Metabolic Interactions Among Environmental Chemicals and Drugs

Environmental chemicals that alter microsomal activity may influence the safety and efficacy of drugs.

A. H. Conney and J. J. Burns

Twenty years ago, Richardson and his associates tried to increase the incidence of cancers in rats by feeding two carcinogens simultaneously. They were surprised to find that the hepatocarcinogenic action of 3′-methyl-4-dimethylaminoazobenzene was abolished when this aminoazo dye was fed with 3-methylcholanthrene, a carcinogenic polycyclic hydrocarbon (*1*). An explanation for this observation came from the finding that 3-methylcholanthrene induced the synthesis of liver microsomal enzymes that metabolize aminoazo dyes by *N*-demethylation and azo link reduction to noncarcinogenic products (Fig. 1) (*2, 3*). Subsequent studies revealed that many drugs and environmental chemicals stimulate or inhibit microsomal enzyme function in animals, and this is reflected in vivo by an altered metabolism and action of drugs, carcinogens, and various normal body constituents, such as steroid hormones, thyroxin, and bilirubin (*4, 5*). Chemicals found in man's environment that alter the action of drugs by stimulating microsomal enzyme activity in animals include halogenated hydrocarbon insecticides (*6, 7*), urea herbicides (*8*), volatile oils (*9*), polycyclic aromatic hydrocarbons (*3, 10–12*), dyes used as coloring agents (*13*), nicotine and other alkaloids (*14*), food preservatives (*15*), and substances such as safrole (*16*), β-ionone (*16*), xanthines (*17*), flavones (*18*), and organic peroxides (*2*) that occur in food. Environmental chemicals that inhibit microsomal function in animals include organophosphorus insecticides (*19, 20*), pesticide synergists of the methylenedioxyphenyl type (*21*), carbon tetrachloride (*22–24*), ozone (*25*), and carbon monoxide (*26*). In this article we describe some of the effects of drugs and environmental chemicals on the activity of microsomal enzymes in animals and man and indicate the pharmacological and toxicological significance of these effects.

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Drug Metabolism

Patients are often given several drugs at the same time, and sometimes the combination results in an undesirable effect because one drug inhibits or stimulates the metabolism of the other. For example, phenylbutazone, sulfaphenazole, phenyramidol, bishydroxycoumarin, and chloramphenicol inhibit the metabolic inactivation of tolbutamide in man, and this effect can result in serious hypoglycemia. Numerous drugs inhibit the metabolism of other drugs in animals and man, and this problem is discussed in more detail elsewhere (*27, 28*). Phenobarbital, on the other hand, decreases the action of other drugs by increasing the rate of which they are metabolized to pharmacologically inactive substances. The enhancement of drug metabolism by phenobarbital is but one example of a phenomenon that has important implications to human health. Several hundred drugs, insecticides, carcinogens, steroid hormones, and other endogenous or foreign chemicals are now known to stimulate drug metabolism in animals (*4, 28, 29*), and many of these compounds have been shown to stimulate the metabolism of drugs and normal body constituents in man (Table 1).

The magnitude of the change in drug action that may occur after enzyme induction in animals is illustrated by data obtained from rats given the muscle-relaxant drug zoxazolamine, which is metabolized by liver microsomal enzymes to the inactive compound, 6-hydroxyzoxazolamine (Fig. 2). A high dose of zoxazolamine paralyzes rats for more than 11 hours, but if they are treated with phenobarbital for 4 days before being given zoxazolamine, they are paralyzed for only 102 minutes; if they are treated with benzo[*a*]pyrene 24 hours before the test, they are paralyzed for only 17 minutes with the same dose of zoxazolamine (*30*). The biological half-life of zoxazolamine in vivo is 9 hours in control rats, 48 minutes in rats treated with phenobarbital, and 10 minutes in rats treated with benzo[*a*]pyrene.

Treatment of rats with phenobarbital for several days increases the activity of liver microsomal enzymes that metabolize the anticoagulant drugs bishydroxycoumarin and warfarin (*31, 32*). In accordance with these observations, the administration of phenobarbital to man decreases the concentration of bishydroxycoumarin and warfarin in the plasma and reduces their pharmacological action (*31, 33*). The hazards of this interaction were investigated (*34*), and the results of a representative study in the dog are shown in Fig. 3. A dog was given 1 milligram of bishydroxycoumarin per kilogram of body weight every 48 hours for several weeks until a constant concentration of drug in the plasma and a constant anticoagulant effect (prothrombin time) were achieved. When phenobarbital was administered to the dog without the bishydroxycoumarin regimen being changed, the concentration of bishydroxycoumarin in the plasma decreased and the anticoagulant effect of the drug was abolished. Even when there was a fivefold increase in the dose of bishydroxycoumarin, adequate anticoagulant therapy and an adequate concentration of bishydroxycoumarin in the plasma were not achieved while phenobarbital treatment was continued. When phenobarbital administration was discontinued, the concentration in the plasma and the anticoagulant effect of bishydroxycoumarin increased during the next few days to such an extent that the dog bled severely and required vitamin K to save its life. These results indicate

that combined therapy with a coumarin anticoagulant and a stimulator of drug metabolism can be hazardous if the enzyme stimulator is withdrawn and therapy with the anticoagulant is continued without an appropriate decrease in the dose.

Ethanol, when consumed habitually, stimulates its own metabolism and the metabolism of various drugs in man (Table 1). Alcoholics metabolize tolbutamide more rapidly than nonalcoholics, and this should be considered when alcoholics are given tolbutamide for the treatment of diabetes. Alcoholics also have an increased concentration of the hepatic enzyme that metabolizes pentobarbital; they metabolize pentobarbital, meprobamate, diphenylhydantoin, warfarin, and antipyrine more rapidly than nonalcoholics, and this helps explain the increased tolerance of alcoholics to barbiturates and other sedatives when sober. A single large dose of ethanol, however, inhibits drug metabolism, and this effect—in addition to the central-depressant action of ethanol—helps explain the enhanced sensitivity of inebriated individuals to barbiturates and other sedatives (*35*).

Not only does the long-term administration of drugs stimulate the metabolism of other compounds, but often the drug stimulates its own metabolism. Examples of drugs that stimulate their own metabolism in dogs include phenylbutazone, tolbutamide, probenecid, chlorcyclizine, and hexobarbital. The development of tolerance to glutethimide in man results from the ability of glutethimide to stimulate its own metabolism, and this may also be true for ethanol and meprobamate (Table 1). Tolerance to narcotics such as morphine and meperidine, on the other hand, does not result from their metabolism being enhanced.

The stimulatory effect of halogenated hydrocarbon insecticides on drug metabolism was discovered accidentally by Hart *et al.* after their animal quarters were treated with chlordane (*36*). Studies on the metabolism and action of drugs were disrupted, and the effects of chlordane persisted for several weeks, even though insecticide treatment had stopped. Examples of insecticides that stimulate drug metabolism in rats include chlordane, DDT, methoxychlor, aldrin, endrin, dieldrin, heptachlor, and benzene hexachloride (*7, 37*). Two days after the intraperitoneal administration of either 1 or 2 mg of DDT per kilogram of body weight, the duration of sleep produced by a dose of pentobarbital was decreased by 25 percent and 50 percent, respectively, and the corresponding concentrations of DDT in the fat were 9.4 and 15.5 μg/g (*38*). Since many human beings possess these concentrations of DDT and other halogenated hydrocarbon insecticides in fat (*39*), it is important to evaluate carefully the effects of DDT on drug and steroid metabolism in man. People exposed to large amounts of DDT and lindane in a pesticide factory metabolize antipyrine about twice as rapidly as a control population (Fig. 4) (*40*). More recently, the effect of intensive occupational exposure to only DDT on drug and steroid metabolism was studied. In a population of DDT-factory workers with a serum and fat concentration of DDT-related substances 20- to 30-fold higher than a control population, the half-life of phenylbutazone in the serum was 19 percent lower, and the urinary excretion of 6β-hydroxycortisol was 57 percent higher than in the control population (*41*). Although it is not known whether DDT storage in the general population is sufficient to stimulate the metabolism of drugs or the metabolism of steroid hormones, the magnitude of the changes obtained in the DDT-factory workers suggests that the extent of possible changes in these parameters in the general population would be small.

Piperonyl butoxide, a pesticide synergist that inhibits the microsomal oxidation of pesticides in insects, also inhibits the activity of microsomal enzymes in mammalian liver (*21, 42*). This effect explains the ability of piperonyl butoxide to (i) prolong the action of barbiturates and zoxazolamine (*43*), (ii) slow the metabolism of benzo[*a*]pyrene in vivo (*44*), and (iii) enhance the acute toxicity of benzo[*a*]pyrene and griseofulvin (*45*). In addition, combined administration of piperonyl butoxide and Freons to newborn mice produces synergistic acute toxicity and hepatocarcinogenicity (*46*). In the rat, however, a very high dose of piperonyl butoxide is needed for inhibition of antipyrine and benzo[*a*]pyrene metabolism and for the potentiation of pentobarbital and zoxazolamine action (*47, 48*). The rat requires more than a 100-fold higher dose of piperonyl butoxide than the mouse for inhibition of antipyrine metabolism, and studies in man reveal that the oral administration

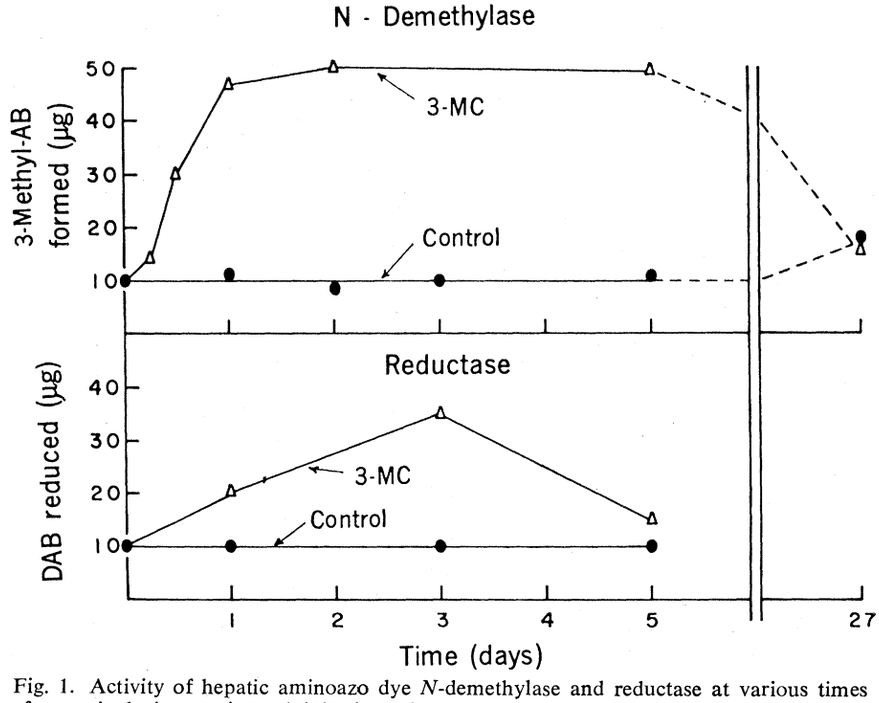

Fig. 1. Activity of hepatic aminoazo dye *N*-demethylase and reductase at various times after a single intraperitoneal injection of 1 mg of 3-methylcholanthrene (*3-MC*) into 50-g male rats (*3*). *N*-demethylase activity was determined by measuring the conversion of 3-methyl-4-monomethylaminoazobenzene to 3-methyl-4-aminoazobenzene (*3-methyl-AB*). Reductase activity was determined by measuring the reduction of the azo linkage of 4-dimethylaminoazobenzene (*DAB*). Demethylase activity is expressed as micrograms of 3-methyl-AB formed per 50 mg of liver per 30 minutes. Reductase activity is expressed as micrograms of DAB reduced per 30 mg of liver per 30 minutes.

of 0.7 mg/kg of piperonyl butoxide does not influence antipyrine metabolism (*47, 48*). Since this dose of piperonyl butoxide is more than 50-fold greater than the daily exposure received by individuals using sprays containing this compound, it is unlikely that environmental exposure of people to piperonyl butoxide inhibits the function of their microsomal enzymes.

Carcinogen Metabolism

People are exposed to polycyclic hydrocarbons, nitrosamines, aflatoxins, and many other chemical carcinogens in their environment (*49*), and factors that inhibit or stimulate the metabolism of these substances may have importance in the formation of human cancers. Enzymes that *N*-demethylate aminoazo dyes, hydroxylate benzo[*a*]pyrene and *N*-demethylate dimethylnitrosamine are present in human liver (*50, 51*), and an enzyme that hydroxylates benzo[*a*]-pyrene is present in human skin (*52*) and placenta (*11, 53*). The cofactor requirements and the microsomal distribution of benzo[*a*]pyrene hydroxylase in human liver are similar to those previously reported for rat liver (*50, 54*).

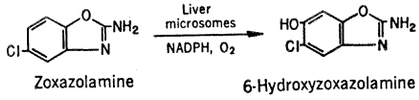

Fig. 2. Metabolism of zoxazolamine to 6-hydroxyzoxazolamine.

The administration of benzo[*a*]pyrene or other environmental polycyclic hydrocarbons to rats induces the synthesis of an enzyme system in liver microsomes that hydroxylates benzo[*a*]pyrene (*54*). The induction of benzo[*a*]pyrene hydroxylase occurs not only in the liver, but also in several other organs of the rat, such as the gastrointestinal tract, lung, kidney, skin, and placenta (*11, 12, 55*). The stimulatory effect of several polycyclic hydrocarbons on benzo[*a*]-pyrene hydroxylase activity in rats is reflected in vivo by enhanced metabolism of benzo[a]pyrene, a decreased blood and tissue concentration of this carcinogen, and enhanced biliary excretion of its metabolites (*56–58*). The stimulatory effect of benzo[*a*]pyrene on its own metabolism is illustrated by a decreased tissue concentration of this compound when it is administered over a long period of time. At 24 hours after a single oral dose of 1 mg of ^{3}H-labeled benzo[*a*]pyrene to adult rats, the concentration of this hydrocarbon in fat was 249 nanograms per gram, whereas at 24 hours after seven daily doses, the concentration in fat was only 24 ng/g (*56*). Inhibitors of microsomal enzyme activity, such as carbon tetrachloride, β-diethylaminoethyl diphenylpropylacetate (SKF 525-A), and piperonyl butoxide, inhibit the metabolism of benzo[*a*]pyrene in vivo and potentiate the acute toxicity of this polycyclic hydrocarbon in rodents (*45, 46, 58, 59*).

The induction of microsomal hydroxylases in rodents provides protection from the carcinogenic effects of benzo[*a*]pyrene (*60*), 7,12-dimenthylbenz[*a*]anthracene (*61*), *N*-2-fluorenylacetamide (*62*), 4-dimethylaminostilbene (*63*), urethane (*64*), aflatoxin (*65*), diethylnitrosamine (*66*), and aminoazo dyes (*1, 62, 67*). Although these studies indicate that the induction of hydroxylating enzymes inhibits the formation of cancer by several unrelated carcinogens, further work is required to evaluate the effects of enzyme induction on chemical carcinogenesis under varying conditions. These studies are important because of observations suggesting that metabolism of polycyclic hydrocarbons and other carcinogens may be required for their carcinogenicity (*68, 69*). Reactive intermediates—perhaps epoxides—capable of interacting with DNA or other macromolecules are formed during the aromatic hydroxylation of polycyclic hydrocarbons (*70*), and hydroxylated metabolites of benzo[*a*]pyrene are more

Table 1. Enzyme induction in man. Decreased concentrations in the plasma were used as criteria for enhanced metabolism of bilirubin and most drugs. Increased urinary excretion of 6β-hydroxycortisol or polar metabolites of testosterone was used as an index of steroid hydroxylation. Enhanced enzymatic oxidation of pentobarbital by human liver and enhanced metabolism of benzo[*a*]pyrene and aminoazo dye by enzymes in human placenta were used as the criteria for accelerated metabolism of these compounds.

Stimulator	Enhanced metabolism
Phenobarbital and other barbiturates	Coumarin anticoagulants (*31, 33, 165*)
	Diphenylhydantoin (*31, 166*)
	Digitoxin (*167*)
	Quinine (*168*)
	Dipyrone (*169*)
	Desmethylimipramine (*170*)
	Chlorpromazine (*171*)
	Phenylbutazone (*172*)
	Cortisol (*114*)
	Testosterone (*118*)
	Bilirubin (*155, 156*)
	DDT (*88*)
Anticonvulsant mixture	Lidocaine (*173*)
	DDT (*88, 90*)
Glutethimide	Glutethimide (*174*)
	Warfarin (*33*)
	Dipyrone (*169*)
Phenylbutazone	Aminopyrine (*175*)
	Digitoxin (*176*)
	Cortisol (*115, 117*)
Antipyrine	Warfarin (*177*)
	Cortisol (*177*)
Meprobamate	Meprobamate (*178*)
Ethanol	Ethanol (*35, 179*)
	Pentobarbital (*35*)
	Meprobamate (*35*)
	Warfarin (*180*)
	Diphenylhydantoin (*180*)
	Tolbutamide (*180, 181*)
	Antipyrine (*182*)
	Bilirubin (*183*)
Diethylnicotinamide (Coramine)	Bilirubin (*184*)
Diphenylhydantoin	Digitoxin (*176*)
	Dexamethasone (*185*)
	DDT (*88, 186*)
	Dieldrin (*186*)
	Cortisol (*112*)
	Thyroxin (*187*)
o,p'-DDD	Cortisol (*113*)
Eucalyptol	Aminopyrine (*9*)
Cigarette smoke	Benzo[*a*]pyrene (*11, 73*)
	3-Methyl-4-monomethylaminoazobenzene (*11*)
	Nicotine (*76*)
	Phenacetin (*77*)
Marihuana smoke	Δ^9-Tetrahydrocannabinol (*78*)
DDT, lindane	Antipyrine (*40*)
	Phenylbutazone (*41*)
	Cortisol (*41*)
	Bilirubin (*158*)

cytotoxic than benzo[*a*]pyrene in tissue culture. In agreement with these observations, benzo[*a*]pyrene is more toxic to cells that possess high hydroxylase activity than to cells with low enzyme activity (*68, 71*).

Since benzo[*a*]pyrene and other polycyclic hydrocarbons are present in cigarette smoke, studies were initiated to determine the effects of cigarette smoke on the concentration of benzo[*a*]pyrene hydroxylase in several tissues. The results of studies in the rat indicated that cigarette smoke stimulates the hydroxylase activity in the lung, placenta, intestine, and maternal liver (Table 2) (*72*). Increased activity was also found in fetal liver, indicating that enzyme inducers in cigarette smoke pass through the placenta and reach the fetus.

A stimulatory effect of cigarette smoking on benzo[*a*]pyrene hydroxylase and aminoazo dye *N*-demethylase activity was observed in the human placenta (*11, 48, 73, 74*). Little or no benzo[*a*]pyrene hydroxylase or aminoazo dye *N*-demethylase activity was detected in human placentas obtained at term after childbirth from nonsmokers, but these enzymes were found in placentas obtained from women who smoked 10 to 40 cigarettes a day. Among the subjects who smoked 15 to 20 cigarettes per day, placental benzo[*a*]pyrene hydroxylase activity varied over a 70-fold range (Table 3).

It would be of considerable interest to know what causes the marked variability in the induction of benzo[*a*]pyrene hydroxylase activity in cigarette smokers and to determine whether this variability can explain why some people develop cancer when exposed to cigarette smoke and others do not. Variability in the basal activity and in the induction of benzo[*a*]pyrene hydroxylase activity in placenta, skin, or other human tissues in culture may provide a way of detecting genetic differences in the concentrations of carcinogen-metabolizing enzymes in different people. Initial studies to determine the feasibility of this approach have been encouraging and have revealed that benz[*a*]anthracene, a polycyclic hydrocarbon in cigarette smoke, induces benzo[*a*]pyrene hydroxylase activity in human foreskin tissue culture (*52, 75*).

The smoking of cigarettes enhances the metabolism of nicotine in man (*76*), which may explain the tolerance to nicotine that occurs in smokers. These results, along with earlier observations indicating a stimulatory effect of polycyclic hydrocarbons on drug metabolism in animals, suggest that cigarette smoking may alter the metabolism and action of some commonly used drugs in man. Indeed, cigarette smokers administered phenacetin have markedly lower concentrations of this drug in the plasma than nonsmokers (*77*), and long-term marijuana smokers metabolize Δ^9-tetrahydrocannabinol more rapidly than nonsmokers (*78*).

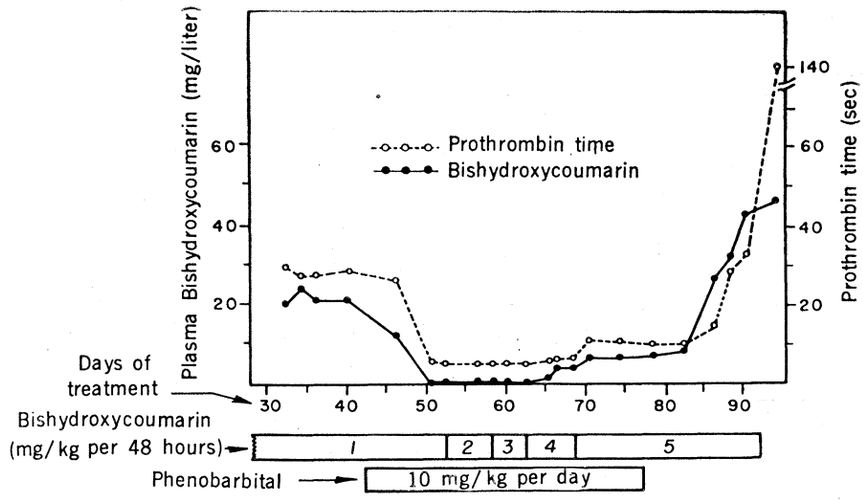

Fig. 3. Effect of phenobarbital on the plasma concentration and anticoagulant action (prothrombin time) of bishydroxycoumarin in the dog (*34*).

Insecticide Metabolism in Mammals

Treatment of rodents with phenobarbital or steroids that induce microsomal enzymes decreased the toxicity of several cholinergic organophosphorous pesticides commonly used in agriculture (*79*). In rats treated with an enzyme inducer, the toxicity of parathion, *O-p*-nitrophenyl phenylphosphonothioate (EPN), systox, di-syston, delnav, phosdrin, ethion, trithion, and malathion was decreased. In contrast to these studies, enzyme induction increased the toxicity of Schradan (*80*), an organic thiophosphate that is relatively nontoxic until it is metabolized by liver microsomes to a potent cholinesterase inhibitor.

Since many halogenated hydrocarbon insecticides are metabolized by enzymes in liver microsomes, the possibility of inducers of liver microsomal enzymes decreasing the storage of these pesticides in body fat was considered. Street and his coworkers (*81–83*) found that in rats given dieldrin or heptachlor epoxide, storage of these substances in the adipose tissue was markedly depressed when DDT was administered simultaneously. Fifty parts per million of DDT in the feed caused a 15-fold reduction in the amount of dieldrin stored in the adipose tissue of rats fed 1 ppm of dieldrin. Although DDT decreased the storage of dieldrin in rats, swine, and fish, it had no effect in chickens (*83*). Other stimulators of liver microsomal enzymes, such as phenobarbital, tolbutamide, heptabarbital, phenylbutazone, and methoxychlor, also decreased the storage of dieldrin in the body fat of rats (*82, 84*), and phenobarbital treatment accelerated the elimination of metabolites of hexachlorocyclohexane (*85*).

Enzyme inducers have been used for lowering insecticide residues in cattle, and recent studies indicate that enzyme

Table 2. Effect of cigarette smoke on benzo[*a*]pyrene hydroxylase activity in various organs from pregnant rats. Rats pregnant for 17 days and weighing 225 to 250 g were placed in a chamber and exposed to cigarette smoke for 5 hours each day for 3 days, with a 1-hour rest period between each hourly exposure. Various organs were examined for benzo[*a*]pyrene hydroxylase activity (mean ± standard error) (*72*).

Organ	Hydroxybenzo[*a*]pyrene formed (ng g^{-1} $hour^{-1}$)		Increase in enzyme activity (%)
	Control	Experimental	
Lung	584 ± 116	7644 ± 1108	1200
Placenta	136 ± 28	676 ± 60	400
Intestine	9396 ± 2024	20368 ± 5956	120
Maternal liver	40988 ± 632	91276 ± 5852	120
Fetal liver	484 ± 72	1112 ± 104	130

inducers can decrease the body burden of halogenated hydrocarbon insecticides in man. Treatment with phenobarbital stimulates hepatic drug-metabolizing enzymes in the cow, sheep, goat, calf, and pig (*86*), and repeated administration of low doses of phenobarbital to dairy cows given DDT for 2 months resulted in a significant decrease in the content of DDT-related substances in the milk (*87*). Administration of phenobarbital also increased the urinary excretion of DDA in bulls and rats administered DDT (*87*) and stimulated the in vitro metabolism of DDT to DDD in rat liver (*87*). Human beings ingesting phenobarbital, diphenylhydantoin, or a mixture of anticonvulsants had a markedly lower concentration of DDE in the blood than a control population (*88, 89*); anticonvulsants also reduced the concentration of DDE in the blood of people occupationally exposed to large amounts of DDT (*90*).

Insecticide Metabolism in Insects

Like mammalian organisms, houseflies and other insects can detoxify pesticides by microsomal hydroxylation (*91*). Certain strains of houseflies resistant to DDT show high DDT and naphthalene hydroxylase activity (*92, 93*), and it appears that the concentrations of microsomal enzymes and DDT-dehydrochlorinase are important in explaining differences in the resistance of various strains of insects to DDT and unrelated insecticides (*92*). Piperonyl butoxide and other methylenedioxyphenyl derivatives inhibit the activity of microsomal enzymes in insects that detoxify pyrethrins, carbamates, and naphthalene (*94*). This effect explains the usefulness of methylenedioxyphenyl derivatives for the potentiation of pyrethrins and other insecticides.

Microsomal enzymes are inducible in some, but not all, insects. DDT induces the microsomal metabolism of DDT in several strains of houseflies (*92*), and phenobarbital induces the metabolism of DDT in *Triatoma infestans* (*95*). Phenobarbital, butylated hydroxytoluene, and triphenylphosphate increase the concentration of cytochrome P-450 and induce microsomal oxidase activity in several varieties of houseflies (*96*). Treatment of wax moth larvae with phenobarbital or chlorcyclizine decreases the toxicity of parathion and increases by several times the rate of EPN detoxification, *p*-nitroanisole *O*-demethylation, and the activity of reduced

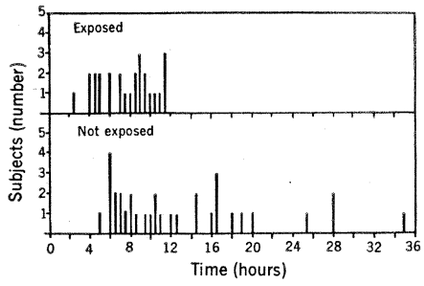

Fig. 4. The half-life of antipyrine in the plasma of human subjects exposed to insecticides and in the plasma of control subjects (*40*).

nicotinamide adenine dinucleotide (NADPH)-neotetrazolium (NT)-reductase in gut homogenate from wax moth larvae (*97*). However, microsomal oxidase activity was not induced in several other insects treated with drugs and insecticides (*98*). Exposure of the housefly, *Musca domestica* L., to DDT or dieldrin enhanced the metabolism of DDT, aldrin, allethrin, propoxur, and diazinon (*99*). The microsomal oxidation of heptachlor and naphthalene was increased severalfold in dieldrin-resistant houseflies exposed to sublethal doses of dieldrin (*100*), and the susceptibility of these insects to carbaryl was decreased. The ability of

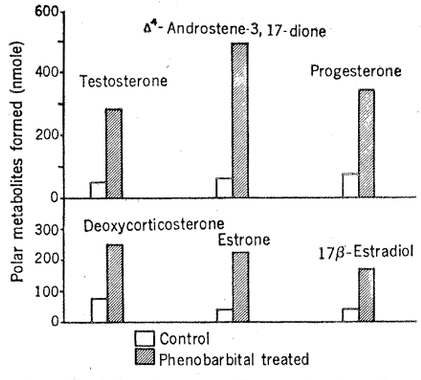

Fig. 5. Stimulatory effect of phenobarbital on steroid hydroxylation by rat liver microsomes (*102–104*). Immature rats were injected intraperitoneally with 37 mg of sodium phenobarbital per kilogram of body weight twice daily for 4 days. The animals were killed the following day, and microsomes from 330 mg of male rat liver were incubated with 700 nmole of [4-^{14}C]testosterone, Δ^4[4-^{14}C]androstene-3,-17-dione, [4-^{14}C]progesterone, or [4-^{14}C]-deoxycorticosterone for 5 minutes at 37°C in the presence of an NADPH-generating system. Microsomes from 330 mg of female rat liver were incubated with 700 nmole of [4-^{14}C]estradiol or [4-^{14}C]estrone for 15 minutes in the presence of an NADPH-generating system. Formation of polar metabolites with the chromatographic mobility of hydroxylated substrate was measured.

halogenated hydrocarbon pesticides to stimulate their own metabolism and the metabolism of other pesticides by microsomal enzymes suggests that the resistance and cross-resistance that occurs in insects after they have been sprayed with various chemicals may, in part, result from the induction of enzymes that detoxify pesticides in insect microsomes.

Environmental Chemicals and Steroid Metabolism

The hydroxylation of steroids by liver microsomes is influenced by the same factors that affect drug oxidations, suggesting that drugs and steroids are substrates for the same hydroxylating enzymes (*4, 5, 101*). Treatment of rats with phenobarbital for several days increases the activity of enzymes in liver microsomes that hydroxylate androgens, estrogens, progestational steroids, and adrenocortical steroids (Fig. 5). The administration of as little as 1 mg/kg of sodium phenobarbital to rats twice daily for 4 days increases the activity of liver microsomal enzymes that hydroxylate 17β-estradiol and estrone (*102*). Several structurally unrelated chemicals that stimulate the activity of drug-metabolizing enzymes also stimulate steroid hydroxylase activity. Examples of such compounds include phenobarbital, diphenylhydantoin, chlorcyclizine, norchlorcyclizine, orphenadrine, phenylbutazone, and several halogenated hydrocarbon insecticides (*101, 102–105*).

The accelerated hydroxylation of steroid hormones by liver microsomal enzymes of rats treated with drugs and insecticides is reflected in vivo by an accelerated metabolism and altered physiologic action of steroids. The increased progesterone hydroxylase activity induced by phenobarbital, chlordane, and DDT is associated with a decrease in the anesthetic action of large doses of progesterone and a lowered concentration of progesterone and its metabolites in the brain and total body of the rat (*104*). Long-term treatment with phenobarbital reduces the anesthetic action of deoxycorticosterone, androsterone, and Δ^4-androstene-3,17-dione and accelerates their metabolism by liver microsomes. Treatment of immature male rats with phenobarbital or chlordane for several days prior to an injection of testosterone or testosterone propionate inhibits the growth-promoting effect of these androgens on the seminal vesicles (*106*).

Halogenated hydrocarbon insecticides are potent stimulators of 17β-estradiol and estrone metabolism, and these inducers decrease the action of estrogens on the uterus (*19, 101, 102, 105, 107*). When immature female rats are treated with chlordane, dieldrin, heptachlor, lindane, *p,p'*-DDD, *p,p'*-DDE, or toxaphene for several days before they are given estrone, the increase in uterine wet weight caused by this estrogen is inhibited. The inhibitory effect of chlordane and phenobarbital on the uterotropic action of [^{3}H]estrone is associated with a decreased concentration of tritiated estrogen in the uterus (Table 4). Long-term treatment of rats with phenobarbital and other microsomal enzyme inducers also inhibits the uterotropic action of ethynyl estradiol-3-methylether (mestranol), norethindrone, and norethynodrel (*108*)—compounds used extensively as oral contraceptives—but the significance of these drug interactions for humans is not known.

Compounds that inhibit drug-metabolizing enzymes in liver microsomes also inhibit steroid metabolism and augment the action of steroids in animals. SKF 525-A potentiates the action of many drugs by inhibiting their microsomal metabolism (*109*), and this compound potentiates the action of estrone on the rat uterus (Table 5) and the induction by cortisol of hepatic tyrosine transaminase in the rat (*110*). Treatment of rats with carbon tetrachloride impairs the oxidation of several drugs in vitro and in vivo, and this effect is associated with a decreased concentration of cytochrome P-450 in liver microsomes (*22, 23, 111*). The activity of drug-metabolizing enzymes declined to about 10 percent of normal within 8 hours after the administration of carbon tetrachloride, and enzyme activity remained low for about 24 hours before gradually returning to the control value during the next 7 days. In rats treated with 0.06 to 0.67 milliliter of carbon tetrachloride per kilogram 24 hours before being killed there was marked inhibition of the microsomal metabolism of estrone and 17β-estradiol (*24*). The inhibitory effect of carbon tetrachloride on the metabolism of estrogens in vitro was reflected in vivo by an enhanced uterotropic action of 17β-estradiol and estrone in animals treated with carbon tetrachloride. The effect of carbon tetrachloride on the action of estrone is shown in Table 5.

Compounds that stimulate the hydroxylation of steroids by liver microsomes in animals also alter pathways of steroid metabolism in man. Treatment of human subjects with phenobarbital, *N*-phenylbarbital, diphenylhydantoin, phenylbutazone, antipyrine, *o,p'*-DDD, or the environmental exposure of people to DDT in a DDT factory, markedly stimulates the metabolism of cortisol to 6β-hydroxycortisol, a minor metabolite of cortisol (*41, 112–117*), and treatment with *N*-phenylbarbital alters the relative amounts of testosterone metabolites excreted in the urine (*118*). Since stimulators of liver microsomal hydroxylases increase the urinary excretion of 6β-hydroxycortisol in man, the measurement of this substance in urine deserves additional study as a possible index of man's ability to hydroxylate drugs and steroids. Although numerous drugs and environmental chemicals enhance the hydroxylation of steroids and alter the relative proportion of steroid metabolites in man, more work is needed to determine the physiological importance of these changes in steroid hydroxylation.

Table 3. Variability in the induction of benzo[*a*]pyrene hydroxylase activity in human placenta. All subjects smoked 15 to 20 cigarettes daily during pregnancy. Variability in benzo[*a*]pyrene hydroxylase activity was not related to medication taken during or prior to delivery (*11, 48*).

Subject	Hydroxybenzo[*a*]pyrene formed by placenta (ng g^{-1} hour^{-1})
L.B.	240
G.A.	260
P.C.	547
C.G.	643
A.T.	1,269
J.K.	1,317
L.C.	1,860
C.J.	4,289
E.R.	4,390
D.B.	5,267
D.A.	15,181
H.J.	16,524
M.N.	17,100

Estrogenic Action of DDT and Other Environmental Chemicals

During investigations on the inhibitory effect of halogenated hydrocarbon insecticides on the action of estrogens, we unexpectedly found that technical grade DDT, methoxychlor, and *o,p'*-DDT, a major component of technical grade DDT, possessed estrogenic activity in the rat (*119, 120*). A similar estrogenic action of *o,p'*-DDT and some related compounds was also observed by Bitman and his associates in studies with rats, chickens, and quail (*121–123*), and by Duby *et al.* in studies with mink (*124*). The uterotropic action of technical grade DDT in the immature female rat is shown in Fig. 6. A smaller response was observed after administration of purified *p,p'*-DDT, and little or no estrogenic activity was observed with *o,p'*-DDD, *m,p'*-DDD, *p,p'*-DDD or *p,p'*-DDE. The intraperitoneal injection of as little as 5 mg of technical grade DDT or 1 mg of *o,p'*-DDT, per kilogram of body weight, caused a significant increase in uterine wet weight in the immature female rat. Technical grade DDT or *o,p'*-DDT also increased uterine wet weight in ovariectomized adult rats, indicating that the effect of the DDT analogs was not mediated through the ovaries. Technical grade DDT or purified *o,p'*-DDT administered 2 hours before an injection of 17β-[6,7-^{3}H]-estradiol inhibited the uptake of this steroid by the uterus in vivo, probably

Table 4. Effect of stimulators of estrogen hydroxylation on the uterine response to estrone.

Treatment	Estrone	Uterine wet weight (mg)	Inhibition of response (%)	Estrone in the uterus (pg-eq)	Decrease (%)
		*Experiment 1**			
Control	−	19.5 ± 0.6			
	+	30.8 ± 1.8		42.8 ± 1.4	
Phenobarbital	−	18.7 ± 0.2			
	+	19.7 ± 0.5	91	13.0 ± 0.4	70
		Experiment 2†			
Control	−	27.3 ± 0.9			
	+	40.2 ± 1.7		21.4 ± 0.8	
Chlordane	−	27.4 ± 1.1			
	+	28.3 ± 1.5	93	10.9 ± 0.9	49

* In experiment 1, immature female rats were injected with 37 mg of sodium phenobarbital per kilogram twice daily for 4 days. On the fifth day, 0.3 μg of tritiated estrone was injected intraperitoneally. The rats were killed 4 hours later, the uteri weighed, and radioactivity in the uteri determined. Each value represents the average ± standard error from 6 to 8 rats (*102*). † In experiment 2, immature female rats were injected intraperitoneally with 25 mg of chlordane per kilogram once daily for 7 days. Twenty-four hours after the last injection, 0.2 μg of tritiated estrone was injected intraperitoneally, and the rats were killed 4 hours later (*105*).

by competing for sites that bind 17β-estradiol (*119, 120*).

In rats treated with carbon tetrachloride, a potent inhibitor of drug metabolism, the uterotropic action of *o,p'*-DDT and technical grade DDT is inhibited, suggesting that the action of *o,p'*-DDT on the uterus may depend on conversion of this substance to estrogenic metabolites (*120*). The administration of *o,p'*-DDT, like 17β-estradiol, increases glycogen (*122, 125*) and RNA synthesis (*120*) and augments the activities of several glycolytic and hexose monophosphate shunt enzymes in the uterus of the ovariectomized rat, and these effects are blocked by actinomycin and cycloheximide (*125*). The estrogenic activity of *o,p'*-DDT in the female rat is about 1/10,000 that of 17β-estradiol (*121*). Because *o,p'*-DDT probably owes its action to a hydroxylated metabolite, and because marked species differences in the hydroxylation of foreign compounds are well known, it would be of interest to determine the relative estrogenic activity of *o,p'*-DDT in various mammalian and avian species.

Bitman and Cecil studied 52 compounds related to DDT, using the 18-hour glycogen response of the immature rat uterus as an index of estrogen action (*122*). Diphenylmethane, diphenylethane, and triphenylmethane compounds were active when a *p-* or *p'*-position was unoccupied or occupied by a hydroxy or methoxy group. Polychlorinated biphenyls and polychlorinated triphenyls (compounds which are environmental pollutants of industrial origin) and phenolthalol and phenophthalein (compounds which are used as laxatives in man) were estrogenically active.

Effects of Environmental Contaminants on Reproduction

The role of DDT and other pesticides in saving lives by controlling disease-carrying pests is well known (*126*), but the significance to public health and wildlife of the pollution of our environment with microsomal enzyme inducers or inhibitors and weakly estrogenic analogs of DDT, polychlorinated biphenyls, polychlorinated triphenyls, and other halogenated hydrocarbon insecticides is not known. The decline of certain species of birds that is attributed to the use of DDT, polychlorinated biphenyls, and various chlorinated hydrocarbon insecticides (*127, 128*) may be caused, in part, by thin eggshells resulting from enhanced metabolism of estrogens and other steroid hormones. An adverse effect of DDT on eggshell thickness and calcium deposition was reported in the Japanese quail (*129*) and Alaskan peregrine falcon (*130*). The deposition of medullary bone, the chief source of calcium during egg and eggshell formation, is largely controlled by 17β-estradiol (*131*), and enhanced estrogen metabolism, or the occupation of estrogen-binding sites by weakly estrogenic DDT metabolites, might result in impaired eggshell formation. Administration of DDT to pigeons enhances the hepatic metabolism of 17β-estradiol, progesterone, and testosterone (*132*), and polychlorinated biphenyls (Arochlor 1254 and Arochlor 1262) stimulate hepatic 17β-estradiol metabolism in the pigeon and American kestrel (*128, 133*). Additional studies in birds suggest that halogenated hydrocarbon insecticides may enhance the metabolism of endogenous estrogens in vivo. In ring doves fed 10 ppm of DDT, hepatic estrogen metabolism was increased, and the concentration of 17β-estradiol in the blood was decreased, which can explain the decreased deposition of medullary bone calcium and the delay in egg laying observed in the DDT-fed birds (*134*).

In beagle dogs, the daily administration of 6 to 12 mg/kg of *p,p'*-DDT or 0.15 to 0.3 mg/kg of aldrin, for 5 days a week for 14 months, caused adverse effects on reproduction 2 weeks to 16 months after discontinuation of the insecticides (*135*). The primary deleterious effects were delayed estrus, reduction in the libido of males, stillbirths, lack of mammary development, reduced milk production, and a high mortality rate in the offspring.

The chlorinated insecticide Kepone (chlordecone) interferes with reproduction in birds and mammals [cited in (*136*)], causes constant estrus in mice (*137*) and has a marked estrogenic effect in quail (*136*). Studies of reproduction in rodents revealed that chlordane decreases fertility in female rats (*138*) and mice (*105*), and that aldrin disturbs the estrus cycle of rats (*139*). Bernard and Gaertner (*140*) reported a decrease in the reproductive success of C57 black mice when they were fed 200 to 300 ppm of technical grade DDT, but no adverse effect on fertility was observed in rats fed 20 to 200 ppm (*141*) or in mice fed 7 ppm of this insecticide (*142*). No detrimental effect on reproduction occurred when rats were fed 1 to 15 ppm of *p,p'*-DDT or *o,p'*-DDT (*124, 143*), and the injection of 900 μg of *p,p'*-DDT or *o,p'*-DDT on days 1, 2, and 3 of pregnancy did not influence the number of embryos surviving to day 10 of pregnancy in the rat (*124*).

Exposure of newborn female rats to exogenous estrogens or androgens induces permanent sterility with polycystic ovaries, anovulation, persistent vaginal estrus, and absence of female mating behavior (*144*). Clomiphene, a chemical with weak estrogenic properties, also produces permanent sterility (*145*), and a recent study conducted by Heinrichs *et al.* indicated that the injection of 1 mg of *o,p'*-DDT into rats on the second, third, and fourth day of life significantly advanced puberty, induced persistent vaginal estrus after a period of normal estrus cycles, and caused the development of follicular cysts in the ovaries and a reduction in the number of corpora lutea (*146*). Heinrichs *et al.* suggested that the syn-

Table 5. Effect of inhibitors of estrogen hydroxylation on the uterine response to estrone.

Treatment	Estrone	Uterine wet weight (mg)	Response increase (%)	Estrone in the uterus (pg-eq)	Increase (%)
		*Experiment 1**			
Control	−	18.4 ± 0.3			
	+	20.3 ± 0.9		7.9 ± 0.6	
SKF 525-A	−	19.5 ± 0.3			
	+	25.0 ± 0.7	189	15.3 ± 1.9	94
		Experiment 2†			
Control	−	19.9 ± 0.5			
	+	23.1 ± 0.7		9.7 ± 1.2	
CCl_4	−	20.0 ± 0.7			
	+	28.0 ± 1.1	148	65.8 ± 15.7	580

* In experiment 1, immature female rats were injected intraperitoneally with 25 mg of SKF 525-A (β-diethylaminoethyl diphenylpropylacetate) per kilogram, and 0.1 μg of tritiated estrone was injected intraperitoneally 30 minutes later. The rats were killed 4 hours after the dose of estrone, the uteri weighed, and radioactivity in the uteri determined. † In experiment 2, immature female rats were given oral doses of 0.67 ml of carbon tetrachloride per kilogram, and 0.1 μg of tritiated estrone was injected intraperitoneally 24 hours later. All rats were killed 4 hours after the administration of estrone. Each value represents the average ± standard error from 6 to 8 rats (*24*).

Table 6. Effect of phenobarbital received by women during pregnancy on the concentration of total bilirubin in the serum of their newborn babies. Twelve pregnant women were treated with sodium phenobarbital (average dose, 60 mg/day) for 2 weeks or longer prior to delivery. The concentration of total serum bilirubin in the serum of their offspring and in 16 control babies was compared during the first 4 days of life. Rh- and ABO-sensitized and premature babies were excluded. All babies in this study received vitamin K shortly after birth (*160*).

Day	Serum bilirubin (milligrams per 100 ml)	
	Control	Phenobarbital
1	3.8 ± 0.4	2.1 ± 0.4
2	5.0 ± 0.6	2.5 ± 0.4
3	5.7 ± 0.7	2.2 ± 0.4
4	5.2 ± 0.8	1.8 ± 0.4

drome observed in rats treated with *o,p'*-DDT resembled the polycystic ovary syndrome and sterility found in some women (*147*), and that the presence of DDT in the environment of the fetus and newborn might play a role in the development of the human syndrome. However, the dose of *o,p'*-DDT used in newborn rats was large, and it would be important to determine the amount of *o,p'*-DDT that is required in the newborn for abnormal development of the reproductive system to occur.

Environmental Chemicals, Lipid-Soluble Vitamins, and Bilirubin

The induction of microsomal enzymes may alter the metabolism and action of lipid-soluble vitamins. Long-term anticonvulsant therapy has been associated with osteomalacia and with reduced concentrations of calcium and elevated concentrations of alkaline phosphatase in the serum. It has been suggested that drug-mediated enzyme induction may be responsible for the osteomalacia by causing an increased metabolic inactivation of vitamin D (*148*). Administration of vitamin D to patients receiving anticonvulsants resulted in a return toward normal concentrations of calcium and alkaline phosphatase in the serum. Further evidence that enzyme induction can decrease the action of vitamin D came from the finding that rats treated with phenobarbital are protected from loss of weight, hypercalcemia, and renal calcinosis produced by the administration of a single large dose of calciferol (*149*).

Spironolactone, a stimulator of hepatic microsomal enzyme activity, decreases the bone absorption caused by overdoses of vitamin A in rats and decreases the concentration of vitamin A in the serum (*150*). It has also been found that DDT lowers the concentration of vitamin A in rat serum (*151*).

Hemorrhagic episodes occur in some infants born to mothers taking anticonvulsants for epilepsy (*152*). The coagulation defect is similar to that found in vitamin K deficiency and is prevented by the administration of vitamin K. These results suggest that inducers of hepatic enzymes may influence the metabolism of vitamin K.

Many normal body constituents possessing high lipid solubility are substrates for inducible drug-metabolizing enzymes (*5*), and this discovery has opened up new possibilities for the use of suitable enzyme inducers for the treatment of human diseases. The administration of barbiturates to animals enhances the enzymatic glucuronidation of bilirubin by liver microsomes, stimulates bile flow, and accelerates the metabolism of bilirubin in vivo (*153*). Studies in man indicate that long-term administration of phenobarbital lowers the concentration of bilirubin in the serum of patients with chronic intrahepatic cholestasis (*154*) and in the serum of jaundiced infants (*155–157*). The decrease in plasma concentration of bilirubin in subjects treated with phenobarbital was associated with a decreased half-life of bilirubin (*156*). The effectiveness of phenobarbital in lowering the concentration of serum bilirubin in infants with congenital nonhemolytic jaundice suggested that these infants did not have a complete genetic block in their ability to synthesize the enzymes involved in bilirubin metabolism. This observation is of considerable importance, for it suggests that some "genetic diseases" might be treated with a suitable enzyme inducer. Thompson *et al.* (*158*) showed that the administration of DDT to a subject with nonhemolytic jaundice also decreased the concentration of bilirubin in the serum; after this treatment was stopped, the concentration of bilirubin remained low for several months, possibly because of the prolonged storage of DDT and its metabolites in fat. The mechanism of this effect appears similar to that postulated for barbiturates, since, in rats, DDT increased hepatic glucuronyl transferase activity. In some patients with hyperbilirubinemia, phenobarbital

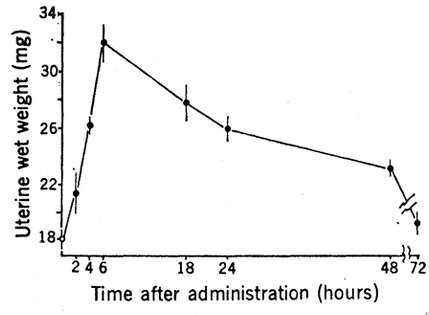

Fig. 6. Effect of technical-grade DDT on uterine wet weight (*120*). Immature female rats were injected intraperitoneally with 50 mg/kg of technical-grade DDT.

treatment did not lower the concentration of bilirubin (*157*), and such results are similar to those obtained with the homozygous Gunn rat (*159*).

Treatment of pregnant animals with phenobarbital increases the concentrations of enzymes that metabolize drugs and bilirubin in the newborn, and it appears that this effect also occurs in human beings (*160, 161*). Administration of 60 mg of phenobarbital to pregnant women daily for 2 weeks or longer before delivery markedly inhibited the transient hyperbilirubinemia that normally occurs in the newborn during the first few days of life (Table 6)—presumably by stimulating hepatic enzymes in the newborn that metabolize bilirubin. Studies by Boggs *et al.* (*162*) indicate a positive relationship between increasing concentrations of bilirubin in the serum of newborn babies and the incidence of low motor and low mental scores attained at 8 months of age. These relationships do not begin abruptly at high concentrations of bilirubin, but the incidence of adverse effects rises gradually and becomes substantial at a concentration of 16 to 19 mg of bilirubin per 100 ml of serum. The results suggest that relatively low levels of bilirubin may adversely affect the central nervous system, and that it may be desirable to prevent or decrease the neonatal jaundice that occurs normally in human beings during the first few days of life. It would be important to know if prevention of the transient hyperbilirubinemia that occurs in the newborn would decrease the incidence of minimal neurological deficits, or perhaps even enhance human intelligence. Studies on the use of phenobarbital or other microsomal enzyme inducers to lower serum bilirubin should proceed cautiously, however, since these compounds may stimulate the activity of liver microsomal

enzymes that metabolize steroid hormones, lipid-soluble vitamins and other endogenous substances. Indeed, a coagulation defect that occurs in some newborn babies from women treated with anticonvulsants during pregnancy (*152, 163*) may be caused by the induction of microsomal enzymes that metabolize vitamin K, since the coagulation defect is prevented by administration of this vitamin.

Conclusions

It is evident that metabolic interactions can occur among drugs, insecticides, food additives, carcinogenic hydrocarbons, and a variety of environmental chemicals. A common denominator governing these effects is the versatile nature of the liver microsomal enzymes that metabolize chemicals with diverse structures and biological activities, and the fact that these enzymes can be stimulated or inhibited by other chemicals administered simultaneously. The discovery of these particular enzymes in the 1950's laid the groundwork for the current research on metabolic interactions. Such research provides information that is helpful in the evaluation of the safety and efficacy of drugs and environmental chemicals, and suggests new directions for further research. Some examples are as follows.

1) The ability of a drug to stimulate or inhibit the metabolism of another drug can explain some of the side effects that occur in clinical practice. Although these interactions have been well documented during therapy with coumarin anticoagulants and several other therapeutic agents, more research is needed in view of the large number of drugs a patient may receive simultaneously.

2) Tolerance to certain drugs after prolonged exposure to them may be explained by enzyme induction, but the true significance of induction must be further explored. Enzyme induction must obviously be considered in the design of safety studies for new drugs (*164*).

3) The ability of environmental chemicals to modify drug action provides another area for further investigation. That such interactions are important in animals is emphasized by the fact that the first observation of this phenomenon was made by chance when an animal colony was sprayed with chlordane. Because phenobarbital administration to dairy cows lowers the concentration of DDT-related substances in milk, the potential use of enzyme inducers to reduce insecticide contamination in food-producing animals should be further explored. There is evidence that some insecticides stimulate whereas others inhibit drug metabolism, but the significance of these effects remains to be established. Ethanol, which may be considered an environmental chemical, has been shown to influence the metabolism of some drugs and thus modify their action. The smoking of cigarettes appears to stimulate the metabolism of nicotine, lower the concentration of phenacetin in the plasma, and induce enzymes in the placenta that hydroxylate benzo[*a*]pyrene.

4) Minor metabolites may be responsible for adverse reactions to drugs, and these pathways may be stimulated or inhibited by the simultaneous administration of another drug or exposure to an environmental chemical. The role of epoxides as active metabolites of carcinogens should be further investigated.

5) The effect of drugs on the metabolism of steroids, lipid-soluble vitamins, and other normal body constituents has opened new areas of investigation. Symptoms of vitamins D and K deficiencies have been observed following therapy with anticonvulsant drugs. Enzyme induction has been explored for the treatment of certain metabolic diseases, such as hyperbilirubinemia. The effect of insecticides on fertility in animals may be explained, at least in part, by the induction of enzymes that metabolize progesterone and other steroids.

A considerable amount of information has already been obtained on the metabolic interactions between environmental chemicals and drugs. Much more research must be done, however, and it must include basic studies of tissue enzymes that may explain the effects of many of the observed interactions, as well as clinical studies in man that may help to establish the relevance to public health of the results obtained in vitro and in vivo with animals. In recent years, the National Academy of Sciences, the World Health Organization, the Food and Drug Administration, and the National Institutes of Health, among other groups, have recognized the importance of such investigations and have emphasized the need for a concerted effort by scientists in many disciplines to determine the importance to public health of the interactions that occur among the multitude of environmental chemicals to which we are all exposed.

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Reflections on Campus Pessimism

Grounds for pessimism about universities are well known; there are also grounds for cautious optimism.

Samuel Gorovitz

In "Whither United States Universities?" (*1*), George Pake provides a compact and perceptive overview of problems facing higher education in the United States. His account is provocative and pessimistic—and thus is, in the end, saddening. In this article, I discuss some of the issues with respect to which Pake is provocative, and I argue that his grounds for pessimism, although all too real, are nonetheless misleading and that the picture he paints is therefore unnecessarily bleak.

I should emphasize that Pake's remarks about the functions and values of universities, the power elements that affect them, the pivotal issues that confront them, and the problems of academic freedom, equality of opportunity, and internal governance all give evidence (in spite of his disclaimer) of a profound understanding of higher education and of a corresponding commitment to nurturing it. I agree with a great deal of what he says. Yet what he says is unsatisfying, not just in that one wishes that much of it were not true, but also in that it focuses on the problems and weaknesses of higher education without a comparable acknowledgment of its opportunities and strengths.

The multiple crises that have beset universities have been mixed blessings. They have given the impression, largely justified, that universities are widely in

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