Corneal Opacification in Infancy

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Corneal opacification in the newborn and in infancy is often not sufficiently recognized, and its importance in the diagnosis of a more complicated systemic disease can easily be overlooked.

A quick search in the standard textbooks for this specific topic is often unrewarding because only a few textbooks would devote more than a few paragraphs on the subject (23).

The purpose of this paper is to present a systematic classification of the more important conditions that can manifest as corneal opacification in early infancy and to state its differential diagnostic significance.

CAUSES OF CORNEAL OPACIFICATION IN INFANCY:

I. Congenital Malformations

1. *Anterior chamber cleavage syndromes*
   a. *Congenital central anterior synechiae*
   b. *Rieger's syndrome*
   c. *Axenfeld's syndrome*
   d. *Peters' anomaly*
   e. *Congenital anterior staphyloma*
2. *Sclerocornea*
3. *Congenital glaucoma*
4. *Dermoid tumors*

II. Birth Trauma

III. Corneal Dystrophy

Congenital hereditary corneal dystrophy

IV. Inflammatory Processes

1. *Interstitial keratitis*
2. *Herpes simplex*
3. *Riley-Day syndrome*
4. *Rubella syndrome*

V. Inborn Errors of Metabolism

1. *Mucopolysaccharidoses*
   a. *Hurler's (type I)*
   b. *Scheie's (type V)*
   c. *Maroteaux-Lamy (type VI)*
2. *Lowe's syndrome*

VI. Chromosomal Aberrations

1. *Mongolism (Down's syndrome)*
2. *Trisomy 13–15 (Patau's syndrome)*

I. Congenital Malformations.

1. *Anterior chamber cleavage syndrome:* In his second Edwin B. Dunphy lecture, Reese made a plea toward simplification in the nomenclature of a group of various clinical syndromes, congenital in nature, characterized by varying degrees of iridocorneal adhesions, iris and iridocorneal angle changes, and marked prominence of the Schwalbe's line (posterior embryotoxon) with or without accompanying corneal opacities and glaucoma. He suggested calling these groups the anterior chamber cleavage syndrome, believing that these various syndromes represent varying degrees of involvement due to a "faulty cleavage" of the anterior chamber during its developmental stage.

   a. *Congenital central anterior synechiae:* Reese and Ellsworth (27) consider this condition the most severe form of anterior chamber cleavage abnormality. This is clinically characterized by central corneal opacification, with or without edema, occurring at the site of the adhesions of the iris to the posterior surface of the cornea. The iris adhesion may be focal or circumferential involving the iris collarette or, less commonly,

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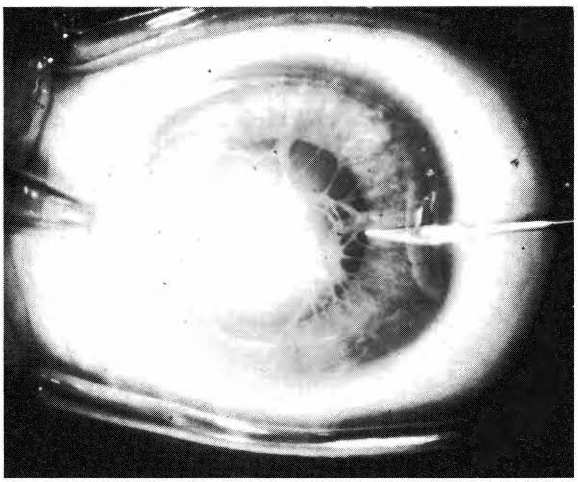

Fig. 1—Congenital central anterior synechiae showing dense central corneal opacification with central synechiae bridging from the iris collarette. (Courtesy of M. M. Parks, M.D.)

points peripheral to the collarette (fig. 1). The cornea may have a ground glass appearance in the early stages due to edema caused by defects in Descemet's membrane formed by the iris adhesions. If there is no accompanying glaucoma or if the glaucoma is controlled, the defect in Descemet's membrane is sealed, and the cornea clears somewhat, leaving a well demarcated scar. Thus, clinically some patients will show progression of the opacification and in some, clearing of the opacification.

Glaucoma was present in 70% of Reese and Ellsworth's cases. Although most of their cases had narrow angles accompanying the forward displacement of the iris due to the adhesions to the cornea, the glaucoma was probably related to the cleavage defects in the angle rather than the narrow angles (27, 3, 20). The condition is bilateral in 80% of the cases (27), and the involvement is usually symmetrical in the two eyes.

Therapy depends on the extent of the anomaly. Glaucoma control, if present, and improvement of visual acuity are the goals of therapy in such cases.

b. *Rieger's syndrome:* This syndrome was first described and termed dysgenesis mesodermalis corneae et irides (28). Some authors consider this syndrome different from the anterior chamber cleavage syndrome of Reese and Ellsworth on the basis that central corneal opacities are not common in Rieger's syndrome. It is probably transmitted as an autosomal dominant gene with high penetrance. Primary ocular findings consist of hypoplasia of the anterior leaf of the iris, iridocorneal angle adhesions, and posterior embryotoxon. The first feature mentioned above is considered by many investigators as the sine qua non of the syndrome. Associated abnormalities include high degrees of myopia, hyperopia, and astigmatism. Strabismus may be present with exotropia occurring more often than esotropia (13, 1, 15, 31).

c. *Axenfeld's syndrome:* This syndrome was first described by Axenfeld in 1920 (2), as consisting of a prominent, thickened, and centrally displaced Schwalbe's line. He termed this specific feature posterior embryotoxon. Currently, most authors describe Axenfeld's syndrome as a milder form of Rieger's syndrome with only posterior embryotoxon and iridocorneal angle adhesions (fig. 2b), with or without glaucoma (5) (fig. 2a).

d. *Peters' anomaly:* As described by Peters in 1906, this syndrome consists of a well defined defect of the deepest stromal layer of the cornea and Descemet's membrane and a

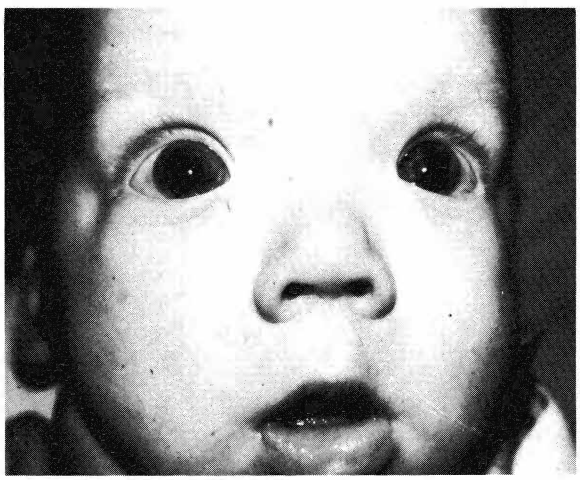

Fig. 2a—Child with Axenfeld's syndrome showing the external appearance of the iridocorneal angle adhesions. (Courtesy of M. M. Parks, M.D.)

Fig. 2b—Gonioscopic view of the angle in Axenfeld's syndrome showing the adhesions. (Courtesy of M. M. Parks, M.D.)

central corneal opacity occurring with or without adhesions or remnants of adhesions to the iris (fig. 3).

Although this syndrome is considered by most investigators as belonging to anterior chamber cleavage syndrome (13), recent studies question this. Brown and Nakanishi (22) published a report on the electron-microscopic study of a patient with Peters' anomaly. They described the finding of Bowman's membrane defect in addition to the defect in Descemet's membrane, thus favoring Alkemeade's (1) suggestion that Peters' anomaly is not strictly a part of an anterior chamber cleavage defect because the portion of the cornea involved does not normally develop during the formation of the anterior chamber embryologically. Of the reported cases, 80% are bilateral. The occurrence of glaucoma is frequently encountered. Less frequently associated abnormalities include anterior polar cataract and other forms of congenital cataract, microphthalmos, and sclerocornea.

e. *Congenital anterior staphyloma:* This condition is characterized by a conical protrusion of a diffusely scarred, usually opacified cornea, lined by iris internally (fig. 4). Most authors consider this a part of the anterior chamber cleavage syndrome, although others have ascribed this condition to intrauterine inflammation. This condition can be bilateral or unilateral. The cornea of the affected eye is usually severely damaged with the iris adherent to the cornea. The lens is usually cataractous and the ciliary body is atrophic.

2. *Sclerocornea:* This condition is defined as a congenital anomaly in which the cornea assumes an opaque appearance approaching that of the sclera. Sclerocornea commonly occurs in conjunction with cornea plana, although it can occur as an isolated congenital anomaly as described by Rollet in 1933 (30). The scleralization may involve the whole or part of the cornea (fig. 5). It can occur in either eye or both eyes. Generally, the cornea is vascularized but can be differentiated from interstitial keratitis by the absence of inflammation and the conspicuous presence of arcades of superficial scleral vessels that extend into the opacified area. Associated ocular findings include nystagmus, strabis-

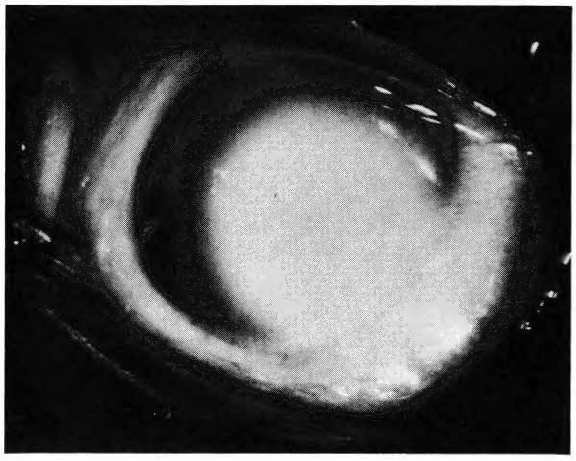

Fig. 3—Peters' anomaly with dense central opacification.

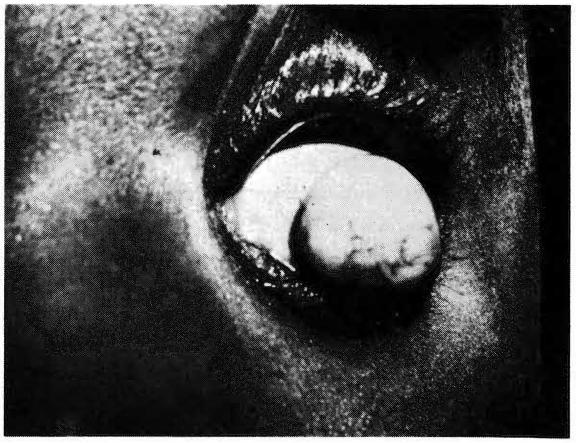

Fig. 4—Severe form of congenital anterior staphyloma.

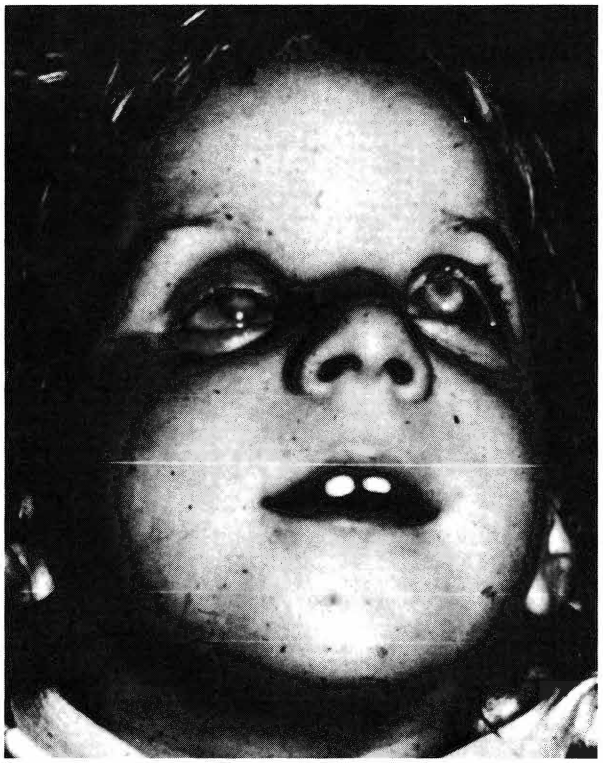

Fig. 5—Bilateral partial scleralization of the cornea in a young male.

mus, glaucoma, microphthalmos and microcornea, embryotoxon, cornea plana, and aniridia. Associated systemic manifestations include malformation of the skin, face, and ears; mental retardation and cerebellar dysfunction; cryptochidism, and brachycephaly (10).

Treatment varies depending on the degree of corneal scleralization and the associated abnormalities. Paufique (24) reported treatment with keratoplasty in 1952.

3. *Primary congenital glaucoma:* Primary congenital glaucoma is the most common hereditary glaucoma of childhood. The disease is diagnosed in over 60% of cases within the first six months of life and in over 80% of cases within the first year (15). There is a small difference in sex incidence with the males predominating in 65% of cases. Unilateral involvement is seen in 25–30% of the cases (31). The anomaly of congenital glaucoma is inherited as an autosomal recessive gene with approximately 80% penetrance (31). Although most cases show this mode of inheritance, clinically in a significant number of cases, the condition does exhibit a sporadic character (31).

Photophobia is probably the earliest symptom in infantile glaucoma. This is due to irritation of the corneal nerve endings from stretching of the cornea due to the increased intraocular tension. Blepharospasm and epiphora are also early signs and symptoms of the condition and should arouse the suspicion of pediatricians and ophthalmologists seeing the patient for the first time. Unfortunately, these findings are occasionally dismissed as physiologic for the age of the patients, passed unnoticed, or mistaken for a less serious condition such as a blocked naso-lacrimal system, especially in the absence of moderately advanced changes such as corneal edema and corneal enlargement. In blocked tear ducts, the nostril in the same side is usually dry unless there is coincidental rhinitis. The finding of epiphora with nasal discharge on the same side should make the physician look closer at the eyes.

More often, when these patients are first seen, definite pressure related changes are already present including ground glass looking cornea (fig. 6a), buphthalmos (fig. 6b), tears in Descemet's membrane, and deep anterior chamber. Cupping of the disc, which is now recognized as an early sign of the condition, has been shown to be reversible to a certain degree with the control of the intraocular tension (31). Late changes include bullous keratopathy of the cornea, optic atrophy, and even phthisis bulbi.

Seemingly unrelated organ system anomalies are also relatively common. Pyloric stenosis, deafness, mental deficiency, and cardiac anomalies have been described (31). Congenital cataract can be found occasionally.

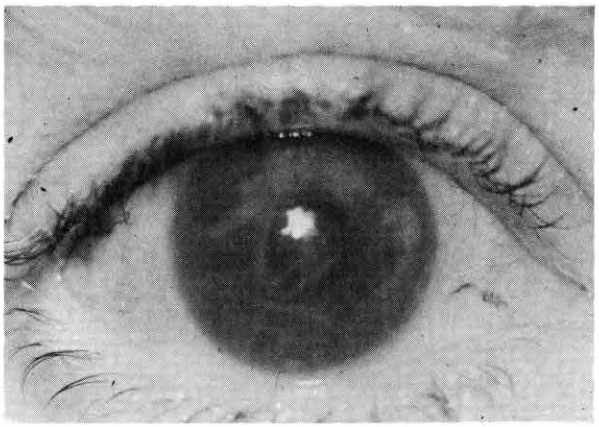

Fig. 6a—Photograph of an eye with congenital glaucoma showing the ground glass appearance and several breaks in Descemet's membrane.

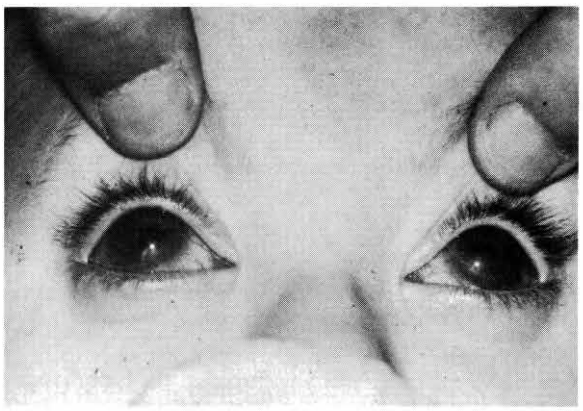

Fig. 6b—Buphthalmos in a case of congenital glaucoma.

The importance of early diagnosis and prompt therapy, either medical or surgical, cannot be overemphasized. A variety of surgical procedures have been used to control the intraocular tension in these patients. Of these, the procedure of choice at the present time is goniotomy. This procedure is aimed at opening the superficial layer of the trabecular meshwork to allow better aqueous drainage into Schlemm's canal. The exact mechanism of its pressure lowering effect is still unsettled.

Of the newer procedures, the external trabeculotomy [Harms and Dannheim. Epicritical Consideration of 300 Cases of Trabeculotomy of Externo; quoted by Shaffer and Weiss (31)] and the external trabeculectomy (16) hold promise in the treatment of this condition, especially in cases where dense opacities of cornea precluding anterior chamber visualization are present. However, long-term results from both procedures are still forthcoming.

4. *Dermoid tumors:* Dermoid tumors can either be cystic or solid. They are congenital misplacements and represent inclusions of epidermal and associated connective tissues during the closure of the fetal clefts. When occurring in the cornea (fig. 7), they may be composed of fibrofatty masses with projecting hairs (12). They are also most commonly located in the inferotemporal quadrant when occurring in the cornea. When involvement of the cornea is severe, they can easily be mistaken for sclerocornea and microcornea. When coincidental ear abnormalities are noted, search for associated vertebral column and other abnormalities should be made because of the possibility of Goldenhar syndrome (9). Excision is generally the rule in the management of this condition.

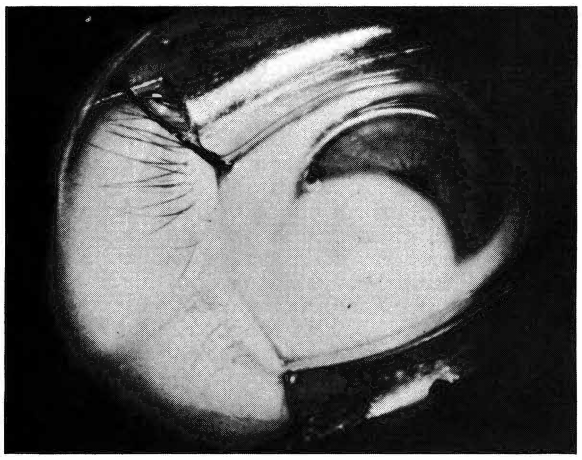

Fig. 7—Dermoid tumor occurring in the cornea and the sclera.

II. Birth Trauma. A few ocular abnormalities at birth have been ascribed to birth trauma (7), and corneal injury is one of them. These injuries commonly result from compression of the globe between the roof and superior margin of the orbit and poorly applied forceps. Cases of corneal injuries occurring in non-forceps delivery have also been described. Lloyd reported that this condition is more common in the left eye. This occurrence has been explained on the basis of the relative frequency of left occiput anterior (LOA) presentation at delivery (7).

Clinically, these patients may present with varying degrees of corneal injury. Transient diffuse corneal opacity can occur due to edema from the direct trauma. Permanent diffuse corneal opacity can occur due to secondary inflammation in the anterior chamber with keratic precipitate formation. Permanent opacity due to rupture of Descemet's membrane and overlying cornea may exist. Cyst formation and formation of glassy membranes in the anterior chamber have also been reported. The appearance of Descemet's tears is also characteristic of corneal injuries. These tears are usually parallel to one another in a vertical or oblique direction; whereas, tears that occur in congenital glaucoma are usually horizontal in direction.

The usual sequelae of these injuries are amblyopia, ,strabismus, myopia, astigmatism, endothelial dystrophy, and bullous keratopathy.

III. Corneal Dystrophy.

Congenital hereditary corneal dystrophy. This condition was originally described by Laurence in

1863 as corneitis interstitialis in utero. However, its true clinical character was determined by Franceschetti and Babel in 1945 as bilateral, symmetrical corneal dystrophy present at birth. Maumenee speculated that the possible mechanism for abnormal corneal hydration in these patients could be either an abnormal embryonic development of the corneal stroma itself, or a congenital form of endothelial dystrophy. More recently, Kenyon, *et al.* (14) performed electronmicroscopic studies on a patient with congenital hereditary dystrophy. They speculated that the disease starts as a primary degeneration of the corneal endothelium as early as the fifth month of gestation, later progressing peripherally. The clinically apparent clouding of the cornea is due to diffuse stromal and epithelial edema occurring secondarily.

Clinically, patients present with a diffusely cloudy, ground glass appearing cornea at birth or soon after. The cloudiness is usually denser in the axial region and in the superficial layers of the stroma. Epithelial edema may be present in some cases, but epithelial bullae are rarely seen. Vascularization usually does not occur. These patients rarely exhibit photophobia or any evidence of inflammation in the eye. Pearce (25) reported the occurrence of congenital nystagmus in patients with this condition. Penetrating keratoplasty has been tried in cases with some success (fig. 8).

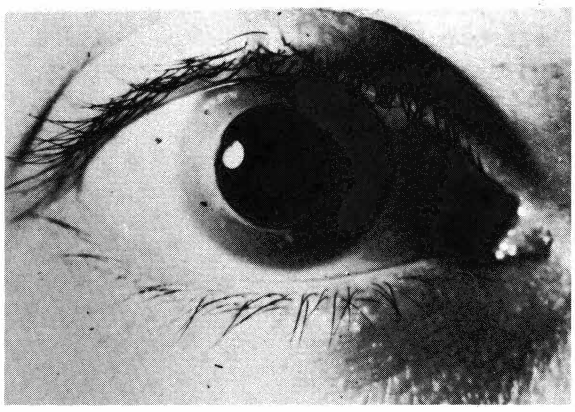

Fig. 8—Congenital hereditary corneal dystrophy successfully treated with a penetrating corneal graft showing contrast between clear donor cornea and cloudy recipient cornea. (Courtesy of D. S. Friendly, M.D.)

IV. Inflammatory Processes.

1. *Interstitial keratitis:* Interstitial keratitis in itself is nonspecific and denotes an inflammation of the deeper portion of the cornea. It is caused by a multitude of etiologic agents including Treponema pallidum, M. tuberculosis, and M. Leprae. Syphilitic interstitial keratitis is usually not present at birth and may develop during the early adolescent period. The latter two can occur early in life but are relatively rare. The condition is almost always bilateral with the second eye manifesting the same process within a month or two of the onset.

Clinically, the condition usually starts as a uveitis and keratitis with early development of endothelial bedewing and keratitic precipitates. Then the stroma develops edema which is later followed by vascularization. At this point, the cornea has a ground glass appearance. The cornea gradually clears, especially with treatment, but leaves residual signs like ill defined areas of deep corneal haze, mostly axial, and attenuated vessels in the deep layers of the stroma later turning into "ghost vessels." These ghost vessels are blood vessels devoid of blood and are best seen during slit lamp examination.

Treatment consists of topical steroids, mydriatics, and specific therapy of the underlying infectious process.

2. *Herpes simplex:* Herpes simplex is the most common cause of keratitis in children. The infection can occur very early, even shortly after birth. The incidence and severity of this condition appears to be increasing, especially with the increasing use of local and systemic steroids.

The infection may involve mainly the epithelium or the stroma of the cornea. In both forms, the cornea may have a hazy appearance because of inflammatory infiltration and edema when severe. Epithelial forms such as discrete dentritic ulcers or diffuse epithelial lesions may be seen. Stromal lesions can have a disciform pattern and may occur with or without epithelial ulcers. The onset is usually acute with pain and intense photophobia. Decrease in corneal sensation is a common finding. Anterior uveitis is a frequent complication.

The current treatment of choice is either epithelial debridement or IDU (Idoxuridine) in epithelial lesions and IDU combined with cautious use of topical steroids in stromal forms. Cycloplegics are used to provide comfort to the patient.

3. *Riley-Day syndrome:* This syndrome was first described by Riley and co-workers in 1949 (29). It is a central autonomic nervous system dysfunction that occurs predominantly in children of Jewish parentage.

The patients may present in early infancy with retarded development and weight gain, difficulty in swallowing, and frequent bouts of respiratory infection with an exaggerated febrile response. The child shows marked indifference to pain, poor motor coordination, postural hypertension, cold hands and feet, emotional instability, dysarthria, and profuse sweating.

Most of the ocular problems of these children result from reduced or absent tear formation during crying, in spite of the presence of normal lacrimal glands, and from corneal anesthesia due to absence of corneal nerves.

Clinically, the corneal involvement may occur in varying degrees of severity (17) and can appear as a severe central corneal ulceration resembling neuroparalytic keratitis. Keratomalacia in a mild form may resemble exposure keratitis in its location and appearance, and a faint scarring resembling etched glass in the lower cornea may be present.

Dunnington, in 1954 (6), described three cases of familial dysautonomia, one of which was brought to the physician because of corneal haziness noted by the parents. Early diagnosis of the condition is important since it will allow for early treatment and prevention of the many complications.

Diagnosis is based upon the findings of the absence of tear formation, corneal anesthesia, exodeviation, miosis induced by 2.5% metacholine, elevated ratio of urinary homovanillic acid to vanillyl mandelic acid, absence of intradermal histamine flare, myopia, anisometropia, ptosis, and anisocoria.

Treatment consists of parenteral antibiotics and supportive measures systemically, and artificial tears and bland ophthalmic ointments to prevent drying of the cornea. Topical antibiotics and tarsorrhaphy may be indicated in some cases.

4. *Rubella syndrome:* Gregg (11) first emphasized the relation between maternal rubella and multiple infantile anomalies. The syndrome results from maternal infection with rubella during the early part of pregnancy. The rubella virus can be cultured from the infant for many months from the time of birth.

Early corneal opacification can occur as a result of the glaucoma, breaks in the Descemet's membrane with edema probably due to previous episodes of acute elevations of intraocular tension, and transient edema probably due to accompanying intraocular inflammation. Sometimes only a transient corneal haze is noted.

Systemic abnormalities include malformation of the heart, hearing defects, mental retardation, and dental defects.

Affected children may present with one or more of the following ocular findings: cataracts (bilateral in 75%), glaucoma, peripheral "salt and pepper" retinopathy, central retinal pigmentation, subnormal ERG, hypoplasia of iris with small pupils, vitreous haze, nystagmus, microphthalmos, and waxy atrophy of the optic disc.

V. Inborn Errors of Metabolism.

1. *Mucopolysaccharidoses:* This is a group of inherited metabolic disorders of mucopolysaccharide metabolism resulting in deposition of the substance in various parts of the body. Of the six syndromes already described in the literature, only three are associated with early corneal opacification.

Recent biochemical studies on these groups of conditions have revealed enzyme deficiencies. Some authors [O'Brien. San Filippo Syndrome: Profound Deficiency of Alpha Acetyl Glucosaminidase Activity in Organs and Skin Fibroblast from Type B Patients. (In Press) and Matalon and Dorfman] have actually pinpointed the actual enzyme responsible in some of these diseases, thus opening the horizon for more extensive clinical studies.

a. *Hurler's syndrome (type I):* This syndrome is transmitted as an autosomal recessive gene. Besides early corneal clouding, ocular changes include pigmentary retinal degeneration with an abnormal ERG. Histopathologically, the corneal clouding is explained by the presence of corneal corpuscles in the stromal connective tissue distended with the acid mucopolysaccharide. The corneal corpuscles are also surrounded by a thick rim of electron opaque homogenous material which permeates Bowman's membrane.

Other clinical findings include gargoyle physical characteristics, mental retardation, parchment-like skin, deformities of the fingers, hepatosplenomegaly, frequent upper respiratory tract infections, and cardiac decompensation leading to congestive heart failure.

Laboratory tests reveal increased urinary excretion of chondroitin sulfate B and heparitin sulfate.

Treatment of this condition with plasma infusion has been reported by some authors with limited success (4).

TABLE 1.

DIFFERENTIAL CHARACTERISTICS OF SYSTEMIC MUCOPOLYSACCHARIDOSES

Syndrome	Type	Transmission	Cornea	ERG	Substance increased in urine	Other Findings
Hurler's	I	autosomal recessive	early clouding	affected	chondroitin sulfate B heparitin sulfate	skeletal deformities, hepatosplenomegaly, infantilism, mental deficiency
Hunter's	II	sex-linked recessive	not cloudy	affected	chondroitin sulfate B heparitin sulfate	dwarfism, hepatosplenomegaly, deafness, mental deficiency
San Fillipo's	III	autosomal recessive	not cloudy	affected	heparitin sulfate	mental deficiency, seizures, mild gargoyle features
Morquio's	IV	autosomal recessive	grossly cloudy by age 10	not affected	kerato sulfate	dwarfism, skeletal deformities, decreased muscle tone
Scheie's	V	autosomal recessive	early clouding	affected	chondroitin sulfate B	aortic valvular disease, thickened joints
Maroteaux-Lamy's	VI	autosomal recessive	early clouding	not affected	chondroitin sulfate B	normal cardiovascular status usually

b. *Scheie's syndrome (type V):* This syndrome is also transmitted as an autosomal recessive gene. This condition is considered by most authors as a forme fruste of Hurler's syndrome, and signs and symptoms of the latter can show up at eight or nine years of age. Clinically, the cornea exhibits early progressive corneal haze which may or may not be present at birth.

Intellectual development is usually normal or above normal. Cardial abnormalities and pigmentary retinal degeneration may also be present. The urine shows increased levels of chondroitin sulfate B.

c. *Maroteaux-Lamy's syndrome (type VI):* This syndrome is transmitted as an autosomal recessive gene. There is early diffuse corneal clouding. Systemically, they can manifest severe osseous abnormalities and hepatosplenomegaly usually without cardiac abnormalities. These children are usually of normal intelligence.

Laboratory tests show increased urinary chondroitin sulfate B excretion.

2. *Lowe's syndrome:* This syndrome was first described by Lowe and co-workers in 1952 (18). The disease is probably transmitted as a sex-linked recessive gene since all the cases reported thus far have been in boys. The essential enzyme or protein abnormalities are unknown.

Systemic abnormalities include vitamin D resistance rickets, aminoaciduria, proteinuria; mental, psychomotor, and growth retardation; cryptorchism; and musculoskeletal abnormalities including hypotonia and hyporeflexia.

Besides corneal opacities, ocular changes consist of nystagmus, glaucoma, malformation of anterior chamber angle and iris, and cataracts.

VI. Chromosomal Aberrations.

1. *Mongolism (Down's syndrome):* This condition is due to trisomy of the 21 chromosome, although involvement of the 22 chromosome has been claimed by other authors. This disease probably results from maternal primary nondisjunction related to age dependent factors. Corneal changes include hypertelorism, oblique eyelid fissures, epicanthus, blepharitis, ectropion, nystagmus, convergent strabismus, high myopia, hyperopia,

color blindness, Brushfield's spots, blepharoconjunctivitis, and cataracts. Other ocular findings are keratoconus, acute corneal hydrops, corneal edema, corneal ectasia, and corneal leukoma. The systemic findings in this condition are well known and will not be discussed here.

2. *Trisomy 13–15 (Patau's syndrome):* As the name denotes, this syndrome occurs as a result of trisomy of any of the 13–15 chromosomes.

Ocular changes are best seen histologically. There is usually disorganization of the globe. The anterior chamber and iris are usually not well defined, and retinal dysplasia is a frequent finding. Microphthalmus and atrophy of the optic nerve and ganglion cell layer of the retina are common findings. Intraocular cartilage has been reported in half of the cases studied. Uveal colobomas are also frequent.

The importance of this condition to our discussion lies in the fact that the cornea (fig. 9c) may appear poorly defined and may resemble the sclera or it may be opaque as part of the microphthalmia and poorly developed eyes.

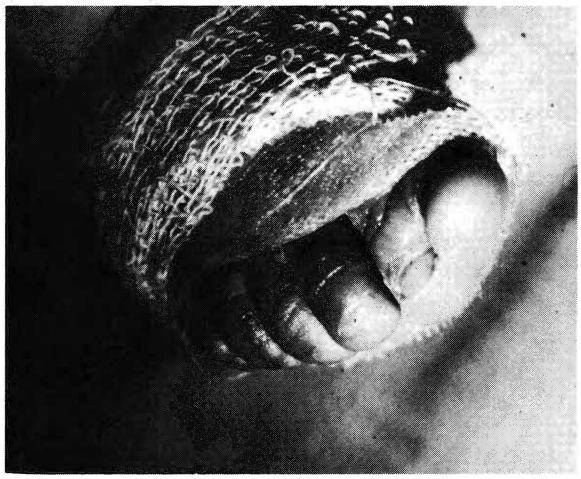

Fig. 9b—Polydactyly in trisomy 13–15.

Systemic abnormalities (figs. 9a and 9b) include harelip, cleft palate, polydactyly, umbilical hernia, and malformation of the heart and central nervous system. Children affected seldom survive for more than a few weeks.

Conclusion. There are many conditions that can present with corneal opacification in infancy. Some are vision-threatening conditions that require early diagnosis and prompt treatment; others, although not posing any immediate deleterious effect on vision, may serve as important differential diag-

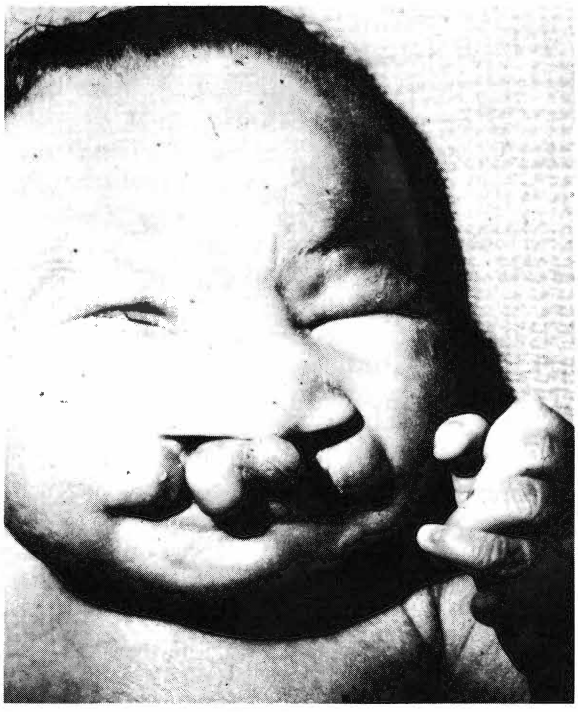

Fig. 9a—External features of trisomy 13–15. (Courtesy of D. S. Friendly, M.D.)

Fig. 9c—Photograph of a trisomy 13–15 patient showing microphthalmos and a poorly differentiated partially opaque cornea.

nostic points in the diagnosis of more serious systemic diseases.

Undoubtedly, the list presented can be expanded to include other conditions. Only the more important and relatively common conditions were included.

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