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Some Test Findings Associated with Susceptibility to Psychosis Induced by Lysergic Acid Diethylamide

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THE EXPERIMENTAL psychosis produced by lysergic acid diethylamide (LSD) offers a means of testing predictions about phenomena associated with acute psychotic states. The present study was initially undertaken to test two such predictions concerning the amobarbital "sleep" threshold and the autokinetic phenomenon. The design involved using each subject as his own control by administering varying doses of LSD on different occasions to produce psychotic and nonpsychotic reactions. This design seemed practical in view of the findings of Isbell et al.[1] that the effects of LSD are dose-related and the expectation generated by the term "psychotomimetic," that, given adequate dosage, all subjects should develop a psychotic reaction. However, even with high doses of LSD, we were unable to produce reactions meeting our criteria of psychosis in half of our subjects. This finding shifted the emphasis of the study toward an examination of changes reflecting susceptibility to the LSD psychosis. The Bender-Gestalt test, which was used together with some other psychological measures to supplement the clinical examination of mental status, was found to be of particular interest as an indicator of susceptibility.

The "sleep" threshold is the amount of amobarbital, injected at constant rate, required to produce unresponsiveness to verbal stimulation.[2] Autokinesis refers to the perceived motion of a stationary pinpoint of light in a dark room. Both of these measures have been reported to discriminate between acute psychotic reactions and neurotic states involving anxiety, with lower thresholds and less autokinesis in the psychoses.[3,4] Insofar as the prepsychotic reactions to LSD are described as characterized by anxiety-like symptoms, it would be predicted that LSD would first increase the "sleep" threshold and autokinesis and then decrease them as a psychotic reaction appeared. These predictions were tested, but not confirmed, in the present study.

METHODS

Subjects.—Fourteen in-patients at the Iowa State Psychopathic Hospital served as subjects. Criteria for selection were, availability, willingness to cooperate, and absence of: psychotic symptomatology, evidence of brain syndrome, mental deficiency, or obvious physical disease. There were 8 men and 6 women, ranging in age from 19 to 37, with a mean age of 22.5 years. Two patients were diagnosed as psychoneurosis, anxiety reaction; the remaining 12 were in the personality disorder group (emotionally unstable, 4; antisocial reaction, 3; sexual deviation, 2; passive-aggressive, 2; schizoid, 1). Mean education level was 13 years and ranged from 10 to 20 years. No patient was receiving medications during the experimental period. The subjects seemed to be relatively unaware of the publicized effects of LSD.

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Administration of LSD.—LSD was given intravenously, diluted with water to a standard quantity of solution. Each subject received at least 3 injections; 5 subjects received 4, and 2 received 5 injections. The interval between injections ranged from 2 to 40 days, with half ranging from 4 to 7 days. Table 1 shows the range and mean of LSD doses in different tests for each subject, in order of magnitude. Dose was not completely standardized, as the aim was to achieve three different LSD reaction states in each subject, corresponding to minimal and moderate nonpsychotic and psychotic reactions. Order of dosage was not fixed; it could be higher or lower in successive tests. The purpose of the study was explained to the subjects and they were informed that they might have some unusual experiences following the LSD injection. All observations except for specific tests took place in the same two rooms, one for males and one for females. The investigator remained with the subjects at all times and attempted to adhere uniformly to an attitude of interest and reassurance.

Clinical Observations.—Observation was continuous, but certain evaluation procedures were carried out three times in a standardized manner: before LSD administration; at one and two hour intervals after the injection. These procedures consisted of Jarvik's questionnaire,[5] mental status examination, and estimation of pupil size, patellar reflex, blood pressure, and pulse rate. Jarvik's questionnaire consists of 59 items involving frequent symptoms of the LSD state. The questions were read to the subjects and they were instructed to reply to each item with "yes" or "no," and then to rate each affirmative response as mild, moderate or severe. Responses were graded on a scale from zero, indicating a negative response, to 3, indicating a "severe" rating. The psychiatric mental status examination was designed to evaluate briefly the subject's memory, orientation, calculation ability, thought processes, mood, and affect.

The criteria for a psychotic reaction were determined at the outset of the study and demanded the presence of one or more of the following phenomena. (1) Hallucinations with "reality like" projection into the surrounding environment; elementary visual color and form images, illusionary phenomena, and fantasy experiences were not included. (2) Delusions. (3) Catatonic phenomena. (4) Psychotic depression in the sense of a depressed mood dominating the subject's thought and behavior so that the reality situation is misinterpreted and there are phenomena such as suicidal preoccupation. (5) Manic behavior to the extent of poor judgement. (6) Toxic-organic symptoms, such as marked changes in judgement, orientation, memory and comprehension.

Bender-Gestalt Test.—This test requires the subject to copy 9 designs.[6] It was administered after the one hour clinical appraisal was completed. It was scored according to the method described by Pascal and Suttell,[7] higher scores indicating poorer performance. Scoring was done in a random order at the end of the experiment, and the scorer standardized his method using the sample tests in the Pascal and Suttell manual, attaining a very high level of agreement with the authors' scores.

Figure Drawing.—This test was given immediately after the Bender-Gestalt. The subject was instructed to draw the figure of a person. At the end of the experiment the tests were scored according to the Goodenough outline.[8] A high score by this scheme indicates a higher level of intellectual performance. After LSD, subjects frequently required considerable persuasion to carry out the Bender and Figure Drawing tests, but most were able to do so.

Table 1.—*LSD Dosage for Different Response Levels*

Dose Level	Psychotic Reaction			No Psychotic Reaction			Total	
	Dose (mcg) Range	Dose (mcg) Mean	mcg/Kg Mean	Dose (mcg) Range	Dose (mcg) Mean	mcg/Kg Mean	Dose (mcg) Mean	mcg/Kg Mean
Low	15–40	26.7	0.40	17–100	38.3	0.50	32.5	0.45
Medium	29–200	95.6	1.46	45–200	122.1	1.73	108.9	1.59
High	90–400	221.4*	3.40	90–300	232.8	3.36	227.1	3.38
Very High	——		—	140–500	336.1	5.43	—	—

*Dose producing psychotic reaction.

Autokinetic Test.—The procedure employed has been described by Schwartz and Shagass,[9] who used Voth's[3] method of testing and scoring. The method involves having the subjects draw with a pencil on a large sheet of paper the movement he perceives when he fixates a pinpoint of light in a completely dark room for a period of 10 minutes. This test was administered after the Figure Drawing test.

"Sleep" Threshold.—This was the last procedure applied, as the injection of amobarbital antagonizes the effect of LSD. The method described by Shagass and Kerenyi[2] was used. The amobarbital solution was prepared so that each cc. would contain 0.5 mg./Kg. body weight. One cc. was injected rapidly intravenously at the beginning of every 40 seconds. The injection was continued until the subject was unable to respond verbally; the amount required to reach this point was taken as the "sleep" threshold.

Statistical Evaluation.—Unless otherwise indicated, a non-parametric sign test was employed to assess statistical reliability,[10] and the 5 per cent level of confidence was taken as significant.

Results

Psychotic Reactions to LSD

Only 7 of 14 subjects developed a psychotic reaction according to our criteria. Delusional ideas were the predominant characteristics in four instances. One patient felt that the examiner would kill him and launched a violent physical attack upon him; another threatened to behave in the same way, and two others manifested extreme suspicion. Two subjects experienced true hallucinations with a marked affective reaction to them and also demonstrated a brief catatonic state. One subject was confused and disorientated as well as hallucinated for about 30 minutes and later developed delusions about the procedure. A psychotic reaction was not manifested by any of the other 7 subjects, even when as much as 9 micrograms/per kilogram of LSD was administered. All 14 subjects experienced many symptoms characteristic of the LSD state with medium or higher level doses.

No known characteristic, such as diagnosis, age, sex or education was related to development of a psychotic reaction to LSD. Table 1 shows that the patients reacting with and without psychosis received approximately the same dose of LSD in their first three tests, while the nonpsychotic reactors received much more LSD in their last tests.

Jarvik Questionnaire.—Table 2 shows the relevant data. As there was no apparent difference between the results obtained after one and two hours, or between the unweighted and weighted scores, only the unweighted scores at one hour are given. The number of symptoms reported increased significantly from baseline after the lowest dose and further increased after the medium dose. No

Table 2.—*LSD Dose and Mean Jarvik Questionnaire Scores (Unweighted) One Hour After LSD*

Dose Level	Psychotic	Nonpsychotic	Total
Before LSD (mean of 1st 3)	6.9	3.4	5.2
Low	13.7*	11.1*	12.4*
Medium	21.1*	19.7*	20.4*
High	23.0	21.0	22.0
Very High	—	25.3	—

*Higher than mean at next lower dose ($P < .05$).

further significant increases were obtained at higher levels. The scores for the psychotic reactors were about the same as those of the remaining subjects, indicating that the questionnaire scores did not reflect the psychotic reactions.

Physical Measures.—Changes in pupil size, patellar reflex response, systolic and diastolic blood pressure, and pulse rate were found to be highly variable. Only pupil size was consistently changed by LSD, with increased dilatation averaging 1.6 mm. However, there was little difference between the effects at varying dose levels. At the high dose level there were significant increases in patellar reflex response and systolic blood pressure over baseline levels. No physical measures discriminated significantly between psychotic and nonpsychotic reactors, or between different doses of LSD.

Bender-Gestalt Test.—Mean standard scores, based on Pascal and Suttell's method for scoring the tests, are given in table 3. With increasing doses of LSD the mean scores increased, but this was so mainly in the psychotic reaction group. Those failing to develop a psychotic reaction required very high dose levels for a significant decrement in performance. Figure 1 plots the changes in Bender scores for individual subjects. The score for the lowest dose administered is plotted as zero. The graph shows that Bender-Gestalt performance tended to deteriorate more rapidly in those subjects who developed psychotic reactions. It seemed that susceptibility to LSD psychosis might be reflected by the rate of change in Bender scores as a function of dose. This was tested by calculating for each subject the slope of the best-fitting straight line relating Bender score to dose level. The slope values ranged from 3.2 to 79.5 (mean, 30.5) for the psychotic reactors and from −9.0 to 13.9 (mean, 1.1) for the nonreactors. One case in each group overlapped with the other. The "t" test showed the mean difference to be significant at the 5 per cent level.

Figure Drawings.—Inspection of the drawings obtained at different dose levels suggested a tendency for poorer organization with higher doses. This impression was checked by having 4 psychiatrists rate the drawings for the three lowest dose tests on each subject. Judges were informed which drawings belonged to a given subject, but did not know the dose levels. The ratings so obtained corresponded significantly to dose level. The general impression of poorer organization or more primitive drawing performance with higher LSD dose was confirmed by the Goodenough scores (table 4). It should be noted that significant decrease at the high dose level occurred mainly because of the changes displayed by the psychotic reactors.

Autokinesis.—No significant changes in Voth's index of autokinesis were found in relation to dose of LSD or to susceptibility to psychotic reaction. Median values at different dose levels actually corresponded to prediction, but

Table 3.—*LSD Dose and Bender-Gestalt Performance (Mean Score)*

Dose Level	Psychotic	Nonpsychotic	Total
Low	58.3	61.1	59.7
Medium	78.4*	63.9	71.1*
High	108.2*	68.9	87.0*
Very High	—	84.0*	—

*Higher than mean at low dose ($P < .05$).

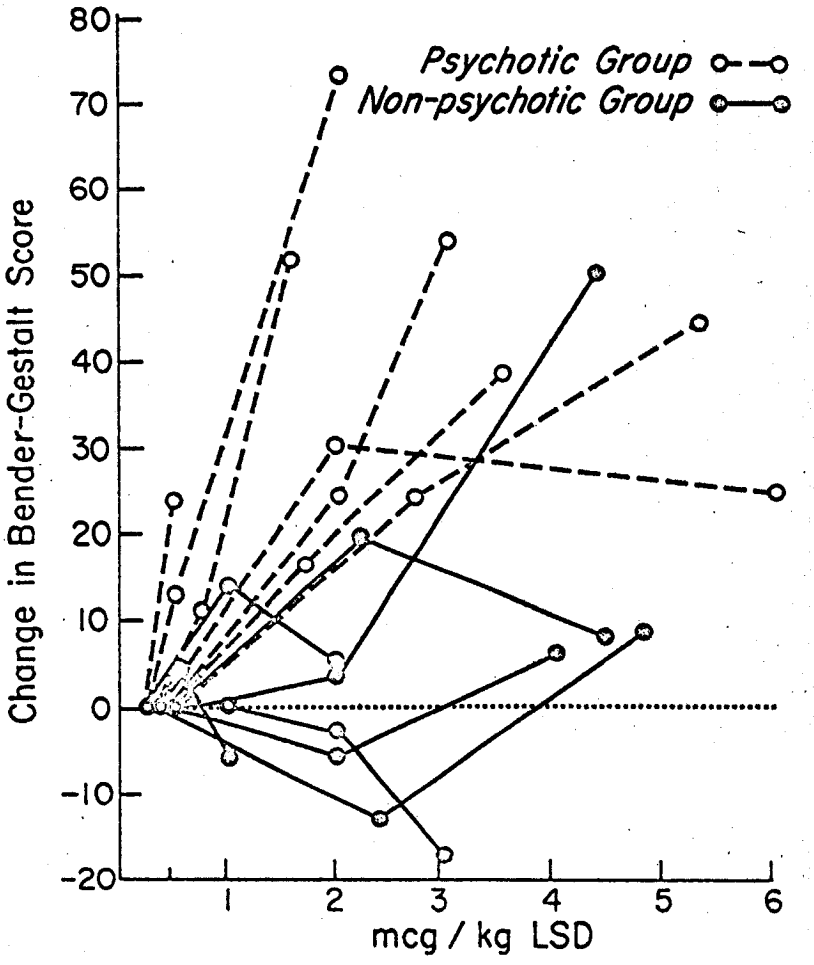

Fig. 1.—Changes in Bender-Gestalt scores as a function of LSD dosage. The score for the lowest dose given each subject is plotted as zero. The first three tests for each subject are shown and joined by lines.

this was found to be due to a few subjects with much higher scores than the remainder.

"Sleep" Threshold.—There were no significant changes in "sleep" threshold related either to LSD dose or display of psychotic reaction.

Discussion

This study failed in its original intent of comparing psychotic and nonpsychotic reactions to LSD in the same subjects. Because only half of the subjects met our criteria of a psychotic reaction, we found it more interesting to concentrate upon test changes associated with susceptibility to such a reaction. Such changes appeared primarily in the Bender-Gestalt and Figure Drawing tests, which involve visuomotor performances. Psychotic reactors showed greater and earlier deterioration of performance, particularly on the Bender

Table 4.—*LSD Dose and Figure Drawing Performance (Mean Goodenough Score)*

Dose Level	Psychotic*	Nonpsychotic	Total
Low	23.7	26.4	25.4
Medium	17.7	19.4	18.3
High	7.2†	22.6	15.5†

*6 Cases only.
†Lower than mean at low dose ($p < .05$).

test. No other measures used here, including the Jarvik questionnaire, reflected the difference between psychotic and nonpsychotic reactions.

Some possible reasons may be advanced for our difficulty in inducing LSD psychosis. An important one is that our criteria of psychosis were perhaps more demanding than those usually employed. However, it seems justifiable to apply criteria which cannot be criticized on the grounds of permitting confusion with other phenomena. Furthermore, the Bender-Gestalt data offer *post hoc* support for such criteria, as they would not be expected to discriminate between reactors and nonreactors if the two groups were really one. One may also query the nature of the experimental population, as others have found that nonpatient subjects are more prone to develop psychotic phenomena with LSD than psychiatric patients.[11] The extent to which the greater susceptibility of nonpatients depends upon suggestibility and "placebo" effect or upon different reactivity characteristics associated with psychiatric disorder is not clear. The patients studied here were relatively naive concerning LSD, but as a group they would certainly be considered at least as suggestible as any nonpatient sample. Also the repeated exposures to LSD and frequent questioning as to symptoms experienced should have served to maximize effects based on suggestion. The investigator's attitude could also be considered to favor psychotic reactions based on suggestion, as we had set out to produce such a reaction in all subjects, and were confident that this was possible. In view of these facts, it seems reasonable to assume that our criteria of psychosis were such as to reduce the significance of "placebo" effect and to emphasize reactivity factors. Unfortunately we were unable to discover any clinical characteristics which would predict reactivity in our group before administration of LSD.

Abramson et al.[12] studied the effects of placebo and LSD in 50 and 100 microgram doses on the scored Bender. They found that performance became worse with LSD in relation to dose. However, the changes were not great enough to demonstrate specific psychotic modes of responding. This is not surprising since very large doses were required to produce significant changes in our patients who did react with overt psychotic symptoms.

Our qualitative results with Figure Drawing seemed grossly similar to those recently reported by Machover and Liebert,[13] although we did not regard ourselves as competent to undertake a dynamic analysis of changes. Present Goodenough scores were lower than would have been the case had we insisted that the whole body be drawn. Several subjects drew only heads; this did not affect measures of change, but lowered the scores. Making allowance for artificially low values, it is still noteworthy that the mean Goodenough

mental age for the psychotic reactors changed from about 9 to about 4.5 years from the low to the high dose of LSD. This suggests marked impairment, compatible with the notion of a "toxic-organic" reaction. Such an interpretation is further supported by the fact that only about 30 per cent of Pascal and Suttel's psychotic population obtained Bender scores as high as the lowest score in our group of psychotic reactors. On the other hand, the symptoms of psychosis were typically "organic" in only one of our subjects; they were schizophrenic-like in the others. Our clinical data thus seem to go along with the idea that LSD produces a reaction resembling schizophrenia, although the test data are more in favor of the "toxic-organic" interpretation. Further evidence is required, but it seems reasonable to suggest that the drawing tests may reflect alteration of the sensorium before it is revealed by clinical examination and that the delusions, hallucinations, and catatonic symptoms are not incompatible with an exogenous type of psychotic reaction.

One wishes that the design had required tests to be administered before any LSD was given, although most test findings at low doses of LSD do not seem to have differed greatly from results expected in a similar population without drugs. It seems possible that, if one were to do the Bender test before and after administration of a moderate dose of LSD, e.g., 1.5 micrograms per kilogram, the change in score could be used to select those subjects most susceptible to LSD psychosis. The change in Bender performance would thus serve as an indicator of sensitivity to "ego function" impairment by LSD. The Bender test seems more useful for this purpose than Figure Drawing, as it involves less initial variability between subjects.

The results failed to confirm our predictions concerning changes in the "sleep" threshold and autokinesis. The findings were so clearly negative as to make it likely that a very much larger sample would be required to reverse them. The negative autokinetic results are in accord with the recent failure of Schwartz and Shagass[9] to confirm Voth's earlier findings regarding differences between psychiatric diagnostic groups.[3] The negative "sleep" threshold findings could perhaps be due to reversal of LSD effects early in the amobarbital injection. If this were so, the "sleep" threshold would not be a suitable indicator of LSD effects.

Summary

Changes associated with a psychotic reaction to LSD were studied in 14 psychiatric patients, each of whom received at least 3 injections of LSD at varying dose levels. Evaluation procedures included: the Jarvik questionnaire, certain physical measures (pupil size, patellar reflex, blood pressure, pulse rate), Bender-Gestalt test, Figure Drawing test, amobarbital "sleep" threshold, and autokinesis. Even though subjects received as much as 9 micrograms per kilogram of LSD, a reaction meeting our criteria of psychosis was induced in only 7 subjects. Only the Bender-Gestalt test and, to a lesser extent, Figure Drawing, provided data correlated with the appearance of a psychotic reaction. Susceptibility to the LSD psychosis seemed to be reflected mainly in early disturbance of performance in drawing tasks.

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