of a common channel at the sphincter of Oddi is occasionally seen in patients with biliary tract disease. Perfusion of the common bile duct with this solution demonstrated relatively little digestion ranging from 0 to 2 + (Table I C) over the 2-hour period of the study. On one occasion a 3 + erosion was noted. Whether one or both of the major hepatic ducts were ligated did not appear to influence the degree of digestive changes.

Summary. 1. The glandular mucosa of common bile duct shows a sensitivity to acid-peptic digestion at least as great as that of the esophagus. 2. Admixture of bile and pancreatic juice incubated from ½ to 48 hours failed to demonstrate evidence of digestive injury to either the common bile duct or the esophagus during a 2-hour period of perfusion. 3. There would appear to be a possibility that acid-peptic erosion of the biliary papilla may play a role in the genesis of stricture of the bile duct in some disease states.

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Tolerance and Withdrawal Hyperexcitability Induced in Mice by Chronic Administration of Phenaglycodol.* (23707)

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Several clinical reports(1-5) reveal that abrupt withdrawal of meprobamate (Miltown, Equanil) medication in patients who have ingested large doses of this drug may precipitate nervousness, insomnia, and convulsions. Work in our laboratories(6) indicates that tolerance and withdrawal hyperexcitability result from chronic administration of large doses of meprobamate to mice, as measured by the technic of McQuarrie and Fingl(7). Tolerance and withdrawal convulsions were also observed to occur after administration of large doses of this drug in dogs, by Essig and Ainslie(4). Since both meprobamate and phenaglycodol (Ultran) are substituted propanediols and have similar pharmacological activities in experimental animals(8,9), it was of interest to determine the effect of chronic administration of large doses of phenaglycodol and of its subsequent abrupt withdrawal on central nervous excitability in mice. In the absence of positive evidence that this drug induces tolerance and physical dependence in man, it was anticipated that such a study might predict the effects of abrupt withdrawal of phenaglycodol in patients who have been chronically ingesting large doses. The results obtained provide the basis for this report.

Methods. Male albino mice (Carworth Farms, CF #1 strain, 21 to 32 g in weight) were randomly divided into 2 groups of 50 animals each. Phenaglycodol† was administered orally to one group as a 2 or 3% suspension in 6% acacia solution, in a total daily dose of 600 mg/kg (200 mg/kg at 7 a. m., 3 p. m., and 12 midnight) for 6 days. Because of the development of tolerance, following the 7 a. m. treatment on day 7 each dose was increased by 50% to make a total daily dose of 900 mg/kg; this higher daily

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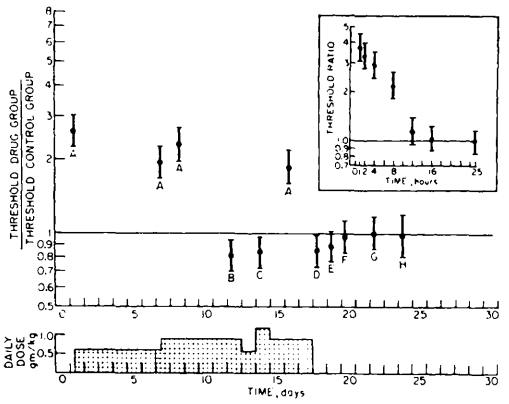

FIG. 1. Effects of chronic administration of phenaglycodol (Ultran) on threshold for low-frequency electroshock seizures in mice. Time in days is indicated on the abscissa. Seizure threshold ratio (threshold drug group/threshold control group) is shown on upper ordinate and total daily dose of phenaglycodol administered is shown below. Vertical bracketed lines indicate 95% fiducial limits. A, ratio 1 hour after a 7 a.m. dose; B, ratio 8 hours after the 11 p.m. dose; C, ratio 16 hours after the 3 p.m. dose. Following the 16-hour interval, the animals were given a double dose in order to maintain the average daily dose of 900 mg/kg. D, E, F, G, and H, ratios at 8, 32, 56, 104, and 152 hours, respectively, after the final dose of drug. The inset illustrates the duration (hours) of the effect of a single dose of phenaglycodol (300 mg/kg) on seizure threshold in nontolerant mice.

dosage was continued for 11 days, except as indicated in Fig. 1. The other group served as a control and was given the requisite volume of 6% acacia solution at the appropriate intervals. Low-frequency electroshock seizure threshold was determined for both groups at the times indicated in the legend to Fig. 1. Seizures were induced through corneal electrodes by means of a Grass stimulator (model S4B). The stimulus parameters employed were the same as those previously described (10), namely, unidirectional pulses of 0.2 msec. duration delivered for 3 seconds at a frequency of 6 pulses per second. The mice were shocked at various voltages which were selected by the staircase procedure(11), and the voltage required to evoke convulsions in 50% of each group was determined; the 95% fiducial limits were calculated by the method of Litchfield and Wilcoxon(12). Results are presented as the threshold ratio (threshold of drug group/threshold of control group). In a separate series of experiments, 80 mice were divided into 2 equal groups. One group was given orally 300 mg/kg of phenaglycodol, the other group the requisite volume of 6% acacia solution; the seizure threshold of each group was determined 1 hour after drug administration. This procedure was repeated at intervals of 4 to 9 days in the same group of mice until the seizure threshold was established at 1, 2, 4, 8, 12, 16, and 25 hours after drug administration.

Results. Administration of a single 300 mg/kg dose of phenaglycodol to nontolerant animals increased the threshold 3.7-fold (see inset, Fig. 1), whereas, after treatment for 6 days with 600 mg/kg/day, and then for 11 days with 900 mg/kg/day, this drug increased the threshold only 1.9-fold (see A, day 16, Fig. 1). Thus, tolerance develops to the threshold-raising effect of phenaglycodol.

The figure also shows that, 8 hours after the 11 p.m. dose on day 11, 16 hours after the 3 p. m. dose on day 13, and 8 hours after the final dose on day 17 (see B, C, and D, Fig. 1), the seizure threshold in phenaglycodol-treated mice was only 0.81, 0.84, and 0.85, respectively, that of control animals. Since the seizure threshold 8 hours after administration of a single dose of 300 mg/kg to nontolerant animals was still 2.19-fold that of control mice (see inset, Fig. 1), the reduction in threshold observed in tolerant animals must be attributed to the chronic administration of phenaglycodol.

Discussion. Since the objectives of this study were to determine whether tolerance develops during chronic administration of phenaglycodol and whether abrupt withdrawal is followed by increased excitability of the central nervous system, only high dose levels of phenaglycodol were employed. The use of large doses is also justified on the basis that excessive amounts are taken by patients who abuse drugs and such quantities are usually necessary to demonstrate physical dependence on ethanol and barbiturates in man(13,14).

The data presented indicate that tolerance and withdrawal hyperexcitability follow chronic administration of large doses of phenaglycodol to mice. Tolerance is shown by the fact that the threshold-raising effect of phenaglycodol is reduced by 50% in animals receiving the drug chronically. Withdrawal hyperexcitability is shown by the fact that

8 hours after the 11 p. m. dose on day 11 and 8 hours after the final dose on day 17 (see B and D, Fig. 1), the seizure threshold in phenaglycodol-treated mice was only 0.81 and 0.85, respectively, that of control animals; a similar decrease in threshold was also observed 16 hours after the 3 p. m. dose on day 13 (see C, Fig. 1). Since seizure threshold is still elevated 8 hours after the single administration of this same dose of phenaglycodol to nontolerant animals, it must be concluded that the reduction in threshold represents withdrawal hyperexcitability attributable to the chronic administration of this agent.

Because of their common chemical derivation and similar pharmacological properties, it is of interest to compare meprobamate and phenaglycodol for ability to induce tolerance and withdrawal hyperexcitability in mice. With regard to tolerance, previous work in our laboratories(6) has shown that the threshold-raising effect of 300 mg/kg of meprobamate is reduced by at least 75% in animals treated for 6 days with 1200 mg/kg/day and for 10 days with 1800 mg/kg/day. The data presented in this study indicate that the threshold-raising effect of 300 mg/kg of phenaglycodol is reduced by 50% in animals treated for 6 days with 600 mg/kg/day and for 11 days with 900 mg/kg/day. With regard to withdrawal effects, hyperexcitability in mice following the chronic administration of meprobamate is detectable 4 and 8 hours after drug withdrawal and subsides within 28 hours(6). In the present studies, hyperexcitability in mice following chronic administration of phenaglycodol is detectable 8 and 16 hours after drug withdrawal and subsides within 32 hours. Thus, there is considerable similarity both in the extent of the tolerance developed during chronic administration of these agents and in the time course of the hyperexcitability following their abrupt withdrawal.

In view of the above observations, certain clinical implications require mention. The similarity in the withdrawal hyperexcitability induced in mice by the chronic administration of either phenaglycodol or meprobamate and the evidence that continued ingestion of large doses of meprobamate can cause physical dependence in both animals and man(6,4) suggest that phenaglycodol should be held suspect, even though there have as yet been no clinical reports describing physical dependence to this drug. It is possible that patients taking large doses of the drug for extended periods of time may exhibit withdrawal effects which the physician may erroneously interpret as due to a return of pre-treatment symptoms. The drug should not be used for trivial complaints and the dose should not be excessive. Precautions should be taken in patients to minimize both the possibility of development of physical dependence on phenaglycodol and the possibility of a withdrawal syndrome. Thus, large doses of phenaglycodol should be avoided if possible, and the drug should be withdrawn slowly, rather than abruptly, from patients who have been ingesting large doses chronically.

These data and those previously reported for ethanol and meprobamate(7,6) indicate that the technics employed herein may be useful as a presumptive test for screening candidate drugs for physical dependence liability. Although preliminary data are in agreement with this suggestion, the predictive value of this test can only be determined after more laboratory and clinical results have been accumulated on a larger number of centrally active drugs

Summary. Tolerance and withdrawal hyperexcitability were observed to follow the chronic administration of large doses of phenaglycodol (Ultran) in mice. Tolerance was shown by the fact that the threshold-raising effect of this agent is reduced by 50%, as measured by the low-frequency electroshock technic. Withdrawal hyperexcitability was shown by the fact that, 8 hours after the final dose of phenaglycodol, the seizure threshold is reduced by approximately 20%. The clinical implications of these observations are discussed.

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