# A NEW DRUG CAUSING SYMPTOMS OF SENSORY DEPRIVATION

## NEUROLOGICAL, ELECTROENCEPHALOGRAPHIC AND PHARMALOGICAL EFFECTS OF SERNYL

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During the clinical evaluation of the compound 1-(phenylcyclohexyl) piperidine, monohydrochloride (Figure 1) named Sernyl® for possible therapeutic use by the Departments of Neurology and Anesthesiology

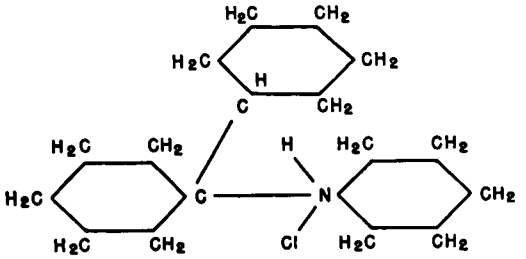

FIG. 1. Structural formula of Sernyl.

of Wayne State University, College of Medicine it was noted that administration of the drug occasionally resulted in symptoms similar to those observed in individuals subjected to sensory deprivation (1, 3, 5). As judged by our clinical observations in man this drug is presumed to have a relatively selective action on sensory cortex, thalamus and midbrain resulting in demonstrable impairment of pain, touch, proprioception and discriminative aspects of sensation. Motor function is unimpaired until high doses are administered, when ataxia and nystagmus result. Subjects in whom sensory deprivation has been induced by Sernyl regularly report feelings of anxiety, depression or fear together with difficulty in thinking and concentration. In higher dosage illusional, delusional and hallucinatory experience and a sensation of displacement commonly occur.

Because of the potential importance of these phenomena in relation to the physiological effects of perceptual isolation and the potential usefulness of this drug in experimental psychology and psychiatry, it is considered appropriate to report our observations.

### MATERIAL AND METHODS

One hundred and two patients have been observed during and after administration of Sernyl. Eighty patients received the drug intravenously while lying prone on a table in a quiet operating room prior to various surgical procedures. In some of them neurological examinations were made before, during and after administration of the drug together with concurrent records of electroencephalogram, blood pressure, respirations and electrocardiogram. Electroencephalograms were recorded using bipolar technique with an 8 channel type 3D Grass electroencephalograph. Ten conventional electrode placements were made on the scalp. Blood pressure was recorded through an arterial canula inserted into the brachial artery and connected to a Statham transducer. Blood pressure and electrocardiogram were recorded with a Sanborn polygraph. Respirations were measured with the subjects breathing room air through a one-way nonrebreathing valve. The expired gases were collected in a self-recording Tissot spirometer. The remaining 22 patients suffered from neurological disorders and were given Sernyl orally in various doses to evaluate the possible usefulness of the drug in thalamic pain, atypical facial pain, postherpetic neuralgia, post-encephalitic Park-

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inson's disease, paralysis agitans, Huntington's chorea, rubral tremor, benign familial tremor and double athetosis. Of the 80 subjects who received large doses of the drug intravenously, thirteen developed a confusional psychosis of 12–72 hours duration characterized by feelings of unreality, depression, anxiety and delusional and illusional experience. One patient who received a larger dose than the others had a perceptual disorder that persisted for four days. In some of these subjects observations of behavior and neurological examination were made during the psychotic episode and were compared with the subject's memory of the experience after the drug had been excreted and behavior had returned to normal.

Of the 22 subjects administered oral preparation of the drug for neurological disorders, eight showed evidence of impaired mentation. None of these subjects had any impairment of mentation prior to the administration of the drug but one patient with benign familial tremor was blind due to glaucoma. All the patients who received the drug by mouth were ambulatory and were observed on the ward or in the outpatient department.

## RESULTS

### NEUROLOGICAL OBSERVATIONS

Intravenous administration of Sernyl regularly produced significant sensory change after 7.5 mgs. of the drug had been administered. Pin-prick was no longer appreciated as painful and response to all forms of sensory stimulation was either appreciably slowed or diminished. After receiving 8 mgs. of the drug one patient was unable to read the time or recognize a painful stimulus, but was able to identify a packet of cigarettes and a key, this very slowly. When 9.5 mgs. of the drug had been administered, vertical nystagmus and bilateral ptosis commonly occurred. After 10.5 mgs. drowsiness appeared and common objects could not be identified by vision or touch, although motor movement was preserved. In higher dosage ptosis, vertical and horizontal nystagmus, dysarthria and crowing respiration were common and the corneal and pupillary light reflexes became depressed. At this stage there was no response to any form of stimulation, but spontaneous movements of the extremities often occurred. The tendon jerks became increased and the plantar reflexes could not be elicited. The visual fields were demonstrated to be intact although recognition of objects was impaired. At this stage minor surgical procedures could be carried out without discomfort.

After recovery from intravenous injection of 7 mgs. of Sernyl, patients were able to recall events clearly. At higher dosage objects seemed to "float away" and the subjects had the sensation that the body went numb and was displaced. The sensation of displacement of the body in relation to the environment was consistently noted by those patients receiving more than 7 mgs. of Sernyl by intravenous injection. After 10 mgs. hallucinatory experiences were commonly noted which appeared to be patterned according to the personality structure and past behavioral experience of the subject. Many of our patients with strong religious backgrounds reported that "God was taking them away" or that they were being "carried up into the clouds." Rarely were feelings of persecution reported.

### CONFUSIONAL PSYCHOSIS

Several patients were examined who remained confused for 12–96 hours after the injection of the drug. The confusional state was characterized by feelings of unreality, depersonalization, persecution, depression and intense anxiety. Some became agitated and anxious. During these states of confusional psychosis defects in sensory perception were demonstrable. Pin-prick sensation was regularly impaired and a partial visual agnosia was occasionally demonstrable. In many instances objects were falsely interpreted and the stimuli responsible for an il-

lusional reaction could be identified. There was also disorientation to time and place. For example, one patient of stoical and cooperative personality structure was being observed in the neurological ward with a diagnosis of pituitary tumor. Carotid angiography was performed under intravenous Sernyl anesthesia. Several hours after the patient had been returned to the ward he became restless and noisy attempting to leave the ward and making accusatory remarks to the nurses and attendants. When he had recovered he explained that he recalled the intravenous drip being started, then his body became numb and he was carried up into the clouds where a group of guards were shouting orders (there were orders being made by the surgeon to the radiology staff during the procedure) then the "guards" attempted to transfix his chest with a massive "spike" (probably the arterial needle). After his recovery the patient explained that during this period of psychotic behavior he was under the impression that "the guards were trying to capture and kill me."

The most prolonged state of confusional psychosis we have seen persisted for four days. The subject was a 45 year old woman who received 0.3 mg. of Sernyl per kilogram of body weight for anesthesia during cholecystectomy. On recovery from anesthesia she was confused, disoriented and failed to recognize people; she tended to lapse into sleep if left alone. She required catheterization because her bladder became distended without discomfort. She talked to relatives who were not present and visual hallucinations occurred. She responded when called by name and stated that she was willing to get out of bed, but felt sleepy. Speech was slightly slurred. She did not know where she was because she was "all mixed up." She recognized the side-boards on her bed, but believed that she was at home. She could not recognize her family because "I cannot think." She stated that the date was 1898 and she had virtually no recent memory at all. When asked her name she gave her maiden name and could not recall her husband's name. She knew her age, the color of a lemon, but not the color of an orange. She was unable to read the time on a clock face. Simple calculation was grossly impaired and she could not read or write. She obeyed simple motor commands with ease. She was unable to recognize a flower. The visual fields were intact since she responded to threats by blinking, but she could not identify common objects presented to her. Nystagmus was present and there was no response to pin prick over the entire body. Although motor strength was entirely normal, position sense was poor and vibration sense was absent. Seven days after operation, neurological and mental examination were entirely normal and she was ambulatory.

Subjects who received the drug by mouth developed milder degrees of mental disorder which were investigated in detail. Two ambulatory and working patients who were being treated with 7.5 mgs. of Sernyl daily for pain, reported relief of pain but inability to think or solve problems. For example, one of them who was an engineer complained that he sat looking at blueprints all day, but was unable to solve a simple problem that usually required thirty minute's work. Another subject treated with Sernyl for postherpetic neuralgia reported that an oral dose of 12.5 mgs. daily abolishd her pain, but in addition produced a feeling as though she were "dying," a "sinking sensation." She said that all her "senses" disappeared and she had no feeling. Her thinking became void; and objects appeared smaller than normal. The beds in the ward appeared to be "as small as marbles" and looked as though they were "stuck to the ceiling." In her case, everything seemed displaced upward and she was displaced downward. Her entire body was numb and as her "senses" came back her hands "looked square." This situation lasted for 3–4 hours and during this time pin-prick sensation was demon-

strably absent, but she could identify coins by palpation, slowly but correctly. Two-point discrimination was also slowly, but correctly perceived.

Subjects with post-encephalitic Parkinsonism tolerated the drug very poorly and became withdrawn, dull and apathetic. Presumably, this decreased tolerance to the drug is due to already existing damage to midbrain and thalamus by the disease process itself. One patient who received 7.5 mgs. daily for six weeks became semi-stuporous and catatonic. His limbs would persist if placed in abnormal postures for several minutes. When the drug was discontinued recovery was prompt. Another patient with post-encephalitic Parkinsonism, receiving 7.5 mgs. daily, reported that this produced a "novocaine" sensation over her entire body and she seemed to be floating in air. It is of interest that patients with paralysis agitans do not appear to show the same degree of sensitivity to the drug, and tremor has been reduced or abolished in several patients.

There also appears to be a lowered threshold to the drug in blind individuals. A colored patient with benign familial tremor and blindness due to glaucoma was treated for seven days with 7.5 mgs. of Sernyl daily, without improvement of his tremor. On the seventh day this previously quiet and placid individual became delusional with a strikingly religious flavor. He began clapping his hands in time to non-existent banjo-music and saying, "Brother, let me tell you how I've been saved." When the drug was discontinued these symptoms rapidly cleared.

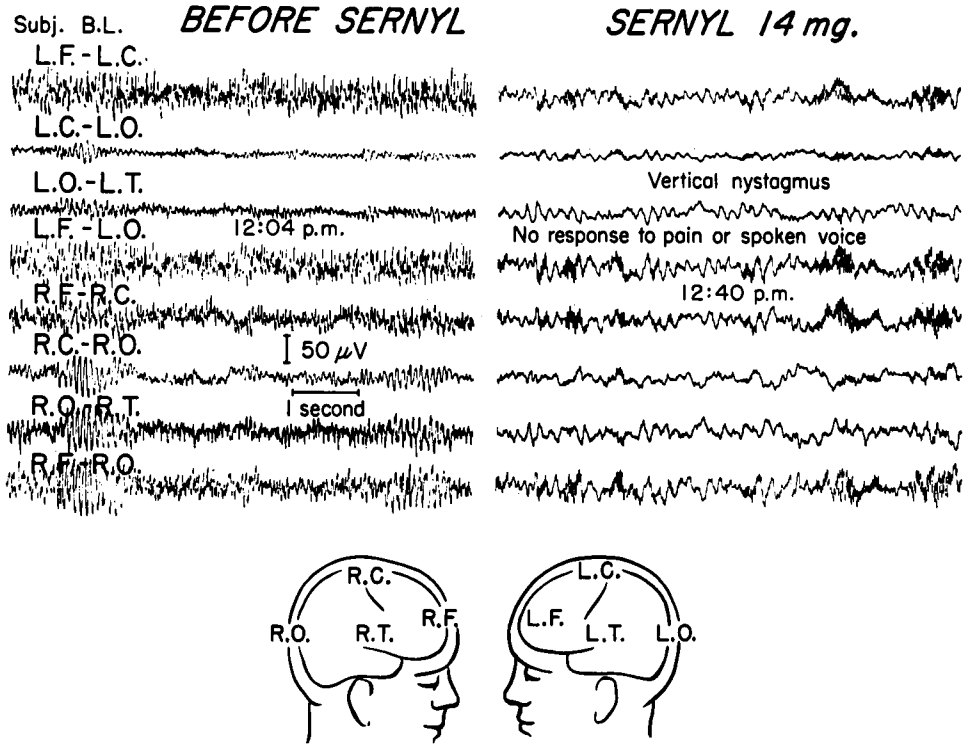


FIG. 2. Samples of continuous EEG recorded from a 49 year old woman weighing 170 lbs. while receiving Sernyl intravenously prior to excision of a lipoma of the left arm. In the record to left, prior to the administration of Sernyl there is alpha activity except in the frontal regions where there is beta rhythm. After 14 mgs. of Sernyl there is no response to pain or spoken voice and vertical nystagmus is present. The EEG shows diffuse slowing in the theta and delta bands.

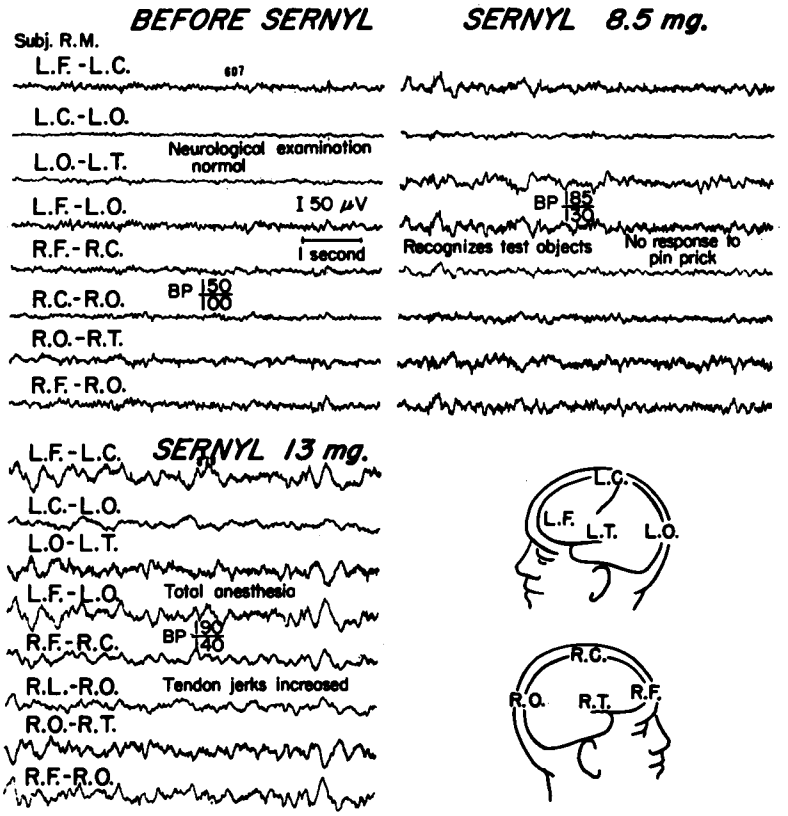


FIG. 3. Samples of continuous EEG recorded from a 33 year old woman while receiving Sernyl intravenously prior to diagnostic curettage of the uterus for menometrorhagia. Before Sernyl the record shows low voltage beta activity. After 8.5 mgs. of Sernyl the BP is elevated and there is no response to pin-prick, but she can identify visual test objects. There is slowing in all regions except the central regions.

After 13 mgs. of Sernyl there is high voltage showing in the delta range and there is no response to all types of stimulation, the blood pressure and tendon-jerks are increased.

ELECTROENCEPHALOGRAPHIC CHANGES

After intravenous administration of 7.5 mgs. of Sernyl, changes consistently appear in the EEG. First there is a disappearance of alpha and beta activity and the appearance of slowing in the theta range in all regions except the central ones. In higher dosage theta and delta slowing becomes diffuse and there is an increase in amplitude (Figures 2, 3, 4).

CHANGES IN BLOOD PRESSURE, RESPIRATION AND HEART RATE

The effects of Sernyl on blood pressure, respiration, and the electrocardiogram were studied on seven volunteer subjects.

Sernyl was administered intravenously in a 0.1% solution at the rate of 5 c.c. per minute until a total dose of 0.25 mgm./kg. had been given.

The effect on respiration is shown in Table 1. As the blood concentration of the drug is increased, the minute volume of respiration is increased. At 0.25 mg./kg. the average increase is of the order of 1140 ± 907 cc. for the seven subjects. Rate and depth of respiration both increase with increasing minute volume, although these changes also appear to be small. At 0.25 mg./kg., six of the seven subjects exhibited a tidal volume equal to or greater than the

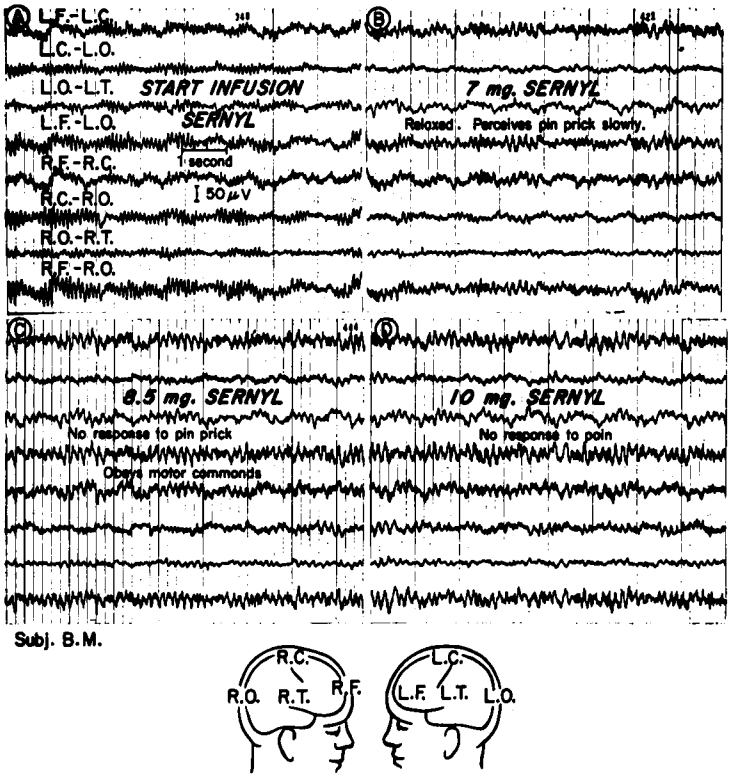


FIG. 4. Samples of a continuous electroencephalographic record made on a patient while receiving Sernyl intravenously. A. Prior to infusion there is alpha activity. B. After 7 mgs. slowing appears and pain sense is diminished. C. and D. shows progressive changes in EEG at higher dosage, which were never marked.

TABLE 1

*Respiratory Response to Sernyl*

| Mg./kg. | 0.06 | 1.125 | 0.19 | 0.25 |
|---|---|---|---|---|
| Min. Vol. | 140 ± 407 | 640 ± 407 | 640 ± 957 | 1140 ± 907* |
| Tidal Vol. | 16.7 ± 39.5 | 27.1 ± 50 | 27.4 ± 66.9 | 15.3 ± 52.9 |
| Resp. Rate | 1.86 ± 1.81 | 1.43 ± 2.61 | 3.43 ± 1.79 | 2.57 ± 3.82 |

* The ± deviations represent confidence values and not standard deviation from the mean. (P = 0.01)

TABLE 2

*Circulatory Response to Sernyl—mm. hg. Change from Normal*

| Mg./kg. | 0.06 | 0.125 | 0.19 | 0.25 |
|---|---|---|---|---|
| Systolic B.P. | 7.9 ± 6.07 | 23 ± 14.4 | 26 ± 9.8 | 25.7 ± 12.9* |
| Diastolic B.P. | 7.43 ± 4.43 | 18.6 ± 9.3 | 17.7 ± 4.6 | 19 ± 5 |
| Pulse rate | 0.33 ± 4.68 | 8 ± 13.2 | 7.8 ± 8.4 | 5.1 ± 14.9 |

* The ± deviations represent confidence values and not standard deviation from the mean (P = 0.01)

control value, and five of seven an increase in respiratory rate.

Circulatory changes are shown in Table 2 and a typical tracing representative of the blood pressure changes are depicted in Figure 5. Both diastolic and systolic blood pressure increased slightly over the control values until approximately half the total dose had been given. At this point a plateau was reached and the blood pressure maintained at this new level for approximately thirty minutes.

Pulse rate changes were not as consistent.

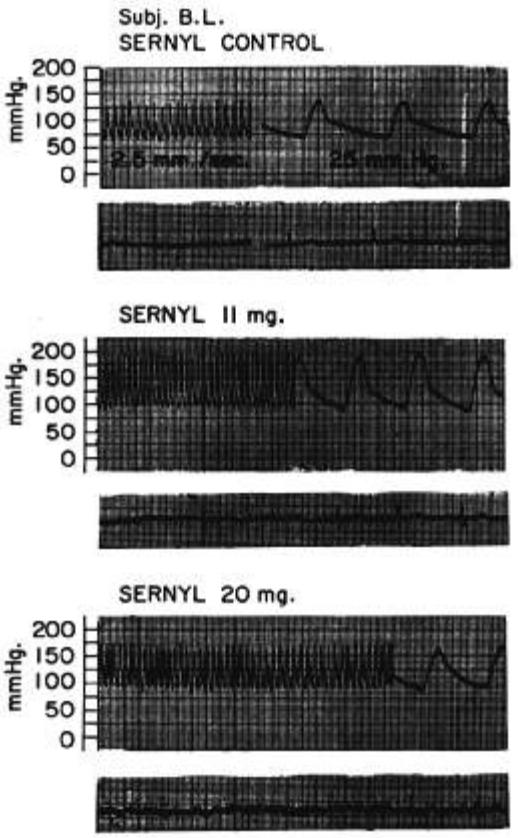


FIG. 5. Records of blood pressure and electrocardiogram before Sernyl (top trace) after 11 mg. (middle trace) and after 20 mg. (bottom trace) of Sernyl intravenously. (See text.)

Four of seven subjects showed a slight increase in pulse rate, while the remaining three exhibited a mild bradycardia after 0.25 mg./kg. had been given.

The electrocardiogram exhibited no arrhythmias or other abnormal patterns, although changes in the EKG have been demonstrated in lower species.

## DISCUSSION

It appears from our data that Sernyl produces a form of sensory deprivation due to the action of the drug on the central nervous system interfering with sensory perception. The type of sensory loss and the associated changes in cranial nerves, blood pressure and reflexes suggest that the drug acts primarily on the sensory cortex, brain-stem and thalamus. This concept is further supported by the fact that subjects with disorders that are known to affect the brain-stem and thalamus (such as post-encephalitic Parkinsonism) show a marked sensitivity to the drug. In addition we have treated four cases of thalamic pain with the drug, with partial or complete relief of pain. The drug does not affect rubral tremor (one subject) or the involuntary movements of Huntington's chorea (five patients). In a few patients with paralysis agitans and in one case of double athetosis the involuntary movements were improved, but care must be taken in dosage to avoid the unpleasant side effects of sensory deprivation. Similarly, patients suffering from post-herpetic neuralgia, atypical facial pain due to syringomyelia were afforded relief, but often found themselves unable to think clearly and became anxious or depressed. Toxic effects on bone marrow, liver and kidney have not been noted in any of our patients or in experimental animals (2, 4).

After higher doses of Sernyl a deficit in sensation is demonstrable and symptoms appear that are similar to those reported during sensory deprivation on normal volunteers (1, 3, 5). We have seen similar symptoms in patients with porphyric and post-infectious polyneuritis who have been treated in a tank-type respirator for prolonged periods of time, in individuals immobilized with Crutchfield tongs for treatment of cervical fracture and in immobilized and temporarily blinded patients following ophthalmological surgery. The concept that the "psychotic states" produced by Sernyl are related to the phenomenon of sensory deprivation is further supported by the fact that in one of our patients who was blind, symptoms of confusional psychosis were produced by doses of Sernyl which did not produce symptoms in individuals with intact vision.

## SUMMARY

Neurological, electroencephalographic and pharmacological data have been presented

on over 100 individuals who have been treated with Sernyl, a drug that appears to exert a blocking action on the thalamus and midbrain. This drug eventually produces a blocking of all forms of sensation with pain sensation disappearing first. Motor movement is not impaired, except for ataxia, until the patient becomes unconscious. Blood pressure and reflexes are increased and vertical nystagmus appear in high dosage of the drug. Early and sometimes prolonged symptoms appear that are similar to those reported in sensory deprivation studies; namely, anxiety, illusional, delusional and hallucinatory phenomena with a feeling of displacement. Interference with thinking processes is an early complaint. It is concluded that Sernyl produces a "centrally mediated" sensory-deprivation syndrome.

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