extraneuronal non-specifically bound ^{3}H-NA, since the same phenomenon was not observed with ^{3}H-MA. The decline in outflow of ^{3}H-NA cannot be due to lack of this amine in the artery since 91% of ^{3}H-NA remained in the vessel after the first period of stimulation. The difference between outflow of ^{3}H-NA and ^{3}H-MA is probably not due to the use of stereoisomers with different optic activity ((−)-isomer of ^{3}H-NA and (±)-isomer of ^{3}H-MA), since the outflow of (−)- and (±)-isomers of ^{3}H-NA was the same (unpublished). We confirmed the observation (Su & Bevan, 1970) that there is a clear dissociation between the stimulus-induced ^{3}H-NA outflow and contraction height (Fig. 1). While the former decreased, the latter remained constant with repeated stimulation. This was not the case with ^{3}H-MA. These results indicate that the ratio tritium outflow/endogenous non-radioactive noradrenaline is variable for tissue preloaded with ^{3}H-NA but constant for that preincubated with ^{3}H-MA.

Tyramine (10^{-4}M) released ^{3}H-NA and ^{3}H-MA (Fig. 1). Tyramine-induced outflow of these [^{3}H] amines was much higher (up to 138 times) than that seen with field stimulation (Table 1). In contrast to the latter treatment (first period of stimulation) tyramine caused a higher (about 3 times) outflow of ^{3}H-MA than of ^{3}H-NA. This may possibly in part be due to a difference in intraneuronal disposition of these [^{3}H] amines. The tyramine-induced outflow of [^{3}H] amines and contraction height showed an inverse relation (Fig. 1).

The present results indicate that the differences in release of ^{3}H-NA and ^{3}H-MA must be taken into account when metaraminol is used instead of noradrenaline as an experimental tool.

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Myocardial depressant action of ethyl acetate

Ethyl acetate is one of the most frequently used organic solvents (see, for example, Deichmann & Gerarde, 1969), but in spite of its extensive use and its not infrequent abuse (Smart, Fejer & Alexander, 1972), information on its toxicological properties is scanty (Beintker, 1928; Smyth & Smyth, 1928; Blina, 1933; Mancini, Noferi & others, 1943).

We have investigated the effect of ethyl acetate on myocardial contractility in guinea-pig isolated ventricular strips to compare its toxicity with that of ethanol.

Guinea-pigs of either sex, of about 500 g, were killed by cervical dislocation. The hearts were removed immediately and the right ventricle excised. The ventricular strip (1 × 10 mm) was suspended in a bath containing oxygenated Ringer-Locke solution (32°; pH 7·3) through which a gas mixture of 5% CO_2 in oxygen was bubbled

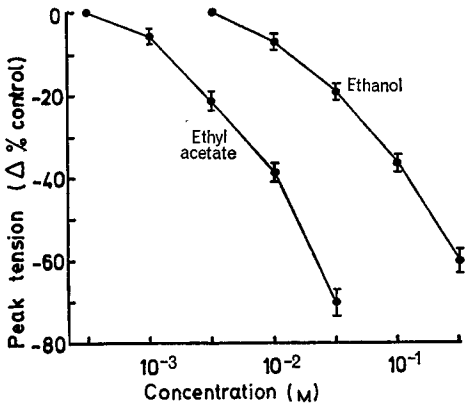

FIG. 1. Effect of graded concentrations of ethanol and ethyl acetate on the myocardial contractile force (peak tension) in the isolated guinea-pig ventricular strip. Each dot represents the mean value of the parameters. Standard errors of the means are indicated by vertical bars.

(Nakano, Holloway & Shackford, 1969). The frequency of ventricular contraction was maintained at a rate of 90 min^{-1} using a Grass stimulator (Model S4). The force of ventricular contraction was measured and recorded continuously using a Grass force-displacement transducer (FT-03), and a Grass polygraph (Model 5), respectively.

As summarized in Fig. 1, graded concentrations (3×10^{-2} to 3×10^{-1} M) of ethanol progressively depressed the peak tension control force ($0{\cdot}37 \pm 0{\cdot}02$ g) of ventricular strip contraction as the ethanol concentration increased. A qualitatively similar negative inotropic action was observed with graded concentrations of ethyl acetate. The magnitude of the myocardial depressant action of ethyl acetate was approximately 10 times greater than that of ethanol.

No information has been published previously on the cardiovascular toxicity of ethyl acetate in either animals or in man. We have found that ethyl acetate is a more potent cardiovascular depressant agent than ethanol on the guinea-pig ventricular strip. It has been well established that ethanol exerts a negative inotropic action in animals and in man (Gimeno, Gimeno & Webb, 1962; Spann, Mason & others, 1968; Nakano & others, 1969; Nakano & Moore, 1972). The precise biochemical mechanism responsible for the myocardial depressant action of either ethanol or ethyl acetate remains uncertain. However, it is conceivable that, being an excellent lipid solvent, ethyl acetate readily penetrates into the lipid layer of the cell membrane and interfers with cellular functions in the myocardium. In a preliminary study we have found that ouabain antagonizes the cardiovascular depressant action of ethyl acetate or ethanol in the guinea-pig ventricular strip preparation (Nakano & Moore, unpublished work).

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A simple screening test for drugs of potential use in ethanol withdrawal

Recently, models for ethanol dependence utilizing mice have been described and these are obviously of interest as screening tests for drugs which may be useful in the treatment of alcohol withdrawal. The administration of ethanol for several days followed by its withdrawal is associated with a characteristic syndrome (Freund, 1969; Goldstein & Pal, 1971; Griffiths, Littleton & Ortiz, 1973) which can be scored for severity in the way described by Goldstein (1972a). Many drugs which are currently used in therapy of ethanol withdrawal states also show effects in the animal model of withdrawal similar to those seen in the clinical condition (Goldstein, 1972b). We now wish to report that the acute administration of acetaldehyde to mice is associated with a transient behavioural change which shares many characteristics with the ethanol withdrawal syndrome and that this may serve as an alternative simple screening test.

The ethanol withdrawal syndrome in mice includes tremor, piloerection and convulsions on handling the animals. All these signs are shown after the injection of acetaldehyde (200 mg kg^{-1} i.p.) as illustrated in Fig. 1a. The peak intensity of ethanol withdrawal signs in mice occurs at a time when blood and brain ethanol concentrations are very low, similarly these aspects of the behavioural change after acetaldehyde occur at a time when blood and brain acetaldehyde concentrations have fallen to low levels (Fig. 1b).

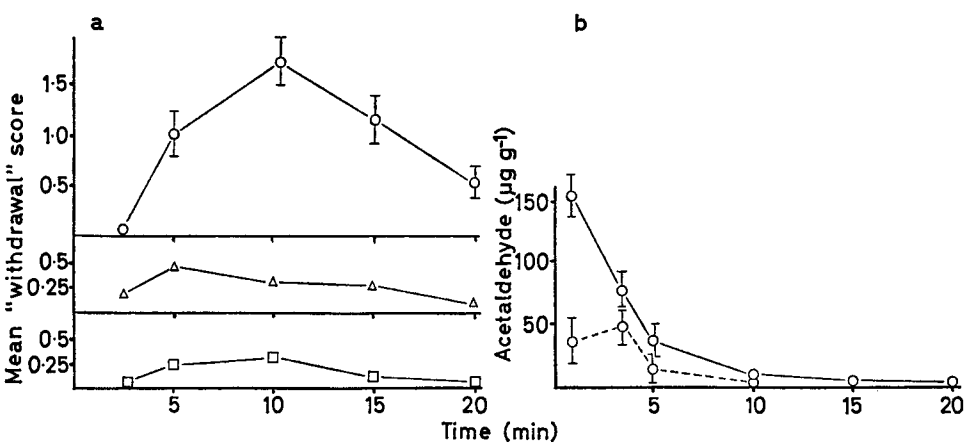

FIG. 1. (a) Behavioural change in mice after the administration of acetaldehyde (200 mg kg^{-1} i.p.). Male white mice (18–20 g) were used and the behavioural change was assessed in the way described by Goldstein & Pal (1971) and Goldstein (1971) ○, Handling convulsions; △, piloerection; □, tremor. Each point represents the mean score of 20 mice. Vertical bars represent standard errors.

(b) Blood and brain acetaldehyde concentrations in mice after the administration of acetaldehyde (200 mg kg^{-1} i.p.). Blood concentration (solid lines) and brain concentration (dotted lines) were measured in the way described by Griffiths & others (1974). Vertical bars represent standard errors of the mean of at least 5 determinations.