DOYNE LECTURE KERATOCONUS

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For a physician specialising in the cornea, corneal dystrophies pose several basic questions regarding clinical identification, anatomic characteristics, and aetiological diagnosis. Corneal dystrophies are most often accompanied by a distinctive distribution of opacities and of a localised deposition of abnormal material (MPS, amylosis).

Keratoconus presents between the ages of ten and twenty years as do many corneal dystrophies but the corneal stroma remains transparent for a long time. Progression is marked by a slow deformation of the cornea. It is histologically very different from other dystrophies and a wide variety of questions arise concerning its aetiology. Over the twenty years that we have had the opportunity of studying corneal pathology in both its clinical and fundamental aspects, we have never stopped investigating Keratoconus and this occasion offers an opportunity to present our concepts concerning a subject particularly dear to me.

Keratoconus has interested a considerable number of ophthalmologists since it was recognised as a pathological entity in the middle of the Eighteenth Century. (Mauchart, 1748; Taylor, 1766). About a century later keratoconus was differentiated from other corneal ectatic disorders. Nottingham (1854) defined its essential clinical features.

Since then, a considerable amount of work has been published on the subject, most addressing either the clinical or the aetiological aspects of the disorder. Their references are listed in bibliographies of general reviews dedicated to keratoconus. The earliest to be

found is Campinchi and Haye,¹ and more recently in Krachmer and *et al.*²

'Keratoconus or conical cornea is a disease defined as a non-inflammatory protrusion of the cornea in its axial region usually appearing in early adolescence and causing a serious decline in visual acuity due to a high degree of irregular myopic astigmatism' (Duke Elder) (Fig. 1).

If we add that the cornea thins in its centre, that the complaint evolves slowly and that it is usually bilateral and generally very disabling we have summarised a little more completely the clinical characteristics of the disease. Many important questions arise:

- relationship to heredity
- aetiology
- relationship to certain local disorders (atopic disease, contact lens wearing) or general disorders
- characteristics which differentiate it from other ectatic disorders of the cornea
- treatment

I will try to answer these questions.

Incidence

It is very difficult to estimate the frequency of keratoconus in an average population because it varies greatly from 4 per 100,000 (Amsler^{3,4,5}) to 600 per 100,000 (Hofstetter⁶). The average is 50 to 230 per 100,000 by Feder,² who has summarised the known statistics. The variation in figures is done in variation of diagnostic criteria and for national and above all regional differences. All races are implicated, but keratoconus appears to be

Fig. 1. Three clinical forms of corneal deformation on slit-lamp examination, (a) eccentric, (b) more or less pointed and (c) thinning of the deformed cornea.

more widely spread in Mediterranean countries rather than in northern Europe, and there is a higher incidence in French people of predominantly Celtic origin (western France), and in females compared with males.

Keratoconus is generally a bilateral condition. Amsler reported 14.3 per cent of cases to be unilateral. Bilaterality may only become apparent with time, the second eye usually being affected a few years after the first.

The disorder most often appears in a patient between ten and twenty years of age. The exact beginning of the disease is often missed by the clinician for the diagnosis is often made a long time after the first signs of trouble. It evolves slowly and it is difficult to be precise about the average interval between the early changes and the stage at which there is sufficient handicap to justify keratoplasty; an average of ten years (Pouliquen).⁴⁰ There are early cases of surgery on record of children younger than ten years and late cases of patients over thirty.

Keratoconus and Heredity

Keratoconus occurring in two members of the same family raises the question of heredity; but, two people in the same family may have shared the same environmental factors. Consequently assessing the precise role of heredity in keratoconus is difficult. However, several cases of identical twins suffering from keratoconus have been reported. We have performed surgery on male twins. In this case, it is difficult to disprove a genetic factor in the pathogenesis of the disease. Numerous authors have attempted to define the frequency and manner of transmitting the disease.

- (1) Waardenburg⁷ cites seven cases of keratoconus involving blood relatives and thus suspects a recessive genetic factor.
- (2) Hallerman⁸ and Wilson think that the frequency of hereditary factors is at least 7 per cent and that the mode of transmission has multiple causes.
- (3) Hammerstein⁹ in studying 52 families with

keratoconus determined that hereditary influence occurs in the order of 20 per cent of cases.

Clinical Diagnosis of Keratoconus

In most cases the clinical diagnosis of keratoconus is easy because it presents as advanced disease. An adolescent comes for consultation because of a decline in visual acuity, intermittent misty vision and distortion. These symptoms are particularly prominent for distance vision and are frequently associated with ocular irritation. The examination reveals high and irregular myopic astigmatism, and irregularity of the mires can be identified by keratometry. Observation of the pupil confirms the existence of a shadow thrown by the cornea on the major horizontal axis. In well developed cases a downward glance causes angulation of the lower eyelid (Munson's sign).

On slit lamp examination, one notes the existence of corneal striae deeply seated in the

corneal stroma.^{10,11} Generally oblique and very fine, they disappear with external pressure on the globe (Fig. 2). They doubtless correspond to the reflection due to the displacement of posterior stromal lamellae with respect to the anterior stromal lamellae. (Katz,¹² offers a theoretical explanation). These reversible striae are very different from the scarring of the subepithelial anterior stroma at the cone apex; these are the real corneal opacities, resulting from ruptures of Bowman's membrane (Fig. 3). The lesions which are of variable size, may contribute to the visual loss in advanced keratoconus. Following rupture of Descemet's membrane in acute hydrops, one observes other folds after clearing of the cornea. Several further biomicroscopic features can still be noted; the existence of Fleischer's ring. This is a more or less complete rust-brown ring, encircling the base of the cone. It is composed of hemosiderine deposited in the deep layers of the corneal epithelium. Only its form is special

Fig. 2. Three central abnormalities of the cornea, (a) folds of Elschnig or Vogt, (b) the fine white parallel striations are situated in the deep stromal cornea and (c) which disappear when pressed in the globe.

Fig. 3. Two forms of central sub-epithelial opacities seen in advanced keratoconus.

because it does not differ in nature from the lines of Hudson-Stähli, Stocker etc . . . It is sometimes accompanied by fine white lines in concentric curves situated in the interior of the ring.¹³ Hypertrophic nerves can sometimes be seen in the cornea. Corneal sensitivity may be variable.

Clinical Forms of Keratoconus

Early stage

The above description can lead one to conclude that it is easy to diagnose advanced keratoconus. This is not always so and it is often difficult to diagnose in the early stages of development. In the first stage only the existence of astigmatism which we are certain did not previously exist, leads to suspicion of the possibility of keratoconus and foresee its development. All the other diagnostic changes such as thinning, protrusion, striae, etc. are lacking. Keratometry is thus of major importance. There are always limitations with classic keratometers because measurements are difficult outside of the central cornea. The alterations of the curve in keratoconus are

paracentric and inferior. Keratometry has been carried out to document evolution of corneal steepening and its slow development. Marechal-Courtois¹⁴ has emphasised that inferior steepening is a characteristic early change of keratoconus and pointed out the need of a topographic keratometry.

The mean at the disposal of an ophthalmologist to determine the changes on the curvature of keratoconus is the Placido disk. It provides qualitative topographical information, which Amsler subdivided into four stages. Although the hand held keratoscope or Placido disk are subject to error, the photokeratoscope (invented by Placido) provides an available method of measurement by which the greater part of the corneal area can be photographed precisely. The alteration of reflected ring contours permits a fairly precise appraisal of corneal distortion. In this manner the keratoscope used by Rowsey allowed early detection of keratoconus which starts with steepening of the inferotemporal cornea, then peripheral steepening subsequently involving the inferonasal quadrant and then

the superotemporal and superonasal area. Using automatic measurement of corneal thickness, Mandell¹⁵ thought he could determine the pathognomonic signs of early keratoconus by establishing a difference of greater than 0.085 mm between the position of minimum thickness and a point of 35 degrees from this position along the horizontal axis of the cornea.

Acute Hydrops

This is not rare during the development of keratoconus. We deduce that there is a rupture in Descemet's membrane in developed keratoconus at the site of very thin stroma. Circumstances might help to provoke it such as trauma to the eye and chronic eye rubbing. Eye rubbing has even been implicated as a primary cause (see below) as well as being a contributing factor in the pathogenesis of acute keratoconus. There is little doubt of its importance in the case of Down's Syndrome. The acute syndrome, spontaneous or provoked, results in a decline of visual acuity,

sharp pain, and watering eyes. The diagnosis can be made on the basis of the whitish discoidal corneal oedema occupying the centre of the cornea, dissecting corneal stroma, with formation, sometimes, of a large intrastromal vesicle (Fig. 4). The reabsorption of the oedema is slow, following healing of Descemet's membrane by endothelial cells leaving fine and diffuse opacity of the central cornea.¹⁶ Surgical treatment may be necessary to restore vision. Acute keratoconus, usually occurs in the young, but may arise much later, (in one case at 80 years).

Topographic Forms

Pellucid marginal degeneration is rare and should not be separated from classical keratoconus. It has almost all of the clinical characteristics of classical keratoconus, except that the apex of the cone is eccentric. Marginal and inferior protrusion bilaterally often with considerable thinning, leading to flattening of vertical axis of the cornea without loss of transparency (Fig. 5). The microscopic

Fig. 4. Acute keratoconus with white discoid opacity due to oedema of the cornea (a) with separation of the corneal lamellae (b) following rupture of Descemet's membrane.

Fig. 5. *Marginal or pellucidal degeneration. Cornea is flattened in its vertical axis and the lateral thin cornea is ectatic.*

and ultrastructural changes that we have reported¹⁷ do not differ from those of keratoconus. The surgical correction requires large diameter keratoplasty and is not simple.

Aetiology

If most keratoconus appears to be spontaneous, it is occasionally precipitated by factors such as repeated eye trauma and contact lens wearing. Eyerubbing, ascribed to nervousness or irritation, has been cited in related literature (spring keratoconjunctivitis, ocular diseases and tics) as factors predisposing to progressive deformation of the cornea, although, it is difficult to identify the relative importance of these factors.

Contact lens wearing may cause repeated minor trauma in itself. Harstein,¹⁸ reports four cases of keratocones developing in myopic patients who wore contact lenses (hard lenses) three of them for unilateral correction. The debate has since been open on the role played by contact lenses and their possible influence in the development of keratoconus. For the time being it is difficult to ascribe

blame, and the only advice we can give to physicians who prescribe PMMA lenses is to take account of initial corneal parameters and carefully follow any developments. If changes occur, the replacement of the hard lenses with soft ones may be indicated. But it is not true that contact lens wearers admit to frequently rubbing their eyes after removing the lenses?

Hormonal problems have been considered as possible contributing factors, for instance, puberty, male or female, and particularly pregnancy, and thyroid insufficiency or hypophysis diencephalic dysfunction. A psychological profile typified by anxiety, tendencies towards introversion or over scrupulous behaviour, as well as religious vocations (priests, nuns, rabbis), have also been recognised by some as being common in patients with keratoconus.

Related Disorders

Ocular

These are numerous and varied. The most common association of vernal conjunctivitis, more frequent in tropical or mid-eastern cli-

mates than in temperate zones, was well established by Bietti.¹⁹ It falls into the category of allergic diseases associated with keratoconus (see below). The other ocular associations are more rare: megalocornea (Fig. 6), ectopia lentis, blue sclera, cataract or retinal detachment.

Generally related diseases

Allergy: Evidence linking keratoconus to allergy is frequently cited. Rahi *et al.*²⁰ found a positive history of atopic disease (asthma, eczema, hay fever) in 35 per cent of 182 keratoconus patients as opposed to 12 per cent in 100 control patients. However, this association was not found by Wachtmeister *et al.*²¹ They also failed to identify a correlation between HLA and keratoconus.

Connective tissue disorders

Association between keratoconus and connective tissue disease is not rare. Hyperlaxity of the joints has been noted in 50 per cent of cases (Robertson).²² According to Paton (personal correspondence) of 57 patients with keratoconus, 19 per cent had a scleral rigidity below normal. Beardsley²³ reports a 38 per cent incidence of prolapse of the mitral valve in keratoconus patients, abnormality found equally in the Marfan's syndrome and Ehlers-Danlos Type I to VI or osteogenesis imper-

fecta, as compared with 13 per cent in a control group.

Trisomy 21 (Down's Syndrome)

The relation between trisomy 21 and keratoconus was mentioned for the first time by Rados.²⁴ Most studies put the incidence at about 5 per cent; it is among this 5 per cent that acute keratoconus is most frequent.

Anatomy Pathology and Biochemistry

As with other corneal dystrophies, the results of electron microscopy and clinico-pathological correlates are crucial to the understanding of the pathogenetic mechanisms in keratoconus, which cause thinning of corneal stroma without affecting its transparency. The first characteristic of histological cross-sections is the central thinning of the corneal stroma. With Hamada²⁵ we studied the lamellar (or pseudolamellar) structure of the stroma in polarised light, comparing the number of lamellae of normal corneas with that of keratoconus. We concluded that the number of central lamellae were considerably reduced in keratoconus (180 as compared to 300). However with an improvement in methods of measurement, the number of lamellae in the centre of normal corneas was revised to 200, such that the differences lost their significance. This caused Paton (per-

Fig. 6. Bilateral megalocornea with keratoconus.

sonal communication) to remark that the number of lamellae in the thinned centre is the same as in the periphery. In the past, we have tried to study systematically the superposed lamellae without success. The results are inconsistent between one section and another of the same cornea, and between one keratoconus specimen and another. A new approach to this subject with a precise methodology confirms our initial results. A great number of slides of the central corneas obtained from 4 keratoconus patients (Amsler Stage IV) were examined by polarised light. It was possible to demonstrate a direct but moderate relationship between the central thinning of the stroma and the number of the connective lamellae (Table I).

Apart from thinning, the most typical microscopic change is irregularity of the epithelium, an alteration of its basal lamina, and rupture in Bowman's membrane (Fig. 7). These ruptures are replaced by scar tissue

between the epithelium and Bowman's membrane. The thinned tissue generally appears as crinkling of the connective tissue lamellae. Scarring occurs only in the subepithelial part of the cornea.

Generally speaking, apart from in acute keratoconus, Descemet's membrane and endothelium are normal. Nevertheless, endothelial specular microscopic studies and double-staining of buttons excised at keratoplasty show some cellular modifications which may have a part in the development of the pathologic changes in keratoconus.^{26,27}

The Electron microscopic studies of keratoconus resolve a few problems. These show changes of basal cells with alteration of the basal lamina which may be multilayered or disrupted.^{28,29} These findings led to a hypothesis in which it was suggested that there was an active collagenase activity at the level of Bowman's membrane and the anterior stroma. The alterations in the stroma are qualitatively

Fig. 7. Three characteristic appearances of Bowman's membrane in keratoconus. The membrane is folded and ruptured and may be replaced by scar tissue between the two edges of the rupture.

of little significance (Fig. 8). We have described^{30,31,32} an abnormality of keratocytes and the accumulation of an abnormal quantity of granular substance around their membrane (Fig. 9). In view of the paucity of evidence concerning these lesions, we have undertaken a rigorous quantimetric analysis of the corneal stroma in keratoconus and normal tissue.³³ This study indicates a slow alteration of the diameter of the collagen fibrils and of the interfibrillar distance. The changes are subtle in the early stage, but become more evident later, particularly in the posterior and central zones of the cornea. There is a significant increase in the average diameter of the fibrils and of the interfibrillary distance (Tables II and III). The hexagonal arrangement is retained which would account for the conservation of corneal transparency (Fig. 10). This result, confirmed many times, contrasts with those of Paton who thinks that the interfibrillar distances are diminished in keratoconus thus explaining the decrease in the thickness of the corneal lamellae. We suggest that there are thicker fibrils in the lamellae, increase in the interfibrillar substance but fewer lamellae.

Neither transmission nor scanning electron microscopy show significant changes in Descemet's membrane; endothelial cells show slight changes but their significance is not clear (Fig. 11).

Pathogenesis

Based on anatomic findings the theories of the pathogenesis of keratoconus can be divided into two main hypotheses:

*Epithelial*²⁸ in which it is suggested that dysfunction at the level of the basal cells of the epithelium cause destruction of the basal lamina of Bowman's membrane, and of the anterior stroma which progresses posteriorly with time.

Stromal which is supported by most authors who believe that there is a slow defect of fibrillogenesis. This a theory shared by Robert,²⁵ which shows an increase in the structural glycoprotein production and a decrease of the collagen synthesis. Some authors,³⁴ have found that the glycosaminoglycan production by the cultured keratoconus keratocytes was altered. The distribution of collagen may be abnormal; whereas 90 per cent of collagen is type I

Fig. 8. Electron microscopy of the corneal stroma. The lamellae appear thin, often to the thickness of a few fibrils with deposition between the lamellae of electron dense granular material.

Fig. 9. Electron microscopy of the granulosomatous material seen in abundance around corneal fibrocytes. These deposits are similar in structure to those seen between the fibrils and lamellae in the stroma. (See Fig. 8.)

in normal cornea, significant quantities of collagen type III is found in keratoconus. Paton has shown that the ratio of α chains to β chains in the triple helix of collagen is 4 to 7 times higher than normal. The resultant alteration of the cross linkage could explain the decrease in the tensile strength of the stroma in keratoconus. The biochemical abnormality in keratoconus may be due to enzymatic deficits or collagenolytic activity. Kim and Hassard³⁵ have shown a deficiency in the glucose-6-phosphate dehydrogenase in keratoconus which can prevent collagen formation. Rehany *et al.*³⁶ have demonstrated, moreover, that there is more intense collagenolytic activity in the keratoconus than in the normal cornea.

In conclusion, we believe that the initial disturbance in keratoconus lies in an alteration of the fibrocyte synthesis. The decreased mass of collagen and increasing hexosamines in the matrix would support this view. An alteration in corneal curvature would be caused by stromal tension induced by intraocular pressure. Numerous studies have been

undertaken to identify the initial enzymatic problem, to characterise the exact biochemical defect and to define the intracorneal origin of the early lesion which is usually central but sometimes eccentric.

Table I Results

	Age	n	Corneal thickness	Total lamellae nb.
Normal cornea	1 17	40	0.45	179
	2 63	72	0.43	162
Keratoconus	1 42	40	0.187	125
	2 29	50	0.247	165
Keratoconus	3 31	36	0.242	151
Keratoconus	4 23	60	0.174	134
Keratoconus	5 23	60	0.231	145

Total lamellae number in the thin central part of the keratoconus cornea in four cases, compared to two normal corneas (central part) n = number of $\frac{1}{2}$ thin-sections studied for each case. The corneal thickness is evaluated after fixation.

Table II Fibrillar diameters

Normal cornea:

Ant. = Middle = Post. = $220 \pm 10 \text{ \AA}$

Keratoconus Stage I-II:

Ant. = Middle = Post. = $220 \pm 10 \text{ \AA}$

Keratoconus Stage III:

Ant. = Middle $\xrightarrow{+4\%}$ Post.
 $230 \pm 15 \text{ \AA}$ $240 \pm 15 \text{ \AA}$

Keratoconus Stage IV:

Ant. $\xrightarrow{+6\%}$ Middle $\xrightarrow{+4\%}$ Post.
 $230 \pm 10 \text{ \AA}$ $245 \pm 10 \text{ \AA}$ $255 \pm 20 \text{ \AA}$

Table III Interfibrillar distances

Normal cornea:

Ant. = Middle = Post. = $440 \pm 30 \text{ \AA}$

Keratoconus Stage I-II:

Ant. = Middle = Post. = $440 \pm 30 \text{ \AA}$

Keratoconus Stage III:

Ant. $\xrightarrow{+2\%}$ Middle $\xrightarrow{+4\%}$ Post.
 $450 \pm 30 \text{ \AA}$ $450 \pm 50 \text{ \AA}$ $480 \pm 35 \text{ \AA}$

Keratoconus Stage IV:

Ant. $\xrightarrow{+10\%}$ Middle $\xrightarrow{+8\%}$ Post.
 $435 \pm 30 \text{ \AA}$ $480 \pm 20 \text{ \AA}$ $520 \pm 50 \text{ \AA}$

NORMAL CORNEA

KERATOCONUS (IV)

Fig. 10. Electron microscopy comparing the anterior (a, c) and posterior (b, d) of the stroma in the normal cornea (a, b) and in keratoconus (c, d). The lamellar organisation appears similar between normal and abnormal but the lamellae are thinner in keratoconus. These differences have been analysed quantitatively (see Tables II and III).

Differential Diagnosis

We believe that Pellucid marginal degeneration is a clinical form of keratoconus, and must be differentiated from Terrien's disease and Mooren's ulcer.

Keratoglobus is, perhaps, the clinical term for longstanding keratoconus. Keratoconus-keratoglobus has much in common histologically with keratoconus³⁷ including the presence of rupture in Bowman's membrane and stroma. Congenital keratoglobus differs radically from keratoconus anatomically with absence of Bowman's membrane, structural changes in corneal stroma and Descemet's membrane. *Posterior keratoconus* is a developmental abnormality of the cornea characterised by localised thinning of the posterior layers of the cornea. Unilateral and bilateral cases have been described. These are linked to abnormalities of anterior chamber cleavage.

Treatment

This consists of three stages in the great majority of cases: correction by glasses, contact lenses, and finally surgery. The transition from the first to second stages depends on tolerance of correction of the high astigmatism by glasses. With the progression of keratoconus, contact lenses become necessary which usually provide years of relief for patients. Contact lenses fitting demands minute examination since the deformation takes various forms and refraction is difficult. The higher the cone the more difficult it is to fit. Initially, a hard lens of small or large diameter may be adequate.

PMMA lenses generally result in good vision, but gas permeable lenses or cellulose acetate butyrate are equally useful. In case of intolerance provoked sometimes by associated follicular conjunctivitis, or recurrent ero-

Fig. 11. Electron microscopic appearance of the endothelial cells in keratoconus. Compared with the normal corneal endothelium (END) and Descemet's membrane (D) (A) the endothelial cells appear flattened (END) and Descemet's membrane (D) is irregular in thickness (B).

sion, at the summit of the cone, we can advocate use of soft lenses. Koliopoulos³⁸ obtained a visual acuity of 20/50 in 74 per cent of cases with soft lenses. The piggy back lens system is useful in very difficult cases, as are scleral contact lenses.

Surgery becomes necessary in cases of intolerance to contact lenses or if the distortion of the cone does not permit a lens to be worn comfortably for any length of time. Though some authors recommend lamellar keratoplasty, we have found it a difficult technique and that the results do not compare well with penetrating keratoplasty. As yet not all the post operative complications of epikeratoplasty have been resolved (Kaufman *et al.*³⁹).

*Penetrating Keratoplasty*⁴⁰ gives excellent results. Ninety percent or more clear grafts have been achieved in most reported series. Visual acuity is equal to or better than 6/12 in 75 per cent of cases. The technique is well described using a trephine of between 8.00

and 8.5 mm. Subsequent care is not easy, rejection being reported in about 30 per cent of cases; in the majority of cases this can be controlled by corticosteroids.

*Urrets-Zavalía*⁴¹ syndrome with acute iris dilation has been reported especially in keratoconus, but does it exist?⁴²

Post operative astigmatism is important post operatively in keratoconus patients and this may be modified by the removal of sutures. Sometimes correction by contact lenses is required or even further surgery. Progressive astigmatism may imply the persistence of keratoconus in the stroma to the peripheral graft or exceptionally a recurrence may develop in the donor.⁴³ Penetrating keratoplasty remains the best treatment for keratoconus. There is little justification for conservative methods such as thermokeratoplasty,⁴⁴ whose beneficial effect on corneal distortion and visual acuity is outweighed by the problems of post operative chronic epithelial recurrent erosion.

This long discussion on keratoconus has addressed certain key questions concerning this curious disease. Without false optimism, we look forward to the day when we discover the unique mechanism, or the combination of many influences, responsible for altering the corneal stroma. Hopefully an appropriate medical therapy will become available that will relieve the long anxiety which haunts the adolescence and sometimes the whole life of our patients.

References

- ¹ Campinchi R and Haye C: *Bul. Soc. Ophtal. Franç.* Rapport année 1962.
- ² Krachmer JH, Feder RS and Belin MN: Keratoconus and related non inflammatory corneal thinning disorders. *Surv. Ophthalmol.* 1984, **28**: 4.
- ³ Amsler M: Frühdiagnose und mikrosymptome. *Ophthalmologica* 1965, **149**: 438-46.
- ⁴ Amsler M: Le kratocne fruste au javal. *Ophthalmologica* 1938, **96**: 77-83.
- ⁵ Amsler M: Quelques donnes du problme. *Bull. Soc. Belge. Ophthal.* 1961, **129**: 331-54.
- ⁶ Hofstetter H: A keratoscopic survey of 13,395 eyes. *Am. J. Optom. Am. Acad. Optom.* 1959, **36**: 3-11.
- ⁷ Waardenburg PJ, Franceschetti A and Klein D: *Genetics and Ophthalmology*. Springfield Charles C Thomas 1961, 452-6.
- ⁸ Hallermann W and Wilson EJ: *Genetische*

- betrachtungen über den keratokonus. *Klin. Monatsbl. Augenheilkd.* 1977, **170**: 906-8.
- ⁹ Hammerstein W: Zur genetik des keratokonus. A. v. Graefes. *Arch. Klin. Exp. Ophthalmol.* 1974, **190**: 293-308.
 - ¹⁰ Elschnig A: Über den keratokonus. *Klin. Monatsbl. Augenheilkd.* 1984, **32**: 25-56.
 - ¹¹ Vogt A: Reflexlinien durch faltung spiegelnder grenzflächen im bereiche von corneo, linsenkapsel und netzhaut. A. v. Graefes. *Arch. Ophthalmol.* 1919, **96**: 296-338.
 - ¹² Katz HH: A hypothesis for the formation of vertical corneal striae as observed in the wearing of soft lens contact lenses and in keratoconus. *Am. J. Optom. Physiol. Opt.* 1976, **53**: 420-1.
 - ¹³ Bron AJ, Lobascher DJ, Dixon WS *et al.*: Fibrillary lines of the cornea. A clinical sign in keratoconus. *Br. J. Ophthalmol.* 1975, **59**: 136-40.
 - ¹⁴ Marechal-Courtois C: Topographic study of the corneal at different stages development of keratoconus. *Bull. Soc. Belge. Ophthalmol.* 1967, **147**: 495-505.
 - ¹⁵ Mandell RB and Polse KA: Keratoconus: spatial variation of corneal thickness as a diagnostic test. *Arch. Ophthalmol.* 1969, **82**: 182-8.
 - ¹⁶ Pouliquen Y, Chauvaud D and Savoldelli M: Kératocône aigu. Une étude ultrastructurale. *J. Fr. Ophthalmol.* 1978, **1**: 111-8.
 - ¹⁷ Pouliquen Y, Chauvaud D, Lacombe E, Amiet F and Savoldelli M: Dégénérescence pellucide marginale de la cornée ou kératocône marginal. *J. Fr. Ophthalmol.* 1980, **32**: 109-14.
 - ¹⁸ Harstein J: Keratoconus that developed in patients wearing corneal contact lenses. *Arch. Ophthalmol.* 1968, **80**: 345-5.
 - ¹⁹ Bietti GB and Ferraboschi C: Sur l'association du kératocône avec le cataracte printanier et sur son évidence statistique. *Bull. Mem. Soc. Fr. Ophthalmol.* 1958, **71**: 185-98.
 - ²⁰ Rahi A, Davies P, Ruben M *et al.*: Keratoconus and coexisting atopic disease. *Br. J. Ophthalmol.* 1977, **61**: 761-4.
 - ²¹ Wachtmeister L, Ingemansson S and Möller E: Atopy and HLA antigens in patients with patients with keratoconus. *Acta Ophthalmol.* 1982, **60**: 113-22.
 - ²² Robertson I: Keratoconus and the Ehlers-Danlos syndrome. A new aspect of keratoconus. *Med. J. Aust.* 1975, **1**: 571-3.
 - ²³ Beardsley TL and Foulks GN: An association of keratoconus and mitral valve prolapse. *Ophthalmology* 1982, **89**: 35-7.
 - ²⁴ Rados A: Conical cornea and mongolism. *Arch. Ophthalmol.* 1948, **40**: 454-78.
 - ²⁵ Pouliquen Y, Graf B, Hamada R *et al.*: [Fibrocytes in keratoconus. Morphological appearance and changes in the extracellular spaces. Optical and electron-microscopic study.] *Arch. Ophthalmol.* (Paris) 1972, **32**: (8-9), 571-86.
 - ²⁶ Laing RA, Sandstrom MM *et al.*: The human corneal endothelium in keratoconus. *Arch. Ophthalmol.* 1979, **97**: 1867-9.
 - ²⁷ Goichot-Bonnat L and Renard G: Aspects comparatifs de l'endothélium du kératocône en microscopie électronique à balayage et en microscopie optique avec double coloration vitale. *Bull. Mem. Soc. Fr. Ophthalmol.* 1986, **97**: 410.
 - ²⁸ Teng CC: Electron microscope study of the pathology of keratoconus: Part I. *Am. J. Ophthalmol.* 1963, **55**: 18-47.
 - ²⁹ Iwamoto T and De Voc AG: [Particulate structures in keratoconus.] *Arch. Ophthalmol.* (Paris) 1975, **35**: 65-72.
 - ³⁰ Pouliquen Y, Faure JP, Limon S and Bisson J: [Extracellular deposits in the corneal stroma of keratoconus. An electron microscopic study.] *Arch Ophthalmol* (Paris) 1968, **28**: 283-94.
 - ³¹ Pouliquen Y, Graf B, de Kozak Y *et al.*: Etude morphologique du kératocône (1). *Arch. Ophthalmol.* (Paris) 1970, **30**: (6-7), 497-532.
 - ³² Pouliquen Y, Graf B, Frouin MA *et al.*: [An attempt at interpretation of the histological and ultrastructural lesions of the cornea in keratoconus.]. *Ber. Zusammenkunft. Dtsch. Ophthalm. Ges.* 1972, **71**: 52-57.
 - ³³ Patey A, Savoldelli M and Pouliquen Y: Keratoconus and normal cornea. A comparative study of the collagenous fibers of the corneal stroma by image analysis. (Submitted to *Cornea*) 1984.
 - ³⁴ Bleckman H and Kresse H: Studies on the glycosaminoglycan metabolism of cultured fibroblasts from human keratoconus corneas. *Exp. Eye Res.* 1980, **30**: 215-9.
 - ³⁵ Kim JO and Hassard D: On the enzymology of the cornea. A new enzyme deficiency in keratoconus. *Can. J. Ophthalmol.* 1972, **7**: 176-80.
 - ³⁶ Rehany U, Lahay M and Shoshan S: Collagenolytic activity in keratoconus. *Ann. Ophthalmol.* 1982, **14**: 751-4.
 - ³⁷ Pouliquen Y, Dhermy P, Espinasse MA and Savoldelli M: Le kératoglobule. (Submitted to *J. Fr. Ophthalmol.*) 1984.
 - ³⁸ Koliopoulos J and Tragakis M: Visual correction of keratoconus with soft contact lenses. *Ann. Ophthalmol.* 1981, **13**: 835-7.
 - ³⁹ Kaufman HA and Werblin TP: Epikeratophakia for the treatment of keratoconus. *Am. J. Ophthalmol.* 1982, **93**, 432-7.
 - ⁴⁰ Pouliquen Y, Bellivet J, Lecoq PJ and Clay C: Kératoplastie transfixiante dans le traitement du kératocône. *Arch. Ophthalmol* (Paris) 1972, **32**, 735-44.
 - ⁴¹ Urrets-Zavalía A: Fixed, dilated pupil iris atrophy and secondary glaucoma. A distinct clinical entity following penetrating keratoplasty in keratoconus. *Am. J. Ophthalmol.* 1963, **56**: 257-65.
 - ⁴² Pouliquen Y, Guimaraes R, Petroutsos G and Lac-

ombe E: Le syndrome d'Urrets-Zavalía existe-t-il encore? *J. Fr. Ophthalmol.* 1983, **6** (3): 325–6.

⁴³ Nirankari VS, Karesh J *et al.*: Recurrence of keratoconus in donor cornea 22 years after successful

keratoplasty. *Br. J. Ophthalmol.* 1983, **67**, 23–8.

⁴⁴ Gasset AR and Kaufman HE: Thermokeratoplasty in the treatment of keratoconus. *Am. J. Ophthalmol.* 1975, **79**: 226–32.