

TABLE 5.—Admission rates (per 100 infants) by diagnosis, birth weight, and maternal smoking.

Diagnosis	Birth weight (g)						Total	
	<2,999		3,000-3,499		3,500+		(including unknown)	
	S (297)	NS (2,326)	S (415)	NS (4,098)	S (264)	NS (3,195)	S (986)	NS (9,686)
Bronchitis and pneumonia	19.2	12.3	9.6	8.2	12.1	9.0	13.1	9.5
All other	22.6	19.9	14.5	14.6	15.2	13.3	16.9	15.5
Total	41.8	32.2	24.1	22.8	27.3	22.3	30.0	24.9

NOTE. — S = Smokers; NS = Nonsmokers. Absolute numbers in parentheses.
SOURCE: Harlap and Davies (42).

which may exist between smoking and factors such as parental neglect or socioeconomic class. In addition, hospital admission rates may not be an accurate index of infant morbidity.

Colley, et al. (22) and Leeder, et al. (54) studied the incidence of pneumonia and bronchitis in 2,205 children over the first 5 years of life in relation to the smoking habits of both parents. They found that a relationship between parental smoking habits and respiratory infection in children occurred only during the first year of life (Table 6). They also showed a relationship between parental cough and phlegm production and infant infection (Table 6) which was found to be independent of the effect of parental smoking habits. The relationship between parental smoking and infant infection was greater when both parents smoked and increased with increasing number of cigarettes smoked per day. The relationship persisted after controlling for social class and birth weight.

Thus, respiratory infections during the first year of life are related to parental smoking habits independently of parental symptoms, social class, and birth weight. Because of the dose-response relationship between parental smoking and infant respiratory infection established by Colley, et al. (22), it is reasonable to suspect that cigarette smoke in the atmosphere of the home may be the cause of these infections; however, other factors such as parental neglect may also play a role.

Summary

1. Tobacco smoke can be a significant source of atmospheric pollution in enclosed areas. Occasionally, under conditions of heavy smoking and poor ventilation, the maximum limit for an 8-hour work exposure to carbon monoxide (50 ppm) may be exceeded. The upper limit for CO in ambient air (9 ppm) may be exceeded even in cases where ventilation is adequate. For an individual located close to a cigarette that is being smoked by someone else, the pollution exposure

TABLE 6.—Pneumonia and bronchitis in the first 5 years of life, by parents' smoking habit and morning phlegm.

Annual incidence of pneumonia and bronchitis per 100 children (Absolute numbers in parentheses)											
Year of followup	Both nonsmokers		One smoker		Both smokers		Both ex-smokers or one ex-smoker or smoking habit changed		All		
	N	O/B	N	O/B	N	O/B	N	O/B	N	O/B	
1	7.6 (343)	10.3 (29)	10.4 (424)	14.8 (128)	15.3 (339)	23.0 (139)	8.2 (546)	13.2 (129)	10.1 (1,652)	16.7 (425)	
2	8.1 (322)	8.3 (36)	7.1 (365)	15.5 (129)	8.7 (286)	9.2 (152)	6.5 (599)	10.7 (159)	7.4 (1,572)	11.3 (476)	
3	6.9 (305)	8.1 (37)	10.5 (353)	9.4 (107)	7.9 (242)	11.0 (154)	8.2 (661)	11.6 (173)	8.4 (1,561)	10.6 (471)	
4	8.0 (287)	11.1 (36)	7.5 (306)	10.8 (102)	7.6 (236)	11.6 (121)	8.2 (695)	9.1 (187)	7.9 (1,524)	10.3 (446)	
5	6.7 (285)	14.7 (34)	5.6 (267)	9.4 (107)	3.9 (208)	10.6 (132)	6.4 (737)	7.3 (219)	5.9 (1,497)	9.1 (492)	

NOTE.—N = neither with winter morning phlegm; O/B = one or both with winter morning phlegm.
SOURCE: Colley, J.R.T. (#2).

may be greater than would be expected from atmospheric measurements.

2. Carbon monoxide, at levels occasionally found in cigarette smoke-filled environments, has been shown to produce slight deterioration in some tests of psychomotor performance, especially attentiveness and cognitive function. It is unclear whether these levels impair complex psychomotor activities such as driving a car. The effects produced by CO may become important when added to factors such as fatigue and alcohol which are known to have an effect on the ability to operate a motor vehicle.

3. Unrestricted smoking on buses and planes is reported to be annoying to the majority of nonsmoking passengers, even under conditions of adequate ventilation.

4. Children of parents who smoke are more likely to have bronchitis and pneumonia during the first year of life, and this may be due to their being exposed to cigarette smoke in the atmosphere.

5. Levels of carbon monoxide which can be reached in cigarette smoke-filled environments have been shown to decrease the exercise duration required to induce angina pectoris in patients with coronary artery disease. These levels of CO also have been shown to reduce the exercise time until onset of dyspnea in patients with hypoxic chronic lung disease.

Recommendations

There has been a long-term research interest in the health effects of voluntary smoking, and substantial relevant data have accumulated. Attention to involuntary smoking is of recent vintage, and only limited information regarding the health effects of such exposure upon the nonsmoker is available. Therefore, research is needed to define these effects.

The initial research priorities with respect to involuntary smoking should be focused on those populations which might be considered at particular risk of negative health effects based on the information now available; namely, children, patients with coronary artery disease, patients with hyperactive airways, and patients with chronic lung diseases. In addition, the potential effects of involuntary smoking on psychomotor performance merit priority attention because of their possible importance in certain circumstances (e.g., driving). More specifically:

1. Prospective studies are needed to define the relationship between parental smoking and the prevalence of respiratory illness and symptoms and pulmonary function status in children. Care should be taken to consider such confounding factors as socioeconomic status and the smoking habits of the children.
2. Further in-depth studies are needed on patients with demonstrable coronary artery disease to assess the effects of carefully-defined carbon monoxide and involuntary smoking exposures upon angina and other indicators of myocardial ischemia and performance.
3. The clinical (symptomatic) and physiologic responses to involuntary smoking exposure should be investigated in patients with demonstrably hyperactive airways ("asthmatics") and chronic lung diseases.

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**12. INTERACTIONS OF SMOKING WITH
DRUGS, FOOD CONSTITUENTS, AND
RESPONSES TO DIAGNOSTIC TESTS.**

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Metabolism

Most drugs are metabolized in the liver, and metabolizing enzymes can occur in the soluble, mitochondrial, or microsomal fractions. The most common routes of drug metabolism involve oxidation, reduction, hydrolysis, and conjugation (34).

Mechanisms of Tobacco-Drug Interactions

Cigarette smoke is a complex mixture of noxious materials. Only a few of its components have been studied with respect to modifying drug disposition in animal, tissue, or enzyme systems. In this regard, polycyclic aromatic hydrocarbons (PAHs), nicotine, cadmium, and some pesticides have been reported to be enzyme inducers, and carbon monoxide (CO), nicotine, cadmium, some pesticides, hydrogen cyanide, and acrolein have been reported to be enzyme inhibitors (23).

The buccal and pulmonary bioavailability of most inhaled materials in cigarette smoke is relatively high. Dalhamn, et al. (9) found 86 to 99 percent retention of several components of cigarette smoke (acetaldehyde, isoprene, acetone, acetonitrile, toluene, and particulate matter) while CO absorption was only 54 percent. Mitchell (38) determined that appreciable retention of cigarette smoke occurs regardless of depth of inhalation. There was a mean retention of 37 percent of smoke in the buccal cavity, 82 percent during short inhalation (5 sec), and 97 percent during long inhalation (30 sec).

Aryl Hydrocarbon Hydroxylase

Aryl hydrocarbon hydroxylase (AHH), sometimes referred to as benzo(a)pyrene hydroxylase, is a mixed-function oxidase enzyme found in human and animal tissues. An extensive literature and many reviews cover the subject (5, 13, 49). AHH activity in many tissues is increased markedly by a variety of foreign compounds present in tobacco smoke, including most of the PAHs. Many carcinogens are biotransformed by AHH into reactive intermediates, such as epoxides, which can elicit cell transformation, mutagenicity, and cytotoxicity.

Inducers of microsomal oxidase enzymes can be classified according to their effects on various components of the enzyme system. The simplest categorization includes phenobarbital and many other drugs as stimulators of cytochrome P-450, while methylcholanthrene and PAHs produce an increase of a modified form of cytochrome P-450, namely cytochrome P-448 or cytochrome P₁-450. A summary of the primary biochemical and pharmacological differences between the two main classes of inducers is provided in Table 1. Steroids form a third group of compounds that can induce liver microsomal enzyme activity under certain conditions. These data, derived entirely from animal systems, led the authors to expect that, to the degree to which PAH constitutes the main enzyme inducer in cigarette smoke, only some

TABLE 1.—Differences between hepatic effect of phenobarbital and polycyclic hydrocarbons

Characteristic	Phenobarbital	Polycyclic aromatic hydrocarbons
Onset of effects	8-12 hr	3-6 hr
Time of maximum effect	3-4 hr	24 hr
Liver enlargement	Marked	Slight
Protein synthesis	Large increase	Small increase
Phospholipid synthesis	Marked increase	No effect
Liver blood flow	Increase	No effect
Ligandin content	Increase	Slight increase
Biliary flow	Increase	No effect
Enzyme components		
Cytochrome P-450	Increase	No effect
Cytochrome P-448	No effect	Increase
NADPH ₂ -cytochrome C reductase	Increase	No effect
Substrate specificity		
N-Demethylation of ethylmorphine and meperidine	Increase	No effect
N-Demethylation of 3-methyl-4-methyl-aminobenzene	Increase	Increase
Aliphatic hydroxylation of hexobarbital and pentobarbital	Increase	No effect
Aromatic hydroxylation of benzo(a)pyrene and zoxazolamine	Increase	Large increase
4-Hydroxylation of biphenyl	Increase	Increase
2-Hydroxylation of biphenyl	Slight increase	Increase
Dehalogenation of halothane	Increase	No effect
Glucuronidation of bilirubin	Increase	Increase
Sulfoxidation of chlorpromazine	Increase	No effect

SOURCE: Jusko, W. (25).

drug disposition pathways will be modified by use of tobacco. Unlike phenobarbital, which affects diverse aspects of liver function, including blood and biliary flow, the actions of PAHs seem to be limited to the induction of selected drug-metabolizing enzymes (5, 13, 27, 28, 42, 49).

Studies with human tissues demonstrate a correlation between cigarette smoking, increased AHH activity, and enhanced biotransformation of numerous—but selected—drugs that share both the P-450 and P-448 mixed-function oxidase pathways. Kapitulnik, et al. (25) found strong correlations between AHH activity in autopsied human livers and the metabolism rates of drugs, including hydroxylation of antipyrine, hexobarbital, and zoxazolamine. The hydroxylation of coumarin and the O-dealkylation of 7-ethoxycoumarin correlated more poorly. Nebert, et al. (41) and Welch, et al. (65) found significantly

higher levels of placental AHH in women with a history of cigarette smoking. The latter investigators also found an increase in aminoazo dye N-demethylase activity in placentas from smokers. Placental tissues show an excellent correlation between zoxazolamine and benzo(a)pyrene (BP) hydroxylation. The largest activities were found in cigarette smokers (24), although the stimulation of O-dealkylation of 7-ethoxycoumarin was less marked while oxidative aromatization (by steroid hydroxylase) of Δ^4 -androstene-3,17-dione to estradiol and estrone was not affected. Much of these data show various degrees of correlation of drug and AHH activity and reflect the presence of several distinct monooxygenase systems.

Other than liver, human tissues which metabolize benzo(a)pyrene include lung, skin, lymphocytes, and some fetal tissues (51). The presence of inducible AHH activity in almost every animal tissue indicates the ubiquitous distribution of this enzyme (50). The liver is the most active tissue per unit weight in hydroxylating BP. Furthermore, its large size and blood flow, relative to other organs, make it the most dominant and important organ in BP-induced drug metabolism. Thus, most changes in drug biotransformation in response to smoking are presumed to occur in the liver. Welch, et al. (64, 66) were able to rule out much of an effect of intestinal metabolism in the enhanced first-pass metabolism of phenacetin. However, the potential for alteration of drug disposition via induction of drug metabolism in other major perfusion sites such as the kidney should not be ignored. Several animal studies have shown that PAHs are effective inducers of renal drug metabolism in rats and rabbits (21, 63).

The data obtained from animal systems reflecting the physiological and substrate specificity of PAH induction somewhat parallel the role of cigarette smoking in altering drug disposition in man. The selective increase in aliphatic hydroxylation of various drugs in smokers (antipyrine, pentazocine), which does not occur in animals, may either reflect species differences or be caused by the myriad other compounds in smoke capable of inducing oxidative enzymes. Alternatively, a rate-limiting process other than enzymatic activity (protein binding, blood flow) may control disposition of these drugs. For example, the rate of aromatic hydroxylation of phenytoin is saturable and is appreciably dependent on diffusion of free drug from plasma in man, while animals generally form different ring-hydroxylated metabolites and exhibit product inhibition in overall biotransformation of the metabolite (22).

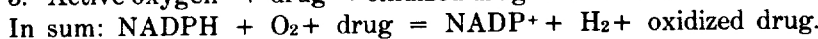
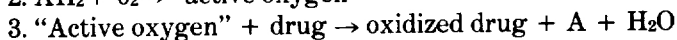
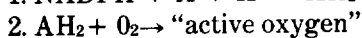
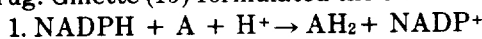
The absence of an effect of smoking on liver size appears to be common in man and animals. Lewis, et al. (30) examined body organ weights in relation to smoking habits in 172 autopsied subjects. Mean liver weights were 1111 g/m²bsa in male nonsmokers versus 980 g/m²bsa in heavy smokers. On the other hand, the nonsmokers tended to have lighter kidneys and lungs than the smokers.

Microsomal Enzyme Systems Which Catalyze Drug Metabolism

Mueller and Miller (39, 40) first described the metabolism of a foreign compound by hepatic microsomes. They showed that the microsomal fraction of a liver homogenate catalyzed both the reductive splitting of the azo linkage and the oxidative N-demethylation of aminoazo dyes. The reactions required nicotinamide-adenine dinucleotide phosphate (NADP), nicotinamide-adenine dinucleotide (NAD), and molecular oxygen. A wide variety of oxidative reactions are known to occur in microsomes: deamination, O-, N-, and S-dealkylation, epoxidation, hydroxylation of alkyl and aryl hydrocarbons, formation of alkyl derivatives, N-hydroxylation, N- and S-oxidation and dehalogenation. Azo- and nitro-reductase activities are also found in hepatic microsomes. The reactions are visualized more simply as different kinds of hydroxylation reactions (3, 14, 16): aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, deamination, sulfoxidation, and N-oxidation. (See Mannering (35) for a thorough discussion of the microsomal enzyme systems which catalyze drug metabolism.)

Drug Metabolizing Systems of the Hepatic Endoplasmic Reticulum

The microsomal drug metabolizing system is thought of as a mixed function oxidase mechanism whereby nicotinamide-adenine dinucleotide phosphate reductase (NADPH) reduces a component in microsomes which then reacts with molecular oxygen to form an "active oxygen" intermediate. The "active oxygen" is then transferred to the drug. Gillette (15) formulated the overall reaction as follows:



Key enzymes in the overall reactions are nicotinamide-adenine dinucleotide phosphate reductase (NADPH)-cytochrome C reductase, the flavin enzyme involved in the oxidation of NADPH, cytochrome P-450, which in its reduced form is generally considered to be A, and NADPH cytochrome P-450 reductase, which functions in the reduction of oxidized cytochrome P-450.

This mechanism requires that equivalent amounts of NADPH, oxygen, and substrate be utilized in the reaction. Stoichiometric relationships have been obtained for the hydroxylation of phenylalanine by hepatic microsomes (26) and the hydroxylation of 17-hydroxyprogesterone by adrenal microsomes (8). Trimethylamine has been reported to stimulate NADPH oxidation by an amount equivalent to the amount of trimethylamine oxide formed (2), and hexobarbital was found to increase NADPH oxidation in accordance with stoichiometric expectations (62). However, in several studies (14, 15, 16, 17) Gillette and coworkers found that some drugs had no effect on NADPH

oxidation, whereas others had more of an effect than could be accounted for by the metabolism of the drug. Microsomes contain enzymes which oxidize NADPH and utilize molecular oxygen in the absence of drugs, greatly complicating the analysis. Whether or not a drug stimulates or depresses NADPH oxidation would seem to depend upon whether or not it stimulates or depresses cytochrome P-450 reductase activity; this, in turn, would seem to depend upon whether the drug combines with cytochrome P-450 as a type I or as a type II compound (17, 18, 19) as discussed below. Ernster and Orrenius (10) demonstrated a 1:1:1 stoichiometry of oxygen utilization, NADPH disappearances, and formaldehyde formation from the oxidative demethylation of aminopyrine. However, Estabrook and Cohen (11) found that stoichiometry did not support the basic assumption of a mixed function oxidase reaction, that a mole of NADPH be oxidized for each mole of formaldehyde formed; two moles of nicotine-adenine dinucleotide phosphate (NADP) were formed per mole of formaldehyde, suggesting that the reaction is more complex than anticipated. Sasame, as cited in Mannering (37), did not find a stoichiometric relationship between NADPH and hexobarbital oxidation; the amount of NADPH oxidized was about 50 percent greater than the amount of hexobarbital metabolized.

Figure 1 shows the electron transfer system involving cytochrome P-450 as conceived by Omura, et al. (43, 48).

The first description of the microsomal system responsible for drug metabolism (39, 40) included a role of nicotinamide-adenine dinucleotide reductase (NADH) as well as NADPH. From time to time since then, NADH has been implicated in reactions involving drug metabolism (6, 42, 62). Using the mechanism of peroxidase action as a model, Estabrook and Cohen (11) suggested a way in which NADH might contribute to the reaction (Figure 2). NADPH may serve as an electron donor, via a respiratory chain, direct to cytochrome P-450 with an associated branched pathway to cytochrome b_5 , the only cytochrome other than cytochrome P-450 found in microsomes. In this way, cytochrome b_5 might serve as a second electron donor to cytochrome P-450 and thus satisfy the requirement of two electrons for the overall reaction.

Sih and coworkers (57, 58) question the function of NADPH as solely to provide the reducing equivalents for cytochrome P-450 via the electron transfer system as shown in Figure 1. Mannering (35) discusses the three lines of evidence leading to the scheme given in Figure 3, which visualizes a dual role of NADPH in the oxidation of corticosteroids by mitochondria of the adrenal cortex.

Much of the speculation regarding the components of the microsomal drug metabolizing system existed because attempts to solubilize cytochrome P-450 in active form had failed, and it was necessary to employ crude microsomal preparations. In various studies (7, 31, 32, 33)

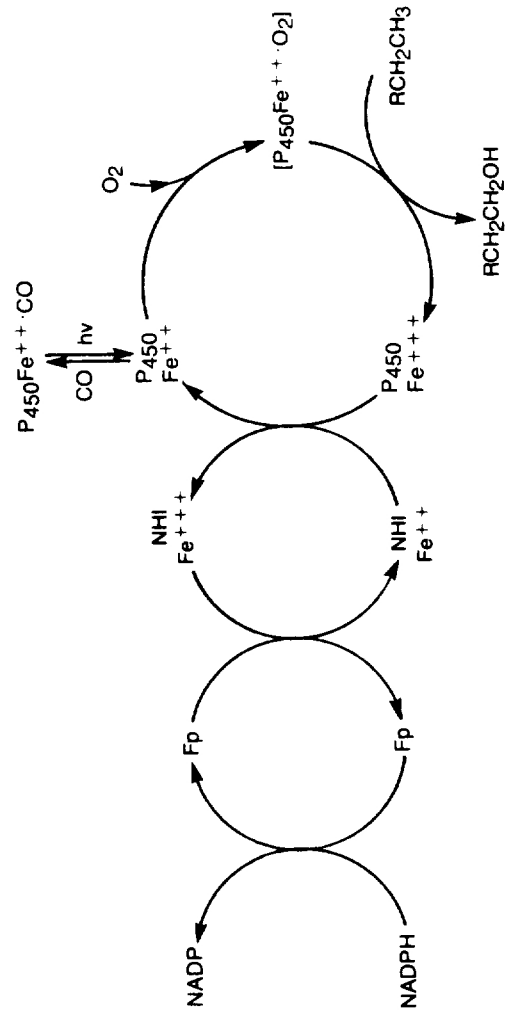


FIGURE 1.—Proposed electron transfer system employed in the microsomal metabolism of drugs. F_p = flavoprotein (in the liver, cytochrome C reductase; in the adrenal, adrenodoxin reductase); $NHIP$ = non-heme iron protein (in the adrenal, adrenodoxin)

SOURCE: Omura, T. (43,48).

Coon and Lu and their associates did much toward solving this problem.

Solubilization of hepatic microsomes from the rabbit with a mixture of glycerol, dithiothreitol, and sodium deoxycholate in a potassium citrate buffer produced an extract which was resolved into a fraction

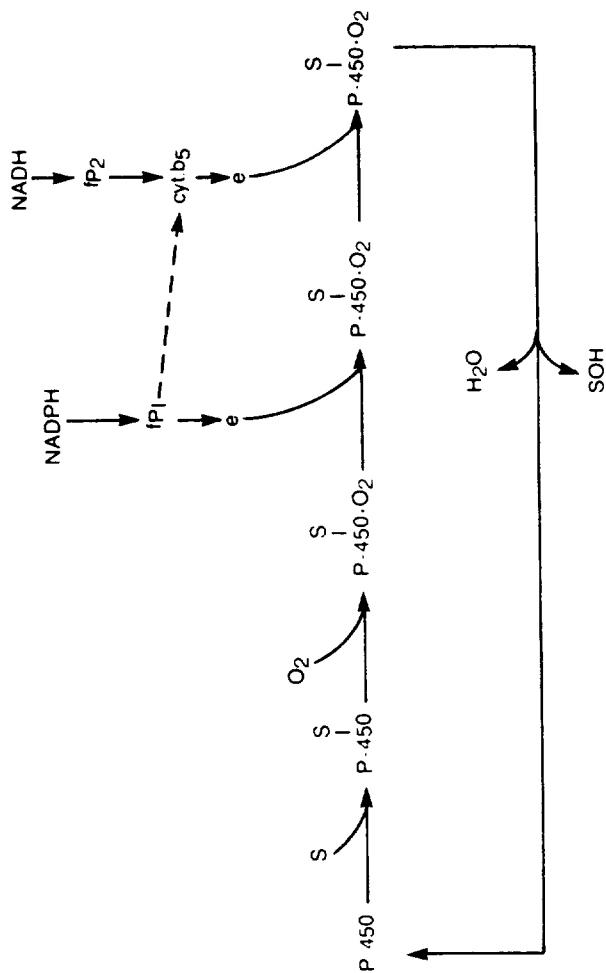


FIGURE 2.—Scheme showing how NADH and cytochrome b_5 might contribute to the electron transfer system employed in the microsomal metabolism of drugs

SOURCE: Estabrook, R. (11).

containing cytochrome P-450, a fraction containing a NADPH reductase, and a fat soluble, heat stable fraction. All three fractions were necessary for the maximal oxidation of drugs (benzphetamine, aminopyrine, ethylmorphine, hexobarbital, norcodeine, p-nitroanisole) or for the ω -hydroxylation of lurate. The criterion for the solubilization of cytochrome P-450 was that it remained in the supernatant fraction

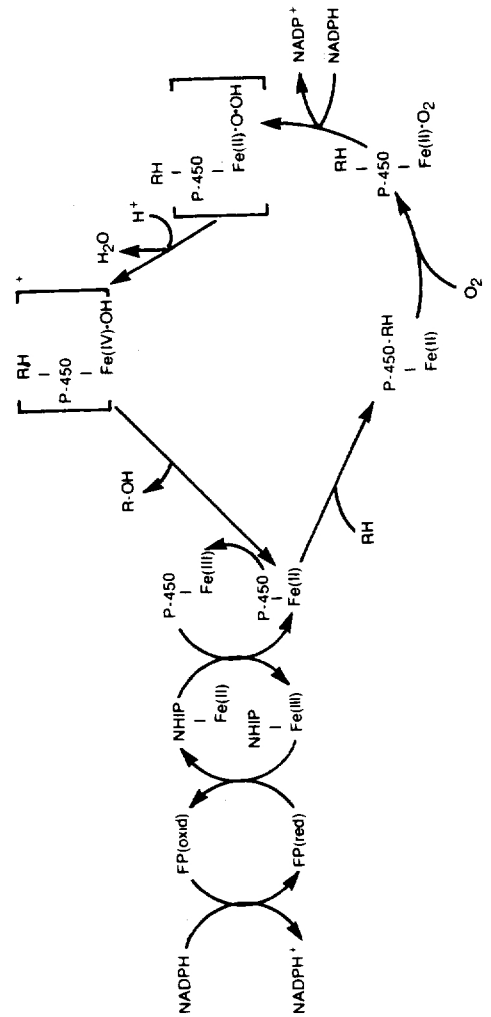


FIGURE 3.—Scheme illustrating a proposed dual role of NADPH in the oxidation of corticosteroids by mitochondria on the adrenal cortex. FP = flavoprotein (adrenodoxin); NHIP = non-heme iron protein (adrenodoxin reductase)

SOURCE: Sih, C. (57,58)

of the preparation after centrifugation at $105,000 \times g$ for 2 hours. These fractions may provide the opportunity for purification and identification of the components of the system.

Both NADH and NADPH can act as the electron donor in the reduction of nitro compounds. The reaction is presumed to proceed to the primary amine through the formation of nitroso and hydroxyl-

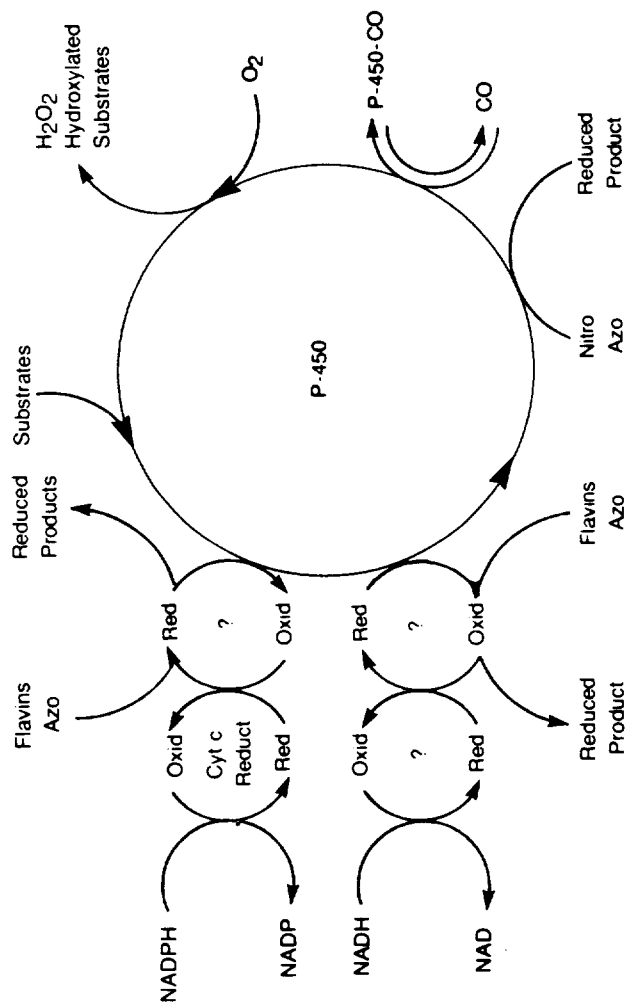


FIGURE 4.—Scheme showing how the microsomal electron transfer system might function in both the oxidation and reduction of drugs

SOURCE: Gillette, J.R. (19).

amine derivatives. Nitroreductase is active only under anaerobic conditions. Sensitivity to oxygen may be due in part to the auto-oxidation of the hydroxylamine intermediate (19). In studies which employed p-nitrobenzoate as a substrate, Gillette, et al. (19) concluded that the reduction was mediated by cytochrome P-450. These investigators proposed an electron transport system which would explain both the oxidative and the reductive function of the microsomal drug-metabolizing system (Figure 4).

Cytochrome P-450, earlier referred to as the CO-binding pigment, was first described by Klingenberg (29), Garfinkel (12), and Omura and Sato (44, 45, 46, 47). It is found in abundance not only in hepatic microsomes, but also in the microsomes and mitochondria from the adrenal cortex where it functions in the hydroxylation of steroids (11, 48), although not in the oxidation of most drugs. Lesser amounts are found in the kidney and intestinal mucosa (37). The presence of cytochrome P-450 has also been reported in mitochondria from the corpus luteum (67).

Factors concerning cytochrome P-450 include (35): (1) its spectral characteristics; (2) its conversion to cytochrome P-420 by a wide variety of compounds, such as phospholipase A, sodium deoxycholate and urea; and (3) its concentration in hepatic microsomes, which is influenced by various drugs, varies with age and sex, and is reported to rise after fasting. Drugs and other foreign compounds bind to hepatic cytochrome P-450 to produce different spectra of two general types, type I and type II. Type I compounds give a different spectrum with a λ max in the general range of 385-390 m μ and λ min in the equally broad range of 418-427 m μ ; the λ max and min given by type II compounds are 425-435 and 390-405 m μ , respectively (54). Thus, with opposing λ max and λ min, type I and type II spectra are approximate mirror images of each other. Figure 5 presents type I (hexobarbital) and type II (aniline) spectra.

Compounds that induce microsomal drug metabolism tend to be type I compounds, such as aminopyrine, 3,4 benzpyrene, coumarin, DDT, ethylmorphine, hexobarbital, and progesterone; one exception is nicotine, a type II compound, which is reported to be an inducing agent. Mannering (35) presents a thorough discussion of the significance of the binding of cytochrome P-450 to compounds.

Cytochrome P₁-450 (P-448, P-446, High Spin P-450, Type a P-450)

The mechanism by which phenobarbital and many other drugs stimulate the synthesis of the microsomal drug metabolizing system has long been considered to be different from the mechanism whereby PAHs produce their inductive effects (36). This early assumption was based on the knowledge that drugs such as phenobarbital induce the increased metabolism of a much larger number of drugs and other foreign substances than do the PAHs such as 3-methylcholanthrene (3-MC) or 3,4-benzpyrene (BP). Attempts to measure some of the differences between the two inductive processes led to the conclusion that PAHs cause the synthesis of a modified cytochrome P-450. For lack of a more suitable nomenclature for the microsomal hemoproteins, the hemoprotein cytochrome was named P₁-450 (37, 55, 59, 60, 61).

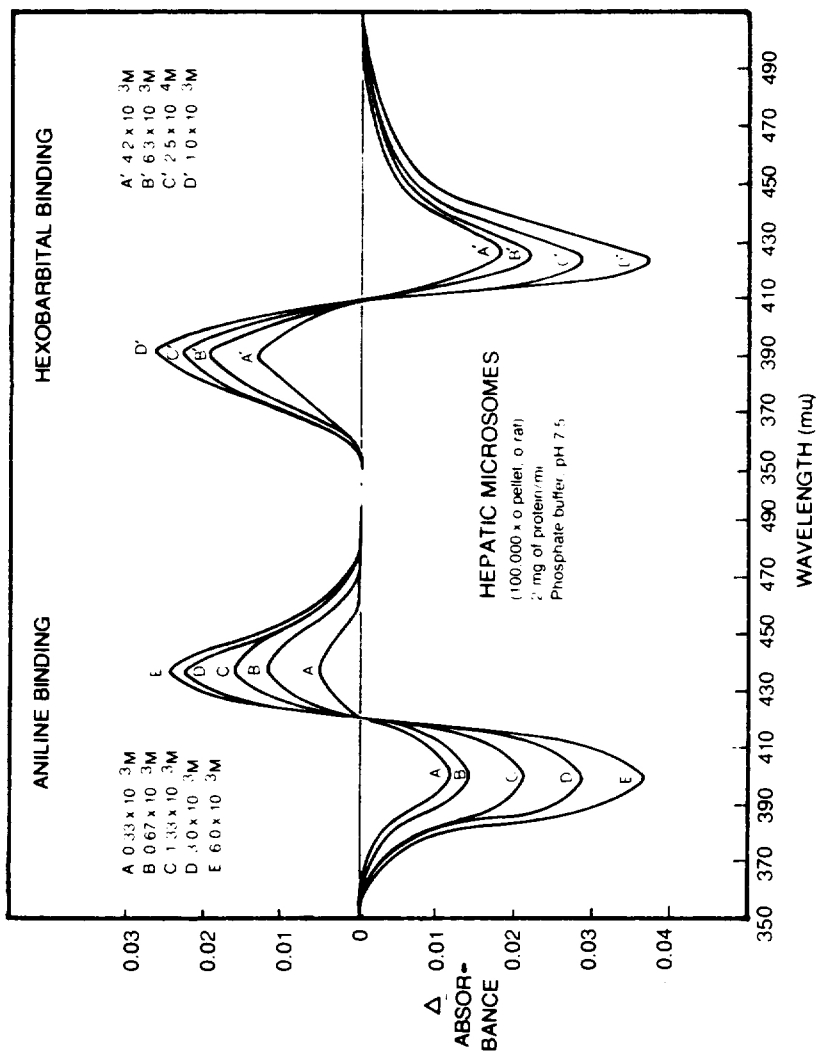


FIGURE 5.—Type I and type II binding spectra given by different concentrations of typical type I and type II compounds (hexobarbital, type I; aniline, type II)

SOURCE: Mannering, G. (35).

Because Alvares, et al. (1) observed a λ max at 448 m μ , cytochrome P₁-450 is sometimes called cytochrome P-448.

Although it is agreed that the administration of PAHs affect microsomal hemoprotein, there is much controversy as to whether the change reflects the formation or revelation of a new molecular species of hemoprotein, or is simply an alteration in the relative amounts of