

CLINICAL AND LABORATORY OBSERVATIONS ON LSD-25¹

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Lysergic acid diethylamide was synthesized, in 1937, by Stoll and Hofmann (13-15). At present there seems to be agreement by most investigators on the clinically observed responses of human patients to the drug. The remaining questions seem to be, "How does it work?" and "What to do with it?" The first question implies an anatomic, biochemical and physiologic response. The second, almost anything from distorting spider webs and scaring salamanders to "shaking up" psychologic trainees or having LSD-25 social parties, to curing schizophrenia (2, 4, 5). *Ergo*, the research done is dependent upon the facilities available and/or the interests of the investigators. Our facilities, consisting of a 70 bed acute, intensive treatment section of a general medical and surgical Veterans Administration teaching hospital, lend themselves well to a twofold purpose: training residents and treating patients.

No animal laboratory is available to us. The only basic science help afforded our particular section is biochemistry, so that our laboratory work is necessarily limited to this field. We have attempted to utilize these facilities to answer in part the two questions posed.

Anxiety is accepted by most psychiatrists as being basic to all mental illnesses. The constellation of symptoms presented is thought of as the effort of the organism to defend itself against a threat. We do not mean to discuss the meaning of anxiety, or whether it is due to a twinge in the ascending reticular activating system or to

castration fear, but rather are considering it as an accepted phenomenon and a useful construct. Moreover, we feel that the continuous repetition of any thought process is the form of all mental illnesses; that it is upon this we make the diagnosis of an illness. The content of the repetition gives us the type. Many authors have taken note of this process and have given it many names, such as circuitous firing circuits and positive feedback mechanisms, or (in a broad sense) Freud's "repetition compulsion neurosis." If one is to treat successfully a psychiatric illness this pattern must be disrupted. The analyst does this over a long period of time and occasionally finds himself repeating word for word a session that occurred a year previously with the same patient. Most important is the transference which he utilizes along with free association in an attempt to break up this obsessive thinking and activity, in order that the organism (ego) may go on to more constructive activity. Electroshock therapy, through the process of a thalamic and cortical discharge "blanks" the cortex; and we hope when cerebation returns that these pathologic thought processes will no longer be present. We have attempted (borrowing from both methods) to use LSD-25 as a therapeutic tool in the treatment of non-psychotic patients. We may hypothesize that the modification of obsessiveness in reaction to LSD-25 occurs by way of an alteration of "reverberating circuits." This could be produced within the reticular activating system through a process of inhibition of the axodentric synapses with a concomitant facilitation of the axosomatic synapses (11), thereby altering the external stimuli available to the cortex.

In our preliminary work with LSD-25,

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using physicians and psychology trainees as subjects, one of the first things noted, besides the obvious hallucinogenic qualities of the drug, was the rapid transference formed by the subject to the investigator. This transference was of a very strong nature and lasted throughout the test situation. Others have also written of this, notably Harold Abramson in his paper, *LSD-25 Effect on Transference* (1). Of special note was the fact that the transference gained was not dependent upon the experience or skill of the "therapist." This immediately opened the way to two methods of procedure, the most obvious being that of therapy with a patient. The second, that of teaching the handling and utilization of the transference process to residents and trainees. The latter may eventually prove to be more important than any therapeutic effect which may take place in the patient. Considering how best to use this transference, it was decided that Rosen's direct, interpretative technique would be the most efficacious and logical, since we were dealing with a psychotic process in which hallucinations, delusions, reality distortions, etc., were prominent. It was found that the patients readily accepted the interpretations and readily gained insight. Examples will be given in the case histories. Marked improvement was seen in psychoneurotic and nonpsychotic "obsessiveness" patients (nonstandardized nomenclature referring to chronic symptom complainers). An additional group of brain syndromes were treated but with no results.

An obvious objection to this method is that perhaps we have what is known as "transference cures." Aside from the fact that we accept readily any type of improvement or cure in the patient from whatever cause, Alexander has stated that he believes that some of his cures promulgated by two or three psychotherapeutic sessions were not of a "transference cure" nature but that the therapy formed a "wedge into the ego" as it were, and the ego was then able

to go on and develop, thereby causing relief of symptoms in the same manner as any prolonged therapy might do. We hoped our therapy with LSD-25 would do just this, allow the ego to develop and expand, thereby forming the basis of a permanent change in the personality structure—or at the very least mitigate the crippling psychiatric condition.

A severe obsessive-compulsive patient was chosen (the extreme of obsessiveness) to demonstrate the ability of LSD-25 in breaking up circuitous thinking and activities. The description and results are given in Case 1. This case readily demonstrated our first hypothesis, and in so doing gave us an inkling of another type of therapy for the obsessive-compulsive patient, namely, "deconditioning." During the height of the reaction the patient was cajoled into doing things that ordinarily would cause an overwhelming amount of anxiety. This process was repeated over and over again. The most common response from the patient to this was, "I don't know how I can do this now. I don't understand this. I feel no anxiety at all and ordinarily it would frighten me a great deal." Following treatment it was found the patient could go on for days performing activities which were previously impossible for him. We hope to study more patients of this type, and to further our work along these lines. Few such patients are to be found in our institution.

METHOD OF TREATMENT

All patients were given complete physical and neurologic examinations, liver function tests, glucose tolerance tests and routine laboratory work. The standard dose of 100 μ g. of LSD-25 (Delysid), furnished by Sandoz Pharmaceutical Company, Hanover, New Jersey, in a fourth of a glass of distilled water was used uniformly. Treatment was given once weekly. If proper reaction did not occur the dose was doubled. On the morning of the treatment breakfast

was withheld. Each patient was placed in an individual room and assigned a primary therapist who stayed with the patient in periods ranging from 2 to 6 hours. No drug termination was made. The reaction was allowed to run its natural course. Control was accomplished using placebos. The same physician gave the drug at all times, and it was he who determined whether the drug or placebo(3) was being used. No one else was aware of whether the patient had water or LSD-25 until the reports were in at the end of the day.

A great latitude of freedom was afforded the therapist and the patient, *i.e.*, they ate together, smoked together and, if the patient wished he could get up and walk away from his therapist. Treatment was attempted in some 18 cases with a total of 52 treatments. The least number of treatments given was 1; the most for any one patient was 8. The total patient and treatment number does not include that carried out with the staff as subjects. Six cases are presented with their results. One should bear in mind that all of these patients had had extensive previous treatment with other methods without improvement. All had personality difficulties which would make improvement very unlikely, so that the staff considered any improvement a significant achievement.

Case Histories

Case 1. J. J. M., a 41 year old white, single, male veteran had classical symptoms of obsessive compulsive neurosis. He complained only of his inability to overcome his compulsive handwashing, of his avoidance of crowds for fear of "getting their germs," and of his compulsive doubting. He wore his trousers and sleeves rolled up, avoided shaking hands with anyone to avoid contamination and was first in the dining room and showers to be sure the food and water would not be "infected." His condition was of 14 years' duration and he had received a complete psychoanalysis, complete course of insulin and electroshock therapy and, of course, the gamut of drugs and various types of psy-

chotherapy. He was placed on LSD-25 treatments, eight in number. His symptoms were treated at the height of the effect of the drug at each treatment; he was given direct interpretive psychotherapy and strong suggestion. Subsequently he shook hands without hesitation to bid farewell to other departing patients. He ate more regularly with concomitant gain in weight. His handwashing was definitely at a minimum. During additional LSD-25 treatments, direct psychotherapy was continued to break up his obsessiveness and "recondition" his patterns of thinking. His improvement at first was dramatic and sustained, but after termination of treatments he displayed recurrences, even though he was satisfied that, "At least I'm not as tense and anxious anymore." His improvement was minimal.

Case 2. M. E. E. W., a 35 year old Negro, married truck driver, complained of gastralgia, severe generalized cephalgia, general tenseness, vague myalgias and easy provocation to anger at work and at home; all since 1943. The symptoms were relieved, usually promptly, by taking an antacid and walking away from or avoiding situations in which he felt irritable. At times, however, he acted out his anger and became involved in occasional fisticuffs. None of the complaints were typical in their course, frequency, location or severity. These behavior patterns never interfered with his sleep or vacations. There was no relationship to any specific marital, social or other interpersonal problem. Since 1943, he had entered several hospitals and always (including his current admission) his blood and serologic examinations, x-rays of the chest and skull, upper gastrointestinal series and electroencephalogram disclosed no pathologic conditions.

His past history included the presence of headaches most of his life. He was reared under strict, paternal discipline. He perpetuated a strong, passive-dependent relationship with his mother although there was conspicuous ambivalence toward her and subsequent female figures. His life theme throughout his adolescence and adult life was a striving for objects to gratify and sustain his state of dependency. Whenever his dependency was threatened, he showed sensitiveness, temper outbursts and at other times vacillated toward attitudinizing, aloofness and withholding his anger. In school

he managed to progress to about the eighth grade despite truancy and disinterest in his studies. In interpersonal associations he had little ability to give or sustain affection and exploited relationships chiefly for narcissistic gains. Occupationally, he displayed emotional instability resulting in frequent job changes.

In the hospital he was inclined to demonstrate a parasitic social existence. At times he was charming and confidence-inspiring, then at other times, surly, complaining and resentful. He frequently complained of his symptoms which were seldom consistent. He never remarked on relief despite participation in psychotherapy, tranquilizing medication and the ancillary therapies.

During the LSD-25 treatments the patient had an intensification of his somatic symptoms. At the peak of effect of the drug he became wide eyed with undescrivable fear. He re-experienced strained interpersonal situations during which he recalled arguing with authority figures. He reported he was in communication with Jesus Christ and, as he states, "I felt like I was walking in the shadow of the valley of death and, like Him, was being born all over again." At this point he was given the interpretation that he had repressed considerable hostility toward his father and basically had always felt the absence of a healthy identification with him or other substitute figures; this defect in psychosexual development was presented along with his passive-dependent relationship with his mother which the patient accepted with further remembrances of situations to confirm this. After four such treatments he requested to leave the hospital to attempt an extramural adjustment in a productive role once more. He has sustained improvement to this date.

Case 3. J. B. K., a 26 year old Greek-American man, married two years, began to notice the onset of headaches, chest pains, fluttering of the heart, and generalized weakness about the time of the birth of his first child. His longitudinal development revealed early childhood restrictions under a patriarchal atmosphere with a compromising, indulgent mother. A strict moral code and social obedience fostered suppression of heterosexual relationships along with feelings of indecisiveness and marginal self-confidence. His family had always

been financially secure and provided the patient with employment in their restaurant. This dependency state was further intensified by frequent childhood illnesses such as allergies and an above average number of mild ailments. He could never assert himself within the family circle or among his peers. By repression and suppression, and the assumption of passive, conforming behavior, the patient was reasonably successful in controlling his hostility. His marriage was an attempt to emancipate himself from this infantilized role. He was assured continued employment with his family's support and he could not turn his back on his parents' "helpful" advice.

The patient was involved in a minor truck accident during which he suffered mild muscle injuries to the back. This apparently had considerable meaning to him as he repeatedly referred to it as the etiology of his current difficulties.

Prior to the birth of their first child he realized that overwhelming and anxiety-provoking responsibilities were forthcoming. His anxiety was bound by somatization and affective channeling through the autonomic system, in the form of the initial symptoms. He responded to none of the psychotherapeutic or other ancillary therapies or to ataractic medication. His complaints were frequent and irregular throughout the day and night. They varied at times and "never were quite gone..."

Under LSD-25, he relived the experience of the truck accident and developed a paraplegia in extension which was quickly relieved by direct interpretation of his wish to remain completely helpless and dependent. He also abreacted emotional tension and apprehension which he had experienced and which had been repressed since the accident. He received three LSD-25 treatments and his progress has been stable.

Case 4. E. P. is a 26 year old, unmarried, Mexican-American male veteran with a 10 year history of atypical symptoms of headache, nausea, myalgias, gingival discomfort, temper outbursts and vague tinnitus. The personality development was passive-dependent. Identification was with an emotionally demonstrative, weak mother. He avoided heterosexual relationships except with prostitutes. School and work adjustment were unstable and characteristically

acceptable only with those who granted him favors and condoned his mediocre talents. He had several hospitalizations and had received various types of psychotherapy and various medications.

Under LSD-25 treatments the patient experienced a visitation of the Virgin Mary standing on a pedestal which was interpreted as symbolic of the purity he saw in women, especially his mother. The relationship between this and his evasions of marriage or of mature love was pointed out. His improvement has also sustained itself to this date.

Case 5. R. M. M., a 34 year old Mexican man, married, with five children, complained of intractable aerophagia, chest pain, gastralgia and flatus over a period of several years. His longitudinal history indicated tumultuous family influences with rejecting and depriving parents and much sibling rivalry. His school and work histories were likewise poor and under any increased stress in ordinary interpersonal relationships his frustration could only be quelled with the use of alcoholic beverages. He received much psychotherapy, hospitalization, specially arranged ancillary therapy and carefully planned and scheduled medical regimen. Laboratory reports were negative. No improvement was ever admitted by the patient or discerned by the staff.

Under LSD-25 treatment the patient reported living again as an infant. The interpretation was made that he was "still sucking on the bottle, just as an infant, and that in this state he need not be concerned about his expected obligations to his family, etc." During the subsequent treatments, he slowly accepted the meaning of his infantilized behavior and need to be nursed and cared for. The aerophagic symptom disappeared although his chest pain persisted. His response was considered good. Then he developed a depression characterized by crying spells and thoughts of suicide. He received a course of electroshock therapy and reported a remission of his chest pain along with the depression. He was improved enough to be discharged.

Case 6. E. S. N., a 43 year old white, married man, retired from the Marine Corps, complained of severe, cervical muscle spasm of about 1½ years' duration. His laboratory and x-ray reports were all normal. He did not respond to

psychotherapy, hypnotherapy or tranquilizing drugs. His past history was without definite emotional disturbances from the patient's point of view. He was exposed to a strict Roman Catholic family milieu. He extricated himself from a yoke of religious limits by enlisting in the U. S. Marine Corps and dissociating himself from Catholicism.

Under the LSD-25 treatments the patient experienced an intensification of his muscular tension and reported visual hallucinations. These were described as follows: "I saw my wife and children standing next to my mother's grave... just to one side God was also present; I felt as though I were a spectator to a scene full of meaning to me." He remarked that he felt as though he was "crying on the inside" all during this time. It was interesting that this patient was repeatedly urinating at intervals during the treatment. He unhesitatingly accepted the interpretations that this "scene" evoked repressed guilt feelings; as he exclaimed, "This is the way I've felt ever since I lost my faith; I let my mother and God down..." Following three such treatments the patient was no longer troubled with insomnia and felt markedly tranquil, although his muscle spasm was not entirely relieved. The degree of improvement was also fair, to the point of his preparing for release from the hospital and a return to his religion.

LABORATORY DATA

Most of the individuals receiving LSD-25 were sampled for circulating eosinophils before, and 1 and 4 hours after the ingestion of the drug. Eosinophil counts were obtained using the Randolph technique (12). Fifteen subjects were tested; 10 of them received 0.1 mg. LSD-25 orally, 2 to 6 times at weekly intervals. Control days with no placebo or medicant, placebo days and stimulant controls with adrenaline and/or ACTH were run.

All normal individuals and all patients but one responded with a decrease (40 per cent or more) in eosinophils following the ingestion of 0.1 mg. of LSD-25. The one patient who failed to respond to 0.1 mg. subsequently lost 75 per cent eosinophils

after 0.2 mg. LSD-25. A block or tolerance to the medicant was observed upon repeated weekly doses. This occurred in one patient on his third course of LSD-25. At this time he also failed to respond to 0.3 ml., 1 to 1000 adrenaline, s.q., but did produce an eosinopenia with 25 units of ACTH, i.m. Prior to this block he had developed decrease in eosinophils following adrenaline. A second patient also failed to show a response on the second course of the medicant. The first 0.1 mg. resulted in a decrease in eosinophils followed by a failure to respond to adrenaline. The next weekly LSD-25 treatment failed to produce a significant decrease as did adrenaline and ACTH. The following week satisfactory decreases were obtained with 0.2 mg. of LSD-25 and 40 units of ACTH but he still did not react to 0.6 ml. of adrenaline. A third patient developed an eosinopenic response to LSD-25 but did not react to the standard dose of adrenaline.

Chronic use of reserpine has previously been shown (7) to be able to block the eosinopenia normally produced by adrenaline.

All placebo procedures failed to produce an eosinopenia even in a patient who subjectively reported a "terrific reaction," "Strongest dose I've had yet." The primary therapist however reported no response in agreement with the physiologic observation.

DISCUSSION

LSD-25 (0.1 mg. orally) initiates a series of events of which one, a physiologic response, is a decrease in circulating eosinophils. It has been shown by Porter (10) that the eosinopenic response in cats can be evoked by stimulation of the tuberal or mammillary areas of the central nervous system and can be blocked by an electric lesion in the posterior hypothalamus. The mechanism of the eosinopenia can be initiated by adrenaline or a nonspecific stress acting in the hypothalamic area. This stimulates the pituitary to release ACTH ac-

tivating the release of adrenal corticoids that results in the decrease in eosinophils. The development of a block in this response by LSD-25 that also blocked the response to adrenaline but not to ACTH suggests that the pathway for this action of LSD-25 may be the same or similar to that of adrenaline.

The two examples of an eosinopenic response to LSD-25 with failure to react to adrenaline may demonstrate a differential sensitivity to the two stimulating agents. There is also the possibility that the adrenaline is inactivated or that its stimulus is blocked prior to the point at which LSD-25 is effective.

Recent animal work of K. Killam (8) implicates the thalamus in the central nervous system's response to LSD-25. These data were obtained by electrode placement in unanesthetized curarized cats.

Further data focusing on the central nervous system have been reported by Olds, Killam and Eiduson (9). Their test preparation is the implanted electrode in rats and the measure of response is a press bar rate. This system gives reproducible results and allows for accurate electrode placement. Their results indicate that the primary response of LSD-25 is a general decrease in press bar rate. The response in the olfactory tubercle of the forebrain and tuber cinereum of the hypothalamus region can be completely blocked with serotonin while the stimulus in lateral placements was not antagonized. Brom LSD-25 was only effective in areas where serotonin blocked LSD-25.

One is tempted to relate the LSD-25 symptomatology, the eosinopenia and its blockade in man to this animal work and to the cortical projection system from the midbrain, subthalamus and hypothalamus of French *et al.* (6). This projection system also involves the cortical sensory responses of sound and sight which also strongly respond to LSD-25.

All of the following responses of LSD-25

can be directly or indirectly related to the hypothalamus-thalamus area of the central nervous system. The constellation of clinical symptoms primarily centered around the hallucinations with the senses of sight and sound having a significant part. The production of an eosinopenia, its affiliation with adrenaline and the blockade of LSD-25 on both stimuli as it was demonstrated in man, the observations by electrode placement in both cats and rats all point to this region as the site of LSD-25 action in the central nervous system.

For what it may be worth, we have had two cases of "hypothalamic syndrome" both of which were preceded by symptomatology similar to that seen during an LSD-25 intoxication. In one case the hallucinatory phenomena appeared 5 days before the other symptoms. These consisted of temperature of over 109° C., status epilepticus and hematemesis. All symptomatology, including the hallucinations, completely cleared within 24 hours. As an incidental result there has been a complete personality change in the patient for the better.

The second case was a paraplegic who, immediately after his accident, had hallucinations, diabetes insipidus and loss of temperature control. All three cleared simultaneously. One could postulate that the focus of irritation was acting at the same level as did the LSD-25.

CONCLUSIONS

1. LSD-25 can be used to demonstrate the integration of basic neurophysiology with well known concepts of psychopathology.

2. LSD-25 has the astonishing quality of bringing into focus the patient's repressed emotional attitudes, conflicts, etc., and permits their reactivation. The hallucinatory experiences are not always symbolic, but in the majority of the patients these were not difficult to interpret with knowledge

of the patient's developmental history, defenses, etc.

3. The intense transference develops and may be capitalized on with direct, interpretive, Rosen type psychotherapy centering on the reexperiences as well as for reconditioning or "breaking up" of obsessional circuits in favor of more appropriate thinking circuits. Improvement was also produced by psychocatharsis.

4. LSD-25 effects are mediated through the reticular activating substance and hypothalamic-pituitary-adrenal axis, as demonstrated physiologically.

5. In the number of cases presented, most had placebos for control and all except the chronic brain syndromes demonstrated some degree of improvement in the sense that they were able to return to society and their families in a more productive capacity.

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