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Does LSD Induce Chromosomal Damage and Malformations? A Review of the Literature [1]

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ABSTRACT Although there are reports of five children with limb defects among 161 children from parents who took LSD (lysergic acid diethylamide) this review of the literature indicates that LSD does not cause chromosome breakage and that there is no strong evidence of teratogenicity in animals.

There has been concern during the past several years that lysergic acid diethylamide (LSD) might cause chromosomal breakage and mutations and thus endanger future generations, and that LSD taken during pregnancy might cause malformations. The purpose of this review was to examine the possibility of direct or indirect effects on children, a topic that has not been thoroughly covered yet (Dishotsky et al., '71).

This paper is a distillation of the existing reports concerning only the genetic and teratogenic effects of LSD and represents an attempt to resolve much conflicting evidence. Reports dealing with other effects of LSD are not considered here.

DOES LSD BREAK CHROMOSOMES?

Studies on cells exposed to LSD in vitro

The first indication that LSD might be genetically dangerous came from reports that LSD caused chromosome breaks when added to cell cultures (Cohen et al., '67b). Though the effects were inconsistent, most authors reported a significant increase in the number of chromosome breaks.

A hallucinogenic dose of LSD (100 μg for a 70-kg man; 1.4 μg/kg) produces a serum concentration of 0.001 μg/ml (Loughman et al., '67). Even this low concentration of LSD caused breaks when added directly to the culture medium (Cohen et al., '67b). When it was increased to 0.01–10.0 μg/ml breaks were found in lymphocytes from people (Cohen et al., '67a,b; Jarvik and Kato, '68; Jarvik et al., '68; Corey et al., '70), rhesus monkeys (Egozcue and Irwin, '69), and rat kangaroos (Bick, '70). On the other hand, there were reports of no increase in breaks after 0.4–45.0 μg/ml LSD added to Syrian hamster embryo cells (DiPaolo et al., '68), Chinese hamster lung cells (Sturelid and Kihlman, '69), and human lymphocytes (Sturelid and Kihlman, '69).

Studies on in vivo *effects of LSD*

To determine whether the chromosome-damaging effects seen *in vitro* occurred *in vivo* investigations were made of chromosomes from subjects who had used LSD. In addition some chromosome studies were made of subjects both before and after they ingested LSD (table 1).

Previously exposed users of LSD. The original investigations were carried out on blood samples collected from users of illicit LSD, hereafter termed "LSD users." The drawbacks to such studies are that the number of doses, the amount, and the purity of the LSD were unknown, and that a large proportion of subjects also took unknown amounts of other compounds. In addition other variables such as recent viral infections, other contagious diseases, and nutritional factors were uncontrolled. Studies were also made of selected groups of hospitalized psychiatric patients whose past treatment with LSD and other drugs had been recorded.

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TABLE 1

Number of LSD users and patients treated with LSD in whom the frequency of chromosome breaks fell beyond the range of breaks in the control subjects ("+" indicates values higher than the control range, "−" values within the control range. The percentages of breaks are listed as means and the ranges are in parentheses).

LSD Users				Patients treated with LSD				Controls		
No. +	% breaks	No. −	% breaks	No. +	% breaks	No. −	% breaks	No.	% breaks	Reference
				1	12.0					Cohen et al., '67b
13	9.1 (6.4–25.1)	2	5.4 (5.3–5.5)					12	3.8 (2.0–5.5)	Cohen et al., '67a
16	8.4 (3.7–20.3)	1	1.0					9	1.5 (0–2.0)	Cohen et al., '68
		2	3.0 (2.8–3.3)							Hsu et al., '70
6	27.4 (21.0–38.0)	2	12.2 (12.0–12.5)					7	9.4 (7.0–13.5)	Irwin and Egozcue, '67
34	21.5 (14.0–45.0)	12	11.0 (8.0–13.5)					13	8.6 (6.0–13.5)	Irwin and Egozcue, '68
2	11.6 (6.6–16.6)									Zellweger et al., '67
5	11.7 (10.0–13.3)		4.1 (3.3–6.6)					32	3.5 (0.0–6.6)	Abbo et al., '68
10	2.5 (none given)			9	4.3 (none given)			41	0.2 and 0.5 (none given)	Nielsen et al., '68a,b
		8	0.0					19	0.2 (0.0–3.3)	Loughman et al., '67
		1	1.0					1	1.0	Sato and Pergament, '68
		5	2.0 (none given)					5	2.0 (none given)	Bender and Sankar, '68
		4	2.2 (0.9–2.4)			4	1.5 (0.4–0.25)	4	1.6 (0.8–2.2)	Sparkes et al., '68
		3	5.7 (2.0–12)					5	1.6 (0.0–6.0)	Hulten et al., '68
				1	3.8	11	1.1 (0–2.1)	8	1.1 (0–1.9)	Stenchever and Jarvis, '70
		14	0.6 (0.0–2.0)					10	0.8 (0–2.0)	Dorrance et al., '70
		17	1.0 (0–11.4)					8	0.7 (0–5.7)	Judd et al., '69
						11	7.0 (2.0–12.0)	13	7.0 (2.0–17.0)	Corey et al., '70
Total number of subjects 86		75		11		26		187		

These studies yielded contradictory results. Among 161 LSD users 53% had chromosome-break frequencies that exceeded the control range, and the same was true for 30% of 37 patients treated with LSD. These percentages include all the reported cases [all 19 cases reported by Nielsen et al. ('68a,b, '69) were included in the group of high-frequency chromosome breaks in table 1 even though the frequencies of breaks for the individual subjects were not itemized]. An examination of reports concluding that LSD led to a significant increase in chromosome breaks (Anonymous, '67c; Abbo et al., '68; Grossbard et al., '68; Jarvik and Kato, '68; Jarvik et al., '68; Garson and Robson, '69; Aase et al., '70) shows that this increase was found in only 81% of 119 exposed subjects. Furthermore, there was no correlation between the number of breaks and the total amount, number of doses, and time between the last dose of LSD and blood sampling.

There was a wide variation in the frequency of cells with chromosome breaks, which are relevant of course only in relation to the controls in each study. But there was also a surprisingly wide range of mean control values of cells with chromosome breaks (0.0–11.9%). These variations could have been due to differences in culture procedures and in ascertainment of control and exposed subjects. In addition some studies were made with relatively small numbers of cells and coding randomization of slides were not always carefully done. The method sometimes used to randomize uncoded slides did not entirely exclude the possibility of bias in choosing the cells for photography. More importantly, although the same parameters were scored, different workers were not equally stringent in their definition of breaks. Still, there might have been true differences in the frequency of breaks among the different control groups. The reasons for this are indeterminate. Some control subjects were excluded from the studies because of high frequencies of breaks associated with recent viral infections or therapeutic X-ray treatment (Irwin and Egozcue, '67; Cohen et al., '67a; Egozcue et al., '68). Perhaps viral infections, commonly used drugs, or predisposition to chromosome breaks might have played some unsuspected role. Nevertheless, it remains that the increase in the frequencies of breaks in relation to the control values was significant in some of the LSD-exposed subjects, although it may be debated whether the increase was due to the LSD (to which some subjects may be more susceptible than others), to impurities in the illicit LSD (Irwin and Egozcue, '68), or to some other factors such as the concurrent use of other compounds (Rappaport, '68; Gilmour et al., '71).

Concerning numerical chromosome abnormalities, aneuploid and polyploid cells were noted occasionally, but the finding was not consistent (Abbo et al., '68; Hultén et al., '68; Nielsen et al., '68a,b, '69; Sato and Pergament, '68; Hsu et al., '70).

Chromosome studies on the same subject before and after LSD use. This approach may control the individual differences in the frequencies of chromosome breaks and provide a control for the amounts and purities of other drugs used. This type of study has been made on psychiatric patients scheduled to be treated with LSD. Blood samples were taken soon before the administration of LSD and 1–10 days later. In two studies there were no differences in the frequencies of breaks in 42 patients (Tjio et al., '69a,b; Corey et al., '70), but in another (Hungerford et al., '68) three of four patients showed a transitory increase in chromosome breaks which returned to normal when a follow-up study was made within 6 months.

Two longitudinal studies were made with rhesus monkeys. One showed a tendency towards a transitory increase in breaks, but too few cells were analyzed to allow complete evaluation (Egozcue and Irwin, '69). The other study did not include a true, pre-LSD sample, the original frequency of breaks was unusually high (15–16%), the last blood samples were taken immediately after the last dose, and there was no follow-up study. An increase in frequency of breaks was noted in one, possibly two, of the three monkeys (Kato et al., '70).

In studies on previous LSD users, Abbo et al. ('68) and Nielsen et al. ('68a,b) reported a possible long-term association between LSD ingestion and increased frequency of chromosome breaks in some

individuals. However, the evidence gathered from the 46 patients sampled before and after LSD did not support this contention, though there may have been a transitory increase in breaks (Hultén et al., '68; Hungerford et al., '68; Kato et al., '70).

Studies of LSD effects on meiotic chromosomes

There are two methods of studying whether chromosomal damage is transmitted to the following generation. The first is to examine children of parents who took LSD before conception, and the other is to examine meiotic chromosomes. This has been done in men, rhesus monkeys, and mice.

In studies of male meiosis there was no increase in the frequency of chromosome abnormalities in testicular material from one man (Hultén et al., '68), seven rhesus monkeys (Egozcue and Irwin, '69), and 49 mice (Egozcue and Irwin, '69; Jagiello and Polani, '69; Skakkebaek and Beatty, '70), but it was seen in other mice (Cohen and Mukherjee, '68; Skakkebaek et al., '68). The meiotic cells showed relatively lower frequencies of chromosome abnormalities than somatic cells from the same animals.

To my knowledge only one study of female meiosis has been made (Jagiello and Polani, '69). There was no increased frequency of chromosomal abnormalities in the ova from mice receiving acute or chronic treatment with LSD, and there was no increase when ova were incubated with LSD *in vitro*.

Cytogenetic studies of children whose parents took LSD

Chromosome analyses were made on 78 children and one spontaneous abortion whose parents took LSD before or during pregnancy, or both. Seventeen children and the abortus had an increased frequency of chromosome breaks (table 2). Cohen et al. ('67a, '68) found the greatest increases in children whose parents took LSD during pregnancy. A transitory increase was reported in one child, but whether this is a general phenomenon cannot be determined because only one sample each was taken from the other children. Jacobson et al. ('70) reported a patient in whom there was a gradual decrease in chromosome breaks with time. They also mentioned four embryos with brain malformations and increases in chromosomal abnormalities, the validity of which can only be estimated when a more detailed report is made.

In 21 cases LSD was ingested before pregnancy. One child had a nonfamilial D/D translocation (Hsu et al., '70). Few parental cells were analyzed so it is difficult to determine whether they had an increased frequency of breaks which could have supported the possibility of an LSD-induced translocation.

There was an increased frequency of chromosome breaks in a third of the apparently healthy children of women who had taken LSD during pregnancy, but the frequency of breaks seemed to parallel that in their mothers (Cohen et al., '68; Egozcue et al., '68). This observation suggests that a follow-up should be carried out on these children and their mothers to determine whether this increase was transitory.

There was no increase in chromosome breaks in cells from rat fetuses exposed to LSD on the 4th or 8th day of pregnancy, and there were no alterations seen in bone marrow from some of these rats at 8–15 weeks (Sato et al., '69, '71).

Finally, there was no increase in chromosome breaks in a series of 14 rhesus monkey fetuses exposed to LSD *in utero* (Wilson, private communication); and Kato et al. ('70) examined the chromosomes of three rhesus monkey fetuses and found a high level of chromosome breakage in the LSD-exposed fetus as well as in one of the two controls.

Studies of relation of LSD, chromosome breakage, and leukemia

Even though there has been concern that LSD might cause somatic damage to the user, there have been reports of only two cases in which leukemic patients had previously been exposed to LSD (Grossbard et al., '68; Garson and Robson, '69), and there seem to be no reports in the literature that associate other types of neoplasia with LSD use.

TABLE 2

Number of children exposed to LSD in which studies of chromosome breaks were made

Group	No increase in chromosome breaks No.	Increase in breaks			Reference
		No.	% breaks in LSD children	% breaks in controls	
LSD taken before conception	1(D/D)				Hsu et al., '70
		1 (abortion)	—	—	Jacobson et al., '70
		4	2.0	1.0	Cohen et al., '68
			2.5	1.0	Cohen et al., '68
			2.9	1.0	Cohen et al., '68
			8.7	1.0	Cohen et al., '68
LSD taken before and during pregnancy	1				Assemany et al., '70
	1				Jeanbart and Bérard, '71
	1				Sato and Pergament, '68
	1				Warren et al., '70
	1				Cohen et al., '68
	41				Dumars, '71
		8	1.3	1.0	Cohen et al., '68
			2.0	1.0	Cohen et al., '68
			4.0	1.0	Cohen et al., '67a, '68
			5.3	1.0	Cohen et al., '68
			7.3	1.0	Cohen et al., '68
			7.5	1.0	Cohen et al., '67a, '68
			13.0	1.0	Cohen et al., '67a, '68
			19.0	1.0	Cohen et al., '67a, '68
		1	12.0	1.6	Hultén et al., '68
		1	20.0	5.0	Jacobson et al., '70
LSD taken during pregnancy	10				Aase et al., '70
	1				Carakushansky et al., '69
	1				Stenchever and Jarvis, '70
	1				Zellweger et al., '67
	1				Egozcue et al., '68
		3	22.0	9.0	Egozcue et al., '68
			26.0	9.0	Egozcue et al., '68
			28.0	9.0	Egozcue et al., '68
Total	61	18			

Obviously these two cases are too few to determine whether there is a causal relation between LSD and leukemia or whether this is a mere coincidence. Furthermore, the types of leukemia were different in the two cases (myelocytic and lymphoblastic), and the family history in the second case suggested a predisposition to malignant disorders. Further, the type of chromosome changes were not the same in the two cases and the LSD was of known origin in only one case.

The implied relation of LSD, chromosomal breakage, and malignancies is based mainly on the observations that persons with Bloom's syndrome and Fanconi's anemia demonstrate an increased frequency of chromosome breaks (Schroeder, '66), and that a proportion of these patients also develop acute leukemia (Swift, '71). The chromosome abnormalities in Bloom's syndrome and Fanconi's anemia are found only in cultured lymphocytes and not in direct bone marrow aspirates (Schmid et al., '65). Even if an agent can induce chromosome abnormalities in somatic cells the biological significance of this observation is presently not known.

IS LSD TERATOGENIC?

Studies in human beings

To date there are reports of 161 children of parents who took LSD before or during pregnancy (table 3): 138 apparently normal children, seven with familial defects, and 16 with sporadic congenital disorders. Among the 16 there were one with D_1-trisomy (unbalanced D/D translocation), three with recognized genetic defects but without a family history of the condition (pyloric stenosis, cystic fibrosis,

and spondylothoracic dysplasia), five limb deficiencies, two "turned-in feet," one rubella syndrome, one megacolon, one bladder exstrophy, one pulmonary edema, and one hyaline membrane disease.

The four children with known genetic defects but no family history (2.5% of the 161) raise the question of increased frequency of nondisjunction and mutation, but the data do not suggest an increased frequency although the number of cases reported is too small to allow a firm conclusion. The question of teratogenicity of LSD does not need to be considered for the rubella syndrome, and for the common defects of turned-in feet, pulmonary edema, and hyaline membrane disease.

This leaves only seven children (4.3%) whose defects must be considered in relation to the mothers' intake of LSD and its implied teratogenic effect. Zellweger et al. ('67) reported a case of fibular aplasia. The mother had taken LSD once on the 25th day and three times between the 45th and 98th days after the last menstrual period. Hecht et al. ('68) reported a child with an absent right hand whose mother had taken unknown quantities of both LSD and cannabis at unspecified times before and during pregnancy, when she had also taken three antinausea drugs. Carakushansky et al. ('69) reported a child with defects of all hands and feet, "whose mother is believed to have been exposed to lysergide and cannabis during pregnancy," and Assemany et al. ('70) reported a child with one finger and toe absent whose mother had taken unknown amounts of LSD and had had three episodes of suspected hepatitis during pregnancy. Jeanbart and Bérard ('71a,b) reported a child with bilateral clubfoot, short humeri, and aplasia of fingers on both hands. The mother had taken LSD before and during the first 2 months of pregnancy, and also cannabis and methedrine. When she was 6 months pregnant she weighed only 83 pounds even though she was 63 inches tall. Gelehrter ('70) reported a child with exstrophy of the bladder whose mother had taken 12–15 doses of LSD during the first 2½ months of gestation and the 2 months prior to that. Last, an editorial (Anonymous, '67c) mentioned a child with megacolon whose

TABLE 3

Anomalies observed among 161 children whose parents ingested LSD [1]

Time of LSD ingestion	Additional drugs [2]	References
LSD ingestion only prior to conception		
104 apparently normal children	Some used Ca, Ha, Me, Pe, and/or Ps	Cohen et al., '68; McGlothlin et al., '70
15 children with congenital defects		
3 children with nonfamilial genetic defects		
1 unbalanced D/D translocation	A, B, Ca	Hsu et al., '70
1 cystic fibrosis	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
1 pyloric stenosis	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
1 child with a rubella syndrome	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
7 children with familial defects	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
1 crimped ureter	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
4 turned-in, -out feet	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
2 tibial rotation	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
4 children with nonfamilial defects of unknown etiology	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
2 turned-in feet	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
1 premature with pulmonary edema	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
1 premature with hyaline membrane disease	Some used Ca, Ha, Me, Pe, and/or Ps	McGlothlin et al., '70
LSD ingestion prior to and during pregnancy		
19 apparently normal children	8 used A, Ca, Co, H, P, and/or Sp	Cohen et al., '67, '68
4 children with nonfamilial defects of unknown		Hultén et al., '68; Jacobson et al., '70

LSD ingestion prior to and during pregnancy		
19 apparently normal children	8 used A, Ca, Co, H, P, and/or Sp	Cohen et al., '67, '68 Hultén et al., '68; Jacobson et al., '70 McGlothlin et al., '70; Sato and Pergament, '68; Warren et al., '70
4 children with nonfamilial defects of unknown etiology		
1 absent right hand (details of LSD ingestion unknown)	Ca, 3 antinausea drugs	Hecht et al., '68
1 absent right third finger and third left toe (details of LSD ingestion unknown)	3 episodes of hepatitis	Assemany et al., '70
1 exstrophy of bladder (LSD ingested 12–15 times in the 2 months before and first 2½ months of pregnancy)	Ca, Ms	Gelehrter, '70
1 bilateral cleft foot and bilateral missing fingers (LSD-25 taken before and during first 2 months of pregnancy)	A, Ca	Jeanbart and Bérard, '71a,b
LSD ingestion only during pregnancy		
15 apparently normal children	4 used A, B, Ca, D, Me, and/or O	Aase et al., '70, Egozcue et al., '68, Stenchever and Jarvis, '70
4 children with congenital defects		
1 child with a nonfamilial genetic defect		
1 spondylothoracic dysplasia (LSD once near conception)	estrogen and medroxyprogesterone	Eller and Morton, '70
3 children with nonfamilial defects of unknown etiology		
1 unilateral fibular aplasia, short femur and congenital dislocated hip (LSD four times, 25th day and between 45th–98th days after last menstrual period)	None	Zellweger et al., '67
1 talipes left, webbed toes right, missing phalangeal bones on both hands (details of LSD ingestion unknown)	Ca	Carakushansky et al., '69
1 megacolon (details of LSD ingestion unknown)	None mentioned	Anonymous, '67b

[1] Dumars ('71) reported 8 children with malformations, but gave no individual data on the parental use of LSD, so they are not considered in this paper.

[2] Abbreviations of drugs: A, amphetamines; B, barbiturates; Ca, cannabis (marihuana, hashhish); Co, cocaine; D, dimethyltryptamine; G, glutethimide; H, hallucinogens (mushrooms, peyote, morning glory seeds); Me, mescaline; Ms, mephentermine sulfate; Mt, minor tranquilizers (chlordiazepoxide, diazepam); O, opiates (morphine, heroin); P, phenothiazines (chlorpromazine, thioridazine); Ps, psilocybin; Sp, sequential contraceptive pills.

mother took LSD during the first month of pregnancy.

Blanc et al. ('71) suggested that the limb amputations seen in the three cases reported by Assemany et al. ('70), Carakushansky et al. ('69), and Hecht et al. ('68) closely resemble the typical amniotic-band syndrome.

The presence of limb deficiencies in five of the 161 children is striking, but still are not necessarily attributable to LSD since reduction deformities of limbs may occur as often as 1.78/1000 births, syndactyly 0.72/1000 births, and other digital anomalies as often as 0.54/1000 births (Lilienfeld, '70). Proof of correlation of limb defects with LSD usage requires avoidance of the bias resulting from malformed children whose parents took LSD being reported more often than normal children of such parents or malformed children whose parents did not take LSD.

In some of the 161 cases LSD had been taken at times during pregnancy when organogenesis was complete. The presence of many children who were apparently normal and healthy may represent cases of LSD taken late in gestation when no teratogenic effect would necessarily have been expected. Hoffer ('68) mentioned a survey of many women treated with LSD in Saskatchewan who later had babies. He reported that there were no malformations, though numbers, doses, and other details were not stated.

In summary there is little evidence at present that LSD has teratogenic effects in human beings. In searching for a teratogenic effect one must look for a consistent pattern of malformations, a sensitive time during pregnancy, and a critical dose level. The five cases of limb deficiencies hardly present enough evidence for a pattern of malformations or to define a sensitive period. Furthermore, the doses taken were not completely known, and thus do not allow an evaluation of the dose required for teratogenic action. Nevertheless, even if there is no clear evidence of a teratogenic effect in people, we should keep these five cases in mind, continue to screen more pregnancies for drug use, and make prospective studies of LSD use in pregnancy.

So far only liveborn children have been studied, but the question of teratogenicity should extend to abortuses also. McGlothlin et al. ('70) found a higher abortion rate (37%) among mothers who took LSD illicitly in addition to doing so medically, whereas the 15% abortion rate among women exposed to LSD only medically was not higher than expected for the general population. This might point to factors in illicit LSD use that contribute to abortions. However, in both groups there were more abortions when the mother, rather than the father, had taken LSD. A preliminary report by Jacobson et al. ('70) mentioned four first-trimester abortuses with central nervous system defects from a population of LSD users and indicated that the frequency of these defects was higher than among their other abortion material.

Studies in laboratory animals

The possible teratogenic effects of LSD have been tested in rats, mice, hamsters, rabbits, and rhesus monkeys (table 4). The doses were based on the estimated blood concentration of a hallucinogenic dose in human beings. This gives a blood concentration after 30 min of 0.4 μg/kg (Loughman et al., '67). However, this estimate, in turn, was originally extrapolated from data on ^{14}C-LSD metabolism studies in mice (Stoll et al., '55) which may not at all be the same as the blood levels in man. Furthermore, there is great variation in the metabolism of LSD which has, for example, a half-life of 175 min in human plasma and only 7 min in mice (Aghajanian and Bing, '64). Despite these limitations there is evidence that LSD enters fetuses during different stages of gestation as seen from studies on ^{14}C-labeled LSD in mice and hamsters (Idänpään-Heikkilä and Schoolar, '69a,b).

Alexander et al. ('67, '70) reported increased percentages of resorption, stillbirth, and growth retardation, but no malformations in rats. However when Warkany and Takacs ('68), Nosal ('69), and Roux et al. ('70) tried to repeat these experiments they found no effects on litter size or fetal weight. The inconsistency of these results may have arisen from the use of the word "resorptions" by Alexander et al. In their studies the rats were given LSD on the 4th day of gestation and

implantation does not occur until the 7th day. They observed young at birth, and female rats with no litters were considered to have resorbed their young. Since they performed no laparotomies it was impossible for them to know whether the rats had been pregnant from the beginning, whether implantation had been interrupted, or whether the embryos had been resorbed.

Auerbach and Rugowski ('67) injected LSD into pregnant mice on the 7th or 8th day and found 57% brain and facial malformations in embryos examined several days later. DiPaolo et al. ('68) and Roux et al. ('70) were unable to confirm these results in offspring examined near term. Hanaway ('69b) noted histological defects of the mouse lens after LSD treatment.

Low frequencies (5–8%) of defects were reported for hamster fetuses from females treated with LSD by Geber ('67). But these effects were not found when the experiment was repeated by DiPaolo et al. ('68) and Roux et al. ('70).

In rabbits Fabro and Sieber ('68) found no malformations or changes in resorption rate or litter size.

A report on six rhesus monkey fetuses showed no malformations (Wilson, '69). Wilson (personal communication) expanded this study to include a total of 14 pregnancies and concluded that there was no embryotoxicity of consequence.

Another report on rhesus monkeys implied that LSD given during the last quarter of gestation was responsible for two stillbirths with undescribed facial deformities, one rejected infant which died of pneumonia at the age of 1 month, and a possible prolongation of gestation (Kato et al., '70). However, no such conclusions can be drawn because the time of treatment during gestation was imprecisely known. During early pregnancy the animals were in transit from Asia, and the treatment with LSD was given long after the organogenetic period. There seems to be no evidence that the observations on the infants can be related to the LSD administration.

In all of these animal studies there was no dose-response effect. A significant number of malformations was reported only once for mice, yet the papers by Alexander ('67), Auerbach ('67), and Geber ('67) have been cited several times as supporting that LSD is teratogenic, although the more recent reports showed no teratogenic action of LSD.

DISCUSSION AND CONCLUSIONS

The postulated genetic and teratogenic hazards of LSD have prompted much speculation and research. It is interesting to compare the wide range of interpretations and conclusions drawn from more or less the same body of data. Some foresee the possibility of genetic damage to future generations (Anonymous, '67c, '68b) and others see unquestionable evidence that LSD is dangerous either as a chromosome-breaking or a teratogenic agent (Anonymous, '67a,b; Houston, '69). Others call for more critical evaluation of the data, some suggesting that the dire predictions are not justified and that there are no indications so serious as to preclude the continued therapeutic use of LSD (Denson, '68; Fitzgerald and Dobson, '68a,b; Malleson, '68; Friedel, '70; Hoey, '70; Dishotsky et al., '71), whereas others review the data but draw no conclusions (Anonymous, '68a, '69; Hoffer, '68; Smart and Bateman, '68; Blaine, '70; Greenblatt and Shader, '70).

Most of the data reviewed in this paper can be summarized as follows. LSD added to cells *in vitro*, even in doses estimated to correspond to plasma levels, almost always resulted in increased chromosome breakage. Cultured lymphocytes from LSD users, patients treated with LSD, and children exposed to LSD *in utero* showed an increase in chromosome breakage in about half the cases. However, longitudinal studies made before, during, and after LSD treatment, showed either no effect, or only a transitory increase in chromosome breaks.

The *in vitro* system is the farthest from ideal and resulted in the highest proportion of breaks. As the techniques and methods approached the *in vivo* situation the incidence of breaks decreased. Studies on cultured lymphocytes from subjects who had taken LSD should not be regarded as true *in vivo* studies because the lymphocytes divided at least once in culture. Even if there was chromosome breakage

TABLE 4

Teratogenicity of LSD in animals

Species (stock or strain)	Dose of LSD and route of administration [1]	Day(s) of gestation administered [2]	Age and number of litters examined	Authors' interpretation of the effects on the fetuses	Reference
Rats (Wistar)	5 μg/kg, sc [3]	4th	newborn 10	No malformations. Stillbirths and retarded postnatal growth in some of the 85 offspring.	Alexander et al., '67
		7th, 8th, 10th, 13th, or 16th	5	All fetuses normal.	
Rats (Wistar)	5 μg/kg, sc 20 or 100 μg/kg, po	1st, 2nd, 3rd, or 4th	newborn 26	No malformations. Increased resorptions, small litters, stillborn, and postnatal deaths (11% compared to 2% in controls). This was especially apparent when LSD given on the 4th day, but when given on the 8th day all offspring were normal. Dose-response effect with oral doses. Offspring were raised. Matings of rats exposed to LSD *in utero* resulted in higher fetal mortality than matings between controls or of control × LSD exposed." Some pregnant "LSD exposed" rats died indicating "some hidden damage not visible until the demands of pregnancy brought it to the surface." Only visible effect of LSD at autopsy was increase in vascularity.	Alexander et al., '70
		4th	29		
Rats (Wistar)	1.5–300 μg/kg, ip, po [4]	7th, 8th, or 9th	21st day	Nonsignificant malformation rate.	Warkany and Takas, '68
		7th–12th	55	4/508 fetuses had defects (hydocephalus, syndactyly, and 2 small fetuses). This falls within control range.	
		4th or 5th	34	No evidence of malformation, stunting, or resorption when LSD given prior to organogenesis. 1/335 fetuses stunted, 2 litters small. This is within control range.	
Rats (Sprague-Dawley	5, 10, 25, 50 μg/kg ip	4th	19th day ?	No malformation, stunting, small litters or resorption	Nosal, '69
Rats (Wistar)	5–500 μg/kg, sc		21st day	Nonsignificant malformation rate in 1003 fetuses. Weight and mortality	Roux et al., '70

Rats (Wistar)	5–500 μg/kg, sc	4th 7th 4th–10th 7th–13th	21st day 11 10 31 46	Nonsignificant malformation rate in 1003 fetuses. Weight and mortality normal. 6/99 given 5 μg/kg on 4th day were edematous and 4/117 given 50 μg/kg on 4–10th days had cataracts, but these were not significant (10–20% mortality among the controls. Enormous doses had no effect). No abortifacient, teratogenic, or growth retarding effects.	Roux et al., '70
Rats (Sprague-Dawley)	100 μg/kg, po, sc	4th or 5th 4th or 8th	14–15th day 3 18–15 weeks	No malformations in 28 fetuses and no chromosomal aberrations in bone marrow cells from 4 young rats. LSD given at different times during gestation did not affect litter size.	Sato et al., '69, '70
Rats (Sprague-Dawley)	1, 10, or 100 μg/kg, po	1–3, 4, 8, 9–12, 13–15, 18–21, or 1–21	40th and 80th days ?	No gross organ malformations, no data on litter size, stillbirth, or resorption. Among the 42–84 rats used there was significant lowering of brain 5-hydroxytryptamine but not of norepinephrine. Suppression of hexobarbital oxidase and o-demethylase liver activity in females but not in some males.	Nair et al., '70
Mice BALB, C3H, C57BL/6, and (BALB × C57) F_1	0.05–1.0 μg, ip	8th 7th, 9th or 10th day	12th day 20 ?	57% malformations in 158 fetuses (10% in 64 controls), mostly midbrain enlargements, shifts, or improper closures; changes in face shape correlated with abnormal eyes and lower jaws. Similar effects seen with treatment on 7th day, but fetuses normal after 9th or 10th-day treatment.	Auerbach and Rugowski, '67
Mice (NIH, A/Cum)	0.5–30 μg, ip	as above	12th or 15th day 22 NIH 14 A/Cum	All 167 NIH fetuses normal; 19% of 79 A/Cum had cleft lip/palate or micrognathia (3% of 66 controls had similar malformations). The malformations were the same as in controls even though the dose was 25–1000 times the human dose, implying not a teratogenic effect, but potentiation of a threshold difference to this defect in these mice.	DiPaolo et al., '68

TABLE 4 (Continued)

Teratogenicity of LSD in animals

Species (stock or strain)	Dose of LSD and route of administration [1]	Day(s) of gestation administered [2]	Age and number of litters examined	Authors' interpretation of the effects on the fetuses	Reference
Mice (Swiss-Webster)	5 μg, ip	7th, 8th, 9th, or 10th	19th day 18	In 120 fetuses there was high percentage of subcapsular lens defects resembling X-ray-induced cataract: 7th day–81%, 8th–65%, 9th–55%, and 10th–79%. All lenses normal in controls. Summary of extended study in progress (Hanaway, '69a) indicated no gross malformations.	Hanaway, '69b
Mice (Yale Swiss)	9900 μg/kg ^{14}C-labeled LSD-25, iv		animals killed 5–120 min after injection	Unmetabolized ^{14}C-LSD entered embryos. During early pregnancy 2.3% of the labeled LSD entered whereas only 5% entered during last week. Decreasing concentration in lung, liver, intestine, brain, myocardium. Lowest in blood.	Idänpään-Heikkilä and Schoolar, '69b
		1st week	3		
		3rd week	3		
Mice (Swiss)	5–500 μg/kg, sc	4th–10th or 6th–13th	19th day 25	No malformations, increase in mortality, or weight change in 521 fetuses.	Roux et al., '70
Hamsters (randombred)	0.8–2.4 μg/kg, sc		12th day	5–8% abnormalities seen in 378 fetuses, may have included exencephaly, spina bifida, meningocele, hydrocephalus, myelocele, edema along spinal axis and other areas, hemorrhages of local brain areas, and omphalocele. There was a correlation between dose and resorbed or dead fetuses but not between dose and abnormalities. Mescaline and bromo-LSD also given, but no indication of which abnormalities found after which treatment.	Geber, '67
		8th	37		
Hamsters (Syrian)	10, 100, 200, or 300 μg, ip		15th day	No teratogenic effects in 168 fetuses. One treated fetus had microphthalmia, but there was exencephaly among controls. He points out that Geber could not show a dose-response curve, and his percentage of abnormalities is too low to be considered as positive results.	DiPaolo et al., '68
		7th, 8th, or 9th	12		
		8th, 9th, and 10th	1		
Hamsters (Syrian)	500 and 50,000 μg/kg ^{14}C-LSD, ip, sc	5th and 6th	15 min–24 h after injection	Labeled LSD entered fetus. With low dose young embryos had twice the activity, and with the high dose 4–5 times as much radioactivity as did	Idänpään-Heikkilä and Schoolar, '69a
		15th and 16th	39		

Hamsters (Syrian)	500 and 50,000 μg/kg ^{14}C-LSD, ip, sc	5th and 6th 15th and 16th	15 min–24 h after injection 39	Labeled LSD entered fetus. With low dose young embryos had twice the activity, and with the high dose 4–5 times as much radioactivity as did older fetuses. They conclude that the placenta slows down transfer of LSD during last week of pregnancy, however difference in uptake in early and late pregnancy may be related to differences in function of yolk sac in early and chorioallantoic placenta in late gestation.	Idänpään-Heikkilä and Schoolar, '69a
Hamsters			15th day	No malformations, weight changes, or increased mortality in 189 fetuses	Roux et al., '70
	50 μg/kg, sc	7th–13th	14		
	500 μg/kg, sc	4th–12th	8		
Rabbits (New Zealand White)	20 μg/kg, po		28th day	No malformations, reduced litter size, or resorption in 118 fetuses. Slight reduction in fetal weight.	Fabro and Sieber, '68
	100 μg/kg, po	4th–7th	2		
		8th–12th	9		
		7th–9th	3		
Monkeys (*Macaca mulatta*)	75, 100, 200 μg, po	23rd, 26th, 28th, or 30th	100th day 4	Five fetuses normal. One mother given 3 doses of 200 μg severely anemic and fetus retarded, though normal.	Wilson, '69
	200 μg on 3 days	25th, 27th, and 29th, and 23rd, 25th and 27th	2		
Monkeys (*Macaca mulatta*)	900–9000 μg/kg, sc, in 4–11 doses.	during last 6 weeks of gestation	4	Only 1/4 LSD-exposed fetuses lived. Two were stillborn and had "facial deformities." These were offspring of the mothers given lowest and a high dose of LSD. One infant rejected by mother died of pneumonia in first month. Fourth LSD-exposed infant was normal. At 7 months there was a high frequency of chromosomal breaks which returned to normal by 13 months. Two control infants were normal. One LSD infant showed elevated breaks and a quadriradial. Parturition may have been delayed by LSD because birth of treated infants was much later than supplier had estimated. All females were pregnant while in transit from Asia.	Kato et al., '70

[1] ip, intraperitoneal; iv, intravenous; po, per os; sc, subcutaneous.
[2] Where possible, in this table the day the vaginal plug was found is called day 1 of pregnancy (Kalter, '68).
[3] This dose corresponds to a human hallucinogenic dose per body weight.
[4] This dose corresponds to a total human hallucinogenic dose.

in the cultured cells this does not necessarily simulate the situation in the body. The only presently available *in vivo* approach would involve the use of fresh bone marrow aspirates; and Amarose and Schuster ('71) who examined bone marrow aspirates and lymphocytes from illicit drug users found no increase in chromosome breaks in bone marrow even though there was a significant difference in the lymphocytes between the drug users and controls.

It is unrealistic to ascribe to LSD the chromosome breaks found in prior LSD users since there was no correlation between the percentage of breaks and the amount of LSD, number of doses, or time between the last dose and blood sampling, and considering that other plausible agents were present and that only one sample was analyzed from each subject. A transitory increase in breaks was indicated in a few cases. This may account for some of the breakage seen in LSD users and children exposed *in utero*, though this cannot explain the high frequencies of breaks seen after 2 years in some subjects.

In general, then, there does not appear to be well-documented evidence that LSD can cause chromosome breaks that may persist for lengthy periods of time, the risk for future generations seems small in light of the negative, albeit rather limited, meiotic data and there is no strong evidence of teratogenic action of LSD in animals or man, though the five cases of limb deficiencies warrant continued surveillance.

These conclusions do not mean that LSD deserves a clean bill of health or that it should be used by pregnant women, but that the publicity given to the possible adverse side effects of LSD is not justified by the available evidence. Thus, if LSD is to be considered for therapeutic administration, one must weigh the strength of the indications for its use against any possible risks. The choice of whether it has therapeutic benefit rests with those who would use it in the clinics, and the risk of possible side effects discussed in the present paper seems small enough to give the clinicians the choice.

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