**Effects of inhibition and induction of the liver microsomal enzyme system on the narcotic activity of ethanol in mice**

SIR,—It is generally accepted that ethanol is largely metabolized in the liver by alcohol dehydrogenase. However, Forney, Hughes, Hulpieu & Clark (1962) have reported that ethanol is metabolized more rapidly during the first 30 min after administration than during subsequent 30 min periods, and they have discussed the possibility that this could be because during this time ethanol is not metabolized by the dehydrogenase route alone, but also by the liver microsomal enzyme system. This has also been suggested from results of *in vitro* experiments (Orme-Johnson & Ziegler, 1965). We therefore considered the possibility that drugs known to affect this microsomal enzyme system, either by inhibiting or inducing activity, might thereby alter the pharmacological effectiveness of ethanol. Induction of ethanol-metabolizing activity of liver slices has recently been reported as a result of prior treatment with ethanol (Ryan & Cornish, 1966).

A series of experiments was made to determine the effect of various pretreatments on the narcotic activity of ethanol in mice as measured by the sleeping time. Groups of 10 Schneider female mice were used for each treatment and they were kept at 32° throughout the experiment, sleeping times being measured at this temperature. Ethanol was injected intraperitoneally as 20% v/v solution in water.

An inhibitor of liver microsomal enzymes, SKF 525A (β-diethylaminoethyl-diphenylpropyl acetate) (Brodie 1956), injected in a dose of 25 mg/kg intraperitoneally 45 min before the ethanol, resulted in a fourfold prolongation of sleeping time, a potentiation which was significant at the 95% probability level (Table 1). This was associated with a potency increase of 1·1 (1·083–1·139).

TABLE 1. THE PROLONGATION OF ETHANOL SLEEPING TIME IN MICE BY SKF 525A, 25 MG/KG I.P.

| Treatment | Ethanol, g/kg i.p. | Sleeping time, min |
|---|---|---|
| SKF 525A + ethanol | 4·5 | 11·3 ± 2·5 |
| SKF 525A + ethanol | 5·0 | 30·5 ± 3·6 |
| Ethanol only | 5·0 | 7·0 ± 1·1 |
| Ethanol only | 5·25 | 24·0 ± 3·9 |

TABLE 2. EFFECT OF OVERNIGHT PRETREATMENT WITH VARIOUS DRUGS ON THE SLEEPING TIME DUE TO ETHANOL IN MICE

| Pretreatment | | | Sleeping time, min | |
|---|---|---|---|---|
| Drug | Dose mg/kg i.p. | Ethanol g/kg i.p. | Treated | Control |
| Chlorpromazine .. | 2 | 5·5 | 18·7 ± 3·2 | 43·5 ± 6·1 |
| Pentobarbitone .. | 50 | 5·5 | 22·4 ± 4·7 | 43·5 ± 6·1 |
| Amitriptyline .. | 10 | 5·75 | 43·0 ± 5·9 | 35·4 ± 6·4 |
| Amitriptyline .. | 20 | 5·75 | 10·9 ± 3·3 | 44·7 ± 6·4 |
| Imipramine .. | 40 | 5·75 | 26·3 ± 4·5 | 34·6 ± 7·6 |

The great increase in sleeping time associated with only a 10% increase in potency reflects the steepness of the dose-response relation for ethanol in mice (Fig. 1). Thus, only a small alteration in enzyme activity is necessary to alter considerably the effectiveness of ethanol.

Numerous agents have been shown to induce liver microsomal enzyme activity, attenuating the effectiveness of other drugs metabolized by this system (Fouts, 1965). These inducing agents include barbiturates and chlorpromazine (Kato & Chiesara 1962). These drugs were given as a pretreatment 21 hr before ethanol in an attempt to affect the sleeping times by enzyme induction (Table 2).

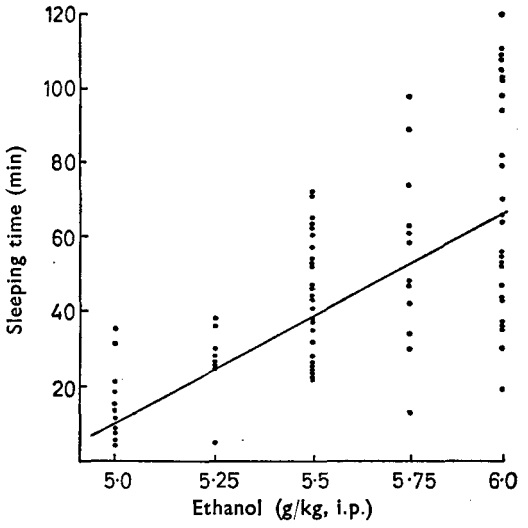


FIG. 1. The sleeping time, in min, of mice injected intraperitoneally with various doses (g/kg) of ethanol in 20% v/v solution in water. Slope of log dose-response relation, $b = 710$; $S_b = 78{\cdot}1$; $P < 0{\cdot}001$ ($n = 120$).

The sleeping time due to ethanol was much shortened by pretreatment with chlorpromazine, 2 mg/kg, and pentobarbitone, 50 mg/kg. Amitriptyline at 20 mg/kg also shortened ethanol sleeping times in mice although imipramine at 40 mg/kg did not cause a significant effect. Kato & Chiesara (1962) reported that imipramine (dose not stated) did not shorten pentobarbitone sleeping time in rats. We have found however, (unpublished) that both imipramine at 5 mg/kg, i.p. and amitriptyline at 20 mg/kg, shortened pentobarbitone sleeping times in mice.

These results support the suggestion that the non-specific oxidizing enzyme system of the liver microsomes contributes to inactivation of ethanol in mice and that agents known to inhibit or induce the activity of this system can cause significant potentiation or reduction in the narcotic effectiveness of ethanol.

Pharmacological Laboratory,
Research Department,
Roche Products Ltd.,
Welwyn Garden City,
Herts.

NORMA LIND
M. W. PARKES

November 3, 1966

## References

Brodie, B. B. (1956). *J. Pharm. Pharmac.*, **7**, 1–17.
Forney, R. B., Hughes, F. W., Hulpieu, H. R. & Clark, W. C. (1962). *Toxic. appl. Pharmac.*, **4**, 253–256.
Fouts, J. R. (1965). *Drugs & Enzymes.* pp. 261–276, editors, Brodie, B. B. & Gillette, J. R., London: Pergamon.
Kato, R. & Chiesara, E. (1962). *Br. J. Pharmac. Chemother.*, **18**, 29–38.
Orme-Johnson, W. H. & Ziegler, D. M. (1965). *Biochem. Biophys. Res. Comm.*, **21**, 78–82.
Ryan, R. C. & Cornish, H. H. (1966). *Toxic. appl. Pharmac.*, **8**, 352–353.