# REHABILITATION OF A CHILD WITH PARTIAL UNILATERAL CRYPTOPHTHALMOS AND MULTIPLE CONGENITAL ANOMALIES*

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**ABSTRACT**

*Purpose:* This paper describes the surgical rehabilitation of a child with craniofacial anomalies, unilateral syndactyly, and partial unilateral cryptophthalmos associated with inferior colobomata of the iris and optic nerve and agenesis of the inferior rectus and inferior oblique muscles. The clinical presentation of cryptophthalmos is described.

*Methods:* The medical literature since the original description of cryptophthalmos in 1872 was reviewed to define patterns of inheritance and the incidence of associated anomalies.

*Results:* Including this patient, 149 case reports of cryptophthalmos were identified. In two families transmission from parent to child suggests dominant inheritance. None of the five dominant cases had any other anomalies, and all had bilateral complete cryptophthalmos. The incidence of cryptophthalmos in the remaining families is consistent with autosomal recessive inheritance. This group includes patients with bilateral, unilateral, and partial cryptophthalmos. Other anomalies are common, including those of the ear and nose, limbs, genitourinary system, and mouth and palate. Mortality in the perinatal period is associated with renal agenesis, laryngeal atresia, and pulmonary hypoplasia.

*Conclusions:* Cryptophthalmos is a rare congenital anomaly with two patterns of inheritance.

## INTRODUCTION

Cryptophthalmos, or "hidden eye," a term coined by Zehender and Manz in 1872, is defined as ablepharon with corneal replacement by fibrovascular tissue and skin.[1,2] Since their original description, approximately 149 cases of complete or partial cryptophthalmos have appeared in the world litera-

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ture (Table I).[1,3-100] In complete cryptophthalmos the cornea and lids are replaced by undifferentiated fibrous tissue, and surgical reconstruction of the lids and globe is not possible. Cilia generally are absent, although a small depression, prominence, or scar at the line of lid fusion may be seen. The globe may move and have light perception, but generally is microphthalmic and may have retinal or optic nerve colobomata. Cryptophthalmos may be bilateral or unilateral, and unilateral cases may have associated abnormalities of the other eye, including microphthalmos, upper lid medial coloboma, small palpebral fissure, iris coloboma, cataract, blepharophimosis, anophthalmos, and symblepharon. Cryptophthalmos may be associated with other anomalies, including displacement of the hairline, malformed conchae, syndactyly of the hands and feet, genitourinary anomalies, renal agenesis, cleft palate, cleft lip, facial cleft, umbilical hernia, anal atresia, laryngeal atresia, mental retardation, and others.[1,2,20,101] Mortality in the perinatal period has been associated with laryngeal atresia, pulmonary hypoplasia, and/or bilateral renal agenesis.[7,8,12,19] In 1962 Fraser [101] described the recurring constellation of cases of cryptophthalmos with other congenital abnormalities, and in 1986 Thomas and associates [20] developed criteria with which to classify the congenital anomalies into Fraser's syndrome (Table II). Cases that satisfied two major criteria and one minor criterion or one major criterion and four minor criteria were classified as Fraser's syndrome. The inheritance of cryptophthalmos with Fraser's syndrome is autosomal recessive. In addition, cases of isolated cryptophthalmos and cryptophthalmos occurring with other anomalies insufficient to satisfy the criteria of Fraser's syndrome have been reported. Some cases of isolated cryptophthalmos may be autosomal dominant.[5,11,80,87]

Partial or incomplete cryptophthalmos in which only a portion of the eye is affected also has been described.[20,56] True cryptophthalmos is recognized clinically by replacement of normal lid and cornea by fibrous tissue and other associated abnormalities of the anterior and posterior segments, as described previously. In some reports the clinical details or illustrations are insufficient to distinguish partial cryptophthalmos from lid coloboma with symblepharon or ankyloblepharon with symblepharon. These lid abnormalities may represent a spectrum with a common pathogenesis, but for this review we have attempted to distinguish them. Review of the literature suggests that partial unilateral cryptophthalmos, in which only part of one lid and globe is anomalous, is very rare. Fifteen cases of partial cryptophthalmos, of which 13 are unilateral, have been reported; and in an additional 18 cases of complete unilateral cryptophthalmos, the fellow eye appeared to be affected by partial cryptophthalmos (Tables I and III).[3,4,6-7,11-13,20,25,33,35,40,46,48-49,52,56,58,62,68,74,77,88,89,94,95]

Only three reports have described abnormalities of the extraocular muscles, and all were cases of bilateral complete cryptophthalmos. Gupta and Saxena[61] explored the right orbit of an Indian child with bilateral com-

**TABLE I: REVIEW OF CRYPTOPHTHALMOS: 149 CASES**

| AUTHORS | YEAR | SEX* | UL/BL† | OTHER EYE‡ | ASSOC A§ | AGE¶ | SB‖ | CONSANG# | FH** |
|---|---|---|---|---|---|---|---|---|---|
| Konrad et al | 1995 | M | od | 10 | abi | 4 yr | | | m,m |
| Ford et al | 1992 | F | os | NL | abhi | 7 yr | | | NS |
| | | F | BL | | afg | 4 yr | | | NS |
| | | F | BL | | acefhi | 2 yr | | | NS |
| | | M | OS | NS | acfg | 2 yr | | | NS |
| Morax et al | 1992 | M | bl | 3 | ab | 6 mo | | | NS |
| | | M | os | NL | - | 20 yr | | | NS |
| Saal et al †† | 1992 | F† | BL | | - | 2 d | | | Mother |
| | | F | BL | | - | 32 yr | | | Daughter, m |
| Bierich et al | 1991 | M | OS | 1 | ahj | Neo | | cous | NS |
| Ramsing et al | 1990 | F | OS | 1 | bcdfghi | 23 w* | X | | S |
| Schauer et al | 1990 | M | BL | | afgi | 18 w* | X | | F |
| Tilahun et al | 1990 | M | BL | | abghi | Neo | | | m,m |
| Woodhead et al | 1990 | F | BL | | afghi | Neo | | | M,f |
| Bialer et al | 1988 | M | OS | 1 | ahj | Neo | | cous | NS |
| Boyd et al †† | 1988 | M | OD | 1 | abcfghi | 24 w* | X | | n,m |
| | | F | OD | NS | bcfi | 20 w* | X | | n |
| | | F | OD | NS | acfgi | | X | | F |
| | | M | BL | | acdfghi | | X | | m |
| | | M | OS | NL | abcdfghi | | X | | |
| | | F | BL | | acfgi | | X | | |
| | | F | od | NS | acfgi | | X | | f |
| | | I | BL | | acfgh | | | | No sibs |
| | | M | OD | 1,2 | acdfi | | X | | m |
| | | M | BL | | abfghi | | X | | n |
| Gattuso | 1987 | F | os | NL | achi | 6 mo | | | No sibs |
| Konrad et al | 1987 | F | BL | | abg | Neo | X | | NS |
| Boukoffa et al | 1986 | F | BL | | ab | 10 d | | cous | F*,F,M,M,m,m |
| Greenberg et al | 1986 | F | BL | | ag | 2 mo | | | s |
| Guhanandhan et al | 1986 | F | OS | NL | acgi | 10 d | | cous | s,s,s |
| Hancheng †† | 1986 | F | BL | | ak | 33 yr | | | s,s |
| | | F | OD | 3 | ak | 29 yr | | | |
| | | M | BL | | ad | 2 mo | | | |
| Pe'er et al | 1986 | F | BL | | aei | 1 d | | cous | S*,S*,S*,S*,S*, S,S,s,s |
| | | M | BL | | adfgi | | X | | NS |
| Thomas et al †† | 1986 | F | OS | NL | acfghi | | X | | |
| | | F | OD | NL | acgi | | X | | |
| | | F | OD | 4 | acfgi | | X | | |
| | | F | bl | 3 | adfgi | | X | | |
| | | F | OS | 1,3,4 | abcfghi | | X | | f,f |
| | | M | OD | NL | acghi | 20 w* | X | | |
| | | M | BL | | acfghi | Neo | 24h | | n,n,n |
| Kaira et al | 1985 | M | BL | | - | 1 d | | + | NS |
| | | F | BL | | i | Neo | 30h | + | NS |
| Ohtsuka et al | 1985 | F | OD | 3 | a | Neo | | | f |
| Wiznitzer et al | 1985 | M | BL | | abfi | Neo | 30' | cous | NS |
| Levine et al | 1984 | M | BL | | afgi | Neo | | | NS |

**TABLE I: REVIEW OF CRYPTOPHTHALMOS: 149 CASES (CONTINUED)**

| AUTHORS | YEAR | SEX* | UL/BL† | OTHER EYE‡ | ASSOC A§ | AGE¶ | SB ‖ | CONSANG# | FH** |
|---|---|---|---|---|---|---|---|---|---|
| Lurie et al †† | 1984 | F | od | 2,6 | adfgi | | X | | No sibs |
| | | I | BL | | fgi | | X | | n,f |
| | | I | BL | | egi | | X | | |
| | | M | BL | | agi | | X | | |
| | | M | BL | | abcdefghi | | X | | |
| | | M | OD | NL | afgi | | X | | n, m,f |
| | | M | OS | NL | fi | | X | | |
| | | I | OS | NS | afgi | | X | | M* |
| Bieber et al | 1982 | M | BL | | afgi | Neo | 1d | | F* |
| Behrens et al | 1981 | M | OS | 2,5,6 | fgj | 13 yr | | | f |
| Boijal et al | 1981 | M | OD | NL | - | 8 d | | | NS |
| Gupta et al | 1981 | F | BL | | abcefi | 9 mo | | | NS |
| Barry et al | 1980 | F | BL | | cfgi | Neo | 5' | | NS |
| Marback et al | 1980 | M | BL | | ai | 27 yr | | | m,m,m,m |
| | | F | OS | 7 | abegi | 3 mo | | | No Sibs |
| Howard et al | 1979 | M | OS | NL | - | 5 mo | | | f |
| | | F | OS | NL | abj | 13 yr | | | NK |
| Kapoor | 1979 | F | OD | 2,3 | abgi | 3 mo | | + | m,f |
| | | F | od | NL | abei | 5 yr | | | NS |
| Liebl | 1979 | M | OS | 3 | abi | 3 mo | | | NS |
| Butler et al | 1978 | M | OD | 1,2 | acfgij | 3 yr | | | s,s |
| Varnek | 1978 | F | OD | 1 | abfgi | Neo | | | NS |
| Momma et al | 1977 | F | OS | NL | abgi | 13 yr | | cous | NS |
| Sen | 1977 | F | BL | | i | 8 mo | | | S*,S*,s,s,s |
| El Hoshy | 1976 | F | OD | NL | - | 5 mo | | + | m.m,f |
| Emberger et al †† | 1976 | F | BL | | abi | | X | | n,m,f |
| | | M | BL | | ai | | X | | |
| | | F | OD | 1 | afgi | | X | | |
| Filonenko et al | 1976 | F | BL | | - | 3 wk | | | s,s |
| Walbaum et al | 1976 | M | BL | | acfgi | | X | | No sibs |
| Goldhammer et al | 1975 | F | OD | NL | abj | Neo | | | NS |
| Ide | 1975 | F | OS | 3,4 | acfgi | died 7 mo | | | NS |
| Ishak | 1975 | F | OD | NL | ai | 17 yr | | cous | f |
| Waring et al | 1975 | F | os | NL | fi | 2 yr | | | NS |
| Das | 1974 | M | BL | | - | 1 d | | | s,s,s,s,s,s,s |
| Dinno et al | 1974 | F | os | 2,4 | aegi | 14 mo | | | f |
| Azevedo et al †† | 1973 | F | BL | | abgi | 1 mo | | + | f |
| | | F | BL | | agi | 2 d | | cous | n,n,n,n,n,M*,F,F,F, |
| | | F | OS | 1 | agi | 2 d | | cous | m,m,m,m,m,m,f,f,f |
| | | M | BL | | gi | | X | cous | |
| Schoenenberg | 1973 | F | OS | NL | abgi | 10 yr | | cous | m,f |
| Singh | 1973 | M | BL | | - | 1 mo | | | f |
| Chovet et al †† | 1972 | M | OD | 1,2 | ab | 15 yr | | cous | m,m,m,f,f |
| | | M | BL | | - | 7 yr | | cous | f,f |
| | | F | BL | | j | 9 yr | | | |
| | | M | OS | 3,8 | a | 7 mo | | | |
| Parmar et al | 1972 | F | BL | | i | 1 d | | | s |
| Reinecke | 1971 | F | BL | | b | 8 d | | | NS |
| Dada et al | 1969 | M | BL | | - | 17 yr | | | NS |

**TABLE I: REVIEW OF CRYPTOPHTHALMOS: 149 CASES (CONTINUED)**

| AUTHORS | YEAR | SEX* | UL/BL† | OTHER EYE‡ | ASSOC A§ | AGE∏ | SB ĵ | CONSANG# | FH** |
|---|---|---|---|---|---|---|---|---|---|
| Francois †† | 1969 | F | os | NL | abgi | 8 yr | | | m |
| | | M | OS | 1,2 | abfgij | 3 yr | | | |
| Ide et al | 1969 | M | BL | | abcegij | 13 yr | | | S,s |
| Sugar | 1968 | F | OD | 1 | i | 35 yr | | | NS |
| Ehlers | 1966 | M | BL | | af | 1 mo | | | NS |
| Ishwarchandra et al | 1966 | M | BL | | ab | 3 d | | | F* |
| Viallefont et al | 1965 | I | BL | | aeg | Neo | | | NS |
| Gupta et al | 1962 | F | BL | | bj | 9 yr | | + | S,S,M*,M*,M*, M*,m,s |
| Otradovec et al | 1962 | I | os | NL | afgi | 17 mo | | | No sibs |
| Steidl | 1962 | M | BL | | abefghij | 12 yr | | | s,s,s,s,s,s,s,s, s,s,s,s, |
| Dymshyts et al †† | 1960 | F | BL | | bj | 3 yr | | | Uncle,Uncle, s |
| | | M | OS | NL | - | 18 yr | | | |
| Pahwa | 1960 | M | BL | | - | 8 mo | | | M,f |
| | | M | BL | | - | 15 d | | | No sibs |
| Fan | 1959 | M | BL | | - | 7 mo | | 1/2 Sib | s,s,s,s,s,s |
| Zinn et al | 1955 | M | OD | NS | ab | 22 mo | | | s,s |
| Dejean et al | 1954 | F | OS | 1,2 | - | 6 yr | | | m |
| Ghosh et al | 1952 | M | BL | | - | 25 yr | | | NS |
| Han | 1950 | F | BL | | agi | 3 mo | | | NS |
| Rumyantseva †† | 1947 | F | OS | NL | abgi | 21 yr | | | |
| | | M | BL | | hi | Neo | 7 d | | |
| Thorp | 1945 | F | BL | | gi | 1 d | X | | NS |
| Brodsky et al | 1940 | I | BL | | g | 10 d | | | NS |
| Key | 1929 | F | OD | 1,2 | ij | 12 yr | | | NS |
| Avizonis | 1928 | M | BL | | a,i | 4 d | | | F,s,s |
| Chou | 1928 | M | BL | | - | 40 d | | | s |
| Jusefova et al | 1928 | F | od | 3 | agi | 4 mo | | | NS |
| Nichelatti | 1927 | F | BL | | ghi | 22 d | | cous | n,s |
| Mueller | 1922 | NS | UL | 3 | ai | NS | | | NS |
| Magruder | 1921 | M | BL | | NS | 8 yr | | | F,Mother |
| Sinclair | 1918 | M | OD | NL | - | 21mo | | cous | No sibs |
| Snowball | 1918 | NS | UL | NL | NS | NS | | | NS |
| Turowsky | 1916 | M | BL | | - | 3 mo | | | s,s |
| Onishi | 1912 | I | BL | | agi | NS | | | NS |
| Eberhardt | 1911 | F | BL | | a | Neo | | cous | F,m |
| Ginzburg | 1911 | M | OD | NL | NS | 3 mo | | | NS |
| Coover †† | 1910 | F | BL | | - | 24 yr | | | Daughter |
| | | F | BL | | - | 7 mo | | | Mother |
| Guttman | 1909 | NS | od | NL | - | 3 mo | | | NS |
| von Hippel | 1906 | M | OS | 1 | agi | 10 d | | | NS |
| Elliott | 1904 | M | OD | 2 | i | 5 yr | | | m,f |
| Newman | 1904 | M | BL | | NS | NS | | | NS |
| Goldzieher | 1903 | F | BL | | - | 10 yr | | | F |
| Golowin | 1902 | M | OS | 1 | - | 26 yr | | | F |
| | | F | BL | | a | 2 mo | | | F |
| | | F | BL | | a | 4 yr | | | F |
| Blessig | 1900 | M | OS | 1 | j | 2 yr | | | m,m,m |

**TABLE I: REVIEW OF CRYPTOPHTHALMOS: 149 CASES (CONTINUED)**

| AUTHORS | YEAR | SEX* | UL/BL† | OTHER EYE‡ | ASSOC A§ | AGE∏ | SB ¶ | CONSANG# | FH** |
|---|---|---|---|---|---|---|---|---|---|
| Karman | 1895 | NS | BL | | a | 6 wk | | + | F* |
| von Duyse | 1889 | M | BL | | a | 3 wk | | U/N | m,m,m,f |
| Fuchs | 1889 | I | OS | NL | agi | Neo | | | S*,S*,S*,s,s,s |
| Chiari | 1883 | F | OS | NL | abcdfgi | | X | | NS |
| Hocquart | 1881 | F | BL | | NS | 30 yr | | | NS |
| Zehender | 1872 | F | BL | | efgh | 6 mo | | | No sibs |

*F, female; I, indeterminate(ambiguous); M, Male; NS, not specified.
†UL/BL, unilateral/ bilateral cryptophthalmos: OD/OS, right/ left complete unilateral cryptophthalmos; bl, bilateral partial cryptophthalmos; od/os, right/ left partial cryptophthalmos.
‡Involvement of noncryptophthalmic eye: NL, normal; NS, not specified; 1, partial cryptophthalmos; 2, microphthalmos; 3, upper-lid medial coloboma; 4, small palpebral fissure; 5, iris coloboma; 6, cataract; 7, blepharophimosis; 8, anophthalmos; 9, symblepharon; 10, dermoid.
§Associated systemic anomalies: a, external ear abnormalities, cleft nose; b, cleft lip/palate/oral; c, laryngeal atresia; d, pulmonary hypoplasia; e, umbilical hernia; f, urinary tract agenesis (renal/ureteral/bladder); g, genital abnormalities (cryptorchidism, microphallus, hypospadias, meatal absence, ambiguous genitalia, clitoromegaly, hypoplastic or stenotic labiae, vaginal stenosis, cervical stenosis, ovarian/oviductal/uterine agenesis, bicornuate uterus); h, anal atresia, bowel malrotation, absent appendix; i, syndactyly/polydactlyly hand/foot; j, mental retardation.
∏Age at report: w*, weeks of gestation at time of spontaneous abortion or voluntary termination of pregnancy(VTOP).
¶Sb, Stillborn.
#Consanguinity of patient's parents: cous, cousins; 1/2 Sib, half-siblings, U/N, uncle/niece; +, nonspecific.
**Family history: n, spontaneous abortion or VTOP; M/F/I, male/female/indeterminate sibling affected with cryptophthalmos, S, sex not specified; M*/F*/S*, sibling with abnormalities excluding cryptophthalmos/stillborn/abortion; m/f, normal sibling, s, sex not specified; Mother/Daughter/Uncle, mother/daughter/uncle affected with cryptophthalmos.
††Cases from one author grouped by bracket are siblings from same family.

**TABLE II: DIAGNOSTIC CRITERIA FOR CRYPTOPHTHALMOS SYNDROME**

**MAJOR**

1. Cryptophthalmos
2. Syndactyly
3. Abnormal genitalia
4. Sibling with cryptophthalmos syndrome

**MINOR**

1. Congenital malformations of nose
2. Congenital malformations of ears
3. Congenital malformation of larynx
4. Cleft lip and/or palate
5. Skeletal defects
6. Umbilical hernia
7. Renal agenesis
8. Mental retardation

From Thomas et al.[20]

**TABLE III: SUMMARY OF 149 CASES OF CRYPTOPHTHALMOS**

| | | |
|---|---|---|
| Bilateral complete | | 78 |
| Unilateral complete | | 56 |
| Condition of fellow eye: | | |
| Normal | 22 | |
| Partial cryptophthalmos | 18 | |
| Other anomalies | 11 | |
| Not stated | 5 | |
| Bilateral partial | | 2 |
| Unilateral partial | | 13 |
| Condition of fellow eye: | | |
| Normal | 6 | |
| Anomalous | 3 | |
| Not stated | 4 | |

plete cryptophthalmos and found that the extraocular muscles inserted 3 mm posterior to the equator; the oblique muscles could not be identified. Fan[66] explored both orbits of a Chinese child with bilateral complete cryptophthalmos and found complete absence of the extraocular muscles in both orbits. Coover [87] explored the right orbit of a female infant with apparently isolated bilateral cryptophthalmos and found no extrinsic eye muscles "macroscopically."

This study describes a child with partial unilateral cryptophthalmos associated with absence of the inferior rectus and inferior oblique muscles, craniofacial abnormalities, and unilateral syndactyly and reviews 149 cases of cryptophthalmos and its associated anomalies.

## CASE REPORT

The third son of a 28-year-old mother and 35-year-old father was born in the Dominican Republic April 17, 1983. His two brothers are said to be normal. No other family members have been examined, and no details of the family medical history or pregnancies are known. At age 3 he was brought to the United States by Heal the Children (Fig 1).

The child was small for his age, weighed 17.9 kg, and was 100 cm tall. Initial examination revealed right oral-orbital cleft, repaired bilateral complete cleft lip, complete cleft palate, and right syndactyly. The right medial canthus was displaced inferiorly, and the right globe appeared 4 to 5 mm lower than the left. The lateral right lower lid was normal but ended abruptly

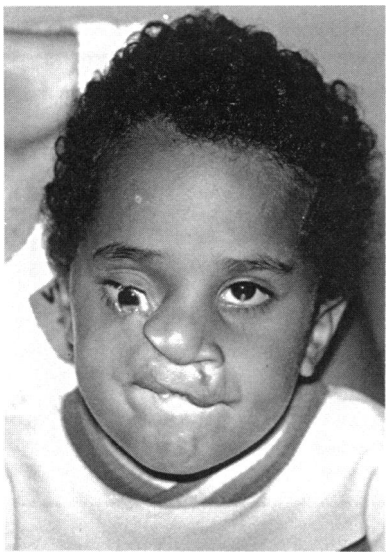

FIGURE 1
Child at age 3 years 4 months. Note right oral-orbital cleft, bilateral repaired cleft lip, incomplete development of right lower lid, and left corneal dermoid.

at the lateral limbus, where a small blind punctum and small caruncle were seen. The nasal lower lid was replaced by firm tissue without muscle function and was adherent to the globe. The inferior fornix ended at the lateral limbus (Fig 2). The horizontal corneal diameter was 11 mm OD and 12 mm OS, and the inferior cornea OD was replaced by fibrous tissue and skin. The pupils reacted directly to light with a right relative afferent defect. An inferior iris coloboma OD was noted. The lens was clear OU. The right optic nerve was small and truncated inferiorly. Inferior to the disc OD the pigment epithelium was mottled (Figs 3 and 4). The right globe was restricted in movement in medial and lateral gaze and did not elevate or depress.

The left eye moved normally, and the lids and fornices were normal. A dermoid protruded from the inferior central clear cornea (Fig 5). A single artery and vein arising from the nasal angle ran on the endothelium to the dermoid. The child fixed and followed well OS and objected vigorously to covering the left eye. Net retinoscopy was +4.00 +2.50 x 180 OD and 0.50 + 1.00 x 180 OS.

After the child was treated for anemia due to intestinal parasites, the cleft palate was repaired, carious teeth were removed or repaired, and the

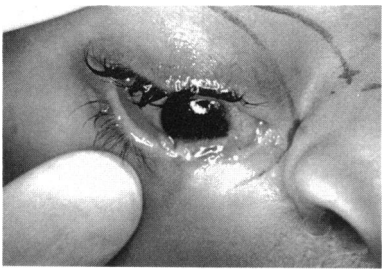

FIGURE 2
Right eye. Caruncle is seen at lateral limbus. Nasal lower lid is undifferentiated and fused with globe.

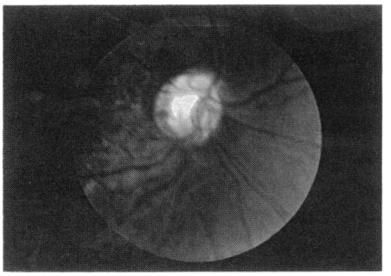

FIGURE 3
Small right optic nerve with inferior coloboma, May 1989.

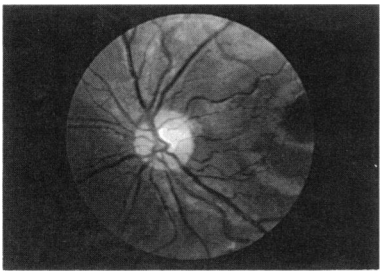

FIGURE 4
Normal left optic nerve, May 1989.

left corneal dermoid was excised on October 21, 1987.

On December 9, 1987, the child underwent craniofacial surgery to elevate the right orbit and to repair the right medial canthal displacement, the right lower lid and fornix, and the nose (Fig 6). Nasal aberrant lid tissue was dissected free from the underlying globe. No sclera was found in this sector, and the inferior oblique and inferior rectus muscles were absent. Via a bicoronal incision, osteotomies were created through the zygoma, the inferior orbital rim, and the lateral orbital wall to the inferior orbital fissure.

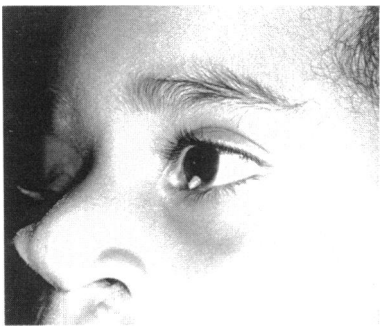

FIGURE 5
Left corneal dermoid.

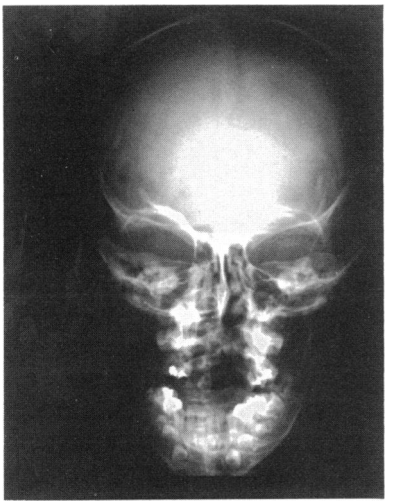

FIGURE 6
Skull film showing that right orbit is only slightly smaller than left.

A fracture was created across the orbital floor to the medial wall, and along the nasal bone to the nasal frontal suture. Via a bifrontal craniotomy, osteotomies were created across the orbital roof. A strip of bone 6 mm in width was removed above the frontal osteotomy, and the freed orbit was elevated and fixed with miniplates (Figs 7 and 8). A bone graft was placed on the orbital floor to elevate the right globe, and bone grafts were placed in the zygomatic osteotomy and medially in the cleft between nasal bridge and medial orbital wall. The medial canthus was secured transnasally with a 30-gauge wire. The lateral canthus was dissected free and repositioned with a 30-gauge wire through two lateral drill holes. Double Z-plasties were used

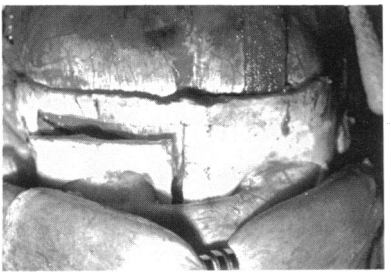

FIGURE 7
Bone removed from right orbit, Dec. 9, 1987.

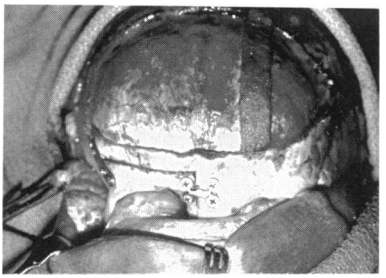

FIGURE 8
Repair of orbit with mini-plates.

to lower the right ala and reconstruct the right lower lid. The fibrotic tissue in the nasal right lower lid was partially resected and the lateral lower lid advanced. A conjunctival graft harvested from the left eye was then used to cover the scleral defect on the inferior right globe (Fig 9).

The inferior conjunctival graft was edematous postoperatively, presumably from to filtration through the eye. Schiotz tonometry readings were 12 OD and 21 OS. On January 20, 1988, preserved sclera (12 x 14 mm) was used to reinforce the inferior globe. The sector of scleral agenesis extended as far posteriorly as was dissected and presumably extended to the optic nerve (Figs 10 and 11). Postoperatively the edema resolved in the repaired sector of the globe, and the child returned home.

In May 1989, he returned to New York. The visual acuity was hand motions OD and 20/30 uncorrected OS. The right globe moved well horizontally but elevated poorly and did not infraduct at all. The applanation tension was 16 OU. The nasal inferior fornix was replaced by loose symblepharon. Levator function was normal OU. On May 31, 1989, after revision of the right lip and nose, the adhesion to the lower lid was mobilized. The underlying scleral graft was intact. A conjunctival graft was used to cover the inferior globe, and the lateral normal lid was secured to the area of the medial canthus.

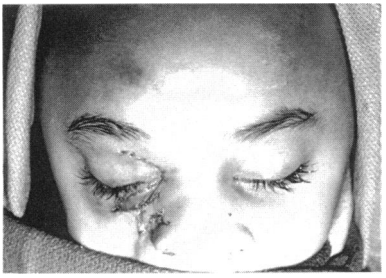

FIGURE 9
Postoperative appearance, Dec. 9, 1987, after craniofacial surgery and repair of right lower lid, right medial canthus, and nose.

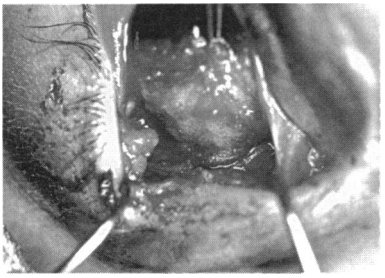

FIGURE 10
Release of nasal lower lid from globe. Sclera is thin and blue reflex of choroid is visible inferiorly.

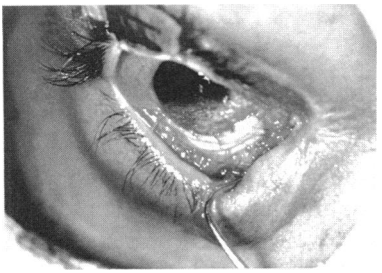

FIGURE 11
Scleral graft to right inferior globe, Jan. 20, 1988.

The child returned to New York in 1990 (Fig 12). The applanation tension was 14 OD and 17 OS. The inferior cornea OD was scarred and vascularized, and a nasal adhesion had developed again to the globe. Biometry revealed an axial length of 22.15 mm OU. On October 2, 1990, the columella was reconstructed by rotation of a previously banked fork flap, and the second and fourth web spaces of the right hand were deepened.

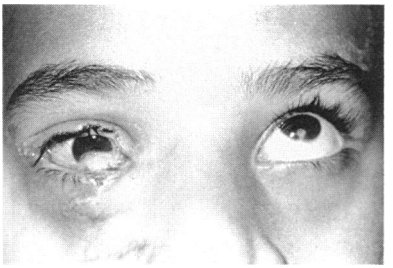

FIGURE 12
Oct. 12, 1990. Right eye does not elevate and inferior cornea is scarred. Scar from dermoid excision seen on left inferior cornea.

The symblepharon OD was cut; the underlying sclera was intact. The lateral canthus was mobilized, and the lateral right lower lid advanced nasally. Redundant skin of the lower lid was excised.

The child returned to New York in 1991. On September 11, 1991, the right inferior fornix was revised; right third and fourth digits were separated with full-thickness skin grafts, the nose and lip were revised, and bilateral myringotomies were performed. In December 1991, the child's weight was 27.7 kg and height 127.5 cm (less than 5th percentile for age). Because of the child's relatively small stature, he was evaluated by a pediatric endocrinologist to rule out hypopituitarism associated with septo-optic dysplasia.[102] Physical examination was completely normal, and endocrinologic studies also were normal.

From September 1991 to May 1992 the child was enrolled in the first grade in the United States. Details of his life in the Dominican Republic are not known, but he did not attend school regularly there. By May 1992 a symblepharon had reformed inferonasally OD, and the inferior cornea was scarred and opaque. The intraocular pressure was 20 OD and 14 OS. Because he was returning to the Dominican Republic, where he could not be examined regularly, he was not a candidate for a cosmetic lens. In March 1993 the bilateral alveolar palatal cleft was repaired with iliac crest, and an oronasal fistula was closed.

He returned to the United States in May 1994 (Fig 13) and in September 1994 began the second grade at age 11. He was unable to read before he began school in the United States, but by spring 1995 he read English at a third-grade level. In March 1995 he developed mild asthma prior to further reconstructive nasal surgery. He weighed 46.3 kg (25th percentile) and was 142.25 cm tall (10th percentile). His karyotype was normal.

## DISCUSSION

Approximately 149 cases of cryptophthalmos have been described in the

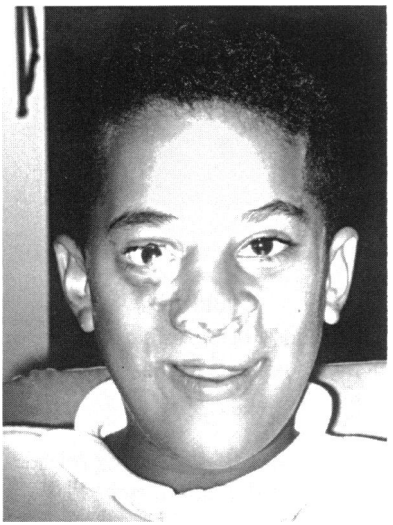

FIGURE 13
Child at age 11, June 1994. Level of globes is nearly symmetric.

American, European, and Asian literature (Table I). Only cases with documented agenesis of at least part of the normal cornea, sclera, and lid were included, and these were divided into three categories: bilateral complete (78), unilateral complete (56), and partial cryptophthalmos (15) (Table III). Some cases previously reported as cryptophthalmos appeared to be colobomata with symblepharon or microblepharon. Although such cases may be different manifestations of the same embryologic misstep, they were excluded from the review. Also, cases of Fraser's syndrome without cryptophthalmos were excluded. This series thus may not exactly match other series.[20] To our knowledge, this is the only reported case of partial cryptophthalmos with agenesis of the extraocular muscles normally found in this section of the orbit.

Of the 140 reports which describe both eyes, 112 (80%) have anomalies of both eyes. Anomalies of the fellow eye are described in approximately half the cases of unilateral complete cryptophthalmos and one third of cases of unilateral partial cryptophthalmos (Table III). The review suggests that complete cryptophthalmos is more common than partial cryptophthalmos. Because complete cryptophthalmos is dramatic and more likely to stimulate a case report than milder anomalies, and the distinction between partial cryptophthalmos and coloboma with symblepharon is not clear, the true incidence of bilateral complete, unilateral complete, and partial cryptophthalmos is not known.

In 1910 Coover [87] reported bilateral crytptophthalmos in a mother and

her daughter. In 1921 Magruder [80] described her son, who also had bilateral cryptophthalmos, without photographic documentation. In 1992 Saal and associates[5] reported a mother and her daughter with bilateral cryptophthalmos. These five individuals had no nonocular anomalies. This rare familial form of isolated cryptophthalmos appears to be autosomal dominant and is distinct from cryptophthalmos with Fraser's syndrome.

The incidence of major nonocular anomalies associated with the remaining 144 cases of cryptophthalmos is summarized in Table IV. Some of these cases may be isolated cryptophthalmos, and the incidence of major anomalies in syndromic cryptophthalmos may be understated. Anomalies of the external ear and nose and syndactyly affected over half of cases. Anomalies of the external genitalia were reported in just under half of cases, and anomalies of the kidneys and urinary system were found in approximately one third of cases. Cleft lip and palate were noted in approximately one fourth of cases. The incidence of the anomalies appeared to be similar with bilateral, unilateral, and partial cryptophthalmos, but it is not known if the severity of the associated anomalies is related to the severity of the cryptophthalmos. In 40 of the 144 cases of nondominant cryptophthalmos,

**TABLE IV: INCIDENCE OF MAJOR ANOMALIES ASSOCIATED WITH NONDOMINANT CRYPTOPHTHALMOS**

| | Bilateral Complete (n=73) | Unilateral complete (n=56) | Partial (n=15) |
|---|---|---|---|
| Not stated/none | 15 | 7 | 2 |
| Ear/nose | 42(58%) | 39(70%) | 12(80%) |
| Syndactyly | 37(51%) | 35(63%) | 12(80%) |
| Genital | 32(44%) | 28(50%) | 7(47%) |
| Urinary | 21(29%) | 20(36%) | 5(33%) |
| Cleft lip/palate | 15(21%) | 19(34%) | 5(33%) |
| Gastrointestinal | 12(16%) | 8(14%) | 2(13%) |
| Laryngeal atresia | 10(14%) | 16(29%) | 2(13%) |
| Umbilical hernia | 9(12%) | 1(2%) | 2(13%) |
| Mental retardation | 5(7%) | 9(16%) | 0 |
| Pulmonary hypoplasia | 3(4%) | 4(7%) | 2(13%) |

infants were stillborn or died within 1 week of birth: 21 of the 73 cases of bilateral complete cryptophthalmos (28%), 16 of 56 cases of unilateral cryptophthalmos (29%), and 3 of 15 cases of partial cryptophthalmos (20%). Six families with at least one child with bilateral cryptophthalmos and one with unilateral cryptophthalmos have been described.[12,18,49,52,64,71] Two families with one child with unilateral cryptophthalmos and one with partial cryptophthalmos and another two families with one child with right unilateral cryptophthalmos and one with left unilateral cryptophthalmos also were identified.[20,25,56] The occurrence of bilateral, unilateral, and partial cryptophthalmos in the same family and the similar incidence of associated anomalies in these groups suggest that bilateral, unilateral, and partial cryptophthalmos are different manifestations of the same genetic defect.

Because the genetic defect is unknown, the sex distribution of cases was examined (Table V) to aid in defining inheritance. Of the presumed isolated dominant cases, 4 of 5 are female. Of the remaining 144 cases, 63 are male, 68 female, and 13 indeterminate or not known. Thus, sex does not appear to be a predisposing factor in nondominant cryptophthalmos.

The number of affected siblings of the 144 presumed syndromal cases also was determined. In 54 reports there were no siblings or sibling information. The remaining 90 case reports came from 70 families, and 120 normal children and 19 other siblings with cryptophthalmos were counted in these reports. In addition, 20 siblings with anomalies other than cryptophthalmos were described. These included a female with Klippel-Trénaunay syndrome; a female with left facial palsy, atrioseptal defect, and abnormal ear; a stillborn male with upper-lid coloboma, syndactyly, and genitourinary and bowel anomalies; a male with cleft palate, syndactyly, and cryptorchidism; a female who died at age 2 months with "lagophthalmos"; 2 term stillborn infants; a term stillborn child with "ankyloblepharon"; and 12 infants whose early deaths are not explained. Also, 15 first- or second-trimester abortions were described, including 4 with cryptophthalmic features.

To calculate the incidence of cryptophthalmos from these reports, a single proband case was subtracted from each of the 70 family groups, leav-

TABLE V: SEX DISTRIBUTION OF CRYPTOPHTHALMOS

| | Male | Female | Not known or Indeterminate |
|---|---|---|---|
| Dominant cryptophthalmos | 1 | 4 | |
| Bilateral complete | 35 | 31 | 7 |
| Unilateral complete | 25 | 27 | 4 |
| Bilateral partial | 1 | 1 | |
| Unilateral partial | 2 | 9 | 2 |
| **Total** | **64** | **72** | **13** |

ing a total of 39 cases of cryptophthalmos. Using this figure and the 120 normal siblings, the incidence of cryptophthalmos is 24.5%. Some of the siblings with other anomalies probably carry the same genetic defect as the children with cryptophthalmos, and including these cases would affect the incidence of cryptophthalmos slightly. None of the first- or second-trimester abortions were included, since morphologic details are not available.

The incidence of cryptophthalmos among 24 families with known consanguinity also was determined.[6,11,15,17,19,21,23,33,37,39,45,49-50,52,61,66,78,81,85,96-97] These families accounted for 28 of the 144 reports of nondominant cryptophthalmos. In 7 cases there were no siblings or no sibling information. In the remaining 17 families, a total of 46 normal children and 8 siblings with cryptophthalmos was counted. Also, 17 children with other anomalies were described, including the female with Klippel-Trénaunay syndrome; the male with cleft palate, syndactyly, and cryptorchidism; a female with "lagophthalmos"; and 14 infants whose early deaths are not described. Six abortions also were counted in these families. Subtracting a single proband case from each family leaves a total of 12 cases of cryptophthalmos. Using only these cases and the normal siblings yields an incidence of cryptophthalmos of 20.7%. This analysis relied on published case reports, and some tallies of family groups may be incomplete or inaccurate. However, these figures appear to be consistent with autosomal recessive inheritance. It is of interest that a p11q21 inversion of chromosome 9 has been found in two related cases of Fraser's syndrome.[8]

Cryptophthalmos has also been reported in avian and mammalian models, including partial cryptophthalmos in cockatiels, bilateral and unilateral partial cryptophthalmos in the chicken, bilateral complete cryptophthalmos in the pheasant, unilateral complete cryptophthalmos in the pigeon, bilateral and unilateral complete cases in three inbred generations of mice, and right complete/left partial cryptophthalmos in the rabbit.[87,97,103-109]

Several theories have been proposed to account for the pathogenesis of cryptophthalmos and the associated midline and organ system malformations. In 1872 Zehender and Manz proposed "ablepharon by agenesis," failure of eyelid development and keratinization of the preocular ectoderm resulting in differentiation of the cornea into integument to protect the globe.[1] A disturbance in the growth of eyelid mesoderm secondary to failed or faulty induction by abnormal eyelid ectoderm has also been suggested.[110,111] Alternatively, corneal abnormalities associated with cryptophthalmos have been thought to occur when the lids fail to separate in utero at 17 to 21 weeks.[20] The associated anomalous development of the globe and the extraocular muscles suggests that cryptophthalmos is not simply a failure of programmed cell death.

Cranial neural crest cells give rise to many elements of the eye and its adnexae, including corneal endothelium and stroma, iris stroma and pig-

ment, trabecular meshwork, parts of the ciliary body, connective tissue of the extraocular muscles, and part of the bony orbit.[112-115] Studies in amphibian and avian embryo models indicate that cranial neural crest cells give rise to much of the connective tissue of the face and head.[112-115] Other studies of neural crest migration and differentiation indicate that the APUD (amine precursor uptake and decarboxylation) cell, a histochemically argyrophilic neural crest derivative responsible for neuroendocrine production, is ubiquitous and is thought to populate many major organ systems, including the trachea and bronchi, the esophagus, stomach, small and large intestine, the genital tract, and neck of the uterus.[116-117] Other candidate cells of neural crest derivation may include renal parenchyma.[116]

Cleft lip and cleft palate have been shown by Johnston[112] to result from neural crest formation defects, and syndactyly from failure of programmed cell death in the migrative or proliferative stage in avian embryos. However, the embryonic undifferentiated vertebrate limb bud is capable of normal development if transplanted to a favorable ectopic site without the presence of neural crest.[118] Inferior cervical neurotome malformation has been shown in humans to result in anomalies of the upper limbs, trachea, heart, esophagus, and diaphragm, and lumbosacral neurotome malformation to result in anomalies of the lower limbs, bladder, external genitalia, rectum, and anus.[116] More recent studies using tiny transplants of prechordal mesoderm between quail and chick embryos indicate that prechordal mesoderm gives rise to the inferior oblique, inferior rectus, and medial rectus muscles.[119] The median paraxial mesoderm gives rise to the other three extraocular muscles, the mesencephalic meninges, and otic capsules.[119] Using quail-chick chimeras, Couly and colleagues [120] also have described in detail the contributions of the neural crest and mesoderm to the embryonic formation of the skull.

Neural crest cells have been shown to migrate into many of the areas affected by Fraser's syndrome, including cryptophthalmos, and some of the defects associated with cryptophthalmos may be related to a defect in neural crest formation, migration, proliferation, or differentiation. However, it is now thought that pulmonary hypoplasia, the development of striated extraocular muscle, and syndactyly do not result directly from neural crest pathology. Such defects could potentially result from a misstep in reciprocal induction between neural crest and surrounding mesoderm, but the interaction between cell types remains to be defined. In addition, some anomalies associated with cryptophthalmos, such as optic nerve dysplasia, may result from embryonic tissue differentiation before neural crest migration begins. Thus, a defect in neural crest alone is not likely to account for all of the anomalies associated with cryptophthalmos, and the underlying genetic defect appears to affect both mesoderm and neural crest.

Recently, a master control gene for eye development in *Drosophila* was described, and a homologous gene is present in vertebrates.[121] Whether an

error in this gene or other genes involved in eye morphogenesis leads to the different manifestations of cryptophthalmos remains to be determined.

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## DISCUSSION

DR WILLIAM C. FRAYER. Drs Konrad, Merriam, and Jones have presented the results of a painstaking analysis of 149 patients reported in the literature with complete or partial cryptophthalmos. In addition, they have described a patient with partial cryptophthalmos associated with other anomalies that they undertook to treat surgically.

This paper concerning a congenital anomaly affords me with an opportunity to make note of significant anniversary. Dame Ida Mann of London and Perth, Australia, was generally considered in her day to be the premier ophthalmic embryologist and teratologist. Just 50 years ago at the Annual Meeting of the American Ophthalmological Society at The Homestead, she was made an Honorary Member. The meeting that year celebrated the end of World War II. Ida Mann spoke about her wartime experiences as an ophthalmologist.

Experience with complete cryptophthalmos is limited. The condition is very rare. I show you here a picture of a complete cryptophthalmos taken from Ida Mann's text (1956). The anomaly is defined as a condition in which the lid folds never form and therefore leave the cornea entirely exposed. The corneal epithelium is somehow converted by metaplasia to surface epidermis, leaving a continuum of skin across the ocular surface. Lashes are never formed, and associated lid structures are usually absent.

It seems obvious that surgical repair of the complete form is not practical. An attempt at such repair was made some years ago at Children's Hospital of Philadelphia. This attempt followed positive evidence of electroretinal activity through the intact skin. The skin was incised, and a cleavage plane was found between the opaque cornea and the overlying skin. A corneal graft was used to replace the excised cornea. The specimen shows a dense, fibrous membrane, somewhat resembling sclera, with a crystalline lens attached to its posterior surface. The epidermis is missing because it was surgically separated from the underlying structure. There was no conjunctiva. In the absence of conjunctiva and eyelids, the graft became opaque.

Repair of partial cryptophthalmos is another story, as can be seen by the experience of today's essayists. Their case is clearly a partial cryptophthalmos. Except for the significant other anomalies, it might be called a coloboma with symblepharon. Using the criteria established by Thomas, however, their pateint clearly falls within the Fraser's syndrome category. In their patient, associated anomalies were not life-threatening, but the possibility of more serious anomalies in such patients is what makes their study so important.

In their analysis of the 149 reported cases, they have been able to document the incidence of the various manifestations of Fraser's syndrome. The study emphasizes the importance of a very thorough systemic evaluation of such patients. The relatively high incidence of life-threatening associated

anomalies is a highly significant finding.

The mechanism of development of these various forms of cryptophthalmos remains obscure. Early students felt that this was a primary agenesis of the eyelid. As Konrad, Merriam, and Jones have pointed out, however, increasing knowledge concerning the component parts of this complex syndrome only emphasizes the fact that we know so little of its origin. Recent developments in genetics provide background for a better understanding of this type of anomaly, hopefully in the near future.

I wish to thank the authors for permitting me to discuss this interesting paper and for providing me with the manuscript in a timely fashion.

DR ROBERT KENNEDY. This is a most interesting paper and subject. I would like to show slides that are a bit different from exact cryptophthalmos, but they do show some of the unusual corneal defects. This does show unusual brow, hair, and marked upper lid defects with lid epithelium extending over the corneas with blind status. She had an identical twin sister who looked absolutely the same but would not allow photographs to be taken. They were seen in Natal, Brazil on the medical HOPE Ship in 1972. Here is a little boy, age 2, seen in Sao Paulo, Brazil in 1968, with congenital defects involving hair distribution, eyebrows, lids, globes, nose and mouth. This next slide shows a 10 year old boy operated in Afghanistan in 1966. He brought out the necessity for the multispecialty group approach to handle these problems, and taught me to wait to see these patients the day before I was to leave the HOPE Ship, or leave the country so as not to get involved.

The next 2 month old child is shown under anesthesia with a normal right eye and absent left eye with a small left socket except for a little dot of iris/corneal discoloration. There was the nasal defect and marked upper lip defect and severe cleft palate abnormalities. The anesthesia involved x-rays, CT scans in the operating room, normal tear passage evaluation and molding of a prosthesis conformer. While the anesthesia was tolerated satisfactorily, a few weeks after going home, the patient suddenly developed the sudden infant death syndrome (SIDS).

I would like to add that in 1988 Dr. Merriam presented a co-authored paper before this Society, and in the discussion period I presented this case since I had experienced 3 cases of SIDS in patients with various somewhat similar ocular syndromes. At that time there was no audience show of hands of similar experiences. Now after 50 years of practice, my experience has increased to 4 cases and I wonder if anyone has had a similar experience? (No show of hands.) Apparently the syndrome is not very common.

DR IRENE MAUMENEE HUSSELS. I would like add one unsuccessful case of repair. But before doing that I would like to mention Ali Khodadoust's work. I spent time in Shiraz about twenty years ago at which point he was taking care of three sibs all of whom were successfully repaired. He had created a

2 millimeter opening through the lids. These children were then about 8-12 years old. Encouraged by his results, I tried to repair another patient. She has the typical hairline that grows toward the eye. Unfortunately, the opening closed over. A mucous membrane graft from the mouth was also unsuccessful. She is now 6 or 7 and recognizes color. Perhaps she is a candidate for a keratoprosthesis. I follow another such patient who is of Oriental extraction. One can immediately make the diagnosis of cryptophthalmos because all these patients resemble each other like sibs or like all Down's syndrome patients have unmistakable similarities. I am questioning the diagnosis in Dr. Merriam's patient. I think his patient looks different and may have the amniotic band syndrome or a facial clefting syndrome.

DR JULES BAUM. In a large series of patients with Goldenhar's syndrome published over twenty years ago, one child exhibited cryptophthalmos on one side and an unusual type of Goldenhar on the other, in which an ectopic pupil was seen, pulled down behind a large atypical lipodermoid. Because of sensory deprivation, I performed an optical iridectomy. As she grew up, her vision maintained 20/40, and as in storybook fashion, she was graduated from college with honors. This patient and yours, with a dermoid, may represent a subset.

JOHN C MERRIAM, MD. Thank you all for your comments. I appreciate Dr. Frayers' thoughtful discussion. There is a spectrum of anomalous development of the globe in cryptophthalmos. Cases in which the globe is least affected are those which might lend themselves most easily to surgical repair. Although there are only five in literature, the eyes in the dominant cases may be less disorganized and might be repaired with some success. I don't think that Dr. Khodadoust has published his three cases; but I suspect the globes are relatively normal. The presence of some conjunctiva to prevent readhesion of the lids may be a requirement for successful repair of complete cryptophthalmos. Dr. Kennedy showed some interesting cases that he has seen in his very wide experience and wide travels. He mentioned the problem of SIDS. I don't have the answer to that, but children with severe facial anomalies may be unwelcome children, and one can't rule out the possibility of some sort of trauma as the cause of their death.

Dr. Hussels asked about the hairline. Our patient had a normal hairline. If you look at the literature, many children with cryptophthalmos and other anomalies including lid coloboma have an abnormal hairline. Dr. Hussels also suggested amniotic band syndrome or a clefting discorder as alternative diagnoses.

Cryptophthalmos is a clinical term for incomplete differentiation of the lid and globe, and this child certainly has incomplete development of part of the lower lid, sclera, extraocular muscles and optic nerve; and the associated anomalies appear to be consistent with Fraser's syndrome.

The clinical term cryptophthalmos does not tell us about pathogenesis, and as Dr. Baum suggested, there may be subsets of cryptophthalmos. Amniotic band syndrome may produce craniofacial and limb anomalies secondary to constriction. I do not believe that cryptophthalmos has been reported with amniotic band syndrome, and an amniotic band does not seem likely to lead to a coloboma of the optic nerve or to a corneal dermoid. However, while we suspect that our patient's anomalies are due to a recessive genetic defect, we cannot be absolutely certain of their etiology. Without a doubt, he has a clefting disorder. The association of cryptophthalmos with various clefts - lip, palate, nose, lid or globe coloboma - is well documented. The pathogenetic relationship between cryptophthalmos and clefts is not known.

Thank you again for your attention.