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A Genetic View of Corneal Dystrophies

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Corneal dystrophies refer to a group of corneal diseases that are genetically determined. These diseases have been traditionally classified and described according to the layer of cornea involved and the pathological changes observed, respectively. It is now known that this classification does not reflect the underlying pathobiology or genetic defects involved. Most corneal dystrophies are either of autosomal dominant or autosomal recessive inheritance, with some variable degrees of clinical severity and penetrance. However, in some cases (eg, keratoconus), the inheritance pattern is not always clear and is considered "complex." The age of onset of the disease is variable and does not reflect the underlying pathogenic defect. Our understanding of corneal dystrophies is undergoing somewhat of a revolution, since >12 chromosomes have been associated with these corneal diseases and mutations have been identified in at least 14 genes (if anterior segment dysgenesis is included in this group of conditions). However, several dystrophies remain without a gene or a genetic location (locus) and more genetic studies are required. The new molecular information is challenging traditional thinking about these conditions that was usually guided by histopathological findings. The elucidation of the underlying biochemical pathways may allow the possibility of modulating these phenotypes in the future. This issue of *Ophthalmology Rounds* presents new molecular information about the more commonly encountered corneal dystrophies (Table 1). For a comprehensive clinical and historical review of corneal dystrophy, the reader is referred to classic texts.[1-3] To best appreciate the implications of this new knowledge, basic developmental anatomy is also briefly discussed.

Development, structure, and function

The cornea forms into 6 concentric layers between 5 and 6 weeks of gestation. The outer epithelium is anchored to a basement membrane, over the acellular Bowman's layer anterior to the stroma. Constituents of Bowman's membrane are believed to be both synthesized and secreted by epithelial cells and stromal keratocytes. The posterior corneal stroma is lined by the collagenous Descemet's membrane, which is secreted and lined by a monolayer of endothelial cells. These cells are important for the passage of nutrients from the aqueous humor into the cornea and are responsible for maintaining the relatively low level of stromal hydration through the ionic pump activity in the plasma membrane of endothelial cells.

The adult cornea has an average diameter of 12.6 mm horizontally and 11.7 mm vertically. Microcornea is usually defined by a horizontal corneal diameter of <11.00 mm.[4,5] Centrally, the thickness measures 0.52 mm, increasing towards the periphery. The tensile strength and transparency of the cornea results in the close interaction between a complex set of proteins and filaments. The major types of cytoplasmic filaments include keratin (intermediate filaments), actin and microtubules, with keratin predominant. The stroma represents 90% of corneal thickness and consists of highly uniform collagen fibrils (22.5-32 nm in diameter) that are predominantly Type I, III, V, VI, XII, and XIV cross-linking fibrillar, collagen-forming, microfibril networks with keratocytes in-between.[6] The keratocytes secrete the extracellular matrix around the collagen consisting of acidic, negatively-charged proteoglycans, with keratan sulphate and dermatan sulfate predominating.[6,7] The proteoglycans play a role in maintaining the regular collagen fibril spacing. The major functions of the stroma are to maintain the proper curvature of the cornea, provide mechanical resistance to intraocular pressure, and transmit light into the eye without significant absorbance. Adult Descemet's membrane contains fibronectin, laminin, type IV and type VIII collagen, heparan sulfate, and dermatan sulfate proteoglycan.[6]

The dystrophies (Table 1)

Recent molecular knowledge about corneal dystrophies demonstrates that dystrophies involving different layers of the cornea with distinct histopathological changes can share a common genetic background.

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Table 1: Genes involved in corneal dystrophies

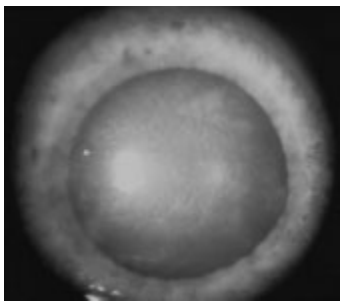
Disease	Heredity	Corneal layer involved	Chromosome	Gene	Function
Meesman	AD	Epithelium	12q	*K3*	Expressed in corneal epithelium, Intermediate filament assembly
	AD	Epithelium	17q	*K12*	Fragility of keratinocytes Intracellular keratin aggregation
Reis-Bückler	AD	Bowman's mbr.	5q	*TGFbI*	
Thiel-Behnke	AD	Bowman's mbr.	5q	*TGFbI*	Keratoepithelin-related amyloid deposits
	AD	Bowman's mbr.	10q23-q24	?	
Granular	AD	Stroma		*TGFbI*	Keratoepithelin-related amyloid deposits
Lattice I	AD	Stroma	5q	*TGFbI*	
Lattice II	AD	Stroma	9	*Gelsolin*	Gelsolin-related amyloid deposits
Lattice IIIa	AD	Stroma	5q	*TGFbI*	Keratoepithelin-related amyloid deposits
Avellino	AD	Stroma	5q	*TGFbI*	Keratoepithelin-related amyloid deposits
Macular	AR	Stroma	16	*CHST6*	Abnormal sulfated keratan sulfate
Gelatinous drop-like	AR	Stroma	1p32	*M1S1 TACSTD2*	Tumour-associated antigen, truncated protein leads to amyloid deposition
Fuchs'	AD	endothelium	1p34-p32	*COL8A2*	Structural role?
PPD	AD	Descemet mbr./ endothelium	20p11-q11, 1p34	*COL8A2 VSX1*	Structural role? Developmental role?
Peters' anomaly	AR	NS	2p	*CYP1B1*	Hydroxylation of 17ß estradiol
	?			*PAX6, PITX2*	Transcription factors
ASMD	AD	NS		*PITX3*	Transcription factors
Cornea plana	AD, AR	NS	12q21	*KERA*	Neural crest cell dev, maintenance of transparency?

Legend: Mbr = membrane, AD = autosomal dominant, AR = autosomal recessive, ASMD = anterior segment mesodermal dysgenesis, dev = development, NS = nonspecific

Reis-Bückler ("geographic") corneal dystrophy, CDBI (OMIM121900)

Reis-Bückler corneal dystrophy is of autosomal dominant inheritance and demonstrates complete penetrance, but variable severity. This condition usually manifests in the first decade of life with variable forms of reticular gray-white opacification forming at the level of Bowman's layer, giving a ground-glass appearance in the intervening areas (Figure 1). The entire cornea is involved, but is most dense axially. Irregularities on the corneal surface can lead to recurrent corneal erosions with reduced corneal sensation. Recurrent attacks of photophobia and irritation become less frequent with increasing age. However, there is progressive visual loss due to secondary corneal opacities; this can be managed with debridement, superficial keratectomy, or phototherapeutic keratectomy.[8] When severe, lamellar or penetrating keratoplasty may be indicated, but recurrence in the graft may be seen, even early. The opacified Bowman's layer is replaced by stratified PAS-positive (Masson's) eosinophillic material, with projections into the epithelium and the anterior stroma,[9] but not involving the epithelial basement membrane. Electron microscopy (EM) shows tubular microfibrils that are crescent- or rod-shaped bodies interspersed between the collagen fibrils in Bowman's layer. Mutations for this condition were identified in transforming growth factor, beta-induced (*TGFBI* or *bIGH3*) (OMIM 601692) located on chromosome 5q31.[10] Despite a strong allelic heterogeneity (ie, >1 mutation in the same gene), some strong phenotype-genotype correlations are observed for mutations such as the R124L change, which is specific to the Reis-Bückler phenotype.

Figure 1: *ßIGH3* related phenotypes; slit lamp example of Reis-Bückler corneal dystrophy

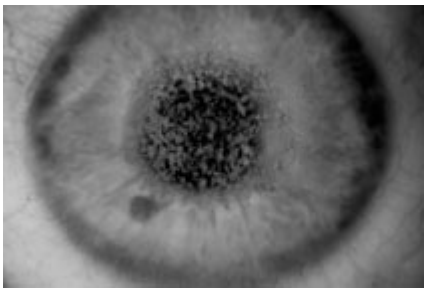


Different mutations in *TGFBI* may also cause granular corneal dystrophy type I (GCD1), GCDII, and GCDIII, lattice corneal dystrophy type I (LCDI), LCDIIIa, intermediate type LCDI/LCDIII and LCD-deep, as well as Thiel-Behnke dystrophy (see below).[11] Mutations involve CpG dinucleotides. *TGFbI* is expressed in keratocytes and encodes for keratoepithelin, a highly conserved 683 amino acid protein. This protein contains an N-terminal secretory signal, 4 domains of internal homology, and an arg-gly-asp (RGD) motif at the C terminus, which is found in many extracellular matrix proteins. The RGD motif modulates cell adhesion and acts as a recognition sequence for integrin binding. Mutations in this gene result in progressive accumulation of corneal deposits shown to contain keratoepithelin. Aggregation of abnormal keratoepithelin isoforms is associated with amyloid or other non-fibrillar deposits, depending on the location and nature of the mutation.

Honeycomb-shaped dystrophy/Thiel-Behnke dystrophy (CDBII) (OMIM 602082)

This autosomal dominant dystrophy usually manifests during the second decade with subepithelial, axial, honeycomb-like opacities with a clear corneal periphery. Recurrent corneal erosions can manifest until the 4^{th}-6^{th} decades. Secondary progressive visual loss can progress to

Figure 2: *ßIGH3* related phenotypes; slit lamp example of granular corneal dystrophy



20/100. However, the corneal surface is usually smooth and the corneal sensation normal. Despite this, the epithelial basement membrane and Bowman's layer may be focally absent. "Curly" collagen fibers seen on electron microscopy (EM)[9] correspond to irregular epithelial and subepithelial PAS-positive fibrocellular deposits. Superficial keratectomy or lamellar or penetrating keratoplasty may be indicated. This condition may recur in the graft, but later than in CBDI.

This "honeycomb dystrophy" phenotype is genetically heterogeneous with mutations in *TGFBI* R555Q, whereas some families are mapped to chromosome 10q24[12] for which the gene is not yet identified.

Granular dystrophy (Groenouw type 1) (OMIM 121900)

This autosomal dominant dystrophy demonstrates complete penetrance and variable clinical severity. The onset of signs occurs in the first and second decade with the appearance of discrete white granular opacities in the central cornea within anterior stroma that may resemble breadcrumbs with clear intervening stroma (Figure 2). With time, the opacities increase in number, density, size, and depth. The peripheral cornea remains clear, whereas the intervening cornea becomes like ground glass. Surface irregularity may develop and sometimes leads to corneal erosions and intense pain. Vision progressively decreases due to scarring and the increase in the density of the deposits, usually by the fourth or fifth decade. Lamellar or penetrating keratoplasty may be required, but recurrences may occur early.

Deposits described as "hyaline" stain bright red with Masson's trichrome. On EM, rod and trapezoid deposits extend into more posterior layers. Mutations in *TGFBI* show strong phenotype-genotype correlations. R555W is a definite hot spot, but R124S is also seen in these patients.[10,11]

Lattice corneal dystrophy

Various subtypes of lattice corneal dystrophy have been distinguished on the basis of their clinical severity and the presence of associated systemic findings. These distinctions are now genetically determined.[10,11]

Lattice corneal dystrophy type 1 CDLI (OMIM 122200)

CDL1 has an autosomal dominant inheritance with complete penetrance and phenotypic variability. Onset usually occurs during the first decade with the appearance of anterior subepithelial white dots and refractile filamentous linear amyloid deposits ± nodules within the stroma. Later, line branching becomes thicker with radial orientation and involves the deeper stroma. Progressive opacification in the central visual axis involves clouding of intervening stroma. Frequent recurrent erosions may present at a young age and may be treated with topical lubrication, patching, or therapeutic contact lenses. When there is scarring, phototherapeutic keratectomy and penetrating keratoplasty may improve vision, but recurrences in grafted corneas are common.

On light microscopy, the epithelium is irregular with a thickened basement membrane and a fragmented Bowman's layer. Fibrillar deposits in anterior stromal layers extend posteriorly, stain intensely with Congo red, and exhibit birefringence and dichroism. Mutations in *TGFBI* are disease specific; R124C.[11]

Lattice corneal dystrophy type 2 CDLII (Familial amyloidosis, Meretoja syndrome, Finnish type, OMIM 105120)

This rare autosomal dominant dystrophy manifests in early adulthood and has systemic findings unlike other forms of lattice dystrophy. The lattice corneal lines are fewer than those seen in CDLI and have a more radial orientation peripherally with relative central sparing. There is reduced corneal sensitivity and recurrent epithelial erosion after age 40, with possible scarring that leads to reduced visual acuity. Dry eyes, pain, and lacrimation are associated with erosions. Overall, symptoms are less severe than those seen in CDLI. Systemic findings are present and include lax skin, peripheral neuropathy, and cardiomyopathy.

The formation of subepithelial scar tissue is associated with linear amyloid material under Bowman's layer, in anterior and midstroma.[13] The amyloid fibrils correspond to an internal degradation product of gelsolin, leading to a progressive loss of corneal sensory nerves and a decrease in the sensation in the cornea, skin, and cranial nerves, predominantly. CDLII maps to chromosome 9q34 and residue D187 of the gelsolin gene (*GSN*) (OMIM 137350) represents a hotspot for disease-causing mutations (D87N, D187Y). *GSN* is widely expressed and encodes for an actin filament modulating (severing and capping) protein,[14] which exerts its action in the presence of submicromolar calcium. The amyloid protein in the Finnish type is a fragment of the actin-filament binding region of a variant gelsolin molecule.[15,16]

Avellino corneal dystrophy (CDA)

CDA is autosomal dominant with complete penetrance and shows highly variable expressivity. It manifests in the second decade with both granular and amyloid linear branching deposits within the stroma. Granular opacities have an earlier onset than amyloid deposits and are located more superficially (Figure 3). Progressive opacification of the central visual axis by deposits may decrease vision enough to require phototherapeutic keratectomy or penetrating keratoplasty. The granular subepithelial to midstromal deposits stain with Masson's trichrome. The fibrillar or fusiform deep stromal deposits containing amyloid stain with Congo red (birefringent).[17,18] The R124H mutation of *TGFbI* is specific to this condition.[11]

Macular dystrophy (MCDI (OMIM 217800), MCDIa, MCDII)

Macular dystrophy is discussed here, not because it is common, but because recent genetic findings are interesting. The different subtypes of macular dystrophy are

Figure 3: *ßIGH3*-related phenotypes; slit lamp example of avellino corneal dystrophy

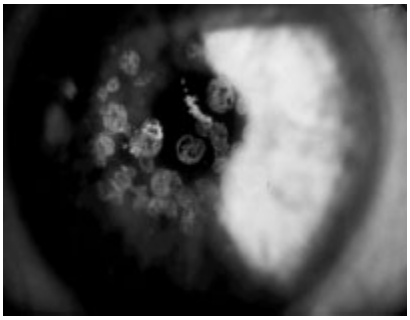
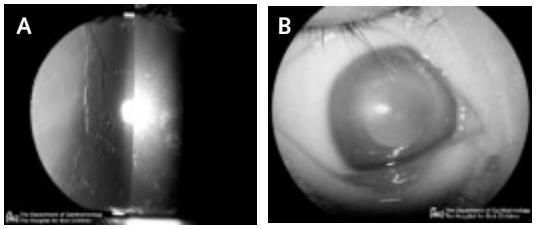


Figure 4: Posterior polymorphous dystrophy (PPD)
A) Slit lamp photograph of a mild case of PPD showing the "snail track sign"
B) Slit lamp photograph of a more severe case of PPD showing corneal opacification



genetically and biochemically determined. The inheritance is autosomal recessive with onset during the first decade of life; there is no significant variability in the phenotype. Early in the course of the disease, the fine opacities have indistinct edges, starting axially in the superficial stroma. The intervening stroma have a ground-glass appearance. Later, opacities extend peripherally and deep into the stroma and the corneal surface becomes irregular with decreased corneal sensation and eventual corneal thinning. Irritation and progressive loss of vision can become severe by the third decade and may require corneal graft with good results.

The characteristic accumulation of glycosaminoglycans (GAGs) stains with Alcian blue and colloidal iron.

MCD1 is characterized by the absence of keratan chain sulfation (KCS) in cornea and cartilage and no appreciable KCS in serum. However, in MCDII, serum and corneal keratan sulphate are detectable and may be reduced, but are often normal. MCD was mapped to chromosome 16q22 and disease-causing mutations involve *CHST6* (OMIM 603797). *CHST6* encodes for carbohydrate sulphotransferase,[19] which is expressed in the cornea, as well as in the trachea and spine. The gene product – corneal N-acetylglucosamine-6-sulphotransferase (C-GlcNAc6ST) – initiates sulfation of keratan sulphate in the cornea.[20] MCD I is due to mutations (missense, deletions, insertions, frameshift) in coding regions of *CHST6*.[19,21] These result in synthesis of an inactive enzyme with the synthesis and secretion of proteoglycans substituted with polylactosamine instead of keratan sulfate. The carrier state is high in Iceland.[20]

MCDIa is seen in families from Saudi Arabia where keratan sulfate is absent in corneal stroma and serum, but present in the keratocyte. The genetic changes in MCDII involve *CHST6* deletions/rearrangements of upstream regions thought to contain gene regulatory elements. These changes affect *CHST6* transcription[19] and reduce sulfation resulting in premature keratan sulfate chain termination.[20]

MCDI and II both have accumulation of other GAGs (chondroitin/dermatan sulfate/hyaluron). Therefore, corneal opacity may result not only from a lack of KCS, but deposition of extra GAGs that may interfere with collagen fibril arrangement.[20] It is important to note that the MCDI (systematic absence of KCS) and II (detectable, but reduced KCS in cornea and serum) phenotypes can occur in the same family.[19,22] In these cases, when an individual has both types of mutations, the MCDII genotype is dominant over MCDI, if a compound heterozygote has a coding mutation and upstream mutation.

Posterior polymorphous dystrophy (PPD) (OMIM 122000, 120252, 605020)

This autosomal dominant dystrophy demonstrates variable expression and variable age of onset. Although it is usually a disease of adulthood (Figure 4a), PPD can be severe and present at birth (Figure 4b). Changes consist of a variable degree of vesicular endothelial lesions and/or basement membrane thickening that may be localized or more diffuse and associated with corneal edema. Vision loss is usually not significant, but is highly variable. Corneal edema can develop to a degree necessitating a corneal graft. There is also an increased risk for glaucoma and keratoconus.[23]

Initially, the abnormal anterior banded layer of Descemet's membrane is lined posteriorly by an abnormal posterior collagenous layer. Multilayering of endothelial cells is seen in the periphery with metaplasia and epithelialization of endothelial cells.[24,25] There is a variable and unpredictable mosaic of better preserved and dystrophic multilayered endothelial cells in the presence or absence of the normal components of Descemet's membrane.

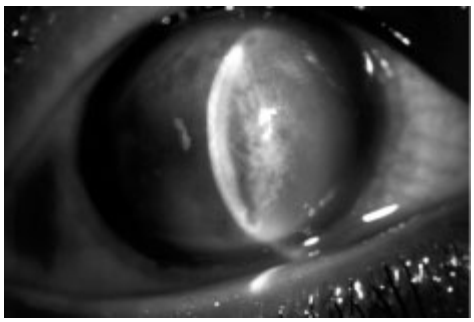
PPD is genetically heterogeneous with mutations identified in *VSX-1* (chromosome 20p11.2-20q11.2)[26,27] and *COL8A2* (chromosome 1p34.3-p32).[28] Data suggest that the chromosome 20 related-PPD is an allelic variant of keratoconus. *VSX-1* appears to play a role in ~9 % of PPD cases and in 4.7% of keratoconus cases. The chromosome 1-related PPD is also an allelic variant of Fuchs' endothelial dystrophy. *Col8A2* could play a role in ~6% of cases of PPD. The role of *Col8A2* in keratoconus has not yet been demonstrated. Changes in *VSX1* have also been associated with an asymptomatic attenuation of cone bipolar cell function in the retina.[27]

Fuchs' endothelial dystrophy (OMIM 136800)

Fuchs' endothelial dystrophy (FECD) is the most common primary disorder of corneal endothelium and may be sporadic or autosomal dominant[29] with

Figure 5: Slit lamp photograph showing the Munson sign, characteristic of keratoconus

Figure 6: Slit lamp photograph showing corneal scarring following hydrops



variable expression. The onset of signs and symptoms is usually from the fourth decade onwards with central cornea guttata, little wart-like protrusions of Descemet's membrane, beaten metal appearance progressing to stromal folds, corneal edema, and endothelial polymegathism. Later, visual loss can be significant and painful because of corneal decompensation. Penetrating keratoplasty in cases of FECD accounts for up to 19% of corneal grafts with a success rate of over 90% in these patients.

Some families affected with FECD have been mapped to chromosome 1p34.3-p32, in which mutations have been identified in *COL8A2* (3.4%).[28] The alpha-2 subunit of type VIII collagen is a member of a family of extracellular matrix proteins[30] and contains an important triple helix repeat, a Proline-rich region that is a site of hydroxylation**.** Mutations within the triple helical domain theoretically disrupt the stability of the supramolecular assembly [28] and have been associated with PPD (~6%) and FECD (~3.4%). The phenotype-genotype correlation is poor as the same mutation can lead to different phenotypes. Mitochondrial mutations have been documented in a case also affected with sensorineural hearing loss, diabetes, cardiac conduction defects, ataxia, and hyperreflexia.[31] The significance of this association is unclear at present.

Developmental and other "corneal dystrophies"

Corneal opacification, central (leucoma), or peripheral (sclerocornea), may manifest in various forms of dysgenesis of the anterior segment. An example is Peters' anomaly, in which mutations are identified in the eye development genes (eg, *PAX6,*[32] *PITX2,*[33] *FOXC1,*[34] and *CYP1B1*.[35] Mutations in *PAX6* can also produce autosomal dominant keratitis.[36]

Keratoconus (OMIM 148300)

Keratoconus can be sporadic or is autosomal dominant in 6%-8% of cases.[37] Its prevalence in first-degree relatives is 15- to 67-times higher than in the general population[38] and it has been observed in identical twins.[39] Onset is around puberty with a progressive ectatic dystrophy leading to corneal thinning and induced irregular myopic astigmatism that may be markedly asymmetrical (Figure 5).[40] Corneal topography is useful for diagnosis and demonstrates an increase in the central Ks. In advanced cases, anterior scarring can be seen and hydrops may occur when Descemet's membrane ruptures with subsequent epithelial and stromal edema (Figure 6). The decreased vision associated with hydrops or corneal scarring may require a corneal graft. For a comprehensive review, see the study by Rabinowitz.[40] Keratoconus is a genetically-determined disorder with a combination of biochemical, structural, and cellular changes.[41-44] It has been associated with several chromosomal anomalies, including Trisomy 21, Turner's syndrome, Ring chromosome 13, trans-location 7;11, connective tissue disorders; Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, mitral valve prolapse, and other ocular diseases (eg, Leber's congenital amaurosis and atopy).[40] As mentioned above, mutations in the *VSX-1* transcription factor were identified in 4.7% of patients with isolated keratoconus.[27] This gene also plays a role in posterior polymorphous dystrophy (see above).

Conclusions

Molecular ophthalmology is redefining our understanding of inherited corneal disorders. This new knowledge indicates that although various conditions are clinically distinct, they may share a common genetic background. Several categories of genes have been identified as playing a role in the determination of corneal transparency and corneal diseases (including those involved in the regulation of eye and corneal development). They may also play a role in determining and maintaining the ultrastructural corneal arrangement and metabolic homeostasis. These genes are part of the molecular pathways currently being characterized, some of which play a role beyond the cornea. Furthermore, some of these genes (ie, *VSX1* and *Col8A2)* link different biological processes such as eye development and aging by the range of phenotypes involved. Understanding of these pathways is critical to the potential modulation of phenotypes. Genetic studies of corneal dystrophies are evolving and are an efficient approach to tie these pathways together and define new therapeutic opportunities.

Electronic address

OMIM: http://www.ncbi.nlm.nih.gov/omim

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Upcoming Scientific Meeting

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Upcoming Events

Department of Ophthalmology and Vision Sciences, University of Toronto

November 25, 2004
VPP - Dr. Stephen Baker, Victoria, BC
Management of orbital infection

December 3, 2004
Walter Wright Day "Ocular Emergencies"
Coordinator – Dr. Dan DeAngelis

December 9, 2004
VPP – Dr. Lelio Baldeschi, Amsterdam, Holland
What the general ophthalmologist needs to know about thyroid disease

February 19, 2005
The Toronto Cataract Course – Course Director, Dr. Ike Ahmed

Note: This year's VPP Rounds will be held at St. Michael's Hospital, 30 Bond Street, Toronto - Paul Marshall Lecture Theatre, B1-Queen, Queen Street entrance (near Second Cup)

Editor's Note: In the August-September issue of *Ophthalmology Rounds* (Pterygium), on page 3 under Mitomycin C (MMC), second paragraph, line 14, the dose of MMC applied should be 0.2 mg/mL.

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