Edited by William H. Spencer, MD
University of California, San Francisco 94122

Multiple Systemic and Ocular Malformations Associated With Maternal LSD Usage

David J. Apple, MD, Thomas O. Bennett, MD

A boy was born with multiple malformations including anencephaly with ectopic placenta, absent left arm, cleft lip and palate, syndactyly, coloboma of the iris, cataract, and corneal opacity with vascularization. The mother had used lysergic acid diethylamide (LSD) before and during pregnancy. The limb amputation deformities are the primary findings in this case. These changes are sufficiently specific to suggest a correlation with other reported cases in which a higher than expected incidence of such deformities are observed in infants following maternal ingestion of the drug. This is only the second recorded case of lens abnormalities associated with maternal LSD ingestion.

It is the purpose of this paper to present a case of multiple birth anomalies including extensive ocular malformations. There was known maternal ingestion of lysergic acid diethylamide (LSD) before and during pregnancy. Although a number of birth defects have been previously reported associated with maternal LSD ingestion, at the present time, the literature fails to delineate the role of this drug in the cause of birth abnormalities. This case is presented to document an association of LSD ingestion and birth abnormalities. A definite cause and effect relationship of maternal LSD ingestion and developmental malformations is not necessarily implied.

Submitted for publication July 13, 1973.

From the Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, Chicago (Drs. Apple and Bennett), and the Department of Pathology, Louisiana State University and Charity Hospital, New Orleans.

Reprint requests to Department of Ophthalmology, University of Illinois Eye and Ear Infirmary, 1855 W Taylor St, Chicago, IL 60612 (Dr. Apple).

Report of a Case

History.—A white male infant was admitted to Charity Hospital in New Orleans on Jan 26, 1970, at the age of 24 hours for evaluation of widespread "congenital anomalies." The infant died shortly after admission following an episode of tonic convulsions and persistent respiratory distress. He died before blood could be drawn for chromosome analysis. The mother, 19 years old, admitted having ingested LSD before and during this (her first and only) pregnancy. No information concerning the father was available. Delivery had been spontaneous with a breech presentation.

Clinical and Autopsy Findings.—All clinical observations were confirmed at autopsy. Both premortem and postmortem findings are described simultaneously. The infant was 43 cm (16.9 in) in length and weighed 2,020 gm (4 lb 7 oz). There was a dorsal defect in the calvarium (Fig 1 and 2). The dorsal cranial bones were absent except for very rudimentary structures in the region of the occipital bones and a small right frontal bone which projected upward from the flat base of the skull. The placenta was adherent dorsally to the rudimentary brain tissue (Fig 2). The umbilical cord (Fig 2) coursed between the navel and the ectopic placenta. Apart from a mild apparent exophthalmos, the right eye was not remarkable. On the left, the cornea was partially opaque, and the lens was cataractous. A fold of skin extended from the region of the right nostril to the vertex of the skull, becoming adherent to the placenta. There was a right-sided cleft lip and palate. The ears were low-set bilaterally and there was a protuberance pointing upward from the left ear. The left scapula was present, but there was complete aplasia of the left arm (Fig 1). The metacarpals of the second, third, and fourth fingers were fused on the right. The testes were small, but descended. The lower extremities were in the "frog" position. The left foot had a rudimentary large toe and second toe. The lateral three toes were fused. The right leg was compressed or grooved medially in the lower one third just above the ankle. The constriction was due to an amniotic band that had been previously removed. Significant internal changes include pulmonary atelectasis, a patent ductus arteriosus, and atrophy of the adrenal cortex.

Ocular Pathology.—The left globe measured 16 × 16 × 16 mm. The cornea was

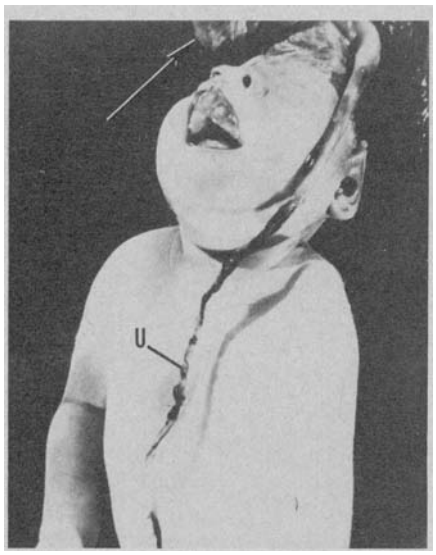

Fig 1.—Postmortem appearance of infant showing anencephaly with ectopic placenta (arrow) and umbilical cord (U). Note facial deformities and musculoskeletal malformations including total aplasia of left upper limb.

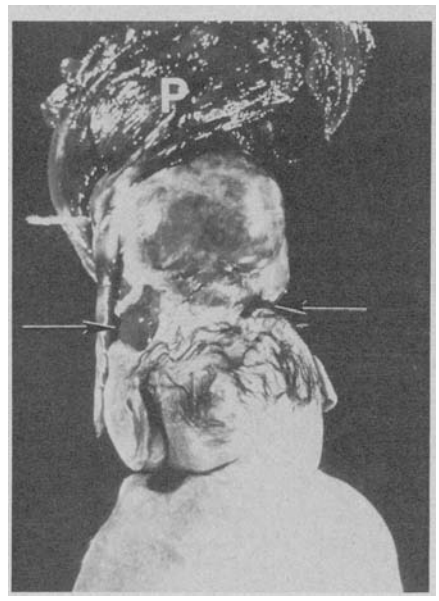

Fig 2.—Posterior appearance of ectopic placenta (P) positioned over defect of calvarium (arrows).

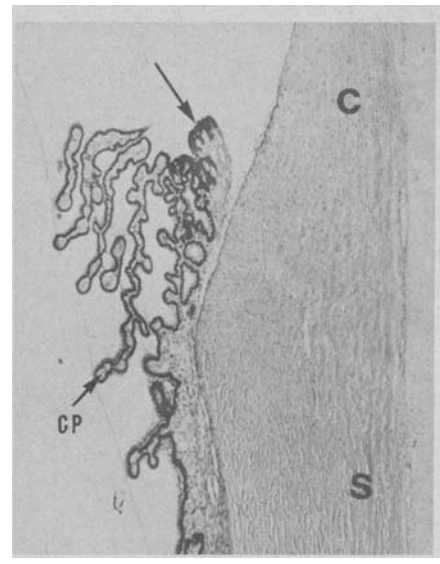

Fig 4.—Angle at 6 o'clock in left eye. Note iris coloboma (arrow) and rudimentary angle. C indicates cornea; S, sclera; CP, hyperplastic ciliary process (hematoxylin-eosin, ×250).

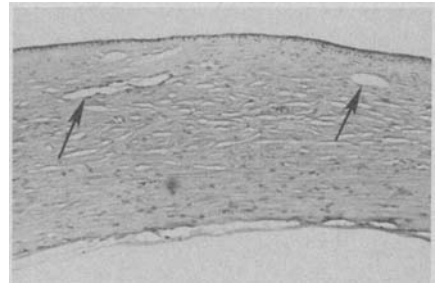

Fig 3.—Left cornea showing irregularity of lamellae and vascularity (arrows) (hematoxylin-eosin, ×250).

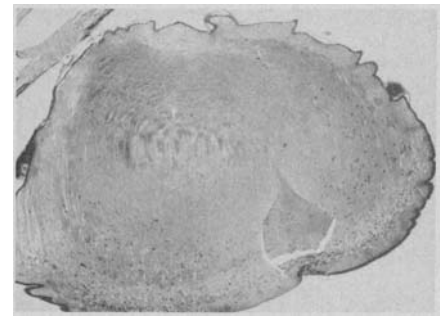

Fig 5.—Marked wrinkling of lens capsule (hematoxylin-eosin, ×120).

opaque and vascularized, particularly centrally and inferiorly. The corneal epithelium was abraded inferiorly so that a superficial sheet of corneal and limbal conjunctival tissue was detached over an arciform area from 3 to 9 o'clock. An inferior coloboma of the iris was noted grossly. Vertical sections revealed the cornea to be pearly-gray and vascularized on cross section. The anterior chamber was deep. The lens was normal in size, but was opaque, and the lens capsule was wrinkled. Apart from the small iris coloboma, the uvea revealed no significant changes. Microscopically (Fig 3), the corneal stromal lamellae were irregular and were composed partially of intertwining bands of dense fibrous tissue. There was moderate superficial stromal vascularization. Except for the region adjacent to the iris coloboma (Fig 4), the anterior chamber angle structures showed normal development. The lens capsule was wrinkled and the lens cortex showed moderate degeneration (Fig 5). There was posterior migration of lens epithelium. The colobomatous iris consisted merely of its root. No differentiation of the corneal-scleral filtering apparatus was evident at the site of the coloboma. The retina exhibited changes typical of anencephaly including absence of the nerve fiber layer, total loss of the ganglion cells, and attenuation of the inner nuclear layer. The optic nerve was reduced to about two thirds of its normal diameter. There was a thickening of pial septae and an apparent increase in vascularity within the optic nerve. The normal parallel rows of glial nuclei were replaced by arrays of haphazardly arranged glial cells that occupied the space normally reserved for nerve fibers.

Right Eye.—Apart from retinal and optic nerve changes identical to those of the left eye, no significant changes were present.

Comment

In addition to the central nervous system (CNS) and eye findings, this case demonstrates malformations involving all four extremities. It is in relation to these limb defects that one might look for a unifying concept regarding the possible effects of this drug on the newborn infant. Two previous reports review 43 cases of infant births to mothers using LSD during pregnancy alone.[1,2] Nine of the 43 infants were born with birth anomalies of unexplained origin. Five of the cases cited showed varying degrees of limb aplasia.[3-7]

Report of Cases Describing 11 Cases in Which Limb Defects Were Associated With Documented Maternal LSD Ingestion

Report	Deformity
1. Zellweger et al[3]	Unilateral fibular aplasia, short femur, dislocated hip
2. Hecht et al[4]	Missing right hand
3. Carakushansky et al[5]	Bilateral absent phalangeal bones of both hands, webbing of toes, talipes equinovarus
4. Assemany et al[6]	Absence of third left toe and third right finger

5. Jeanbart and Berard[7]	Aplastic fingers bilaterally
6. Apple and Bennett (present case)	Aplastic left arm, syndactyly
7. Jacobson and Berlin[8]	Five of 21 embryos analyzed showed limb bud defects

The addition of the present case to the above-mentioned 43 brings the total of limb defects to six out of 44. Furthermore, in a recent and separate series, Jacobson and Berlin[8] refer to five cases showing similar limb amputation defects out of 21 embryos analyzed pathologically after either therapeutic or spontaneous abortion by mothers using LSD.[8] The incidence of limb deformities cited in those reports suggests a rate higher than Lilienfeld's[9] estimate of 1.78 per 1,000 (0.178%) for limb reduction deformities in the general population.

In view of the fact that these figures indicate a higher than expected incidence of limb aberrations following maternal LSD ingestion, it follows that further investigation as to cause and effect relations is warranted. Prospective as well as retrospective analysis of a large series of cases is required to determine the true nature of LSD's effect on human development.

The ocular findings of absent ganglion cell layer and atrophy of nerve fiber layer related to anencephaly are quite nonspecific and occur with sufficient frequency to conclude that they are not necessarily related to LSD usage. Anderson et al[10] in 1967 related anencephaly to ocular development. In 40 eyes from 21 infants, they found that hypoplasia of the ganglion layer and atrophy (hypoplasia) of the nerve fiber layer and optic nerve were characteristically related to the cerebral malformations. Occasionally, colobomata were noted in their study. No specific causative agents could be determined to explain these aberrations.

The present case exhibited lens changes and corneal opacities in the left eye. Hanaway[11] studied the effect of LSD on lens development in fetal mice. He reported the presence of anterior subcapsular lens abnormalities including hyperplastic lens epithelium, with cells migrating posteriorly in infant mice born to mothers treated with LSD. In 1972, Bogdanoff et al[2] reported a case of CNS abnormalities in an infant whose mother ingested LSD throughout pregnancy. There was marked cortical degeneration of the lens anteriorly and posteriorly, with posterior migration of lens epithelium. The overall findings were similar to those in Hanaway's[11] study. In the present case the lens from the left eye also shows moderate degeneration, and there is a posterior migration of lens epithelium. The possibility of LSD causing these lens changes as well as corneal opacities is worthy of further investigation.

Key Words.—Birth anomalies; LSD; anencephaly; iris; coloboma; cataract.

References

1. Long SY: Does LSD induce chromosome damage and malformations? A review of the literature. *Teratology* 6:75-90, 1972.

2. Bogdanoff B, Rorke LB, Yanoff M, et al: Brain and eye abnormalities: Possible sequelae to prenatal use of multiple drugs including LSD. *Am J Dis Child* 123:145-148, 1972.

3. Zellweger H, McDonald JS, Abbo G: Is lysergic acid diethylamide a teratogen? *Lancet* 2:1066-1068, 1967.

4. Hecht F, Beals RK, Lees MH, et al: Lysergic acid diethylamide and cannabis as possible teratogens in man. *Lancet* 2:1087, 1968.

5. Carakushansky G, Neu RL, Gardner LI: Lysergide and cannabis as possible teratogens in man. *Lancet* 1:150-151, 1969.

6. Assemany SR, Neu RL, Gardner LI: Deformities in a child whose mother took LSD. *Lancet* 1:1290, 1970.

7. Jeanbart P, Berard NJ: Congenital abnormalities possibly induced by LSD-25: Review of the literature apropos of a personal case. *Surg Gynecol Obstet* 70:215-230, 1971.

8. Jacobson CB, Berlin CM: Possible reproductive detriment in LSD users. *JAMA* 222:1367-1373, 1972.

9. Lilienfeld AM: 1970 population difference in frequency of malformations at birth, in Fraser FC, McKusick VA (eds): *Congenital Malformations.* Amsterdam, Excerpta Medica, 1970, pp 251-263.

10. Anderson R, Bro-Rasmussen F, Tygstrup I: Anencephaly related to ocular development and malformations. *Am J Ophthalmol* 64:559-566, 1967.

11. Hanaway JK: Lysergic acid diethylamide effects on developing mouse lens. *Science* 164:574-575, 1969.