TERATOLOGY 60:306–321 (1999)

Teratogen Update: Thalidomide: A Review, With a Focus on Ocular Findings and New Potential Uses

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Thalidomide (α-[N-phthalmido]-glutarimide) was synthesized in 1954, in what was then West Germany, by Chemie Grünenthal under the brand name of Contergan and was subsequently licensed in 46 other countries worldwide, covering all continents. It is an odorless white crystalline compound with low solubility in water (McBride, '77; Stirling et al., '97). A number of pharmaceutical companies manufactured thalidomide in various concentrations under several trade names (Stirling et al., '97). 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 (Lenz, '88). Additionally, it was an effective antiemetic in pregnancy (McBride, '77). Thalidomide was first marketed in Germany in October 1957 as an effective, safe, inexpensive sedative, and production in that country reached 14.58 tons by 1960 (Zwingenberger and Wendt, '96). A liquid form was available for children, and some compounds were sold without prescriptions (Stirling et al., '97). Routine screening tests found thalidomide to be nontoxic in rodents, and therefore its potent teratogenicity in humans and higher mammals was not anticipated (Brent and Holmes, '88).

In the early 1960s an increasing number of infants were born with hypoplastic limb defects (Lenz,'85). In fall 1961, Lenz, noting these congenital malformations in the German population, suggested a possible correlation with thalidomide taken during pregnancy. He reported his observations at meetings and in the medical literature (Lenz,'61a,b,'62; Lenz and Knapp, '62). Similar observations were made in England (Smithells, '62) and Australia (McBride, '61). Within a few months of the initially reported cases, the drug was withdrawn from commercial sale by Grünenthal (November 1961), and 9 months later was taken off the market in Japan. It was withdrawn from Great Britain in December 1961 (Kida, '87). The potent teratogenicity appropriately suppressed other uses of thalidomide, such as for anti-inflammatory effects (Somers, '60, Miller et al., '60). The U.S. Food and Drug Administration (FDA) had not approved the drug for unrestricted use because of concerns (primarily about possible peripheral neuropathy) raised by Francis Kelsey, an FDA physician. Thus the number of cases of thalidomide embryopathy in the United States was small (Kelsey, '88). The teratogenic effects of thalidomide contributed to the passage of new regulatory legislation for pharmaceuticals (Stirling et al.,'97). There are many reviews in the literature of various aspects of the thalidomide story (McBride, '77; Fraser, '88; Kelsey, '88; Lenz, '88; Warkany, '88; Lenz, '88).

PERIOD OF GREATEST SENSITIVITY

From the studies of periods of exposure compared with resultant congenital anomalies, it was established that thalidomide was teratogenic primarily between 20 and 36 days after fertilization (34–50 days after the last menstrual cycle) (Lenz and Knapp, '62). Thalidomide differs from some teratogens in that the clinical dosage seems not to be as significant a factor as the time of intake of the drug. It is quite rapidly hydrolyzed and because of this short action time, extreme potency, and the large number of women who took thalidomide, informative histories could be ascertained. Many women knew the exact date of intake and the number of pills they took, and a correlation between time of drug intake and resultant malformations could be constructed (Pliess, '62; Miehlke and Partsch, '63; Papst, '64; Nowack, '65; Lenz, '66). From this information, summary timetables were developed (Nowack, '65; Kida, '87). Additional data came from observing anomalies that seemed to cluster in the individuals with thalidomide embryopathy even if the exact time of intake of the drug was not known (Armimoto, '87; Gilkes, '63; Miehlke and Partsch, '63; Cullen, '64; Schmidt, '64). Nowack did one of the most extensive reviews in 1965 in which he reported 82 completely documented cases out of a total of 945 case histories. He

Grant sponsor: Swedish Medical Research Council; Grant number: K98-17X-10863-05A; Grant sponsor: NEI Core Grant for Vision Research; Grant number: EY01792; Grant sponsor: Research to Prevent Blindness, Inc.; Grant sponsor NIH; Grant number: P01HD35466.

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Received 1 January 1998; Accepted 7 July 1999

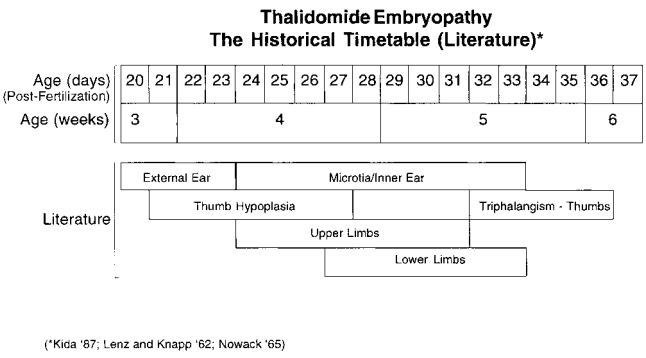

Fig. 1. Summary timetable of thalidomide embryopathy based on observations in the literature. The sensitive period is 20–36 (± 1 day) days after fertilization. If calculated from the last menstrual period, it would be approximately days 34–50.

established the sensitive times for the development of various types of malformations from thalidomide taken between the 34th and 50th day after the last menstrual period (20–36 days postfertilization). He noted that anotia was the first finding occurring at the beginning of the sensitive period, followed by thumb, upper extremities, and later lower extremities, and triphalangeal thumbs. A summary of these and similar observations from the literature (Kida, '87) is shown in Figure 1. Lenz ('66) estimated the total affected cases to be between 5,000 and 7,000, with >3,000 in West Germany alone. Since the survival rate is thought to have been between 40% and 70%, this gives an overall estimate of >10,000 affected embryos (Lenz and Knapp, '62; Lenz, '61a,b, '66).

PHENOTYPIC EFFECTS

Older literature

Thalidomide intake produces a spectrum of malformations often involving craniofacial structures and extremities, but also affecting a wide array of other structures (Nowack, '65; Kida, '88). The most frequently reported anomalies were those of the extremities and ranged from mild limb defects (thenar muscle aplasia, triphalangeal thumbs, shoulder weakness, etc.) to more severe limb anomalies (absent or very hypoplastic thumbs, flexion contractures of middle and index fingers, hypoplasia of radius and ulna, absent phalanges, hip and shoulder hypoplasia). Some cases demonstrated the most severe forms of limb defects (absent radius, phocomelia, and amelia) (Taussing, '62).

Ear malformations and/or hearing loss were very common malformations, showing a spectrum from severe microtia with absent pinna (often referred to as anotia) to mild malformations of the external ear (Takemori et al., '76). Sensorineural deafness secondary to inner ear anomalies with or without external ear involvement was observed, along with some middle ear changes in some individuals. Facial nerve palsy was often reported as a manifestation of a thalidomide effect and could be unilateral, bilateral, or bilateral but asymmetric.

Ocular anomalies, such as uveal coloboma, glaucoma, microphthalmos, refractive error, ptosis, and occasionally cataract were observed, in addition to ocular movement abnormalities, such as sixth nerve palsy and Duane syndrome (Honegger and Pape, '64; Pabst, '64). A rare anomaly of aberrant lacrimation (often called crocodile tears) was also described as a manifestation of this potent teratogen (Takemori et al., '76). External ear, strabismus, facial nerve palsy, and aberrant lacrimation were often noted to occur together.

A wide variety of other anomalies have been reported in review articles (Kajii, '65; Smithells, '73; Newmann, '77; Kida et al., '78). The more frequent were kidney malformations (hypoplasia or positional defects), heart defects, anal atresia or stenosis, spine and chest structural defects, and central nervous system (CNS) defects.

Although cranial nerve abnormalities are common in thalidomide embryopathy, severe CNS structure defects, such as anencephalus or spina bifida, did not seem significantly increased (Leck and Miller, '62). However, not many patients had radiologic imaging, so minor malformations might not be recognized.

In a large Japanese study of thalidomide-affected individuals, mental retardation occurred in 6.6% (Saito and Asahu, '87). Also noted in the study was a significant increase in percentage of abnormal EEG (40%) and epileptic seizures (5.8%). The incidence of heart malformations was higher in newborn infants than in older children, suggesting that cardiac complications may have been responsible for many of the early deaths of infants born to mothers who took the drug (Winberg, '64).

Phenotypic effects: Swedish study (1987–1989)

From 1987 to 1989, a study was conducted to document the ocular findings of 86 thalidomide-affected Swedish individuals who were then 27–30 years of age. In addition to ocular findings, obvious craniofacial anomalies and a summary of the associated systemic anomalies from the patients or medical records were documented (Miller, '91; Miller and Strömland, '91; Strömland and Miller, '92,'93).

Thalidomide was available in Sweden between January 1959 and December 1961. An estimated 150 Swedish infants were affected, of which approximately one-third died in the neonatal period or early infancy (Strömland and Miller, '93). When the association between the drug taken early in pregnancy and the ensuing anomalies was appreciated, the parents of the affected children brought a lawsuit against the Swedish pharmaceutical company that manufactured thalidomide. The resulting trial (which won the plaintiffs financial compensation), plus the well-developed medical system in Sweden, encouraged all families who had affected children to come forward. Physicians determined whether the birth defects were likely to be related to thalidomide and, if so, compensation was

established proportionate to the severity of the problems. In 1969 an agreement was made with the families, and the affected individuals received payments at regular intervals (Strömland and Miller, '93). Since compensation is still given, the affected individuals, now adults, were known and were asked to participate in a study.

At the onset of the study, the number of affected living individuals in Sweden was estimated to be about 100 patients (Strömland and Miller, '93). A few patients had died of other causes, some had left the country, and a few refused examinations, resulting in a final study number of 86. In 14 unexamined patients from the original group of affected children, medical records were usually available and there did not seem to be any evidence that they represented a group with significantly different characteristics from the examined individuals. Other information was available on these Swedish patients from previous studies (d'Avignon and Barr, '64; Winberg, '64; Zetterstrom, '66; d'Avignon et al., '67).

TABLE 1. Limb and systemic anomalies documented in Swedish thalidomide study (N = 86)

Anomalies or site of anomaly	No. (%) affected	
Thumbs	70 (81%)	
Upper limb (excluding thumb)	59 (69%)	
Lower limb	21 (24%)	
Ears/hearing	33 (38%)	
Facial nerve palsy	17 (20%)	
Kidney	12 (14%)	by history or medical record
Cardiovascular	7 (8%)	
Chest/lung	4 (5%)	
Genitalia	3 (3%)	
Anal atresia	4 (5%)	
Choanal atresia	2 (2%)	
Dental anomalies	4 (5%)	
Mental retardation (moderate to severe)	5 (6%)	
Autism	4 (5%)	

Data collection

Because the study focused on the ophthalmic findings and observable or known malformations, complete physical examinations looking for minor variations or less obvious systemic malformations were not performed. Also, patients in the study were resistant to extensive examination, feeling that they had been studied enough over the years. Therefore, the systemic anomalies listed represent those easily observable, those reported by the patients themselves, or those present in the medical records. Four study patients were in special institutions for the deaf and mentally retarded, but most of the other patients lived independently.

Since the thalidomide literature was quite consistent concerning the sensitive period for ear and limb anomalies and these groups of malformations were obvious to the investigators, they were chosen as the basis of comparison for the ophthalmic anomalies noted in our study patients. The correlations between eye malformations and the limb and ear anomalies in the Swedish study were in general agreement with many published observations proposing the sensitive periods for ocular malformations (Arimoto '87; Lenz, '62; Gilkes, '63; Cullen, '64; Papst, '64; Papst and Esslen, '64; Schmidt, '64).

Table 1 shows a breakdown of limb and systemic anomalies in these thalidomide-affected individuals in Sweden. By far, the most common were reduction-type limb defects, with the thumbs the most affected. Thumb anomalies had been noted to be caused by thalidomide taken early in embryogenesis (~days 20–27) and usually of the deficiency-type defect. An exception was triphalangeal thumb, which occurred later in the sensitive period. This was consistent with our observations, but because thumb anomalies were so prevalent and noninformative of the exact time of insult in embryogenesis, they were not used as a basis for comparison when we constructed an ocular timetable. Instead we used the comparison of upper and lower limb anomalies in our comparative timetable.

Figure 2 shows the spectrum of observed thumb anomalies. Tables 2–9 summarize the systemic anomalies and autism in these 86 examined patients based on their history or medical record compared with their associated limb anomalies.

Ear anomalies were very frequent (Fig. 3). True anotia implies no remnants of ears, and this was not observed. However, the term "anotia" as used descriptively in the thalidomide literature often represents extremely severe external ear anomalies. Severe microtia is a better description and was seen in 14 patients. It could be unilateral or bilateral and asymmetry was often observed. A total of 24 patients had external ear anomalies, 30 patients had inner ear malformations, and 32 patients reported some hearing deficit. Additionally, 10 patients said they had been told they had narrow ear canals, but we were not in a position to verify these statements.

Table 10 indicates the observed ocular anomalies. The spectrum of anomalies was consistent with those reported in the literature, but the very high prevalence of an unusual form of strabismus (misalignment of the eyes) was a surprising finding in this study. Although strabismus is a relatively common anomaly occurring in 2–5% of the general population, it is usually an isolated finding, but also can be commonly noted in children with other systemic anomalies of various etiologies. The most common form of strabismus (>90%) is presumed to be due to pathology in higher centers in the brain and does not show any limitation of movement in any field of gaze and is termed *comitant* strabismus. This is contrasted to *incomitant* strabismus, which can be secondary to cranial nerve palsies, restrictive problems, or aberrant innervation. In this type of strabismus, the misalignment changes in the different fields of gaze. Figure 4 shows examples of the most common type of incomitant strabismus, Duane

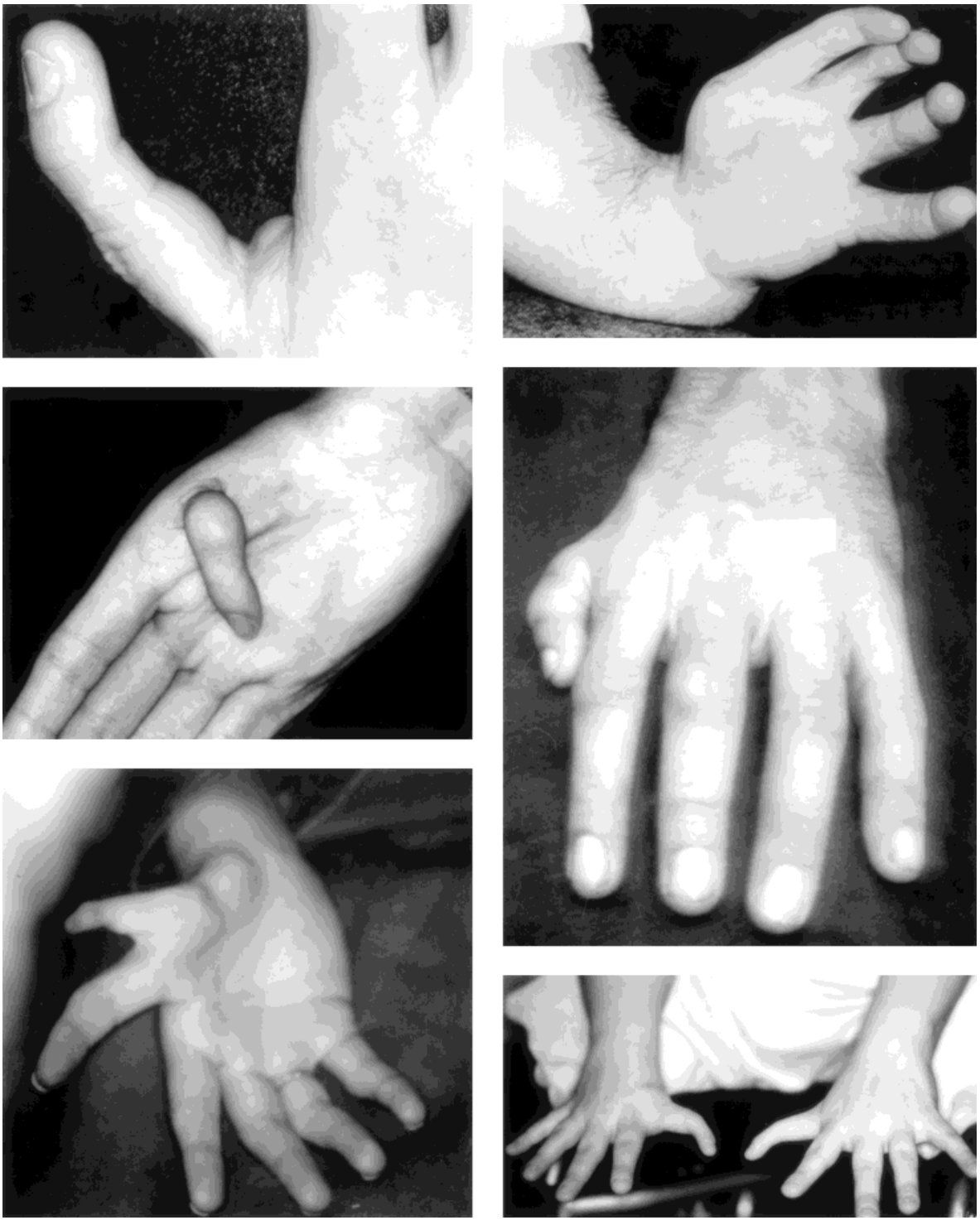

Fig. 2. Spectrum of thumb anomalies: triphalangeal (2), absent, misplaced, hypoplastic, and extra digit.

syndrome. Figure 5 illustrates structural ocular malformations.

Association between certain anomalies and ocular and systemic anomalies were analyzed. Tables 11 and 12 are examples of these comparisons for both. They were aberrant lacrimation and facial nerve palsy. It was apparent from the data in these tables that facial nerve palsy and abnormal lacrimation were almost always associated with incomitant strabismus and external ear anomalies, and rarely lower limb anomalies. This strongly suggested that the early thalidomide effect (days 20–26) was the sensitive period for development

TABLE 2. Kidney malformations* with associated limb anomalies

Case no.	Type of kidney malformation	Sex	Associated limb anomalies** Thumb R	Thumb L	Upper R	Upper L	Lower R	Lower L	Other systemic anomalies
10	Absent (R)	M	0	+ (T)	+	+	0	0	Ear (L)
17	Absent (L)	M	+	+	+	+	0	0	Choanal atresia, 7th nerve, lung, ear (deaf)
18	Horseshoe (L)	M	+	+	+	0	0	0	Deaf (R)
22	One functional	M	+	+	+	+	0	0	Anal atresia; VSD, scoliosis; 7th nerve (mild)
34	Absent (R)	F	+	+	+	+	0	0	VSD, pulmonary atresia, ear
50	Absent (R)	M	+	+	+	+	+	+	
52	Hydronephrosis	F	+	+	+	+	0	0	
56	One absent	F	+	+	+	+	+	+	
69	One dislocated	F	+	+	+	+	+	+	
78	Atresia of one	M	+	+	+	+	0	0	
79	Hypoplastic; transplant	F	0	+	0	+	+	+	
85	Removed (R)	F	+ (T)	+ (T)	0	0	+	+	Hearing

*Determined by history or medical record.
**+ = present; 0 = absent; T = triphalangeal thumb; VSD = ventricular septal defect.

TABLE 3. Cardiovascular malformations* with associated limb anomalies

Case no.	Type of cardiovascular malformation**	Sex	Associated limb anomalies*** Thumb R	Thumb L	Upper R	Upper L	Lower R	Lower L	Other systemic anomalies
12	VSD	M	0	0	0	0	0	0	Ear
16	Irregularity, flutter	M	+	+	+	+	+	+	Scoliosis, chest
22	VSD	M	+	+	+	+	0	0	Kidney, anal atresia, scoliosis, 7th nerve (mild)
34	VSD	F	+	+	+	+	0	0	Pulmonary atresia, ear, one kidney absent
45	Ductus botalli	M	+	+	+	+	+	+	Myelomeningocele, chest, CNS, MR, ear
57	Murmur	F	+	+	+	+	0	0	Absent vagina and uterus
81	VSD	F	0	0	0	0	0	0	Ear

*Determined by history or medical record.
**VSD = ventricular septal defect.
***+ = present; 0 = absent; CNS = central nervous system; MR = mental retardation.

TABLE 4. Pulmonary and chest systemic malformations* with associated limb anomalies

Case no.	Type of pulmonary/ chest malformation	Sex	Associated limb anomalies** Thumb R	Thumb L	Upper R	Upper L	Lower R	Lower L	Other systemic anomalies
17	Cardiovascular anomalies	M	+	+	+	+	0	0	Choanal atresia, kidney
34	Pulmonary atresia	F	+	+	+	+	0	0	VSD, one kidney absent, ear
16	Enlarged chest wall	M	+	+	+	+	+	+	Heart, scoliosis
45 (R)	Chest structural anomaly	M	+	+	+	+	+	+	Myelomeningocele, CNS, heart, ear, 7th nerve (R)

*Determined by history or medical record.
**+ = present; 0 = absent; VSD = ventricular septal defect; CNS = central nervous system.

of these anomalies. This observation was also noted in a large Japanese study (Arimoto, '87). Figure 6 shows an example of the methodology in each patient with Duane syndrome comparing each with the associated limb and ear malformations. The time common to each patient was then observable to be early in the sensitive period. This same approach resulted in summary timetables for ocular motility disturbance, facial nerve palsy, aberrant lacrimation, and ocular structural anomalies (Fig. 7). The exceptions to these summaries were rare.

When all of the individual timetables were grafted together, we derived composite data of the sensitive period common to almost all cases (Fig. 7). The most informative patients were those in which the associated anomalies were few and representative of a narrow time of the sensitive period, suggesting that the mother had taken the drug only for a few sequential days. Equally informative were patients without any ocular anomalies but with observable limb anomalies. The least useful cases were those that had combined anoma-

TABLE 5. Genital malformations* with associated limb anomalies

Case no.	Type of genital malformation	Sex	Associated limb anomalies**						Other systemic anomalies
			Thumb		Upper		Lower		
			R	L	R	L	R	L	
7	Absent uterus and vagina	F	+	+	0	0	0	0	Hearing
57	Absent uterus and vagina	F	+	+	+	+	0	0	Heart murmur
80	Double vagina	F	+	+	+	+	+	+	

*Determined by history.
**+ = present; 0 = absent.

TABLE 6. Gastrointestinal malformations* with associated limb anomalies

Case no.	Type of gastrointestinal malformation	Sex	Associated limb anomalies**						Other systemic anomalies
			Thumb		Upper		Lower		
			R	L	R	L	R	L	
4	Anal atresia	M	+	+	+	+	0	0	
22	Anal atresia	M	+	+	+	+	0	0	Kidney, VSD, scoliosis, 7th nerve (mild)
24	Anal atresia	F	+	+ (T)	0	0	0	+	Submucous cleft, ear (L)
73	Anal atresia	F	+	+	+	+	0	0	Hearing

*Determined by history.
**+ = present; 0 = absent; T = triphalangeal thumb; VSD = ventricular septal defect.

TABLE 7. Choanal atresia malformations* with associated limb anomalies

Case no.	Type of malformation	Sex	Associated limb anomalies**						Other systemic anomalies
			Thumb		Upper		Lower		
			R	L	R	L	R	L	
17	Choanal atresia	M	+	+	+	+	0	0	Kidney, lungs, ear, 7th nerve
59	Choanal atresia	M	+	+	+	+	0	0	Missing teeth, ear

*Determined by history.
**+ = present; 0 = absent.

TABLE 8. Dental malformations* with associated limb anomalies

Case no.	Type of dental malformation	Sex	Associated limb anomalies**						Other systemic anomalies
			Thumb		Upper		Lower		
			R	L	R	L	R	L	
37	Enamel hypoplasia	M	+	+	+	+	0	0	Hearing (R)
43	Enamel hypoplasia	M	+	+	0	+	+	0	
59	Missing teeth	M	+	+	+	+	0	0	Choanal atresia, ear
61	Missing teeth	M	+	+	+	+	0	0	

*Determined by history.
**+ = present; 0 = absent.

lies of the eyes, ears, and upper and lower extremities, implying that the drug had been taken throughout the sensitive period.

Aberrant lacrimation was a somewhat surprising common early finding. The clinical symptoms ranged from isolated lack of emotional tearing to inappropriate tearing when eating, or both. Apparent aberrant innervation was an early effect of thalidomide and was always accompanied by incomitant strabismus, usually with ear anomalies, but never with limb anomalies alone (Table 11).

An unexpected finding in this study was obvious autism in four of the five patients with mental retardation. A more thorough evaluation of the five patients with severe mental retardation was performed later by psychiatrists. Autism was diagnosed in four of the five mentally retarded individuals (Strömland et al., '94). We were able to identify an early sensitive period for this problem based on associated ear and limb anomalies (Fig. 7). This was similar to incomitant strabismus, facial nerve palsy, and aberrant lacrimation.

TABLE 9. Autism and associated anomalies

Case no.	Type of malformation*	Sex	Associated limb anomalies: Thumb R	Thumb L	Upper R	Upper L	Lower R	Lower L	Other systemic anomalies**
36	Autism and MR	F	0	0	0	0	0	0	Ear (deaf), 7th nerve
77	Autism and MR	M	+	+	+	+	0	0	Ear, 7th nerve
84	Autism and MR	M	0	0	0	0	0	0	Ear, 7th nerve
86	Autism and MR	F	0	0	0	0	0	0	Ear (deaf)

*MR = mental retardation (all patients with autism had MR).
**Cases 77, 84, and 86 had incomitant strabismus; cases 77 and 84 had aberrant lacrimation.

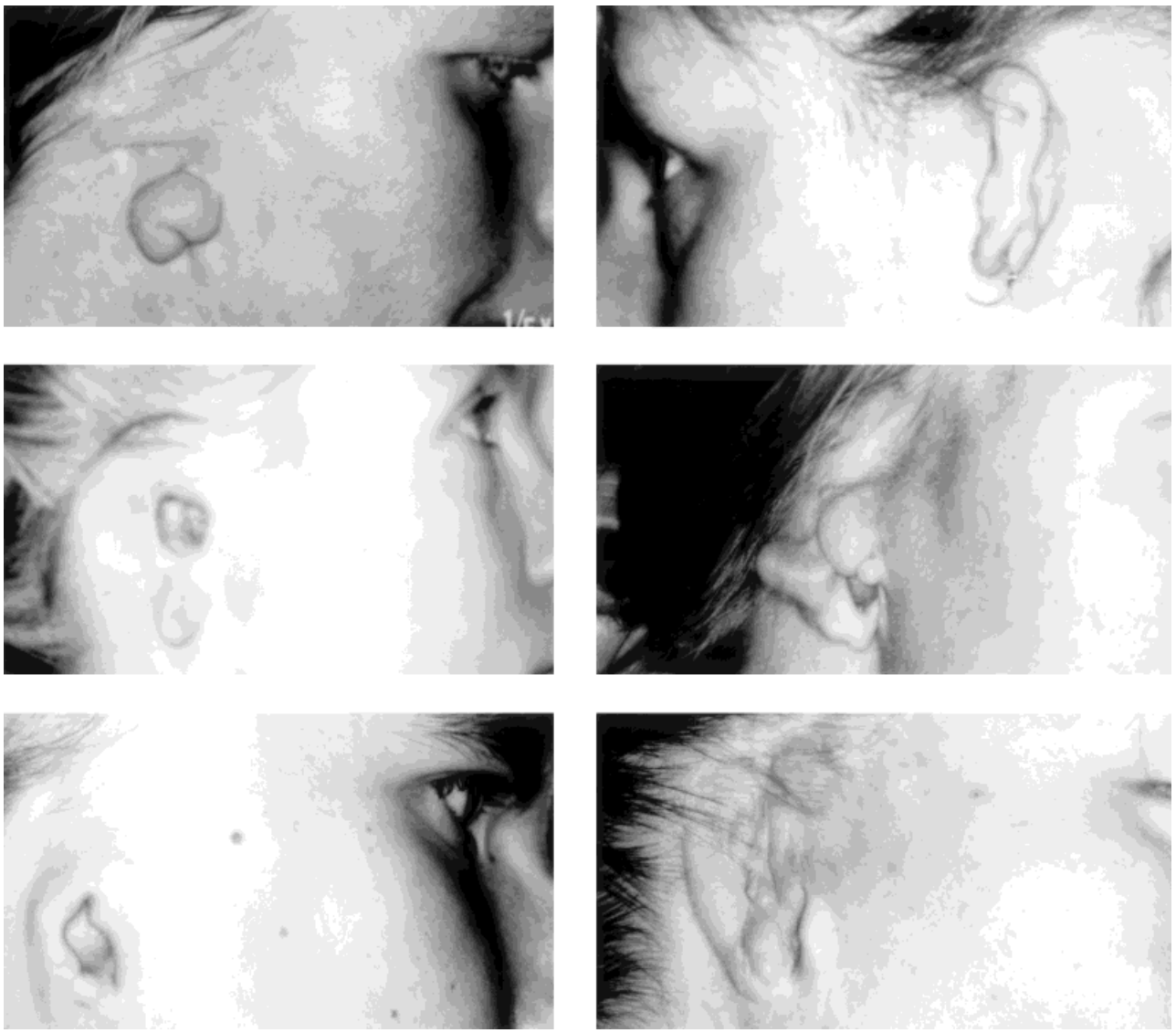

Fig. 3. Examples of observed ear anomalies.

The study design and extent of examinations did not allow a comprehensive evaluation of many systemic anomalies (cardiovascular, kidney, etc.). Anomalies listed in Tables 2–9 were derived from the history given by the patient or from medical records and could be incomplete. Therefore, no attempt was made to develop a definite timetable.

Of the estimated 150 thalidomide-affected children delivered in Sweden, a few were stillborn and 40-plus died in the neonatal period early infancy (Winberg, '64).

TABLE 10. Ocular anomalies documented in Swedish thalidomide study

Anomaly	No. (%) affected*
Strabismus	
Incomitant strabismus (Duane type 26; limitation abduction and adduction [gaze type] 7; abduction deficit only 4)	37 (44%)
Horizontal comitant strabismus (all esotropia)	6 (7%)
Aberrant lacrimation	17 (20%)
Coloboma (uveal or optic disc)	4
Microphthalmos	3
Glaucoma	1
Lipodermoid of conjunctiva	1
Hypertelorism	1
Myelinated nerve fiber	2
Ptosis	2

*N = 86, except strabismus when N = 84.

Some of those with mild skeletal malformations still had serious systemic malformations that may have led to death. There was a very high mortality in children with amelia with only 3 of 21 affected surviving. It was also noted that children with unilateral damage to the radius would survive, whereas about 1/3 of those with bilateral damage died (Winberg, '64). Since the trial in 1969 established the group that is described here, this Swedish study contained only those that were living in that year. Of this group of about 100 individuals, we were able to examine 86. There have been some deaths of the original 100 individuals and a few from the 86 we examined, but there does not seem to be pattern of causation, i.e., one drowned (no details known), one died of colon cancer , one had a malignant tumor of the bladder, one died while in Thailand (no details are known), and one was murdered.

DISCUSSION

Although congenital incomitant strabismus is not frequent, Duane syndrome is the most common form in this group. Duane syndrome is felt to be due to aberrant innervation of the ocular muscles in most cases. The electromyographic data and a few autopsy cases support the concept that a branch of the third cranial nerve (which normally innervates the medial, inferior, and superior rectus and inferior oblique muscles) inappropriately innervates the lateral rectus muscle (normally innervated by the sixth nerve). In these patients there is usually little or no firing of the lateral rectus on attempted abduction, suggesting involvement with the sixth nerve either at the nuclear or peripheral site. This results in limitation of movement in some fields of gaze (incomitant strabismus). There is also narrowing of the palpebral fissure on adduction in the affected eyes probably due to co-firing of the medial and lateral rectus from the aberrant innervation. Different clinical patterns of Duane syndrome occur depending on the balance between (1) the amount of aberrant innervation to the lateral rectus by the third nerve, (2) the degree of the sixth nerve paresis, and (3) the extent of reduced innervation to the medial rectus, from fibers going to the lateral rectus.

Duane syndrome occurs in ~1% of strabismus cases. Usually it is an isolated finding; however, there are many cases of Duane syndrome in the literature that show an association with a wide spectrum of systemic anomalies, such as those found in the Goldenhar-type patients (i.e., spinal cord malformations, upper lid colobomas, conjunctival and limbal dermoids, and ear anomalies).

The presence of Duane syndrome may have been underreported in the thalidomide literature. Some thalidomide patients were described as having abduction defects, which were attributed to a sixth nerve palsy but actually may have had Duane syndrome, since this is a more difficult diagnosis in a young child. In the Swedish thalidomide study, a surprisingly high number of patients had a clinical pattern that was highly compatible with the diagnosis of Duane syndrome with its recognized variations (44%), whereas only six patients (7%) showed common types of comitant strabismus (misalignment without any limitation of ocular movement). The comitant strabismus pattern was seen more in patients with the later occurring limb malformations (Miller, '91).

Congenital paradoxical lacrimation is a very rare anomaly that was present in 17 study patients (20%). This malformation also had been reported as a fairly frequent finding in a Japanese series of thalidomide embryopathy (Arimoto, '87). All of the affected patients in the Swedish study also had incomitant strabismus of the Duane type. Anomalous lacrimation also represents an example of aberrant innervation, although the details of the abnormal neurologic connections are not completely understood. The association of congenital paradoxical lacrimation and Duane syndrome in patients not exposed to thalidomide has been reported previously in the literature (Jampel and Titone, '62; Tachibana et al., '84). Ramsay and Taylor ('80) suggested that the most logical explanation of this combination of findings was nuclear damage or dysgenesis in the vicinity of the abducen nucleus, with the lacrimal findings resulting from aberrant innervation of the lacrimal gland. Most of the patients in the literature or the Swedish series had no evidence of damage to their corneas, which suggests that their basal tear secretion is normal. The term "crocodile tears" is used to describe tearing while eating supposedly because crocodiles seemed sad when they eat their "catch."

Autism was not a finding previously reported with thalidomide embryopathy. This was first noted at the end of the Swedish study when institutionalized patients with severe mental retardation were evaluated. Since the initial study was not designed to evaluate patients with autism or autistic traits, or mild mental retardation, the prevalence of autism-like conditions may have been underestimated. The associated findings in this group of four patients were usually Duane

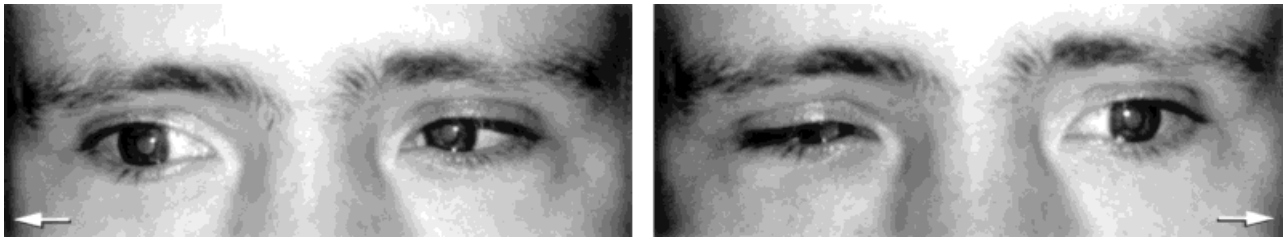

Fig. 4. Incomitant strabismus, Duane type, showing bilateral limitation of abduction with narrowed palpebral fissure on adduction.

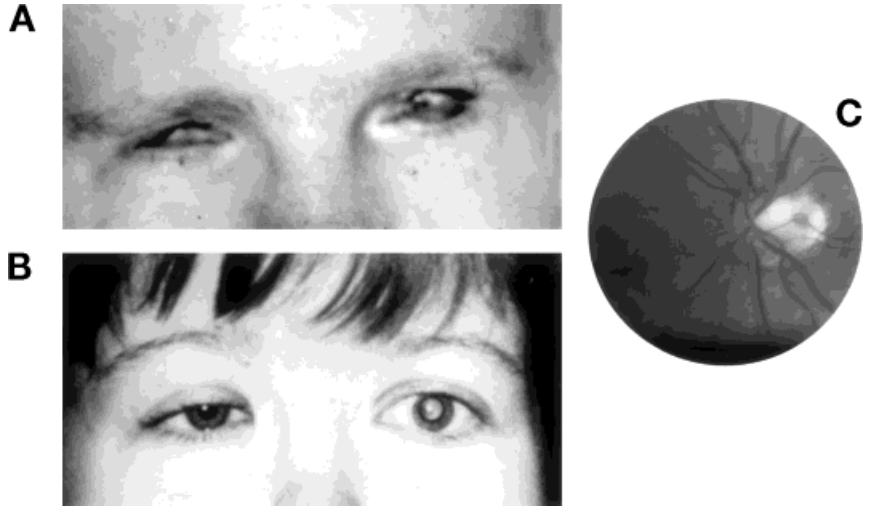

Fig. 5. Structural eye defects: **(a)**bilateral microphthalmia; **(b)** prosthesis in the right eye due to severe microphthalmia; **(c)** optic disc malformation (coloboma).

TABLE 11. Associated anomalies in 17 patients with abnormal lacrimation

Associated anomalies	No. (%) of patients
Horizontal incomitant strabismus	17 (100%)
Hearing deficit	16 (94%)
Facial nerve defect	12 (71%)
External ear malformation	14 (59%)
Hearing/ear without limb anomalies	9 (53%)
Ear and limb anomalies	8 (47%)
Upper/lower limb without ear anomalies	0

TABLE 12. Most common associated anomalies with facial nerve palsy in 17 patients*

Associated anomalies	No. (%) of patients
Horizontal incomitant strabismus	14 (82%)
Abnormal lacrimation	12 (71%)
External ear malformation	16 (94%)
Hearing deficit	16 (94%)

*Nine of the 17 cases were bilateral; seven were right side only, and two were left side only.

syndrome, facial nerve palsy, ear malformations, and aberrant innervation. This suggests autism might represent thalidomide effect occurring early in the sensitive period (Strömland and Miller, '93).

As is necessary in all clinical investigations, serious attention was paid to the ways in which bias may enter the study, such as selection of a nonrepresentative population, inaccuracy of the observations, or unsubstantiated conclusions. As the study proceeded, however, it became obvious that although the prevalence of ocular anomalies in the surviving adult thalidomide victims could be fairly accurately determined, the true incidence of any one type of ocular malformation in the developing embryo might be significantly different because of the estimated 30–40% of neonatal mortality (Lenz, '88), and the spontaneous abortion rate. Since ocular anomalies do not affect the mortality rate, the final prevalence of ocular malformations in the adult compared with the incidence rate of these anomalies in the embryo was influenced "by the company they keep." The more severe ocular anomalies such as microphthalmia and colobomas seemed to have been reported more frequently in the early thalidomide literature than observed in this study. If true, this might be explained by the fact that these ocular malformations occurred at the same time in embryogenesis as life-threatening systemic anomalies (e.g., severe cardiovascular malformation, anal atresia). This could result in the death of the fetus or infant and would indirectly decrease the

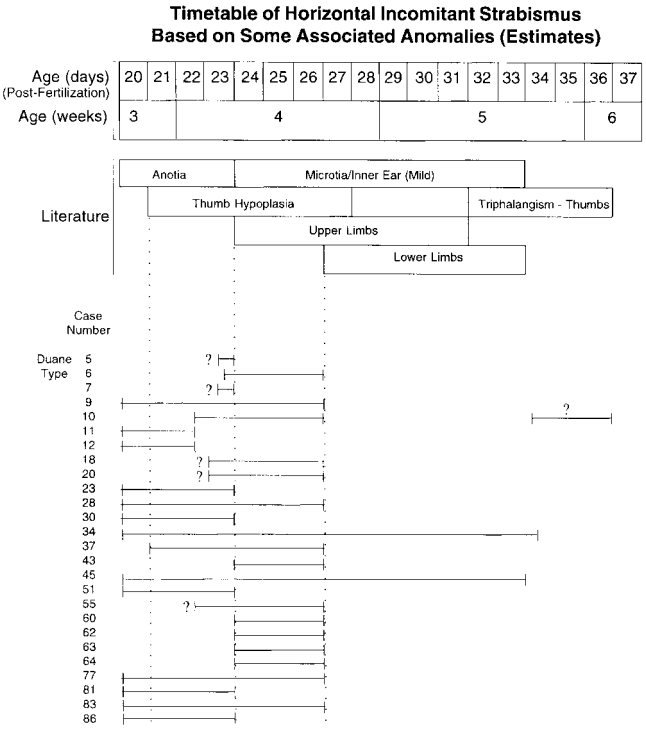

Fig. 6. Swedish Study. Timetable of Duane syndrome (DS) based on associated ear and limb anomalies of each patient compared to the thalidomide timetable established from the literature. For example, patient #9 who had moderate ear anomalies, upper limb but no lower limb malformations suggests that thalidomide was taken in early to midsensitive period. Some of the beginning and endpoints are estimates, e.g., the difficulty in separating anotia from microtia and how to plot the few patients with very mild or questionable limb anomalies. Other problem patients included patients 5 and 7. They only had some malformations. Even with the less clear examples, there was no question that DS was associated with an early thalidomide effect of the 20–36 day overall sensitive period.The individual data for the other types of incomitant strabismus, facial nerve palsy, and aberrant lacrimation were consistent with an early thalidomide effect.

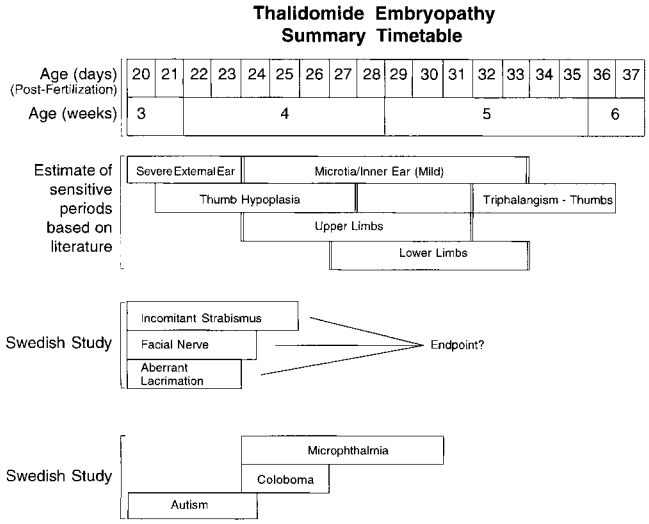

Fig. 7. Summary estimates of sensitive periods for ophthalmic malformations based on associated anomalies manifested by most patients (see Fig. 6 for Duane syndrome, the most frequent incomitant strabismus). The other clinical forms of incomitant strabismus had similar associated anomalies. These sensitive time blocks for the development of eye anomalies and autism are estimations and they may be shorter or slightly longer than indicated. The thalidomide timetable for the ear, thumb, and limb anomalies was derived from the literature (Nowack, '65; Lenz, '66, Kida, '87).

observed prevalence of certain ocular malformations in the older age group in this study. By contrast, ocular movement (motility) disorders were associated with the early thalidomide effects of ear, thumb, and upper limb malformations, which may not be as life threatening to the embryo or the infant. Therefore, severe eye malformations might show a lower prevalence in this cohort than if the cohort had been studied in very early infancy or had included aborted fetuses. Similarly, less severe defects such as ocular motility disorders might have a higher prevalence in surviving adults.

THALIDOMIDE'S USES IN THE 1990s

Thalidomide was the teratogenic scourge of the 1960s. The only redeeming outcome seems to be that it brought greater awareness to the scientific community and public of the potential severe damage to the fetus from exposure to drugs and other environmental agents taken during pregnancy. After the world recognized the high teratogenicity of this drug, it would have seemed unthinkable that it would ever make it back into the marketplace or that any benefit from the drug could ever override the severe risk to women early in their pregnancy. However, thalidomide has actions that have led to its re-evaluation in a large variety of medical conditions and it has become available in some countries. These new insights and more research have suggested new possible modes of activity, although the molecular basis for these actions is often not understood.

Areas of present use include treatment of some of the complications of leprosy, particularly erythema nodosum leprosum (ENL); wasting disease associated with acquired immunodeficiency syndrome (AIDS); a variety of dermatologic conditions; and some immunologic diseases. There is also ongoing research pertaining to its use in some malignancies and diseases in which abnormal angiogenesis is a factor. Other applications undoubtedly will be evaluated through research in the future. Further investigations may be facilitated by the recent decision of the FDA to release thalidomide for use in erythema nodosum leprosum and the serious consideration for less rigid restrictions in other diseases and approval to market is pending (Nightingale, '98).

With increased availability, there needs to be greater attention to safety precautions (see the later section on Safety). There is also concern that the birth defects surveillance systems may not be adequate to detect small changes in a specific defect caused by a teratogen that was being used in a limited way (Yang et al., '97). The consideration of decreasing the restrictions on this

drug has resulted in many debates over the issues of patients' needs and the resultant increased fetal exposure even when significant precautions are taken. A national conference (1997) addressed these issues ("Thalidomide: Potential Benefits and Risks").[1]

Mechanism of action

Thalidomide is a derivative of glutamic acid with two rings (α-[N-phthalmido and glutarimide) and two optically active forms (Tseng et al., '96). After a 200 mg oral dose, it has a mean peak at about 4 hours and a half-life at about 8–9 hours and total body clearance around 11 hours (Tseng, '96). Clearance is primarily by a nonenzymatic hydrolytic mechanism (Tseng et al., '96). It is hydrolyzed into many compounds, and the exact action of each is not established, but most do not appear to have immunological activity (Zwingenberger and Wendt, '96). It is a difficult compound to work with because of this rapid hydrolysis.

After the recognition of the significant teratogenicity of thalidomide, it was studied extensively, but no definite conclusions were absolutely established about its mechanisms of action (Stephens, '88). Recently, more attention has been directed to its effects in vitro and in vivo on the immune system. Comprehensive reviews by Zwingenberger and Wendt ('96) and Tseng et al. ('96) have summarized the present status, and this review highlights only the more clinically oriented aspects.

The immune effect seems best described as immunomodulatory and has been ascribed to the selective inhibition of an inflammatory cytokine, tumor necrosis factor-α (TNF-α), released from monocytes (Klausner et al., '96a; Turk et al., '96). There are a number of speculations as to how this works at a molecular level (Turk et al., '96; Miyachi et al, '96; Santos-Mendoza et al '96; Tavares et al, '97). TNF-α is released with infection, is associated with weight loss, weakness, and fever, and may contribute to tissue damage. There are conflicting reports in the literature about the mechanism and effect of thalidomide on TNF-α (it often enhances another cytokine interleukin-2). Shannon et al. ('97) suggested that the different results may be due to variations in experimental dosages and related to hydrolysis. Some authors suggest the embryogenic action of thalidomide may be related to TNF-α (Argiles et al., '98). The variable effect has been observed to depend both on cell-type and TNF-α production-inducer resulting in both enhancing and inhibiting effects (Hashimoto, '98).

Thalidomide's sedative effect acts by a different mechanism than barbiturates It has not been observed to have respiratory depression or incoordination (Tseng et al, '96).

[1]At the scientific workshop sponsored by the National Institutes of Health, Food and Drug Administration, Centers for Disease Control and Prevention, September 9–10, 1997, Bethesda, MD.

Conditions where thalidomide may have a significant effect

Leprosy. One of the observations that brought thalidomide back to the attention of the medical community was made by Sheskin ('65), dermatologist and leprologist, who noted that a patient with erythema nodosum leprosum (ENL) responded favorably to thalidomide within 1 day. Further clinical trials supported the initial observation (Sheskin, '80). Patients with ENL (Jopling type II leprosy reaction) suffer from painful crops of vasculitis nodules and also may have severe neuritis due to damage to Schwann cells. This immunologic reaction may result in permanent nerve damage. Although very effective in type II leprosy reactions, thalidomide does not work in cell-mediated type I neuritis and has no antimycobacterium activity (Zwingenberger and Wendt, '96).

Sampaio et al. ('93) noted that whereas a large percentage of the patients with ENL had received antibacterial therapy, even untreated patients can get ENL, indicating that there was no one single explanation for the pathophysiology of this inflammatory state. In their study they noted that circulating levels of TNF-α were often associated with ENL, and the severity of reaction partially correlated with the level. Thalidomide in vitro is a selective inhibitor of TNF-α production, and it has been proposed that the reduction of TNF-α is somewhat correlated with the often rapid clinical improvement of patients with ENL.

Leprosy (Hansen's disease) still is a serious affliction in some parts of the world. The relief of some leprotic complications gained by thalidomide has led to greater demand and availability of the drug in areas of South America. Unfortunately, some of the pills became available to pregnant women, and a number of infants were born with the classic findings of thalidomide embryopathy (Teixeira et al., '94; Castilla, '96; Neubert et al., '96).

Angiogenesis. Thalidomide may have an inhibiting effect on new blood vessel formation. This activity has been of interest, particularly to ophthalmologists because of the severe visual complications from neovascularization of ocular structures such as the cornea and retina (D'Amata et al., '94, '97; Joussen et al., '97). Orally administered thalidomide has been shown to inhibit blood vessel growth (D'Amata et al., '94). In a rabbit model in which corneal neovascularization was produced by implanted pellets with proteins containing basic fibroblast growth factor (BFGF), a dose of 200 mg/kg of thalidomide inhibited this angiogenesis. The mechanism is unknown but did not appear related to immunomodulatory action. The authors suggested that this observation should be further tested in ocular conditions associated with abnormal angiogenesis, such as diabetic retinopathy, macular degeneration, and retinopathy of prematurity. Kruse et al. ('98) observed thalidomide had a definite effect against corneal neovascularization induced by vascular endothelial growth factor (VEGF) when used at specific times with a teratogenic dose. In another ophthalmic possible appli-

cation, a clinical trial evaluating use of thalidomide in macular degeneration is being performed (Folkman, '95; Gastl et al., '97).

Bauer et al. ('98) in a series of experiments in different animal models noted that inhibition of angiogenesis by thalidomide was species dependent. They thought that a species-specific metabolite of thalidomide was required. The inhibitory angiogenic action has been offered as a possible explanation of the limb defects of thalidomide embryopathy. D'Amata et al. ('94) suggested that it may work by its effect on FGF-2. Joussen et al. ('97) proposed it works through α-Vβ5 mediated angiogenesis.

The relationship of new angiogenesis in tumor hypervascularity, growth, and metastasis has received recent attention. If this is an important factor in some types of cancer, all potential antiangiogenesis drugs will be closely scrutinized as to their usefulness in cancer chemotherapy (Folkman, '95; Browne et al., '98; Joseph and Isaacs, '98). Some clinical trials are testing these concepts (Barinaga, '97).

Human immunodeficiency virus (HIV) infections

Recently thalidomide has been considered for wider availability in the United States. One of the more outspoken groups supporting freer access to thalidomide are the physicians treating patients with AIDS-related diseases and affected individuals. Thalidomide has been observed to improve the wasting associated with AIDS and induce a better appetite (Soler et al., '96a; Weidle, '96; Brown, '94; Balog, '98). The term "wasting syndrome" describes a clinical condition in which there is a greater than 10% weight loss without clear identifiable causes but believed to be related to a multifactorial process (Centers for Disease Control and Prevention, '93). It is characterized by chronic diarrhea, weakness, and fever. These symptoms in an HIV-seropositive individual establish the diagnosis of AIDS and are an AIDS-related clinical disease (Weinroth et al., '95). Elevated levels of TNF-α are implicated as a causal factor (Tracey and Cerami, '94; Stirling, '95)

Inhibition of the synthesis of TNF-α in vitro and in vivo is the rationale for thalidomide's use in HIV-positive individuals with wasting syndrome. In a randomized clinical trial of 28 adults with advanced HIV disease, thalidomide (100 mg four times a day) was shown to impede the wasting syndrome ($P = .021$) and also improve the Karnofsky Scale of Performance Status (Reyes-Teran et al., '96). There was no effect on the CD4+T or viral load. There is also evidence (Tramontana et al., '95; Klaunser et al.,'96b) that in patients with both HIV-1 and tuberculosis infections, there is a reduction of both the plasma TNF—α and HIV levels and a weight gain. These observations suggest that thalidomide may enhance weight gain by reducing TNF—α and HIV-1 in patients who also have tuberculosis. Moreira et al. ('97) have shown that thalidomide and some analogs reduce HIV type 1 replication in human macrophages.

AIDS-related Kaposi sarcoma has been reported to regress when treated with thalidomide (Soler et al., '96b; Fife et al., '98). Thalidomide has also proven very effective in the treatment of debilitating oropharynx, esophageal, rectal, and genital ulcers associated with HIV infection (Paterson et al.,'95; Soler et al., '96a; Ball et al., '97; Jacobson et al., '97). This is a useful adjunct therapy, especially when steroids are contraindicated or proven ineffective (Gardner-Medwin et al., '94; Verberkmoes et al., '96). The sedative action of thalidomide also was shown to be a benefit in a study done in a group of patients with esophageal ulcers (Alexander and Wilcox, '97). The mechanism of action is unknown, but the inhibition of TNF-α was suggested by these authors. The dosage in this study was 200 mg/day for 1 month.

Modified thalidomide drugs are being studied(see the Safety section below) with the hope of retaining the drug's efficacy but with fewer side effects (Moreira et al., '97).

Dermatologic, autoimmune diseases, and miscellaneous applications

In addition to leprosy and HIV-associated complications, thalidomide has been found effective in various dermatologic conditions and autoimmune disease with varying degrees of success (Calderon et al., '97; Stirling, '98). Considerable attention has been focused on the use of thalidomide in lupus erythematosus (Knop et al., 83; Godfrey et al., '98; Bessis et al., '92; Duna and Cash, '95). Stevens et al. ('97) reported their experience in 16 patients with systemic lupus erythematosus (SLE) and refractory serious rashes. The response was excellent and rapid, but a relapse occurred in most cases upon withdrawal of the drug. They noted low doses (25–50 mg/days) could be used to maintain the response. Sato et al. ('98) also reported good results for the cutaneous lesion of SLE and not responsive to other therapies.

Actinic or nodular prurigo, Behcet syndrome, and erythema nodosum have been reported to respond successfully to thalidomide treatment (Cherouati et al., '96; Tseng et al., '96; Yazici et al., '99). A rare disease, Longerhans cell histiocytosis, was found to respond dramatically to thalidomide in one patient (Lair et al., '98).

Investigations are also ensuing in patients with graft versus host disease (GVHD) (Vogelsang et al., '92; Rovelli et al., '98), or nerve damage resulting from peripheral neuropathy (Tseng et al., '96). Thalidomide has proved effective for treatment of steroid-resistant colitis in Behcet disease (Larsson, '90; Postema, '96) and in experimental animals as a replacement for steroids after lung transplantation (Uthoff et al., '95). This drug has also been suggested for possible use in inflammatory bowel disease (Rhodes et al., '97) and some complications of sarcoid (Lee and Koblenzer, '98; Muller-Quernheim, '98). Minimal efficacy was found by the use of thalidomide in combination with another drug in rheumatoid arthritis (Huizinga et al., '96).

SAFETY

The increasing potential therapeutic uses of thalidomide in many medical conditions as well as pressure from medical practitioners and their patients who might benefit from the drug have turned attention to safety and ethical issues. There is considerable debate on which patients thalidomide should be made available to, especially since it is well accepted that controlling access is exceedingly difficult and many women might inadvertently receive this potent teratogen or might attempt to use it as an abortive agent (Asscher, '94; Robert, '96).

The problem of controlling access is underscored by the fact that new cases of thalidomide embryopathy have occurred when used for medical conditions, especially regarding leprosy. Castilla et al. ('96) reviewed the current use of thalidomide in South America and reported that 34 cases of thalidomide embryopathy were ascertained after 1965 by a network of maternity hospitals that collaborated with the ECLAMC (Latin American Collaborative Study of Congenital Malformations) and other sources. Thalidomide is available in eight South American countries through leprosy treatment centers and in Brazil at some pharmacies. It is presently manufactured in Argentina and Brazil and exported. Brazilian production of thalidomide is estimated to be between 2 and 8 million tablets a year (Cutler, '94). In the review by Castilla et al. ('96), 10 cases of thalidomide embryopathy, primarily ascertained from their limb anomalies, were described in detail. The authors speculated that there are many unrecognized cases because the ECLAMC system covers less than 1% of all births in South America and phocomelia may not be specific enough to identify thalidomide embryopathy; that is, many patients might have only craniofacial anomalies. They concluded that there is a need for a birth defect monitoring system in areas where thalidomide is available.

Since ENL, which is the primary indication for thalidomide, has other successful treatment modalities, there is some question about the use of thalidomide to treat this condition (Crawford, '94a,b). The discussion of thalidomide's use for any condition, however, continues, with strong advocates on both sides of the debate as to how strict the control should be on the availability and distribution of this drug (Bessis et al., '92; Carmichael and Knight, '92; Hawkins, '92; Robert, '96; Therapeutic Teratology Symposium, '96).

There is no question, however, that great care must be taken if thalidomide is given to a woman of childbearing ages. The World Health Organization has recommended that thalidomide be used only in postmenopausal women (WHO, '88). However, the fact that children still are being born with thalidomide embryopathy shows how difficult it is to guarantee safe usage (Cutler, '94). Guidelines for use are available (Asscher, '94) and are outlined in detail by Powell and Gardner-Medwin ('97). Good information on effective contraception should be given by physicians to any woman of childbearing age who has access to teratogenic agents (Trussell, '95) such as thalidomide.

Increasing the availability and production of thalidomide raises many ethical issues that have always faced medicine: the right of the unborn child versus the mother's rights to access to available treatment drugs, inclusion in clinical trials, and procreative privacy. Even with major safety precautions, zero risk is not possible if the drug is available for use. The considerations must include the likelihood of benefit, the severity of the disorder being treated, and the availability of treatment alternatives, weighed against the risk to the unborn child (Frost, '97). If thalidomide is available and children are born with thalidomide embryopathy, legal action can be anticipated, even if precautions are taken.

Robert ('96), in an editorial, compared the potential teratogenic effects of thalidomide to those of a similarly strong teratogen, isotretinoin, which is available for use with strong precaution. The author questioned why the two drugs are handled differently. She also suggested that if thalidomide were to be remarketed, it should keep the same name (thalidomide) as a protection against inappropriate use. This recommendation is presently accepted. However, it has been noted that the name "thalidomide" may have more impact on the older population with some historical memory of the thalidomide tragedy.

Jones ('94) noted that it is unusual for a chemical, such as thalidomide, with such severe side effects, to be continually investigated for new applications. Attempts have been made to develop a derivative that has the immunologic properties without the teratogenic effect. Nogueira et al. ('96) described two derivatives without teratogenicity, but unfortunately they had no effect on white blood cells, which are believed to represent one of the drug's immunologic actions. They postulated that the teratogenic effect of thalidomide may be linked with alterations and expression of adhesion molecules, which they thought were necessary for the anti-inflammatory and immunosuppression actions. Until a less teratogenic derivative is found, many clinicians believe that alternative therapies should be the first choice of prescribed treatment (Jakeman and Smith, '94).

Although most attention has focused on thalidomide's teratogenic effects, the drug has significant side effects of peripheral neuropathy and sedation. The most common side effect, peripheral neuropathy, was reported in 21–50% of patients receiving thalidomide for treatment of dermatologic conditions (Ochonisky et al., '94). The initial manifestation is numbness, but painful paresthesia of the hands and feet sometimes leads to sensory loss in some patients. Only about 25% of the peripheral neuropathy are reversible. It has been suggested that individual susceptibility, perhaps with a genetic predisposition, may explain some variation in the degree of this observed complication. Other investigators have reported this complication (Stevens et al., '97) and one group suggested following up patients for early neuropathy with electrophysiologic tests (Gardner-

Medwin et al., '94). Some investigators have noted thalidomide prolongs experimental autoimmune neuritis (EAN) and suggest this may be related to clinical polyneuropathy (Zhu et al., '98).

Reversible erythroderma has been reported in two cases in which thalidomide was used to treat nodular prurigo due to chronic renal insufficiency (Bielsa et al., '94).

SUMMARY

Thalidomide has changed from a prototypical teratogen, essentially banned from medical usage to a possible useful therapeutic agent in a wide variety of conditions. In some countries it is still considered an experimental drug, but its availability and use are increasing. In regions where the drug is more difficult to control, infants have been born with the devastating findings of thalidomide embryopathy.

Clinicians who desire to use thalidomide must be aware of its teratogenicity and also must appreciate the difficulty of controlling access to at-risk females. It is feared that if thalidomide is available by prescription for a large number of conditions, more cases of thalidomide embryopathy will occur. However, there may be severe cutaneous and systemic diseases for which thalidomide is an effective drug, and physicians and their patients will insist on availability. If this occurs, determining the risks and benefits will be an important challenge for the medical profession.

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