CLINICAL EVALUATION OF A NEW SEDATIVE-HYPNOTIC (3,3-DIETHYL-2,4-DIOXOTETRAHYDROPYRIDINE) IN PSYCHIATRIC CONDITIONS

BY PHILLIP POLATIN, M. D., AND WILLIAM A. HORWITZ, M. D.

Barbiturate medication has been and is being widely prescribed to calm "nervousness" and to induce sleep. Patients frequently disregard the physician's directions and take unduly large doses of these drugs, and this may lead to barbiturate intoxication. These compounds as a group are now the most common suicidal poisons, excepting carbon monoxide. According to Hambourger the national incidence of suicide by means of barbiturates (1932-1936) is 4.2 per cent of that for all poisons (except gases) and the incidence in large cities ranges from 2 to 16 per cent. The fatality rate in hospitalized cases of acute barbiturate poisoning is over 7 per cent, and may rise to 15 per cent in severely poisoned cases.

In many instances, especially in patients with a neurotic disposition, the use of a sedative or hypnotic may become habitual and often lead to frank addiction. The survey by Hambourger, in 1940, indicates that, exclusive of alcohol, barbiturates constituted 10 per cent of all addiction cases admitted to the selected group of larger general hospitals. The incidence of barbiturate addiction in the general population is difficult to evaluate, except by the drug's widespread consumption, although a large part of this may be by occasional rather than habitual users.

Furthermore, in some patients, even after moderate doses of barbiturates, side reactions occur, such as headache, drowsiness or lassitude on awakening, or skin eruptions.

As a consequence of these difficulties, any new drug which offers favorable sedative-hypnotic effects without the disadvantages of the barbiturates would be a welcome addition to the armamentarium of the physician, especially of the neurologist and psychiatrist.

With this in mind, we have undertaken the clinical evaluation of an experimental sedative-hypnotic* submitted to us under the designation of NU-903 and which seemed to offer certain advantages over the barbiturates, as judged by pharmacological findings.

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The drug under consideration is 3,3-diethyl-2,4-dioxotetrahydro-
pyridine and has the structural formula shown in the accompanying diagram.

The substance occurs in the form of colorless crystals, melting at 98° C., is soluble up to 2.5 per cent in water and readily soluble in alcohol, ether, chloroform, glycerin and olive oil.

The pharmacology of the compound has been adequately described by Koppanyi, Herwick, Linegar and Foster. From the wealth of findings presented by these investigators the following data are of particular interest. The drug is characterized as a central nervous system depressant which produces, in appropriate doses, motor paralysis, muscular relaxation, loss of righting reflexes, and deep sleep. The LD50 (lethal dose for 50 per cent of the animals) intravenously for rabbits was 350 mg./kg. The ND50 (narcotic dose for 50 per cent of the animals) intravenously for rabbits was 86 mg./kg. Hence the narcotic index (LD50/ND50) of the pyridine derivative is 4.07, whereas with barbital the safety margin is less, giving an index of 2.96.

There were no manifestations of toxicity when the drug was fed to rabbits daily (for six days out of seven) at doses ranging from 15-400 mg./kg. for from 25 to 86 days. The experimental animals showed no deviations from normal in general appearance and food consumption. Furthermore, there was no evidence of development of tolerance, sensitization or addiction and changes in the blood picture were within normal limits. Similarly, the drug did not produce any detectable histological changes in these animals.

The onset of action in rabbits following intravenous administration of the drug was very rapid (about two minutes after injection), and the duration of action was relatively short. In general it is true that the quick-acting hypnotics have a greater safety margin. In agreement with this, the relative order of safety was found to be: pyridine derivative > barbital. The experimental compound was readily absorbed from the gastro-intestinal tract, the subcutaneous tissues, and the peritoneal cavity. The rate of