

LSD and Chromosomal Damage

KURT HIRSCHHORN *The Mount Sinai School of Medicine*

Both in vivo and in vitro studies have definitely established that the psychotomimetic, hallucinogenic drug lysergic acid diethylamide (LSD-25) can produce profound chromosomal damage in humans and that it does so in some 75% of persons who use it.

The exact implications of these chromosomal changes are not yet

clear, but all evidence to date suggests that they may have far-reaching mutagenic, teratogenic, and carcinogenic consequences. In short, it now appears that the chromosomal damage induced by LSD—and the consequences thereof—may be exactly comparable to that caused by ionizing radiation, certain cytotoxic drugs, such

as Mitomycin C, and certain viruses. Further, there is at least a possibility that other psychotomimetic agents frequently employed by users of LSD may enhance its chromosome-damaging potential, but this is largely unexplored territory.

The in vitro ability of LSD to bring about chromosomal changes like those caused by radiation or potent cytotoxic drugs has been demonstrated in a number of studies, including our own done with Dr. Maimon M. Cohen of State University Medical Center at Buffalo and Dr. William A. Frosch of New York University School of Medicine. In one study, for example, we assayed effects of various levels of LSD on somatic chromosomes, using leukocyte cultures made of cells taken from six normal persons (three of each sex). None, it should be noted, had a history of previous ionizing radiation, LSD ingestion, or recent viral infection. The cells used were from whole blood inoculum grown in microculture. We added LSD at 48, 24, and four hours, in concentrations ranging from 10.0 to .001 $\mu\text{g}/\text{ml}$, before harvesting the cells, reserving untreated cells as controls.

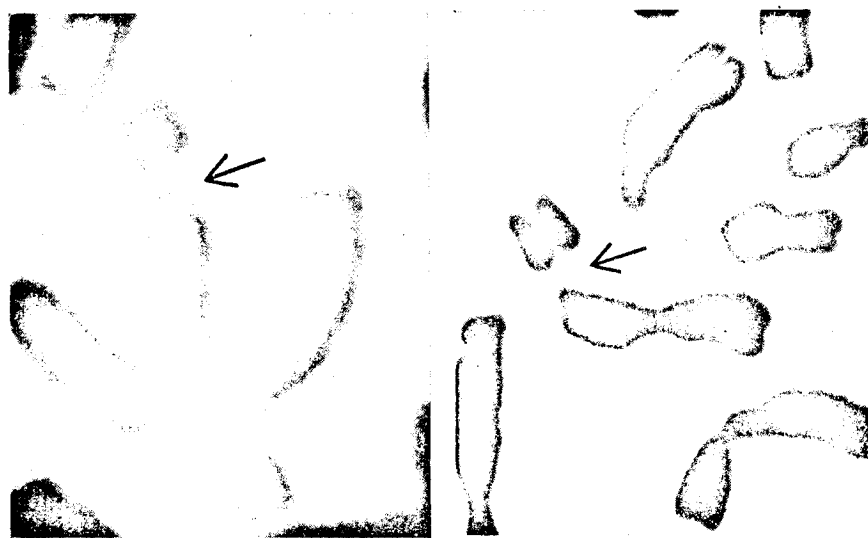
The results clearly showed that LSD significantly inhibited mitosis, regardless of the concentration used. However, the longer the exposure at any given concentration, the greater was the suppression of mitosis.

In the control cultures the spontaneous chromosome breakage rate was 3.9%. In sharp contrast, the lowest frequency of breakage among the treated cells was 7.7%—nearly twice the normal rate—and the highest rate was 17.5%, or more than four times the control level.

Perhaps even more significant, however, from the standpoint of mutagenic, teratogenic, or carcinogenic potential is the fact that only the LSD-treated chromosomes showed such radical chromosomal changes as dicentric chromosomes and exchange figures. Moreover, the LSD-treated



Among chromosomal abnormalities seen in leukocyte cultures treated with LSD were chromatid breaks (arrows), which occurred two to four times more often than in controls.



Isochromatid breaks (arrows) are essentially the same except that both chromatids rather than one are broken at the same level and the distal portions displaced.

cells also showed a large number of small acentric fragments. These breaks, occurring in two chromosomes of the same cell, may be precursors of dicentric chromosomes which are formed in the healing process. Such end-to-end figures are commonly seen early in cultures infected with SV-40 virus, and they are followed at a later stage by large numbers of dicentric chromosomes.

In one of our *in vivo* studies to assess the chromosome-damaging potential of LSD, we used peripheral leukocyte cultures from 22 persons who had either ingested the drug or had been exposed to it in utero. Controls were 14 persons who had not taken the drug. In every instance, a history of LSD ingestion was associated with an increase in chromosomal damage above the mean level of controls. The range was from 5.3% to 25.1%, with a mean of 13.2%, an increase of more than three times the control mean. However, degree of damage did not appear to be correlated with the number of doses, amount per dose, or the time that had elapsed between the last dose and the taking of blood. Also, other drugs taken during the period that LSD was ingested did not seem to affect the rate of chromosomal damage nor the type of breaks that occurred.

As in the *in vitro* studies, most of the abnormalities in LSD-affected individuals were chromatid and isochromatid breaks. But again, there were radical changes among the LSD-treated group and none in the non-LSD group; the former showed 12 dicentric chromosomes and five exchange figures.

Chromosomes of four children born of mothers who had taken LSD during pregnancy showed that offspring exposed to "standard" doses (300 to 600 µg per dose) of LSD during the third and fourth months of pregnancy showed break levels of 13% and 19%. Children who had been exposed in utero to doses of 50 to 100 µg late in pregnancy, however, showed break rates of only 4% and 7.5%. In one instance, where the mother had used "standard" LSD doses early in pregnancy, the child showed a 13% chromosome breakage rate 2½ years after birth. All the children, however, appeared to be normal and healthy.

In another study we investigated the chromosome breakage rate in nine

children exposed to LSD in utero and in four children whose parents had used LSD before, but not during, pregnancy. Once more, we found significantly higher than normal rates of chromosome breakage, with the children who had been exposed in utero showing the highest rate. The LSD-exposed children also showed various chromosomal structural changes, such as dicentric chromosomes and quadriradials, neither of which were found in the control children.

Obviously, of course, it is one thing

to show that a given drug or agent can cause chromosome breakage and quite another to show that the resultant damage is itself deleterious. In the long run, however, it is likely that the chromosomal damage induced by LSD is harmful. Chromosomal breaks are followed by a number of rearrangements, and chromosomal rearrangements in turn have been associated with mutagenesis, carcinogenesis, and teratogenesis.

The evidence for assessing the longer-range effects of LSD-induced

for control of excessive capillary bleeding

Used Pre- and Postoperatively

- to lessen the need for time-consuming, "mechanical" measures during operative procedures
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- to reduce the risk of unexpected, delayed postoperative capillary bleeding

Effective in T & A Surgery

In a controlled surgical study,¹ PREMARIN Intravenous (conjugated estrogens-equine) lessened the bleeding tendency during T & A surgery.

- The treated group consisted of 240 patients (216 children). One injection of PREMARIN Intravenous was given preoperatively (10 mg. under 5 years; 20 mg. over 5 years). The incidence of postoperative bleeding was 0.83%, both primary (within 24 hours) and secondary (after 24 hours).
- In the control series of 198 patients (174 children), the incidence of primary postoperative bleeding was 6.6%, and for secondary bleeding 1.5%.

Bleeding Arrested in Severe Epistaxis

In his experience with over 1,000 cases of epistaxis, Jacobson² considers that "a hor-

monal imbalance which starts with estrogen deprivation is the stimulus that promotes the bleeding state." To demonstrate the effectiveness of PREMARIN Intravenous, the author³ cites 6 cases of very severe epistaxis where bleeding was arrested within 20 to 35 minutes after a single 20 mg. dose. In 4 of these cases where bleeding recurred, a second injection was administered.

Brief Summary

CAUTION: The control of spontaneous bleeding with PREMARIN Intravenous (conjugated estrogens-equine) when it is largely an emergency measure does not preclude the need for determining the etiology of the bleeding. As is true in all hemorrhage cases, whatever the means of control, suitable diagnostic procedures should be taken to establish the underlying pathology and where possible to institute definitive therapy.

SIDE EFFECTS: Throughout years of clinical use no toxic manifestations or untoward effects have been reported other than rare instances of nausea and vomiting, and flushing when the solution is injected too rapidly. Because of rapid excretion and short term therapy for the control of capillary bleeding, sex-linked tissue is not subject to prolonged stimulation.

ADMINISTRATION: The usual precautionary measures governing intravenous administration should be adhered to. Injection should be made SLOWLY to obviate the occurrence of flushes.

chromosomal damage remains fragmentary. However, one case is on record that suggests that induced chromosomal changes may be injurious. This is the case of a youth in whom a Philadelphia-like chromosome was found when he developed acute myelogenous leukemia. He had used several hallucinogens, including LSD, mescaline, and marijuana (as well as amphetamines) over a period of time.

In this instance, of course, no causal relationship could be established between the acute leukemia and

LSD ingestion, nor between the drug and the chromosomal abnormality. The relationship between the drug and the Philadelphia-like chromosome remains purely speculative. Only further studies — defining both the emergence of the abnormal chromosome and its association with myelogenous leukemia, and particularly the appearance of both in a user of LSD — can clearly elucidate the relationship between drug and disease.

Considerable indirect evidence suggests that the types of chromosomal

damage caused by LSD may be directly harmful to the person affected. For example, similar chromosomal aberrations arise spontaneously in three diseases known to be inherited in an autosomal, recessive pattern: Bloom's syndrome, Fanconi's syndrome, and ataxia telangiectasia. Patients with these syndromes also show a high propensity to leukemia and the growth of neoplasms.

Suggestive also is the fact that a number of conditions, such as mongolism, are accompanied by a chromosomal imbalance. Mongoloid children, for instance, have one extra chromosome; they are also more than ordinarily prone to leukemia. An abnormal number of chromosomes has also been reported in chronic myeloproliferative diseases and leukemia.

Cells from neoplasms themselves often show a variety of chromosomal aberrations, much like those following LSD exposure. It should be reiterated, moreover, that such carcinogenic agents as radiation, benzene, and (in animals) viruses also cause chromosomal changes similar to those caused by LSD. Here again, whether chromosomal damage and malignancy are causally related remains unclear, but the association of one with the other is firmly established.

Thus, one of the obvious potential hazards from exposure to LSD or any other chromosome-breaking agent is a possible future increase in leukemia and other neoplasms in exposed individuals. We have, in fact, suggested that conversion from chronic myelogenous leukemia to acute leukemia may result from chromosomal damage superimposed by the cytotoxic agents used in treating the chronic condition.

Although none of the children exposed to LSD in utero have shown any damage other than chromosomal aberrations, the production of congenital defects appears to be a real possibility. Birth defects attributable to LSD ingestion by the mother have been reported, but this observation must be interpreted cautiously in view of the high frequency of birth defects found in the general population.

The teratogenic potential of LSD has, however, been clearly shown in experimental animals. When the drug is injected into rats, hamsters, or mice early in pregnancy it is associated

Use of PREMARIN Intravenous (conjugated estrogens-equine) does not preclude administration of other therapeutic measures employed separately, such as vitamin K, if the practitioner so elects. IT IS NOT COMPATIBLE WITH PROTEIN HYDROLYSATE, ASCORBIC ACID, OR ANY SOLUTION WITH AN ACID pH.

SUGGESTED DOSAGE REGIMENS: For rapid control of spontaneous capillary bleeding—*Adults:* 20 mg. per injection. *Children:* Intravenously or intramuscularly, 5 mg. to 10 mg. per injection. Intravenous use is preferred since more rapid response can be expected from this mode of administration. The intramuscular route may be employed, however, particularly in small children or the difficult patient.

To control spontaneous capillary bleeding: One injection immediately. A response should be noted within one hour. One dose will often suffice to arrest bleeding. However, should hemostasis not be complete, the dose may be repeated at one hour intervals for as many as three doses.

To reduce capillary bleeding in surgery: In the experience of some clinicians, best results were obtained when PREMARIN Intravenous was administered the evening before operation. In patients admitted for early surgery, administration at least one hour preoperatively is desirable.

If bleeding should occur postoperatively, repeat injections may be employed as indicated.

References: 1. Fox, S. L.: Eye Ear Nose Throat Monthly 39:251 (Mar.) 1960. 2. Jacobson, P.: Laryngoscope 77:89 (Jan.) 1967. 3. Jacobson, P.: Arch. Otolaryng. 59:523 (May) 1954.

I.M. or I.V. Premarin® Intravenous (CONJUGATED ESTROGENS-equine)

I.M. for convenience, especially in small children

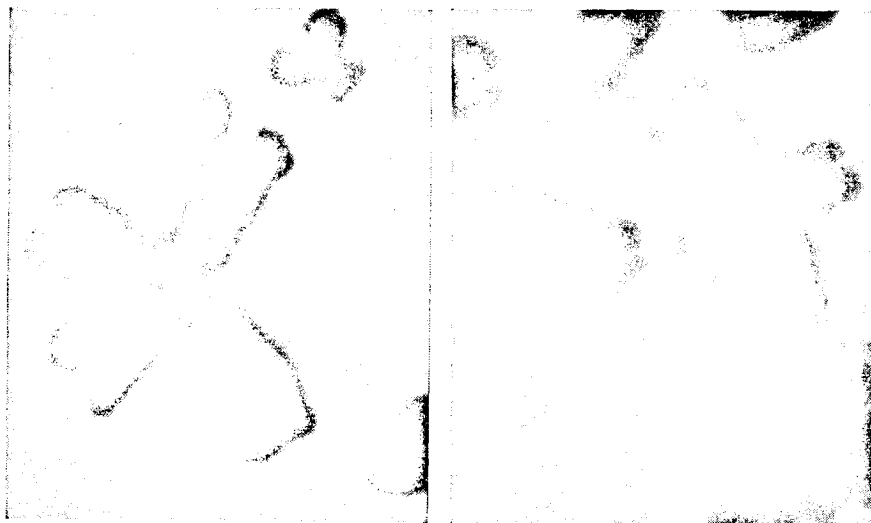
I.V. for rapid response, usually within 30 minutes to one hour after a single injection

COMPATIBILITY...may be used with other therapeutic measures, employed separately—for example, with vitamin K.



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Radical changes like the exchange figures shown above were not seen in control cultures. The findings in both the in vivo and the in vitro studies were identical.

with a wide range of defects in the offspring, including stunted growth in some, severe malformations of the central nervous system and morphologic anomalies in others. These teratogenic effects are most pronounced when the drug is given early in gestation, but they still occur to some extent even when it is given at a later time.

The findings suggest that the drug has a limited, highly specific time period during which it may cause fetal malformation. If this is so, then it may be that many women who have borne normal children even though they took LSD during pregnancy simply did not take the drug at the critical period. Further, if such a critical period does exist for humans and comes very early in gestation, producing severe or gross malformation, the result in most instances may be abortion. The latter, of course, may go unnoticed.

Perhaps the greatest hazard from LSD or any other chromosome-damaging agents arises from potential damage to the gametes. One agent, streptonigrin, has been shown to damage the meiotic chromosomes of the ova of mice. And if chromosomal damage similar to that seen in rodent spermatogenic cells – or in human leukocytes – does occur in human meiotic

cells that give rise to viable gametes, obviously LSD could have a genetic effect. Given the nature of these changes and their mechanism of inheritance, this might of course prove impossible to establish for a number of years. In this connection it may be pointed out that chromosome rearrangements result in structural anomalies including balanced reciprocal translocations. Segregation of such results in chromosomal imbalance associated with fetal wastage and increased incidence of congenital abnormalities and mental retardation. Since the carriers of these balanced translocations are usually clinically normal, the consequences of the chromosomal imbalance may not become apparent for several generations.

There is at least one case suggesting LSD actually does cause balanced translocations of this type. The child involved, born of parents who had taken LSD before the pregnancy, had many of the stigmata of trisomy 13 and died shortly after birth. Cytogenetic analysis showed a modal number of 46 chromosomes, including five members of group D and an extra chromosome resembling chromosome 3. This marker element was taken to be a translocation between two group D chromosomes, with subsequent adjacent segregation during meiosis leading to the trisomic condition. Both parents had karyotypically normal somatic cells, suggesting that the child represented a *de novo* transloca-

tion caused by drug-induced chromosomal breakage in a germ cell.

Whatever may have occurred in this particular instance, it is logical to assume that since it appears in the circulation, LSD has access to the germ cells and presumably may damage them just as it does somatic cells. Actual damage to the germ cells in man could of course be shown only by gonadal biopsy. Barring such studies, as we have indicated it will take some years to measure the total damage to the human population caused by LSD.

Since users of LSD quite often are users of other hallucinogens, the question of whether other drugs may enhance the chromosome-damaging potential of LSD assumes special importance. Unfortunately, we do not have a clear-cut answer. In one study involving children who had been exposed in utero to the hallucinogen Psilocybin as well as to LSD, a higher rate of chromosomal damage was found than in children exposed to LSD alone. Whether Psilocybin potentiated the LSD or vice versa is a matter of speculation; Psilocybin itself has chromosome-damaging potential.

Complicating the picture is the fact that children exposed in utero to marijuana and LSD showed the same rate of chromosomal damage as children exposed to LSD only. Further, some adults who were exposed to both these drugs showed no rise in chromosomal damage at all; it is possible that those covered in this study were among the 25% of LSD users who suffer no chromosomal damage. At the same time, this and other evidence suggests that marijuana as such neither directly damages chromosomes nor potentiates LSD in such action. It should be stressed, however, that no studies with tetrahydrocannabinol, the active principle of marijuana, have been done.

Given what is known of the mechanisms of chromosome breakage, it is reasonable to expect that many agents that are not themselves capable of inducing damage may enhance the ability of others that are. For example, ultraviolet light, which is mutagenic, becomes even more so in bacteria treated with caffeine at levels too low for the caffeine itself to be mutagenic. Quite possibly caffeine and a number of other agents can prevent the normal repair of chromosome breaks that would occur in their absence.

Dr. Hirschhorn is Arthur J. and Nellie Z. Cohen Professor of Genetics and chief of the division of medical genetics, department of pediatrics, the Mount Sinai School of Medicine, New York.

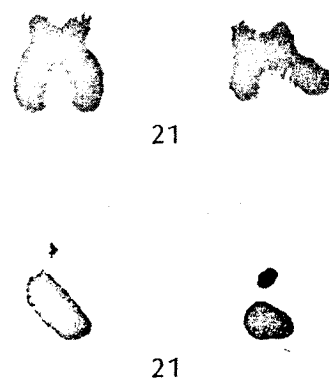
In the final analysis, it may not be the breaks themselves that are of greatest importance but the manner in which they are brought about. Perhaps only through understanding the how and why of chromosome breaks will we come to understand their consequences fully. But we already know that even though some chromosome breaks may appear morphologically alike and be completely nonrandom in distribution, the different agents able to bring about such apparently similar changes act by different mechanisms. We know further that seemingly similar chromosomal aberrations may lead to quite different results, causing carcinogenesis in one instance, teratogenesis in another, mutagenesis in still another.

Several phenomena have been demonstrated to have the capability of damaging chromosomes. They include free radical formation due to ionizing radiation; incorporation of nucleotide analogues into DNA; cross-linking of the DNA molecule by agents such as Mitomycin C; faulty synthesis of protein or precursors needed for repair; and release of lysosomal DNAse and cathepsins by agents that have been incorporated into lysosomes. Thus far the evidence indicates that the chromosome damage caused by LSD probably occurs after the completion of

DNA synthesis and possibly arises directly from metabolic errors or from lysosomal membrane instability. The critical factor in producing long-term effects from chromosome damage appears to be the production of rearrangements (especially exchanges which result in translocations). Simple breaks alone, such as those produced by measles, colds, caffeine, and perhaps even aspirin, disappear within one cell generation, with death of the affected cells, and are probably harmless, except possibly when they occur in the young fetus.

In assessing the chromosome-damaging potential of LSD or of any other agent, the possible effects of other, non-drug, elements in the total environment should not be overlooked. It seems to be a fact that many who use LSD are also likely to suffer from malnutrition, from hepatitis, or from other concomitants of their way of life. These factors may very well affect the chromosome-damaging potential of LSD. But the relative weight of these factors could be established only by rigidly controlled studies — not a likely prospect, given the nature of the problem.

For the present, then, it seems quite obvious that, like radiation and a number of cytotoxic drugs, LSD is potentially dangerous, genetically speak-



Philadelphia chromosome, shown at lower right (normal 21 pair above), has been linked with leukemia; such a chromosome was found in one young LSD user who developed acute myelogenous leukemia.

ing. It is certainly capable of inducing extensive chromosomal changes in man, and it is possible that these in turn may lead to teratogenesis, mutagenesis, or carcinogenesis. It appears almost certain that an undetermined proportion of LSD-induced chromosomal aberrations are detrimental, either to the person immediately involved or to his offspring. These reasons make it all the more important to approach use of LSD, under any circumstances, with extreme caution. □

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Keflin 15-18
Mi-Cebrin T 88, 89

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Valium second cover, 1

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