*Brit. J. Ophthal.* (1964) **48**, 151.

# OCULAR DEFECTS IN THALIDOMIDE BABIES*

BY

J. F. CULLEN

*Department of Ophthalmology, University of Edinburgh*

IN the early reports on congenital abnormalities in thalidomide babies in Great Britain little attention has been paid to the occurrence of ocular defects. A recent survey by the Chief Medical Officer of the Ministry of Health relating to children born with congenital limb deformities during 1960–62, revealed that there were 652 surviving children with such deformities, 244 of whose mothers had definitely or possibly taken thalidomide during pregnancy. Of the children born to these 244 mothers, 146 had gross deformities or absence of two, three, or four limbs, and these included 27 with additional deformities, two-thirds of which affected the eyes or ears or both. Of the remainder 45 had deformities of one limb only, and a further 53 had minor deformities of the hands or feet or both. Gilkes and Strode (1963) have reported on the ocular findings in twenty children with limb deformities of the thalidomide type at Chailey Heritage, Sussex, and they discovered colobomatous defects in five of them. A colobomatous defect is the typical eye deformity to be expected in thalidomide children and can easily be missed unless specifically looked for.

In Edinburgh, in the Summer of 1962, a thalidomide baby (Case 1) was found to have ocular defects. Since then, through the courtesy of Mr. D. W. Lamb, a further eleven thalidomide babies, three males and eight females, who attend a special clinic at the Princess Margaret Rose Orthopaedic Hospital, Edinburgh, have been examined and we have found typical colobomatous defects in two of these, giving a total of three such deformities in twelve children, again an incidence of 25 per cent.

## Case Reports

**Case 1, a girl born on May 26, 1960,** whose mother had taken thalidomide during the first month of pregnancy. The birth weight was 8 lb. 1 oz., and delivery was by forceps at term. It is reported that the child's face was bruised for a few weeks after birth. The child's upper limbs and external ears were rudimentary. There was a haemangiomatosis birth-mark in the centre of the forehead. The lower limbs were normal.

*Ocular Examination.*—The right eye and adnexae were normal and the child appeared to see well with this eye. The direct pupil reaction was present but the consensual reaction was questionable. The optic disc was normal with a small physiological cup. On the left side there was complete ptosis and the eye was 10° divergent and immobile, with apparent paralysis of all the extra-ocular muscles. The pupil measured 3 mm. in diameter, did not react to direct or consensual stimulus, and dilated poorly with mydriatics. The corneal reflex was intact. The media were clear. The optic disc presented an unusual appearance of a very deep physiological cup, almost a coloboma of the disc, there being only a very narrow rim of normal disc tissue between the edge of the cup and the surrounding retina. The remainder of the fundus was normal. The child did not appear to see well with this eye as far as could be assessed at this age.

*Comment.*—The findings in this case are difficult to explain. It would seem that the most likely explanation for the apparent paralysis of the 3rd, 4th, and 6th nerves without regeneration, is that this was the result of birth injury and, if so, the damage must have occurred at the origin of the nerves from the brain stem where they are still devoid of Schwann sheaths and hence cannot regenerate. To explain the small pupil there must also be involvement of the sympathetic fibres.

* Received for publication June 28, 1963.

The appearance of the optic disc fits in with the finding of colobomata of the choroid, retina, and optic disc in other cases. The foetal fissure has closed in this instance, but filling up of the central cavity has been arrested, leaving a deep physiological cup or coloboma of the optic nerve entrance.

**Case 2, a girl born on September 15, 1961,** the birth and pregnancy having been entirely normal. There was no history of the mother having taken thalidomide during the pregnancy, but the deformities present were typical of such drug-induced defects. There was congenital absence of the greater part of all four limbs (Fig. 1) and an anal stricture was present at birth.

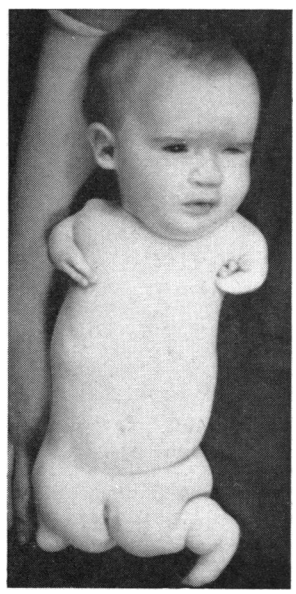

FIG. 1.—Case 2, showing typical limb deformities in a thalidomide baby.

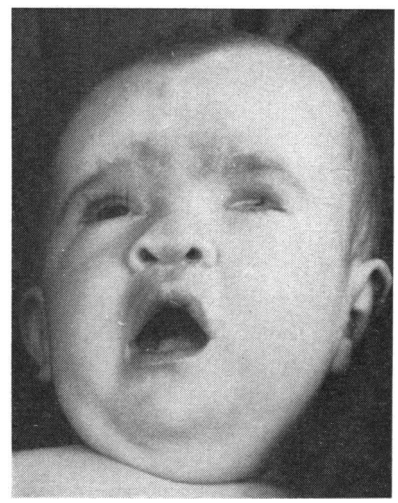

FIG. 2.—Case 2, close-up view of face showing small orbit on left side associated with microphthalmos.

*Ocular Examination.*—The child appeared to see well with the right eye. The eyelids and adnexae were normal. Movements were full. The corneal diameter measured 10–11 mm. There was a keyhole coloboma of the iris in the 6 o'clock position and a large, typical coloboma of the choroid and retina involving the optic disc. The macula was not included in the colobomatous area.

The left orbit seemed underdeveloped compared to the right (Fig. 2), and the left eye was extremely small with a corneal diameter of 4–5 mm. There was a large colobomatous defect in the iris below, involving one-third of its circumference, and it was not possible to get any view of the fundus. The child died from an intercurrent broncho-pneumonia at the age of 16 months, and *post mortem* examination revealed absence of the appendix, a small atrophic left kidney, and a dilated large intestine due to rectal and anal stenosis. The eyes were unfortunately not made available for pathological examination.

*Comment.*—This case illustrates the most extensive deformity associated with failure of closure of the foetal fissure in the left eye and, in such cases, the whole eye may be microphthalmic. The defect in the right eye was less extensive and the eye was of normal size.

**Case 3, a girl born on April 2, 1961,** whose mother had taken thalidomide in the second month of pregnancy. There was agenesis of all four limbs but no other associated defects. The eyes were normal externally as were the pupil reactions and there was good central fixation with each eye. On dilating the pupils a coloboma of the choroid and retina was seen in the right eye extending up to within 6 mm. of the disc. The disc itself and the macula were normal. The left fundus was normal.

## Discussion

The deformities associated with thalidomide ingestion during pregnancy invariably involve the limbs to the greatest extent, so much so that, even without definite evidence of the drug having been taken by the mother, a presumptive diagnosis can be made on the typical appearances of the infant. The usual associated deformities are found in the external ears, as aplasia or absence of the auricles, and in the gastro-intestinal tract, where atresia of the oesophagus, duodenum, or anus, and aplasia of the gall-bladder and appendix are commonly seen. Cardiac anomalies have been reported, and haemangiomata or naevi on the face and elsewhere are often seen. It is significant that no defects of the central nervous system have been reported, and that these children are mentally normal. It is suggested, therefore, that thalidomide and other similar teratogenic agents affect mesenchymal tissues only, and it is now established that the critical period for the production of the deformities is sometime between the 5th and 7th week of gestation when the limb buds are forming.

At this period of development the eyes are also undergoing important changes. The lens vesicle is separating and the embryonic fissure is closing, and this is probably completed by the end of the 6th week. One might have expected to find congenital cataracts in these children but, to date, no such cataract has been reported. The finding of colobomata of the choroid and retina, therefore, is not unexpected and their occurrence confirms the dating of the harmful effect of these drugs between the 5th and 6th week of gestation. It is now fairly universally accepted that the defect causing typical colobomata in the eye is of neuro-ectodermal or epiblastic origin; a mesodermal developmental defect has also been suggested, but von Szily (1924) showed that this theory was untenable, since the entrance of mesoderm through the gap in the fissure occurs after the initial abnormal changes in the ectoderm. It is interesting, therefore, to find this ectodermal defect in the eyes of thalidomide babies in whom all the other defects are found in tissues of mesodermal origin.

## Summary

The occurrence of ocular defects in association with developmental limb abnormalities in thalidomide babies is recorded. Three cases of colobomatous defects in a series of twelve thalidomide children are reported. The origin and dating of the defect are discussed.

I am indebted to Mr. D. W. Lamb for allowing me to examine the thalidomide babies attending his clinic, and to Dr. M. H. Schutt for his assistance. My thanks are also due to Mr. I. S. Kirkland for permission to report Case 1, and to Professor G. I. Scott for his encouragement and advice in the preparation of this paper.

### ADDENDUM

Since this paper was submitted for publication another thalidomide baby has been seen with ocular defects similar to those described in Case 2. This child had agenesis of the upper limbs only. The left eye was microphthalmic with a large typical coloboma of the iris, choroid, and retina and partial persistence of the pupillary membrane. The right eye showed a typical coloboma of the iris below, and a large coloboma of the choroid and retina. which extended up to and included the optic disc. The macula was not involved in the defect.

### REFERENCES

GILKES, M. J. and STRODE, M. *Lancet*, **1**, 1026.
Ministry of Health: CENSUS OF THALIDOMIDE BABIES (1962). *Brit. med. J.*, **2**, 1176.
SZILY, A. VON (1924). *Z. Anat. Entwickl.-Gesch.*, **74**, 1.