OCULAR TERATOLOGY
OBSERVATIONS, SPECULATIONS, QUESTIONS, PRINCIPLES REAFFIRMED

MARILYN T. MILLER
Chicago, USA

SUMMARY

Teratology is most simply defined as "the study of environmental agents which disturb development". A more comprehensive definition is "the study of causes, mechanisms, and manifestations of developmental deviation, structural or functional." Teratology has several important purposes. Obviously, the most important is to protect future generations by identifying environmental agents that cause malformations. In this sphere, ophthalmologists are generally not the primary detectors. One notable exception is when Gregg, in 1941, recognised that an increase in congenital cataracts was due to a viral agent and brought rubella embryopathy to the attention of the medical community.[1] Another pertinent reason for teratology is that it gives us insights into normal development. As Harvey said with such flair, "nature is nowhere accustomed more openly to display her secret mysteries than in cases where she shows tracings of her workings apart from the beaten path".[2]

There are two prototypes of well-proven ocular teratogens, alcohol and thalidomide. These are quite contrasting teratogens. Thalidomide produced an iatrogenic medical tragedy in the 1950s, in which 5000–7000 children were born with severe malformations before a cause-effective relationship was established between the drug taken in early gestation and the developmental anomalies noted in the mothers' offspring. As frequently happens with such adverse occurrences, some good has resulted. The susceptibility of the fetus, particularly in the first few months of gestation, to environmental agents and drugs has become better appreciated. More emphasis is now placed on drug testing and on compensation of such victims, and there is more interest in toxicology and teratology. The observed associations of anomalies from a teratogen acting in a short susceptible period have given insight into developmental time windows. Some of this information may explain clusters of malformations noted from other causes, such as local vascular accidents and genetic factors.

Correspondence to: Department of Ophthalmology and Visual Sciences, Eye and Ear Infirmary, University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA.

Alcohol is unquestionably the most serious teratogenic agent in our country and is responsible for producing an enormous number of children who will spend their lifetime with great limitations, both mentally and physically. It is the most frequent *preventable* cause and ranks in the top three causes of mental retardation. Teratologists have attempted to define mechanisms of action, but at this time we are still at an observation and speculation stage. There may well be a variety of mechanisms of action depending on the time of the insult and the amount of the dose.

Thalidomide presented different problems. After the embryotoxic effects of thalidomide were recognised, it was relatively easy to prevent future problems by discontinuing use of the drug. This is, unfortunately, not true with alcohol, in which it is difficult to determine the exact dose or timing of drug intake and in which there has been minimal success in significantly decreasing the future number of affected infants.

Teratogens are used to study normal development in animal models. This has the distinct advantage of identifying specific critical periods for the formation of a particular structure. In 1977, Wilson,[3] in a classic textbook of teratology, elucidated some fundamental principles, which have stood the test of time with few exceptions, and are mentioned in most standard courses in teratology. He suggested that there is a finite number of pathways that mediate all types of defects and insults to organism.

The characteristics of a teratogen, according to Wilson, relate to:

(1) the time of intake,
(2) the tissue specificity and genotype,
(3) the threshold effect,
    a concept Fraser[4] has developed similar to that of multifactorial inheritance.

One of Wilson's principles that is pertinent to thalidomide embryopathy is that of critical time, an old principle in developmental biology. He noted that the "susceptibility of the agent varies with the developmental stage at the time of exposure." The susceptibility can occur throughout intrauterine development but is usually the highest during the period of organogenesis from gestational days

Table I Ocular motility in patients with thalidomide embryopathy

	No. of Patients*	
Incomitant horizontal strabismus	37 (44%)	
Duane type		26 (31%)
Gaze pattern		7 (8%)
Abduction deficit only		4 (5%)
Comitant horizontal strabismus (total)	7 (8%)	
Comitant with vertical limitation: n=2 (all patients with esotropic)		
No strabismus	40 (48%)	

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

18 to 55, or 60 days after fertilisation. The embryo is less vulnerable earlier and reacts usually in an all-or-nothing manner; either death occurs, or it survives and implants with no complications. Later involvement during histogenesis usually results in growth changes or functional impairment but not usually malformations.

Another of Wilson's principles may not apply as much to thalidomide embryopathy: the dose-response relationship as manifestations of deviate development increases in degree as dosage increases from no effect to total lethality. There are a few exceptions to this principle. One is that the dosage necessary for an effect on the embryo might be toxic to the mother. This is not true for either thalidomide or alcohol. Another exception is when a very small dosage of the agent causes a profound effect on the embryo. This is the case in thalidomide but not alcohol, which certainly does have a dose-related curve, even though it is not easy to exactly describe the upper and lower limits.

The number of cases of thalidomide embryopathy was so large that there was a significant subset in which accurate data were available about the exact times of intake and dosage. With these data various investigators constructed timetables of action of this teratogen that proved to be quite consistent. The fact that thalidomide is hydrolysed very rapidly gives it an almost pulse-type action making a timetable more precise.

Miller and Stromland[5,6] examined 86 thalidomide-affected individuals in Sweden and observed clusters of malformations that seemed consistent with those described in the literature. For example, if there was lower limb involvement, the upper limbs and thumbs were frequently abnormal but the ears were not necessarily affected. Obviously in some cases the drug was taken throughout the sensitive period from 20 to 35 days after conception, giving a mixture of effects. Using the developmental timetable in the literature, we constructed our own ocular timetable. For example, if a patient had an affected upper limb but normal lower limb and ears, we estimated that the patient's ocular manifestation occurred between days 22 and 26. We undertook this study to further explore the reported association of Duane syndrome in a number of thalidomide-affected individuals.[5,6]

Duane syndrome is of particular interest as it appears to be caused most frequently by abnormal innervation in which a branch of the third nerve innervates the lateral rectus muscle. Previously it had been suspected on electromyographic studies, and this speculation was substantiated pathologically by noting the innervation of the lateral rectus branch of the third nerve in two patients, both of whom had absence of abducens nuclei and had been noted to have Duane syndrome when they were living. The embryologic timing or location of the insult has not been proved for Duane syndrome, but the association with external and internal ear and cervical spine anomalies made many investigators suspect the 4th or 5th week of embryogenesis. One hypothesis is that Duane syndrome might be a predictable reparative process due to an insult at a specific time and involving specific structures, and

Table II. Ocular motility anomalies.

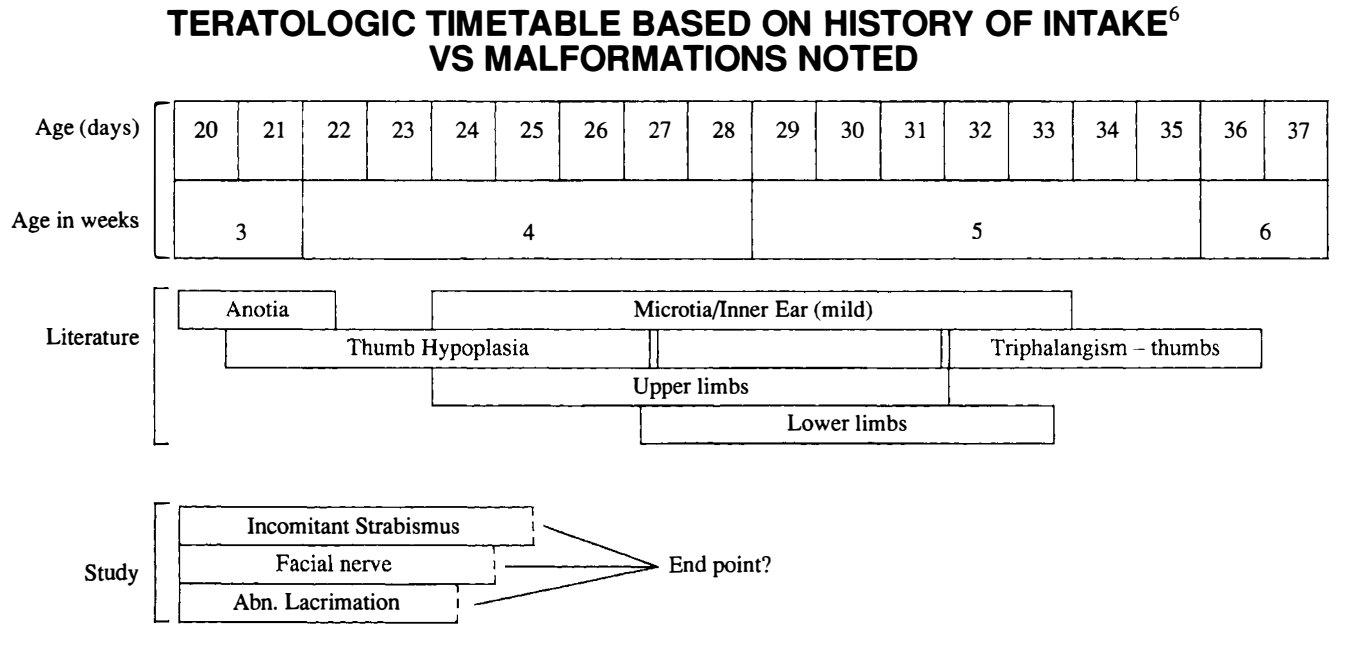
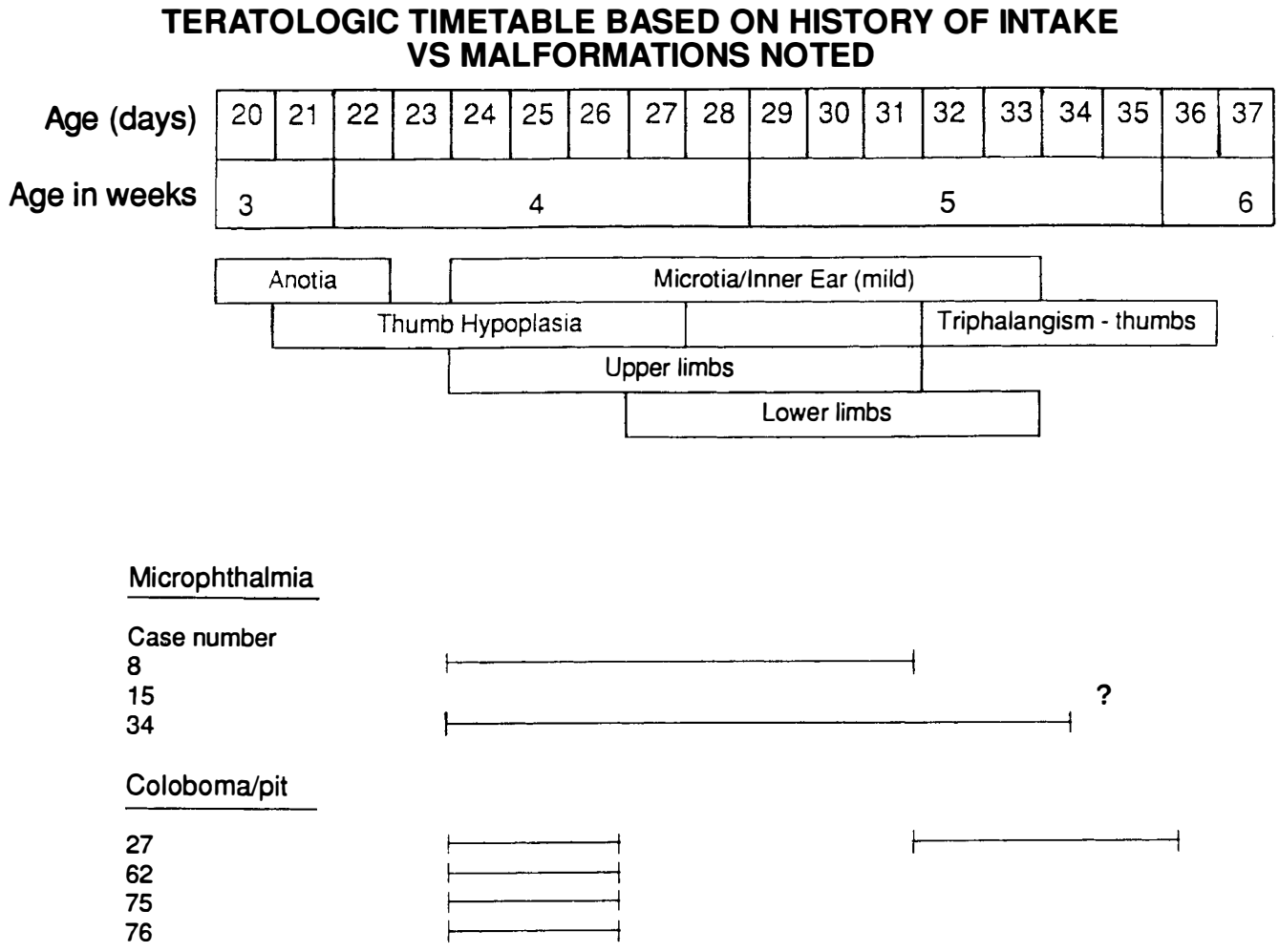


Table III Ocular motility anomalies.



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that insight into this problem could be gained by studying patients with Duane syndrome and associated systemic anomalies. Thalidomide embryopathy offered a clinical model to examine this problem.

Table I is a summary of the strabismus findings showing the extremely large number of cases of incomitant strabismus (usually of the Duane type) seen in patients with thalidomide embryopathy.[6] Additionally, many of these patients showed ear anomalies, facial nerve palsy, and evidence of aberrant lacrimation. Congenital aberrant lacrimation is a rare anomaly but occurs in almost all cases associated with Duane syndrome. The aetiology postulated is aberrant innervation of the lacrimal gland by fibres subserving salivation.

The other ocular anomalies, such as uveal coloboma and microphthalmia, which were less frequent, came with different clusters of systemic anomalies. Using the timetable in the literature of when various anomalies occurred compared with thalidomide intake,[10] we superimposed the ocullar findings that obtained strong evidence that Duane syndrome and similar kinds of comitant strabismus occur 20 to 24 days after conception (Table II).[6] This is much earlier than one could expect with primary involvement of innervation to the muscles, which does not occur until later. In fact, the association of the sixth nerve and seventh nerve and probably the lacrimal nucleus suggests that it is damage to the cells destined to form the brain stem nuclei, which are located very close together in the embryo.

Data are less striking for structural anomalies of the globe noted in individuals with thalidomide embryopathy, but when we apply the same methodology to the malformations of anophthalmia, microphthalmia, or colobomas, there is an association with systemic anomalies that occurs at a slightly later time (Table III).

While the exact mecahnism of action of thalidomide on the ocular structures or the brain stem is not known, the study of patients with thalidomide embryopathy has given us insight into the timetable for one sequence of events that results almost uniformly in Duane syndrome. It also explains the frequent association of Duane syndrome with ear and hearing anomalies, aberrant tearing, and involvement of both the sixth and seventh nerves.

Based on this data one could speculate that the aberrant innervation to the lateral rectus muscle by branch of the third nerve may be a relatively nonspecific but expected reparative process due to an insult early in the 4th week of

development. It is interesting that the patients showing the early effects of thalidomide could manifest a spectrum of motility findings, ranging from what appeared to be a horizontal gaze paresis to a few characteristics abduction defects without a change in the fissue. These appear to be variations of the same process rather than different clinical entities.

The ophthalmologic findings due to alcohol abuse in pregnancy are many and varied. The most common malformation is optic nerve hypoplasia or an abnormal optic disc.[12] This has been reported to occur in 40% to 50% of the affected offspring.[12] The frequency of this type of malformation suggests that it may represent chronic alcohol abuse rather than a single binge drinking phenomenon. Some investigators suggest that optic nerve hypoplasia may be a destructive phenomenon occurring later in embryogenesis rather than during organogenesis. While this is difficult to prove based on the clinical data, it seems consistent with the observations.

Another exciting finding occurred in a much smaller percentage of patients, but it is certainly not a chance association; various types of anterior segment anomalies were observed in patients with fetal alcohol syndrome.[9] Developmental disturbances of the anterior segment result in a wide spectrum of anomalies varying greatly in severity and morphology. They range from mild posterior embryotoxon, which is a normal variant in a number of people, to the more severe Peters, Reiger, and Axenfeld anomalies. These abnormalities were grouped under the umbrella diagnosis of anterior chamber cleavage syndrome by Reese and Ellsworth.[14] They were given a stepladder classification by Waring *et al.*[15] It has been proposed that this group of malformations is the consequence of disturbances occurring at a time when three waves of neural crest cells migrate centrally from the optic cup and should be more appropriately called mesenchymal dysgenesis. This is contrary to the intial concept that they were due to cleavage defects.

We reported eight cases[13] showing a wide spectrum of anomalies in both unilateral and bilateral cases, and there have been more cases noted subsequently. At that time, we were convinced that this was a good example of the alcohol effect on migrating neurocrest cells. Evidence presented by Cook and Sulik[16] suggested that the involvement of the neural crest cells could easily be a secondary phenomenon due to the failure of the lens vesicle to separate from the overlying corneal epithelium. This would implicate the attention for primary involvement of neural crest cells to the effect more related to disturbance in cell migration. They initially did a number of studies on C57BI/6J mice showing that treatment with alcohol on day seven of gestation resulted in a significantly increased number of ocular malformations as well as some of the facial characteristics of fetal alcohol syndrome.[12] The C57BL mouse, however, has a very high underlying percentage of ocular anomalies (11%), which may make it particularly sensitive to teratogenic effects. This is another example of a third principle of Wilson, i.e., the type and degree of effect depends on genotype.

In summary, thalidomide and alcohol are two teratogenic agents with serious and frequent ocular malformations. Both drugs possess very different characteristics in type of malformation and in our ability to prevent future children from being affected.

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