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THE PSYCHOPHARMACOLOGY OF LYSERGIC ACID DIETHYLAMIDE (LSD-25)

LEONARD S. RUBIN

Eastern Pennsylvania Psychiatric Institute

A great deal of interest has been directed recently to the use of drugs as an aid to understanding and establishing a biological or chemical mechanism for the so-called functional psychoses, specifically, schizophrenia. Although no irreversible demonstrable organic or chemical change has as yet been demonstrated for schizophrenia, there is renewed interest in the possibility that new biochemical and physiological methods are available which are more sensitive and can consequently be employed to ascertain subtle changes which previously had eluded investigators searching for a biological fundament. It is claimed (**49**) that although toxic psychoses and endogenous psychoses are not identical, still, there is significant similarity with regard to clinical aspects and subjective symptoms to furnish psychiatry with a controllable toxic state within the nervous system that permits investigation of the endogenous psychosis. Solms (**46**) ventures still further and discusses the possibility that schizophrenia is due to a toxicosis because of this apparent similarity between the behavior engendered by certain drugs and the endogenous psychosis.

The rationale of this approach in studying the functional psychoses is difficult to establish logically. At first it is observed that there are some features common to schizophrenia and the behavior of nonpsychotics intoxicated with a drug. Then, there occurs the gradual identification of the two states by most authors who assume that all elements of the two domains are identical. It should be pointed out that no studies to date have been conducted to establish the identity of these two processes. One searches the literature in vain to find a study requiring a psychiatric team to evaluate and classify a population consisting of previously diagnosed schizophrenics and those under the influence of some "psychotomimetic" drug which concludes that the population was homogeneous or undifferentiable. However, in spite of the fact that the processes have not been shown to be identical, still there are behavioral manifestations of a toxicosis that resemble aspects of the syndrome that characterizes schizophrenia. It is the brave hope of workers in this area that new chemical and biological advances will be made that will permit a greater understanding of the functional disturbances which will result in effective prophylactic and therapeutic procedures.

Psychological Effects

Of the numerous chemical substances that have striking effects on man's behavior, mood, and mental processes, there is one that has been employed most frequently, lysergic acid diethylamide (LSD-25), an indole derivative belonging to the class of ergot alkaloids.

The profound behavioral changes occasioned by LSD intoxication in normal human beings or nonpsychotics have led numerous investigators to call it a psychotomimetic agent, apparently because of the striking similarity they observed be-

tween schizophrenic behavior and the behavior induced by LSD. With a dose as small as 20–50 μg., it has been reported (**7, 13, 47**) that normal subjects manifest euphoria with compulsive laughter, depression, and some degree of confusion. In some cases there are visual illusions, hallucinations resembling those caused by mescaline, disorders of coenesthesia, posture sense, and autonomic difficulties. Rinkel et al. (**38**) reported that psychotic phenomena and alterations of the autonomic nervous system were observed following the administration of LSD to normal subjects. The psychotic phenomena were predominantly schizophrenic-like symptoms that were manifested in disturbances of thought and speech, changes in affect, mood, and perception, production of hallucinations and delusions, as well as depersonalization. Only slight changes were produced by LSD on the EEG and these were principally an increase in the total amount of alpha rhythm. Rorschach tests showed abnormalities principally of the paranoid schizophrenic type. Concrete-abstract thinking tests showed responses similar to those obtained in schizophrenic patients. Arnold (**5**) found that LSD produced disturbances in the body image and regarded this change as a retrogression to an early stage of ontogenetic development, possibly due to an influence on the function of the thalamo-cortical connections. Stoll (**48**) administered the Rorschach test to 11 mentally normal patients with and without previous administration of LSD. Under the influence of LSD there was "a general loosening of mental processes comprising disinhibition of affectivity and fluency of thought processes; the precision and wealth of content were, however, decreased." He concluded that the mixture of psycho-organic and schizophrenic traits corresponded to the clinical picture of a disturbance of the acute exogenous reaction type. Delay et al. (**14**) employed the Rorschach test on normals one week prior to LSD administration and during the effect of LSD (80 μg. orally). Comparison of the two tests showed that under LSD all personality features were intensified and therefore "more readily identifiable." Nevertheless, the authors state that it would be dangerous to draw conclusions as to the real personality of the subject from the findings of the test, for, "the toxic factors distort the picture of the true hypertrophy of the personality." Matefi (**33**) employed only one subject, a physician, to study the effects of LSD and mescaline and reported that they produced different psychopathologic reactions; the former, one of hebephrenic type and the latter catatonic. These clinical impressions were reinforced by means of a drawing test interpreted by the author. Drawings produced under the influences of LSD showed a tendency to expansion, while the "mescaline pictures" showed constriction. The drawings elicited from the subject under the influence of each drug showed "some similarity" to the drawings produced by psychotic patients. Abramson et al. (**4**) administered 25–225 μg. of LSD and placebos orally to 26 nonpsychotic adults and used a questionnaire containing 47 items to indicate changes in physiological and perceptual responses. They found that the characteristic feature of items to which responsiveness was affected under LSD was that they were related to autonomic functions said to be elicited by anxiety. It was of interest to read that the symptoms elicited by placebos were mostly depressive symp-

toms. Abramson et al. (2) also investigated the effect of LSD on the manual and verbal reaction time to auditory and visual stimuli employing 12 nonpsychotic subjects given 50 μg. of LSD orally and found that LSD had little effect on the manual reaction-time tests but significantly impaired the scores on the verbal reaction-time tests. Jarvik et al. (29) studied the effect of 50 and 100 μg. of LSD on arithmetic test performance employing 12 nonpsychotic adults and found that the scores varied inversely with the dose, i.e., the higher the dose the lower the score. Abramson et al. (3) explored the effect of the same doses on two tests of hand-eye coordination and found no statistically significant differences. However, Jarvik et al. (28) found that on 9 tests of recognition and recall significant impairment was found on 6 tests with a dose of 100 μg. whereas no significant impairment of either recall or recognition was manifest with a dose of 50 μg. In another experiment, he (27) evaluated the effects of LSD (50 and 100 μg. orally) and placebo on attention and concentration by means of various psychological tests, e.g., marking of particular figures in a mass of similar figures. Six out of eight tests showed no significant differences between the scores after placebo and after 50 μg. of LSD. Two tests showed a significant difference between the scores after placebo and 100 μg. LSD. The authors feel certain that had they "ruled out" the effects of practice the decrease in performance after LSD would have been even more significant.

Typically, the evidence employed to establish identity between the endogenous functional psychoses and the toxic states has been derived from studies and observations such as these. The reports may be summarized as indicating that various behavior changes which have been characterized as psychotic-like are occasioned by minute quantities of LSD, These conclusions are based either upon clinical impressions or upon uncontrolled Rorschach protocols usually obtained from small samples. The objective studies of Abramson and his associates demonstrate that some cognitive and motor functions are significantly impaired by LSD, but the pattern of impairment has not as yet been compared to that which may characterize the functional psychoses.

Physiological Effects

It is only recently that studies of the electrophysiological effects of the psychotomimetic agents have been undertaken. Marrazzi and Hart (32) studied the effect of LSD on the evoked cortical response of a transcallosal preparation that received 8 μg./kg. and found that the amplitude of the postsynaptic component of the transcallosal response was reduced. Elkes et al. (16) found that cerebral synaptic transmission in the cat is inhibited by adrenaline, amphetamine, mescaline, LSD, and serotonin. Purpura (37) studied the effects of LSD on evoked potentials in the auditory and visual systems. He found that LSD caused facilitation of the primary cortical responses to auditory and visual stimulation in cats. The cortical response to lateral geniculate radiation shock was also facilitated by LSD. Evarts et al. (17) studied the effects of LSD on synaptic transmission in the visual system of the cat. Intracarotid administration of 30 μg./kg. caused a decrease in the amplitude of the geniculate postsynaptic response to a single shock to the optic nerve.

Whereas geniculate transmission was blocked by LSD, transmission within the retina and between geniculate radiation fibers and cortical cells was extremely resistant to inhibition by LSD.

Generally, these studies have demonstrated marked differences in the sensitivity of various synapses to the blocking effects of LSD. Among the most sensitive synapses are those involved in the transcallosal and suprasylvian-striate reactions. The lateral geniculate synapse is less sensitive, whereas the synapses of the retina and those between lateral geniculate radiations and cells in the visual cortex are extremely resistant to the blocking effects of LSD.

Studies of the effects of LSD on spontaneous cortical activity in animals and in man have been reported. The results of Bradley and Elkes (**8**) are typical of the findings reported by other investigators who employed cats or rabbits. In the conscious, unrestrained cat from which electrical activity was recorded with implanted electrodes, LSD (15–25 μg./kg., orally) was followed by an EEG pattern which was not unlike that seen in the normal alert animal. It consisted of diffuse, low-amplitude, fast (from 15–30 counts per second) activity. The EEG of cats that had not received LSD showed higher amplitude and slower activity. Rinkel et al. (**38**) studied the effects of LSD on the EEG in humans and found that LSD caused only slight changes in the EEG, these changes consisting principally of slight increases in the frequency of occurrence of the alpha rhythm.

As yet, no one has attempted to relate any particular behavioral effect of a drug to a demonstrated disturbance of the electrical activity of the nervous system. It is clear that corticocortical responses are sensitive indices of the effect of LSD, at least in animals, but the relationship between inhibition of these responses and the psychological effects of LSD remains obscure.

Mechanism of Action

Intermediate Carbohydrate Metabolism

Mayer-Gross et al. (**34**) hypothesized that the minute dosage required to produce the psychological effect of LSD had as its mode of action some anti-enzyme activity. Since the only substrate known to be metabolized by the brain cell is glucose, an investigation was made of the effect of LSD on carbohydrate metabolism in vivo. The increase in hexosemonophosphate and glucose suggested that there was an increased metabolism of glycogen coupled with a probable block in the breakdown of hexosemonophosphate. The changes in carbohydrate metabolism observed after the intake of LSD are considered responsible for at least part of the psychological symptoms. To test the mechanism that LSD blocked glycogen decomposition at the first phase of hexose-1-phosphate, preventing any further cleavage down to the end products pyruvic acid and lactic acid, Mayer-Gross et. al. (**35**) deduced that application of glucose (which is broken down directly via hexose-6-phosphate) should abolish the toxic symptoms. This seemed to be the case, according to the authors, except that the number of experiments was too small to provide conclusive evidence. Arnold (**6**) also investigated the correlation between subjective sensations and carbohydrate metabolism and concluded that the manner of experiencing an event may be modified by LSD because it produces a toxic disturbance affecting certain cell groups. He found that the

effect of LSD may be either interrupted or retarded for 3 to 5 hours by either glutamic acid (20–100 gm.) or by succinic acid (10 gm.). Neither glutamic acid nor succinic acid is considered a detoxifying substance; instead, they are substances which protect the organic substrate against LSD so long as their concentration in the cellular groups affected is sufficient for protection. Proceeding from the hypothesis that even in acute schizophrenia there is a disturbance in the energy metabolism of certain cell groups, the author investigated the therapeutic effects of glutamic and succinic acids. Employing dosages calculated to suppress the effects of LSD, he could favorably influence certain "labile" symptoms (impulses, passion, emotional tension, etc.) but could not influence symptoms of deficiency or alterations in personality. Fischer et al. (**18**) investigated carbohydrate metabolism by employing standard tests of liver function prior to and after administration of LSD and mescaline. He reported that LSD caused a less intense and transient disturbance in liver function than mescaline. Quick's hippuric-acid test was found to be negative after LSD but positive after mescaline, as it is in most cases of acute schizophrenia. However, the cinnamic-acid test of liver function of Snapper-Saltzman, which is more sensitive, reveals transient disturbances of liver function after the administration of LSD.

Buscaino et al. (**9**) injected two dogs with 1 and 10 μg. LSD, intravenously, and they developed, respectively, psychomotor excitement followed by depression in one case and "catatonia" in the other. In chronic experiments (4 μg. intramuscularly over 23 days, 11.8 μg. intramuscularly over 56 days, and 15.3 μg. orally over 90 days) the animals developed psychomotor excitement initially but were soon normal again. Following administration of LSD the EEG spectrum showed a shift to high frequency waves of low amplitude. Hypoglycaemia and hyperbilirubinaemia were generally noted in the chronic experiments whereas the histochemical phosphatase reactions in the brain were modified in the acute experiments. The liver and kidneys exhibited degenerative changes in the parenchyma. These findings were employed to support a hepatotoxic theory of schizophrenia.

The Pituitary-Adrenal Axis and Reaction to Stress

Hoagland and his associates (**24**) compared the adrenocortical function and urinary phosphate excretion of schizophrenics to normals under the influence of LSD. In normal subjects, LSD (0.5–1.0 μg./kg., orally) reduced the excretion of inorganic urinary phosphates as compared to the control values. While the subjects were under the influence of LSD, 25 mg. corticotropin markedly enhanced the excretion of inorganic phosphate. This increased excretion of inorganic phosphates under the impact of adrenocorticoids in the LSD-treated normal subjects is similar to that found in schizophrenic patients not given LSD. The findings indicate that LSD appears to stimulate the pituitary-adrenal axis and leaves the adrenals somewhat unresponsive to corticotropin. It is suggested that LSD acts on enzyme systems to facilitate the binding of phosphate. Adrenocorticoids may release the phosphate from its bound form and thus account for the marked output of urinary phosphate in schizophrenic patients and in normal sub-

jects under the influence of LSD following the action of corticoids. An endogenous derivative of adrenaline metabolism may act in schizophrenic patients in a similar manner to that in which LSD acts in normal subjects. Thus, this hypothesis proposes that schizophrenia may be due to the production of an endogenous metabolite that modifies phosphorylation. Rinkel et al. (**39**) also found in biochemical studies that LSD seemed to stimulate the pituitary-adrenal axis. With LSD, the adrenals were rendered somewhat unresponsive to adrenocorticotrophic hormone and modified urinary phosphate output (similar conditions prevail in schizophrenia). The authors assume that LSD interferes with the adrenaline cycle and that adrenoxine, a breakdown product of adrenaline, may be involved in psychoses. Sloane et al. (**45**) administered LSD to 11 healthy controls, 12 patients with predominant depression, and 7 patients with schizophrenia. In general, slight although clinically apparent changes due to LSD were difficult to verify objectively. However, spectroscopic oximetry (an estimate of capillary change) indicated increased autonomic lability in the controls and depressives but not in the schizophrenics.

The Antagonism Between LSD and Serotonin

The numerous studies demonstrating the psychotomimetic effect of LSD suggested to some investigators (**22, 46**) that drugs or neurohumors antagonistic to LSD would play a major role in mental activities. The initial research that stimulated this hypothesis was performed by Gaddum (**21**) who found that LSD inhibited or abolished the oxytocic effect of serotonin but not that of oxytocin on the isolated rat uterus. Shore et al. (**44**) studied the interaction of serotonin (5-hydroxytryptamine) and LSD in the central nervous system of the mouse and found that serotonin markedly potentiated the hypnotic effect of hexobarbitone. LSD, which itself had no effect on the hypnosis produced by the barbiturate, markedly diminished the potentiating effect of serotonin. In another study Gaddum (**22**) tested the effects of serotonin and various possible antagonists on the rat uterus, perfused rabbit ear and guinea pig ileum. Of the ergot alkaloids investigated, LSD was the most active and specific antagonist of the action of serotonin. Ginzel et al. (**23**) also found that LSD was a strong antagonist of the constrictor action of serotonin on the pulmonary vessels of the cat and the hind-leg vessels of the cat and dog.

Woolley and Shaw (**50**) described serotonin as a hormone that has a vital role to play in living processes. They postulated that following administration of LSD mental disturbances became apparent because (*a*) the antimetabolic action of LSD on serotonin diminishes the content of this substance in the brain, or (*b*) by increasing the amount of serotonin in the brain by competing for amine oxidase, the accumulation of excessive amounts of serotonin in the brain is permitted. In terms of these hypotheses pertaining to the "model psychosis" produced by LSD, the authors further assert that endogenous psychoses such as schizophrenia may result from either too much or too little serotonin in the brain. A real test of the hypothesis that antimetabolites of serotonin cause behavioral disturbances by interfering with the action of serotonin in the brain would be to determine whether serotonin would overcome the mental

effects of drugs, i.e. various antimetabolites of serotonin. Unfortunately, this test has not been made. Yet, even if it had been made and the hypothesis verified, there would remain the problem of identifying an antimetabolite of serotonin in patients afflicted with an endogenous psychosis.

The Effect of LSD on Psychotics

Although LSD made its impact on psychiatric research because of its psychotomimetic properties, it is interesting to note that it was later employed as a research therapeutic agent. Some investigators curiously felt that drugs capable of engendering a morbid state in normals could have therapeutic value for psychotics.

De Giacomo (**12**) administered 300–500 μg. to 12 mental patients and found that in 5 an initial phase of excitation was followed by catatonia-like symptoms with stupor and catalepsy, resembling that noted after the administration of bulbocapnine. In low dosage, LSD caused mental excitation, but in high dosage, hallucinatory mental confusion and catatonia. Katzenelbogen and Fang (**30**) administered LSD, sodium amytal, and methedrine to 20 schizophrenic patients and found that the physiological reactions to LSD and methedrine were predominantly sympathicotonic, while those to sodium amytal were predominantly vagotonic. Emotional reactions appeared more marked with LSD than with methedrine or amytal. Since the effects of LSD and methedrine lasted considerably longer than those of amytal, there was greater opportunity for emotional catharsis and verbal production. Pennes (**36**) administered amytal, pervitin, mescaline, and LSD to 55 schizophrenic patients and analyzed the results in terms of normalization and intensification of the preexisting clinical symptoms. Amytal was classified as predominantly a normalizer of clinical symptoms, pervitin produced an unstable state with normalization and intensification equally evident while mescaline and LSD acted as intensifiers. Condrau (**11**) administered 100–280 μg. of LSD to 30 mental patients and 7 normal subjects. He found that mental patients showed a much greater resistance to behavioral change following administration of LSD than the normal subjects; moreover, LSD was generally better tolerated by the mental patients than by the normal controls. Whereas a given dose would alter the behavior of a normal individual the same dose produced no observable alteration in the behavior of the psychotic. Forrer and Goldner (**19**) studied the physiological and psychic responses resulting from administration of LSD to schizophrenic patients. The drug produced a slight increase in blood pressure, slight increase in pulse rate, no essential change in respiration, an increase in salivation and lacrimation, dilation of the pupils, an increase in deep reflexes, and slight ataxia. Oral administration produced pupillary dilation of marked degree, whereas conjunctival instillation produced very slight dilation. The total white blood-cell count was increased during the time of action of the drug. Euphoria occurring in outbursts was prominent. "Increased accessibility and availability with increased release of libido and greater accessibility of delusional material" was also observed. Visual hallucinations of the so-called primary type were not noted in two blind patients treated with the drug but were seen in all of the six patients with normal vision. Urinary constituents, the nonprotein nitrogen level, the EEG, cephalin-

cholesterol flocculation, weight, and temperature were not affected by the administration of this drug in doses up to 6 μg. per kilogram.

Hoch et al. (25) found after administration of either LSD or mescaline that the physiological and mental symptoms of schizophrenic patients were markedly aggravated. The changes after LSD were less intense and less diffuse than those after intravenous injection of mescaline but comparable to those after oral administration of mescaline. Visual hallucinations were less frequent after LSD but other perceptual disturbances occurred with about the same frequency. Both drugs magnified the schizophrenic structures in schizophrenic patients. Liddell (31) studied the effects of methedrine and LSD on mental processes and on the blood adrenaline level using patients suffering from various mental disorders. After an initial phase of relaxation, both drugs produced an aggravation of the clinical picture. Rapid mood swings were sometimes observed after LSD but not after methedrine. After both drugs the plasma adrenaline level rose initially, then dropped below the starting level and finally rose again. The effect of LSD on the blood sugar concentration was hardly significant.

Busch and Johnson (10) believe that LSD is a drug which induces a controllable toxic state within the nervous system, that reactivates anxiety and fear with apparently just enough euphoria to permit recall of provoking experiences. It does this, it is claimed, without the sluggishness of speech and speech difficulties so frequently encountered with amytal or the more marked confusion encountered during insulin shock therapy or electric shock therapy. LSD offers a means for more readily gaining access to the chronically withdrawn patient. The authors also believe that LSD may serve as a new tool for shortening psychotherapy. Sandison and his colleagues (41) described the results of LSD therapy in 36 patients suffering from psychoneurosis and allied conditions, 20 of whom had previously received other treatment without effect. The initial dose was usually 25 μg. and at subsequent treatments the dose was gradually increased until an "adequate" reaction was obtained. Thereafter, the drug was administered at approximately weekly intervals. As a result of the LSD therapy, it is claimed, 14 patients recovered (average of 10.4 treatments), 1 was greatly improved (3 treatments), 6 were moderately improved (average of 2 treatments), and 2 were not improved (average of 5 treatments). Eleven patients still under treatment at the time of the report were improved (average of 18.6 treatments). In one case (6 treatments) it was too early to assess the results. One patient refused further treatment after having received one dose of LSD. In another paper (40) Sandison examined the possible psychological mechanism of action of LSD by analyzing the verbal material produced under the influence of LSD and he states that it bore a striking similarity to the dream and fantasy material of patients undergoing deep analysis. LSD, according to Sandison, produced an "upsurge of unconscious material into consciousness" and this material was of great personal significance to the patient. LSD apparently permits unconscious material to become manifest and psychotherapy helps them to assimilate this material. Abramson (1) has also employed LSD as an adjunct to psychotherapy to eliminate fear of homosexuality. He reports a verbatim transcript of a patient under LSD

(40 μg.) who had previously resisted analysis of a dream related to her conflict. Under the influence of LSD the patient acquired more confidence in reconstructing and re-evaluating data for a longer period than had previously been possible without LSD.

Savage (**43**) studied the effects of LSD in 5 normal controls and 15 depressed patients. In the latter group 3 patients recovered and 4 improved after 1 month of LSD treatment (20–100 μg., daily, orally); four patients showed no improvement and treatment was discontinued on the remaining four for various reasons. Frederking (**20**), although reporting the beneficial effect of LSD as an adjunct to psychotherapy, cautions against the use of the drug in anxiety states and schizophrenia. Several other reports suggest the inadvisability of giving LSD to schizophrenic patients. Elkes et al. (**15**) studied the effects of several drugs on catatonic stupor and found that the response to LSD was characterized by unmotivated laughter and crying, bizarre uncontrolled behavior and an apparent activation of hallucinatory and delusional material. Hoch (**26**) reported that LSD (as well as mescaline) disorganizes the psychic integration of the individual. The disorganization is more apparent in schizophrenics and latent schizophrenics than in normal subjects. More specific effects of LSD on schizophrenics are reported by Savage (**42**). He employed doses of 10–100 μg. orally or parenterally, in 6 normals and 32 hospitalized mental patients. In normal subjects an effect was produced by 10 μg. but in acute schizophrenics, 100 μg. was required to produce a much slighter effect. In acute schizophrenics the symptoms caused by LSD appeared to be an exaggeration of symptoms that already existed. Chronic schizophrenics exhibited behavior similar to that observed in acute episodes. Schizoid patients with depression and involutional depressives complained of an intensification of anxiety, depression, and somatic symptoms. Savage, like Hoch, concluded that LSD makes it impossible for the ego to integrate the evidence of its senses and to coordinate its activities.

The evidence presented assigns some unique effects to LSD. On one hand we find that LSD reactivates anxiety and fear which is considered conducive to the elicitation of unconscious material which can be assimilated by the ego. It purportedly facilitates the acquisition of confidence required for reconstruction of personal data. On the other hand, it is reported that LSD disorganizes the psychic integration of the individual. Here then we have a state in which LSD engenders anxiety and fear and disrupts the psychic integration of individuals and yet is considered by some authors as a valuable adjunct to psychotherapy. Although a review of the therapeutic value of LSD for chronic emotional disorders seems inconsistent, there is some agreement that LSD is ineffective for anxiety states and for schizophrenia.

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