dicates a decreased metabolism or an increased "binding" of 5-HT (*6*). Determination of the effects of Δ^9-THC on more refined parameters of amine metabolism, such as turnover, uptake at nerve endings, and localization in critical regional or subcellular compartments, is obviously required to differentiate the various psychoactive drugs which influence brain amine metabolism. For instance, the 5-HT changes should not be interpreted as a specific effect upon 5-HT receptors. The changes reported, although reliable (*15*) and significant, are quite variable and could conceivably be a pharmacologically nonspecific effect and due to stress or stimulation (*16*). Our results indicate that the Δ^9-isomer of tetrahydrocannabinol does produce many of the effects of marihuana in animals, as it does in humans.

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4. Early experiments were performed with a purified extract of marihuana. This extract consisted primarily of Δ^9-THC (approximately 98 percent by weight); by thin-layer chromatography, it was shown also to contain small amounts of two other tetrahydrocannabinol isomers and the other constituents of marihuana which have been described [F. Korte and H. Sieper, *J. Chromatogr.* **13**, 90 (1964)]. The majority of the experiments reported here were carried out with synthetic Δ^9-tetrahydrocannabinol, the purity of which was verified by thin-layer chromatography, according to the procedure of F. Korte and H. Sieper [*J. Chromatogr.* **13**, 90 (1964); *ibid.* **14**, 178 (1965)]. The results of experiments with the Δ^9-THC were quantitatively comparable with respect to effects on behavior and concentration of amine in the brains of mice.
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Alcohol and Amitriptyline Effects on Skills Related to Driving Behavior

Abstract. *Three motor-skill tests related to driving ability were given to 21 healthy young volunteers after administration of various combinations of amitriptyline, placebo, and alcohol. It was found that the tricylic antidepressant added to the deleterious effects of alcohol.*

Drugs which act on the central nervous system are being ever more widely prescribed (*1*), and it has been shown that chlorpromazine has a supplementary and possibly potentiating effect on the impairment of coordination and judgment produced by alcohol (*2*). Although an initial moderate dose of either chlordiazepoxide or meprobamate does not significantly potentiate the effects of alcohol (*3*), there is still little information available concerning the interaction of most prescribed psychotropic drugs with alcohol. Since animal studies indicate that antidepressants may add to the effects of alcohol (*4*), the effects of amitriptyline (a commonly prescribed antidepressant) and alcohol on some skills related to driving behavior were tested in humans.

Healthy medical students (18 men and 3 women; mean age 22.14 years, S.D. = 1.15) volunteered as subjects. Full blood counts and liver function tests were performed on each subject before and after the experiment; no subject on any medication or with a history of recent illness or liver disease was accepted. They were cautioned against drinking and driving for several days after.

The subjects were randomly placed in one of three groups of seven subjects each; however, one woman was allocated to each group. Group A received amitriptyline twice; the first dose on the night before and the second on the morning of the day on which the tests were administered (interval, 12 to 15 hours). Group B received placebo at night and amitriptyline on the test day. Group C received placebo tablets on both occasions. A double-blind technique was used for drug administration and for the recording and scoring of test results. Amitriptyline (0.8 mg per kilogram of body weight) was given in tablet form for each dose.

After a medical examination on the morning of the test day, the subjects received their second issue of tablets, and 2 hours later they were tested with three motor-skill tests given in random order.

The simulated driving task was a modification of a test designed by Gibbs (*5*). The subject was seated before a steering wheel and required to move a pointer to a position in line with one of five horizontal lights placed at eye level. These lights flash on in a random order for 1.27 seconds, and the pointer has to be steered from one light to another as they go on in turn. This tedious and repetitive task is designed to show up the effects of fatigue. Only errors were scored, that is, movements in the wrong direction, omissions, and inadequate or otherwise incorrect steering of the pointer. The test lasted 12 minutes, but only the last 150 seconds were scored. Pen-recording equipment and the observer were based in a room separated from the subject by a one-way screen.

The dot-tracking test required a continuous line to be drawn between small dots that were arranged in an irregular

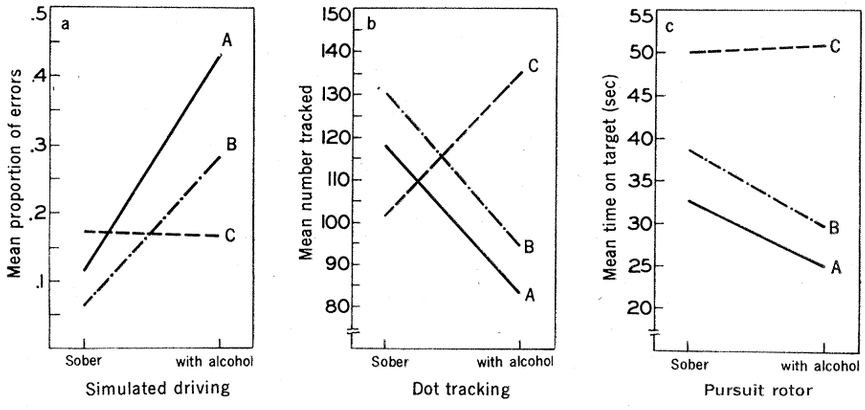

Fig. 1. Mean scores for each motor-skill test before and after alcohol intake. A separate line has been drawn for each condition of drug administration. Drug/drug group (A); placebo/drug group (B); and placebo/placebo group (C).

spiral pattern. The spiral pattern was attached to a slowly rotating turntable, and the subject tracked the dots with a pen through a small aperture cut into the cover of the apparatus. The pattern had to be tracked from the center to the periphery, thus gradually increasing response speed.

The third task was the pursuit rotor test. Near the periphery of a plastic turntable (307 mm in diameter) a metal disk (19 mm) is attached. The turntable rotates at 50 rev/min, and the subject is asked to keep a loose-handled stylus in contact with the metal disk. Every subject was given ten trials of 10-second duration. Two seconds of practice were allowed, and the intertrial interval was 28 seconds. Time on target was electrically recorded.

After completing the tests, subjects were asked to drink their preferred alcoholic beverage over a period of 30 to 45 minutes. Beer, brandy, whisky, and wine were provided; subjects who drank spirits usually diluted their drinks. The amount of liquor given to each subject was meant to be intoxicating and was calculated on the basis of the subject's body weight so as to bring blood alcohol level to approximately 0.08 percent. Fifteen minutes after a subject had stopped drinking, a Breathalyzer test was administered and the tests were repeated. After a meal, coffee, and rest, the subjects were again medically examined, asked to answer a questionnaire, and taken to their homes. Throughout their time in the laboratory hourly checks were made of the subjects' blood pressures and pulse rates.

The proportion of errors to total recorded responses made was used as the score in the simulated driving test; the number of dots tracked accurately was the score in the dot-tracking task; and the total time on target was the score in the pursuit rotor task. The data were tested for statistical significance by analysis of variance.

No significant variations from normal values were found for any of the blood tests or other physiological measures. The mean Breathalyzer reading was 0.093 percent (S.D. = 0.035) (*6*).

The simulated driving test showed that when the subjects were sober the means of the proportions of errors made did not differ significantly between the three treatment groups ($F = 1.263$, d.f. $= 2/18$, $P > .1$). Alcohol consumption did not result in a higher error score by subjects of group C (double placebo condition), but did interact significantly with amitriptyline ($P < .01$). Group B (placebo/amitriptyline condition) had a mean proportion of errors of 0.064 when sober and 0.280 after alcohol ($P < .05$). Group A (double amitriptyline condition) had a mean error score of 0.113 when sober and 0.434 after alcohol ($P < .01$) (Fig. 1a).

In the dot-tracking test, the mean scores of the three groups did not differ significantly when sober ($F = 0.782$, d.f. $= 2/18$, $P > .1$). Subjects in group C showed a practice effect; their mean score after alcohol consumption was 135.0, but it was only 101.1 when they first attempted this task. Subjects given amitriptyline showed a reversal of this trend; the amitriptyline-alcohol interaction completely overcame the practice effect. The mean score for group B was 130.2 when sober and 94.3 after alcohol, whereas for group A the mean scores were 118.0 and 82.9, respectively. This significant interaction effect ($F = 10.086$, d.f. $= 2/18$, $P < .01$) is shown in Fig. 1b.

The results of the pursuit rotor test are shown in Fig. 1c. A statistical evaluation of the data after a logarithmic transformation showed that mean time on target differed significantly between the three experimental groups ($F = 3.752$, d.f. $= 2/18$, $P < .05$) and between conditions of alcohol intake ($F = 6.006$, d.f. $= 2/18$, $P < .05$). The interaction effect approaches statistical significance ($F = 3.034$, d.f. $= 2/18$, $P < .1$).

The results indicate that amitriptyline, a tricylic antidepressant commonly prescribed for out-patients, potentiates the effects of alcohol as judged by performance of subjects given three motor-skill tests related to driving. The interaction was significant after only a single dose of amitriptyline and especially pronounced after two doses. Since it has been found (*7*) that after 3 or 4 days of medication the combined effect of amitriptyline and alcohol does not seriously affect motor skills identical to those used in this study, it seems likely that the patient's chief hazard is during the first day or two of therapy.

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