

CONGENITAL ABNORMALITIES AND METABOLIC DISEASES AFFECTING THE CONJUNCTIVA AND CORNEA

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CONGENITAL ABNORMALITIES

Clinical Aspects

Congenital anomalies of the cornea are the result of abnormal corneal development and are evident as alterations in the morphology of the cornea at birth. This is in contrast to metabolic diseases of the cornea and to corneal dystrophies, which occur in previously normal tissue and appear clinically only some time after birth.

Absence of the Cornea and Agenesis of the Anterior Segment

Agenesis of the cornea is unknown as an isolated abnormality. In such cases, there is usually variable absence of other ocular structures derived from the surface ectoderm (1). The result is a scleral shell lined with choroid, retinal pigment epithelium, and retina, but lacking cornea, anterior chamber, iris, ciliary body, and lens. The affected eye is usually small. Ultrasonography may be used to distinguish this condition from true cryptophthalmos. Embryologically, this abnormality occurs when the optic vesicle forms and invaginates to form the optic cup, but the anterior segment fails to differentiate. This abnormality is a form of microphthalmos because it occurs after the formation of the optic vesicle and because the affected eye is usually small.

Cryptophthalmos

True cryptophthalmos (ablepharon) happens when the lids fail to form (1–3). The exposed cornea undergoes metaplasia to skin and so appears to be absent. Because the skin covering the eye is essentially metaplastic corneal tissue, the brows and lashes are absent, which allows for easy differentiation of cryptophthalmos from pseudocryptophthalmos (total ankyloblepharon), in which brows and lashes are present. In true cryptophthalmos, the lacrimal gland and puncta are likely to be missing as well, and the anterior segment of the globe is

usually disorganized (4). Affected patients have a layer of skin extending from the forehead to the malar region. An *incomplete form* in which only the nasal aspect of the lid fold is involved is recognized. Still another presentation is the *abortive form*, in which the upper eyelid is replaced by a fold of skin that is adherent to the upper third of the cornea; the lower eyelid is normal (5). Even in the complete form, the underlying eye moves and may even show some reaction to bright light in the form of contractions of the periocular skin. However, attempts to treat it are futile, because any incision into the overlying skin will result in entry into the malformed eye. The only advantage of a cutaneous incision may be some slight cosmetic benefit. Embryologically, cryptophthalmos results from a failure of formation of the eyelid folds.

Cryptophthalmos is rare, with only about 50 cases reported. It is usually transmitted as an autosomal-recessive trait and may be unilateral or bilateral. When it is unilateral, the other eye may have symblepharon or coloboma of the eyelid. Males and females are affected equally.

When cryptophthalmos occurs in association with other systemic abnormalities, as it often does, the condition is described as cryptophthalmos syndrome. Associated systemic abnormalities include, most commonly, syndactyly, genitourinary anomalies, and craniofacial anomalies. Less commonly, spina bifida, deformed ears or teeth, cleft palate or lip, laryngeal or anal atresia, ventral hernias, cardiac anomalies, displacement of the nipples or umbilicus, basal encephaloceles, and mental retardation may also occur (2,5–7). Renal agenesis has been documented in siblings of patients with this syndrome.

Total Ankyloblepharon

In this condition, a fully formed eye is covered by skin. The lid folds are formed but fail to separate. Brows and lashes are present. Incision may be of some value, to expose the globe covered by the lid, although the newly formed lids tend to close again (1,8).

Abnormalities of Size

Megalocornea

Megalocornea is characterized by a primarily enlarged diameter of the cornea (more than 13 mm in horizontal diameter) in the absence of previous or concurrent elevated intraocular pressure (1–3). The corneal enlargement may occur as an isolated anomaly (*simple megalocornea*) or in association with enlargement of the ciliary ring and lens (*anterior megalophthalmos*) (9). Simple megalocornea is usually a nonprogressive, usually symmetric, inherited condition. Megalocornea is usually X-linked recessive, with 90% of cases in males, although all forms of inheritance have been reported, including occasionally dominant, less often recessive and germ-line mosaicism also reported (10).

Some patients with megalocornea are myopic because of increased corneal curvature, although the curvature may also be normal. With-the-rule astigmatism is often present when the corneal curvature is increased. Megalocornea can be differentiated from congenital glaucoma by the normal intraocular pressure, the clarity of the cornea, and the normal optic nerve in simple megalocornea. Moreover, megalocornea demonstrates normal endothelial cell population densities on specular microscopy, whereas in congenital glaucoma, these are diminished, ostensibly because of corneal distention (11). Studies have also suggested the use of A-scan ultrasonography to distinguish features of megalocornea that are not present in glaucoma, including increased anterior chamber depth, posterior lens and iris positioning, and short vitreous length (12). Some people believe megalocornea represents congenital glaucoma that has been arrested, but a histopathologic report on an eye with megalocornea did not show the angle abnormalities classically seen in congenital glaucoma. However, both megalocornea and congenital glaucoma have been reported in the same families and even in the same person (13,14).

Anterior megalophthalmos is associated with enlargement of the lens-iris diaphragm and ciliary body in addition to the cornea. This condition may be associated with a large myopic astigmatic error. The iris may demonstrate iris transillumination defects. The condition is usually harmless except for three complications that may appear later in life: ectopia lentis due to the abnormal architecture; glaucoma secondary to lens subluxation; and cataract, which is usually posterior subcapsular but may be nuclear or peripheral. Other associated abnormalities include Marfan's syndrome, Apert's syndrome, and mucopolidosis type II (1–3,14,15).

Megalocornea is probably the result of a failure of the anterior tips of the optic cup to grow sufficiently close to one another, the remaining space being taken up by the cornea. Other possible explanations are that it represents an exaggeration of the normal tendency for the cornea to be large, relative to the rest of the eye, from embryonic life to the age of 7 years; an atavistic regression to the tendency for nonhuman

TABLE 39-1. ABNORMALITIES ASSOCIATED WITH MEGALOCORNEA

Ocular
Myopia
Astigmatism
Arcus juvenilis
Krukenberg's spindle
Mosaic corneal dystrophy
Hypoplasia of iris stroma and pigment epithelium
Miosis (hypoplasia of iris dilator)
Prominent iris processes
Pigmentation of trabecular meshwork
Open-angle glaucoma
Congenital glaucoma (rare)
Cataract (usually posterior subcapsular)
Ectopia lentis
Systemic
Marfan's syndrome
Craniosynostosis
Lamellar ichthyosis
Mental retardation (with recessive megalocornea)

mammals to have larger corneas relative to their globes; or spontaneously arrested congenital glaucoma.

Table 39-1 lists other abnormalities associated with megalocornea.

Microcornea

A microcornea is one that has an adult horizontal diameter of less than 11 mm (1,3). Note that the cornea usually reaches its adult size around 2 years of age. Microcornea can occur as an isolated anomaly, or the whole anterior segment may be small, in which case the term *anterior microphthalmos* applies. *Nanophthalmos* indicates an eye that is small but otherwise normal, and *microphthalmos* refers to a small eye that is also malformed in other ways.

Patients with microcornea are likely to be hyperopic because their corneas are relatively flat, but any kind of refractive error is possible owing to variations in length of the globe. Open-angle glaucoma develops later in life in 20% of patients, and some predisposition to narrow-angle glaucoma also exists because of the shallow anterior chamber with crowding of the anterior chamber structures seen in anterior microphthalmos. Congenital glaucoma coexists occasionally. An eye with microcornea (or microphthalmos) is sometimes misinterpreted as being normal in comparison to its fellow (actually normal) eye, which is thought erroneously to have corneal enlargement from congenital glaucoma. Certain somatic abnormalities have been described in conjunction with microcornea and anterior microphthalmos, including dwarfism and Ehlers-Danlos syndrome. Table 39-2 lists other problems that are sometimes associated with microcornea (1,16,17).

Microcornea is thought to be caused by an overgrowth of the anterior tips of the optic cup, leaving less than normal

TABLE 39-2. ABNORMALITIES ASSOCIATED WITH MICROCORNEA

Ocular
Hyperopia (other refractive errors possible)
Cornea plana
Corneal leukoma
Mesodermal remnants in angle
Aniridia
Uveal coloboma
Corectopia
Persistent pupillary membrane
Congenital cataract
Microphakia
Open-angle glaucoma
Angle-closure glaucoma
Congenital glaucoma
Retinopathy of prematurity
Microblepharon
Small orbit
Systemic
Weill-Marchesani syndrome or similar habitus
Ehlers-Danlos syndrome
Meyer-Schwickerath and Weyers syndrome
Rieger's syndrome
Partial deletion of long arm of chromosome 18
Nance-Horan (X-linked cataract-dental) syndrome

space for the cornea. It may be transmitted as a dominant or recessive trait, the former being more common.

Abnormalities of Shape

Horizontally Oval Cornea

The cornea is normally horizontally oval when viewed from in front, with the horizontal diameter approximately 1 mm larger than the vertical diameter (although it is round when seen from the back). The oval appearance is caused by greater scleral encroachment above and below than in the horizontal meridian. An exaggeration of the normal oval shape usually indicates the presence of some degree of sclerocornea (1,3).

A horizontally oval, bifid cornea attributed to maternal ingestion of large amounts of vitamin A throughout pregnancy has been reported (18). The condition was unilateral and manifested a cornea and iris having roughly the shape of an hourglass lying on its side. Reduplicated but clear crystalline lenses were also present.

Vertically Oval Cornea

A vertically oval cornea sometimes occurs in association with iris coloboma, Turner's syndrome (ovarian dysgenesis, XO karyotype), or intrauterine keratitis (usually from congenital syphilis) (1,13,16,19,20). It is interesting that the luetic interstitial keratitis can appear before or after the observation of the abnormal shape of the cornea.

Abnormalities of Curvature

Cornea Plana

Cornea plana (flat cornea) is seldom an isolated entity. It is more often seen in association with microcornea or sclerocornea (1,4,21). The sclerocornea is likely to be more prominent above and below, so that the cornea appears to be horizontally oval as well. The limbus in cornea plana is usually indistinct, whereas it is typically well defined in simple microcornea.

Cornea plana often produces hyperopia, but the refractive error is unpredictable because the length of the globe varies. The cornea itself must have a radius of curvature of less than 43 diopters if it is to be designated as a cornea plana, but measurements of 30 to 35 D are more common. A keratometry reading of as low as 23 D has been reported (4). A corneal curvature that is the same as that of the sclera is almost pathognomonic for cornea plana. The cornea is even flatter than the sclera in some cases. The anterior chamber is shallow, and angle-closure glaucoma is not uncommon. The incidence of open-angle glaucoma is also increased. Other possible abnormalities are listed in Table 39-3 (1,3,4,21).

Cornea plana is thought to be the result of a developmental arrest in the fourth month of fetal life, when the corneal curvature normally increases relative to that of the sclera. The heredity may be dominant or recessive. The recessive form is more severe and can be complicated by the presence of central corneal opacities. Cornea plana is especially likely to occur in patients of Finnish extraction (4).

TABLE 39-3. ABNORMALITIES ASSOCIATED WITH CORNEA PLANA

Ocular
Hyperopia (other refractive errors possible)
Blue sclera
Sclerocornea
Microcornea
Arcus juvenilis
Nonspecific corneal opacities
Anterior segment dysgenesis
Absence of normal iris markings and collarette
Uveal and retinal coloboma
Aniridia
Congenital cataract
Ectopia lentis
Retinal and macular aplasia
Angle-closure glaucoma
Open-angle glaucoma
Pseudoptosis (Streiff's sign)
Systemic
Osteogenesis imperfecta
Hurler's syndrome (mucopolysaccharidosis I-H)
Maroteaux-Lamy syndrome (mucopolysaccharidosis VI) ^a
Trisomy 13

^aPersonal observation.

Anterior Keratoconus and Keratoglobus

Anterior keratoconus usually develops during the first two decades of life and is only rarely evident at birth. Keratoglobus (globular cornea) is not infrequently congenital, but it, too, can appear after birth. Both of these corneal ectasias are usually classified as corneal dystrophies and so are not discussed here, although some of their features are summarized in Table 39-4.

Generalized Posterior Keratoconus

In this condition, the entire posterior surface of the cornea has an increased curvature, that is, it has a shorter radius of curvature and so is more strongly curved, whereas the contour of the anterior surface remains normal (1,22-24). The differential features of anterior keratoconus, keratoglobus, generalized posterior keratoconus, and circumscribed posterior keratoconus (discussed later) are given in Table 39-4 (1,22-24).

Generalized posterior keratoconus is the least common of the four disorders. It probably represents a developmental arrest, as the posterior surface of the cornea is normally more curved during fetal life (24). Generalized posterior keratoconus is usually unilateral. All examples have been in women, but there is no evidence of hereditary transmission. Central corneal thinning is present, but the condition is nonprogressive, and the vision is normal unless there is associated clouding of the cornea, which seldom occurs.

Kerectasia

Kerectasia is characterized by the presence of a bulging, opaque cornea that protrudes through the palpebral aperture (1,3,25). Most cases are unilateral and are probably the result of intrauterine keratitis; corneal perforation *in utero* causes the cornea to undergo metaplasia to tissue resembling skin (dermoid transformation). The metaplasia involves only

the cornea and does not extend over the entire eye to the area of the lids, as occurs in cryptophthalmos.

Some examples of kerectasia may be caused by a failure of mesenchyme to migrate into the developing cornea, resulting in subsequent corneal thinning, bulging, and metaplasia, with or without preceding perforation.

Congenital Anterior Staphyloma

Congenital anterior staphyloma differs from kerectasia only in that the staphyloma is, by definition, lined by uveal tissue (1,3,25).

Corneal Astigmatism

Corneal astigmatism is usually just a variation, that is, a common and minor deviation from normality, although Duke-Elder considered radii of curvature of less than 6.75 mm or greater than 9.25 mm to be deformities (1,3,25).

Corneal astigmatism is nearly always dominant. Autosomal or X-linked recessive transmission is rare but may occur, especially with high degrees of astigmatism. The approximate amounts, and even the axes, of astigmatism are often remarkably similar in related individuals (3,21).

Abnormalities of Structure

Anterior Segment Dysgenesis

Anterior segment dysgenesis (ASD) was formerly called mesodermal dysgenesis (anterior chamber cleavage syndrome), but evidence indicates that the affected embryonic tissues probably originate from the neuroectoderm of the neural crest rather than from the mesoderm (26,27). These problems may be thought of as a spectrum in which any of several abnormalities may exist alone or in various combinations (1,14,22,25,28-30). Some of the more frequently

TABLE 39-4. COMPARATIVE FEATURES OF ANTERIOR KERATOCONUS, POSTERIOR KERATOCONUS, AND KERATOGLOBUS

Feature	Anterior Keratoconus	Generalized Posterior Keratoconus	Circumscribed Posterior Keratoconus	Keratoglobus
Frequency	Most common	Least common	Third most common	Second most common
Heridity	Uncertain	None	Usually none	Uncertain
Sex predilection	Slightly more females	All females	Mostly females	Uncertain
Laterality	Usually bilateral	Usually unilateral	Usually unilateral	Bilateral
Progression	Yes	No	No	Yes
Decreased acuity	Yes	Rarely	Sometimes	Yes
Corneal clouding	Sometimes	Seldom	Usually	Seldom
Anterior curve	Increased, distorted	Normal	Normal or distorted	Increased, distorted
Posterior curve	Increased	Increased	Increased locally	Increased
Corneal thinning	Central	Central	Variable	Peripheral
Acute hydrops	Occasionally	No	Seldom	Seldom

occurring combinations are given eponymic designations such as Rieger's anomaly, Peters' anomaly, and others.

In trying to understand this subject, it is helpful to review some of the embryology of the anterior segment of the eye (3,22,31). After separation of the lens vesicle, the surface ectoderm forms a layer that becomes corneal epithelium. Three waves of tissue then invade the primary mesenchyme that lies behind the surface ectoderm: the first wave gives rise to corneal endothelium, the second forms corneal stroma, and the third becomes the iris stroma. These waves of tissue (secondary mesenchyme) were once thought to be mesodermal, thus giving rise to the concept of mesodermal dysgenesis, but are now widely held to be of neural crest origin and the term most commonly used now is that of *anterior segment dysgenesis*.

During early development, there is no anterior chamber, the entire area being filled with primary or secondary mesenchyme. This gradually recedes, and its remnant in the form of the pupillary membrane begins to undergo atrophy at about the seventh month. The angle recess does not become fully opened until sometime during the first year after birth.

Three hypotheses have been proposed to explain the disappearance of mesenchyme and the consequent formation of the anterior chamber (25,26,28,32,33). The first idea was that the mesenchyme disappears by means of atrophy and absorption. The next explanation was that it is pulled apart passively as a result of different growth rates of the anterior tissues; there is no evidence to support this idea and so the term *anterior segment cleavage syndrome* is rarely used. The latest, and most plausible, explanation for the abnormalities that occur in conjunction with the development of the anterior chamber is that they represent abnormal migration, proliferation, or final differentiation of secondary mesenchymal cells that originate from the neural crest (26). This concept accounts also for the fact that associated abnormalities of the head and face are often present.

The various ASDs are now classified as follows: (a) abnormalities of neural crest cell migration (congenital glaucoma, posterior embryotoxon, Axenfeld's anomaly and syndrome, Rieger's anomaly and syndrome, Peters' anomaly, and sclerocornea); (b) abnormalities of neural crest cell proliferation (essential iris atrophy, Chandler's syndrome, and Cogan-Reese iris nevus syndrome); and (c) abnormalities of neural crest cell final differentiation (congenital hereditary endothelial dystrophy, posterior polymorphous corneal dystrophy, congenital cornea guttata, and Fuchs' corneal dystrophy). Other abnormalities such as prominent iris processes, dysgenesis of the iris, circumscribed posterior keratoconus (and, perhaps, generalized posterior keratoconus), goniodysgenesis with glaucoma, and iridogoniodysgenesis with cataract are probably also abnormalities of neural crest cell migration or differentiation.

Posterior Embryotoxon

Posterior embryotoxon is an exaggeration of the normal Schwalbe's ring. This structure is a collagenous band that encircles the periphery of the cornea on its posterior surface (34). The collagen fibers of Schwalbe's ring course circumferentially (parallel to the limbus), whereas the fibers elsewhere in the cornea run radially. Schwalbe's ring is bounded anteriorly by the termination of Descemet's membrane and posteriorly by the trabecular meshwork. Gonioscopically, it is seen just above the meshwork and is then referred to as Schwalbe's line. It may be flat and indistinct, or elevated and ridgelike.

In most persons, Schwalbe's ring is not visible biomicroscopically because it lies behind the opaque portion of the limbus; if it is sufficiently prominent and anteriorly displaced as to be visible, it is called a posterior embryotoxon and is present in 15% to 30% of normal eyes. It appears clinically as an arcuate or scalloped translucent membrane on the posterior surface of the cornea just inside the limbus. It is usually seen in the horizontal meridian, nasally and temporally, but may encircle the entire cornea.

Posterior embryotoxon is inherited as a dominant trait. The eye is usually otherwise normal unless Axenfeld's anomaly or syndrome (discussed below) is present. A prominent Schwalbe's line may be associated with other disorders, including primary congenital glaucoma, Alagille's syndrome (arteriohepatic dysplasia), megalocornea, aniridia, corectopia, and Noonan's syndrome.

Even a Schwalbe's ring that is not anteriorly displaced may be visible without gonioscopy if there is a sectoral deficiency of the normal extension of sclera into the superficial tissues of the limbus. This extremely rare anomaly is called the *partial limbal coloboma of Ascher* and exposes Schwalbe's ring and the meshwork to direct view (1).

Axenfeld's Anomaly and Syndrome

Axenfeld's anomaly is the combination of posterior embryotoxon with prominent iris processes. The iris processes extend across the angle and insert into the prominent Schwalbe's line. *Axenfeld syndrome* is the name given to Axenfeld anomaly occurring along with glaucoma (30,38). Both the anomaly and the syndrome are dominantly inherited. Hypertelorism is occasionally present. Systemic abnormalities are rare (10).

Rieger's Anomaly and Syndrome

Rieger's anomaly consists of the changes found in Axenfeld anomaly plus hypoplasia of the anterior iris stroma (28,30,33). Peripheral anterior synechiae, corectopia, and pseudopolyoria are often present also, as is glaucoma in 50% to 60% of cases. Rieger's syndrome is present when the Rieger's anomaly is accompanied by skeletal abnormalities,

such as maxillary hypoplasia, microdontia, and other limb and spine malformations (35). Some patients are mentally retarded.

Rieger's anomaly and syndrome are usually dominant but are occasionally sporadic. One case showed a presumptive isochromosome of the long arm of chromosome 6 (36), and another had a pericentric inversion of chromosome 6 (37). Various systemic associations have been described, such as Down syndrome, Ehlers-Danlos syndrome, Franceschetti's syndrome, Noonan's syndrome, Marfan's syndrome, oculodentodigital dysplasia, and osteogenesis imperfecta.

Examination of these patients must include gonioscopy and tonometry: this not only helps make the differential diagnosis, it also helps direct treatment (especially if intraocular pressure is elevated). The pneumotonometer or Tonopen is preferable to the Perkins, or Schiötz tonometers because the presence of associated corneal abnormalities or small radius of corneal curvature may give false intraocular pressure readings. Also, a thorough assessment of the optic nerve is critical in determining the overall visual prognosis and deciding on the course of future treatment.

Medical therapy can be useful when intraocular pressure is high and needs to be decreased in an urgent manner. However, this disorder generally has a relatively poor surgical prognosis, both for glaucoma control and for corneal opacities, if present. Deciding on the correct balance between chronic administration of medications and performing surgery is difficult. The advent of effective use of antimetabolites for filtration in children may tip the balance in favor of surgery when the optic nerve is threatened significantly. However, this type of treatment in the maturing eye of a child is, itself, embryonic.

Goniodysgenesis with Glaucoma

Goniodysgenesis with glaucoma is probably just a minor form of Rieger's anomaly, lacking only posterior embryotoxon (30,38). Transmission is dominant.

Iridogoniodysgenesis with Cataract

Iridogoniodysgenesis with cataract differs from Rieger's anomaly in that cataract is present, posterior embryotoxon is absent, and the heredity is autosomal recessive (30,38). Iridogoniodysgenesis is not associated with systemic abnormalities, but Conradi's syndrome (congenital stippled epiphyses) sometimes manifests other forms of ASD in association with cataract.

Peters' Anomaly

Peters' anomaly is characterized by a central corneal opacity with corresponding defects in the stroma, Descemet's, and endothelium. Two variants of Peters' anomaly have been

described: in the so-called *mesodermal form* (or, probably more properly, the *neuroectodermal form*) or type I Peter's anomaly, the central cornea has a congenital leukoma with strands of iris adherent to it (1,28,30,33,40-42). The adhesions usually, but not invariably, arise from the iris collarette and represent persisting remnants of the pupillary membrane. The lens, which is ectodermal in origin, is clear in the classic and purely mesodermal (neuroectodermal) form of the anomaly. It is most often sporadic but may be transmitted recessively or as an irregularly dominant trait (39). Approximately 80% of cases are bilateral, and about half include glaucoma. Other associated abnormalities such as microcornea and sclerocornea may be present, although they usually are not. This form of Peters' anomaly is caused by abnormal development of the tissues associated with the central portions of the iris, anterior chamber, and cornea. Descemet's membrane and endothelium are generally absent at the site of the leukoma, as is true also of the other two forms of the anomaly that are discussed below.

Peters' anomaly type II, or the *surface ectodermal form* of the anomaly, is the result of faulty separation of the lens vesicle from surface ectoderm. In addition to the features of the mesodermal (neuroectodermal) type, anterior cataract (polar, subcapsular, or reduplication) is present. This form is usually bilateral and is almost always associated with other more severe manifestations, both ocular and systemic. Fifty percent to 70% of patients have concomitant glaucoma, and other associated abnormalities include microcornea, microphthalmos, cornea plana, sclerocornea, colobomas, aniridia, and dysgenesis of the angle and iris.

The *inflammatory form* follows intrauterine inflammation and so is nonhereditary. The inflammation can interfere with surface ectodermal or neuroectodermal development or both. There is no definitive way to make the diagnosis, although signs of inflammation may still be present after birth, and the iris adhesions are extensive and do not arise only from the vicinity of the collarette. Cases of inflammatory Peters' anomaly nearly always fulfill the criteria for use of the term *von Hippel's posterior corneal ulcer*, namely inflammatory signs in association with congenital defects of Descemet's membrane and endothelium. We have already seen that some examples of circumscribed posterior keratoconus have these same features and so may also be referred to as cases of von Hippel's ulcer; in fact, there seems to be little, if any, difference between the inflammatory form of Peters' anomaly and the inflammatory form of circumscribed posterior keratoconus.

The management of patients with Peters' anomaly is complex, and the outcome of a keratoplasty depends on the ability to control the associated glaucoma.

Prominent Iris Processes

Although prominent iris processes are not corneal anomalies, they should be mentioned because they are part of

the spectrum of ASD and because it is necessary to determine their relationship to the peripheral cornea in order to evaluate their pathologic importance (14).

It is normal for some slender processes (usually fewer than 100) to extend from the peripheral iris to the scleral roll (also known as the scleral spur) at the posterior edge of the trabecular meshwork or, occasionally, even to the central portion of the meshwork itself. Extensions to or beyond Schwalbe's ring are abnormal and are referred to as prominent iris processes. Abnormal processes are often more numerous, in addition to being more prominent and anteriorly displaced, than are normal processes.

Prominent iris processes can occur with any of the other manifestations of ASD. They are also seen in many cases of primary congenital glaucoma and in several systemic disorders that are associated with congenital glaucoma: phakomatosis; homocystinuria; rubella; and Marfan's, Lowe's, Pierre Robin, Hallermann-Streiff, Rubenstein-Taybi, and Turner's syndromes (14).

Anterior Segment Dysgenesis of the Iris

In addition to prominent iris processes, ASD may be associated with congenital peripheral anterior synechiae and a variety of abnormalities of the iris itself, including atrophy of the iris stroma, corectopia, pseudopolyopia, and congenital ectropion uveae.

Posterior Polymorphous Dystrophy

Posterior polymorphous dystrophy may be classified either as a dystrophy or as a congenital anomaly. Its histopathologic features suggest a relationship to ASD, and it not infrequently occurs with other forms of ASD (22,25,43,44). This entity is described in detail elsewhere in this book.

Congenital Cornea Guttata

Cornea guttata can occur, rarely, as a congenital anomaly. It is sometimes familial. A dominant pedigree with associated anterior polar cataract has been described, which suggests an abnormality in the secondary mesenchyme that helps to separate the lens from the surface ectoderm at about the sixth to eighth week of embryonic life (45). Congenital cornea guttata is also described elsewhere in this book.

Congenital Hereditary Endothelial Dystrophy

Congenital hereditary endothelial dystrophy (CHED) is now classified as an ASD. It is characterized by the presence, at birth or soon thereafter, of bilateral corneal edema that is often slightly worse centrally and that is not associated with vascularization or inflammation (44,46–49). Epithelial edema is not prominent, but the stroma may

be swollen to two or three times its normal thickness. Descemet's membrane, when visible, is seen to be thick and opaque, but guttate changes are not present. Intraocular pressures are normal. The corneas are not enlarged.

Two types of CHED with different modes of transmission are recognized (46,49,50). The recessive form is more common, and is usually more severe, than the dominant form. In the recessive disease, the corneas are cloudy at birth, and nystagmus is common. The condition is essentially nonprogressive and is asymptomatic except for severely decreased vision. Deafness is sometimes present; otherwise, there are no related systemic abnormalities (51).

Corneal edema in dominant CHED may not become apparent until sometime during the first or second year after birth (44,46,50). Nystagmus is absent. The edema is likely to progress slowly, and some patients develop pain, photophobia, and tearing.

Histopathologically, the anterior ("banded") portion of Descemet's membrane is normal, but the posterior non-banded layer (which is formed later during development) is abnormal and consists of a variably thickened, or occasionally thinned, layer of aberrant collagen (47,52,53). Guttate excrescences do not form. Endothelial cells are absent or atrophic. The primary abnormality is presumed to be with the endothelial cells and must manifest itself during or after the fifth month of gestation, at which time the endothelial cells begin to form the posterior nonbanded portion of Descemet's membrane.

Asymptomatic relatives of patients with CHED may show corneal changes resembling posterior polymorphous dystrophy (54). An attempt should be made to identify such persons because their children seem to run a greater risk of having CHED.

Circumscribed Posterior Keratoconus

Circumscribed posterior keratoconus may be a localized form of Peter's anomaly. It is characterized by the presence of a localized, crater-like defect (convex toward the stroma) in the posterior surface of the cornea (22,30,40–42,55). Contrary to former belief, Descemet's membrane and endothelium are usually present in the area of the defect, although the collagen of Descemet's membrane may be thinned and abnormal in structure and configuration (22,40,42,55). More than one pit may be present. The overlying stroma often has nonspecific opacities. Most cases are in females, unilateral and sporadic, although familial examples have occurred. It is probably the result of abnormal migration or terminal induction of cells of neural crest origin in the area of involvement, perhaps secondary to some problem with separation of the lens vesicle. Some cases show evidence of being related to intrauterine inflammation: corneal infiltrates and vascularization, keratic precipitates, anterior synechiae, and uveitis; these cases often have defects in Descemet's membrane and endothelium and are

TABLE 39-5. ABNORMALITIES ASSOCIATED WITH CIRCUMSCRIBED POSTERIOR KERATOCONUS

Ocular
Fleischer ring
Aniridia
Anterior segment dysgenesis
Anterior lenticonus
Systemic
Hypertelorism
Poorly developed nasal bridge
Brachydactyly
Bull neck
Mental retardation
Growth retardation

sometimes referred to as *von Hippel's posterior* (or *internal*) *corneal ulcer*.

The characteristics of circumscribed posterior keratoconus, as compared with generalized posterior keratoconus, anterior keratoconus, and keratoglobus, are summarized in Table 39-4. Associated ocular and systemic abnormalities are listed in Table 39-5 (22).

The anterior surface of the cornea is usually normal in these individuals, unless there is enough thinning to cause ectasia. Thus, although the posterior corneal surface may degrade vision to some extent, this is usually not enough to warrant a surgical procedure.

Sclerocornea

Sclerocornea is an abnormality in which the margins of the cornea are not well defined because scleral tissue with conjunctival vessels extends to the margins (56–58). The scleralization may be only peripheral or virtually complete. Even when it is complete, the central cornea is apt to be slightly less opaque than the periphery. Affected areas have fine, superficial vessels that are direct extensions of normal scleral, episcleral, and conjunctival vessels. Sclerocornea is usually bilateral (57).

Histopathologic studies reveal elastic fibers and collagen fibers of increased and variable diameter in the anterior corneal stroma. The deeper collagen fibers have smaller diameters than do the more anterior ones, as is typical of sclera; the reverse is true of normal cornea (58).

About 50% of cases of sclerocornea are sporadic, and the remainder can be dominant or recessive (57). The dominant forms are less severe than the recessive ones (58). Sclerocornea is occasionally caused by chromosomal aberrations. There is no sex predilection. The most common associated finding is cornea plana. Other ocular and systemic associations are given in Table 39-6 (7,57,59,60,61,62). In brief, sclerocornea is associated with cornea plana in about 80% of patients. Other associated ocular abnormalities include microphthalmos, iridocorneal synechiae, persistent

TABLE 39-6. ABNORMALITIES ASSOCIATED WITH SCLEROCORNEA

Ocular
High refractive errors
Blue sclera
Cornea plana
Horizontally oval cornea
Aniridia
Anterior segment dysgenesis
Uveal and retinal coloboma
Cataract
Open-angle glaucoma
Angle-closure glaucoma
Pseudoptosis
Microphthalmos
Systemic
Anomalies of skull and facial bones
Deformities of the external ear
Deafness
Polydactyly
Cerebellar dysfunction
Testicular abnormalities
Hereditary osteo-onychodysplasia
Osteogenesis imperfecta
Others (numerous and variable)

pupillary membrane, dysgenesis of angle and iris, congenital glaucoma, coloboma, and posterior embryotoxon of the fellow eye. Somatic abnormalities sometimes occur along with associated chromosomal abnormalities; they include mental retardation, deafness, and craniofacial, digital, and skin abnormalities.

Other Combined Forms of Anterior Segment Dysgenesis

Although the foregoing disorders are the most frequently encountered combined forms of ASD, it is worth reemphasizing that any combination of features is possible. This is illustrated well by the family reported by Grayson (43), in which some members had all of the following findings: cornea guttata, posterior polymorphous dystrophy, posterior embryotoxon, circumscribed posterior keratoconus, iris atrophy, peripheral anterior synechiae, prominent iris processes, and glaucoma. These patients also developed corneal edema and fibrocalcific band keratopathy.

Congenital Mass Lesions of the Cornea

Metaplasias

A metaplasia is a transformation of tissue from one type to another, usually in response to exposure, inflammation, or trauma (1,63). As mentioned earlier, the cornea can undergo metaplasia to skin (dermoid transformation) in the conditions of keratectasia, corneal staphyloma, and true

cryptophthalmos. The metaplasia is at times of such proportions as to produce an apparent tumor of the cornea.

If the metaplasia is strictly ectodermal, the corneal epithelium is replaced by tissue resembling epidermis, sometimes with related derivatives such as hairs and glandular structures being present. Mesodermal metaplasia brings about the appearance in subepithelial stroma of the fibrofatty elements of dermis, and sometimes cartilage or bone. When the metaplasia consists primarily of a hypertrophic overgrowth of fibrous tissue, the term *corneal keloid* may be used (64).

Choristomas

A choristoma is a mass of tissue that has been displaced during prenatal development from its normal position to a location where it would not normally be found (63).

Corneal, Limbal, and Epibulbar Dermoids

Corneal, limbal and epibulbar dermoids consist of masses of tissue that were destined to become skin but were displaced to the surface of the eye (1,63). They can also occur in the orbit.

Choristomatous dermoids contain ectodermal elements (keratinizing epithelium, hair, sebaceous and sudoriferous glands, nerve, smooth muscle, and, rarely, teeth) and mesodermal derivatives (fibrous tissue, fat, blood vessels, and cartilage) in various combinations. They are called lipoderoids if fatty tissue predominates.

Clinically, an epibulbar dermoid is usually a round or ovoid, yellowish white, dome-like mass. Occasionally, a dermoid may be rather diffuse or may encircle the limbus or peripheral cornea. Hairs often protrude from the lesion. The surface may be pearly or clear and glistening, depending on the presence or absence of epithelial keratinization. The most common location is at the inferotemporal limbus, but dermoids can occur anywhere on the surface of the eye. The central cornea can be affected, although some of these lesions are probably the result of dermoid transformation (metaplastic dermoids) rather than being choristomatous malformations.

The second most common site for a dermoid is the superotemporal orbit. Dermoids usually exhibit little or no growth but do enlarge occasionally, especially at the time of puberty (65). They do not become malignant.

A limbal or corneal dermoid can cause decreased visual acuity by covering the visual axis or by causing astigmatism. An arcuate deposition of lipid often develops along the central (corneal) edge of a limbal dermoid and is another possible source of decreased vision. The lipid sometimes increases as long as the dermoid is present (65).

Limbal dermoids always involve some of the corneal stroma and can even extend into the anterior chamber. Any attempt at excision must be limited merely to shaving away the elevated portion of the lesion, unless one is willing to undertake a corneoscleral graft, which would seldom be

indicated. It is important to explain to the parents, or to the patient who is old enough to understand, that the shaving procedure can only eliminate the elevation and that the corneal opacity will remain. The surgery is not without some difficulty and risk. The cornea may be thin in the area of the dermoid, and perforation is possible. I have observed that if the dermoid covers the anterior portion of the sclera, the underlying extraocular muscles and their insertions may be anomalous and may inadvertently be transected if the surgeon is not careful.

Perhaps 30% of patients who have epibulbar dermoids have other abnormalities (65). These most often consist of some or all of the features of *Goldenhar's syndrome* (Goldenhar-Gorlin syndrome, facioauriculovertebral sequence, oculoauriculovertebral dysplasia) (2,16,65,66). Goldenhar's syndrome is the result of maldevelopment of the first and second branchial arches, which give rise to the maxilla, mandible, malar bone, auricle, and structures of the upper neck. The syndrome comprises a triad of findings: epibulbar (usually limbal) dermoid(s), abnormalities of the ear such as auricular appendages or pretragal fistulas, and anomalies of the vertebral column. Other abnormalities that sometimes occur are listed in Table 39-7 (2,16,65,66,68).

The cause of Goldenhar's syndrome is unknown. It is nearly always sporadic and nonhereditary, although familial examples have been reported twice (69,70). Most isolated epibulbar dermoids are also sporadic, but bilateral corneal dermoids can be hereditary, and dermoids that encircle the limbus (ring dermoid syndrome) can be dominantly transmitted (71,72).

Epibulbar dermoids are occasionally associated with systemic disorders other than Goldenhar's syndrome (Table 39-8) (65,67).

TABLE 39-7. ABNORMALITIES ASSOCIATED WITH GOLDENHAR'S SYNDROME^a

Ocular
Coloboma of upper eyelid
Uveal coloboma
Aniridia
Miliary retinal aneurysms
Duane's retraction strabismus syndrome
Lacrimal stenosis
Microphthalmos
Systemic
Mandibular and malar hypoplasia
Hemifacial microsomia
Other facial and oral abnormalities
Cardiac abnormalities
Renal abnormalities
Gastrointestinal abnormalities
Genitourinary abnormalities
Mental retardation

^aIn addition to the basic triad of epibulbar dermoid(s), anomalies of the ear, and anomalies of the vertebral column.

TABLE 39-8. SYSTEMIC MALFORMATION SYNDROMES SOMETIMES ASSOCIATED WITH EPIBULBAR DERMOIDS

Branchial arch syndromes
Goldenhar's syndrome (oculoauriculovertebral dysplasia)
Franceschetti (or Treacher Collins) syndrome (mandibulofacial dysostosis)
Congenital neurocutaneous syndromes
Bloch-Sulzberger syndrome (incontinentia pigmenti)
Encephalocraniocutaneous lipomatosis
Linear sebaceous nevus syndrome
Chromosomal abnormalities
Cri-du-chat syndrome (deletion of short arm of chromosome 5)

Abnormalities of Transparency

In a heterogeneous group of disorders, the clarity of the cornea is disturbed, but the cornea is not grossly malformed. Loss of transparency can be caused by edema, trauma, inflammation, biochemical depositions, or drying, as well as by any of the various mechanisms that have already been discussed. Many of these problems are not truly congenital anomalies and so are mentioned only briefly.

Edema

Birth Trauma

Mild trauma during birth can damage the corneal epithelium. More severe injury, usually from the use of forceps, can produce ruptures in Descemet's membrane and the endothelium. These ruptures tend to be linear and seem to occur more often in the left eye (when related to the use of forceps) because babies most commonly present in the left-occiput-anterior position; in such a case, the tears would run in an inferonasal-superotemporal axis. As healing ensues, a ridge of hypertrophic Descemet's membrane develops along the line of rupture. The edema may or may not clear and can recur later in life.

Primary or Secondary Congenital Glaucoma

Congenital glaucoma of any cause can produce corneal edema. The cornea enlarges, which causes ruptures of Descemet's membrane and endothelium (Haab's striae) and still more edema (14).

Congenital Hereditary Stromal Dystrophy

Congenital hereditary stromal dystrophy (CHSD) is a rare, dominant condition in which the superficial corneal stroma of both eyes has an ill-defined, feathery cloudiness (73). The haze is more prominent centrally and fades peripherally. There is no edema. CHSD is nonprogressive, but the opacity can be sufficiently dense as to cause substantial loss of vision. Searching nystagmus is usually present. The stromal collagen fibers are abnormal in form, size, and distribution.

Keratitis

Rubella

Rarely, rubella produces keratitis in the form of disciform stromal edema. It more often causes a cloudy cornea by virtue of its association with congenital glaucoma.

Syphilis

Luetic interstitial keratitis may occasionally be present at birth, although it characteristically appears during the first or second decade of life, as does the associated deafness.

Miscellaneous Infections

Many other infectious agents, including gonococcus, staphylococcus, and influenza virus (among others), can cause intrauterine keratitis. If the process is active, the presentation is with inflammatory signs in the cornea; if not, leukoma, keratectasia, or congenital anterior staphyloma may be seen.

Depositions

Arcus Juvenilis

Arcus juvenilis, a deposition of lipid in the peripheral cornea (also known as *anterior embryotoxon*), is the same as corneal arcus, except that the congenital variety is more often unilateral and sectoral in its distribution (3,74). The anomaly is of unknown etiology. When truly congenital, it is not related to elevated levels of serum cholesterol. However, the patient with juvenile arcus is often not seen until sometime after infancy, and it is then uncertain whether the finding was present at birth. In such a case, the serum cholesterol level should be checked because it can be elevated (and associated with premature atherosclerosis) in some cases of developmental juvenile arcus. Arcus juvenilis is sometimes found in association with megalocornea, aniridia, blue sclera, or osteogenesis imperfecta; hereditary nephritis and nerve deafness (Alport's syndrome); or corneal inflammation or malformation from any cause.

Other Depositions

Biochemical deposits can appear in the cornea early in life as a manifestation of any of several systemic diseases, but most of these deposits are not clinically apparent at birth. These diseases are listed in Table 39-9.

Neurotrophic Changes and Drying of the Cornea

The cornea may become dry soon after birth because of decreased corneal sensation, as happens with the Riley-Day syndrome (familial dysautonomia) or with isolated congenital dysfunction of the trigeminal nerve. Other causes of drying include congenital deficiency of tears (which may be idiopathic or may occur as another manifestation of the Riley-Day syndrome) and exposure from lagophthalmos.

TABLE 39-9. SYSTEMIC DISEASES THAT CAUSE CORNEAL OPACITIES EARLY IN LIFE^a

Biochemical deposits
Cystinosis
Fabry's disease (angiokeratoma corporis diffusum)
Mucopolysaccharidosis
Mucopolipidosis
Tyrosinemia
Tangier disease (high-density alpha-lipoprotein deficiency)
Familial plasma lecithin-cholesterol acyltransferase deficiency
Refsum's syndrome (hereditary atactica polyneuritic form)
Schnyder's crystalline corneal dystrophy
Nonspecific (usually patchy or spotty) opacities
Trisomy 13
Trisomy 18
Turner's syndrome (ovarian dysgenesis, XO karyotype)
Phenylketonuria
Chédiak-Higashi syndrome
Genodermatoses

^aMost of these opacities are not clinically apparent at birth.

Chromosomal Aberrations

Corneal anomalies are only occasionally caused by chromosomal aberrations, and most patients who have chromosomal disorders do not manifest corneal abnormalities. Nevertheless, some associations between the two groups of problems are known to exist. Patients who have a trisomy 21 (Down) syndrome have an increased incidence of keratoconus (75). The trisomy 18 (Edwards') syndrome is sometimes associated with abnormalities of the anterior cornea, whereas the chromosome 18 deletion syndromes are more likely to affect the posterior cornea.

No particular corneal anomaly constitutes, by itself, a need for chromosomal studies, but karyotyping may be indicated if some of the following features are also present: hypertelorism, epicanthus, pronounced mongoloid or antimongoloid slant of the palpebral fissures, ptosis, strabismus, ocular colobomas, peculiar facies, multiple systemic malformations, and especially, mental retardation.

The relationships between corneal anomalies and chromosomal aberrations are summarized in Table 39-10 (18,76–78).

METABOLIC DISEASES

Several of the inherited metabolic diseases may be associated with ocular manifestations. In this section, we discuss some of anterior segment manifestations of the metabolic diseases.

Carbohydrate

Diabetes

Until recently there was little awareness of corneal changes among diabetic patients. Slightly decreased corneal sensation

has been noted in most diabetic corneas (79,80). This may be related to irregularities in the basal lamina of Schwann cells and axonal degeneration observed in diabetic animals (81). Punctate corneal staining (82) and neurotrophic corneal ulceration (81,83) have also been reported. Poor healing and persistent epithelial defects occur, most commonly after epithelial removal during vitrectomy (84,85). Poor epithelial healing, especially after vitrectomy, may be related to abnormal corneal innervation (82,85). Alternately reduced numbers of hemidesmosomes (86) and decreased penetration of anchoring fibrils into the stroma (87) have been suggested as contributory factors. Sorbitol accumulation from increased aldose reductase activity may play a role in diabetic corneal pathology as well. Studies of animal diabetic models have shown both structural (polymegathism, pleomorphism) and functional (increased permeability, slower recovery from induced edema) changes in the diabetic corneal epithelium and endothelium, although these have not always been borne out by studies on humans (88).

Oral aldose reductase inhibitor appears promising in the treatment of diabetic epithelial keratopathy, as does an inhibitor eye drop (CT-112) (89,90). Subtle irregularities and hypertrophy of diabetic corneal epithelium have been observed with specular microscopy (91). Increased corneal thickness and persistent stromal edema have occasionally been described, although the presence of increased central corneal thickness in these patients has been disputed by other studies (81,84,92). An abnormal diabetic endothelium, characterized by a decreased frequency of hexagonal cells but a normal age-related cell density, may be responsible for these observations (93). Diabetic corneal endothelium is more permeable to fluorescein and takes longer to recover from cataract surgery than nondiabetic endothelium (94,95). Others have been unable to detect any functional endothelial abnormality in the diabetic cornea (96). Interestingly, corneal autofluorescence has been noted to correlate with the presence of diabetic retinopathy (97).

Mucopolysaccharidoses

Mucopolysaccharide storage diseases (Table 39-11) are in-born errors of metabolism characterized by excessive storage of mucopolysaccharides due to deficiencies of lysosomal acid hydrolases, which degrade mucopolysaccharides. The normal cornea contains 4.0% to 4.5% mucopolysaccharides, of which 50% is keratan sulfate, 25% is chondroitin, and 25% is chondroitin 4-sulfate (98). In the mucopolysaccharidoses (MPSs), excess dermatan and keratan sulfate appear in the cornea, and heparan sulfate accumulates in the retina and central nervous system. This results in corneal opacity. The opacities usually appear during the neonatal period or later, reflecting the availability of maternal enzymes *in utero*. In some diseases, the corneal opacities appear within a few weeks to months of birth, raising the differentials of congenital glaucoma and CHED, and also

TABLE 39-10. CHROMOSOMAL ABERRATIONS THAT HAVE BEEN ASSOCIATED WITH CORNEAL ANOMALIES

Chromosomal Aberration	Corneal Anomaly ^a
Partial duplication of short arm of chromosome 2 (dup[2p21-2p25])	Microcornea, corneal opacities, anterior segment dysgenesis
Deletion of short arm of chromosome 4 (Wolf-Hirschhorn syndrome; 4p-)	Corneal opacities, sclerocornea, microcornea, megalocornea
Deletion of short arm of chromosome 5 (cri-du-chat syndrome; cat's cry syndrome; 5p-)	Megalocornea, epibulbar dermoid
Partial trisomy of short arm of chromosome B (trisomy Bp)	Patchy corneal opacities with vascularization
Isochromosome of long arm of chromosome 6	Rieger's syndrome
Pericentric inversion of chromosome 6	Rieger's syndrome
Trisomy of chromosome 8	Corneal opacity
Partial trisomy of long arm of chromosome 10 (trisomy 10q)	Sclerocornea
Ring chromosome D (Dr)	Retrocorneal mass or membrane
Deletion of long arm of chromosome D (Dq-)	Megalocornea
Deletion of short arm of chromosome 11 (Miller's syndrome; aniridia-Wilms' tumor syndrome; 11p-)	Aniridia ^b (with Wilms' tumor)
Deletion of long arm of chromosome 11 (11q-)	Peters' anomaly
Trisomy of chromosome 13 (Patau's or Bartholin-Patau syndrome)	Clinical anophthalmia, cyclopia, corneal dysgenesis, corneal opacities, sclerocornea
Partial trisomy of long arm of chromosome 16 (trisomy 16q)	Rieger's anomaly and glaucoma
Deletion of short arm of chromosome 18 (18p-)	Posterior keratoconus with deep corneal opacity
Deletion of long arm of chromosome 18 (18q-)	Microcornea, corneal opacities, Peters' anomaly, oval cornea, anterior segment "mesodermal" dysgenesis
Ring chromosome 18 (18r)	Corneal leukomas
Trisomy of chromosome 18 (Edwards' syndrome)	Anterior corneal opacities
Deletion of long arm of chromosome G (Gq-) or ring chromosome G (Gr)	Corneal opacities
Ring chromosome 21 (21r)	Peters' anomaly
Trisomy of chromosome 21 (Down's syndrome)	Keratoconus (occurs fairly often)
XO (Turner's syndrome; presence of only a single X1 sex chromosome)	Corneal opacities, microcornea, vertically oval cornea
Various translocations	Corneal opacities, Peters' anomaly, sclerocornea, megalocornea

^aMost of these corneal anomalies have been reported very rarely, often only once or twice.

^bAniridia is not a corneal anomaly but is often associated eventually with the development of extensive opacification and vascularization (pannus) of the superficial cornea.

may be the first manifestation of the disease. Corneal opacities appear earlier in the MPS IH or Hurler's syndrome, Scheie syndrome, with G_{M1} gangliosidosis type I and in the mucopolidosis (where the opacities are mostly peripheral). In other forms of the MPS, the corneal opacities may appear later in life when the diagnosis is already established.

Hurler's Syndrome

Hurler's syndrome (mucopolysaccharidosis IH) or gargoylism is characterized by moderate dwarfism, protuberant abdomen, joint contractures, and mental retardation. A large head, hypertelorism, and thick lips with a large

TABLE 39-11. OCULAR MANIFESTATIONS OF MUCOPOLYSACCHARIDOSES

Mucopolysaccharidosis	Enzyme Deficiency	Corneal Clouding	RPE Degeneration	Optic Atrophy
Hurler (I-H)	α -L-iduronidase	+	+	+
Scheie (I-S)	α -L-iduronidase (partial)	+	+	+
Hurler-Scheie compound (I-H/S)	α -L-iduronidase (partial)	+	+	+
Hunter A (IIA) (severe phenotype)	Iduronate sulfatase	-	+	+
Hunter B (IIB) (mild phenotype)	Iduronate sulfatase	+	+	+
Sanfilippo A (IIIA)	Heparan sulfatase	-	+	+
Sanfilippo B	N-acetyl-a-D-glucosaminidase	-	+	+
Morquio (IV)	N-acetyl-galactosamine sulfatase	+	-	+
Maroteaux-Lamy A (VIA) (severe phenotype)	Arylsulfatase B	+	-	+
Maroteaux-Lamy B (VIB) (mild phenotype)	Arylsulfatase B	+	-	-
Macular corneal dystrophy (Groenouw type II)	?	+	-	-

+, present; -, absent; RPE, retinal pigment epithelium.

(Modified from Kenyon KR. Lysosomal disorders affecting the ocular anterior segment. In: Nicholson DH, ed., *Ocular pathology update*. New York: Masson, 1980.)

tongue and hypertrophic gums are generally seen. The bridge of the nose is depressed, and the chest is usually enlarged with marked flaring of the lower ribs. The hands are broad and the fingers short and stubby. In the extreme cases, clawhand deformity may arise as well as bony changes in the feet. The skin is usually thickened, and there may be nodules over the scapular region. Hirsutism and deafness are often present. Respiratory disease results from deformity of the nasal and facial bones. Heart damage may be due to specific valvular lesions. Coronary artery and myocardial disease also occurs. Neurologic findings are variable, but spasticity and mental retardation have frequently been reported.

Corneal clouding, which occurs within a few days to months of birth, is a prominent feature of the disease (99) and helps to differentiate it from Hunter's syndrome. The opacities are located first in the anterior stroma and consist of fine gray punctate opacities. Later, the posterior stroma and endothelium become involved. Histologically, grossly ballooned macrophages are found in the cornea (100). Glaucoma has also been documented in these patients and is associated with the presence of the mucopolysaccharide-containing cells in the region of the aqueous drainage channels. Pigmentary retinopathy and optic atrophy are also commonly seen (101,102).

Scheie's Syndrome

Scheie's syndrome (mucopolysaccharidosis IS) is a variant of Hurler's syndrome, with the same enzymatic defect, a deficiency of α -L-iduronidase inherited as an autosomal-recessive trait. Increased amounts of dermatan sulfate and heparan sulfate are excreted in the urine (103). Scheie's syndrome does not have the typical features of Hurler's syndrome except for the clawhand deformity and bony changes in the feet. Physical growth is normal, and mental impairment is minimal or absent (104).

The most prominent ocular feature in Scheie's syndrome is a corneal haze that is often present at birth and very slowly progressive. The cornea appears thickened and somewhat edematous. The cloudiness is more marked in the corneal periphery. This is thought to occur because the stromal fibrils show a large range of sizes unlike normal corneal stroma where the sizes of the fibrils are remarkably similar, and by abnormally large stromal collagen. Mucopolysaccharide deposits are found in the keratocytes, and vacuoles or pleomorphic inclusions are found with electron microscopy (105,106,107). Corneal transplantation may be necessary later in life; however, transplants may do poorly (108).

Other ocular findings include pigmentary disease of the retina and optic nerve atrophy. Acute glaucoma has been reported (109), but the cause is unclear. It may be due to a narrow angle or possibly a thickening of the anterior ocular structures caused by abnormal acid mucopolysaccharide

storage. A thickening and decrease in the elasticity of the conjunctiva have also been observed.

Hunter's Syndrome

Hunter's syndrome (mucopolysaccharidosis II) has clinical and biochemical features similar to those of Hurler's syndrome except Hunter's syndrome is less severe. It is inherited as an X-linked recessive trait and is seen more commonly than Hunter's syndrome. There is a failure to degrade dermatan sulfate and heparan sulfate. Lysosomal storage of these polymers leads to numerous clinical problems including skeletal abnormalities, limitation of joint motion, hepatomegaly, deafness, and cardiovascular disease (99,110). The gross facial features are similar to those in Hurler's syndrome. Mental retardation is less severe than in Hurler's syndrome, and lumbar gibbus does not usually occur. Deafness, however, is a common feature of Hunter's syndrome. Patients usually die in their 20s and 30s because of cardiac involvement with congestive heart failure.

Corneal clouding is generally not present in Hunter's syndrome, although exceptions have been recorded (111). Pathologic studies have also demonstrated the accumulation of mucopolysaccharides in the cornea, conjunctiva, and other ocular tissues (113–116). Two forms of Hunter's syndrome are said to exist. In the mild form, corneal opacities occur later in life but are mild and visually insignificant in contrast to those of other mucopolysaccharidoses. In the severe form, subclinical corneal clouding can be demonstrated histochemically. Thus, although the presence of corneal clouding has been used to distinguish Hurler's syndrome from Hunter's syndrome, this distinction is not always a reliable one. Some Hurler's patients have clear corneas up to the age of 14 years (115); other Hunter's patients have clear corneas until late in life. Retinal pigmentary changes and optic atrophy have been noted in Hunter's syndrome, and the sclera and cilia may also be affected (112,114).

Sanfilippo's Syndrome

Sanfilippo's syndrome (mucopolysaccharidosis III) is an autosomal-recessive disease in which patients excrete only heparan sulfate. It is seen less frequently than the Hurler or Hunter variant. It is characterized by severe mental retardation but fewer craniofacial changes than in Hurler's. Dwarfism is not a prominent feature. Joint movements are restricted, and neurologic symptoms including seizures and athetosis are quite prominent. Death usually occurs by age 14. Corneal cloudiness does not occur in Sanfilippo's syndrome. Retinal pigmentary degeneration and optic atrophy have been observed.

Morquio's Syndrome

Morquio's syndrome (mucopolysaccharidosis IV) is inherited as an autosomal-recessive trait and is associated with

the accumulation of keratan sulfate in the tissues. The patients have a dwarf appearance, with knock-knee, barrel chest with pigeon breast, short neck, and osteoporosis. The facial appearance is characteristic, with a broad mouth, short nose, widely spaced teeth with defective enamel, and a prominent maxilla. Hepatosplenomegaly, deafness, and metachromatic granulation of leukocytes has also been noted. Intelligence is normal, but neurologic symptoms may result from deformity of the spine, and cardiac complications may result from malformation of the chest. Corneal clouding may occur but may not be grossly evident until after the age of 10 years. Cloudiness may consist of a mild stromal haze, or it may be severe (116). Retinopathy and optic nerve changes are not present.

Maroteaux-Lamy Syndrome

Maroteaux-Lamy syndrome (mucopolysaccharidosis VI) is an autosomal-recessive disease in which dermatan sulfate accumulates in the tissues. Skeletal changes are a prominent feature of the syndrome. Lumbar kyphosis, protrusion of the sternum, and genu valgum are found. The facial appearance is abnormal, but not as striking as in Hurler's syndrome. Intellectual function is normal. Corneal opacities occur in all patients, but may be subtle, and a slit-lamp examination may be necessary to see them (117). Histology on a penetrating keratoplasty specimen has shown degenerated epithelial cells with apoptotic nuclei. Proteoglycans were present in epithelial cells, intercellular spaces, swollen desmosomes, and throughout the stroma. Keratocytes showed no cell organelles, were vacuolated, and contained a large quantity of abnormal proteoglycans. Hydrocephalus, papilledema, and optic atrophy may also be seen (117). The accumulation of lipid-like material in the stroma in addition to glycosaminoglycans (118,119) suggests a relationship between Maroteaux-Lamy syndrome and the mucopolipidoses.

In one patient, the affected cornea around a penetrating keratoplasty cleared (120,121).

β -Glucuronidase Deficiency

β -glucuronidase deficiency (mucopolysaccharidosis VII) is an autosomal-recessive trait in which dermatan sulfate accumulates in the tissues. Skeletal dysplasia, hepatosplenomegaly, and mental retardation are known to occur, but no ocular complications have been reported.

Glucose 6-Phosphatase Deficiency

Glucose 6-phosphatase deficiency (von Gierke's disease) is an autosomal-recessive glycogen storage disease caused by the deficiency of glucose-6-phosphatase. Like the other glycogen storage diseases, it is characterized by enlargement of the liver and kidneys and bouts of severe hypoglycemia.

Liver tissue is needed for diagnosis. If patients survive the initial hypoglycemia, the prognosis is good. Xanthomas with prominent lipemia are characteristic. Seizures and vomiting also occur. The cornea may show a faint brown peripheral clouding, and discrete yellow perimacular lesions have also been observed. Although no treatment exists for this disease, early diagnosis and recognition have led to an increased life expectancy.

Lipid

Mucopolipidoses

The mucopolipidoses are inherited metabolic diseases characterized by abnormal accumulation of acid mucopolysaccharides, sphingolipids, and glycolipids. Corneal opacities as well as psychomotor retardation and other systemic abnormalities are associated with this group of diseases.

Clinical Features: General

Mucopolipidosis I is recessively inherited, but the specific enzymatic defect is unknown.

In this condition, physical growth is normal in the first years of life but slows after the age of 10. Hepatosplenomegaly and hernias are sometimes seen. Mental development is slow and patients usually have a moderate degree of mental retardation.

Mucopolipidosis II is also recessively inherited with a deficiency of β -galactosidase. The disease is characterized by severe growth and psychomotor retardation, hepatomegaly, gargoyle-like facies, and thickened skin. The disease is also known as I-cell disease because of the cytoplasmic inclusions in fibroblasts and macrophages of affected persons (122).

Mucopolipidosis III, also known as pseudo-Hurler, is a recessively inherited disease with an unknown enzymatic defect. Musculoskeletal abnormalities including small stature, short neck, scoliosis, hip dysplasia, and restricted joint mobility are seen. Moderate mental retardation is present, and gargoyle-like facies sometimes appear. Neither hepatosplenomegaly, severe psychomotor retardation, nor excessive excretion of mucopolysaccharides in the urine occurs in this disorder.

Mucopolipidosis IV is probably a recessive disorder with an unknown enzymatic defect affecting mainly Ashkenazic Jews. It is characterized clinically by corneal clouding and profound psychomotor retardation but no skeletal or facial deformity, organomegaly, gross neurologic abnormalities, or mucopolysacchariduria.

Clinical Features: Ocular

In mucopolipidosis I, corneal opacities are rarely seen, but when they occur, they are associated with a cherry red spot on the macula (123,124). Corneal opacities have been seen in association with spokelike cataracts, tortuous retinal and conjunctival vessels, and strabismus (124). Histologically,

inclusion vacuoles are seen in the conjunctival and corneal epithelium.

Mucopolidosis II may be associated with bilateral corneal haziness, early cortical cataracts, and bilateral prominence of the eyes (123,125,126). Glaucoma, megalocornea, optic atrophy, absent retinal blood vessels, and severe retinal degeneration have also been described (127). Mucopolidosis III can be associated with fine corneal opacities, which are presumably abnormal storage material around stromal keratocytes (128).

Mucopolidosis IV is characterized by severe corneal clouding, ocular pain, and corneal surface irregularities seen at birth or early infancy (129–132). The severe and early corneal involvement distinguishes type IV from the other mucopolidoses. Light microscopy reveals swollen corneal and conjunctival cells containing foamy cytoplasm and vacuolated keratocytes. This material may represent phospholipids (120). Cataract, outer retinal degeneration, and optic atrophy may also be found. A case report described removal of the affected corneal epithelium and conjunctival transplantation from a related donor resulting in corneal clarity in a 28-month-old patient (133).

Fabry's Disease

Fabry's disease is a sphingolipidosis caused by a lack of α -galactosidase, transmitted as an X-linked recessive trait. The hemizygous male is most seriously affected. Female carriers may be asymptomatic or exhibit mild symptoms. High-performance liquid chromatography is a sensitive method for analyzing the urinary sediment for glycolipids and detecting asymptomatic heterozygotes (134). The skin is affected with clusters of punctate lesions that vary from purple to maroon to brownish but have a very characteristic distribution over the genitalia and lumbosacral area. The genitourinary, central nervous, musculoskeletal, and cardiovascular systems may all be involved. Common neurologic changes include hemiplegia, aphasia, cerebellar disorders, and stroke. Pain in the fingers and toes is common.

Ocular

Ocular findings are frequent and quite characteristic. The most typical ocular feature is cornea verticillata, a fine, whorl-like superficial corneal opacity caused by the accumulation of sphingolipids in the corneal epithelium (135–137). This corneal change can be found in both the affected male patient and the female carrier, and resembles the corneal opacities found after administration of chloroquine and amiodarone. Corneal opacities have been seen as early as the age of 6 months.

Other ocular alterations include dilatation and tortuosity of the conjunctival vessels, sometimes associated with aneurysms. Spoke-like posterior sutural cataracts consisting of nine to 12 spokes are seen in 50% of patients. Cream-colored anterior capsular deposits, sometimes in a

propeller distribution, are also noted (138). Periorbital and retinal edema, optic atrophy and papilledema, and dilatation and tortuosity of the retinal vessels may be present.

The visual prognosis in Fabry's disease is excellent, although severe visual loss caused by central retinal artery occlusion has been reported (138). Internuclear ophthalmoplegia may rarely occur (139).

Without treatment, the disease is compatible with long life; deaths related to cardiovascular, renal, and gastrointestinal complications occur in midlife (140). The Food and Drug Administration (FDA) recently approved a drug for Fabry's disease (Fabrazyme) that works to reduce fat buildup in organs of patients with this condition.

Hyperlipoproteinemias

Five types of hyperlipoproteinemias have been distinguished (141). All the hyperlipoproteinemias may be associated with corneal arcus, xanthelasma, conjunctival xanthomas, and lipid keratopathy, except type I hyperlipoproteinemia, which is not usually associated with corneal arcus (142).

Familial Plasma Cholesterol Ester Deficiency

Familial plasma cholesterol ester deficiency [lecithin-cholesterol acyltransferase (LCAT) deficiency] is characterized by a marked reduction of plasma cholesterol esters and lysolecithin, and an increase in the level of unesterified cholesterol, triglycerides, and phospholipids. The deficiency of LCAT prevents the maintenance of a normal balance between cholesterol and cholesterol esters in cell membranes (143). The cornea shows a nebulous cloudiness and a pronounced annular opacity near the limbus. The opacity, found in the stroma, is composed of innumerable tiny dots and resembles a corneal arcus, but the peripheral border is not as sharply demarcated. It is believed that the corneal opacity is due to lipid deposits as a consequence of abnormal plasma lipid and glycoprotein deposition (144). Occasionally, crystals appear near Descemet's membrane peripheral to the opacity.

Tangier Disease

Tangier disease is an autosomal-recessive disease associated with the complete absence of plasma high-density α -lipoproteins. Corneal involvement consists of stromal clouding caused by deposition of cholesterol esters (145) and many small dots in the posterior stroma, sometimes in a whorl-like distribution. A haze in the peripheral horizontal meridian may be seen, but no arcus is present. Sometimes, visual impairment due to corneal clouding may be significant (146).

Histiocytosis X

In histiocytosis X (Hand-Schüller-Christian disease, Letterer-Siwe disease), large xanthomas or xanthelasma may be present

on the lids. Infrequently a peripheral yellow-white infiltration may be present in all layers of the cornea. Similar corneal lesions may rarely be seen in juvenile xanthogranuloma.

Protein

Porphyria

The term *porphyria* embraces a group of diseases characterized by abnormalities in the enzymes involved in the biosynthesis of heme, resulting in the accumulation of one or more intermediate fluorescent pigments, known as porphyrins. Porphyria can be divided into two general groups: *erythropoietic porphyria*, in which excessive quantities of porphyrins accumulate in red blood cells, and *hepatic porphyria*, in which porphyrins accumulate in the liver. The latter may be subdivided into at least four different types: acute intermittent porphyria, porphyria variegata, porphyria cutanea tarda, and hereditary coproporphyria. Although there is some overlap between the erythropoietic and hepatic groups, specific inherited enzymatic defects have been identified in at least three of the porphyrias (erythropoietic uroporphyria, acute intermittent porphyria, and porphyria cutanea tarda). The enzymatic defects are present in many tissues; however, the resulting metabolic derangements are most prominent in either the liver or erythroid tissue.

Clinical Features

None of the erythropoietic porphyrias have ocular manifestations; the eyelids, however, may be involved as part of the involvement of the skin of the face. In erythropoietic uroporphyria, the skin manifestations take the form of blisters occurring on the skin surfaces exposed to light, especially the face and the hands, starting in childhood. With time, scarring and mutilation occur, with loss of fingers and facial tissues. In erythropoietic protoporphyria, there is skin photosensitivity with intense itching, edema, and erythema of the exposed skin. The disease is usually benign, consisting of chronic skin changes on the hands and face. Oral β -carotene provides effective protection against sun sensitivity but the reason for this is not known.

Of the hepatic porphyrias, acute intermittent porphyria is a rare autosomal-dominant disease, which is not usually associated with ocular manifestations, but which presents with gastrointestinal and neuropsychiatric manifestations.

Porphyria variegata is an autosomal-dominant condition characterized by cutaneous lesions and attacks of colic. It is also associated with ocular manifestations and is therefore discussed in greater detail here. Coproporphyrins and protoporphyrins are excreted in the feces in large amounts. The skin is unusually sensitive to light, and it blisters and abrades easily. Jaundice, colic, and psychosis may occur during acute attacks. Between attacks, there may be no symptoms.

Porphyria cutanea tarda is the most common form of porphyria; it is also associated with ocular manifestations. It is an autosomal-dominant disease and is characterized by photosensitive dermatitis, hyperpigmentation of the skin, liver disease, and hypertrichosis. The skin is sensitive to light and trauma, and blisters, ulcers, and scars may occur on areas exposed to light. Porphyria cutanea tarda may remain latent for several years, only to be precipitated by alcoholic cirrhosis or exposure to drugs or toxins.

Hereditary coproporphyria is an autosomal-dominant disease characterized by increased excretion of coproporphyrin in the urine and feces. Acute attacks may be precipitated by ingestion of barbiturates and other drugs. Symptoms consist of psychiatric crises and skin abnormalities.

Ocular

Acute intermittent porphyria has no ocular manifestations. Ocular involvement tends to occur in porphyria variegata and coproporphyria. The ocular findings in coproporphyria are variable and may affect all tissues of the eye. The eyebrows may be thinned or thickened and may meet in the midline (147). Bullous lesions of the eyelids may be followed by pigmentation and scarring. Ocular manifestations are similar to those of ocular pemphigoid, with blisters developing on the exposed area of the conjunctiva, resulting in symblepharon and shrinkage of the conjunctival sac, and possible stenosis of the punctum and canaliculus (148). Lacrimation, photophobia, and blepharospasm are common features (149). The conjunctiva becomes infiltrated by chronic inflammatory cells and forms adhesions to the underlying sclera, typically in the second or third decade of life.

Corneal complications are the result of cicatricial ectropion or vesiculation of the cornea. Vesicles occur in exposed areas of the cornea and heal forming nebulae or leukomas. Occasionally, the vesicles may lead to perforation (149). The cornea may be thin peripherally, contain numerous crystals in Bowman's layer, and have deep stromal lamellar opacification (150). Lesions resembling phlyctenules may precede corneal ulceration. Exposure keratitis and corneal opacification may result from severe ectropion.

Scleromalacia perforans may occur, with punched-out scleral ulcers occurring most commonly temporally (150). These ulcers may sometimes extend over the limbus onto the cornea. Scleritis is sometimes seen, and red fluorescence has been observed in the sclera, vitreous, and retina. The tissue damage that is seen is probably the result of oxidative or fluorochemical reactions.

Ophthalmoscopic changes include brown cotton-wool patches of edema. After 3 weeks, these become dense, black globular patches. Retinal hemorrhages and discrete annular choroidal lesions are sometimes observed (150). Atrophy of the ganglion cell and nerve fiber layer of the retina has also been described (151). Optic atrophy has been reported (152).

Diagnosis

The conjunctival changes of porphyria must be differentiated from those of cicatricial pemphigoid. The scleral and corneal changes must be distinguished from keratomalacia associated with vitamin A deficiency and peripheral corneal degenerations associated with local and systemic immunologic diseases. The retinal and choroidal lesions of porphyria can be confused with various types of uveitis. The systemic features of porphyria, the excretion of porphyrins, and the fluorescence of skin and ocular tissues will help in making a definitive diagnosis.

Treatment

If ultraviolet exposure causes damage, sunlight should be avoided. β -carotene, 30 mg/day orally, may be of value in reducing dermal sensitivity to sunlight. Crystalline retinopathy does not occur after long-term therapy with β -carotene as it does with canthaxanthin (153,154). Splenectomy and phlebotomy to remove the excess iron load from the liver are effective treatments for certain kinds of porphyria. Slow subcutaneous infusion of desferrioxamine may be helpful when phlebotomy is contraindicated. For acute attacks, a liberal intake of glucose orally or intravenously is the most effective treatment. Supportive therapy, including analgesics, fluids, and respiratory support, is also important for acute attacks.

Treatment of ocular lesions begins with proper medical management of systemic porphyria. Protection from the sun and abstention from alcohol seem to be helpful. Corticosteroids have been recommended for the scleritis of porphyria (150), but surgical treatment with scleral grafting may be necessary.

Gout

Gout is an abnormality of uric acid metabolism characterized by hyperuricemia, that results in the deposition of sodium urate crystals in the joints, soft tissues, and urinary tract. Primary gout occurs due to an inborn error of metabolism. Secondary gout occurs when hyperuricemia occurs as a result of some acquired metabolic derangement (and not an inherited metabolic disorder). Myeloproliferative disorders, high purine intake, alcohol consumption, cytotoxic chemotherapy, obesity, and hypertriglyceridemia can lead to hyperuricemia. The prevalence varies from approximately 0.2% in the United States and Western Europe to 10% in the adult male Maori of New Zealand. One third of patients with gout give a positive family history, and at least 50% are regular alcohol drinkers. Over 90% of gout is found among adult men, but 3% to 7% may occur in postmenopausal women. Secondary gout constitutes 5% to 10% of all cases and usually is a complication of myeloproliferative disorders or hypertensive cardiovascular disease.

Uric acid is formed by oxidation of purine bases, which may be of dietary or biosynthetic origin. In most cases with

primary gout, the major cause of the hyperuricemia is the overproduction of uric acid, but there is also increased excretion. Not all cases of hyperuricemia are associated with the clinical syndrome of gout. Idiopathic hyperuricemia is 10 times more common than gout.

Clinical Features

The natural history of gout consists of three phases: asymptomatic hyperuricemia, acute gouty arthritis, and chronic gouty arthritis. Fifty percent of initial acute attacks involve the great toe (podagra), and 90% of gout patients experience podagra during the course of their disease. Attacks may be precipitated by many kinds of stress. Dietary, physical, and emotional factors have been implicated. Chronic gouty arthritis is associated with a progressive inability to dispose of urate and deposition of urate crystals in the cartilage, synovial membranes, tendons, and soft tissues. Tophaceous deposits may produce irregular swelling over the joints or the helix of the ear. Eventually, destruction of the joints ensues. The incidence of permanent joint change is considerably less now that drugs are available to control uric acid levels.

Ocular

Acute ocular inflammation in gout is characterized by a conjunctivitis and episcleritis adjacent to the limbus. There is marked hyperemia and scanty discharge. The conjunctival vessels are dilated and tortuous (155) and the patient experiences a burning, hot, prickly sensation. This has been referred to by Hutchinson (156) as the "hot eye of gout." Conjunctival tophi have also been reported (157). The inflammation is episodic and associated with acute attacks of gouty arthritis. True scleritis may rarely be associated with gout, and urate crystals occasionally are found in the sclera (157). Clinical gout is present in about 2% of patients with scleritis. Acute iritis has also been reported but is extremely rare (155). The cornea may be affected with the uric acid crystals deposited in the interpalpebral limbal area adjacent to the episcleral blood vessels. Pinguecula-like limbal masses of urate have been described and band keratopathy has also been observed with gout (158); it may be impossible to distinguish this condition from calcific band keratopathy by slit-lamp examination. Monosodium urate crystals may be deposited in the superficial stroma and epithelium of both the conjunctiva and the cornea (159). Corneal scraping reveals urates that can be demonstrated by colorimetry and spectrophotometry (158). Urate crystals occur within the nuclei of the corneal epithelial cells (159). The crystals are needle-like and demonstrate negative birefringence.

Diagnosis

Ocular gout should be distinguished from keratitis urica (160), a localized dystrophic disease of the cornea having an uncertain cause but unassociated with gout. Uric acid

levels, a history of typical attacks of gouty arthritis, and the presence of tophi help in making a correct diagnosis. It must be noted, though, that only 2% of cases with scleritis and 7% with episcleritis may have clinical gout. In the absence of hyperuricemia and the characteristic clinical features of gout, corneal urate deposits must be differentiated from the deposits of other metabolic corneal diseases as well as certain drug depositions. Rheumatoid arthritis, acute rheumatic fever, and osteoarthritis may need to be distinguished from gouty arthritis.

Treatment

Treatment of gouty arthritis is aimed at terminating the acute attack and preventing new recurrences, as well as preventing and reversing uric acid deposition in the joints and kidneys. Colchicine, indomethacin, naproxen, and phenylbutazone are effective in treating the acute gouty arthritis attack. Hydrocortisone may be injected intraarticularly for prompt relief of pain. Drugs that lower the serum level of uric acid include probenecid, salicylates, sulfinpyrazone, and allopurinol (161,162). Allopurinol is a potent inhibitor of xanthinoxidase and has been associated with the development of cataracts (163). In some cases, surgical removal of urate deposits may be necessary. Tophaceous deposits can also be surgically removed from the conjunctiva. Superficial keratectomy may be necessary to remove the urate band keratopathy. Purified uricase may supplement the scraping of the superficial deposits.

Cystinosis

Cystinosis (Lignac-Fanconi syndrome) is a rare autosomal-recessive disorder of cystine storage. French Canada has the highest incidence of cystinosis in the world. The lysosomal cystine transport system is thought to be defective (164), and cystine is found in lipid-storing membranes of circulating leukocytes, fibroblasts, and macrophages (165). Cystinosis usually occurs in childhood in association with Fanconi's syndrome, which is a descriptive term for a group of physiologic abnormalities that include proximal renal tubular dysfunction, notably glucosuria; generalized aminoaciduria; phosphaturia; and renal tubular acidosis. Occasionally, ocular and systemic cystine storage occurs in the adult in the absence of renal disease.

Cystinosis results from the intracellular deposition of crystalline cystine in the reticuloendothelial cells of the bone marrow, liver, spleen, lymphatic system, and kidney.

Clinical Features

Three clinical forms of cystinosis are recognized. The infantile form with Fanconi's syndrome is a severe disorder usually leading to death by the age of 10. Severe rickets with stunting of growth and failure to thrive is evident in the first few months of life and the disorder may be associated with secondary hyperparathyroidism and frequent

pyelonephritis with consequent renal failure. An intermediate form presents in early young adulthood with fever and renal problems. The third, adult form, is benign.

Ocular

Ocular manifestations of cystinosis are characterized by the deposition of cystine crystals in the cornea. These crystals, which are glistening, polychromatic, and needle-like to rectangular, are distributed throughout the anterior stroma with a slight predilection for the periphery. Mild photophobia is the most common ocular symptom and patients may also complain of increased glare sensitivity, decreased contact sensitivity, and decreased vision. In infantile cystinosis, the corneal crystals may appear as early as 6 months of age and can cause intense photophobia. In adult cystinosis, they may be the only manifestation of the disease. Crystals may be found throughout the entire thickness of the corneal stroma (166); if they are extensive, visual acuity may be reduced. The corneal thickness is increased, possibly reflecting subclinical corneal edema (167). Corneal sensitivity is decreased (168).

Intracellular crystals have also been demonstrated within cells of the iris, ciliary body, choroid, and retinal pigment epithelium (165–169). Retinopathy associated with extensive degeneration and loss of the pigment epithelium has also been described (170). These peripheral fundus abnormalities may precede the corneal deposits and prove helpful in making an early diagnosis of cystinosis. Crystalline macular changes may occur as a result of cystine crystals in the choroid or pigment epithelium (171). Retinoschisis and retinal detachment have been reported in conjunction with adult cystinosis (172). In the adolescent form of cystinosis, corneal crystals and nephropathy may be present, but retinopathy is absent (173).

Diagnosis

Cystinosis must be differentiated from other types of corneal depositions, including the paraproteinemias. Conjunctival biopsy is a useful technique in which cystine can be extracted and analyzed by column chromatography (174). In addition, the characteristic retinal lesions may be very useful in making a proper diagnosis (175).

Treatment

Dietary restriction is not successful, because cystine is synthesized from the essential amino acid methionine. Renal transplantation has been carried out successfully in a number of patients. Potassium replacement to reverse chronic acidosis and vitamin D therapy to promote normal calcification of bone are important.

The mainstay of therapy, however, is cysteamine administration (176), which may prevent the development of the complications of cystinosis and remove crystals after they have developed (177,178). The major problem with the drug is its taste and odor. The phosphorothioester of cysteamine,

which is tasteless and odorless, is presently being tested (179). Cysteamine eyedrops prevent the deposition of crystals in the cornea. The adult form of the disease is benign and requires no treatment.

Type II Hypertyrosinemia

Type II hypertyrosinemia is caused by a deficit of the enzyme tyrosine aminotransferase. A dendritic lesion may develop in the cornea (180,181), which must be differentiated from a healing wound and herpetic disease. Other ocular changes include conjunctival plaques, strabismus, and cataracts. A chronic keratitis may develop (182). The systemic findings include hyperkeratotic skin lesions and mental retardation (183,184).

Alkaptonuria

This hereditary metabolic disease is caused by an absence of the enzyme homogentisic acid oxidase, which results in an accumulation of homogentisic acid, a normal intermediary in the metabolism of phenylalanine and tyrosine, in the urine and other tissues including the eye. Oxidation of homogentisic acid produces a form of degenerative arthritis and a dark pigmentary change in connective tissues known as ochronosis.

Clinical Features

The first description of alkaptonuria was by Garrod in 1902 (185). The disease occurs in about 1 in 200,000 births. In the infant, darkening of the urine on a wet diaper may be the first sign. Alkaptonuria is a benign disorder until midlife, when degenerative joint changes begin to take place in the majority of patients, primarily in the large joints and the spine. Ochronotic pigmentation of the ear, nose, and sclera is often seen. Internal structures such as the costochondral junctions, joints, and ligaments have also been noted to have ochronotic pigmentation. A diagnosis is usually made on the basis of the triad of arthritis, ochronotic pigmentation, and urine that darkens on the addition of a strong alkali.

Ocular

Ocular pigmentation is found in the interpalpebral sclera at the insertion of the recti muscles (186). In addition, a more diffuse pigmentation may also be found in the conjunctiva and cornea. The pigmentation may be gray to bluish black but microscopically appears ochre. Corneal pigment is located in the deep epithelium and in Bowman's layer. Pigmentation of the tarsal plates and lids may also be seen.

Treatment

Attempts to treat alkaptonuria with vitamin C and cortisone may delay the onset of arthritis (187). Dietary restriction of

phenylalanine and tyrosine is not practical except for brief periods, and there is no conclusive evidence that it is of benefit. Enzyme replacement and gene transfer therapies are also not available at present.

Amyloidosis

Amyloid is an eosinophilic hyaline material that can be deposited in various tissues of the body, including the eye, as part of a localized or systemic disease. There are at least two different types of amyloid. Type A amyloid (also known as AA) is a nonimmunoglobulin protein of unknown origin. Type B amyloid has been shown to be identical to a fragment of the light chain of immunoglobulin. Amyloid deposits are associated with a structural protein known as P or AP (188).

Amyloidosis is sometimes classified as primary or secondary. Either type A or type B amyloid can occur in both forms. Amyloidosis may also be defined as systemic or localized. A third type of amyloid, known as type C, may be seen adjacent to tumors of neuroectodermal origin and in aging.

Several mechanisms may account for the deposition of amyloid in the tissues of the body, including catabolism by macrophages of deposited antigen-antibody complexes, de novo synthesis of whole immunoglobulins or light chains with reduced solubility, genetic deletions in the light-chain gene producing an anomalous protein of reduced solubility, and separate synthesis of discrete regions of the light chain. Other types of amyloid may be formed by complexing precursors of polypeptide hormones. The reason for amyloid deposition is unknown. It may be a disorder of protein metabolism, an abnormality of the reticuloendothelial system, the result of chronic immunologic stimulation, a disorder of delayed hypersensitivity, or a combination of these defects (189).

Clinical Features

Many classifications of amyloidosis exist. The most widely used classification divides amyloidosis into the following: (a) Primary amyloidosis occurs in the absence of a preexisting disease. (b) Secondary amyloidosis usually follows chronic diseases such as neoplasms, infections, and connective tissue disorders. (c) Tumor-forming amyloid is an isolated mass of amyloid that appears in the skin, eye, or urinary tract. (d) Familial types of amyloidosis affect different organ systems and have different patterns of inheritance. The most common is associated with familial Mediterranean fever, seen mostly in Sephardic Jews.

Virtually any organ system can be affected in amyloidosis. Kidney involvement is usually the main cause of death. Renal involvement is the preponderant manifestation in secondary amyloidosis and in approximately half the patients with primary amyloidosis. Cardiac deposition of amyloid may be asymptomatic or lead to congestive

heart failure. Amyloid may be deposited in any portion of the gastrointestinal tract, from the tongue to the anus. Diagnosis can sometimes be made by biopsy of the rectum, conjunctiva, or gingivae. Amyloid infiltration may also be seen in nearly every other tissue of the body. Involvement is often limited to the walls of small blood vessels, and clinical manifestations may be absent.

Ocular

The skin of the eyelid is a frequent site of amyloid deposition. Small papules with a waxy, yellowish appearance are typical. Conjunctival amyloid nodules, although rarely seen, may mimic various forms of conjunctivitis, including trachoma. Occasionally, large tumor-like conjunctival nodules may be seen in the absence of any apparent predisposing condition (190).

Amyloid may be deposited in the cornea as the result of preexisting chronic inflammation (e.g., in interstitial keratitis patients). Amyloid has been demonstrated in the corneal epithelium of a patient with retinopathy of prematurity (191). It has also been detected in the corneas in seven unsuspected cases of amyloidosis showing corneal scarring and opacification (192). Corneal involvement is characterized by the presence of cobblestone masses of yellowish pink material, which stain bright salmon pink with 0.2% Congo red (193). A gelatinous or drop-like change in the cornea has been described in primary corneal amyloidosis, especially in Japan (194–197). Familial amyloidosis of the cornea has also been described (198) and may be associated with cataracts (which do not contain amyloid). Lattice dystrophy of the cornea is considered a localized form of amyloidosis (199,200), but it may be associated with systemic amyloidosis as well, or with the Meretoja syndrome (201). Type A amyloid has been identified in the cornea of a patient with lattice corneal dystrophy (202).

Amyloid may be deposited in the iris secondary to chronic infection (203), or it may be found in the vitreous where it has a characteristic glass-wool appearance. Most patients with vitreous amyloid have familial amyloidosis, although some have no family history of the disease. Vitreous opacities can be unilateral or bilateral. They may be in contact with the posterior lens surface. Pupillary abnormalities are not uncommon in familial amyloidosis. The irides may show segmented paralysis (204), pupillary dissociation (205), inequality (206), or heterochromia (207). Scalloped pupils are a characteristic feature of familial amyloidosis and may be a helpful clue in making a correct diagnosis (207,208). This pupillary abnormality may be due to infiltration of the sphincter of nonadjacent ciliary nerves with amyloid.

Orbital involvement may be seen in amyloidosis and may lead to proptosis (209,210). Lacrimal gland and extraocular muscle involvement has also been described (209).

Histopathology

Homogeneous amyloid consists of characteristic long fibrils, which measure 80 Å. It is not known whether these

fibrils are synthesized as such or whether they are the result of degradation of intact protein molecules. Clinically suspected amyloidosis must be confirmed by biopsy of appropriate tissues. Amyloid stains with hematoxylin and eosin. It is periodic acid-Schiff (PAS)-positive and stains mahogany brown with iodine, changing to blue with the addition of sulfuric acid. Amyloid stains brown with Congo red and exhibits dichroism and birefringence with polarized light. Amyloid fluoresces yellow green with thioflavine T.

Treatment

In amyloidosis associated with plasma cell tumors, treatment is directed at the tumor; however, regression of the amyloid lesions may be slow or imperceptible. Treatment of an infection or an inflammatory process may cause mobilization of systemic amyloid. Colchicine may abort the febrile episodes of familial Mediterranean fever, a disease often accompanied by amyloidosis. This drug can also prevent the development of amyloidosis in mice (211) and may be useful in far-advanced human disease. Various other agents including steroids, ascorbic acid, and immunosuppressive agents have also been tried, but without clear-cut benefit.

The vitreous deposits associated with amyloidosis may be removed by vitrectomy (212); however, redeposition tends to occur. Corneal transplantation may be necessary in advanced lattice corneal dystrophy or for the localized forms of corneal amyloidosis.

Graves' Disease

Among the metabolic disorders that affect the eye, Graves' disease (thyroid exophthalmopathy) is one of the most common and potentially severe. In this disorder, lymphocytes and plasma cells infiltrate the thyroid gland and retro-orbital tissues. This infiltration may lead to mild or severe exophthalmos and corneal exposure.

Graves' disease is an autoimmune condition. Antibodies to thyroid and other tissues are found in virtually all patients with Graves' disease (213). Other immunoglobulin-containing substances have also been identified in the serum of patients with Graves' disease, and there is evidence of cellular immunity to thyroid antigens in patients with Graves' disease and Hashimoto's thyroiditis (214).

Deposition of mucopolysaccharides, fat hypertrophy, and soft tissue edema lead to exophthalmos in Graves' disease. The exophthalmos may occur in the acute stage of the disease, or may occur while the patient is euthyroid.

Clinical Features

The signs and symptoms of Graves' disease are due to the overproduction of thyroid hormone. Tissue metabolism is increased, and the patient experiences restlessness, heat intolerance, weight loss, and palpitations. The skin is warm, moist, and smooth, and sweating is excessive. A diffusely enlarged thyroid gland may be found on physical examination.

A fine tremor, tachycardia, wide pulse pressure, and muscle weakness are also characteristic.

Ocular

Half the patients with hyperthyroidism have no ocular abnormalities. Common findings include widening of the palpebral fissures owing to retraction of the upper eyelid (the cause remains unknown), lid lag on downward gaze, and infrequent blink. About 20% of patients with Graves' disease exhibit proptosis. This is thought to reflect retro-orbital infiltration and soft tissue swelling. If proptosis and lid retraction are severe enough, exposure keratitis may result. The earliest change is punctate staining of the inferior cornea and conjunctiva. This may indicate nocturnal lagophthalmos. More severe exposure will lead to frank epithelial cell loss and sometimes a persistent epithelial defect. If the exposure is not corrected, corneal stromal ulceration and even corneal perforation may result. This may or may not be accompanied by secondary microbial keratitis. Because the progression of events may be rapid, early recognition of exposure keratitis is important.

The most severe complication associated with Graves' ophthalmopathy is irreversible optic nerve damage caused by pressure on the optic nerve or its blood supply resulting from orbital congestion. Milder forms of this syndrome may result in diplopia, papillitis, retrobulbar neuritis, or papilledema.

Treatment

The treatment of hyperthyroidism associated with Graves' disease may involve removal of the thyroid gland, administration of radioactive iodine, or therapy with antithyroid drugs (215).

Mild ophthalmopathy is relatively easy to treat by keeping the cornea well hydrated with lubricants and preventing exposure keratitis. It may be helpful to tape the lids closed at night after lubricants are instilled. Fishing goggles that create a humidity chamber may be useful. More severe cases may require lid surgery. Tarsorrhaphy or surgical procedures designed to decrease upper eyelid retraction, such as recession of the levator and Müller's muscle, may be effective. However, eyelid procedures are undertaken only after the orbital and muscle issues have been addressed, if surgical decompression of the orbits and muscle surgery is needed.

High-dose systemic steroids may in some instances be successful in reducing exophthalmos. Supervoltage orbital radiation may also be used in acute cases of optic nerve compression (216). Surgical decompression of the orbit is highly effective for severe ophthalmopathy.

Minerals

Calcium

Calcium deposition can occur in the cornea under a wide variety of circumstances ranging from local ocular inflammation to widespread systemic metabolic abnormalities. The most frequent pattern of corneal calcification is band

keratopathy. However, diffuse corneal calcification, sometimes accompanied by conjunctival calcification, is known to occur (217).

Band keratopathy begins in the peripheral cornea in the interpalpebral zones. A clear interval is usually present between the band and the limbus. If severe, the deposit may extend across the visual axis. In many cases, the band simply remains in the periphery. Tiny Swiss cheese-like holes are usually present in the deposit. These are thought to be located in areas where corneal nerves penetrate Bowman's layer.

Histologically, the calcium is deposited in and around Bowman's layer. The early histologic change consists of a basophilic stippling of the epithelial basement membrane followed by deposition and fragmentation within Bowman's layer.

When calcific deposits in the cornea impair visual acuity, they can be removed by a variety of methods (218).

Hyperparathyroidism

Corneal calcification has been studied extensively in both primary and secondary hyperparathyroidism (219,220). Calcium, in the form of hydroxyapatite crystals, is found intracellularly in both the conjunctiva and the cornea. In other cases of band keratopathy, calcium spherules and conglomerates are usually found extracellularly. It has been suggested that parathyroid hormone may have an effect on the intracellular deposition of calcium (219,220).

Hypophosphatasia

Hypophosphatasia is a rare familial disease characterized clinically by multiple skeletal abnormalities, pathologic fractures of long bones, malformation of the skull and orbits, early loss of teeth, failure to thrive, and often early death caused by nephrocalcinosis and the other sequelae of hypercalcemia. Band keratopathy and conjunctival calcification have been noted in this syndrome and may be associated with blue sclera, harlequin orbits, pathologic lid retraction, papilledema, and increased intracranial pressure (221,222).

Dietary Causes

Excessive vitamin D intake in a range of 100,000 to 500,000 IU daily may lead to band keratopathy and nephrocalcinosis in a few months to a few years. Excessive ingestion of antacids, a condition known as the milk-alkali syndrome, has been associated with similar changes.

Renal Failure

Patients with renal failure may demonstrate uremia, hypercalcemia, and band keratopathy. In some cases, renal damage may result from high calcium and alkali intake. Red eyes and conjunctival irritation are sometimes associated with renal failure (223,224). The conjunctival injection and granular appearance of the conjunctiva are due to a deposition of microcrystals of calcium phosphate salts in

the conjunctiva and cornea. Over 80% of severely uremic patients will have corneal and conjunctival calcific deposits. Most of these patients are asymptomatic, and chronic hemodialysis does not seem to have any influence on the deposits (225). Typical conjunctival and corneal changes associated with chronic renal failure consist of diffuse opacification of the peripheral limbal area and the interpalpebral zone (226). Such deposits may regress after kidney transplantation.

Neoplastic and Inflammatory Diseases

Diffuse or bandlike calcific changes may be associated with sarcoidosis and with various malignancies with and without bone metastases. Multiple myeloma and Paget's disease of bone may also lead to band keratopathy.

Corneal Scars

Band keratopathy is frequently associated with chronic ocular inflammation such as trachoma and interstitial keratitis (227). The severity of the band reflects the duration of the inflammation.

Iridocyclitis

Band keratopathy is a well-known complication of chronic iridocyclitis, especially cases occurring in children. The exact mechanism of this deposition is unknown. It has been suggested that gaseous exchange at the surface of the exposed cornea with loss of carbon dioxide and a localized elevation of pH may be an important factor (228). Experimental band keratopathy can regularly be induced in rabbits with immunogenic uveitis that have been given systemic calceferol (229). Lid closure may prevent the development of these calcific deposits.

Dry-Eye Syndrome

Rapid development of band keratopathy has been reported in dry-eye patients with corneal inflammation who use artificial tears frequently (230). Whether this corneal change is due to some component of the artificial tears or another mechanism is still unclear.

Mercurial Compounds

Atypical band keratopathy has been reported in glaucoma patients using pilocarpine with the preservative phenylmercuric nitrate (231,232). The reason for this deposition is unclear, and this preservative is no longer used in eye drops.

Copper

Copper deposition in the eye may be the result of metabolic diseases or intraocular foreign bodies composed of copper or copper alloys. Hepatolenticular degeneration or Wilson's disease is a deficiency of the copper-binding serum protein ceruloplasmin. This condition is characterized by deposition of free copper in nearly all the body's tissues,

especially the liver, basal ganglia of the brain, kidney, and cornea. Patients with Wilson's disease have ataxia, hepatosplenomegaly, cirrhosis of the liver, and progressive neurologic impairment. The disease is inherited as an autosomal-recessive trait. Copper excretion is high, but serum copper is low because the copper is deposited in the tissues. The most characteristic ocular feature of Wilson's disease is the Kayser-Fleischer ring in the peripheral cornea. This ring is a deposition of copper 1 to 3 mm wide in the peripheral cornea. It is green, blue, red, yellow, brown, or a mixture of any of these colors. There is no lucid interval unless an anterior embryotoxon is present. The ring is at the level of Descemet's membrane. It may be absent before the age of 10, and it may also disappear on treatment with chelating agents and restricted copper intake. Anterior subcapsular cataracts, sometimes called sunflower cataracts, may be part of the ocular picture of Wilson's disease.

Copper may also be deposited in the cornea in primary biliary cirrhosis, progressive intrahepatic cholestasis of childhood, and chronic active hepatitis (233).

Intraocular foreign bodies of pure copper produce a marked suppurative reaction and loss of the eye. Copper alloys containing less than 85% copper result in less severe reactions (234,235). Intraocular copper produces a blue-green discoloration between the endothelium and Descemet's membrane, especially in the peripheral cornea. The iris, vitreous, and lens may also be affected. If electroretinographic changes develop, the copper foreign body should be removed and medical treatment with a chelating agent instituted. Penicillamine, 250 mg, can be taken orally four times each day for extended periods.

Gold

Intramuscular gold therapy has been used in the treatment of rheumatoid arthritis and other collagen vascular diseases. The exact therapeutic mode of action is uncertain; however, gold may be capable of inhibiting lysosomal hydrolases. With continued therapy, gold is deposited in various tissues including the kidney, liver, spleen, and eye (236).

Two forms of gold deposition have been reported in the cornea. Corneal chrysiasis consists of numerous, minute, yellowish brown to violet, glistening deposits that are distributed irregularly throughout the cornea at various depths (236–238). Sometimes, the deposits are described as dustlike and are gold to purple violet (239). Deposits may be seen in the deep stroma or in the epithelium (240). Occasionally, a vortex distribution can be seen. Most patients receiving an excess of 1,500 mg of gold or 25 mg/wk for 6 months will demonstrate corneal chrysiasis. Other ocular features include deposition of gold in bulbar conjunctiva and anterior lens capsule. Dermatitis and stomatitis are signs of gold toxicity. Ocular chrysiasis does not usually produce any symptoms, and visual acuity is not ordinarily impaired. A second form of

TABLE 39-12. ADDITIONAL METABOLIC DISEASES THAT AFFECT THE CORNEA

Disease	Enzyme Deficiency	Corneal Findings	Other Ocular Findings	Systemic Findings
Alport's syndrome	Unknown	Lenticonus, cataract, retinal flecks	Arcus, posterior polymorphous dystrophy, granular stroma	Nephritis, deafness
Fish eye syndrome	Unknown	Clouding	None	Hyperlipoproteinemia
Goldberg-Cotlier disease	β -Galactosidase	Clouding	Macular cherry red spot	Gargoylism, skeletal abnormalities, mental retardation, seizures, hearing loss
Lowe's syndrome	Unknown	Keloids	Cataract, glaucoma, miotic pupil	Mental retardation, aminoaciduria
Norrie's disease	Unknown	Band keratopathy	Cataract, retroental membrane, microphthalmos, retinal folds	Hearing loss, mental retardation
Phenylketonuria	Hepatic phenylalanine hydroxylase	Opacities	Strabismus, cataract, albinoid fundus	Seizures, mental retardation, melanin abnormality, gait alteration, microcephaly
Riley-Day syndrome	Dopamine- β -hydroxylase	Anesthesia, epithelial erosion	Dry eye	Familial dysautonomia

ocular disease caused by gold is a possibly allergic response consisting of marginal ulceration and keratitis (240). Painful, white, crescent-shaped ulcers bordering the limbus are seen. Distinct, flat, white, superficial opacities have also been noted.

Corneal gold deposition is not necessarily an indication for discontinuing gold therapy. Deposits tend to resolve when gold treatment is stopped, and penicillamine appears to be effective for the toxic reactions.

Silver

Silver deposition in the cornea, conjunctiva, and lens has been observed during the use of topical silver preparations, such as mild silver protein (Argyrol), and after industrial exposure to organic silver salts. Argyrosis is rare today, although a number of cases have been reported (241–244).

The conjunctiva develops a slate-gray appearance. The nasal portion where the tear pool accumulates may be nearly black. The cornea may contain fine, blue-gray, green, or gold deposits. These are found in the deep stroma and in Descemet's membrane, especially inferiorly. Electron microscopic examination has shown that minute silver deposits are located intracellularly in the connective tissue of the conjunctiva and extracellularly in Descemet's membrane (243). Ocular argyrosis produces only cosmetic changes; it does not impair vision. The skin and the eyelids may develop a slate-gray hue. Argyrosis of the nasolacrimal sac has been reported (244), and iridescent cataracts have been described as well. Severe silver nitrate injury to the cornea has been reported after use of the concentrated applicator sticks (242). Obviously, these applicators should not be used around the eye.

Rare Metabolic Disorders

Parathyroid and thyroid tumors as well as those in the pancreas and adrenal cortex can be associated with the multiple endocrine neoplasia (MEN) syndrome. MEN type I consists of an aggregation of tumors of parathyroid, pancreatic, and pituitary glands. MEN type II consists of medullary carcinomas of the thyroid and pheochromocytoma. Type III includes type II tumors plus mucosal neuromas, intestinal ganglioneuromatosis, marfanoid habitus, thickened eyelids, subconjunctival neuromas, and prominent corneal nerves (245). Refsum's disease, a rare metabolic disorder, can also be associated with prominent corneal nerves.

Corneal abnormalities may be found in several other rare metabolic disorders. For the sake of completeness, some of these are listed in Table 39-12.

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