ceptor blocking drug for three days and were sacrificed 24 h after the last administration. Enzyme activities and cytochrome content were determined in liver microsomes (105,000 g pellet resuspended in 1.15% KCl).

Pretreatment of animals with carcinogens leads to preferential enhancement of the cytochrome P-448-mediated 2-hydroxylation of biphenyl, whereas pretreatment with non-carcinogens enhances only the cytochrome P-450-mediated 4-hydroxylation (Creaven & Parke, 1966; Bridges *et al.*, 1973; McPherson, Bridges & Parke, 1974). None of the β-adrenoceptor blocking agents, at any dose level stimulated the 2-hydroxylation of biphenyl with the exception of propranolol which, at the highest dose of 150 mg/kg, caused a significant increase in the 2-hydroxylation (45%), as well as in the 4-hydroxylation (30%) of biphenyl. The activity of ethoxyresorufin de-ethylase was elevated following pretreatment with propranolol and pronethalol and this appeared to be dose-dependent, the increase being 2-fold at the highest dose (150 mg/kg) for both drugs. Acebutolol also stimulated the activity of this enzyme (65%) at this dose. The carcinogen 3-methylcholanthrene caused a very marked induction of this enzyme (180-fold) (Burke, Prough & Mayer, 1977), many orders of magnitude higher than that observed with the β-adrenoceptor blocking agents in this study.

None of the compounds, at any dose level, affected the demethylation of ethylmorphine, or the concentrations of cytochrome P-450 and cytochrome b_5, or cytochrome c reductase, demonstrating that none of the β-adrenoceptor blocking agents is a potent inducer of the liver microsomal mixed-function oxidase system.

Pronethalol and propranolol show a dose-response inductive effect of ethoxyresorufin de-ethylase in the rat, and propranolol at high dosage also induces biphenyl 2-hydroxylation, suggesting that both drugs might act as weak promoters of carcinogenesis when administered in prolonged high dosage. However, at the normal therapeutic dose (5 mg/kg) there is no inductive effect, although one must bear in mind that rates of drug oxidation in man are generally some 10-fold slower than in smaller animals, such as the rat.

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Quantitative analysis of noradrenaline clearance

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Interindividual variations in plasma noradrenaline may be due to variations in clearance of noradrenaline (NA) as well as to different levels of sympathetic nervous activity (FitzGerald, Davies & Dollery, 1979). The aim of this study was to quantify the relative contributions of uptake$_1$ (UP_1), uptake$_2$ (UP_2), catechol-*O*-methyl transferase (COMT) and monoamine oxidase (MAO) to NA clearance, with a view to establishing whether a defect in any one pathway could lead to significant reduction in clearance. Selective blockade of each pathway was provided by, respectively, desimipramine, metanephrine, pyrogallol and pargyline. Total systemic clearance was measured in 8 rabbits; (−)-NA (3.5 μg kg^{-1} min^{-1}) was infused for 1 h into the left ventricle, and timed samples were then

drawn from the right. Endogenous NA release was blocked by i.v. infusion of pentolinium (0.02 mg kg^{-1} min^{-1}). NA was infused (a) without blockade (b) with blockade of all 4 pathways (c) individual blockade of each pathway.

In (a) NA clearance was 69.37 ± 5.7 ml kg^{-1} min^{-1}. In (b), it was reduced to 15.9 ± 2.1 ml kg^{-1} min^{-1} ($P < 0.001$). In (c), it was reduced by Up_1 blockade to 42.46 ± 4.8 ml kg^{-1} min^{-1} ($P < 0.01$), by COMT blockade to 52 ± 6.3 ml kg^{-1} min^{-1} ($P < 0.01$) and by Up_2 blockade to 59 ± 5.3 ml kg^{-1} min^{-1} ($P < 0.05$). In (a) the elimination of NA after cessation of the infusion appears to be described by a multiexponential function, with a late phase elimination constant of 0.048 min^{-1}. This is not seen after Up_1 blockade, in (b).

Up_1 and COMT appear to be the major pathways in the clearance of infused NA. Some of the NA cleared by Up_1 may be later re-released into the circulation.

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Effect of penicillamine, hydrallazine and phenelzine on the function of pyridoxal-5'-phosphate

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The effect of a number of drugs on vitamin B_6 metabolism has been studied in Lister Hooded rats. Abnormal metabolism was detected by an increased urinary excretion of xanthurenic acid after an oral loading dose of L-tryptophan, a commonly used method of detecting vitamin B_6 deficiency (Sauberlich, *et al.*, 1972), and by measuring liver pyridoxal-5'-phosphate (PLP) content.

Xanthurenic acid excretion was increased, relative to the pretreatment levels, after 14 days' treatment with DL-penicillamine (435% increase), hydrallazine (348% increase) and phenelzine (342% increase). Concurrent treatment with drug and pyridoxine hydrochloride reversed these increases almost completely. However, the liver PLP content was decreased only in the DL-penicillamine-treated rats.

Penicillamine, hydrallazine and phenelzine all react with PLP *in vitro*. However, it has been shown in studies with cycloserine and isonicotinic acid hydrazide that interaction between drug and coenzyme, and excretion of the resulting product from the body, may not be the main mechanism of antagonism of PLP function (Rosen, Mihich, & Nichol, 1964; Krishnamurthy, *et al.*, 1967). Experiments were carried out to determine whether hydrallazine and phenelzine inhibited a PLP-dependent stage in tryptophan metabolism.

The action of penicillamine, hydrallazine and phenelzine on a partially-purified preparation of rat kidney kynurenine aminotransferase (KAT), a PLP-dependent enzyme (Mason, 1957), was investigated using the method of Kilgallon & Shepherd (1977). DL-penicillamine did not inhibit KAT, whilst hydrallazine and phenelzine showed non-competitive inhibition with respect to substrate with K_i values of 1.06×10^{-4} M and 5.07×10^{-5} M respectively. These results agree with those recently reported by Allegri Costa & De Antoni (1979) for the action of D-cycloserine, which also reacts with PLP, on KAT. When the PLP concentration was increased, the inhibition due to phenelzine increased. It is suggested that the hydrazone formed between phenelzine and PLP is a more potent inhibitor of KAT than is phenelzine itself.

Penicillamine, hydrallazine and phenelzine affect the normal functioning of PLP. Hydrallazine and phenelzine inhibit KAT, a PLP-dependent enzyme, whilst penicillamine lowers liver PLP levels, perhaps by an effect on the PLP-producing enzymes, pyridoxal kinase or pyridoxal phosphate oxidase.

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