# LYSERGIC ACID DIETHYLAMIDE (LSD-25)
## XXXI. COMPARISON BY QUESTIONNAIRE OF PSYCHOTOMIMETIC ACTIVITY OF CONGENERS ON NORMAL SUBJECTS AND DRUG ADDICTS*

By

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A GENERALLY acceptable method of comparing psychotomimetic compounds has apparently not been devised. A method of this type would provide the replicability not now available in the newly developed field of psychopharmacology. For example, the method employing the Cold Spring Harbor questionnaire devised by the writer and his co-workers has been criticized as being "too suggestible", "too structured", or "insufficiently cognizant of unconscious processing". It is the purpose of this communication to show that the Cold Spring Harbor questionnaire (1, 2) provides a suitable method of study of the psychotomimetic drugs similar to d-lysergic acid diethylamide (LSD-25). The basis for this statement is the comparison made here of the results of an independent study of a series of congeners of LSD-25 made by Isbell, Miner and Logan (3) in another laboratory, in a different milieu, and on a different population sample. It has been found that the comparative effectiveness of a series of LSD congeners both at Cold Spring Harbor and at Isbell's laboratory in Lexington, Kentucky are the same when the Cold Spring Harbor questionnaire is employed.

### COMPARISON OF PROJECTS

*Questionnaire.* The questionnaire employed at Cold Spring Harbor was that described in detail in a previous paper of this series, and has been in use for eight years (1). The Kentucky project employed essentially the same questionnaire with the questions arranged somewhat differently. However, the differences between the two questionnaires are negligible.

*Subjects.* The Cold Spring Harbor subjects were the five non-psychotic, white subjects used for the past five years in intra-subject studies. They were an engineer, a physician, lawyer, teacher, and housewife. At Lexington the subjects were all Negro, male, drug addicts, serving for violation of the Narcotic Laws. They were in good physical health with no evidence of a major psychosis.

*Drugs.* The congeners of LSD studied were obtained from the same source, Sandoz Pharmaceuticals, Hanover, N.J. At both laboratories fresh solutions of all drugs were administered to subjects in a fasting state as follows: at Cold Spring Harbor the drugs were administered one-half hour before dinner; at Lexington they were given in the morning before breakfast. At Cold Spring Harbor doses were not calculated on the basis of body weight but were given in units of round numbered increments, depending on the threshold dose. At Lexington, doses were calculated in micrograms per kilogram. Experiments

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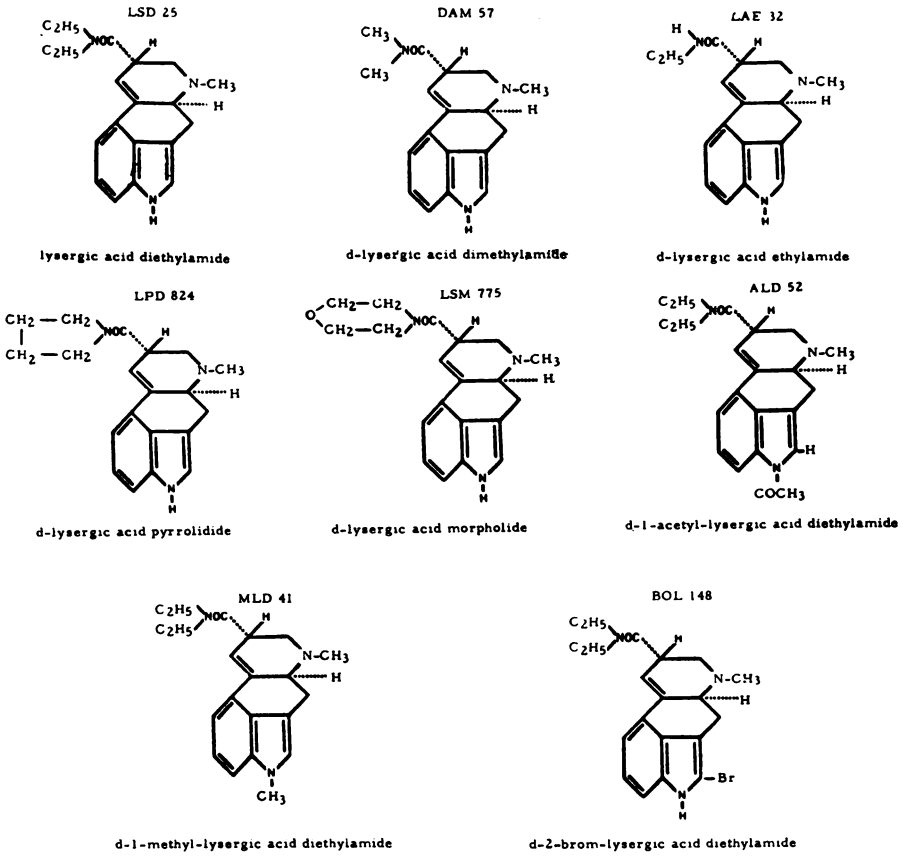


FIG. 1

were usually "single blind" at Cold Spring Harbor, whereas at Lexington neither the subjects nor the observer knew the nature of the drugs under study.

*General Conditions.* At Cold Spring Harbor the experiments were conducted in the home of the writer, under social conditions designed to reduce anxiety (4), whereas at Lexington they were conducted in a special ward devoted to research. The Lexington patients entered the ward in the afternoon prior to the experiment. They were housed in individual rooms but were allowed to leave them and mix with other patients in a common dayroom. At both places experiments were done at weekly intervals. At both laboratories dosages were increased, but to different levels. At Cold Spring Harbor the purpose was to determine the reactivity of the drugs at or near threshold levels, whereas at Lexington a somewhat different procedure was used. The dosage at Lexington in the first trial was always 0·5 microgram per kilogram. This was increased with the congeners of LSD until at least 50 micrograms per kilogram had been reached without evidence of any psychotomimetic reaction. In both laboratories the congeners were compared with LSD, which was administered from time to time.

*Analysis of the Data.* In both cases the number of positive responses to the questionnaire was the basic method of computation, although at Lexington the short mental rating test provided by Part II of the Cold Spring Harbor questionnaire was apparently omitted but was substituted by a clinical grading.

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## Results

The approximate equivalent psychotomimetic doses shown under Table I under Lexington were obtained by Isbell *et al.* by inspecting the data on the

Table I

*Comparison of Relative Values of Effectiveness of LSD Congeners on Narcotic Addicts (Lexington) and Non-psychotic Subjects (Cold Spring Harbor) Using the Cold Spring Harbor Questionnaire*

| Compound | Code | Lexington | Cold Spring Harbor |
|---|---|---|---|
| d-Lysergic acid diethylamide .. .. | LSD-25 | 100 | 100 |
| d-1-Acetyl lysergic acid diethylamide .. | ALD-52 | 100 | 91 |
| d-1-Methyl lysergic acid diethylamide .. | MLD-41 | 33 | 36 |
| d-Lysergic acid morpholide .. .. | LSM-775 | 11 | 11 |
| d-Lysergic acid dimethylamide .. .. | DAM-57 | 10 | 11 |
| d-2-Brom-lysergic acid diethylamide .. | BOL-148 | <2 | 7* |
| d-Lysergic acid pyrrolidide .. .. | LPD-824 | 10 | 5 |
| d-Lysergic acid monoethylamide .. | LAE-32 | 5 | 3 |

* There is variation in different samples of BOL (see, Baron, M. O., Sklarofsky, B., Fremont-Smith, N., and Abramson, H. A., "Lysergic Acid Diethylamide (LSD-25): XXVIII. Assay of 2-Bromo-Lysergic Acid Diethylamide by the Siamese Fighting Fish", *J. Psychol.*, 1958, **46**, 303.)

number of positive answers and clinical grading and selecting the dose of the new drug which most nearly approximated the effect seen or expected from one microgram per kilogram of LSD. These data are obtained from Table I of their paper and give the relative psychotomimetic activity of LSD-25=100.

The method of obtaining the relative activity of congeners of LSD-25 at Cold Spring Harbor was described previously. Briefly, it consists of adding the number of positive responses obtained by means of the questionnaire for three and one-half hours after the drug has been administered (at ½ hour, 1½ hours, 2½ hours, 3½ hours). The sum of the number of positive responses, $n$, is divided by the dose in micrograms and a Response Index=R.I.=$\frac{n}{\text{mcg}}$ is calculated using an experimentally determined value of the threshold dose. For a given dose, therefore, the higher the value of R.I., the greater the response to the drug as measured by the questionnaire. Values of the R.I. for the congeners were obtained similarly, and rather than estimating response as Isbell *et al.*, did by approximating reactions equal to one microgram per kilogram of body weight, group averages of the Response Index for the five non-psychotic subjects were compared and recalculated for the value of the R.I. obtained for LSD=100. The raw data and the method of calculation have already been published (4). In Table I the Cold Spring Harbor data are compared with those of Isbell.

## Discussion

It is remarkable that the order of activity obtained for the series of LSD congeners at Lexington and Cold Spring Harbor are almost identical, with the exception of BOL-148. The work of Isbell, Miner and Logan, therefore, confirms the procedure employed in this Laboratory and indicates that a greater degree of validity can be ascribed to the method of calculation of the comparative effectiveness of these compounds than had hitherto been supposed. Isbell, Miner and Logan's data also indirectly confirms the validity of the

procedure of calculating the R.I., which forms the basis of our calculation of a Tolerance Index*.


## Summary

Data of Isbell, Miner and Logan on Negro narcotic addicts at Lexington, Kentucky are compared with normal non-psychotic, experienced, white test subjects at Cold Spring Harbor. The experiments were performed with a series of congeners of d-lysergic acid diethylamide. The method of comparing the comparative psychotomimetic effectiveness was based upon the use of a questionnaire. Within the limits of error remarkable agreement was obtained on the two different test groups under different experimental settings. The agreement confirms the validity of the method employing the Cold Spring Harbor questionnaire in studies on the comparison of psychotomimetic activity.


* A Tolerance Index may be calculated to compare cross-tolerance produced by different agents. For example, taking the Response Index for LSD as a standard, the ratio of the Response Index for LSD to the Response Index for a test drug will always be more than one if LSD produces the greatest response. We may take, therefore, a measure of effectiveness of cross-tolerance production by MLD to LSD as $\frac{\cdot 47}{\cdot 02} = 23 \cdot 5$, a number expressing the apparent effectiveness of tolerance production not corrected for the dosage of MLD. In the particular experiment the Tolerance Index corrected for dosage turned out to be $20 \cdot 6$, which actually is about ten times that found for BOL. (For data see Abramson, H. A., Sklarofsky, B., Baron, A. B., and Fremont-Smith, N.: Lysergic Acid Diethylamide (LSD-25) Antagonists: II. Development of Tolerance in Man to LSD-25 by Prior Administration of MLD-41 (1-Methyl-d-Lysergic Acid Diethylamide), *A.M.A. Archives of Neurol. and Psychiat.*, 1958, **79**, 201.)

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