These and other findings indicate that cytochrome *P*-450 is the terminal oxidase functioning in the $\omega$-oxidation of fatty acids and also suggest that fatty acids, like steroid hormones, may be physiological substrates for the hydroxylating enzyme system of the liver microsomes.

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## Induction of Drug-Metabolizing Enzymes and Cytochrome *P*-450

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As a result of treatment with certain drugs, animals acquire an increased capacity to metabolize a wide range of drugs administered later. This phenomenon, first observed some 15 years ago, has aroused much interest and a considerable literature exists (Conney, 1967). Several hundred compounds are known to stimulate drug-metabolizing enzymes. They fit into one of two general classes typified by 3-methylcholanthrene and phenobarbital respectively, the former class being restricted almost entirely to polycyclic hydrocarbons, the latter containing many chemically diverse drugs such as barbiturates, phenothiazines, chlorinated insecticides and phenylhydantoins.

The polycyclic hydrocarbons produce a sharp rise in the rate of metabolism of a restricted range of drugs; drugs of the barbiturate type produce a slower increase in the metabolism of a much wider range of drugs. Biosynthesis of protein is involved and inhibitors such as cycloheximide and puromycin prevent induction. Morphological changes in the liver cell, principally a considerable increase in the quantity of smooth endoplasmic reticulum, accompany induction of enzyme activity by barbiturate, but are less noticeable after 3-methylcholanthrene induction. There are marked species, strain and individual variations in the responses of animals to inducing chemicals. All increase in drug-metabolizing capacity is accompanied by increases in the cytochrome *P*-450 content of the microsomal fraction from liver homogenates (Remmer & Merker, 1965). There is evidence that the cytochrome *P*-450 produced after induction has different properties from that present in unstimulated animals, and that that found after 3-methylcholanthrene differs from that found after barbiturate treatment. The spectrophotometric and enzymological evidence advanced to support this view (Sladek & Mannering, 1969*b*; Alvarez, Schilling, Levin & Kunzman, 1967; Hildebrandt, Remmer & Estabrook, 1968; Daly, Jerina, Farnsworth & Guroff, 1969) will be reviewed and implications for assessing the number of distinct drug-metabolizing enzymes present in liver will be considered.

Although increases in cytochrome *P*-450 accompany increased rates of drug metabolism after induction, there is not always a quantitative relationship between the two (Guarino, Gram, Gigon, Greene & Gillette, 1969). Evidence on the extent to which changes in enzyme activity are mirrored by changes in cytochrome *P*-450 concentrations will be reviewed and discussed.

The mechanisms by which drug-metabolizing activity is induced are still uncertain. Gene derepression seems to be involved (Wortham, Wilson, Falk & Geboin, 1967), but there is also evidence that, after induction, catabolism of cytochrome *P*-450 is slowed down (Greim & Remmer, 1969).

The two types of inducer seem to work through different mechanisms, since effects of a compound from one group are additive with those of a compound from the other. Recently more direct evidence for different mechanisms has been provided by the finding that thioacetamide prevents the effects of phenobarbital but not those of 3-methylcholanthrene (Sladek & Mannering, 1969*a*). Evidence bearing on the mechanisms involved, including that for the participation of endogenous intermediates in a de-repression process, will be considered.

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