200 *g* pellet) or in the 100,000 *g* supernatant (this latter measured by equilibrium dialysis).

Further studies of high-affinity binding with parallel metabolism experiments indicated a relationship between high-affinity binding and metabolism. Each was potentiated by oxygen and suppressed by carbon monoxide: drugs which displaced propranolol from high-affinity binding inhibited propranolol metabolism (SKF 525-A, chlorpromazine, imipramine and lignocaine): changes in high-affinity binding with sex and age correlated with changes in metabolism.

This approach may provide another possible method of examining drug-cytochrome P-450 complex, analogous to microsomal difference spectra with the added advantage of providing a capacity term. Although there are some quantitative difficulties in directly correlating this microsomal high-affinity capacity with the threshold of the first-pass phenomenon, it may be the case that such high-affinity subcellular binding is a common property of drugs which undergo first-pass hepatic extraction.

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Changes in renal function following chronic phenobarbitone administration

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Following chronic administration of phenobarbitone (30 mg kg^{-1} day^{-1} i.p.) to rats increases in the urinary excretion of unchanged chlorothiazide were found (Ohnhaus, 1972). As the drug/creatinine clearance ratio for chlorothiazide is similar to that for *p*-amino hippurate (PAH) and therefore to renal plasma flow (Beyer, 1958), phenobarbitone might have an influence on glomerular filtration rate (GFR) or renal plasma flow (RPF).

SRF-male rats were treated intraperitoneally with phenobarbitone (30 mg kg^{-1} day^{-1}) or sodium chloride respectively for 4 days. The latter rats formed a control group. Endogenous creatinine clearance in conscious rats and inulin clearance without induced diuresis under inactin anaesthesia were measured 24 h following the last dose of phenobarbitone. In an additional group of pretreated rats diuresis was induced by infusing 0.9% NaCl + 2% mannitol i.v. for 30 min at 5.0 ml 100 g^{-1} h^{-1} and inulin- and PAH-clearance were measured under the same experimental conditions.

Following 4 days treatment with phenobarbitone endogenous creatinine clearance and inulin-clearance with and without induced diuresis were not significantly different in control and phenobarbitone treated animals; changes in urine volume were not found. In contrast PAH-clearance was significantly increased in the phenobarbitone treated in comparison to the controls from 2.87 ml min^{-1} 100 g^{-1} body weight to 4.84 ml min^{-1} 100 g^{-1} body weight ($P < 0.001$).

These results indicate no changes in the glomerular filtration rate following chronic phenobarbitone administration, whereas the renal plasma flow is increased by about 69%. The increased excretion of chlorothiazide following chronic administration of phenobarbitone can therefore be attributed to changes in renal hemodynamics.

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