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Chromosome Abnormality in Offspring of LSD User

D Trisomy With D/D Translocation

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Congenital abnormalities compatible with D$_1$-trisomy occurred in a newborn girl whose parents had used lysergic acid diethylamide (LSD) prior to conception, but not during the pregnancy. Chromosomal analysis of the infant revealed trisomy 13 with a D/D translocation. Lysergic acid diethylamide may have damaged maternal germ cells prior to fertilization, inducing chromosomal rearrangement. Fertilization of a gamete with unbalanced chromosome complement may be the direct cause of the chromosomal aberration in the offspring.

LYSERGIC acid diethylamide (LSD) has been found to cause chromosomal damage in human leukocytes both in vitro and in vivo[1] although other studies have not always confirmed the in vivo findings.[2] Teratogenicity of LSD in the fetus has been inferred by increased incidence of stillbirths and stunted growth in the offspring of rats receiving LSD on the fourth day of pregnancy, gross cerebral and facial defects in the progeny of mice given LSD on the sixth and seventh days of pregnancy, and multiple malformations, especially of the central nervous system, in offspring of hamsters given LSD on the eighth day of gestation.[3] One study in rats found no such effects.[3] Deformities of extremities have been reported in two infants whose mothers had taken LSD in the first trimester of pregnancy.[4,5] The induction of abnormalities in meiotic chromosomes of healthy male mice by LSD[6,7] suggests that the teratogenic effect of the drug may be mediated by damage to the chromosomes of germ cells, although another study has not confirmed this finding.[8] This possibility is considered in the following report concerning an infant with multiple malformations, whose parents had taken LSD prior to conception only. The infant's karyotype was 46, XX, D−, *t* (Dq, Dq) +, ie, trisomy 13 with D/D translocation. (For identification of nomenclature see *Chicago Conference: Standardization in Human Cytogenetics.*[9]) The infant's karyotype was studied because of multiple anomalies found at birth; subsequent history revealed that both parents were LSD users prior to conception.

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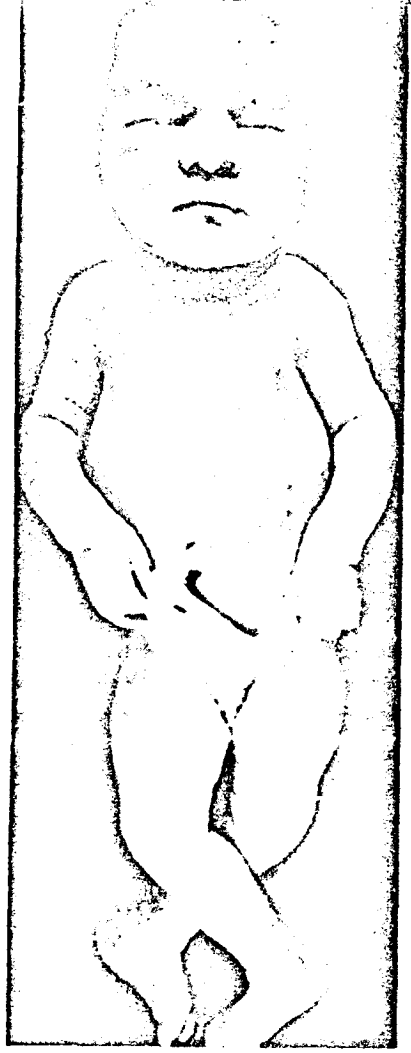
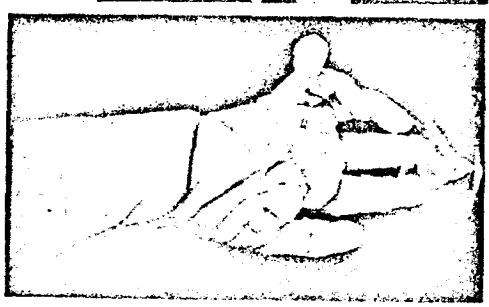
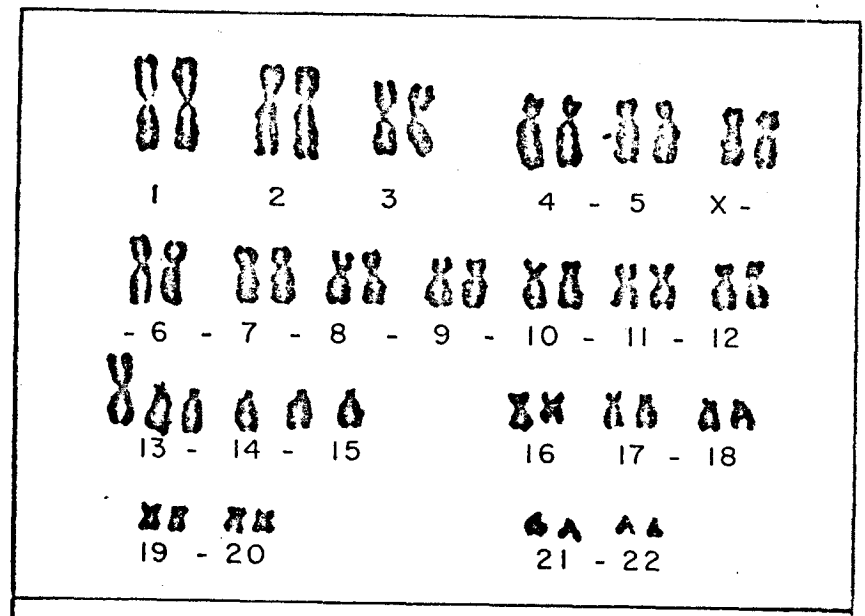
Report of a Case

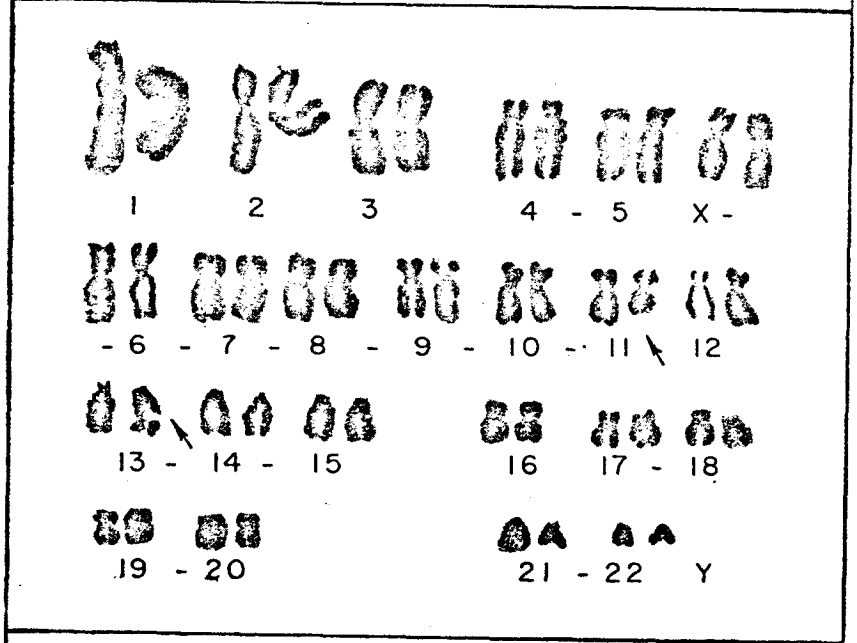
A white girl was born at full term to a 22-year-old primipara who had taken three doses of LSD nine months prior to conception, and one dose three years earlier. Throughout her pregnancy she had taken other drugs including marihuana, barbiturates, and methamphetamine hydrochloride (Methedrine) by inhalation. The father, aged 26 years, had taken two doses of LSD four years prior to the birth of this infant. He had taken marihuana and dextroamphetamine (Dexedrine) sulfate. Neither parent was aware of any other congenital defect in the family.

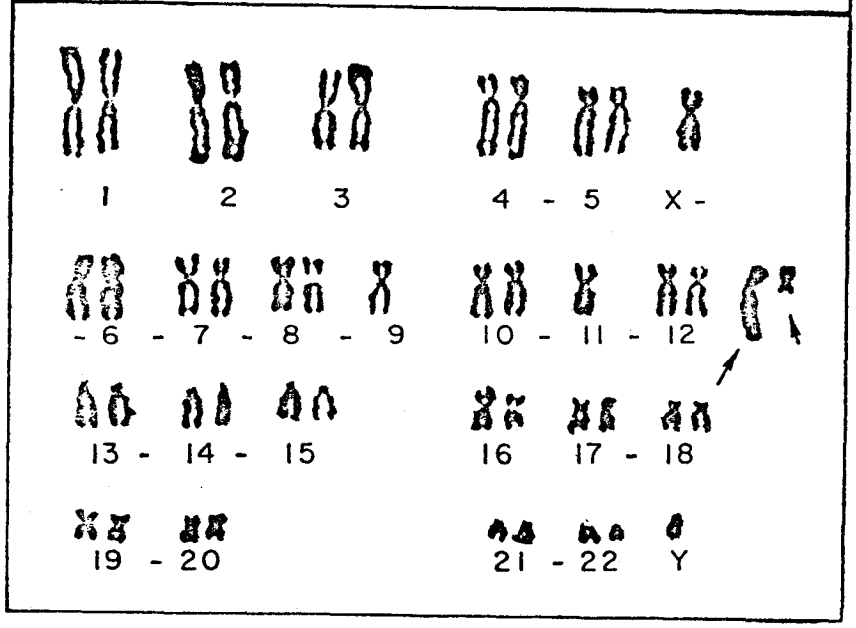
Delivery was spontaneous after nine hours of labor. At birth the infant was limp and apneic, with an Apgar score of 1. She died with severe respiratory distress at the age of 9 hours. The infant weighed only 2,200 gm (5 lb) (< −2 SD) and measured 45 cm (18 in) in length (−2 SD). Head circumference measured 30 cm (12 in). She had a sloping forehead, poorly differentiated, low-set ears, a broad nose with prominent bridge, narrow palpebral fissures, and bilateral epicanthic folds (Fig 1, *top*). The pupils were round and equal, without colobomas. A slight fatty hump was noted at the nape of the neck. The palate was somewhat high-arched, without cleft. Abduction of the thighs at the hips was limited. The wrists were poorly formed; both hands had simian creases. The left hand had four fingers (thumb and three fingers), with ulnar deviation of the second finger, which was held in a flexed position. A rudimentary sixth finger was attached to the ulnar side of the right hand. The skin of both hands appeared excessively loose. Dermatoglyphics showed bilateral distally located palmar triradii (*t*″). Both feet had elongated first toes. The right foot showed a slight valgus deformity and the left a recessed calcaneus (Fig 1, *top, center, and bottom*). A roentgenogram taken after death showed 11 pair of thin ribs, absence of the phalanges of the fourth finger of the left hand, absence of part of the sacrum, and dislocated hips bilaterally. In addition to these abnormalities, the autopsy revealed that the following developmental defects were present: ventricular septal defect with dextroposed, riding aorta without pulmonic stenosis, hypoplasia of crista supraventricularis, right ventricular hypertrophy (Eisenmenger complex), atrial septal defect (ostium









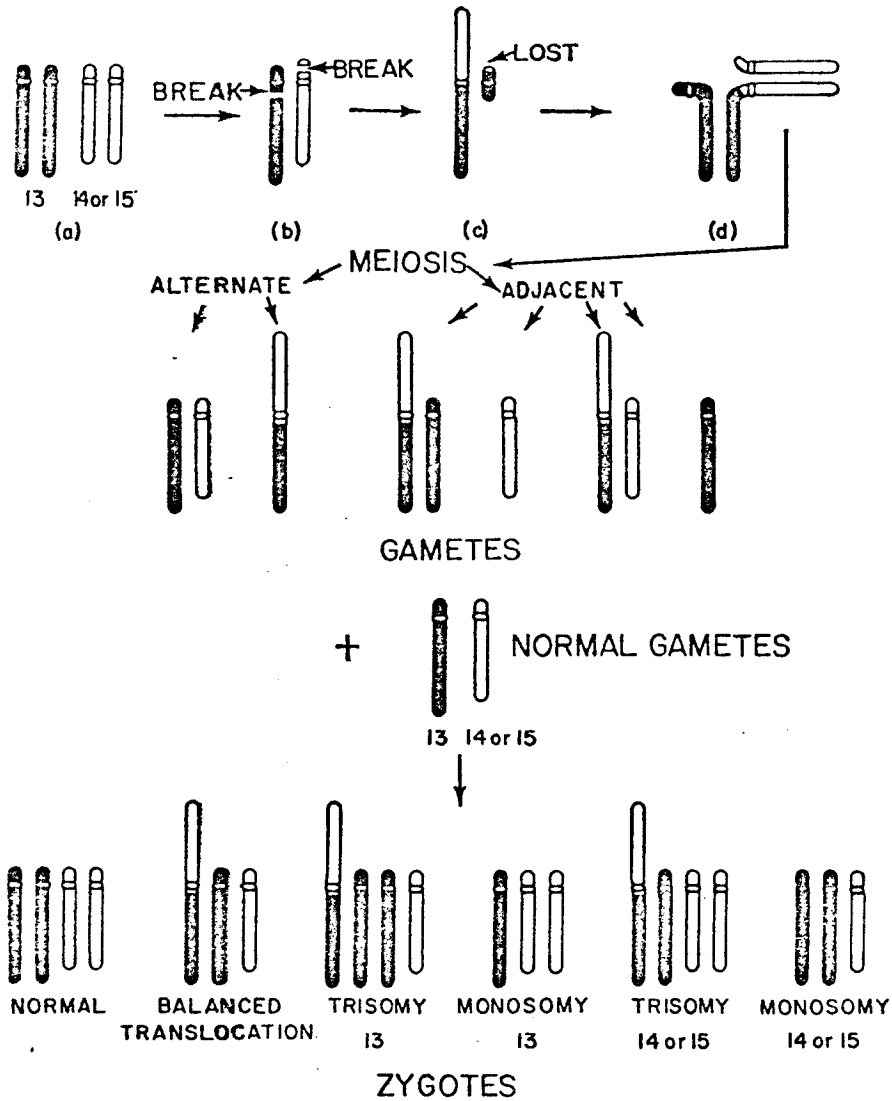


1. *Top*, small stature of infant, and abnormal facies with broad nasal bridge and narrow palpebral fissures. Recessed heel of left foot. *Center*, right hand with abnormal palmar creases, loose skin, and rudimentary accessory digit. *Bottom*, left hand with missing fourth finger and abnormal palmar creases.
2. *Top*, karyotype of patient showing 46, XX, D— t (Dq, Dq)+. *Center*, karyotype of mother showing one unpaired chromosome in the C group (6 — 12+X) and chromatid break of D group chromosome. *Bottom*, karyotype of father showing two obviously unpaired chromosomes in C group (6 — 12+X).

secundum), bilateral accessory arterial supply to kidneys, and venous telangiectasias in the posterior mediastinum; moderate hypoplasia of the lungs, anomalous origin of the upper lobe of the right lung bronchus from trachea, absence of minor fissure of right lung, and venous telangiectasias of left lung; Meckel's diverticulum and mesenterium commune, abnormal configuration of inferior surface of liver with extra lobe obscuring the gallbladder and intrahepatic cholestasis; focal dilation of small pancreatic ducts; bilateral mild hydronephrosis, segmental dysgenesis of left kidney with cortical cysts, thick labia minora pudendi and small folds of labia majora pudendi, septate uterus and vagina, and long thin ovaries with hypoplasia and extramedullary hematopoiesis; short sternum with bifid xiphoid process, small anterior cranial fossa, and shallow sella turcica; dysgenesis of olfactory nerves and posterior cerebellar vermis.

Cytogenetic Studies.—The results of the chromosome analysis of peripheral leukocyte cultures are summarized in the Table. Each of the patient's cells had 46 chromosomes with one chromosome missing in the D group (No. 13 through 15) and one extra chromosome in the A group resembling No. 3. This chromosome was interpreted as a translocation of two D group chromosomes (Fig 2, *top*). She had a normal sex chromosome constitution (XX). No chromatid or chromosome breaks were noted in all 40 metaphases examined.

Autoradiography of the extra group A chromosome revealed one late replicating, heavily labeled arm and one early replicating, lightly labeled arm. The five D group chromosomes in the labeled cells showed two comparatively heavier labeled chromosomes, most likely No. 13, and three lightly labeled D chromosomes which could not be distinguished from each other. Therefore, the extra chromosome in group A was most likely the product of a translocation between a No. 13 and a No. 14 or 15, ie, *t* (13q, 14, or 15q).



3. Diagram of hypothetical events in gametocyte: (a) chromosome breakage and rearrangement; (b) meiotic segregation showing how six different gametes may be produced, and result of fertilization of each gamete with normal gamete.

In the 30 metaphases of the mother's lymphocytes only one chromatid break was observed, but there were two cells with an abnormally short C group chromosome, which suggested the presence of a clone resulting from a translocation involving at least one C group chromosome (Fig 2, *center*). In the 36 cells of the father, there was one chromatid break in a C group chromosome. He also had two cells with two strikingly unpaired chromosomes in the C group, one resembling a B group chromosome and one as small as chromosome No. 17, which again suggested a clone with a reciprocal translocation *t* (Cq, Cq) but different from that found in the mother (Fig 2, *bottom*). No cells with a D/D translocation, as seen in the child, were found in either parent.

Analysis of Chromosomes in Patient and Parents

	Chromosome Count			Sex Chromosome	No. of Chromatid Break (Group of Chromosomes)	No. of Aneuploidy Cells
	45	46	47			
Patient	0	40	0	XX	0	40*
Mother	0	30	0	XX	1 (D)	2†
Father	0	36	0	XY	1 (C)	2‡

*All consisted of five D group chromosomes and one D/D translocation chromosomes.
†Cells of two unpaired chromosomes in the C group.
‡Cells with two strikingly unpaired chromosomes in the C group, having one as big as B group chromosome and one as small as chromosome 17.

Comment

The combination of defects in this patient, including intrauterine growth retardation, facial and skeletal anomalies such as sloping forehead, abnormal ears, narrow palpebral fissures, polydactylia, short sternum, thin ribs, together with cardiovascular defects, absence of olfactory nerves, Meckel's diverticulum, minor renal anomalies with cortical cysts, abnormal labia, and septate uterus and vagina, are strongly compatible with the trisomy 13 syndrome. The chromosomal findings, aided by autoradiographic studies, confirmed that the infant was actually trisomic for chromosome No. 13, but with 46 chromosomes and D/D translocation (46, XX, D−, *t* (Dq, Dq) +).

The D/D translocation has usually been found without associated trisomy with a frequency of one in 1,000 live births.[10] In most instances it is carried in two or more generations of the same family in individuals with normal phenotype,[11-13] but with a history of diminished fertility and repeated miscarriages.[11-12] D/D translocation with trisomy 13 has been reported in offspring of translocation carriers[13] (James R. Miller, written communication, 1965). Occasional de novo D/D translocation with trisomy 13 has been reported.[14-15] This may occur as a result of an unusual sequence of events in the germ cell before fertilization, ie, chromatid breaks, chromatid exchange, adjacent segregation of the translocation chromosome and one of its homologues, and fertilization of the gamete with the unbalanced chromosome complement (Fig 3).

Since neither parent of the patient is a carrier of the D/D translocation chromosome, this must be considered a de novo D/D translocation with trisomy 13. This chromosomal aberration in the infant and the history of LSD ingestion by the parents, both of whom show other chromosomal structural rearrangements in some of their cells, suggests that LSD may have induced abnormal chromosome arrangements in the germ cells of the mother.

Damage to chromosomes in germ cells has been considered as one, perhaps the most important, hazard of LSD use. Other potential dangers are the following: (1) There may be a tendency for leukemia or other neoplastic processes to develop because of chromosomal breaks. This effect of LSD may not be assessable for some time to come. However, two instances of acute leukemia have been reported in users of LSD, one of whom had a Ph^1-like chromosome in the leukemic leukocyte, although he had no chromosome breaks in lymphocytes stimulated with phytohemagglutinin.[16] (2) Chromosomal damage to fetal cells may occur with a potential teratogenic effect, resulting from transplacental passage of LSD. Increased frequency of chromatid breaks in the leukocytes of infants exposed to LSD in utero[17] would support this possibility. However, thus far the infants studied have been phenotypically normal, with no recognizable malformation. Stillbirths and abnormal fetuses have been produced by administration of LSD to pregnant animals.[2] Chromosome studies have not been reported in these experiments. Two deformed infants have been born to mothers who had taken LSD during the first trimester.[4,5] The absence of chromosome breaks in our patient, and no history of LSD ingestion during pregnancy precludes transplacental transport of LSD in this case. On the other hand, damage to chromosomes in the germ cells by LSD must be strongly considered. Lysergic acid diethylamide taken by the mother prior to conception may have damaged the chromosomes in her oocytes during the dictyotene stage. In mammalian females, oocytes begin their first meiotic prophase several weeks before birth, and then remain in the dictyotene stage until ovulation when the first meiotic division is completed. The second meiotic division may not be completed until fertilization. If two chromatids in the dictyotene stage were broken and the broken pieces exchanged, a balanced reciprocal translocation would result. If either translocation chromosome happens to undergo adjacent segregation with one of its homologues, an ovum with an unbalanced chromosome complement would be produced. Either the ovum could be missing a chromosome and if fertilized, would be aborted, or the ovum could contain the translocation chromosome with its homologue, and become trisomic after fertilization (Fig 3). In view of the short life-span of spermatocytes, and the rapid turnover of spermatogonia, paternal origin of the translocation chromosome is a less likely possibility. The other drugs taken by the parents such as marihuana, barbiturates, amphetamines, and methamphetamine have so far not been found to cause chromosomal damage, but this needs further investigation.

While coincidence of a D/D translocation with trisomy 13 and a history of LSD ingestion by the parents cannot be excluded, the possibility of chromosome damage to germ cells by LSD, with production of abnormal offspring, must be emphasized.

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