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Comparison of Phencyclidine Hydrochloride (Sernyl) with Other Drugs

Simulation of Schizophrenic Performance with Phencyclidine Hydrochloride (Sernyl), Lysergic Acid Diethylamide (LSD-25), and Amobarbital (Amytal) Sodium; II. Symbolic and Sequential Thinking

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DETROIT

In a previous report[7] the administration of phencyclidine hydrochloride, a chemical compound with anesthetic and sedative properties, was shown to produce profound disturbances in reaction time, motor learning, and weight discrimination. These findings were obtained with normal subjects who had been given subanesthetic doses of the drug. The degree and pattern of drug-produced deficits closely approximated those found in a group of chronic schizophrenic patients given the same battery of tests without drugs. These psychotomimetic effects could not be attributed solely to the drug's hallucinogenic or to its sedative properties, since other drugs with each of these properties (lysergic acid diethylamide [LSD-25] and amobarbital sodium) produced neither the degree nor the pattern of deficits demonstrated under phencyclidine hydrochloride. It was tentatively concluded that the deficits seen in normal subjects under phencyclidine hydrochloride and in chronic schizophrenia might be attributable to a common underlying disturbance of proprioception which results in impaired ability to perform, and/or to utilize the feedback from, covert intrabodily reactions necessary to the integration of attention and motor tasks.

The present report will compare the performance of normal subjects tested under phencyclidine hydrochloride, LSD-25, and amobarbital sodium with the nondrug performance of chronic schizophrenic patients on tasks requiring symbolic reasoning (proverb interpretation) and sequential thinking (serial sevens). These tasks were considered to be of interest since they tap functions typically impaired in chronic schizophrenia; hence, changes in their performance should provide further evidence

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of the relative psychotomimetic properties of the drugs. A second reason for our interest in these tasks stems from the hypothesis that symbolic reasoning and sequential thinking involve processes which depend on an intact proprioceptive system.

It was anticipated that phencyclidine hydrochloride would prove especially effective in producing deficits in symbolic reasoning because of earlier clinical observations made in our laboratories [5] of disturbances in proverb interpretation. Furthermore, the interpretation of proverbs requires a relatively precise analysis and integration of the social meanings of linguistic stimuli. If phencyclidine hydrochloride impairs the proprioceptive feedback of motor, perceptual, and linguistic responses which serve as the locus of such meanings, this drug would be expected to produce severe impairments in symbolic reasoning. Impairments would not be expected with the other drugs since they apparently have little effect on proprioception.

The presumed deleterious effect of phencyclidine hydrochloride on proprioception also led to the expection that sequential thinking would be severely impaired by this drug. In sequential thinking, as this term will be used in the present report, cues, presumed to involve central or peripheral proprioceptive components, arising from each response in a series control the selection of the specific succeeding response. To measure the efficiency of sequential thinking, the traditional "serial sevens" test was used.

One implication of the hypothesis that phencyclidine hydrochloride blocks or disorganizes proprioception is that Ss under phencyclidine hydrochloride might become especially dependent on external sensory cues for the control of successive responses in a goal-oriented sequence. Consequently, the serial sevens test was administered under ordinary testing conditions and under a condition in which Ss were prevented from receiving the auditory feedback from their successive vocal responses. It was anticipated that phencyclidine hydrochloride-treated Ss and schizophrenic Ss would show particularly severe disruption in sequential thinking when deprived of auditory feedback, since they would thus be unable to compensate for the hypothesized proprioceptive deficit.

Method

Procedure.—The procedures employed in administering the drugs and testing the Ss have been described in detail previously.[7] In general, the design of the study permitted comparisons of the nondrug performance of 10 male chronic schizophrenic Ss with the performance of 3 groups of normal male Ss (college students), both before and after receiving drugs. The dosages of the drugs used and the time interval between drug administration and testing were aimed at producing maximum characteristic drug effects without profound disturbances in consciousness.* The 4 groups of Ss with their drug and testing schedules are shown in Table 1.

The predrug test battery generally required 1 hour, and the postdrug battery 1 to 2 hours. Schizophrenic Ss received the battery only once without drugs and took 1 to 2 hours. The proverb interpretation test was the first and the serial sevens test was the second of the 6 psychological tests contained in the battery. In the postdrug sequence, the testing was preceded by a 15-minute

* Amphetamine sulfate was used in the amobarbital sodium solution to decrease drowsiness and prolong the amobarbital sodium reaction during the testing period, following the procedure recommended by Gottlieb and Coburn.[2]

TABLE 1.—*Drug and Testing Schedules of Schizophrenic and Drug Groups*

Group	N	Drug Administration	Time of Testing
Schizophrenia	10	None	On arrival
Phencyclidine hydrochloride	10	0.1 mg. per kilogram in 150 cc. of 5% dextrose intravenously over 12 min.	Immediately after intravenous injection
LSD-25	10	1.0μg. per kilogram in 50 cc. of water orally	3 hours after drug intake
Amobarbital sodium	5	500 mg. and 15 mg. of amphetamine sulfate in 21 cc. solution intravenously to point of dysarthria and lateral nystagmus	Immediately after intravenous injection

question period designed to evaluate subjective reactions to the drugs.

Symbolic Thinking.—Five of the proverbs contained in Gorham's Proverbs Test[1] were used to measure symbolic thinking. The proverbs were selected for ease of scoring and for tapping various levels of difficulty. These same 5 proverbs were presented both before and after drugs in the following order of increasing difficulty.

1. The proof of the pudding is in the eating.
2. A rolling stone gathers no moss.
3. A drowning man will clutch at a straw.
4. One swallow doesn't make a summer.
5. Great bodies move slowly.

The test was administered orally and usually took 5 minutes. The instructions employed were: "I'm going to say some proverbs and you are to tell me what they mean. For example, the proverb 'Large oaks from little acorns grow' means that great things may have small beginnings. Now I'll say another proverb and you tell me what it means. What do people usually *mean* when they say:"

Responses to the proverbs were recorded verbatim and scored 0, 1, or 2 points for degree of abstraction on the basis of sample answers provided by Gorham's scoring cards. All responses were scored independently by 2 raters, and the points for the 5 proverbs were summed to obtain individual scores. The interrater reliability was determined by correlating 62 pairs of such summed scores (25 drug Ss before and after, 10 schizophrenics, and 1 preliminary drug S before and after); r was 0.848. The proverb interpretation score for each S employed in further data analyses was the mean of the 2 raters' individual scores.

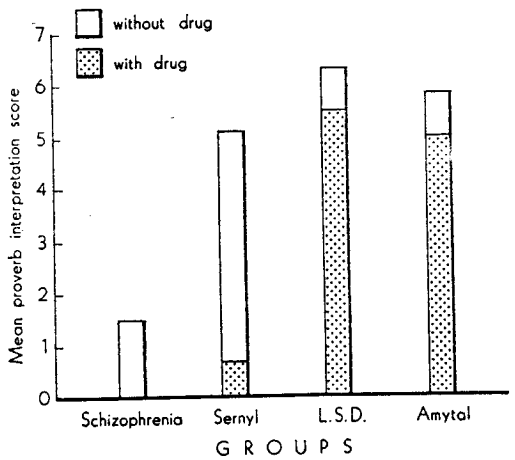
Sequential Thinking.—The standard serial sevens task frequently employed in psychiatric mental status examinations[10] was initially administered with the following instructions: "I want you to count *backwards* from 100 by 7's. Start with 100 and subtract 7; then subtract 7 again and so on, as far down as you can go. Do it out loud so that I can hear each of your answers. Ready? Begin."

The test was then readministered to all subjects under a condition in which a masking noise was used to minimize response-produced auditory feedback. Ss were instructed: "This time I want you to do the same thing; count backwards by 7's starting with 100. I am going to put these earphones on you so you will not be able to hear me. Start when I wave my hand like this." In this condition Ss were fitted with a pair of earphones through which was fed the hum of an electric fan amplified to a level at which normal speech was inaudible to the S.

All responses were recorded verbatim on both test administrations, and the length of time required to complete the series of sevens was recorded to the nearest second. Two measures of performance in sequential thinking were obtained: (*a*) the length of time required to complete the series within a 120 sec. time limit, and (*b*) the percentage of correct subtractions emitted within the series. In computing this second measure, a perfect score would result from 14 correct serial subtractions: thus 14 was used as the denominator in determining the per cent correct for Ss who made fewer than 14 subtractions. The actual number of subtractions was used as the denominator for Ss who made more than 14. The percentage score proved more efficacious than a simple error score in taking into account errors committed within the series which modified both the nature and the total number of responses emitted.

Results

Proverb Interpretation.—The results of schizophrenia and the 3 drugs on symbolic thinking are shown in the proverb interpretation data, presented as the Figure. Inspection of the Figure indicates that the schizophrenic Ss earned a mean proverb interpretation score of 1.5 out of a possible 10 for all 5 proverbs, while the normal groups had means of 5.1 (phencyclidine hydrochloride), 6.2 (LSD-25), and 5.8 (amobarbital sodium) prior to drug administration. A simple analysis of variance of these data revealed a significant between groups effect ($P<0.001$). Separate t-tests based on the analysis of variance showed that the schizophrenics were significantly poorer in proverb interpretation than the 3 normal groups ($P<0.001$ for all 3 com-



Abstraction levels of schizophrenic and drug groups on proverb interpretation.

parisons), while the normal groups were not significantly different from one another without drugs.

The shaded bars in the Figure show the effects of the 3 drugs on proverb scores. Analysis of variance of these data showed that following drug administration the phencyclidine hydrochloride group performed significantly more poorly than the LSD-25 and amobarbital sodium groups. In addition, there was no significant difference between the schizophrenic and the phencyclidine hydrochloride-drugged Ss in proverb interpretation, while the other 2 drug groups were significantly better than the schizophrenic group. Thus phencyclidine hydrochloride appears to have produced a quantitative deficit in symbolic thinking which closely simulates that found in schizophrenia.

Despite the effects of practice on the same 5 proverbs, which should have benefited performance under the drug condition, the drop in proverb scores under phencyclidine hydrochloride was significant at less than the 0.001 level. While the LSD-25 and amobarbital sodium groups also showed small decrements in mean proverb score under the drugs, neither of these decrements was statistically significant.

Serial Sevens.—The effect of drugs and noise on the performance of the 4 groups in sequential thinking is shown in Tables 2 and 3. Inspection of Table 2 shows that the 3 normal groups all performed at approximately 90% correct prior to drug administration. This finding is in keeping with the results of Ruesch,[8] who reported a

TABLE 2.—*Mean Per Cent Correct for Schizophrenic and Drug Groups on Serial Sevens*

	Without Drug		With Drug	
	Without Noise	With Noise	Without Noise	With Noise
Schizophrenia	49.9	50.7		
Phencyclidine hydrochloride	93.7	94.4	32.1	34.2
LSD-25	87.2	81.5	75.7	82.3
Amobarbital sodium	90.0	94.2	91.4	82.8

TABLE 3.—*Mean Time Scores in Seconds of Schizophrenic and Drug Groups on Serial Sevens*

	Without Drug		With Drug	
	Without Noise	With Noise	Without Noise	With Noise
Schizophrenia	82.5	85.2		
Phencyclidine hydrochloride	53.6	48.7	102.2	97.5
LSD-25	57.6	51.2	53.0	44.7
Amobarbital sodium	33.2	31.2	37.6	40.6

mean error score of 2 (out of a possible 14) in a group of adults of average intelligence. On the other hand, the schizophrenics showed a clear deficit in sequential thinking with both means very close to 50% correct. Analysis of variance of these data indicated that the schizophrenics were significantly different from the 3 groups of normal Ss on the per cent correct measure ($P<0.01$).

Highly similar results may be observed for the time scores without drugs in Table 3, except that the amobarbital sodium group appeared to perform more rapidly than the other 2 normal groups. Statistical analyses of these data, however, again showed that the 3 normal groups did not differ significantly from one another and all were significantly faster than the schizophrenic Ss ($P<0.01$).

When the groups were compared for their performance under the drug condition, the phencyclidine hydrochloride Ss showed a drop in per cent correct and slower time scores, their efficiency being reduced to a level not significantly different from that of the schizophrenic Ss without drugs. In contrast with phencyclidine hydrochloride, amobarbital sodium produced a small, statistically insignificant decline in performance; while the LSD-25 group showed no appreciable change in per cent correct, a slight improvement in speed occurred under the noise condition which reached the 0.05 level.

The hypothesis that reduced auditory feedback would particularly interfere with sequential thinking in the schizophrenic and phencyclidine hydrochloride-drugged Ss was not supported. By inspection of Tables 2 and

3 and statistical analyses of the noise effect, none of the groups showed any decrement in either of the serial sevens measures as a result of the noise condition.

Comment

There is little question that phencyclidine hydrochloride, in the dosage administered, produces severe incapacity in the symbolic cognition and sequential thinking required by the proverb interpretation and serial sevens tasks. Neither LSD-25 nor amobarbital sodium, administered in clinically effective dosages,† produces comparable deficits. Quantitative comparisons with the scores of chronic schizophrenics showed that phencyclidine hydrochloride, in contrast to the other drugs, simulated closely the level of impairment of the schizophrenic group.

Qualitative comparisons of the responses of schizophrenic Ss and normal Ss under phencyclidine hydrochloride also show striking similarities in thinking deficit. Illustrative of the proverb interpretations of the 2 groups are these typical responses to the "rolling stone" proverb: (*a*) phencyclidine hydrochloride Ss—"Well, if a person keeps moving . . . you know . . . ah . . . a rolling stone gathers no moss . . . it keeps moving" or "Once you start going . . . a stone keeps rolling . . . you do not stop"; (*b*) schizophrenic S—"A stone don't gather no moss while it rolls." Some characteristic responses to the "proof of the pudding" proverb were: (*a*) phencyclidine hydrochloride S—"Things are proved anywhere unless they're eaten"; (*b*) schizophrenic Ss—"Good food is worth eating" or "The eating of the pudding . . . the eating will prove itself." Qualitative similarities in the thinking deficit of the 2 groups on the serial sevens task included the ability to produce 2 or 3 successful subtractions followed by a tendency to count backward by one, forward by one, to repeat the last response, or mixtures of these response patterns.

Examination of these qualitative resemblances suggests that the concreteness in proverb interpretation common to both groups stemmed from the inability to respond to the proverb stimuli with meaningful associations. This inability was dramatically illustrated by one phencyclidine hydrochloride S who asked, after several false starts on a proverb interpretation, "What does 'mean' mean?" In the serial sevens task, Ss appeared to be unable to sustain effective, goal-oriented chains of responses, even when initial responses were appropriate.

These observations of similar thinking deficits in schizophrenic and phencyclidine hydrochloride Ss are consistent with the hypothesis of a common proprioceptive disturbance. That the results cannot be attributed simply to the sedative properties of phencyclidine hydrochloride is indicated by the comparison with amobarbital sodium; that they cannot be attributed to some general psychotomimetic factor is indicated by comparison with the effects of LSD-25. It should also be noted that the absence of thinking disorder in the LSD-25 group is in keeping with our earlier observation[5] that LSD-25 mimics the secondary or restitutional symptoms of schizophrenia, while only minimally impairing the primary symptoms of association, affect, and attention.

On the other hand, the failure to find increased disruption in the schizophrenic and phencyclidine hydrochloride Ss on the serial sevens task under reduced auditory feedback does not support the hypothesis of a common proprioceptive dysfunction. One important condition which may have generated this negative finding was the uniform tendency for all Ss to raise their voices automatically when the masking noise was present. This raised voice level may have negated the effect of the masking noise either by reaching the level of audibility or

† While no appreciable disturbance in proverb interpretation or serial sevens was noted in these Ss, both the LSD-25 and amobarbital sodium subjects displayed the characteristic clinical reactions that have usually been obtained with these drugs. A separate report is currently being prepared comparing the subjective sensory changes, frequency of hallucinatory and delusional reactions, and alterations in emotional responsiveness observed with the 3 drugs in this investigation.

by increasing the kinesthetic feedback from more vigorous vocal responses to a level that would compensate for the reduced auditory feedback. It is also possible that the disturbance in the capacity to respond meaningfully to external stimuli, as indicated by the proverb data for the chronic schizophrenics and phencyclidine hydrochloride-treated Ss, was so profound as to have rendered the masking noise superfluous; that is, the noise may have been masking already meaningless stimuli.

Proprioception and Thinking Disorder.—The problem posed by these results is to specify similarities between the underlying psychoneurological state of the normal S under phencyclidine hydrochloride and that of the chronic schizophrenic. One hypothesis is that both states are characterized by a weakened capacity of the organism to perform chains of implicit cue-producing responses controlled by verbal goals (i.e., instructionally specified end-objectives). This hypothesis may be elaborated by coordinating these mediating processes with proprioceptive processes, whether centrally or peripherally located. Osgood has advanced essentially this hypothesis in his theory of meaning, asserting further that peripheral proprioceptive responses originally representing meaning might become ". . . telescoped to a largely central representation in the mature individual." [6]

Disturbances in thinking therefore would result from disruptions in the functioning of the proprioceptive system. The proprioceptively impaired individual would manifest: (*a*) inefficient evocation of the necessary implicit responses with which an organism *appreciates the meaning* of an external stimulus (symbolic deficit); and/or (*b*) inefficiencies in the ability to select appropriate responses to stimuli produced by the S's own previous reactions in a goal-oriented chain (sequential deficit). In either instance, impaired proprioception makes it difficult to respond to cues in sufficiently articulated form to permit the subsequent production of firm, well organized, goal-relevant responses. Put another way, the S is impaired in his ability to provide himself with those response-produced cues which normally function to enhance stimulus discrimination and relevant response selection.

The hypothesis that phencyclidine hydrochloride impairs proprioceptive sensory transmission is consistent with recent neurophysiological evidence indicating that the drug acts to disrupt neural processes at the level of the sensory cortex.[9] Support for the notion of a deficit in proprioceptive acuity is also provided by our previously reported results [7] showing raised weight discrimination thresholds in normals under phencyclidine hydrochloride and in chronic schizophrenics. In view of the role of proprioception in explanations of both drive arousal [4] and acquired drive mechanisms,[3] the possibility that disturbances in this system may produce motivational as well as associational decrements in schizophrenic and phencyclidine hydrochloride-treated Ss also warrants further inquiry.

Summary

This report extends previous findings on the relative psychotomimetic properties of phencyclidine hydrochloride (Sernyl), lysergic acid diethylamide (LSD-25), and amobarbital (Amytal) sodium. The earlier report showed that phencyclidine hydrochloride was the only drug to produce impairments in attention, motor function, and proprioception approximating those seen in a target group of chronic schizophrenics. The present study concerned the effects of these drugs on symbolic and sequential thinking.

Three groups of normal Ss were tested before and after receiving phencyclidine hydrochloride (N=10), LSD-25 (N=10), or amobarbital sodium (N=5), and their performance compared with a group of chronic schizophrenics (N=10). Symbolic thinking was assessed by means of a proverb interpretation task; sequential thinking by means of a serial sevens task. This latter task was administered under ordinary conditions and with masking noise to test for S's depend-

ence on auditory feedback during sequential thinking. Proverb responses were scored for abstraction level by 2 independent raters. Serial sevens were scored for percentage of correct subtractions and for speed.

Without drugs, all normal groups were superior to the schizophrenic group on all measures. With drugs, the phencyclidine hydrochloride group scores were significantly inferior to those of the other drug groups and approximated the mean scores of the target group of schizophrenics. LSD-25 and amobarbital sodium produced slight but insignificant decrements in performance. LSD-25 produced an increase in speed under the masking noise condition.

The data are consistent with the hypothesis that phencyclidine hydrochloride produces a deficit state which simulates the primary thinking disorder shown by chronic schizophrenics. A disturbance in proprioceptive sensory transmission with consequent effects on meaning is proposed as a common mechanism linking the phencyclidine hydrochloride state to chronic schizophrenia.

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