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CLINICAL REACTIONS AND TOLERANCE TO LSD IN CHRONIC SCHIZOPHRENIA

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HISTORICAL REVIEW

Since Hofmann's (15) description in 1943 of the altered state of consciousness produced by LSD, a number of attempts have been made to elucidate the relationship between LSD and psychotic reactions. Because the LSD state manifests many of the characteristics of the schizophrenic reactions, considerable emphasis has been placed on comparing and evaluating this similarity. The experimental value of a drug which could produce a controlled schizophrenic state would be inestimable. It stimulates the imagination to conceive the creation of a model psychosis which can be studied psychodynamically, biochemically and subjectively at once. The hope for an ingress into the mysteries of schizophrenia has resulted in studying this problem from many differing viewpoints.

Some investigators have studied the effect of this drug on the chronic schizophrenic patient. Many of them describe a diminished response in these patients compared with normals. Stoll (15) gave LSD 20 times to six schizophrenics who had proven immune to therapy and found: 1) "the effects were relatively sparse and less colorful than in normal subjects"; 2) relatively higher doses were required to produce an effect; 3) the reaction of one patient to 100 μg. was much weaker the second time he received it than the first time; 4) there was no doubt as to which were functional and which were toxic symptoms. He concluded that in view of the very small doses required, LSD might be considered a trace element in the development of endogenous psychoses. He mentioned the possibility that the weaker reactivity might be either immunity to the drug or schizophrenic negativism. Condrau (4) found, in general, 1) that psychotics were more resistant to LSD, 2) that the course of LSD intoxication was blander, and 3) that the disturbances in perception, consciousness and ego feeling were less in the psychotic patients. He also proposed the question that the psychotic patient had a specific immunity to the LSD. He hypothesized that psychoses might be produced by a substance similar to LSD, possibly produced in significant concentrations in the body.

Manfred Bleuler pointed out (2) that LSD was most interesting because of the relatively higher doses required to produce an effect in psychotics than were required by normal subjects. He did not feel that the effect was sufficiently discrete to serve as a diagnostic criterion.

De Giacomo (5) confirmed Condrau's opinion that psychotics are very resistant to LSD. He studied relatively high doses, 300–500 μg. on 12 patients, 9 schizophrenics and 3 oligophrenics, and was able to produce excited catatonic states in non-catatonic patients.

Belsanti (1) in 1952 gave 80–480 μg. of LSD to 14 schizophrenics and 2 oligophrenics. He concluded that LSD has a specific schizogenic action, that it heightens the symptoms in schizophrenics and produces them anew in oligophrenics.

In England Mayer-Gross (11) gave LSD to 13 schizophrenic patients and found that the

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psychological effects were minimal although his tabulated results show that seven developed euphoria and one showed outbursts of anger.

Liddell and Weil-Malherbe (10) gave IV LSD to six schizophrenic patients. They observed aggravation of the clinical picture blocking, incoherence, perseveration, echolalia and poor production of material in these patients. They also noted rapid mood swings. Two of the schizophrenic patients gave evidence of visual and auditory hallucinations. They were frightened and completely inaccessible.

Sloan and Doust (14) gave LSD to 7 patients with schizophrenia and found slight although clinically apparent changes due to LSD that were difficult to verify objectively.

In this country Busch and Johnson (3) studied 18 schizophrenic patients and noted the chief effect of LSD to be excitation. These patients moved more, showed greater interest, responded more, talked more, exhibited more emotion, and expressed more psychopathology verbally. Some had short periods of disorientation, confusion and occasional temporary visual hallucinations. Most of them showed euphoria.

Forrer and Goldner (6) gave LSD to 6 schizophrenics who had failed to respond to treatment. Five of the six showed euphoria and increased verbal productivity; all patients showed hallucinations although these could not be determined at the time the patients were under the influence of the drug. Increased sexual material was apparent in three patients.

Hoch, Cattell, and Pennes (7) studied 21 schizophrenic patients and observed mental changes if more than 60 μg. were used. They found perceptual disturbances, including hallucinations and illusions, unreality feelings, disturbance of time sense, disturbances of thought and language process in every patient when the doses exceeded 10 μg. Emotional disturbances were common including anxiety, depression and euphoria. There was an intensification of catatonic and paranoid pictures. They state "the well-preserved pseudoneurotic schizophrenics and the undeteriorated or moderately deteriorated overt schizophrenics showed the more intense over emotional reactions to the drug."

In the group of severely deteriorated schizophrenic patients, the emotional response was at times intense, but often no content was verbalized and gross catatonic withdrawals ensued. Deteriorated schizophrenic patients respond differently than do well-preserved schizophrenic patients.

They commented that "schizophrenic patients whose reality contacts have already been impaired are seemingly more vulnerable to drugs that have a disorganizing effect on reality perceptions."

Pennes (12) gave LSD to 25 schizophrenics and found symptom intensification in 64%, while 24% had a biphasic reaction of normalization and intensification.

Hoch, Cattell and Pennes (7) in comparing schizophrenia with the drug induced psychoses feel that there are differences and that these differences do not permit an analogy to be drawn to the two conditions. This is in contrast to the view of Hoffer, Osmond and Smythies (9) and Rinkel, Hyde, and Solomon (13) who feel that they are analogous.

Hoch (8) states that LSD shows a marked difference of response between acute schizophrenic and deteriorated schizophrenic patients. He says "while acute schizophrenic patients respond with great intensity to LSD and mescaline which reinforce and underscore their symptomatology, most of the deteriorated schizophrenics show very little response to the drug."

Present Studies[3]

The first part of the present study was directed at ascertaining what reaction chronic, regressed, schizophrenic patients would show to LSD inasmuch as the results in the literature differed. This was preliminary to a later study designed to assess the possible therapeutic use of this drug. This presentation will describe some methods used for studying the effects of LSD on chronic schizophrenic patients and some of the associated phenomena which were encountered in the course of this study.

Method

As far as we could ascertain, LSD has not been previously administered intramuscularly.

[3] The lysergic acid diethylamide (LSD-25) used in this study was furnished through the courtesy of the Sandoz Chemical Works, Inc. New York.

However, this route seemed preferable for administration to chronic schizophrenic patients. It overcomes the problem of oral administration where negativism might result in failure to swallow all of the drug. Also there would be no question concerning intestinal absorption. Intravenous administration with chronic schizophrenic patients is sometimes difficult to accomplish.

A simple behavior rating scale was assembled which could be completed by relatively uneducated aide personnel. It was essentially a gleaning of items from the many rating scales now in existence, which would highlight behavioral manifestations of psychological state. (table 1).

These observation forms were filled out by each aide in charge of each patient for every shift. An observer whose only task was to fill out the rating scales, saw the patients each evening for 3 hours. The ward psychiatrist and another hospital psychiatrist each saw the patients three times a week. They made clinical notes and filled out Lorr Rating Scales.

The first four female patients who satisfied the following criteria were picked as subjects from a review of their records. They must 1) have been in the State Hospital for 15 years without parole; 2) relatively stable in their symptomatology for the past 5 years; 3) be under the age of 40; 4) be classified as chronic regressed schizophrenic patients; 5) have graduated from grammar school; 6) have spent some time in this ward within the past year without benefit. These patients were transferred to the new ward where they could be better studied and observed.

There was a period of 3 weeks' observation before any injections were given. This was followed by a 3-week period when only placebo was given. Thus it was possible to rate the effects of the change of ward and to assess the effects of the IM needle.

After this time, 100 μg. of LSD were given to 2 patients, and placebo was continued with the other 2 patients. No one in any way associated with these studies, including the investigator, knew which patients were to get the drug and which the placebo. The Sandoz Company had kindly prepared vials of saline to serve as placebos which were identical in appearance with the LSD vials.

This experimental design was not absolutely necessary in the light of the later results, for, on the day the first dose of LSD was given, it seemed clearly evident which 2 of the patients were receiving something new.

Clinical Reactions

One catatonic patient who had been mute for some years suddenly burst into loud wailing sobs which were shortly followed by overwhelming bursts of laughter starting 35 minutes after the drug was given. This patient seemed most distressed and shaken. Intermittently she would open her mouth as if she were trying desperately to talk or at least to exercise the muscles of her mouth. She also expressed a state of acute anguish with her body movements. When asked why she was crying, she said, "You should never leave the farm." A half hour after the crying started, the wails seemed to end in a giggle. Soon the tears diminished, and she had almost continuous waves of laughing for another hour or so. The patient then began to walk about the ward studying the walls and the windows as though she were seeing them for the first time. She seemed to respond to hallucinations, for she began to talk to non-present individuals. Every few moments for the next few hours she would shake with laughter, and then she might talk a little. Her speech was never particularly coherent, and she soon became preoccupied with the fact that something or somebody was tickling her. She often said she enjoyed things very much and that this was a nice ward, etc.

Three hours after the drug was given, the patient was prancing about the ward and still bursting into gales of laughter. She could hardly eat since she said she had no appetite. That afternoon she played basketball for the first time since she was admitted to the hospital although the opportunity had been offered to her many times. She seemed interested in the effort and was pleased at her attempts. She walked about briskly, smiling broadly, and occasionally laughing. That evening she went to a dance and danced with another patient for the first time. She continued talking until bedtime. The next morning when she awoke, she was her old catatonic self, unable to

TABLE 1.—OBSERVATION CHART FOR WARD PERSONNEL

Name of Patient _____ Date _____

Name of Observer _____ Shift _____

This chart is organized to get your *daily* impression of your patient's behavior. The answers are arranged under the line so you can check the place that best describes the patient's behavior today. Some of the answers will be hard to decide upon. Don't worry about it! Do the best you can; we know it won't be easy. Sometimes the answers will lie between two points on the line. If so, check between the points.

If you don't know the answer, mark (x) in the don't know box in the corner. If you want to, you can write a few words saying why it's hard to answer that question.

At the end of the paper you should mention anything unusual you noticed about the patient.

Also remember, this is a description of how your patient acted *today*.

NOTE: *If you didn't see much of the patient,* mention *it at the end of the chart.*

Each aide should make a chart out for each *of the four patients each day—there are special charts for the night shift.*

Example: Patient who soiled herself 3 or 4 times today, but also went to the toilet.

TIDINESS—TOILET _____Don't know

X

Went to toilet when she had to. No mess	One accident today	Sometimes went to toilet. Sometimes soiled self	Soiled self a lot. Did not attempt to go to toilet	Smeared feces

ACTIVITY _____Don't know

Didn't move at all	Hardly moved at all	Stayed in one place most of shift	Moved a little, less than average	Was as active as normal person would be	Little overactive	Quite restless and overactive	Hardly rested at all	Always moving around, no stopping her

SPEECH—AMOUNT _____Don't know

Didn't talk at all	Hardly talked at all. Even when spoken to	Would only talk when spoken to	Kind of quiet. Didn't talk much	Average amount of talking	Kind of talkative	Talked a lot	Talked almost all shift	Talking all the time

MOOD CONTENT _____Don't know

Extremely depressed and unhappy (or cried a lot)	Very sad or maybe crying	Seemed quite sad or unhappy	A little blue	Pleasant	Overly cheerful	Happy and laughing much more than average	So happy and laughing she bothered others	Wouldn't stop laughing no matter what happened

SPEECH—LOUDNESS _____Don't know

Could never hear what she said	Often did not hear what she said because she spoke quietly	Spoke very quietly	Occasionally spoke very softly	Normal tone of voice	Raised her voice sometimes	Talked too loudly often	Talked too loud whenever she said anything	Screaming whenever she spoke

TABLE 1.—*Continued*

EATING—DESIRE _____Don't know

Ate anything she saw, including objects on floor	Grabbed to eat anything on table	Asked for 2 or 3 extra helpings	Ate an extra amount	Ate average amount	Ate by herself but needed a little coaxing	Ate very little even with coaxing	Had to be spoon-fed	Had to be tube fed

DESTRUCTIVENESS _____Don't know

Didn't tear anything	Tore a magazine or clothes once	Tore a few things today	Tore many things today	Tore anything she could get her hands on

TIDINESS—CLOTHES _____Don't know
_____Didn't get clothes

Dressed neatly	A little messy	Clothes very disorderly	Dressed bizarrely or partially undressed	Completely undressed

TOILET HABITS _____Don't know
_____No B.M.

Went to toilet when she had to. No mess	Soiled self once today	Sometimes went to toilet sometimes soiled self	Soiled self a lot. Did not attempt to go to toilet	Smeared feces

SPEECH _____Don't know
_____Didn't speak

Always spoke sensibly	Sometimes hard to understand	Often hard to understand	Hardly speaks sensibly all shift	Never spoke sensibly today

SOCIABILITY _____Don't know
_____In seclusion

Paid an ordinary amount of attention to others	Paid only a little attention to others	Paid practically no attention to others	Paid no attention to anyone else	Avoided everyone

MOOD—CHANGES _____Don't know

Same mood all day	Slight changes in mood	Occasional mood changes	Often changing mood	Constantly changing moods

TEMPER—CONTROL _____Don't know

Didn't get angry today	Was occasionally angry for some good reason	Flies off the handle with the slightest excuse	Sometimes angry with no excuse, often had temper tantrums	Many temper tantrums. Angry all day long

EATING HABITS _____Don't know

Good eating habits	Used spoon but somewhat sloppy	Used spoon but messy and slobbers	Ate with fingers, bad manners	Ate with fingers, slobbering like an animal

TABLE 1.—*Continued*

COOPERATION

				Don't know
Comes readily when called	Takes her time when answering call	Required calling a number of times	Refused to come when called (Unless seemed she would be forced)	Required force to get her to do anything

EROTICISM

Scratch out item that doesn't apply. Don't know

Never see her basturbate or talk about sex	Occasionally she masturbates or talks about sex	Often masturbating or talks about sex	Usually masturbating or talking about sex	Always masturbating or talking about sex

Did you see much of the patient? _____

Did you notice any behavior unusual for this patient? _____

If so, what was it? _____

Did the patient fight today? _____

NIGHT SHIFT

Aides: Please fill this chart at the end of your duty.

AROUSAL

				Don't know
Got up herself before call, or on first call	Awoke when called a couple of times	Needed extra attention to get up	Responded slowly to awakening needed prodding	Very difficult to awaken. Needed a lot of attention

DRESSING

				Don't know
Dressed self	Dressed with a little help	Needed much help to dress	Hard to get her to dress	Impossible to get her dressed

SLEEP—AMOUNT

				Don't know
Slept normal amount of hours	Slept most of night	Slept about half of night	Hardly slept (2 hours)	Didn't sleep at all

SLEEP—PEACEFULNESS

				Don't know
Calm sleep	Rare tossing and turning	Some tossing and turning	Quite a bit of tossing and turning	Always tossing and turning

SLEEP—TALKING

				Don't know
Quiet sleep	Occasional talking	Some talking	Quite a lot of talking	Always talking in sleep

SLEEP—DEPTH

				Don't know
Deep sleep not disturbed	Slept calmly but awakened with noise	Light sleeper	Awoke easily with outside noise	Half asleep and half awake

NIGHT—ACTIVITY

				Don't know
Stayed in bed all night	Got up to walk around once	Got up a few times	Out of bed much of the night	Couldn't get her to stay in bed

TABLE 1.—*Concluded*

NIGHT—TOILET _____Don't know

Did not go to toilet after bedtime	Went to the toilet once during the night	Went to the toilet a few times tonight	Many trips to toilet	Wanted to go to the toilet all night

Note anything unusual, such as—gave sedation (how much) _____
(any extra) _____

Wet bed_____ Nightmares_____
Walked in sleep_____ Pleasant dreams_____

speak, unable to show interest in anything about her, and quite withdrawn.

On this day the patient received another injection. She laughed a little at first, spoke a few words, but a few hours later lapsed into her previous mute and withdrawn behavior. Thus on the second day we had slight evidence of change from her previous behavior, however, much less than the change observed on the first day the drug was given.

When the patient received the same dosage the third morning, she showed no response at all.

Miss B., the second patient who received LSD, was diagnosed a hebephrenic schizophrenic. She had been in the hospital for 15 years. She commonly stood about the ward with her clothes in bizarre disarray, constantly giggling and laughing about the birds and the flowers in May. However, one-half hour after receiving her first 100 μg. dose of LSD, the silliness and laughter disappeared entirely. She became very serious, and while much of her communication was incoherent and bizarre, there was no giggling or laughter associated with it. In fact, she seemed quite serious. That morning she called her ward doctor by his correct name for the first time. She said "Dr. X, this is serious business—, we are pathetic people—don't play with us."

This is a most unusual type of statement from this patient. The psychiatrist who had been seeing her 3 times a week for the past 6 weeks also had the impression that she was responding to hallucinations. He had never been conscious of this with her before. She looked off into space in a dreamy way and talked to someone out there. She soon was rather seriously calling for help because she was in a very difficult situation. On that day she soiled her dress and tore off her clothes. About 3 hours after the drug was given, Miss B. assaulted the aides and later attempted to embrace and make sexual overtures to the chief nurse. This kind of behavior had never been noted before. On this day she did something characteristic of her only on the days she was reacting to LSD, namely, to get on a chair and hang on the screen of the dayroom. That night the patient kept chattering constantly and even at 1 o'clock in the morning was making and remaking her bed. She was given barbiturates and shortly after this went to sleep.

The next morning she awoke again giggling and silly. About a half hour after 100 μg. of LSD were given, she began talking in the same manner she had the previous day and again hung on the screen. However, this patient also did not show as marked an effect on the second day. On the third day the same dose of drug was given to this patient with no effect. The drug was continued daily for 2 weeks with no noticeable difference in behavior from the observation or placebo period.

The 2 patients who received placebos showed no major changes, either clinically or on the rating scale. They seemed puzzled by the changed behavior of the other patients, but this did not seem to affect their behavior. Later when they received the drug, marked responses were seen. One of these patients who was commonly assaultive and almost constantly in seclusion became calm, friendly and laughed when under the influence of the drug. Of course she would be taken out of seclusion at these times. She wanted to kiss one of the female aides. When she was asked how she was feeling, she often said "I feel crazy."

The other patient who was huddled in the corner nude and masturbating, unable to talk or look at anyone, moving about every few hours, also changed considerably when LSD

was given to her. First, she started smiling very broadly, began to pat people on the shoulder, touched them and desired to make some type of quiet contact. Then she put her head in the investigator's lap and indicated that she wanted him to pat her head. This went on for a long time. She would laugh intermittently. On the second day of drug administration, the effect seemed to be diminished. On the third day of LSD administration there seemed to be no response in either of these 2 patients.

Thus, in each of our first four patients we saw a marked change in behavior on the first day of drug administration. It seemed to diminish on the second day the drug was given, and on subsequent administrations was not noticeable. We continued giving the drug in 100 μg. doses for a period of 2 weeks, and no further effect was noted. We therefore felt we were dealing with the phenomenon of tolerance to the drug; tolerance that was manifested on the second daily dose and was complete on the third day of drug administration.

Tolerance

It then seemed desirable to study some of the characteristics of this rapidly developing tolerance. It is unusual that tolerance to a drug occurs on the second and is complete on the third dose. Our first attempts were to observe whether the tolerance decreases with a drug-free time interval. After experimentally varying the time interval between drug administration, it was noted that a reaction similar to the strong first reaction to LSD would be shown if approximately 5 days were allowed to elapse between LSD injections. Some patients seemed to show a slight reaction to the drug after a 4-day drug-free interval. However, this was not the same order of reaction that was manifested on the first day. By the fifth day about all showed a strong reaction to the drug. One of our patients, however, showed a somewhat lesser reaction to the drug on the fifth day and a stronger reaction on the sixth day.

Later, in an attempt to overcome the tolerance manifested by these 4 patients the dosage was increased by 100 μg. daily. Thus, each patient would receive 100 μg. the 1st day, 200 μg. the 2nd day, 300 μg. the 3rd day, 400 μg. the 4th day, and 500 μg. the 5th day. The response to this dosage schedule was as follows: The 1st day there was a large response, the 2nd day there was a lesser response, the 3rd day and the 4th day there was no response. A very questionable response was suggested on the 5th day with 500 μg. We did not attempt to give dosages larger than 500 μg. to any of our patients. It might, however, have been possible to overcome the tolerance by using higher dosages.

Cross-Tolerance

In an effort to test the cross-tolerance between the various LSD derivatives, LSD was tested with LAE and brom-lysergic acid. A cross-tolerance was noted in these 3 drugs; that is, the patients who would not respond to LSD because they had developed a tolerance to that drug also did not respond to LAE and brom-lysergic acid. However, it was noted that one of our patients showed a marked gastric upset to LAE, vomiting and manifesting signs of nausea and pain in her stomach, even though she showed none of the psychological manifestations that would indicate the hallucinatory experiences she showed with LAE in the non-tolerant state.

In an effort to test the hypothesis that this tolerance was psychological in nature, a hypothesis that these patients could adjust in this short time to the psychic effects of LSD, an attempt was made to alternate LSD and mescaline. Mescaline hydrochloride rather than mescaline sulfate was used since it was more soluble and more easily prepared for intramuscular administration. The records showed that patients who were tolerant to LSD did not manifest the same tolerance to mescaline. In other words, if they were given LSD on Monday and Tuesday and normally would show no response to LSD on Wednesday, they would be given mescaline on Wednesday instead. They showed their usual response to mescaline at this time. This indicates that tolerance to LSD is not transferred to mescaline HCl, whereas it is transferred to other lysergic acid compounds.

The order and type of behavioral response to LSD and mescaline seemed to be very similar. However, their physiological mechanics must be different insofar as tolerance to LSD does not indicate tolerance to mes-

caline. If tolerance were the result of psychological encapsulation of the anxiety produced by LSD, would they not show this same encapsulation to a similar psychological upset caused by mescaline? Of course the question of whether the psychic upset is really similar in these two drugs cannot be answered at present. The fact that they did not show this type of cross-tolerance between the two drugs, while there was cross-tolerance between the various LSD derivatives, would suggest, however, that the tolerance has a physiological basis rather than a psychological one. Certainly, our numbers are not large enough to state this with any finality; we simply wish to point out the indications from this limited study.

Other Clinical Reactions

In order to assess the reaction to LSD in other age ranges of hospital population, other groups of patients were studied in a similar manner. A few of the typical clinical reactions were as follows:

Two older male patients were given LSD, Mr. G., age 60, and Mr. K., age 57. Mr. G. responded with wild bursts of laughter which was most unusual for him since Mr. G. never spoke. Mr. K., who stands tensely rigid and uncooperative, seemed to become very flushed, retched a few times and then went to bed. He was occasionally heard to speak at these periods. Later, these patients were given doses of 200 μg. of LSD, and the same reactions and the same tolerance described above were manifested to this dose.

However, it is to be noted that as time went on and these patients were given drugs, they seemed to show a markedly diminishing effect to the drugs even after their tolerance period, despite the larger dose of 200 μg.

Four young males were given this drug, using 100 μg. of LSD. These patients were schizophrenics who had been in the hospital for a few years, and who ranged in age from 22 to 30. Two of these patients responded to the drug by going to sleep on the floor of their noisy ward, something they had not done previously. One of these was a markedly overactive, pacing, agitated patient. The other, a quiet, inhibited, withdrawn young man, seemed to withdraw even further with the administration of LSD.

Another young man, who has usually been aggressive, occasionally assaults aides and doctors, often spits in the doctor's face, began to laugh hilariously 30 minutes after the drug was administered. His explanation for his laughter was that he was so happy. No aggressive outbursts were ever noted while he was responding to LSD.

Some patients were then studied more intensively by daily interviews with a psychiatrist. One patient was a 36-year-old woman who for the four years preceding her admission had the chronic fixed delusion that she was dead and had no body. In addition she was depressed, phobic, and had become increasingly withdrawn and remote. After one month of study, she received 50 μg. of LSD. Initially she complained of giddiness and wanted to lie down but refused to lie down in front of the doctor. She became more hypochondriacal and complained of dying and not having a body. She laughed and said happily, "I shouldn't be laughing."

Later she developed a strong sexual feeling. "It's not stimulating me exactly; it's just that I like you, you know and naturally you want to—I don't know—I'm not very good at anything like this under these circumstances; I'd be better if I had a body and was out in the moonlight with you" (laughs); "I'm hopeless and incurable; hopeless in love and incurable; you're so cute; it's a good thing I don't have a body, I'd really go overboard." She commented this would be wonderful for treating the emotionally ill; it relaxes, yet it stimulates.

This upsurge of libidinal feelings with its associated euphoria was subsequently anxiety provoking, and the anxiety expressed itself in terms of increased somatic preoccupation and complaint, with reinforcement of the delusion of having no body. She then became self-accusatory and depressed, and profound quiet feelings were experienced. She soon reexperienced her reactions during the acute phase of her illness.

Summary

Of the 20 patients who received LSD the following general categories of reaction to LSD were noted:

1. *Covert*—while some patients at first glance show no apparent reaction to LSD,

closer scrutiny often leads to the conclusion that there is a marked albeit subtle effect. *Each* of our subjects showed some unusual behavioral manifestation as a result of the drug administration.

For example, one patient lay in a fetal posture, mute, withdrawn, and staring. After 200 μg. of LSD she continued mute, withdrawn, and staring. She was listed as having no reaction except for pupillary dilation. Subsequently the night nurse reported that she wept bitterly all evening, a mode of reaction foreign to her usual one.

Another patient was described as having no reaction and during the interview situation appeared his usual absent-minded, preoccupied restless self. However, it turned out that this man, who usually tears off his clothes and paces the ward like a panther, had curled up and slept peacefully on the floor for an hour after the LSD took effect. This was an obvious reversal of his usual behavior.

A third patient was at first considered to have no reaction. After 100 μg. of LSD he seemed to remain rigid, mute, withdrawn in a state of waxy catatonia. Yet, actually he too had a reversal. He became preoccupied with the ward activities, dancing frequent, furtive and appealing glances about him instead of keeping his eyes glued shut. In addition, he accepted and smoked a cigarette, something he had not done for four years even though they were offered to him often.

The assessment of LSD effects by objective observation of behavior is more reliable than subjective reports where negativism, withdrawal and denial may lead to the erroneous conclusion that LSD has no effect.

2. *Intensification*—some patients show an intensification of their usual symptomatology and behavior patterns. This may express itself as an intensification of the prevailing mood, increase in anxiety, increase in withdrawal, increased agitation, increased preoccupation with delusion and somatic complaints. Our observations indicate that intensification is more common in the more acute schizophrenic patients. For example: A young lady who was only mildly suspicious became sure people were looking at her through the door, she was being raped, and was much more panic stricken than usual.

A man who was very quiet, bemused and withdrawn lay on the floor and slept in the dayroom with noise all about him when given 100 μg. of LSD.

3. *Reversal*—striking reversals of accustomed behavior often occurred. Patients who were mute became talkative, those who were hyperactive fell asleep, those who were hostile became friendly and warm. Such a reversal may be followed by a subsequent intensification. One of our patients showed a reversal reaction consisting of elation, increased communication, with pleasant sexual fantasies and rather forward behavior followed by intensification of depression and anxiety and phobias, increased somatic complaints and delusion formation, and finally withdrawal.

In a study which will be reported at a later time, 6 patients who had been in a state hospital for from 10 to 20 years, who were under the age of 40, and who were relatively stable in their symptomatology for the past 5 years were taken to the better equipped wards of the Clinical Center of the National Institutes of Health.

These patients were studied closely for a period of 2 months before any LSD was given to them. In the very permissive and understanding environment utilizing an unusually high nursing-patient ratio, considerable change was noted in the patients' behavior. Presumably this was a result of this change milieu during the 2 months of the initial study.

It is interesting to note that these patients, who had been living in the back wards of state hospitals for a number of years, showed this change as a result of the change of physical and social environment. When these patients were given 100 μg. of LSD, there was considerably less behavioral change noted than the changes outlined in the patients reported above. There were no outbursts of laughter in any of the 6; there were fewer marked behavioral changes that were so clearly evident above. These patients were under constant surveillance and were well observed.

The question then arises whether this difference in response is related to the change in environment, or related to the fact that these patients have so recently undergone a major change. Could it be that after having undergone a major change, the patients do not

respond so strongly to LSD because change has already been accomplished, or their personalities are already in flux? It is also possible that they felt more comfortable in the acceptance and relative freedom of this friendly environment, and consequently the psychic upset resulting from LSD did not raise as much anxiety and turmoil as with the other patients.

Conclusions

1. LSD can be given intramuscularly over a protracted period without untoward effects. Consistent results are obtained from intramuscular injections of LSD. The intramuscular route is useful for studying the effects of LSD on chronic schizophrenics, and reactions are noted in approximately 30 minutes.

2. Tolerance to LSD in chronic schizophrenics is evidenced on the second and complete on the third day of drug administration. A period of 4 to 6 days free of LSD is necessary to reinstate the original reaction to LSD.

3. The gross behavioral reactions of chronic schizophrenics affords a useful index of tolerance. Estimates of the LSD effect can be made with the use of the rating scale which has been described.

4. The behavioral difference between intramuscular LSD and intramuscular mescaline is not pronounced in chronic regressed schizophrenic patients. That tolerance is not purely psychologic is indicated by the fact that there is no cross-tolerance between mescaline and LSD, whereas cross-tolerance is shown between LSD and LAE, and brom-lysergic acid.

5. Clinical responses of chronic schizophrenics to LSD can be categorized as: (a) *covert:* In which the patient may show a delayed reaction; (b) *intensification:* where the patient reacts by a regression to earlier forms of behavior, or a magnification of symptoms; (c) *reversal:* in which the manifestations of the drug reaction are quite the reverse of the usual behavior.

6. While the reaction to LSD is shown by the use of control studies to be due to the LSD rather than the experimental procedure itself, nevertheless there are indications that the reaction may be determined in part by the milieu.

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