Comparison of Sernyl with Other Drugs

Simulation of Schizophrenic Performance with Sernyl, LSD-25, and Amobarbital (Amytal) Sodium; I. Attention, Motor Function, and Proprioception

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Study of the pathological mechanisms implicated in schizophrenia has recently been accelerated by the production of model psychoses through the use of psychotomimetic drugs. Our laboratories have previously reported[6] psychotomimetic effects with Sernyl, 1-(1-phenylcyclohexyl) piperidine monohydrochloride. This drug is one of a class of new chemical compounds which function as sensory blocking agents, with anesthetic and sedative properties. It was found to produce severe disturbances in body image, affect, attention, and thinking which closely approximated the primary symptoms of schizophrenia. Depersonalization, feelings of isolation and estrangement, concreteness, hypnagogic states, and repetitive motor behavior occurred in patients following intravenous infusion of this drug.

The present studies were conducted in an attempt to isolate the mechanism responsible for the effects of Sernyl and its relevance to the psychopathology of schizophrenia. A number of psychological functions characteristically associated with the primary pathology of schizophrenia were systematically evaluated in schizophrenic patients and in normal subjects receiving Sernyl and other drugs. This report presents comparative data on the relative effectiveness of Sernyl, lysergic acid diethylamide (LSD-25), and amobarbital (Amytal) sodium in simulating attention and motor deficits characteristically found in schizophrenia. Additional data are reported showing the effects of schizophrenia and of these drugs on proprioception. It is hypothesized that blocking of the proprioceptive inputs required for normal behavioral integration may be the pathological mechanism mediating impairments found in schizophrenia and those produced by Sernyl.

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Method

Experimental Design.—Ten chronic schizophrenic patients with illnesses of at least three years' duration were compared with three groups of normal subjects. Of these normal subjects, 10 later received Sernyl; 10 received LSD-25, and 5 received amobarbital sodium. All subjects were tested on a battery which included measures of attention (reaction time), motor function (rotary pursuit), and proprioceptive acuity (weight discrimination). LSD-25 was used to permit comparison of Sernyl with a well-known psychotomimetic drug. The amobarbital sodium group provided a control index for the sedative effects of Sernyl. All normal subjects were pretested before drug administration to provide a base line against which the drug effects could be evaluated. Schizophrenic patients were tested only without drugs. This design permitted comparisons of the relative effects of the three drugs and the extent to which performance under each drug simulated schizophrenic performance.

Administration of Drugs.—Sernyl was administered intravenously in a subanesthetic dose of 0.1 mg. per kilogram in 150 cc. of 5% dextrose over a period of 12 minutes. One microgram of LSD-25 in 50 cc. of water per kg. of body weight was administered orally. An average dose of 500 mg. of amobarbital sodium and 15 mg. of amphetamine sulfate mixed in a 21 cc. solution was administered intravenously to the point of slurring of speech and lateral nystagmus. The test battery was begun immediately following injection for the Sernyl and amobarbital groups and three hours

following injection for the LSD-25 group, at the height of the LSD-25 reaction.[11] The dosages of the comparative drugs were based on an attempt to produce maximum sedative and psychotomimetic effects without profound disturbance in consciousness.

Testing Procedure.—The postdrug test battery was administered to the normal subjects two to four hours following the pretest battery. The administration of the predrug test battery required one hour, while the postdrug battery required one to two hours. Schizophrenic subjects usually required one to two hours to complete the battery, which they received only once without drugs. The complete battery contained a number of tests of thinking functions and questionnaires designed to evaluate subjective reactions to the drugs. The total battery included six psychological tests presented serially so that the weight-discrimination test occurred fourth, the reaction-time test fifth, and the rotary-pursuit task sixth. In the postdrug test sequence, these tests occurred 30, 60, and 75 minutes after the onset of testing.

Measurement of Attention.—A modification of the reaction-time technique previously employed by Huston and Senf[4] for measuring deficits in level and maintenance of attention in schizophrenia was used in the present study. The reaction-time apparatus employed has been described elsewhere.[9] Subjects were required to release a telegraph key at the sound of a buzzer following a 10-second preparatory interval. All subjects were given 20 reaction-time trials. On the first 10 trials, subjects were socially motivated by instructions to react as rapidly as possible, whereas the last 10 trials were biologically motivated by a 50-volt shock to the reacting finger accompanying the buzzer signal to react. Median reaction times obtained on the first and last 10 trials served as measures of attention under the two conditions of motivation.

Measurement of Motor Function.—A rotary-pursuit task was employed to evaluate motor performance. This task has previously been used to show that schizophrenic patients perform below the level of manic-depressive and normal subjects, both in initial level of motor functioning and in improvement with practice.[5] The apparatus was a Lafayette Instrument Co. Pursuit Rotor. The task requires the subject to keep a prod-stylus in contact with a small metallic target, set in a phonograph-type disk, revolving at 60 rpm. Score on a given trial is the total time on target during a 20-second period, the trial being followed immediately by 20 seconds of rest. In order to assess several attributes of motor performance, the complete motor task consisted of 2 initial trials with the nonpreferred hand; then 10 trials with the preferred hand, interrupted by one min. of rest between the 5th and the 6th trial, and, finally, 2 additional trials with the nonpreferred hand. This procedure provided separate scores for total motor efficiency, motor learning, reminiscence effects, and bilateral transfer.

Measurement of Proprioception.—A weight-discrimination procedure was employed to measure proprioceptive acuity. The procedure was a modification of the method of constant stimuli, in which upper difference thresholds were obtained from a 44 gm. standard weight. Subjects received eight trials with each of four comparison weights of 52, 50, 48, and 46 gm., respectively, in that order. On each trial, subjects were required to "heft" the standard stimulus and comparison weight successively and to designate whether the first or the second weight was heavier. The order of presentation of the standard stimulus as the first or second weight was randomized within each block of eight trials. The time requirements of the total test battery precluded obtaining difference thresholds in more than one direction. The present procedure proved satisfactory for obtaining reasonably stable thresholds over a wide-enough range of stimuli to reflect individual changes in proprioceptive acuity.

Results

Reaction Time (RT).—The effects of schizophrenia and the three drugs on attention are shown in the RT data, presented as Figure 1. The upper portion of the Figure shows the medians obtained from the four groups under ordinary social motivation to react without shock. Inspection of the Figure and analysis of variance of these data indicate that the nonshock RT scores of the schizophrenic group were significantly slower ($P<0.001$) than those for the three normal groups prior to drug administration. With drugs, as shown in the solid bars on

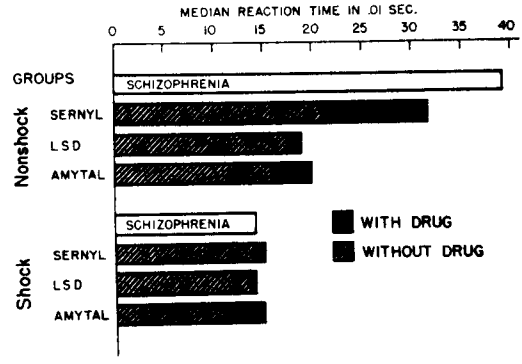

Fig. 1.—Reaction times of schizophrenic and drug groups under shock and nonshock conditions.

the figure, the Serynl, LSD-25, and amobarbital groups differed significantly ($P<0.05$). Separate *t*-tests revealed that this difference was attributable to a marked slowing of the Sernyl group RT's ($P<0.01$). In addition, there was no significant difference between the schizophrenic and the drugged Sernyl subjects in nonshock RT's, while the RT's of the other two drug groups were significantly faster than those of the schizophrenic group.

Analysis of the shock RT's, presented in the lower portion of Figure 1, showed no significant differences among any of the four groups, with or without drugs. This finding is in keeping with previous results [10] showing that characteristic disturbances in schizophrenic reaction time can be eliminated under shock motivation. The similarity in the nature of the attention deficits produced by Sernyl and schizophrenia is clearly reflected in the fact that the slowing of RT produced by Sernyl was likewise eliminated with shock stimulation.

In striking contrast to the schizophrenomimetic effects of Sernyl, LSD-25 produced no significant changes from the predrug level in either shock or nonshock reaction time. Amobarbital produced a significant slowing of RT under both the shock ($P<0.05$) and the nonshock ($P<0.05$) condition, but the disturbance in nonshock RT never approached the schizophrenic level. Thus, amobarbital sedation appears to result in mildly reduced reactivity to both biological and social motivation, while Sernyl and schizophrenia produced marked disturbances in attention under social motivation and normal maintenance of attention with shock motivation.

Rotary Pursuit.—The motor performance of the four groups with and without drugs is presented in Figure 2. The trials with the nonpreferred hand are not presented, as these data did not show clear bilateral transfer effects and were too variable to be systematically related to schizophrenia or any of the drug conditions. The rise from the fifth to the sixth trials indicates that

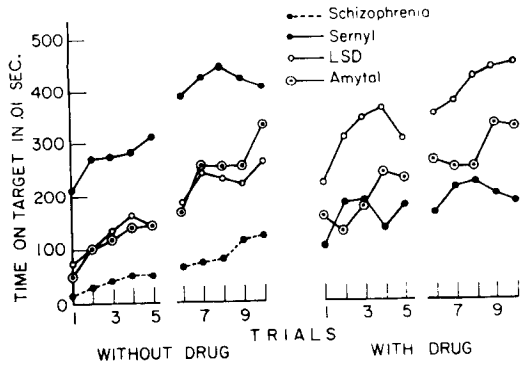

Fig. 2.—Rotary-pursuit learning of schizophrenic and drug groups.

most groups showed characteristic reminiscence effects. However, the individual reminiscence scores proved to be extremely variable and unrelated to schizophrenia or drug effects.

The principal objectives in analyzing the rotary pursuit data were (*a*) to confirm previous findings that schizophrenic patients show a deficit in level of motor proficiency and in improvement with practice, and (*b*) to determine whether any of the drugs would simulate schizophrenic deficits in motor function. Examination of Figure 2 clearly indicates that prior to drug administration the schizophrenic group showed poorer rotary-pursuit scores than the other three groups. Statistical analyses of these data, utilizing all 14 rotary-pursuit trials with both hands, indicated that without drugs the four groups were significantly different ($P<0.01$). While this difference was largely attributable to the poorer performance of the schizophrenic group, further analysis revealed that the subjects who later received Sernyl were significantly better than the other two normal groups ($P<0.01$). Since the subjects in the three drug groups were selected at random, this initial difference in motor function among the three normal groups appears to be the result of a sampling artifact.

When these three groups are compared after drug administration, the differential effects of the drugs are clearly apparent. The Sernyl subjects showed a significant

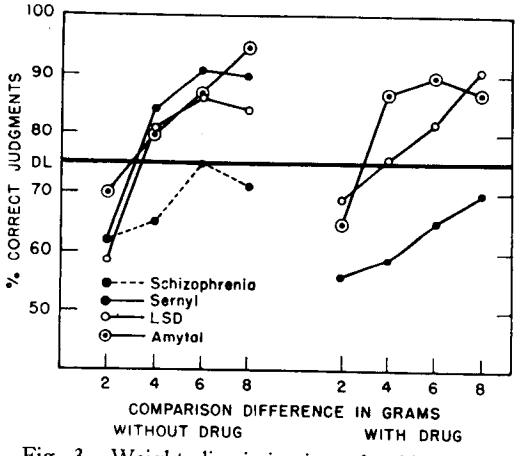

Fig. 3.—Weight discrimination of schizophrenic and drug groups.

drop in performance from their predrug level ($P<0.01$), approaching the level of the schizophrenic group. The amobarbital subjects continued to function at a level approximating their predrug performance. The LSD-25 subjects showed a significant acceleration of their motor learning curve ($P<0.01$), which rises well above the predrug level.

In general, the schizophrenic patients showed a lower level of motor proficiency and little improvement with practice. Sernyl produced a decline in motor function which closely approximated the flat motor-learning curve of the schizophrenic patients. Amobarbital resulted in no significant change in motor function, while LSD-25 produced significant improvement and acceleration of motor learning.

Weight Discrimination.—The weight-discrimination curves presented in Figure 3 are compatible with the hypothesized deficit in proprioceptive acuity both in chronic schizophrenia and in normal subjects under Sernyl. Examination of the Figure indicates that the upper difference limen (75% correct judgments) was reached within 4 gm. by each of the three normal groups without drugs. On the other hand, the estimated difference limen was 9.48 gm. for the schizophrenic group and 10.46 gm. for the normal subjects under Sernyl. Statistical analyses of these data showed that the schizophrenic group and the Sernyl group with drug differed significantly ($P<0.001$) from the other drug groups, but did not differ from each other.

Comment

The present results demonstrate the capacity of Sernyl to simulate in several significant details the symptomatology characteristically found in schizophrenia. This new compound, like LSD-25, produces a model psychosis resembling schizophrenia, in that subjects are able to communicate sensory experiences and bodily sensations despite the occurrence of hallucinatory and delusional sequelae. In the dosages used, neither drug results in the typical disorientative, amnesic delirium syndrome usually found in toxic states. Unlike LSD-25, Sernyl results in schizophrenic-like impairments of primary attention and motor functions, in addition to the secondary symptoms of depersonalization, subjective disorganization, and hallucination found with other psychomimetics.

The present findings indicate that both schizophrenics and normal subjects receiving Sernyl showed abnormally slow reaction times under social motivation and a deficit in the level and amount of motor learning. These results cannot be attributed solely to the hallucinogenic or sedative properties of Sernyl, since other drugs with each of these properties failed to simulate these schizophrenic impairments. Sedation with amobarbital resulted in a generalized reduction of attention and motor efficiency, but the resulting impairment did not exhibit the characteristic features of schizophrenia and was considerably less extensive. Similarly, the hallucinogen, LSD-25, failed to affect reaction-time measures of attention and appears to have benefited motor learning.

The possibility that the underlying pathological mechanisms common to schizophrenia and the Serynl-produced state is a disturbance in proprioception was supported by the weight-discrimination data. Neurological findings [8] that Sernyl produces demonstrable

impairment in proprioception, pain, and touch add further credence to this hypothesis. It has also been suggested in a previous paper [6] that the body-image disturbance typically found with schizophrenia and Sernyl may be a direct reflection of disturbances in proprioception.

While these data suggest that the proprioceptive deficit produced by Sernyl may also be present in schizophrenia, the nature of the performance deficits obtained is also consonant with a social-learning theory of schizophrenia. In a previous study, Rosenbaum, Mackavey, and Grisell [10] have shown that schizophrenic disturbances in attention on a reaction-time task performed under social motivation can be eliminated by the arousal of biological-pain motivation. Similarly, Cohen [2] and Huston and Shakow [5] have shown that defective motor learning in the chronic schizophrenic patient may be attributable to poor social cooperation and insufficient drive arousal. The present results confirm these previous findings on the nature of the performance deficit in schizophrenia, but indicate further that Sernyl produces an almost identical deficit in these performance functions.

If schizophrenia is conceptualized as the end-product of a long-term process of social disarticulation, as suggested in the theories of Cameron [1] and Sullivan,[12] how could a drug like Sernyl have produced immediate effects closely simulating the primary pathology of this illness? Our findings on the effects of Sernyl suggest that it tends to block and disorganize the basic proprioceptive mechanism through which social meanings and motives are normally integrated. This formulation means, in effect, that the acquisition of social motives ordinarily requires the development of habitual acts and thoughts which elicit response-produced proprioceptive stimuli, serving, in turn, to energize and direct appropriate social behavior. These stimuli, arising from the feedback of motor, linguistic, and perceptual reactions, presumably serve as the locus of socially shared meanings and provide the motivation for effective interpersonal communication.* Disturbances in this system of socially acquired meanings and motives could then result either (*a*) from inadequate social reinforcement of these mediating reactions in the social development of the schizophrenic or (*b*) from the direct action of Sernyl on the proprioceptive mechanism.

An alternative formulation of the process of social disarticulation in the schizophrenic patient would assume that the proprioceptive deficit represents a primary biological defect, constitutionally or genetically based. Disturbance in the acquisition of social motives and meanings would then arise from physiologically determined distortions in the proprioceptive system.

The assumption that reduced proprioceptive stimulation results in the performance deficits found in schizophrenia suggests the additional possibility that increases in proprioceptive stimulation could reverse these effects. Techniques for directly modifying the amount and type of proprioceptive stimulation and its effects on performance and meaning in schizophrenic patients are currently being developed.

Summary

The performance of a group of chronic schizophrenic patients on attention (reaction time), motor function (rotary pursuit), and proprioception (weight discrimination) was compared with the corresponding functions of groups of normal subjects receiving Sernyl, lysergic acid diethylamide (LSD-25), and amobarbital (Amytal) respectively. Sernyl was the only one of the three drugs which produced disturbances in these functions approaching the deficit level shown by the schizophrenics. It is concluded that Sernyl results in schizophrenic-like impairments of primary attention and motor functions, whereas LSD-25 simulates only the secondary symptoms of schizophrenia. The data are interpreted as evidence for the

* This notion is further elaborated in personality theory by Dollard and Miller [3] and in the analysis of language and meaning by Osgood.[7]

hypothesis that disturbances in proprioception may be the pathological mechanism mediating impairments in performance and motivation found in schizophrenia and produced by Sernyl.

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