Clinical Use of Psychotomimetic Drugs

By Louis A. Faillace

THERE HAS BEEN an increased scientific interest in the psychotomimetic (psychodysleptic) drugs, primarily represented by lysergic acid diethylamide (LSD) and several pharmacologically similar compounds such as psilocybin, psilocin, mescaline, dimethyltryptamine, and diethyltryptamine. These drugs are controversial and have gained attention in and out of the medical profession. There have been many commentaries and reviews reported in the literature.[9,15,17,20,21,26,33,44,51] Several symposia have been held concerning their use and therapeutic potentialities.[1,10] Unfortunately, there was widespread unfavorable publicity in many national popular magazines[28,32,54] due to the indiscriminate use of these potentially harmful agents.

The literature is replete with vivid descriptions of the striking and varied effects produced by these compounds.[16,29,35,45,46] These include marked alterations in sensory perception, with an apparent intensification of the brightness and beauty of colors, true visual hallucinations, and marked lability of emotional experiences with rapid shifts from elation to depression. Alteration in body image occurs, with parts of the body appearing larger or smaller. Subjects describe feelings of depersonalization and derealization. Occasionally they lose insight into the temporary nature of the drug reaction and develop paranoid delusions. The passage of time becomes distorted. Anxiety is present, ranging from mild apprehension to panic.

Because of these striking effects and their questionable safety and efficacy, the Food and Drug Administration has classified these drugs as investigational. At present, the pharmaceutical companies provide them only for scientific study by investigators functioning with federal or state agencies with formal approval of the agencies, or to investigators doing research under grants from these agencies.[9] Apparently there has been a proliferation of illicit trade in major urban centers.[7,9] Official attempts to control the source of the psychodysleptics has not deterred individuals from seeking new substances which alter the state of consciousness and perception. Ingram[27] has commented on the use of morning glory seed as a psychotomimetic agent and reported a case of excessive ingestion by a university student. Cohen[6] described a suicide related to morning glory ingestion.

The terminology associated with these drugs is new and at times confusing. The terms psychotomimetic, psychosomimetic, hallucinogenic, and psychodysleptic describe psychotic-like symptoms. Psychedelic, a word introduced by Osmond in 1957,[36] means mind-manifesting. A psychedelic compound is one which will enrich the mind, enlarge the vision, and create a kind of mystical experience in which insight is gained. According to Sandison,[40] the term

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psycholytic was first suggested and adopted by the European investigators at the Gottingen Conference in 1960. They were of the opinion that the hallucinogenic drugs should be renamed "the psycholytic drugs" because of their ability to allow the total experience of the unconscious to be brought into awareness. They thought that this name would be free from many of the objections attached to the word "hallucinogenic."

Compounds which affect man's thinking and emotions have been used since antiquity. The Aztecs of Central America had a rich culture in which these drugs played a prominent part. R. Gordon Wasson[53] in an enlightening monograph describes the four great divinatory plants of Mexico at the time of the Spanish conquest: picietl is a sister species of ordinary tobacco; peyotl is a cactus whose active ingredient is mescaline; teonanacatl, the sacred mushroom, contains psilocybin and psilocin, which accounts for its psychodysleptic properties; and ololuihqui, which is the morning glory seed *rivea corymbosa.* Wasson attributes the lack of knowledge, until recently, of the remarkable properties of these compounds to the Spaniards, who looked upon them with horrór, and during their years of colonization simply ignored them.

Jean Delay[11] credits Moreau in 1845 as the first in the Western world to explore the hallucinogenic drugs in a paper entitled "Hashish and Mental Illness." Moreau conducted drug studies on normal subjects and highly gifted individuals. He concluded that in using Hashish it was possible to reproduce the primary aspects of mental illness.

The toxicologist Louis Lewin in 1888[34] classified the plant, peyotl, botanically. Prentiss and Morgan in 1895,[37] Weir Mitchell in 1896,[35] and Havelock Ellis in 1897[16] subsequently described its dramatic psychological effects. Since then an enormous bibliography on peyotl has accrued.

Guttman and Maclay in 1936[22] first suggested using mescaline as an adjunct to psychotherapy after employing it in a study on depersonalization. Stockings in 1940[45] described in detail the symptoms of mescaline psychosis and pointed out the similarities and dissimilarities to the psychogenic psychoses. He postulated that the psychogenic psychoses were caused by a toxic amine, probably related to mescaline. This is of interest, since Friedhoff and Van Winkle[19] have reported on the presence of 3,4-dimethoxyphenylethylamine in the urine of schizophrenic patients.

In 1943 the discovery of the hallucinogenic properties of LSD by Hofmann, and the subsequent classic report of the drug's psychologic effects by Stoll,[46] gave emphasis and new dimension to the psychodysleptic drugs. In the late 40's and early 50's, the initial emphases of LSD research were in comparing the drug to schizophrenia and exploring the possibility of the drug being used as a model for the psychogenic psychoses. The studies of Rinkel and co-workers[13,38,39] were most prominent. Wikler,[55] after reviewing the literature, concluded that in all probability no simple relationship existed between clinical and model psychoses. In 1950, Busch and Johnson[3] published the first paper suggesting that LSD might be helpful in the treatment of psychiatric illness. Since then, numerous reports have been published concerning the use of the psychodysleptic drugs in the treatment of illness.[1,4,10,18,41,42]

Investigators using psychotomimetic drugs can be roughly divided into three groups: the Psycholytic group, the Psychedelic group, and, for lack of a better term, the Behaviorists.

The psycholytic group are those interested in using these drugs, especially LSD, as adjuncts to a psychoanalytically oriented type of psychotherapy. The difference between psycholytic and psychoanalytic therapy is the rapidity with which deep unconscious material is brought to awareness. Sandison[40] contends that there is abundant evidence that the psychological basis of LSD-treatment lies in its peculiar property of releasing unconscious material. He states that the participants at the first European Symposium on LSD therapy in Gottingen, 1960, were unanimous that this theory is the only satisfactory explanation for the quality of the LSD subjective experience and, thus, of its healing effects on the individual. He also maintains that psycholytic treatment is most beneficial for obsessional neurosis, character disorders, and psychopaths. Sandison further reports that there is general agreement among investigators from many countries concerning what constitutes psycholytic therapy. Drug sessions are given once or twice a week. Each treatment lasts four to eight hours and usually is attenuated with drugs, either a barbiturate derivative or one of the phenothiazines. The average dose of LSD is between 50–200 μg. The setting of the treatment should be in a special area of the hospital. The environment should be secure, but permissive, and be manipulated to increase the drug response. A darkened room, expressive pictures, appropriate music and manikins help intensify the patient's reaction. Physicians and nurses associated with the treatment program should have careful training in order to handle any contingencies which might arise. The course of treatment is usually eight weeks to several months.

The psychedelic group consists of those investigators primarily interested in the treatment of alcoholism. A most succinct explanation of the rationale for treatment was given by Savage in 1962.[43] He quoted William James, who suggested that one of the motivations for drinking is to achieve an actual mystic experience. He also quoted Fromm, who stated that the alcoholic suffers from alienation from the "sickness of the soul." Savage goes on to say that LSD may help the alcoholic by providing a genuine mystic or transcendental experience. By abolishing the distinctions between subject and object, conscious and unconscious self and the world, there is a lessening of alienation, a rediscovery of the self, a learning of a new set of values and a new beginning.

Psychedelic therapy[52] usually consists of a thorough psychological evaluation for approximately two weeks, with emphasis on the exploration of the patient's difficulty with alcohol and priming him for one intensive psychedelic experience. The therapist sees the patient daily for varying lengths of time and is with him for the entire LSD experience. Treatment is done in a special area of the hospital. The drug session may last from 12 to 16 hours and is not attenuated with drugs. The dosage of LSD is large, usually 400 μg. or more, in order to insure an overwhelming transcendental experience. The environment is much the same as in psycholytic treatment, with appropriate manipula-

tion to increase the drug response. Due to the intensive reaction produced by large doses of these drugs in a very short period of time and their ability to uncover deep unconscious material, the therapist should be specially trained to conduct this type of therapy. The patient, following his treatment, remains in the hospital for approximately two weeks before discharge.

The third group, the Behaviorists, in contrast to the other two groups, is not principally interested in treatment but is trying objectively to determine the actions of these drugs. A great many investigators from many divergent disciplines are included in this group. Only a few examples of some of the research will be discussed.

Hoch, Cattell and Pennes[24,25] reported their studies with schizophrenic patients, using mescaline and LSD. They concluded that these drugs aggravated schizophrenic symptoms. Hoch[23] questioned the claims made for LSD. He compared LSD to amytal, amphetamine, CO_2, ether and mescaline, and pointed out that when these compounds were introduced, great claims of success also were made for them. He went on to say that all basically accomplished something similar in conjunction with psychotherapy. They produced euphoria, were disinhibiting, relaxing, activating or stimulating, and some caused anxiety. He observed that patients under these pharmacologically dissimilar drugs brought forth the same psychodynamic material, and there did not appear to be any marked specific effect exhibited by any of these drugs.

Isbell and the group associated with him at the Addiction Research Center at Lexington, Kentucky, conducted a series of investigations on former narcotic addicts serving sentences for violations of the Federal narcotic laws. They reported[29] the development of psychologic and physiologic symptoms in this unique patient population similar to those in nonaddicts. They also observed the rapid development of tolerance to LSD. This was rapidly lost after discontinuance of the drug. They have also conducted studies[30] which showed the development of cross tolerance between LSD and psilocybin, and confirmed the work of Balestrieri and Fontanari[2] on the cross tolerance between mescaline and LSD.[56] This group[57] also compared the strengths of psilocin with psylocibin, mescaline and LSD. One μg/Kg. of LSD tartrate is equivalent to approximately 45 μg/Kg. of psilocin; 1 μg/Kg. of psilocin is approximately equivalent to 66 μg/Kg. of mescaline. Psilocin is approximately 1.4 times as potent as psilocybin.

Delay and co-workers[12] have carried on intensive studies with psilocybin, which is the first phosphorylated indole compound found in nature. The phosphorylation probably does not contribute to its psychodysleptic action. Psilocin, the dephosphorylated compound derived from psilocybin, has the same psychodysleptic properties. These studies included 90 mental patients and 47 normals. Symptoms produced by the drug lasted approximately four hours. The peak effect was reached at two hours. The psychologic manifestations are similar to the other psychodysleptics. Delay[11] suggests that this drug offers diagnostic possibilities. Since the underlying psychotic or psychoneurotic symptoms are intensified by psilocybin, he suggests that it may be helpful in facilitating the diagnosis of difficult clinical cases. He gives as example a case

of anorexia nervosa which had failed to respond to treatment. Following the administration of psilocybin, the patient developed a typical hebephrenic reaction which was then successfully treated with a phenothiazine derivative.

Szara has conducted a detailed series of investigations with the psychotomimetic tryptamine derivatives, particularly N.N-dimethyltryptamine (DMT) and N.N-diethyltryptamine (DET). In 1957,[47] he reported that DMT and DET rapidly produced sympathomimetic autonomic effects, perceptual, mood and cognitive disturbances similar to those exhibited after the administration of LSD and mescaline. These symptoms last for approximately one hour with DMT and two and one-half hours for DET. In contrast, the effects of LSD and mescaline last six to eight hours or more. In the course of his experiments, Szara[48,50] came to the conclusion that 6-hydroxylation of the indole ring might be an important pathway for the metabolism of DET. In order to provide further evidence that this might be an important biologic mechanism, Kalir and Szara[31] prepared a series of compounds blocked at the 6-position. One of these synthesized compounds, a 6-fluoro derivative of DET, was reported to produce autonomic symptoms and mood changes in humans but without the characteristic perceptual and thinking disturbances usually observed with psychotomimetic agents. Szara[49] has postulated that this fluorinated derivative of DET, which so closely mimics some of the actions of the psychodysleptic drugs, might be useful as an "active" placebo in clinical studies.

Suicide and prolonged psychosis are the potentially serious adverse reactions of psychotomimetic drugs. Cohen[5] in 1960 sent a questionnaire to 62 investigators using LSD and mescaline; 44 responded. This group had given these drugs to 5000 individuals, using a total of 25,000 doses. The number of doses per subject varied from 1 to 80 and the dose range from 25 to 1500 μg of LSD and 200–1200 mg. of mescaline. The incidence of psychosis lasting over 48 hours was 0.08 per cent for experimental subjects, and 0.18 per cent for patients in therapy. The successful suicide rate was 0.04 per cent for the latter. There were no reported successful suicides in experimental subjects. In a followup report, Cohen and Ditman[8] are of the opinion that patients who have serious complications are usually emotionally labile, often hysterical or paranoid personalities, and many are in treatment and hope to obtain an instantaneous magical cure. The authors also contend that the majority of patients who develop adverse reactions usually have obtained the drugs from improper sources. They further state that the actual incidence of serious complications following LSD is not known. They believe that complications are infrequent, and despite the profound psychological experience produced by LSD, adverse residuals are rare.

A critical assessment of the reports in the literature is most difficult. Many investigators are overly enthusiastic and make consistent and dramatic claims. All too frequently, euphoric testimonials for the efficacy of the drugs are given instead of cautious scientific observations, making objective analysis of results questionable. Ditman, Hayman and Whittlesey,[14] in their paper, *Nature and Frequency of Claims following LSD,* concluded: "Perhaps LSD is unique in

that it prompts so many claims, not only from subjects and patients, but from investigators themselves." At present, the therapeutic value of these agents has not been adequately proven. Many reports of the drugs' beneficial effects have not been based on carefully controlled studies designed to be free of bias and the investigator's enthusiasm. To do a carefully controlled study, it is of the utmost importance to establish a method which will separate what the drug does from the effect of the environment and psychotherapy. The development of an effective placebo would help to facilitate evaluation of the efficacy of these drugs. At present, there is no adequate one available. The effects of the psychodysleptic drugs are so dramatic that both the patient and the therapist immediately know if a placebo has been given. Further research is thus necessary. Any drug, either alone or combined with therapy, which can produce such striking phenomena and motivate otherwise apparently hopeless psychiatric patients, even if only temporarily, warrants careful evaluation.

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