REVIEW ARTICLE

The Chromosomal and Teratogenic Effects of Lysergic Acid Diethylamide:

A Review of the Current Literature

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A RECENT review by the authors[14] summarized the reported adverse effects of LSD; this was chiefly a review of psychological and psychiatric effects. Since that article was prepared a number of studies have been concerned with damage to chromosomes and with abnormalities in the offspring of females given LSD during pregnancy. It is important to clarify the chromosomal and teratogenic effects of LSD for purely scientific reasons and to educate illicit users about its dangers. There are some at least who believe that publicity about these effects is discouraging illicit use of LSD and a definite consensus on this issue could probably further reduce its use.[16] However, the same publicity may make LSD difficult to obtain for research purposes, and it is probably too early to suspend research in LSD unless it is clearly harmful in all circumstances. Unfortunately, the studies available provide no obvious consensus; both positive and negative findings have been reported for chromosomal and for teratogenic effects. The purposes of this paper are (i) to review and analyze the relevant studies in an attempt to explain the apparent inconsistencies in findings and (ii) to indicate areas for further research. A more general purpose is to discuss the overall importance of these physical effects for various types of LSD users.

I. Chromosomal Studies

Eight papers have examined the effects of various doses of LSD on chromosomes[3-6, 9, 10, 12, 17] and in all but one of these[12] human leukocytes were studied. Six of the papers[4-6, 9, 12, 17] concluded that LSD did damage chromosomes and two[3, 10] concluded that they did not. Because of their complexities the main features of these studies are shown in Table I. Those which did find that LSD had a deleterious effect reported breaks in as many as 45% of the chromosomes studied.

Two *in vitro* studies have been carried out in which leukocytes have been exposed to various concentrations of LSD. The first paper in this series was by Cohen, Marinello and Back.[4] They obtained cells from two individuals and examined the chromosomes after treatment with various amounts of LSD. Cultures of leukocytes were exposed for 4, 24 or 48 hours to a solution containing 10, 1, 0.1, 0.01 and 0.001 μg. per ml. of LSD. Untreated leukocytes for the control group were taken from the two experimental subjects and from four additional persons. It was found that the number of breaks in the LSD-treated groups was double that found in the untreated, and the rate of breakage ranged from 5 to 36.8%. An exception, however, was the group exposed to a level of 0.001 μg. per ml. for four hours; it showed no increase in breaks. The highest concentration brought about the greatest number of breaks at the shortest incubation time. Unfortunately, time-dose relationships for the other groups were more confused, but the four-hour exposure produced the fewest overall number of breaks.

In a later study Cohen, Hirschhorn and Frosch[5] obtained similar findings with larger samples. Leukocytes from six persons were exposed to the same LSD dosages for the same lengths of time. The breakage rate varied from 7.7 to 17.5%, compared to 3.9% for the control group. In addition, the group exposed for four hours to a level of 0.001 μg. per ml. had 11.2% breaks compared to 3.9% for the control group —a significant difference. Virtually no time-dose relationship is apparent from these data.

The *in vitro* findings led to a search for chromosome abnormalities in the cells of users. Cohen, Marinello and Back[4] also reported data from a single male schizophrenic who had re-

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TABLE I.—STUDIES OF THE EFFECTS OF LSD ON CHROMOSOMES

	Number of individuals		*Number of cells examined for abnormalities*		*Dosage of LSD*		*Percentage of cells showing chromosome abnormalities*	
	LSD group	*Control group*	*LSD group*	*Control group*	*Size*	*Frequency*	*LSD group*	*Control group*
In vitro								
Cohen, Marinello, and Back[4]	2	6 (2 same as LSD group)	2678	925	.001 to 10 μg./ml.	1	14.3	3.7
Cohen, Hirschhorn, and Frosch[5]	6	6 (all same as LSD group)	7735	1680	.001 to 10 μg./ml.	1	13.0	3.9
In vivo								
Cohen, Marinello, and Back[4]	1 treated	—	200	—	80, 20, 200 μg.	15	12.0	—
Cohen, Hirschhorn, and Frosch[5]	(a) 18 LSD users	(a) 2 non-users	(a) 4282	(a) 2674	Unknown	2 to 300	(a) 13.2	(a) 3.8
	(b) 4 children exposed in utero	(b) 2 non-users with viral infection	(b) 1000	(b) 300			(b) 11.9	(b) 19.6
		(c) 6 users of other drugs		(c) 1361				(c) 11.8
Irwin and Egozcue[9]	8 LSD users	(a) 6 non-users	1600	(a) 1200	200 to 600 μg.	4 to 200	23.6	(a) 9.4
		(b) 2 non-users exposed to x-rays		(b) 400				(b) 20.8
Zellweger, McDonald and Abbo[17]	1 exposed in utero	—	60	—	Unknown	4	5.0	—
Egozcue, Irwin, and Maruffo[6]	(a) 46 LSD users	14 "drug-free" controls	(a) 9140	2800	100 to 1000 μg.	1 to 300	(a) 18.8	9.0
	(b) 4 children exposed in utero		(b) 800				(b) 21.5	
Loughman, Sargent and Israelstam[10]	8 LSD users	1 non-user	245	112	100 to 4000 μg.	12 to 100	.76	0
Bender and Sankar[8]	7 children	20 untreated	50 (from only 5 children)	50 (from only 5 children)	100 to 150 μg.	approx. 170 to 1050	2	2
Skakkebaek, Phillip and Rafaelsen[12]	6 mice	6 mice	400	300	1 mg./kg.	1 to 8	7.8	1.7

ceived 15 LSD treatments with doses from 80 to 200 μg. Leukocyte cultures prepared eight months after the last treatment showed a breakage rate of 12% compared to an expected value of only 3.7%.

The finding was corroborated by Irwin and Egozcue[9] in their study of LSD users. They compared the number of choromosome abnormalities found in eight LSD users with that in nine non-users. The users had taken LSD on 4 to 200 occasions with peak dose intakes of 400 to 2800 μg. As expected, the LSD users showed far more breaks ($\overline{X} = 23.6\%$ of the cells) than did the controls ($\overline{X} = 9.4\%$ when those who had a recent radiograph were disregarded). Again, there was little correlation between dosage and frequency of abnormalities.

The most extensive study of LSD-induced chromosome breaks was made by Egozcue, Irwin and Maruffo,[6] who studied 50 LSD users and 14 non-user controls. The LSD users had a mean breakage rate twice as high as that of the non-users (18.99% compared to 9.03%), although there was considerable overlap in the distributions. This study also contained chromosome data from four children born to mothers who had ingested LSD during pregnancy. Two of the mothers had taken LSD early in pregnancy and two somewhat later. Three of the four showed high levels of chromosome breaks (22 to 28%) but one did not (9.5%). There was a limited relationship between total dosage, or interval between last dose and chromosome sampling, and the incidence of chromosome breakage.

Cohen, Hirschhorn and Frosch[5] also found a high frequency of abnormalities in LSD users. They studied 22 persons who had taken LSD on 20 to 300 occasions; these had an average of 13.5% chromosomal breaks compared to 3.8% in the 12 controls used. There was negligible correlation between dosage or time of exposure and frequency of abnormalities. They also examined the chromosomes of four children born to three mothers who took LSD during pregnancy. Two of the children whose mothers took LSD during the third and fourth months (300 to 600 μg.) had a high frequency of breaks (13.0 and 19.0%), but two exposed to low doses late in pregnancy showed 4.0 and 7.5% breaks. Comparable data for the offspring of non-LSD users were not presented.

An interesting study of the offspring of a father and mother who took LSD has been reported by Zellweger, McDonald and Abbo.[17] Both parents had taken LSD, the mother four times during early pregnancy (the last occasion was on the 98th day). They had a child with a deformed leg. Both parents and child had chromosome breaks, but only small leukocyte samples were used.

The latest study of LSD and chromosomes was performed with the sperm of mice.[12] Six mice were injected with 1 mg. per kg. of LSD

on one to eight occasions, and germ cells in meiosis were examined for chromosome breaks. Comparisons were made with six control mice; two of them were injected eight times with saline and four were not injected at all. Far more gaps, breaks and fragments were found in the LSD-treated group (7.8% of cells) than in the control group (1.7% of cells). It is worth emphasizing that the dose received was very high —about 500 times as high as the usual human dose (1.4 to 2 μg. per kg.). Naturally, questions will be raised about the precipitation of such abnormalities after smaller doses. This study, however, is concerned with germ cells, and unlike those with leukocytes, the relevance of its results for congenital malformations can be readily appreciated.

Two studies have failed to find an effect of LSD on the chromosomes of users. Loughman, Sargent and Israelstam[10] studied the chromosomes of eight persons who had ingested LSD on 12 to 100 occasions, including doses up to 4000 μg.* They found an incidence of abnormalities no higher than in 19 non-user controls. Only one of these controls was supplied by the authors; the others appear to have been drawn from other sources. Similar findings were reported by Bender and Sankar[3] for seven children who received 100 to 150 μg. of LSD for 5½ to 35 months. Chromosome breakages in these children amounted to only 2%, the same as in 20 controls.

An important question concerns the reasons for the inconsistent results. Certain differences in the preparation of cultures or in the counting of "abnormalities" may account for the discrepancies. However, similar methods of preparation and observation have been described,[4, 6, 9, 10] and photographs of the abnormalities[4-6, 9] suggest that similar items are being counted. An exception is that Cohen, Marinello and Back[4] did not report each type of break separately, whereas others did.

Loughman, Sargent and Israelstam[10] suggested that the studies with positive results may have administered doses of LSD much higher than usual. They found no chromosomal abnormalities in their users and point out that Cohen, Marinello and Back[4] found abnormalities *in vitro* only with exposure to levels above 0.001 μg. per ml. (four hours' exposure). Their point is that 100 μg. of LSD given to a man weighing 70 kg. would result in a concentration not higher than .0014 μg. per g. and that after 30 minutes this would fall to 0.0004 μg. per g. They conclude that "no chromosome breakage is to be expected in humans given doses of LSD of 100 μg.". However, a later study by Cohen, Hirschhorn and Frosch[5] did find a substantial (11.2%) number of abnormalities in cultures exposed to 0.001 μg. per ml. for four hours. This study included 578 leukocytes in the 0.001 μg. per ml. group as compared to only 200 in the earlier study. It could be argued that greater confidence should be placed in the results from the larger sample. A further problem with this argument is that the concentration data were based on studies done with mice. The actual concentrations of LSD in various body fluids at specified times after oral administration are not known for man. All of these points suggest that Loughman, Sargent and Israelstam's explanation[10] of the conflicting results is premature. It should be noted, too, that 100 μg. is probably a very low dose in illicit or therapeutic settings.

Irwin and Egozcue[9] have argued that Bender and Sankar[3] failed to find chromosomal abnormalities in LSD takers because of the long interval between the last LSD dose and the examination of leukocytes, or because of the small number of chromosomes studied. Bender and Sankar[3] studied children who had their last LSD dose 20 to 48 months before their chromosomes were examined. Irwin and Egozcue[9] have argued that this period is too long because the average life of lymphocytes has been found to be 15 to 20 months.[11]

However, Cohen, Hirschhorn and Frosch[5] found high frequencies of chromosome abnormalities in the offspring of LSD users up to 5½ years after LSD was taken during pregnancy. The sample size is small, but these findings raise some doubts about the argument based on the life span of lymphocytes. Unfortunately no study other than that of Bender and Sankar[3] examined users as long as 20 months after their last LSD dose. Elevated rates of abnormalities have been found six,[9] seven and eight months[5] and 12 months[6] after the last dose. Clearly, some studies of LSD users who stopped using it several years before their chromosomes were examined would add substantially to our knowledge.

A more convincing argument adduced by Irwin and Egozcue[9] is that Bender and Sankar[3] may have obtained false negative findings because they studied only 10 metaphases per subject in contrast to 200 in their own studies. Nevertheless, Loughman, Sargent and Israelstam[10] found negative results when they examined an average of 87 cells per user (697 cells for eight users). It has been suggested by Irwin and Egozcue[9] that it is necessary to examine 100 metaphases per subject and, in fact,

*The statistical criticisms of this article by Slatis[13] do not materially affect the conclusions.

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in all of those studies where abnormalities after LSD use have been found, about 200 have been examined. The small sample size could contribute to the lack of positive findings in the papers of Bender and Sankar and of Loughman, Sargent and Israelstam.

There is little agreement about the "control" or basal level of chromosome abnormalities with which LSD-induced changes should be compared. The two *in vitro* studies found rates of 3.7%[4] and 3.9%[5] for abnormalities in the untreated leukocytes. However, Loughman, Sargent and Israelstam[10] have argued that these figures are too high and that the rate based on earlier studies and their own controls should be 0.76% to 1.1%. Similarly, Bender and Sankar[3] found an abnormality rate of 2% in their untreated controls. However, Irwin and Egozcue[9] found an abnormality rate of 11.9% in nine controls or 9.4% if two persons are dropped who had recent diagnostic radiographs and previous x-ray therapy. This high rate for untreated persons is difficult to explain, and if it had occurred in other studies[3, 10] different conclusions would have been drawn by their authors, even that LSD protects against chromosome breaks. More information is needed about the rates of chromosome abnormalities occurring in untreated controls and the variables which affect those rates. It has been suggested that sampling biases have affected results, as the highest control rate is noticed in the study[9] with a small sample size. The wide range of accepted basal rates of abnormality must lead to reduced confidence in the conclusions about the effects of LSD.

It has also been suggested that the chromosome abnormalities found in LSD users could be incidental to their use of LSD, but related to the use of some other drug. The *in vitro* findings would seem to cast doubt on this possibility. Nevertheless, many illicit users of LSD experiment with or even prefer a variety of other drugs, such as morphine, marijuana, amphetamines and tranquillizers. For example, most LSD users in the chromosome studies had taken other psychoactive or hallucinogenic drugs. Only one LSD user in Loughman, Sargent and Israelstam's study[10] had not used any other drug. However, the study by Egozcue, Irwin and Maruffo[6] contained two persons who had taken only LSD and both had high rates of breakage. No information on drug use other than LSD was reported by Irwin and Egozcue or Bender and Sankar. Since chlorpromazine is often used to terminate prolonged LSD experience, it is difficult to believe that subjects in the studies mentioned had no experiences with other drugs.

Cohen, Hirschhorn and Frosch[5] reported high rates of chromosome damage (average incidence breaks : 12.6%) in six patients who had taken psychoactive drugs (chlorpromazine, amphetamines and diphenhydramine) but no LSD. Three of the four patients who took chlorpromazine showed very elevated rates of breakage. In fact, the chlorpromazine users had slightly higher rates of abnormalities than did the LSD users (14.2% compared to 13.2%). However, in an earlier study Cohen, Marinello and Back stated that "screening of chromosomes from 35 schizophrenic patients, some of whom were treated with these tranquilizers (thorazine, librium) revealed no increase in the frequency of chromosome breakage over that in untreated individuals". Other than these two contradictory studies it has been impossible to find any evidence in the literature that marijuana, morphine, amphetamines or tranquillizers can create chromosome damage. It may be that many or all of the chromosome breaks in LSD users are attributable to their use of drugs other than LSD but the current literature neither confirms nor denies this proposition.*

In summary, it is difficult to reach a clear decision about the chromosomal damage caused by LSD. Two *in vitro* studies have found clear evidence of increased damage when doses above 0.01 μg. per ml. are added to leukocyte cultures. However, the evidence is ambiguous for levels of 0.001 μg. per ml. which correspond more closely to the blood levels achieved in human use. The study with negative results for 0.001 μg. per ml. used a sample size smaller than did the study with positive results but one usually taken to be adequate for the purpose.[9] Clearly, more studies with levels that range between 0.01 and 0.001 μg. per ml. are required before an adequate decision can be made. There is some evidence in one of the *in vitro* studies, but very little evidence in the other, that the extent of damage depends on dosage.

When the effects on the chromosomes of human users are examined, there are positive and negative findings which are difficult to reconcile. Unfortunately, the two negative studies involve a somewhat smaller total of users (15) than do the ones with the positive results (78). One of the negative studies may also be criticized because only 10 metaphases per subject were counted. The basal or untreated level of chromosome breaks varies unpredictably from one study to another (0.76% to 11%). Also,

*A review of Index Medicus for 1960-1968 failed to reveal any studies of the effects of marijuana, morphine, amphetamines or the major tranquillizers on chromosome breakage. The exceptions are the two studies referred to above.

chromosome abnormalities in LSD users may eventually be found to be due to their extensive and varied drug usage. Once more, evidence on this point is ambiguous and incomplete. Most of the studies on human users have been made with persons who received a very large number of doses, up to 300. This means that the findings may have little relevance for persons who received one or two doses in therapeutic or experimental settings. At present, the case for the chromosomal effects of LSD in human users is not proved although sufficient evidence exists to justify the expectation that further studies may confirm such an effect.

II. TERATOGENIC EFECTS OF LSD

Concern attaches to the chromosome damage caused by LSD partly because it may cause some abnormality in the offspring of users. Several studies have examined the effects of LSD on the offspring of rodents and positive and negative results have been found, with no obvious explanation of the differences. Only one study[17] has collected data on the chromosomes of parents and the physical condition of their child.

Alexander *et al.*[1] reported three experiments in which LSD was given to pregnant rats. In two of these 5 μg. per kg. of LSD was given to 10 rats on the fourth day of pregnancy; in the third experiment it was given on the seventh to sixteenth days. This dose would be equivalent to about 300 μg. for a person weighing 60 kg. Rats which received LSD early in pregnancy produced small litters with higher rates of stillbirths, abortions and stunted offspring compared to controls treated with saline. However, rats given LSD late in pregnancy produced normal offspring but somewhat smaller litters.

A similar study by Warkany and Takacs[15] failed to corroborate these results even though very large doses were given. They performed three experiments in which rats received: (i) single doses of 1.5 to 300 μg. of LSD on the seventh to ninth days of pregnancy, (ii) multiple doses on the seventh to twelfth days, and (iii) doses of 1 to 100 μg. on the fourth or fifth day. As in the study by Alexander and his colleagues,[1] no teratogenic effect of LSD was found for the doses given after the seventh day. Neither was there any effect from doses given early in pregnancy, so that the finding of the earlier study was not confirmed.

In the last study most of the young (296 out of 335) were removed on the twenty-first day by cesarean section. Thus, the earlier finding[1] that the number of stillbirths was very high after LSD could not be corroborated. Those delivered by cesarean section showed no evidence of resorption or stunting greater than expected. It is not clear whether litter sizes were smaller than expected in the rats receiving LSD. Warkany and Takacs[15] refer generally to "control animals", but in none of their experiments is there any indication of the size of these groups or how they were treated in comparison with the experimental animals. It is worth noting that in their studies doses up to 300 μg. (equivalent to human doses) were used, although these would be 200 to 300 times as high on a weight basis. No ready explanation for the conflict between these two sets of findings is apparent. The type of LSD used and the size of the rats were diferent, but no clear conclusion can be based on these factors.

A study by Geber[7] with hamsters obtained results similar to those of Alexander *et al.*[1] even though they used very small doses. Pregnant females were given injections of 0.000084 to 0.24 μg. per kg. of LSD or 0.9 saline on the eighth day of pregnancy. Compared to the controls the experimental animals produced offspring with higher rates of congenital abnormalities, resorptions, dead fetuses and runts. Positive correlations appeared between dosage and the number of resorptions and between dosage and the number of dead fetuses but not between dosage and the number of abnormalities or runts.

Auerbach and Rugowski[2] have published the only report on the effects of LSD on embryos. They gave doses of 0.05 to 5 μg. to pregnant mice on the sixth, seventh, eighth and ninth days of pregnancy. Fifty-seven per cent of the embryos from those injected on day 7 were deformed, compared to only 10% in the control groups injected with Tyrode's solution. However, there were "no gross observable effects when injection occurred later than day 7 of pregnancy". In all cases the abnormalities involved "characteristic brain defects", abnormalities of the lower jaw, shifts in the position of the eyes and modification of facial contours. This paper has reported the largest percentage to date of abnormalities possibly due to LSD.

In conclusion, the significance of these teratogenic studies is difficult to assess. Three studies have found a teratogenic effect of LSD given early in pregnancy but one has not. It is unfortunate that the study with negative results contains so little information on control groups. However, the incidence of abnormalities in the experimental group is so low that if control observations from other studies were substituted

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they would lead to the conclusion that LSD had no effect. There seems to be general agreement from animal studies that only when LSD is given early in pregnancy is there a teratogenic effect; however, some human studies[6] have found chromosome breaks in offspring exposed to LSD in the fifth to sixth months. One child showed only a normal breakage rate, even though it was exposed to LSD early in intrauterine life.[6]

III. CONCLUSIONS

As it stands now, the evidence for a teratogenic effect of LSD is very strong but not unanimous. Certainly, it is strong enough to warrant a great deal of further research on the whole topic. Studies of the effect of LSD given before pregnancy and at various stages during pregnancy are needed. To date, all teratogenic studies have been concerned with LSD given during pregnancy, and its effects on subsequent pregnancies when given to non-pregnant females are unknown. More human studies are also needed in which the teratogenic effects of LSD use by both parents are investigated. So far, only one study has included a father, but it is likely that among illicit human users of LSD both parents have taken the drug both before and during the mother's pregnancy. Studies are also needed in which chromosome examinations are made of parents and offspring to determine the relationship between chromosomal and teratogenic effects. Eventually, too, the almost exclusive dependence on human leukocytes for chromosome data should cease and a wider variety of human cells, including germ cells, should be studied. The single study using germ cells applied such large amounts of LSD that its relevance to human LSD use is uncertain.[12]

It is difficult to decide what significance for the human user of LSD can be attached to the two types of study already available. Only one[16] has attempted to correlate chromosomal and teratogenic effects, and many more such studies are needed. So far, those individuals receiving one dose in the course of therapeutic and experimental studies, provided they are not pregnant, expose their offspring to unknown risks and perhaps to none at all. So few studies have included persons who had a single dose of LSD that its effect is unknown. Hoffer[8] has stated that "there have been no malformed babies born in Saskatchewan to women given LSD", but no details about the number of cases treated, dosages given and control groups studied are given. Pregnancy was a contraindication for giving LSD in Saskatchewan, and probably few received it during early pregnancy when the teratogenic effects seem most striking. Pregnant women may be exposed to some risk of having a deformed child if LSD is taken early enough. This risk may be substantial among frequent users of LSD, possibly because of their use of other psychoactive drugs. However, pregnancy and birth seem to be uncommon among illicit users of LSD. For example, in a psychological study of 100 such users, the group contained only one person who had children and one who was pregnant, even though most of them were young and somewhat promiscuous.

All persons who take LSD are exposed to its chromosomal effects, although the evidence for a harmful effect on chromosomes from small doses is insufficient. Until questions concerning the normal level of chromosome abnormalities, the minimal sample size required for dependable analysis and the contribution of drugs other than LSD to abnormalities are answered, this evidence will be difficult to establish. Whatever damage does occur may well be temporary, although studies with cells other than leukocytes may yield different conclusions.

ADDENDUM

Since this article was prepared three additional studies of LSD and chromosomes have been published.[18-20] One study of LSD users[19] showed elevated rates of chromosome breakage and one did not. An *in vitro* study[20] of drosophila cells treated with LSD found no increase in abnormalities. In general, these studies fail to decide the issues raised in this paper although they contribute useful data.

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