OBSERVATION ON TWO PSYCHOTOMIMETIC DRUGS OF PIPERIDINE DERIVATION—CI 395 (SERNYL) AND CI 400 [1]

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This report describes the sensory blocking action of two anaesthetic drugs CI 395 and CI 400. CI 395 is Sernyl :—1—(1-phenylcyclohexyl) piperidine monohydrochloride, and CI 400 which is N-ethyl—1 phenylcyclohexylamine monohydrochloride. The phenylcyclohexyl nucleus is common to both drugs.

PROCEDURE

Four schizophrenic and 14 patients with mixed psychoneurosis were given both drugs in dosage of 0.05 to 0.2 mg. per kg. of body weight. Intravenous injections produced the most striking effects within minutes ; intramuscular injections were less marked but more prolonged ; oral administration was least effective.

Sernyl produced tachycardia, sweating, excessive salivation, disturbances of consciousness, cerebellar signs, motor effects, loss of deep pain sensation and anaesthesia. These changes were mild or absent with CI 400, which caused disorder of thought with apathy but no body-image disturbance. Both drugs produced mild hypertension.

With Sernyl psychoneurotic patients showed apathy, then anxiety, followed by disturbance of body-image, feelings of unreality and depersonalization, together with thought disorder, disorganization of intellectual processes and difficulty of comprehension.

Two patients became hostile and paranoid and one experienced auditory hallucinations. Euphoria occurred in 6 patients after intravenous injection.

The body-image disturbance which occurred in all patients was well recalled after effects of Sernyl had disappeared. Feelings of "floating in outer space" were frequently described. A tendency for patients to maintain catatonic limb postures was present with Sernyl and absent with CI 400.

Chlorpromazine, 50 mg. intramuscularly seemed to antagonize the psychotomimetic effects of Sernyl and produced a return to normal body-image.

In the 4 schizophrenic patients, Sernyl produced an increase in the schizophrenic symptoms with exaggeration of thought block, body-image disturbance and depersonalization. Two of these patients who received LSD 25 previously, described their reaction to Sernyl as different to LSD 25. CI 400 on the other hand, produced an alleviation of symptoms and mild clinical improvement.

COMMENTS AND SUMMARY

Based on the work of Elkes and Shore, Sernyl appears to exert its action by the release of adrenaline and noradrenaline in association with the depression of the availability of serotonin in the brain. This is consistent with Brodie's hypothesis(1) that serotonin and noradrenaline are antagonistic chemical mediators regulating the central autonomic system.

The importance of kinaesthetic input in preserving the intactness of the body-image is well recognized in studies of the effects of sensory deprivation(2). Nocturnal delusions of the senium due to loss of familiarity with surroundings is also a well recognized phenomenon(3). Hence, disturbance of kinaesthetic input, whether taking place primarily within the brain, due to externally administered agents such as CI 395, or outside the brain as in sensory deprivation, leads to psychotic behaviour with features similar to schizophrenia. "Information input underload" and the disturbance of coding or integration of sensory stimuli at a higher level may be the possible cause of psychotic behaviour.

The reversibility of the psychotomimetic effects produced by Sernyl with chlorpro-

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mazine, suggests a common mechanism with that seen in temporary psychotic states, such as acute paranoid or schizophrenic reactions. This would support the tentative hypothesis of Luby and associates(4) "that certain primary symptoms of schizophrenia may have their basis in a dys-synchrony or defect in proprioceptive feedback."

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REPORT OF HYPOMANIC EXCITEMENT WITH IMIPRAMINE TREATMENT OF DEPRESSION

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With the recent flood of anti-depressive drugs, many reports have appeared concerning their physical side-effects and toxicity. But the psychic side-effects need to be kept in mind because they can create serious problems requiring hospitalization or other immediate treatment. Psychomotor and psychological changes of a pathological sort, in fact, have been mentioned briefly in earlier articles on imipramine. Lehmann reports visual hallucinations or hypomanic excitement appearing in 7 of 84 patients treated with that drug(1). The commercial description of imipramine lists agitation as the commonest side-effect requiring discontinuance of therapy—25 times more common than any other psychic or physical reaction(2). Azima describes elation or hypomania in 10 patients out of 145 given the drug(3).

This paper deals specifically with the occurrence of hypomania during imipramine treatment. At this hospital, 88 patients have been given imipramine in the usual dosages. Among these, 6 instances of hypomanic excitement appeared, with such typical features as elated mood, grandiose schemes, pressure of speech, restlessness, and combativeness. In some instances this behavior stopped a few days after the drug was stopped ; in other patients, it continued for more than 8 weeks after stopping imipramine. A patient report follows :

A 58-year-old white woman became gloomy, apathetic, unable to do household tasks, anorexic, sleepless, and suicidal beginning in June, 1958. She lost 30 pounds and became more depressed in spite of treatment with a combination of amphetamine and amobarbital. No previous episodes of depression or hypomania were admitted. When first seen in the outpatient department, in June, 1959, she was given imipramine 25 mgm. q.i.d., and in two or three days rapidly changed. She visited and irritated others by her excessive enthusiasm and constant calls, and was admitted to hospital on July 2, 1959. Imipramine was discontinued and the ward physician gave her large doses of trifluoperazine for her overactivity. By July 7, she showed extrapyramidal signs, but was still over-talkative, distractible, and verbosely enthusiastic for the hospital and the staff. An EEG and routine laboratory tests were normal. Psychological test performance was impaired by her inability to sit still and finish ; the tests showed euphoria, defects of attention, flight of ideas, and pressure of speech. On July 17, psychological tests still showed minimal organic changes and the defects of attention noted ten days earlier. Proclorperazine was substituted as the patient became calmer, but even when discharged on September 4, she still showed signs of hypomania, although no longer taking imipramine for two months.

This case illustrates several important problems in imipramine treatment. Is the hypomania a drug-induced reaction, or is it merely a variant, an equivalent of the depression ? Is this altered behavior truly a side-effect of the drug, or, since it continued long after imipramine was stopped, merely another pathological expression of the same basic excess of anxiety, permitted or provoked by the effect of imipramine ?

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