REVIEW

Keratoconus and Related Noninflammatory Corneal Thinning Disorders

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Abstract. Keratoconus and other noninflammatory corneal thinning disordes (keratoglobus, pellucid marginal degeneration and posterior keratoconus) are characterized by progressive corneal thinning, protrusion and scarring; the result is distorted and decreased vision. The etiology and pathogenesis of these disorders are unknown but may be associated with a variety of factors, including contact lens wear, eye rubbing, Down's syndrome, atopic disease, connective tissue disease, tapetoretinal degeneration and inheritance. Recent advances in techniques for biochemical and pathological investigation are now allowing further exploration in these areas. Early diagnosis is aided by the finding of irregular corneal astigmatism with inferior corneal steepening. Treatment ranges from simple spectacle correction to keratoplasty. In this review, the past and present literature on corneal thinning disorders is reviewed and practical approaches to diagnosis and management are outlined (**Surv Ophthalmol 28:**293–322, 1984)

Key words. atopic disease • contact lenses • corneal thinning disorder • Down's syndrome • keratoconus • keratoglobus • keratometry • pellucid marginal degeneration • penetrating keratoplasty • posterior keratoconus

A great deal has been written about keratoconus. Recent advances in contact lens technology, corneal surgery, and laboratory methodology have provided the means to better understand and treat the disorder. Without extensive experience in examining, treating, or performing research on keratoconus it is difficult to evaluate the current literature. Key questions commonly arise. How do you diagnose early keratoconus? What kind of contact lenses should be used? When is surgery indicated? Can contact lenses cause keratoconus? Is keratoconus inherited? What information can be found in the research literature to help us understand the etiology of keratoconus?

There are other noninflammatory corneal thinning disorders that can closely resemble keratoconus. In some cases they might merely be different clinical manifestations of the same underlying problem. We have seen patients who have features of both keratoconus and pellucid marginal degeneration in one eye. Nevertheless, these conditions typically present with distinct slit lamp characteristics.

This review was the joint effort of three authors. Section I, "Keratoconus," was authored primarily by Dr. Feder and Section II, "Related Noninflammatory Corneal Thinning Disorders," was written primarily by Dr. Belin.

I. Keratoconus

Keratoconus is a clinical term used to describe a condition in which the cornea assumes a conical shape because of thinning and protrusion. The process is noninflammatory. Cellular infiltration and vascularization do not occur. It is usually bilateral, and although it involves the central two-thirds of the cornea, it is usually centered just below the visual axis. This disease process results in mild to marked impairment of the quality of vision. In most cases the area of conical protrusion is surrounded by a superficial iron ring, contains scars and fine posterior folds, and may result in high irregular astigmatism. The development of conical cornea can occur in the presence of a variety of clinical settings or, more commonly, it can occur

without any known associated conditions. Patients with Ehlers-Danlos syndrome and atopic individuals have a higher incidence of keratoconus. Keratoconus can occur with other ocular diseases such as Leber's congenital amaurosis. It may result from various forms of ocular trauma such as contact lens wear or eye rubbing, although this is uncertain.

Confusion exists as to the etiology, heredity, pathogenesis, pathology, and biochemistry of keratoconus, and it is possible that keratoconus is an end result or final common pathway of many different clinical conditions, such as systemic collagen disease, trauma, or pre-existing abnormal cornea tissue (Fig. 1). Unfortunately, previous studies have not separated cases of keratoconus into groups according to the clinical setting. Therefore, the discussion which follows is presented as if keratoconus is the same disorder in all clinical settings.

A. PREVALENCE, DISTRIBUTION AND COURSE

Reported estimates of the frequency of keratoconus vary widely. Commonly quoted figures range from 4[59] to 600[108] per 100,000. Most estimates fall between 50 and 230 per 100,000.[9,50,70,173] Why the inconsistency? Duke-Elder observed that the incidence appears to vary in different countries.[59] Another perhaps more important explanation involves the criteria for the diagnosis of keratoconus. (The difficulties encountered in diagnosing subtle cases of conical cornea will be discussed in the Diagnosis section of this review). If all cases of high astigmatism are included in a group of keratoconus patients the incidence will be artifactually elevated. The highest incidence (600/100,000) was reported by Hofstetter,[108] who surveyed 13,395 eyes. Conical cornea was diagnosed by keratoscopy alone.

Keratoconus occurs in people of all races. A female predominance has been observed in most studies; however, the ratio varies. In 300 cases, Hammerstein found 199 women and 101 men or a 2 to 1 ratio.[97] In Amsler's study of 600 keratoconus patients 59.2% were women.[4] Other studies have shown 66.7%,[19] 65%,[238] and 57%[142] of keratoconus patients to be female. Contrary to the above, Palimeris et al discovered a majority of males with the disease (69.8%) in 86 keratoconus patients.[180]

Keratoconus usually occurs bilaterally. In a large series[4] only 14.3% had unilateral disease. Although we are convinced that unilateral cases do exist, we think that their frequency might be even lower than reported above if diagnostic criteria and examination techniques allowed the detection of very early keratoconus in the fellow eye. A diligent search for early signs such as inferior corneal steepening or irregular astigmatism might reveal the presence of very mild disease in the "normal" eye.

Knowing the natural course of keratoconus is very important because nearly all patients will ask what to expect regarding the rate and severity of visual malfunction. However, it is difficult to know the natural course of the disorder because usually the corneal changes have begun before the patient is first seen and, after that, treatment may modify the natural course. The patient begins with either a spherical cornea or regular corneal astigmatism. At about the age of puberty, the cornea begins to thin and protrude resulting in irregular astigmatism with what is usually a steep curvature. Usually, over a period of the next 10 to 20 years, the process continues until the progression gradually stops. If a faint broad iron ring was present, it becomes a thinner more discrete ring. The rate of progression is variable. The severity of the disorder at the time progression stops can range from very mild irregular astigmatism to severe thinning and protrusion and scarring requiring keratoplasty. The concept of progression with age was documented in a study of 386 eyes followed over a 3–8-year period by Amsler.[4]

B. HEREDITY

It is important to distinguish between the terms "heritable" and "familial" in describing a condition. The discussion which follows uses the term "inheritance" in a loose fashion. The reader should be aware that the occurrence of keratoconus in two members of a family does not demonstrate Mendelian inheritance. The cause may be environmental. If one supposes, for example, that eye rubbing can cause keratoconus and that excessive habitual eye rubbing is a prominent characteristic in a family, then keratoconus might occur in more than one member.

The etiological role of heredity in the development of keratoconus has not been clearly established. The available literature must be interpreted cautiously. One must consider many factors before drawing inferences from these studies. What were the author's diagnostic criteria for determining which members of a given pedigree have keratoconus? Waardenburg et al[247] point out that identifying the abortive forms of keratoconus by photokeratography might aid in the elaboration of a more precise pedigree, thus clarifying the mode of transmission. On the other hand, a study in which keratoconus is only loosely defined might inappropriately identify affected or unaffected individuals in each generation.

The significance of heredity must be evaluated independently of other potential systemic or local risk factors for the disease. The importance of heredity in a keratoconus patient with atopic disease is diffi-

cult to determine, because of a possible direct association between the two diseases. Studies in which the relatives of keratoconus patients were examined are difficult to interpret if the proband was a long-term contact lens wearer. Was the keratoconus a result of lens wear, inheritance, or both? With the above considerations in mind, a number of studies have furnished information regarding the heredity of keratoconus.

A total of five sets of identical twins with conical cornea have been reported in the literature.[63,71,98,252] In most sets, the disease was not equally severe in both twins. The occurrence of keratoconus in this particular setting would appear to be under genetic control.

A number of investigators have attempted to elucidate the frequency and mode of transmission of the disease. The possibility of some form of sex-linked transmission has been advanced by authors pointing to the predominance of females with the keratoconus.[97,217] Waardenburg et al[247] cite seven reports in which parental consanguinity was observed. This was believed to be suggestive of a recessive inheritance pattern.

Hallerman and Wilson[96] reviewed 304 cases retrospectively. Twenty-two of these patients had at least one other blood relative with keratoconus. They concluded that the frequency of inheritance was at least 7% (22/304). The mode of transmission was believed to be multifactorial because of the many associated conditions and the various forms of the corneal disease. Isolated dominant or recessive cases could not be excluded.

Several reports attempt to document autosomal dominant inheritance.[65,98,201] Falls and Allen[65] collected 20 cases reported in the literature in which keratoconus was detected in at least two generations. The method of diagnosis was not specified. They concluded that autosomal dominant transmission with variable penetrance was likely.

The largest prospective study was performed by Hammerstein.[98] The detection of irregular mires on keratometry was considered diagnostic of early keratoconus. He examined 52 families, each containing a proband with keratoconus. A total of 236 subjects included the 52 probands, 162 blood relatives, and 22 spouses of probands. In 10 of the 52 families (19%), keratoconus was detected in two or more relatives. Of the 162 blood relatives, 13 (8%) had keratoconus. Conical cornea was found in 5 of 49 siblings. Assuming autosomal dominant transmission with complete penetrance one would expect 25 of 49 siblings to have the disease. Because only 1/5 of the expected figure was found they believed the degree of penetrance was approximately 20%.

Patients commonly ask if keratoconus is inherited and if their children will develop the disorder. Based on available information, we have formulated a response. We tell them the chances are less than one in ten that a blood relative would have the disease.

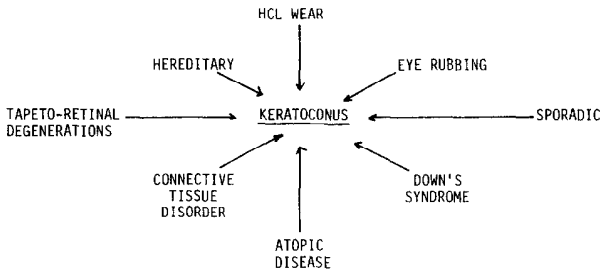


Fig. 1. Clinical settings in which keratoconus occurs.

C. ETIOLOGY

Over the years many theories have been postulated regarding the etiology of keratoconus. Nevertheless the cause of this corneal thinning disorder remains an enigma. Various laboratory studies performed on conical corneas shed light on the pathogenesis of keratoconus. A multitude of clinical reports have linked keratoconus with various systemic diseases, leading many to conclude that keratoconus is a manifestation of a systemic disorder. Results from both laboratory and clinical studies have provided useful clues as to the etiology.

Evidence from histopathological studies led Teng[235] to conclude that the earliest pathologic changes occur in the basal layer of the corneal epithelium. Enzymes released by these degenerating cells cause the fragmentation of the basement membrane, fibrillation of Bowman's membrane, and loss of collagen fibrils. According to Teng's analysis, keratoconus is primarily a disease of the ectodermal layer of the cornea. Underlying tissues of mesodermal origin (corneal stroma) are affected secondarily. This contradicts the hypothesis of Galin and Berger reported in 1958.[73] Recognizing that the slit lamp findings in keratoconus were predominantly in the nonectodermal layers, they concluded that a defect should exist in mesenchymal development or maintenance. The epithelial changes were thought to occur secondarily.

Sabiston[215] found similarities between Teng's work and the histopathological findings in atopic dermatitis. Atopic disease is known to be associated with certain cases of keratoconus. Because both disease processes primarily effect tissues of ectodermal origin, Sabiston implicated a single etiological factor. Mohan[173] suggested the possibility of an ectodermal syndrome to explain the coexistence of keratoconus (affecting surface ectoderm) with retinitis

pigmentosa and macular coloboma (involving neuroectoderm).

When one considers the strong association between keratoconus and noninflammatory connective tissue disease, the question of etiology must be examined from a different perspective. Maumenee considers keratoconus to be a heterogeneous group of conditions. At least in some instances it would appear to be caused by abnormalities of connective tissue.[163] In contrast to atopic disease these abnormalities would primarily affect the corneal tissue of mesodermal origin — the stroma. Observed biochemical abnormalities in the synthesis and degradation of stromal collagen and glycoprotein are detailed in the Biochemistry section of this review.

Perhaps the changes in corneal structure that occur in keratoconus are under direct genetic control. Certainly the disorder is inherited in some families. Many of the systemic diseases with which keratoconus is associated are inherited as well, e.g., trisomy 21, Ehlers-Danlos syndrome, and osteogenesis imperfecta. Freedman and Gombos[72] reported the association of keratoconus with bilateral macular coloboma and retinitis pigmentosa. They propose that a single gene produces all these defects.

Many studies of possible relationships between ocular disorders and the major histocompatibility system (HLA) have been reported. An attempt has been made to correlate certain HLA types with keratoconus.[26,79,121,218] At present we feel the results are inconclusive.

Genetic control over the maldevelopment of the corneal substructure in keratoconus remains unproven. It is merely one etiological possibility. Perhaps the genetic influence is more subtle, requiring the effects of environmental stimuli to produce the phenotypic picture characteristic of keratoconus. Mild chronic corneal trauma induced by contact lenses or eye rubbing are considered by many to be significant etiological factors in the development of keratoconus. The relationship between keratoconus and contact lenses will be reviewed in detail in the next section.

Several reports have implicated eye rubbing as an important etiological factor in the development of keratoconus.[50,75,125,199,205] Ridley hypothesized a cause and effect relationship in corneas already weakened by antecedent inflammation or posterior keratoconus.[205] The induced corneal trauma caused by eye rubbing allows these corneas to undergo conical change. A direct cause and effect relationship has not been proven. The association is implied by the high percentage of keratoconus patients with a positive history of eye rubbing. The reported prevalence ranges from 66%[50] to 73%.[125] Eye rubbing may be the etiological link between conical cornea and associated systemic and ocular diseases. Itching, ocular irritation, and eye rubbing are common features of vernal catarrh and atopic disease. Perhaps the chronic ocular massage is responsible for the increased occurence of keratoconus in these patients. Trisomy 21 (Down's syndrome) is known to be associated with keratoconus. Vigorous eye rubbing has been frequently observed in Down's patients. The relatively high incidence of corneal hydrops in patients with trisomy 21 may be related to corneal trauma associated with intense digital ocular massage. Finally, eye rubbing is said to be a common feature of Leber's tapeto-retinal degeneration.[125] Up to one-third of patients with this disorder develop keratoconus.[1]

The etiological significance of eye rubbing in keratoconus is not known, and the evidence for this behavior's being a risk factor is circumstantial. As Gasset et al[75] point out, it is based only on clinical observation and subjective responses. However, there does seem to be some observation and until more conclusive answers are found, we recommend advising patients against vigorous or prolonged rubbing of their eyes.

Hormonal influence has for some time been advanced as a possible cause of conical cornea.[59,70] The usual onset around puberty, the predominance of affected females[9] and the tendency to progress during pregnancy[50] all support this supposition. King reported the onset of bilateral keratoconus in two women following thyriodectomy.[135] Again there is no evidence to prove a cause and effect relationship. Finally, Duke-Elder[59] cited associations with thymus dysfunction and a hypophysis diencephalic disturbance.

D. CONTACT LENSES AND KERATOCONUS

In 1968 Hartstein reported four cases of keratoconus that developed in myopic patients wearing hard contact lenses.[101] Three of the four were unilateral cases. He suggested that this was a strong indication of contact lens-induced disease. So began a controversy which has persisted to the present. Does hard contact lens wear have etiological significance in the development of keratoconus? Since that initial observation, many authors have described isolated cases of conical cornea occurring unilaterally and bilaterally in the presence of hard contact lens wear.[18,31,102,103,161,230]

Two large retrospective studies addressed this issue. Gasset et al compared 162 keratoconus patients with 1248 soft contact lens wearing patients.[76] Of those with keratoconus, 26.5% had worn hard contact lenses prior to the diagnosis. The average duration of lens wear was seven years. Only one of the soft lens wearing group developed conical cornea

over a one to six year follow-up. Brightbill and Steiner examined 120 consecutive keratoconus patients. A history of contact lens wear prior to the diagnosis of their corneal disease was found in 21 patients or 17.5%.[33] They could not relate the development of keratoconus to the fitting technique or lens specifications. No control group was studied.

The importance of a control population should be emphasized. A random group of cosmetic hard contact lens wearers are largely composed of young myopic individuals. Gasset et al[76] point out that many keratoconus patients become myopic before the disease becomes manifest. The spontaneous development of keratoconus in a group of young myopes might occur with increased frequency independent of contact lens use. These authors are better able to refute this argument because their control group of soft contact lens wearers (1248 patients of similar age and refractive error) did not show an increased incidence of keratoconus.

While retrospective studies of this type suggest a circumstantial association between contact lens wear and keratoconus, they do not prove a cause and effect relationship. A large prospective randomized study with controls matched for age, sex, and refraction is needed. The protocol would require complete evaluation including initial and periodic refraction, keratometry (central and topographical), photokeratoscopy, and slit lamp examinations. A multicenter approach would provide the large patient numbers needed.

The onset of keratoconus while wearing hard contact lenses would seem to disprove the hypothesis that lenses arrest the development of keratoconus. Once the disease becomes manifest the influence of contact lens wear on the rate of progression is unknown.

Several authors have linked the development of keratoconus to the presence of decreased ocular rigidity.[76,105,111] It was suggested that low ocular rigidity might predispose some hard contact lens wearers to develop high astigmatic errors and/or keratoconus. It has further been advanced that early measurement of ocular rigidity might identify a high risk patient group.

Foster and Yamamato reached a different conclusion after reviewing the results of their study on ocular rigidity.[69] They emphasize that corneal thinning may artifactually reduce the determined value of ocular rigidity. Ocular rigidity was determined in four groups. The groups included 84 eyes of 55 patients with keratoconus, 80 normal age-matched eyes, 28 eyes of 24 patients who had undergone penetrating keratoplasty for keratoconus, and 11 eyes of 11 patients who had undergone penetrating keratoplasty for corneal scarring from dystrophic disease. A specific technique was employed in an effort to minimize the potential for artifact induced by a thinned cornea. The coefficient of ocular rigidity in keratoconus patients with less than 60% corneal thinning was not significantly different from the normal controls. In those with corneal thinning greater than 60%, the coefficient of ocular rigidity was artifactually quite low. After the thinning had been corrected by performing cornea transplant surgery, the determination of ocular rigidity returned to normal. The authors concluded that no generalizations about ocular rigidity in a patient with keratoconus were possible with present day instrumentation.

It is important to distinguish the contact lens patient who develops keratoconus from the one with only corneal molding or warping. Corneal warping due to wearing hard contact lenses was first described in 1965.[102] Since then others have reported a similar experience.[145,213] Corneal warping refers to an alteration in corneal contour with resultant change in refraction. This change may last for only a few days, weeks, or months or it may be permanent. Because the astigmatism is characteristically irregular, patients are dissatisfied with the vision achieved through spectacles. Corneal astigmatism does not progress once the lenses have been discontinued. Punctate staining and corneal edema were not described in the previously mentioned reports. In fact, the lens may appear to fit well.

According to Mandell the patient with corneal "molding" often manifests significant corneal edema.[155] The induced refractive change typically recedes, but may do so slowly. Aside from the presence of edema, molding seems quite similar to corneal warping. Persistent significant changes in corneal contour have not been described with oxygen permeable hard lenses or soft lenses.

There are several features which usually distinguish keratoconus from corneal warping or molding. Keratoconus tends to progress once it begins. Increasing myopia is a common characteristic. While the presence of corneal edema is atypical, other slit lamp findings are virtually pathognomonic. These features will be discussed in the Diagnosis section of this review. In some cases, the diagnosis of warpage versus keratoconus will depend on the definition of keratoconus in its earliest stages.

At the present time there is no proof of a cause and effect relationship between the prolonged use of polymethylmethacrylate (PMMA) lenses and the development of keratoconus. There is no question that in some patients PMMA lenses produce permanent high irregular corneal astigmatism. Whether these lenses can also lead to corneal thinning and scarring which would not have occurred without the

TABLE 1

Characteristic Signs of Keratoconus

Retinoscopy
Myopic astigmatism
Scissors reflex
Slit lamp findings
Central or eccentric corneal protrusion
Stromal thinning at cone apex
Fleischer ring at base of cone
Subepithelial fibrillary lines
Prominent corneal nerves
Scarring of Bowman's membrane
Anterior stromal clear lines
Striae anterior to Descemet's membrane (Striae disappear with external pressure)
Keratometry
Irregular mires
Degree of central steepness variable
Increased central steepening over time
Inferior steepening
Placido disc
Irregular rings
Inferior steepening

lenses is not known. In our opinion it seems likely that they can.

When fitting PMMA lenses, certain precautions should be taken to identify early corneal curvature problems. Prior to fitting of PMMA lenses the corneal contour should be evaluated as completely as possible. Patients already wearing PMMA lenses should have follow-up examinations at least yearly. The fitter should be on the lookout for changes in corneal curvature. We suggest careful refraction, keratometry (topographic if possible), keratoscopy, and slit lamp examination. If moderate alterations are detected, the patient should be refit with soft or gas permeable hard lenses. When changes are more substantial, the patient should be instructed to discontinue lens wear for several weeks. Then if the corneal curvature has reverted back, the patient can then be refit.

If the patient does not return to his prelens refractive status, it is possible that the cornea would recover given more time without lenses. The trial period without lenses should be extended only if the patient's visual needs and desires permit him to function with spectacles alone. If the corneal changes are permanent, without progression or recovery, the patient should be refit with a hard contact lens and watched for evidence of progression. Keratoconus may already be present. Examine the patient carefully for the characteristic signs of this disorder (Table 1). Once the diagnosis of keratoconus is made, the patient should be managed as detailed in the Treatment section of this review. A patient with the onset of irregular astigmatism may go on to develop keratoconus and should be watched carefully for the typical signs.

Fig. 2. Angulation of the lower lid on downgaze caused by corneal protrusion in advanced keratoconus is referred to as Munson's sign.

E. DIAGNOSIS (TABLE 1)

The diagnosis of keratoconus in the more advanced form can generally be made without much difficulty. Typically, a patient in the teens or 20's will consult an ophthalmologist for symptoms of progressive visual blurring and/or distortion. It is important to realize that the patient with keratoconus can experience reduction of visual function before visual acuity loss can be measured.[42] Photophobia, glare, and ocular irritation may be noted as well. Examination reveals high, irregular myopic astigmatism. A scissoring reflex is commonly seen on retinoscopy. The irregular corneal astigmatism is confirmed when keratometry is performed and the central mires can not be superimposed. In advanced keratoconus, the corneal protrusion may cause angulation of the lower lid on downgaze (Fig. 2). This has been referred to as Munson's sign.[9] Usually, the diagnosis of keratoconus is made long before Munson's sign is evident.

Slit lamp examination reveals characteristic findings (Table 1). An eccentrically located ectatic protrusion of the cornea is noted (Fig. 3). The apex is usually inferior to a horizontal through the pupillary axis. Corneal thinning from one-half to one-fifth of normal thickness is observed in the apex of the protrusion.[59] Perry et al[184] have distinguished two types of cones in advanced keratoconus. The round or nipple-shaped cone is more common. It is of smaller diameter. The center lies mostly inferonasally. These corneas are more easily fit with contact lenses. The oval or sagging cone is larger and lies predominantly inferotemporally. This cone is more often associated with hydrops, scarring, and contact lens fitting problems.

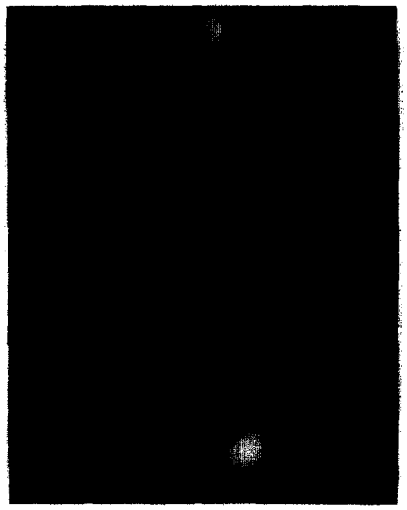


Fig. 3. An eccentric area of corneal protrusion and thinning is characteristic of keratoconus.

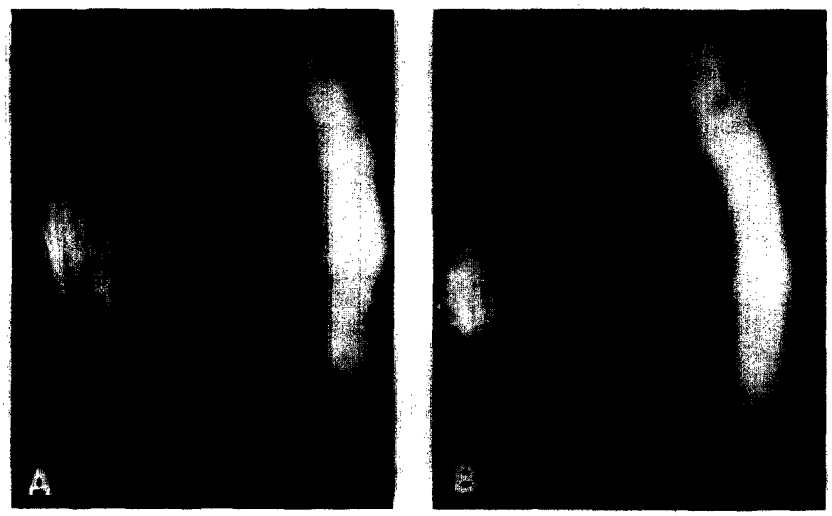


Fig. 4. Corneal striae in keratoconus. A: Striae occur in the posterior stroma and Descemet's membrane. B: Striae disappear when external pressure is applied to the globe.

Corneal striae are usually found within the deep stroma and Descemet's membrane of the cone (Fig. 4A and Fig. 6). These were observed by Elschnig[62] in 1894 and described by Vogt[246] in 1919. The striae occur in the posterior corneal stroma, just anterior to Descemet's membrane.[9,59,88,219] They are often oriented vertically, but usually are aligned in the meridian of greatest curvature.[212,219] When the intraocular pressure is transiently raised by applying external pressure to the globe, the folds disappear (Fig. 4B).[126,212] The fine striae described are to be distinguished from the superficial linear scars seen at the corneal apex (Figs. 5 and 6). These are caused by ruptures in Bowman's layer.[9,59] Very anterior

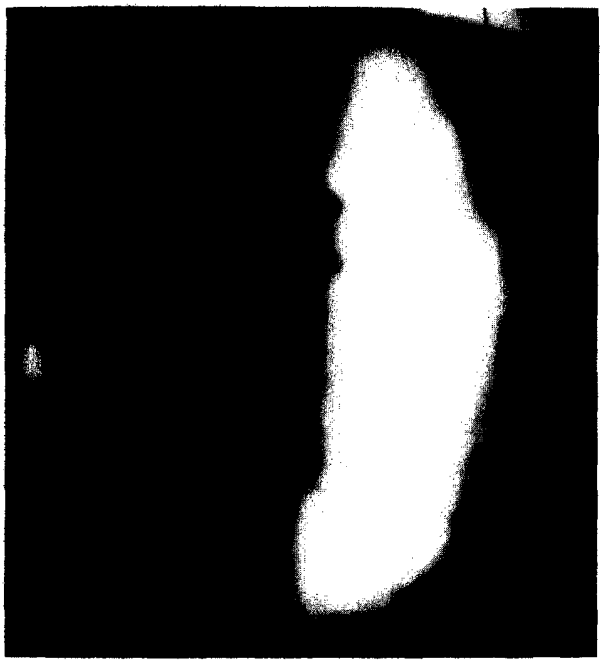


Fig. 5. Scars occurring in the corneal apex at Bowman's layer are characteristically seen.

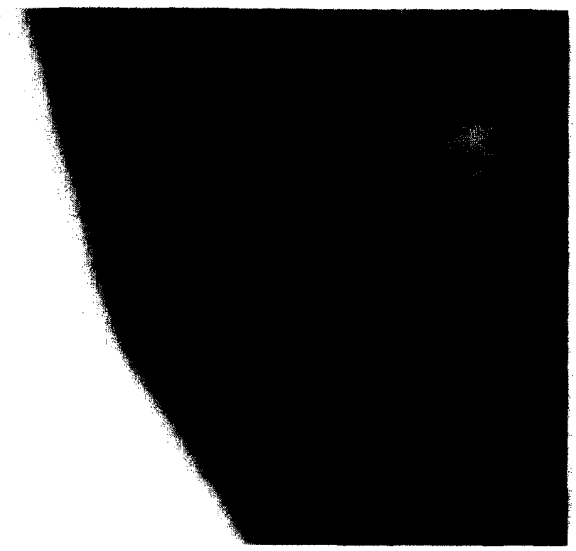


Fig. 6. Large black arrow points to striae of the posterior stroma and Descemet's membrane. Small black arrow indicates an area of corneal scarring at the level of Bowman's membrane. White arrows illustrate short clear zones believed to correspond to ruptures in Bowman's layer.

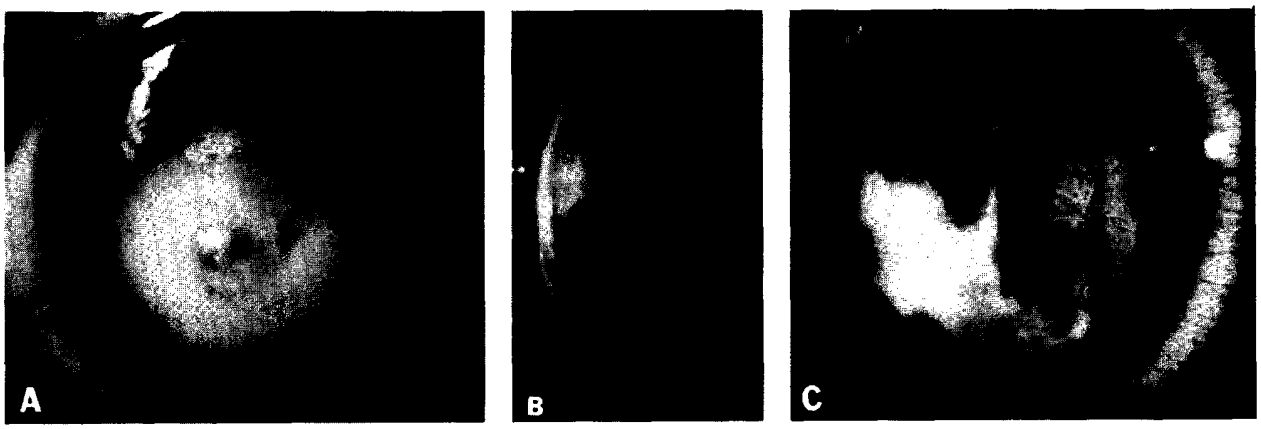


Fig. 7. Corneal hydrops. A: Corneal edema results from stromal imbibation of aqueous through ruptures in Descemet's membrane. B: Slit beam demonstrates the area of corneal thickening. C: In most cases the area is eventually replaced by scarring.

clear lines forming networks are sometimes seen by extremely close inspection (Fig. 6). Possibly they represent interruptions in Bowman's layer before scar tissue fills the breaks.

In more advanced cases, deeper opacities can be seen at the apex resulting from ruptures in Descemet's membrane. Acute keratoconus or corneal hydrops results from stromal imbibation of aqueous through these defects (Figs. 7A and B). This was described by Terrien in 1906.[236] Bellows[66] has observed that 40% of keratoconus patients with corneal hydrops will develop acute keratoconus in the fellow eye within ten years. The edema may persist for weeks or months, usually diminishing gradually. Eventually, it is replaced by scarring (Fig. 7C).

Fleischer's ring is a partial or complete annular line commonly seen at the base of the cone (Color Plate 1). The ring is formed from hemosiderin pigment deposited deep in the epithelium. As the ectasia progresses, the ring tends to become more densely pigmented, narrower, and may become complete. It is present in approximately 50% of cases.[59,88] Assuming subtle incomplete annular pigment lines are included in the definition of Fleischer's ring, it is our impression that a careful search will uncover a pigmented ring in the vast majority of keratoconus patients.

Bron et al[34] has described fine, white subepithelial fibrillary lines in concentric bundles lying just inside the Fleischer's ring. These are best seen under high magnification with a broad, oblique slit beam. The pattern is characteristic of keratoconus and occurs in approximately one-third of patients with this disease.

Prominent corneal nerve fibers forming a network of gray lines with fine white dots are also sometimes seen. Vogt, in 1919, postulated that increased visability of corneal nerves resulted from the outward

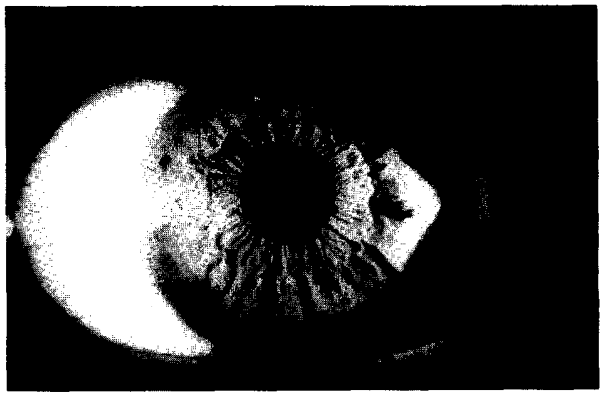


Fig. 8. Ruzzuti illumination test. Light shined from the temporal aspect of the eye is focused by the cone.

bowing and thinning of the ectatic cornea.[246] Bron points out that although there is no relationship between the presence of fibrillary lines and the prominence of stromal nerves, connections between deep stromal nerves and fibrils have been observed. Corneal hyperaesthesia can be detected early in the course of the disease.[130] Later the cone becomes relatively less sensitive.[59]

Various light reflexes are observed in the cornea of keratoconus patients. An endothelial reflex may appear at the peak of the cone due to the increased concavity of the posterior corneal surface.[189] An annular dark shadow separates the bright reflex of the cone from the reflex of the corneal periphery (Color Plate 2). This shadow results from total internal light reflection induced by the corneal ectasia. It is best demonstrated using the direct ophthalmoscope.[59] Shaw et al[221] used the ophthalmoscopic image of the cone, viewing the red reflex through a fully dilated pupil, to aid in the diagnosis of early

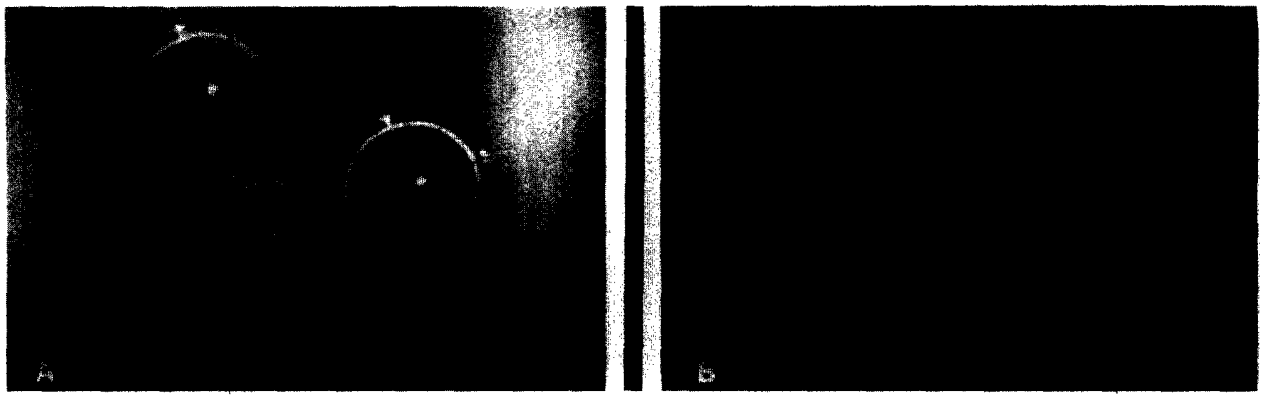


Fig. 9. Inferior steepening is a characteristic finding in keratoconus. A: Central keratometry of a conical cornea. Notice the central location of the fixation light and the mildly irregular mires. B: In this case on upgaze the curvature of the inferior cornea steepened 8 diopters. Notice that the fixation light is now reflected inferiorly. The superior mires splay apart and the mires become increasingly elliptical.

keratoconus. He describes a photographic technique for documenting the size, location, and contour of the cone. Rizzuti[206] demonstrated a simple illumination test for the diagnosis of keratoconus. With a penlight shining on the temporal side anterior to the iris plane, light rays illuminate the nasal limbal area evenly in the normal eye. In mild keratoconus, the ectatic cornea focuses the light sharply inside the nasal limbus (Fig. 8). In more advanced states, the light may be focused at the nasal limbus or even beyond. Rizzuti cautions that this response can also be elicited in patients with severe refractive errors.

The diagnosis of early keratoconus depends on assessment of the topography of the central and paracentral cornea. The keratometer is an invaluable tool for measuring the central corneal curvature, but it is difficult to measure the corneal contour outside this area unless certain modifications are made. Soper et al[227] has described a topographic keratometer which measures paracentral curvature. Using this device, inferior corneal steepening (Figs. 9A and B) — early sign of keratoconus — can be detected earlier and subtle progression can be followed. The need for topographic keratometry to detect inferior steepening has been discussed by Marechal-Courtois.[159] Inferior steepening can be measured without a topographic keratometer. While viewing the cornea through a standard keratometer, the patient is asked to slowly look up and then fix on a target in upward gaze. At this point the keratometer is centered on the inferior cornea. If inferior steepening is present, the vertical mires will splay apart. The degree of steepening is determined by aligning the mires and then turning the appropriate drum until they are superimposed.

The standard keratometer is limited in another way. In keratoconus, the degree of corneal steepening often exceeds the upper limit of the instrument. Miller et al[170] and Manning[158] have described a method of extending the range of the keratometer by applying spherical lenses to the sighting aperture of the device.

Is there a keratometric value beyond which the diagnosis of keratoconus is definite? This question is commonly asked of corneal surgeons. No cutoff value can be given. There are patients with steep corneas and high astigmatic errors who do not have keratoconus and, conversely, patients with keratoconus who have central corneas of normal steepness. We have even seen one patient with definite keratoconus in the 36 diopter range. Irregular astigmatism and inferior steepening are more suggestive clues to the diagnosis.

The handheld keratoscope or Placido disc provides qualitative topographical information (Fig. 10). Amsler[2,3] used the Placido disc to describe a forme fruste of keratoconus. This type was stationary and thought to be an aborted form of the disease. A downward deviation of the horizontal axis of the Placido disc reflection was measured in degrees. Amsler classified the forme fruste as less than or equal to 4 degrees of downward deflection. With greater than 4 degrees of deflection, the diagnosis of mild keratoconus was made. Only a slight degree of asymmetric oblique astigmatism was seen in the forme fruste. Levene[144] and Mandell and Polse[156]

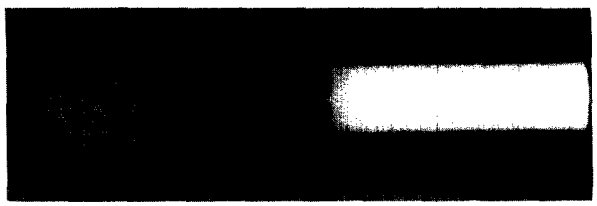
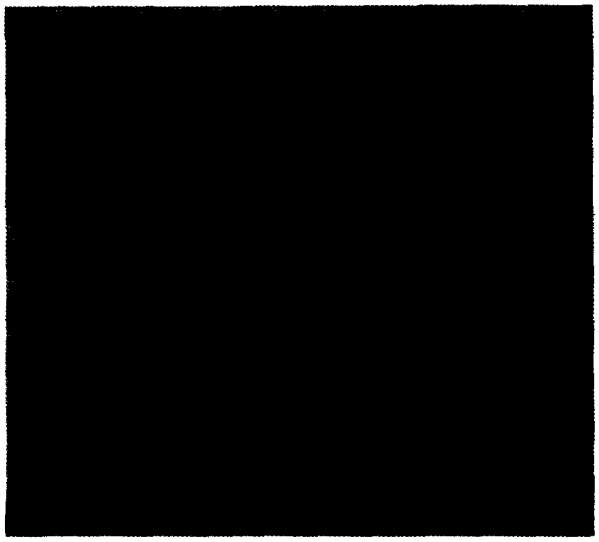


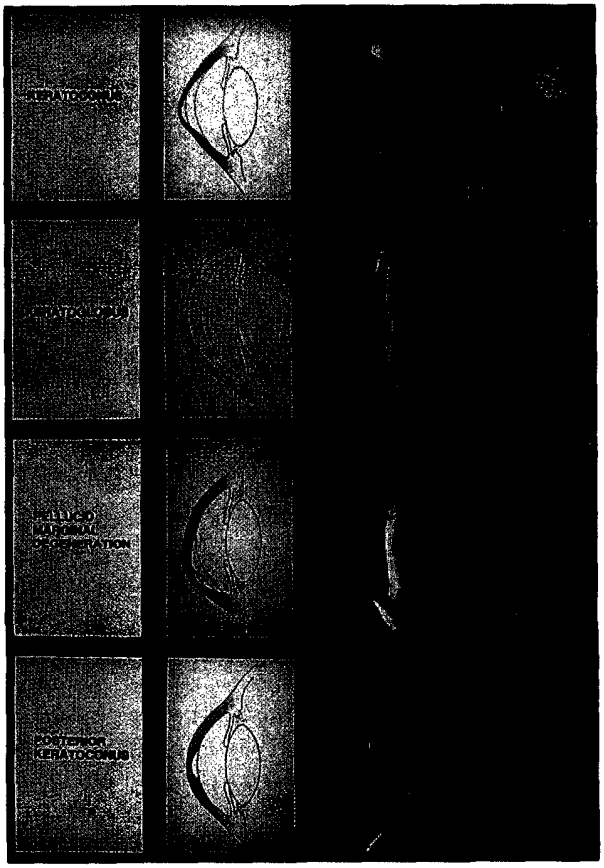
Fig. 10. Klein handheld keratoscope.

Color Plate 1. The Fleischer ring is a partial or complete, brown, annular, iron line found at the base of the cone.

Color Plate 2. Characteristic appearance of a conical cornea viewed with slit lamp retroillumination.



Color Plate 3. Iron deposited in the basal layer of the epithelium is colored blue in this Prussian blue stain of a Fleischer ring. (Prussian blue, × 288)



Color Plate 4. The clinical appearance of keratoconus, keratoglobus, pellucid marginal degeneration, and posterior keratoconus are compared. Keratoconus is characterized by thinning and protrusion of the paracentral cornea. On slit lamp examination maximal thinning is noted at the apex of the cone. External photography shows the typical conical shape when viewed from the side. In keratoglobus, diffuse thinning occurs. On slit lamp examination thinning extends to the limbus. The cornea assumes a globular contour on side view. Pellucid marginal degeneration is recognized by inferior thinning 1–2mm in width, 1–2mm from the limbus. Corneal protrusion occurs above the area of maximal thinning. Flattening of the vertical meridian above the area of thinning, with an abrupt steepening of the inferior cornea, is seen on side view. In posterior keratoconus the anterior surface is relatively normal. Slit lamp examination reveals a crater-like depression on the posterior corneal surface with surrounding stromal haze. Because the anterior surface is not significantly affected, the external appearance is normal.

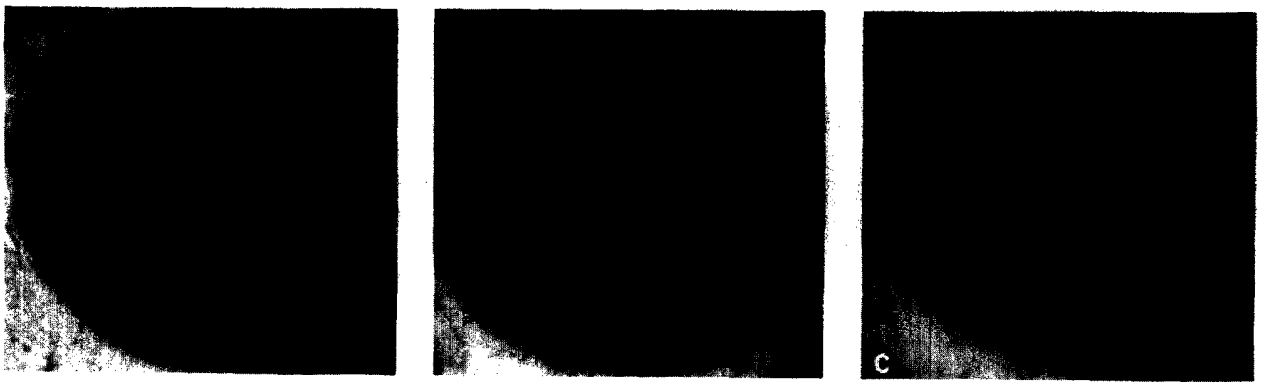


Fig. 11. The corneoscope aids in the diagnosis of keratoconus. (Courtesy of James J. Rowsey, M.D.) A: Steepening of the inferior cornea, one of the earliest signs, is indicated by the closer ring spacing inferiorly. B: With progression, the steepening extends peripherally. C: With further progression, every quadrant may show involvement.

point out that observations made using a handheld keratoscope may be subject to large error from poor instrument alignment or tilt.

The photokeratoscope, invented by Placido and popularized by Gullstrand,[111] has undergone many modifications over the years.[55,189,212] This instrument provides a photographic record of 55–80%[55,212] of the total corneal contour. Donaldson[62] described the photokeratoscopic rings in keratoconus as showing loss of concentricity without breaks in the pattern. Closer ring spacing inferiorly indicates corneal steepening. Quantitative determination of the radius of curvature can also be performed using a photokeratoscope. Rowsey et al[212] analyzed keratoconus and its progression in 827 patients using a topographic corneoscope. They concluded that with the corneoscope one could detect the earliest stages of keratoconus. The earliest sign was steepening of the inferotemporal cornea (Fig. 11A). As the condition progressed, the steepening extended peripherally (Fig. 11B). Subsequently it would involve the inferonasal quadrant and then the superotemporal area. Involvement of the superonasal quadrant was mild and was last to occur (Fig. 11C). With corneoscopic examination of the peripheral cornea, contact lens-induced irregularities in corneal curvature were distinguished from early or progressive keratoconus in a patient wearing contact lenses.

Mandell et al[156] has reported the use of differential corneal thickness measurements with early keratoconus. An automatic recording device was added to a standard keratometer. A difference of greater than 0.085 mm between the position of minimum thickness and a point of 35 degrees from this position along a horizontal appeared to be pathognomonic of keratoconus.

The diagnosis of keratoconus in a more advanced form is relatively easy to make. It is based on characteristic slit lamp findings in the clinical setting of a young adult with progressive irregular myopic astigmatism. Subtle forms of keratoconus present a diagnostic challenge. The ophthalmologist should make use of all the available modalities to carefully evaluate the topography of the paracentral as well as the central cornea. A documented increase in corneal curvature over time remains a most sensitive indicator of keratoconus.

F. ASSOCIATED SYSTEMIC DISEASES

1. Atopic Disease

Over the past forty years much has been written linking keratoconus to atopic disease. Atopy includes such conditions as eczema, asthma, and hay fever. Despite Hilgartner's mention in 1937 of "allergic eczema" in a patient with keratoconus,[107] Berestone and Baer[21] were actually first to suggest a relationship between the two. Sabiston[213] described pathological similarities between the primary skin lesion in atopic dermatitis and the corneal changes in keratoconus. Early papers described a limited number of patients with keratoconus who manifested atopic disease.[36,73,228] In 1956 Ridley[204] reviewed the allergy history from 92 patients diagnosed as having keratoconus. He found 15.2% gave a positive history of allergy compared to 4.2% of 2000 nonkeratoconus patients seen in a contact lens clinic. A criterion for the diagnosis of keratoconus was not described. Gasset[75] questioned keratoconus patients with regard to atopic disease. He found a much higher prevalence of atopy in the keratoconus population than in the general population. In a series of 100 keratoconus patients Copeman[50] found 32 with some form of eczema. This compared to an incidence of 3% in the general population. He concluded that the prevalence of atopic disease among keratoconus patients was 10 times that expected.

Lowell and Carrol[148] are credited with the first

controlled clinical study comparing the prevalence of atopy in a keratoconus population with that of a normal control population. The number of patients was very small, 31 with keratoconus and 30 controls. No bias was obvious in the method of inclusion in the study. On the basis of careful allergy history, skin testing to various allergens, and cosinophil count, the authors concluded that the two groups did not significantly differ with respect to atopic characteristics. It was emphasized that personal and family history taken from a keratoconus patient may be colored by the individual's past medical experience and concern with illness.

A negative correlation between keratoconus and history of atopic disease was also found in a recent work by Wachtmeister et al.[218] Thirty keratoconus patients were compared with thirty age and sex matched control patients having regular astigmatism. The paper specifies the authors' criteria for the diagnosis of keratoconus. This important information is only rarely included in the available literature on this subject. The conclusions drawn in this communication are again based on small numbers.

The largest controlled study, performed at the University of London,[52,199] revealed a positive correlation between keratoconus and atopic disease. Of 182 keratoconus patients, Rahi et al[52,199] found a positive history of atopic disease (asthma, eczema, and/or hay fever) in 35%. This was compared to 12% in 100 normal control patients.

In 1969 Juhlin et al[119] discovered a significant elevation of IgE in the serum of patients with atopic dermatitis. This was not seen in patients with urticaria, nonatopic dermatitis or other dermatological conditions. No correlation was found between IgE level and a history of asthma or hay fever. The immunological profile of keratoconus patients has been studied by several authors searching for correlations with atopic disease.[52,60,199,248] Wachtmeister et al[248] found no statistically significant elevation in serum IgE in their series of 30 keratoconus patients. In a similar number of keratoconus patients, Easty et al,[60] using immunodiffusion plates, found elevated IgE levels in 17%. He observed that those with elevated IgE were also atopic individuals. Rahi et al[199] performed an immunoglobulin survey on their large keratoconus and control populations, using the immunodiffusion technique. The number of keratoconus patients with elevated serum IgE levels was statistically significant compared with normal controls. Among keratoconus patients with atopic disease an even higher percentage of patients were found to have elevated serum IgE. Elevations in serum IgM and IgG were also found in higher proportions among keratoconus patients. No significant difference was present when tears were assayed for IgE.

These observations are most interesting from a research perspective. One must wonder if a common mechanism explains the elevation of serum immunoglobulins and the characteristics of some cases of keratoconus. From a clinical perspective, the difference between the two groups is not enough to warrant recommending serum immunoglobulin assay as a helpful diagnostic test.

Turner et al[213] have documented that clinical manifestations of atopic disease are related to HLA antigen combinations. Based on this knowledge Wachtmeister et al[248] wondered whether a connection might exist between the major histocompatability system and keratoconus. She and her coworkers had postulated that the correlation between atopy and HLA antigens might represent a genetically controlled mechanism. This mechanism might be responsible for the tissue changes occurring in keratoconus associated with atopic disease. Unfortunately, no correlation between keratoconus and specific HLA antigens was found in Wachtmeister's relatively small number of keratoconus patients.

Based on our experience and the available literature, we believe that the prevalence of atopic disease is higher among keratoconus patients. This correlation is clinically important for several reasons. Ophthalmologists must be aware that a thorough evaluation of the keratoconus patient should include a complete history of atopy. If significant atopic disease is newly revealed, the patient may benefit by referral to the appropriate consultant. The ophthalmologist must be informed if steroid preparations are to be used. Steroid induced cataract or glaucoma could potentially compound the patient's visual disability. Allergic lid and conjunctival disease can affect contact lens tolerance adversely. Penetrating keratoplasty may be required earlier in the course of the disease to effect visual rehabilitation.

Dermatologists, allergists, and internists should be aware of a possible increase in prevalence of keratoconus among their atopic patients. At the minimum, an ocular history should be obtained from these patients.

2. Down's Syndrome

Down's syndrome or trisomy 21 is the most common of the chromosomal anomalies. It is widely known that most cases result from an extra chromosome 21. A small percentage result from the translocation of genetic material to a D chromosome or another G chromosome.[237]

Rados[198] was the first to report an association between Down's syndrome and keratoconus in 1948. The many eye findings observed in trisomy 21 were detailed by Skeller and Oster in 1951.[222] In their

series of 81 such cases the incidence of keratoconus was 6%. Most series report the incidence between 5.5% and 8%.[51,171,186] Conflicting data was presented by Rochels et al.[209] Of 1047 people with Down's syndrome, only 0.5% had keratoconus.

The occurrence of acute hydrops in the normal keratoconus patient is relatively uncommon. Pierse and Eustace[186] cite many reports of corneal hydrops occurring in patients with Down's syndrome. They state that acute hydrops occurs with increased frequency in keratoconus patients with mongolism or other forms of mental deficiency.

How is this increased frequency of hydrops explained? Pierse and Eustace,[186] referring to a paper by Ridley,[205] suggested that ruptures in Descemet's membrane occur in these patients because of eye rubbing. Boger et al[28] reported four cases of keratoconus with acute or previous corneal hydrops. Each patient had congenital rubella syndrome, mental retardation, and vigorously rubbed and poked their eyes. Again the corneal changes were attributed to "chronic traumatizing mannerisms" observed in each of these patients.

3. Connective Tissue Diseases

Keratoconus is known to occur in noninflammatory connective tissue disorders.[165] Most notable among these are Ehlers-Danlos syndrome and osteogenesis imperfecta.

The basic defect in Ehlers-Danlos syndrome is abnormal cross linkage of collagen. Seven forms have been described.[140,163,166] Maumenee[163] reports that only in type VI are ocular tissues defective. The basic defect in this autosomal recessive form is a lysyl hydroxylase deficiency. It is suggested that collagen in ocular structures is affected more by the lack of lysyl hydroxylase than by deficiencies of other enzymes required by cross linkage of collagen. Besides keratoconus, ocular findings can consist of ectopia lentis, microcornea or megalocornea, corneal thinning, retinal detachment and cataract.

Robertson[208] examined 44 consecutive keratoconus patients for the following features: hypermobility of joints, blue sclera, hyperextensibility of skin, fragile tissues, bleeding diatheses, and a family history of keratoconus. The prevalence of hypermobility of the joints was 50% (22/44). He diagnosed these patients as having Ehlers-Danlos type II, because findings centered around joint hyperextensibility. In 44 age-matched controls without keratoconus this trait was not present. Kuming and Joffe[140] reported a single case of keratoconus in a patient they classified as Ehlers-Danlos type IV. The characteristic skin changes of this category were described.

Osteogenesis imperfecta is a hereditary disease characterized by bone fragility, deafness, relaxation of ligaments and skeletal muscles, and other abnormalities related to mesodermal tissues.[214] The most consistent ocular feature of osteogenesis imperfecta is the "robin's egg" blue scleral discoloration. McKusik[165] mentioned a single case of keratoconus occurring in a patient with osteogenesis imperfecta. He suggested that the corneal changes were probably closely related to the defect in scleral connective tissue.

Greenfield et al[91] presented two siblings with blue sclerae, middle ear bony conduction defects and spondylolisthesis. One had keratoconus and the other keratoglobus. The report is clouded by the presence of vernal conjunctivitis in both cases. Vernal conjunctivitis itself has been related to keratoconus.[9,21,59,82,89] Aside from the two patients described above, 11 cases were collected from the literature.[91] In each, keratoconus and blue sclerae were present in association with other connective tissue disease.

Keratoconus has been associated with other disorders of connective tissue such as oculodentodigital syndrome, Rieger's syndrome,[91] anetoderma,[92] and focal dermal hypoplasia.[200] It has been reported in the following bone and connective tissue dysplasias: nail-patella syndrome,[91] Apert's syndrome,[80] and cranio-facial dysostosis (Crouzon's syndrome),[254] and Marfan's syndrome.[16]

Beardsley and Foulks have described an association of keratoconus with mitral valve prolapse.[20] The prevalence of mitral valve prolapse in 32 consecutive keratoconus patients was 28% compared with a prevalence of 13% in an age and sex-matched control group. Again the possibility of abnormal collagen metabolism as an etiological factor was considered for both conditions.

It is unlikely that a relationship between conical cornea and connective tissue disorders is purely coincidental. A common defect in the synthesis of connective tissue probably is responsible for this association. This defect could take the form of an imbalance of the biosynthesis of collagen and glycoproteins, improper post synthesis assembly of collagen fibrils, or inappropriately rapid turnover.

4. Other Systemic Diseases

Isolated case reports appear in the literature associating keratoconus with other systemic diseases. Examples are Laurence-Moon-Biedl syndrome,[249] neurofibromatosis,[249] pseudoxanthoma elasticum,[249] Noonan's syndrome[220] (an inherited disorder characterized by a phenotype similar to that in Turner's syndrome with a normal karyotype), and ichthyosis.[70] The association of keratoconus with these other systemic diseases can be considered strongly only after many confirmatory cases have been reported.

G. ASSOCIATED OCULAR DISEASE

As previously discussed, keratoconus may accompany the characteristic ocular findings of a multitude of systemic disorders. For example, in a patient with noninflammatory connective tissue disease keratoconus could occur concomitantly with ectopia lentis, blue sclera, cataract, or retinal detachment. Conical cornea might be found in an atopic individual with cataract.

Keratoconus can also appear in the presence of isolated ocular pathology. A classic example is retinitis pigmentosa. Many authors, enumerated by Franceschetti,[70] and Duke-Elder[59] have reported this association. The statistical significance of this correlation between keratoconus and retinitis pigmentosa was emphasized by Bietti et al[23] in 1962. Macular coloboma has been described in patients with keratoconus. In one report bilateral macular coloboma was seen in a patient with bilateral keratoconus and retinitis pigmentosa.[72]

Infantile tapetoretinal degeneration (Leber's congenital amaurosis) is frequently complicated by keratoconus and cataract, according to Walsh and Hoyt.[249] They refer to a large study (175 cases) by Alstrom and Olson,[1] in which keratoconus was observed in 2% of patients younger than age 15. The prevalence was 30% in patients between 15 and 45. Of those older than 45, more than one-third had keratoconus. In a study of 42 patients with Leber's congenital amaurosis, followed for 2–18 years, Karel[123] also found an increased frequency of keratoconus with age. His patients tended to have an earlier onset with 21% manifesting keratoconus between ages 4 and 10. The prevalence was 57.1% in patients older than 15 years. The keratoconus was always bilateral. The frequency of corneal hydrops was 44% in comparison to that of isolated conical cornea (16/1600 or 2.6%).[70] Godel et al[81] reported Leber's congenital amaurosis in two siblings with familial juvenile nepheronophtisis. One child was severely mentally retarded. The other child had bilateral keratoconus. No mention of eye rubbing in this blind youngster was made.

Leighton and Harris[143] present two cases of retinal aplasia complicated by keratoconus and macular coloboma. Five cases of keratoconus associated with retrolental fibroplasia have appeared in the recent literature.[122,147] Each case of keratoconus was unilateral. Four of the five presented with acute hydrops. Karel[122] implicated digital trauma as an important etiological factor for the development of acute keratoconus in his two patients. Aside from retrolental fibroplasia and Leber's congenital amaurosis (both causes of blindness in childhood), the frequency of acute hydrops is increased in Down's syndrome and other mental deficiency states. An increased prevalence of digital trauma in mentally retarded people and blind children might explain the observed higher incidence of acute keratoconus.

Aniridia is usually included in lists of ocular disorders associated with keratoconus.[59,70,133] Mackman reviewed the corneal changes in aniridia.[150] Keratoconus was not included as one of the changes. Grove et al[93] examined 40 aniridic patients. Corneal changes ranged from a mild haze to a diffusely dense opacity. Keratoconus was not discovered in these cases. In 1938 conical cornea was mentioned as occurring in cases of aniridia.[177] However, keratoconus was not present in the case descriptions. Based on our experience and the available literature, there is little evidence to support a strong correlation between keratoconus and aniridia.

A possible link between low scleral rigidity and keratoconus was put forth by Hartstein and Becker.[106] This relationship has since been questioned by Foster and Yamamoto.[69] They suggest that the method employed to test scleral rigidity may have resulted in artifactually lowered measurements.

An association between vernal conjunctivitis (spring catarrh) and keratoconus is widely reported.[24,59,70,82,89] In 1958 this relationship was statistically proved by Bietti and Ferraboschi.[24] More than one statistical method was employed. Grayson[89] points out that keratoconus can also be seen in atopic keratoconjunctivitis.

H. BIOCHEMISTRY

The biochemical constituents of the normal cornea have recently been reviewed.[224] Collagen is the predominant protein in the cornea, accounting for 71% of its dry weight. The molecular configuration of this ubiquitous structural protein is dependent on a high concentration of carefully arranged glycine, proline, and hydroxyproline. The regular arrangement of collagen fibers in the corneal stroma is essential for corneal transparency. Five types of collagen have been described by collagen biochemists. Between 80 and 90% of the stromal collagen fibers is composed of type I collagen. Type III and type V collagen may also be present in the stroma. Type IV collagen is found in Descemet's membrane and the basement membrane of the epithelium. Type II is not found in the cornea.

The nonfibrillar extracellular matrix is primarily composed of glycosaminoglycan proteoglycans. These are acid mucopolysaccharides attached to a relatively small protein core. The glycosaminoglycans (GAG's) most prevalent in the normal cornea are keratan sulfate (about 65%) and chondroiton-4-sulfate (about 30%). The proteoglycans are neces-

sary for the normal structure and transparency of the cornea. Their presence also influences the imbibation of water by the cornea.

In the past fifteen years research on the biochemistry of the normal and diseased cornea has become increasingly sophisticated. In the case of keratoconus more recent work tends to contradict the results of earlier investigations.

The biochemical evaluation of the conical cornea has been approached from several directions. The amount of collagen and proteoglycan present in normal and conical corneas has been determined in a multitude of studies. The early investigators reported a decrease in the dry weight of collagen compared to that in the normal cornea.[194,207,253] A diminished level of hydroxyproline suggested a decrease in fibrillogenesis in the corneal stroma.[253] A theory was advanced that keratoconus resulted from a metabolic shift by dystrophic keratocytes toward decreased collagen synthesis and increased glycoprotein production.[207] Different results have been obtained by recent work. Two studies have shown similar amounts of collagen in the corneal stroma of normal and keratoconus patients.[178,259] A third study revealed no difference in the concentration of hydroxyproline.[5]

Two early reports described decreased levels of sulfated mucopolysaccharides (now known as glycosaminoglycans or GAG's) in the stroma of conical corneas.[194,253] At the same time Anseth reported no quantitative or qualitative difference in the GAG's of keratoconus corneal buttons.[7] The synthesis of glycosaminoglycans by keratoconus stromacytes in cell culture has recently been examined. A decade after the original studies the debate continues. Yue et al[258] report similar amounts of sulfated GAG's, while Bleckmann and Kresse[27] found diminished levels of sulfated GAG's synthesized by the keratoconus stromacytes. Cell culture studies evaluating the synthesis of heparan sulfate, a GAG associated with cell surfaces, yield conflicting results. Compared to that in normal stromacytes, the production of heparan sulfate by keratoconus stromacytes was elevated in one study[27] and decreased in another.[258]

Several investigators have attempted to compare the type of stromal collagen in keratoconus to that found in normals. Maumenee reported increased levels of type III collagen in two patients with keratoconus.[164] Alterations were obtained in the relative proportion of type I collagen and A,B chains synthesized by cultured keratoconus stromacytes.[259] The most recent study of cultured keratocytes from keratoconus buttons has revealed the synthesis of collagen to be normal in type and amount.[178] These authors concluded that if keratoconus is in reality a disease of collagen, the defect results from an error in collagen assembly or control of collagen turnover.

Abnormalities of collagen crosslinkage are known to occur in Ehlers-Danlos syndrome, a connective tissue disease sometimes associated with keratoconus. Collagen crosslinks in the keratoconus cornea have recently been examined in patients without generalized connective tissue disease.[41] Much greater amounts of lysinonorleucine were discovered in corneas with keratoconus than in normal age-matched controls. This seemed to suggest a change in the hydroxylation of certain lysyl residues of normal collagen or the possible synthesis of an abnormal collagen. To our knowledge, the results reported in this study have not yet been confirmed by other investigators.

The biomechanical properties of keratoconus and normal corneas have recently been compared.[5] It was found that the mechanical strength of the cornea was reduced in keratoconus. The authors suggested that the relatively small load values for keratoconus corneas are only partially explained by corneal thinning. Qualitative differences in the keratoconus cornea were a significant factor in explaining their relatively reduced strength. Decreased mechanical resistance may play a role in the protrusion of the conical cornea.

Enzymatic assays have been performed on corneal buttons from keratoconus patients. A relative deficiency in glucose-6-phosphate dehydrogenase (G-6-PD) was uncovered by two independent investigations.[131,197] Kim and Hassard explain how a deficiency in this enzyme might indirectly lead to impairment of stromal collagen formation.[131] This deficiency might also lead to a decrease in reduced glutathione. Resultant peroxidation of the lipid-rich epithelial basement membrane could perhaps play a role in the pathogenesis of keratoconus.

Rehany et al[202] recently performed assays for collagenolytic activity.[202] The assays were done on organ culture media from which keratoconus corneal buttons had been incubated. Compared with normal corneas, conical corneas had higher levels of collagenolytic activity. The presence of a high level of collagenase in an active form might be an important factor in the development of keratoconus.

An important question has yet to be addressed. Are all cases of keratoconus biochemically equivalent? For example, would biochemical assays in an Ehlers-Danlos patient with keratoconus be similar to those in an atopic individual with conical cornea? Prior to evaluation the corneal specimens should be grouped according to environmental or genetic setting in which the disease occurred. These groups should then be studied individually. Treating cases individually with our increasingly sophisticated methodology might provide insight into the patho-

TABLE 2

Pathology of Keratoconus

Epithelium
Disruption of epithelial basement membrane
Downgrowth of epithelium into Bowman's membrane
Thickened subepithelial basement membrane-like layer
Particles (on EM) between basal epithelial cells and on surface of Bowman's membrane
Iron ring: ferritin particles within and between epithelial cells
Bowman's Membrane
Breaks in Bowman's layer filled by eruptions of stromal collagen
Z-shaped interruptions at the level of Bowman's membrane
PAS positive nodules on Bowman's membrane
Reticular scarring
Stroma
Compaction and loss of random arrangement of fibrils
Decreased number of collagen lamellae
Normal and degenerating fibroblasts in addition to keratocytes
Fine granular and microfibrillar material associated with keratocytes
Descemet's Membrane
Breaks in Descemet's membrane
Endothelium
May be normal
Intracellular "dark structures"
Increased cellular pleomorphism
Elongation of cells with long axis toward cone

genesis of various cases of keratoconus.

I. PATHOLOGY

Since the first report of the pathology of keratoconus in 1859, a great deal has been written about the subject. Electron microscopy has aided in the description of fine detail. Combined with biochemical analysis, electron microscopy has given us a great deal of information concerning the pathogenesis of keratoconus.

Depending on the stage of the disease, every layer and tissue of the cornea can become involved in the pathological process (Table 2). Early degeneration of the basal epithelial cells can be followed by disruption of the basement membrane of the epithelium.[235] Breaks in the epithelial layer are sometimes accompanied by a downgrowth of the epithelium into Bowman's membrane (Fig. 12).[117,120] On electron microscopy, particles have been seen within a thickened subepithelial basement membrane-like layer.[113] Others have seen the particles between the basal epithelial cells and on the surface of Bowman's layer.[181] It is not certain what these particles represent. They might contain collagenase and be involved with disintegration of collagen fibrils.[113]

A hallmark of keratoconus is the Fleischer ring which surrounds the base of the cone (Color Plate 1). The brown iron ring is more commonly seen histologically than clinically.[167] Light and electron microscopy reveal that ferritin particles accumulate within and between epithelial cells (Color Plate 3). They are most prominent in the basal layer of the epithelium.[112]

Bowman's layer is also involved early in keratoconus. Breaks in Bowman's layer are filled by eruptions of underlying stromal collagen.[117,181] These ruptures in Bowman's layer are more common in oval (sagging) cones than in round cones.[184] Nodules, which are PAS positive, have been seen on Bowman's layer.[167]

A classic finding in keratoconus is Z-shaped interruptions at the level of Bowman's layer. The two triangles of the Z are filled with epithelium growing posteriorly and stromal collagen growing anteriorly. Included in these interruptions are deposits of fine granular PAS positive material.[207] Polack believes that the Z-shaped areas are due to the separation of two collagen bundles.[187]

The pathology of collagen fibrils in keratoconus has been extensively studied. An early change is compaction and loss of random arrangement of fibrils of the anterior stroma.[35] It had been thought that there was thinning of individual collagen lamellae.[117] However, more recently, Pouliquen et al found normal sized collagen fibers with a decrease in the number of collagen lamellae.[193] In their study of the keratoconus cornea, they found the number of lamellae outside the cone to be 340, in the periphery of the cone 220, and within the central portion of the cone 140. Others have noted an unfolding of collagen bundles.[192] Polack believes that collagen lamellae are released from their attachments to other lamellae or to Bowman's membrane and slide, giving a thinning of the cornea without actual collagenolysis.[187] He thinks that the release results from alterations in the composition of the ground substance. Caffi found that anterior fibrillar degeneration preceded epithelial changes.[40]

A variety of keratocytes are found in keratoconus. Pouliquen et al[195] have carefully described several types. They found normal keratocytes in the anterior third of the stroma and in the periphery. Fibroblasts were seen beneath the epithelium and around scars. Fibrocytes with microgranular accumulations along their surface were seen in the anterior and mid-stroma. Degenerating fibrocytes were the least common variety of keratocytes and were found mostly in the posterior layers.

Granular and microfibrillar material have been documented in multiple publications. Fine granular material closely associated with keratocytes was felt to be produced by the keratocytes.[207] Some have felt that the extracellular microfibrillary material was the precursor of collagen fibrils.[192] Amyloid deposits

were found by McPherson and Kiffney,[167] suggesting degenerative changes. This finding was not confirmed by Pouliquen et al.[193]

Some investigators have studied corneal hydrops. Breaks in Descemet's membrane and stromal edema are resolved when endothelium covers the defect and lays down a new Descemet's membrane. There has been debate as to whether the endothelial repair takes place mainly by the sliding of endothelial cells[191] or by endothelial cell regeneration.[233] Perhaps the relative contribution of regeneration or sliding depends on the severity of the break.

Corneal scarring in keratoconus takes many forms.[35] Reticular branching opacities at the level of Bowman's layer is an early form of scarring. These opacities are felt to be preceded by short clear zones in Bowman's layer which are thought to be ruptures in this layer (Fig. 6). Fine scars form in the clear breaks which consolidate resulting in reticular scarring. Small focal scars may appear anywhere in the stroma. Extensive scarring over the cone may resemble a Maltese cross.

Many theories have been proposed regarding the pathogenesis of keratoconus. Among these are theories which either implicate alterations in the basal epithelial cells as the initial change, the junction between Bowman's layer and the anterior stroma as the first change, or the possible existence of primary pathology of keratocytes. Teng felt that the process begins in the basal epithelial cells.[235] Following degeneration of these cells the basement membrane disintegrates with resulting breaks. PAS positive material from the basement membrane spreads into Bowman's layer and the anterior stroma. Enzymes from the degenerated basal epithelial cells attack the collagen fibers of Bowman's layer resulting in fibrillation and liquefaction. The enzymatic degradation reaches progressively deeper into the stroma and eventually includes Descemet's membrane. Teng therefore considers keratoconus to be primarily a lesion of basal epithelial cells with secondary destruction in a posterior direction.[235]

McTigue found the earliest changes in keratoconus to be located between Bowman's layer and the anterior stroma.[168] In that area, he found aggregations of collagen fibrils and fibroblastic keratocytes. The next change was the anterior movement of fibroblasts. The production of more basement membrane by the epithelium followed as a reparative process. He theorized that this process of fragmentation and repair continued in cyclic fashion.

More recent authors favor the theory of primary keratocyte pathology. Some feel that there is an enzymatic defect in fibrogenesis.[85,193] Others feel that keratocytes undergo a change which results in the modification of the synthesis of collagen fibers and ground substance which then results in a decrease in the number of collagen lamellae and an increase in the ground substance along with the accumulation of granular deposits.[160]

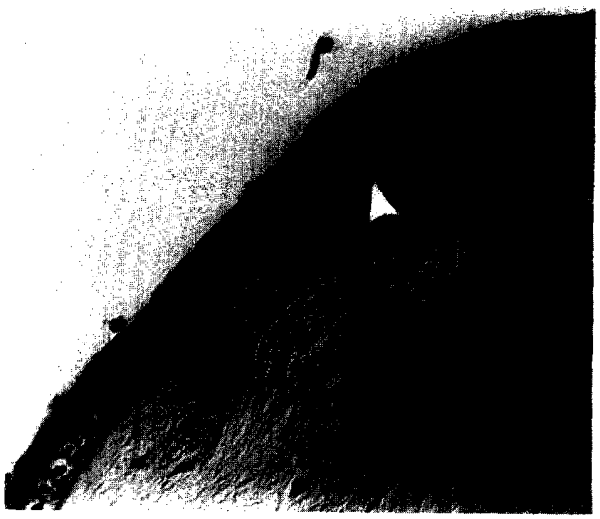


Fig. 12. The downgrowth of epithelium into Bowman's membrane (arrow) is a characteristic histopathological finding. (hematoxylin and eosin, × 132)

Although much has been written regarding the pathology of keratoconus, we still have a great deal to learn about the pathogenesis. Perhaps the pathogenesis of an individual case is dependent on its etiology.

J. TREATMENT

The management of keratoconus is a spectrum of therapy progressing from no treatment to correction with glasses to contact lenses and finally to surgery. The appropriate treatment depends on the severity of the disease and visual requirements. Mild forms of the disease are treated with spectacles or corneal contact lenses. Contact lens wear becomes necessary when cone progression increases the degree of irregular astigmatism. Penetrating keratoplasty is performed when the patient can no longer tolerate or achieve satisfactory vision with contact lenses.

1. Historical Review

In 1869, Wells reviewed the spectrum of therapy available at the time.[251] Medical treatment consisted of using spherocylindrical spectacle lenses and stenopeic slit devices. Various tonics prescribed were believed to be of little benefit. Patients were cautioned against sewing or reading, as it was suspected that protracted near work would contribute to the conical condition. Numerous surgical procedures were recommended. In some patients lens extraction was performed in an effort to neutralize induced

myopia. Frequent anterior chamber paracenteses was recommended for others. The most successful procedures were an iridectomy or an iridesis procedure. Iris surgery was performed in order to allow vision through a less distorted portion of the cornea or to form a stenopeic slit. In addition, it was felt that lowered intraocular pressure resulting from the procedure might retard the progression of the disease.

Reference is made to a procedure advocated by von Graefe designed to produce scarring and subsequent flattening of the conical apex. After performing a lamellar keratectomy, silver nitrate was applied to the bare stroma. The desired result occurred five to six weeks after the induced keratitis healed.

By 1936[9] the use of miotics and various tonics were in vogue. Thyroid and ovarian extracts were believed to be of benefit in the early stages of keratoconus. Knapp[136] suggested the systemic use of vitamin-D complex in the therapy of keratoconus.

Scleral lenses of ground or blown glass were being used. It comes as no surprise that intolerance was the most significant problem with these lenses. Corneal lenses were not introduced until the late 1940s.[81] These lenses allowed patients more comfortable, extended wear time. Only in hopeless situations was surgery advised.

Appelbaum[9] described a technique of flattening the corneal apex by excising a full thickness elliptical piece of corneal tissue. Electrocautery both with and without perforation was widely advocated. Hilgartner[107] mentioned the application of radium to the conical cornea. Sato[217] performed posterior corneal incisions through Descemet's membrane in an effort to flatten the conical cornea, avoiding the leukoma caused by chemical cautery or electrocautery.

In 1936 Castroviejo reported the use of keratoplasty in a case of advanced keratoconus.[41] This represented an important milestone in the development of the current day approach. The concept of completely excising the misshapen corneal tissue and replacing it with clear donor corneal tissue of normal thickness was radically different from the other recommended surgical techniques. By 1949[43] Castroviejo had performed more than 200 keratoplasties for advanced keratoconus. He reported success in over 80%.

In the decades that followed, improved lathing techniques, new lens materials, and better fitting procedures increased the success rate of contact lens wear in keratoconus patients. In addition, great strides have been made in corneal transplantation surgery. The development of microsurgical techniques and instrumentation, modern methods of corneal preservation, and more effective postoperative care have all led to an extremely high success rate for penetrating keratoplasty in the keratoconus patient.

2. Contact Lenses

As keratoconus progresses, the degree of irregular corneal astigmatism increases. Eventually patients become unable to achieve satisfactory vision with spectacle correction alone. A contact lens provides a new regular refractive surface, eliminating much of the irregular corneal astigmatism. As described previously, early lenses were scleral or optic lenses. Some details of scleral lens preparation and fit are described elsewhere.[131,204] In the United States most fitters now use exclusively corneal lenses.

The prefit evaluation should include refraction, extended keratometry, keratoscopy and an assessment as to the type of cone, nipple shaped or the oval, sagging type (see Diagnosis section). Keratoconus patients requiring contact lenses are difficult to refract. Prefit accuracy is not critical because final lens power is determined by overrefraction. Assessment of the cone type is helpful. If an oval or sagging cone is present a more difficult fit can be anticipated. In a patient with a sagging cone the initial lens in our trial fit is usually a large diameter single cut PMMA hard contact lens. The diameter is in the range of 8.5 mm to 9.0 mm. We aim for a flat fit by choosing a central posterior curve equal to the flattest keratometry reading plus one fourth of the difference between the flattest and steepest reading. Slight apical touch and peripheral touch determined on fluorescein pattern is desirable. Excessive apical touch should be avoided. On the other hand, if a patient with moderate touch is fit steeper so that there is less touch or even vaulting of the cone, visual acuity is often decreased.

The superior portion of the lens is often supported by the upper lid. This support is important because the irregular corneal contour and the proclivity for inferior lens lift-off tend to destabilize the lens. The lens stability should always be checked in extreme gaze positions. Lens movement with the blink usually provides adequate tear exchange. Kemmetmüller[130] reported the results of 555 eyes of keratoconus patients with large diameter flat fitting hard lenses. He observed that in 68.4% of these cases, regular lens wear resulted in arresting progression of the cone. We have not had the same experience as Kemmetmüller, but we do advocate this type of lens when fitting an oval or sagging cone.

In the case of a round or nipple-shaped cone, our initial step is to try a smaller diameter lens with a steeper central posterior curve (diameter 8.0–8.5mm and base curve midway between the two keratometry readings). The steeper base curve

minimizes apical touch. Less inferior lift-off is observed with lenses of smaller diameter. Good movement and, therefore, tear exchange are also benefits of smaller lenses. Adequate centration is sometimes a problem. Fluctuating vision is experienced by the patient if on blinking the lens edge moves into the visual axis.

Arias[101] has developed a lens which is an extension of this smaller lens concept. The minikeratoconus lens is designed to fit the apex of the cone. We have used this lens with success. Surprisingly, lens stability and complaints of fluctuating vision have not been a problem. This type of lens is also a better choice for a round or nipple-shaped cone.

Good vision is usually achieved with the PMMA lens. Lens intolerance can limit the duration of lens wear. This occurs most commonly when excessive apical touch is present. Our experience, as well as others,[81,172] has been that these patients are more apt to tolerate lenses of gas permeable material. Lenses made from a silicon-PMMA mixture are particularly well suited. The Polycon™ lens is composed of this material and is our choice for patients with complaints of lens intolerance. Akashi[81] points out that lenses of cellulose acetate butyrate (CAB), another gas permeable material, tend to flatten with time and mold to the cornea. In addition, they are easily scratched.[141] Mobilia and Foster[172] used Polycon™ lenses to refit 96 eyes of 56 keratoconus patients intolerant of PMMA lenses. The partially gas permeable Polycon™ lenses were successfully worn in 73% of these patients.

When the above techniques fail, we have had success fitting a Soper lens.[130] The posterior surface of the lens has two different curvatures. The steeper, central curve is designed to fit the cone, while the flatter peripheral lens curve fits the more normal peripheral corneal curvature. By increasing the diameter of the central curve the saggital depth is increased. An increased saggital depth will provide more effective vaulting of the cone. This can be a difficult lens to fit. The sharp junction between the two curves can interfere with proper tear exchange. The lack of an adequate blend between the central and peripheral curves may explain lens failure in patients with advanced cones.

Based on reports of successful fits some authors have advocated the use of soft contact lenses for keratoconus patients.[109,119,230] Koliopoulos and Tragakis[137] fit 96 eyes of 52 keratoconus patients with soft lenses. Most of these patients were unable to tolerate hard lenses. They found 74% of the patients obtained visual acuity of 20/50 or better with soft contact lenses alone or in combination with spectacles to correct residual astigmatism. Baldone[17] points out that it is difficult to predict which keratoconus patients will attain good visual acuity with soft contact lenses. It seems logical to assume that the less astigmatism present (especially irregular astigmatism) the better the chances for good vision with soft lenses and spectacles. Massin et al[162] recommend prescribing soft lenses when the keratoconus patient can no longer tolerate hard lenses. They recommend large diameter lenses (14–15mm) with base curve between 7.50 mm and 8.60 mm. In our experience soft lenses do not mask enough irregular astigmatism to allow satisfactory vision even with a spectacle overcorrection. We have used semiflexible lenses such as the Dura-T™ lens described by Gasset and Lobo.[78] This lens is thinner and lighter than a PMMA lens. The weight reduction is said to assist with lens centering and patient tolerance. Our patients have not obtained satisfactory visual acuity with this lens.

If the other methods fail, a piggyback lens system can be tried. A large diameter low minus soft lens is placed on the cornea. A hard lens (PMMA or gas permeable) is placed on top of the soft lens. Generally, a hard lens diameter of 9.0 mm–9.5 mm seems to work best. We use this method as a last resort prior to recommending surgery. Most patients find this system cumbersome, but others feel it is a reasonable alternative to a surgical procedure.

Fitting contact lenses in the keratoconus patient is a challenging and often frustrating endeavor. Both the patient and the fitter must be willing to invest a great deal of time, patience, and motivation toward the goal of a successful lens fit. An ideal lens fit is frequently not possible, therefore, the capacity for compromise becomes increasingly important. As the disease progresses, the patient may need to accept some degree of lens awareness and/or distorted or blurred vision. The fitter compromises by attempting to minimize apical touch while, at the same time, providing stable lens fit.

A patient with progressive keratoconus must never be forced to continue wearing lenses when satisfactory visual function with a comfortable fit becomes unobtainable. It is the art of ophthalmology to help the patient determine when this point has been reached. Surgical intervention should then be recommended.

In the case of a retarded patient, the management should always be tailored to the individual. Mildly handicapped patients may be capable of wearing contact lenses. When penetrating keratoplasty is contemplated, the surgeon must weigh potential benefits against the risks of ocular trauma and improper management at home postoperatively. Slusher et al[223] point out that every effort should be made to maintain visual function in these patients, as poor vision increases the level of sensory depriva-

tion already present.

3. Surgery

a. Penetrating Keratoplasty

In the United States, penetrating keratoplasty is the most commonly employed surgical technique for rehabilitating the patient with keratoconus. Keratoplasty is indicated when the patient becomes unable to tolerate contact lenses or when the vision obtained is not satisfactory. It should always be kept in mind that performance on the Snellen chart does not accurately reflect the visual function of a patient with irregular astigmatism. Another frequently mentioned indication for keratoplasty is progression of cone size toward the limbus, necessitating a larger desirable graft. It has been our experience that poor vision or lens intolerance occurs before that happens.

Acute corneal hydrops is not an indication for penetrating keratoplasty nor does its occurrence constitute an ophthalmic emergency. A proper treatment regimen includes shortterm pressure patching, cycloplegia topical hyperosomotic ointment or drops, and topical pressure lowering agents. Most effective, however, are patient reassurance and "tincture of time." In our experience the stromal edema usually resolves within weeks to months. After healing, the residual stromal scar may actually lessen the degree of conical protrusion. Rarely, it can be permanent, necessitating surgery.

The results of cornea transplant are generally excellent. A clear graft is obtained in greater than 90% of cases. Reports include rates of 90%,[99] 93% (48 grafts),[29] 95% (34 grafts, 3 months to 4 year follow-up),[38] 98% (87 grafts),[8] 100% (50 grafts, 9 months to 8 year follow-up),[6] and 100% (27 grafts, 1 to 6 year follow-up).[129] The largest series was that of Paglen et al,[179] who reported clear grafts in 90% of 326 eyes grafted for phakic keratoconus. The follow-up ranged from 5 to 34 years with a mean of 11.3 years. Visual prognosis post keratoplasty is also quite good. Reports of the percentage of keratoconus patients with a visual acuity of 20/40 or better range from 73–100%.[6,56,129,179,211] The degree of postoperative astigmatism or anisometropia is very important information that is routinely omitted from studies of post transplant vision.

Most corneal surgeons prefer to use younger donor material for keratoconus grafts hoping to achieve the best possible longterm result. However, the literature does not contain data to support that custom. Linn et al[146] recently studied the endothelial morphology in 55 keratoconus grafts. Follow-up time ranged from 2.5 to 35 years. No statistical correlation was found between donor age and endothelial cell count. Younger recipients seemed to have better endothelial cell survival than older recipients regardless of the age of the donor tissue.

Technically, a penetrating keratoplasty is similar to other grafts done for nonvascularized corneal diseases. We generally select the smallest trephine that will encompass the entire cone and still allow an adequate optical zone free from sutures. Usually we use a trephine between 8.0 mm and 8.5 mm. The Fleischer ring is used as the limit of the conical cornea. Most corneal surgeons believe that recurrence within the graft is a result of incomplete excision initially. Abelson et al[146] reported a case of recurrent keratoconus studied histopathologically.

High post-keratoplasty astigmatism is probably the most frequent complication of cornea transplant surgery. To date there is no surgical technique that insures an anastigmatic cornea after penetrating keratoplasty for keratoconus.[241] Fortunately, keratoconus patients are accustomed to contact lens wear and can usually tolerate a large degree of regular astigmatism in a spectacle correction.

The reported frequency of endothelial graft rejection in keratoconus ranges from 8%[129] to 39%.[46] Chandler and Kaufman[47] studied 41 grafted keratoconus patients. Endothelial graft rejection reactions occurred in 38%. Fifty percent of the endothelial rejection reactions occurred within the first two postoperative months.

Two questions commonly arise when transplant surgery is contemplated for the second eye. Is the rate of graft rejection significantly increased by performing a second keratoplasty? Will the second transplant jeopardize the integrity of the first? Donshik et al[56] studied 100 keratoconus patients postkeratoplasty. Twenty-four had undergone bilateral cornea transplantation. Nearly a four-fold increase in the risk of rejection for a second graft was found (10% for the first versus 38% for the second). The first graft was also at higher risk for immune reaction when a second transplant was performed. The authors concluded that the second operation should be postponed as long as possible. They suggest the use of topical steroids bilaterally in the immediate postoperative period.

This increased rate of rejection has not been experienced by others.[39,46,152] One report included 30 keratoconus patients with bilateral transplants (60 grafted eyes).[152] No statistically significant difference in immune rejection was observed when unilateral grafts were compared with the first or second eye of the bilaterally grafted patient. These authors concluded that fear of immune rejection should not contraindicate performing a transplant in the fellow eye.

We generally do not graft the second eye until the first eye has been completely rehabilitated. At the time of second eye surgery topical steroids are not

given bilaterally unless rejection phenomena have occurred in the first eye.

Vannas performed HLA typing in 56 grafted keratoconus patients and 900 normal controls.[245] Those avascular keratoconus patients with HLA-B12 and HLA-B27 were at significantly increased risk for developing a rejection reaction. The number of grafted patients included in this study were unfortunately too small to interpret the significance of this report.

The number of grafts lost because of repeated or severe rejection phenomena can be minimized by diagnosing the problem early and treating aggressively. Early diagnosis depends on patient recognition of the warning signs — injection, discomfort, and decreased vision. It is the surgeon's responsibility to continually emphasize to the patient the necessity for early recognition of these signs. We treat rejection reactions aggressively. When stromal edema is seen in the presence of subepithelial infiltrates, keratic precipitates, or anterior chamber cells, our regimen includes hourly topical steroids, steroid ointment at bedtime, subconjunctival and systemic steroids, as well as close observation. Fortunately, the vast majority of endothelial rejections treated early are reversible.

Postoperative topical steroids must be judiciously used to avoid the development of posterior subcapsular cataracts. Cataract extraction poses a potential threat to the integrity of the graft. The patient must also contend with the problems associated with monocular aphakia. In two studies, the frequency of post-keratoplasty posterior subcapsular cataract in the keratoconus patient was approximately 30% with a follow-up of up to five years.[56,57] Fortunately, early cataracts often do not cause significant visual impairment. These cataracts usually progress slowly, and usually will stabilize if steroids are discontinued. Steroid dose should be tapered and discontinued as rapidly as is feasible.

A complication of particular importance after keratoplasty for keratoconus is permanent mydriasis. Urrets-Zavalia was the first to document and describe this condition in the literature.[241] He pointed out an association with iris atrophy and secondary glaucoma and emphasized its occurrence especially when strong mydriatics were used postoperatively. Since this first publication in 1963, many have reported permanent mydriasis following corneal transplant for keratoconus.[30,53,74,99,190]

The most detailed description is that of Davies and Ruben.[53] In their series of 140 grafts done for keratoconus over a six-year period, 11 (7.8%) developed a fixed dilated pupil. Over an 18-week period, two patients completely recovered and two partially recovered. Seven remained permanently dilated. All of these had focal or sector iris atrophy. A partially dilated, sluggish pupil was found in the operated eye in 19% of 94 cases. In a control group of 246 age and sex-matched nonkeratoconic grafts, permanent mydriasis was found in only two cases (0.8%).

The reported incidence in patients grafted for keratoconus varies from 5.8%[74] to 17.7%.[22] Bilateral involvement has been described.[190] Davies and Ruben[53] attributed the occurrence of this condition to preoperative iris abnormalities and traumatic strangulation of the iris sphincter by pressure against the posterior corneal wound edge. Our experience after several hundred penetrating keratoplasties for keratoconus has been quite different. We have not had a single case of permanent mydriasis. Our usual postoperative cycloplegia regimen includes either 1% cyclopentolate hydrochloride or 1% tropicamide.

Factors that might reduce the risk of permanent mydriasis have been suggested. These include avoiding air to reform the anterior chamber at the conclusion of the operation[30,99] and performing a peripheral iridectomy.[53,190] It would seem logical to avoid strong mydriatics, although this condition has been described when no mydriatics had been used.[22,30,53,180]

b. Other Surgical Procedures

Surgical procedures for keratoconus other than penetrating keratoplasty are performed. These include thermokeratoplasty, lamellar keratoplasty, and epikeratophakia. Thermokeratoplasty has been used as an alternative surgical modality. Flattening of the conical cornea is achieved by thermal shrinkage of stromal collagen. Arentson and Laibson recommended this technique for a small group of well selected patients.[13] It is suggested for poor surgical candidates who are unable to wear contact lenses. Ideally, the apex of the cone should be below the visual axis. The cornea is preferably greater than 50% of normal thickness with absent to moderate axial corneal scarring. In addition, Aquavella et al[11] have advocated thermokeratoplasty in the treatment of persistent corneal hydrops. This represents an alternative to the recommended conservative approach discussed earlier. A group of 59 cases without hydrops were treated by Gasset and Kaufman.[77] Most achieved a visual acuity of at least 20/30, with a follow-up of 2–24 months. Over time, the altered corneal curvature can return toward its pretreatment value. For this reason, the length of follow-up becomes an important factor in the evaluation of these reports. In one report corneal curvature reverted to the pretreatment measurements in seven of nine patients.[128] After thermokeratoplasty, recurrent epithelial breakdown can be a problem.[12] This is probably related to the disruption and defective

regeneration of the epithelial basement membrane.[12,14,67]

Lamellar keratoplasty is another surgical alternative to penetrating keratoplasty.[151,153,203,256] The advantages of this procedure are several. It is not an intraocular procedure and therefore avoids some of the complications associated with penetrating keratoplasty. The criteria for acceptable donor tissue are not as stringent for a lamellar graft and, therefore, potentially usable tissue should be more available. Following lamellar keratoplasty, postoperative astigmatism is generally less than that obtained after a full-thickness corneal graft.[203,256] Richard et al[203] compared 50 consecutive keratoconus cases treated by lamellar keratoplasty to 50 cases in which penetrating grafts were performed. The surgical techniques employed are detailed in the report. The percent of cases with final corneal astigmatism greater than 3 diopters was 58.6% for the penetrating keratoplasties compared with 36.9% for the lamellar grafts.

Lamellar grafts can be technically difficult if relatively large areas of marked thinning are present. The final visual acuity obtained after lamellar keratoplasty is generally worse than with a penetrating graft.[151,154,203,256] Again analyzing the data of Richard et al,[203] 88% of patients achieved a vision of 20/30 or better after penetrating keratoplasty. Only 67% achieved this level of vision after lamellar graft.

Epikeratophakia is a new surgical approach to the treatment of conical cornea. With this technique a piece of donor tissue is lathed to a constant thickness, i.e., without refractive power. The host epithelium is removed and the donor tissue is placed over the cone and sutured tightly to a previously trephined groove. This cap graft provides structural support to the cornea and results in flattening of the cone with a reduction in astigmatism.

Kaufman and Werblin have described many advantages of this procedure.[127] Epikeratophakia is safer than lamellar or penetrating keratoplasty. Aside from the initial peripheral host trephination, no other dissection of host corneal stroma is performed. The risk of precipitous entry into the anterior chamber is therefore greatly reduced. Large grafts can be used and can be sutured to the thicker limbal tissue. The risk of rejection reaction is the same as for a standard lamellar keratoplasty.

This procedure is not without complications. Problems of epithelialization, graft dehiscence, infection, and persistent haziness of the graft have been reported.[225] Although this procedure results in dramatic corneal flattening, significant residual astigmatism may persist.[127] Epithelialization problems may prevent the successful use of a contact lens postoperatively. Nevertheless, with technical improvements and large longterm clinical investigations, epikeratophakia may prove to be a valuable addition to our surgical armamentarium.

II. Related Noninflammatory Corneal Thinning Disorders

Although other non-inflammatory corneal thinning disorders exist (i.e. dellen, furrow degeneration, post-irradiation thinning), three disorders have a distinct clinical expression and warrant separate discussion (Table 3). These are keratoglobus, pellucid marginal degeneration, and posterior keratoconus. Each has a characteristic clinical appearance different from keratoconus (Color Plate 4). Posterior keratoconus is usually a developmental anomaly. Pellucid degeneration and keratoglobus might well be a variation in expression of underlying pathology similar to that of keratoconus.

A. KERATOGLOBUS

Keratoglobus is a rare bilateral condition in which the cornea assumes a globular contour. The cornea is transparent and shows a generalized thinning often most pronounced in the periphery. The thinning can approach 20% of normal thickness. Minimal if any scarring is present and no iron ring is found. The corneal diameter is usually normal or slightly increased.

Elschnig[61] and Prelat[196] both believed that keratoglobus was related to infantile glaucoma while Duke-Elder[58] thought it was a variant of megalocornea. Cavara[45] was the first to consider keratoglobus a distinct corneal ectasia. Jacobs et al[114] reported a patient with thyroid ophthalmolopathy and adult acquired keratoglobus. When present at birth, keratoglobus must be differentiated from megalocornea and congenital glaucoma. Megalocornea represents a nonprogressive symmetric enlargement of the cornea (greater than 12 mm in horizontal diameter) without a significant change in corneal thickness or contour.[132] In contrast to congenital glaucoma, keratoglobus is not associated with elevated intraocular pressure, a cloudy cornea, changes in the optic disc or generalized enlargement of the eye.

Keratoglobus may be genetically related to keratoconus. No definite inheritance pattern has been observed for keratoglobus. Cavara[45] reported one family in which the father had keratoglobus and the son had keratoconus.

In contrast to keratoconus, keratoglobus is nonprogressive or minimally progressive. The corneal thinning is diffuse and greatest in the periphery as compared to axial thinning in keratoconus. Keratoglobus may also be associated with scleral thinning.[25] Ruptures of Descemet's membrane and acute hydrops are less common than in keratoconus.

TABLE 3

Features That Differentiate Keratoconus from Related Non-Inflammatory Corneal Thinning Disorders

	Keratoconus	Marginal Keratoglobus	Pellucid Posterior Degeneration	Keratoconus
Frequency	Most common	3rd most common	2nd most common	Least common
Hereditary	At times familial	Usually none	Usually none	Usually none
Laterality	Usually bilateral	Usually bilateral	Usually bilateral	Usually unilateral
Progression	Yes	Yes	Yes	No
Corneal scarring	Sometimes	Rare	Rare	Yes, in localized
Iron ring	Usually	No	No	Common, in localized
Anterior curve	Increased	Increased in periphery	Flat above Steep below	Normal, or slightly irregular
Posterior curve	Increased	Increased in periphery	Flat above Steep below	Increased

Keratoconus has been associated with a number of systemic abnormalities such as atopic dermatitis and Down's syndrome. These disorders have not been associated with keratoglobus.[132]

Corneal perforations and/or ruptures are rare in keratoconus. Patients with keratoglobus, however, are very prone to corneal ruptures from minimal trauma and often no antecedent history of trauma can be elicited.[92,110,231] A theoretical basis for the increased incidence of corneal perforations was proposed by Poole.[188] The amount of stress on the corneal tissue can be calculated using Laplace's formula. If the radius of curvature (r), the corneal thickness (t), and the intraocular pressure (p) are known, then the corneal stress can be calculated from the formula:[183]

$$\text{corneal stress} = pr/2t$$

One can see that corneal stress is directly proportional to the radius of curvature and inversely proportional to the corneal thickness. At equal thicknesses, the radius of curvature for keratoglobus is much greater than for keratoconus and so the corneal stress is much greater. This leads to a smaller tolerance to trauma-induced pressure elevations and an increased incidence of corneal rupture.

Since 1913, numerous reports[15,25,92,110,200,231,242] have related keratoglobus, blue sclera, and one or more of the following features: moderate hyperextensibility of joints, abnormal teeth, reduced hearing (both conductive and sensorineural), frequent bone fractures, and consanguinity. Hyams et al[110] were the first to propose that these patients had a distinct hereditary disorder of connective tissue. Greenfield et al[91] suggested an autosomal recessive inheritance and a probable disorder of collagen biosynthesis. Though the above syndrome shares some clinical features with the ocular variety of Ehlers-Danlos syndrome, the patients lack skin hyperelasticity, extreme joint laxity, microcornea, and reduction in skin collagen hydroxylysine characteristic of Ehlers-Danlos.[25]

Treatment of keratoglobus does not differ significantly from keratoconus. Spectacle correction and contact lenses are utilized as long as they provide adequate correction. Penetrating keratoplasty is performed when visual needs are not satisfied by the above. Transplant surgery is complicated by the need to use very large grafts to encompass the area of extensive peripheral corneal thinning. In addition there is usually greater graft/host thickness disparity than is seen in keratoconus and the proximity of the limbus to the surgical wound may increase the risk of graft rejection. Because of the increased risk of traumatic corneal rupture in patients with keratoglobus, adequate ocular protection is recommended during sporting, occupational, or household tasks on which accidental trauma is more likely.

B. PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration is a bilateral, clear, inferior (usually from 4–8 o'clock), peripheral corneal-thinning disorder. It is characterized by a narrow band of corneal thinning (approaching 20% normal thickness) 1 to 2 mm in width. There is an uninvolved area between the thinned section of cornea and the limbus, usually 1–2 mm in width. The cornea protrudes above the area of thinning, which results in high and irregular astigmatism. The cornea above the band of thinning is of normal thickness and has the most marked anterior displacement just above the band. The resultant astigmatism depends on the location in which it is measured. Above the band of thinning there is a flattening of the vertical meridian and "against the rule" astigmatism. However, the cornea steepens inferiorly with increased curvature of as much as 20D.[138] If the increased inferior curvature becomes steeper than the horizontal curvature, the inferior cornea might be described as having "with the rule"

astigmatism.

Pellucid marginal degeneration is usually detected between the second and fifth decade of life. There appears to be no sex predeliction. Evidence for hereditary transmission is lacking, though moderate or high astigmatism has been found in family members by some authors.[176,229]

There is no iron ring, cone, or lipid deposition. Corneal sensation is normal. Descemet's folds ("stress lines") can develop and are seen concentric with the inferior limbus and disappear with pressure. Acute hydrops can develop leading to inferior edema, scarring, and vascularization. These corneas are otherwise clear and avascular.[138]

Although not well recognized in the American literature, similar conditions have been described under a variety of names, including marginal degeneration of the cornea,[174,216] cylindrical protrusion of the cornea,[68,118] and corneal piriformis and pellucid marginal dystrophy.[69,218] Schlaeppi[218] was the first to coin the term "pellucid" (meaning clear) to describe the bilateral inferior, peripheral, corneal thinning disorder.

The differential diagnosis of pellucid marginal degeneration includes other peripheral corneal diseases such as Terrien's corneal degeneration and Mooren's ulcer, and keratoconus. Terrien's corneal degeneration also results in high astigmatism and afflicts a similar age group. However it affects both the superior and inferior cornea and has vascular invasion and lipid deposition. Mooren's ulcer and other peripheral ulcerative diseases are easy to differentiate because they are ulcerative and are followed by scarring, vascularization, and often a lipid deposition. In contrast to keratoconus, patients with pellucid marginal degeneration have no iron ring, "cone," or scarring in the protruding cornea. The corneal protrusion is located above rather than in the area of thinning.

The first histopathologic report of pellucid marginal degeneration was by Zucchini[261] who found normal epithelium, absent Bowman's layer, and increased stromal ground substance rich in mucopolysaccharides. Descemet's membrane and the endothelium were normal. Rodrigues et al[210] noted normal or focally disrupted Bowman's layer. Electron microscopy in the peripherally thinned region revealed unusual electron-dense areas of fibrous long-spacing (FLS) collagen with a periodicity of 100–110 nm as opposed to normal collagen with a period of 60–64 nm. Such FLS collagen has been observed elsewhere including advanced keratoconus,[210] but not in normal corneal stroma. Similar findings of FLS collagen in human atherosclerosis may account for arterial weakening and dilitation.[175] It is postulated that weakening in the area of FLS collagen in the cornea could result in the thinning seen in pellucid marginal degeneration.[210]

Spectacle correction of pellucid marginal degeneration is usually inadequate unless the case is mild. The high irregular astigmatism is not adequately corrected. Hard contact lenses, while offering excellent optical correction, are difficult to fit. The flat central vertical meridian and the sharp inferior steepening make the lens difficult to center and prone to lens lift off.

Penetrating keratoplasty is often required for visual rehabilitation. Larger than normal grafts are needed to encompass the area of inferior thinning and still provide a clear central visual axis. Corneal grafts 9.0 mm or larger are usually required. In addition, the proximity to the inferior limbus makes graft vascularization and early suture erosion more common. Lamellar keratoplasty reportedly gives good results.[95] Others have advocated diathermy[261] or thermokeratoplasty.[138]

C. POSTERIOR KERATOCONUS

Posterior keratoconus is a rare noninflammatory corneal disorder which is usually a developmental anomaly. First described by Butler,[37] it is characterized by a total (keratoconus posticus generalis) or localized (keratoconus posticus circumscriptus) thinning of the cornea. In the generalis type there is an increase in the curvature of the entire posterior corneal surface, the cornea usually remaining clear. In keratoconus posticus circumscriptus, there is a localized central or paracentral indentation of the posterior cornea without any protrusion of the anterior surface, often with a variable amount of overlying stromal scarring. The anterior corneal curvature may be astigmatic but it does not show the same high irregular astigmatism that is seen in anterior keratoconus.[139] Loss of stromal substance can lead to corneal thinning approaching ⅓ normal. The stromal scarring associated with the localized variety varies significantly in severity. Cornea guttata is commonly seen within the involved portion of the cornea,[139] and in some cases pigment surrounds the edges of the posterior depression.

Because the aqueous and cornea differ only slightly in refractive index, changes of the posterior corneal surface do not have the same consequences as changes on the anterior surface. Posterior keratoconus is usually congenital, unilateral, and nonprogressive. Bilateral cases have been described.[83,100,124,139] Traumatic cases[116] and familial cases[19,100,115] have also been reported. Posterior keratoconus has no known association to anterior keratoconus and no reported cases of posterior keratoconus have progressed to anterior keratoconus.[124]

These disorders are included in the discussion of anterior keratoconus because of similarity in name and clinical appearance.

A variety of ocular abnormalities have been observed in association with posterior keratoconus. Choroidal and/or retinal sclerosis[49,54,211] are frequently mentioned as are anterior segment anomalies, including cleavage anomalies, aniridia, ectropion uvea, iris atrophy, glaucoma, anterior lenticonus, ectopia lentis, and anterior lens opacities.[48,87,90,91,124] Three cases of posterior keratoconus associated with systemic abnormalities have been described. Haney and Falls[100] reported a brother and sister and Streeten et al[234] described a young female with brachydactyly, hyperteleorism, a flattened nasal bridge, upward displacement of the latoral canthi, webbed neck, stunted growth, abnormal gait, and localized posterior keratoconus. In addition, the case described by Streeten et al showed median facial clefting (cleft lip and palate) and genitourinary abnormalities (ectopic hydroureter and ureto-vaginal fistula). Chromosomal analysis in the latter case was normal. Migeon[169] reported a child with unilateral posterior keratoconus and a short-arm deletion of the 17–18 chromosome. The case described by Migeon and the sister of the siblings had unilateral posterior keratoconus. Therefore, unilaterality does not exclude the possibility of genetic or familial disease.

Histopathologic descriptions of posterior keratoconus have been documented in the literature.[139,234] Corneal buttons removed during penetrating keratoplasty were examined by both light and electron microscopy. Light microscopy revealed a thin central zone covered by an irregular epithelium. The epithelial basement membrane showed focal disruption, and Bowman's layer was replaced by fibroblastic proliferation. The stroma was thinned and the lamellae were disorganized. Descemet's membrane appeared unremarkable centrally, but posterior excrescences were noted paracentrally. The endothelium was intact and attenuated adjacent to the guttata. Electron microscopy of Descemet's membrane demonstrated a multilaminar configuration and abnormal anterior banding. Since anterior banding of Descemet's membrane usually begins at about six months and is complete by eight months of gestation, abnormal development resulting in posterior keratoconus must begin prior to this time.[257]

The exact pathogenesis of posterior keratoconus remains obscure. Since the curve of the embryonic cornea is more pronounced, Mann in 1930 proposed that posterior keratoconus represented an arrest of fetal development with a persistence of the embryonic characteristics.[157] Green[41] in 1945 and Hagedoorn and Velzebaer[94] in 1959 felt that the delayed separation of the lens from the cornea was the cause and that the axial fetal lenticular opacities supported this. This does not explain the majority of cases where no lens pathology is noted. Jacobs[115] in 1957 and DeRosa[54] in 1959 felt that an underdevelopment of the central corneal endothelium was an obstacle to normal migration of mesodermal cells. Most recently, posterior keratoconus has been considered a variant of the anterior chamber cleavage syndromes supported by the frequent association of other anterior chamber anomalies with posterior keratoconus.[250] Clinically, cases of posterior keratoconus with central scarring and anterior chamber anomalies resemble Peter's anomaly; however, pathologic specimens from Peter's anomaly have shown either an absence[232,239] or marked thinning[141] of Descemet's membrane and corneal endothelium. The normal appearance of Descemet's membrane by light microscopy and the abnormal anterior banding demonstrated by electron microscopy suggest that endothelial cell changes in posterior keratoconus occur early in gestation prior to the fifth or sixth month.[139]

The majority of cases of posterior keratoconus require no treatment. The irregularity of the posterior corneal surface has little effect on vision because the posterior surface makes only a small contribution to total corneal refraction. Spectacles or contact lenses do not adequately correct posterior corneal changes. Central corneal scarring in localized posterior keratoconus and/or associated ocular anomalies are usually the cause for decreased vision. Penetrating keratoplasty can be performed when indicated by poor vision. However, amblyopia may preclude a good visual outcome.

III. Summary

Keratoconus is manifested by progressive corneal thinning, protrusion and scarring, resulting in distorted and decreased vision. The pathology is usually just below the visual axis and is surrounded by an epithelial iron ring. In 90% of cases it is bilateral. Keratoconus is familial in less than 20% of cases. The pathogenesis is unknown but might depend on whether or not the case is sporadic or associated with contact lens wear, eye rubbing, Down's syndrome, atopic disease, connective tissue disease, tapetoretinal degeneration, or inheritance. Hard contact lens wear in some individuals probably can lead to keratoconus. Early diagnosis is aided by the finding of irregular corneal astigmatism with inferior corneal steepening. Biochemical and pathological studies have been inconsistent in identifying abnormal collagen in a keratoconus cornea. There does seem to be a decrease in the number of stromal lamellae. The treatment of the disorder ranges from spectacle correction to keratoplasty. Contact lens

fitting for keratoconus is a compromise between the ideal lens fit and the patient's requirements for vision and comfort. Central touch, occasional air bubbles, and peripheral lens lift-off are typical. The fit is accomplished by trial and error using a variety of lenses. Corneal transplant surgery is indicated when the patient cannot wear contact lenses or when the vision, even with a contact lens, is unsatisfactory. In over 90% of penetrating keratoplasties for keratoconus the graft remains clear. The large majority have 20/40 or better corrected visual acuity.

Other noninflammatory corneal thinning disorders which resemble keratoconus are keratoglobus, pellucid marginal degeneration, and posterior keratoconus. Keratoglobus is often associated with systemic collagen abnormalities. Thinning extends over the entire cornea to the limbus. Corneal surgery is not required as often as for keratoconus because astigmatism and scarring are usually not as great. Pellucid marginal degeneration is manifested by corneal thinning 1–2 mm from the limbus and 1–2 mm in width in the inferior cornea from the 4 o'clock to the 8 o'clock position. Protrusion of the cornea above the area of thinning results in high against-the-rule astigmatism. Visual correction is usually adequate by spectacles or contact lenses. Occasionally a large penetrating keratoplasty is required to encompass the pathological area and still provide an optical zone free from wound or suture scars. Because there are families in which combinations of keratoconus, keratoglobus, and pellucid marginal degeneration are seen, the pathogenesis of these conditions is probably related. Therefore, these disorders may represent varied clinical presentations of the same basic underlying abnormality.

Posterior keratoconus is usually a developmental abnormality. The anterior corneal curvature is relatively normal while the posterior curvature is steep in either a localized area or over the entire posterior surface. Scarring, slight irregular astigmatism, and amblyopia can all reduce vision. Penetrating keratoplasty has a guarded prognosis in congenital cases because of amblyopia.

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Outline

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III. Summary

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