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REVIEW ARTICLE

Unfavourable Reactions to LSD:

A Review and Analysis of the Available Case Reports

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LYSERGIC acid diethylamide (LSD) is one of several hallucinogens which have lately become prominent as therapeutic agents and as psychedelic drugs. LSD is similar in its main effects to drugs such as mescaline found in peyote cactus, harmine in vines, bufotenine in mushrooms, and the more recently developed synthetics such as psylocybin and dimethyltryptamine. Of these, LSD is the most frequently used for scientific and therapeutic investigations. It is also the most popular of the hallucinogens used for "kicks", self-exploration, or religio-philosophic experiences by college students and other members of the intelligentsia.

Until recently, both the proponents of the therapeutic uses[18, 33] and psychedelic uses of LSD[17, 22] have promised that LSD is relatively safe. Sometimes the dangers are made into a virtue, as Leary[22] has said that "it becomes necessary for us to go out of our minds in order for us to use our heads". Heard[17] tells us that "the hallucinogens are less harmful than aspirin or alcohol, less dangerous than riding in a motor car". Despite these assurances, it now appears that a variety of serious complications can result from both the therapeutic and non-therapeutic uses of LSD. Reports of these complications have grown from only a few before 1960 to six in 1966 and early 1967 containing 158 cases. This is a remarkable increase which calls into doubt the early confidence in the safety of LSD, especially because several of the latest reports are of complications arising from controlled therapeutic trials. So far, these complications have not been reviewed or analyzed for the necessary and sufficient conditions on which they depend. In this paper, the intent is to review all of the reported unfavourable reactions and to establish their frequency and origin in the personality of the user or in the features of his LSD experience. An effort will also be made to describe the persons who use LSD for "kicks" or psychedelic purposes. Because many of the reported complications appear in these people, their backgrounds are of special interest.

The most serious complications include prolonged psychotic reactions, recurrent LSD experiences, disturbed non-psychotic reactions, and, less frequently, suicide, homicide and convulsions. It has also been suggested that the acute toxic effects of LSD could lead to death. Without a clear demonstration, some persons have speculated that LSD users could develop addiction or physical dependence and that they could be led to try drugs such as heroin or morphine.

By June of 1967 there were 21 reports which contained the details of 225 adverse reactions to LSD.* Although this may not include all reported cases, it is believed that coverage is nearly complete, as all of the usual abstracting services in addition to the Addiction Research Foundation Archive of Drug Literature have been searched.† The main features of these adverse reactions and the social characteristics of those affected will be discussed in this paper. There were 142 cases of prolonged psychotic reactions, 63 non-psychotic reactions, 11 spontaneous recurrences, 19 attempted suicides, four attempted homicides, 11 successful suicides and one successful homicide. An additional nine cases showed possible suicidal intent. There were no clear cases reported in the clinical literature of dependency, addiction or death due to toxic effects. There are six cases of convulsions which may be seen as toxic reactions.‡

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*The authors have reduced the overlap between reports by counting each person only once, when they have been reported in two separate papers.

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‡On request, the authors will send a mimeographed table summarizing the details of all LSD reactions reported in this paper.

1. TOXIC REACTIONS

With any drug having such striking physical and behavioural effects as LSD there is always the question of lethal toxicity. Until recently the acute toxic effects from LSD appeared to be of minor importance, provided the drug is relatively pure, and the dose taken is small (100 to 300 μg.). However, the possibilities that LSD can result in convulsions[3] and in chromosomal damage[5] have been reported. Poisonings from LSD have not been reported in man, except from morning-glory seeds and they contain a variety of substances in addition to LSD. The possibility that ergotism (marked by vasoconstriction and peripheral coldness) can result from taking these seeds has been described by Hoffer.[18]

The lethal dose of LSD for man is not known, as no human death from an overdose has been reported. Almost all studies of lethality in non-human species have used acute intravenous doses. This provides a useful analogy to the therapeutic and experimental uses, but LSD taken in unsupervised settings is usually eaten with sugar cubes, or dissolved in a drink.[24] The intravenous and ingestive lethal doses could be quite different, as with drugs such as morphine. Another consideration is that toxic overdoses are least likely in therapeutic and experimental trials and most likely in unsupervised settings for which we do not know the lethal dose.

Rothlin[28] has reviewed the toxicity studies of LSD based on animals up to 1957. LSD poisoning results in "mydriasis, piloerection, vomiting, increased reflex activity, ataxia and spastic paresis; death results from respiratory failure". The intravenous acute LD_{50} (dose at which 50 of 100 will die) varies inversely with the size of the species. The LD_{50} for mice is 46 mg. per kg., for rats 16.5 mg. per kg., and for rabbits 0.3 mg. per kg. An elephant was killed with a dose of 0.1 mg. per kg.[37] Hoffer[18] has suggested that the LD_{50} for man should be 0.2 mg. per kg., but some humans have been given 1 mg. per kg. safely. Thus, the lethal dose for man remains uncertain, even for acute intravenous doses and still less is known about lethal ingestive doses.

The long-term toxic effects of LSD have yet to be studied in man. Rats have been given 2.5 mg. per kg. intravenously for 30 days. They show increased reflex responses, mydriasis, piloerection and slowing of growth. Long-term lethality studies have been made only with rats, and they appear to show no accumulation of effects over long periods of time. Rats chronically exposed to LSD show the same LD_{100} as do unexposed animals.[28] What is clear from all of these studies is that the acute lethal dose for man is probably many times the usual therapeutic or psychedelic dose of 100 to 300 μg. However, whether or not there is an accumulation of toxic effects after a long series of doses is unknown.

LSD has been found by a few investigators to produce convulsions;[3, 6] these represent the only clear instance of a toxic response to LSD in man, but they are a rare occurrence. Baker[3] has reported five grand mal seizures following LSD treatment with 150 patients. Sandison and Whitelaw[29] reported a single case of convulsions, but no other cases arising from therapeutic or psychedelic use have been reported. If these convulsions are a true toxic reaction rather than a peculiar response of certain individuals, it is surprising that the reports are so infrequent. Long-term neural toxicity studies have not been made with LSD. Such studies would be useful if only because of the unknown purity of LSD from illicit manufacture or botanical origin (e.g. morning-glory seeds).

A recent study by Cohen, Marinello and Back[5] has shown that human leukocytes exposed to LSD have a very high rate of chromosome breaks during cell division. Cytological studies of the blood of a single person who had taken LSD 15 times also showed a large number of chromosomal breaks. Obviously, these investigations should be repeated with a large number of LSD users and with their offspring.

II. PROLONGED PSYCHOTIC REACTIONS

The usual responses to LSD include bizarre visual experiences such as heightening of brightness and colour perception, distortions in the perception of real objects, and visual delusions or hallucinations. The emotional effects are often shifting and may involve apprehension, panic, elation or depression. Although LSD was believed, originally, to mimic real schizophrenic episodes, it is generally accepted now that the experience is more personal and emotional than truly schizophrenic.[26] Nevertheless, a number of cases have been reported in which LSD has produced prolonged psychotic episodes or at least profoundly disturbing states. Sometimes these episodes are self-limiting but often they need to be treated with tranquillizers or long periods in hospital. In several instances they have been cleared up, only to make a mysterious reappearance a few weeks later. The prevalence rate of prolonged psychoses in persons taking LSD in various settings is difficult to establish, as are the necessary and sufficient conditions for their occurrence.

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Of the 225 adverse reactions, there were 142 cases of prolonged psychotic reactions to LSD, including those in therapeutic, experimental and unsupervised settings. The most typical symptoms seem to be paranoid delusions,[8, 36] schizophrenic-like hallucinations[15, 27] and overwhelming fear.[27, 34] The majority of these psychoses have required special tranquillizer medication or hospitalization lasting from a few days to several years. Ungerleider, Fisher and Fuller[36] reported that 68% of their 70 cases required more than one month in hospital, but five to six months is not unusual in isolated cases.[9, 27, 34] Psychiatrists at the Bellevue Hospital in New York[34] found that 30 of 52 patients with prolonged psychosis became normal within 48 hours. A further 11 patients required two to seven days and six others a longer period of time. Surprisingly, five of this latter group of six patients "had no psychiatric history or had previous psychiatric history but were adequately integrated".[34] It is clear then that serious prolonged psychoses may result from LSD use.

Cohen[6] sent questionnaires to 62 investigators who had used LSD in therapeutic or experimental trials. He obtained 44 replies containing information on the complications resulting from 25,000 LSD administrations to about 5000 persons. Psychotic reactions lasting more than 48 hours had a rate of 0.8 per 1000 among experimental subjects and 1.8 per 1000 in patients obtaining therapy. Unfortunately, replies were received from only 70% of those contacted and some conservative biases may have resulted. Also, many therapeutic and experimental studies do not have a routine follow-up and hence all but the most immediate adverse reactions could have been missed.

Somewhat higher rates of prolonged psychosis have been recently reported. Opitz[25] observed two cases in 66 patients—one of them a "motor-excitatory" state and the other a "confused or manic psychosis". Fink *et al.*[14] precipitated three prolonged psychoses in 65 mental hospital patients, but these occurred in persons with a variety of psychiatric disturbances. Baker[3] precipitated four psychoses lasting three or four days in 150 patients who received up to 10 LSD sessions. Also, Leuner[23] found three prolonged psychotic reactions among 82 patients given an average of 27 LSD sessions. It may be that the rate of prolonged reactions reported by Cohen[6] is spuriously low, especially when severely disturbed persons are involved. Rates of prolonged reactions could certainly be reduced by excluding psychotic or pre-psychotic persons. It would be valuable to know which personality or social characteristics and which conditions surrounding the use of LSD are associated with prolonged psychotic reactions.

Only 27 of the 142 persons (19%) with prolonged psychotic reactions took their LSD in supervised settings.[9, 14] Two persons[15, 27] began their LSD experience in a supervised therapeutic or experimental setting and took self-administered doses thereafter. Of the 27, the three described by Fink *et al.*[14] had histories of psychosis and were mental hospital patients at the time of receiving LSD.

It appears that some persons who experienced prolonged psychoses after illicit use of LSD had previous psychiatric diagnoses. Frosch, Robbins and Stern[15] found that five out of 12 were definitely psychotic, although the others had "some degree of personality difficulty". Ungerleider, Fisher and Fuller[36] found that 27 out of 70 persons with both mixed psychotic and non-psychotic reactions had previous psychiatric treatment; 25 (36%) had been diagnosed as psychotic before taking LSD. The Bellevue series contained only 12 out of 52 persons (23%) who were psychotic or schizoid personalities and of these seven were "adequately integrated into society".[34] It is clear that these rates of pre-LSD psychoses are much higher than in the general population; however, we are uncertain how many psychotics can take LSD without a prolonged psychotic episode. A more important point is that LSD is precipitating prolonged psychoses in many persons who cannot be diagnosed as psychotic, or who have only minor personality disturbances or none at all. In fact, about 77% of the prolonged psychoses from LSD in the Bellevue study[34] could not have been predicted from previous psychotic disturbances.

Further conditions associated with the occurrence of prolonged psychoses are difficult to define. In most therapeutic cases, the dosage taken was not abnormally large, although many studies of non-medical use fail to specify exactly what it was. About 15% in the Bellevue study[34] and 53% in the Los Angeles study[36] developed a prolonged psychosis after a series of doses (more than five). However, a surprising proportion—30 to 50%—had a prolonged psychosis after only one LSD experience.[34, 36] It appears that for many persons even a single dose of LSD is sufficient to produce a psychosis, especially when it is taken in unsupervised settings.

III. SPONTANEOUS RECURRENCES

A further complication, for which there is no adequate explanation, is the spontaneous re-

currence of parts of the LSD experience. In at least 11 cases, frightening delusions or hallucinations have reappeared weeks or months after the last ingestion of LSD and after an interval of normality.[7, 8, 10, 15, 23, 27] Cohen and Ditman[10] reported this phenomenon in a patient who had spontaneous daily recurrences of frightening LSD experiences (after 200 to 300 doses), and in one who had "periodic illusions" while under stress. A spontaneous recurrence also reported by Cohen[7] seems to have resulted in suicide four weeks after LSD was taken.

Frosch, Robbins and Stern[15] reported the largest proportion of recurrences—three out of 12 persons with LSD complications. Two of these persons experienced recurring depersonalization and perceptual distortions one to two months after taking the drug. The third had transient episodes of catatonia and visual hallucinations more than a year after taking LSD for the last time.

Leuner[23] described three spontaneous recurrences among his patients, who are generally given a very long series of LSD sessions, usually at least 27.

The most completely described case of a spontaneous recurrence in an LSD user was reported by Rosenthal.[27] This user had spontaneous hallucinations, such as pleasant panels of moving light and colour, but also terrifying illusions of people decomposing in front of her. These continued for about five months after her last use of LSD.

The possible mechanisms for spontaneous recurrences are difficult to identify at present. Pharmacological studies make it clear that LSD is rapidly absorbed and most of it is rapidly destroyed. Studies summarized by Rothlin[28] show that the half-life of LSD in rats is only 35 minutes and after two hours only "traces" can be found in the blood or organs. The half-life of LSD in larger mammals is longer (100 minutes in the monkey and 130 in the cat), but apparently most LSD passes quickly from the blood. LSD moves from the blood to the brain and other organs and then into bile. Even though LSD itself may not be present to trigger spontaneous hallucinations, some of its neurological and neurochemical effects may be sufficiently long lasting to do so. Rosenthal[27] has reviewed the work in these areas, but unfortunately most studies are of the acute effects of a single dose. He has proposed that some LSD effects related to retinal functioning, synaptic transmission or "some yet undiscovered reaction" may result in spontaneous recurrences.

What has not been noted so far is the connection between spontaneous recurrences and the frequency with which LSD has been taken. Of the 11 persons with recurrent experiences, six had taken LSD numerous times; for five of them exact doses have not been stated,[7, 23] but a recurrence reported by Leuner[23] followed an "accidental overdose". In six persons exact doses were reported and these had taken LSD (or similar hallucinogens) on 9, 10 to 12, 15, 25, 200 to 300, and over 200 occasions. This is much more frequent than that found for persons experiencing only prolonged psychoses, about half of whom have taken it only once or on a few occasions.[34, 36] The connection between frequent ingestion of LSD and recurrent experiences suggests that LSD itself or some of its effects may persist or build up over repeated administrations sufficiently to cause a recurring experience, particularly under stress.

IV. PROLONGED NON-PSYCHOTIC REACTIONS TO LSD

In addition to psychoses and recurrent experiences, LSD has resulted in a variety of disturbed reactions which are difficult to classify. In all, 63 cases of non-psychotic prolonged reactions to LSD have been described. These may be classified as 39 cases of acute panic or confused reactions,[8, 11, 15, 24, 30, 36] 17 cases marked by depression,[10, 36] five cases of antisocial or psychopathic behaviour,[8-10] one case of a "motor-excitatory state"[25] and one case of chronic anxiety.[8] The non-psychotic cases presented by Ungerleider, Fisher and Fuller[36] are difficult to classify as only the frequencies of presenting symptoms are given, with several symptoms possible for each person.

Panic reactions are the most frequent non-psychotic adverse reaction to LSD. The most common features are dissociation, terror, confusion, fear of going insane and fear of not being able to return to normality. Most of these acute reactions are terminated within a few days,[15] but Cohen[8] has described a chronic anxiety reaction which required long-term psychotherapy and tranquillizers.

Purely depressive reactions are apparently rare and depression is most likely to occur with anxiety, confusion and panic, as in the patients of Ungerleider, Fisher and Fuller.[36]

In some persons LSD seems to have released psychopathic personality trends and made asocial, criminal and sociopathic behaviour possible.[8, 9, 34] The number of prolonged non-psychotic reactions described here is small and most of them have appeared in persons with asocial or psychopathic predispositions.

Virtually all of the non-psychotic reactions occurred in persons who took LSD alone or in un-

supervised settings. The doses taken do not seem to be abnormally large, except for those who had psychopathic reactions. They tended to take large doses or to have taken LSD very frequently (up to 2000 μg. weekly for three years in the case described by Cohen[8]). Where the information is given, most had previous personality disturbances.

V. SUICIDE

Depressions accompanied by suicide have often been reported as a complication of LSD administration. The first study of such suicides was made by Cohen[6] who queried 62 LSD therapists about the complications seen. Only 44 therapists replied; nonetheless, they had administered LSD or mescaline to 5000 persons. Five attempted suicides had resulted, but four of these occurred many months after the LSD session. Only two of these suicides were believed by Cohen to be directly attributable to the LSD experience.[2] This rate of suicide has been taken to be very small, and Cohen's study has been widely reported as supporting the proposition that LSD does not lead to suicide.[18, 33] Hoffer[18] has even concluded that "it is likely that LSD decreased the rate since in such a group of subjects I would expect a higher mortality rate by suicide."

There are a number of reasons to doubt Cohen's estimate of LSD-related suicides. First, many (18 out of 62) LSD therapists did not respond to the query about complications and their rates of complications may have been higher. Second, many studies of LSD have used very short follow-up periods or none at all. For example, studies of LSD therapy with alcoholics[32] report follow-up periods varying from two months to three years, and similarly wide variations can be found in studies with other types of patients. Some therapeutic studies[4] have involved no follow-up beyond the LSD experience. In addition, routine follow-ups are not at all common in studies investigating the basic psychological effects of LSD in a non-therapeutic setting.[26] These considerations raise questions about the validity of present estimates of LSD-related suicides. The incidence of five cases in 5000 may be a gross under-reporting of the true incidence.

Since Cohen's questionnaire study,[5] there have been reports of 14 attempted and six successful suicides, and of nine persons with possible suicidal intent. The successful suicides were all males except one;[30] two were college students and both had taken LSD in an unprotected setting. Two of the successful suicides and four of the attempted suicides occurred during or soon after therapy with LSD.[16] These six suicidal persons were part of a group of 129 patients who were diagnosed chiefly as neurotics and character disorders. This is the highest rate of suicide found in LSD therapy.

Little information is available concerning the personality of the two college students before they took LSD. The suicide reported by Cohen[7] occurred four weeks after a 24-year-old student had ingested 200-300 μg. of LSD in morning-glory seeds. The experience included feelings of depersonalization, hallucinations, feelings of wonderment and "grandiose fantasies about saving the world," and it lasted about 24 hours. For three weeks after the ingestion he was exhilarated, but he experienced a recurrence without taking more LSD. About four weeks after the first experience "he awoke and was very upset because he was out of balance again". Soon afterwards he crashed his car into a house at high speed.

Only two suicides have occurred during an LSD episode.[16, 19] Keeler and Reifler[19] described the only case resulting from illicit use. A 20-year-old student, who had frequently taken LSD with friends, disrobed and jumped from a window shortly after taking an unknown dose of LSD. Six months before his death he had complained of anxiety and inability to study, but was diagnosed psychiatrically as only moderately disturbed. Severe depression or suicidal behaviour was not observed before his death; he stayed in school and talked of his future. The authors concluded that "the circumstances strongly suggest that he would not have died at the time he did if he were not in a state of LSD intoxication".

Geert-Jörgensen *et al.*[16] reported the only completed suicide during a supervised LSD session. In this case a young man committed suicide within a few hours of taking LSD for therapeutic purposes.

In addition to these successful suicides, Cohen[8] has reported two cases of accidental death which may have been suicides. In one case a young man walked into traffic shouting "halt" after he had taken LSD. In the other a frequent user of LSD was drowned soon after he had taken LSD alone on a beach.

The cases of attempted suicide are less adequately described than are the successful ones. The four probable suicide attempts reported by Ludwig and Levine[24] were gathered from the reports of narcotic addicts and were not seen by the investigators themselves. There is no information on age, dosage used or frequency of

experience with LSD. The five attempted suicides presented by Ungerleider, Fisher and Fuller[36] have been integrated with the other 65 cases with regard to age, sex, occupation and previous experience with LSD. The Bellevue study[34] reported one suicide attempt in 52 persons with LSD psychoses. The manner in which suicidal persons or their LSD experience differs from those who did not make suicidal attempts is uncertain. It is clear, though, that all of these persons had taken LSD alone or with friends in unprotected settings.

More details have been presented for the cases described by Cohen and Ditman[10] and by Fink *et al.*[14] The latter found one attempted suicide among 65 psychotic patients who were given LSD—a 25-year-old man with "mixed psychosis and psychopathy". He made a suicide attempt three days after the administration of only 40 μg. of LSD. During his session he had been restless, agitated and paranoid.

Cohen and Ditman[10] and Knudsen[20] have reported the only suicide attempts in females; both of these occurred as a result of LSD therapy. Cohen and Ditman's patient was a 41-year-old woman who had had a chaotic life and early family situation, marked by a murder-suicide involving her parents. She attempted suicide both before and after eight sessions which were given as therapy. Her last suicide attempt was probably not directly attributable to LSD but to larger personality and adjustment problems. The suicide attempt by Knudsen's female patient occurred after only 50 μg. of LSD; later this patient murdered her boy friend.

In summary, suicide attempts are an important complication of LSD administration. About one-third of them occurred in persons who took LSD in non-medical settings, although seven successful and 12 unsuccessful suicides have occurred as a result of therapy. There is, of course, difficulty in attributing all of these suicides to LSD therapy, as it is typically given to disturbed persons already prone to suicide. Probably no more than half of the suicides would be directly attributed to LSD by the therapists involved.

It is difficult to specify further the conditions leading to LSD-related suicides. There were two female suicide attempts out of 10 and three successful suicides in 10 for whom sex was stated. This merely reflects the higher proportion of males in the total population of adverse reactions and no sex difference is apparent.

The dosage likely to lead to attempted suicide cannot be specified, but it may be as low as 40 μg. for severely disturbed persons.[14] Almost nothing is known about suicide rates among persons who take LSD in unprotected settings, although rates for those given LSD in therapy appear to be low, if they have not been under-reported.

VI. Homicide and Assault

Some persons have been found[29] to react to LSD with increased emotionality and aggressiveness.[1] In at least four persons this has led to homicidal attempts or threats and in one case to a completed homicide.

Cohen and Ditman[10] described a psychologist who had taken LSD three times (75-125 μg.). He became grandiose for several weeks afterwards, threatened his wife with a gun and then went to live in a desert.

Cohen[8] also described a man who became intensely suspicious after taking 200-300 μg. of LSD for the first time. He became convinced that friends were plotting against him and attacked them; he caused one to flee and inflicted a severe beating on the other. The beaten man later fell or was pushed out of a fourth-floor window. The Bellevue study[34] also reported two attempted homicides, but specific details were not given.

Only one case of successful homicide has occurred after treatment with LSD. Knudsen[20] described a 25-year-old woman who murdered her boy friend two days after the last of five LSD sessions. The murder was not committed during the acute effects of LSD, but a close connection is apparent, as the desire to kill the boy friend was expressed during at least one LSD session. In this patient LSD appeared to release aggressive drives and to weaken self-control. She had been diagnosed as a psychopathic personality with chronic alcoholism, and previous disturbances may have contributed to her lack of control after LSD.

VII. Addiction and Dependence

Addiction and dependence on LSD have been mentioned as possible complications, with few indications that they actually occur. Farnsworth[13] has also stated that "until we know otherwise, it is prudent for us to assume, further, that regular use of the hallucinogens will prepare individuals to 'move up' to other and more powerful drugs such as morphine or diacetylmorphine (heroin)".

Addiction can be understood as a state of physical dependence marked by increased tolerance and physiological withdrawal symptoms. Tolerance to LSD develops rapidly, but it also dissipates rapidly.[18, 28] Many volunteers for

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LSD studies do not wish to take the drug again, particularly if it is not given as a therapeutic agent.[2, 35] Consequently, few would have the chance to develop tolerance to it. No studies of the use of LSD in humans have included tolerance over a long period of time (e.g. several years), and hence the practical importance of tolerance studies with lower animals is difficult to assess.

There are numerous reports of persons taking a long series of LSD administrations.[10, 15] However, no cases of pharmacological addiction to LSD have been reported as yet. Also, the literature on the peyote cult among Indians[1, 21, 31] contains no cases of peyote addiction. In fact, the alleged non-addictive nature of peyote became an argument for maintaining its freedom from legal control.[31] If LSD is addicting at all, its addictive liability is probably slight.

Questions have also been raised about long-term dependence on LSD and about the creation of psychological or social damage (such as personality changes, damage to employability, family relationships and moral and ethical controls). Again, clear cases of dependency over a long period of time have rarely been reported. Perhaps the only such case involved a woman who took LSD 200 to 300 times in a year;[10] she developed psychological dependence on it, but no withdrawal symptoms were described. Social and psychological damage resulting from LSD use has been described above in the sections on prolonged reactions, suicide and homicide, but many of these cases arose out of short-term rather than long-term use. No studies have been made of psychological or social damage resulting from long-term use.

As mentioned previously, at least one writer[13] has suggested that LSD may encourage users to try the more seriously addictive drugs such as heroin. As yet, there is no evidence to support this fear, since few LSD users take heroin as well. A study by Ludwig and Levine,[24] however, showed that at least some heroin users also take hallucinogenic drugs, but percentages or other indications of multiple drug use were not given. Both Cohen and Ditman[9] and the Bellevue psychiatrists[34] have described cases of "multihabituation". In all, 13 cases of habituation to a wide variety of sedatives, amphetamines and hallucinogens have been reported. Unfortunately, details about the use of these drugs or the order in which they were tried have not been stated. It could well be that the use of LSD tends to encourage a variety of experiments with psychoactive drugs. It may be argued that LSD has not been available long enough to have created very many heroin users and none have been reported. Long-term studies of LSD users would be needed to clarify these questions about multihabituation, the primacy of LSD in initiating it, and the relation between the use of LSD and narcotic addiction.

VIII. The Basis for Unfavourable Reactions to LSD

This review has provided a number of clues to predisposing factors for unfavourable reactions to LSD. These should be seen as clues, not conditions, because studies of the responses of persons who have taken LSD in unsupervised settings have not been made. The reported cases may appear to reflect a striking social problem to the observer, but it is uncertain what proportion of the total LSD sessions results in adverse reactions. Reports of adverse reactions, however, give some indication about the persons who are likely to volunteer to take LSD. They also help to indicate the nature and distribution of hallucinogenic usage.

Several conditions are associated with unfavourable reactions. Most of the reactions in every category described occur most frequently in persons taking LSD in unprotected settings alone, with friends, or with others who are taking LSD. About 80% of the prolonged psychotic and virtually all of the non-psychotic reactions were outside therapeutic and experimental use. Only three of 11 recurrences took place after therapeutic use. However, almost two-thirds of the suicidal attempts and the only successful homicide occurred in carefully protected settings; this poses an enigma for LSD therapists. There have not been sufficiently detailed follow-up studies to be certain that LSD therapy is as safe as reported by Cohen,[6] particularly with regard to the precipitation of suicidal thoughts and behaviour.

Although many of those with prolonged psychotic reactions had previous personality disturbances, the proportion may be as low as 23%, as in the Bellevue study.[34] Spontaneous recurrences and psychopathic reactions appear almost exclusively in very heavy users, but many of the other reactions appear after a single, relatively moderate dose. Judging from the reactions reported so far, no one is able to guarantee a safe dosage, a safe series of doses, or a personality which is certain to create no unfavourable reaction to LSD. Many cases have been reported in which a single, moderate dose of LSD led to a profoundly adverse reaction in otherwise normal persons, especially where the dose had been taken in an unprotected situation. Even when other persons have been with the one taking

LSD, supposedly protecting him, suicide and psychotic reactions have occurred. As yet, the dose being taken in unprotected settings is uncertain—it could be similar to the therapeutic doses or much larger, depending on the quality control exercised by the supplier and the determination of the user to succeed in obtaining a given effect.

The analysis of adverse reactions also contributes to knowledge of the manner in which LSD users differ from the general population. The users appear to be a young population of male students, former students and college graduates. The majority are in their early 20's; out of 112 for whom age was definitely stated, 82 were under 25. Only five persons older than 40 were found and none over 50. Most of them are men—132 of 180 for whom sex is stated. At least half of the illicit users of LSD are college students or former students, and their previous personality instabilities have been mentioned earlier. Unfortunately, the motivations of these persons for taking LSD are not stated, nor are other details about their social class, life problems or coping mechanisms. In summary, the LSD users would appear to be mainly young male college students or former students, some of whom have had previous personality problems of a psychotic or neurotic type.

These special characteristics make it likely that, at present, illicit use of LSD is an urban phenomenon. All studies of unfavourable reactions to date came from large cities—Los Angeles, New York and Boston, with the exception of a single report from a small university city, Chapel Hill.[19] It cannot be assumed that LSD is being used only in these cities, but its connection with urbanism and university facilities is probably not an artifact of the reporting so far.

The present state of knowledge makes it difficult to assess the reasons for the psychedelic use of LSD. Not a single study has been made of the motivations of illicit LSD users who have not had complications. However, Esecover, Malitz and Wilkens[12] found that paid volunteers for a hallucinogenic study had high rates of personality disturbances. Forty-one per cent were diagnosed as needing psychiatric treatment and 20% had received such treatment in the past. Without control groups such data are merely suggestive, but they appear to indicate the importance of personality problems in the seeking of the LSD experience. More sophisticated motivational studies of the illicit LSD-using population are required.

Much research on the adverse effects of LSD remains to be done. More studies of the long-term effects of LSD are needed—studies of both the effects of long LSD series and of the development and progress of unfavourable reactions. Data on the frequency of illicit use are unavailable at present, so prevalence rates of adverse reactions for this type of use cannot be estimated. It is also important to understand something of the attraction of LSD for the male population in college. Currently, we know very little of the reinforcements for taking LSD, nor do we know the personality and social needs which are served by the hallucinogens in general. Until some of these basic psychological investigations are made, many of the adverse reactions to LSD will remain enigmas.

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