Studies on the Diethylamide of Lysergic Acid (LSD-25)

II. Effects of Chlorpromazine, Azacyclonol, and Reserpin on the Intensity of the LSD-Reaction

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The effects of "tranquilizing" drugs on the abnormal mental state induced by the diethylamide of lysergic acid (LSD-25) are of interest from several points of view. Some means of mitigating too severe a reaction is needed in using LSD-25 experimentally or therapeutically. Since the LSD reaction is measurable and reproducible, it might be possible to use the LSD psychosis as a screen for predicting the potential clinical value of new tranquilizing drugs. In addition, such studies might be useful in elucidating the mechanisms of action of both the tranquilizers and the psychotogenic drugs. The purpose of the present paper is to present the results of experiments in which attempts were made to block (prevent) or reverse (treat) the LSD reaction with chlorpromazine, azacyclonol (Frenquel), and reserpin.

Methods

Subjects.—The subjects used in these experiments were all adult male drug addicts who were serving sentences for violation of the Harrison Narcotic Act. All subjects volunteered for the experiment; none were psychotic, and the majority had been diagnosed as having character disorders or inadequate personalities. All had been abstinent from opiates for three months or more prior to serving in the experiments. The LSD reaction in such subjects has been shown to be similar to or identical with that in persons who have never been addicted to narcotics.1

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Means of Measurements and Analysis.—These have previously been described in detail.1 The patellar reflex, pupillary size, and resting systolic blood pressure were measured hourly for two hours prior to and eight hours after administration of the LSD. The data were plotted on graph paper; the average of the two pre-LSD measurements was used as a base line and the area under the curve measured with a planimeter, thus converting all the data for that particular subject and that particular day to one figure. The mental effects were assessed by administering the questionnaire devised by Jarvik et al., hourly, two hours before and eight hours after administration of LSD. The number of positive responses after LSD were counted, eliminating any positive answers that were also scored positively prior to administration of the drug. The intensity of the reaction was graded on a 4-point scale, using criteria previously described. The grade was based on a short psychiatric examination which was carried out either at the height of the reaction or hourly.

Drugs.—LSD and an LSD placebo were given orally to fasting patients in doses specified below. Chlorpromazine and azacyclonol were administered either before (blocking experiment) or at the height of the reaction after LSD (reversal experiment). Only blocking experiments were conducted with reserpin. The specific doses of the tranquilizers, routes of administration, and times are described below under the specific experiments. Experiments were conducted at least one week apart in order to prevent the development of tolerance to LSD.

Experimental Design.—A "cross-over" design, in which each person served as his own control, was used. Study of any tranquilizer always involved four separate drug combinations in the same group of subjects: LSD placebo plus tranquilizer placebo; LSD plus tranquilizer; LSD placebo plus tranquilizer; LSD plus tranquilizer placebo. The "double-blind" pro-
TRANQUILIZING DRUGS AND LSD

TABLE 1 Effect of Chlorpromazine in "Blocking" the LSD Reaction

<table>
<thead>
<tr>
<th>NUMBER OF SUBJECTS</th>
<th>DOSE OF LSD (MCG)</th>
<th>DOSE OF CHLORPROMAZINE (MG)</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>40</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>60</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

(1) GIVEN AS A SINGLE DOSE ORALLY, 30 MINUTES PRIOR TO LSD

Procedure was followed throughout. Both the observers and the subjects were unaware of the medication that had been administered. The order in which the various combinations of LSD and tranquilizers were given was randomized by using random numbers and a Latin-square design.

Results

Chlorpromazine—Four blocking experiments were done with chlorpromazine, which was given orally 30 minutes prior to LSD. The timing was such that maximal effects of chlorpromazine and LSD developed simultaneously. The drug combinations used were 50 mg. of chlorpromazine HCl against 40γ of LSD-25; 75 mg. of chlorpromazine HCl against 40γ of LSD-25; 75 mg. of chlorpromazine HCl against 60γ of LSD-25, and 100 mg. of chlorpromazine HCl against 60γ of LSD-25. The data are summarized in Table 1. A significant reduc-

![Graph](image-url)

**Fig. 1.** Effect of 75 mg. of chlorpromazine HCl given 30 minutes before LSD. For details see text.
tion in intensity of the mental effects produced by LSD was observed in all experiments. Detailed results of the largest experiment, in which 75 mg. of chlorpromazine HCl was given 30 minutes prior to 60γ of LSD-25 in 19 subjects, are shown in Figure 1. In this, and in subsequent figures, the means of the various measurements under the four treatment conditions are represented by the heights of the bars. The kinds of treatments are identified by differing hatching on the bars. The heavy lines with brackets at the top of the bars depict two standard errors above and below the mean of that particular measurement and treatment combination. In order to show a statistically significant difference between LSD alone and tranquilizer plus LSD, the bracketed lines of the two center bars should not overlap. In Figure 1, the size of the pupil and the clinical grade of reaction after LSD plus chlorpromazine are significantly reduced, as compared with LSD plus chlorpromazine placebo. Although the knee jerk, blood pressure, and number of positive answers were not diminished significantly, a trend to reduction in these measurements was present.

In the doses used, chlorpromazine did not abolish the mental effects of LSD completely. Anxiety, increased psychomotor activity, and nervousness were less prominent, and fewer patients reported visual perceptual distortion and hallucinations. Confusion and difficulty in concentration and thinking, however, persisted despite the chlorpromazine.

Two reversal experiments with chlorpromazine are summarized in Table 2. In the first experiment 75 mg. of chlorpromazine HCl was given orally one and one-half hours after 60γ of LSD-25. Although pupillary size was reduced by the chlorpromazine, the over-all course of the mental reaction was not significantly affected. Since chlorpromazine given orally requires about two hours to develop maximal effects, and since the LSD reaction is already beginning to subside by the time the chlorpromazine would have exerted its maximal effect in this experiment, the failure to show any change in the total course of the reaction is not surprising. Significant amelioration was attained in the second experiment, in which 25 gm. of chlorpromazine HCl was given intramuscularly one and one-half hours after a variable dose of LSD-25. Results with chlorpromazine intramuscularly are particularly significant, since the dose of chlorpromazine was not large and the dose of LSD was sufficient to induce a Grade 3 reaction in all subjects.

Azacyclonol.—One blocking (preventive) experiment was done with azacyclonol. Twelve patients received 20 mg. of azacyclonol HCl orally (or placebo) every eight hours for seven days and an additional 20 mg. of azacyclonol HCl two hours before administration of 60γ of LSD-25 on the day of the experiment. The tests were carried

<table>
<thead>
<tr>
<th>TABLE 2—Effect of Chlorpromazine in “Blocking” the LSD Reaction</th>
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<tbody>
<tr>
<td>NUMBER OF SUBJECTS</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>12</td>
</tr>
</tbody>
</table>

(1) GIVEN 1/2 HOURS AFTER LSD
(2) "O" REFERS TO ORAL ROUTE OF ADMINISTRATION;
"I.M." TO THE INTRAMUSCULAR ROUTE
out at intervals of two weeks in order to permit "washout" of azacyclonol, which has been reported by Fabing 2 to have an effect persisting for a week. Results in this experiment are shown in Figure 2. No reduction in any aspect of the LSD reaction occurred. In this experiment, the mean degree of mental effect after LSD alone was not great, being only slightly above Grade 1. Two of the twelve patients, however, had hallu-
solutions regardless of whether or not they had received azacyclol.

In a reversal experiment, 12 patients received varying doses of LSD-25 (2γ-3γ kg.) The dose was chosen individually in order to induce a Grade 3 (hallucination) reaction in all subjects. Sixty milligrams of azacyclol HCl (or an azacyclol placebo) was given intravenously two hours after LSD. An additional 40 mg. of azacyclol HCl (or placebo) was given intravenously three hours after LSD. The results are shown in Figure 3. No significant diminution in any aspect of the LSD reaction could be demonstrated after azacyclol. Detailed statistical analysis of the effect of azacyclol on the time course of the reaction as reflected by the number of positive answers reported each hour or by determination of the clinical grade hourly showed no significant change.

Reserpine.—Because of the slow onset of action of reserpine, only blocking experiments were attempted with this drug. The combinations used were as follows: 1 mg. of reserpine orally two hours prior to administration of LSD; 2.5 mg. of reserpine orally, 10 and 2 hours prior to LSD-25; 2.5 mg. of reserpine orally, 22, 10, and 2 hours prior to 60γ/kg. of LSD-25; 2 mg. of reserpine intramuscularly, 22, 10, and 2 hours prior to 60γ/kg. of LSD-25; 2 mg. of reserpine intramuscularly, 22, 10, and 2 hours prior to 0.5γ/kg. of LSD-25. The results are summarized in Table 3. There was no evidence of any mitigation of the LSD reaction by reserpine in any of the experiments. In fact, the patients seemed to be worse after receiving the larger doses of reserpine plus LSD than after LSD alone. The details of the experiment in which 6 mg. of reserpine (total dose) in 22 hours against 0.5γ/kg. of LSD are shown in Figure 4. The increase in the number of positive answers and in the clinical grade may be noted. This experiment was particularly significant, since the dose of LSD was small, so that beneficial effect of reserpine should have been easily detected.

The combinations of reserpine and LSD were so disagreeable that the patients were persuaded to complete all the experiments only with the greatest difficulty. In addition to the usual symptoms experienced after LSD, the patients reported other symptoms, which seemed to be of two sorts: first, the usual side-effects of reserpine, such as nasal stuffiness, nausea, diarrhea, vomiting, lethargy, weakness, and dizziness on standing; second, severe mental effects. The latter included nervousness and confusion, which exceeded that experienced after LSD alone. A specific kind of hallucination was frequently reported after the combination of LSD and reserpine, which the patients termed “jets” or “jet propulsion.”

<table>
<thead>
<tr>
<th>NUMBER OF SUBJECTS</th>
<th>DOSE OF LSD MCG</th>
<th>TOTAL DOSE OF RESERPINE MG AND ROUTE</th>
<th>RESULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>60</td>
<td>(1) 2.0 “O”(4)</td>
<td>NO BLOCKING</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>(2) 5.0 “O”</td>
<td>NO BLOCKING</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>(3) 7.5 “O”</td>
<td>NO BLOCKING; PATIENTS WORSE</td>
</tr>
<tr>
<td>12</td>
<td>60</td>
<td>(3) 6.0 “I.M.”(4)</td>
<td>NO BLOCKING; PATIENTS WORSE</td>
</tr>
<tr>
<td>12</td>
<td>0.5/KG</td>
<td>(3) 6.0 “I.M.”</td>
<td>NO BLOCKING; PATIENTS WORSE</td>
</tr>
</tbody>
</table>

(1) GIVEN IN ONE DOSE 2 HOURS PRIOR TO LSD
(2) DIVIDED IN 2 DOES 10 HOURS AND 2 HOURS PRIOR TO LSD
(3) DIVIDED INTO 3 DOES 22, 10 AND 2 HOURS PRIOR TO LSD
(4) “O” REFERS TO ORAL ADMINISTRATION;
“I.M.” TO INTRAMUSCULAR
hallucination consisted of a repeated hissing sound which seemed to start in the back of the head and culminated in an expanding flash of light. Simultaneously, patients had a sensation of being hurled or of flying through the air. This particular hallucination was not observed under either LSD alone or reserpine alone.

The subjective effects of the large doses of reserpine in nonpsychotic patients are of some interest. While they were in no way as severe or as unpleasant as those after the combination of reserpine plus LSD, they were, under the circumstances of the experiments, very disagreeable to the subjects. In addition to the expected side-effects of reserpine, such as nausea, the patients were nervous and apprehensive, even though they were lethargic and weak. Mental confusion, depression of mood, and irritability were consistently reported. Most patients heard buzzing sounds, which did not culminate in the flash of light customarily reported with the combination of LSD and reserpine. Two of the twelve patients reported illusions of lights with the eyes closed. These lights were shimmering little dots of white light and differed from the kaleidoscopic play of colors seen when under the influence of LSD. To what extent the subjective effects of reserpine were colored by the fact that all the patients received LSD cannot be determined.

In addition to increased subjective complaints, neurological changes were enhanced after the combination of LSD and reserpine. These consisted of gross tremors at rest, involving large muscle groups in arms and legs in 7 of the 12 patients who received 60g of LSD-25 plus 6.0 mg. of reserpine intramuscularly. While such tremors may occur after larger doses of LSD alone,
they were not present after 60% of LSD-25 alone in these patients.

Comment

Of the three drugs tested, only chlorpromazine reduced the intensity of the LSD reaction significantly. This appeared to be due to the sedative effects of the chlorpromazine and was not due to a specific antagonistic action, such as is observed when nalorphine (X-allylnormorphine) is administered after morphine. The results with chlorpromazine are in agreement with those reported by Hoch; Schwarz, Bickford, and Rome, and Giberti and Gregoretti.

Failure of azacyclonol to alleviate the LSD reaction is puzzling in view of the enthusiastic reports of Fabing. We have no explanation for the differences in our results and those of Fabing except differences attributable to the type of subjects, the experimental environment, and the experimental design.

Failure of reserpine to mitigate the LSD reaction is in agreement with the results of Hoch, but in disagreement with those of Giberti and Gregoretti. The differences between the results reported here and those of these authors are possibly due to differences in the dosage of reserpine and methods of measurement and experimental design.

A number of hypotheses are currently being advanced which relate serotonin to mental functioning and the LSD psychosis to some interference with, or enhancement of, serotonin effects within the central nervous system. Woolley and Shaw postulated, on the basis of similarity in chemical structure of LSD and serotonin, and of antagonistic effects of the two drugs on isolated smooth muscle preparations, that LSD might cause a psychosis by interfering with serotonin within the central nervous system. In this first paper Woolley and Shaw mention only the possibility of deficiency of serotonin produced by competition of serotonin with LSD for receptor sites in neurons, but in a latter paper they state that an alternative hypothesis is possible which relates the LSD psychosis to an excess of serotonin caused by inhibition of amine oxidase by serotonin antagonists. Shore, Silver, and Brodie have shown that both reserpine and serotonin prolonged sleeping time after hexobarbital in mice and that LSD abolished the prolongation. These authors suggest that serotonin has an important function in the brain and that LSD produces its mental disturbances by suppression of some central action of serotonin. In other experiments the same group of investigators have demonstrated that reserpine reduces the concentration of serotonin in the brain, as well as in the intestine and blood platelets. The hypothesis advanced by these workers has, however, been greatly weakened by demonstrations that 2-brom-β-lysergic acid diethylamide (BOL), a substance which does not induce a psychosis in man, both blocks the smooth muscle spasm induced by serotonin and abolishes serotonin or reserpine-induced enhancement of sleeping time in mice and rats. Obviously these phenomena can have no relationship to the psychomimetic effect of LSD in man.

Costa found that in low concentrations, such as would be found in clinical experimentation, LSD enhanced the spasmogenic action of LSD on the excised rat uterus, while higher concentrations blocked this effect. Mescaline always augmented serotonin-induced uterine contractions, whereas azacyclonol, reserpine, and chlorpromazine inhibited the uterine spasm caused by serotonin. On this basis, Rinaldi, Rudy, and Hinwich suggested that the psychogenic effects of LSD and mescaline were due to their serotonin-facilitating properties and that the correction of LSD-evoked psychosis by azacyclonol was due to inhibition of serotonin.

If, as seems probable, reserpine caused a release of serotonin from nerve tissue in our patients, this additional serotonin had no ameliorating effect on the LSD reaction. Since our patients were worse after reserpine, our results favor the hy-
hypothesis which relates the LSD psychosis to an excess of serotonin rather than the hypothesis which postulates a deficiency of serotonin. Such an interpretation, however, should be viewed with caution, since reserpine alone did not produce a psychosis identical with that caused by LSD, as would be expected if excess of serotonin-like action were the only mechanism of the LSD effect. In addition, it was not possible in our experiments to determine whether the increased objective and subjective effects seen after the combination of LSD and reserpine were due to a specific enhancement of the LSD effect by reserpine, or were due merely to a combination of two kinds of drug toxicity.

Winter and Flataker have found that both LSD and reserpine impair the ability of hungry rats to climb a rope in order to obtain food. Serotonin blocked this effect of LSD, whereas reserpine enhanced the impairment of performance after LSD. Winter's results with the combination of reserpine and LSD are in the same direction (enhancement of the LSD effect by reserpine) as those reported here. Since, however, serotonin ameliorated the LSD reaction in rats, the serotonin presumably "released" by the reserpine must have been prevented from blocking the LSD response because of some other action of reserpine. At the moment there is no single hypothesis which explains satisfactorily all the data on the interrelationships of LSD, serotonin, and reserpine.

Correlation of results in our experiments and those obtained in experiments utilizing isolated smooth muscle or neurophysiological techniques in animals are very poor. For example, Costa found that azacyclonol, reserpine, and chlorpromazine all antagonized serotonin-evoked contraction in the isolated rat uterus. Since in our experiments only chlorpromazine reduced the intensity of the LSD psychosis, these results seem to have little bearing on the mechanism of the LSD effect in man. Rinaldi and Himwich found that azacyclonol reversed the LSD- and mescaline-induced electroencephalographic changes in the rabbit; yet it is clear that azacyclonol had no ameliorative effect on the LSD psychosis in man. Purpura found that reserpine antagonized both LSD-induced facilitation and depression of electrical responses in the cortex of the cat which were evoked by auditory stimuli. Since reserpine does not block the psychotogenic effect of LSD in man, the significance of this observation is obscure.

The results with reserpine make it unlikely that the LSD psychosis can be used as an effective screen for drugs that might be useful in the pharmacotherapy of mental illness.

Summary

1. Chlorpromazine ameliorates partially the abnormal mental state induced by the diethylamide of lysergic acid (LSD-25) in man. Chlorpromazine has this effect when administered before or after LSD.

2. Azacyclonol (Frenquel) does not reduce the intensity of the LSD psychosis in man.

3. Reserpine does not mitigate the LSD psychosis in man. Patients receiving a combination of reserpine and LSD have severer symptoms than when receiving either drug alone.

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REFERENCES


