Ocular Colobomata

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Abstract. Ocular colobomata present diagnostic and therapeutic challenges in patients of all ages, but especially in young children. The “typical” coloboma, caused by defective closure of the fetal fissure, is located in the inferonasal quadrant, and it may affect any part of the globe traversed by the fissure from the iris to the optic nerve. Ocular colobomata are often associated with microphthalmia, and they may be idiopathic or associated with various syndromes. Types and severity of complications vary depending on the location and size of the coloboma. This article reviews the pathogeneses, categorization, genetic bases, differential diagnoses and management of ocular coloboma. (Surv Ophthalmol 45:175–194, 2000. © 2000 Elsevier Science Inc. All rights reserved.)

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Ocular colobomata are caused by defective embryogenesis. All layers of the eye can be involved, including the cornea,53,102 iris, zonule and ciliary body, choroid, retina, and optic nerve. Eyelid “coloboma” has been described.85,157,168 Colobomata can be “typical” or “atypical,” and complete or incomplete; affected eyes are frequently microphthalmic. The etiologies of colobomata are varied, and visual prognosis is related to location and associated features.

I. Definition and Pathogenesis

Coloboma (plural: colobomata) is derived from the Greek koloboma,56 meaning mutilated or curtailed. The malformation refers to a notch, gap, hole, or fissure in any of the ocular structures.151,157 As used in this review, the term applies primarily to embryologic defects, although it is occasionally used to describe acquired iris abnormalities.

The earliest report of uveal coloboma was written in 1673 by Thomas Bartholin (Bartholin the younger), a Danish anatomist, who described hereditary iris coloboma.12,14 Coloboma is frequently associated with microphthalmia. In a prospective study of more than 50,000 pregnancies in the United States,192 the incidence of anophthalmia or microphthalmia or both was found to be 0.22 per 1,000 births, and the incidence of coloboma was 0.26 per 1,000. Incidence rates found in an epidemiological study of congenital eye malformations in 131,760 consecutive births were 1.8 per 10,000 for microphthalmia, 0.3 per 10,000 for anophthalmia, and 0.7 per 10,000 for coloboma.232,260 The prevalence of coloboma among blind adults has been calculated at 0.6–1.9%,146 among children, it accounts for a greater proportion of blindness (3.2–11.2%).83,86 Differences in prevalence may reflect the race or population studied; the highest prevalence (11.2%) was found in visually-impaired Japanese school children.86
Colobomata generally result from a failure of the fetal or choroidal fissure to close\textsuperscript{61,123,171,199} during the 5th to 7th week of fetal life, at the 7–14 mm stage.\textsuperscript{61,123,151,248,283} This is the period between the invagination of the optic vesicle and the closure of the fetal fissure. Almost any ocular structure may be involved, including the cornea\textsuperscript{35,102} iris, ciliary body,\textsuperscript{189} zonule (lens),\textsuperscript{3,11} choroid, retina, optic disk, and/or optic nerve. Although formation of the eyelids is induced by the developing globe, there is no clear evidence that the presence of eyelid coloboma is secondary to globe abnormalities.\textsuperscript{85,157,168} A rare case of coloboma involving the inferior rectus muscle has been reported.\textsuperscript{17} Orbital involvement may occur with cyst formation and/or reduced orbital volume because of a microphthalmic eye. The mechanism of cyst formation is poorly understood, but some authors have speculated that it results from prolapse of intraocular contents through a scleral defect (microphthalmia with cyst).\textsuperscript{6,154,148,266} A more plausible explanation is that microphthalmia with cyst represents ectasia of the colobomatous globe.\textsuperscript{9}

The eye develops from three embryonic layers: neural ectoderm, neural crest, and surface ectoderm, with minor contribution from the mesoderm, which gives rise to striated extraocular muscles and vascular endothelia.\textsuperscript{183} The neural ectoderm gives rise to the optic vesicle and optic cup. It contributes cells for the formation of the retinal pigment epithelium, the iris sphincter and dilator muscles, the posterior iris neuro-epithelium, the pigmented and nonpigmented ciliary epithelium, and the optic nerve fibers and glia. The lens, the corneal epithelium, the lacrimal gland, the surface epidermis of the lids, and the epithelium of the adnexal glands and conjunctiva all arise from the surface ectoderm. The cranial neural crest is the origin of the corneal keratocytes; the endothelium of the cornea and trabecular meshwork; the iris and choroidal stroma, including pigmented and nonpigmented ciliary epithelium, and the ciliary smooth muscle; the fibroblasts of the sclera; and the optic nerve meninges.\textsuperscript{179} Orbital fibroadipose tissues, the satellite cells of the extraocular muscles, the orbital nerves and their associated Schwann cells, the trigeminal ganglion, and the orbital cartilage and bone also originate from the neural crest.\textsuperscript{183}

Ocular development begins at the cranial end in a thickened zone in the differentiating central nervous system, which forms the neural folds of the early embryo. Optic pits appear about 21 days after conception as two depressions on the surface of the neural fold, one on each side of the neural groove.\textsuperscript{149,183} It has been suggested that, during development, the eye begins as a median structure, but it is notable that the optic pits are symmetrical and paired right from the outset.\textsuperscript{149} These optic pits give rise to the two optic grooves (sulci), which, by the beginning of the fourth week, are recognizable in the neural folds located on each side of, and parallel to, the neural groove at the cranial end of the embryo. As these folds close, neural ectoderm evaginates from each groove toward the surface. The resulting spherical projections from the sides of the forebrain are recognizable by the 25th day of development as the optic vesicles,\textsuperscript{183} thought to be induced by the adjacent mesenchyme.\textsuperscript{171} Each vesicle is connected to the forebrain by an optic stalk, the canal for the future optic nerve and the hyaloid vessels. Cells of the optic stalk eventually form the neuroglial supporting tissue of the actual optic nerve fibers, which are axons of the developing retinal ganglion cells, the nerve sheaths and septa being derived from the surrounding mesoderm. At the same stage, the surface ectoderm overlying each vesicle thickens to form a lens plate (placode). Under the sustaining influence of the adjacent optic vesicle, this structure subsequently invaginates to form a lens pit.\textsuperscript{81,109} The fusion of the edges of the lens pit gives rise to the lens vesicle.

The optic vesicle then invaginates—the original outer wall approaching the inner wall—giving rise to a double-layered optic cup. The lens vesicle, which by the fourth week or 9-mm stage has been “pinched off” the surface ectoderm, comes to lie within the optic cup (Fig.1). The simultaneous linear invagination of the ventral surface of the optic stalk and vesicle results in the formation of the fetal or choroidal fissure. Blood vessels from vascular mesoderm grow into the mesenchyme of the choroidal fissure. These are the hyaloid vessels of the vitreous cavity, and their proximal portions are destined to become the central retinal artery and vein. The margins of the optic cup then grow around the choroidal fissure. As invagination progresses, the fetal fissure narrows and closes during the fifth or sixth week. Although closure of the fetal fissure commences during the fifth week, it may not be complete until after the sixth week (17-mm stage).\textsuperscript{183} A permanent opening left at the anterior end of the optic stalk permits passage of the hyaloid vessels.

Failure of a portion of the fetal fissure to close results in the defect we recognize as an ocular coloboma; disk coloboma results from nonclosure of the most anterior portion of the optic stalk.\textsuperscript{10,244,246} Efforts to understand the pathogenesis of aberrant closure have included the use of animal models. In rabbits, prospective colobomatous embryos showed failure of the optic fissure to fuse,\textsuperscript{253} as well as deformities in the shape of the entire cup. Disturbed growth ratios of the outer and inner layers of the optic cup occurred, with the outer layer lagging behind. As a result, the presumptive retinal tissue be-
came everted around the margin of the fissure, partially duplicating the retina in the outer layer of the cup. In the experimental cinnamon mouse, homozygous for the microphthalmia gene, abnormal growth and invagination led to delayed apposition of fissure margins; a failure of basement membrane disintegration at the margins of the fissure was visible by electron microscopy. It was suggested that phagocytic cells may be fewer in number or may lack sufficient enzymes for breaking down basement membrane. In any case, the combination of delayed apposition and failure of basement membrane disintegration is thought to give rise to coloboma formation.

The eyelids develop from surface mesoderm as mesoblastic folds, which first appear at 4–5 weeks and extend from above and below to meet at the palpebral fissure. Fusion begins in the inner canthus region at the 32-mm stage, extends laterally, and is complete at the 37–45 mm stage. Structures of the lid margin (Meibomian glands, glands of Moll and Zeiss, cilia, muscle fibers, and tarsal plates) differentiate while the lids are fused. Epithelial adhesion of the lids begins to break down by the end of the fifth month. Failure of adhesion of the lid folds or localized breakdown of the adhesion caused by maternal virus infection during pregnancy may result in coloboma. It has been suggested that symmetric temporal lower eyelid coloboma may result from a deficiency in migration or excessive death of neural crest cells. Eyelid coloboma may be vascular in some cases.

Coloboma of the eyelids can be partial or full thickness, presenting as a quadrilateral or triangular gap, broadest at the lid margin; W-shaped and irregular defects are also possible. They may range in size from minute, scalloped notches to absence of most of the lid. Lid coloboma may involve the orbital margin with localized absence of the eyebrow; an anomalous wedge of scalp hair has been described extending down the forehead toward the coloboma. Lacrimal drainage anomalies may be associated.

II. Clinical Features and Complications

A. TYPICAL/ATYPICAL

The “typical” coloboma is in the inferonasal quadrant, caused by defective closure of the fetal fissure. It is so named because it is the most frequent. It may affect any part of the globe traversed by the fissure from the iris to the optic nerve. Although iris coloboma may be an isolated phenomenon, it is frequently associated with coloboma of the ciliary body, zonule, choroid, retina, and optic nerve.

Coloboma located anywhere other than the inferonasal quadrant of the globe is termed “atypical” (Fig. 2); the embryologic basis of this malformation is still unclear, although several theories have been suggested. It may represent a “rotation” of the fetal fissure or a result of an intrauterine inflammatory process. Atypical ciliary body coloboma may be caused by persistence of mesodermal tissue from the
embryonic vascular system.\textsuperscript{165} This tissue may block the forward growth of the neuroectoderm, producing a defect in the ciliary body and iris.\textsuperscript{165} Other ocular defects, such as Peters anomaly, Rieger anomaly/syndrome, and aniridia may be associated.\textsuperscript{91,158,160,261}

Optic nerve pits may be caused by a fetal fissure malformation.\textsuperscript{157,236} These crater-like holes or indentations in the surface of the optic disk occur most frequently in the temporal aspect of the disk and, at least, in dogs, are more commonly seen in left eyes.\textsuperscript{20} In a series reported in humans, 57\% of optic pits occurred in the left eye and 43\% in the right.\textsuperscript{137,236} The reported incidence is approximately 1:10,000, with no gender predilection.\textsuperscript{236} Whether or not optic pits are colobomatous in origin is controversial. Many authors regard them as incomplete or partial colobomata of the optic nerve head, perhaps atypical, because of their frequent association with other colobomata and with inferior optic nerve crescents.\textsuperscript{36,100,137}

The pathogenesis of optic pits may involve the faulty closure of an aberrant fetal fissure, although this has been a subject of debate. They are usually asymptomatic, but they may be associated with central serous retinopathy or exudative retinal detachment.\textsuperscript{20,136,236,239} It has been postulated that a communication between the vitreous and/or retina and the subretinal space may develop through the pit in such cases.

Histologically, optic nerve pits are herniations of dysplastic retina into a collagen-lined pocket, which often extends posteriorly into the subarachnoid space through a defect in the lamina cribrosa.\textsuperscript{23,163} These herniations are frequently associated with aberrant nerve fibers and pigmented cells, which resemble pigment epithelium, together with glial tissue and some branches of retinal or cilioretinal blood vessels.\textsuperscript{236} Edema and cystoid degeneration of the outer plexiform layer have also been described in the macula.\textsuperscript{77}

In dogs, the collective term dysplasia has been applied to abnormal development of ocular embryonal tissue.\textsuperscript{20} The phenotypic manifestation includes optic nerve pits and typical colobomata, as well as the pathological occurrence of pigmented cells within the optic nerve and a variety of meningeal and neural tissue anomalies.\textsuperscript{20,236,271}

B. COMPLETE/INCOMPLETE

A complete iris coloboma is a full thickness defect, involving both the pigment epithelium and the iris stroma.\textsuperscript{184} It may be total, extending to the iris root and giving rise to the “keyhole pupil” (Fig.3), or partial, involving only the pupillary margin and causing a slightly oval pupil. Small strands of mesodermal tissue are occasionally seen bridging the coloboma and forming multiple pupils, or polycoria. Such strands may extend to the lens as a persistent pupillary membrane.\textsuperscript{151}

An incomplete iris coloboma is usually partial thickness, involving either the pigment epithelium or the iris stroma.\textsuperscript{123} It tends to be wedge-shaped and is best demonstrated by iris transillumination. Heterochromia iridis and colobomata have occurred simultaneously;\textsuperscript{58} however, whether heterochromia represents a mild form of incomplete iris coloboma is speculative.\textsuperscript{184,260}

C. LENS “COLOBOMA”

At the 26-mm stage of embryological development, the secondary vitreous begins to form around the primary vitreous, arising either from the terminal fibers of Mueller cells or, possibly, from the lens.\textsuperscript{60,150,282} Organization of mesodermal tissue in the paralenticular area results in the appearance of a specialized region of the anterior secondary vitreous.
called the marginal bundle of Druault, or *faisceau isthmique*. The tertiary vitreous, or zonules, develop within this structure at 3 to 4 months’ gestation (Fig. 4). However, there is no general agreement about whether the zonules result from local condensation and differentiation of the vitreous substance or, alternatively, are “induced” by the lens and proceed across the marginal bundle.114,150,183

Segmentally defective or absent development of the zonules results in a “coloboma” of the lens secondary to flattening of the equator in the region of the zonular defect.3,15,64,114 The absence of zonular fibers releases tension on the lens capsule, causing the lens to contract segmentally with a notch in the affected region. Occasionally, normal lenses in young people can be seen to have indentations at the equator between zonular insertions.69,123,162,284 The term *lens coloboma* is, thus, a misnomer because there is no actual loss of lens substance. There were no associated abnormalities in the filtration angle, iris, or uveal tract in the series reported by Hovland and colleagues.114 On the other hand, a ciliary body coloboma is often seen in the area where the zonules are defective. Lens coloboma is, therefore, more accurately referred to as *coloboma of the zonule and/or ciliary body*.3,15

D. POSTERIOR SEGMENT COLOBOMA

In contrast to iris malformations, posterior segment colobomata are more closely related to visual prognosis. The inner layers of the fetal fissure, comprising progenitor neuroretinal cells, are approximated at its margins, normally closing during the 5th or 6th week of gestation. The neuroretinal cells then completely cover the inside of the globe. Failure of simultaneous fusion of the outer layers—the future retinal pigment epithelium (RPE)—leads to coloboma involving both the RPE and the neurosensory retina. The choroid also fails to differentiate in areas in which the RPE is absent, although the cause and the effect of the associated choroidal involvement are uncertain.107,151 The defect represents an area of bare sclera devoid of overlying normally differentiated retina or choroid. However, undifferentiated retinal remnants may persist as a membrane, sometimes with associated retinal vessels. The sclera in the affected area may bulge posteriorly, forming a staphyloma which may involve the entire posterior pole.11,126

The term *choroidal coloboma* is synonymous with *retinochoroidal coloboma*.258 Coloboma of the choroid is infrequent, occurring in only 0.14% in one large hospital series.126 Histological findings include absence of the RPE.9,258 The overlying retina is hypoplastic and gliotic, and sometimes has rosettes. Where retinal tissue is recognizable, the retinal layers are reversed, with the rods and cones facing inward and the nerve fiber layer adjacent to the sclera.9 Underlying choroid is either hypoplastic or absent altogether. On the other hand, the RPE at the edge of the defect is hyperplastic. The thin sclera may have cystic spaces filled with glial proliferation, sometimes exuberant enough to resemble a neoplasm.61,210,285

Fig. 4. Normal development of the zonule.
Retinochoroidal colobomata can occur as multiples, with intervening areas of normal retina (Fig. 5). Clinically, they may be identified by parents or primary care physicians because of leukocoria. They usually appear glistening white with definable borders, frequently with irregular clumps of pigment along the rim. The white reflex is caused by absence of the choroid; the underlying sclera is visible because of the atrophic or absent retina and RPE. A retinochoroidal coloboma is often discovered on examination that has been undertaken because of a more obvious iris defect; in some cases, however, the iris is not involved. Rarely, it presents in adulthood with visual loss related to retinal detachment.

A typical coloboma is located in the inferonasal quadrant and may extend to include part or all of the optic disk (see section I.E). Clinically, chorioretinal coloboma may be totally asymptomatic, may present early in life as leukocoria, or may be diagnosed later in life because of loss of visual acuity or visual field.

Macular colobomata can be isolated. By definition, such defects are atypical and unrelated to choroidal fissure closure. Macular colobomata are usually bilateral, symmetrical, circumscribed and excavated defects that involve both the choroid and retina. They have been classified into three main types: pigmented macular coloboma, nonpigmented macular coloboma, and macular coloboma associated with abnormal vessels. Differentiation of isolated macular colobomata from inflammatory lesions, such as toxoplasmosis, and from Leber’s congenital amaurosis can be difficult. A unilateral macular “scar,” with or without pigmentation, in the absence of a positive family history or parental consanguinity, may be consistent with healed toxoplasma choroiditis or healed chorioretinitis secondary to *Toxocara canis* or *Toxocara cati*. Specific serum antibody titers would be confirmatory. Retinal findings in Leber’s congenital amaurosis vary from normal appearance to severe pigmentary retinopathy. Evidence of a widespread photoreceptor disorder is provided by an absent or markedly diminished electroretinogram (ERG).

The visual prognosis depends primarily on the involvement of the optic nerve, macula, and papilomacular bundle. If these structures are seriously compromised, severe visual loss is inevitable. Bilateral cases may present in infancy with poor visual function and nystagmus. Unilateral cases may develop a sensory strabismus, perhaps with superimposed “organic amblyopia.” If the macula is spared and the optic nerve and papilomacular bundle are not severely involved, typical choroidal colobomata may remain asymptomatic.

Retinochoroidal colobomata induce absolute scotomata if they are severe. Macular colobomata are associated with loss of central vision. Useful peripheral vision may be preserved if the lesion is small.

**E. OPTIC NERVE**

Retinochoroidal colobomata can involve both the macula and the optic nerve to varying degrees. Isolated optic disk colobomata present as enlarged, white, sharply delineated, bowl-shaped excavations of the disk, 2–8 diopters in depth. Usually, a rim of neural tissue is preserved superiorly (Fig. 6). Optic disk involvement has been classified into six types, increasing in severity from a normal disk outside the chorioretinal coloboma as the mildest form to a nonidentifiable disk shape with blood vessels emerging from the superior border of a large chorioretinal coloboma. This classification is helpful for predicting the degree of visual impairment in optic disk colobomata, particularly in infants and young children whose visual acuity can be difficult to measure. Although the visual prognosis depends on the severity of optic nerve involvement, some eyes with apparently extensive optic nerve damage maintain surprisingly good vision.

Of special importance is the association of disk malformations, especially the morning glory disk anomaly, and congenital forebrain anomalies. Basal encephaloceles, or herniations of brain tissue, can present as pulsating exophthalmos or as a mass in the medial portion of the upper lid with or without hypertelorism. Biopsy of such masses should be avoided. Other craniofacial associations include cleft lip and palate, agenesis of the corpus colosum, defects in the sella turcica, and endocrine dysfunction.
F. THE MORNING GLORY DISK ANOMALY

Morning glory syndrome was first described in 1970 in ten unrelated children with an unusual congenital disk anomaly. The morning glory anomaly appears as a large, excavated, funnel-shaped disk with a prominent elevated rim or ring of peripapillary tissue sometimes associated with peripapillary pigmentary mottling (Fig. 7). The emerging vessels characteristically form a radiating pattern as they fan out from the disk, giving the appearance of a flower—hence, the name morning glory. As originally described, the condition occurred unilaterally and was associated with either strabismus or poor visual acuity in the affected eye. However, it may be bilateral, and it is not always associated with markedly diminished vision. The precise nature of this developmental anomaly is still debated. While several authors presume that a different embryologic fault is involved, the morning glory anomaly is considered by others to be a type of optic disk coloboma, and optic pits are thought to be caused by anomalous closure of the fetal fissure involving the disk.

Of interest are rare case reports of morning glory syndrome with spontaneous contractile movements of a choroidal neovascular membrane, which change the configuration of the optic disk. The clinical significance of this phenomenon is unclear. The movements have been ascribed to an anomalous communication between the subretinal and subarachnoid spaces, allowing fluid flux between the two compartments to cause variable retinal elevation within the excavated part of the lesion.

G. MICROPHTHALMIA/ANOPHTHALMIA AND CYST

The term microphthalmia (or microphthalmos) describes a congenital ocular malformation in which the volume of the globe is smaller than normal. It has been defined as an eye with an axial length at least 2 standard deviations below the mean for that age group. Simple microphthalmia refers to a globe that is small but otherwise normal, whereas in complex or complicated microphthalmia there are other associated abnormalities, including retinochoroidal coloboma. Axial length at birth has been estimated to be 18 mm, and tables of “normal values” exist for both axial length and corneal diameters, although accuracy of these figures remains a subject of debate. High resolution ultrasonography, computerized tomography, and magnetic resonance imaging as means of measurement should prove helpful in defining normal values.

The microphthalmic eye has an axial length less than 19.2 mm at 1 year of age and less than 20.9 mm in adulthood. These compare with average adult inner sagittal diameter of 22.12 mm and outer sagittal diameter of 24.15 mm. The term clinical anophthalmia (or anophthalmos) is generally applied to extreme microphthalmia in which ocular structures are identifiable only histopathologically.

The normal development of the lens depends upon apposition between the surface ectoderm and the optic vesicle, following resorption of the intervening mesenchyme. In the absence of this apposition, residual mesenchyme proliferates, with eventual resorption of the developing globe, causing anophthalmia. If the lens has reached a critical size, it is retained within the optic cup and the eye becomes microphthalmic. Studies of the homozygous microphthalmic (mi/mi) mouse have shown that the cause of microphthalmia was failure of secondary vit-
reous to develop. Although this sequence has been observed primarily in animal models, it is possible that similar events occur in the human.

Microcornea frequently occurs in association with microphthalmia. The natural history of the growth of the cornea in microphthalmia is not known, but it may be similar to that in the normal eye. At birth, the normal cornea has an average horizontal diameter of 9.8 mm, and it attains its average adult dimension of 11.8 mm by the age of 2 years.

The horizontal and vertical corneal diameters may be different in microphthalmia, resulting in an oval-shaped cornea.

Animal studies and pedigree analyses of human families support the concept that retinochoroidal coloboma and orbital cyst are the result of the same mechanism. Both are considered parts of the clinical spectrum, which includes anophthalmia and microphthalmia. The embryologic relationship between coloboma and microphthalmia is such that causes of coloboma can also result in microphthalmia; however, the reverse is not true. Clinical anophthalmia is uncommon and total anophthalmia, with no evidence of ocular tissue on histological study, is extremely rare.

Orbital cysts present in a variety of forms. A posterior cyst may cause proptosis of the microphthalmic eye and orbital contents, and an anterior cyst may be visible as a bluish bulge in the lower lid adjacent to the microphthalmic eye. Cysts may be attached to the optic nerve posterior to a normal globe. Histologic examination of orbital cysts reveals an outer layer of sclera and an inner layer of variably differentiated retina, with or without retinal folds. A thin-walled cyst may be devoid of discernible differentiated ocular structures.

H. COMPLICATIONS

Retinal detachment and cataract are the most common complications associated with retinochoroidal coloboma. Rhegmatogenous retinal detachments have been reported in 4–40% of cases, usually because of breaks within or adjacent to the coloboma. Occasionally, breaks are remote from the coloboma. Of all cases of retinal detachment, 0.6–1.7% are associated with retinochoroidal coloboma. While some detachments may be congenital, resulting from incomplete attachment at the margins of the colobomatous defect, acquired retinal detachment is more common. One factor contributing to such detachments may be absence of the normal RPE pump. Additionally, colobomatous eyes are frequently myopic and have vitreous syneresis, which increases vitreous traction. Histologic sections indicate that a central break in the inner layer of the retina and a break in the outer layer at the margin of the coloboma are both necessary to produce rhegmatogenous detachment. Retinal vascular ischemia or scleral stretching could explain the break in the inner layer. The outer layer break is thought to be secondary either to vitreous traction at the margin of the coloboma or to extension of an initially isolated detachment to the margin of the coloboma, where there is less glial support.

Hovland and associates reported eight cases of bilateral, congenital retinal detachments in association with nasal “coloboma of the lens.” The detachments were caused by giant retinal tears ranging in size from 90–360°. Other retinal holes also were located posterior to the giant tears in four eyes. Such tears most commonly involved the nasal quadrants and were related to abnormal formation of the zonules, with adherence between the peripheral retina and the lens. The authors postulated that failure of the normal recession of the marginal bundle of Drault, together with persistence of the tunica vasculosa lentis and associated mesoderm, could have caused such adherence and prevented the normal apposition of the inner sensory and outer pigment epithelial layers of the optic cup. Retinal detachment may accompany even subtle defects in the lens/zonule/ciliary body complex, because fluid can gain access to the subretinal space through a break in the nonpigmented epithelium of the ciliary body. Excavated defects of the optic disk, including congenital pits, optic nerve coloboma, and the morning glory syndrome, have all been associated with retinal detachment.

Nonrhegmatogenous retinal detachment occurs, usually after infancy, in two-thirds of individuals with autosomal dominant, isolated optic nerve coloboma. Savell and Cook found this condition to be heterogeneous, the incidence of nonrhegmatogenous retinal detachment varying with the type of optic nerve coloboma. Counseling of such patients should therefore be guarded. The incidence of retinal detachment in nonhereditary cases of optic nerve coloboma is unknown.

Eyes with optic nerve pits are especially at risk of retinal detachment. In such cases, a hole has been identified in tissue within the optic cup, which presumably provides an anomalous fluid communication between the developing subretinal and either the subarachnoid space or the vitreous compartment. Dog studies have documented congenital colobomata associated with scleral ectasia and extensive retinal detachment. In some, “crater-like holes” were present in the optic disk. Retinal dysplasias are commonly noted at the border of retinochoroidal colobomata, and may be associated with intrauterine or neonatal retinal detach-
ments. Coloboma with retinal glioma has been described in tuberous sclerosis. Although both retinoblastoma and uveal coloboma are part of the 13q-deletion syndrome, this combination has occasionally been reported in patients with a normal karyotype. In addition to a high resolution karyotype, a molecular genetic examination may be necessary to eliminate the possibility of a 13q-deletion in a patient with retinoblastoma and microphthalmia or coloboma. Subretinal neovascularization causing serous macular detachment has also been reported in a number of adults and at least one infant as a complication of retinocochoroidal coloboma. For unknown reasons, the neovascular membrane tends to develop at the superotemporal edge of the coloboma. It is comparable to the choroidal neovascularization associated with high myopia, angiod streaks, choroidal ruptures, and choroiditis. It is thought that the abrupt termination and abnormal architecture of the RPE and Bruch’s membrane at the margin may predispose to the development of subretinal neovascularization. Treatment with laser photocoagulation may preserve good vision in affected eyes.

A variety of cataracts have been associated with coloboma, including isolated pigment clumping on the lens capsule at the equator, subcapsular and cortical opacification, anterior and posterior polar cataracts, and total opacification. Lens subluxation occurs infrequently. Secondary glaucoma (and related angle abnormalities), amblyopia, anisometropia, and sensory strabismus may occur. Finally, a large upper eyelid coloboma may be associated with exposure keratopathy and even corneal ulceration if left untreated.

III. Etiology and Patterns of Inheritance

A. ISOLATED OCULAR MONOGENIC SYNDROMES

1. Autosomal Dominant Inheritance

Autosomal dominant colobomatous microphthalmia without associated systemic malformations has been well established. Variable expressivity, from small iris or choroidal coloboma to clinical anophthalmia or orbital cyst, has been reported; incomplete penetrance is common. The parents of children with isolated colobomatous microphthalmia should be examined carefully for minor ocular malformations. Incomplete penetrance reduces the risk that the offspring of an affected individual will have colobomatous microphthalmia. In a family with an autosomal dominant inheritance pattern, it was estimated that any individual with a normal ocular examination has an 8.6% chance of having an affected child. Macular coloboma may be inherited as an autosomal dominant disorder and usually is not associated with microphthalmia. Although autosomal dominant transmission is most common, autosomal recessive colobomatous microphthalmia has been reported as a syndrome associated with skeletal anomalies.

Coloboma of the optic nerve is usually unilateral, but some cases are bilateral and may be asymmetric. Both optic nerve and uveal coloboma may be inherited as autosomal dominant syndromes, as illustrated by the colobomatous microphthalmia with microcornea syndrome. However, autosomal recessive and X-linked recessive inheritance patterns have been described. In most cases, a hereditary pattern cannot be established.

2. Autosomal Recessive Inheritance

Pedigrees supporting nonsyndromal autosomal recessive inheritance of microphthalmia are few, and many lack careful documentation of the ocular status of the parents. Several consanguineous Israeli families established this form of inheritance. Additional evidence is from the study of more than 1300 Japanese patients with microphthalmia; segregation analysis indicated a recessive form of inheritance. However, there was no distinction between the colobomatous and noncolobomatous forms and associated malformations were not discussed.

B. MULTISYSTEM MONOGENIC SYNDROMES

1. Autosomal Dominant Inheritance

The basal cell nevus (carcinoma) syndrome is characterized by multiple basal cell carcinomas, dyskeratotic cysts of the jaw, rib and spinal anomalies, and pits of the hands and feet; mental retardation may be present. Penetrance is high; variable expressivity has been observed, and the diagnosis may be made if two major features are present. This syndrome may be associated with multiple ocular anomalies. The basal cell carcinomas, which cannot be differentiated histologically from nongenetic forms, usually appear in childhood and frequently involve the eyelids. AFFECTED individuals should be monitored for malignant transformation of nevi. Colobomatous microphthalmia, as well as congenital cataract and strabismus, have been recorded in this syndrome. The gene has been mapped to the long arm of chromosome 9.

Congenital contractural arachnodactyly, characterized by a Marfanoid body habitus and multiple congenital joint contractures, may be associated with uveal coloboma. Dislocated lenses are not a feature of this syndrome. The gene defect is in the connective tissue protein fibrillin and has been mapped to chromosome 5.
Optic nerve coloboma combined with renal anomalies has recently been described. In addition to renal hypoplasia and vesico-ureteral reflux, patients may have genital anomalies, high-frequency hearing loss, and central nervous system anomalies. Mutation in the PAX 2 gene is thought to be responsible.

2. Autosomal Recessive Inheritance

The Meckel-Gruber syndrome, which consists of microcephaly; occipital encephalocoele; congenital heart defects; polydactyly; facial clefts; and polycystic disease of the kidneys, liver, and pancreas is commonly associated with colobomatous microphthalmia. This syndrome, phenotypically similar to trisomy 13, usually is fatal during the first few weeks of life. Microphthalmia, with or without coloboma, occurs in approximately 15% of patients.

The Sjogren-Larsson syndrome, described in 1949, is characterized by colobomatous microphthalmia and mental retardation. This syndrome is not associated with other systemic abnormalities. Few subsequent reports have appeared.

Humeroradial synostosis, characterized by reduced or absent flexion and extension at the elbow, may be associated with microcephaly, occipital meningocele, and colobomatous microphthalmia. The inheritance pattern has not yet been confirmed, although an autosomal recessive form has been suggested.

Hunter and colleagues have described two siblings, a boy and a girl, with multiple minor dysmorphic features (frontal bossing, high arched palate, anteverted nares, hypertelorism, and carp mouth), colobomatous microphthalmia, congenital hepatic fibrosis, polycystic kidney disease, and diffuse encephalopathy. Autosomal recessive inheritance is presumed. However, the nonocular manifestations may be similar to those found in both the Zellweger and the Meckel-Gruber syndromes; the Zellweger syndrome has not been associated with uveal coloboma.

Cohen and coworkers described several children with mental retardation and retinitis pigmentosa, who also had hypotonia, obesity, prominent incisors, and colobomatous microphthalmia. Inheritance was presumed to be autosomal recessive, as male and female siblings were affected.

An autosomal recessive form of the oral-facial-digital syndrome (type VIII) may be associated with uveal coloboma.

Rarely, colobomatous microphthalmia may be associated with an autosomal recessive chondrodysplasia punctata syndrome.

Walker-Warburg syndrome, or type II (Walker) lissencephaly, includes optic nerve coloboma, hydrocephalus, and agyria. Other ocular anomalies include Peters anomaly, persistent hyperplastic primary vitreous, retinal dysplasia, retinal detachment, and optic nerve hypoplasia. Magnetic resonance imaging shows a smooth cerebral surface and cerebellar hypoplasia with absence of the posterior vermis. The disorder is usually fatal before the first birthday.

3. X-Linked Inheritance

The Lenz microphthalmia syndrome is inherited as an X-linked recessive disorder. Carrier females are not phenotypically identifiable, although they may have early cataracts. Microphthalmia, with or without coloboma, is a fundamental manifestation of the disorder; congenital cataracts and clinical anophthalmia also have been reported. The ocular manifestations are relatively consistent within a family, as are short stature, cylindrical thorax, and widely spaced teeth. Additional features in affected males may include mental retardation, microcephaly, asymmetric or dysmorphic ears, and dental anomalies. Genitourinary abnormalities, such as renal agenesis or hypospadias, also have been described. It is not yet clear whether more than one genetic locus is involved or whether the variability reflects different alleles (mutations) at the same site.

The Aicardi syndrome includes optic disk and/or iris colobomata in association with chororetinal lacunae. Other ocular abnormalities include microphthalmia, orbital cyst, pseudoglioma or retinal detachment, and cataract. Systemic findings include vertebral anomalies, dysmorphic features, microcephaly, and mental retardation. The inheritance is thought to be X-linked dominant, the mutation lethal in males.

Focal dermal hypoplasia is an X-linked dominant lethal in males. Carrier females have the MLS syndrome (microphthalmia with linear skin defects). Most affected individuals are female and it has been postulated that the trait is lethal in males. Colobomatous microphthalmia is a common manifestation.

MIDAS syndrome (an acronym for microphthalmia, dermal aplasia, and sclerocornea) is a term that has been proposed for an X-linked dominant male-lethal trait distinct from focal dermal hypoplasia. The gene defect can be assigned to Xp22.3. Clinical features include bilateral microphthalmia with blepharophimosis, linear lesions of dermal aplasia involving the face, and microcephaly; major congenital heart defects also may be associated. It is often called the MLS syndrome (microphthalmia with linear skin defects).

The Catel-Manzke syndrome, characterized by index finger hyperphalangy with the Pierre-Robin se-
OCULAR COLOBOMATA

quence, has been associated with colobomata. An X-linked recessive pattern has been postulated.

A male with an X-linked recessive oto-palatal-digital syndrome (type II) with cerebellar hypoplasia/hydrocephalus and iris colobomata has been reported. The patient had two similarly affected maternal uncles, who died as neonates. The authors postulated a chromosomal deletion, but this could not be confirmed microscopically.

4. Unknown Etiology

The CHARGE association derives its acronym from the nonrandom grouping of a series of features: colobomatous microphthalmia, heart defects, choanal atresia, retarded growth, genital anomalies, and ear anomalies or deafness. Generally, at least three of the features are necessary for the diagnosis. Cranial nerve paresis or palsy is common. The cardiac defects are varied and may be lethal. It has been postulated that the syndrome is caused by an insult during the second month of gestation or that it is genetic with autosomal dominant inheritance. Sporadic and autosomal recessive inheritance patterns also have been described. Some chromosomal syndromes, including trisomies 13 (Patau syndrome) and 18 (Edwards syndrome), 4p- (Wolf-Hirschhorn syndrome), and the cat-eye syndrome, exhibit some similar features and a chromosomal analysis should be performed.

The epidermal nevus syndrome (also known as the linear sebaceous nevus syndrome, or nevus sebaceous of Jadassohn) is characterized by one or more linear epidermal nevi. Some individuals also have a seizure disorder and developmental delay. The diagnosis is usually is evidenced at birth by the presence of the sebaceous nevus, a yellowish lesion with abundant sebaceous glands and immature hair follicles. A midline lesion on the face is common. At puberty, papillomatous epidermal hyperplasia develops. Malignant transformation may occur in the postpubertal period. Rarely, colobomatous microphthalmia may be an associated finding.

Colobomatous microphthalmia may occur uncommonly in association with the Rubinstein-Taybi syndrome. Affected individuals have characteristic facies, including a broad nasal bridge, prominent forehead, beaked nose, broad thumbs and first toes, and mental retardation. The etiology is unknown and none of the affected individuals have reproduced offspring.

Two unrelated children with macrosomia, obesity, macrocrania, and colobomata have been described. The acronym MOMO was suggested and the authors postulated an autosomal dominant form of inheritance.

Many individuals with the Pai syndrome have colobomatous microphthalmia. Affected individuals have medial cleft of the upper lip, cutaneous facial polyps, and lipoma of the corpus callosum; the inheritance pattern is uncertain and may be autosomal dominant.

Frontonasal dysplasia may be associated with mental retardation and uveal colobomata.

5. Chromosomal Aberrations

Multiple chromosomal aberrations that have been associated with colobomatous microphthalmia are summarized in Table 1.

Although some disorders, such as trisomy 13 or the 4p-syndrome, have specific clinical features that may alert the physician to the diagnosis, many of these syndromes are nonspecific. The physician, whether an ophthalmologist or a primary care physician, should consider the possibility of a chromosomal disorder in individuals who have colobomatous microphthalmia with developmental delay or any other malformation. A high resolution karyotype should be performed.

### Table 1
Chromosomal Aberrations That Have Been Associated with Colobomatous Microphthalmia

<table>
<thead>
<tr>
<th>Type</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triploidy</td>
<td></td>
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<tr>
<td>Trisomies</td>
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<td>Trisomy 13</td>
<td>54</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>173</td>
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<tr>
<td>Trisomy 22</td>
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<td>251</td>
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<tr>
<td>Duplication 9p</td>
<td>197</td>
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<tr>
<td>Duplication 9p+q</td>
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</tr>
<tr>
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<td>115</td>
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</tr>
<tr>
<td>Deletion 4p-</td>
<td>274</td>
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<tr>
<td>Deletion 4r</td>
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<tr>
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<tr>
<td>Deletion Dq</td>
<td>35</td>
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<td>Deletion Dr</td>
<td>279</td>
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<tr>
<td>Deletion 18r</td>
<td>286</td>
</tr>
<tr>
<td>Pericentric Inversions</td>
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</tr>
<tr>
<td>Inv(6)(p23q23.1)</td>
<td>272</td>
</tr>
<tr>
<td>XY Anomalies</td>
<td>XY</td>
</tr>
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</table>
C. ENVIRONMENTAL CAUSES AND INTRAUTERINE INSULTS

Although environmental influences would seem plausible in sporadic cases of colobomatus microphthalmia, few specific embryopathic agents have been identified. To date, thalidomide "A" is the only documented environmental cause of coloboma in humans with or without phocomelia. A prospective study of individuals with established thalidomide embryopathy documented two patients with isolated coloboma of the optic disk, and another with coloboma of both the uvea and optic disk. The effect of thalidomide was thought to have occurred early in the teratogenic period, perhaps during the 4th week of development.

Intrauterine vitamin A deficiency in humans also has been implicated. This observation has been supported by the finding of colobomatous microphthalmia in the offspring of rats deprived of vitamin A during pregnancy.

Use of anticonvulsants in pregnancy, notably diphenyl hydantoin and carbamazapine, has been associated with increased risk of systemic and ocular abnormalities, including cardiovascular and renal defects, cleft lip and palate, hypertelorism, ptosis, strabismus, and retinochoroidal colobomata.

A variety of ocular anomalies have also been related to the fetal alcohol syndrome, including microphthalmia, microcornea, and uveal colobomata.

Infectious embryopathic agents, such as cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, and herpes virus, may be associated with noncolobomatous microphthalmia. Although their causality is controversial, maternal fever during pregnancy and prenatal irradiation have been implicated. In animal models, ocular teratogens causing noncolobomatous microphthalmia have included folic acid deficiencies (rat), irradiation (rat), exposure to nickel carbonyl (rat), and elevated incubation temperatures (chick).

Several mechanisms have been proposed for the formation of lid colobomata in utero. The craniofacial and limb abnormalities in the amniotic band syndrome are caused by constrictive intrauterine bands. Pressure over the eyelid and eye may cause an eyelid coloboma or microphthalmia. As described in the Goldenhar syndrome, eyelid hematomas may be responsible for asymmetric eyelid defects. Bilateral defects are more likely to have a genetic basis. The gene for Treacher-Collins syndrome has been localized to chromosome 7, but its relationship to eye anomalies is unclear. Lower lid colobomas often are associated with cleft lip and palate, hypertelorism, ptosis, strabismus, and retinochoroidal colobomata.

IV. Evaluation and Treatment

A. EYELIDS

Congenital defects in the eyelid are not related to the fetal fissure. Upper lid colobomata are more common and, with the exception of an association with Goldenhar syndrome, are generally isolated. They occur at the junction of the inner and middle thirds, tend to be full thickness, and have normal adjacent lid margins. In contrast, lower lid colobomata, sometimes symmetrical, are often associated with mandibulofacial dysostosis (Treacher-Collins Syndrome). They occur most frequently at the junction of the middle and lateral thirds, and tend to be partial thickness, involving preferentially the anterior lamella. Notably, eyelid colobomata have not been associated with focal dermal hypoplasia (Goltz-Gorlin syndrome), which affects tissues of meso-ectodermal origin, despite its ocular associations that include other lid abnormalities.

Treatment of eyelid defects depends on the extent of involvement and the risk of corneal decompensation. Infants generally tolerate relatively large defects well, especially if only the lower lid is involved. Initial therapy should be conservative, consisting of topical lubricants, bandage contact lenses, and/or moisture chambers fabricated with plastic food wrap and ointment. Surgical repair is warranted if corneal decompensation is caused by dehydration and/or trichiasis. Eyelid sharing procedures should be considered carefully in young children because of the risk of occlusion amblyopia during the healing phase. Infants generally tolerate relatively large defects well, especially if only the lower lid is involved. Closure of larger defects may necessitate a sliding myocutaneous flap or a full-thickness lid-sharing operation, such as the Cutler-Beard procedure or modifications.

B. IRIS

Because the iris defects themselves impose no visual defect, treatment is indicated only for cosmesis. One useful approach is to fit a cosmetic contact lens (Fig.8) that resembles a normal iris and is designed to match the fellow eye in appearance. Such lenses can be optically corrective. Cosmetic contact lenses also are useful for microcornea associated with coloboma and microphthalmia.

Surgical treatment of iris colobomata may be undertaken as part of cataract extraction or penetrating keratoplasty at any age. Surgical repair is not generally performed unless other intraocular
surgery is indicated. After implantation, the coloboma may be repaired with nonabsorbable sutures. Posterior chamber lens implantation in the capsular bag is preferred by many cataract surgeons. If zonular integrity is insufficient, sulcus placement or anterior chamber implantation could be considered. Ideally, haptics should be placed 90 degrees from the defect to stabilize the implant, and larger lens implants are preferred to minimize glare. Repair of iris colobomata is helpful to provide a stable platform for anterior chamber lens implantation and may prevent progressive synechiae formation and secondary angle closure.

Intraocular surgery in patients with cataract and microphthalmia may be complicated by postoperative uveal effusion, retinal detachment, intraocular hemorrhage, and malignant glaucoma. Prophylactic previous or simultaneous sclerotomy or sclerectomy has been advocated to reduce the incidence of postoperative uveal effusion.

C. ZONULE AND CILIARY BODY

“Coloboma” of the lens is secondary to zonular and ciliary body defects; no lens tissue is missing. In rare cases, coloboma affecting the zonule is associated with superior lens subluxation. Lens extraction is indicated for cataract or subluxation if visual function is sufficiently compromised. Coloboma is the most common congenital defect in the ciliary body, involving both mesodermal and neuroectodermal elements. Ciliary body coloboma may be visible through the overlying iris coloboma as white lesions with varying degrees of pigmentation at the margins related to hyperplasia of pigment epithelial cells.

There is no specific treatment for ciliary body colobomata and restoration of defective zonules is not possible. Lens implant surgery may be higher risk because of absent zonules.

D. RETINOCHOROIDAL

Retinal detachments have long been a recognized risk of retinochoroidal colobomata, with an incidence of 23–42%. In patients under 30 years of age, coloboma-associated retinal detachments are more common in males. The incidence of retinal breaks is doubtless higher, as many of these may be asymptomatic and unassociated with detachments. Most holes are atrophic, without operculae, and may be hidden near the edge of the coloboma or under a hemorrhage. These breaks may therefore be difficult to localize, because there is little contrast in the colobomatous area, and patients may have nystagmus. Additional technical difficulties include ectatic sclera, absence of choroid, and thinned retina.

Prophylactic laser treatment applied posteriorly along the edge of the coloboma and cryopexy anteriorly has been recommended. A complication of such treatment is the creation of nerve fiber bundle defects in eyes with already compromised visual fields.

In cases requiring surgery, the preferred initial treatment is laser photocoagulation. Vitrectomy and air-fluid exchange with a buckle may be indicated subsequently, and are more successful than scleral buckling alone. Colobomatous eyes tolerate buckling surgery poorly, with success rates ranging from 37% to 70%. One useful technique to localize retinal holes during vitrectomy is to aspirate subretinal fluid from within the vitreous; the yellow color indicates the location of the break. The prognosis following vitrectomy is better in older patients, who are able to tolerate the face-down head positioning after surgery. Optic nerve sheath fenestration has reportedly led to reattachment in a few cases of optic nerve pit associated detachment; however, these successes are difficult to validate, because spontaneous retinal reattachment can occur.

In cases with associated severe microphthalmia, treatment during infancy with cosmetic scleral shells may be helpful. With periodic refitting, this method may promote the development of symmetrical ocular appearance without the need for surgery.

In colobomatous microphthalmia the size of the orbit varies from normal or near normal to very small. An eye with normal function is more likely to have normal-sized fornices and orbit. When indicated, gradual expansion of the fornices may be accomplished by the use of progressively enlarged ring-type prostheses from the age of a few months, so that a specially shaped normal size prosthesis can eventually be fitted in the socket. Orbital growth
has been successfully induced by the implantation of a 4-ml spherical intraorbital tissue expander with a remote saline injection port in a series of patients between the ages of 4 months and 8 years. Dermis-fat graft implantation and intraorbital balloon techniques also have been employed.

E. OPTIC NERVE

Colobomata, pits, and morning glory malformation of the optic nerve have all been associated with serous retinal detachments. These detachments are nonrhegmatogenous, and spontaneous reattachment has been known to occur. Optic nerve sheath fenestration has been advocated by some.

F. GENERAL

Evaluation should be performed expeditiously if there is a threat of corneal decompensation from an eyelid coloboma. Meticulous evaluation of infants with colobomata is typically difficult, given their lack of cooperation, nystagmus and microphthalmos. Indeed, effective examination may be impossible without general anesthesia. Slit-lamp examination can then aid in defining anterior segment manifestations. Choroidal, retinal, and optic nerve involvement can be studied with direct and indirect ophthalmoscopy. Accurate refraction is essential, as amblyopia can be induced by anisometropia or by bilateral high ametropia. Computerized tomography or magnetic resonance imaging can be useful in defining microphthalmia and associated CNS malformations. Axial length can be measured by high resolution ultrasonography. Older patients can have their visual fields assessed. Inferior retinal colobomata are associated with superior defects.

Fundamental in the treatment of children with colobomata is a determination regarding visual prognosis. It is advisable for the parents to be included in this discussion from an early stage, and for them to have the benefit of second opinions if it is determined that an eye will not be visually useful. Such determination, however, can facilitate cosmetic treatment of severe microphthalmia with scleral shells. With periodic refitting, this method may promote the development of symmetrical ocular appearance without the need for surgery. When indicated, gradual expansion of the fornices may be accomplished by the use of ring-type prostheses. Orbital growth has also been induced by the implantation of spherical intraorbital tissue expanders with remote saline injection ports, intraorbital balloon devices, and dermis grafts. Children with severely limited visual prognosis in one eye should be fitted with safety glasses by the time they are independently active, and should wear goggles for sports. Although amblyopia may be untreatable, in some cases a trial of part-time occlusion may help to show the parents the inevitability of poor vision in the affected eye. Strabismus can be treated surgically if necessary. In some cases, spectacle correction of hyperopia in the normal eye may correct accommodative esotropia. Children with nystagmus can be treated surgically, especially if a compensatory face turn is induced.

V. Differential Diagnosis

Colobomata of the eyelids can be mistaken for congenital amniotic band syndrome, eyelid trauma, entropion and, in cases presenting with involvement of the lacrimal drainage system, blocked tear ducts. Iris abnormalities in aniridia, heterochromia irides, iris nevi, iris trauma, iris atrophy, and Rieger syndrome can mimic a coloboma. In young people, normal lenses with indentations at the equator between zonular insertions can be mistaken for “coloboma” of the lens. Retinochoroidal colobomata are easily differentiated from inflammatory lesions and all the other causes of leukocoria.

The morning glory disk anomaly has been occasionally confused with optic nerve coloboma. A differential diagnosis has been published by Brodsky, Baker, and Hammel. Morning glory disks are surrounded by an annular zone of pigmented disturbance, whereas colobomatous disks have a paracentral defect, typically inferior, with minimal parapapillary pigmentary disturbance. Morning glory disks have anomalous retinal vessels and a central glial tuft, neither of which is typical of colobomatous disks.

Congenital optic pits and optic nerve staphylomata can also be confused with optic nerve coloboma. A staphylosa is a deep fundus excavation surrounding the optic disk, which itself may be normal or show only mild temporal pallor. Optic pits are round or oval gray, white, or yellowish depressions within the substance of the optic nerve. Some believe they are similar to colobomata in that they may represent anomalous closure of the fetal fissure involving the disk.

Optic nerve coloboma, congenital optic pits, and the morning glory disk anomaly may be confused with each other and with staphyloma of the optic nerve.

In most cases the diagnosis is made clinically based on the appearance of the lesions themselves. Imaging studies are sometimes required. In the case of inflammatory lesions, specific titers or appropriate cultures can be helpful diagnostically.

VI. Conclusion

Ocular colobomata are often associated with microphthalmia. They are common congenital malfor-
mations which may occur as an isolated ocular anomaly or in association with multisystem anomalies. Although most cases are idiopathic, there are many associated syndromes.

There is wide variation in severity, ranging from a small iris coloboma to a defect that causes profound visual impairment. Treatment is dependent on location and severity. A genetic evaluation is warranted in all cases.

Method of Literature Search

Medline and Ovid were used to search literature from 1966 to the present. Supplemental sources included Index Medicus and references in identified articles. Key words used were coloboma, microphthalmia, and named syndromes. One Russian article was translated. The English abstracts of other foreign language articles were used.

References

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   C. Lens "coloboma"
   D. Posterior segment coloboma
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