tested, had such acute-chronic differences. The latter drug could be compared with fluoxetine, also a selective serotonin uptake inhibitor, that following chronic treatment neither reduced the noradrenaline-sensitive adenylate-cyclase response[22] nor β-adrenergic receptor binding[23]. The correlation between pineal and plasma melatonin is useful in considering clinical studies. Although in the rat plasma melatonin appears to be entirely pineal in origin[24], this is not yet clarified for other species, including man. However, post-mortem pineal synthetic enzymes in man do follow the circadian pattern of circulating melatonin[25]. Thus, these animal data showing melatonin increase following the administration of antidepressant drugs, indicate the possible potential of plasma melatonin measurements in man.

A number of questions arise from these observations: is there a common mechanism of action of antidepressant drugs related to their ability to acutely elevate pineal melatonin? Is this elevation of melatonin related to their β-adrenergic agonist properties? If so, is β-adrenergic stimulation a necessary and/or sufficient pharmacological characteristic of an antidepressant drug, as has recently been suggested[26]? Furthermore, is the difference between chronic clomipramine, which reduced the pineal melatonin response, and L-5HTP and Ro 11-2465 which did not, meaningful with respect to differences in clinical antidepressant efficacy? The answers to these questions may lead to a better understanding of the mechanism of action of antidepressant drugs.

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Dexamethasone protection against the acute lethality of ethanol in mice[1]

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Summary. The administration of dexamethasone (DXM, 2.00 mg/kg) 1 h prior to the injection of lethal doses of ethanol was found to offer complete protection against ethanol toxicity at doses up to 5.25 g/kg and partial protection using higher doses. It is suggested that DXM central action might be involved in the protection against ethanol toxicity.

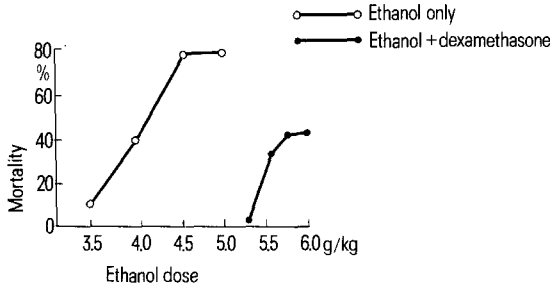
Ethanol toxicity in mice which is mainly due to respiratory depression[3], can be reversed by the administration of a β-adrenoceptive antagonist[3,4]. On the other hand dexamethasone (DXM) (9- α fluoro-16,α methyl prednisolone, DXM) was suggested to act via inhibiting β-receptors activity[5]. The reversal of ethanol central depression would imply therapeutic potential but β-antagonist usually have deterimental cardiovascular effects. Therefore, it was of interest to study the protective effect of a drug that antagonize ethanol toxicity with minimum side effects.

Materials and methods. In this experiment Swiss-Webster male mice, 25–35 g, had food and water available ad libitum. They were maintained under controlled temperature conditions (23±1 °C) and 12:12 light-dark cycle (lights were on 09.00 h). Animals were kept in these conditions for a period of at least 3 weeks prior to experimentation. Various doses of ethanol were chosen randomly in attempting to find the lethal dose. DXM (2.0 mg/kg, Sigma) was injected 1 h prior to the administration of ethanol. The vehicle for DXM was an equal mixture of propylene glycol and saline and was injected i.p. Likewise ethanol was diluted with saline and was injected using 25% ethanol concentration. Animals treated with ethanol was injected with DXM vehicle to be used as control. Animals were

observed following drug(s) administration and the counts were made of the numbers that died or recovered after a 24-h-period.

Results. The figure shows that pretreatment with DXM shifted the mortality rate curve to the right. Maximum mortality rate using ethanol alone reached 80% using 4.5 or 5 g/kg of ethanol. Meanwhile the mortality rate was 40% using 5.75 g/kg or 6 g/kg of ethanol in animals pretreated with DXM 1 h prior the administration of ethanol. The difference in mortality rate between the 2 groups was found to be significant ($p<0.01$). It is of interest to note that using ethanol alone there was a linear relationship between the mortality rate and doses ranged between 3.5 and 4.5 g/kg. The same relationship was obvious in the DXM pretreated mice with higher levels of ethanol (between 5.25 and 5.75 g/kg). The figure also shows that no mortality in DXM pretreated animals, treated with 5.25 g/kg of ethanol. Lower dosage proved to be not lethal in the pretreated animals.

Discussion. It is clear from these results that DXM administration to mice prior to ethanol injection protected the animals from the lethal effect of ethanol. Since ethanol toxicity is directly related to respiratory depression[3], it might be suggested that DXM offers this protection through its central action. The central action of DXM was reported earlier[6]. The action of DXM might be brough about through the β-antagonist properties of the drug[5], by modulating brain biogenic amines concentrations. An inverse relationship has been found between circulating glucocorticoid levels and brain serotonin levels[7,8]. Meanwhile, ethanol effect has been known to be related to the increase of norepinephrine level in different brain regions[9].



The effect of dexamethasone pretreatment on ethanol toxicity. Each point represents the results on 12 animals.

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N″-cyano-N-4-pyridyl-N′-1,2,2-trimethylpropylguanidine, monohydrate (P 1134): A new, potent vasodilator

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Summary. N″-cyano-N-4-pyridyl-N′-1,2,2-trimethylpropylguanidine, monohydrate (P 1134) is a new agent which induces a marked and sustained hypotensive response in normotensive and renal, neurogenic, and spontaneously hypertensive rats, as well as in normotensive and renal hypertensive dogs. The overall potency of this compound is 2–3 times greater than that of hydralazine. The fall of blood pressure is accompanied by an increase in heart rate and cardiac output and a decrease in total peripheral resistance. The hypotensive effect appears to be due primarily to a direct relaxant effect on vascular smooth muscle.

Recent effort has concentrated on the development of agents which lower blood pressure by relaxation of vascular smooth muscle. The resultant vascular effect may correct the major hemodynamic disturbance in most hypertensive patients, i.e. the marked elevation of vascular resistance, without adding further abnormalities – as, for example, depression of cardiac output or impairment of sympathetic activity[2].

Following the observation some years ago that certain N-alkyl-N′-pyridylthioureas possess pronounced hypotensive activity[3] a series of N-alkyl-N″-cyano-N′-pyridylguanidines were synthesized[4]. P 1134, racemic N″-cyano-N-4-pyridyl-N′-1,2,2-trimethylpropylguanidine, monohydrate is a member of this series (figure 1). The present report describes its cardiovascular effects.

Materials and methods. Blood pressure was measured in conscious rats by an indirect method, by application to the tail of the animals of a Gartner cuff connected to an 8000 BP recorder (W+W Electronic, Basel).

In conscious dogs the following parameters were measured: a) Blood pressure, by an indirect method using ultrasonic Doppler detection of caudal artery wall motion during deflation of an occlusive cuff with a manometer (Roche Arteriosonde 1010). Heart rate was simultaneously recorded. b) Cardiac output, according to the thermodilution method of Ganz et al.[5] by means of an Edwards Labs. model 9500 computer with a Swan-Ganz thermodilution catheter No. 93-118-7F inserted in a jugular vein. c) From the cardiac output (=CO, l/min) and the mean arterial blood pressure (=MABP, mmHg) mean total peripheral resistance (=MTPR, mmHg/l/min) was calculated by the formula: MTPR=MABP/CO. d) Renal blood flow, by an indirect method, i.e. the clearance of para-amino-hippuric acid (PAH) and inulin, according to standard methods. e) Plasma renin activity, by radioimmunoassay using a modification of the technique of Haber et al.[6].

In anaesthetized dogs (Na pentobarbital 30 mg/kg i.v.) the blood pressure was measured by means of a Statham