MAJOR REVIEW

Keratoconus

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Abstract. Keratoconus is a bilateral noninflammatory corneal ectasia with an incidence of approximately 1 per 2,000 in the general population. It has well-described clinical signs, but early forms of the disease may go undetected unless the anterior corneal topography is studied. Early disease is now best detected with videokeratography. Classic histopathologic features include stromal thinning, iron deposition in the epithelial basement membrane, and breaks in Bowman’s layer. Keratoconus is most commonly an isolated disorder, although several reports describe an association with Down syndrome, Leber’s congenital amaurosis, and mitral valve prolapse. The differential diagnosis of keratoconus includes keratoglobus, pellucid marginal degeneration and Terrien’s marginal degeneration. Contact lenses are the most common treatment modality. When contact lenses fail, corneal transplant is the best and most successful surgical option. Despite intensive clinical and laboratory investigation, the etiology of keratoconus remains unclear. Clinical studies provide strong indications of a major role for genes in its etiology. Videokeratography is playing an increasing role in defining the genetics of keratoconus, since early forms of the disease can be more accurately detected and potentially quantified in a reproducible manner. Laboratory studies suggest a role for degradative enzymes and proteinase inhibitors and a possible role for the interleukin-1 system in its pathogenesis, but these roles need to be more clearly defined. Genes suggested by these studies, as well as collagen genes and their regulatory products, could potentially be used as candidate genes to study patients with familial keratoconus. Such studies may provide the clues needed to enable us to better understand the underlying mechanisms that cause the corneal thinning in this disorder. (Surv Ophthalmol 42:297–319, 1998. © 1998 by Elsevier Science Inc. All rights reserved.)

Key words. collagen genes • contact lenses • corneal thinning disorder • genetics • keratoconus • penetrating keratoplasty • segregation analysis • videokeratography

In 1984 a review on keratoconus and related noninflammatory corneal thinning disorders by Krachmer et al. was published in this journal. It remains one of the most comprehensive and complete clinical descriptions on this subject. In the past 14 years, computer technology and biotechnology have had a major impact in improving our understanding of keratoconus and may ultimately allow us to devise a medical therapy to retard its progression. Computer-assisted videokeratoscopes are now used in clinical practice, and videokeratography has enhanced our ability to detect early keratoconus in a quantifiable and reproducible manner. This will allow us to accurately construct family pedigrees with the familial forms of keratoconus. Biotechnology may allow us to identify a gene or genes that play a major role in the pathogenesis of this disorder. This review focuses on these advances as they relate to our understanding of keratoconus and provides an update on biochemical and clinical research studies and management options developed since the last major clinical review.66

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I. Epidemiology

Keratoconus, classically, has its onset at puberty and is progressive until the third to fourth decade of life, when it usually arrests. It may, however, commence later in life and progress or arrest at any age. Rarely it may be congenital. It is most commonly an isolated condition, despite multiple singular reports of coexistence with other disorders (Table 1). Commonly recognized associations include Down syndrome, Leber's congenital amaurosis, and connective tissue disorders. For example, patients with advanced keratoconus have been reported to have a high incidence of mitral valve prolapse (58%). Atopy, eye rubbing, and hard contact lenses have also been reported to be highly associated with this disorder, and 6–8% of reported cases have a positive family history or show evidence of familial transmission (Table 2). The reported incidence of keratoconus varies, with most estimates being between 50 and 230 per 100,000 in the general population (approximately 1 per 2,000). Prevalence is 54.5 per 100,000. The variability in the reported incidence reflects the subjective criteria often used to establish the diagnosis, allowing subtle forms to be often overlooked. Keratoconus occurs in all ethnic groups with no male or female preponderance.

II. Clinical Features

Keratoconus is a condition in which the cornea assumes a conical shape as a result of noninflammatory thinning of the corneal stroma. The corneal thinning induces irregular astigmatism, myopia, and protrusion, leading to mild to marked impairment in the quality of vision. It is a progressive disorder.

| TABLE 1 |
| Diseases Reported in Association With Keratoconus |

<table>
<thead>
<tr>
<th>Multisystem Disorders</th>
<th>Ocular Disorders (Noncorneal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aaglle's syndrome</td>
<td>Aniridia</td>
</tr>
<tr>
<td>Albers-Schonberg disease</td>
<td>Anetoderma and bilateral subcapsular cataracts</td>
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<tr>
<td>Angleman syndrome</td>
<td>Ankyloblepharon</td>
</tr>
<tr>
<td>Apert's syndrome</td>
<td>Bilateral macular coloboma</td>
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<tr>
<td>Autographism</td>
<td>Blue sclerae</td>
</tr>
<tr>
<td>Anetoderma</td>
<td>Congenital cataract</td>
</tr>
<tr>
<td>Bardet-Biedl syndrome</td>
<td>Ectodermal and mesodermal anomalies</td>
</tr>
<tr>
<td>Crouzon's syndrome</td>
<td>Floppy eyelid syndrome</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Gyrate atrophy</td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome</td>
<td>Iridoschisis</td>
</tr>
<tr>
<td>Goltz-Gorlin syndrome</td>
<td>Lebers congenital amaurosis</td>
</tr>
<tr>
<td>Hyperornithemia</td>
<td>Persistent pupillary membrane</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>Posterior lenticusitis</td>
</tr>
<tr>
<td>Kurz syndrome</td>
<td>Retinitis pigmentosa</td>
</tr>
<tr>
<td>Laurence-Moon-Bardet-Biedl syndrome</td>
<td>Retinal dissection syndrome</td>
</tr>
<tr>
<td>Marfan's syndrome</td>
<td>Retrolental fibroplasia</td>
</tr>
<tr>
<td>Muhwili-Smith syndrome</td>
<td>Vernal conjunctivitis</td>
</tr>
<tr>
<td>Nail patella syndrome</td>
<td>Ocular Disorders (Noncorneal)</td>
</tr>
<tr>
<td>Neurocutaneous angiomatos</td>
<td>Aniridia</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>Anetoderma and bilateral subcapsular cataracts</td>
</tr>
<tr>
<td>Noonan's syndrome</td>
<td>Ankyloblepharon</td>
</tr>
<tr>
<td>Osteogenesis imperfecta</td>
<td>Bilateral macular coloboma</td>
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<tr>
<td>Oculodentodigital syndrome</td>
<td>Blue sclerae</td>
</tr>
<tr>
<td>Pseudoxanthoma elasticum</td>
<td>Congenital cataract</td>
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<tr>
<td>Rieger's syndrome</td>
<td>Ectodermal and mesodermal anomalies</td>
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<tr>
<td>Rothmund's syndrome</td>
<td>Floppy eyelid syndrome</td>
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<td>Torette's disease</td>
<td>Gyrate atrophy</td>
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<tr>
<td>Turner's syndrome</td>
<td>Iridoschisis</td>
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<tr>
<td>Xeroderma pigmentosa</td>
<td>Lebers congenital amaurosis</td>
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<table>
<thead>
<tr>
<th>Other Systemic Disorders</th>
<th>Corneal Disorders</th>
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<tbody>
<tr>
<td>Congenital hip dysplasia</td>
<td>Atopic keratoconjunctivitis</td>
</tr>
<tr>
<td>False chordae tendinae of left ventricle</td>
<td>Axenfeld's anomaly</td>
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<tr>
<td>Joint hypermobility</td>
<td>Aveilino's dystrophy</td>
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<tr>
<td>Mitral valve prolapse</td>
<td>Chandler's syndrome</td>
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<tr>
<td>Measles retinopathy</td>
<td>Corneal amyloidosis</td>
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<tr>
<td>Ocular hypertension</td>
<td>Deep filliform corneal dystrophy</td>
</tr>
<tr>
<td>Thalassasemia</td>
<td>Essential iris atrophy</td>
</tr>
<tr>
<td>Malignancies</td>
<td>Fleck corneal dystrophy</td>
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<tr>
<td>Neurofibromatosis</td>
<td>Fuchs corneal dystrophy</td>
</tr>
<tr>
<td>Primary open angle glaucoma</td>
<td>Iridocorneal dysgenesis</td>
</tr>
<tr>
<td>Phenylketonuria</td>
<td>Lattice dystrophy</td>
</tr>
<tr>
<td>Photoallergy</td>
<td>Microcornea</td>
</tr>
<tr>
<td>Pellucid marginal degeneration</td>
<td>Posterior polymorphous dystrophy</td>
</tr>
<tr>
<td>Posterolateral keratolysis</td>
<td>Terriens marginal degeneration</td>
</tr>
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Reference numbers in superscript.
TABLE 2

Signs of Keratoconus

<table>
<thead>
<tr>
<th>External signs</th>
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<tbody>
<tr>
<td>Munson’s sign</td>
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<tr>
<td>Rizzuti phenomenon</td>
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<tr>
<td>Slit-lamp findings</td>
</tr>
<tr>
<td>Stromal thinning</td>
</tr>
<tr>
<td>Posterior stress lines (Vogt’s striae)</td>
</tr>
<tr>
<td>Iron ring (Fleischer ring)</td>
</tr>
<tr>
<td>Scarring—epithelial or subepithelial</td>
</tr>
<tr>
<td>Retroillumination signs</td>
</tr>
<tr>
<td>Scissoring on retinoscopy</td>
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<tr>
<td>Oil droplet sign (“Charleaux”)</td>
</tr>
<tr>
<td>Photokeratoscopy signs</td>
</tr>
<tr>
<td>Compression of mires inferotemporally</td>
</tr>
<tr>
<td>(“egg-shaped” mires)</td>
</tr>
<tr>
<td>Compression of mires inferiorly or centrally</td>
</tr>
<tr>
<td>Videokeratography signs</td>
</tr>
<tr>
<td>Localized increased surface power</td>
</tr>
<tr>
<td>Inferior superior dioptric asymmetry</td>
</tr>
<tr>
<td>Relative skewing of the steepest radial axes above and below the horizontal meridian (Fig. 6)</td>
</tr>
</tbody>
</table>

ultimately affecting both eyes, although only one eye may be affected initially.\textsuperscript{71,105}

Symptoms are highly variable and, in part, depend on the stage of the progression of the disorder. Early in the disease there may be no symptoms, and keratoconus may be noted by the ophthalmologist simply because the patient cannot be refracted to a clear 20/20 corrected vision. In advanced disease there is significant distortion of vision accompanied by profound visual loss. Patients with keratoconus fortunately never become totally blind from their disease.

Clinical signs also differ depending on the severity of the disease (Table 2). In moderate to advanced disease any one or combination of the following signs may be detectable by slit-lamp examination of the cornea: stromal thinning (centrally or paracentrally, most commonly inferiorly or inferotemporally (Fig. 1A)); conical protrusion; an iron line partially or completely surrounding the cone (Fleischer’s ring); and fine vertical lines in the deep stroma and Descemet’s membrane that parallel the axis of the cone and disappear transiently on gentle digital pressure (Vogt’s striae [Fig. 2]). Other accompanying signs might include epithelial nebulae, anterior stromal scars, enlarged corneal nerves, and increased intensity of the corneal endothelial reflex and subepithelial fibrillary lines.\textsuperscript{66,80}

Munson’s sign and Rizzuti’s sign are also useful adjunctive external signs associated with keratoconus.\textsuperscript{90} Munson’s sign is a V-shaped conformation of the lower lid produced by the ectatic cornea in downgaze. Rizzuti’s sign is a sharply focused beam of light near the nasal limbus, produced by lateral illumination of the cornea in patients with advanced keratoconus.

Patients with advanced disease may occasionally present with a sudden onset of visual loss accompanied by pain. On slit-lamp examination the conjunctiva may be injected and a diffuse stromal opacity is noted in the cornea. This condition, referred to as “hydrops,” is caused by breaks in Descemet’s membrane with stromal imbition of aqueous through these breaks (Fig. 3A). The edema may persist for weeks or months, usually diminishing gradually, with relief of pain and resolution of the redness and cor-

\textbf{Fig. 1.} Ectatic dystrophies, the arrows point to the areas of maximal thinning. \textit{Top:} Keratoconus-paracentral corneal thinning. \textit{Center:} Pellucid marginal degeneration—inferior thinning from 4 to 8 o’clock. \textit{Bottom:} Keratoglobus: thinning of the whole cornea from limbus to limbus.
neal edema ultimately being replaced by scarring (Fig. 3B).

Early in the disease process the cornea may appear normal on slit-lamp biomicroscopy; however, there may be slight distortion or steepening of keratometry mires centrally or inferiorly. In such instances it is useful to dilate the pupil. Retroillumination techniques and scissoring of the retinoscopic reflex or the “Charleux” oil droplet sign are useful clinical signs to confirm the diagnosis in suspicious cases. In these early cases, where the cornea appears normal but keratoconus is suspected, measuring the anterior topography of the central and para-central cornea is also extremely useful to confirm the diagnosis.66

Several devices are currently available for detecting early keratoconus by measuring anterior corneal topography. These range from simple inexpensive devices, such as handheld keratoscopes (placido disks), to expensive sophisticated devices, such as computer-assisted videokeratoscopes. With the hand-held keratoscopes, such as the Klein keratoscope, early keratoconus is characterized by a downward deviation of the horizontal axis of the Placido disk reflection (Fig. 4). Until recently, nine-ring photo-keratoscopes, such as the Corneascope (Kera Corporation, Santa Clara, CA), were commonly used by cornea specialists. With this device early keratoconus is depicted by compression of the mires inferiorly or inferotemporally120 (Fig. 5).

Computer-assisted videokeratoscopes, which generate color-coded maps and topographic indices, are currently the most sensitive and sophisticated devices for confirming the diagnosis of keratoconus. (A more detailed discussion is provided in “V. Topographic Studies of Keratoconus.”) With such devices, keratoconus appears as an area of increased surface power surrounded by concentric zones of decreasing surface power. Three features are common to keratoconus videokeratographs that use sag-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Collagen Type</th>
<th>Chain</th>
<th>Gene</th>
<th>Chromosomal Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>alpha 1 (I)</td>
<td>COL1A1</td>
<td>17q21-q22</td>
</tr>
<tr>
<td></td>
<td>alpha 2 (I)</td>
<td>COL1A2</td>
<td>7q21-q22</td>
</tr>
<tr>
<td>III</td>
<td>alpha 1 (III)</td>
<td>COL3A1</td>
<td>2q31-q32</td>
</tr>
<tr>
<td>IV</td>
<td>alpha 1 (IV)</td>
<td>COL4A1</td>
<td>13q33-q34</td>
</tr>
<tr>
<td></td>
<td>alpha 2 (IV)</td>
<td>COL4A2</td>
<td>13q33-q34</td>
</tr>
<tr>
<td></td>
<td>alpha 3 (IV)</td>
<td>COL4A3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>alpha 4 (IV)</td>
<td>COL4A4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>alpha 5 (IV)</td>
<td>COL4A5</td>
<td>X</td>
</tr>
<tr>
<td>V</td>
<td>alpha 1 (V)</td>
<td>COL5A1</td>
<td>2q31-q32</td>
</tr>
<tr>
<td></td>
<td>alpha 2 (V)</td>
<td>COL5A2</td>
<td>9p</td>
</tr>
<tr>
<td></td>
<td>alpha 3 (V)</td>
<td>COL5A3</td>
<td>2q31-q32</td>
</tr>
<tr>
<td>VI</td>
<td>alpha 1 (VI)</td>
<td>COL6A1</td>
<td>22q</td>
</tr>
<tr>
<td></td>
<td>alpha 2 (VI)</td>
<td>COL6A2</td>
<td>22q</td>
</tr>
<tr>
<td></td>
<td>alpha 3 (VI)</td>
<td>COL6A3</td>
<td>6</td>
</tr>
<tr>
<td>VII</td>
<td>alpha (VII)</td>
<td>COL7A1</td>
<td>3q</td>
</tr>
<tr>
<td>VIII</td>
<td>alpha (VIII)</td>
<td>COL8A1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>alpha (VIII)</td>
<td>COL8A2</td>
<td>1</td>
</tr>
</tbody>
</table>
ittal topography, a localized area of increased surface power, inferior-superior power asymmetry, and skewed steep radial axes above and below the horizontal meridian (depicting irregular astigmatism, the hallmark of keratoconus [Fig. 6]).

Ultrasonic pachymetry may be useful to confirm corneal thinning in patients with suspected keratoconus on slit-lamp examination or videokeratography; however, it cannot be solely relied on to make the diagnosis because of the large range and variation of pachymetry readings both centrally and para-centrally in the normal population.

III. Histopathology

Thinning of the corneal stroma, breaks in Bowman’s layer, and deposition of iron in the basal layers of the corneal epithelium comprise a triad of the classical histopathologic features found in keratoconus (Fig. 7). Depending on the stage of the disease, every layer and tissue of the cornea can, however, become involved in the pathological process. Fine details of these processes are most clearly appreciated by electron microscopy.

The epithelium may show degeneration of its basal cells, breaks accompanied by downgrowth of epithelium into Bowman’s layer, particles within a thickened subepithelial basement membrandlike layer and between basal epithelial cells, and accumulation of ferritin particles within and between epithelial cells most prominently in the basal layer of the epithelium. Histopathologic features detected in Bowman’s layer may include breaks filled by eruptions of underlying stromal collagen, periodic acid Schiff–positive nodules, and Z-shaped interruptions, possibly due to separation of collagen bundles and reticular scarring. Features noted in the stroma are compaction and loss of arrangement of fibrils in the anterior stroma, decrease in the number of collagen lamellae, normal and degenerating fibroblasts in addition to keratocytes, and fine granular and microfibrillar material associated with the keratocytes.

Descemet’s membrane is rarely affected except for breaks seen in acute hydrops. The endothelium is usually normal. However, some abnormalities have been reported, including intracellular “dark structures,” pleomorphism, and elongation of cells with their long axis toward the cone. Gross histopathologic analysis of corneal buttons undergoing penetrating keratoplasty for keratoconus has revealed the presence of two types of cone morphology: “nipple”-
type cones, located centrally, and “oval”-(sagging) type cones, located inferiorly or inferotemporally. These types of cones often can be distinguished on slit-lamp examination or evaluation of the anterior corneal topography in keratoconus patients.

Histopathologic examination of corneal buttons in patients who have had acute hydrops reveals stromal edema. Descemet’s membrane separates from the posterior surface and retracts into scrolls, ledges, or ridges. During the repair process, corneal endothelium extends over the anterior and posterior surfaces of the detached Descemet’s membrane and denuded stroma: endothelial integrity is usually reestablished 3–4 months after the acute event.

IV. Etiology and Pathogenesis

A. ASSOCIATED DISORDERS

Keratoconus has been reported in various clinical settings. It may be an isolated sporadic disorder, or it may be associated with other rare genetic disorders, with Down syndrome and Leber’s congenital amaurosis, with connective tissue disorders, with hard contact lens wear and eye rubbing, and with a positive family history of the disorder.

By far the most common presentation of keratoconus is as an isolated sporadic disorder with no other associated systemic or ocular disease detectable by clinical evaluation. Of 300 consecutive keratoconus patients screened for a genetic research study at the Cedars-Sinai Medical Center in Los Angeles, 2 (0.6%) had Down syndrome, 2 (0.6%) had neurofibromatosis, and 296 (99%) were isolated with no associated genetic disease.

Table 1 summarizes conditions reported to be associated with keratoconus. For the most part, these associations should be considered to have occurred by chance. For example, the incidence of keratoconus is 1 per 2,000 and the incidence of neurofibromatosis type 1 is 1 per 4,000 in the general population; thus, there is a 1 in 8,000,000 chance that these two disorders would occur together (30 potential cases in the USA). Rare associations with keratoconus are important, particularly if they occur as a result of a chromosomal translocation; if the associated disorder cosegregates with keratoconus it might provide clues as to the chromosomal location of the inherited form of keratoconus. Therefore, it is worthwhile to perform cytogenetic studies in patients who have mental retardation or rare genetic
disorders attributed to chromosomal translocations and associated with keratoconus.

Down syndrome has been reported to have a high association with keratoconus, with reported incidence ranging from 0.5% to 15% (i.e., 10-300 times more common than in the general population).\(^2\) Similarly, there is a high incidence of keratoconus in patients with Leber's congenital amaurosis (up to 30% of patients older than 15 years).\(^2\) The frequent occurrence of keratoconus has been attributed to a high incidence of eye rubbing in these two disorders, owing to increased blepharitis in Down syndrome and an oculo-digital sign in Leber’s congenital amaurosis. However, a recent study of children in a school for the blind by Elder\(^2\) contradicts this theory and suggests that the association with keratoconus might be due to genetic factors rather than eye rubbing.

Several reports suggest an association between keratoconus and connective tissue disorders.\(^5,8,6,2,3,8,4,1,1,7\) This is based on rare reports of associations of keratoconus with disorders of collagen metabolism, such as Osteogenesis Imperfecta and subtypes of Ehlers-Danlos syndrome, and on a study that reported joint hypermobility in 22 of 44 (50%) keratoconus patients. Two recent studies, however, dispute this high association of joint hypermobility, one by an Emory University (Atlanta, GA) group\(^13\) and one by our group at the Cedars-Sinai Medical Center. In our study 34 of 218 (15%) keratoconus patients compared to 10 of 183 (12%) normal age-matched controls had joint hypermobility (not statistically significant \(P = 0.304\)).\(^11\) Other compelling evidence in support of a connective tissue abnormality in keratoconus does, however, exist, based on two reports of an association between patients with advanced keratoconus and mitral valve prolapse—a 1982 study by Beardley and Foulks\(^7\) and a more recent study by Sharif et al.\(^12\) which suggests that 58% of keratoconus patients requiring surgery have mitral valve prolapse versus 7% of normal controls.

Mechanical trauma has also been implicated in the pathogenesis of keratoconus. Although a number of studies report a high association of eye rubbing with keratoconus, a cause-and-effect relationship is difficult to prove.\(^6\) A recent preliminary study at our institution, however, suggests that keratoconus patients do rub their eyes more often than normal controls (174 of 218 [80%] versus 106 of 183 [58%] \(P < 0.001\)).\(^11\) Contact lenses are also suggested as a source of mechanical trauma related to keratoconus.\(^4,2,3,3,0\) Because early in the disease process patients have mild myopic astigmatism with clinically normal-looking corneas and their vision is best corrected with rigid contact lenses, it is extremely difficult to determine which came first, the keratoconus or contact lens wear. In none of the reports citing these associations were topographic studies performed prior to contact lens fitting to determine whether the patients had early disease before wearing contact lenses. It is possible that mechanical trauma induced by eye rubbing and hard contact lens wear act as environmental factors that enhance the progression of the disorder in genetically predisposed individuals.

Atopy is often cited as being highly associated with keratoconus. A review of the literature reveals con-
B. BIOCHEMICAL STUDIES

Despite intensive biochemical investigation into the pathogenesis of keratoconus, the underlying biochemical process and its etiologic basis remain poorly understood. Corneal thinning appears to result from loss of structural components in the cornea, but why this occurs is not clear. Theoretically, the cornea can thin because it has fewer collagen lamellae than normal, fewer collagen fibrils per lamella, closer packing of collagen fibrils, or various combinations of these factors. These conditions may result from defective formation of extracellular constituents of corneal tissue, a destruction of previously formed components, an increased distensibility of corneal tissue with sliding collagen fibers or collagen lamellae, or a combination of these mechanisms.

Early biochemical studies demonstrated that collagen composition in corneas with keratoconus was unaltered. Recent biochemical assays and immunohistochemical studies of corneas with keratoconus suggest that the loss of corneal stroma after digestion by proteolytic enzymes could be caused by increased levels of proteases and other catabolic enzymes or decreased levels of proteinase inhibitors. Observations of corneal α1 proteinase inhibitor and α2 macroglobulin (also a major proteinase inhibitor) confer further support to the hypothesis that the degradation process may be aberrant in keratoconus. Both inhibitors can be demonstrated immunohistochemically in the epithelium, stroma, and endothelium of normal and pathologic human corneas. In contrast to normal corneas and corneas with other pathologic conditions, the staining intensity in the corneal epithelium of keratoconus corneas was markedly diminished. This decrease in α2 macroglobulin in the cornea and stroma was confirmed by Western blot assays. Another proteinase inhibitor (TIMP-1) that inhibits matrix metalloproteinase was found not to contribute to the increased levels of gelatinolytic activity noted in prior biochemical studies of the cornea. These proteases and inhibitors require further study to clarify their precise role in the pathogenesis of keratoconus.

The preceding biochemical findings may merely be signs of a more generalized keratocyte abnormality in keratoconus. Wilson and coworkers demonstrated that the loss of anterior stromal keratocytes, which accompanies corneal epithelial abrasion or subepithelial ablation, is likely due to apoptotic cell death. They point out that both the corneal epithelium and endothelium produce interleukin-1 (IL-1) and that keratocytes can be shown to express the IL-1 receptor. Interleukin-1 induces keratocyte death in vitro and negatively regulates keratocyte chemotaxis, and it can upregulate hepatocyte and keratinocyte growth factors. It can also regulate the expression of keratocyte metalloproteinases collagenase and complement factors. On the basis of this, IL-1 is postulated to be a modulator of epithelial stromal interactions, with a role in the regulation of corneal cell proliferation, differentiation, and death.

Wilson et al have proposed a role for an IL-1 system in the cornea in the pathogenesis of keratoconus. It has previously been demonstrated that keratocytes from keratoconus corneas have a fourfold greater number of IL-1 receptors than normal corneas; Wilson et al suggest that the increased expression of the IL-1 receptor sensitizes the keratocytes to IL-1 released from the epithelium or endothelium, causing a loss of keratocytes through apoptosis and a decrease in stromal mass over time. This hypothesis makes sense of the occurrence of keratoconus in relation to eye rubbing, contact lens wear, and atopy, if it is presumed that epithelial microtrauma leads to an increased release of IL-1 from the epithelium. Wilson et al have also suggested that abnormalities in the processes that regulate apoptosis, besides the IL-1 system, could be the cause of keratoconus, even in the absence of epithelial cell injury.

C. GENETICS
1. Twin Studies

Although formal genetic analyses using current methodology have not been reported for keratoconus, review of the published literature provides strong pointers to suggest genetic influences in the pathogenesis of this disorder. This includes at least eight reports of its occurrence in both identical twins, with the bilaterality of the disorder, the high degree of nonsuperimposable mirror image symmetry in the location of topographic alterations between two eyes of an individual patient, and multiple reports of its occurrence in family members in two and three generations.

Twin studies have a special place in the study of human genetics because of their usefulness in comparing the effects of genes and environment. The importance of twin studies for comparison of the effects of nature and nurture was originally pointed out by Galton in 1875. Diseases caused wholly or partly by genetic factors have a higher concordance rate in monozygotic twins than in dizygotic twins. In situations where a condition does not show a simple genetic pattern, comparison of its incidence in
monozygotic and dizygotic twin pairs can reveal that heredity is involved; moreover, if monozygotic twins are not fully concordant for a given condition, nongenetic factors must also play a part in its etiology.

Nine cases of keratoconus in monozygous twins have been reported in the literature; in all instances but one, both twins had keratoconus. In the one who did not have keratoconus, videokeratography had not been performed. We have observed at least two sets of twins in which one had clinical keratoconus while the other was affected only as shown by videokeratography, and two sets of dizygotic twins in which one was affected and the other normal as shown both clinically and by videokeratography. These observations present very strong support for genetic influences in keratoconus; however, a formal prospective twin study comparing monozygotic versus dizygotic twins without ascertainment bias is necessary to confirm the conclusions drawn from such observations.21,106

2. Family Studies

Several large series, including our own study at Cedars-Sinai Medical Center, have reported a positive family history in 6-10% of patients with keratoconus.31,141 The majority of reported studies suggested an autosomal dominant mode of inheritance with variable expression and included subtle forms of the disorder, such as keratoconus fruste or mild irregular astigmatism, in order to resolve the mode of inheritance. At least 74 such instances have been reported in the ophthalmologic literature: 21 cases cited by Falls and Allen,44 including one by Falls; 24 cases examined by Ihlailinen in a Finnish study,56 and 10 families examined by Hammerstien.51 In Hammerstien's study of 52 families, keratoconus was detected in 2 or more relatives in 10 of the families (19%). The degree of penetrance was approximately 20%. The disease was characterized by complete penetrance and variable expressivity. Seven pedigrees were reported by Redmond,115 who suggested that keratoconus fruste and high degrees of astigmatism represent incomplete expression of the keratoconus gene and should be taken into account in pedigree analysis. Five families of patients with keratoconus were reported by Rabinowitz et al.101 who used videokeratography to detect abortive topographic abnormalities in the disorder. In these five families, hereditary patterns were consistent with autosomal dominant transmission with variable expressivity (Fig. 8). Gonzalez and McDonnell16 detected videokeratographic abnormalities in at least one parent of seven sets of clinically normal parents of patients with keratoconus. Although there are several reports in the literature that suggest recessive inheritance,96 none show clear evidence that three generations were examined or

Fig. 8. Family pedigrees of subjects studied with videokeratography. Subtle topographic abnormalities in clinically normal family members detectable by videokeratography only suggests a hereditary pattern consistent with autosomal dominance and variable expression. (Reprinted from Rabinowitz et al.101 with permission of the American Medical Association.)

that subtle forms of the disorder were sought for inclusion in the pedigree analysis.

3. Formal Genetic Analyses

Although most studies suggest a dominant mode of inheritance, formal genetic analyses are needed to accurately define hereditary patterns for various subtypes of keratoconus and elucidate the role genetic influences may play in its pathogenesis. Formal genetic analyses of a disease or trait are used to test whether there is a significant genetic influence in the etiology of the disease and to identify both the modes of inheritance of any responsible genes and their locations in the human genome. In a genetic analysis, the first question to be investigated is whether familial aggregation is the result of genetic factors.

a. Molecular Genetic Studies

Once genetic factors have been established, the goal of further analysis is to investigate the number of genes that influence the disease (one, two, or many), the relative contribution of each of the genes to the development of the disease, the mode of in-
heritance of the genes, the presence or absence of genetic heterogeneity (one or more diseases with a similar phenotype), and the chromosomal location of the gene(s). Such information has not yet formally been attained for keratoconus, but with the rapid development of molecular and statistical methods, these goals are now achievable and are currently being pursued at our institution.\(^{21,110}\)

Segregation analysis is a statistical method used to evaluate the mode of inheritance of a trait or disease.\(^{21,31,86}\) A particular mode of inheritance is postulated for the disease, and data on the presence or absence of the disease are collected from families with affected members. These data are used to test whether the expression of the disease is consistent with the proposed mode of inheritance. The variables analyzed in classic segregation analysis are the presence or absence of disease, which can be based on a qualitative or discrete (quantitative) trait. Qualitative criteria for diagnosis of keratoconus include corneal thinning, Vogt's striae, Fleischer rings, and scissoring of the retinoscopic reflex with a dilated pupil. For quantitative traits, for which clear cutoff points for affection status are required and complex, segregation analyses using computer programs are preferred because such methods glean more information from the data.\(^{115}\) For discrete cutoff points for diagnosis using quantitative traits, videokeratcopy indices can be used. To develop these cutoff points, a clear, quantifiable, and reproducible definition of early keratoconus by videokeratcopy in the absence of clinical signs is necessary. Because keratoconus appears to be a complex disorder, not always following simple mendelian modes of inheritance, videokeratcopy research to provide minimal topographic criteria for determining affection status provides a unique opportunity to determine true modes of inheritance and ultimately construct pedigrees for molecular genetic analysis in appropriate families with keratoconus.\(^{115}\) Before expensive molecular studies are undertaken to investigate the heredity and genetics of keratoconus, several areas must be clarified through formal analysis. A definition of the disorder must be established. The influence of associated systemic conditions and the effect of mechanical trauma must be determined, and topographical changes in contact lens wearers must be identified.\(^{120}\) After these factors are understood, the relationship of expressivity to age and the potential heterogeneity of keratoconus can be determined.

Once the early phenotype has been characterized and segregation analysis has been performed, accurate family pedigrees with familial keratoconus can be constructed. This may open new avenues for investigating the pathobiology of keratoconus through gene-linkage analysis.\(^{29,135}\) A random marker approach with polymorphic microsatellite markers or a candidate-gene approach could be used in appropriate families to identify a gene locus (or multiple loci) and answer some important questions that have been suggested by clinical and biochemical observations. Is keratoconus caused by degradative enzymes, as suggested by biochemical studies? Is there a role for the IL-1 system as previously outlined? Is keratoconus caused by a structural abnormality of collagen or products involved in its regulation, as suggested by clinical observations?

To provide answers to some of the questions raised by findings in biochemical studies, cDNAs of the proteinase inhibitors, proteases, or components of the IL-1 system could be used as candidate genes in appropriate linkage studies of appropriate keratoconus families. Such studies may provide more definitive support for their role in the thinning process resulting in keratoconus.

### b. Collagen Genes as Candidate Genes

The role of collagen and products involved in its regulation is receiving intense scrutiny at our institution. The high association of advanced keratoconus and mitral valve prolapse, prior reports of an association between Osteogenesis imperfecta, and a recent report in which keratoconus cosegregates with familial osteogenesis imperfecta in three generations points to a genetic abnormality of connective tissue being responsible for at least some forms of keratoconus.\(^{8,120}\) Different subtypes of Osteogenesis imperfecta have been shown to be caused by mutations in the COL1A1 and COL1A2 genes.\(^{118}\) To test the hypothesis that some forms of keratoconus may result from a mutation in one of the fibrillar collagens in the cornea, we are using the complementary DNAs of the fibrillar collagens to study one large family with autosomal dominant keratoconus, using a candidate-gene approach.\(^{110}\)

The collagens form a multigene family with more than 28 members, the genes for which are known to be dispersed to at least 12 chromosomes. As a family of proteins, the collagens are the most abundant in the body. The vast majority of collagen in the body is type I collagen, which is ubiquitously distributed and is the major protein in bone, skin, ligament, sclera, cornea, blood vessels, and hollow organs. Mutations that affect the structure or processing of the chains of type I collagen are often expressed as generalized, connective tissue disorders, although the specific tissue in which the major effect is seen may vary and determines the clinical phenotype. With the exception of types III, V, and VI collagen, which are also distributed in virtually all tissues, most other collagens have tissue-specific or structure-specific distribution.\(^{26}\) Types II, IX, X, and XI are found in hya-
line cartilage and the vitreous of the eye, type IV collagens are found in basement membranes, and type VII collagen is found at some epithelial-mesenchymal junctions in anchoring fibril structures. Because of differences in structure, expression, and tissue distribution, the collagens perform different functions; in different tissues the same collagen may perform different functions.  

Collagens throughout the body function in a number of ways. They provide tensile strength, facilitate transparency, provide form during embryonic and fetal development, interact with other proteins to build tissues and organs, separate cell layers during and after development, and provide filtration barriers between spaces. It is likely that some of the functions are achieved as a direct result of collagen structure, while others depend on interactions with additional matrix macromolecules.  

Collagens type I, III, IV, V, VI, VII, and VIII are scattered throughout different layers of the cornea (Fig. 9). The chromosomal location of the genes encoding these collagens have been identified (Table 3). These genes thus serve as excellent candidate genes for studying keratoconus. Their inclusion or exclusion could yield valuable information. Preliminary studies at our institution using molecular genetic approaches have excluded several collagen genes (Table 4). COL1A1 and COL1A2 remain excellent candidates and are currently being investigated in more detail, as are new markers distal to COL6A1 and COL6A2 on the telomere of chromosome 21.

4. Summary

Clinical observations, topographic studies, and preliminary segregation analyses of families of patients with keratoconus suggest that genes play a major role in the etiology of keratoconus. Environmental factors such as eye rubbing and hard contact lens wear may cause progression of this disorder in genetically susceptible individuals. The heterogeneous nature of the disease suggests that different genetic subtypes might result from different mutations and that not all families with keratoconus will follow classical mendelian patterns of inheritance. Despite the fact that to date we have made very little progress toward understanding what causes keratoconus, molecular genetic approaches with DNA markers of families with keratoconus have great potential for providing pointers to an underlying genetic abnormality that causes the noninflammatory corneal thinning found in keratoconus. This may ultimately lay the foundation for possible gene therapy to retard progression of the disorder in high-risk individuals.

V. Topographic Studies of Keratoconus

A. Placido Disk Studies

In 1938 Marc Amsler, using a photographic placido disk, was the first to describe early corneal topographic changes in keratoconus before clinical or biomicroscopic signs could be detected. His classical studies on the natural history of keratoconus docu-
mented its progression from minor corneal surface distortions to clinically detectable keratoconus. He classified keratoconus into clinically recognizable stages and an earlier latent stage recognizable only by plaido disk examination of corneal topography. These early stages were subdivided into two categories: keratoconus fruste, in which there is a 1-4 degree deviation of the horizontal axis of the plaido disk, and early or mild keratoconus, which has a 4-8 degree deviation. Only slight degrees of asymmetric oblique astigmatism could be detected in these early forms. Similar findings were absent in patients with regular astigmatism.3,5

In Amsler’s study of 600 patients, 22% had clinically obvious keratoconus in both eyes, 26% had clinical keratoconus in one eye and latent keratoconus in the other, and 52% had latent keratoconus bilaterally. Progression was highly variable and most often asymmetric. The cone could remain stationary, progress rapidly over 3-5 years, and arrest or progress intermittently over an extended period of time. When Amsler reexamined 286 eyes 3-8 years after the diagnosis, only 20% of the entire group, including 66% of the latent cases, had progressed. Progression was most likely to occur in patients between 10 and 20 years of age, decreased slightly between ages 20 and 30, and was less likely to increase after age 50.3,5

Levene suggests that instrument tilt or poor alignment with respect to the corneal plane in hand held keratoscopes may result in incorrect interpretation of the deviation of the horizontal axis.72 Reproducibility thus poses a potential problem with this device.

B. PHOTOKERATOSCOPY

The photokeratoscope produces a topographic record of 55-80% of the total corneal contour, but it provides little or no information about the central 3 mm of the cornea. Rowsey et al used this instrument to study keratoconus and its progression in 827 patients.25,129 The earliest sign detected, in the absence of biomicroscopic signs, was steepening of the inferotemporal cornea, extending peripherally over time to involve the inferonasal, superotemporal and, last, the superonasal quadrant.

C. KERATOMETRY

The ophthalmometer (keratometer), which provides information about only 2-3 points approximately 5 mm apart, can detect keratoconus by showing distortion of its mires or central or inferior steepening. While steep corneas might suggest keratoconus, there are patients with steep corneas and high degrees of regular astigmatism who do not have keratoconus. Conversely, there are patients who have keratoconus with normal central corneal curvatures but irregular astigmatism or inferior steepening only. A documented increase in corneal curvature over time as seen by keratometry is a sensitive indicator of keratoconus.40

D. COMPUTER-ASSISTED VIDEOKERATOSCOPY

Over the past 7 years computer-assisted videokeratoscopes have gained rapid acceptance in clinical practice.65 Many such devices are currently available, most using plaido disk principles, although other technologies are rapidly emerging. (For a detailed discussion of computer-assisted videokeratoscopes, refer to “Corneal Topography” in The Clinical Atlas, by Lucio Burrato.38)

The instrument we have used primarily in our topography studies is the Topographic Modeling System (TMS-1, Computed Anatomy, New York, NY). It consists of a plaido disk-type nose cone, capturing the plaido disk image into a computer-based system, which can rapidly analyze data accurately and reproducibly. Both the central and paracentral cornea can be measured in one sitting. This device, which uses spherically biased algorithms (sagittal topography), has previously been described in detail and has been shown to be highly accurate and reproducible on spherical surfaces and in the central two thirds of normal human corneas.17,128,139 Topographic data points in polar coordinates using 256 radial lines scanning across 25 rings are examined and approximately 7,000 data points are generated.
A color-coded map that allows easy appreciation of changes in the corneal curvature is generated. The 25-ring photokeratoscope mires can be superimposed on the maps for qualitative interpretation, and a series of quantitative indices, including simulated keratometry readings, are part of the data output. Because placido disk-based computer videokeratoscopes, such as the TMS-I, have the combined features of both a kerometer and photokeratoscope, recording curvature changes in both the central and paracentral cornea, they are ideally suited for detecting subtle topographic changes present in early keratoconus and for documenting their progression by serial topographic analysis.

E. VIDEokeratography STUDIES OF KERATOCONUS

Several studies have been performed to characterize the topographic phenotype of clinically detectable keratoconus by videokeratography, The majority of patients have peripheral cones, with steepening extending into the periphery. The steepening in this group is usually confined to one or two quadrants. A smaller group of patients have central topographic alterations. Many central cones have a bow tie configuration similar to that found in naturally occurring astigmatism. In the keratoconus patients, however, the bow tie pattern is asymmetric, with the inferior loop being larger in most instances. In contrast to eyes having the rule astigmatism, the steep radial axes above and below the horizontal meridian in keratoconus appear skewed, giving the bow tie a lazy-eight configuration. Another pattern found in central cones is more symmetric steepening without a bow tie appearance. The pattern is usually the same in both eyes, although it may be more advanced in one eye than in the other. The peripheral and central cones probably correspond roughly to the oval sagging and nipple-shaped cones described by Perry et al. In summary, keratoconus has three characteristics seen by videokeratography that are not present in normals: an increased area of corneal power surrounded by concentric areas of decreasing power, inferior-superior power asymmetry, and skewing of the steepest radial axes above and below the horizontal meridian (Fig. 6).

F. VIDEokeratography PATTERN RECOGNITION: NORMAL Versus KERATOCONUS

Similar patterns have been noted in clinically normal family members of keratoconus patients and in the clinically normal fellow eyes of patients with clinically unilateral keratoconus. These patterns are, however, milder (as measured by dioptric power) than the patterns noted in clinically obvious keratoconus (Fig. 10).

While it is relatively easy to recognize patterns with color-coded maps once a practitioner has gained experience through observing many topographic maps, it is confusing and difficult for clinicians who are inexperienced with this technique to identify the minimal topographic criteria required for a diagnosis of keratoconus based on pattern recognition of a videokeratograph alone. Therefore, it

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Fig. 10: Videokeratograph of forme fruste keratoconus in a clinically normal family member of a patient with familial keratoconus (see Fig. 8, A-I-5). This videokeratograph has similar but milder features than those noted in keratoconus.
has been recommended that maps that look suspicious for keratoconus in the presence of a clinically normal eye be labelled "keratoconus suspect" until progression to keratoconus can be documented.\textsuperscript{151} One way to become proficient in recognizing subtle pathology is to print maps of all patients examined in the absolute scale (in the TMS-1 this scale divides the cornea into 1.5 diopter [D] intervals between 35 and 50 D and 5 D intervals outside of this range).\textsuperscript{47,155} This singular scale allows the clinician to get used to patterns descriptive of normal topography, allowing earlier recognition of subtle abnormal topography. The normalized scale in this device, which divides the cornea into 11 equal colors, is confusing, and many clinically normal patients with slight inferior steepening might inadvertently be labelled as suspect using this scale. For the purposes of our research in trying to define an early keratoconus phenotype by videokeratography, we have compiled a database of normal videokeratography patterns of 195 normal individuals using this absolute scale (Fig. 11). This baseline database of videokeratography patterns (sagittal topography) to be used as a reference for our longitudinal topographic studies of keratoconus family members can also help the clinician in determining whether subtle deviations in corneal topography exist in a particular patient observed at any time. While it has not yet been determined which patterns ultimately progress to keratoconus, our database of videokeratography patterns suggests that only 1 in 195 (0.5%) normal patients have mild topographic features similar to, but milder than, those seen in clinically detectable keratoconus asymmetric bow tie with skewed radial axes ([AB/SRAX] pattern, Fig. 11).\textsuperscript{108} 

G. VIDEOKERATOGRAPHIC "PSEUDOKERATOCONUS"

Another source of confusion in assigning minimal topographic criteria for keratoconus are videokeratography patterns simulating keratoconus (videokeratographic pseudokeratoconus).\textsuperscript{102,134,157} The most common culprit is contact lens wear (both hard and soft), which induces patterns of inferior steepening that may be very difficult to distinguish from keratoconus.\textsuperscript{157} These patterns, however, disappear with time after contact lens wear is discontinued. Videokeratographic pseudokeratoconus may also result from technical errors during videocapturing, such as inferior eyeball compression, misalignment of the eye with inferior or superior rotation of the globe (Fig. 12), and incomplete digitization of mires, causing formation of dry spots, which simulates inferior steepening. Early pellucid marginal degeneration, inflammatory corneal thinning, and previous ocular surgery can all induce patterns that simulate keratoconus by videokeratography.\textsuperscript{59} Awareness of the conditions that may simulate early keratoconus videokeratographically will enhance the clinician's ability to recognize true topographic changes in early keratoconus.

H. QUANTITATIVE DESCRIPTORS

Developing quantitative descriptors of videokeratography patterns in keratoconus would allow for easier recognition of patterns and enable us to develop a quantitative phenotype that could be universally used to formulate minimal topographic criteria for diagnosing keratoconus.\textsuperscript{111} In a small preliminary study, we developed three indices that dis-
Fig. 12. Pseudokeratoconus error pattern (with EySys instrument) induced from misalignment of a normal eye resulting in a pattern simulating a keratoconus videokeratograph (right); videokeratograph of early keratoconus for comparison (left). (Courtesy of R. E. Hubbe, MD, and Gary Foulks, MD.)

tingished eyes with keratoconus from normals: central K (descriptive of central steepening); I-S values (inferior-superior dioptric asymmetry); and R versus L (difference between right and left central corneal power). Videokeratography studies on 28 family members of five patients with keratoconus revealed that 75% of the subjects had mild topographic abnormalities and at least one index greater than two standard deviations from their normal control group. These abnormalities were similar to, but less severe than, those found in the patients with keratoconus. It is possible that these indices are descriptive of the earliest stages of keratoconus in normal eyes before they progress to keratoconus, and these abnormalities might represent variable expression of a keratoconus gene in these families. However, longitudinal studies and serial topographic analysis are required to confirm this. Since the original study, the indices have been modified and embodied into a computer software program where they are analyzed with our baseline database (constructed from 195 normals). A new index has also been developed that is more specific to keratoconus and that quantifies the irregular astigmatism that typifies the keratoconus videokeratograph, the SRAX index (Fig. 6). Using a combination of four indices, Central K, I-S value, Sim K, and the SRAX index, 98% of keratoconus videokeratographs could be distinguished from a group of normal controls. These indices were, however, useful only in patients with 1.5 D or more of astigmatism as measured by the simulated keratometry readings. Work is currently in progress to formulate a single numeric value derived from these indices to provide minimal topographic criteria for assigning affection status to keratoconus family members for use in formal pedigree analyses such as complex segregation analysis.

Analyses of videokeratography data described thus far are based on data generated by sagittal algorithms, which are spherically biased. Recent preliminary studies suggest that tangential algorithms may have more promise for identifying the early topographic features of keratoconus. Studies are currently in progress to determine whether such algorithms might be the preferred method for studying keratoconus.

I. VIDEKERATOGRAPHY SCREENING FOR REFRACTIVE SURGERY

With the recent approval in the USA of the excimer laser for the correction of myopia, detecting early keratoconus in the absence of slit-lamp findings has assumed increasing importance. In some instances, unpredictable results and patient dissatisfaction have been attributed to the existence of undiagnosed early keratoconus in refractive surgery patients. Because these patients do not achieve high-quality vision with either glasses or contact lenses, they tend to seek out refractive surgery. Recent reports suggest that patients with early keratoconus or keratoconus suspects comprise 2–5% of patients presenting for refractive surgery for myopia.

Videokeratography screening allows the clinician to rule out these early ectasias and other topographic abnormalities before embarking on refractive surgery. It is difficult to identify which subtle keratoconus-like topographic patterns truly represent early keratoconus, hence the need to formulate quantitative indices derived from patients who have clinical signs of disease.
Two software systems using quantitative indices for detecting keratoconus are currently available on some corneal topographers, the one developed by Rabinowitz and another developed by Maeda and Klyce at the LSU Eye Center in New Orleans, Louisiana. Using TMS-I videokeratographs, the LSU group computed 11 quantitative criteria for each map and trained a three-layer neural network using 108 maps from 7 separate diagnostic categories. The overall accuracy of the trained neural network was 80%. Based on eight of the quantitative criteria, Maeda and Klyce designed an "expert system" to detect keratoconus. The system, which is based on linear discriminant analysis and a binary decision tree, identifies the map as representing keratoconus or nonkeratoconus and, based on a value from the discriminant analysis (the KPI), assigns the map an index expressed as a percentage that suggests the severity of keratoconus (the KCI, Fig. 15). This system was able to differentiate keratoconus from a wide variety of other pathologies with a false positive rate of 1 out of 43 and a false negative rate of 2 in 130.

The Rabinowitz software differs from the Maeda/Klyce system in several respects: it attempts only to differentiate keratoconus from normals, not from other pathologies in a noncontact lens wearing population; it relies on both eyes, not a single eye in its evaluation; its indices are derived from videokeratographs of patients who have clinical signs of keratoconus, not from videokeratographs judged by experts to have keratoconus without regard to clinical signs; and it provides clear quantitative cutoff points based on its indices as to which videokeratographs should be labeled normal or keratoconus.

Both software programs were designed to aid the clinician in identifying abnormal topography and were not intended as a substitute for a history, thorough ocular evaluation, and good clinical judgment when a patient is being evaluated as a candidate for refractive surgery.

VI. Differential Diagnosis

It is important to distinguish keratoconus from other ectatic dystrophies and thinning disorders, such as pellucid marginal degeneration, Terrien's marginal degeneration, and keratoglobus, because the management and prognosis in these disorders differ markedly from keratoconus. The distinction can usually be made by careful slit-lamp evaluation, but corneal topography evaluation is a useful adjunct to differentiate these disorders in subtle or early cases.

A. PELLUCID MARGINAL DEGENERATION

Pellucid marginal degeneration is characterized by a peripheral band of thinning of the inferior cornea from the 4 to the 8 o'clock position. There is 1-2-mm uninvolved area between the thinning and the limbus (Fig. 1B). The corneal protrusion is most marked above the area of thinning, and the thickness of the central cornea is usually normal. Like keratoconus, pellucid marginal degeneration is a progressive disorder affecting both eyes, although eyes may be asymmetrically affected. In moderate cases it can easily be differentiated from keratoconus by slit-lamp evaluation because of the classical location of the thinning. In early cases the cornea may look relatively normal, and in advanced cases it may be difficult to distinguish from keratoconus because the thinning may involve most if not all of the inferior cornea. In both instances videokeratography is very useful to make the distinction. The videokeratograph has a classical "butterfly" appearance (Fig. 13A), demonstrating large amounts of against-the-rule astigmatism, as measured by simulated keratometry.

Pellucid marginal degeneration can be differentiated from other peripheral corneal thinning disorders, such as Terrien's marginal degeneration, because the area of thinning is always epithelialized, clear, avascular, and without lipid deposition. Terrien's corneal degeneration affects a similar age group and also causes high astigmatism; however, it may affect both the superior and inferior cornea and is accompanied by lipid deposition and vascular invasion. Videokeratography can also be used to differentiate these two disorders because they have distinctly different topographic patterns.

Because of the large amounts of against-the-rule astigmatism, patients with pellucid marginal degeneration are much more difficult to fit with contact lenses than patients with keratoconus, although spherical or aspheric contact lenses with large overall diameter should initially be attempted in early-to-moderate cases. Surgery may be considered for patients whose vision is not adequately corrected by contact lenses or in patients who are contact lens-intolerant. Patients with pellucid marginal degeneration, however, are typically poor candidates for penetrating keratoplasty for two reasons. First, thinning occurs so near the limbus that the donor cornea must be placed very close to the corneal limbus, thus increasing the chances of graft rejection. Second, because of the extreme thinning and the location of the thinning, penetrating keratoplasty typically induces large amounts of postoperative astigmatism, which may be extremely difficult to correct because of disparity in graft-host thickness.

Crescentic lamellar keratoplasty is a useful initial surgical procedure in patients with pellucid marginal degeneration. This procedure involves removing a crescentic inferior layer of ectatic tissue by lamellar dissection and replacing it with a thicker
B. KERATOGLOSSUS

Kerato glossus is a rare disorder in which the entire cornea is thinned most markedly near the corneal limbus (Fig. 1C), in contrast to the localized thinning centrally or paracentrally in keratoconus. This will, in most cases, eliminate large amounts of against-the-rule astigmatism. In some cases, the patient may become contact lens intolerant, thus obviating a full-thickness procedure. In contact lens failures, a full-thickness centrally located penetrating keratoplasty can subsequently be performed, encompassing part of the lamellar graft and significantly reducing the risk of graft rejection and postkeratoplasty astigmatism (Fig. 13B).

The cornea may be thinned to as little as 20% of normal thickness, and it assumes a globular shape. In advanced keratoconus, the entire cornea can also be thinned and globular-shaped, making it difficult to distinguish these two entities. However, even in very advanced keratoconus there may be a small area of uninvolved cornea superiorly that approaches normal corneal thickness.

Kerato glossus is bilateral, but it is usually present from birth and tends to be nonprogressive. It can be distinguished from megalocornea and congenital glaucoma because the cornea is usually of normal diameter. It is a recessive disorder and is often associated with blue sclerae and other systemic features, in contrast to keratoconus, which is most commonly an isolated disorder. In contrast to keratoconus, the corneas in kerato glossus are prone to corneal rupture from even minimal trauma. Thus, hard contact lenses are contraindicated and protective spectacles should be strongly encouraged. If the cornea is extremely thin, a tectonic limbus-to-limbus lamellar keratoplasty should be considered to strengthen the cornea. A subsequent central penetrating keratoplasty may be considered if adequate visual rehabilitation cannot be achieved with glasses.

VII. MANAGEMENT OF KERATOCONUS
A. CONTACT LENSES

The management of keratoconus varies depending on the state of progression of the disease. In very early cases, spectacles may provide adequate visual correction, but because spectacles do not conform to the unusual shape of the cornea and the resultant

Fig. 13. Pellucid marginal degeneration: A: Videokeratograph with typical butterfly-shaped appearance. B: Postoperative slit-lamp photo after combined peripheral crescentic lamellar keratoplasty and central penetrating keratoplasty.
induced irregular astigmatism, contact lenses provide better correction. Contact lenses are the mainstay of therapy in this disorder and represent the treatment of choice in 90% of patients.\textsuperscript{17,18}

The type of contact lens used varies depending on the stage of keratoconus. Early in the disease, soft lenses of toric design are adequate. As the disease progresses, more complex rigid gas permeable lenses are used; these include multicurve spherical-based lenses, aspheric lenses, and biaxialpheric lenses. A hybrid lens, which has a rigid central portion for obtaining best optics and a soft hydrophilic peripheral skirt, is also popular with some practitioners.\textsuperscript{19,19,19,19,19}

Fitting contact lenses in keratoconus is a complex task embraced by few contact lens practitioners. The challenge is to keep the patient contact lens-tolerant with good visual acuity in a cornea that may be changing in shape over time. Common complications from lenses include induced corneal abrasion, apical scarring, neovascularization from induced hypoxia, lens discomfort, and lenses not staying on the cornea for adequate periods of time. While some reports suggest that rigid contact lenses induce keratoconus and anecdotal reports contend that keratoconus can be arrested by good contact lens fitting, good evidence does not exist that supports either of these contentions. With the new contact lenses currently available and with good fitting techniques, many patients with 20/40 spectacle correction may enjoy stable 20/20–20/25 contact lens correction.
for many years. I believe that no keratoconus patient who can tolerate contact lenses should be denied the good visual rehabilitation afforded by them because of fear that they may enhance the progression of the disease.

B. CORNEAL TRANSPLANT

1. Indications

Corneal transplant (penetrating keratoplasty) is the best and most successful surgical option for keratoconus patients who cannot tolerate contact lenses or are not adequately visually rehabilitated by them. Central scarring may preclude good vision from contact lenses, even when they are tolerated. A patient with keratoconus has an approximately 10–20% chance over his/her lifetime of needing a corneal transplant.\textsuperscript{132,143} Corneas in keratoconus almost never perforate; thus, advanced thinning by itself is not necessarily an indication for surgery.

Acute hydrops is not necessarily an indication for penetrating keratoplasty, because in many instances the hydrops resolves and the resultant scar is outside the visual axis. The scarring may flatten the cornea, allowing the patient to tolerate contact lenses and achieve good vision. Patients with hydrops can be treated initially with cycloplegics, steroids or nonsteroidal anti-inflammatory agents, 5% sodium chloride solution (Muro 128), and, in rare instances, with bandage contact lenses.\textsuperscript{144}

Buzard and Fundingsland have recently suggested that because of improved corneal transplant techniques and new and improved modalities to correct refractive error after corneal transplantation, patients whose best corrected spectacle visual acuity is 20/40 or worse should be offered cornea transplants in lieu of contact lens fitting.\textsuperscript{143} Considering the good visual acuity afforded to many patients who are successful contact lens wearers, this approach would be regarded by many as being too aggressive.

2. Procedures and Success Rate

Because of the avascular nature of the cornea, corneal transplant has a success rate of 93–96%.\textsuperscript{132,139,144,152} Advances in both eyebanking and surgical techniques now allow this procedure to be done on an outpatient basis with minimal incapacitation of the patient. Complete visual recovery may, however, take as long as 6 months.

Patients who are candidates for penetrating keratoplasty should be counseled that in spite of the high success rate of surgery there is still a 50% chance that they may need contact lenses, either because of residual myopia or postkeratoplasty astigmatism. To decrease the amount of myopia, several surgeons are performing keratoplasties with the donor and host trephines of equal size (usually 7.5 mm; the incidence of rejection is slightly higher with larger size grafts).\textsuperscript{143,144} While in many instances this reduces the amount of myopia, patients who are axial myopes may still be left with large amounts of residual myopia.\textsuperscript{145}

Large amounts of postkeratoplasty astigmatism may remain even after all the sutures are removed. This can be corrected with a combination of relaxing incisions and compression sutures while videokeratography is used as a guide. The residual astigmatism is then small and and can be corrected well with rigid gas permeable lenses (Fig. 14).\textsuperscript{147} It is desirable to leave a small amount of with-the-rule astigmatism, as the patients tolerate this better and it allows for easier contact lens fitting than against-the-rule astigmatism.
3. Complications

In compliant patients, complications after penetrating keratoplasty are rare. These may include rejection, postoperative astigmatism, a fixed dilated pupil, and recurrence of keratoconus.1,67,89,142,149 Graft rejection rates in keratoconus are low and may be reversed with medication if treated early. There have been isolated reports of keratoconus recurring in the graft decades after surgery. These reports are extremely rare, and it is not clear whether keratoconus actually recurred in the graft or whether there was mild, undetected keratoconus in the donor button.1,67,89 Patients will, however, often ask about recurrence, and these isolated reports should be mentioned within this context.

C. EPIKERA TOPLASTY

Epikeratoplasty for a while gained acceptance as a mode of treatment for patients with keratoconus with a clear visual axis. Although good long-term results have been reported,67,149 the procedure has for the most part been abandoned in favor of penetrating keratoplasty because of the superior quality of vision afforded by the latter procedure. There still is a role for epikeratoplasty in select high-risk circumstances. For instance, in keratoconus patients with Down syndrome, epikeratoplasty might be preferable to a penetrating keratoplasty because of its non-invasive nature and the decreased potential for corneal graft rejection.

D. EXCIMER LASER PHOTOTHERAPEUTIC KERATECTOMY

Excimer laser phototherapeutic keratectomy has been demonstrated to be useful in the management of patients with keratoconus who have nodular subepithelial corneal scars and who are contact lens-intolerant.196 This technique provides a smooth corneal surface, allowing patients to regain contact lens tolerance. The nodules may also be removed at the slit-lamp with a sharp handheld blade, potentially with a similar result, albeit with less precision. A recent small study, with short-term data only, suggests that the excimer laser might be useful for providing an improved refractive effect and delaying the need for penetrating keratoplasty in patients with advanced keratoconus.80 This suggested mode of treatment for keratoconus is not currently commonly accepted and should be approached with extreme caution until long-term data on outcomes become available. Performing this procedure on an already thinned and irregular cornea could be hazardous and has the potential for immediate complications exceeding the long-term therapeutic effect.

Method of Literature Search

All articles in Medline up to March 1997 were reviewed. Those considered relevant and that contributed scientifically to the topics covered were included in this article.

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