The Effects of LSD on Chromosomes, Genetic Mutation, Fetal Development and Malignancy

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In the last decade, a serious new dimension has been added to the LSD controversy. A number of scientific papers have been published indicating that LSD might cause structural changes in the chromosomes, genetic mutations, disturbances of embryonic development, and malignant degeneration of cells. However a comparable number of publications question the accuracy of these allegations. Some are independent experimental studies which have yielded negative results, others criticize the original papers for serious conceptual and methodological inadequacies. Despite all the experimental work done in this area, and the vast expenditure of time and energy, the results are ambiguous and contradictory. It seems appropriate to include in this book a critical review of all the relevant research because the issue is extraordinarily important to the future of LSD psychotherapy.

The following discussion is based almost exclusively on careful study of the existing literature. I have limited firsthand research experience in this area, and genetics is not my primary field of interest and expertise. In the LSD study conducted in the Psychiatric Research Institute in Prague we did not examine the effect of LSD on the chromosomes or its implications for heredity; there were at that time no experimental or clinical observations that

would suggest the need for such studies. The first paper that attracted the attention of scientists to this area did not appear until the late 1960's. (22)* After my arrival in the United States, I participated in a major study concentrating on structural changes of the chromosomes in the white blood cells following LSD administration. This was one of the few genetic studies using pure pharmaceutical LSD, a double-blind approach, and comparison of the samples before and after the administration of the drug. (106)

The material discussed in this review will be divided into several thematic groups. The first group includes papers describing structural changes of the chromosomes produced by LSD *in vitro*,** in these experiments various concentrations of LSD are added to cultures of cells from human, animal, or plant tissues in a test-tube. The second group involves *in vivo* studies of LSD; in this type of research the effect of LSD is studied after the substance has been ingested by or injected into animals or humans. The papers in the third group describe the results of experiments studying the influence of LSD on the genes, and its mutagenic effects. It includes a small number of papers dealing with the detailed mechanism of the action of LSD on the deoxyribonucleic acid (DNA), the most important constituent of the chromosomes. The fourth group consists of publications describing the consequences of LSD administration on the growth, development and differentiation of human and animal embryos. Finally, the fifth group comprises papers focusing on the possible link between LSD and the development of malignant changes in cells, especially in the case of leukemia.

In the following sections, the most relevant findings in these five thematic categories will be briefly reviewed and critically evaluated.

THE EFFECT OF LSD ON CHROMOSOMAL STRUCTURE

The possibility of inducing structural changes in the chromosomes by exogenous agents such as radiation, viruses, and a variety of chemicals, has been a subject of great scientific interest for a long time. The genetic controversy about LSD started in 1967 when *Cohen, Marinello and Back* (22) published a paper suggesting that LSD should be added to the list of substances capable of causing abnormalities in the chromosomes. Because of the widespread use of LSD, this information created vivid interest in scientific circles, and a number of investigators focused their attention on this area. Two major approaches were used in these studies; in some the effect of LSD on the chromosomes was studied in the test tube *(in vitro),* in others in the living organism *(in vivo).* The cells studied were in most cases human white blood cells (lymphocytes).

In the *in vitro* studies, the blood samples were drawn from normal, healthy persons with no history of prior drug injection, radiation exposure, or recent viral infection. After incubation at 37° centigrade in appropriate media, colcemide was added to stop the cell division at the stage of metaphase. The cells were then harvested, made into specifically stained cytological preparations and examined with phase contrast microscopy. During the period of incubation,

LSD dissolved in sterile distilled water was added to the experimental cultures in various concentrations.

In the *in vivo* studies, the blood samples were drawn from subjects who had been exposed to either "street acid" (illicit material allegedly containing LSD) or pharmaceutically pure LSD. In most of these studies, the chromosomes were examined after the exposure to LSD (retrospective approach); in a minority of these studies, the checkups were done both before and after the administration of the drug (prospective approach). The technical procedure employed in the *in vivo* studies did not differ significantly from that described for the *in vitro* approach. A special and rather important subgroup of the *in vivo* studies are reports about the influence of LSD on the chromosomes of the germinal cells (meiotic chromosomes).

IN VITRO STUDIES

Cohen, Marinello and Back (22) added LSD to cultured human leucocytes obtained from two healthy individuals. They used five concentrations ranging from 0.001 to 10.0 micrograms of LSD per cubic centimeter (cc), and the time of exposure was 4, 24, and 48 hours. The incidence of chromosome breaks for treated cells was at least twice that of control cells for all treatments, except at the lowest concentration and time (0.001 micrograms of LSD per cc for four hours) where no difference existed between treated and control cells. There was no simple linear relationship between the frequency of these aberrations and the LSD dosage or duration of exposure. In a later study, *Cohen, Hirschhorn and Frosch* (20) described the results of a larger study in which they used peripheral leucocyte cultures from six normal, healthy persons; the concentrations of LSD and the times of exposure were the same as in the original study. They found a significant inhibition of cellular division (mitosis) on addition of the drug in any concentration. The suppression of mitosis was directly proportional to the duration of exposure. The lowest frequency of chromosomal breakage among the controls was 3.9 percent of cells; among the treated cultures, the lowest frequency was almost twice the control (7.7 percent) and ranged to over four times the control value (17.5 percent).

In 1968, *Jarvik et al*. (63) tried to replicate some of the *in vitro* experiments of Cohen's group. In addition to LSD, they used as testing substances ergonovine (a drug commonly used in obstetric practice), aspirin, and streptonigrine. They found a higher incidence of chromosome breaks in the LSD samples (10.2 percent with the range 0.0-15.0) as compared to the control samples (5.2 percent with the range from 0.0-9.0). They found, however, approximately the same breakage rate with aspirin (10.0 percent) and ergonovine (9.6 percent). The concentration of LSD in blood used in this study approximates the level reached one to four hours after injection of 1,000 micrograms of LSD. On the other hand, the level of aspirin used was considerably below the common therapeutic level. Streptonigrine, a substance with a well-known dramatic effect on the chromosomes, induced chromosome breakage in 35 percent of the examined cells. It is interesting to note that two of the eight

cases described in this paper did not respond to LSD with an increase in chromosome breaks.

Corey et al. (24) performed an *in vitro* study in ten individuals; 1 microgram per cc of LSD was added to the culture during the last twenty-four hours of incubation. The authors found an increase in chromosome breaks in all ten subjects. Although the *in vitro* concentration of LSD was much greater than any known comparable ingested dosage, the mean increase of 4.65 breaks per 100 cells was small compared to the range of frequencies (0.0-15.2) observed in the untreated cultures.

In this connection it is interesting to mention that *Singh, Kalia and Jain* (92) found an increased incidence of chromosome breakage in the cells of barley root as a result of exposure to LSD in the concentration 25 micrograms per cc. On the other hand, *MacKenzie and Stone* (73) reported negative results of experiments on lymphocytes, hamster fibroblasts and on the plant *Vicia faba*.

The above-mentioned findings of structural changes in chromosomes following LSD administration became the basis of speculations concerning the possible influence of this drug on genetic mutations, fetal development and malignancy. In the atmosphere of national hysteria then existing, the original report of *Cohen, Marinello and Back* (22) was widely publicized by the mass media. As a result, the significance of their findings was considerably over-emphasized, and many premature conclusions were drawn for which there was not sufficient scientific justification.

Several important facts have to be taken into consideration before we can draw any substantial conclusions from the findings of increased chromosome breakage associated with LSD in the *in vitro* experiments. It must be emphasized that the findings themselves were not completely consistent. In several studies there were no indications of increased chromosome breakage following the exposure to LSD. (27, 73, 105). In addition, the concentrations of LSD and durations of exposure used in these studies were usually much greater than those occurring in the human organism after the ingestion of LSD in the commonly used dosages. *Cohen, Marinello and Back* (22) themselves did not find increased breakage of chromosomes at the lowest concentration and time (0.001 micrograms of LSD per cc for four hours). *Loughman et al.* (70) emphasized that it is precisely the lowest concentration and duration of exposure used in this study that most closely approximates the expected concentration in blood, liver and other organs after a dose of 100 micrograms of LSD ingested by a man weighing 70 kg. If the metabolic degradation of LSD is considered, then the effective concentration *in vivo* of unchanged LSD would be considerably less than this, approximating 0.0001 micrograms per cca concentration used only by *Kato and Jarvik,* (65) who found no increase in breakage at this dosage.

In general, special caution is required in extrapolating the *in vitro* findings to the situation in the living organism. The intact human organism differs from isolated cells in the test tube in its enormous complexity and in its ability to detoxify and excrete noxious compounds.

Substances that are toxic *in vitro* do not necessarily have the same effect *in vivo*. In addition, some of the techniques used in the in vitro studies can create an artificial situation and introduce factors that do not exist in the living organism. This issue has been discussed in detail in an excellent review on LSD and genetic damage by *Dishotsky et al.* (28) These authors point to the fact that all the studies on cultured lymphocytes have used modifications of a technique in which the lymphocytes are stimulated by phytohemagglutinin to enter the reproductive cell cycle. In the normal state *in vivo*, small lymphocytes are in a phase of growth which precedes DNA synthesis; they do not grow, divide or enter the cell cycle. Thus, in the studies *in vitro*, lymphocytes are exposed to chemical agents during developmental stages of the cell cycle, including the synthesis of DNA, which do not normally occur in these cells in the body. Damage to a lymphocyte in this phase generally will not manifest itself as chromatid-type change in a subsequent division. Most, if not all chromatid-type changes are initiated by technical procedures, and the great majority of lesions reported in the *in vitro* and *in vivo* studies were of the chromatid type. The findings of an increased rate of chromosomal breakage in lymphocytes exposed to LSD *in vitro* must therefore be interpreted with great caution.

Many recent studies concerning the structural changes caused in chromosomes by LSD gave the impression that this effect was something specific and unique. Most of these reports have silently bypassed a fact that would have made the issue much less interesting and sensational. The changes in chromosomal structure described are not exclusively caused by LSD; they can be induced by a variety of other conditions and substances. Factors that have been known to cause chromosomal breakage *in vitro* include radiation, changes in temperature, variations in oxygen pressure, impurities in tap water unless it is distilled twice, and a variety of common viruses. The long list of chemical substances that increase the chromosomal breakage rates contains many commonly used drugs, including aspirin and other salicylates, artificial sweeteners, the insecticide DDT, morphine, caffeine, theobromine, theophylline, tranquilizers of the phenothiazine type, some vitamins and hormones, and many antibiotics such as aureomycin, chloromycetin, terramycin, streptomycin and penicillin.

In this connection it is interesting to quote *Sharma and Sharma,* (91) who have written an extensive summary of the literature on chemically induced chromosome breaks: "Since the first induction of chromosomal mutations by chemicals and the demonstration of definite chromosome breakage by Oehlkers, such a vast multitude of chemicals have been shown to possess chromosome breaking properties that the problem has become increasingly complex." *Jarvik,* (61) discussing the paper by *Judd, Brandkamp and McGlothlin*, (64) was even more explicit: "... and it is likely that any compound added at the appropriate time, in the appropriate amount, to the appropriate cell type, will cause chromosome breaks."

IN VIVO STUDIES

Because of the limitations of the *in vitro* approach, *in vivo* studies are preferred for

assessing the possible genetic dangers associated with administration of LSD. Unfortunately, of the twenty-one reports that have been published by seventeen laboratories many have serious methodological shortcomings and are more or less inadequate, while individual reports contradict each other and their overall results are inconclusive. Two major approaches have been used in the *in vivo* studies. In fourteen of these projects, subjects were exposed to illicit substances of unknown composition and potency, some of which were alleged to be LSD. In eleven studies, individuals were exposed to known quantities of pharmaceutically pure LSD in experimental or therapeutic settings.

Dishotsky et al. (28) published a review in which they presented a synopsis of the studies of this kind conducted prior to 1971. According to this review, of a total of 310 subjects studied, only 126 were treated with pure LSD; the other 184 subjects were exposed to illicit or "alleged" LSD. Eighteen of the 126 subjects (14.29 percent) in the group given pure LSD showed a higher frequency of chromosome aberration than the controls. In contrast, 89 of the 184 subjects (48.9 percent) in the group taking illicit LSD showed an increased incidence of aberrationsmore than three times the frequence reported for subjects given pharmacologically pure LSD. Only 16.67 percent (18 of 108) of all the subjects reported to have chromosome damage, were given pure LSD. There is, therefore, good reason to discuss the two categories of *in vivo* studies, those with pure and those with "alleged" LSD, separately.

Illicit LSD and Chromosomal Damage

The initial findings of chromosomal damage in illicit LSD users were reported by *Irwin and Egozcue*. (57) They compared a group of eight illicit LSD users with a group of nine controls. The users had a mean breakage rate of 23.4 percent, more than double the 11.0 percent rate in the controls. Only two of the eight users did not have increased breakage rates. In a later and more extensive study carried out by *Egozcue, Irwin and Maruffo,* (33) the mean breakage rate in forty-six illicit LSD users was 18.76 percent (with a range between 8 and 45 percent); this was more than double the rate of 9.03 percent found in control cells. Only three of the forty-six users did not have a breakage rate higher than the mean control rate In addition, the authors studied the chromosomes of four infants exposed to LSD *in utero*. All four showed breakage rates above the mean control value. There was no evidence of disease or physical malformation in any of these children.

These findings were supported by *Cohen, Hirschhorn and Frosch*, (20) who studied eighteen subjects exposed to illicit LSD. They described an increased chromosomal breakage in this group (mean 13.2 percent) which was more than triple that of the control group (3.8 percent). The authors also examined the chromosomes of four children born to three mothers who took LSD during pregnancy. The frequency of chromosome breaks was elevated in all four, and was greater in the two children who were exposed to LSD during the third and fourth months of pregnancy than in the two infants exposed to low doses of LSD late in pregnancy.

In a later paper, *Cohen et al*. (21) reported that thirteen adults exposed to illicit LSD showed chromosome breakage rates that were above the control mean. In nine children exposed to illicit LSD *in utero*, they found a mean breakage of 9.2 percent, as compared with 4.0 percent in four children whose mothers had used illicit LSD before but not during pregnancy. The breakage rate in the control group was 1.0 percent. All but two children had been exposed to other drugs during pregnancy; all were in good health and showed no birth defects.

Nielsen, Friedrich and Tsuboi (82) found that their ten subjects exposed to illicit LSD had a mean breakage rate of 2.5 percent; this was significantly higher than that of the control group (0.2 percent). However, the allegedly pathological 2.5 percent rate is lower than that of the controls in other positive studies.

A number of investigators have not been able to demonstrate increased chromosome breakage in LSD users. The synoptic paper by *Dishotsky et al*. (28), quotes nine groups of researchers who reported negative results of similar studies. At the present time, therefore, the results of the in vivo studies are considered rather controversial and at best inconclusive.

Many investigators have attempted to offer explanations for the existing discrepancies between positive and negative reports. Some have criticized the breakage rate for controls in the studies by *Cohen et al.* (21) (3.8 percent) and *Irwin and Egozcue* (57) (11.9 percent and 9.03 percent) as being unusually high. Others have suggested that the high control values could have resulted from viral contamination of the cultures, insufficiently fortified media interfering with chromosome repair, technical variation in cell culturing, and the approach to chromosome evaluation. It was also pointed out that in these studies, chromosome-type and chromatid-type changes were not reported separately but were combined and then converted to "equivalent numbers of breaks." Combining the two types of aberrations in a single index obscures the distinction between real chromosome damage occurring in vivo and damage arising in the course of cell culture.

However, these factors cannot account for the discrepancies between the findings of various teams of investigators. If they did, the aberrations resulting from these effects would be randomly distributed between groups exposed to illicit LSD and control groups. Since the distribution is uneven, these factors do not explain the significantly elevated breakage rates in eighty of the eighty-six subjects exposed to illicit LSD studied by Cohen et al. and by Irwin and Egozcue.

A much more important clue to the understanding of this controversy seems to be related to certain characteristics of the group of the "LSD users." In this type of research, the investigators depend on the recall and reliability of the subjects in determining the type of drugs they have used in the past, the number and frequency of exposures, the alleged dosages, and interval since last exposure. Even in cases where the reports are accurate, the subjects usually do not know the content and the quality of the samples they are using. The

content of pure LSD in the illicit LSD samples is almost always questionable, and various impurities and admixtures rather frequent. The samples analyzed in the past have been demonstrated to contain amphetamines, mescaline, DOM (4-methyl-2, 5-dimethoxyamphetamine, also called STP), phencyclidine (phenylcyclohexylpiperidine, PCP or "angel dust"), benactyzine and even strychnine. In addition, all the subjects tested used or abused drugs other than street LSD. These drugs included, among others, Ritaline, phenothiazines, alcohol, amphetamines, cocaine, barbiturates, heroin and other opiates, and various psychedelic substances such as marihuana, hashish, psilocybin, mescaline, STP, methylenedioxyamphetamine (MDA), and dimethyltryptamine (DMT). Under the circumstances, one questions the logic of referring to this group in scientific papers as "LSD users." Most of these subjects were actually multiple-drug users or abusers exposed to a variety of chemicals of unknown composition, quality and potency.

In addition, it has been repeatedly reported that this population suffered from malnutrition and had very high rates of venereal disease, hepatitis and various other viral infections. It was mentioned above that viruses are one of the most common factors causing chromosomal damage; the possible role of malnutrition remains to be evaluated. *Dishotsky et al.* (28) conclude their review of the *in vivo* studies involving illicit LSD by relating the findings of increased chromosome breakage to a combination of factors such as long-term excessive exposure to illicit chemical agents, the presence of toxic contaminants, the intravenous route of administration, and the physical debility of many drug abusers. According to them, positive results, when found, are related to the more general effects of drug abuse and not, as initially reported, specifically to the use of LSD.

Pure LSD and Chromosomal Damage

Chromosomal studies of persons who received pharmaceutically pure LSD in an experimental or therapeutic framework are much more relevant and reliable as a source of information than the studies of illicit drug users. In these studies, there is no uncertainty concerning purity, dosage, frequency of exposure and the interval between the latest exposure and blood sampling. Two different approaches can be distinguished in the chromosome studies using pure LSD. The studies of the first type are *retrospective* and use a "post hoc" design; they examine the chromosomal changes in subjects who were exposed to pure LSD in the past. The studies of the second type are *prospective*; the chromosomal patterns are examined both before and after the exposure to LSD, and each subject serves as his own control.

Retrospective Studies of Chromosomal Changes in Pure LSD Users. A review of the studies in this category reveals that only two groups of investigators have reported an increased rate of chromosome breakage in their subjects. Five other teams failed to confirm these positive findings.

Cohen, Marinello and Back (22) reported in their initial study that they found

chromosomal damage in the white blood cells of one paranoid schizophrenic patient who had been treated fifteen times in the past with LSD in dosages between 80 and 200 micrograms. *Nielsen, Friedrich and Tsuboi* (80) examined the chromosomes of five persons treated with LSD and found "no correlation between any specific drug and the frequency of gaps, breaks, and hyperdiploid cells." The authors later regrouped their data, forming smaller groups on the basis of age and sex. (81) After this revision of the original material, they concluded that LSD induced chromosomal damage. *Tjio, Pahnke and Kurland* (106) criticized this study on the basis of the insufficient number of cells analyzed for a reliable determination of breakage rates. Three of the five LSD subjects studied had no chromosomal aberrations, and the two remaining subjects accounted for all six breaks found. In addition, the 1.7 percent breakage rate is still within the values reported for the general population. Another study by *Nielsen, Friedrich and Tsuboi* (82) which reported an increased breakage rate of 4.3 percent in a group of nine former LSD users has been criticized by *Dishotsky et al.* (28) on the basis of its unusual approach to data analysis.

Sparkes, Melnyk and Bozzetti (99) did not find an increase in chromosomal breakage in four patients treated with LSD in the past for medical reasons Negative results were also reported by *Bender and Siva Sankar*, (11) who examined the chromosomes of seven schizophrenic children who had been treated in the past by prolonged administration of LSD. These children received LSD daily in two divided dosages of 100 to 150 micrograms for a period of weeks or months. The frequency of chromosome breakage in this group was less than 2 percent and did not differ from that of the control group.

Siva Sankar, Rozsa and Geisler (93) studied the chromosome patterns in fifteen children with psychiatric problems who had been given LSD, UML or a combination of both. LSD was administered daily; the average dose for the whole group was 142.4 micrograms per day per patient, and the duration of therapy varied from 2 to 1,366 days. The breakage rate for the group treated with LSD was 0.8 percent, for the group treated with both LSD and UML 1.00 percent. This was not significantly higher than the rate of breakage in the controls. The patients in this study received LSD two to four years prior to the chromosome studies. The authors admitted that the effects of LSD on the leucocyte chromosomes might have been rectified over such a long period of time. In any case, this would indicate that LSD therapy has no long-lasting effects on the chromosomes.

Tjio, Pahnke and Kurland (106) published the results of chromosome analysis of a group of eight "normal" subjects who had received pure LSD in research experiments one to twenty-six times, two to fifteen months prior to giving the blood sample. The mean total chromosomal aberration rate for this group was 2.8 percent, and the individual rate in none of them exceeded the pre-LSD mean of 4.3 percent found in the patient sample.

Corey et al. (24) reported the result of a retrospective chromosomal study of sixteen patients, five of whom had been treated with LSD only, five with mescaline only, and six with

LSD plus mescaline. In the eleven individuals who were clinically treated with LSD dosages ranging from 200 micrograms to 4,350 micrograms, frequency of chromosome breaks did not differ from that found in the thirteen controls. The respective frequencies were 7.8 percent for LSD, 5.6 percent for mescaline, 6.4 percent for LSD plus mescaline, and 7.0 percent for the control group.

In an unpublished study, *Dishotsky et al.* examined the chromosomes of five subjects exposed in the past to pure LSD. The mean breakage rate in this group (0.40 percent) was not significantly different from that of the eight control persons (0.63 percent). In their review paper, *Dishotsky et al.* (28) indicate that fifty-eight of seventy (82.9 percent) of the subjects studied after treatment with pure LSD did not have chromosome damage. Because of incomplete data on nine of the remaining twelve subjects, they were not able to compute the precise percentage of subjects with elevated breakage rates. However, they estimated that this figure would range between 17.1 percent and 4.9 percent. All but one of the twelve subjects were reported by a single team of investigators. The authors concluded that in view of the procedures, incomplete data, questionable re-analysis of the data, and low breakage rates reported, there is no definite evidence from this type of experiment that pure LSD causes chromosome damage.

Prospective Studies of Chromosomal Changes in Pure LSD Users. The studies comparing the chromosomal changes before and after exposure to pure LSD represent the most adequate scientific approach to the problem from the methodological point of view, and are the most reliable source of scientific information. The first report in this category was published in 1968 by *Hungerford et al.* (55) who examined the chromosomes of three psychiatric patients before and after repeated therapeutic administrations of LSD. Blood samples were taken from all patients before any LSD therapy, one hour before and one and fourteen hours after each dose; follow-up samples were taken at intervals of one to six months. An increase in chromosome aberrations was observed after each of three intravenous injections of LSD. The increase was small in two of the three subjects; however, dicentric and multiradial figures appeared only after treatment, and acentric fragments appeared more frequently after treatment. In the follow-up study, a return to earlier levels was observed in all three patients. The data from this study indicated that pure LSD may produce transitory increases of chromosome abnormalities, but that these are no longer evident one month after administration of the final dose. The results were slightly complicated by the administration of chlorpromazine (Thorazine), which in itself can produce chromosomal aberrations. It is interesting to note that Hungerford's study is the only one in which LSD was administered intravenously.

Tjio, Pahnke and Kurland (106) reported the results of a study of thirty-two hospitalized alcoholic or neurotic patients treated with LSD in the framework of a double-blind controlled study at the Maryland Psychiatric Research Center. The dosage of LSD was 50 micrograms

in eleven patients and 250-450 micrograms in twenty-one patients. The number of cells observed in this study (22,500) was more than twice the total number of cells observed in all other studies of pure LSD users. The amount of breakage was not directly proportional to the dosage; actually those in the low-dose range showed greater increases than those on high dosage. The authors also examined a group of five persons who had taken illicit LSD from four to thirty-six times before the study. In these subjects, blood samples were drawn for seven to ten consecutive days before, during and after treatment with pure LSD either two or three times. Statistical analysis revealed no significant difference in the chromosomal aberration before and after LSD. In another prospective study, *Corey et al.* (24) examined the chromosomes of ten persons before and after the administration of 200-600 micrograms of pure LSD. The authors found no significant difference in the rate of chromosome breakage between the pre- and post-samples and confirmed the negative findings of the previous study.

It is interesting to mention in this connection two prospective studies of LSD-related chromosomal damage which were conducted in Rhesus monkeys *(Macaca mulatta);* the results of both studies were rather inconclusive. *Egozcue and Irwin* (32) administered high dosages of LSD (40 micrograms per kg.) four times at ten day intervals. Two of their animals showed increased chromosomal breaks, whereas the other two stayed within normal values. *Kato et al.* (66) described transitory changes in chromosomes after multiple, subcutaneous injections of LSD in high doses (125-1000 micrograms per kg. per injection) in Rhesus monkeys. The authors have not provided a statistical evaluation of the results; *Dishotsky et al.,* (28) who later analyzed their data, found them statistically nonsignificant.

Dishotsky et al. (28) also offered a synoptic evaluation of the prospective LSD studies. According to them, only six of the fifty-six patients (10.7 percent) studied before and after treatment with pure LSD had elevated breakage rates; of these, three received LSD intravenously and one had a viral infection. Of these six subjects, one individual was not available for follow-up determinations; in the remaining five, breakage returned to that observed before treatment. From the total number of subjects studied before and after treatment, 89.3 percent did not have chromosome damage. The results of the prospective LSD studies are thus in agreement with the negative conclusion of five of the seven teams that studied subjects only after LSD treatment.

Chromosomal Changes in Germinal Cells

In the past, the positive findings of some chromosomal studies have been used as a basis for far-reaching speculations concerning the hereditary dangers associated with LSD. Journalists, and also several scientific workers, described their rather apocalyptic visions of the offspring of LSD users. Such speculations were rather premature, and insufficiently substantiated by experimental data. The reasoning that refers to structural abnormalities of the chromosomes as "damage" and relates them automatically to genetic hazards has serious gaps in its logic. In reality, it is not quite clear whether or not the structural changes in the

chromosomes of the white blood cells have any functional significance, and whether they are associated with genetic abnormalities. There exist many chemical substances that cause chromosomal breaks but have no adverse effects on genetic mutation or fetal development. The complexity of this problem can be illustrated by the case of viruses. A variety of virus diseases (such as herpes simplex and shingles, measles, chicken pox, influenza, yellow fever, and possibly mumps) induce marked chromosomal damage without causing fetal malformations. According to *Nichols*, (79) one of the exceptions is rubella (German measles), a disease that is notorious for causing severe fetal malformations when acquired by the mother in the first trimester of pregnancy.

In addition to the methodological problems involved and the inconsistency of the findings discussed above, one more important fact has to be taken into consideration. In all the studies quoted, the effect of illicit or pure LSD, *in vitro* or *in vivo*, was assessed in the chromosomes of the white blood cells. No direct conclusions about the hereditary dangers associated with the administration of LSD can be drawn on the basis of these studies since the lymphocytes are not involved in the reproductive processes. Speculations about such dangers could be made only on the basis of chromosomal findings in germ cells such as the spermatozoids and ova, or their precursor cells. Unfortunately, the few existing studies of the chromosomes of germinal cells (the so-called meiotic chromosomes) yielded as inconclusive results as the studies of the chromosomes of somatic cells.

Skakkebaek, Phillip and Rafaelsen (95) studied meiotic chromosomes from six healthy male mice injected with large dosages of LSD (1,000 micrograms per kg); the number of injections and intervals between exposures varied. Several chromosomal breaks, gaps and unidentifiable fragments were found in the treated animals but, with a few exceptions, not in the control animals. The authors consider their finding tentative evidence that high doses of LSD may influence meiotic chromosomes in mice. They admitted that the number of abnormalities was small and technical errors could not be excluded, but concluded that the changes found could have influence on fertility, size of the litter, and the number of congenital malformations. In a later study, *Skakkebaek and Beatty* (94) injected four mice subcutaneously with dosages of 1,000 micrograms per kg of LSD twice a week for five weeks. Analysis carried out on a blind basis showed a high frequency of abnormalities in two of the treated mice. In addition, the spermatozoa of LSD-treated mice also showed morphological differences, with a more rounded convex side of the head and broader heads in general. The practical significance of these findings is considerably reduced by the fact that the dosages used far exceed anything used in clinical practice. A comparable dose in humans would come to 60,000-100,000 micrograms per person, which is 100 to 1,000 times more than the dosages commonly used in experimental and clinical work with LSD.

Another positive finding of meiotic chromosome damage induced by LSD was reported by *Cohen and Mukherjee.* (23) These authors injected thirteen male mice with a single dose of

LSD at a concentration of 25 micrograms per kg. In this study the meiotic cells were apparently less vulnerable than somatic cells. However, there was an obvious tenfold increase in chromosome damage among the mice treated with LSD. This reached a maximum between two and seven days after injection, with a subsequent decrease and return to almost normal levels after three weeks. On the basis of evidence from clinical human cytogenetic studies, the authors concluded that chromosome anomalies of this type may lead to reduced fertility, congenital abnormalities and fetal wastage.

The other existing studies of the effect of LSD on meiotic cells brought essentially negative results. *Egozcue and Irwin* (32) studied the effects of LSD administration in mice and Rhesus monkeys. The mice in this study received 5 micrograms per kg of LSD daily in a number of injections increasing from one to ten. Four adult male Rhesus macaques ingested doses of either 5, 10, 20 or 40 micrograms per kg of LSD. Six months after their single dose of LSD, three of the monkeys received four doses each, at ten-day intervals, of 40 micrograms per kg of LSD per dose. The authors reported essentially negative results in both the mice and the monkeys. In mice, occasional chromosomal breaks and fragments were observed in similar proportions in the control and the experimental groups. In the Rhesus monkeys, no significant differences were found before or after acute or chronic treatment.

Jagiello and Polani (60) published the results of a detailed and sophisticated study of the effect of LSD on mouse germ cells. They performed acute and chronic experiments on both male and female mice. The dosage of LSD in the chronic experiments ranged between 0.5-5.0 micrograms; in the acute experiments a single subcutaneous dose of 1,000 micrograms per kg of LSD was administered. The results of this study were essentially negative. The authors attributed the discrepancies with other studies to mode of administration, dosage and the animal strain involved.

In two of the existing studies, the effects of LSD on the meiotic chromosomes were tested in the banana fly, *Drosophila melanogaster*, an organism that has played an important role in the history of genetics. In one of these studies, *Grace, Carlson and Goodman* (44) injected male flies in concentrations of 1, 100 and 500 micrograms per cc. The dosage used is equivalent to approximately one liter of the same solution in humans (1,000, 100,000 and 500,000 micrograms respectively). No chromosomal breaks were observed in premeiotic, meiotic or postmeiotic sperm. The authors concluded that LSD is in a class quite distinct from that of ionizing radiation and mustard gas. If it is a mutagenic or radiomimetic agent in human chromosomes, it is not a very powerful one. In another study, *Markowitz, Brosseau and Markowitz* (74) fed LSD to male fruit flies in a 1 percent sucrose solution for twenty-four hours; the concentrations used were 100, 5,000, and 10,000 micrograms per cc. In these experiments, LSD had no detectable effect on chromosome breakage. The authors concluded that LSD is a relatively ineffective chromosome breaking agent in *Drosophila*.

Considerable caution is required in extrapolating the data about the effect of LSD on

meiotic chromosomes obtained from animal experiments to humans, because of rather wide interspecies variability. The only report about the effect of LSD on human germ cells was published by *Hulten et al.* (54) These authors examined the testicular biopsy in a patient who had used massive doses of illicit LSD in the past, up to an alleged 1,000 micrograms. For a period of four weeks he practiced the administration of these dosages daily. There was no evidence of an increased frequency of structural chromosome aberrations in the germinal tissue of the testicles.

Concluding this discussion of the effects of LSD on chromosomal structure, we can say that the results of the existing studies are inconclusive despite the fact that the dosages used in many experiments far exceed the doses used in clinical practice. Whether LSD causes structural changes in the chromosomes or not remains an open question. If it does, the circumstances and dosage range in which these occur have not been established, and the interpretation of these changes and their functional significance is even more problematic. This question could not be answered even on the basis of results of methodologically perfect chromosomal studies. In future research, much more emphasis should be put on the study of the effect of LSD on genetic mutation and embryonal development.

MUTAGENIC EFFECTS OF LSD

In the past, the classic experimental animal for the study of genetic mutations has been the banana fly, *Drosophila melanogaster*. Several studies exist in which the effect of LSD on genetic mutation has been observed in this fly. *Grace, Carlson and Goodman* (44) studied the mutagenic effects of intra-abdominal injections of LSD in concentrations ranging from 1 to 500 micrograms per cc. They have not found an increase in induced mutations in the LSD-treated group. On the basis of these negative findings, the authors consider it improbable that LSD induces mutation in humans. *Markowitz, Brosseau and Markowitz* (74) fed LSD to male flies in concentrations of 100, 5,000 and 10,000 micrograms per cc. In this experiment, LSD produced a significant increase in the frequency of sex-linked recessive lethal mutations. The authors concluded that LSD at high concentrations is a weak mutagen in *Drosophila*.

In several studies performed in Drosophila flies, lower concentrations of LSD had no mutagenic effects, but an increased frequency of induced mutations was observed after excessive dosages. *Vann* (111) reported that dosages of 24,000 micrograms per kg produced no significant increase in the frequency of recessive lethals, whereas a dosage of 470,000 micrograms per kg did. *Browning* (15) administered intraperitoneal injections of 0.3 microliters of a solution containing 10,000 micrograms per cc of LSD; this dosage corresponds to about 4,000,000 micrograms per kg of body weight. Out of seventy-five flies, only fifteen survived this procedure, and ten were fertile. Under these circumstances, a significant increase in recessive lethal mutations in the X-chromosome of male flies was observed by the author. A 1:1 dilution of the original solution, when injected into one

hundred males, resulted in thirty-five survivors of which thirty were fertile; the frequency of mutations markedly dropped. *Sram* (101) concluded on the basis of his experiments with LSD in the Drosophila fly that LSD is a weak mutagen producing gene and chromosome mutations only when used in very high concentrations; this finding is in basic agreement with the existing literature on the mutagenic effects of LSD.

The effects of LSD were also tested on another standard genetic system, namely the fungus *Ophistoma multiannulatum*. *Zetterberg* (118) exposed the cells of this fungus to 20-50 micrograms per cc of LSD; he did not find any difference between treated and control cells. The data on Drosophila flies and fungi suggest that LSD is a weak mutagenic agent that is effective only in doses far exceeding those commonly used by human subjects.

There are several interesting studies focusing on the interaction of LSD with deoxyribonucleic acid (DNA) and ribonucleic acid (RNA); these studies could contribute to our understanding of the mechanism of interaction between LSD and the chromosomes or genes. *Yielding and Sterglanz* (115), using spectrophotometric methods, were able to demonstrate binding of LSD, its inactive optical isomer, and its inactive brominated analogue by helical DNA of the calf thymus. Binding did not take place with yeast RNA or nonhelical DNA, suggesting that this binding is specific for helical DNA.

Wagner (112) concluded on the basis of his experiments that LSD interacts directly with purified calf thymus DNA, probably by intercalation, causing conformational changes in the DNA. According to him, it is unlikely that this could influence the internal stability of the DNA helix enough to cause chromosomal breakage. However, it may lead to the dissociation of histones, which could render DNA susceptible to enzymatic attack. *Smythies and Antun* (98) performed similar experiments and arrived at the conclusion that LSD binds to nucleic acids by intercalation. According to *Dishotsky et al.,* (28) this evidence of LSD intercalation into the DNA helix provides a clue to the physical mechanism involved in the mutagenic effects of high doses of LSD in Drosophila and the fungus, as reviewed above.

Nosal (83) investigated the effects of LSD on the Purkinje cells of the cerebellum of growing rats. These studies were specifically focused on the action of the ribonucleoproteins (RNP) of the differentiating nucleus-ribosome system. Only large doses of LSD (100-500 micrograms per kg) seemed to induce changes in the structure and staining properties of this cellular system.

Obviously, much more research is needed for the final clarification of the interesting interaction between LSD and various chemical substances involved in the genetic mechanisms.

TERATOGENIC EFFECTS OF LSD

It has been frequently hypothesized in the past that LSD may be a potential cause of abortions, fetal wastage and congenital malformations. The actual experimental studies of the

effect of LSD on embryonic development have been made primarily in rodents. Since free transplacental transfer of LSD has been demonstrated in an autoradiographic study performed by *Idanpään-Heikkilä and Schoolar*, (56) it is conceivable that it might influence the developing fetus. In this study, the injected LSD rapidly passed the placental barrier into the fetus; however, according to the authors, the relatively high affinity of LSD for the maternal organs seemed to diminish the amount of the drug available for transfer into the fetus itself.

The experimental data from mice, rats and hamsters have been rather controversial. *Auerbach and Rugowski* (10) reported a high rate of embryonal malformations in mice following relatively low doses of LSD administered early in pregnancy. In all cases the induced malformations involved characteristic brain defects. Abnormalities of the lower jaw, shifts in the position of the eyes, and modifications of the facial contour were frequently associated with these defects. There was no observable effect on the embryonic development if the LSD exposure occurred later than the seventh day of gestation. These findings were partially supported by *Hanaway* (47) who experimented with LSD in mice of a different strain. Using comparable dosages, he described a high incidence of lens abnormalities; however, he was unable to discover any malformation of the central nervous system, even on histological examination. *DiPaolo, Givelber and Erwin* (27) administered LSD to pregnant mice and hamsters. The total amount of LSD injected in mice ranged from 0.5 micrograms to 30 micrograms per pregnant animal; Syrian hamsters were injected with a single dose ranging between 10 and 300 micrograms. The authors concluded that their investigation failed to demonstrate that LSD is teratogenic for mice and Syrian hamsters. They interpreted the increased frequency of malformed embryos in some of the experiments as an indication of a potentiating effect of LSD on individual threshold differences. It is necessary to emphasize that the doses used in this study were 25 to 1,000 times the human dosage. *Alexander et al.* (4) administered 5 micrograms per kg of LSD to pregnant rats. They described a significantly increased frequency of stillbirth and stunting in two of their experiments where LSD was administered early in pregnancy. In the third experiment, where the animals received similar single injections of LSD late in pregnancy, there was no obvious effect on the offspring. *Geber* (42) reported a study in pregnant hamsters in which he administered LSD, mescaline and a brominated derivative of LSD. He described a markedly increased frequency of runts, dead fetuses and reabsorbed fetuses in the experimental groups. In addition, he observed a variety of malformations of the central nervous system such as exencephaly, spina bifida, interparietal meningocele, omphalocele, hydrocephalus, myelocele and hemorrhages of local brain areas, as well as edema along the spinal axis and in various other body regions. The dosages of LSD used in this experiment ranged between 0.8 micrograms per kg and 240 micrograms per kg. However, there was no correlation between the dose and the percentage of congenital malformation. LSD and mescaline produced similar malformations; mescaline appeared to be a less potent teratogen, as judged by the dose.

There exist a number of studies in which negative results were reported in all the species mentioned. *Roux, Dupois and Aubry* (88) administered LSD in dosages from 5-500 micrograms per kg per day to mice, rats and hamsters. There was no increase in fetal mortality or decrease in the mean weight of the fetuses for any group of experimental animals. There was no significant increase in the incidence of external malformations, and sections performed in approximately 40 percent of the experimental animals showed no visceral malformations. The authors concluded, on the basis of the results, that in the three species studied, no abortificient, teratogenic or embryonic growth-depressing factors were observed, even after enormous doses.

At least four studies of the teratogenic effect of LSD carried out on rats brought negative results. *Warkany and Takacz* (113) found no abnormalities in their experimental Wistar rats, despite the fact that they used large doses of LSD (up to eighty times those given by Alexander et al.). (4) The only finding was a reduction in size in one of the young. *Nosal* (83) administered LSD to pregnant rats in dosages of 5, 25, and 50 micrograms per kg on the fourth and seventh days of gestation. He did not observe any external malformations of the head, vertebral column and extremities, or macroscopic lesions of the central nervous system and viscera. There were no differences from the controls as to mortality and fetal resorption or reduced number and size of the offspring, even with higher dosages. Negative results were also obtained in two studies performed and published by *Uyeno*. (109, 110)

Fabro and Sieber (35) studied the effect of LSD and thalidomide on the fetal development of white rabbits. Thalidomide had a marked embryotoxic effect and produced an increased incidence of resorptions, decreased the mean fetal weight, and induced malformations of fetuses. Pregnant rabbits given LSD in a dosage of 20 or 100 micrograms per kg of body weight produced litters which were not significantly different from the controls. Decrease of the mean fetal weight at twenty-eight days was the only effect which could be detected in the litters of does treated with daily doses as high as 100 micrograms per kg.

As emphasized by *Dishotsky et al.,* (28) an overall view of the rodent studies indicates a wide range of individual, strain, and species susceptibility to the effects of LSD. The effect, when found, occurs at a highly specific time early in gestation; no effect was reported with exposures occurring late in pregnancy. Extreme caution is required in extrapolating results from the rodent studies to the human situation, since fetal development and growth in these species is markedly different. Rodents lack the chorionic villi in the placenta, so that the fetal blood is separated from the maternal sinuses only by endothelial walls. This makes the rodents much more sensitive than humans to the teratogenic potential of any given substance.

In the only existing experimental study in primates, *Kato et al.* (66) administered multiple subcutaneous injections of LSD to pregnant Rhesus monkeys. Of four animals treated, one delivered a normal infant, two were stillborn with facial deformities and one died at one month. The two control animals delivered normal offspring. The dosage used in this study

was more than 100 times the usual experimental dose for humans. The authors themselves concluded that the small size of their sample made it impossible to draw any definite conclusion.

The information about the influence of LSD on the development of human embryos is scanty and exists only in the form of clinical observations. For obvious reasons, this problem cannot be approached in an experimental manner in humans. There are six reported cases of malformed infants born to women who ingested illicit LSD prior to or during pregnancy. *Abbo, Norris and Zellweger* (2) described a child born with a congenital limb anomaly. Both parents of the child had taken alleged LSD of unknown purity and amount from an unidentified source on an indefinite number of occasions. The mother took LSD four times during pregnancy, twice during the first three months, which is the time at which the limbs are differentiated. *Zellweger, McDonald and Abbo* (117) reported the case of a child born with a complex unilateral deformity of the leg. This anomaly, the so-called fibular aplastic syndrome, includes absence of fibula, anterior bowing of the shortened tibia, absence of lateral rays of the foot, shortening of the femur, and dislocation of the hip. The parents of this child took illicit LSD, the mother on the 25th day and three times between the 45th and 98th day after her last menstrual period. The authors emphasized the fact that the seventh week of gestation is the period of most active differentiation of the lower limbs; this was also established for the thalidomide embryopathy. *Hecht et al.* (49) observed malformation of the arm in the case of a child whose parents had taken LSD and smoked marijuana. The mother took unknown amounts of LSD before and during early pregnancy. The authors concluded that the relation of the deformity to LSD in this case is unclear. *Carakushansky, Neu and Gardner* (16) reported a similar case. It involved an infant with a terminal transverse deficit of portions of fingers on the left hand and syndactyly of the right hand with shortened fingers. This malformation is characterized by a failure of the fingers to separate and function independently. The mother was believed to have been exposed to LSD and cannabis during pregnancy. *Eller and Morton* (34) gave a report of a severely deformed baby with an anomaly involving defective development of the thoracic part of the skeleton (spondylothoracic dysplasia). This rare condition had previously been described only in infants of Puerto Rican parents. The mother in this case happened to take LSD once around the time of conception. The authors question the causal relationship between LSD and the deformity. Finally, *Hsu, Strauss and Hirschhorn* (53) published the report of a female infant born with multiple malformations, to parents who were both LSD users prior to conception. During pregnancy the mother also took marijuana, barbiturates and methedrine. The malformations in this case were associated with chromosomal aberrations indicating the so-called trisomy 13 syndrome.

Berlin and Jacobson (12) studied 127 pregnancies in 112 women where one or both of the parents admitted taking LSD before or after the infant's conception. According to the authors, sixty-two pregnancies resulted in live birth, six of these infants had congenital abnormalities,

with one neonatal death. One of the fifty-six normal newborns died from an intrapulmonary hemorrhage. Sixty-five pregnancies were terminated by abortion; seven abortions were spontaneous and four of these fetuses were abnormal. Out of fourteen therapeutic abortions, there were four abnormal fetuses. The rate of defects of the central nervous system was about sixteen times that in the normal population. One of the findings in all the abortion specimens was failure of fusion of the cortex. Three of the six abnormal children born alive had myelomeningocele and hydrocephalus; one had hydrocephalus only. The authors themselves emphasized that the mothers in this study were a very high risk obstetric population for many reasons. In addition to ingestion of alleged LSD, there was multiple drug use (15 percent used narcotics), infectious diseases and malnutrition. Most of the therapeutic abortions were done for psychiatric reasons. Thirty-six percent of the women had undergone extensive radiological investigations for abdominal complaints.

Berlin and Jacobson's study, as well as all the previously mentioned case reports of fetal abnormalities, involve infants born to parents who ingested illicit substances of unknown dosage and origin that were considered to be LSD; to date there is no report of congenital malformations in human offspring exposed to pure LSD. In addition, as *Blaine* (13) pointed out in his rather bitter and emphatic criticism of the paper by *Eller and Morton,* (34) there is no scientific evidence in these individual case histories of a causal relation between the ingestion of illicit substances and the subsequent development of the embryonal malformation. The findings could represent pure coincidences and be related to any number of situations that contribute to congenital abnormalities, such as maternal nutrition, physiological, psychological and pathological states, socio-economic circumstances, or various cultural practices. Differences in type and severity of malformations may be due to genetic factors, both embryonic and parental.

There exists a considerable amount of clinical evidence contradicting or limiting the above findings. Three studies focusing primarily on the frequency of chromosome breaks in children exposed to illicit LSD *in utero* reported elevated breakage rates of the chromosomes. (27, 33, 54) However, all fourteen infants studied were in good health and had no indications of birth defects. It is interesting to note in this context that the hypothesis of the possible teratogenic action of LSD was originally derived from observations of increased chromosomal breakage. In the majority of the reported cases of actual congenital malformations attributed to LSD, the chromosomal findings were normal. Conversely, the children exposed to LSD *in utero* and reported as having chromosome damage did not show any physical abnormalities. Although it is not common, for obvious reasons, to publish case histories with negative results, *Sato and Pergament* (89) presented one in their discussion of the case of *Zellweger et al.,* (117) They described a newborn whose mother had taken LSD before and during early pregnancy six times. The pregnancy was uneventful, and she gave birth to a full-term, healthy girl. The doses of alleged LSD taken by the mother were

sufficient to produce a psychedelic effect. She took LSD during the critical stage for production of limb deformities, as in Zellweger's case, but no fetal deformities developed.

Aase, Laestadius and Smith (1) observed a group of ten pregnant women who were ascertained as having ingested LSD in hallucinatory dosages. These women subsequently delivered ten living and healthy children. There was no evidence of teratogenic effects or chromosomal damage in any of these ten babies considered to have been exposed to LSD in utero. The authors point out a most interesting fact, that all of the delivered children were girls. The low probability of this being a random event suggests that LSD may have an influence on the sex ratio. *Healy and Van Houten* (48) calculated that the probability of the entire series of ten pregnancies resulting in children of the same sex is 1:1024. They suggested that LSD might enhance the basic immunological incompatibility between male fetuses and their maternal hosts; this results in the detection of the fetal tissue as antigenic. A similar hypothesis was offered in the past as an explanation of the observation that women who became schizophrenic within one month of conception gave birth to female offspring only.

McClothlin, Sparkes and Arnold (76) studied 148 human pregnancies following ingestion of LSD; this was part of a larger study of 300 persons randomly drawn from a population of 750 who received LSD orally in either an experimental or psychotherapeutic setting. The number of sessions ranged between one and eighty-five, and the usual dosages were 25-400 micrograms. For twenty-seven pregnancies, there was additional use of LSD under non-medical conditions. In a small percentage marihuana (8 percent) and strong psychedelics such as peyote, mescaline and psilocybin were also used. The authors found no evidence that the use of LSD in reasonable doses by men before intercourse leading to conception, is related to an increase in the rate of abortions, premature births or birth defects. However, they found some evidence that the use of LSD by women prior to conception may increase the incidence of spontaneous abortions; the causal connection between these two events is not clear and requires further research. There was little to suggest that exposure of either parent to LSD prior to conception and in the amounts described in this study increased the risk of having a child with a congenital defect. The only increased risk observed in this study, therefore, was a possible higher incidence of spontaneous abortions among women exposed to LSD. Spontaneous abortions occurred significantly more often when the mother had taken LSD than when the father only had taken it. The authors offered two explanations for this finding: (1) The period required for the maturation process of the ova is very long; it takes several years, as compared to a few weeks for the spermatozoa. (2) In one-half of the cases the mothers were given medical LSD for therapeutic purposes. It is a well-known fact that greater emotional stress in neurotic patients increases the incidence of abortions, and this suggests that the connection found in this survey between LSD and abortion might not be causal at all, but purely coincidental.

Arendsen-Hein (7) presented at the Congress of the European Medical Association for Psycholytic Therapy at Wurzburg in 1969 data about the offspring of 4,815 former LSD patients from several European countries, including England. Of 170 children born to these patients after they had completed LSD therapy, frequently involving multiple exposures, only two showed congenital anomalies. One child had a dislocation of the left hip joint; another child, born to a couple where the father used LSD, had the little finger and ring finger on one hand grown together (syndactyly). Two women from this sample took LSD within fourteen days after conception (in one case 400 micrograms), and both children were normal. Thus, out of 170 infants, only two showed pathology; the author felt that even in these two cases the anomalies were of a common kind and could not be attributed to LSD for any sound reason.

The experimental and clinical evidence for the teratogenic effects of LSD can be summarized as follows. Increased incidence of congenital malformation has been reported in mice, rats and hamsters; however, there exist a number of papers contradicting these findings. The information from experiments on lower primates, although preliminary, suggests a possible teratogenic effect and deserves further investigation. There exist several case reports of malformed children born to users of illicit LSD, and one study suggesting a high incidence of birth defects and abortions in this group. The causal relation of these malformations to the use of LSD is not established. The unknown chemical composition of the samples of alleged LSD, as well as the existence of many other important variables characterizing the group of "LSD users" (such as infections, malnutrition, multiple drug use, and emotional disorders) leave all the conclusions open to question. There are indications of an increased risk of spontaneous abortions related to the use of LSD. There is no evidence at present that pure LSD causes birth defects or fetal wastage in humans. However, for practical clinical purposes pregnancy should be considered a contraindication for the administration of LSD. This is not something unique and specific to LSD; similar caution is required in regard to many other substances. The balance between the maternal organism and the developing fetus, especially in the first trimester of pregnancy, is very precarious and can be disturbed by a wide variety of external influences.

CARCINOGENIC EFFECTS OF LSD

It has repeatedly been mentioned in the literature that LSD might have carcinogenic potential. This speculation appeared for the first time in the paper by *Cohen, Marinello and Back*. (22) The authors drew this conclusion from their findings of a markedly increased frequency of chromosomal breakage and a quadriradial chromosome exchange figure in a patient with paranoid schizophrenia who had undergone extensive LSD psychotherapy. This is a combination occurring in three inherited disorders: Bloom's syndrome, Fanconi's anemia and ataxia teleangiectatica. These disorders are connected with a high incidence of leukemia and other neoplastic diseases. The authors also pointed out that cells of neoplastic origin

show a variety of chromosomal aberrations, many of which are not unlike those they had found in subjects after ingestion of LSD. In addition, some of the agents known to produce similar-chromosome aberrations, such as radiation and various viruses, are known carcinogens.

The carcinogenic hypothesis was supported by the finding of *Irwin and Egozcue* (57) that nine subjects who had taken illicit LSD had chromosomal fragments resembling the so-called Philadelphia (Ph.) chromosome, often associated with chronic granulocytic leukemia. *Grossbard et al.* (46) found a Ph1-like chromosome in all thirty-five peripheral leukocytes from an individual who had used illicit LSD and other drugs and who later developed acute leukemia.

Several serious objections can be raised against this hypothesis. First, the evidence that pure LSD causes chromosomal aberrations is rather problematic and inconclusive. Second, the cause of the chromosomal lesions in the above mentioned inherited disorders is not known, nor has it been established whether these lesions have any relation to subsequent neoplastic developments. There exist many chromosome breaking agents which are not associated with leukemia, and quadriradial and other rearrangement figures have also been found in the white blood cells of normal individuals. Third, Cohen's comparison of the effects of LSD with those of radiation does not seem to be well substantiated by experimental and clinical findings. According to *Dishotsky et al.,* (28) long-term chromosomal damage following LSD injection has been reported in three retrospective studies. In two reports of subjects studied before and after. they took LSD (prospective approach), the occasional damage that was found was without exception transitory, suggesting a reversibility of effect unlike that associated with radiation. Fourth, the Ph1-like chromosome was reported in only two studies; in both of them it was found in peripheral leucocytes. In chronic granulocytic leukemia, the Ph1 chromosome is characteristic only of myeloid and erythroid cells, which normally do not divide in peripheral blood. *Dishotsky et al.* (28) quote *Nowell and Hungerford* (84) who initially described this lesion: "A chromosome compatible with the Ph. would have to be observed in blood cells other than lymphocytes to be relevant to the question of chronic granulocytic leukemia."

Only two cases of leukemia have been reported in individuals who were treated in the past with pure LSD. (41, 108) In both of them it remains to be established whether the association represents a causal relation or a coincidence. In one of these cases, reported by *Garson and Robson*, (41) there was a "remarkable incidence of childhood malignancies strongly suggestive of a familial predisposition to malignant disease." At the present time the carcinogenic hypothesis seems to be rather poorly supported by experimental and clinical data and remains in the realm of pure speculation. There appears to be no definite evidence that LSD is a carcinogenic agent.

SUMMARY AND CONCLUSION

Two-thirds of the existing in vitro studies have reported some degree of increased chromosomal breakage following exposure to illicit or pure LSD. With one exception, these changes were observed with concentrations of LSD and durations of exposure that far exceeded the dosages commonly used in humans. In none of the studies was there a clear dosage-response relationship. Since similar findings have been reported with many commonly used substances, including artificial sweeteners, aspirin, caffeine, phenothiazine tranquilizers and antibiotics, there is no reason why LSD should be singled out and put in a special category. There is no justification for referring to the structural changes of the chromosomes as "chromosomal damage"; their functional relevance and relation to heredity remains to be established. In addition, the fact that the *in vitro* experiments bypass the excretory and detoxifying systems present in the integral organism casts doubt on the overall relevance of the *in vitro* results.

In the *in vivo* chromosomal studies, the majority of positive findings was reported in persons who had been exposed to illicit, "alleged" LSD. *Dishotsky et al.* (28) in their excellent synoptic review of the chromosomal studies made in the past, summarized the existing evidence in the *in vivo* papers as follows: "In twenty-one *in vivo* chromosomal studies, a total of 310 subjects were reported. Of these, 126 were treated with pure LSD; the other 184 were exposed to illicit, alleged LSD. Only 18 of 126 (14.3 percent) of the subjects in the pure LSD group were reported to have chromosomal aberration frequencies above mean control rates. In contrast, 89 of 184 (48.9 percent) of the subjects in the illicit LSD group had elevated aberration frequencies. Of all the subjects reported to have chromosomal damage, only 18 of 108 (16.7 percent) were exposed to pure LSD. The frequency of individuals with chromosomal damage reported among illicit drug users was nearly triple that associated with the use of pharmacologically pure LSD." These findings indicate that chromosomal aberrations when found were related to the more general effects of drug abuse and not to LSD *per se*; it is highly improbable that pure LSD ingested in moderate dosages produces chromosomal aberrations in the white blood cells.

The positive findings in some of the chromosomal studies using human leucocytes were interpreted as indicating genetic damage and danger to future generations. To be of direct genetic relevance, however, the chromosomal damage would have to be demonstrated in the germinal cells, the sperms and ova, or their precursor cells. Several existing studies of the effect of LSD on the meiotic chromosomes have been inconclusive despite the use of excessive dosages. The mutation studies in *Drosophila melanogaster* indicate no mutagenic effect from 0.28 to 500 micrograms of LSD per cc and a definite mutagenic effect from 2,000-10,000 micrograms of LSD per cc. The fact that truly astronomic dosages have to be used to induce mutations in Drosophila shows LSD as a rather weak mutagen that is unlikely to be mutagenic in any concentration used by human subjects.

In some of the early studies, LSD was implicated as a potential cause of congenital malformations, abortions and fetal wastage. The original reports of teratogenic effects in hamsters, rats and mice have not been confirmed by later studies. The experiments in rodents indicated a rather wide range of individual strain and species susceptibility to the effects of LSD. It is highly questionable whether and to what extent the results of such investigations can be extrapolated to the situation in humans. There have been six individual cases reported of malformed children born to parents who have used illicit LSD. Only one team of workers reported an increased frequency of congenital malformations in the offspring of illicit LSD users. In regard to the high frequency of unexplained "spontaneous" birth defects and the wide-spread abuse of LSD, the above observations may be coincidental. The increased occurrence of malformations in the LSD users reported in one of the studies may be explained by many other variables characterizing this group, and there is no logical reason to implicate LSD as the single or most important factor. At the present time there is no clear evidence that pure LSD is teratogenic in humans. However, in view of the high vulnerability of the developing fetus to a great variety of substances and conditions, the administration of LSD is contraindicated for the gestation period.

There is no clinical or experimental data demonstrating that LSD has carcinogenic properties, as suggested by some of the early studies. No increase in the incidence of tumors among LSD users has ever been detected. Case reports of leukemia and malignant tumors in the population of LSD users have been exceedingly rare. In the three existing case reports of leukemia, there has been no proof or even indication of a causal relationship, and the association of leukemia with LSD use may have been merely a coincidence.

As this review shows, no convincing experimental or clinical evidence exists to prove that the commonly used dosages of pure LSD produce genetic mutations, congenital malformations or malignant growths. As far as illicit LSD is concerned, the situation is much more complex, and the results of the studies of illicit LSD users should not be considered relevant to the question of the biological dangers of LSD. Uncertainties about the dosage, and the contamination of black-market samples of psychedelic drugs by various impurities and additives contribute a very important dimension to the already serious psychological hazards associated with unsupervised self-experimentation.

There is absolutely no indication in the research data currently available that responsible experimental and therapeutic use of LSD by experienced professionals should be discontinued.

Footnotes

*Numbers apply to references that appear [in the original publication]. (back)

**_In vitro_ literally means in glass, and refers to experiments conducted in test-tubes; _in vivo_ is a medical term for experiments in living organisms. (back)