Exhibit P-64

OBSERVATIONS ON THE ACTION OF SERNYL — A NEW PSYCHOTROPIC DRUG

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It is possible to divide psychoactive drugs into psychotomimetic, inhibitory and excitatory agents(7). Psychotomimetics or hallucinogens are those chemicals which cause a transitory psychotic-like state or "model psychosis" through dissociation of the usual association pathways. Drugs that produce inhibition are the well known older sedatives and the whole group of new tranquilizing, neuroleptic or ataractic agents. Many of this group have physiological depressant actions of varying degree. Drugs that produce excitation are those central stimulants which produce increased alertness, increased speed of reaction, promote wakefulness and reduce the subjective sensation of fatigue(6). An entirely new group of psychoactive drugs are the anti-depressant substances. Most of the recent phenotropic drugs belong to one of these groups, while Sernyl (CI 395), a relatively new compound of Parke, Davis & Company, does not fit into any of the above four categories since it may exhibit different characteristics at different dose levels.

Pharmacological and Clinical Data

1-(1-Phenylcyclohexyl) piperidine monohydrochloride (Sernyl) is a white, stable, glistening, solid chemical with a melting point of 234-236°C, soluble in water and ethanol. It immobilizes animals, produces a marked blocking of all sensory stimuli, causes no adrenergic or ganglionic blocking and shows no anticholinergic or anti-histaminic action.

The first clinical application of Sernyl was made by Greifenstein and associates when they introduced it as an intravenously administered anesthetic agent. Given in an 0.1% solution by continuous ¹From the Verdun Protestant Hospital, Verdun, Que. infusion at a rate of approximately 5 cc/min. in a dose of 0.25 mg/kg body weight, the infusion brought about a complete analgesia after 8-11 mgms. of the drug had been given. At this point a slight increase in the minute volume of respiration and a consistent and significant rise in both systolic and diastolic blood pressure were observed as well as a slight increase of the pulse rate. Postoperatively, 10 out of 64 cases exhibited severe degrees of manic behaviour and a number of the remaining group appeared to be euphoric and disoriented as if intoxicated. It was also observed by the same authors that larger doses of the drug, 0.5-1.0 mgm/kg of body weight, produced a state of agitation, and still larger doses, convulsive seizures (5). Because laboratory observations indicated that phenicyclidine possesses central nervous system depressant properties associated with an improvement of mood, investigations were also carried out along this line.

Bodi and his associates noted improvement in 25 of their 32 psychiatric patients. According to these authors, Sernyl appeared to be most effective when given to patients with anxiety symptoms in mild to moderately severe degree, but was less effective in patients with personality disorders or with residual schizophrenic symptoms(1).

Luby et al. described the sensory and cognitive deviations produced by the drug and compared them with schizophrenic symptomatology. They introduced the term schizophreno-mimetic and applied it to Sernyl. These workers gave 0.1 mgm/kg in 150 cc of 5% dextrose administered over a period of 12 minutes. Psychological and neurological changes were observed and the former were grouped under the headings of body image changes, estrangement, disorganization of thought, negativism and hostility, drowsiness and apathy, hypnagogic state, feelings of inebriation and repetitive motor behaviour (10).

Review of Literature

The possible use of intravenous Sernyl in psychiatry extends to three areas: 1) to control excited patients, having an advantage over barbiturates in that it does not depress blood pressure and respiratory rate, 2) as a diagnostic test for schizophrenia, since schizophrenics seem to be most susceptible to this drug, and 3) as an abreactive agent(15). In regard to the second possibility Luby and his collaborators on the basis of their studies, conclude that the model psychosis produced by Sernyl, as well as certain primary symptoms of schizophrenia, may have their basis in a dysynchrony or defect in proprioceptive feedback. According to these authors "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" (10). This hypothesis was based on the findings of severe disturbances in body image, affect, attention and thinking, essentially the primary symptoms of schizophrenia. Further studies along these lines were carried out by Rosenbaum and associates, who found that in contrast to LSD 25 and amobarbital, Sernyl produces disturbances in attention, motor function and proprioception, approaching the deficit level shown by schizophrenics. It was concluded by the same authors that Sernyl administration results in schizophrenia-like impairments of primary attention and motor function, whereas LSD 25 stimulates only the secondary symptoms. This was interpreted as evidence for the hypothesis that disturbance in proprioception may be the pathological mechanism mediating the impairments in performance and motivation found in schizophrenia and produced by Sernyl(12).

Experimental Procedure

The drug was administered to a group of 55 patients, 21 females and 34 males. All patients were chosen from the inpatient population of a mental hospital. The length of hospitalization varied from a few days up to many years. The mean age of subjects was 35.9 years with a range of 18-50. While all 55 sample members received varying dosages of Sernyl, 30 other drug interviews were conducted on six patients including LSD 25, Mescaline Sulfate, Sodium Amytal and Desoxyn HC1.

In all cases, patients on medication were only tested after a minimum of 72 hours without medication and in all cases pretest physical examinations indicated no intercurrent disease. The patients fell into the following diagnostic categories: 1) 43 schizophrenia, 2) 3 paranoid state, 3) 3 manic depressive psychosis, 4) 5 alcohol dependency and 5) 1 mental deficiency. The test drug Sernyl was administered intravenously as were all other test drugs, except for Mescaline SO₄ and LSD 25. Sernyl dosage ranged from 0.01 mgm/kg to a maximum dosage of 0.1 mgm/kg, except in one of the first cases, who received a dose of 0.12 mgms/kg. The time of administration ranged from 1 minute to 10 minutes. The test drug Sernyl was administered in the dilution recommended by the manufacturer, 0.1% and after completion of the test, patients were replaced on their usual medications. Only in three isolated cases was special sedation required within the post-test 24 hours.

The actual test period from the time of drug administration to the return of the patient to the ward varied from 4-8 hours. During this time, the patient remained in a single room, attended by two nurses or nursing attendants, one of them taking detailed notes with verbatim samples of the patients speech, the other charting regularly the patient's blood pressure, respiration and pulse rate as well as his physical activity. Some of the experiments were recorded on a recording device. In most of the experiments the patients were given minimal pre-test instructions, but were encouraged to verbalize and express subjective changes.

Data accumulated were primarily of two orders: 1) objective-the observations of the psychiatrist and the nursing staff, neurological examinations and a series of psychomotor and perceptual test procedures 2) subjective-data obtained from the patient via introspection as well as projective data through the administration of a multiple choice Rorschach test. The psychophysiological tests used were those described by Lehmann and Knight (9) for the determination of basic perceptual functions, psychomotor discharge, capacity of recall, attention, concentration and learning(9). Critical flicker fusion frequency, after image disappearance level, tapping speed, reaction time, hand steadiness, digit span, digit symbol substitution, cancellation and spiral after effect were employed as a test battery(8). In addition a neuropsychiatric check list was used to compile observational data.

General Observations

1. The effects of varying dosage and time of administration were studied separately by: a) administering Sernyl in increasing concentration intravenously from 0.01-0.1 mgm/kg, b) decreasing the time of administration from 10-1 minute. It was noted that in low concentration the drug seemed to have a disinhibiting potential, but never to the extent seen with Sodium Amytal or other barbiturates.

On increasing the dose or decreasing the time of administration, the picture became increasingly dependent on and related to the subject's psychopathology. The intensity of reaction was in direct relationship to the amount of drug administered with individual variations depending on ego-strength and ego-defenses up to a critical value beyond which any further increase of dose or decrease of the time of administration resulted in an uniform inhibitory action. These general impressions led us to choose 0.07 mgms/ kg as the standard dosage and seven minutes as the standard time of drug administration in our further studies.

2. The effects of Sernyl administration were compared to the reactions to Mescaline Sulfate and LSD 25. Our psychophysiological tests did not provide data which allowed for measurable differentiation between the different drug response patterns. It was felt by the authors that whereas the reactions to Mescaline and LSD 25 were the expected "drug or personality specific" manifestations, the total response pictures to Sernyl were to a greater degree "pathology specific". This is in accordance with the findings of Luby and his associates, who found that, while LSD 25 and Mescaline SO₄ "might be said to mimic the secondary or restitutional symptoms of schizophrenia" Sernyl "uniformly intensifies the primary symptoms of a small group of schizophrenic patients". It was our opinion that the Sernyl reactions we noted in our cases were "pathology specific" both as to form and content.

Physiological Findings

Sernyl was originally employed as an anaesthetic agent and previous investigators have reported anaesthesia and hypaesthesia as occurring consistently in the human (5) (10). Decrease of sensory discrimination of varying degree, as well as paraesthesia, were consistent findings in our study. Deep reflexes i.e. biceps, triceps, knee, ankle jerks, were uniformly increased, but not necessarily in proportion to the dosage. Nystagmus was present in less than 10% of our cases and while all patients complained of vertigo, of unsteady and slapping gait and swaying, repeated testing of cerebellar function did not establish a specific or consistent response pattern.

In regard to the autonomic nervous system, nausea occurred in 90% of our cases either during administration or within 30 minutes thereafter. This was

aggravated by activity, especially, if the patient was asked to stand up. Approximately one half of our patients vomited and, in two cases, there was fecal incontinence. The latter occurred in moderately deteriorated schizophrenics. Ten percent of the patients complained of a dry mouth and thirst. A uniform elevation of the systolic blood pressure was noted, the mean elevation being 10-20 mm/HG with the maximum rise occurring within 30-45 minutes after Sernyl administration and then subsiding slowly within 2 hours. A rise in the pulse rate was associated with the blood pressure elevation. In a number of patients fluctuation of blood pressure and pulse was observed, but in our series hypotension did not develop to the degree of producing syncope. We were prepared to deal with respiratory system emergencies, but these did not occur in our material. Twenty percent of our cases showed a slight increase in respiratory rate.

Psychological Testing

Psychophysiological testing and multiple choice Rorschach was administered. Thirty per cent of the subjects were unable to complete the full battery. All data were tabulated for purposes of comparison, but no significant or internally consistent response pattern was apparent in those areas of functioning for which the tests used were accepted as valid. The one exception was lengthened simple reaction time. It was noted that in 3 alcohol-dependent patients a decreased reaction time occurred with an increased tapping speed while critical flicker fusion frequency and after-image-disappearance-level were diminished.

Behavioural Observations

All patients were known to the interviewers previous to the drug experiments and psychopathology, character traits and ward behaviour were known to us on the basis of daily observation of behaviour on the ward. In every case it was evident that a patient given intravenous Sernyl was undergoing a maximal stress situation

in terms of threat to the total self-organization. This personality disorganization was most evident at the dose level we had chosen for our final testing (0.07 mgm/kg in seven minutes) and was particularly dramatic and striking in patients who had recently recovered from acute schizophrenic episodes. Within $\frac{1}{2}$ hour after drug administration, the intensity of reaction was at its maximum, subsiding within 3-4 hours, residual anxiety and apprehension lasting for 8-12 hours. In order of frequency the occurrence of disorientation, emotional outbursts of rage or sorrow with weeping and erratic behaviour were observed. Varying degrees of anxiety, restlessness and tenseness to the point of panic were apparent in 41 of our cases. Only 3 patients became euphoric, laughed with inappropriate affect or expressed evidence of pleasure during the Sernyl experience. Patients manifested suspiciousness in cases where projective mechanisms were a significant feature of the psychopathology. Most prevalent was an expression of fearful expectancy, puzzlement and foreboding of disaster with a pathetic turning to the observer for reassurance and relief.

It was of particular interest to note that in 2 cases, there was a gradual observable emergence of the original acute psychotic state. Both these cases were young females and both had been diagnosed as paranoid schizophrenia. This was most clearly seen in a patient, who some months prior to the Sernyl experience had been floridly psychotic, with visual and auditory hallucinations. At the onset of the interview, she was appropriate, talkative and friendly. Following Sernyl administration she became progressively more restless, silent, suspicious, first of faint noises outside the interview room and then of her immediate environment and of persons present. Within 3 hours, she was withdrawn, silent and overtly hallucinating. The re-activated psychotic state lasted for 3 days, then she responded to Phenothiazine therapy and rapidly returned to her pre-Sernyl

level of integration. In interviews later on she was able to discuss with lucidity and some insight her disturbed state.

Subjective Material

1. The Sernyl experience was uniformly described as unpleasant and extremely frightening on later questioning. It was a common occurrence for the patients to spontaneously request that they never be exposed to such an experience again. The experiential nature of the internal phenomena consequent to Sernyl administration was evidently of ego-alien quality. This was particularly noted in patients who had undergone LSD 25 and Mescaline experiences as well. Such patients recalled and distinguished clearly the frightening nature of the drug reaction on a certain test day. Invariably, the drug referred to by these patients was Sernyl. Patients, trembling with terror, would repeatedly ask "where am I?, what is happening to me?, something is happening, I feel terrible", etc, but content was invariably absent. During these states, patients would turn to staff with pleas for assistance and relief from this state of nameless and undefined apprehension.

2. Preoccupation with death was a common finding. This took various forms: expressing fear of death "I don't want to die", requesting reassurance that death was not imminent or re-statements of desire to live, ambivalence about living or dying or the expressed desire to die. In one of these cases referred to above as re-experiencing a previous psychotic state, resignation and acceptance of impending death was presented dramatically. This was coupled with a deeply personal re-evaluation of her past and with questioning of the nature of her personal existence in a dramatic manner, e.g.: "I suppose my mother had me-I don't know-I did not ask her to have me -I didn't want to be born" and "please kill me, be a good man and kill me, kill me please, I want to die. I don't want to live any longer-I didn't want to be born -it was an accident" and "no wonder, I

am insane-I am free-I feel free as a breeze-you can throw me in the river". Sandison and associates (1954) refer to the intense reliving of repressed personal memories during the LSD 25 experience as "the surging up of repressed experiences" and Stocking (1940) in speaking of the Mescaline psychosis refers to this phenomenon as "a tremendous volcanic eruption of the subconscious with the repressing force in complete abeyance" (14)(15). Observations made on our patients would indicate that Sernyl administered in certain doses may have similar potentialities for reviving repressed significant events and affects, with the implied therapeutic possibilities.

3. Body image disturbances occurred in the majority of our cases, usually associated with unreality feelings. Many patients spoke of feeling weightless, e.g. "floating on top of the world" and "like a feather". These sensations did not appear to be alarming. Disturbances of the body image were in reference to the whole body rather than to discrete body parts, e.g. "I am a baby", "now I don't know what to do, I am a little boy of 3 years". Feelings of estrangement from the immediate environment were frequent, patients freely expressing their puzzlement that people and things about them had changed their expression, had become "a different world". It was of interest that certain aspects of the patients' personality appeared to be observing the whole procedure and to be able to relate to the interviewer even during maximal stress.

Site of Action

1.) Clinical and Neurological Evidence.

The site of action of Sernyl in the central nervous system is not yet defined. According to the clinical observations made by Meyer, Greifenstein and De Vault the thalamus and mid brain are involved. This is based on the demonstrable impairment of pain, touch, proprioception and discrimination and the observation that large doses produce ataxia, rotatory nystagmus, bilateral ptosis (10) and suppression of the pupillary light reflexes. The increase of blood pressure may also be an indication of this(5).

2.) Pathological Evidence.

No characteristic brain pathology has been observed in animals following Sernyl administration(1).

3.) Electroencephalographic Evidence.

a.) The effect on the cortical EEG of Macaca mulatta monkeys was dependent on dosage. The effects varied in direct proportion to dosage from minimal or no change, to medium voltage, fast waves, or high voltage delta activity. Photic driving responses were decreased in amplitude(10).

b.) On human subjects the EEG showed some slowing, most pronounced in theta activity and a decrease in fast activity after the infusion of 2-3 mgms. of the drug(5). According to recent literature, the result obtained after a large dose (0.2 mgms/kg) is marked theta activity, after a medium dose (0.1 mgm/kg) slowing in the 5-8 c/sec. frequency range and after a minimal dose (0.03 mgm/kg) a slight theta slowing or no apparent change. It was also pointed out by Rodin and associates that the psychotomimetic effects (severe depersonalization, feeling of unreality, thought defect characterized by concreteness and looseness of association, hypnagogic states, repetitive motor phenomena and feeling of inebriation) were observed also in the absence of definitive EEG changes. (1, 11, 16). On the basis of the EEG changes reported, site and mode of Sernyl action must still be considered obscure.

"Meditatio mortis"

We have already referred to the remarkable preoccupation with death and dying apparent in our test subjects. This phenomenon attracted our particular attention and the literature was consulted. Morgagni is said to have referred to the fear of dying as angor molestus and Seneca's physician employed the term meditatio mortis, presumably in reference

to thoughts on impeding death. Gowers (1907) noted the frequency with which this phenomenon occurred in association with vagal and vasovagal attacks(4). This observation has been made earlier by Nothnagel describing it as "angina vasomotoria" and by Bonnier referring to "Syndromes medullaires" (2) (1904)Gowers described vagal attacks as recurrent seizures of sudden onset, usually without loss of consciousness, the symptoms being mostly sensory and subjective. Subjective symptoms were those of gastric, respiratory and cardiac discomfort associated with a sense of impending death. Clinical cases were presented by this author, but the etiology was not clarified. The following description is given: "With the dyspnoic or the cardiac sensation or both is often associated a sense of impending death, so intense that no recollection of its falsity in preceding attacks prevents the conviction of its present reality"(4).

Sensations of dying in association with vagal attacks were reported by Ryle. He uses the term angor animi and notes that this sensation has been reported in labyrinthine vertigo, tumors invading the vagus nerve and also in cerebral tumors. In attempting to explain this subjective symptom, he states "it must surely be a powerful medullary stimulus of some kind", and further uses the term "medullary storm". He views angor animi as "the aura of a nervous storm having its origin in those medullary centres upon which the act of living depends". At the date of writing (1928) Ryle could not refer to the reticular activating system, since the latter's functional activity and importance was not then known(13).

David and associates (1946) reported that manipulation of the medulla oblongata produced a sudden sense of dying, the patient stating: "I am going to die" (3). Cairns (1952) noted that following accidental needle puncture of the medulla oblongata, the patient lost consciousness and later said: "I wish I had been quite killed." This author refers to the sense of dying as being one of "symptoms, related to bulbar lesions which seem primarily disturbances of vital forces, breathing, heart beat, body awareness and of being alive"(2). The above observations would indicate that the lower brain stem must be considered as a possible area of investigation in regard to the site of action of Sernyl.

Summary

Sernyl was administered to 55 patients, chosen at random from the population of a mental hospital.

Its disinhibiting potential appears to be related to the dose. Sernyl in doses of 0.07 mgms/kg administered in 7 minutes by the intravenous route activated the patients specific psychopathology to a greater degree than known psychotomimetics (LSD 25 and Mescaline Sulfate). Physiological and neurological observations, psychological tests and behavioural observations were made and correlated with the collection of subjective data. The unpleasant and extremely frightening nature of the experience, the preoccupation with death and body image disturbances were the most characteristic features observed. The history of the feeling of impending death as a symptom ("meditatio mortis") has been reviewed and it is suggested that the lower brain stem may be considered as a possible site of action.

Judging from our findings, Sernyl would not appear to be a psychotomimetic or schizophrenomimetic drug in the true sense, although certain aspects of the response picture obtained in psychiatric patients resemble the primary symptoms of schizophrenia. The drug seems to possess no particular therapeutic value, at least not at the present state of our knowledge.

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Résumé

Du Sernyl (1.-Phenylcyclohexyl) piperidine monohydrochloride) fut administré à 55 sujets choisis au hazard parmi les patients d'un hôpital mental.

L'effet disinhibiteur du produit dépend essentiellement de la dose utilisée. Administré par voie i.v. à raison de 0.07 mg/kg de poids corporel (injection lente étalée sur 7 minutes), le Sernyl jouit de la propriété d'activer la psychopathologie spécifique des patients à un plus haut degré que les psychotomimetiques connus (LSD 25 et sulfate de Mescaline). L'administration de ces derniers, en effet, produit un tableau spécifique de la drogue administrée, alors que la symptomatologie déclanchée par le Sernyl serait plus spécifique de la pathologie du patient.

L'évaluation de l'action du produit est basée sur les réactions physiologiques et neurologiques, les données des tests psychologiques, l'observation du comportement de nos patients, et nous avons confronté le tout avec les phénomenes subjectifs qu'ils nous rapportaient.—Le caractére pénible et effrayant de l'expérience, la hantise de la mort, ("meditatio mortis") et les altérations du schéma corporel dans son ensemble furent les plus caractéristiques des phénomènes subjectifs observés.

En ce qui a trait au lieu d'action du Sernyl, nous présentons d'abord ici une brève revue de la littérature relative au "sentiment de la mort imminante" au tant que symptôme localisateur. Bien que les indications fournies par les examens electroencephalographiques et anatomopathologiques soient essentiellement nonspecifiques, nos observations sur le plan psychiatrique nous portent à considerer la partie inferieure du tronc cérébral comme lieu d'action possible du Sernyl.

Par ailleurs, il ne nous semble pas que le Sernyl puisse être considéré comme un psychotomimetique ou un schizo-phrénomimetique au vrai sens du terme, bien qu'il produise chez le malade mental un tableau rappelant dans une certaine mesure les symptômes primaires de la schizophrénie.—Ajoutons enfin que ce produit ne nous semble posséder aucune valeur thérapeutique particulière, du moins dans l'état actuel de nos connaissances.

