The distribution and induction of some drug-metabolizing enzymes in man

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The activities of certain drug-metabolizing enzymes were measured in visibly and histologically normal hepatic and extrahepatic surgical tissues. Fresh material was homogenized and sub-cellular fractions prepared using standard techniques. Two fractions, namely the supernatant of the 10,000 g×10 min fraction and the 105,000 g× 60 min (microsomal) fraction were used as sources of the various enzymes. Cytochrome P_{450}, hexobarbitone oxidase, ethylmorphine-N-demethylase, *p*-nitroreductase, UDP-glucuronyl transferase and the L-leucyl-β-naphthylamide splitting enzyme were chosen as representatives of the major classes of enzyme systems, namely oxidation, reduction, conjugation and hydrolysis, involved in the metabolism of foreign substances in the human body.

Enzyme activities were measured by standard methods in liver, kidney, placenta, lung, stomach, colon, spleen and prostate. For example, hexobarbitone oxidase was found in all tissues except prostate and had relative activities varying from 18·9% in the colon to 104% in the placenta (liver=100%). Ethylmorphine N-demethylase, however, was found only in the kidney and had a relative activity of 7·5% while cytochrome P_{450} was not detected in extrahepatic tissues. On the other hand, *p*-nitroreductase and UDP-glucuronyl transferase were found in most extrahepatic tissues but at levels less than 50% of the activities of the liver. The relative activities of L-leucyl-β-naphthylamide splitting enzyme which is considered to be involved in the metabolism of exogenous insulin varied from 35% in the lung to 352% in the kidney. Activities of the various hepatic drug-metabolizing enzymes as measured in the present work were higher than those obtained previously by Darby, Newnes & Price Evans (1970) from post-mortem specimens but were of the same order as those of Schoene, Fleischmann, Remmer & Oldershausen (1972) obtained in needle biopsy material. Comparison of the activities of hepatic microsomal enzymes between man and rat showed that they were higher in the latter species.

Preliminary results in 6 patients who received phenobarbitone before surgery suggests that daily divided doses of 90 mg for up to 10 days do not appear to induce drug-metabolizing enzymes in extrahepatic tissues.

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Dose-dependent enzyme induction

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Many drugs and other chemicals have been classified as inducers or non-inducers of liver microsomal drug metabolizing enzymes based on studies at one dose level. The purpose of the present study was to investigate if it is more meaningful to perform such studies at several dose levels. This has been done by administering varying doses of inducing agents to both man and rat and observing the degree of enzyme induction produced.

Administration of quinalbarbitone 100 mg nightly for 33 days caused a significant ($P<0·01$) fall in the steady state plasma warfarin concentration and rise in thrombotest