tion of expired air demonstrated 5% deacetylation, although desacetylpractolol was not detected in urine, confirming previous observations (Bodem & Chidsey, 1973). Human adverse reactions do not appear to be associated with gross differences in practolol metabolism.

Of eight animal species studied, mouse, rat and dog most closely resemble man in metabolic profile. Minimal deacetylation (5–14% dose) occurs in all species except marmoset (51%). In other species, practolol was recovered largely unchanged in urine, except hamster, which eliminated practolol primarily as 3-hydroxypractolol and its glucuronide (35% dose).

Microsomal studies (Orton & Lowery, 1977) have been extended to show that hepatic enzymes from several species produce intermediary metabolites which bind to proteins. Hamster microsomes produced the highest binding rate although with marked inter-animal variation (0.44–2.44 nmoles bound mg protein^{-1} 30 min^{-1}). Inhibition and stimulation (53–448% control) were observed in the presence of sodium fluoride, stimulation being the major finding. Tricyclopropene oxide, an epoxide hydratase inhibitor, caused no significant change in binding. *Bis*-[*p*-nitrophenyl] phosphate both inhibited deacetylation *in vitro* and reduced binding. These results suggest, but do not prove, that N-hydroxylation may give rise to the intermediary metabolite(s). Microsomal activation has been utilized immunologically to screen for anti-practolol metabolite antibodies in patients' sera (Amos, Lake & Atkinson, 1977).

The relevance of any hypothesis implicating bound metabolites remains unclear as no toxic signs related to those seen in man were found in albino mouse (18 months, doses up to 100 mg/kg), black (C57 BL/10J) mouse (21 months, 300 mg/kg), rat (24 months, 300 mg/kg), Beagle dog (12 months, 200 mg/kg) and marmoset (6 months, 400 mg/kg). A hamster study reported to us gave rise to no relevant toxic sign. Thus, to date, no animal model for the human adverse reactions is known.

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Paraquat-induced formation of hydroperoxide in mouse liver microsomes

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The activation of oxygen is considered to be the underlying mechanism of paraquat (PQ) toxicity. Bus, Aust & Gibson (1974) demonstrated the formation of superoxide anion and an increased perioxidation of microsomal lipids in a system consisting of NADPH-cytochrome c-reductase, microsomal lipids and a NADPH-regenerating system whereas other authors (Ilett, Stripp, Menard, Reid & Gillette, 1974; Montgomery, 1976) observed a diminished formation of malondialdehyde (MDA).

Mouse liver microsomes were incubated at 37°C in a Soerensen buffer (pH 7.4) with NADPH and a NADPH regenerating system. Oxygen uptake was measured polarographically and MDA formation by the 2-thiobarbitone acid method. Oxygen uptake was increased by PQ in a dose-dependent fashion (K_m 3×10^{-4} M); microsomes from animals pretreated with phenobarbitone had a higher oxygen uptake than microsomes from control animals. MDA formation was decreased by PQ (K_i 6×10^{-5} M) and was not affected by phenobarbitone pretreatment. In the absence of PQ about 1 mole of NADPH was oxidized per mole oxygen. In the presence of PQ (1 mM) the ratio was 2. Addition of NaN_3 (1mM) shifted the NADPH/O_2 ratio towards 1 and increased the speed