EXHIBIT 19

Psychopharmacological Studies of Lysergic Acid Diethylamide (LSD-25) Intoxication

Effects of Premedication with BOL-128 (2-Bromo-d-Lysergic Acid Diethylamide), Mescaline, Atropine, Amobarbital, and Chlorpromazine

LINCOLN D. CLARK, M.D., and EUGENE L. BLISS, M.D., Salt Lake City

One consequence of the recent interest in psychotomimetic drugs has been a search for pharmacological agents that will "block" drug-induced psychological disturbances and hallucinations. Fabing [1] reported that azacyclonol (Frenquel) in small doses prevented the occurrence of lysergic acid diethylamide (LSD-25) "psychoses" in man, although one of us (L. D. C.) was unable to verify this observation.[2] Other investigators have reported that LSD-25 intoxication is ameliorated by premedication with chlorpromazine,[3,4] serotonin,[5] and reserpine.[4] However, it has also been reported that serotonin [6] and reserpine [3] intensify LSD-25 effects. Hoch [7] found that premedication with amobarbital (Amytal) sodium and chlorpromazine did not prevent LSD-25 or mescaline intoxication but pointed out that such drugs produced suppressive effects when given at the height of the intoxication.

Several reasons exist for this confusing state of affairs. There has been a failure to distinguish between true pharmacological antagonism (blocking) and suppression. For example, in studying the effects upon the LSD-25 state of drugs with potent depressive action, such as amobarbital or chlorpromazine, one must differentiate between evidence of specific blocking from modest doses and masking or suppression secondary to impaired awareness in heavily premedicated subjects. Another source of difficulty is that LSD-25 intoxication is a complex condition, offering a wide variety of behavioral and psychological changes that may be observed and measured. When the object of the study is the modification of LSD-25 intoxication by other drugs, the choice made of what is to be measured may lead to appreciably different results. For example, if an investigator were to regard nausea as an important aspect of LSD-25 intoxication, he would probably find chlorpromazine to be an effective "blocking" agent. Other investigators emphasize the prevention of LSD-25 "psychosis" as though the latter were a predictable occurrence. This may be justified if one defines "psychosis" as the appearance of the typical LSD-25 perceptual disturbances. However, in our experience, psychosis in the sense of real behavioral disorganization occurs in only occasional experimental subjects given LSD-25 in the usual 1γ/kg. dose.

The experiments to be described in this paper were further attempts to assay the effectiveness of various drugs as blocking agents against LSD-25. Since there is little precise knowledge of the locus or mechanism of action of LSD-25, the choice of potential antagonists, while obviously guided by the experience of other workers, was frankly

Submitted for publication July 9, 1957.

From the Department of Psychiatry, University of Utah College of Medicine, and Veterans' Administration Hospital, Fort Douglas Division.

Assistant Professor of Psychiatry (Dr. Clark). Associate Professor of Psychiatry (Dr. Bliss), University of Utah College of Medicine.

The LSD-25 and BOL-148 used in these experiments were supplied by Mr. Harry Althouse, of Sandoz Pharmaceuticals. The mescaline sulfate was supplied as a research grant from S. B. Penick & Company, New York.

speculative and arbitrary. Tap water was employed as a control. BOL-148 (2-bromo-*d*-lysergic acid diethylamide) was used, since it is structurally similar to LSD-25 but lacks the latter's hallucinogenic properties. Consequently, it was assumed that it might displace the LSD-25 at some hypothetical site of action in the central nervous system. On the other hand, mescaline sulfate, a drug with hallucinogenic activity similar to that of LSD-25, was given in the subhallucinogenic dose of 0.1 gm. on the assumption that this quantity might be sufficient to preempt a common site of action. Amobarbital sodium, 0.3 gm., as a central nervous system depressant, and chlorpromazine, 50 mg., as a tranquilizer-depressant, were studied as drugs which might be expected to antagonize the stimulating effects of LSD-25. Finally, atropine sulfate, 1.2 mg., was used as an autonomic blocking agent which might modify those aspects of the LSD-25 experience due to parasympathetic discharge. All medications were given orally.

Modest doses of premedication were chosen on the assumption that if true pharmacological antagonism occurred, as is exemplified by the model of nalorphine-morphine, such amounts would suffice to produce recognizable "blocking" effects. There were also other advantages in this choice. High doses of mescaline or atropine would have produced effects which could easily be confused with those of LSD-25, while excessive amounts of amobarbital or chlorpromazine would have obscured LSD-25 effects by producing nonspecific cortical depression.

The subjects were six medical students. A "double-blind" design was followed, so that neither the subjects nor the observers knew the exact order of the administration of drugs. All premedications were dispensed in 200 ml. of tap water to fasting subjects at 8:30 a. m., and LSD-25 was given at 10:00 a. m.

A modification of the extensive questionnaire for LSD-25 effects devised by Jarvik et al.[8] was completed by the subjects before the premedication, at 10:00 a. m., and 11:30 a. m. In addition, we made independent behavioral observations and mental-status evaluations at 15-minute intervals throughout each experiment. An effort was made to observe a broad spectrum of the physiological, perceptual, and psychological effects which may be produced by LSD-25. The subjects were also asked to record at regular intervals their perception of any somatic and psychological changes. These notes were later organized by the subjects into lengthy introspective reports.

The initial dose of LSD-25 was 1γ/kg. of body weight. However, after the first experiment this was reduced to 0.5γ/kg. There were two reasons for this change. First, one of the subjects experienced a severe "psychotic" LSD-25 reaction, which represented a real management problem. Second, it became apparent that the large dose produced such disruptive effects that the subjects were unable to complete the LSD-25 questionnaire accurately or to maintain an adequate introspective record of their experience. While there were minor differences from one subject to another, the smaller dose of LSD-25 produced mild but characteristic effects. These consistently included feelings of depersonalization, various paresthesias, a persistent urge to stretch, feelings of nervousness or general stimulation, and transient visual imagery when the eyes were closed. The effects of the larger dose were largely an extension of these effects, including more elaborate and persistent visual and somatic disturbances.

After three experiments, during which each of the subjects received three different premedications, a tabulation of the responses to the questionnaire and an analysis of the observer's protocols and the subjects' reports were made. With the possible exception of atropine, where fewer responses to the questionnaire occurred, the premedications failed to modify significantly any aspect of the LSD-25 intoxications. To check the significance of the observation on

atropine, three more experiments were run. All six subjects were studied under the influence of LSD-25 0.5γ/kg. alone, atropine 1.2 mg. alone, and atropine followed by LSD-25. These experiments failed to confirm the initial impression. Atropine did not decrease the response to LSD-25 but, instead, caused additional disagreeable autonomic effects, which actually made the experience more unpleasant.

Summary

Premedication with moderate amounts of BOL-148 (2-bromo-*d*-lysergic acid diethylamide), amobarbital sodium, chlorpromazine, mescaline sulfate, and atropine sulfate did not significantly influence the somatic and psychological disturbances induced by either large or small doses of lysergic acid diethylamide (LSD-25). There was no evidence of a blocking effect, such as might have been anticipated if these agents had any specific pharmacological antagonism toward LSD-25.

156 Westminster Ave. (15).

REFERENCES

1. Fabing, H. D.: Nerve Blocking Agent Against the Development of LSD-25 Psychosis, Science 121:208, 1955.

2. Clark, L. D.: Further Studies of the Psychological Effects of Frenquel and a Critical Review of Previous Reports, J. Nerv. & Ment. Dis. 123:557, 1956.

3. Isbell, H.: Effect of Chlorpromazine, Reserpine, and "Frenquel" on LSD Reaction, Fed. Proc. 15:442, 1956.

4. Giberti, F., and Gregoretti, L.: Prime Esperienze di antagonismo psicofarmacologico, Sistema nerv. 7:301, 1955.

5. Montanari, C., and Tonini, G.: Azioni della 5-idrossitriptamina sul sistema nervoso centrale: suo impiego in psichiatria sperimentale, Riv. sper. freniat. 79:465, 1955.

6. Poloni, A.: Serotonina e schizofrenia: Osservazioni sulle interferenze fra l'azione della serotonina e della dietilamide dell'acido lisergico (LSD-25), mescalina e bulbocaprina nell'uomo e nell'animale, Cervello 31:271, 1955.

7. Hoch, P. H.: Experimental Psychiatry, Comments, Am. J. Psychiat. 111:787, 1955.

8. Jarvik, M. E.; Abramson, H. A., and Hirsch, N. W. Comparative Subjective Effects of Seven Drugs Including Lysergic Acid Diethylamide (LSD-25), J. Abnorm. & Social Psychol. 51:657, 1955.