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LYSERGIC ACID DIETHYLAMIDE (*LSD*-25): XXX. THE QUESTIONNAIRE TECHNIQUE WITH NOTES ON ITS USE*

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A. INTRODUCTION

In response to numerous inquiries and to resolve misunderstandings, the questionnaire (3), which forms the basis of practically all of the publications on *LSD*-25 by the writer and his colleagues, is herewith discussed. This questionnaire (Tables 1-2) was used in the form published here in the first paper and subsequent papers of this series, with one exception. It is also the test method of assessment in another series on *LSD* antagonists (2, 6). In the first paper published, only Part I of the questionnaire was analyzed statistically. Data were obtained, however, using Part II of the questionnaire, which was employed as the basis of a short mental rating test. Responses to Part II were later analyzed by Dr. Kornetsky (5).

The modified questionnaire, which we do not use, classified questions under physiological, perceptual, and cognitive (8). The writer feels that this type of classification robs the questionnaire of a certain degree of randomization that the original questionnaire possesses. The original questionnaire was composed by the writer and his assistant, Mrs. E. Teige, when the *LSD* Project was started about eight years ago. Mrs. Teige and the writer surveyed the literature on *LSD*-25 and listed all the symptoms and signs reported. These symptoms and some of the signs, really the psychological signs, comprised the questionnaire now in use. As was expected, subsequent statistical studies revealed that certain of the questions were not so significant for the *LSD* reaction as were others. Another reason for using the questionnaire in its original form has to do with the nature of Part II, which as mentioned, can be used as a short mental rating test. Dependent on the experimental design, subjects may fill in Part I and Part II of the questionnaire, but they are also questioned by the observer. Additional

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TABLE 1

Half an hour after administration and at hourly intervals thereafter, the following direct questions are put to the subject. His rating is accepted, if possible, on a + to +++++ basis.

PART I QUESTION	½ Hr.	1½ Hrs.	2½ Hrs.	3½ Hrs.	4½ Hrs.	4½ Hrs.
1. Do you feel ill in any way?						
2. Are you nauseated?						
3. Have you a feeling of choking?						
4. Is salivation increased?						
5. Or decreased?						
6. Is your appetite increased?						
7. Or decreased?						
8. Do you have a "dry" taste in your mouth?						
9. Do you have a funny taste in your mouth?						
10. Is it a bitter taste?						
11. Are your lips numb?						
12. Or drawn back as if you were smiling?						
13. Does your head ache?						
14. Are things moving around you?						
15. Do you feel dizzy?						
16. Or unsteady?						
17. Is there difficulty in breathing?						
18. Do you pass more urine than usual?						
19. Are you aware of your heart beat?						
20. Is it faster than usual?						
21. Are you sweating?						
22. Are you hot?						
23. Or cold?						
24. Are your palms moist?						
25. Or dry?						
26. Or cold?						
27. Is your skin sensitive?						
28. Do you have funny feelings on your skin?						
29. Do your hands and feet feel peculiar?						
30. Do they feel heavy?						
31. Or light?						
32. Is there pressure in your ears?						
33. Is your hearing abnormal?						
34. Is it more acute than usual?						
35. Is your eyesight blurred?						
36. Do you have difficulty in focusing your vision?						
37. Do you see double?						
38. Are shapes & colors altered in any way?						
39. Does light bother you?						
40. Do things seem too close?						
41. Or too far away?						
42. Do you tremble inside?						
43. Do you feel weak?						
44. Or fatigued?						
45. Do you feel drowsy?						
46. Do you feel as if in a dream?						
47. Are you anxious?						

notes are made on the back of the cardboard test sheet (9.5″ x 11.5″) by the subjects themselves. Using Part I in this way, the questionnaire loses disadvantages often inherent in a strictly structured test situation and provides both the replicability of a questionnaire and the flexibility of a clinical assessment in addition.

TABLE 2

Half an hour after administration and at hourly intervals thereafter, the following qualitative ratings are made on the subject by the experimenter aided by the subject's comments.

PART II

1. Motor Behavior:	2. Control:	3. Consciousness:
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later
Concentration:	**5. Mood (Euphoria - Depression):**	**6. Attitude to Environment:**
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later
7. Orientation:	8. Memory:	9. Hallucinations:
½ Hr.	½ Hr.	½ Hr.
1½ Hrs.	1½ Hrs.	1½ Hrs.
2½ Hrs.	2½ Hrs.	2½ Hrs.
3½ Hrs.	3½ Hrs.	3½ Hrs.
4½ Hrs.	4½ Hrs.	4½ Hrs.
Later	Later	Later

B. Problems

1. *Placebo Reactivity*

Only inadequate studies of psychotomimetic drugs can be made if poor communication exists between observer and test subject. It is recommended, therefore, that non-psychotic subjects be made aware of the content of the questionnaire before experiments are begun. Analysis of the data obtained on randomly selected, essentially non-psychotic subjects, showed the fre-

quency of placebo reactors to be high (3, 4). This demonstrated that the questionnaire technique screened out placebo positive subjects. It became apparent that one of the prerequisites for the study of the reaction of man to psychotomimetic drugs was to have essentially placebo-negative subjects. Indeed, even subjects who have been placebo negative may respond with symptoms in part characteristic of the *LSD* psychosis in times of psychological stress. Stress may exist either within or without the experimental situation. For this reason, repeated testing with placebos, or to save time and expense, with threshold doses of new compounds, is necessary.

2. *Subject to Subject Variability*

The questionnaire is useful in detecting the fact that in psychologic studies large differences in reactivity to *LSD* and its congeners exist from subject to subject. These differences cannot be readily correlated with known variables. Various compounds may be given to each subject more than once, making two or three separate comparisons at separate dose levels for each drug, and thus have not only subject to subject data but also within subject studies (7). Although the effect of each drug will not be known as precisely as possible, these procedures by the use of the questionnaire provide us with adequate data. Subject to subject variability as well as within subject variability is illustrated in Table 3. For test Subject P.B.,

TABLE 3
THE EFFECT OF PSILOCYBIN ON TWO NON-PSYCHOTIC SUBJECTS

Subject	Experiment	Psilocybin (mg)	Questionnaire response (n)
P.B.	1	3	4
	2	6	2
	3	6	14
	4	6	13
	5	6	23
D.V.G.	1	6	16
	2	6	10
	3	6	10
	4	8	14

in a recent study of Psilocybin, the following data were obtained using Parts I and II of the questionnaire. The data disclose the wide variability in n, the number of responses, for Subject P.B. Compare these data of P.B. with studies on Subject D.V.G. with Psilocybin. Subject D.V.G. shows

much less within subject variability. These data are typical of the variability which may be disclosed using the questionnaire.

Our method of using the questionnaire enables us to compute a standard analysis of variance with three components: (*a*) Average difference between drugs for all subjects. (*b*) Subject to subject variation of psychotomimetic effects of the drugs. (*c*) An overall estimate of experimental error for each subject.

The real effectiveness of psychotomimetic differences from subject to subject can then be estimated.

3. *Subject Sophistication and Anxiety*

It must be recognized that a test group, on being used repeatedly, becomes somewhat sophisticated in their evaluation of symptom production. For example, in studying the effect of Prednisone on the *LSD* reaction, members of the test group could almost invariably detect whether or not Prednisone was being administered in advance by the occurrence of typical euphoria produced by Presnisone in the doses employed (2). This sophistication demonstrates, to a certain extent, the psychological threat invoked by the possibility of going psychotic in the test situation. In tests of tolerance and cross-tolerance, where subjects take large doses of psychotomimetic drugs for 10 days before the test situation itself, severe symptoms may occur. For example, following are verbatim remarks of Subjects R.B. and C.G. taken from the back of the questionnaire regarding the effects of Psilocybin during a 14-day tolerance experiment:

> *Subject R.B.:* A considerable quantity of symptoms were experienced during the past week. The peak was reached on Monday and Tuesday of this week, having started on Saturday. The physical symptoms generally experienced were contraction of scalp, hollow feeling in pit of stomach, and unsteadiness. To walk purposefully was an effort. Monday I experienced great difficulty in concentrating on the conversations of others but was able to concentrate on work not involving others. A change in plans involving dinner preparations, in which I was to participate, completely "threw" me. I took some time to regain my composure. My temper was short throughout the day.
>
> Tuesday I completely lost control of my temper at my child in the morning. Concentrated effort to avoid conflicts carried me through the rest of the day and since. Since Tuesday, the physical symptoms have been present, but the emotional symptoms were less severe. Yesterday and today I was able to carry on work involving others fairly well. Noontime symptoms are less severe than morning and evening symptoms. One must presume that some tolerance has been built up since symptoms have not increased with increasing dosages.

Subject C.G.: Saturday, Sunday, and Monday I had no particular reaction except wakefulness at night. Tuesday morning I had a two-and-a-half-hour reaction during which time I had nausea, dizziness, buzzing in the ears, light hands and feet, and considerable loss of time consciousness. Tuesday night I had the same feelings only they were worse, and I found I was unable to read a child's book with any coherency or sequence. The ideas weren't coming through.

Wednesday morning's reaction was worst of all. I sat at my desk, gazing out of the window for three hours, physically and mentally paralyzed. I felt as if I were anaesthetized. I couldn't answer questions or discuss anything. Wednesday night I split the dose in two parts, which was better. Thursday I split the dose in three parts in the morning and two parts in the evening, with only a slight effect each time. Friday the single dose had no effect at all.

Factors similar to the foregoing may structure the experiment on psychotomimetic drugs for the production of anxiety in the test subjects, independent of the drug itself. This situation is perhaps best illustrated by the fact that the queries of the questionnaire are very different indeed from the usual therapeutic trial where the expectation of the patient is to be helped, not to be threatened. For this reason, every effort is made to eliminate or dilute the anxiety, *which must be engendered by the test situation, no matter how dedicated or experienced the test subject may be.* A social milieu as free of stress as possible, with two or more subjects, is fairly anxiety free. Interaction by the members of the test group or their wives or husbands, who may be permitted to be present, diminishes anxiety because of the common bond produced by the test situation. It is of interest that during a television demonstration of the *LSD* psychosis by the writer the test subject wished his wife in the same room both before and during his television appearance (9).

To further prevent contamination of the test situation no visitors are permitted unless unanimous consent is obtained from members of the group. Test subjects are encouraged to verbalize recent experiences, which they feel may be anxiety producing, e.g., death of a close friend, occupational stress or nightmares. It has been found necessary to disclose occasionally to one member of the group information that partially destroys the "blind" or "double-blind" character of the experimental design. Thus, a test subject may be aware that he is really one of the first humans to have ever ingested a new congener of *LSD*. The test subject may ask, "Is this a new one?" This question should be answered with a noncommittal answer designed to reduce anxiety, but without disclosing precisely what is going on. A suitable answer might be, "Yes, but you are getting a low dose," or, "Yes,

but only an oxymethyl group has been added." It has been our experience that almost any answer will do, but rejection of the question must be avoided.

Ideally speaking, double-blind experiments may be desirable. However, a single-blind design produces much less anxiety. Tension arises in a subject unless he knows that someone responsible is consciously aware of his travail, incidental to the experiment. It is believed, therefore, that blind experiments are in general more suitable, although double-blind may be necessary at times.

It may be argued that continued experience with the same drug changes the reaction to the drug. However, as illustrated in Table 3, often the opposite may occur. For example, in recent experiments with Psilocybin, our subject P.B., for reasons unknown, during the first Psilocybin experience to 6 mg responded with only two positive responses on the questionnaire, whereas in the three subsequent Psilocybin experiments with 6 mg, the number of responses was 14, 13, and 23 respectively.

C. Methods

1. *High Doses*

Too much reliance cannot be laid on Part I of the questionnaire with high doses. The greater the dose of a psychotomimetic drug, the more difficult it may be to communicate with the subject. In our present test group, used for the past five years, the threshold dose of *LSD* employed is about 25 mcgm. At 100 mcgm withdrawal symptoms with certain members of the group are great enough to produce symptoms so severe that problems arise. The second part of the questionnaire must be emphasized under these circumstances with the observer's evaluation often more important than the numerical value of the responses.

2. *Within Subject Studies*

Our first use of the questionnaire attempted to obtain a study of subject to subject variability with different doses. We have found that the questionnaire was especially useful for comparisons of psychotomimetic effects if studies were made within placebo negative subjects rather than between subjects. The method becomes sensitive if each subject receives all of the compounds at all of the dosage levels unless, as occasionally arises, a subject has a very low threshold and very severe reactions at higher doses. We believe that with this method variations within the response from subject to subject cancel out when response averages are compared. This leads to a gain in precision.

Since the questions of the questionnaire are constructed so that a positive

response constitutes one response, by adding the number of responses a number, *n*, is obtained. It is obvious that, if the same drug is used in all experiments, different values of *n* may be compared. However, if *LSD* is to be compared with its congeners and derivatives, the significance of *n* only becomes important when the dose administered is introduced into the comparison. I have called the ratio of *n* divided by the dose in micrograms the Response Index, or

$$Response\ Index = R.I. = n/mcgm$$

For a given dose, therefore, the higher the value of *R.I.*, the greater the response of the drug. The use of the *R.I.* increases the sensitivity of the questionnaire and provides a suitable method of comparing psychotomimetic activity at threshold levels, or slightly above threshold levels, of various compounds related structurally. By obtaining the group average of the *R.I.*, a more representative value of psychotomimetic activity is established (1).

3. *Cross-Over Designs*

It is feasible to utilize a cross-over design in the study of various derivatives of *LSD*, varying the compounds within the group. The method has been especially effective in our present preliminary comparison of *LSD* and Psilocybin by administering both drugs to our test group double-blind. It may be mentioned that our test subjects cannot usually distinguish between *LSD* and Psilocybin taken orally, unless doses are near the threshold level.

4. *Grouping in Between Subject Comparisons*

We have found that age, sex, weight, occupation, psychological testing, pretest interviews, and screening by outside observers of pretest interviews did not provide adequate replicable groups. We are planning to explore this subject by comparing identical and nonidentical twins, both in our test group and also independently.

D. Summary

The questionnaire used in assessing the effects of *LSD*-25 and other psychotomimetic compounds in non-psychotic test subjects is discussed in detail. Its value in estimating placebo reactivity, subject to subject variability, subject sophistication and anxiety, within subject studies, and evaluation of a Response Index, is illustrated.

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