Notes and Abstracts

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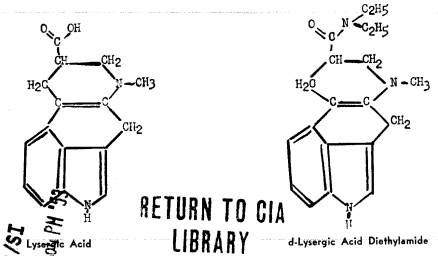
The CNS Action of D-Lysergic Acid Diethylamide (L.S.D.-25)

ERGOT of rye has long been of great interest to medical science and there is some evidence that ergot was used in the Eighteenth Century by the French midwives to hasten labor. The specific alkaloid involved is ergonovine which produces contractions of the human uterus. The ingestion of large quantities of ergotized rye produces an acute toxic effect to which Mezerary in his history of France gave the name St. Anthony's Fire when describing epidemics of ergotism. The constituents of ergot have been divided by chemists into two classes, *i.e.* the alkaloids (active and inactive), and the amines and other nitrogenous compounds. It is from the active alkaloid ergonovine, alluded to, that d-lysergic acid diethylamide is derived. Lysergic acid is the base of this compound as it is of all the ergot group. The substance under consideration is the synthetic amide of d-lysergic acid with diethylamine. The structural formulas of d-lysergic acid and of d-lysergic acid diethylamide are shown below.

The diethylamide was obtained for the first time in 1938 by W. A. Stoll and A. Hofmann.

The quantities of this drug necessary to produce a demonstrable effect are extremely minute; it was established by Stoll that an oral dose of 0.000020 gm. (20 micrograms) administered in water solution was sufficient to obtain threshold effects. The usual doses administered are from 10 to 60 micrograms. The effects of the drug are noticeable in one-half to one and one-half hours, with the maximum effectiveness in from two to two and one-half hours, and usually persists for four hours. While the drug effect may persist for as long as eight hours, this is unusual. There are sometimes demonstrable after-effects lasting as long as a week. Forrer and Goldner report from studies carried out on laboratory animals that the lethal dose intravenously is 65 mg. per kilogram and the lethal subcutaneous dose 285 mg. per kilogram. This indicates that d-lysergic acid diethylamide is a relatively nontoxic drug. It appears to be quite safe since the usual dosage is from 10 to 60 micrograms.



Lysergic Acid

d-Lysergic Acid Diethylamide

[Note that the OH group of the terminal carbon atom has been replaced by $N(C_2H_5)$ 2.]

PHYSIOLOGICAL EFFECTS

The systemic effects of the drug, as reported in the literature, are varied and often contradictory. Most investigators seem to be in agreement that a dilation of the pupils is produced and Forrer and Goldner noticed only a slight dilation when L.S.D.-25 was instilled directly into the conjunctival sac, which observation indicates that the dilation is due primarily to the central effects of the drug. The pulse rate increases, and hypersalivation occurs, the latter increasing directly with the amount of the drug administered. Gastric distress, nausea and occasional vomiting have often been reported, as have skin flushing and a slight ataxia. Increased lacrimation, hyperreflexia, chilliness, muscle irritability and hot and cold "flashes" may also occasionally be noted. Stoll mentions indistinct and blurred speech and vision as well as disturbances in tactile perception. No urinary changes were noticed but a dose of 1 microgram per kilogram was reported by Forrer and Goldner to produce a definite leukocytosis. These investigators also found that atropine did not produce its customary drying of the mucous membranes of the mouth when the atropine was followed by L.S.D.-25.

Reprinted from The MODERN HOSPITAL, January 1953

DeSchon, Rinkel and Solomon reported that the autonomic nervous system exhibited signs of greater lability during the height of the reaction to the drug. The tests were carried out with adrenalin and atropine. They, as well as other investigators, report slight changes in the electroencephalogram records of patients under the influence of L.S.D.-25 but these changes seem insignificant when compared to the magnitude of the clinical reaction.

Undoubtedly, the most striking physiological effect of the drug is the production of vivid visual hallucinations in a large number of the cases reported. These are actually pseudo-hallucinations since the subjects are aware that these images are subjective. These hallucinations are best experienced in a darkened room and are rather specific in character. That is, they consist mostly of geometrical patterns and designs and of flashing whirling and dancing patterns of light. All of these forms are perceived as being in motion and, in addition, this motion seems either to flow toward the subject or away from him. Brilliant hues and colors characterize these images and they may best be approximated by indicating their similarity to the images that are seen in part of Walt Disney's motion picture "Fantasia."

Stoll noticed that the colors are definitely influenced by the mood of the subject, being bright when the subject is euphoric and mostly confined to somber hues of blue and dark green when a psychic depression is experienced. Less frequently, the hallucinations are more organized, landscapes, vistas and buildings being perceived. In the light, the incidence of hallucinations is lessened and often visual illusions take their place. Objects are perceived as very tiny and distant or distorted and out of proportion. Gross disturbances of perspective are reported. It has also been reported by Stoll that there are occasionally synesthetic effects of noise upon visual hallucinations.

In addition to distortions and disturbances of visual perception, there are, although less frequently encountered, auditory hallucinations and illusions of a simple nature and a hypersensitivity to auditory stimuli in general. Some gustatory hallucinations (metallic taste) are also reported. Tactile hyperesthesia and paresthesia have already been alluded to.

PSYCHIC EFFECTS

L.S.D.-25 produces a marked euphoria of mood with increased amiability and alterness. This euphoria, however, alters easily and may be transformed into a depression in which suicidal tendencies appear. Whether in a euphoric state (by far the most common) or a depressed state, the mood may be either agitated or apathetic. Time perception is often disturbed with a feeling that a tremendous amount of time has elapsed since the first administration of the drug. Temporal perception may also be considerably shortened and, in some instances, there is reported a feeling of the cessation of time.

These temporal distortions are similar to those observed in marihuana intoxication. The thought processes are accelerated but there is noticed an increased distractability and a difficulty in concentrating. Moreover, the thought processes often become jumpy and exhibit little coherence. A certain clouding of consciousness may occur but this is not very pronounced and the subjects seem at all times to be in good contact with their environment. Self-observation is often distorted with feelings of curious detachment and estrangement; the subjects often report a feeling of being outside of themselves.

At times, in contrast to a flight of ideas, a distinct poverty of thought and apathy paralleling certain schizophrenic states may be induced by L.S.D.-25. One group of experimenters administered a Rorschach examination to five normal subjects, four of whom had control while in a normal state. All of the tests showed distinct abnormalities during the height of L.S.D. intoxication. Three records were definitely schizoid; one frankly paranoid record was obtained, and one record indicated borderline symptoms not definitely assignable to any psychiatric classification. These results lead one to ponder the possibility that perhaps the endogenous release of a similarly acting compound might account for schizophrenic reaction types. In addition, the use of L.S.D.-25 may have use in the further investigation of the Rorschach test itself. Another often reported effect of the drug is the irrepressible desire to smile and laugh although no humorous situation has occurred. Self-control can not at times be adequately maintained. Euphoria is the most pronounced and most often reported psychic effect.

PSYCHOTHERAPEUTIC CONSIDERATIONS

The administration of L.S.D.-25 to schizophrenic patients, as reported by Scholl, Forrer and Goldner and Busch and Johnson, may produce striking effects. The chief changes seem to be an increased activity and euphoria and an increased effect. In addition, they exhibit evidence of having visual hallucinations and they undergo most of the physiological effects seen in normal persons although they seem to have a higher tolerance and the total picture is blander than in normal persons. Patients have seemed to exhibit a more adequate response to external stimuli and seem to come into closer contact with their environment. Some who had previously refused discussed their difficulties at length. The changes produced, while not always predictable, seem to have in common an increased and more realistic effect. Patients were able to experience and express relevant emotion, and many patients, following administration of the drug, strive to establish interpersonal relationships which they had hitherto ignored. The patients thus become more accessible to the psychiatrist and better able to reveal and discuss their problems. This may lead to a shortened term of psychotherapy. The toxic effect of the drug seems to break down the barriers of repression.

In general, according to W. A. Stoll, the effects of d-lysergic acid diethylamide seem to be those of a delirious intoxication. This intoxication has many features which parallel the actions of ethyl alcohol, marihuana, mescaline, opium and cocaine. Perhaps it produces a depression as does ethyl alcohol since the euphoria, increased emotional lability, dilation of the pupils, increased deep reflexes, and increased salivation seem to indicate this. The blocking of cortical inhibition would produce some of the effects noticed during the height of the reaction to this drug. Some investigators envision a selective inhibitory effect upon the sympathetic intracortical circuits and/or sympathetic projections to or from the telencephalon. Brodman areas 18 (secondary visual cortex) and 19 (tertiary visual area), the stimulation of which produces unformed hallucinations of light and hallucinations of formed images, respectively, appear to be particularly involved. Since some auditory and gustatory phenomena are also encountered, it is probable that the cortical areas involving these functions are also affected.

It seems from the foregoing that the effects of L.S.D. are not specific since the symptomatology observed may also be seen following the administration of mescaline and other phantastica. One very important difference is to be noted, however, and that is the minute amount of L.S.D. required to produce an effect. In regard to this, it may be possible to trace L.S.D. in its course through the organism by radioactive tagging as suggested by W. A. Stoll. Research on the effects of the drug will probably follow two main courses. First, the drug will be administered to patients suffering from mental illness as it has some demonstrable therapeutic effects in that it renders schizophrenics more accessible and increases in some patients the ability to relive past traumatic experiences and to reevaluate their present difficulties in terms of recalled past experience. Research with the drug is also indicated with psychoneurotics and with forms of psychoses other than schizophrenia. The second main line of research will probably be concerned with the effects of L.S.D. on normal individuals especially in regard to the reproduction of schizophrenic-like reaction types. The use of psychological tests of personality, intelligence and learning in conjunction with L.S.D. on normal subjects would seem to be fruitful and a start in this direction has already been made. More purely physiological testing of reaction times and reflex actions are also desirable. Finally, an attempt must be made to trace the drug through the organisms and to determine, if possible, its site of action and method of action. Animal experimentation is imperative. L.S.D. is a drug of extreme interest, especially from a psychiatric standpoint; further intensive research is definitely indicated.—RICHARD SMITH, B.A.

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