

## COMPARATIVE SUBJECTIVE EFFECTS OF SEVEN DRUGS INCLUDING LYSERGIC ACID DIETHYLAMIDE (LSD-25)<sup>1</sup>

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THERE has been increasing interest in recent years in drugs which are capable of producing disturbances in behavior and thought in otherwise normal subjects (Ss) (1, 7, 9). Elucidation of the action of these drugs holds the hope of revealing biochemical mechanisms underlying the forms of behavior so affected. One of the most dramatic agents under study is LSD-25 (lysergic acid diethylamide), a substance which in minute doses produces psychotic-like symptoms (8, 12, 14). Many better known drugs also produce behavioral changes, so that a comparison between the subjective effects of LSD-25 and those of some of these other drugs seemed desirable. There are extremely few comparative studies utilizing drugs with primarily psychological effects. Even fewer have been those in which the same Ss were intensively studied under a series of drugs, because of the practical problems incident to such an experiment (4, 6).

The present experiment was performed as part of a much more extensive study concerned with the behavioral effects of LSD-25 (lysergic acid diethylamide) and illustrates the relative potency of this chemical when compared with a few other commonly used drugs in producing subjective behavioral changes. A few selected Ss, taken from a much larger population, were intensively studied for a few weeks. While they were in a drugged and normal state, numerous physiological and psychological measurements were made. While most of the measures were primarily objective in nature, one of the subjective measures used was a questionnaire, and it is the analysis of these questionnaire results that will be discussed.

One of the serious objections to questionnaires is that the validity of individual items is doubtful. Nevertheless, there are many items

whose validity cannot be pushed further than a subjective response. Unfortunately, the only way to tell whether a person has hallucinations, or a headache, for that matter, is to ask him. As our science progresses, more objective tests for these phenomena may be evolved. In the meantime, it would seem that the proper course for the scientific psychologist to follow lies somewhere between complete dependence upon verbal reports of individuals and complete rejection of such material. It should be emphasized that the small number of Ss used in this study was necessary because of the intensive nature of the individual objective tests, the results of which will be reported elsewhere. We must stress the tentative nature of the results, which are presented for the sake of their uniqueness.

### METHOD

#### *Subjects*

Five paid adult volunteers (three men and two women), considered nonpsychotic on the basis of a psychiatric interview, their responses on psychological tests, and the opinion of a clinical psychologist, served as Ss. They were between 24 and 32 years of age, and weighed from 130 to 180 pounds. Three were graduate students, one a photographer, and the other an advertising trainee. All were cooperative and above average in intelligence.

#### *Drugs*

Each S received seven different drugs and two tap water placebos, each on a different day. The drugs used were d-lysergic acid diethylamide (LSD-25), d-1-brom lysergic acid diethylamide (BOL-148), d-lysergic acid monoethylamide (LAE-32), ergometrine (Ergonovine), scopolamine (hyoscine), methamphetamine hydrochloride (Pervitin or Methedrine), and ethyl alcohol. The properties of these drugs are discussed elsewhere (3, 5, 10, 13). These particular drugs were chosen because either they are known to produce subjective and behavioral changes or are related chemically to LSD.

The dose of each drug that was used in this experiment is presented in Figure 1. Here, for each drug, the logarithm of the concentration actually used in this experiment is indicated. For example, it can be seen that the concentration of alcohol was about a million times as great, expressed in terms of weight, as the concentration of LSD. In terms of molecules, this difference was even greater since the molecular

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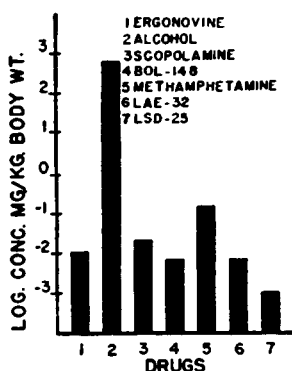


FIG. 1. LOGARITHM OF THE CONCENTRATION OF EACH DRUG USED IN THIS EXPERIMENT EXPRESSED AS MILLIGRAMS PER KILOGRAM OF S'S BODY WEIGHT

weight of LSD is relatively large, whereas that of alcohol is relatively small. The reason for the tremendous difference of potency of these agents is still not known.

### Questionnaire

In order to elicit the symptoms experienced by each S on each of the experimental days, a modification of the questionnaire previously described by the present authors (2) was utilized. The questions were divided into three categories, physiological, perceptual, and cognitive. These are indicated in Table 1.

### Procedure

The five Ss were tested together during nine experimental days, spread over a period of approximately one month. They started at 9 o'clock in the morning, were given a drug or placebo at 9:30, and were tested and observed during the rest of the day until 5 P.M. On

TABLE 1  
QUESTIONS IN EACH OF THREE CATEGORIES

| Physiological                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Perceptual                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Cognitive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>Question</p> <ol style="list-style-type: none"> <li>1. Do you feel peculiar in any way?</li> <li>26. Do you feel ill?</li> <li>27. Are you nauseated?</li> <li>28. Do you feel abnormally hungry?</li> <li>29. Are you hot?</li> <li>30. Are you cold?</li> <li>31. Are you sweating?</li> <li>32. Are your palms moist?</li> <li>33. Are you aware of your heart-beat?</li> <li>34. Have you a headache?</li> <li>35. Do you tremble inside?</li> <li>36. Is breathing difficult?</li> <li>37. Is swallowing difficult?</li> <li>38. Do you have trouble moving about?</li> <li>39. Do you feel weak?</li> <li>40. Do you feel muscular fatigue?</li> <li>41. Do you feel drowsy?</li> <li>42. Do your movements lack control?</li> <li>43. Are your movements incoordinated?</li> </ol> | <p>Question</p> <ol style="list-style-type: none"> <li>2. Is your eyesight blurred?</li> <li>3. Does it take long to focus your eyes?</li> <li>4. Do colors seem changed?</li> <li>5. Do shapes seem changed?</li> <li>6. Do things look too close?</li> <li>7. Do things feel too close?</li> <li>8. Do things look too far away?</li> <li>9. Do things feel too far away?</li> <li>10. Do objects look distorted?</li> <li>11. Do you see anything which isn't there?</li> <li>12. Do you have visual hallucinations?</li> <li>13. Are things moving to and from you?</li> <li>14. Is your hearing abnormal?</li> <li>15. Do you have auditory hallucinations?</li> <li>16. Is your hearing less acute than usual?</li> <li>17. Is your skin sensitive?</li> <li>18. Do you have funny feelings on your skin?</li> <li>19. Do your clothes feel peculiar?</li> <li>20. Do your arms feel peculiar when you move them?</li> <li>21. Do your legs feel peculiar when you move them?</li> <li>22. Do you feel dizzy?</li> <li>23. Do you feel unsteady on standing?</li> <li>24. Do things seem to move?</li> <li>25. Does the room seem to move around you?</li> </ol> | <p>Question</p> <ol style="list-style-type: none"> <li>44. Are you laughing more than usual?</li> <li>45. Are you crying more than usual?</li> <li>46. Do you feel more happy than usual?</li> <li>47. Do you feel more sad than usual?</li> <li>48. Are you unsure of where you are?</li> <li>49. Do you have difficulty in concentrating?</li> <li>50. Do strange things seem familiar?</li> <li>51. Do familiar things seem strange?</li> <li>52. Do you feel as if in a dream?</li> <li>53. Are you anxious?</li> <li>54. Does time seem to be passing more quickly than usual?</li> <li>55. Does time seem to be passing more slowly than usual?</li> <li>56. Do thoughts crowd your mind?</li> <li>57. Do unpleasant thoughts occur more often?</li> <li>58. Do you feel friendly?</li> <li>59. Do you have difficulty in expressing yourself as clearly as usual?</li> </ol> |

TABLE 2  
DRUGS RECEIVED ON EACH EXPERIMENTAL DAY BY EACH SUBJECT

| Experimental Day | Subjects        |                 |                 |                 |                 |
|------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | A               | B               | C               | D               | E               |
| 1                | placebo         | placebo         | placebo         | placebo         | placebo         |
| 2                | LAE-32          | BOL-148         | Ergonovine      | placebo         | methamphetamine |
| 3                | scopolamine     | alcohol         | LAE-32          | methamphetamine | LSD-25          |
| 4                | placebo         | Ergonovine      | scopolamine     | LSD-25          | BOL-148         |
| 5                | methamphetamine | LAE-32          | placebo         | BOL-148         | alcohol         |
| 6                | LSD-25          | scopolamine     | methamphetamine | alcohol         | Ergonovine      |
| 7                | BOL-148         | placebo         | LSD-25          | Ergonovine      | LAE-32          |
| 8                | alcohol         | methamphetamine | BOL-148         | LAE-32          | scopolamine     |
| 9                | Ergonovine      | LSD-25          | alcohol         | scopolamine     | placebo         |

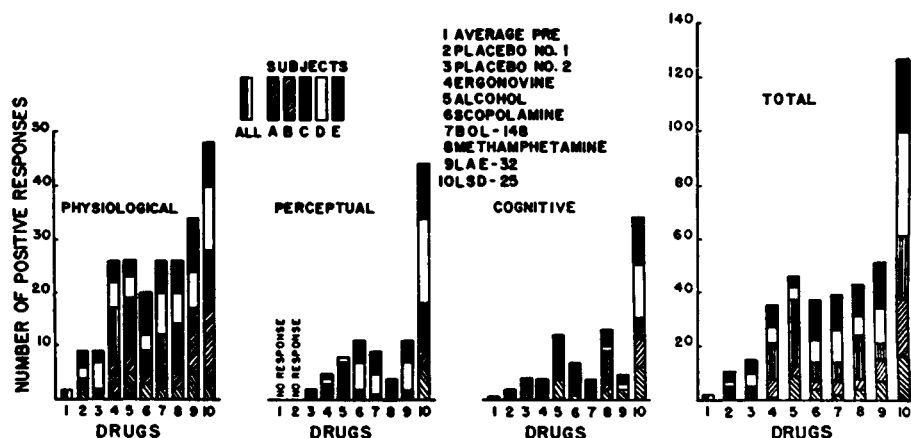


FIG. 2. NUMBER OF POSITIVE RESPONSES TO QUESTIONNAIRE GIVEN UNDER TEN DIFFERENT CONDITIONS BY FIVE Ss

the first experimental day a placebo consisting of 200 cc of tap water was given to all Ss. The order of drug administration is shown in Table 2. The dose of each drug is indicated in Figure 1, and it can be seen how widely they differed. Since only one dose of each drug was given to each S, it was necessary to be somewhat arbitrary. Therefore, commonly accepted average effective doses were used. A double-blind procedure was followed.

The following instructions were given: "Answer the following questions with zero if your answer is no; 1 for slight, 2 for moderate, and 3 for severe positive answers." The Ss answered the questionnaire about 15 minutes prior to and  $\frac{1}{2}$ ,  $2\frac{1}{2}$ , and  $4\frac{1}{2}$  hours after receiving the drug or placebo. During the major part of the day, the Ss were intensively tested with a variety of physiological and psychological measures.

### RESULTS

The total number of positive responses on the questionnaire given under the influence of

each drug is indicated in Figure 2. The results from these questions are divided, as were the questions (see Table 1) into the three categories: physiological, perceptual, and cognitive. It can be seen in Figure 2 that for all three categories the number of positive responses was greatest for LSD. This is most striking in the perceptual sphere. It should be pointed out that the average "pre" scores are derived from the nine sets of responses given at approximately 9:15 A.M.; that is, 15 minutes before the drug was administered. A most suggestive finding is that the number of responses given under the "pre" condition is below that under placebos for two of the three categories; that the scores under placebos are lower than those under any of the drugs (with a slight exception for cognitive symptoms for two Ss), and that the responses under all other

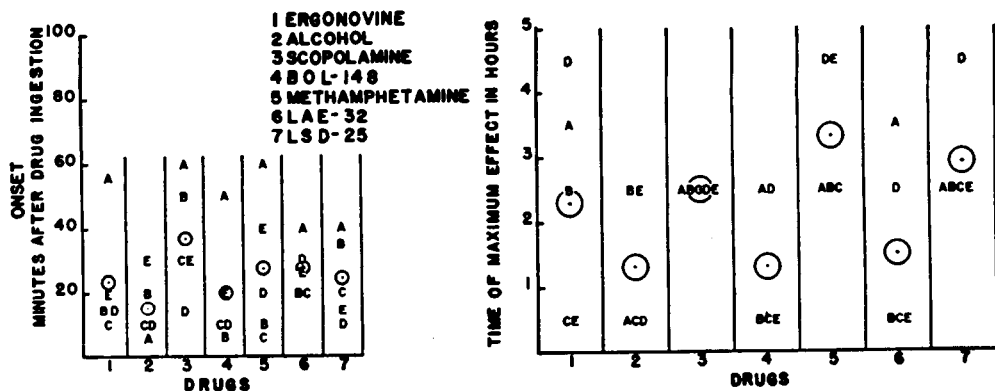


FIG. 3. SUBJECTIVE ONSET OF ACTION OF EACH OF SEVEN DRUGS EXPRESSED IN TERMS OF MINUTES AFTER ORAL ADMINISTRATION. TIME OF MAXIMUM EFFECT IN HOURS AS DETERMINED BY THE GREATEST NUMBER OF RESPONSES TO THE QUESTIONNAIRE

drugs are considerably fewer than those under LSD.

The subjective onset of action of each drug is indicated in Figure 3. It would appear from these results that the onset of the subjective effects of alcohol is relatively rapid, whereas the onset of scopolamine is relatively slow. The time of maximum effect was obtained by determining when the greatest number of positive responses occurred. Again it would seem that the time required to attain maximum effect for alcohol is rather short, whereas methamphetamine took the longest to reach its peak.

It is beyond the scope of this paper to consider an analysis of all the individual questions. However, the responses to a few which seemed especially interesting will be considered. One question which received a positive response by all Ss under most drugs was No. 1, "Do you feel peculiar in any way?" All Ss answered this question positively while under five of the seven drugs, and four of the Ss answered positively under the remaining two drugs. One S gave a positive response with both placebos and another with one of them. No Ss, however, gave positive responses to this question in the "pre" state. Just what the precise determinant of a positive response to this item is cannot be defined at present. The fact that it was occasionally answered positively with a placebo shows that it is not unambiguous, but it is likely that it is sufficiently differently answered by Ss in a drugged state and in a normal state to be of diagnostic value.

In view of the present interest in the reticular activating system (11), we may examine the responses to question #41, "Do you feel drowsy?" Subject A responded to this item positively on 30 of the 35 times that he answered this question. This is not particularly discriminating for him. He responded positively to this item just as many times when under methamphetamine (which is ordinarily considered a stimulant) as when under alcohol (which is a depressant). This is not the case with the remaining four Ss. Both of the other two male Ss responded positively to this item only with alcohol and not with methamphetamine. The same was true of the two female Ss, neither of whom responded positively with methamphetamine, but both of whom responded positively with alcohol. It would seem worthwhile to explore the subjective experience underlying the response to such an item which differentiates two drugs.

Some of the individual differences between Ss in their responses to this questionnaire are especially interesting. Subject A gave relatively few responses in the nine experiments; furthermore, his responses were usually "slight." It is interesting to note that he was also slow to react to the drugs, and in all cases, except when he received alcohol, he first felt a change between 40 minutes and one hour after the ingestion of the drug (see letters designating Ss in Fig. 3). On almost every occasion he reported that he felt abnormally hungry. Subject B also gave very few responses, and only under LSD were there a

large number of +2 and +3 responses. The other three Ss gave relatively more responses, with Subject E giving the most responses. Clearly there are individual differences in responsiveness to these drugs. How these differences are related to other personal traits is of considerable interest, but outside the scope of this paper.

#### DISCUSSION

In comparing the effects of seven different chemicals and two tap water placebos upon the responses to a questionnaire, it is apparent that the chemical structure of the compound ingested is of paramount importance in determining responses to these questionnaires. Of course, we must be cautious with generalizations when we have a population of only five Ss even though every S took the questionnaire 35 times including 9 preingestion testings. We would expect any effect due to suggestion, fatigue, transitory illness, or factors other than the drug to appear also in the placebo or the pretesting situations. It can be seen that the differences obtained between these sessions and the drug sessions are quite marked. It should be remembered that in the "pre" sessions the Ss knew that they had not received a drug, whereas under the placebo conditions, there was no way of their knowing whether or not they had received a drug other than their own subjective experience.

On the basis of the number of replies given to the questionnaire, it is possible for us to differentiate LSD-25 from the other drugs and to differentiate the other drugs from the placebos. The placebos, in turn, can be differentiated from the "pre" responses. It is interesting that three of the other drugs used; namely, Ergonovine, BOL-148, and LAE-32 are only slightly different chemically from LSD-25. LAE-32 is the monoethylamide instead of diethylamide, and BOL-148 has one of the hydrogens replaced by a bromine atom. Ergonovine has a slightly different amide linkage. On the other hand, alcohol, scopolamine, and methamphetamine are quite unrelated chemically. It is noteworthy that ethyl alcohol, a depressant, and methamphetamine, a stimulant, give rise to approximately the same type of results on our questionnaire.

The fact that different Ss responded differently to the same questions with the same

drugs may have a biochemical basis, but it may also be ascribed to certain psychological propensities. Just as in a psychophysical experiment at or near threshold values, whether an S reports a sensation or not depends to a great extent upon his attitude, so in these experiments the feelings, which were frequently rather ambiguous in nature, might be reported by some Ss and not by others even though if they could have been objectively measured they might have been the same. Unfortunately, unlike psychophysical measures, there is no physical correlate of the subjective responses here. Only as our neurophysiological techniques improve, may we hope that sensations and perceptions may be objectively demonstrated.

#### SUMMARY AND CONCLUSIONS

Five Ss were tested on nine occasions under two placebos of tap water and under an average effective dose of seven drugs—ergometrine (Ergonovine), ethyl alcohol, scopolamine (hyoscine), d-1-brom lysergic acid diethylamide (BOL-148), methamphetamine hydrochloride (Methedrine or Pervitin), lysergic acid monoethylamide (LAE-32), and lysergic acid diethylamide (LSD-25) during nine different experimental sessions. Except for the first experimental day on which all Ss received the tap-water placebo, a double-blind procedure was followed, wherein neither Ss nor E knew the order of administration of the substances. The Ss completed a questionnaire inquiring about their perceptual, physiological and cognitive state, before they received the drug or placebo and  $\frac{1}{2}$ ,  $2\frac{1}{2}$ , and  $4\frac{1}{2}$  hours after receiving it. The substance receiving the lowest number and the mildest types of positive responses was for all Ss the tap-water placebo. Although differentiation between three lysergic-acid derivatives, Ergonovine, LAE-32, and BOL-148 and between alcohol, methamphetamine, and scopolamine was not clear-cut, the number of responses to the questionnaire under these drugs was clearly greater than those given under water. In turn, the number of symptoms elicited in the preceding period was quite apparently less than that elicited by a tap-water placebo. LSD-25 clearly produced the most frequent and the largest positive responses. Under this drug occurred the greatest agreement among Ss,

the greatest variety of symptoms, the greatest number of responses, and the most extreme responses to the questions.

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