THALIDOMIDE EMBRYOPATHY: A MODEL FOR THE STUDY OF CONGENITAL INCOMITANT HORIZONTAL STRABISMUS*

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INTRODUCTION

THE PRIME GOAL OF CLINICAL TERATOLOGY IS TO IDENTIFY AND CHARACterize environmental agents responsible for damage to the developing embryo, thus facilitating the removal of these agents from possible contact with the pregnant woman. This removal is possible for agents that are controllable or are nonvital medications, such as thalidomide, a drug that because of its teratogenic effects is no longer available except for its limited use in the treatment of some dermatologic and immune diseases.[1-3] The adverse effect of a few necessary drugs, and certain nutritional states of the woman, such as in diabetes, can only be modified but not eliminated as a potential hazard to the fetus. It is particularly difficult to prevent pregnant women from using alcohol, cocaine, and other similar drugs commonly found in certain social settings.

The discipline of teratology, however, has a wider application; it is the study of causes of congenital malformations. Known or suspected teratogenic agents are analyzed for their action and effect on normal and abnormal development. In this way, greater insights are obtained into human development and the factors necessary for normal differentiation of cells, tissues, and organs. In this thesis thalidomide embryopathy will be used as a model to gain insight into the time and location of developmental disturbances responsible for certain forms of congenital incomitant strabismus.

Duane syndrome[4] is the most extensively studied and best understood of the types of congenital incomitant strabismus. However, other forms do exist, such as abduction deficiency associated with seventh nerve palsy in the Möbius syndrome complex and, more rarely, horizontal gaze paresis,

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isolated lateral rectus palsy, and abduction deficiencies with vertical limitations that do not show a clear paretic pattern. The clinical separation between these conditions is frequently hazy, and in syndromes such as Möbius there are examples of the complete spectrum of these types of horizontal incomitant movement.[5]

Little clinical information has been added to Duane's original description in 1906 of patients with abduction weakness associated with narrowing of the palpebral fissure and retraction of the globe on adduction.[4] He observed that some patients exhibited more adduction than abduction deficit, and he noted various secondary characteristics such as upshoot and downshoot on adduction in some patients. These different motility patterns were placed into various classifications,[6,7] but the pathophysiology of the condition remained confusing; some reports described normal anatomy of the lateral rectus muscle, whereas others described fibrotic changes.[8,9] Similarly, there was no agreement on whether the abducens nucleus or nerve was absent, hypoplastic, or normal.[10-12] The mystery about the observed clinical findings began to unwind with the emergence of electromyographic data that suggested cocontracture of muscles on adduction.[13-23] The electromyographic patterns observed aided in understanding the variety of clinical pictures.[24-27] Similarly, although there has been a number of reported cases of abnormal innervation of the lateral rectus,[11,12] the implication of this finding was better appreciated in subsequent autopsies on known clinical cases of Duane syndrome.[28,29] The cause of retraction, upshoot, and downshoot is not completely established, and some experimental data conflict.[23,26,30]

Duane syndrome is an uncommon but not rare form of motility disturbance, occurring in about 1% of strabismus cases.[31] It seems surprising that nature would make this type of primary innervational error so frequently, since other probable examples of congenital aberrant innervation, such as Marcus Gunn jaw-winking syndrome and crocodile tears, occur infrequently.

Although most cases of Duane syndrome are an isolated finding occurring sporadically, about 10% show a hereditary pattern.[7,31-37] Additionally, a significant number of cases of Duane syndrome or "abduction weakness" occur in association with other anomalies.[38-57] The types of congenital malformations reported suggest that many of these anomalies may be associated with a developmental disturbance in the fourth through seventh weeks after conception.[38,39,58] This led us to examine, in a preliminary study, our own cases of Duane syndrome with systemic anomalies and to review some informative cases in the literature. Our purpose was to attempt to narrow the period of suspected disturbance by

analyzing the associated anomalies and also to gain a better understanding of the factors that contribute to this syndrome. Although the findings reported herein provided greater insight into the association between Duane syndrome and systemic anomalies, there were not enough cases that involved one syndrome or that showed a common cluster of anomalies to allow us to draw definite conclusions. The ocular motility patterns varied considerably in our cases, and some patients had no lid retraction.

Review of previous cases of Möbius-type syndromes reported in the literature showed that there are a number of different patterns of motility disturbances other than isolated abduction weakness that occur in the syndrome complex of which Möbius is a component.[5,59] The literature also indicated that there are many cases diagnosed as congenital lateral rectus palsy associated with thalidomide ingestion early in pregnancy[60-70]; however, when the articles contained good descriptions of ocular motility, the authors noted that some cases had Duane syndrome or complete limitation of horizontal movement.[60,71,72] Additionally, a seventh nerve palsy was found in many thalidomide patients who presented a Möbius-type picture.[73] In one report from Sweden, 17 of 34 young children had a sixth nerve palsy.[67]

We therefore decided to use thalidomide embryopathy as a model for studying ocular malformations. The questions addressed in this thesis are as follows: (1) Are the various patterns of congenital horizontal incomitant strabismus (ie, Duane syndrome, isolated abduction deficiency, gaze paresis, and motility disturbances of Möbius syndrome) interrelated and based on a similar pathophysiologic defect? (2) Can we obtain more information about the time and location of embryonic (or fetal) disturbance by studying the associated ocular and systemic malformations? (3) Is thalidomide embryopathy a good model for studying ocular malformations, particularly horizontal incomitant forms of strabismus?

A review of pertinent literature and a history of thalidomide embryopathy will be presented first.

LITERATURE ON THE ASSOCIATION OF DUANE SYNDROME AND OTHER ANOMALIES

Many series in the literature indicate a number of skeletal conditions in patients with Duane syndrome.[38,39,45,49]

In a review of 186 cases of Duane syndrome seen at the Mayo Clinic, Pfaffenbach and associates[39] noted congenital hearing and ear anomalies in 14 patients (7.5%). Although this series may be biased toward patients with syndromes, the distribution of pathologic conditions is noteworthy. The authors also found radiologic evidence of spinal abnormalities in 16% of the patients. After reviewing the literature, they proposed that patients

with Duane syndrome are 10 to 20 times more at risk for skeletal anomalies of the ear than is the general population.[39]

In a survey of 500 deaf children, Alexander[41] noted 7 cases of Duane syndrome. Four additional patients demonstrated a restriction of horizontal movement of all four horizontal muscles, a gaze-type pattern.

Although Duane syndrome occurs with many craniofacial malformations, such as macrostomia, microsomia, cleft palate, and oral and systemic anomalies, this association is most often noted in two syndrome complexes—Wildervanck syndrome and hemifacial microsomia, particularly the Goldenhar variant. Wildervanck[74] designated the triad of Duane syndrome associated with Klippel-Feil anomalies of the spine and sensorineural deafness as cervico-oculo-acoustic syndrome. The frequency of the isolated forms of Duane syndrome is higher in females (60% to 70%), and there is an almost complete predominance of females in Wildervanck syndrome.[74-80] Kirkham[31] reviewed 112 cases of Duane syndrome and noted 12 cases with perceptive deafness, 5 with Klippel-Feil anomaly, and only 2 with the complete triad. Wildervanck also observed variable expressivity of this syndrome and suggested that only two characteristics of the triad are needed to make the diagnosis. In Fraser and MacGillivray's[75] review of the literature, there were four case reports of dermoids. These authors concluded that intermediate forms exist between cervico-oculo-acoustic syndrome and other first arch syndromes such as Goldenhar.

The deafness noted in Wildervanck syndrome is often secondary to a congenital inner ear anomaly, although mixed forms have been described. Tomography and computed tomography (CT) of otologic structures have demonstrated frequent abnormalities of the middle ear structures and semicircular canals. Although not necessarily present in all cases, Duane syndrome is a diagnostic characteristic of Wildervanck syndrome. A less impressive but still definite association occurs between Duane syndrome and hemifacial microsomia. More than 20 cases are cited in the literature, and since the diagnosis is somewhat difficult without ophthalmologic expertise, the number is probably underreported.[7,39,40,42,45-47,50]

"Hemifacial microsomia" is the term that Gorlin and colleagues[81] used to characterize a spectrum of malformations of the ear, mandible, mouth, eye, and often the cervical spine. These abnormalities occur unilaterally in most patients. Gorlin and co-workers[81,82] proposed that Goldenhar syndrome (oculo-auriculo-vertebral dysplasia) represents a variant of hemifacial microsomia. Goldenhar[83] described the triad of epibulbar dermoids, lipodermoids, and preauricular skin tags and fistulas. Later the association of upper lid coloboma and vertebral anomalies with this triad

was well documented. According to a review of this syndrome, Duane syndrome has occurred both bilaterally (even in cases showing unilateral hypoplasia of facial bones) and unilaterally. When found in the hemifacial microsomia group, Duane syndrome appears to occur most frequently in the patient with a Goldenhar-type syndrome who usually manifests epibulbar dermoids and lipodermoids.[38,40,43,45,47,49,50,84-88]

Although retraction of the globes on adduction is an identifying finding in Duane syndrome, it is not present in all cases that have electromyographic characteristics of Duane syndrome. However, without retraction, the clinical diagnosis is difficult and patients appear to have a gaze paresis. One such patient had a Klippel-Feil anomaly, unilateral deafness, and cleft palate.[57]

The frequent association of Duane syndrome with limb malformations is less clear. In the series of Pfaffenbach and co-workers[39] of 186 cases at the Mayo Clinic, 13 cases had skeletal deformities involving the extremities; the most frequent anomaly was of the feet (six patients), but one patient was missing a thumb. There are a few other syndromes (discussed later) with limb anomalies and incomitant strabismus.

LITERATURE ON MÖBIUS AND MÖBIUS-TYPE SYNDROME

The association of cranial nerve palsies with craniofacial and limb malformations is well recognized in the literature, occurring in a number of syndromes. The differentiation between many of these syndromes is not distinct, however, and they have been grouped under the collective heading of "oromandibular limb hypogenesis syndromes."[82] The following syndromes were included in that group: Möbius, Hanhart, hypoglossia-hypodactyly (aglossia/adactyly), glossopalatine anklyosis and Charlie M. Observed limb anomalies ranged from mild changes such as syndactyly to amputation defects of the limb. Since the proximal limb structures were characteristically normal or near normal, Temtamy and McKusick[89] referred to this group of syndromes as "terminal transverse defects with orofacial malformations (TTV-OFM)" and added to this group another entity, ectrodactyly with orofacial malformations.

Cranial nerve palsies may occur in any of these entities but the combination of sixth and seventh nerve palsies becomes the distinguishing criterion for Möbius syndrome. Paresis of the sixth or seventh cranial nerve is usually bilateral, but unilateral involvement of either nerve can occur. Systemic findings are frequent, and it is the patients with severe systemic findings plus cranial nerve palsies in whom syndrome delineation is confusing and frequently somewhat arbitrary. Deficiency of the sternal head of the pectoralis major (Poland anomaly) is at times associated

with an ipsilateral hand deformity (Poland syndrome).

There is no proven single etiology for the syndromes of terminal transverse defects with orofacial malformations. Most cases are sporadic, although there are reports in the literature[90-93] of families with Möbius syndrome that demonstrate autosomal dominant, recessive, and multifactorial patterns of transmission. Occasional cases seem to have resulted from a teratogenic action or some environmental influence in the pregnancy.[73,94-97]

Some investigators have proposed that these conditions fall into a formal genesis syndrome: that is, "syndromes that have similar mechanisms of production of anomalies but are etiologically heterogeneous."[98,99] Formal genesis syndromes frequently show a pattern of anomalies that implicate multiple nonspecific developmental field disturbances.[99,100]

Vascular interruption is another possible mechanism responsible for the constellation of malformations seen in these Möbius-type syndromes.[101,102] The cause of the vascular interruptions may be multiple—environmental, genetic, or local accidents in development—but the result is ischemia, edema, and hypoxia to the embryonic tissues or cranial nerve nuclei supplied by that vessel. The hypothesis of asphyxia as a cause has been strengthened by some of the reported pathologic findings obtained at autopsy, and this theory supports the concept of a formal genesis syndrome with a final common pathway.[103,104]

HISTORICAL BACKGROUND OF THALIDOMIDE EMBRYOPATHY

Thalidomide (α[N-phthalmido] - glutarimide) was introduced on the market in 1957 in West Germany under the brand name of Contergan and was subsequently licensed in 46 other countries on the European, Asian, and African continents. Other pharmaceutical companies manufactured thalidomide in different concentrations under other trade names. Advertisements for the drug claimed that it was helpful in treating anxiety, insomnia, gastritis, and tension and that it was safe and harmless for pregnant women.[105-108] Thalidomide was not found to be very teratogenic in rodents, and routine screening tests of the drug did not reveal its high teratogenicity in humans and higher mammals.[109]

Four years after thalidomide was first sold, Lenz noted an increase in congenital malformations of the extremities in the West German population. He later made the correlation that the mothers of some of these children with birth defects had received thalidomide during pregnancy.[70,108] Within a few months of the initially reported observation, the drug was withdrawn from commercial sale in Europe and 9 months later was taken off the market in Japan.[105]

From the studies of periods of exposure compared to resultant congenital anomalies, it was established that thalidomide is teratogenic primarily between 20 and 35 days after conception (34 to 50 days after the last menstrual cycle). During this period thalidomide intake produces a wide spectrum of malformations, most frequently those involving craniofacial structures and extremities. These malformations can be summarized as follows[70,105-136].

Upper Extremity Anomalies

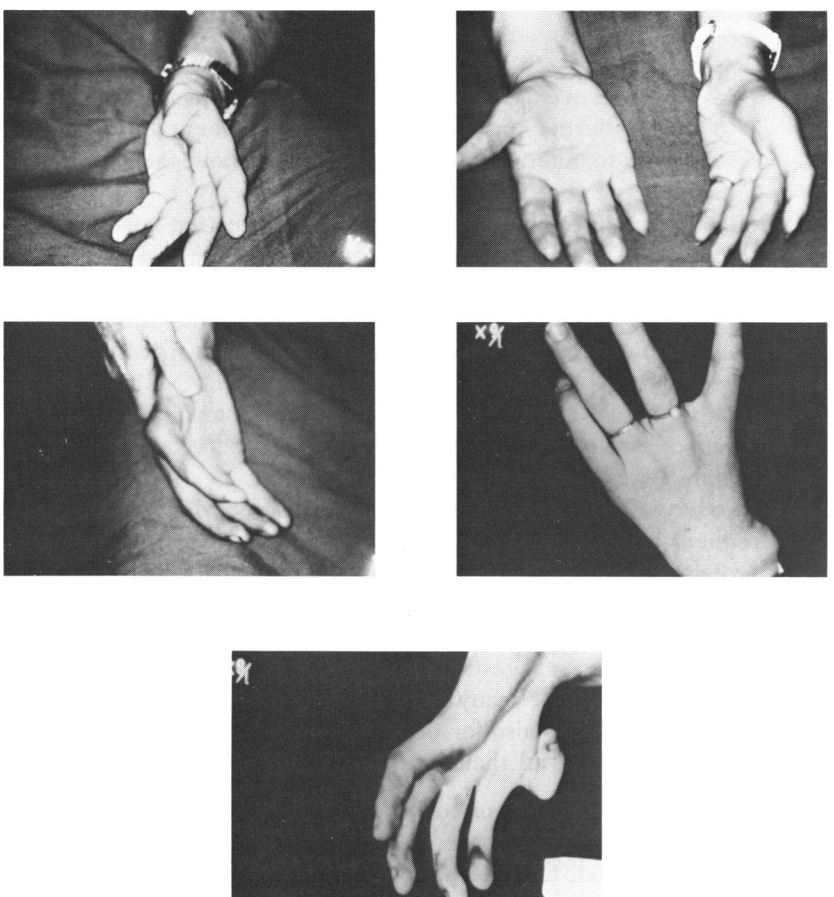


FIGURE 1
Thalidomide embryopathy. Various types of hand and thumb anomalies. Note absence of thumbs (*upper right*, *middle right*), which occurs in early midpart of sensitive period, and triphalangeal thumbs (*middle left*), which result from thalidomide intake late in the sensitive period.

A. Dysmelia abnormal development of the limbs) (Fig 1)
   1. Mild dysmelia: thenar muscle aplasia, triphalangeal thumbs (thumb has an extra joint), shoulder weakness.
   2. Moderate dysmelia: absent or very hypoplastic thumbs, flexion contractures of middle and index fingers, hypoplasia of radius and ulna, absent phalanges, hip and shoulder hypoplasia.
   3. Severe dysmelia: absent radius, phocomelia (hands attached directly to shoulders), amelia (absent upper or lower extremity), severe shoulder and hip anomalies.

B. Facial Anomalies
   1. Involvement of external and internal ear, ranging from anotia to mild malformations of ear, and also sensorineural deafness secondary to inner ear anomalies with or without external ear involvement (Fig 2).
   2. Ocular motility abnormalities primarily affecting horizontal movement, ranging from limitation of abduction to a Duane-type motility pattern.
   3. Facial nerve palsy: unilateral or bilateral, partial or severe.
   4. Abnormal lacrimation, most frequently tearing when eating or sucking, but also lack of emotional tearing.
   5. Other ocular anomalies, such as uveal coloboma, glaucoma, microphthalmos, refractive error, ptosis, and cataract.

C. Systemic Anomalies

   A variety of systemic anomalies have been reported, the most frequent being kidney malformations (hypoplasia or positional), cardiac anomalies, anal atresia, spinal anomalies, chest abnormalities, and central nervous system (CNS) complications. The incidence of heart anomalies was higher in newborn infants than in older children, suggesting that a cardiac condition may have been responsible for many of the stillbirths or early deaths of infants and perhaps also for the spontaneous abortions in some women who received thalidomide.

Thalidomide differs from many teratogens in that dosage seems not to be as significant a factor compared to time of intake of the drug. It is rapidly hydrolyzed and, therefore, shows a "pulse" type action on developing structures. It was possible to document a correlation of drug intake versus the observed malformations because many women took only a few pills and remembered on what days they took the drug when they were asked soon after delivery. These correlations became more accurate as the number of affected babies increased. The number of cases was estimated

Ear Anomalies

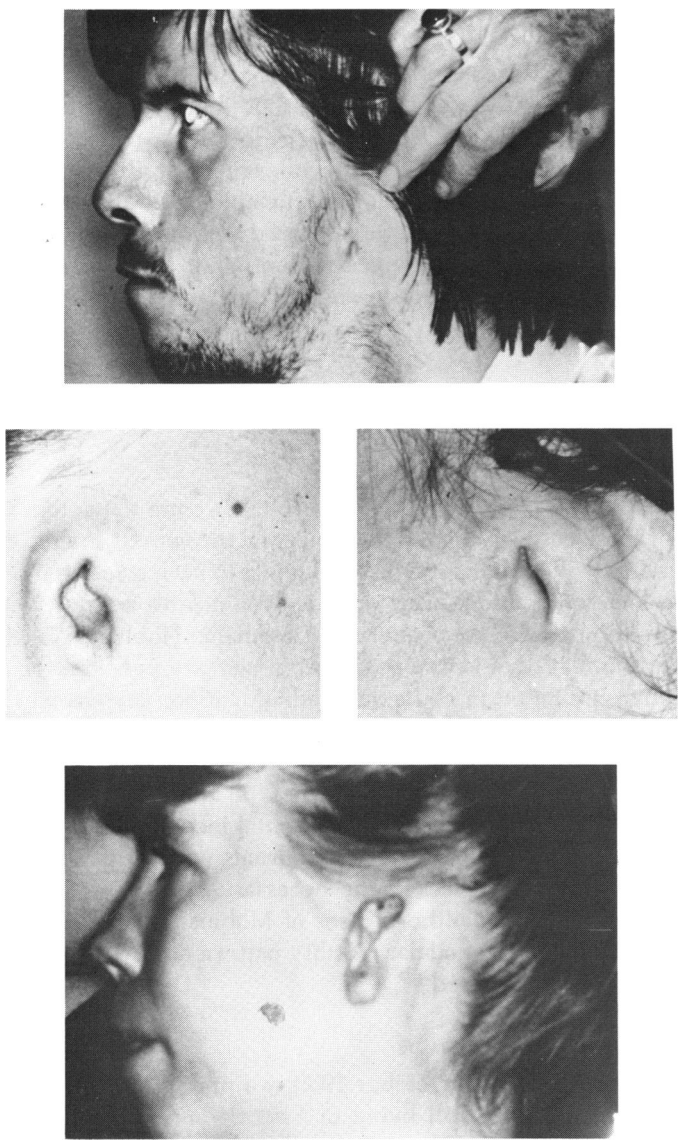


FIGURE 2
Thalidomide embryopathy. Various types of severe ear anomalies, ranging from anotia to severe microtia.

by Lenz to be between 5000 and 7000,[106,108] with greater than 3000 in West Germany alone. Since the survival rate is thought to have been between 40% and 70%,[105-107] this gives an overall estimate of 10,000 affected embryos. The timetables that various authors constructed on the sensitive periods for each type of anomaly are surprisingly consistent, and we will attempt to interpret the ocular motility data from our study of reported timetables.[70,71,105,130]

With the collaboration of a Swedish colleague, a study was undertaken to prospectively examine as many as possible of the known Swedish patients with thalidomide embryopathy who were available for examination. In this thesis we paid special attention to the observed ocular motility patterns in an attempt to answer the three questions proposed earlier.

PATIENTS AND METHODS

PRELIMINARY STUDY

In the preliminary study, most cases were taken from the author's clinic. Eleven of these cases of congenital horizontal incomitant squint, thought to be primarily of the Duane type and known to have associated congenital anomalies, were studied retrospectively and prospectively, with particular attention paid to the clustering of anomalies (Table I). We recorded the ocular motility, that is, the deviation in primary position, the degree of horizontal limitation in abduction and adduction, any changes in palpebral fissure, and vertical muscle involvement. Refractive errors, visual deficits, and other ocular anomalies were noted, if significant.

The literature was reviewed for types of anomalies reported with Duane syndrome or other forms of horizontal incomitant strabismus. An exhaustive review of foreign-language journals was not undertaken, nor were cases included that lacked the necessary detailed information.

In addition, 16 of the author's cases of Möbius-type syndromes were reviewed, and the type of ocular motility pattern and types of associated anomalies were summarized.[5]

THALIDOMIDE EMBRYOPATHY STUDY

Between August 1987 and October 1989, we prospectively examined 86 of 100 Swedish patients still living in Sweden and known to show the manifestations of thalidomide embryopathy. All patients were 26 to 29 years of age, since thalidomide was on the market for just less than 3 years (1959-1962) in Sweden, and thus only children conceived in those 3 years

could show manifestations of thalidomide embryopathy. The estimated number of living affected individuals in that country is believed to be accurate, since the medical community made substantial efforts to identify all affected children, and since convincing documentation of thalidomide intake during the sensitive gestational period was established at a public trial held a few years after the teratogenic effect of the drug was appreciated. After the trial a yearly compensation was awarded to the affected individuals based on the severity and type of their anomalies. The names of the children and information on the levels of their yearly monetary compensation were available to us, and we obtained permission to contact these individuals and offer ophthalmologic evaluation. Past medical records for these 100 individuals were reviewed, including the 14 not participating in the study. The 14 cases that we were not able to examine did not seem to represent any significant bias as to type or severity of malformations.

Eighty-six patients agreed to participate in our study. Eighty-four were examined in government eye clinics in six locations in Sweden, and two additional patients received a somewhat less complete examination in residential homes for the mentally retarded and deaf.

In addition to taking a thorough medical history, we performed the following examinations on almost all patients: visual acuity (corrected and uncorrected); inspection of facial structures, adnexa, and lids; examination of the anterior chamber by biomicroscopy; testing of pupillary reaction; evaluation of ocular motility by the Hirschberg method, prism cover test, Urist version reflex measurements, versions, ductions, ocular deviation in the up and down positions of gaze, fissure abnormalities and changes, and Wirt stereopsis test; corneal sensitivity; and ophthalmoscopy. Standard measurements included cycloplegic refraction with 1% cyclopentolate hydrochloride (Cyclogyl); applanation tonometry; canthal and pupillary distances; head circumference; height, weight, and shoe size obtained from the medical records; keratometry; and ultrasonography. Photographic documentation was made of ocular motility, systemic malformations of extremities and ear, and fundus examination of the posterior pole of the eye. Videotape documentation of ocular motility was performed on most patients with strabismus.

We did not do certain tests such as forced ductions because of the reluctance of many patients to agree to this type of examination. Some were even hesitant about undergoing a cycloplegic refraction. Because of frequent communication among all of the patients with thalidomide embryopathy in Sweden, we believe it would jeopardize further recruitment if we included tests that some patients did not wish to undergo because

TABLE I: PRELIMINARY STUDY: PATIENTS WITH INCOMITANT HORIZONTAL SQUINT (DUANE TYPE) PLUS OTHER OTHER OR SYSTEMIC MALFORMATIONS

CASE/ SEX	EXTERNAL OR INTERNAL EAR ANOMALIES	OTHER SYSTEMIC ANOMALIES	PRIMARY	LIMITATION ABDUCTION	LIMITATION ADDUCTION	FISSURE CHANGE	STEREOPSIS	OTHER OCULAR ANOMALIES	CLINICAL DIAGNOSIS
1/F	+ +	Preauricular tags; facial hypoplasia	St	+ + OS ± OD	0	+ + OS	—	Epibulbar dermoid OS	Duane syndrome + Goldenhar
2/F	+ +	Facial palsy (L side); mandibular hypoplasia; fusion C_2C_3	ET	+ + OS	+ OS	+ + OS	0	Conjunctival dermoid OS	Duane syndrome OS + Goldenhar
3/F	0	0	St	+ + OS	+ OS	+ + OS	—	Epibulbar dermoids; astigmatism OS; conjunctival dermoids OS	Duane syndrome OS + ocular dermoids
4/F	+ +	Slight asymmetry R side face	ET	+ + OU	+ + OU	0	0	Abnormal lacrimation conjunctival dermoids OU	Duane syndrome OU + Goldenhar
5/M	+ +	Submucous cleft; hypertelorism; cervical spine anomaly	ET	+ + OU	+ OU	+ + OU	0	Coloboma upper lid OS; conjunctival dermoid OU	Duane syndrome OU + Goldenhar
6/F	0	Hypertelorism	ET	+ + OU	0	+ + OU	0	Coloboma upper lid OS; corneal pannus OU, conjunctival dermoid	Duane syndrome OU + median facial cleft syndrome
7/F	+ + (deaf)	Klippel-Feil	St	+ + OD	+ OD	+ + OD	+	0	Wildervanck syndrome
8/F	+	Mild facial palsy	XT	+ + OD	+ + OD	+ OD	+	Abnormal lacrimation	Duane syndrome OD + crocodile tears
9/M		Lower limb (mild)	ET	+ + OU	+ + OS	+ + OU	+	Coloboma of choroid and iris OD	Duane syndrome OU + uveal coloboma

TABLE I: PRELIMINARY STUDY: PATIENTS WITH INCOMITANT HORIZONTAL SQUINT (DUANE TYPE) PLUS OTHER OTHER OR SYSTEMIC MALFORMATIONS (CONT'D)

CASE/ SEX	EXTERNAL OR INTERNAL EAR ANOMALIES	OTHER SYSTEMIC ANOMALIES	PRIMARY	LIMITATION ABDUCTION	LIMITATION ADDUCTION	FISSURE CHANGE	STEREOPSIS	OTHER OCULAR ANOMALIES	CLINICAL DIAGNOSIS
10/F	0	Lower limb (mild); mental retardation (mild)	ET; RH	+ + OS	0	+ OS	0	Choroidal coloboma OU	Duane syndrome OS + uveal coloboma
11/M	0	Mental retardation; broad thumbs and toes	St	+ OS	0	+ OS	—	0	Duane syndrome OS + Rubinstein-Taybi syndrome

+, Mild to moderate involvement; + +, moderate to severe involvement; 0, absent; —, information not available; ET, esotropia; St, straight (orthophoric).

they considered them uncomfortable or bothersome to driving a vehicle. Although we were able to persuade a remarkably large number of this group to undergo a 2-hour examination, we encountered significant reservations about additional medical evaluations. Many explained that they felt "over-studied" in their lifetime. We respected and were sympathetic to this viewpoint.

We decided that the most pertinent data were related to observation of the frequency and variety of ocular motility patterns and associated ocular and systemic anomalies as determined by history, examination, and medical records. We were able to obtain thorough histories, as we found the patients to be very well informed about their medical conditions.

RESULTS

PRELIMINARY STUDY

Duane "Plus" Patients

Table I summarizes the findings in our 11 patients with systemic anomalies associated with a congenital incomitant horizontal strabismus, primarily of the Duane variety. Cases 1 to 6 demonstrated to varying degrees the stigmata of hemifacial microsomia, Goldenhar variant, which is characterized by epibulbar dermoids or lipodermoids, upper lid colobomas, and malformations of the ear, facial bones, and cervical spine (Table II). Cases

TABLE II: PATIENTS WITH DUANE SYNDROME AND OCULAR DERMOIDS (EPIBULBAR OR LIPODERMOIDS) (n = 24)*

ANOMALY	NO OF PATIENTS
Ear anomalies	20
Preauricular nodes or fistula	10
External	8
Internal	3
Hearing deficit	8
Spinal anomalies	12
Cervical spine fusion anomalies or Klippel-Feil	11
Other	4
Other anomalies	
Tearing abnormalities	3
Seventh nerve palsy	3
Facial asymmetry	6
Cleft palate	5

*Cases 1 to 6 from the present study and 18 cases from the literature.[38,40,43,45-47,50,86-88,151] Eleven were male and 13 were female.

5 (Fig 3) and 6 (Fig 4) additionally had significant hypertelorism, with case 6 manifesting those findings associated with median facial cleft syndrome (hypertelorism, cleft lip and palate, etc).

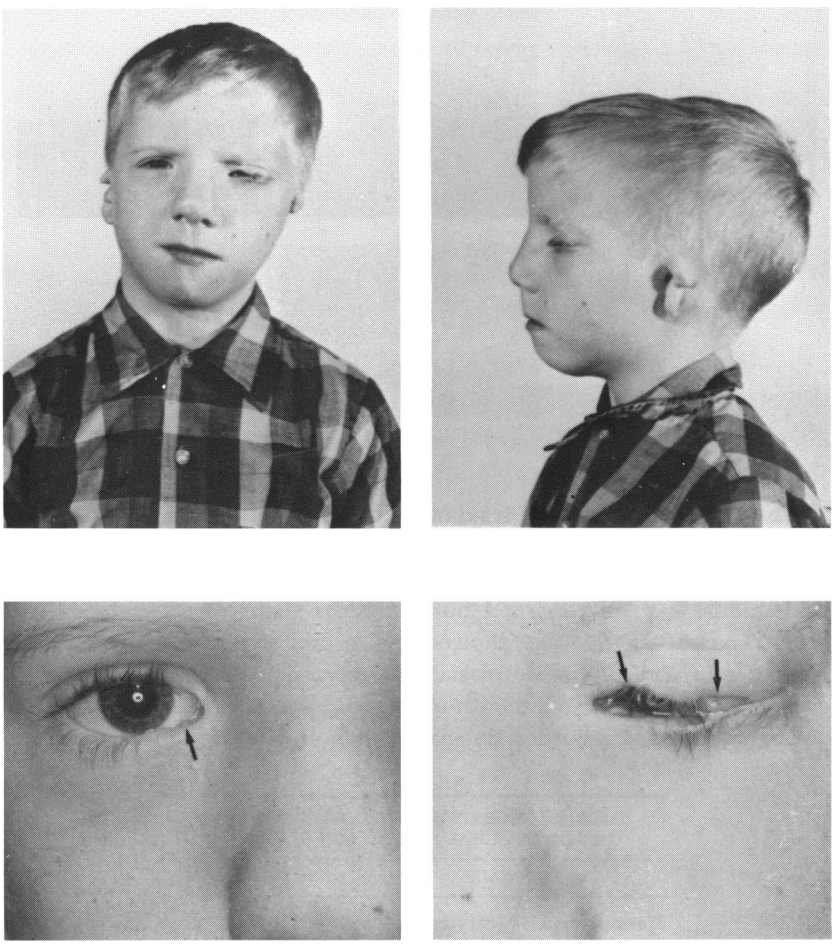
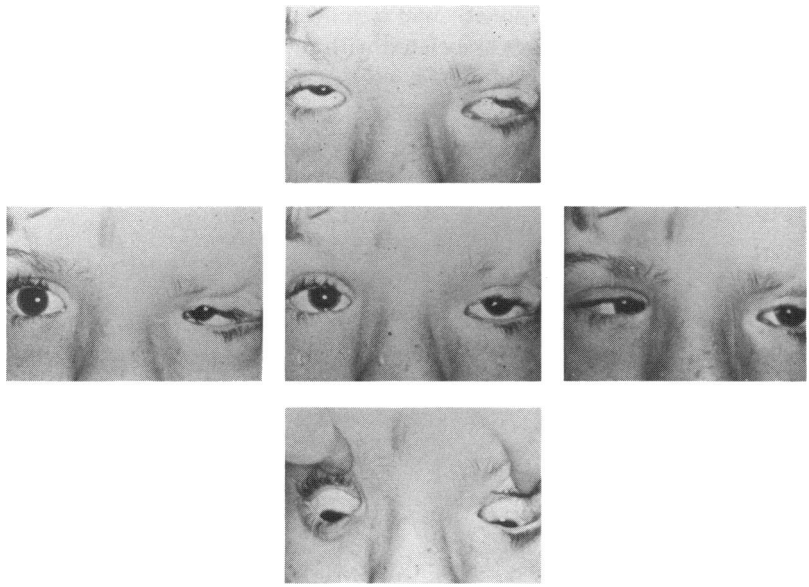


FIGURE 3

Duane-type anomalies, case 5. Hemifacial microsomia Goldenhar variant. A: Full-face photograph showing bilateral microsomia, ptosis, and coloboma of the left upper lid. Patient also had submucous cleft and mild hypertelorism. B: Lipodermoid (*arrow*) of right eye and coloboma of left eye (*arrows*). C: Motility views showing bilateral Duane syndrome and repaired coloboma.



Case 7 had the complete triad of Wildervanck syndrome: sensorineural deafness, Klippel-Feil anomaly of the spine, and Duane syndrome, although the motility finding was only unilateral (Table III). The external and middle ear were normal but inner ear structures were very malformed. The CT findings showed cystic and hypoplastic cochlea and vestibule (Mandini-type dysplasia) and abnormalities of the semicircular canal. In case 8 (Fig 5) a 3-month-old baby showed lacrimation of the right eye when sucking a bottle, associated with unilateral (right) Duane syn-

TABLE III: PATIENTS WITH DUANE SYNDROME AND SENSORINEURAL HEARING LOSS (n = 19)*

ANOMALY	NO OF PATIENTS
Spinal anomalies (cervical fusion or Klippel-Feil)	18
Facial asymmetry	6
Seventh nerve palsy	3
Cleft palate	5
Ocular dermoids (any type)	3

*Cases 4 and 7 from the preliminary study and 17 cases from the literature.[38,49,74,75,77,78,80] Two were male and 17 were female.

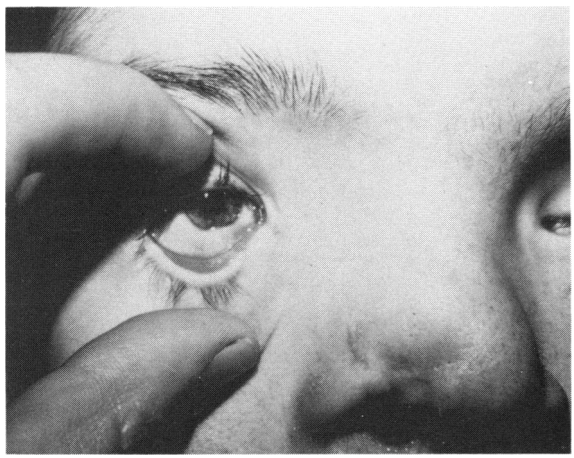
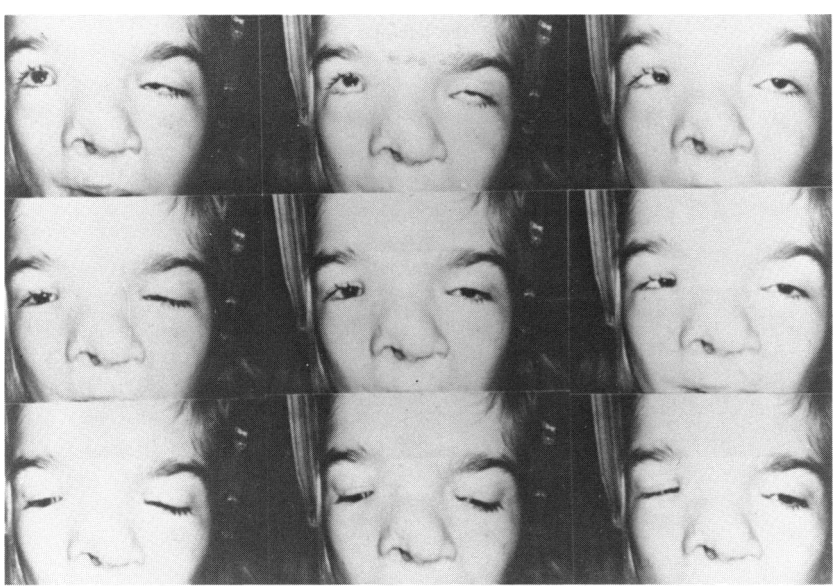


FIGURE 4
Duane-type anomalies, case 6. Median facial cleft. Patient had a repaired coloboma of the left upper lid, conjunctival dermoid of the right eye (*A*), and bilateral Duane syndrome (*B*).



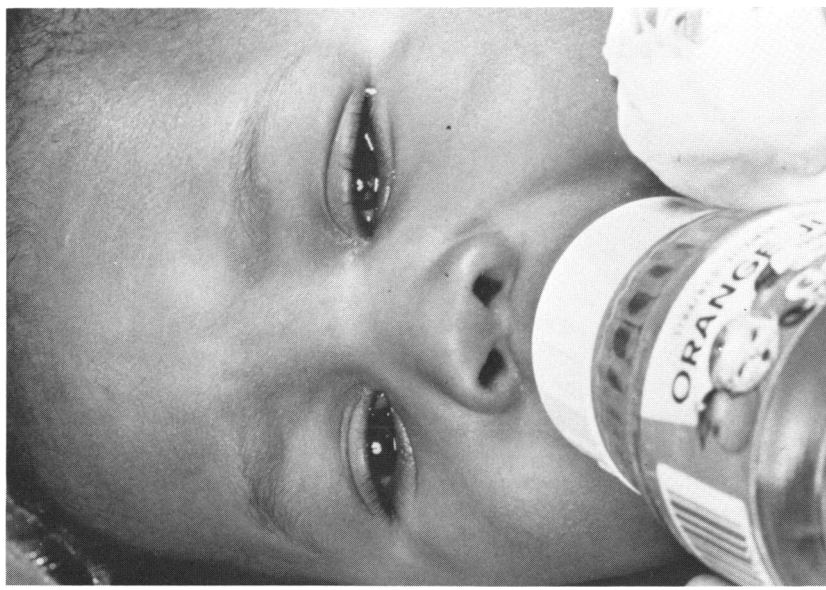
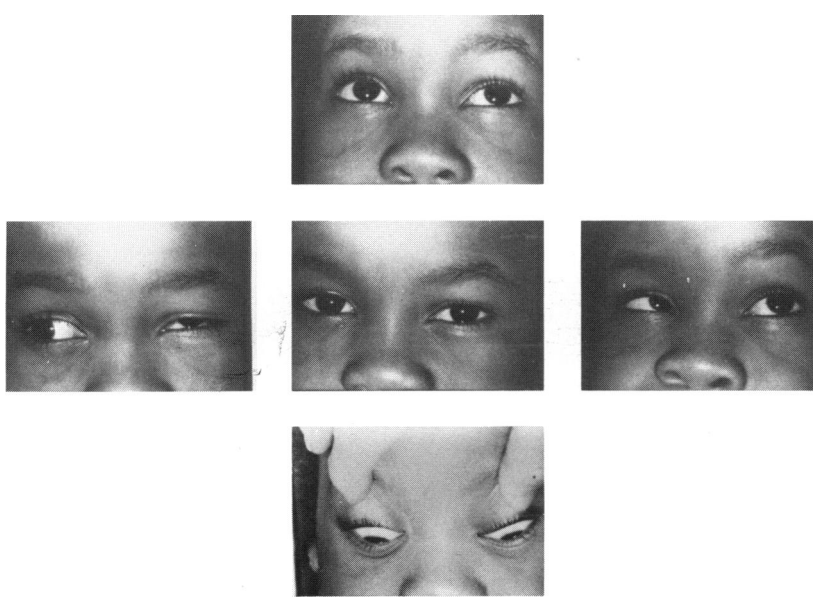


FIGURE 5

Duane-type anomalies, case 8. Paradoxical lacrimation. A: In infancy, tearing of the left eye occurred when the patient sucked a bottle. B: Patient at 5 years, showing Duane syndrome in the left eye.



drome (Table IV). This abnormal lacrimation was not noted by the parent and could not be elicited when the baby was chewing, sucking, or drinking.

TABLE IV: PATIENTS WITH APPARENT DUANE SYNDROME AND PARADOXICAL LACRIMATION (n = 10)*

ANOMALY	NO OF PATIENTS
Ear anomalies	3/6
Preauricular tags	3/6
External	2/6
Hearing loss	2/6
Spinal anomalies	
Klippel-Feil	1/6
Scoliosis	3/6
Other anomalies	
Systemic anomalies	2/6
Ocular dermoids	0/6

*Case 8 from the preliminary study and nine cases from the literature.[48,51,52,54,148] Four were male and six were female. No information about the type of anomalies was available on four of the ten patients.

Two of our patients (cases 9 and 10) had uveal and retinal colobomas. In one patient the coloboma was unilateral and the motility anomaly was bilateral (Fig 6); the other had unilateral Duane syndrome with bilateral colobomas. The combination of uveal colobomas, optic nerve anomalies, and Duane syndrome has been previously reported.[49,137,138] These two patients manifested minimal craniofacial abnormalities but had mild anomalies of the extremities.

One of our patients (case 11) had Rubinstein-Taybi syndrome. First described in 1963,[139] this syndrome is characterized primarily by mental and physical developmental delay, broad thumbs and toes, short stature, and facial abnormalities. Less frequent systemic findings are skeletal abnormalities of the cervical spine and sternum, electroencephalographic disturbances, nevus flammeus, cardiac murmurs, and respiratory problems. Ocular findings include antimongoloid slant to palpebral fissure, epicanthal folds, cataract, glaucoma, long eyelashes, hypertelorism, high arched brows, coloboma of the iris and choroid, lacrimal system abnormalities, refractive errors, and nystagmus.[140,141] Strabismus was noted in 72% of cases of Rubinstein-Taybi syndrome in a review of the literature by Roy and associates,[141] with exotropia of a concomitant variety most frequently noted. The possibility of Duane syndrome being a chance occurrence in our case 11 cannot be ruled out at this time.

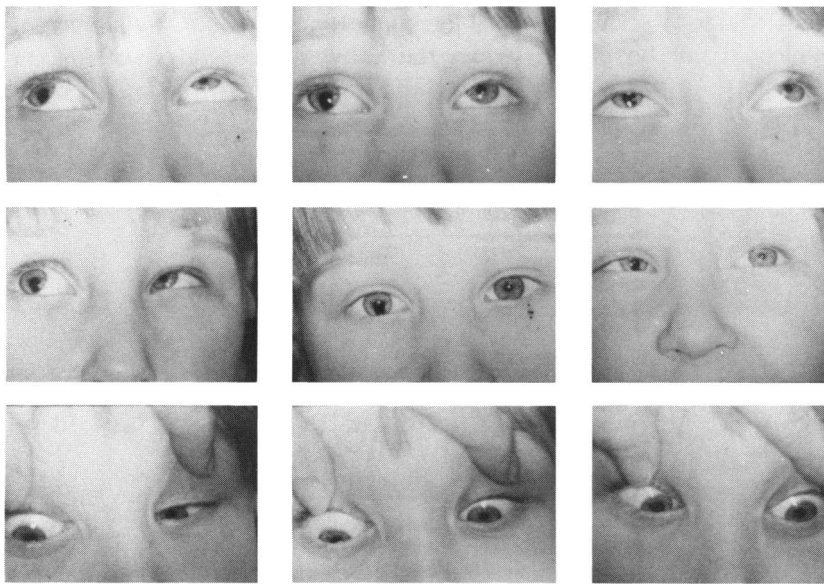


FIGURE 6
Duane-type anomalies, case 9. Uveal coloboma of the right eye involving iris and retina. Motility views show bilateral Duane syndrome.

Tables II to IV summarize different clusters of anomalies in our study and cases reported in the literature.

Möbius and Associated Syndromes

Our 16 cases of Möbius and Möbius-type syndromes are summarized in Table V. Although they demonstrated all types of horizontal incomitant strabismus (ranging from isolated abduction weakness to more of a clinical Duane syndrome [Fig 7] or horizontal gaze syndrome, occasionally with vertical involvement), there were significant differences in the frequency of each clinical pattern and associated systemic anomalies (Fig 7). There were a few patients with severe craniofacial deformities or ear malformations, but more had anomalies of the limb, tongue, and pectoralis muscle (Poland anomaly). Since seventh nerve palsy is a diagnostic characteristic for the patients with "pure" Möbius syndrome, it is not surprising that this was a predominant finding, although it was not always bilateral.

THALIDOMIDE STUDY

Tables VI to XI summarize the data on 86 Swedish individuals who demonstrated the malformations resulting from thalidomide embryopa-

thy. Table VI includes all significant findings on the 86 patients examined as well as information on the 14 patients not examined, which was obtained from old medical records.

Based on our findings of major malformations and on those in the literature, we initially divided our patients into three groups: Group 1 included those patients with external ear malformations or significant hearing anomalies but without limb involvement; group 2, those with limb malformations but normal external ears and no significant hearing loss; and group 3, those who showed a mixture of the anomalies of the first two groups. Since thumb involvement is an early and late finding and was present in so many of our patients, we elected to not consider this criterion when placing patients into group 1 or 2. Therefore, we needed another group (group 4) that consisted of patients in which the only malformations were tabulated but did not form the basis for classification into the four groups.

Ocular motility patterns were analyzed in 84 patients (Table VII). The motility patterns of the 52% of patients with strabismus indicate the very high prevalence (44%) of horizontal incomitant types (Figs 8 and 9) and a relatively low prevalence (8%) of comitant horizontal strabismus. There were a few patients with combined horizontal and vertical incomitant strabismus, and two patients with comitant horizontal strabismus with vertical involvement.

When ocular motility patterns were analyzed according to the four groups of thalidomide patients, the association became even more striking (Table X). Group 1, those patients showing only the effects of early thalidomide intake, had an 80% prevalence of strabismus, all with the horizontal incomitant variety. In group 2, patients who manifested only the later effects of thalidomide (days 24 to 37 after conception), the number of horizontal incomitant cases decreased markedly (22%), replaced by some comitant forms of horizontal strabismus (12%) and normal ocular motility (61%). Group 3, patients with both early and late effects, showed a mixed picture, whereas group 4 was a miscellaneous group and was not associated with a narrow period of effect.

Similarly, facial nerve palsy and abnormal lacrimation showed a very strong correlation with early effects of thalidomide and with patients with external ear malformations and severe hearing deficits that usually are associated with inner ear involvement (Tables VIII and IX).

We proposed a timetable (Tables XII to XIV) for determining the probable period of development of incomitant strabismus, facial nerve palsy, and abnormal lacrimation based on the patients in our thalidomide study. This timetable was compared to the timetables of other malforma-

TABLE V: PATIENTS WITH MÖBIUS-TYPE SYNDROMES†

CASE	CLINICAL DIAGNOSIS	FACIAL PALSY	LIMB ANOMALIES	OTHER SYSTEMIC ANOMALY	STRABISMUS			FISSURE CHANGE	OTHER OCULAR FINDINGS
					PRIMARY	LIMITATION ABDUCTION	LIMITATION ADDUCTION		
1	Poland-Möbius	R,L	Club feet syndactyly (R)	Poland	St	+ +	+ +	0	Exposure keratitis; astigmatism (moderate)
2	Möbius*	R,L	Clinodactyly; mild feet anomalies	Renal dysgenesis hypoplasia midface	St previous surgery	+ +	+ +	0	Vertical muscle limitation OS; exposure keratitis; inversus of retinal vessels; myopic astigmatism
3	Hypoplasia-hypodactylia*	0	Absent lower portion arms and legs	Microphthalmia; tongue	St	+	+	+	
4	Möbius	R>L	Small hands, feet	Tongue	R XT	+ +	+ +	0	Ptosis; limited movements in all fields of gaze
5	Möbius*	R,L	Clinodactyly of 5th fingers	0	St	+	0	—	
6	Ectrodactyly with orofacial malformations*	R,L	Absent 2nd, 3rd, 4th phalanges both hands	Tongue; facial asymmetry	St	+ +	+	+	Mild myopia
7	Möbius*	R,L	Normal	Micrognathia	St	+	0	0	
8	Arthrogryposis "plus"	R,L	Arthrogryposis	0	ET to XT	+ +	+ +	0	Vertical muscle limitation; head tilt; ptosis; moderate astigmatism; tortuous retinal vessels; miotic pupils
9	Möbius*	L	Clinodactyly	Preauricular tags (R)	0	+	0	—	
10	Hanhart*	0	Clinodactyly 5th finger; right leg shorter; toe anomaly	Microglossia; scoliosis	10° LH	+ +	+	—	

TABLE V: PATIENTS WITH MÖBIUS-TYPE SYNDROMES (CONT'D)

CASE	CLINICAL DIAGNOSIS	FACIAL PALSY	LIMB ANOMALIES	OTHER SYSTEMIC ANOMALY	STRABISMUS			FISSURE CHANGE	OTHER OCULAR FINDINGS
					PRIMARY	LIMITATION ABDUCTION	LIMITATION ADDUCTION		
11	Hanhart*	R,L	Absent lower extremities and lower part of arms bilaterally	Microphthalmia	St	—	—	—	
12	Terminal transverse defects with orofacial malformations	L	0	Kidney micrognathia; VSD	XT	+ +	+ +	—	Vertical muscle limitation; tortuous retinal vessels; exposure keratitis
13	Möbius*	R,L	0		XT	+ +	+	—	
14	Poland-Möbius*	R,L	Brachydactyly	Microglossia	AET	+ +	+	0	
15	Poland-Möbius*	R,L	Clinodactyly	Microglossia	AET	+ +	+	0	
16	Möbius*	R,L	Clinodactyly	Microglossia	AET	+ +	+	+	

+, Mild to moderate involvement; + +, moderate to severe involvement, 0, absent; —, information not available; St, straight (orthophoric); XT, exotropia; ET, esotropia; VSD, ventricular septal defect.
*Included in syndrome complex called terminal transverse defects with orofacial malformations.
†From Miller et al: Möbius and Möbius like syndromes. *J Pediatr Ophthalmol Strabismus* 1989; 26:176-188.

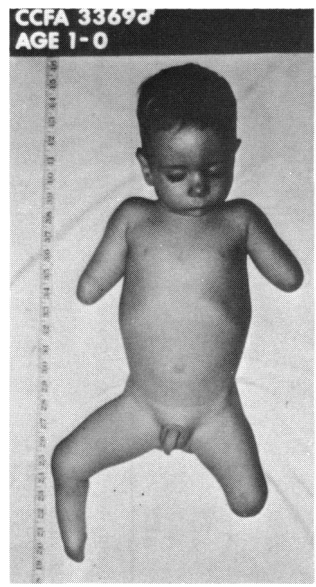
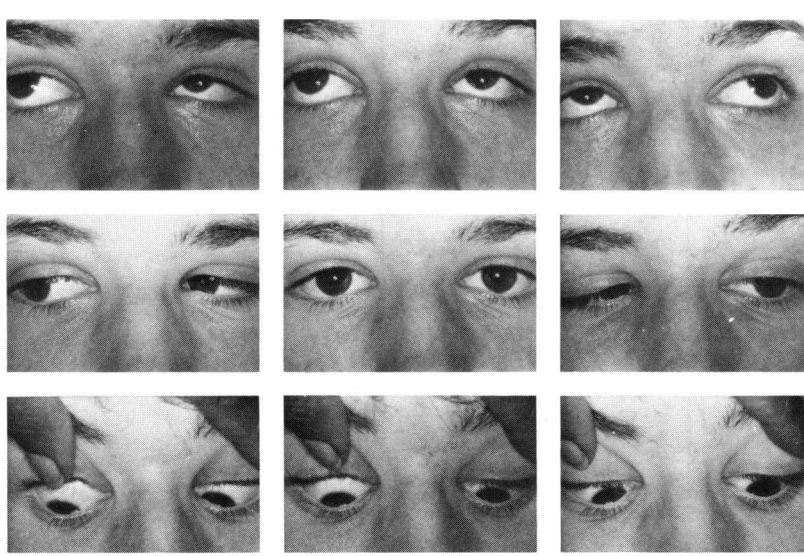


FIGURE 7
Möbius-type anomalies, case 4. Hypoglossia-hypodactylia. A: In infancy, demonstrating amputation deformity of arms and legs. B: At age 12, Duane syndrome with limitation of abduction, mild limitation of adduction, and narrowing of both fissures.



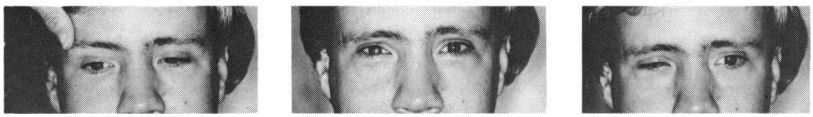


FIGURE 8
Thalidomide embryopathy. Typical Duane pattern.

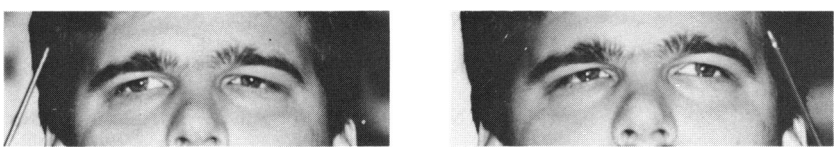


FIGURE 9
Thalidomide embryopathy. A: An example of horizontal motility in a patient described as having a "gaze" pattern. There was little horizontal movement, a normal vertical pattern, and minimal lid changes. This is probably a variation of Duane syndrome. B: Another patient with minimal horizontal movements and better but not normal vertical excursions.

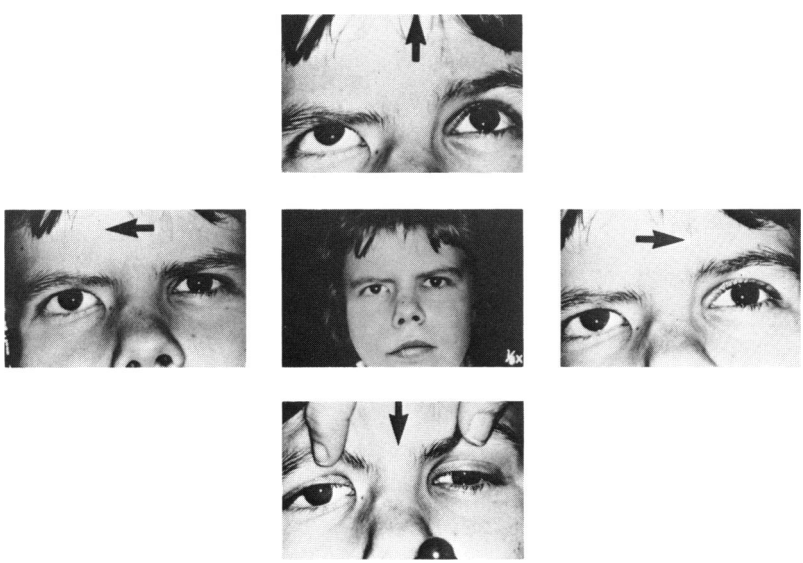


TABLE VI: THALIDOMIDE

CASE/ SEX	EAR ANOMALY		7th FACIAL NERVE PALSY	TEARING WHEN EATING	OCULAR MOTILITY		
	EXT'L	HEARING DEFICIT			PRIMARY POSITION	TYPE OF HORIZONTAL STRABISMUS	STEREOPSIS
1/F	+ +	+ + (R>L)	R	Yes (Emot 0)	St	Incomitant (gaze OU)	Yes
2/F	0	0	No	No	St	0	Yes
3/M	0	0	No	No	6° ET	Comitant (decreased RIO)	No
4/M	0	0	No	No	12° LH	Comitant (decreased RIO)	No
5/M	0	0	No	No (Emot 0)	St	Incomitant (Duane OU)	Yes
6/M	0	0	No	No	St	Incomitant (Duane OD)	—
7/F	0	+	No	No	St	Incomitant (Duane OU)	Yes
8/M	0	0	No	No	Unable to evaluate	Unable to evaluate	No
9/M	+ +	+ +	R>L	Yes (Emot 0)	4° XT	Incomitant (Duane OU)	No
10/M	0	+ (L)	No	Yes (Emot 0)	4° XT	Incomitant (Duane OU)	No
11/F	+ +	+ +	L	No	St	Incomitant (Duane OU)	Yes
12/M	+ +	+ +	L>R	Yes (Emot 0)	St	Incomitant (Duane OU)	Yes
13/M	0	0	No	No	15° ET	Incomitant (abduction weakness)	No
14/M	0	+ + (deaf)	No	Yes (Emot 0)	St	Incomitant (gaze OU)	Yes
15/M	0	0	No	No	Unable to evaluate	Unable to evaluate	No
16/M	0	0	No	No	16° ET	Comitant ET (DVD)	No
17/M	+ +	+ + (deaf)	L>R	Yes (Emot 0)	20° XT	Incomitant (gaze)	No
18/M	+ +	+ + R 0 L	No	Yes	St	Incomitant (Duane OU)	Yes
19/F	0	0	No	No	St	0	Yes
20/F	0	0	No	No	St	Incomitant (Duane L)	Yes

EMBRYOPATHY STUDY RESULTS

CASE/ SEX	DECREASED VISION	OTHER OCULAR FINDINGS	LIMB ANOMALY			OTHER SYSTEMIC ANOMALIES AND MISCELLANEOUS	GROUP
			THUMB	UPPER	LOWER		
1/F	OD (amblyopia)	0	0	0	0		1
2/F	0	0	+	+	0		2
3/M	0	0 Astigmatism OU	+	++	++		2
4/M	OU (mild)	Hyperopia	+	+	0	Anal atresia	2
5/M	OD (amblyopia)	0	+	0	0	1-2 pills total; atresia cricoid cartilage	4
6/M	0	0	+	+	0		2
7/F	OD (amblyopia)	0	+	0	0	2-3 pills total	1
8/M	NLP OD; LP OS; (prosthesis)	Microphthalmia OU; corneal opacification OU	+	++	+ R 0 L		2
9/M	0	Astigmatism OU; tortuous retinal vessels	+	+	0	Hypoplastic maxilla	3
10/M	0	Myopia OU	+ T (R)	+	0	Absent right kidney	3
11/F	OS (mild)	Myopia OU; astigmatism OU	0	0	0	2 pills on one day; esophageal; vaginal	1
12/M	0	0	0	0	0	VSD	1
13/M	0	0	+	+	0		2
14/M	0	0	+ R	+	0	CNS	3
15/M	NLP OD; LP OS	Microphthalmia OD; glaucoma OS; cloudy cornea OU	0	0	0	Pills late; ? past sensitive period	4
16/M	Myopia OU; 0	Astigmatism OU	+	+	++	Heart irregularity; scoliosis	2
17/M	OS (amblyopia); NLD obstruction; myopia OU	Astigmatism OU	+	+	0	Choanal atresia; kidney; lung	3
18/M	OS (mild)	Large optic cup; OT borderline	+	+	0	Kidney	3
19/F	0	0	+ T (R,L)	+	++	6 digits R hand; 1-2 pills	2
20/F	0	0	+	+		1-2 pills	2

TABLE VI: THALIDOMIDE EMBRYOPATHY

CASE/ SEX	EAR ANOMALY		7th FACIAL NERVE PALSY	TEARING WHEN EATING	OCULAR MOTILITY		
	EXT'L	HEARING DEFICIT			PRIMARY POSITION	TYPE OF HORIZONTAL STRABISMUS	STEREOPSIS
21/M	+ +	+ +	L	Yes (Emot 0)	St	Incomitant (gaze OU)	Yes
22/M	0	0	Mild	No	St	0	Yes
23/M	+ +	+ +	R	Yes (Emot 0)	0-8° ET	Incomitant (Duane OU)	Yes
24/F	0	+ L	No	No	St	Incomitant (gaze L)	Yes
25/M	0	0	No	No	St	0	Yes
26/M	0	0	No	No	St	0	Yes
27/M	0	0	No	No	St	0	Yes
28/M	+	0	No	No	6° RH	Incomitant (Duane OU)	Yes (down)
29/M	+ +	+ +	R	Yes (R)	8° LH	Incomitant (abduction weakness OD)	Yes (down)
30/F	+ +	+ +	L	Yes (R) (Emot 0 R)	20° XT 4° RH	Incomitant (Duane OU; DVD)	No
31/F	0	+ L (slight)	No	No	8° LET	Incomitant (abduction weakness OS)	No
32/F	+ + R	+ R	R (mild)	No	St	0	Yes
33/F	0	+ + R + L	No	No	St	0	Yes
34/F	+ (low set)	+ +	No	No	Unable	Incomitant OS; (Duane OS)	No
35/M	0	0	No	No	St	0	Yes
36/F	+ +	+ + (deaf)	Yes	No	St	0	Unable to evaluate
37/M	0	+ R 0 L	No	No	St	Incomitant (Duane)	Yes
38/M	0	0	No	No	St	0	Yes
39/M	0	0	No	No	0-4° ET	Slight incomitant (slight abduction weakness OS)	Yes
40/F	0	0	No	No	St	0	Yes
41/M	0	0	No	No	St	0	Yes

STUDY RESULTS (CONT'D)

CASE/ SEX	DECREASED VISION	OTHER OCULAR FINDINGS	LIMB ANOMALY			OTHER SYSTEMIC ANOMALIES AND MISCELLANEOUS	GROUP
			THUMB	UPPER	LOWER		
21/M	0	Myelinated nerve fibers	0	0	0	Few pills only; kidney	1
22/M	0	0	+	+	0	Kidney; anal atresia; VSD; scoliosis	2
23/M	0	0	0	0	0		1
24/F	0	Ptosis OS	+	0	+	Submucous cleft; anal atresia; mental retardation (mild)	3
25/M	0	0	+	+	0		2
26/M	0	0	+	++	0		2
27/M	0	Coloboma disc (mild)	+ T (R)	+	0	6 digits R hand	2
28/M	0	Limitation of up gaze; decreased SR OU; decreased RIR; myopic astigmatism	+	+	0		3
29/M	0	Hyperopia; amblyopia (bilateral)	+	+	+	Heart murmur	3
30/F	OU (OS>OD) (amblyopia)	Decreased SR OU (slight); myopic astigmatism	0	0	0		1
31/F	OS (amblyopia)	0	+R	+R	+L		3
32/F	0	Conjunctival lipodermoid OU	0	0	0	OD appears large	1
33/F	0	0	+ T (R,L)	++		3	
34/F	NLP OD (prosthesis)	Microphthalmia OD; abnormal vessels of disc OS	+	++	0	VSD; pulmonary atresia	3
35/M	0	Myelinated nerve fibers OU	+	++	0	Lung; kidney	2
36/F	Difficult but not grossly abnormal	0	0	0	0	Mental retardation; has unaffected ? twin (case 82)	1
37/M	OD (amblyopia)		+	+ R	0	Enamel hypoplasia	3
38/M	0	0	+	+	0		2
39/M	0	0	+	++	0		2
40/F	0	0	+	0	0		4
41/M	0	0	+ T (R,L)	0	0	1/2 tablet	4

TABLE VI: THALIDOMIDE EMBRYOPATHY

CASE/ SEX	EAR ANOMALY		7th FACIAL NERVE PALSY	TEARING WHEN EATING	OCULAR MOTILITY		
	EXT'L	HEARING DEFICIT			PRIMARY POSITION	TYPE OF HORIZONTAL STRABISMUS	STEREOPSIS
42/F	0	0	No	No	St	0	Yes
43/M	0	0	No	No	4° XT 10° RH	Incomitant (Duane OU)	No
44/F	0	0	No	No	St	0	Yes
45/M	++R 0 L	+ R 0 L	+ R	No (Emot 0)	12° ET 4° LH	Incomitant (Duane OU; DVD)	No
46/M	0	0	No	No	St	0	Yes
47/F	++ R + L	+ R	No	No	St	0	Yes
48/F	+	++	No	Yes	St	Incomitant (gaze OU)	Yes
49/M	0	0	No	No	St	0	Yes
50/M	0	0	No	No	St	0	Yes
51/M	++	++	+(slight)	No	St	Incomitant (Duane OU)	Yes
52/F	0	0	No	No	0	0	Yes
53/M	0	0	No	No	St	0	Yes
54/F	0	0	No	No	St	0	Yes
55/F	0	L>R	No	No	St	Incomitant (Duane OU)	Yes
56/F	0	0	No	No	8° ET	Comitant ET	No
57/F	0	0	No	No	St	0	Yes
58/M	0	0	No	No	St	0	Yes (?)
59/M	+R	++R	No	No	St	0	Yes
60/F	0	0	No	No	St	Incomitant (Duane ?)	Yes
61/M	0	0	No	No	St	0	Yes
62/F	0	0	No	No	St	Incomitant (Duane OU)	Yes
63/M	0	0	No	No	St	Incomitant (Duane OU)	Yes
64/M	0	0	No	No	2° ET	Incomitant (Duane OU)	Yes
65/M	0	0	No	No	St	0	Yes
66/F	0	0	No	No	St	0	Yes
67/F	0	0	No	No	St	0	Yes
68/M	0	0	No	No	4° ET	0 (Acquired bilateral SO) [trauma]	Yes

STUDY RESULTS (CONT'D)

CASE/ SEX	DECREASED VISION	OTHER OCULAR FINDINGS	LIMB ANOMALY			OTHER SYSTEMIC ANOMALIES AND MISCELLANEOUS	GROUP
			THUMB	UPPER	LOWER		
42/F	0	0	+ R	0	0		4
43/M	0	Hypertelorism	+	+ L	+ + R	Enamel hypoplasia	2
44/F	0	0	+	+ +	0		2
45/M	OS (amblyopia)	0	+	+ +	+ +	Meningomyelocele; chest; CNS; heart	3
46/M	0	0	+	+ +	+ R	Chest; genitalia	2
47/F	0	0	0	0	0	Dental	1
48/F	0	0	0	0	0	Ear tags	1
49/M	0	0	+	0	0		4
50/M	0	0	+ T (R,L)	+ +	+ +	Absent kidney	2
51/M	0	0	0	0	0		1
52/F	0	0	+	+ + (amelia)	0	Kidney; ectopic nipple	2
53/M	0	0	+	+ +	0		2
54/F	0	0	+	+	0	Vertebral	2
55/F	0	0	+	+ +	0	Accessory nipple; missing teeth	3
56/F	0D (amblyopia)	Hyperopia	+ T (R,L)	+ +	+ +	Kidney	2
57/F	0	0	+	+ +	0	Absent uterus and vagina	2
58/M	Small macular cyst (OS)	0	+	0	0	0	4
59/M	0	Mild ptosis; telecanthus; downward slant fissure	+	+ +	+	Choanal atresia; missing teeth	3
60/F	0	0	+	+ +	0	1-2 pills	2
61/M	0	Overaction RIO	+	+ +	0	Missing teeth	2
62/F	0	Pigment area inferiorly OS; myopia; astigmatism	+	+ +	0		2
63/M	0	0	+	+ +	0		2
64/M	0	Hypertelorism (IPD 66)	+	+ +	0		2
65/M	0	0	±	+ R	+ R	Cerebral palsy; retarded	2
66/F	0	± hypertelorism (IPD 65)	+ T (R,L)	0	0		4
67/F	0	0	+	+ +	0		2
68/M	0	0	+ T (R)	+	0	0	4

TABLE VI: THALIDOMIDE EMBRYOPATHY

CASE/ SEX	EAR ANOMALY		7th FACIAL NERVE PALSY	TEARING WHEN EATING	OCULAR MOTILITY		
	EXT'L	HEARING DEFICIT			PRIMARY POSITION	TYPE OF HORIZONTAL STRABISMUS	STEREOPSIS
69/F	0	0	No	No	St	0	Yes
70/F	0	0	No	No	St	0	Yes
71/F	0	0	No	No	St	0	Yes
72/M	0	0	No	No	16° ET	Comitant ET (A pattern)	Yes (down)
73/F	0	+ (narrow canal)	No	No	St	0	Yes
74/M	0	0	No	No	St	0	Yes
75/M	0	0	No	No	2° RET	Comitant (microtropia)	Yes
76/M	0	0	No	No	St	0	Yes
77/M	+ +	+ +	L>R	Yes	8° XT	Incomitant (Duane OS)	Yes
78/M	0	0	No	No	St	0	Yes
79/F	0	0	No	No	St	0	Yes
80/F	0	0	No	No	St	0	St
81/F	+ +	+ +	R	Yes	St	Incomitant (Duane OU)	Yes
82/M	0	0	No	No	ET	Comitant	No
83/F	+	+ +	No	Yes (R)	4° XT	Incomitant (Duane OU)	Yes (down)
84/M	+ +	+ + (deaf)	L>R	yes	St	Incomitant (gaze)	—
85/F	0	+	No	No	0	0	Yes
86/F	+ +	+ (deaf)	No	—	12° XT 4° RH	Incomitant (Duane OU)	No
							RESULTS IN PATIENTS
87/F	0	0	No	—	—	—	—
88/F	0	0	No	—	—	—	—
89/M	0	0	—	—	—	—	—
90/F	R	R	R	—	0	Incomitant	—

STUDY RESULTS (CONT'D)

CASE/ SEX	DECREASED VISION	OTHER OCULAR FINDINGS	LIMB ANOMALY			OTHER SYSTEMIC ANOMALIES AND MISCELLANEOUS	GROUP
			THUMB	UPPER	LOWER		
69/F	0	0	+	++	+	Kidney	2
70/F	0	0	+	++	0	No vagina or uterus	2
71/F	0	0	+ T (L)	+	0		2
72/M	0	0	+	++	++		2
73/F	OU (slight) (high myopia)	Myopic astigmatism	+	++	9	Anal atresia	3
74/M	0	0	+ T (R,L)	0	0		4
75/M	OD (slight) amblyopia	Coloboma disc OS	+	++	0		2
76/M	0	Optic pit OD; abnormal vessel disc	+ (R,L)	+R	0		2
77/M	0	0	++	+L	0	Autistic; retarded	3
78/M	0	0	+	++	0	Kidney	2
79/F	0	0	+L	+L	++	Hypoplastic kidney; transplant	2
80/F	0	0	+	++	++	Double vagina	2
81/F	0	0	0	0	0	VSD	1
82/M	0	Hyperopia	0	0	0	Twin of case 36	4
83/F	0	0	+	++	0		3
84/M	—	—	0	0	0	Retarded; autistic	1
85/F	0	0	+ T (R,L)	0	++	Kidney	3
86/F	—	—	0	0	0	Retarded	1

NOT EXAMINED

87/F	—	—	+	++	++	Anal atresia	2
88/F	—	—	+	0	++		2
89/M	—	0	+	++	0		2
90/F	0		+	0	0	Spina bifida	1

TABLE VI: THALIDOMIDE EMBRYOPATHY

CASE/ SEX	EAR ANOMALY		7th FACIAL NERVE PALSY	TEARING WHEN EATING	OCULAR MOTILITY		
	EXT'L	HEARING DEFICIT			PRIMARY POSITION	TYPE OF HORIZONTAL STRABISMUS	STEREOPSIS
91/M	0	0	No	No	St	0	—
92/F	0	0	No	—	St	0	—
93/M	0	0	No	—	St	0	—
94/F	L	L	R	No	—	Incomitant (gaze OU)	—
95/F	0	R	—	—	—	—	—
96/F	0	0	No	—	—	—	—
97/M	0	0	No	—	—	—	—
98/M	—	—	—	—	—	—	—
99/M	+ +	+ +	No	Yes	—	Incomitant	—
100/M	—	—	—	—	—	Incomitant	—

Information on cases 87-100 was obtained from records.
0, absent; —, information not available; VSD, ventricular septal defect; NLD, nasal lacrimal duct; Emot 0, no emotional tearing.
Types of horizontal strabismus: Duane = limitation of abduction and/or adduction with obvious narrowing of palpebral fissure on adduction. Gaze = limitation of abduction and adduction in contralateral eye with no change in fissures; usually bilateral. St = orthotropia. Abduction weakness = definite limitation in abduction with no change in fissure on adduction. DVD = dissociated vertical deviation.
Thumb: +, abnormality; T, triphalangeal thumb. Limb (upper/lower): +, mild to moderate involvement; + +, moderate to severe involvement.

TABLE VII: OCULAR MOTILITY IN PATIENTS WITH THALIDOMIDE EMBRYOPATHY

MOTILITY	NO OF PATIENTS* (%)
Incomitant horizontal strabismus	37 (44%)
Duane type	26 (31%)
Gaze pattern	7 (8%)
Abduction deficit only	4 (5%)
Comitant horizontal strabismus	7 (8%)
Comitant with vertical limitation (n = 2) (all patients were esotropic)	
No strabismus	40 (48%)

*Only 84 of the total 86 patients could be evaluated for ocular motility.

STUDY RESULTS (CONT'D)

CASE/ SEX	DECREASED VISION	OTHER OCULAR FINDINGS	LIMB ANOMALY			OTHER SYSTEMIC ANOMALIES AND MISCELLANEOUS	GROUP
			THUMB	UPPER	LOWER		
91/M	—	0		0	+		2
92/F	—	0	+	+ +	+ +	Genitalia; anal stenosis	2
93/M	—	0	+	+ +	+ +	Anal atresia	2
94/F	—	—	—	0	+		3
95/F	—	—	+ T (R,L)	0	0	Heart	3
96/F	—	—	+	0		Duodenal atresia	2 or 4
97/M	—	0	+	+ +	0	Genitalia	2
98/M	—	—	+	+ +	—		?
99/M	0	0	+	+ +	—	Anal atresia; heart; died (drowning)	3
100/M	—	—	+ T (R,L)	+	—	—	?

Miscellaneous: data on pills related to the amount of thalidomide ingested by the mother, as given in history.

Group: 1, Patients with external ear or significant hearing loss and no limb anomalies (thumbs excluded); 2, Patients with limb anomalies (thumbs not considered) and no ear or hearing malformations; 3, Patients with both ear and limb anomalies; 4, 6 patients with anomalies of thumbs but no hearing problems or malformations of external ear or other limb; 1 patient with glaucoma only.

TABLE VIII: PATIENTS WITH ABNORMAL LACRIMATION
(n = 18; 21% of TOTAL 86)

ASSOCIATED ANOMALIES	NO OF PATIENTS (%)
Horizontal incomitant strabismus	18 (100%)
Facial nerve defect	12 (67%)
External ear malformation	16 (89%)
Hearing deficit	17 (94%)
Hearing/ear without limb anomalies* (group 1)	9 (50%)
Upper/lower limb* without ear anomalies (group 2)	0 (0%)
Ear and limb anomalies (group 3)	8 (44%)
Thumb only (group 4)	1 (6%)

*Thumb anomaly not in criteria.

tions proposed in the literature.[70,71,105,129] The criteria for recording the suspected sensitive period of various anomalies in our cases were as follows: (1) severe external ear anomalies and/or hearing deficits—days 20 to 23 after conception (Fig 2); (2) mild inner ear and external ear anoma-

TABLE IX: PATIENTS WITH FACIAL NERVE PALSY (n = 17; 20% of TOTAL 86)*

ASSOCIATED ANOMALIES	NO OF PATIENTS (%)
Horizontal incomitant strabismus	14 (82%)
No strabismus	3 (18%)
Abnormal lacrimation	12 (71%)
External ear malformation	16 (94%)
Hearing deficit	16 (94%)
Ear/hearing without limb anomalies* (group 1)	10 (59%)
Limb without ear/hearing anomalies† (group 2)	1 (6%)
Ear/hearing and limb anomalies (group 3)	6 (35%)

*Nine of the 17 cases were bilateral; 7 were right side only and 2 were left side only.
†Thumb anomaly not in criteria.

TABLE X: MOTILITY PATTERNS IN THALIDOMIDE EMBRYOPATHY BY GROUP

GROUP	NO. OF PATIENTS (MALE/FEMALE)	STRABISMUS*		NO STRABISMUS*
		HORIZONTAL INCOMITANT	HORIZONTAL COMITANT	
1 (early effect)	15 (5/10)	12 (80%)	0	3 (20%)
2 (mid to later effect)	31 (24/17)	9 (22%)	6 (12%)	25 (61%)
3 (early and later effect)	19 (11/8)	15 (80%)	0	4 (21%)
4 (miscellaneous)	11 (8/3)	1 (9%)	1 (10%)	8 (73%)
Total	86 (48/38) (56% M) (44% F)	37 (44%)	7 (8%)	40 (48%)

*Calculations were performed in 84 patients for whom we were able to determine ocular motility; 1 patient in group 2 had bilateral microphthalmos and I patient had congenital glaucoma (group 4).
Group 1: Patients with external ear anomalies or significant hearing loss and no limb anomalies (thumbs excluded).
Group 2: Patients with limb anomalies (thumbs not considered) and no ear or hearing malformations.
Group 3: Patients with both ear and limb anomalies.
Group 4: 6 patients with anomalies of thumbs but no hearing problems or malformations of external ear or other limb and 1 patient with glaucoma only.

lies—days 24 to 34; (3) thumb hypoplasia—days 21 to 28; (4) upper limb—days 24 to 32; (5) lower limb—days 27 to 34; and (6) triphalangeal thumbs—days 32 to 37. For example, a patient with severe external ear and upper limb anomalies but no involvement of the lower limbs would be recorded as the product of possible anomaly intake between days 20 and 27 after conception.

This timetable must be regarded as a rough estimate since the literature is not completely consistent in the sensitive period for each developing organ and our classification is difficult in many cases because of minor or questionable involvement of the limbs or ears. Also, the group 3 cases, with evidence of thalidomide taken over a greater duration of the sensitive period, are much less informative than those cases in group 1 or 2. However, this timetable reinforces the observation that incomitant strabismus occurs from thalidomide taken in both the early and midsensitive period, with gaze paresis occurring primarily in the very early period and the isolated abduction deficiencies resulting from slightly later intake. Lacrimation anomalies and facial nerve palsy appear to be primarily due to early effects of thalidomide.

DISCUSSION

Classic principles or observations in teratology are dramatized by some of the findings in our thalidomide study. For example, the development of the thumb appears to be extremely sensitive to being disturbed by thalidomide, and there is a very high correlation between hypoplastic or absent thumbs and horizontal incomitant strabismus in our patients (Table XI). It has been postulated that the development of the thumb starts at about the 21st day after conception and, therefore, overlaps the time at which this form of strabismus occurs. However, a different type of abnormal development of the thumb—an extra joint, producing a triphalangeal thumb—is a result of disturbance in the later sensitive period (days 30 to 34). Four patients (cases 19, 27, 33, and 41) had triphalangeal thumbs, none had an incomitant strabismus, and only one had a comitant esotropia. This underlines the association of incomitant strabismus with the early effect of thalidomide. Because thalidomide is short acting and some pregnant women took an apparently minimal dosage of the drug, the resulting birth defects may represent very small or narrow disturbances in development. For example, patient 41 had only a thumb anomaly and, according to the history, his mother had stated that she took only one half of a thalidomide tablet.

Patient 36 was of particular interest in that she had very severe external

TABLE XI: THALIDOMIDE ANOMALIES ASSOCIATED WITH INCOMITANT STRABISMUS

ASSOCIATED ANOMALY	DUANE (n = 26)	GAZE (n = 7)	ABDUCTION ONLY (n = 4)	TOTAL NO. OF PATIENTS WITH INCOMITANT STRABISMUS AND THE ANOMALY	% OF PATIENTS WITH ANOMALY WHO HAVE INCOMITANT STRABISMUS
Aberrant lacrimation (n = 18; 21%)	11 (42%)	6 (86%)	1 (25%)	18	100
Facial nerve palsy (n = 17; 20%)	9 (35%)	4 (58%)	1 (25%)	14	82
External ear malformations (n = 23; 27%)	13 (50%)	5 (71%)	1 (25%)	19	83
Hearing (n = 33; 38%)	17 (65%)	7 (100%)	2 (50%)	26	79
Hypoplastic thumb (n = 70; 81%)	19 (73%)	3 (43%)	4 (100%)	26	37
Upper limb (n = 58; 67%)	17 (65%)	2 (29%)	4 (100%)	23	40
Lower limb (n = 20; 23%)	2 (8%)	1 (14%)	2 (50%0)	5	25

ear anomalies, deafness, and marked facial asymmetry of anomalies. Additionally, she had a twin brother (case 82) who was reported as being unaffected, although when we examined him he had hyperopia with esotropia, which may be a chance occurrence and not related to the thalidomide exposure.

There are a few explanations for the possible occurrence of twins in which one child is affected and one is unaffected by a teratogenic agent. One theory is that there is a different genetic background on which the teratogen is acting, and, therefore, the effect is variable. Thalidomide, however, has been postulated to affect a very high percentage of the offspring of women known to have taken the drug, and most twins were concordant.

Another, more intriguing, explanation is that the two embryos were at a slightly different stage of development, between the sensitive period and the insensitive period, that is, 20 to 21 days, and that a drug taken on this borderline day might affect one twin but not the other. There are two observations that somewhat supported this theory: (1) the very earliest effect of thalidomide embryopathy is anotia (an absent or severely hypoplastic external ear), and (2) Lenz reported a few other similar cases of affected/unaffected twins.[108]

Further speculation as to how only one twin might be affected is that incomitant strabismus might start to develop shortly after anotia—that is, on day 21 after conception—and, therefore, not be present in twin 1 if the

drug was taken only on day 20. Whether thalidomide precipitated a squint in an "at risk" individual (twin 2) would be impossible to prove.

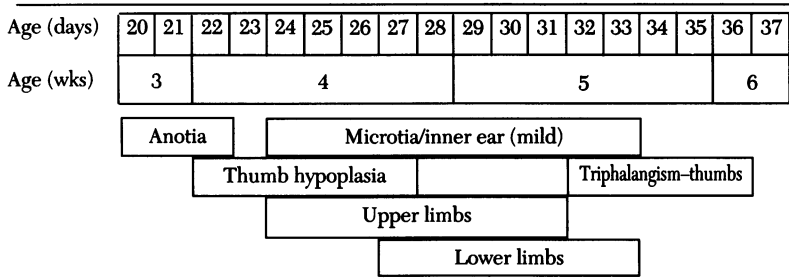
In the construction of timetables of sensitive periods for different developing organ systems or structures, it is necessary to look for clusters of anomalies (Tables VI to XIV). Patients with only a few associated anomalies are frequently more informative than those with a wide array of malformations, the latter suggesting intake of the teratogen over a greater proportion of the sensitive period. Since there were a large number of individuals with thalidomide embryopathy, these developmental timetables are quite accurate, and there was considerable consistency with the literature as related to the major malformations.[70,71,105,129]

By comparing the prevalence of Duane syndrome with various types of systemic malformations whose developmental timetable is quite accurately established, it became evident that a disturbance in development in days 21 to about 26 repeatedly results in Duane syndrome. The presence of other forms of congenital incomitant strabismus (eg, isolated lateral rectus palsies or gaze paresis) with the same malformations in this model system leads to the conclusion that there is a spectrum of incomitant motility patterns that may occur from the same insult to the embryo during a narrow time frame. Furthermore, there is a suggestion that slight variations within this period may result in a gaze paresis in some patients and in isolated lateral rectus palsy later in the sensitive period (Table XII). Differences in dosage of the teratogenic agent could also be responsible for the variation.

Electromyographic data, supported by a few autopsy specimens and the other associated innervational errors reported in the literature, strongly suggest that Duane types of strabismus result from inappropriate neuronal connections. The clustering of anomalies associated with the early effect of thalidomide implicates the location of disturbed development near the sixth, seventh, and lacrimal nucleus. The observation that incomitant strabismus occurred in most patients showing the early effect suggests that these inappropriate neuronal connections may not be a primary programming error but rather the result of a predictable "normal" reparative process, with branches of the third cranial nerve supplying the developing uninnervated lateral rectus muscle. This is consistent with the previous observations that the lateral rectus frequently had normal anatomy and yet no evidence of abducting ability. These findings suggest that the muscle must be innervated by a nerve other than the sixth. Conversely, areas of fibrosis or hypoplasia of the muscle may be due to failure of secondary innervation to that region of the muscle.

An alternative speculation is that branches of the third cranial nerve are

TABLE XII: TIMETABLE OF HORIZONTAL INCOMITANT STRABISMUS BASED ON SOME ASSOCIATED ANOMALIES (ESTIMATES)



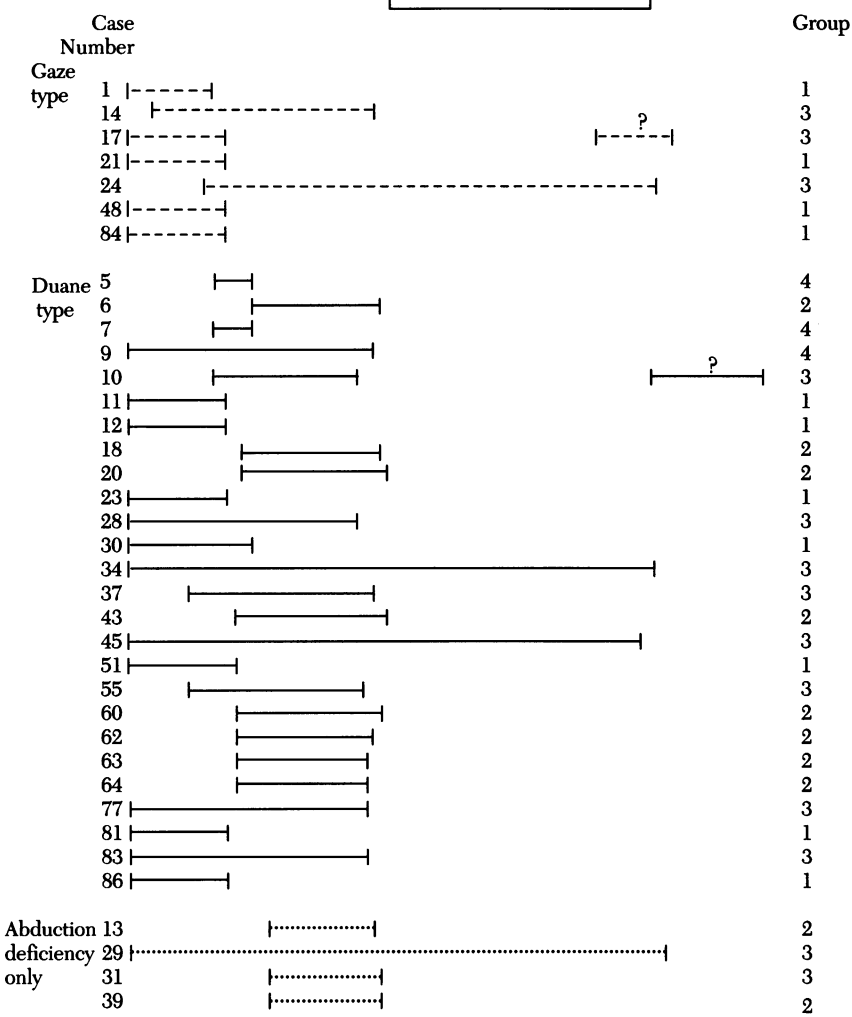
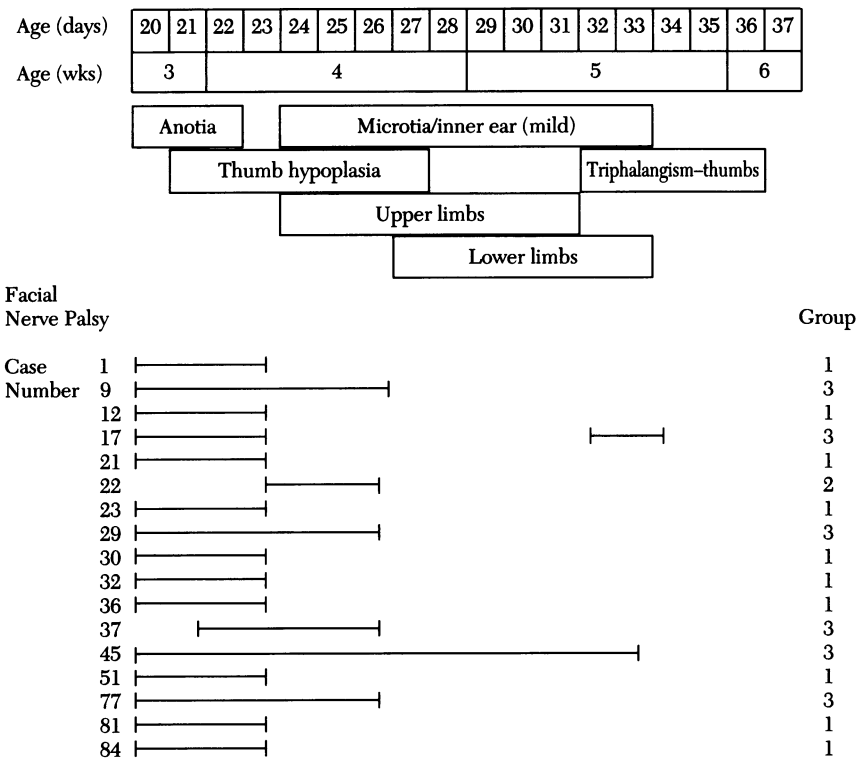


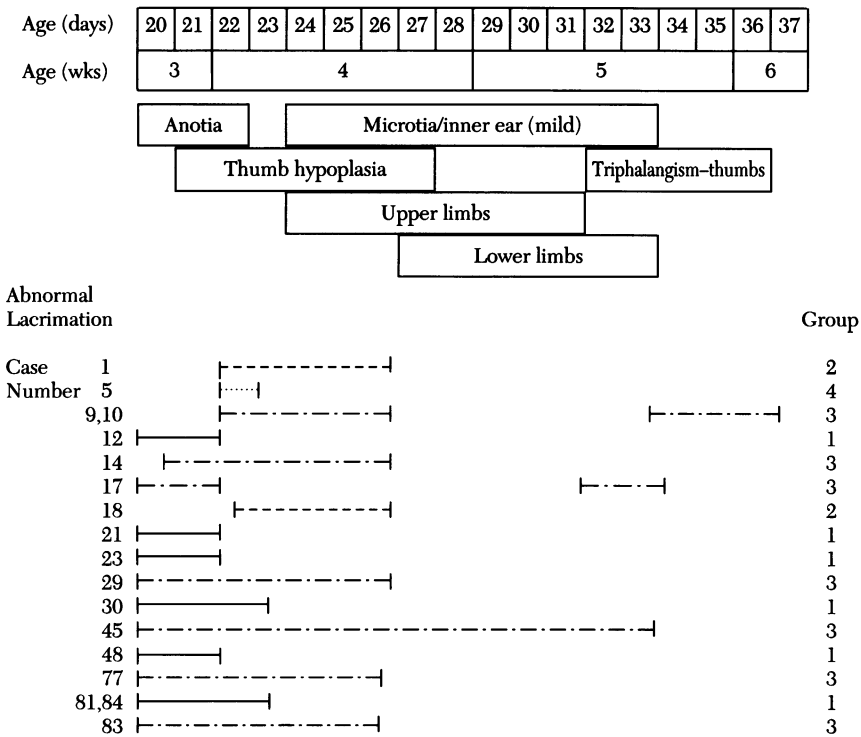
TABLE XIII: TIMETABLE FACIAL NERVE PALSY (ESTIMATES)



always "available" for innervation of the lateral rectus, but that thalidomide somehow interferes with the programmed cell death process. While the thalidomide model strongly suggests damage to the abducens nucleus because of the early time of insult, it does not rule out the possibility that damage to the sixth cranial nerve more distally (from a different etiology) could result in the same reparative process and the same clinical picture.

There are a number of cases in the literature in which the associated anomalies resemble those seen in thalidomide embryopathy. Patients with Holt-Oram syndrome,[142] an autosomal dominant condition characterized by cardiac and upper limb anomalies, cannot be differentiated from cases of thalidomide embryopathy. In one family with Holt-Oram syndrome, Duane syndrome was noted to be associated with hypoplasia of the left thenar muscle of the thumb.[143] Okihiro and co-workers[144] reported three generations of a family in which Duane syndrome was present in

TABLE XIV: TIMETABLE OF ABNORMAL LACRIMATION (ESTIMATES)



five individuals, four of whom also had congenital hypoplasia of the thumb but no cardiac lesions. A similar case of Duane syndrome plus hypoplasia of the thumb occurred in a patient with a proven hypoplastic radial artery, suggesting a vascular basis for this condition.[145] Seven individuals from three generations of a French-Canadian family all had varying degrees of thumb hypoplasia and urinary tract anomalies. Three of these patients had ocular anomalies: one with Duane syndrome and ptosis, one with bilateral uveal colobomas, and one with unilateral coloboma.[146] It is interesting that Duane syndrome and uveal colobomas occurred in the same familial syndrome but not in the same patient.

A more complex picture of strabismus appeared in a large pedigree that showed an autosomal dominant-type transmission manifested by radial ray hypoplasia (thumb and radial bones), mixed-type hearing loss, and thrombocytopenia. Almost all affected individuals demonstrated external ophthalmoloplegia that varied in type and degree but predominantly

involved lateral movements more than vertical, although no retraction of the globes was observed.[147] Whether these patients represent examples of abnormal innervation to the ocular muscles cannot be proven from the available information, but such speculation seems valid because of the existence of similar cases in the literature with clinical documented Duane syndrome.

One of the most intriguing associations with Duane syndrome is that of inappropriate lacrimation.[51,52,148-152] This condition has a variety of names, such as paradoxical gustatory lacrimal reflex or the more colorful designation "crocodile tears," an expression derived from the legend that the crocodile sheds tears before devouring its victim. The symptom is not always mentioned during a history taking because the parents and patients either do not appreciate the association with the patients' other problems or do not consider it a serious defect.

In our preliminary study, the finding of inappropriate lacrimation in case 8 became known only after many examinations of this child, in whom the diagnosis of Duane syndrome was initially not obvious; as an aside, the mother informed us that the child always tears when sucking. The patient was then unavailable for follow-up for 6 years, and on his return to us the symptom no longer existed or could not be elicited by sucking or chewing stimuli. A different form of abnormal lacrimation occurred in case 4 (preliminary study), a girl who had never been observed to tear from any type of stimulus. These two cases plus all of those that we observed in the thalidomide study had no evidence of secondary corneal damage, indicating basal tear production. The 18 patients with abnormal tearing all had horizontal incomitant strabismus.

In the present study the lack of emotional tearing that a number of our patients experienced was a curious finding, but the tearing when eating (especially in public) proved to be a greater problem socially for the patients. Most patients partially control this symptom by eating very slowly.

The syndrome of anomalous lacrimation while eating is almost always acquired and only rarely congenital. In the acquired form it appears weeks or months after a facial nerve palsy during its period of remission.[154] In the rare congenital cases in the literature, almost all have been associated with abduction deficiencies. A number of these cases were described as Duane syndrome, and one may question whether all of the cases represent Duane syndrome. As in Duane syndrome, the proposed etiology of anomalous lacrimation is an aberrant innervation, although location of the abnormality is not completely agreed on in the literature. The previous reports of this association in the cases not involving

thalidomide embryopathy number less than 15 cases, so our group of thalidomide patients represents a noteworthy addition.

Table VIII reviews the associated findings noted in the non-thalidomide cases that are similar to the patients with hemifacial microsomia/Goldenhar syndrome. The acquired form of anomalous lacrimation is not thought to imply a lesion in the same location as the congenital type. A study of one patient by Jampel and Titone[148] showed that whereas salivation could be produced by chewing, sucking, and gustation, the chewing and sucking were primarily responsible for the abnormal lacrimation. From this observation the authors believed that the symptom should be renamed the paradoxical salivary lacrimal reflex. Ramsay and Taylor[51] also thought that the most logical explanation of this combination was nuclear damage or dysgenesis in the vicinity of the abducens nucleus, with the lacrimal finding being the result of innervation of the lacrimal gland by fibers subserving salivation. The observations in thalidomide embryopathy of an overwhelming association with facial nerve palsy, horizontal incomitant strabismus, and aberrant tearing strongly support the theory of a nuclear location. Another rare example of miswiring conditions is that of Duane syndrome with Marcus Gunn jaw-winking phenomenon.[150,155,156]

The common association of seventh nerve palsy and abduction weakness noted in the patients with thalidomide embryopathy has led many authors to designate this group of patients as having Möbius syndrome or Möbius-like anomalies. We observed almost the same types of clinical motility patterns in the review of patients with Möbius-like anomalies as we did in the thalidomide patients except for differences in the frequency of each type of anomaly. Although the etiologies are certainly different, it is tempting to believe that the pathophysiology producing a Möbius syndrome is similar to an insult with thalidomide during a certain period.

The frequent association of limb anomalies in Möbius syndrome also supports this view. However, there are many findings that make significant differences among this group of patients even though the patients may share some commonality of appearance. Similarly, Hickey and Wagoner[158] described a patient with no recognized syndrome but who had congenital bilateral horizontal gaze palsy not associated with fissure changes. On autopsy they found lack of an abducens nucleus or nerve but innervation of the lateral recti by a division of the third nerve. These authors also hypothesized that there may be a spectrum of clinical presentations (including Möbius syndrome) in patients who have abnormal innervation as the cause of their limitation of horizontal ocular motility.

Many reports in the literature on thalidomide embryopathy mention hemangiomas of the lid and face as being frequent findings in infants. The

absence of this finding in all of our patients underlines the natural history of hemangiomas, which is to disappear with increasing age. Occasionally patients gave a history of prior hemangiomas, but most did not mention it. Therefore, little can be concluded from our data regarding time/event versus presence of hemangioma.

Another interesting associated anomaly is ocular dermoids, particularly lipodermoid of the conjunctiva. Ocular dermoids were prominent in the preliminary study of the Goldenhar variant of hemifacial microsomia but were infrequent in the patients with thalidomide embryopathy. One patient in the thalidomide group had a lipodermoid, and there have been others mentioned in the thalidomide literature,[60] but this association is not nearly as striking as that with external ear anomalies, also a component of the Goldenhar syndrome complex. The reason for these differences in frequency is not yet clear.

CONCLUSION

The sensitivity of the embryo to thalidomide is well documented to occur between the 20th and 35th days after conception, resulting in a wide spectrum of anomalies. The most prevalent anomalies involve the extremities, producing various degrees of dysmelia ranging from almost total absence of arms and legs (amelia) to weakness or mild hypoplasia of the thumbs. Next to malformations of the extremities, the most frequent group of anomalies involves the face, with external and internal ear abnormalities, facial nerve palsy, strabismus, and abnormal tearing. The facial involvement can be associated with thalidomide ingestion early in pregnancy, anotia (an absent or severely hypoplastic external ear) occurring in days 20 to 22 or 23 after conception and less severe ear anomalies occurring in days 24 to 29.

In patients with thalidomide embryopathy, severe external ear anomalies were almost always associated with horizontal incomitant forms of strabismus, usually clinical Duane syndrome, although the period of vulnerability was longer for the motility disturbance than for the external ear. There appeared to be a slightly different time span in which internal ear anomalies and subsequent deafness (the combination found in Wildervanck syndrome) were noted with Duane syndrome.

In the early midpart of the thalidomide-sensitive period, associated malformations of the upper extremity and the thumb were observed in incomitant forms of strabismus, usually of the Duane syndrome type or isolated abduction deficits. This may give insight into some of the syndromes reported in the literature in which Duane syndrome has been

noted with upper limb and thumb anomalies. The concordance of seventh nerve palsy with Duane syndrome or similar types of incomitant strabismus raises the question of whether Möbius syndrome is not closely related to Duane syndrome. The oromandibular limb hypogenesis group of syndromes, to which Möbius syndrome may belong, has frequent and severe limb anomalies. Other forms of congenital lateral rectus dysfunction that more closely resemble a gaze paresis were also found in our review of patients with Möbius syndrome.

Incomitant strabismus was uncommon in the later part of the sensitive period. There were a few cases with comitant strabismus, but most had not strabismus.

Thalidomide embryopathy also results in more severe types of ocular pathology, such as uveal colobomas, microphthalmia, and glaucoma. These result from teratogenic action later in the sensitive period, ie, the 28th to 24th days, as determined by the other associated limb and systemic anomalies. The combination of Duane syndrome plus uveal colobomas was noted in two cases in our preliminary study and occasionally was reported in the literature. One explanation for the association is that the sensitive periods for producing each type of malformation may overlap slightly or, more probably, the teratogen was acting in both sensitive periods.

Since teratogens vary in their mode and time of action, it is not possible to conclude from our thalidomide study that all forms of horizontal incomitant squint are due to disturbances at exactly the same time or to the same mechanism. However, the period of developmental insult suggested by our thalidomide model is compatible with the timetables proposed in other syndromes manifesting Duane syndrome because of the commonality of the associated malformations noted in the case reports in the literature. It also suggests that patients with this type of motility disturbance should receive a careful evaluation to rule out associated malformations, especially of the ear.

The study of patients manifesting the effects of thalidomide embryopathy has offered an excellent model for examining unusual patterns of incomitant horizontal strabismus and the association with systemic anomalies. It has provided much information toward answering the questions set forth in the thesis by strongly suggesting that the various patterns of thalidomide horizontal strabismus are closely interrelated and can result from a developmental disturbance beginning early in the fourth week and extending over the next 4 to 5 days. There may be slight variations in time and severity that modify the patterns. Furthermore, our findings indicated that certain rare combinations, such as Duane syndrome plus abnor-

mal lacrimation, were "real" associations.

The tragedy of birth defects such as those related to thalidomide exposure, one hopes, will not occur again with another drug, but less potent teratogens must still be suspected as possible etiologic agents for some patients manifesting these patterns of malformations.

ACKNOWLEDGMENT

I want to thank Dr Kerstin Strömland, my friend and colleague, who arranged the details that allowed the clinical research project to be done, and was a co-investigator throughout all aspects of the thalidomide study.

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