age groups.

Table 7.10

Using 1940 census data to estimate expected frequencies

Keratoconus Patients (N = 55)	Maternal Age (Years)							
	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	3	2	16	17	11	4	2	55
(%)	(5.45)	(3.64)	(29.09)	(30.91)	(20.00)	(7.27)	(3.64)	(100)
Number expected	2.46	13.17	17.84	12.45	6.76	2.13	0.18	55
(%)	(4.48)	(23.95)	(32.43)	(22.63)	(12.29)	(3.88)	(0.33)	(100)

$$X^2 = \frac{(5 - 15.63)^2}{15.63} + \frac{(16 - 17.84)^2}{17.84} + \frac{(17 - 12.45)^2}{12.45} + \frac{(17 - 9.07)^2}{9.07} \quad \text{deg. freed} = 3$$

$$= 7.2295 + 0.1898 + 1.6629 + 6.9333 = 16.015 \qquad p < 0.005$$

Inference: Maternal Age distribution of Keratoconus sample significantly different from maternal age distribution described in 1940 Registrar General's Population data.

Using 1950 census data

Table 7.11

Keratoconus Patients (N = 55)	Maternal Age (Years)							
	<20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	3	2	16	17	11	4	2	55
(%)	(5.45)	(3.64)	(29.09)	(30.91)	(20.00)	(7.27)	(3.64)	(100)
Number expected	2.40	15.13	18.46	10.32	6.60	1.95	0.14	55
(%)	(4.36)	(27.51)	(33.57)	(18.77)	(12.00)	(3.54)	(0.25)	(100)

$$X^2 = \frac{(5 - 17.53)^2}{17.53} + \frac{(16 - 18.46)^2}{18.46} + \frac{(17 - 10.32)^2}{10.32} + \frac{(17 - 8.69)^2}{8.69} \text{ deg. freed} = 3$$

$= 8.9561 + 0.3278 + 4.3239 + 7.9466 = 21.554 \quad p < 0.001$

Using 1960 census data

Table 7.12

Keratoconus Patients (N = 55)	Maternal Age (Years) <20	20 - 24	25 - 29	30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	3	2	16	17	11	4	2	55
(%)	(5.45)	(3.64)	(29.09)	(30.91)	(20.00)	(7.27)	(3.64)	(100)
Number expected	3.38	16.83	17.17	10.54	5.68	1.30	0.10	55
(%)	(6.15)	(30.60)	(31.21)	(19.17)	(10.32)	(2.37)	(0.18)	(100)

$$X^2 = \frac{(5 - 20.21)^2}{20.21} + \frac{(16 - 17.17)^2}{17.17} + \frac{(17 - 10.54)^2}{10.54} + \frac{(17 - 7.08)^2}{7.08} \text{ deg. freed} = 3$$

$= 11.4470 + 0.0797 + 3.9594 + 13.8992 = 29.385 \quad p < 0.001$

Note the major contributions to the X^2 come from the extremes, the Keratoconus sample having significantly less young mothers (< 25) and significantly more older ones (> 35).

There is no difference in the proportion of mothers in the (25 - 29) category.

Chi-squared Goodness of Fit Tests — Larger Sample (N = 150)

Note: Not necessary to combine so many categories in this larger sample.

Using 1940 census data

Table 7.13.

Keratoconus Patients (N = 150)	<20	20 - 24	25 - 29	Maternal Age (Years) 30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	5	18	37	47	33	8	2	150
(%)	(3.33)	(12.00)	(24.67)	(31.33)	(22.00)	(5.33)	(1.33)	(100)
Number expected	6.72	35.93	48.65	33.95	18.44	5.82	0.49	150
(%)	(4.48)	(23.95)	(32.43)	(22.63)	(12.29)	(3.88)	(0.33)	(100)

$$\chi^2 = \frac{(5 - 6.72)^2}{6.72} + \frac{(18 - 35.93)^2}{35.93} + \frac{(37 - 48.65)^2}{48.65} + \frac{(47 - 33.95)^2}{33.95} + \frac{(33 - 18.44)^2}{18.44} + \frac{(10 - 6.31)^2}{6.31}$$

$= 0.4402 + 8.9475 + 2.7898 + 5.0163 + 11.4964 + 2.1579 = 30.8481$ degrees of freedom = 5

$p < 0.001$ Note: < 20 classes not significantly different.

Using 1950 census data

Table 7.14

Keratoconus Patients (N = 150)	< 20	20 - 24	25 - 29	Maternal Age (Years) 30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	5	18	37	47	33	8	2	150
(%)	(3.33)	(12.00)	(24.67)	(31.33)	(22.00)	(5.33)	(1.33)	(100)
Number expected	6.54	41.26	50.35	28.15	18.00	5.31	0.38	150
(%)	(4.36)	(27.51)	(33.57)	(18.77)	(12.00)	(3.54)	(0.25)	(100)

$$x^2 = \frac{(5 - 6.54)^2}{6.54} + \frac{(18 - 41.26)^2}{41.26} + \frac{(37 - 50.35)^2}{50.35} + \frac{(47 - 28.15)^2}{28.15} + \frac{(33 - 18)^2}{18} + \frac{(10 - 5.69)^2}{5.69}$$

$= 0.3626 + 13.1126 + 3.5397 + 12.6225 + 12.500 + 3.2647 = 45.402$ degrees of freedom = 5

$p < 0.001$

Using 1960 census data

Table 7.15

Keratoconus Patients (N = 150)	< 20	20 - 24	25 - 29	Maternal Age (Years) 30 - 34	35 - 39	40 - 44	45 - 49	TOTAL
Number observed	5	18	37	47	33	8	2	150
(%)	(3.33)	(12.00)	(24.67)	(31.33)	(22.00)	(5.33)	(1.33)	(100)
Number expected	9.23	45.90	46.82	28.76	15.48	3.56	0.27	150
(%)	(6.15)	(30.60)	(31.21)	(19.17)	(10.32)	(2.37)	(0.18)	(100)

$$x^2 = \frac{(5 - 9.23)^2}{9.23} + \frac{(18 - 45.90)^2}{45.90} + \frac{(37.46.82)^2}{46.82} + \frac{(47 - 28.76)^2}{28.76} + \frac{(33 - 15.48)^2}{15.48} + \frac{(10 - 3.83)^2}{3.83}$$

$= 1.9386 + 16.9588 + 2.0588 + 11.5681 + 19.8288 + 9.9397$

$= 62.2936$ degrees of freedom = 5 $p < 0.001$

As in the smaller sample - little difference in the 25 - 29 category. Greatest differences seen in the (20 - 24) group and the (30 - 34) and (35 - 39) groups, wherein up to 30% are expected, but over 50% are found, in the Keratoconus group.

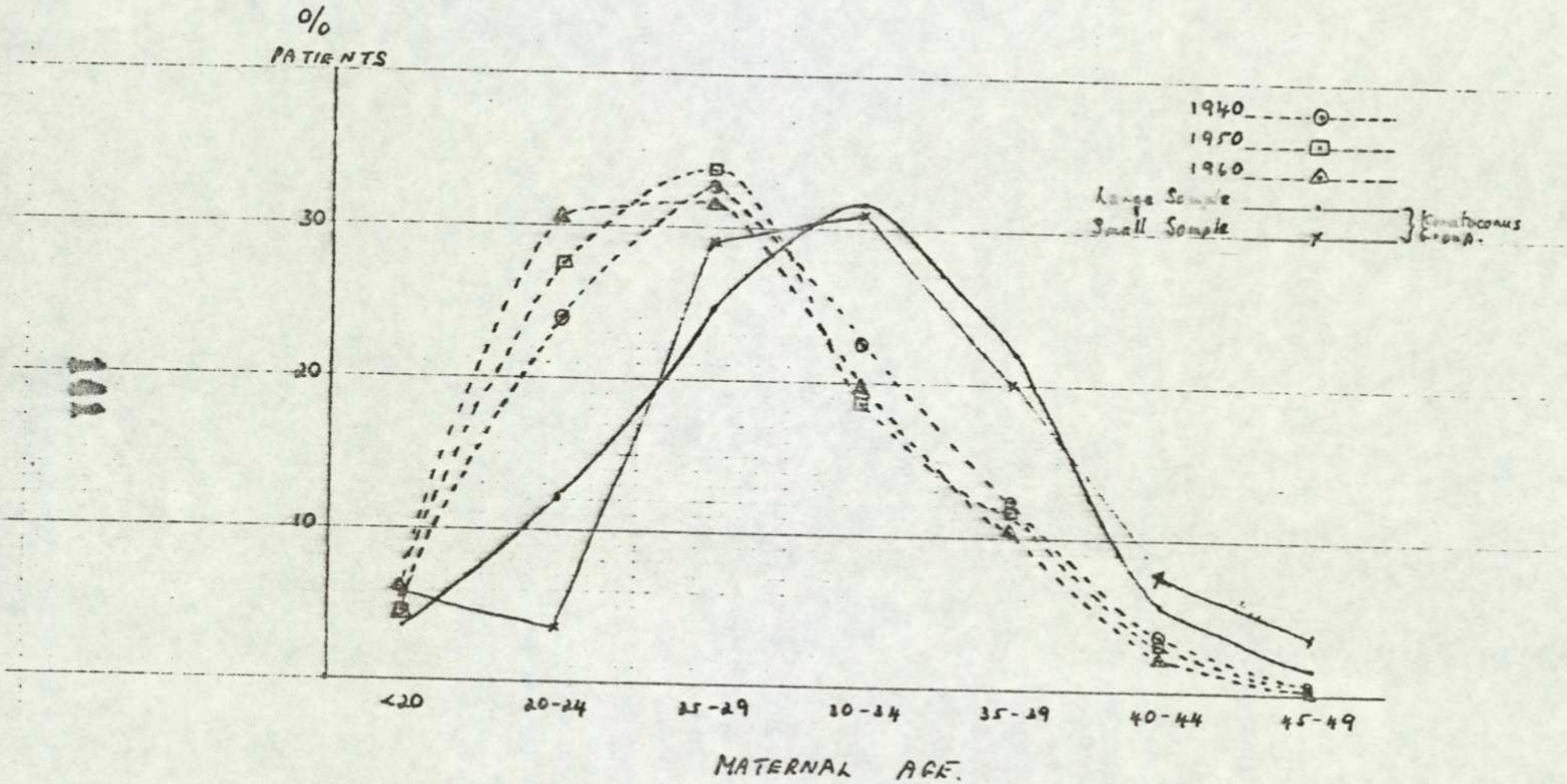
Accumulative Data (%)

Table 7.16

Actual (large sample)			1940		1950		1960	
<20	3.33	3.33	4.48	4.48	4.36	4.36	6.15	6.15
<25	12.00	15.33	23.95	28.43	27.51	31.87	30.60	36.75
<30	24.67	40.00	32.43	60.86	33.57	65.44	31.21	67.96
<35	31.33	71.33	22.63	83.49	18.77	84.21	19.17	87.13
<40	22.00	93.33	12.29	95.78	12.00	96.21	10.32	97.45
<45	5.33	98.66	3.88	99.66	3.54	99.75	2.37	99.82
<50	1.33	99.99	0.33	99.99	0.25	100.00	0.18	100.00

Small sample		
<20	5.45	5.45
<25	3.64	9.09
<30	29.09	38.18
<35	30.91	69.09
<40	20.00	89.09
<45	7.27	96.36
<50	3.64	100

Plot accumulative % against midpoint of age group category (see graph 7.2) or actual % against midpoint (see graph 7.3).


0/0
PATIENTS
30
20
10
1940
1950
1960
Large Sample
Small Sample
Hematocrit
<20
20-24
25-29
30-34
35-39
40-44
45-49
MATERNAL AGE.

GRAPH 4.3

The X^2 test can also be used to compare frequencies for mothers of less then 30 years of age and more than 30 years of age.

Table 7.17

	<30	30 and over		<30	30 and over	Large sample
Number	21	34	55	60	90	150
(%)	(38.18)	(61.82)	(100)	(40%)	(60%)	(100%)
1940 Number Expected	33.47	21.53	55	91.29	58.71	150
(%)	(60.86)	(39.14)	(100)	(60.86)	(39.14)	(100%)
1950 Number Expected	35.99	19.01	55	98.16	51.84	150
(%)	(65.44)	(34.56)	(100)	(65.44)	(34.56)	(100%)
1960 Number Expected	37.38	17.62	55	101.94	48.06	150
(%)	(67.96)	(32.04)	(100)	(67.96)	(32.04)	(100%)

	Small Sample	Large Sample
1940 comparison	$X^2 = 11.86$	$X^2 = 27.40$
1950 comparison	$X^2 = 10.06$	$X^2 = 42.92$
1960 comparison	$X^2 = 22.40$	$X^2 = 53.85$
	All 1 degree of freedom	All significant of $< p$ 0.001

There is therefore no doubt that both samples show a statistically significant excess of older mothers as compared with that expected on the basis of the Registrar General's data. The only reservation that could be made is the possibility that other factors associated with older mothers might influence choice or chance of patients presenting at Moorfields Eye Hospital. This is one reason why it is not possible to present a complete view of the factors influencing the condition and its incidence.

Discussion

As noticed in the introduction to this thesis the association of Down's Syndrome with Keratoconus has been reported by many authors including Hofman (1956), Stucchi and Erpelding (1960) Zajacz (1963) and Cullen and Butler (1963). Like Keratoconus Down's Syndrome has been identified for many years and yet definitive knowledge of the aetiology is far from complete. It is 112 years since Langdon Down identified Mongolism and chromosomes were first incriminated by Waardenberg in 1932. The following year this was related to the fact that Down's Syndrome was frequently associated with births to older women by Jenkins (1933) and Penrose (1933).

Epidemiological and clinical research has demonstrated the increased risk of Down's Syndrome with increasing maternal age, Collman and Stoller (1962) and Mikkelsen and Stene (1970).

However the comparison between Keratoconus and Down's Syndrome cannot be carried too far because if the rate per live birth is plotted against maternal age studies of Down's Syndrome show a monotonically increasing rate with advancing maternal age and at age 49 is as high as 106.76 per 1000 live births, Hook and Lindsjo (1978). Possibly if more adolescents and adults suffering from Down's Syndrome were to be examined for Keratoconus our figures would be modified. It also appears that the incidence to Down's Syndrome amongst very young mothers may be high: for maternal ages 15 years or less the rates seem to be equivalent to those found at 30 - 35, Erikson (1978), there were no maternal ages as low as this in the present study although 3 patients who were asked their mothers age at their birth were adopted and had no exact knowledge but used such descriptions as 'very young', so possibly such a parallel does exist.

The birth of a mongol baby becomes apparent at a fairly early

stage but the development of Keratoconus 15 or 20 years later in the child of an unusually young mother would be much less likely to be recorded.

Other conditions showing this 'U' shaped risk curve with maternal age are Anencephaly, Janerich (1972) and Spina Bifida, Janerich (1973) in both these conditions the lowest incidence is with mothers in the 25 - 29 age group.

Jayasekara and Street (1978) have written on dyslexia and concluded that increased maternal age contributes to a greater incidence of the condition. Table 2 from their paper is reproduced below.

Table 7.18

Maternal age at birth of dyslexic boys.

Dyslexic boys	Maternal Age (years)				
(N = 48)	<20	20 - 24	25 - 29	30 - 34	35+
No affected	0	5	16	17	10
% affected	0	10.42	33.33	35.42	20.83
No expected	3	14.77	14.62	9.23	6.30
% expected	6.26	30.77	19.23	19.23	13.29

As can be seen 56% of the cases had mothers who were over 30 years of age when they were born, this compares well with the 59% found in the Keratoconus study. Although there was a smaller sample the authors from the Department of Human Genetics, University of Newcastle-upon-Tyne concluded that there must be a genetic element in the aetiology.

Many examples can be quoted of maternal age related incidence of conditions. For example the possibility of an association between maternal age and sex chromosomal aneuploidies was suggested by Caruthers et al (1978) by analogy with Down's Syndrome and such an association was found to exist. Penrose and Smith (1966), Lenz et al (1959), Ferguson-Smith et al (1964), Court Brown, Law and Smith (1969) Bargaonkor and Mules (1970) and Tumba (1974) have all reported an increased maternal age at birth for sex chromosomal abnormality as compared with control groups.

In the study of human genetics the age specific risk (or relative frequency) in each age group for a specific condition is often quoted. In this study it would be calculated by dividing the percentage of mothers producing children who eventually develope Keratoconus by the percentage of mothers of this age group in the population as a whole.

If this figure is calculated for the study using the 1950 population figures the results are as follows:-

Table No. 7.19

Maternal Age	Live Births %	Keratoconus Group %	Relative Frequency
20	4.36	3.33	0.76
20 - 24	27.51	12.00	0.44
25 - 29	33.57	24.67	0.73
30 - 34	18.77	31.33	1.67
35 - 39	12.00	22.00	1.83
40 - 44	3.54	5.33	1.51
45	0.25	1.33	5.32

This specific risk distribution is typical of a maternally age related condition such as D.E. and X trisomy or the XXY condition. Lenz, Pfeiffer and Tunte (1967).

As has been discussed in the introduction to this thesis it has long been known that there can be an hereditary occurrence of Keratoconus and classically Franceschetti et al (1958) described concordance of the corneal distortion in Keratoconus occuring in identical twins. In a recent paper Rochels (1979) describes 10 cases of acute Keratoconus in mongols, and considers the aetiology of acute Keratoconus to be chromosomal in all these cases.

However, it is the writers suggestion that the similarity of the findings of maternal age distributions in the present study with all these conditions which are known to be or thought to be due to chromosomal abberations is circumstantial evidence of chromosomal implication in ALL cases of Keratoconus.

The investigation of a possible genetic nature of the condition is rendered very difficult by the probability of the condition presenting as forme fruste in most cases. Some family studies were carried out in the keratoconus clinic but they were limited to keratometry and slit lamp examination, possibly if corneal pachometry had been performed more cases may have been found where the cornea was thinner than usual.

The postulation of a genetic cause for all cases of keratoconus could explain some of the large variations in the reported incidence of the condition, although variations in the standard of diagnosis with socio-economic and ethnic conditions are inevitable.

Nevertheless demographic patterns must have some effect. It is known in Europe that when socio-economic status decreases the fertility

of the youngest maternal age group increases and this is reflected in the incidence of Downs Syndrome, Stene and Stene 1978, Lowry et al 1976. A similar pattern could possibly apply in the case of Keratoconus. Within developed countries which might be expected to have roughly equal standards of ophthalmic disease diagnosis there is considerable variation in child bearing patterns.

Table 7.20

Maternal Age Distribution for all live births during 1962 in various countries. (Source Demographic Yearbook. 15th Edition. New York 1964)

Maternal Age (years)	U.S.A. N = 4167362	CANADA N = 453959	ENGLAND & WALES N = 838736	FRANCE N = 822191	SWEDEN N = 104501	WEST GERMANY N = 994278
< 20	14.6	8.7	8.0	4.6	10.4	4.6
20 - 24	24.7	30.4	31.1	27.4	29.2	31.3
25 - 29	25.1	27.3	30.6	32.7	28.9	32.4
30 - 34	15.3	19.2	18.4	21.3	18.6	18.4
35 - 39	8.0	10.7	9.1	10.6	9.8	10.0
40 - 44	2.2	3.4	2.7	3.2	2.9	3.2
> 45	0.1	0.2	0.2	0.2	0.2	0.1
TOTAL	100	99.9	100.1	100	100	100

As can be seen, in 1962 of the live births in the U.S.A. 25.6% were to women over 30 whereas in France the figure was 35.3%. If Keratoconus isof chromosomal origin the incidence of the disease must be related to these factors. Another contributory factor may be consangunity, in discussion with Norwegian ophthalmologists the writer has been told there is a high incidence of Keratoconus in the Lofoten islands where there are extremely isolated fishing communities where marriage of cousins is a common occurrence

However bearing in mind Galton's strictures on the acceptance of general impressions as unquestionable tenets, speculation must not be carried too far. Suffice it to say that although the relatively low incidence of keratoconus in the general population makes genetic investigation very difficult the inference is that all Keratoconus is chromosomally determined through inheritance or mutation. It is of course possible that the genetic mechanism may act synergistically with another mechanism such as allergy which may itself be independently chromosomally determined. Although outside the scope of this thesis further investigation into the family history of this group of patients would be rewarding. Several of the index cases had known positive family histories including two pairs of siblings and in these a more detailed genetic investigation would seem justified.

References

BARGAONKOR D.S. and MULES E. (1970) — J Med. Genet. 7. 345 - 350

CARUTHERS A.D. COLLYER S. DE MEY R. & FRACKIEWICZ A. (1978) — Parental Age and birth order in the aetiology of some sex chromosome aneuploidies

COLLMAN R.D. & STOLLER A. (1962) — A survey of mongoloid births in Victoria, Australia, 1942 - 1957. American Journal of Public Health 52, 813 - 829.

COURT-BROWN W.M. LOW P. and SMITH P.G. (1969) — 'Sex chromosome aneuploidy and parental age' Ann. Hum. Genet. 33. 1 - 14

CULLEN J.F. & BUTLER H.J. (1963) — "Mongolism (Downs Syndrome) and Keratoconus" Brit. J. Ophthal 47.6 321 - 330

ERIKSON A.J. (1978) — 'Down Syndrome, paternal age, maternal age and birth order' Ann. Hum. Genet. 41,289

FERGUSON-SMITH M.A. MACK W.S. ELLIS P.M. DICKSON M. SANGER R. and RACE R.R. (1946) — Lancet (i) 46

FRANCESCHETTIA, LISCH and KLEIN — Klin Mbl. Augenheilk 133,15.

HOFMAN (1956) — 'Klin. Mbl. Augenheilk 129,756

HOOK E.B. & LINDSJO A. (1978) — Downs Syndrome in live births by single year maternal age interval in a Swedish study. Am. J. Hum Genet 30: 19 - 27

JANERICH D.T. (1972) — 'Anencephaly and maternal age' Am. J. Epidemiol 95 (4) : 319 - 326

'Maternal age and spina bifida' Am. J. Epidemiol 96 (6) 389 - 395

JAYASEKARA R. & STREET. J. (1978) — 'Parental Age and Parity in Dyslexic Boys' J. biosoc Sci 10, 255 - 261

JENKINS R.L.
(1933)
'Etiology of Mongolism'
American Journal of Disturbed
Children 45, 506 - 519

LENZ W. NOWAKOWSKI H.
PRADER A. and SCHIRREN C.
(1959)
Schweiz. Med. Wachschr.
89. 727 - 731

LENZ W. PFEIFFER R.A.
& TUNTE W.
(1967)
Ger. Med. Mon
12 (1) 27 - 30

LOWRY R.B. JONES D.C.
RENWICK D.H.G. and
TRIMBLE B.K.
(1976)
Teratology
24 29 - 34

MIKKELSEN M. &
STENE J.
(1970)
Genetic counselling in Downs Syndrome
Human Heredity 20 457 - 464

PENROSE L.S.
(1933)
"The relative effect of paternal and
maternal age in mongolism"
Journal of Genetics 27, 219 - 224

PENROSE L.S. &
SMITH G.F.
(1966)
"Downs Anomaly"
London

ROCHELS R.
(1979)
Graefes Archiv. Oph.
212 (2) 117 - 129

STENE J. &
STENE E.
(1978)
Ann. Hum. Genet
41, 465 - 468

STUCCHI & ERPELDING
(1966)
'Confin. neurol. 20, 376

TUMBA A.
(1974)
J. Genet. Hum. (22) 1 73 - 97

WAARDENBERG P.F.
(1932)
"Das Menschlicke Auge und Seine
Erbanlangen"
Martinus Nighoff. Haag.

ZAJACZ
(1963)
Kiln. Mbl. Augenheilk 143, 503.

B. EDUCATION

Educational Attainments of Patients in the Study

After a considerable number of years fitting patients suffering from Keratoconus with contact lenses the writer had formed the impression that their educational attainments were well above those of the general population.

It was thus decided to include in the information recorded the extent of the patients' education to see if this impression was based on fact or was a false one.

As a basis for comparison the "Report of the Ministry of Education and statistics of Public Education for England and Wales" was consulted. These reports made yearly are available at the Department of Education and Science Library, Elizabeth House, York Road, Waterloo. The method of presenting statistics has varied over the years, but for every year there is a breakdown of children leaving school to either higher education or paid employment. So it was decided to use this rather basic differentiation because it had remained unchanged over the period in which the writer was interested. If, for example, it had been attempted to break it down further into technical colleges, polytechnics and universities anomalies would have arisen because during the period concerned some polytechnics became first, colleges of advanced technology and finally universities. It was thus felt that the simple breakdown would give the most reliable analysis, particularly as the minimum school leaving age was raised to 15 in 1947 and 16 in 1972 which also distorted the figures to some degree.

It was appreciated that even this analysis was not as straightforward as would first appear. The oldest patient in the study was born in 1935 and the youngest in 1962. During this 27 years significant social changes had ocurred which had to be taken into account.

The oldest patient in the study left school in 1953 and several were still at school at the commencement of the study. For this group a prediction was made on the basis of the examination they were preparing to take.

The data from the Ministry of Education was analysed for every year from 1953 unti the latest information available (1976 at the time of writing) and the following figures obtained.

Table 7.21.

Children Leaving School

	To Higher Education	To Paid Employment, etc.
1953	31,260	454,947
1954	32,971	475,096
1955	35,619	440,443
1956	38,988	414,025
1957	43,339	445,368
1958	48,659	472,480
1959	56,973	497,466
1960	49,934	526,051
1961	60,540	535,740
1962	61,360	576,440
1963	60,840	552,180
1964	59,280	529,280
1965	57,420	508,230
1966	61,680	475,200
1967	63,470	478,630
1968	69,610	486,620
1969	62,940	482,130
1970	61,550	476,660
1971	63,500	443,240
1972	67,800	446,360
1973	66,700	469,240
1974	89,030	542,430
1975	88,670	546,280
1976	96,240	581,120

As can be seen there is a steady increase in the number of school leavers to higher education both in absolute numbers and as a percentage of total leavers. These figures were then compared with the Keratoconus sample.

Keratoconus Sample.	Number proceeding to full time		
	Higher Education	33	60%
	Employment	22	40%

Table 7.22.

Report of the Minister of Education and Statistics of Public Education for England and Wales.

School Leavers

Year	To full time H.E.		To Paid Employment	Total
1953	31,260	(6.36%)	459,947	491,207
1958	48,659	(9.34%)	472,480	521,139
1963	60,840	(9.92%)	552,180	613,020
1968	69,610	(12.5%)	486,620	556,230
1973	66,700	(12.45%)	469,240	535,940
1976 (latest figures available)	96,240	(14.21%)	581,120	677,360

The years covered included the school leaving years of 46 out of the 55 patients in the study.

Comment

In view of the social class the patients in the study these results are not surprising. They do seem to confirm the impression that the writer and other clinicians had formed concerning keratoconus patients. This higher educational attainment might possibly explain the reputation that Keratoconus patients have gained amongst contact lens practitioners, nursing staff and reception clerks for being somewhat awkward and pernickerty patients. Compared with the typical ophthalmic patient they are much more articulate, younger and more willing to voice their doubts and fears concerning the management of their condition. **However too much reliance must not be placed on anecdotal material.**

French ophthalmologists in discussion often describe Keratoconus patients as typically being aesthetes, but there seemed no valid scientific method of confirming this. Standards of taste, discrimination and sophistication being notoriously subjective and not amenable to objective assessment.

RESULTS OF PARAMETRIC CHANGES OVER TRIAL PERIOD

I have no faith in anything except actual measurements and the Rule of Three.

Charles Darwin
(Life and Letters Vol. II p.51).

The results of anterior chamber depth measurements.

A.

Initial measurements of anterior chamber depth were taken on 110 eyes, second measurements on 104 eyes, third measurements on 100 and fourth measurements on 100 eyes also. These measurements were taken over a period spanning two years. The results obtained are given in Appendix 2 and plotted on graph 8(A) 1 and 2.

The mean and standard deviation for each visit was as follows:-

Table 8.1

	1	2	3	4
Mean	3.08	3.18	3.20	3.22
Standard Deviation	0.33	0.33	0.34	0.36

Depth at initial visit

It is interesting to compare the figure for the first visit with other workers on normal eyes Tornquist (1953) obtained:

Table 8.2

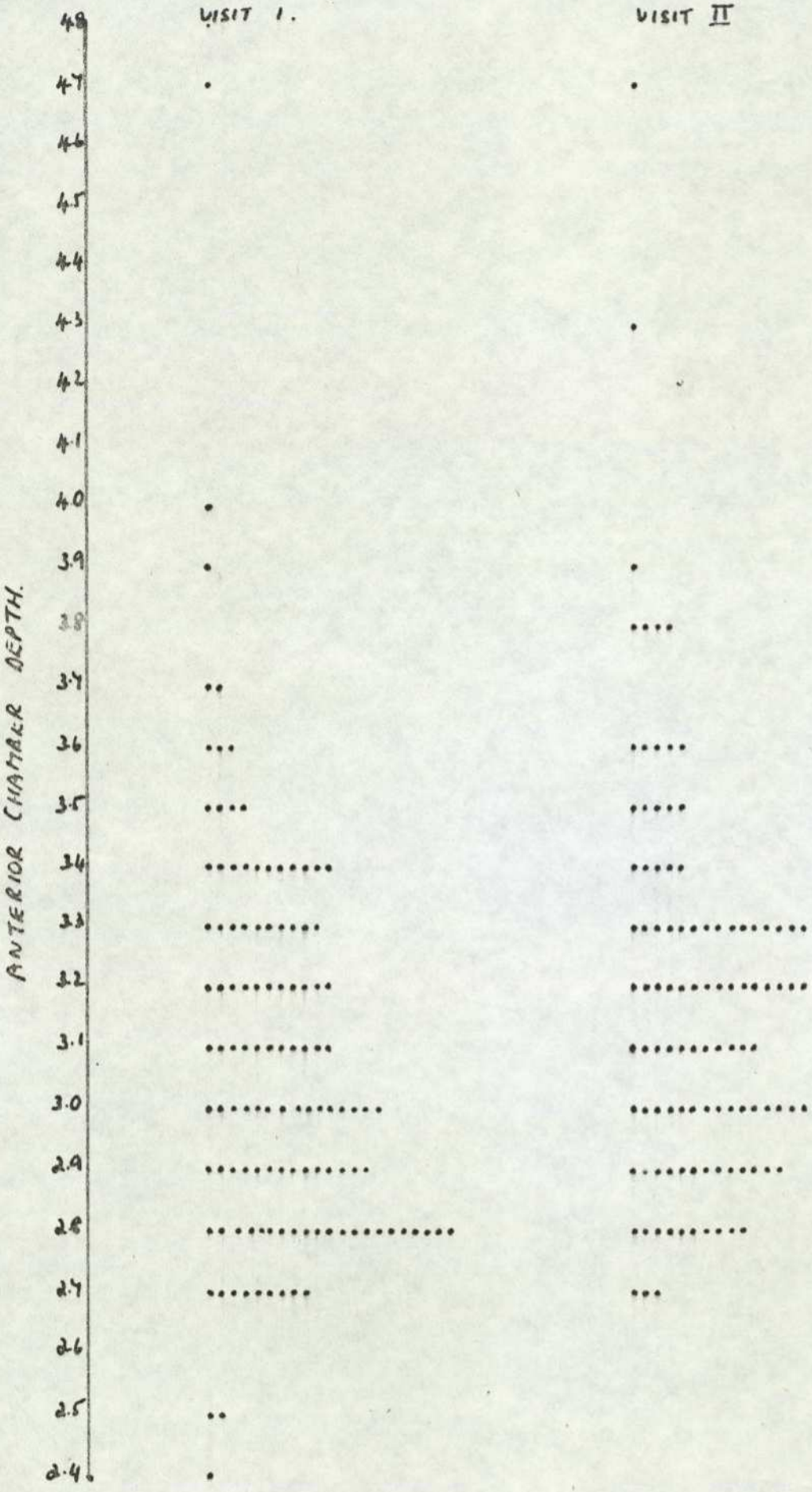
Age	19 - 21 years		34 - 36 years	
	Male	Female	Male	Female
Number	50	50	50	50
Mean	3.18	3.10	2.98	2.86
Standard Deviation	0.31	0.37	0.33	0.30

Stenstrom (1946) investigating material of 1000 patients between the ages of 20 - 35 found the average value to be 3.70 mm for males and 3.65 mm for females. Stenstroms method included the thickness of the cornea so the comparable values for the mean on the normal eyes would be of the order of 3.18 for males and 3.13 for females.

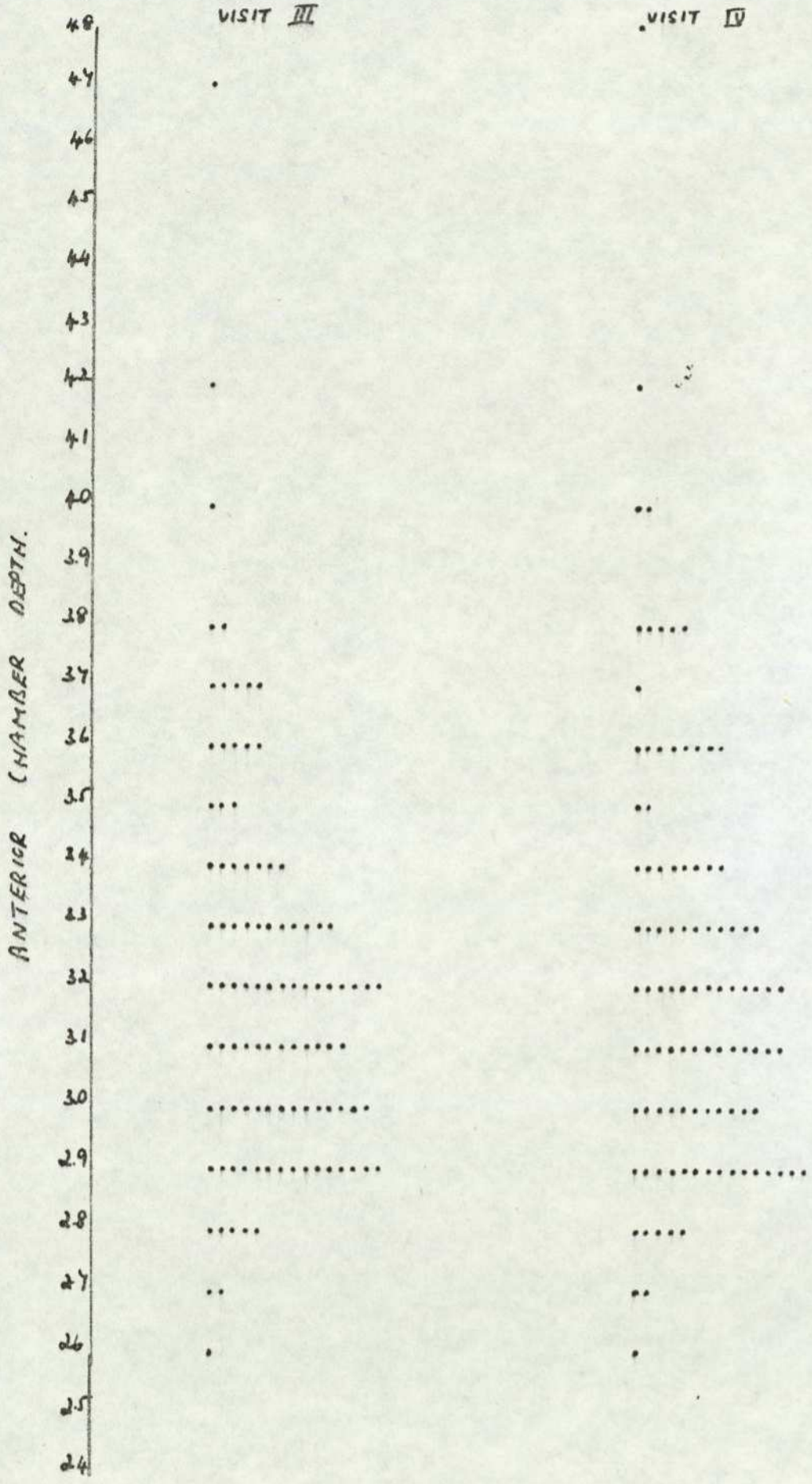
Rosengren (1931) investigated 810 eyes and at the age of 25 years the average value was 3.61 again allowing for corneal thickness the mean would be 3.09. The values of the standard deviation obtained were 0.31 (Rosengern) and 0.29 (Stenstrom). Thus agreement for this value was apparent with the three workers and with the writers results.

All three writers found a normal distribution of the anterior chamber depth. Graph 8A1 shows the distribution of anterior chamber depth at the first visit in the present study and if consideration is given to the fact that a fifth of the sample had Keratoconus diagnosed more than 2 years previously a distribution that is only slightly skewed can be seen.

GRAPH 8(A) I.


VISIT I.
VISIT II
ANTERIOR CHAMBER DEPTH.
4.8
4.7
4.6
4.5
4.4
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4

GRAPH 8 (A) 2.


VISIT III
VISIT IV
ANTERIOR CHAMBER DEPTH.
48
47
46
45
44
43
42
41
40
39
38
37
36
35
34
33
32
31
30
29
28
27
26
25
24

Weekers et al (1973) studied 2395 eyes and gave a breakdown of anterior chamber depth as a function of age and refraction as follows:

Table 8.3

	Number of Eyes	Age 16 - 20	21 - 40
Hypermetropia	725	2.98	2.87
Emmetropia	1149	3.26	3.04
Myopia	521	3.40	3.39
All	2395	3.22	3.10

This is the largest patient sample of which the writer is aware and the results obtained accord well with other workers who have investigated anterior chamber depth as a function of age and refraction such as Calmette, Deodati, Huron and Bechac (1958).

If these results of other workers are compared with the present study where the mean age was 24.45 years it can be said that the anterior chamber depths of the Keratoconic eyes at the first visit had the same distribution as those found with normal eyes. Again bearing in mind that the patients were not all newly diagnosed it must be some years after the onset of the disease that corneal ectasia is sufficient to produce a measurable increase in anterior chamber depth.

Furthermore the idea of a Keratoconus posticus occuring as a precursor of distortion appearing on the anterior corneal surface is not supported by any of the results in this study.

Keratoconus posticus is thought to be due to a disturbance of the corneal endothelium or Descemets membrance at an early stage due to prenatal, natal or neonatal trauma or inflamation, involving a failure in the formation or an absorption of the deeper corneal lamellae, Jacobs (1957). Other cases of Keratoconus posticus have been ascribed to trauma shortly after birth (Stallard 1930, Butler 1932) and later in life by Walter and Haney (1963). The rare condition of Keratoglobus where the whole cornea is steeper but still spherical in contour is a primary degeneration of the cornea, Ruben (1975).

Therefore although Keratoconus is described as a primary Kerectasia the ectasia occurs sometime after corneal thinning and is not usually present in the earlier stage of the condition to a measurable degree. This means that such diagnostic signs as "Munsons" only appear when the condition has been present for some time and Keratometry and pachometry are much more important in diagnosing the condition in its early stages.

Changes in chamber depth in the patients studied.

As can be seen the anterior chamber depth of the group increased during the study which is as would be expected. To analyse this further the chamber depth of groups of eyes according to Keratometry was compared at the first and last visit. The Keratometry value taken was that of the steeper meridian.

Table No. 8.4

Visit I

	Keratometry	Anterior Chamber depth Number of Eyes	Mean	S.D.
1.	> 7.50	23	2.91	0.21
2.	7.00 - 7.49	28	3.06	0.27
3.	6.50 - 6.99	28	3.02	0.24
4.	6.00 - 6.49	13	3.21	0.33
5.	5.50 - 5.99	14	3.34	0.56
6.	< 5.49	4	3.30	0.09
		110		

As can be seen anterior chamber depth increases with a steepening cornea which is quite predictable. Group 6 with only 4 eyes in it is of doubtful significance.

Table No. 8.5

Visit IV

	Keratometry	Anterior Chamber depth Number of Eyes	Mean	S.D.
1.	> 7.50	15	2.96	0.22
2.	7.00 - 7.49	29	3.09	0.18
3.	6.50 - 6.99	21	3.26	0.33
4.	6.00 - 6.49	18	3.32	0.34
5.	5.50 - 5.99	8	3.56	0.62
6.	< 5.49	8	3.56	0.28
		99		

(the grafted eye has been excluded from this analysis)

Comparing this with the previous table two points emerge. Firstly, again as anticipated chamber depth increases with steepening corneae but now the difference between the mean of the flatter corneae and that of the steeper group is 0.60 mm compared with 0.39 at the first visit. The difference of 0.21 is almost certainly accounted for by corneal thinning. For every group the anterior chamber depth was greater at

the fourth visit compared with the first visit even in groups of comparable corneal radii. This means that corneal thinning does occur without necessarily showing corneal anterior surface curvature changes and this is confirmed by results given in later chapters.

However too much cannot be inferred from this because of the unknowns introduced by many of the patients having worn contact lenses. As stated earlier ideally all patients would not have worn lenses for at least 48 hours prior to measurement but many of the patients in the study could not have lead their normal lives without wearing their contact lenses so this approach was impracticable.

Because of these unknowns it was decided to analyse separately the 10 patients who were not wearing contact lenses at the end of the study. These comprised two groups of five.

Group I patient wearing spectacles at the end of the study.

Table 8.6

	Visit I		Visit IV	
	R.	L.	R.	L.
1	3.26	3.12	3.29	3.39
2	2.80	3.00	3.05	3.02
3	2.89	2.95	2.91	2.86
4	2.95	3.19	2.90	3.13
5	2.84	2.90	2.84	2.90
	Mean 2.99		Mean 3.04	
	S.D. 0.15		S.D. 0.21	

As can be seen the mean chamber depth at the last visit was less than that for the whole group at the same visit. The increase in chamber depth during the study was 0.05 mm as against 0.14 for the whole group. As the systematic error of the method on normal eyes is in the region of $\pm$0.03 mm one can say that there was no significant increase in anterior chamber depth in the group wearing spectacles at the end of the study. However there was an increase in the standard deviation so the group was becoming less coherent. Even so the standard deviation at both first and last visits was lower than for the whole sample.

These results are not surprising in that one would expect eyes which retained an acceptable level of visual acuity to be relatively dimensionally stable.

Group II patients wearing no optical correction at end of study.

Table 8.7

	Visit 1		Visit IV		
	R.	L.	R.	L.	
1	2.82	2.88	3.03	3.10	
2	2.86	3.25	3.30	3.17	
3	3.47	3.65	3.64	3.33	(Graft excluded)
4	2.74	2.88	2.80	3.03	
5	3.20	3.07	4.00	3.32	
	Mean 3.08		Mean 3.27		
	S.D. 0.30		S.D. 0.36		

In this group the means and standard deviations at both first and last visits corresponded closely with the sample as a whole. The explanation of this is probably that, as stated in the section dealing with the patient sample, the patients were people who had a marked difference in the severity of the condition in the two eyes.

The group who were successfully wearing spectacles had more equal anterior chamber depths than the patients in Group II. One could hypothesize that this gave them less difference in retinal image size and hence a better chance of tolerating a spectacle correction. But investigation of this is outside the scope of this study.

References Anterior Chamber

BUTLER (1932) — Brit. J. Ophthal 16.30

CALMETTES, DEODATI, HURON and BECHAC (1958) — Archives Opthalmologie 18 : 514 - 542

JACOBS M.G. (1957) — Brit. J. Ophthal 41.31

ROSENGREN B. (1931) — Acta Ophthalmologic (Kbh) 9,103

RUBEN C.M. (1975) — "Contact Lense Practice" Bailliere Tindall London p.278

STALLARD (1930) — Trans. ophthal Soc. U.K. 50,566

STENSTROM S. (1946) — Untersuchungen uber die Varcation und Kovarcation der optischen Elemente des monschliohen Auges. Acta Ophthalmologic (Kbh) Suppl XXVI

TORNQUIST R. (1953) — Acta Ophthalmologic (Kbh) Supp. XXXIX p.42

WEEKER R. DELMARSELLE Y. COLLIGNON J. and LUYCKC J. (1973) — Documenta Opthalmologica 34 : 413 - 434

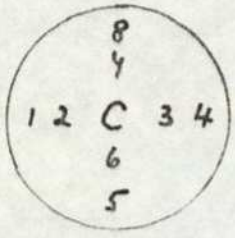
WOLTER & HANEY (1963) — Arch. Ophthal (Chicago) 69,357

The Results of Corneal Thickness Measurements.

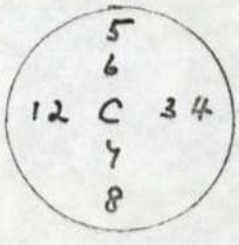
B.

As described in the section on Instrumentation it was possible to measure the thickness of the cornea of the subjects at nine different points at each visit.

The L.E.D. positions were numbered in the following manner:



This meant that measurements were taken in the following positions when the patient fixated the L.E.D.s



As can be seen for the right eye, positions 3 and 4 would be nasal and for the left positions 1 and 2. The mid peripheral measurements would always be at positions 2,3,6 and 7, 8 would always be inferior and 5 superior.

A discussion as to the position of the measurement points on the cornea can be found in the instrumentation section.

Patients were seen four times over a two year period. 50 patients attended on all four occasions and full results were obtained on 50 right eyes; as one patient in the study underwent a left keratoplasty during the two year period full results were only obtained on 49 left eyes. These results are given in Appendix 3.

As Keratometry was taken at each visit the patients were classified in Keratometry groups as in the anterior chamber depth study i.e. Table 8.8

Group	Steeper Meridian
1	> 7.50
2	7.00 - 7.49
3	6.50 - 6.99
4	6.00 - 6.49
5	5.50 - 5.99
6	< 5.49

The keratometry group at the initial and final visits are also given in Appendix 4 as are the age of the patient at diagnosis and at first visit.

The 99 eyes on which a complete set of corneal thickness measurements had been taken over the two year period were then split into three groups for statistical analysis.

Group 1. Considered to have a significant thinning i.e. 0.04 mm or more.

Group 11. No significant change i.e. less than 0.04mm.

Group 111. Significant thickening i.e. 0.04 mm or more.

With this classification the number in the groups were as follows:

1	Significant thinning	47
11	No significant change	45
111	Significant thickening	7
		99

The basis for choosing the figure of 0.04 mm was as follows. The tolerances for measurement of corneal thickness by the modified Haag-Streit pachometer are $\pm$ 0.01, but as a considerable number of patients had been wearing contact lenses variations due to post wear oedema could not be discounted, an allowance $\pm$ 0.03 mm corresponds to approximately 7% on a keratoconic cornea. Typical figures for the greatest contact lens induced changes for steeply fitted hard corneal lenses are of this order (see Chapter on corneal thickness changes).

As corneal lenses fitted for keratoconus could hardly ever be described as steeply fitting it was felt that 0.04 mm was a suitably conservative figure constituting significant change.

The best visual acuity obtainable at each visit was also recorded and is given in Appendices No. 5 and 6 according to whether or not a

contact lens had been worn in the eye at that visit. The keratometry group at each visit is also given in the appendix 4.

The results obtained were analysed for the following correlations.

1. Age of diagnosis/Corneal thinning over trial period.
2. Years since diagnosis/Corneal thinning.
3. Rate of change centre/Rate of change periphery.
4. Central thickness/Keratometry group initial and final visit.
5. Rate of change centre/Keratometry group.
6. Rate of change/Measurement position.
7. Visual acuity/thinnest corneal position a) wearing contact lenses.
   b) not wearing contact lenses.

Statistical Analysis

Age of diagnosis versus corneal thinning over trial period

This was investigated in two ways, firstly by comparing the three groups described earlier with age of diagnosis.

Group 1 = Significant thinning

Group 11 = No significant change

Group 111 = Significant thickening

Table 8.9

Distribution of age of diagnois with group

(taking worse eye to classify patients group)

	1		11		111		Total	Overall
Age group	N	(%)	N	(%)	N	(%)	N	(%)
< 15 years	3	(21%)	5	(16%)	1	(20%)	9	(18%)
16 to 20 years	4	(29%)	12	(39%)	1	(20%)	16	(32%)
21 to 25 years	2	(14%)	6	(19%)	1	(20%)	10	(20%)
26 to 30 years	3	(21%)	4	(13%)	2	(40%)	9	(18%)
31 to 35 years	0		2	(6%)			2	(4%)
36 to 40 years	2	(14%)	1	(3%)			3	(6%)
41 to 45 years	0		1	(3%)			1	(2%)
Total	14		31		5		50	100

There was no correlation found between age of diagnosis and centre thinning over trial period.

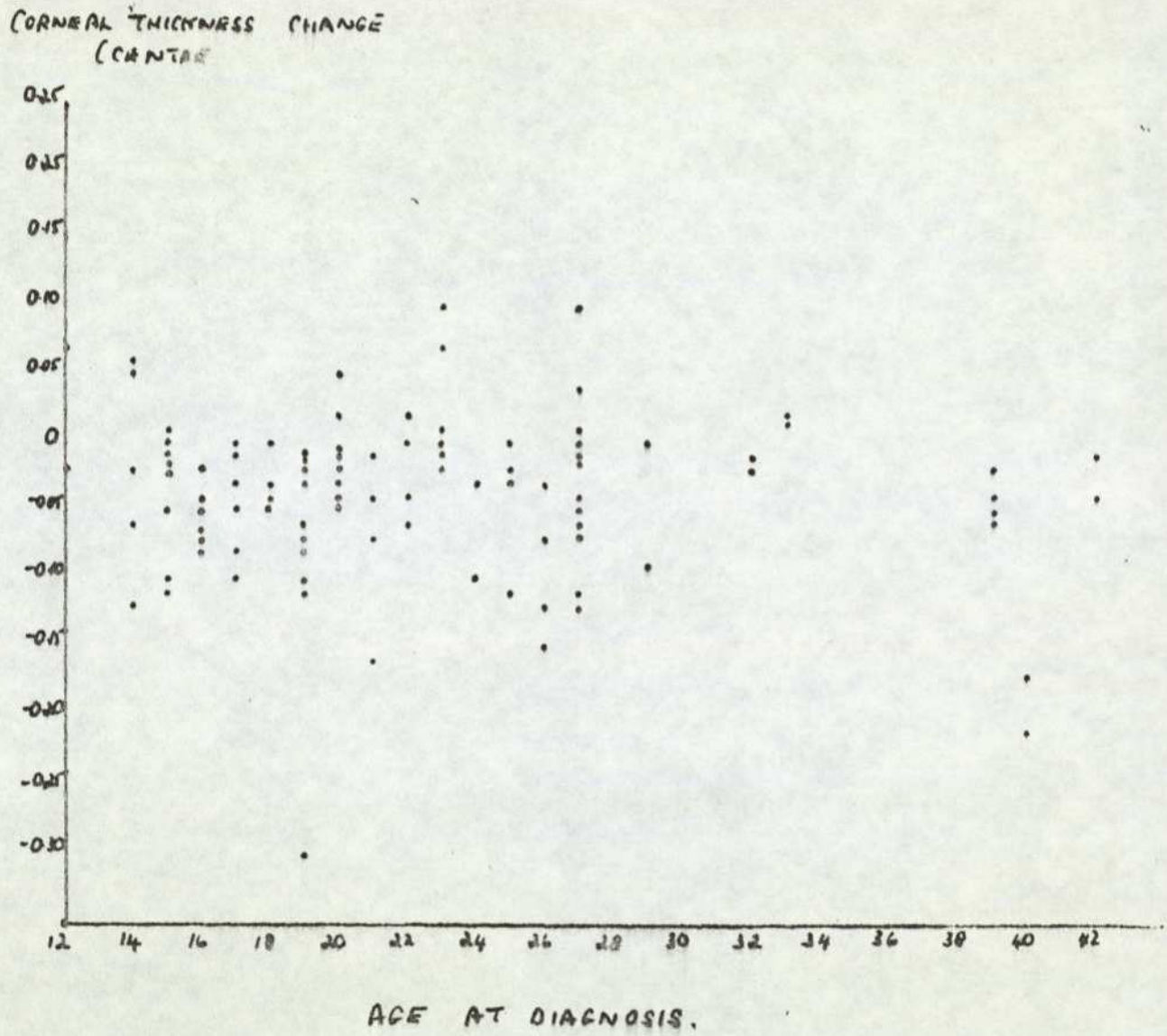
Instead of using the three groups, absolute measurements of central corneal thinning were then plotted against age of diagnosis and again no correlation could be found. See Graph No. 8.1.

Lower values for corneal thinning were found for the older patients but there were insufficient older patients to explore any correlation with age of diagnosis and change in corneal thickness over a wide age group.

The majority of the patients were diagnosed between the ages of 12 and 28, here all that can be said is, that there is possibly a thinning peak at approximately 20 years.

It would perhaps be surprising if a definite correlation were found because fundamentally we are comparing different stages of the disease for different patients. Even if all the patients were seen immediately they were diagnosed it would by no means signify that measurement had started at the onset of the disease.

GRAPH. 8.1.


CORNEAL THICKNESS CHANGE
(CENTRE
0.25
0.20
0.15
0.10
0.05
0
-0.05
-0.10
-0.15
-0.20
-0.25
-0.30
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
AGE AT DIAGNOSIS.

Years since diagnosis at start of trial versus corneal thinning

In this analysis patients were placed in to five groups on the basis of time elapsing between diagnosis and the first measurements.

The groups were:

1. More than 4 years
2. 3 and 4 years
3. 2 years
4. 1 year
5. the same year

For full breakdown see Appendix 7.

Table 8.10

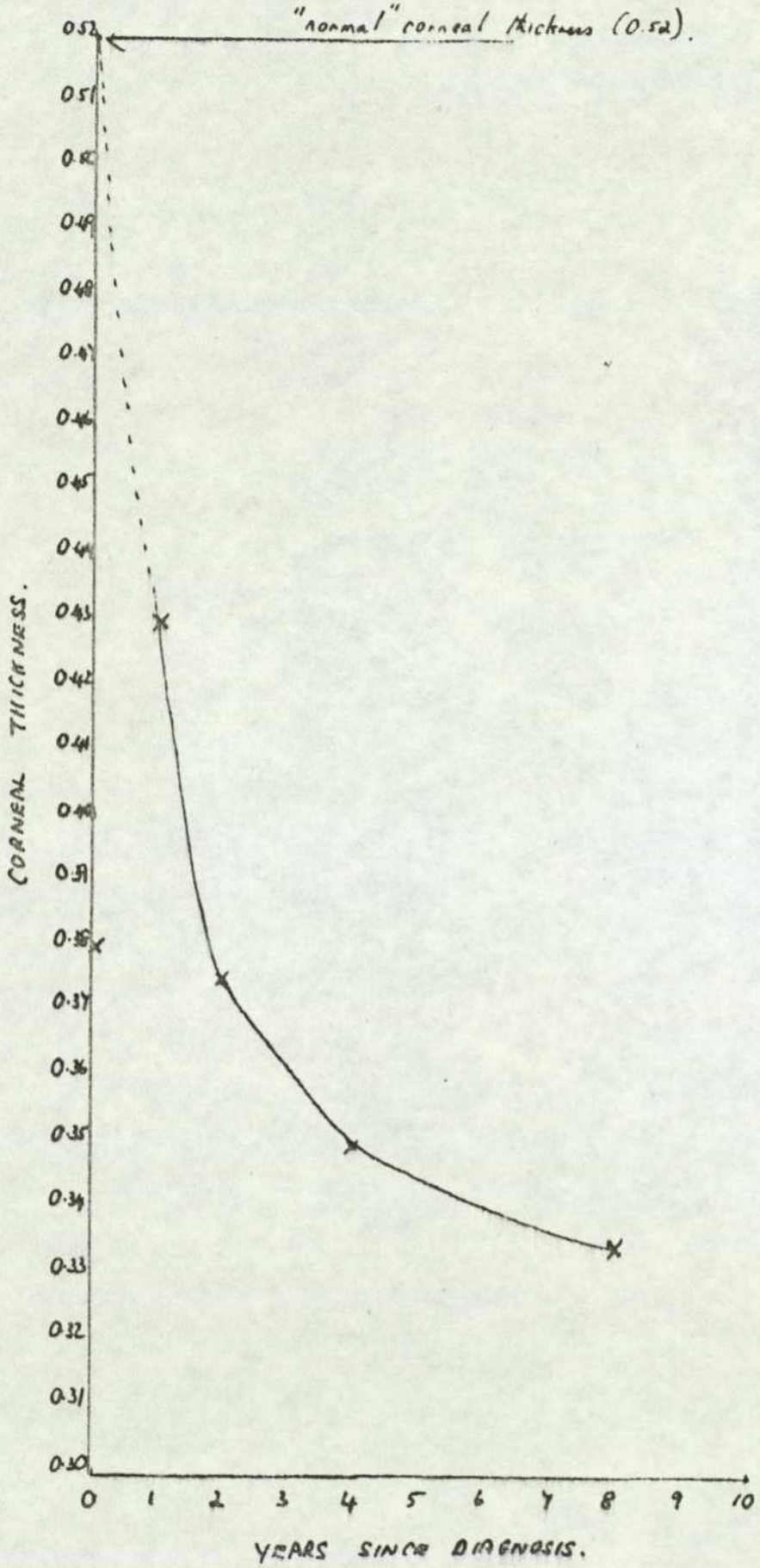
		Corneal Thickness (thinnest)			
Elapsed Time	Number of Patients	Mean	Median	Min.	Max.
4 years	6	0.32	0.32,0.34	0.17	0.45
3 and 4 years	6	0.360	0.35	0.26	0.50
2 years	8	0.366	0.37,0.38	0.29	0.45
1 year	10	0.416	0.43	0.35	0.51
1 year	19	0.376	0.38	0.30	0.51

The median corneal thickness was then plotted against years since diagnosis (Graph No. 8.2).

As can be seen a curve is obtained with regression towards the normal corneal thickness of 0.52 at year 0 with the exception of the first plot.

The explanation of this must again lie in the variation of the age of diagnosis as against the age of onset. It can be seen that in the two groups that had been diagnosed for the least period of time the maximum thickness was 0.51 mm in both groups whereas the minimum thickness was 0.30 for the group diagnosed the same year, as against 0.35 for the group diagnosed for one year. This would suggest that in the newly diagnosed group there was a significant number of cases where the disease was fairly advanced and hence the off curve plot was obtained. However, as the disease progresses the difference between the age of onset and age of diagnosis becomes less significant and a smooth curve is obtained.

GRAPH 8.2.


"normal" corneal thickness (0.52).
0.52
0.51
0.50
0.49
0.48
0.47
0.46
0.45
0.44
0.43
0.42
0.41
0.40
0.39
0.38
0.37
0.36
0.35
0.34
0.33
0.32
0.31
0.30
CORNEAL THICKNESS.
0 1 2 3 4 5 6 7 8 9 10
YEARS SINCE DIAGNOSIS.

Rate of change centre cornea/Rate of change peripheral cornea

The thinning at the centre of the cornea was plotted against thinning at the periphery of the cornea using the point of maximum thinning at the periphery see Graph 8.3.

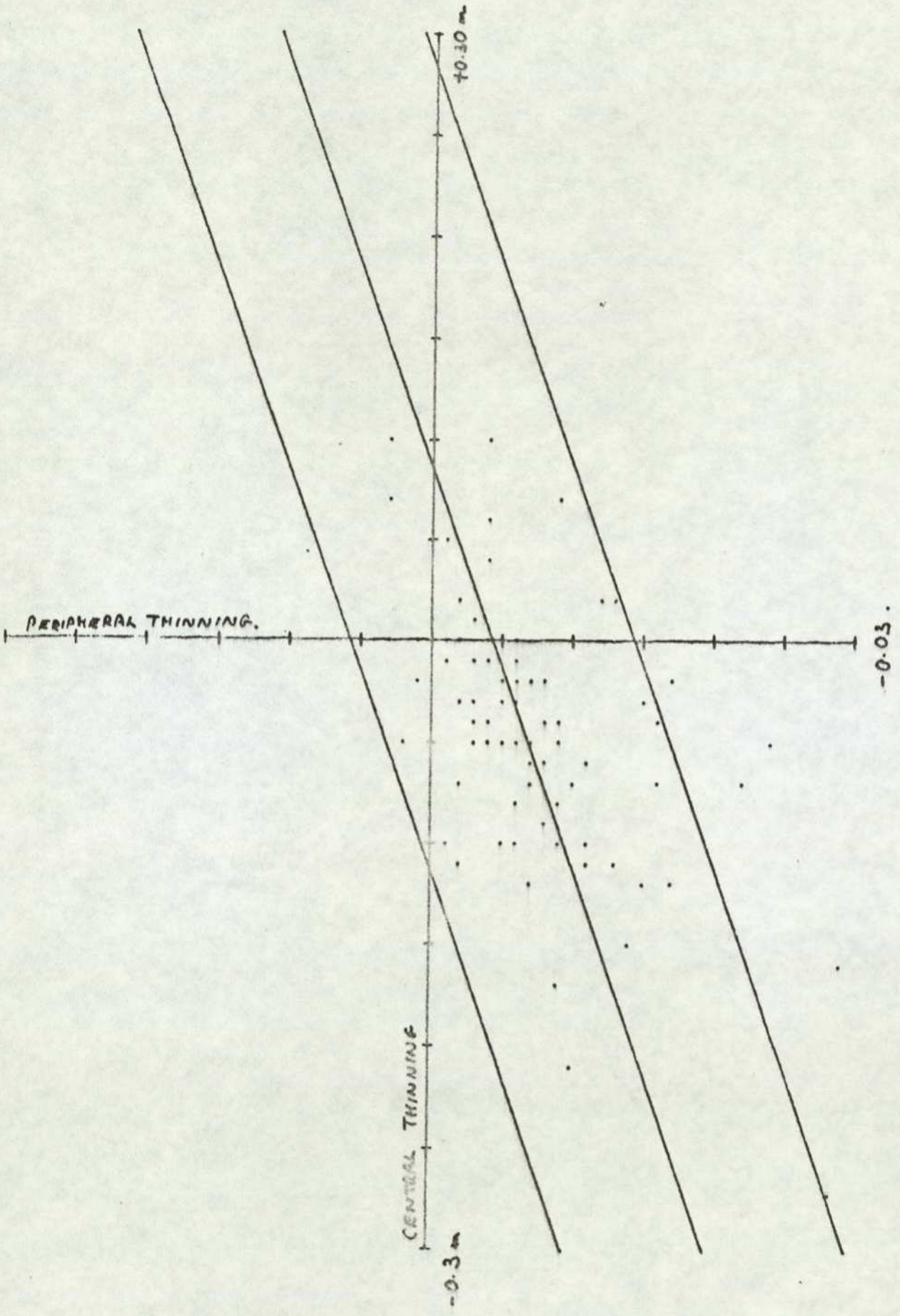
Table 8.11

A significant correlation was found as follows:

Slope	=	0.508 691
Intercept	=	-0.043 070
Correlation co-efficient	=	0.479 510
Probability	=	0.001
Degree of freedom	=	97
Confidence limits		$\pm$0.1007 74

This indicates that at its thinnest position the peripheral cornea is thinning at approximately half the rate of the central cornea over the period of measurement. (i.e. slope = 0.50). However this assumes that the two zones started thinning at the same time, as we are dealing with a specific period of time it could be that the periphery started thinning later than the centre.

GRAPH. B.3.



Central corneal thickness/Keratometry group

The central corneal thicknesses found were plotted against the Keratometry groups for both the initial and final visits (Graphs 8.4 8.5).

Again a significant correlation was found.

Table 8.12

Initial visit:	Slope	=	- 13.5221
	Intercept	=	8.284
	Correlation co-efficient	=	- 0.5943
	Degree of freedom	=	96

Table 8.13

Final visit:	Slope	=	- 8.7045
	Intercept	=	6.5242
	Correlation co-efficient	=	- 0.4606
	Degree of freedom	=	98

It is of course known clinically that thinning of the cornea accompanies steepening. It can be seen that the correlation was greater at the first visit than the final visit. This is almost certainly because by the final visit a large number of patients had been wearing contact lenses which had produced some degree of corneal flattening for sometime after wear.

GRAPH 9.4.

KERATOMETRY GROUP

0 I II III IV

0.00 .10 .20 .30 .40 .50 .60

CENTRAL THICKNESS. VISIT 1

GRAPH 8.5.
CORNEAL THICKNESS (FINAL VISIT)
.00
.10
.20
.30
.40
.50
.60
0
1
2
3
4
5
TONOMETRY GROUP

Rate of thinning at Centre/Change in Keratometry Group

Data was analysed in two ways, firstly by plotting central corneal thickness changes over the trial period against change in keratometry group. See graph 8.6.

No significant correlation was found (c.c. = -0.118).

The final Keratometry group was then plotted against corneal thickness changes over the trial period and again no significant correlation was found. See graph 8.7.

The interpretation of this is that over the trial period a steeper cornea was no more likely to thin than a less steep one or vice versa. Although the previous analysis has shown that there is a general relationship between corneal thickness and keratometry (the thinner the steeper) the rates of change of the two were not related at least over the period of trial. Here again the effect of wearing contact lenses is almost certainly significant. Were it possible to use a group not wearing lenses a relationship might have been found.

.18
.16
.14
.12
.10
.08
.06
.04
.02
.00
-.02
-.04
-.06
-.08
-.10
-.12
-.14
-.16
-.18
CORNEAL THICKNESS
-3
-2
-1
0
1
2
KERATOMETRY GROUP

GRAPH 8.6.

KERATOMETRY GROUP (FINAL VISIT).

GRAPH 8.4

Rates of change/Position on Cornea.

The advice of a statistician was that in this kind of analysis the danger of bias due to the odd extreme result could be reduced by using non parametric analytical techniques. It is the impression of the writer that in keratoconus areas of localised transient corneal oedema do occur particularly when contact lenses are worn, this could give the odd extreme result hence a non parametric method was used initially. The parametric method of calculating mean corneal thinning was also used and this gave the same order of thinning for the right eyes but a slightly different order for the left eyes (see graphs 8.8, 8.9, 8.10, 8.11, 8.12, 8.13, 8.14, 8.15, 8.16).

The non parametric method used was one whereby for each eye, positions of the cornea were ranked in order of greatest thinning and alloted scores i.e. 1 to the position showing greatest thinning, 2 to the next, through to 9 for the position showing least thinning. For each position, all rank scores were totalled for each eye and divided by the number of eyes involved (50 right eyes 49 left eyes). A complete agreement of ordering of positions would result in average rank scores of 1,2,3 --- 9. If there were no difference between positions as regards thinning, fairly average scores for each position would be obtained 5,5,5 --- 5.

The results obtained showed that position 3 was the most favoured thinning position for both right and left eyes then the other mid peripheral positions and finally the peripheral positions 4,5,1 and 8 showing least thinning.

Table No. 8.14

Right Eyes (N - 50)

	1. Ranking method		2. Calculation of mean changes	
Position	Rank Total	Average Rank Score	Mean	Standard Deviation
3	167.5	3.35	-0.062	0.059
2	204.0	4.08	-0.052	0.062
7	220.5	4.41	-0.049	0.068
C	221.5	4.43	-0.0402	0.050
6	248.0	4.96	-0.0396	0.060
4	257.5	5.15	-0.029	0.060
1	284.0	5.68	-0.020	0.061
5	319.5	6.39	-0.014	0.052
8	327.5	6.55	-0.011	0.054

Note: Some orders of positions obtained by both methods.

Table No. 8.15

Left Eyes (N= 49)

	1. Ranking method		2. Calculation of mean changes	
Position	Rank Total	Average Rank Score	Mean	Standard Deviation
3	153	3.12	-0.061	0.070
6	198.5	4.02	-0.044	0.063
2	209.5	4.28	-0.046	0.071
7	219	4.47	-0.043	0.068
C	248.5	5.07	-0.032	0.058
4	269	5.49	-0.033	0.070
5	277.5	5.66	-0.016	0.059
1	307.5	6.28	-0.006	0.061
8	322.5	6.58	-0.012	0.066

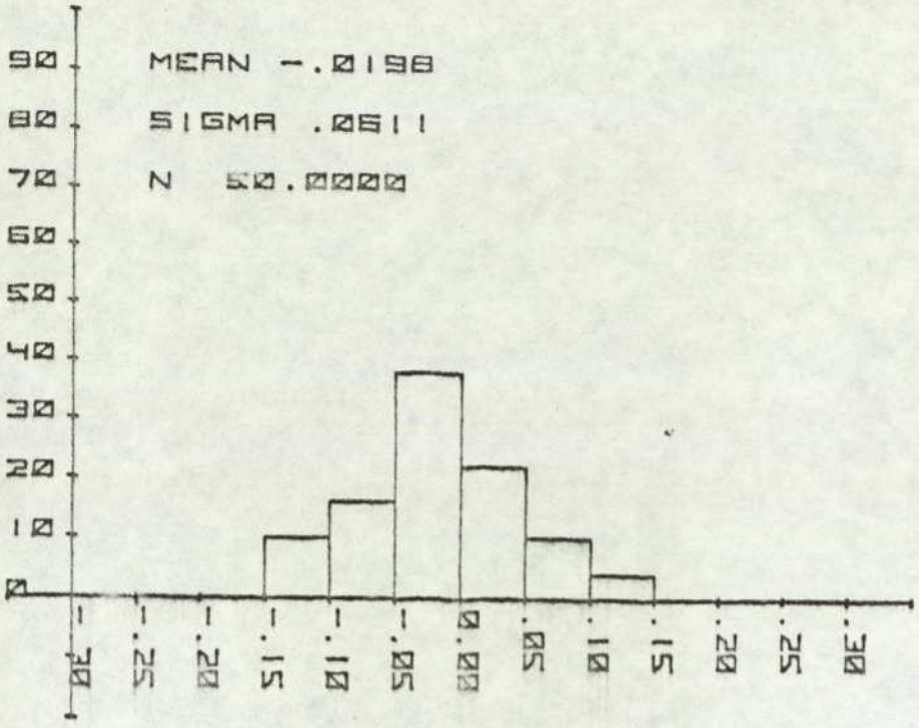
Note: Not quite the same order obtained - also slightly more variation in these results - note larger standard deviation. Method 2 gives the order 3,2,6,7,4,C,5,8,1.

As can be seen by both methods position 3 shows the greatest amount of thinning for both eyes. This is somewhat surprising because this represents a mid peripheral nasal position for the right eye but a mid peripheral temporal position for the left eye.

This does not accord with conventional clinical opinion but of course measurements were only taken at 9 discreet points on the cornea, a deliberate search for the thinnest point of the cornea was not made as there was no way of measuring at the same position at subsequent visits. Therefore, the results only represent various rates of thinning at points on the cornea, not necessarily the thinning at the thinnest point.

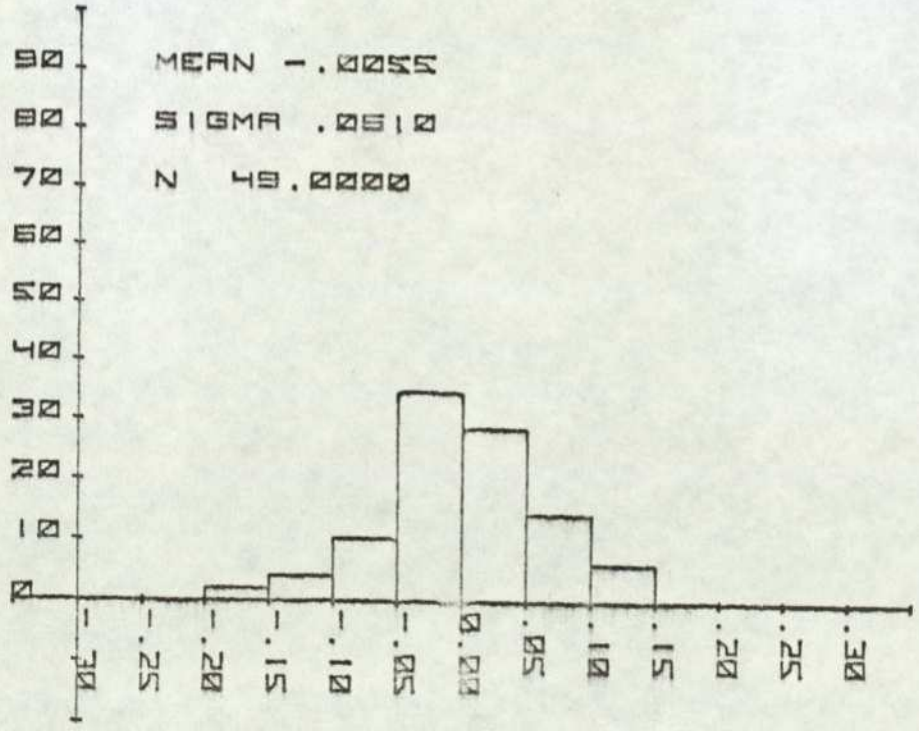
By the non parametric method of ranking the 5 central points showed the greatest range of thinning (this would accord with clinical experience) and by all analytical methods the greatest rate of thinning was shown at positions eccentric on the cornea.

Graph 8.8.



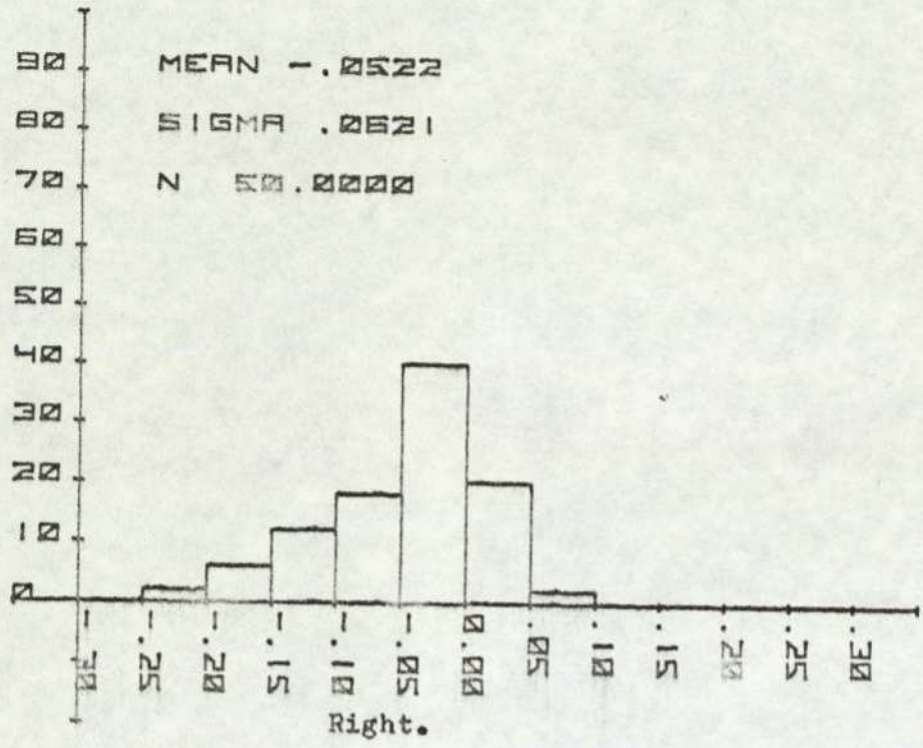
Right

Position 1.

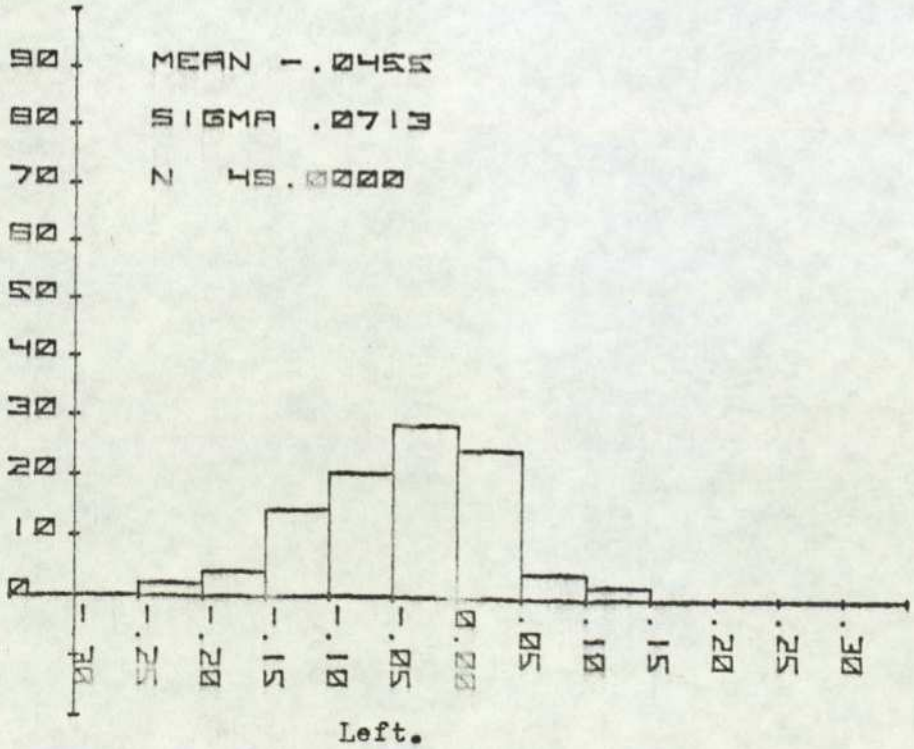


Left.

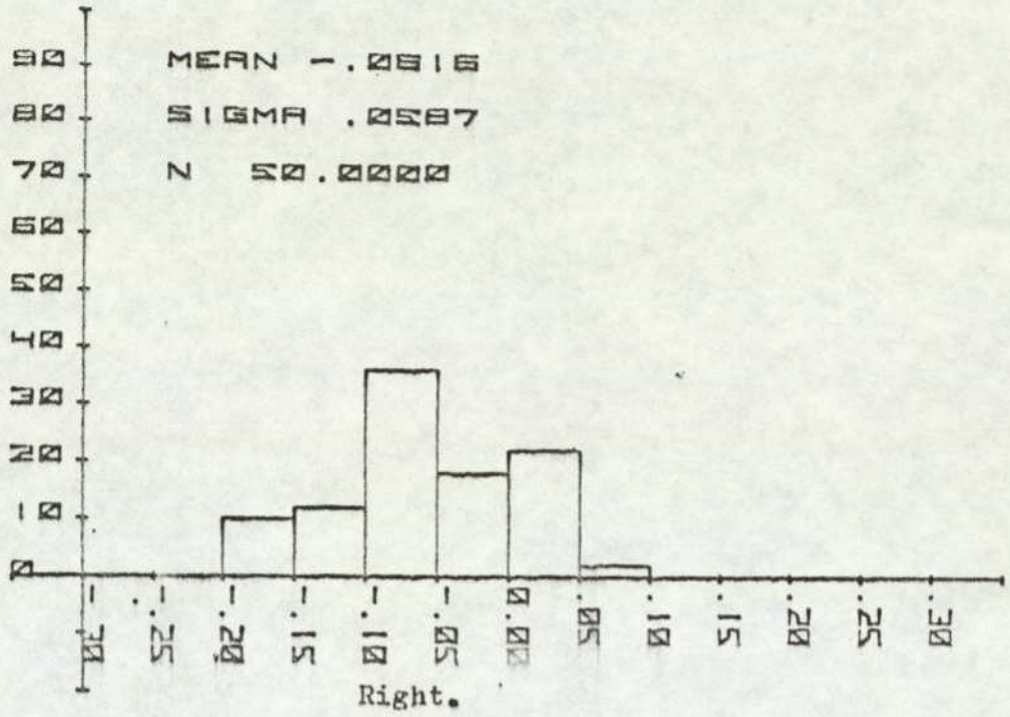
Graph 8.9.



Position 2.

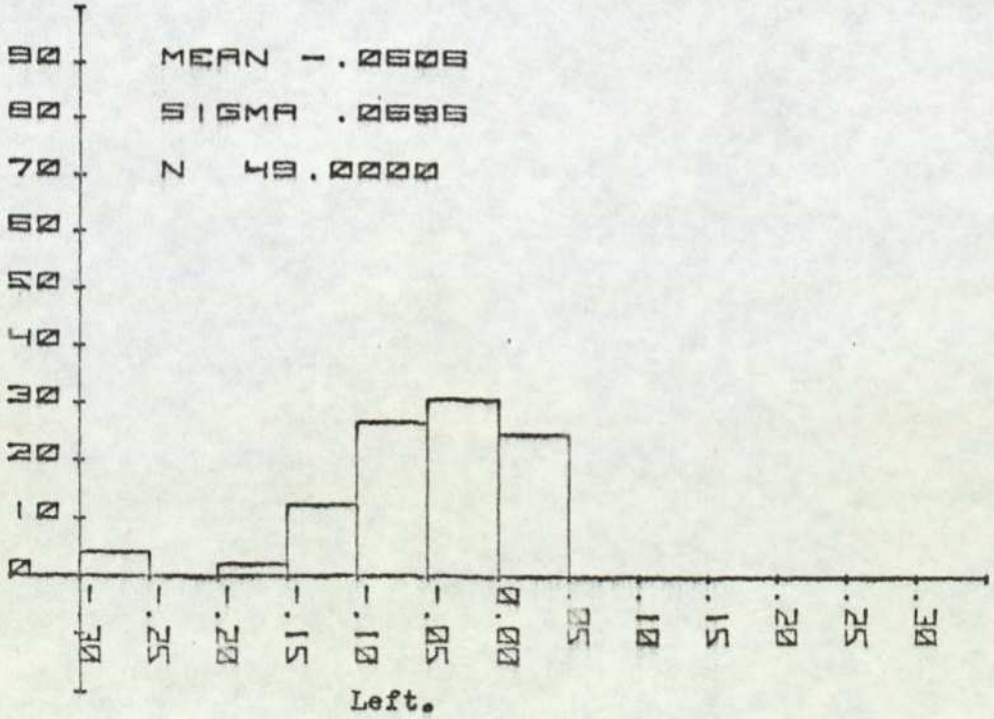


Graph 8.10.



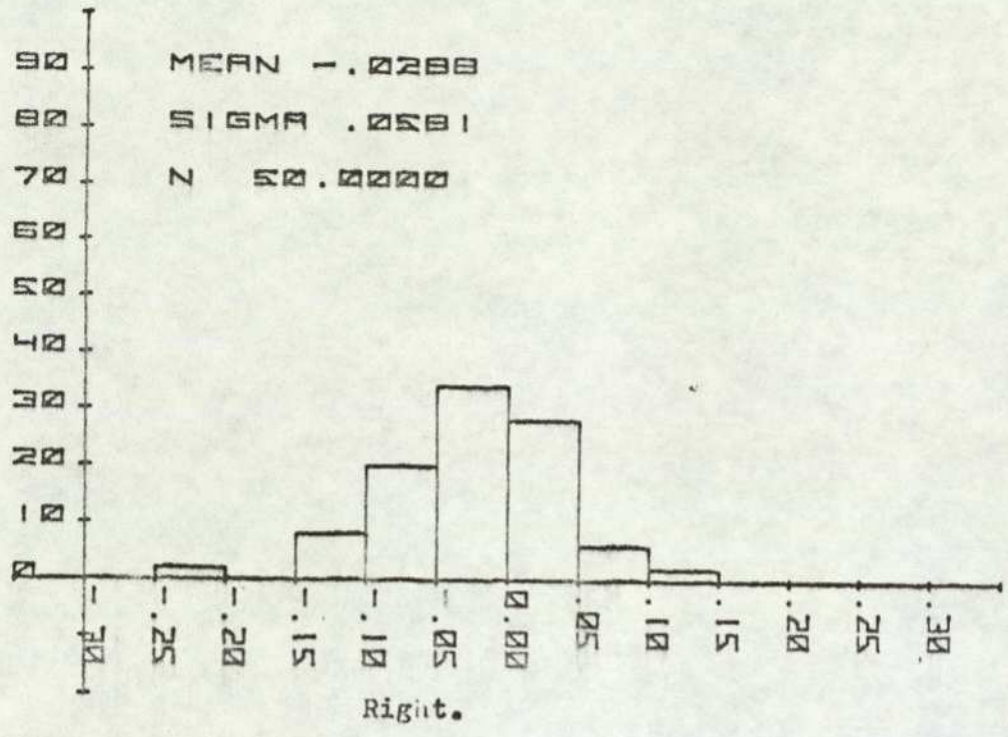
Right.

Position 3.



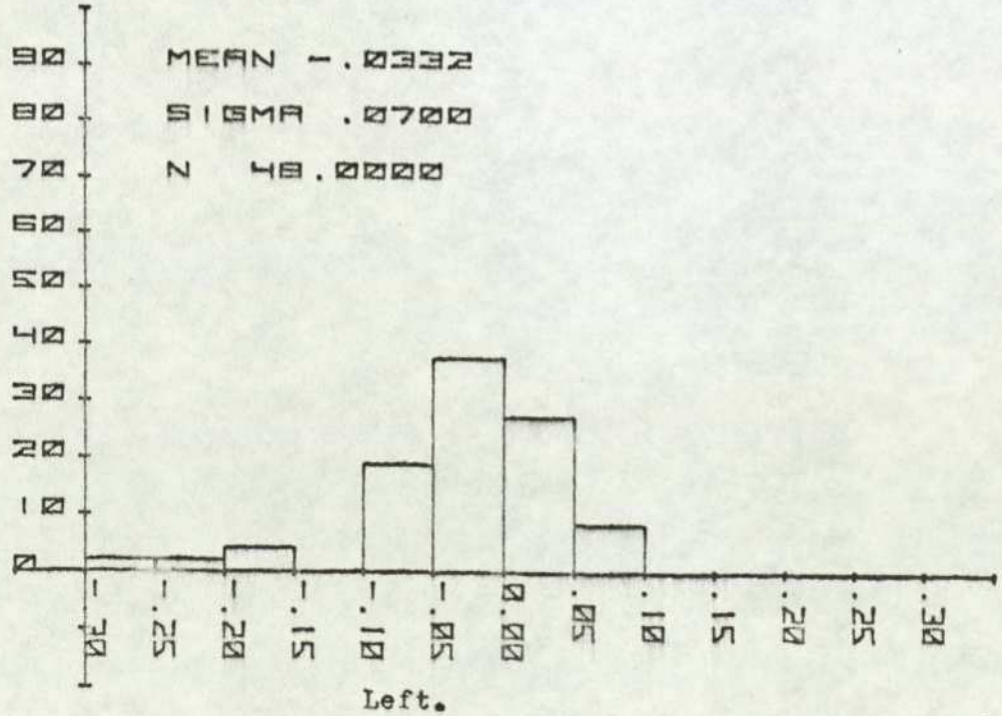
Left.

Graph 8.11.



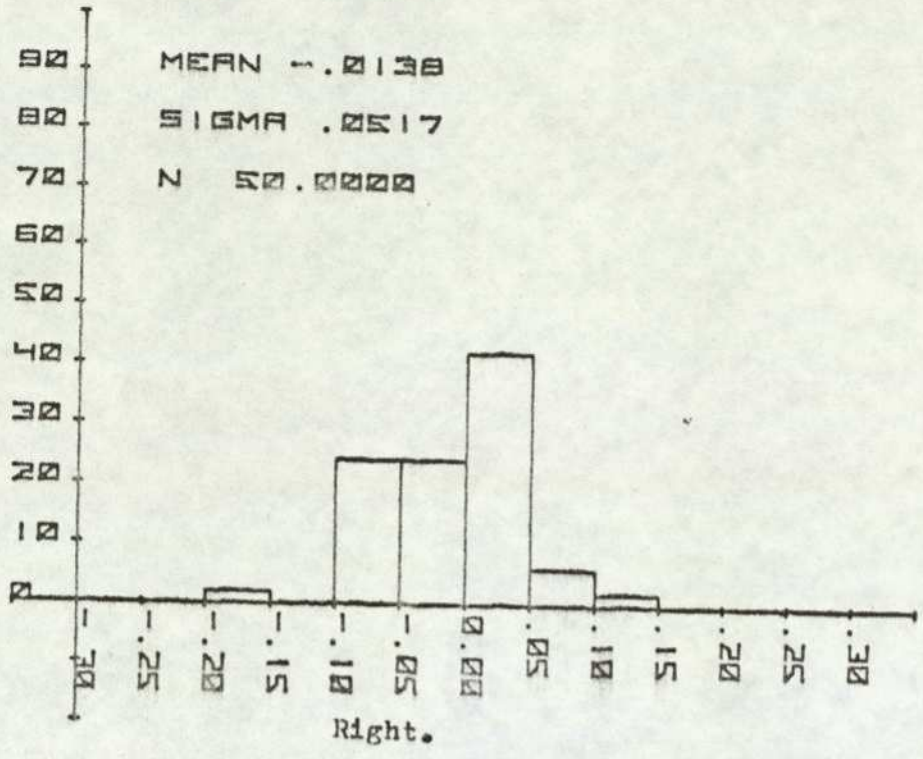
Right.

Position 4.



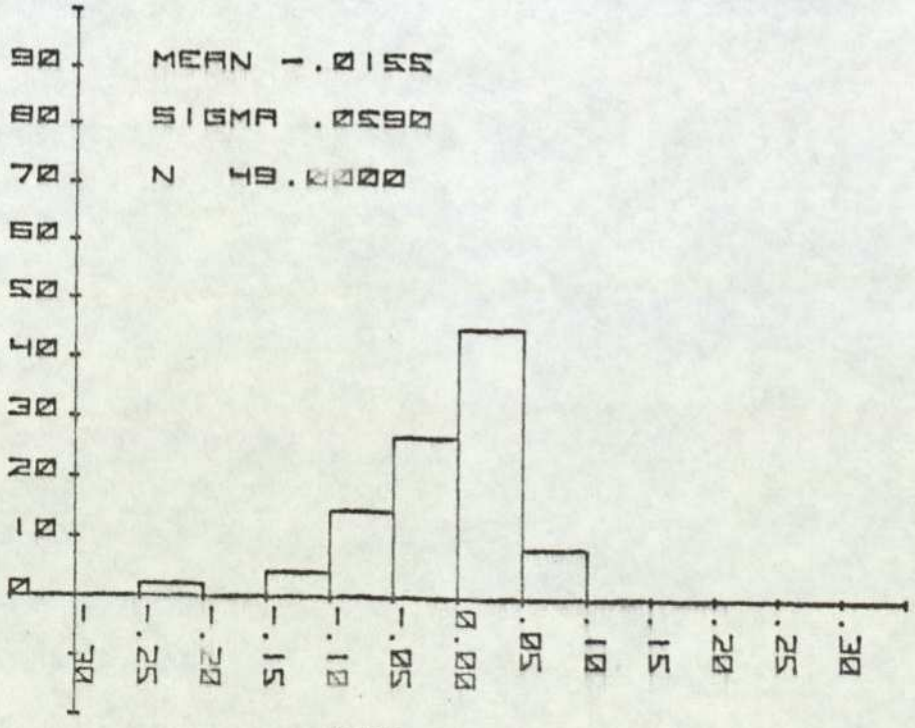
Left.

Graph 8.12.



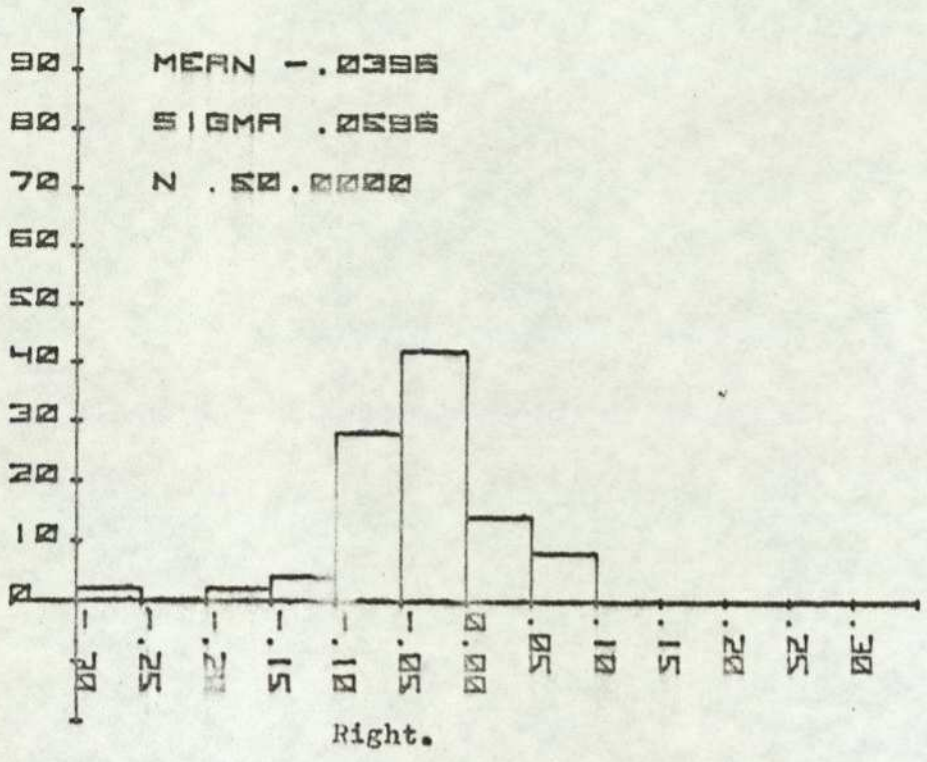
Right.

Position 5.



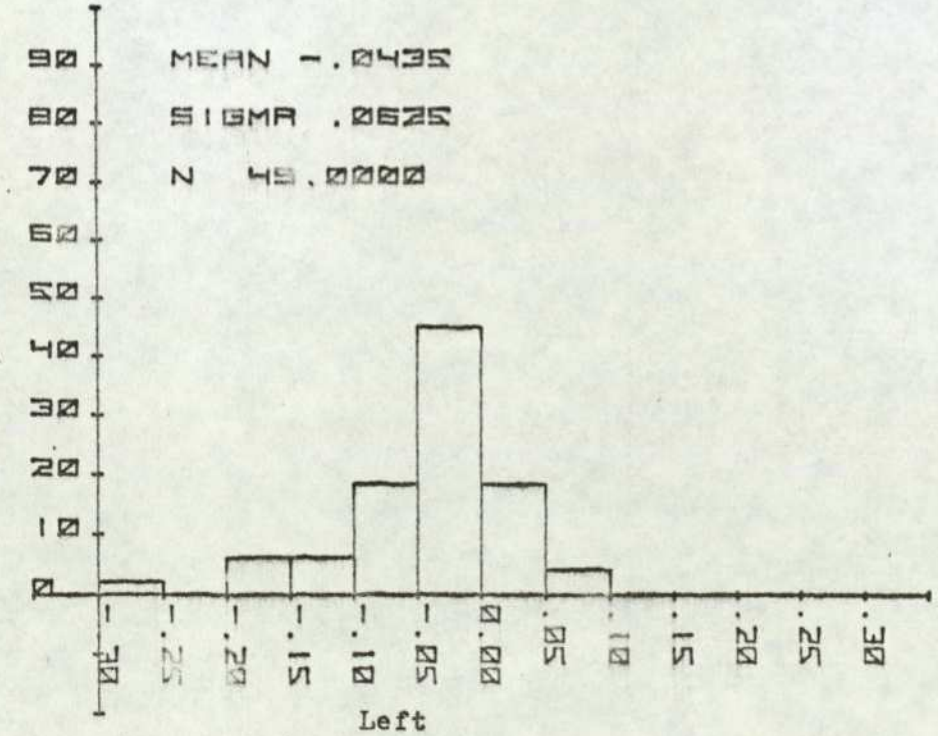
Left.

Graph 8.13.



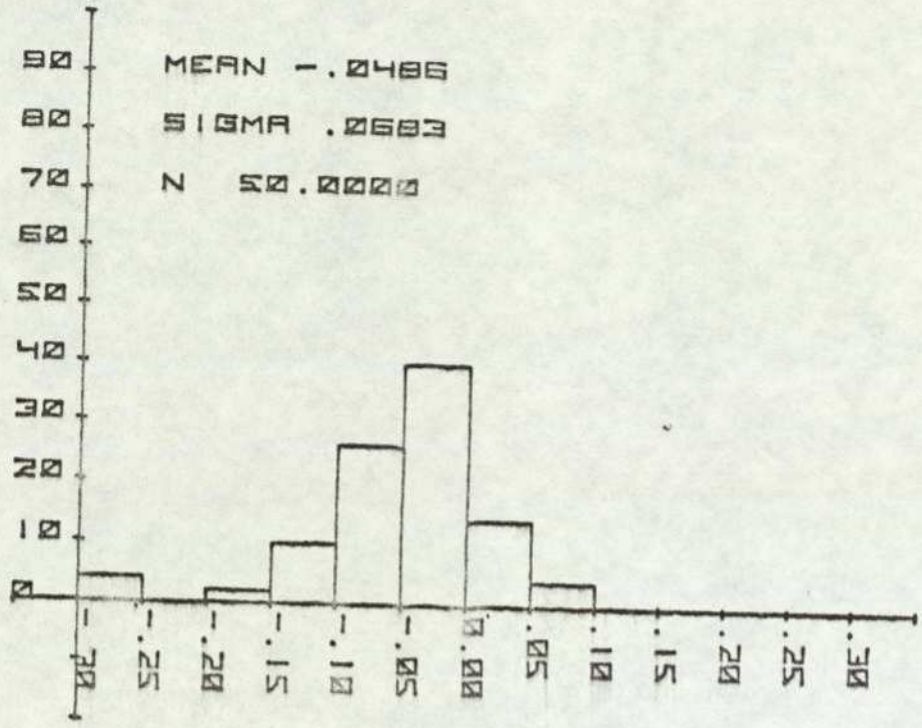
Right.

Position 6.



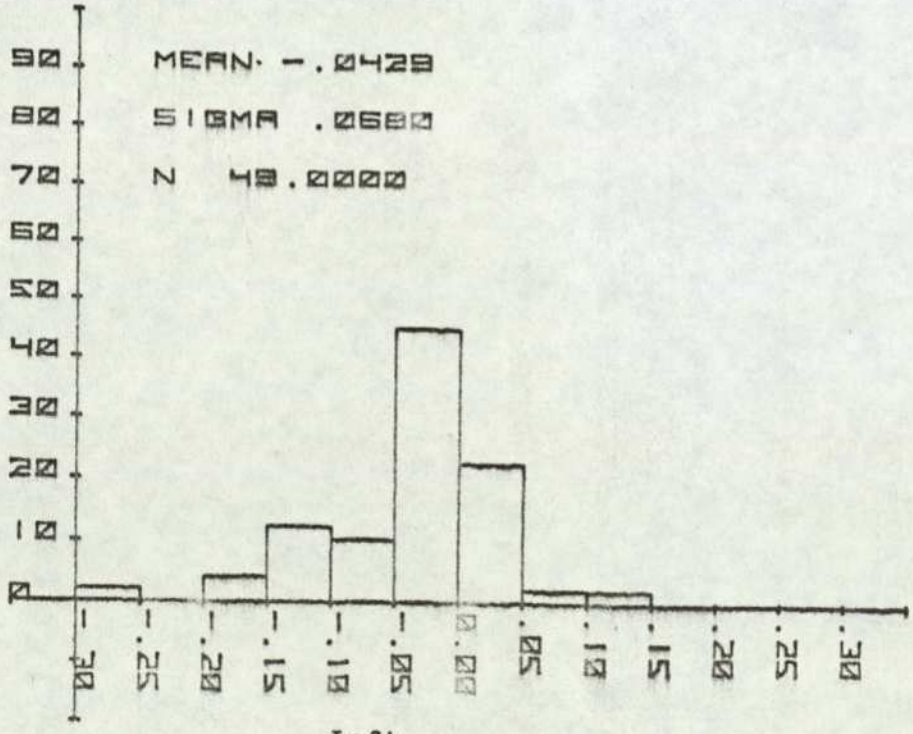
Left

Graph 8.14.



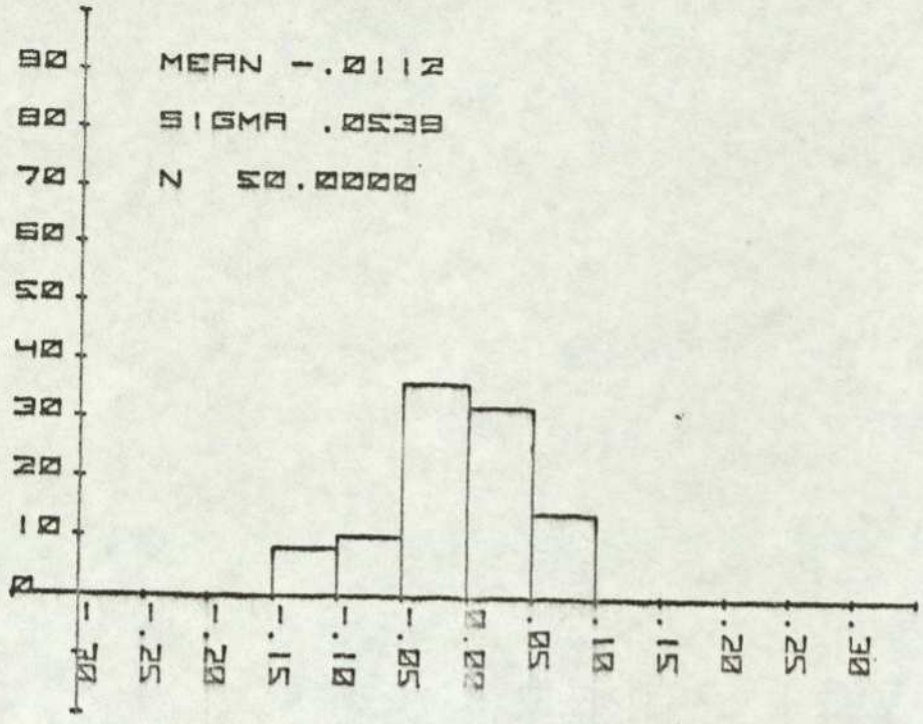
Right

Position 7.



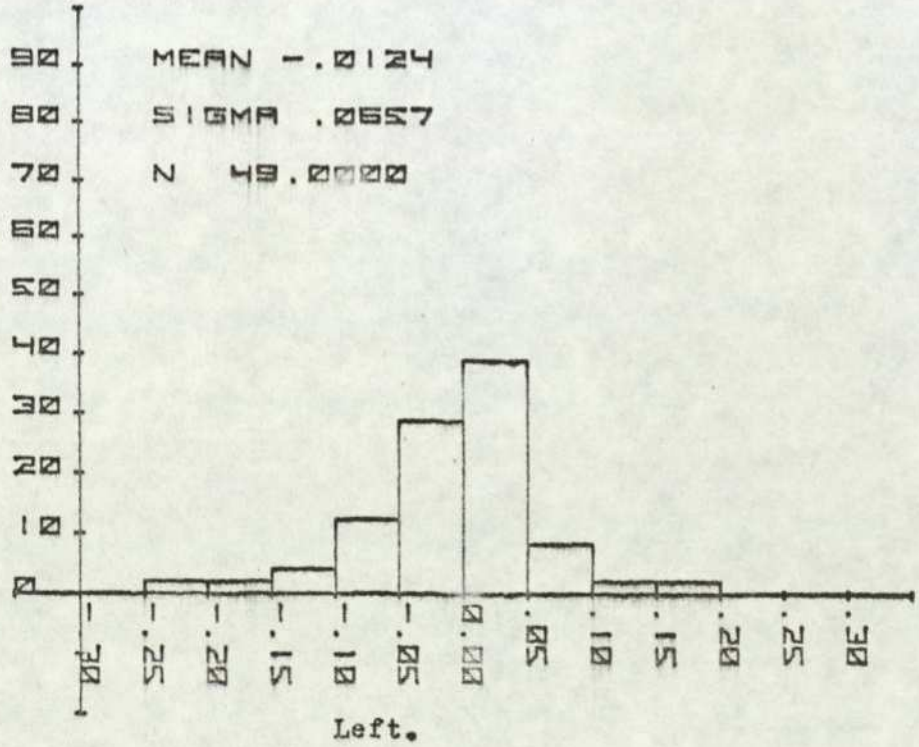
Left.

Graph 8.15.



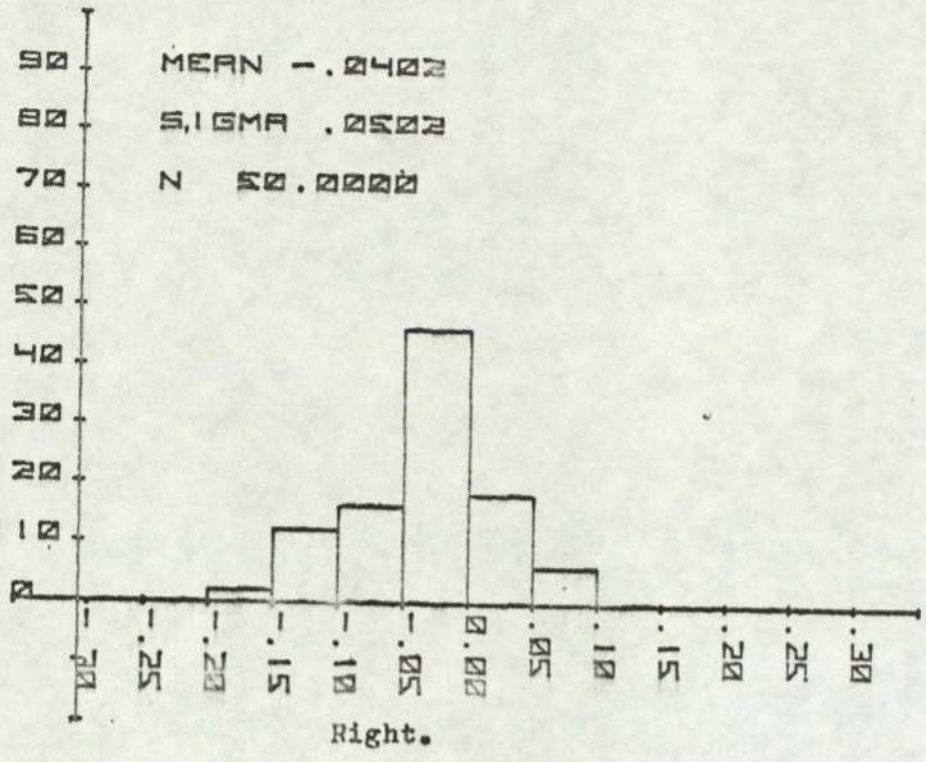
Right.

Position 8.



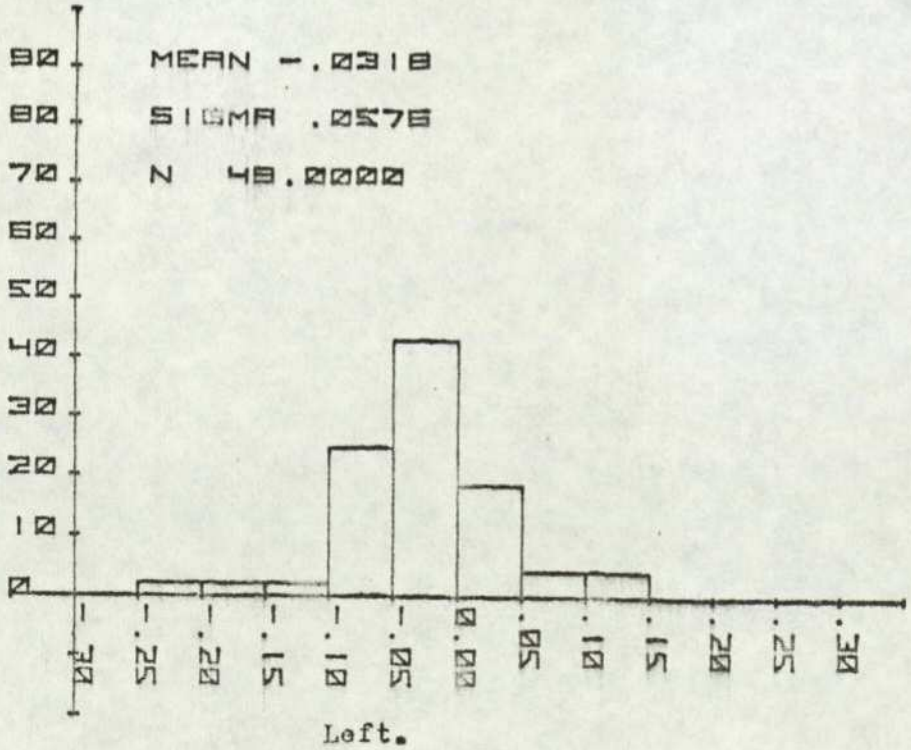
Left.

Graph 8.16.



Right.

Position 9.(centre)



Left.

Visual acuity/corneal thinning

The best visual acuity obtainable with spectacle lenses or contact lenses was recorded at each visit according to mode of correction being worn at each visit.

For results see Appendices 5 and 6.

The results were then plotted on two graphs. Graph 8.17 for eyes wearing contact lenses and Graph 8.18 for eyes corrected with spectacles.

In both cases a positive correlation was found between corneal thickness and visual acuity.

Table 8.16

For eyes wearing contact lenses:

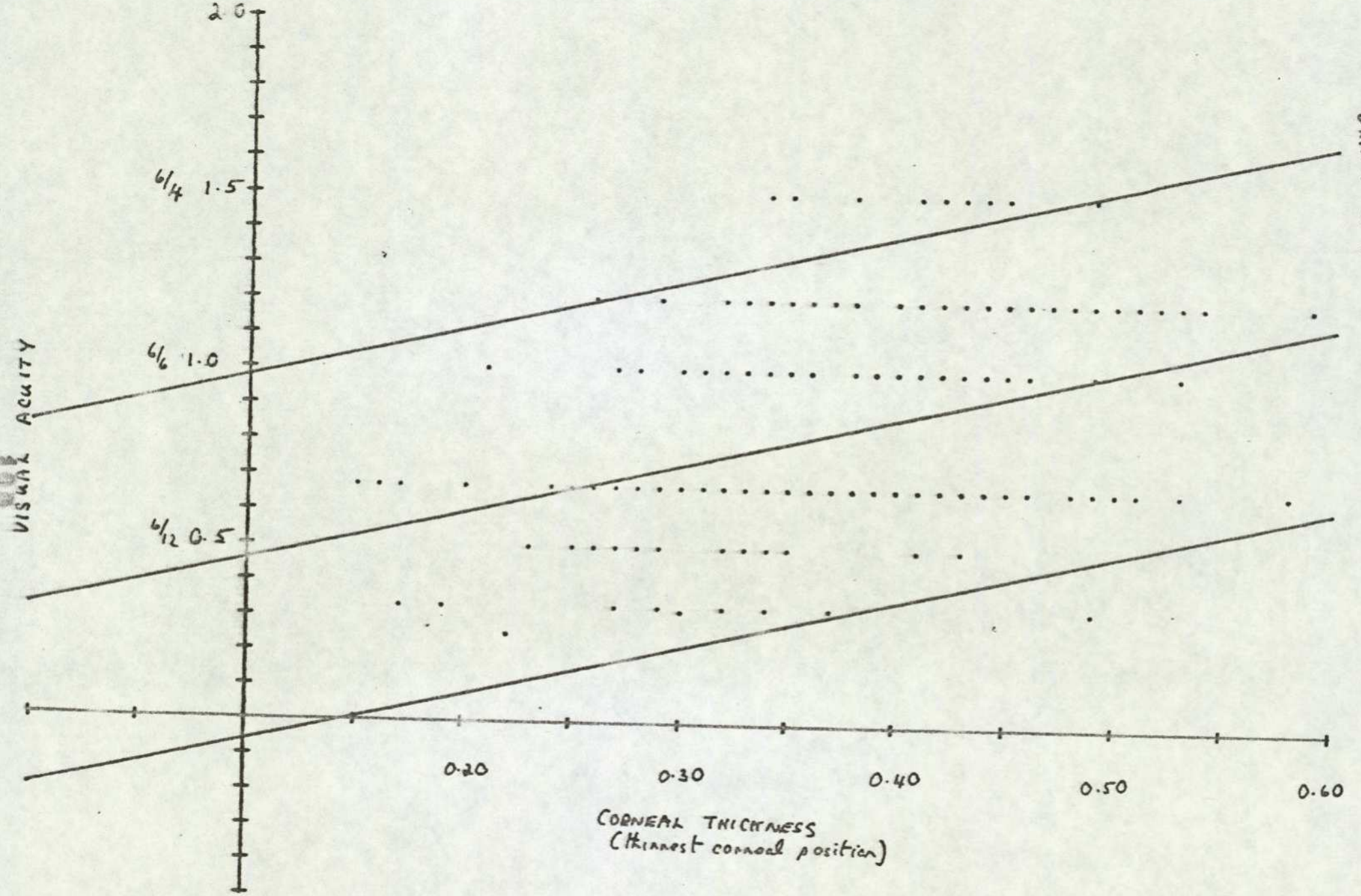
Slope	=	1.382	
Intercept	=	0.318	
Correlation co-efficient	=	0.3646	$p < 0.001$
Degree of freedom	=	247	
Confidence limit	=	$\pm$0.5167	

Table 8.17

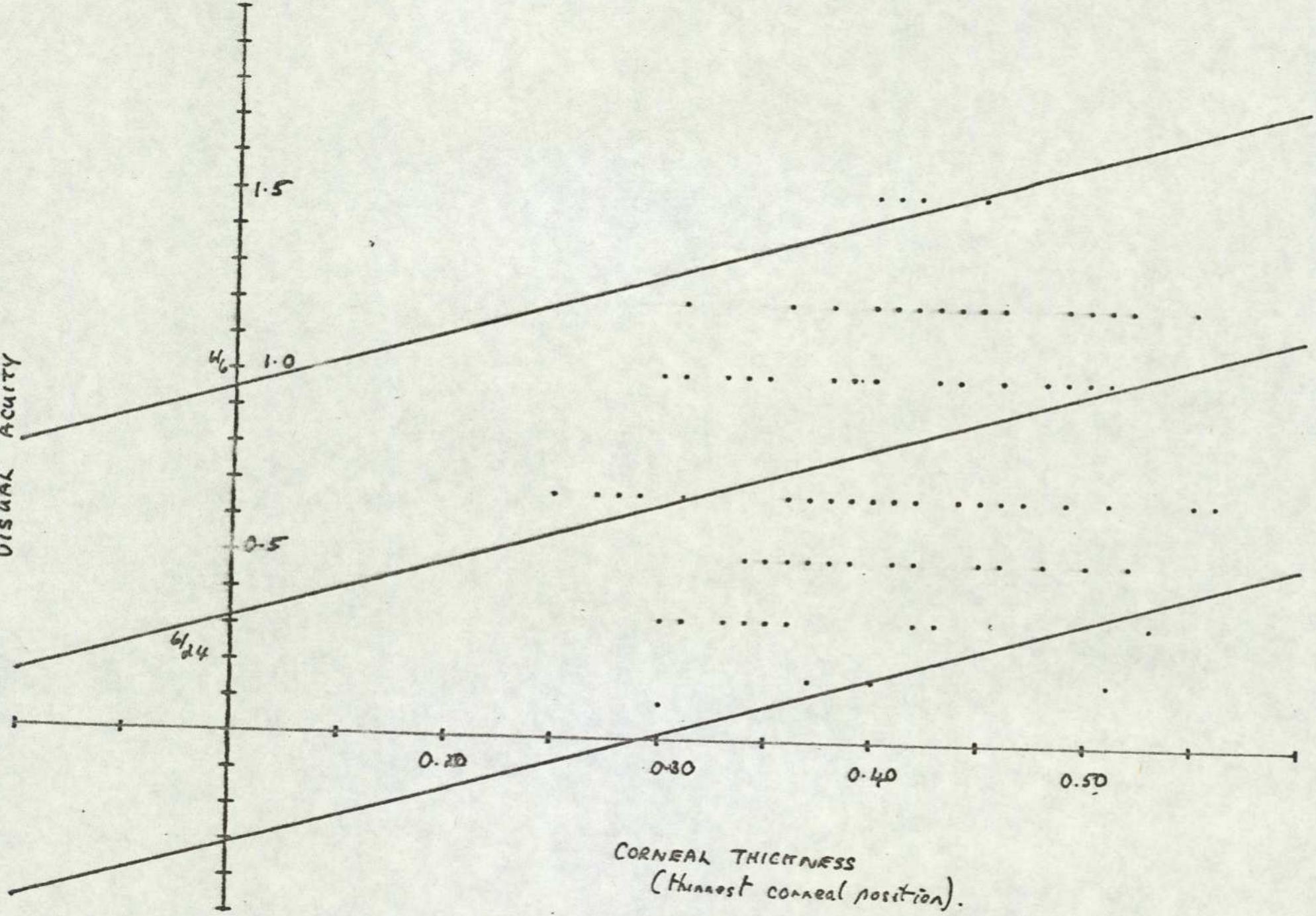
For eyes corrected with spectacle lenses:

Slope	=	1.626	
Intercept	=	0.155	
Correlation co-efficient	=	0.294	$p < 0.005$
Degree of freedom	=	159	
Confidence limit	=	$\pm$0.629	

The greater slope found in the group corrected with spectacles is as expected because of the effect of corneal thickness on anterior corneal surface aatigmatism. Where this is mainly corrected by a contact lens, there is a better correlation between thickness and acuity as indicated by the correlation co-efficients.


2.0
6/4 1.5
6/6 1.0
6/12 0.5
VISUAL ACUITY
0.20
0.30
0.40
0.50
0.60
CORNEAL THICKNESS
(thinnest corneal position)
41.8 HARRS

GRAPH 8.18


VISUAL ACUITY
1.5
6/6 1.0
0.5
6/24
0.20
0.30
0.40
0.50
CORNEAL THICKNESS
(Thinnest corneal position).

Results of Corneal Thickness Measurements.

Discussion

Looking first at the trial period in relation to the progression of the condition it was shown:

(a) there was no correlation between age at diagnosis and thinning over the trial period;

(b) there was a correlation between years since diagnosis and thinning over the trial period.

The first finding tends to contradict the clinical impression that many ophthalmologists and optometrists have. It has often been said the earlier in life the condition present the faster it progresses, this was not the case in this sample. Three of the patient sample were in the 14-15 age group at the commencement of the study, but as mentioned earlier the group as a whole was perhaps a little older than other writers have suggested would be usual for a relatively newly diagnosed group. However this was a representative sample of patients attending the clinic at Moorfields. Possibly this clinical impression had arisen because only the more extreme cases of the condition had been diagnosed in earlier days and mild cases of the disease in younger patients were not being detected.

The second finding showed a greater rate of thinning in the first two or three years and thereafter the rate of thinning steadily decreasing. It is self evident that in absolute terms if the cornea carried on thinning at the same yearly rate most of them would perforate. But it is quite clear that most cases do tend to stabilise and cease further thinning after a certain period of time. Possibly this occurs when the ocular rigidity falls below a certain level. This point of corneal stabilisation appears to occur usually when the corneal thickness is in the region between 0.35 and 0.30mm.

There thus emerges a picture of a condition that tends to pursue a course of corneal thinning and then stablises, the rate of corneal thinning being unrelated to the age of onset. The corneal thickness at which the cornea stabilises varies but tends to be about 60% of normal thickness.

The measurement of the ectasia that the corneal thinning produces shows somewhat contradictory results. Although for a given visit there was found to be a correlation between keratometry group and

corneal thickness, that is to say the thinner the cornea the steeper its anterior surface. No correlation was found between keratometry groups and rates of changes of corneal thickness over the trial period, as indicated in the relevant section this is almost certainly due to the part wear distortion effect of contact lens wear.

For a given cornea the rate of corneal thinning shows a variation with position. The central corneal area is thinning at approximately twice the rate of the peripheral cornea. The central measurement points showing the greatest rate of thinning are the eccentric ones. This would accord with experience of most practitioners.

It is known from the work of Martola & Baum (1968) (See Section 2C) that the normal peripheral cornea does undergo thickness changes with time, i.e. it thins. However these workers, who measured 209 eyes at the Refraction Clinic at the Massachusetts Eye and Ear Infirmary, found that peripheral corneal thickness changes did not become statistically significant until after the age of 50 years. The oldest patient in the study was 42 at its commencement.

A correlation was shown between corneal thinning and reductions in visual acuity, but there is still a wide variation in visual acuity for a given corneal thickness. The amount of visual acuity reductions for a given corneal thinning might be constant but after factors such as the positions of any scarring and the eccentricity of the cone must have a significant effect.

Contemporaneous Writings on Keratoconus

This may be considered under two headings, textbooks and single scientific papers.

The two most recent textbooks currently used for basic ophthalmalogical training, Newell (1974) and Miller (1978) devote very little space to the condition, perhaps reflecting its relative rarity compared with other eye conditions. Furthermore, as these books are multi-edition the section dealing with keratoconus seems to have been revised hardly at all compared with such entities as **uveitis** and retinopathies. The section dealing with keratoconus in Duke Elder's System of Ophthalmology was published in 1965 and does not seem likely to be revised in the forseeable future.

The teaching in the two current textbooks is that keratoconus is due to a congenital weakness of the cornea and both books report it as being more common in women, whereas more specialist workers in corneal diseases have reported the opposite of late. Both books also suggest that the condition may be detected earliest by the use of a Placido disc, a conclusion with which the writer would not agree. As far as treatment is concerned contact lenses are suggested for the management of the condition and if these do not prove successful penetrating keratoplasty is advocated.

The fact that in a general ophthalmology text book of around 600 pages there is rarely more than one page on Keratoconus does perhaps indicate its importance or rarity in the eyes of the general ophthalmologist. Even in Duke Elder's system where the section on corneal diseases is all but 400 pages long, only 12 pages are devoted to keratoconus, so within the spectrum of corneal diseases it is not considered particularly significant in text books.

As would be anticipated more detailed references to the condition are found in textbooks and symposia reports devoted solely to the cornea. But here again there is not a wealth of detail given and some surprising statements are made. For example Grayson and Keates (1969) also consider the condition to be more commonly found in females and frequently self limiting as they write "It is often manifests itself at puberty progresses slowly for about five years and then stops".

In order to evaluate keratoconus in the current literature a computer search was carried out through BLAISE (British Library

Automated Information Service) using the Medline file.

The number of citations printed for the various time intervals was as follows:

Years	Citations
66 - 68	35
69 - 71	58
72 - 74	50
75 - 76	64
77	22
78	22

As can be seen there tend to be about 20 papers a year published on the condition. However many of these relate to descriptions of single cases usually where the condition is associated with other conditions, e.g. Singh and Mather 1968 who wrote a paper entitled "Atopic erythroderma with bilateral cataract, unilateral keratoconus and iridocyclitis and undescended testes". Or Freedman J. and Gombos G.M. (1971) on "Bilateral macular coloboma, keratoconus and retinitis pigmentosa."

After the description of single cases the most common topic is the fitting of contact lenses in keratoconus. Here usually only a small number of cases are described and rarely are the findings submitted to any form of statisical analysis.

The idea that contact lens wear can actually precipitate keratoconus surfaces now and again in the literature. Gasset, Haude and Garcia Bengochea (1978) compared the number of patients in their clinics who developed keratoconus after having worn hard and soft contact lenses and went on to claim an association between hard contact lens wear and the risk of keratoconus. This to the writer is unconvincing, as the soft lens wearers were analysed prospectively whilst they were contrasted with a retrospective analysis of a group of patients already wearing hard contact lenses for some time. The authors control group seems suspect although they say the refractive errors of the two groups were comparable. Although this may have been true for their spherical equivalents it seems unlikely that the proportion of cases with irregular or high degrees of astigmatism were similar, since these conditions would suggest the use of hard contact lenses. In the early stages of keratoconus before the diagnosis is clear a significant

proportion of cases will suffer irregular or high degrees of astigmatism. A population of hard contact lens wearers, will therefore automatically contain a larger proportion of future keratoconus patients than a population of soft lens wearers.

Hartstein and Becker (1970) suggested that hard contact lens wearing could induce keratoconus in patients with low ocular rigidity. However Foster and Yamamoto (1978) found that ocular rigidity in Keratoconic eyes was within normal limits until the cornea was thinned by more than 60%. Furthermore replacement of a markedly thin cornea by keratoplasty results in normal ocular rigidity co-efficients.

Several writers have attempted to sub-classify the condition of keratoconus. Gormaz (1970) considers there to be some patients who have true Keratoconus (genotype) but many who have a secondary form of the disease i.e. phenotype. In his view the secondary keratoconus (phenotype) follows spring catarrh and is possibly associated with the marked increase in mucopolysaccharide content his workers found in the conjunctival secretion of patients with spring catarrh. He thus concludes that there are two forms of Keratoconus one a degenerative condition genetically conditioned and the other a process whereby the corneal tectonics are secondarily altered by a local process affecting both the conjunctiva and the cornea. The statistical evidence in this thesis would not support this contention but suggests that keratoconus is always chromosomally determined although there is possibly another mechanism acting synergistically, such as allergy which may itself be independently genetically determined.

In a large study Itoi (1978) found a higher incidence in males and concluded that Japanese keratoconus is somewhat different from Caucasian keratoconus. He divides the disease into "anterior type" and "posterior type". The posterior type is described as being more common in Japanese than Caucasians, occuring later (between 20 and 35) and usually unilateral. This is unlike the writers experience who has never seen a true case of unilateral keratoconus there always being minimal signs or changes in the other eye even though vision may be quite normal. However there were no Asians in the writers study all being Caucasian, with the exception of one Negro.

The design of the posterior surface of Japanese contact lenses does suggest that Japanese corneal topography must be different from

Caucasian with a slower rate of corneal flattening when proceeding from centre to periphery.

The condition is managed in Japan initially by hard contact lenses with a similar fitting philosophy to the one prevailing in England at the present time, Nakayana et al (1978). Should this be unsuccessful, thermokeratoplasty is often used as there is an acute shortage of donor eyes in Japan for use in penetrating keratoplasty and this procedure is only used as a last resort. The probe of the thermopencil is used at a lower temperature (80°c) as compared with American workers such as Gasset (1973) who used temperatures in the region of 100°c.

There are of course many papers on the associations of keratoconus. Bron et al (1978) includes in their list of associations.

Ehlers-Danlos VI
Ehlers-Danlos (Oxford)
Keratoconus - blue sclera
Keratoconus - cataract
Leber's Disease
Mongolism

Rahi et al (1977) have written a comprehensive survey on keratoconus and co-existing atopic disease.

A number of non associations have also been reported in recent years, for example Gasset et al (1978) investigated the blood groups of keratoconus patients as it is generally accepted that blood groups may be associated with susceptibility or resistance to certain categories of disease, however they found no associations with keratoconus.

Many papers have been published on keratoplasty in keratoconus and in an interesting paper Danshik et al (1979) found a statistically significant difference in graft rejection rates between bilateral and unilateral grafts. Graft rejections occured twice as frequently in bilaterally grafted patients (27%) as in unilaterally grafted (13%). The other major post-operative complication they reported was a high incidence (32%) of posterior subcapular cataracts which they ascribe to steroid immunosuppressive treatment.

Ruben, Colebrook and Guillon (1979) examined 51 grafts using the non contact photographic method described by Zantos and Holden (1978). Endothelial cell density was found to be lower for the corneal graft patients than for any patient in a control group. The range of corneal graft densities was 814 to 1817 cells/mm^2 and that of the control

group 2787 to 3666 cells/mm^2. The mean **density** of the control group was 2.67× that of the graft group but without any significant effect on the corrected visual acuity or corneal thickness. These workers also found an increase in cellular plemorphism compared with the control group.

There is some variation in opinion as to the site of the earliest changes in Keratoconus. Teng (1963) considered them to be in the basal epithelium whilst McTigue (1967) placed them between Bowman's membrane and the superficial stroma. McPherson and Kiffney (1968) found sub epithelial amyloid deposits as an early sign.

Biochemical investigation of keratoconic cornea are showing abnormal collagen cross linking. The rate of collagen synthesis is normal but there appears to be an intrusion of other types of collagen not normally seen in the cornea, Cannon and Foster (1978). Some workers consider the primary defect in Keratoconus as a **desynchronisation** of the relative rates of biosynthesis, of collagen proteoglycan and structural glycoprotein by the keratocytes, Pouliquen (1975). A full review of current views on corneal structure and biochemistry has been given by Bron et al (1978).

The writer of this thesis was pleased to see a recent letter to the American Journal of Ophthalmology, Ederer and Ferris (1979) discussing the role of environmental factors in disease aetiology, in which the following statement was made:

'A clinical trial comparing the progression of keratoconus with and without hard contact lenses may be feasible'.

The writer would say it is feasible but would not give one group the benefit of the best visual acuity possible.

BRON A.J. TRIPATHI R.C. HARDING J.J. & CRABBE (1978) — Trans. O.S.U.K. 98(3): 393 - 6

DONSHIK P.C., CAVANAGH H.D. BORUCHOFF S.A. & DOHLMAN (1979) — Am. J. Ophthal 87(6): 823 - 6

CANNON D.J. & FOSTER C.C. (1978) — Invest Ophthal Vis. Sci. 17(1): 63:5

EDERER F. & FERRIS F.L. (1979) — Am. J. Ophthal (letter) 87(3) 434 - 5

FOSTER C.S. & YAMAMOTO G.K. (1978) — Am. J. Ophthal 86(6) 802 - 6

FREEDMAN J. & GOMBOS G.M. (1971) — Ann. Ophthal 3(6): 664 - 665

GASSET A.R., HAUDE W.L., GARCIA-BENGOCHEA (1978) — Am. J. Ophthal 85(3) 339 - 4

GASSET A.R., HINSON W.A. & FRIAS J.L. (1978) — Ann. Ophthal 10(5): 601 - 2

GASSET A.R., SHAW E.L., & KAUFMAN (1973) — Trans. Amer. Acad. Ophthal 77: 441 - 445

GORMAZ A. (1970) — "Corneal & External Diseases of the Eye" First Inter-American Symposium Pub. C.C. Thomas. Springfields Illinais 155-163

GRAYSON M & KEATES R.H. (1969) — "Diseases of the Cornea" Churchill London pp 87 - 93

HARDIE B. & HARTSTEIN J. (1970) — Arch. Ophthal 84,728

HARTSTEIN J. & BECKER B. (1970) — Arch. Ophthal 40: 84(6) 728 - 729

ITOI M. (1978) — Proceedings of the Symposium of the International Society for Corneal Research Kyoto 1978. Documenta Ophthalmologica Proceedings Series volume 20 pp. 193 - 200

KRACHMER J.H. & RODRIGUES M.M. (1978) — Arch. Ophthal 96(10) 1867 - 73

LAING R.A., SANDSTROM M.M. BERROSPI A.R., LEIBOWITZ H.M. (1979) — Arch. Ophthal 97 1867 - 1869

MILLER S.J.H. (1978) — "Parsons' Diseases of the Eye" Churchill Livingstone London & New York pp 225 - 226

McPHERSON S.D. & KIFFNEY G.T. (1968) — Arch. Ophthal (Chicago) 79:669

McTIGUE J.W. (1967) — Trans. Amer. Ophthal Soc. 65:626

NAKAYAMA C. KUYAMA H. & ITOI M. (1978) — "Contact lens fitting for Keratoconus patients" Fourth International Medical Contact lens Symposium Kytoo May 78.

NEWELL F.W. & ERNEST J.T. (1974) — "Ophthalmology, Principles and Concepts" C.V. Mosby. St. Louis. pp 221 - 222

POULIQUEN Y. (1975) — Arch. Opthal (Paris) 35,37

RAHI A, DAVIES P, RUBEN M. LOBASCHER D. & MENON J. (1977) — B. J. Ophthal 61(12) 761 - 4

RUBEN M. COLEBROOK E. & GUILLON M. (1979) — Brit. J. Ophthal 63 790 - 793

SINGH G. & MATHUR J.S. (1968) — Brit. J. Ophthal 52(1): 61 - 3

TENG C.C. (1963) — Am. Ophthal 55,18

ZANTOS S. & HOLDEN B. (1978) — International Contact Lens Clinic 5, 10 - 14

SUGGESTIONS FOR FURTHER RESEARCH

The finding in this study of a well-established association between increased maternal age and the incidence of keratoconus suggests that further investigations into the genetic history of the patients would be a useful field of research. In the main, family studies have been confined to siblings and children of patients but the investigation of patients parents might show that some "lazy" eyes were in fact forme fruste keratoconus. Many contemporary workers in this fields such as Gasset, Hinson and Frias (1978) consider keratoconus to be caused by multifactorial modes of inheritance and in a personal communication Dr. Marcus Pembrey of the Paediatric Genetics Section of the Institute of Child Health (University of London), writes that he feels a detailed genetic investigation should be carried out in cases where there is a positive family history such as an affected sibling. At the Bristol Eye Hospital an investigation into the association between allergy, keratoconus and family history is currently in progress.

The results in this study have shown that a mild degree of keratoconus could easily be missed as corneal thinning can precede significant distortion of the keratometer mires, or any loss of acuity, by some time. The work of Kornerup and Ladin (1959) showed a significantly high incidence of cases where the principal meridians of an astigmatic cornea were not mutually at right angles, in cases of atopic dermatitis, although they found no evidence of keratoconus. This suggests to the writer that had they performed topographical pachometry it is possible that some mild cases of keratoconus may have been detected.

An investigation of a group of patients who had a known family history of atopic manifestations in which keratometry and topographical pachometry were carried out and compared with a normal population could given an indication of the extent of undiagnosed keratoconus in the general population. The sample of patients could well be drawn from a dermatological department rather than those attending an eye hospital.

The analysis of paternal age and birth order could also be a fruitful field of research, as it is well reported that these can be significant in conditions due to chromosomal abberations, Erickson

(1978). The season of conception is also known to affect the incidence of genetic defects, Iffy et al, (1978). A computer analysis of the months of birth of all patients who have attended the keratoconus clinic might reveal a significant pattern, particularly if it could be compared with a group of keratoconus patients known to have been born in the southern hemisphere.

The refinement of techniques for evaluating corneal morphology which have emerged with new instrumentation in the last two years also indicates fresh fields of research.

Bron and Brown (1974) studied the corneal endothelium of six eyes with keratoconus using a non contact technique. The endothelial cell desities that they found in the keratoconic corneae (2,858 cells/mm^2 $\pm$ 282) were considered to be similar to normal corneae. This was the first report of a successful attempt to quantitate endothelial cell density in the living human subject by photographic means, it was thus a harbinger of techniques which have only recently been exploited commercially in the form of readily available instruments.

As it was a non contact photographic method, as is the one described by Zantos and Holden (1978), it is necessary to consider the effect of differing corneal curvature on cell density measurements particularly if the use of the technique in keratoconus is contemplated.

Olsen (1979) has written that using the non contact techniques of Holm (1978) provided that the angle of observation is kept at a small value ($< 23°$) the curvature of the cornea varies the zone observed by less than 1%. With his apparatus he concludes that a standard correction factor of x 0.959 can be applied in all cases when comparing with contact specular microscopy. However in many cases of keratoconus it may not be possible to visualise the corneal endothelium at this angle.

Guillon (1979) in a paper read at the Cardiff Corneal Workshop and as yet unpublished, discusses the effect of varying corneal curvature and thickness on magnification. The theoretical results when applied to keratoconic cornea are somewhat fortuitous. Compared to an applanated cornea, a cornea of radius 7.8 mm would have a magnification of 1.78%, whereas a cornea of radius 6.00mm would produce a magnification of 2.33% i.e. an increase in magnification of 0.55%. However, when changes in corneal thickness are considered, a cornea

of 0.50mm thickness would give a magnification of 1.78%, whereas a cornea of thickness 0.30mm, gives a magnification of 1.06% i.e. a decrease in magnification of 0.72%. Thus in a thinning and simultaneously steepening cornea the optical effects produced are opposite and to a great extent self correcting. The same considerations also apply on normal cornea when passing from centre to periphery i.e. to thicker and flatter areas of the cornea.

However these theoretical findings do not mean that the endothelium can be satisfactorily visualised and photographed in all cases of keratoconus. Furthermore the problems of locating the exact area photographed, discussed in Section 5 of this thesis, still apply if attempts are made to obtain topographic results by varying the fixation.

In keratoconus when the applanating specular microscope is used the problem of varying magnification, owing to abrupt changes in corneal curvature does not arise. However there is the suspicion that, in itself, the flattening of the cornea could cause changes in the appearance of the endothelial cells. In a recent paper Laing and his co-workers using a clinical specular photomicroscope (Bio-Optics - 76) examined twelve case of keratoconus. They found an increase in cellular pleomorphism with many cells smaller than normal distributed throughout the endothelial cell population. There were also large elongated cells whose axes seemed orientated towards the apex of the cone, the cells appearing to have been stretched by the ectatic process. (See Fig. 27). In an eye which had a history of acute corneal hydrops they found cells up to 10x larger than normal in the region of the scar, but the mean cell area in other regions of this cornea was not signficantly different from normal.

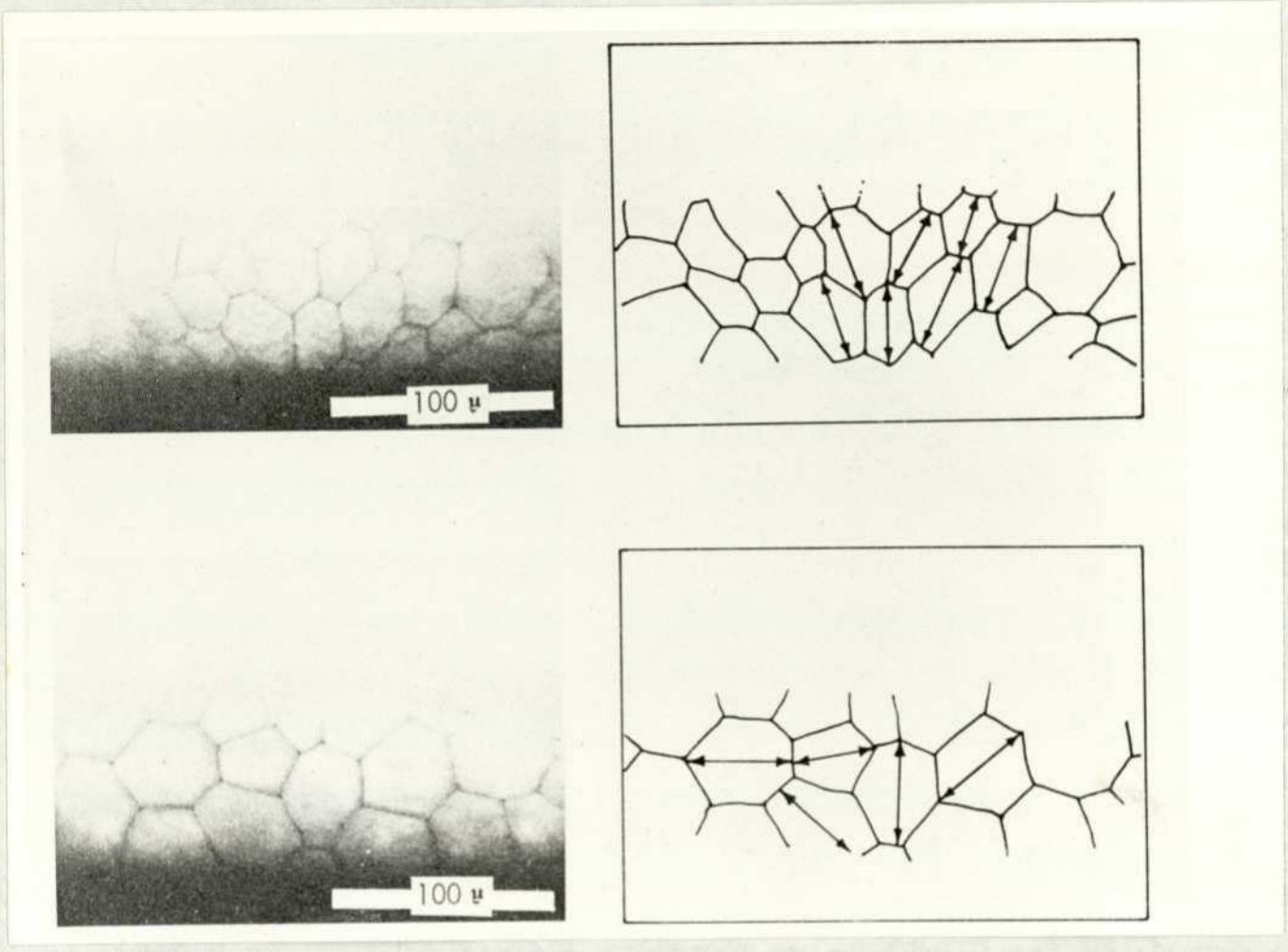


Fig. 27 Enlarged endothelial cells in keratoconus (Upper) and in a graft (lower). (from Laing et al 1979)

Like Bron and Brown (1974) they did not find the mean cell count to be significantly different from that of a group of an age-matched normal subjects. This suggests to the writer that if research is to be directed towards acquiring evidence that will incriminate the endothelium as a primary site in the pathogenesis of keratoconus, it will be necessary to use a large sample and compare the degree of pleomorphism rather than the cells per square m.m. A method of evaluating the regularity of the endothelial mosaic by some form of scanning reader which would measure the thickness of silver on the photographic emulsion and quantify its regularity of deposition, would be a useful addition to the researchers armamentarium. Cell counts on their own are obviously too crude to evaluate early changes in corneal function. For example the wearing of both soft and hard contact lenses is known to produce irregularities of the corneal mosaic but does not appear to alter the mean cell count, Guillon (1979).

The use of the specular microscope has caused Krachmer and Rodriques (1978) to speculate on the probable aetiology of keratoconus posticus. They consider the probable mechanism to be an early pathogenic one prior to the fifth or sixth month of gestation. This results in the peripheral endothelium migrating in a normal fashion but then failing to migrate centrally or to differentiate normally.

Findings of endothelial abnormalities in eyes which subsequently become keratonic but before any signs of the disease appeared would be of great significance in the investigation of the pathogenesis of keratoconus. This could be done by investigating the endothelium of the contralateral eye in cases of early unilateral keratoconus as of course most cases become bilateral eventually. As it could be several years before the disease manifested itself a full study would of necessity become a long term one. Perhaps over this period a more sophisticated technique of evaluating endothelial mosaic regularity will have evolved.

A control study of Moorfields non Keratoconus patients in terms of maternal age, social class, education etc. would determine if there was any selection bias in the samples used in this study.

SUGGESTIONS FOR FURTHER RESEARCH

References

BERROSAI A.R., & LEIBOWITZ H.M. (1979)	Arch. Ophthal. 97. 1867 - 1869
BRON A.J. & BROWN N.A.P. (1974)	Tans O.S.U.K. 94, 863
ERICKSON J.D. (1978)	Ann. Hum Genet 41, 289
GASSET A.R., HINSON W.A. & FRIAS J.L. (1978)	Ann. Ophthal. 10 (8) 991 - 4
GUILLON M. (1979)	"Topographical Endothelial Photography" Paper read at the Cardiff Corneal Workshop 5.10.79 awaiting publication
HOLM O. (1978)	Acta. Ophthal. (Kbh) 56 475 - 476
IFFY L. LAVEMAR M., KAMINETZKY H.A., JONGBLOET P.H., WINGATE M.B., & JAKOBVITS A. (1978)	Int. J. Gynaecol. Obstet 16 210 224
KORNERUP T. LODIN A. (1959)	Acta. Ophth. (Kbh) 37 508
KRACHMER J.H. & RODRIGUES M.M. (1978)	Arch. Ophthal. 96 (10) 1867 - 73
LAING R.A., SANDSTROM M.M. BERROSAI A.R., & LEIBOWITZ H.M. (1979)	Arch. Ophthal. 97. 1867 - 1869
OLSEN T. (1979)	Acta. Ophthal. (Kbh) 57, 860 - 868
ZANTOS S. & HOLDEN B. (1978)	Internation Contact Lens Clinic 5, 10-14

APPENDICES

1. Maternal age of patients in initial and expanded sample.

2. Anterior chamber depth measurements of sample group.

3. Corneal thickness of sample group and changes over trial period.

4. Ages of patients at diagnosis and first visit. Keratometry groups first and last visits.

5. Visual acuity at each visit. Eyes wearing contact lenses.

6. Visual acuity at each visit. Eyes not wearing contact lenses.

7. Time elapsed between diagnosis and first visit and thinnest corneal measurement.

APPENDIX 1

Study No.	Hospital No.	Sex	Year of Birth	Age of Mother at Birth
1	[redacted]	M	1949	18
2		M	1956	35
3		F	1936	27
4		F	1961	28
5		M	1961	28
6		M	1949	38
7		M	1953	27
8		M	1962	39
9		F	1951	33
10		M	1950	30
11		M	1953	32
12		M	1958	28
13		M	1937	45
14		F	1957	34
15		F	1954	41
16		M	1951	29
17		M	1957	24
18		M	1954	41
19		M	1953	37
20		F	1937	45
21		M	1935	32
22		F	1956	29
23		F	1944	25
24		F	1960	39
25		M	1960	29
26		F	1950	27
27		M	1952	41
28		M	1950	29
29		M	1950	37
30		F	1947	44
31		F	1951	38

Appendix I (continued)

Study No.	Hospital No.	Sex	Year of Birth	Age of Mother at Birth
32	[redacted]	M	1956	26
33		M	1959	30
34		M	1954	38
35		F	1950	33
36		M	1961	25
37		M	1959	19
38		F	1940	30
39		F	1944	32
40		M	1950	33
41		M	1939	30
42		F	1947	35
43		M	1944	29
44		F	1961	27
45		M	1959	30
46		M	1954	29
47		F	1949	27
48		M	1959	38
49		F	1957	25
50		M	1960	31
51		M	1948	29
52		M	1957	33
53		F	1940	30
54		F	1953	24
55		F	1960	33
56		M	1928	40
57		M	1940	37
58		M	1941	22
59		F	1957	32
60		M	1949	26
61		M	1960	32

Appendix I (continued)

Study No.	Hospital No.	Sex	Year of Birth	Age of Mother at Birth
62	[redacted]	F	1955	31
63		F	1941	38
64		F	1963	30
65		M	1956	21
66		M	1947	30
67		M	1949	34
68		M	1948	37
69		F	1955	21
70		F	1953	20
71		M	1928	42
72		F	1943	34
73		M	1954	19
74		F	1913	39
75		M	1959	38
76		M	1960	27
77		M	1949	37
78		M	1946	29
79		M	1962	34
80		M	1961	21
81		F	1927	36
82		F	1957	32
83		M	1963	37
84		F	1944	35
85		F	1955	18
86		F	1943	40
87		F	1955	30
88		M	1951	27
89		M	1950	33
90		M	1941	28
91		F	1941	36
92		M	1942	31
93		M	1942	36

Appendix I (continued)

Study No.	Hospital No.	Sex	Year of Birth	Age of Mother at Birth
94	[redacted]	M	1941	38
95		M	1962	39
96		M	1954	31
97		M	1948	37
98		M	1965	32
99		F	1943	39
100		M	1949	25
101		M	1961	29
102		F	1952	30
103		M	1945	25
104		M	1947	24
105		M	1939	29
106		M	1935	29
107		F	1942	30
108		F	1952	30
109		F	1930	27
110		M	1929	33
111		F	1944	32
112		F	1939	26
113		M	1939	30
114		F	1952	29
115		M	1961	28
116		F	1950	32
117		M	1959	21
118		M	1958	30
119		G	1951	22
120		F	1909	35
121		M	1942	24
122		M	1953	27

Appendix I (continued)

Study No.	Hospital No.	Sex	Year of Birth	Age of Mother at Birth
123	[redacted]	M	1944	27
124		F	1960	39
125		M	1959	30
126		M	1954	39
127		M	1958	25
128		M	1932	39
129		M	1961	22
130		M	1949	24
131		M	1949	26
132		M	1945	22
133		M	1944	31
134		F	1954	30
135		F	1958	35
136		M	1946	26
137		F	1955	30
138		M	1959	23
139		M	1948	27
140		M	1946	37
141		M	1919	32
142		M	1938	32
143		M	1937	30
144		F	1964	31
145		M	1956	38
146		F	1938	42
147		M	1947	27
148		M	1961	33
149		F	1933	23
150		F	1940	24

APPENDIX 2

Anterior chamber depth

Patient No.	Eye	Visit 1	Visit 2	Visit 3	Visit 4
1	R	3.53	3.63	3.73	3.85
	L	3.38	3.61	3.65	3.72
2	R	2.78	2.89	2.93	2.94
	L	2.81	3.25	3.26	3.25
3	R	2.82	2.97	3.03	3.03
	L	2.88	3.07	3.10	3.10
4	R	2.86	3.15	3.24	3.30
	L	3.05	3.19	3.19	3.17
5	R	3.01	3.05		
	L	3.17	3.32		
6	R	2.89	3.16	3.14	3.17
	L	2.86	3.06	3.11	3.10
7	R	2.84	3.10	3.10	3.10
	L	2.43	2.80	2.82	2.86
8	R	3.47	3.54	3.65	3.64
	L	3.65	3.76	3.33 (a)	3.33 (a)
9	R	3.01	3.02	3.12	3.12
	L	3.05	3.06	3.06	3.06
10	R	3.47	3.75	3.70	3.77
	L	3.64	3.78	3.71	3.79
11	R	2.88	2.95	2.94	2.95
	L	2.85	2.95	2.95	2.96
12	R	3.05	3.32	3.32	3.40
	L	2.80	3.08	3.15	3.24
13	R	2.75	2.94	2.91	2.85
	L	2.87	3.32	3.41	3.42

(a) Post Keratoplasty measurements

Appendix 2 (continued)

Anterior chamber depth

Patient No.	Eye	Visit 1	Visit 2	Visit 3	Visit 4
14	R	2.81	2.88	2.96	2.89
	L	2.81	3.16	3.24	3.18
15	R	3.42	3.62	3.67	3.65
	L	3.24	3.39	3.39	3.47
16	R	3.26	3.33	3.38	3.39
	L	3.12	3.36	3.36	3.39
17	R	2.73	2.94	2.96	2.94
	L	2.93	3.01	3.09	3.11
18	R	3.42	3.27	3.33	3.38
	L	3.20	3.46	3.50	3.57
19	R	2.97	2.98	2.95	2.97
	L	2.90	3.04	3.00	3.02
20	R	3.07	3.25	3.28	3.26
	L	3.04	3.28	3.41	3.31
21	R	2.84	2.84	2.90	2.92
	L	2.69	2.69	2.69	2.71
22	R	2.80	2.95	2.99	3.05
	L	3.00	2.99	2.99	3.02
23	R	2.90	2.90	2.97	2.98
	L	2.71	2.85	2.85	2.91
24	R	3.30	3.51	3.77	4.00
	L	3.07	3.21	3.29	3.32
25	R	3.02	2.97	2.98	3.02
	L	2.53	2.88	2.88	2.93
26	R	3.10	3.18	3.18	3.15
	L	3.02	3.08	3.09	3.08
27	R	2.53	2.66	2.65	2.64
	L	2.67	2.67	2.66	2.67

Appendix 2 (continued)

Anterior chamber depth

Patient No.	Eye	Visit 1	Visit 2	Visit 3	Visit 4
28	R	3.19	3.32	3.33	3.34
	L	2.82	3.13	3.05	3.04
29	R	3.06	3.07	3.07	3.11
	L	2.83	2.84	2.88	2.89
30	R	2.80			
	L	2.72			
31	R	2.82	3.28		
	L	2.76	2.98		
32	R	3.20	2.93	3.16	3.20
	L	2.85	2.93	2.99	2.97
33	R	3.56	3.63	3.69	3.75
	L	3.71	3.76	3.77	3.81
34	R	3.03	3.13	3.10	3.11
	L	3.45	3.46	3.45	3.56
35	R	2.83	2.84	2.84	2.84
	L	3.09	3.07	3.07	3.08
36	R	3.52	3.52	3.52	3.59
	L	3.45	3.44	3.56	3.55
37	R	3.26	3.25	3.25	3.32
	L	3.35	3.45	3.59	3.65
38	R	2.99	3.10	3.10	3.17
	L	3.08	3.13	3.21	3.21
39	R	2.89	2.89	2.91	2.91
	L	2.95	3.02	2.86	2.86
40	R	2.76	2.79	2.90	2.91
	L	3.26	3.27	3.24	3.26
41	R	3.30	3.63	3.60	3.62
	L	2.84	2.88	2.86	2.86

Appendix 2 (continued)

		Anterior chamber depth			
Patient No.	Eye	Visit 1	Visit 2	Visit 3	Visit 4
42	R	4.71	4.73	4.74	4.78
	L	4.02	4.28	4.25	4.20
43	R	2.85	2.86	2.89	2.85
	L	2.86	2.84	2.91	2.95
44	R	3.18	3.32	3.33	3.38
	L	3.15	3.14	3.24	3.25
45	R	3.17			
	L	3.68			
46	R	3.37	3.21	3.21	3.20
	L	3.39	3.34	3.33	3.29
47	R	2.74	2.76	2.78	2.80
	L	2.88	2.98	2.97	3.03
48	R	2.95	2.94	2.92	2.90
	L	3.19	3.15	3.16	3.13
49	R	3.35	3.35	3.30	3.40
	L	3.30	3.30	3.28	3.31
50	R	3.26	3.24	3.32	3.33
	L	3.86	3.90	3.98	4.03
51	R	3.29	3.30	3.28	3.29
	L	3.13	3.20	3.20	3.22
52	R	2.80	2.80	2.80	2.80
	L	2.80	2.80	2.90	2.90
53	R	3.08			
	L	3.28			
54	R	2.84	2.84	2.86	2.84
	L	2.90	2.96	2.97	2.97
55	R	3.25	3.30	3.45	3.42
	L	3.43	3.30	3.50	3.50
	Mean	3.08	3.18	3.20	3.22
	S.D.	0.33	0.33	0.34	0.36

APPENDIX 3

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.42	0.56	0.51	0 60	0.59	0.54	0.46	0.59	0.60
1 (R)	2	I	0	−0.10	+0.01	−0.12	−0.20	+0.05	−0.06	−0.04	−0.10
	3		+0.02	−0.10	0	−0.09	−0.20	−0.01	+0.05	−0.04	−0.12
	4		−0.12	−0.16	−0.07	−0.20	−0.27	−0.11	−0.02	−0.10	−0.15
	1		0.42	0.58	0.52	0.51	0.47	0.59	0.52	−.54	0.58
1 (L)	2	I	+0.02	−0.10	−0.09	0	−0.03	−0.07	+0.01	+0.04	−0.08
	3		+0.01	−0.09	−0.08	+0.01	−0.03	−0.04	+0.02	+0.04	−0.09
	4		−0.04	−0.19	−0.19	−0.05	−0.09	−0.09	−0.10	−0.03	−0.16
	1		0.54	0.51	0.53	0.54	0.55	0.59	0.54	0.60	0.57
2 (R)	2	II	−0.03	+0.03	+0.02	+0.05	−0.01	+0.01	+0.01	+0.02	+0.01
	3		−0.07	−0.01	−0.06	0	−0.04	−0.05	+0.01	+0.01	+0.01
	4		−0.03	+0.03	+0.02	+0.01	−0.04	−0.02	+0.01	+0.01	+0.01
	1		0.50	0.59	0.57	0.55	0.55	0.63	0.58	0.61	0.56
2 (L)	2	I	−0.10	−0.07	−0.12	+0.02	+0.02	−0.10	0	−0.01	−0.04
	3		−0.11	−0.12	−0.13	−0.02	−0.02	−0.09	−0.08	−0.01	−0.01
	4		−0.10	−0.11	−0.14	−0.02	−0.02	−0.05	−0.09	−0.05	−0.02

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.54	0.57	0.55	0.51	0.58	0.60	0.62	0.61	0.54
3 (R)	2	I	-0.16	-0.11	-0.12	-0.07	-0.16	-0.03	-0.10	-0.08	+0.01
	3		-0.17	-0.09	-0.10	-0.02	-0.11	-0.05	-0.08	-0.09	+0.03
	4		-0.17	-0.11	-0.11	-0.05	-0.13	-0.04	-0.06	-0.09	+0.02
	1		0.61	0.62	0.55	0.59	0.58	0.53	0.55	0.65	0.62
3 (L)	2	I	-0.18	-0.16	-0.13	-0.17	-0.09	-0.02	-0.08	-0.13	-0.08
	3		-0.21	-0.12	-0.13	-0.15	-0.16	-0.01	-0.04	-0.11	-0.07
	4		-0.21	-0.15	-0.13	-0.16	-0.16	0	-0.03	-0.10	-0.07
	1		0.57	0.63	0.62	0.62	0.58	0.62	0.56	0.61	0.70
4 (R)	2	I	-0.12	-0.15	-0.15	-0.09	-0.08	-0.03	-0.04	-0.03	-0.15
	3		-0.11	-0.11	-0.13	-0.03	-0.08	-0.02	+0.04	+0.03	-0.08
	4		-0.12	-0.12	-0.10	-0.08	-0.08	-0.02	+0.02	+0.02	-0.07
	1		0.55	0.71	-.79	0.71	0.67	0.74	0.74	0.76	0.70
4 (L)	2	II	-0.04	-0.14	-0.27	-0.17	-0.18	-0.13	-0.17	-0.13	-0.15
	3		-0.04	-0.13	-0.28	-0.13	-0.17	-0.12	-0.15	-0.11	-0.08
	4		-0.02	-0.12	-0.28	-0.16	-0.14	-0.08	-0.17	-0.15	-0.07

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.44	0.51	0.52	0.52	0.48	0.58	0.62	0.59	0.51
6 (R)	2	I	-0.10	-0.08	-0.12	-0.08	-0.10	-0.11	-0.13	-0.09	-0.02
	3		-0.08	-0.09	-0.08	-0.06	-0.11	-0.10	-0.11	-0.05	-0.02
	4		-0.11	-0.09	-0.12	-0.06	-0.12	-0.10	-0.13	-0.06	-0.02
	1		0.46	0.58	0.47	0.57	0.58	0.64	0.51	0.53	0.59
6 (L)	2	I	-0.02	-0.11	-0.04	-0.11	-0.16	-0.09	-0.06	-0.02	-0.10
	3		-0.07	-0.11	-0.08	-0.12	-0.17	-0.09	-0.08	0	-0.10
	4		-0.06	-0.11	-0.09	-0.13	-0.20	-0.08	-0.06	+0.01	-0.07
	1		0.44	0.65	0.44	0.73	0.68	0.63	0.54	0.74	0.67
7 (R)	2	I	-0.07	-0.23	-0.03	-0.29	-0.27	-0.14	-0.07	-0.22	-0.17
	3		-0.07	-0.17	0	-0.28	-0.22	-0.12	0	-0.20	-0.18
	4		-0.07	-0.22	+0.01	-0.27	-0.26	-0.11	0	-0.16	-0.15
	1		0.55	0.74	0.76	0.74	0.75	0.75	0.77	0.78	0.77
7 (L)	2	I	-0.15	-0.30	-0.36	-0.27	-0.31	-0.27	-0.33	-0.26	-0.30
	3		-0.17	-0.25	-0.32	-0.26	-0.29	-0.25	-0.29	-0.27	-0.27
	4		-0.16	-0.25	-0.31	-0.26	-0.26	-0.18	-0.29	-0.24	-0.23

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.43	0.49	0.43	0.48	0.47	0.54	0.55	0.56	0.53
8 (R)	2	I	-0.07	-0.07	-0.06	-0.11	-0.18	-0.08	-0.10	-0.10	-0.12
	3		-0.06	-0.08	-0.06	-0.11	-0.16	0	-0.11	-0.12	-0.12
	4		-0.06	-0.09	-0.07	-0.06	-0.12	-0.06	-0.11	-0.08	-0.05
	1		0.43	0.53	0.55	0.52	0.45	0.59	0.55	0.58	0.55
8 (L)	2		-0.11	-0.12	-0.37	-0.12	-0.12	-0.12	-0.13	-0.09	-0.12
	3				Keratoplasty Sutures on Situ						
	4		0.52					-0.05	-0.01	-0.09	0
	1		0.49	0.52	0.60	0.60	0.49	0.53	0.60	0.61	0.57
9 (R)	2	I	-0.01	-0.03	-0.06	-0.09	-0.08	+0.01	-0.01	0	+0.01
	3		-0.06	-0.05	-0.06	-0.06	-0.06	-0.01	0	+0.01	+0.02
	4		-0.06	-0.04	-0.06	-0.04	-0.06	+0.05	0	+0.01	+0.03
	1		0.53	0.58	0.57	0.59	0.54	0.62	0.59	0.62	0.59
9 (L)	2	I	-0.04	-0.04	-0.08	-0.04	-0.04	-0.03	-0.05	-0.01	+0.01
	3		-0.04	-0.11	-0.08	-0.05	-0.04	-0.02	-0.03	+0.01	0
	4		-0.04	-0.10	-0.07	-0.06	-0.04	-0.02	-0.04	+0.02	+0.02

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.34	0.47	0.45	0.44	0.29	0.57	0.47	0.58	0.42
10 (R)	2	I	-0.19	-0.17	-0.17	-0.10	-0.09	-0.17	-0.08	-0.13	-0.10
	3		-0.04	-0.06	-0.09	-0.09	-0.04	-0.04	-0.06	-0.06	-0.12
	4		-0.11	-0.16	-0.09	-0.09	-0.08	-0.10	-0.05	-0.10	-0.11
	1		0.38	0.43	0.37	0.48	0.31	0.45	0.59	0.56	0.42
10 (L)	2	I	-0.06	-0.06	-0.17	-0.10	-0.04	0	-0.30	-0.18	-0.10
	3		-0.04	-0.03	-0.04	-0.06	-0.05	-0.04	-0.27	-0.17	-0.08
	4		-0.07	-0.07	-0.11	-0.08	-0.11	+0.07	-0.22	-0.11	-0.01
	1		0.44	0.50	0.47	0.48	0.41	0.51	0.52	0.53	0.48
11 (R)	2	I	-0.04	-0.04	+0.02	-0.02	+0.01	0	+0.01	-0.01	+0.02
	3		-0.03	-0.10	-0.02	-0.01	-0.01	-0.02	0	+0.02	+0.03
	4		-0.04	-0.12	+0.01	-0.02	-0.02	-0.03	-0.02	-0.01	+0.02
	1		0.45	0.53	0.47	0.45	0.47	0.56	0.46	0.49	0.55
11 (L)	2	II	0	-0.01	-0.02	+0.02	+0.02	-0.04	+0.03	0	0
	3		0	-0.02	-0.03	+0.02	-0.03	-0.02	+0.02	+0.01	-0.04
	4		-0.01	-0.14	0	0	-0.03	-0.01	+0.05	+0.02	-0.03

Appendix 3 (contimued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
12 (R)	1	II	0.38	0.57	0.54	0.53	0.47	0.63	0.56	0.56	0.56
	2		0	-0.16	-0.10	-0.11	-0.12	-0.15	-0.12	-0.02	-0.08
	3		0	-0.21	-0.17	-0.12	-0.12	-0.16	-0.08	-0.01	-0.07
	4		-0.03	-0.20	-0.17	-0.08	-0.11	-0.15	-0.03	+0.03	-0.03
12 (L)	1	II	0.47	0.54	0.49	0.52	0.49	0.57	0.55	0.61	0.56
	2		-0.05	-0.07	-0.04	-0.08	-0.05	-0.02	-0.05	-0.05	-0.02
	3		-0.02	-0.02	-0.07	-0.02	-0.04	-0.10	-0.06	0	-0.02
	4		-0.01	-0.02	-0.07	-0.02	-0.01	+0.03	-0.06	+0.02	+0.01
13 (R)	1	I	0.40	0.48	0.53	0.48	0.45	0.63	0.59	0.52	0.50
	2		-0.14	-0.10	-0.13	-0.10	-0.09	-0.17	-0.15	-0.03	-0.04
	3		-0.11	-0.10	-0.19	-0.06	-0.12	-0.19	-0.07	+0.01	0
	4		-0.05	-0.10	-0.17	-0.13	-0.10	-0.14	-0.24	-0.07	-0.03
13 (L)	1	I	0.34	0.51	0.37	0.50	0.46	0.58	0.40	0.56	0.55
	2		-0.06	-0.14	-0.07	-0.11	-0.11	-0.11	-0.01	-0.09	-0.10
	3		-0.05	-0.07	-0.06	-0.08	-0.11	-0.06	-0.01	-0.07	-0.10
	4		-0.06	-0.13	-0.08	-0.08	-0.10	-0.11	-0.01	-0.05	-0.11

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.39	0.49	0.44	0.44	0.47	0.51	0.50	0.51	0.52
14 (R)	2	II	-0.02	-0.05	-0.01	0	-0.02	+0.04	+0.04	+0.05	0
	3		-0.10	-0.13	-0.08	-0.05	-0.06	-0.03	+0.04	+0.03	+0.03
	4		-0.03	-0.12	-0.09	-0.01	-0.08	-0.03	-0.01	+0.01	+0.01
	1		0.44	0.55	0.39	0.49	0.48	0.58	0.47	0.52	0.53
14 (L)	2	II	0	-0.05	0	0	-0.02	-0.03	+0.01	+0.02	+0.01
	3		-0.08	-0.19	-0.01	-0.03	-0.13	-0.07	-0.02	+0.02	-0.03
	4		-0.02	-0.18	-0.05	-0.02	-0.06	0	-0.05	+0.03	-0.01
	1		0.38	0.51	0.43	0.51	0.47	0.58	0.51	0.58	0.51
15 (R)	2	II	0	-0.06	+0.03	-0.01	-0.02	-0.04	+0.01	+0.02	+0.03
	3		0	-0.07	-0.04	0	-0.02	-0.03	+0.05	+0.02	-0.01
	4		+0.02	-0.05	+0.01	0	-0.01	-0.02	+0.01	+0.02	+0.01
	1		0.46	0.52	0.43	0.53	0.50	0.61	0.50	0.56	0.58
15 (L)	2	II	0	-0.02	+0.04	-0.02	-0.02	-0.01	+0.04	+0.01	0
	3		0	-0.02	+0.07	-0.01	-0.11	-0.05	+0.04	+0.02	+0.01
	4		-0.03	-0.02	-0.01	-0.07	-0.12	-0.05	+0.01	+0.02	-0.02

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.44	0.48	0.46	0.49	0.46	0.54	0.51	0.53	0.55
16 (R)	2	II	-0.02	-0.02	-0.01	-0.02	-0.03	-0.01	-0.01	+0.01	-0.02
	3		-0.02	0	-0.02	0	-0.03	0	0	+0.01	+0.02
	4		-0.03	-0.03	-0.03	-0.05	-0.02	-0.01	-0.02	+0.03	0
	1		0.48	0.54	0.48	0.51	0.48	0.58	0.54	0.56	0.55
16 (L)	2	I	-0.04	-0.02	-0.02	-0.05	-0.01	-0.02	-0.04	+0.02	-0.02
	3		-0.04	+0.01	-0.05	-0 02	+0.01	+0.01	0	+0.06	0
	4		-0.07	-0.04	-0.05	-0.02	+0.02	-0.01	-0.02	+0.02	+0.01
	1		0.45	0.52	0.55	0.54	0.50	0.61	0.58	0.57	0.60
17 (R)	2	I	-0.04	-0.04	-0.11	-0.07	-0.09	-0.06	-0.09	-0.01	-0.07
	3		-0.05	-0.02	-0.10	-0.08	-0.08	-0.06	-0.04	-0.01	-0.08
	4		-0.04	-0.05	-0.22	-0.08	-0.08	-0.09	-0.01	+0.01	-0.06
	1		0.45	0.52	0.49	0.51	0.50	0.54	0.51	0.55	0.54
17 (L)	2	II	-0.06	-0.06	-0.08	-0.04	-0.11	-0.04	-0.01	-0.03	-0.02
	3		-0.04	-0.03	-0.08	-0.03	-0.12	-0.02	-0.05	-0.01	0
	4		-0.01	-0.05	-0.10	-0.03	-0.11	0	-0.03	-0.01	-0.01

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.28	0.48	0.44	0.45	0.35	0.49	0.50	0.53	0.36
18 (R)	2	II	0	-0.01	+0.05	0	-0.09	-0.04	+0.01	+0.01	+0.02
	3		-0.01	-0.11	-0.04	+0.02	-0.09	-0.01	+0.01	+0.01	+0.03
	4		-0.01	-0.11	-0.07	-0.02	-0.09	+0.01	-0.04	-0.01	+0.06
	1		0.40	0.49	0.44	0.47	0.40	0.52	0.42	0.60	0.42
18 (L)	2	II	+0.04	0	-0.01	+0.05	+0.05	+0.03	+0.09	+0.01	+0.12
	3		0	+0.01	+0.05	+0.03	+0.03	+0.04	+0.05	-0.05	+0.06
	4		-0.02	0	-0.08	+0.01	+0.02	+0.05	0	-0.07	+0.07
	1		0.43	0.49	0.54	0.50	0.48	0.54	0.55	0.54	0.56
19 (R)	2	II	-0.01	-0.01	-0.05	+0.04	0	+0.01	+0.02	+0.04	-0.04
	3		+0.02	-0.01	-0.05	+0.01	-0.01	+0.05	+0.01	+0.05	-0.07
			0	-0.01	-0.06	-0.01	-0.01	+0.05	+0.05	+0.07	-0.04
	1		0.45	0.50	0.47	0.51	0.45	0.54	0.48	0.51	0.51
19 (L)	2	II	-0.01	+0.04	0	-0.01	0	+0.02	+0.02	+0.04	-0.05
	3		0	+0.01	-0.01	+0.02	+0.01	+0.03	+0.05	+0.06	0
	4		-0.02	+0.01	-0.03	+0.01	0	+0.05	+0.07	+0.07	+0.01

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.43	0.53	0.43	0.49	0.53	0.60	0.52	0.52	0.48
20 (R)	2	I	-0.03	-0.08	0	-0.05	-0.19	-0.10	0	0	+0.01
	3		-0.06	-0.15	-0.07	-0.07	-0.23	-0.14	-0.02	-0.03	-0.07
	4		-0.04	-0.08	0	-0.05	-0.18	-0.09	-0.06	+0.02	-0.06
	1		0.46	0.55	0.44	0.49	0.49	0.60	0.53	0.53	0.49
20 (L)	2	II	-0.04	-0.08	-0.03	-0.02	-0.05	-0.06	-0.08	-0.01	+0.01
	3		-0.12	-0.13	-0.06	-0.05	-0.12	-0.14	-0.08	+0.01	-0.05
	4		-0.02	-0.08	+0.01	-0.03	-0.14	-0.06	-0.08	+0.04	+0.01
	1		0.46	0.57	0.56	0.59	0.48	0.58	0.62	0.62	0.56
21 (R)	2	I	0	0	-0.02	-0.01	+0.02	0	0	-0.02	0
	3		-0.06	-0.09	-0.05	-0.05	+0.01	+0.01	-0.09	-0.02	-0.04
	4		-0.04	-0.07	-0.07	-0.06	-0.02	0	-0.08	-0.02	-0.02
	1		0.51	0.55	0.52	0.57	0.49	0.62	0.57	0.62	0.54
21 (L)	2	II	0	-0.01	-0.01	+0.01	0	0	+0.01	0	0
	3		0	-0.01	-0.01	-0.04	0	-0.05	-0.01	0	+0.02
	4		-0.01	-0.01	-0.04	-0.03	+0.01	-0.03	-0.03	-0.01	+0.03

Appendix 3 (continued)

Patient No.	Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
			2	3	6	7	1	4	5	8
1		0.40	0.52	0.46	0.48	0.46	0.55	0.50	0.55	0.53
22 (R) 2	I	0	-0.03	-0.01	+0.04	-0.01	+0.01	+0.02	+0.04	0
3		-0.04	-0.08	0	-0.01	-0.01	-0.07	+0.02	+0.02	+0.02
4		-0.05	-0.07	-0.07	-0.02	-0.04	-0.03	+0.03	0	+0.03
1		0.40	0.52	0.45	0.49	0.53	0.62	0.47	0.58	0.55
22 (L) 2	II	+0.01	0	-0.02	-0.02	-0.06	-0.04	+0.02	0	+0.03
3		-0.04	-0.03	-0.05	-0.01	-0.09	-0.02	-0.04	-0.04	+0.01
4		0	-0.10	-0.07	-0.06	-0.06	-0.05	+0.01	-0.06	+0.01
1		0.35	0.49	0.48	0.48	0.42	0.58	0.49	0.53	0.49
23 (R) 2	II	0	-0.08	-0.01	0	-0.06	-0.08	-0.01	+0.02	0
3		-0.02	-0.04	-0.03	0	-0.04	+0.01	+0.01	+0.05	-0.02
4		-0.03	-0.03	-0.03	-0.02	-0.04	-0.06	+0.02	+0.02	-0.02
1		0.44	0.51	0.49	0.46	0.43	0.59	0.50	0.62	0.52
23 (L) 2	I	-0.09	-0.04	-0.09	+0.02	-0.03	-0.07	-0.02	-0.06	-0.04
3		-0.04	-0.06	-0.09	+0.02	0	-0.07	0	-0.04	-0.02
4		-0.10	-0.07	-0.13	+0.03	-0.04	+0.06	+0.02	-0.05	0

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.40	0.46	0.53	0.55	0.37	0.50	0.57	0.57	0.51
24 (R)	2	I	-0.01	-0.04	-0.02	0	0	-0.04	-0.01	+0.05	+0.01
	3		-0.07	-0.06	-0.17	-0.07	-0.08	+0.06	+0.01	+0.04	+0.05
	4		-0.10	-0.03	-0.19	-0.06	-0.07	+0.04	-0.11	-0.01	+0.02
	1		0.48	0.57	0.51	0.56	0.51	0.59	0.58	0.62	0.59
24 (L)	2	I	-0.04	-0.02	-0.01	-0.03	-0.02	+0.01	0	+0.01	-0.01
	3		-0.07	-0.05	-0.04	-0.03	-0.11	+0.02	-0.02	+0.01	0
	4		-0.10	-0.06	-0.10	-0.02	-0.13	+0.02	-0.05	+0.03	-0.05
	1		0.38	0.54	0.51	0.56	0.44	0.55	0.59	0.60	0.52
25 (R)	2	II	+0.05	-0.03	+0.01	+0.01	-0.01	+0.05	+0.02	-0.01	+0.02
	3		+0.04	-0.05	0	0	0	+0.07	+0.03	+0.01	+0.02
	4		0	-0.04	0	-0.08	-0.02	+0.09	+0.03	+0.03	+0.03
	1		0.57	0.55	0.45	0.54	0.47	0.61	0.54	0.62	0.54
25 (L)	2	I	-0.05	+0.01	+0.02	+0.04	+0.02	-0.01	-0.01	+0.01	+0.03
	3		-0.05	+0.01	-0.01	+0.04	+0.02	+0.02	+0.02	+0.02	+0.02
			-0.10	-0.01	-0.02	0	+0.03	+0.03	-0.01	+0.02	+0.02

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.40	0.44	0.43	0.49	0.42	0.51	0.55	0.56	0.48
26 (R)	2	I	−0.08	+0.02	+0.01	−0.01	−0.01	−0.01	−0.02	+0.02	0
	3		−0.08	−0.01	−0.03	−0.01	+0.01	−0.02	−0.09	−0.06	+0.01
	4		−0.05	0	−0.03	−0.03	−0.02	+0.01	−0.07	−0.02	+0.05
	1		0.48	0.52	0.45	0.48	0.46	0.54	0.45	0.50	0.50
26 (L)	2	I	−0.06	−0.04	−0.03	+0.01	−0.01	−0.02	+0.04	+0.05	+0.05
	3		−0.09	−0.04	−0.01	+0.03	−0.01	−0.03	+0.05	+0.05	+0.03
	4		−0.08	−0.06	−0.04	−0.01	−0.04	0	+0.03	+0.03	+0.03
	1		0.62	0.60	0.60	0.62	0.59	0.63	0.66	0.66	0.63
27 (R)	2	I	−0.13	0	−0.01	−0.03	−0.03	+0.05	0	0	0
	3		−0.12	−0.02	−0.04	−0.08	−0.04	+0.02	−0.02	+0.01	−0.01
	4		−0.11	−0.02	−0.06	−0.04	−0.03	+0.03	−0.02	+0.01	−0.02
	1		0.53	0 59	0.56	0.62	0.58	0.62	0.57	0.66	0.63
27 (L)	2	II	0	+0.02	−0.01	−0.01	−0.01	+0.04	+0.02	+0.01	0
	3		+0.01	+0.03	−0.01	−0.05	−0.02	+0.04	+0.05	+0.01	−0.03
	4		0	+0.02	−0.04	−0.04	−0.04	+0.06	+0.05	+0.01	−0.04

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	2	3	6	7	1	4	5	8
	1		0.51	0.61	0.54	0.58	0.56	0.57	0.61	0.66	0.66
28 (R)	2	I	−0.13	−0.12	−0.08	−0.07	−0.09	+0.05	−0.10	−0.08	−0.07
	3		−0.14	−0.13	−0.08	−0.06	−0.13	+0.02	−0.10	−0.08	−0.10
	4		−0.15	−0.14	−0.07	−0.08	−0.13	+0.02	−0.11	−0.10	−0.14
	1		0.58	0.62	0.59	0.60	0.62	0.73	0.62	0.64	0.68
28 (L)	2	I	−0.11	−0.08	−0.14	−0.09	−0.14	−0.14	−0.11	−0.05	−0.14
	3		−0.13	−0.12	−0.14	−0.11	−0.14	−0.14	−0.17	−0.05	−0.09
	4		−0.12	−0.08	−0.13	−0.12	−0.14	−0.14	−0.17	−0.07	−0.10
	1		0.44	0.53	0.54	0.57	0.42	0.58	0.57	0.63	0.48
29 (R)	2	I	−0.01	+0.02	+0.01	+0.01	0	+0.05	+0.04	0	+0.06
	3		−0.01	0	−0.08	+0.02	+0.02	+0.05	+0.04	+0.01	+0.09
	4		−0.05	−0.01	−0.07	−0.03	+0.02	−0.01	−0.04	−0.04	+0.06
	1		0.52	0.57	0.55	0.63	0.52	0.60	0.57	0.63	0.60
29 (L)	2	II	−0.01	−0.01	−0.01	−0.04	+0.02	+0.01	+0.01	+0.01	+0.01
	3		0	+0.01	+0.01	−0.02	+0.06	+0.03	+0.01	−0.04	+0.01
	4		−0.01	−0.05	−0.02	−0.04	+0.02	−0.01	−0.04	−0.01	−0.02

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.40	0.49	0.50	0.49	0.42	0.55	0.58	0.55	0.51
32 (R)	2	I	+0.12	+0.10	+0.12	+0.11	+0.12	+0.11	+0.10	+0.15	+0.15
	3		−0.01	−0.08	−0.05	0	+0.02	0	−0.02	+0.02	0
	4		−0.05	−0.04	−0.05	−0.03	−0.02	−0.04	−0.06	0	−0.01
	1		0.45	0.51	0.44	0.52	0.47	0.57	0.55	0.58	0.48
32 (L)	2	II	+0.11	+0.10	+0.11	+0.10	+0.12	+0.10	+0.08	+0.12	+0.13
	3		−0.04	+0.01	−0.05	−0.03	−0.03	−0.04	−0.07	−0.01	−0.01
	4		−0.02	−0.02	−0.06	−0.06	−0.05	−0.05	−0.07	−0.02	+0.02
	1		0.44	0.57	0.52	0.58	0.44	0.65	0.62	0.66	0.60
33 (R)	2	I	−0.07	−0.09	−0.04	−0.03	+0.02	−0.15	0	−0.03	−0.05
	3		−0.03	−0.09	−0.05	−0.02	0	−0.07	−0.02	−0.03	−0.02
	4		−0.08	−0.08	−0.08	−0.06	−0.06	−0.06	−0.03	−0.04	−0.03
	1		0.49	0.44	0.45	0.57	0.47	0.62	0.54	0.69	0.54
33 (L)	2	I	−0.05	+0.08	+0.01	−0.03	+0.01	−0.02	+0.04	−0.06	+0.01
	3		−0.01	+0.10	+0.02	−0.06	−0.03	0	−0.01	−0.04	−0.02
	4		−0.05	+0.10	−0.05	−0.08	−0.04	0	−0.02	−0.09	−0.04

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.42	0.44	0.55	0.47	0.41	0.54	0.62	0.61	0.51
34 (R)	2		-0.10	-0.01	-0.10	0	-0.06	-0.02	-0.06	-0.02	-0.05
	3		-0.07	-0.02	-0.09	+0.03	-0.06	+0.01	-0.02	-0.01	-0.03
	4		-0.08	-0.04	-0.12	-0.04	-0.07	-0.03	-0.09	-0.05	-0.02
	1		0.35	0.46	0.39	0.51	0.37	0.57	0.50	0.58	0.48
34 (L)	2	I	-0.01	0	-0.07	-0.04	-0.01	-0.04	-0.05	+0.01	-0.04
	3		0	+0.04	-0.06	-0.06	-0.04	+0.04	-0.04	+0.03	-0.02
	4		-0.06	-0.03	-0.09	-0.17	-0.03	-0.01	-0.07	-0.07	-0.03
	1		0.42	0.52	0.48	0.49	0.49	0.55	0.54	0.58	0.53
35 (R)	2	II	-0.01	-0.02	0	+0.03	0	-0.02	0	0	0
	3		-0.01	-0.02	+0.01	+0.03	0	-0.02	+0.05	+0.01	+0.03
	4		-0.01	-0.10	-0.04	-0.02	-0.01	-0.03	-0.01	-0.03	+0.01
	1		0.41	0.54	0.45	0.51	0.47	0.59	0.48	0.58	0.58
35 (L)	2	II	+0.02	-0.03	+0.01	+0.02	+0.06	-0.02	+0.04	0	-0.01
	3		+0.02	-0.05	-0.03	+0.01	+0.02	-0.03	+0.02	-0.03	+0.01
	4		+0.01	-0.05	-0.05	-0.04	+0.03	-0.03	+0.03	0	0

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.33	0.41	0.46	0.45	0.37	0.45	0.52	0.57	0.48
36 (R)	2	II	0	+0.02	−0.03	0	+0.05	+0.02	0	−0.03	0
	3		0	−0.03	−0.09	−0.07	−0.01	+0.04	−0.07	−0.07	−0.05
	4		−0.02	−0.04	−0.11	−0.06	−0.06	+0.04	−0.07	−0.06	−0.03
	1		0.40	0.48	0.41	0.52	0.41	0.55	0.45	0.56	0.46
36 (L)	2	I	+0.01	+0.03	0	0	0	+0.02	−0.02	+0.03	0
	3		−0.06	−0.06	−0.05	−0.04	−0.06	−0.03	−0.05	−0.02	0
	4		−0.05	−0.06	−0.04	−0.10	−0.05	−0.02	−0.04	−0.04	0
	1		0.45	0.53	0.45	0.49	0.47	0.54	0.52	0.48	0.56
37 (R)	2	I	0	−0.05	0	−0.02	−0.01	−0.02	+0.01	+0.07	−0.03
	3		0	−0.06	0	−0.02	−0.01	0	+0.03	+0.06	−0.03
	4		−0.07	−0.10	0	−0.06	−0.05	−0.04	−0.02	+0.06	−0.07
	1		0.40	0.44	0.41	0.47	0.44	0.49	0.50	0.56	0.50
37 (L)	2		0	+0.04	0	+0.02	−0.01	+0.06	+0.02	−0.02	+0.07
	3		+0.01	+0.03	0	+0.02	+0.02	+0.07	+0.02	+0.02	+0.08
	4		−0.05	+0.04	0	−0.01	−0.02	+0.07	−0.04	−0.04	+0.01

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.36	0.41	0.42	0.45	0.35	0.59	0.49	0.54	0.48
38 (R)	2	II	+0.04	+0.01	−0.04	−0.04	+0.02	−0.12	−0.02	−0.07	−0.06
	3		+0.04	+0.03	−0.04	−0.01	+0.01	−0.16	−0.01	−0.08	−0.07
	4		+0.02	0	−0.04	0	+0.03	−0.13	−0.01	−0.06	−0.04
	1		0.37	0.42	0.35	0.40	0.34	0.52	0.44	0.45	0.56
38 (L)	2	II	0	+0.02	+0.04	+0.02	+0.07	−0.04	+0.06	+0.01	−0.07
	3		+0.02	+0.01	+0.04	+0.03	+0.02	−0.02	+0.05	+0.04	−0.09
	4		+0.02	+0.04	0	+0.04	+0.02	−0.02	−0.02	+0.03	−0.12
	1		0.41	0.47	0.52	0.52	0.43	0.55	0.60	0.57	−0.50
39 (R)	2	II	0	−0.04	−0.05	−0.04	−0.01	−0.03	−0.04	0	−0.01
	3		−0.02	−0.05	−0.08	−0.04	−0.02	−0.07	−0.08	−0.01	−0.01
	4		−0.02	−0.04	−0.09	−0.06	−0.01	−0.06	−0.08	−0.01	−0.03
	1		0.45	0.50	0.47	0.49	0.46	0.56	0.47	0.57	0.54
39 (L)	2	II	−0.02	−0.05	0	0	0	−0.04	+0.01	−0.03	−0.03
	3		−0.01	−0.08	−0.03	−0.03	−0.03	−0.02	+0.01	−0.03	−0.04
	4		−0.01	−0.01	−0.07	−0.05	−0.04	−0.02	−0.01	−0.03	−0.03

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.44	0.49	0.49	0.50	0.38	0.52	0.62	0.58	0.50
40 (R)	2	I	−0.03	−0.02	−0.03	+0.02	+0.05	+0.03	−0.02	+0.04	+0.04
	3		−0.04	−0.08	−0.03	+0.01	+0.04	+0.03	−0.08	+0.04	+0.02
	4		−0.05	−0.03	−0.04	−0.03	+0.03	+0.02	−0.05	+0.03	0
	1		0.34	0.50	0.39	0.53	0.42	0.57	0.51	0.63	0.54
40 (L)	2	III	+0.04	+0.02	0	−0.01	+0.03	−0.03	+0.01	0	+0.02
	3		+0.07	+0.02	−0.03	−0.03	−0.03	−0.01	−0.05	−0.02	0
	4		+0.10	+0.01	0	−0.03	−0.01	+0.01	−0.03	−0.04	−0.01
	1		0.30	0.41	0.45	0.45	0.26	0.51	0.54	0.58	0.42
41 (R)	2	II	−0.03	+0.07	−0.10	0	+0.08	+0.01	−0.01	−0.01	+0.03
	3		0	+0.04	−0.05	−0.08	+0.03	+0.01	+0.02	−0.03	−0.02
	4		−0.02	−0.01	−0.19	−0.01	+0.03	−0.03	0	−0.06	−0.02
	1		0.46	0.53	0.47	0.50	0.48	0.59	0.54	0.53	0.55
41 (L)	2	II	−0.04	−0.08	+0.01	−0.05	−0.09	−0.05	0	+0.05	−0.07
	3		−0.02	−0.01	−0.02	−0.02	−0.01	+0.01	−0.05	+0.01	−0.01
	4		−0.02	−0.04	−0.08	−0.03	−0.01	−0.02	−0.07	+0.02	0

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.19	0.33	0.26	0.28	0.21	0.51	0.47	0.48	0.45
42 (R)	2	II	−0.02	−0.02	+0.05	−0.01	+0.05	−0.06	+0.03	+0.05	+0.05
	3		−0.03	−0.01	0	+0.02	+0.05	−0.03	−0.03	+0.01	−0.02
	4		−0.02	+0.01	−0.03	+0.01	+0.06	−0.03	−0.05	+0.02	−0.01
	1		0.23	0.38	0.22	0.37	0.31	0.47	0.39	0.55	0.41
42 (L)	2	I	−0.01	+0.07	+0.01	−0.05	+0.02	+0.08	−0.13	−0.03	+0.01
	3		+0.02	+0.09	+0.03	−0.05	+0.04	+0.03	−0.13	−0.03	+0.03
	4		+0.07	+0.09	+0.01	+0.04	+0.03	+0.10	−0.09	+0.02	+0.07
	1		0.40	0.47	0.42	0.47	0.42	0.59	0.49	0.55	0.52
43 (R)	2	II	+0.09	−0.01	+0.04	+0.01	+0.01	−0.04	+0.03	+0.03	+0.06
	3		−0.04	−0.02	+0.06	+0.03	+0.02	−0.08	+0.06	−0.06	+0.05
	4		0	+0.02	+0.05	+0.04	0	−0.02	+0.06	−0.06	+0.07
	1		0.44	0.53	0.47	0.54	0.51	0.59	0.52	0.55	0.55
43 (L)	2	II	+0.02	−0.05	0	−0.04	−0.01	0	+0.03	+0.03	+0.03
	3		0	0	−0.01	−0.05	−0.02	0	−0.01	+0.02	+0.02
	4		+0.01	−0.04	+0.01	−0.05	−0.01	+0.02	0	+0.06	+0.04

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.42	0.42	0.48	0.50	0.39	0.48	0.54	0.54	0.53
44 (R)	2	I	−0.04	+0.01	−0.05	−0.04	+0.02	+0.05	+0.01	+0.02	−0.03
	3		−0.05	+0.01	−0.05	−0.02	−0.03	+0.10	0	+0.04	−0.01
	4		−0.05	+0.01	−0.07	−0.03	−0.03	+0.11	+0.03	+0.05	+0.02
	1		0.45	0.48	0.46	0.50	0.48	0.50	0.54	0.60	0.55
44 (L)	2	II	+0.01	0	+0.01	−0.01	0	+0.07	0	−0.04	+0.02
	3		+0.01	+0.05	+0.02	−0.02	−0.02	+0.12	0	−0.06	0
	4		0	0	0	−0.02	−0.04	+0.13	+0.02	0	+0.03
	1		0.38	0.44	0.45	0.43	0.38	0.52	0.46	0.49	0.47
46 (R)	2	III	+0.06	+0.04	+0.07	+0.08	+0.11	−0.02	+0.11	+0.10	+0.10
	3		+0.06	+0.03	+0.04	+0.08	+0.06	+0.02	+0.11	+0.12	+0.05
	4		+0.07	+0.04	+0.03	+0.07	+0.08	+0.03	+0.10	+0.10	+0.03
	1		0.36	0.44	0.38	0.44	0.36	0.45	0.47	0.56	0.50
46 (L)	2	III	+0.05	+0.05	+0.08	+0.12	+0.04	+0.07	+0.03	+0.04	+0.02
	3		+0.06	+0.03	+0.02	+0.10	+0.04	+0.10	+0.04	+0.04	0
	4		+0.10	+0.04	+0.04	+0.08	+0.06	+0.12	+0.05	+0.04	+0.03

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.36	0.47	0.56	0.42	0.42	0.55	0.53	0.51	0.43
47 (R)	2	III	+0.08	−0.01	−0.08	+0.05	+0.04	−0.07	−0.05	+0.03	+0.03
	3		+0.06	−0.03	−0.10	+0.05	+0.03	−0.06	−0.04	+0.02	+0.08
	4		+0.04	−0.03	−0.10	+0.05	+0.03	−0.01	−0.04	+0.02	+0.09
	1		0.37	0.48	0.41	0.44	0.37	0.52	0.49	0.49	0.46
47 (L)	2	II	0	0	−0.01	+0.01	+0.06	+0.02	−0.03	+0.06	+0.06
	3		+0.01	−0.01	0	0	+0.05	+0.03	0	+0.06	+0.06
			0	−0.01	−0.02	+0.01	−0.01	+0.03	0	+0.06	+0.06
	1		0.30	0.42	0.43	0.44	0.40	0.54	0.51	0.57	0.49
48 (R)	2	III	+0.01	+0.02	0	+0.01	+0.01	0	0	+0.03	+0.05
	3		+0.03	0	+0.02	+0.03	−0.01	−0.02	+0.03	+0.02	+0.03
	4		+0.05	+0.04	+0.03	+0.05	−0.01	−0.01	0	+0.02	+0.03
	1		0.31	0.41	0.36	0.43	0.34	0.53	0.46	0.55	0.42
48 (L)	2	III	+0.04	+0.04	0	+0.02	+0.02	+0.02	+0.02	+0.01	+0.13
	3		+0.03	−0.01	0	+0.01	+0.07	0	+0.03	+0.01	+0.10
			+0.06	−0.11	0	+0.06	+0.10	−0.01	−0.04	+0.01	+0.15

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.25	0.33	0.40	0.41	0.36	0.44	0.49	0.52	0.40
49 (R)	2	III	0	+0.02	−0.03	+0.03	−0.01	+0.06	+0.05	0	+0.05
	3		+0.05	−0.04	−0.03	+0.04	+0.03	+0.06	+0.03	+0.02	+0.06
	4		+0.05	+0.05	−0.02	+0.06	−0.02	+0.11	0	+0.03	+0.05
	1		0.35	0.45	0.31	0.41	0.37	0.48	0.43	0.52	0.41
49 (L)	2	II	0	+0.01	0	+0.05	0	+0.09	−0.03	+0.04	0
	3		+0.02	+0.02	+0.02	+0.03	+0.04	+0.02	−0.01	+0.06	+0.06
	4		−0.01	0	+0.02	+0.02	+0.04	+0.07	−0.01	+0.06	+0.13
	1		0.44	0.45	0.55	0.54	0.44	0.61	0.62	0.62	0.44
50 (R)	2	I	+0.02	+0.01	−0.07	+0.01	0	−0.03	−0.04	+0.01	+0.02
	3		−0.06	−0.01	−0.16	−0.11	−0.04	−0.04	−0.10	−0.08	−0.06
	4		−0.07	−0.01	−0.16	−0.13	−0.06	−0.05	−0.10	−0.09	−0.07
	1		0.44	0.53	0.44	0.54	0.34	0.63	0.50	0.60	0.44
50 (L)	2	I	−0.04	−0.03	−0.02	−0.01	−0.02	0	−0.01	+0.03	−0.04
	3		−0.02	−0.07	−0.13	−0.12	0	−0.09	−0.04	−0.06	−0.02
	4		−0.07	−0.09	−0.13	−0.12	0	−0.01	+0.04	−0.05	−0.07

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peropheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.31	0.41	0.41	0.38	0.32	0.48	0.59	0.57	0.38
51 (R)	2	II	-0.01	+0.04	-0.02	+0.02	+0.02	+0.08	0	-0.05	+0.04
	3		+0.02	0	-0.08	+0.02	-0.01	+0.06	0	-0.03	+0.05
	4		0	0	-0.08	+0.02	-0.02	+0.08	+0.01	-0.02	+0.06
	1		0.47	0.49	0.41	0.49	0.43	0.59	0.50	0.61	0.54
51 (L)	2	I	-0.07	+0.02	0	-0.06	-0.01	0	-0.02	-0.05	+0.01
	3		-0.07	-0.01	-0.02	-0.04	-0.03	0	+0.03	-0.07	0
	4		-0.09	0	-0.02	-0.05	-0.03	0	+0.04	-0.07	-0.08
	1		0.45	0.49	0.48	0.53	0.50	0.57	0.59	0.60	0.60
52 (R)	2	II	0	+0.03	+0.01	+0.03	+0.01	+0.05	0	+0.03	+0.03
	3		0	+0.03	+0.01	0	+0.02	+0.04	+0.01	+0.03	+0.04
	4		0	+0.03	+0.01	+0.01	+0.02	+0.05	+0.03	+0.03	+0.04
	1		0.45	0.55	0.47	0.54	0.59	0.62	0.48	0.63	0.63
52 (L)	2	II	0	0	+0.01	+0.01	-0.05	+0.01	+0.01	+0.01	+0.02
	3		0	-0.01	+0.01	-0.02	-0.07	+0.02	+0.03	+0.02	+0.01
	4		0	0	+0.02	-0.02	-0.05	+0.02	+0.04	+0.01	+0.01

Appendix 3 (continued)

Patient No.		Type	Centre Thickness	Mid Peripheral Thickness				Peripheral Thickness			
				2	3	6	7	1	4	5	8
	1		0.46	0.48	0.52	0.53	0.51	0.54	0.56	0.59	0.60
54 (R)	2	II	0	+0.03	−0.02	+0.01	0	+0.03	+0.02	+0.05	0
	3		−0.02	−0.04	−0.01	−0.01	−0.03	+0.02	+0.06	+0.03	−0.02
	4		0	−0.01	0	−0.01	−0.02	+0.03	+0.06	+0.03	−0.01
	1		0.50	0.54	0.53	0.55	0.62	0.62	0.55	0.63	0.58
54 (L)	2	II	−0.01	0	−0.01	−0.04	−0.04	0	+0.03	0	−0.01
	3		−0.02	0	−0.02	−0.03	−0.03	0	+0.04	0	0
	4		+0.01	+0.01	−0.01	−0.03	−0.04	0	+0.04	+0.01	+0.01
	1		0.35	0.42	0.50	0.47	0.42	0.48	0.54	0.56	0.51
55 (R)	2	II	0	−0.03	−0.09	−0.01	0	+0.01	+0.03	+0.01	−0.02
	3		−0.05	−0.05	−0.13	−0.08	−0.08	−0.04	−0.08	−0.03	−0.01
	4		−0.02	−0.04	−0.12	−0.04	−0.07	0	−0.06	−0.02	+0.02
	1		0.37	0.37	0.47	0.47	0.43	0.46	0.47	0.51	0.55
55 (L)	2	II	−0.02	+0.07	−0.05	+0.01	−0.01	+0.08	+0.02	+0.06	−0.01
	3		−0.02	+0.07	−0.13	−0.06	−0.02	+0.07	−0.06	+0.03	−0.03
	4		−0.02	+0.07	−0.09	−0.06	−0.05	+0.07	−0.05	+0.04	−0.03

APPENDIX 4

Patient No.	Age at First Visit	Age at Diagnosis		Keratometry Group Visit 1	Visit 4
1	27	27	R	2	4
			L	2	4
2	20	19	R	2	2
			L	5	4
3	40	40	R	3	4
			L	4	4
4	15	14	R	3	3
			L	1	2
5	15	15	R	1	4
			L	1	4
6	27	27	R	3	2
			L	3	2
7	23	21	R	5	5
			L	3	4
8	14	14	R	3	6
			L	5	2
9	25	22	R	3	3
			L	2	2
10	26	19	R	3	4
			L	5	6
11	23	21	R	3	4
			L	2	2
12	18	17	R	3	5
			L	1	2
13	39	39	R	2	1
			L	5	4

Appendix 4 (continued)

Patient No.	Age at First Visit	Age at Diagnosis		Keratometry Group Visit 1	Visit 4
14	20	18	R	1	2
			L	3	2
15	23	20	R	4	3
			L	2	3
16	26	26	R	1	2
			L	1	1
17	20	20	R	1	1
			L	2	3
18	23	19	R	6	6
			L	6	3
19	24	23	R	2	2
			L	2	2
20	40	39	R	3	3
			L	2	2
21	42	42	R	3	3
			L	1	1
22	18	18	R	2	3
			L	2	2
23	33	24	R	2	3
			L	2	2
24	17	15	R	6	6
			L	2	5
25	17	17	R	5	4
			L	5	5
26	17	17	R	3	3
			L	1	1
27	25	25	R	1	1
			L	1	1

Appendix 4 (continued)

Patient No.	Age at First Visit	Age at Diagnosis		Keratometry Group Visit 1	Visit 4
28	27	26	R	3	4
			L	1	2
29	27	27	R	2	2
			L	1	1
30	30	12	R	3	
			L	2	
31	26	23	R	3	1
			L	3	1
32	21	20	R	5	4
			L	4	3
33	18	16	R	2	3
			L	2	4
34	23	19	R	2	2
			L	4	4
35	27	27	R	2	2
			L	3	2
36	16	16	R	5	6
			L	3	3
37	18	18	R	1	2
			L	2	4
38	37	33	R	3	3
			L	4	3
39	33	32	R	3	3
			L	2	2
40	27	27	R	1	1
			L	2	3

Appendix 4 (continued)

Patient No.	Age at First Visit	Age at Diagnosis		Keratometry Group Visit 1	Visit 4
41	38	25	R	5	6
			L	1	1
42	30	12	R	5	5
			L	5	5
43	23	22	R	1	2
			L	1	1
44	16	15	R	3	4
			L	1	1
45	18	17	R	3	
			L	4	
46	23	23	R	2	2
			L	2	2
47	28	27	R	4	4
			L	3	3
48	18	14	R	3	3
			L	4	6
49	20	20	R	5	5
			L	5	5
50	17	15	R	2	2
			L	4	3
51	29	29	R	6	6
			L	3	1
52	20	15	R	3	3
			L	4	4
53	37	34	R	3	
			L	4	
54	24	23	R	1	1
			L	1	2

Appendix 4 (continued)

Patient No.	Age at First Visit	Age at Diagnosis		Keratometry Group Visit 1	Visit 4
55	17	15	R	4	2
			L	3	3

Keratometry

Group	Steepest Meridan
1	>7.50
2	7.00 - 7.49
3	6.50 - 6.99
4	6.00 - 6.49
5	5.50 - 5.99
6	< 5.49

APPENDIX 5

EYES WEARING CONTACT LENSES

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
1	R	2	0.39	6/6	1
1	L	2	0.44	6/6	2
1	R	3	0.39	6/6	2
1	L	3	0.44	6/9	2
1	R	4	0.30	6/9	3
1	L	4	0.38	6/9	4
2	R	2	0.51	6/5	2
2	L	2	0.40	6/9	4
2	R	3	0.47	6/5	1
2	L	3	0.39	6/6	3
2	R	4	0.51	6/5	2
2	L	4	0.40	6/5	4
6	R	2	0.34	6/9	3
6	L	2	0.42	6/6	3
6	R	3	0.36	6/6	2
6	L	3	0.39	6/6	2
6	R	4	0.33	6/6	2
6	L	4	0.38	6/6	2
7	R	2	0.35	6/9	5
7	L	2	0.40	6/9	3
7	R	3	0.35	6/9	5
7	L	3	0.38	6/9	4
7	R	4	0.35	6/9	5
7	L	4	0.39	6/9	4
8	R	1	0.43	6/9	3
8	L	1	0.43	6/12	5
9	R	1	0.49	6/18	3
9	L	1	0.53	6/9	2
9	R	2	0.41	6/12	4
9	L	2	0.50	6/9	2
9	R	3	0.43	6/9	3
9	L	3	0.50	6/9	2
9	R	4	0.43	6/9	3
9	L	4	0.49	6/6	2
10	R	1	0.29	6/9	3
10	L	1	0.31	6/9	5
10	R	2	0.15	6/9	4
10	L	2	0.20	6/9	6
10	R	3	0.27	6/6	4
10	L	3	0.26	6/12	6
10	R	4	0.21	6/6	4

Appendix 5 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
10	L	4	0.24	6/9	6
11	R	1	0.41	6/6	3
11	R	2	0.40	6/5	2
11	R	3	0.40	6/6	3
11	R	4	0.39	6/6	4
12	R	2	0.35	6/9	3
12	L	2	0.42	6/9	1
12	R	3	0.35	6/9	5
12	L	3	0.42	6/9	2
12	R	4	0.35	6/9	5
12	L	4	0.42	6/9	2
13	R	2	0.26	6/5	1
13	L	2	0.28	6/12	5
13	R	3	0.29	6/5	2
13	L	3	0.29	6/12	5
13	R	4	0.35	6/6	1
13	L	4	0.28	6/9	5
14	R	2	0.37	6/5	1
14	L	2	0.39	6/9	3
14	R	3	0.29	6/5	1
14	L	3	0.38	6/9	3
14	R	4	0.36	6/5	1
14	L	4	0.34	6/9	2
15	R	1	0.38	6/9	4
15	L	1	0.38	6/9	2
15	R	2	0.38	6/9	4
15	L	2	0.46	6/9	2
15	R	3	0.38	6/9	4
15	L	3	0.39	6/9	3
15	R	4	0.40	6/9	3
15	L	4	0.40	6/9	3
17	L	2	0.41	6/6	3
17	L	3	0.40	6/6	1
17	L	4	0.39	6/6	3
18	R	2	0.28	6/12	6
18	L	2	0.28	6/6	4
18	R	3	0.27	6/12	6
18	L	3	0.40	6/6	4
18	R	4	0.27	6/18	6
18	L	4	0.38	6/6	3
19	R	2	0.42	6/4	2

Appendix 5 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
19	L	2	0.41	6/4	2
19	R	3	0.45	6/4	2
19	L	3	0.45	6/6	2
19	R	4	0.43	6/4	2
19	L	4	0.43	6/6	2
20	R	2	0.40	6/6	2
20	L	2	0.41	6/6	2
20	R	3	0.36	6/6	3
20	L	3	0.34	6/5	2
20	R	4	0.35	6/9	3
20	L	4	0.44	6/6	2
21	R	2	0.46	6/6	3
21	L	2	0.49	6/6	1
21	R	3	0.40	6/9	3
21	L	3	0.49	6/5	1
21	R	4	0.42	6/6	3
21	L	4	0.48	6/9	1
23	R	1	0.35	6/9	2
23	L	1	0.44	6/5	2
23	R	2	0.35	6/12	2
23	L	2	0.40	6/9	2
23	R	3	0.33	6/12	3
23	L	3	0.40	6/9	2
23	R	4	0.32	6/12	3
23	L	4	0.34	6/12	2
24	R	1	0.37	6/9	6
24	L	1	0.48	6/5	2
24	R	2	0.37	6/18	6
24	L	2	0.44	6/6	3
24	R	3	0.29	6/18	6
24	L	3	0.40	6/6	3
25	R	2	0.43	6/9	5
25	L	2	0.49	6/9	5
25	R	3	0.42	6/9	4
25	L	3	0.44	6/9	4
25	R	4	0.38	6/9	4
25	L	4	0.43	6/9	5
26	R	2	0.32	6/9	2
26	R	3	0.32	6/9	3
26	L	4	0.35	6/9	3
27	R	1	0.59	6/5	1
27	L	1	0.53	6/6	1

Appendix 5 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
27	R	2	0.49	6/5	1
27	L	2	0.53	6/5	1
27	R	3	0.50	6/5	1
27	L	3	0.54	6/5	1
27	R	4	0.51	6/5	1
27	L	4	0.52	6/5	1
28	R	1	0.51	6/9	3
28	L	1	0.58	6/9	1
28	R	2	0.38	6/9	3
28	L	2	0.45	6/9	1
28	R	3	0.37	6/9	4
28	L	3	0.45	6/9	1
28	R	4	0.36	6/9	4
28	L	4	0.46	6/9	1
29	R	2	0.43	6/9	2
29	R	3	0.43	6/9	2
29	R	4	0.39	6/9	2
30	R	1	0.45	6/5	3
30	L	1	0.46	6/5	2
31	R	1	0.38	6/5	3
31	L	1	0.43	6/5	1
31	R	2	0.32	6/5	3
31	L	2	0.42	6/5	1
33	R	1	0.44	6/5	2
33	L	1	0.44	6/6	2
33	R	2	0.37	6/9	3
33	L	2	0.44	6/9	4
33	R	3	0.41	6/9	3
33	L	3	0.44	6/9	4
33	R	4	0.36	6/9	3
33	L	4	0.40	6/9	4
34	R	1	0.41	6/6	2
34	L	1	0.35	6/12	4
34	R	2	0.32	6/6	2
34	L	2	0.32	6/12	4
34	R	3	0.35	6/5	2
34	L	3	0.33	6/5	4
34	R	4	0.34	6/5	2
34	L	4	0.29	6/5	4
35	L	2	0.43	6/9	3
35	L	3	0.42	6/9	3

Appendix 5 (continued)

Case No.	Eye	Visits	Thinnest Cornea	V/a	K. Group
35	L	4	0.40	6/9	4
36	R	2	0.33	6/6	5
36	L	2	0.41	6/6	3
36	R	3	0.33	6/6	5
36	L	3	0.34	6/4	3
36	R	4	0.31	6/6	5
36	L	4	0.35	6/4	3
37	L	2	0.40	6/9	2
37	L	3	0.41	6/9	4
37	L	4	0.35	6/9	4
38	R	1	0.36	6/9	3
38	L	2	0.34	6/9	4
38	R	2	0.37	6/9	2
38	L	2	0.37	6/9	3
38	R	3	0.36	6/9	2
38	L	3	0.36	6/9	3
38	R	4	0.38	6/9	3
38	L	4	0.35	6/9	3
40	R	2	0.41	6/9	1
40	L	2	0.38	6/9	3
40	R	3	0.40	6/6	1
40	L	3	0.36	6/6	4
40	R	4	0.39	6/6	1
40	L	4	0.39	6/6	2
41	R	1	0.30	6/9	5
41	R	2	0.27	6/9	6
41	R	3	0.29	6/9	6
41	R	4	0.26	6/9	6
42	R	1	0.19	6/18	5
42	L	1	0.22	6/24	5
42	R	2	0.17	6/18	5
42	L	2	0.22	6/24	5
42	R	3	0.16	6/9	5
42	L	3	0.25	6/12	5
42	R	4	0.17	6/9	5
42	L	4	0.23	6/12	5
43	R	2	0.43	6/9	1
43	R	3	0.36	6/9	1
43	L	4	0.40	6/9	2
44	R	1	0.39	6/9	3
44	L	1	0.46	6/5	1

Appendix 5 (continued)

Case No.	Eye	Visits	Thinnest Cornea	V/a	K. Group
44	R	2	0.38	6/9	4
44	L	2	0.46	6/5	1
44	R	3	0.36	6/6	4
44	L	3	0.46	6/5	1
44	R	4	0.37	6/9	4
44	L	4	0.44	6/5	1
45	R	1	0.33	6/6	3
45	L	1	0.32	6/9	4
46	R	1	0.38	6/4	1
46	L	1	0.36	6/5	1
46	R	2	0.44	6/5	1
46	L	2	0.41	6/5	2
46	R	3	0.44	6/5	1
46	L	3	0.40	6/6	2
46	R	4	0.45	6/9	1
46	L	4	0.42	6/9	2
49	R	2	0.25	6/9	5
49	L	2	0.35	6/6	6
49	R	3	0.30	6/9	5
49	L	3	0.33	6/6	4
49	R	4	0.30	6/18	5
49	L	4	0.33	6/6	5
50	R	1	0.44	6/6	2
50	L	1	0.34	6/18	5
50	R	2	0.44	6/9	2
50	L	2	0.32	6/18	5
50	R	3	0.38	6/5	2
50	L	3	0.29	6/18	5
50	R	4	0.37	6/5	2
50	L	4	0.29	6/18	5
51	R	4	0.30	6/9	6
51	L	4	0.38	6/6	1
52	L	1	0.45	6/5	4
52	L	2	0.45	6/5	4
52	L	3	0.45	6/5	4
52	L	4	0.45	6/5	4
53	R	1	0.37	6/9	3
53	L	1	0.32	6/9	4
55	R	1	0.35	6/5	3
55	L	1	0.37	6/5	3

Appendix 5 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
55	R	2	0.30	6/6	4
55	L	2	0.34	6/6	4
55	R	3	0.33	6/9	2
55	L	3	0.35	6/6	3

APPENDIX 6

EYES NOT WEARING CONTACT LENSES

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
1	R	1	0.42	6/9	2
1	L	1	0.42	6/9	2
2	R	1	0.51	6/9	2
2	L	1	0.50	6/12	5
3	R	1	0.51	6/36	3
3	L	1	0.53	6/18	4
3	R	2	0.43	6/18	3
3	L	2	0.42	6/18	4
3	R	3	0.37	6/36	4
3	L	3	0.40	6/36	4
3	R	4	0.37	6/36	4
3	L	4	0.40	6/36	4
4	R	1	0.56	6/9	3
4	L	1	0.55	6/5	2
4	R	2	0.45	6/12	3
4	L	2	0.49	6/5	2
4	R	3	0.46	6/12	3
4	L	3	0.50	6/5	2
4	R	4	0.45	6/12	3
4	L	4	0.51	6/5	2
5	R	1	0.48	6/6	1
5	L	1	0.50	6/12	4
5	R	2	0.50	6/6	1
5	L	2	0.48	6/12	4
6	R	1	0.44	6/9	3
6	L	2	0.46	6/6	3
7	R	1	0.44	6/9	5
7	L	1	0.55	6/9	3
8	R	2	0.29	6/9	3
8	L	2	0.36	6/12	5
8	R	3	0.31	6/18	5
8	L	3	0.51	6/6	1
8	R	4	0.35	6/18	6
8	L	4	0.50	6/6	2
11	L	1	0.45	6/5	2
11	L	2	0.45	6/5	2
11	L	3	0.44	6/6	2
11	L	4	0.44	6/6	2

Appendix 6 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
12	R	1	0.38	6/9	3
12	L	1	0.47	6/9	1
13	R	1	0.40	6/5	2
13	L	1	0.34	6/12	5
14	R	1	0.39	6/6	1
14	L	1	0.44	6/9	3
16	R	1	0.44	6/6	1
16	L	1	0.48	6/6	1
16	R	3	0.42	6/12	2
16	L	3	0.44	6/9	1
16	R	4	0.41	6/12	2
16	L	4	0.41	6/9	1
16	R	1	0.45	6/5	1
17	L	1	0.45	6/5	2
17	R	2	0.41	6/5	1
17	R	3	0.40	6/9	1
17	R	4	0.40	6/9	1
18	R	1	0.28	6/9	6
18	L	1	0.40	6/6	6
19	R	1	0.43	6/5	2
19	L	1	0.45	6/9	2
20	R	1	0.43	6/5	3
20	L	1	0.46	6/5	2
21	R	1	0.46	6/9	3
21	L	1	0.49	6/9	1
22	R	1	0.40	6/5	2
22	L	1	0.40	6/9	2
22	R	2	0.40	6/9	3
22	L	2	0.41	6/9	2
22	R	3	0.36	6/9	3
22	L	3	0.41	6/9	2
22	R	4	0.35	6/18	3
22	L	4	0.38	6/9	2
24	R	4	0.30	6/30	6
24	L	4	0.38	6/6	5
25	R	1	0.38	6/12	5
25	L	2	0.45	6/9	5

Appendix 6 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
26	R	1	0.40	6/6	3
26	L	1	0.45	6/4	1
26	L	2	0.42	6/5	1
26	L	3	0.41	6/5	1
26	L	4	0.41	6/5	1
29	R	1	0.42	6/9	2
29	L	1	0.52	6/5	1
29	L	2	0.51	6/5	1
29	L	3	0.52	6/5	1
29	L	4	0.51	6/5	1
32	R	1	0.40	6/9	5
32	L	1	0.44	6/6	3
32	R	2	0.52	6/12	4
32	L	2	0.55	6/9	3
32	R	3	0.39	6/12	4
32	L	3	0.41	6/9	3
32	R	4	0.35	6/12	4
32	L	4	0.39	6/9	3
35	R	1	0.42	6/4	2
35	L	1	0.41	6/9	3
35	R	2	0.41	6/4	1
35	R	3	0.41	6/5	2
35	L	4	0.41	6/5	2
36	R	1	0.33	6/18	5
36	L	1	0.40	6/5	3
37	R	1	0.45	6/5	1
37	L	1	0.40	6/5	2
37	R	2	0.45	6/5	1
37	R	3	0.40	6/5	1
37	R	4	0.38	6/5	1
39	R	1	0.41	6/9	3
39	L	1	0.45	6/9	3
39	R	2	0.41	6/9	3
39	L	2	0.43	6/6	2
39	R	3	0.39	6/9	4
39	L	3	0.43	6/6	3
39	R	4	0.39	6/9	3
39	L	4	0.40	6/9	3
40	R	1	0.38	6/6	1
40	L	1	0.34	6/6	3

Appendix 6 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
41	L	1	0.46	6/5	1
41	L	2	0.39	6/6	1
41	L	3	0.44	6/6	1
41	L	4	0.39	6/6	1
43	R	1	0.40	6/5	1
43	L	1	0.44	6/5	1
43	L	2	0.46	6/5	1
43	L	3	0.44	6/5	1
43	L	4	0.45	6/5	1
47	R	1	0.36	6/5	2
47	L	1	0.37	6/9	4
47	R	2	0.44	6/5	2
47	L	2	0.37	6/9	4
47	R	3	0.42	6/4	2
47	L	3	0.38	6/12	4
47	R	4	0.40	6/4	2
47	L	4	0.37	6/12	4
48	R	1	0.30	6/6	3
48	L	1	0.31	6/18	4
48	R	2	0.31	6/6	3
48	L	2	0.35	6/18	4
48	R	3	0.33	6/6	3
48	L	3	0.34	6/18	5
48	R	4	0.35	6/6	3
48	L	4	0.36	6/18	6
49	R	1	0.25	6/9	5
49	L	1	0.31	6/5	5
51	R	1	0.31	6/9	6
51	L	1	0.4	6/9	3
51	R	2	0.30	6/18	6
51	L	2	0.40	6/9	3
51	R	3	0.31	6/18	6
51	L	3	0.40	6/9	3
52	R	1	0.45	6/5	3
52	R	2	0.45	6/5	3
52	R	3	0.45	6/5	3
52	R	4	0.45	6/5	3
54	R	1	0.46	6/6	1
54	L	1	0.50	6/6	1
54	R	2	0.46	6/6	1
54	L	2	0.49	6/6	1

Appendix 6 (continued)

Case No.	Eye	Visit	Thinnest Cornea	V/a	K. Group
54	R	3	0.44	6/6	1
54	L	3	0.48	6/6	1
54	R	4	0.46	6/6	1
54	L	4	0.51	6/6	1
55	R	1	0.35	6/12	4
55	L	2	0.37	6/9	3

APPENDIX 7

Patient No.	Age at Diagnosis	Age at First Visit	Elapsed Time	Thinnest Corneal Position R	L
42	12	30	18	0.17	0.23
41	25	38	13	0.26	0.37
23	24	33	9	0.32	0.34
10	19	26	7	0.21	0.24
39	32	39	7	0.39	0.40
42	18	20	5	0.43	0.44
34	19	23	4	0.34	0.30
38	33	37	4	0.38	0.35
48	14	18	4	0.35	0.37
18	19	23	4	0.26	0.36
9	22	25	3	0.43	0.30
15	20	23	3	0.35	0.34
7	21	23	2	0.35	0.39
11	21	23	2	0.38	0.39
14	18	20	2	0.40	0.40
28	26	28	2	0.36	0.45
33	16	18	2	0.36	0.40
30	15	17	2	0.37	0.29
35	15	17	2	0.33	0.31
43	22	23	1	0.40	0.45
2	19	20	1	0.51	0.40
4	14	15	1	0.45	0.51
12	17	18	1	0.35	0.42
19	23	24	1	0.43	0.43
20	37	38	1	0.35	0.43
32	20	21	1	0.35	0.39
44	15	16	1	0.34	0.44
42	27	28	1	0.40	0.34
54	23	24	1	0.46	0.43
37	18	18	0	0.38	0.35
40	27	27	0	0.39	0.39
46	23	23	0	0.45	0.42
49	20	20	0	0.30	0.33
51	24	24	0	0.30	0.38

Appendix 7 (continued)

Patient No.	Age at Diagnosis	Age at First Visit	Elapsed Time	Thinnest Corneal Position R	Thinnest Corneal Position L
1	27	27	0	0.30	0.33
3	40	40	0	0.37	0.40
6	27	27	0	0.33	0.38
8	14	14	0	0.36	Graft
13	39	39	0	0.35	0.39
16	20	20	0	0.41	0.48
17	20	20	0	0.41	0.38
21	42	42	0	0.42	0.48
22	18	18	0	0.35	0.38
25	17	17	0	0.38	0.43
26	17	17	0	0.35	0.41
29	27	27	0	0.39	0.51
35	27	27	0	0.41	0.40
36	16	16	0	0.31	0.31