

Study of a New Schizophrenomimetic Drug—Sernyl

ELLIOT D. LUBY, M.D.; BERTRAM D. COHEN, Ph.D.; GERALD ROSENBAUM, Ph.D.; JACQUES S. GOTTLIEB, M.D.,
and ROBERT KELLEY, M.A., Detroit

Introduction

The production of model psychoses has been employed as a technique for testing hypotheses relevant to the causes, correlates, and treatment of schizophrenia since 1921, when De Jong demonstrated experimental catatonia by giving bulbocapnine to animals.⁵ This method of study has received considerable impetus with the discovery of the hallucinogenic properties of lysergic acid diethylamide (LSD-25)²² and other psychotomimetic agents.

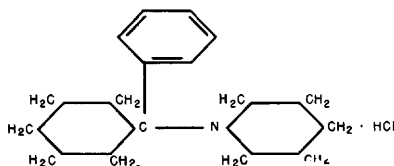
Objections have since been raised to the drawing of premature analogies between the psychotic-like states produced by drugs and the psychopathology of schizophrenia. Ebaugh has pointed out that "the difference between these pseudopsychoses and schizophrenia is so striking that such experimentation seems to have only tenuous relevance to the problem of schizophrenia."⁷ On the other hand, Wikler has asserted that "from the standpoint of the development of dynamic (causal) concepts about human behavior, it matters little whether or not model psychoses resemble schizophrenia. Drugs which modify sensing, feeling, wishing, ideating, etc., can be used as tools to detect and manipulate the biochemical, physiological, and psychological variables that regulate these functions."²³ We assume that availability of laboratory techniques for inducing psychotic behavior portends the accelerated development of control over the basic biopsychological processes implicated in the psychoses.

Submitted for publication July 17, 1958.

Parke, Davis & Company supplied the Sernyl used in this study.

From the Lafayette Clinic and Wayne State University College of Medicine.

This report describes the schizophrenic-like behavioral effects of Sernyl, a new drug chemically unrelated to other psychotomimetic agents and with unique neuropharmacologic properties. Sernyl, 1-(1-phenylcyclohexyl) piperidine monohydrochloride,³ is one of a class of sensory-blocking agents recently developed for anesthesiology (Figure). Griefenstein et al.



Structural formula of Sernyl.

have used it in this way with 41 patients and believe that its action is unlike that of any other known anesthetic.¹² It produced complete analgesia; yet patients were still awake, with eyes open. Sernyl became of psychiatric interest when Meyer, Griefenstein, and DeVault observed the postoperative development of transient psychotic states.¹⁶

The sites of action of this drug in the central nervous system have not been identified. As judged by the clinical observations of Meyer, "the drug is presumed to have a relatively selective action on thalamus and mid-brain, resulting in demonstrable impairment of pain, touch, proprioception and discriminative aspects of sensation."¹⁶ Motor function is relatively unimpaired until with large doses ataxia, rotatory nystagmus, and bilateral ptosis result. Domino, in preliminary studies, reported: "In unanesthetized beagle dogs and *Macaca mulatta* monkeys with chronic electrode implants, variable effects on the cortical EEG were obtained, depending upon the dose of

Sernyl administered and the individual animal. These effects varied with increasing dosage from minimal to no change in the EEG, to medium-voltage fast waves, to high-voltage delta activity. Photic-driving responses were decreased in amplitude, as were electrical discharges synchronous with respiration recorded in the olfactory bulb and medial amygdala."⁶

The purposes of the present report are (1) to describe the sensory and cognitive deviations produced by the drug; (2) to compare these deviations with schizophrenic symptomatology; (3) to propose a hypothesis concerning a mechanism which may be operative in both the model psychosis produced by Sernyl and certain symptoms of the schizophrenic process.

Method

Nine normal subjects and nine patients were selected for this study. The normal subjects included six medical students, two residents in psychiatry, and one attendant. Four patients were suffering from chronic schizophrenia, with illnesses of 8 to 10 years' duration, and one was an acute catatonic schizophrenic ill for four months. Of the remaining four patients, two had "pseudoneurotic" schizophrenia, while the other two had character disorders with neurotic features.

Sernyl was given intravenously in a subanesthetic dose of 0.1 mg. per kilogram in 150 cc. of 5% dextrose over a period of 12 minutes. Marked reactions to the drug began in three minutes and usually persisted up to one hour. During this time the subjects were interviewed, given selected psychological tests, and evaluated neurologically. A continuous recording of the content of each interview was made. Tape recordings and stenographic records were used. In addition, some nonpsychotic subjects wrote retrospective accounts of their drug experiences. The patients were kept under daily observation following drug administration to record any changes in behavior.

Results

The general psychological effects of Sernyl on the normal and patient groups are summarized in the accompanying Table.

Psychological Changes

Body-Image Changes.—Alteration in body image was the earliest and most characteristic reaction to the drug. It was reported

Incidence of Sensory and Cognitive Deviations Produced by Sernyl in Normal Subjects and Patients

Deviations	Percentages	
	Normals (N=9)	Patients (N=9)
Body-image changes	100	100
Estrangement	100	100
Disorganization of thought	100	100
Negativism and hostility	67	67
Drowsiness and apathy	100	100
Hypnagogic states	56	33
Feelings of inebriation	78	22
Repetitive motor behavior	29	44

clearly by all 16 subjects who were able to communicate adequately. The remaining two subjects were chronic schizophrenics who were unable to provide definite information as to their subjective states under the drug. The body-image disturbances were accompanied by a loss of "ego boundaries," impaired ability to distinguish between self and nonself stimuli, feelings of depersonalization, and a sense of unreality.

A normal subject reported: "I feel far away; now I'm coming back. My arms and legs feel distant." A medical student in recall stated: "Before I realized it, I was standing, but I didn't feel like I was standing. I didn't know where my feet were, and I didn't feel myself get up. I know I got up fast because my body felt light, just as though my legs didn't have much to support. When I began to walk, I didn't know where my feet were. I could feel my shoes on my feet, the pants around my legs, a slightly numb sensation like that in my arms, but I couldn't feel them move."

Another nonpatient subject stated: "My arm feels like a 20-mile pole with a pin at the end." The experience of floating "in and out, up and down," together with feelings of flying, was repeatedly described. There were prolonged sensations of subjective vertigo, associated with alternate contraction and expansion of body size. There were feelings of "selflessness," of not being human, and of being an "empty nobody." "I am a small . . . not human . . . just a block of something in a great big laboratory."

A disturbing sense of unreality accompanied the body-image distortions. TAT cards became "real," and some subjects literally attempted to relate themselves physically to the figure in the picture. One male patient became enraged at the young man in Card 6BM and belted the card across the room. In response to TAT Card 13MF, which depicts a standing male figure and a woman lying with breasts exposed, he remarked on the woman's sadness and cradled the picture in his arms while uttering soothing phrases.

Estrangement.—There was a commonly experienced profound sense of aloneness or isolation. The sense of being completely detached from all environmental objects and tensions was reported by several subjects directly, and implied by others who were not able to verbalize so clearly. This experience involved a sense of loneliness, but was not always accompanied by fear or anxiety. While the experience was a strange one for the subjects, they sometimes appeared to become passive and relaxed.

The loneliness was sometimes accompanied by an intensification of dependency feelings. There was a desire for the presence of a supportive figure, with indications of rejection-sensitivity and resentment when the subject was left alone by the experimenter.

A normal subject became angry when he was left alone in the experimental room. He stated reproachfully, when the examiner returned: "I trusted you and then you left me alone. Why did you leave me? I should have brought my wife along." Another normal subject, as he was recovering from the effects of the drug, described feeling as though the examiner were at a "great distance" from him. A normal subject, who wished to be left alone to sleep when the drug was wearing off, still preferred that the door to the experimental room be left open.

Disorganization of Thought.—Consistent deficits in the organization and direction of thought was a marked attribute of the drug state. This was seen in all subjects. Most

striking was the inability to maintain a set, frequent loss of goal ideas, and impairment of the "abstract attitude." Some subjects showed blocking, neologisms, word salad, and echolalia. The subjects appeared to be struggling to describe feeling states which they were unable to define except in fragmentary phrases. To obtain information at the height of the drug effects, the examiner was forced to ask extremely simple and direct questions.

Proverbs were interpreted in a fragmentary, concrete manner, or were simply repeated as though this implied meaning. Without the drug, in response to "a drowning man will clutch at a straw," a subject responded: "A person who is desperate will grab at anything regardless of its value to him." In the drug state, he answered: "I think it is—a drowning man . . . will clutch at a straw. It means a drowning man will clutch." The loose and asyndetic quality of thinking is illustrated by the following response to TAT Card 8BM: "Oh, there is a doctor and a surgeon and a boy and a gun and a boy, boy, boy, boy, boy, boy, knife, gun, man, card, surgeon . . ." The performance of serial 7's became an impossible task for most subjects.

Negativism and Hostility.—These reactions were seen in many subjects. Oppositional behavior was observed, varying from subtle expressions of hostility, in the more sophisticated subjects, to child-like negativism and catatonic-like reactions, in more naïve and characterologically immature patient subjects. One medical student, while in the recovery phase, told of his feelings of futile anger. He felt hostility toward the examiner, but was completely impotent to express it. A passive-aggressive man became stubborn and resistive to instructions. He held his eyes tightly closed and pursed his lips, refusing to attend to tasks in which visual signals and verbal responses were required. Subjects often responded with a "no" when asked if they could hear.

Drowsiness and Apathy.—All subjects exhibited progressively increasing drowsi-

ness. At times, some appeared to fall asleep but remained immediately responsive to questioning. In their retrospective accounts, they recalled being able to hear questions and instructions and to comprehend what was expected of them, but felt no special compulsion to comply with the examiner's requests. They verbalized this as an "I don't care" attitude. Their appearance, especially toward the latter stages of the examination session, became more and more strikingly apathetic.

Hypnagogic State.—These phenomena were reported both by patients and by normal subjects. These were dream-like productions, which occurred in a waking state and which usually had a basis in the subject's past. The subjects reported feeling as though they were in some specific setting and were able to describe it in detail. While the reports typically had reference to past events, they were expressed as though the experiences were taking place at the moment. The lack of time-boundedness was reminiscent of dreaming. As in dreams, multiple shifts occurred in the settings experienced by the subjects, sometimes in rapid succession.

A pseudoneurotic schizophrenic male patient reported that he was "in a swing," which he proceeded to draw for the examiner. Shortly thereafter, he stated that he was in his third-grade classroom, which he described elaborately, including the recognition of an old friend in the classroom. At another time, he felt that he was on his ward, and was able to enumerate and point out the locations of various objects there.

In each of these experiences, the subject responded as though he were an integral part of the perceived setting, rather than an observer of detached, projected images. Insight into the unreality of these perceptions was sometimes clear, and at other times vague. In his retrospective account, a medical student subject formulated his impression of this type of experience vividly. He reported: "I was afraid at the height of these experiences that this would never end, and this was me as I always was and

always would be. I felt as though I was in the midst of a horrible and dreadful nightmare, to compare it with something I've experienced before. The walls at times became long, and I thought I was walking through a long corridor. I thought of where I was, in the heart of Detroit away from home and friends and nobody knew what I was doing at the time. I felt all alone. I thought of my girl friend by her name only. I relived the experience of walking through the first floor of the new City-County Building, which I had done two hours before the experiment began. I thought at that time: Is this real? Did I really do this, or did I dream that I went to the City-County Building? I remember clearly that I couldn't answer those questions."

In addition to the neutral content of the hypnagogic responses mentioned above, more intense experiences relevant to central conflict areas were evoked in patient subjects. In contrast to the predominantly visual-spatial reference of the neutral responses, affectivity was the outstanding feature of these abreactive responses.

A patient recalled a disturbing childhood event, involving a head injury to his twin brother, who had smashed his head against a steel bar. As the patient remembered his brother's bloody head, he experienced the various "weird and creepy" feelings associated with the event. Another patient tearfully abreacted his mother's death, a precipitating factor in his illness. These illustrations were taken from patient protocols. In general, normal subjects did not report experiences relevant to areas of deep personal conflict.

Feelings of Inebriation.—Occasional euphoria was seen. When it occurred, the subjects would often smile vacuously and compare their feelings to those resulting from several Martinis. "This is a cheap hang-over" and "I feel half-plastered" were characteristic responses. The majority of this group were normal subjects who were moderate social drinkers. In this connection, Griefenstein gave Sernyl as an anes-

thetic to a patient who developed a full-blown delirium tremens. He later discovered that the man was a chronic alcoholic.¹¹

Repetitive Motor Behavior.—There were many reactions which appeared to function as facilitators of sensory feedback. Body movements of a rhythmic type were demonstrated by both normal subjects and patients. These included rocking, head-rolling, and, less frequently, grimacing. A normal subject reported in his retrospective account: "I kept shaking the bottles up and down because it felt good. Then I discovered that it also felt good to make my arms move in a figure eight." There was a definite tendency to focus on those stimuli which could still be appreciated. The same normal subject stated: "I started to rub my lips and my face. I could feel my fingers on my face, my lips rubbing each other, and my fingers rubbing each other. It felt pleasant to stroke my face and smack my lips against each other." It was almost as though the intact sensory modalities were overvalued, if not erotized. Perhaps the same general interpretation could be applied to the instances of repetitive, chanting speech observed in several subjects.

Neurological Changes

With the dose of 0.1 mg. per kilogram, the neurological changes were not as severe as those reported by Meyer et al.¹⁶ Diminution in pain, touch, and position sense occurred uniformly. All subjects displayed rotatory nystagmus and ataxic, slapping gait. Some subjects showed diplopia. There were a slight increase in muscle tone and minimal to mild impairment in motor strength. There was also a mild diminution in auditory and visual acuity. A centrally produced nausea occurred in several subjects.

Drug Effects on Schizophrenic Patients

Sernyl was given to four chronic schizophrenic subjects with illnesses of 8 to 10 years' duration, and one acute, mute, unresponsive catatonic patient. In the chroni-

cally ill patients, there was an intensification of the thought disorder, together with the stimulation of considerable affect. It was as though in these patients the acute phase of the illness had been reinstated. Sexual acting out, with professions of love toward personnel, was observed. One patient kept screaming: "I want to fuck; I love to eat; I love to fuck. Can I help it?" Another wanted to be kissed and fondled; however, the warmth and amiability were transient. The chronic patients generally became more assertive, hostile, and unmanageable. Withdrawal was less in evidence, and they tended to relate more to other patients and personnel, although in a meddlesome and aggressive manner. It was interesting that all four chronic patients manifested behavioral changes, which have continued for one month. The acute catatonic patient seemed completely unresponsive to the drug, his catatonia, if anything, being intensified. Four days later, he spontaneously emerged from his stuporous state and was able to recall his drug experience. He had been aware of the infusion and remembered feeling as though he were "returning to earth from another planet." His improvement was maintained for six weeks.

Comment

There is an impressive similarity between the psychopathology resulting from the intravenous administration of Sernyl and certain primary symptoms of the schizophrenic process. The disturbance in associations, inability to maintain a set, and concreteness produced by the drug were accompanied by none of the kaleidoscopic, visual, hallucinatory phenomena so characteristic of LSD-25 and mescaline.^{13,21} This would seem to distinguish Sernyl from these psychotomimetic agents, which might be said to mimic the secondary or restitutional symptoms of schizophrenia, while only minimally impairing the ability to associate, abstract, and maintain attention.^{4,10,22} The fact that the drug uniformly intensified the primary symptoms of a small group of schizophrenic patients also suggests that it

may act in a way fundamentally different from LSD or mescaline. Patients with chronic schizophrenia are highly resistant to the latter drugs and are able to discriminate between the drug effects and the usual manifestations of the psychosis.⁴ In contrast, Sernyl exaggerated their associational defect, and frequently their inappropriate affectivity. It also resulted in feelings which were more characteristic of the acute and earlier phases of the illness. In these patients, it is puzzling that behavioral changes persisted for weeks following Sernyl administration; this suggests that the action of the drug may touch upon some fundamental aspect of the disease.

Comparisons can be drawn between the effects of Sernyl and those changes occurring with environmental sensory isolation.¹⁵ In both experimental settings there is an attempt to diminish sensory input. With sensory isolation this effort is relatively successful with respect to exteroceptive stimuli, but inadequate with respect to proprioceptive stimuli. Prominence of personal reverie, impairment of directed thinking, and occasional disturbances in body image have been reported in these studies.^{2,18,20} With Sernyl the changes observed were similar, but far more intense, particularly with respect to distortions of body image and thinking.

The sequence in which symptoms became manifest following Sernyl infusion may be of particular importance. The first to appear was a disturbance in body image, with feelings of unreality, estrangement, and depersonalization. Then the disturbance in thinking emerged, characterized by inability to maintain a set, concreteness, blocking, and disordered linguistic expression. Following this, hostility and negativism were noted. Throughout the sequence, apathy became increasingly prominent.

The mechanisms by which Sernyl produces these changes are as yet obscure. It can be speculated that impaired transmission or central integration of proprioceptive feedback constitutes a necessary condition for the process observed. The nuclear im-

portance of the body image in psychological functioning has been repeatedly emphasized. Freud stated that "the ego is primarily a bodily thing, that is, the perception of one's own body. The body image is the nucleus of the ego."⁹ Schilder¹⁹ and Angyal¹ emphasized the significance of kinesthetic input and the postural model in neurosis and psychosis. Federn considered depersonalization to be the core of the schizophrenic process.⁸ In this connection he pointed out that "it could be clearly recognized that the bodily ego is formed by the proprioceptions transmitted through the sensorial nerves plus a uniting cathexis."⁸ Kubie has long emphasized the bipolar nature of the symbolic process with its anchor in the body image: "Thus the earliest learning builds on intrabodily experience, and the expanding knowledge of the external world relates itself automatically to those body impressions which have already been experienced internally."¹⁴

The experiments of Roger, Rossi, and Zirondoli present further evidence indicating the dependence of conscious states upon the maintenance of intact proprioception.¹⁷ These authors studied the effects of suppression of various afferent sources on EEG alertness patterns in *encéphale isolé* cats. EEG was maintained when olfactory, visual, acoustic, vestibular, or vagal sources were cut. EEG sleep rhythms resulted, however, from bilateral destruction of the Gasserian ganglion. Thus, a muscular origin of afferent feedback may be essential to the maintenance of normal states of wakefulness.

These considerations suggest that both the model psychosis induced by Sernyl and certain primary symptoms of schizophrenia may have their basis in a dysynchrony or defect in proprioceptive feedback. This tentative formulation is consonant with psychological hypotheses emphasizing the role of kinesthesia in thinking and affect.

This hypothesis is a tentative one, and it is understandable that other meaningful hypotheses regarding the action of Sernyl

and the pathophysiology of schizophrenia may be postulated. For example, the direct action of this drug on the cerebral cortex may be of crucial significance for the production of the thinking disturbance observed. Experiments to clarify the validity of these various hypotheses are being developed.

Lafayette Clinic, 951 E. Lafayette St. (Dr. Gottlieb).

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