Discuss in details the factors affecting drug metabolism.

Drugs can be metabolised by many different pathways and many factors can determine which pathway is used by which drug and to what extent a particular drug is biotransformed by a particular pathway. The relative amount of any particular metabolite is determined by the concentration and activity of the enzyme(s) responsible for the biotransformation as well as dose, frequency, route of administration, tissue distribution and protein binding of the drug. The rate of metabolism of a drug is particularly important for its pharmacological action as well as its toxicity. For example, if the rate of metabolism of a drug is decreased, this generally increases the intensity and duration of the drug action. In addition, decreased metabolic elimination may lead to accumulation of toxic levels of the drug. Conversely, an increased rate of metabolism decreases the intensity and duration of action as well as the drug's efficacy. These factors range from the species of organism studied to the environment in which that organism lives. Factors affecting drug metabolism can be split into internal (i.e. physiological and pathological) factors and external factors. These are, of course, purely arbitrary divisions and much interaction exists between the various factors (cf. hormonal, sex and age influences)

Internal:

* species
* genetic (strain)
* age
* sex
* hormones
* disease
* Enzyme induction and enzyme inhibition.

External:

* diet
* environment

**INTERNAL FACTORS**

**Age Differences**

Age-related differences in drug metabolism are generally quite apparent in the newborn. In most fetal and newborn animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability seen. In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months. An illustration of the influence of age on drug metabolism is seen in the duration of action (sleep time) of hexobarbital in new-born and adult mice. When given a dose of 10 mg/kg of body weight, the new-born mouse sleeps more than 6 hours. In contrast, the adult mouse sleeps for fewer than 5 minutes when given the same dose.

In humans, oxidative and conjugative (e.g., glucuronida-tion) capabilities of newborns are also low compared with those of adults. For example, the oxidative (CYP) metabolism of tolbutamide appears to be markedly lower in new-borns. Compared with the half-life of 8 hours in adults, the plasma half-life of tolbutamide in infants is more than 40 hours. As discussed previously, infants possess poor glucuronidating ability because of a deficiency in glucuronyltransferase activity. The inability of infants to conjugate chloramphenicol with glucuronic acid appears to be responsible for the accumulation of toxic levels of this antibiotic, resulting in the so-called gray baby syndrome. Similarly, neonatal hyperbilirubin-emia (or kernicterus) results from the inability of newborn babies to glucuronidate bilirubin.

In elderly persons, the liver size is reduced, the microsomal enzyme activity is decreased and hepatic blood flow also declines as a result of reduced cardiac output, all of which contributes to decreased metabolism of drugs. For example, chlomethiazole shows a high bioavailability within the elderly, therefore they require a lower dose. There is some evidence in animals and humans that drug metabolism diminish with old age. Much of the evidence, however, is based on prolonged plasma half-lives of drugs that are metabolized totally or mainly by hepatic microsomal enzymes (e.g., antipyrine, phenobarbital, acetaminophen). In evaluating the effect of age on drug metabolism, one must differentiate between "normal" loss of enzymatic activity with aging and the effect of a diseased liver from [hepatitis](https://www.pharmacologicalsciences.us/hepatitis.html), [cirrhosis](https://www.pharmacologicalsciences.us/cirrhosis.html), etc., plus decreased renal function, because much of the water-soluble conjugation products are excreted in the liver. There is a strong correlation between age and renal clearance: for example, the renal excretion rate of an 80-year-old is about 50% of that of a 30-year-old. This is why patient age is an important factor to consider when prescribing drugs.

**Species and Strain Differences**

The metabolism of many drugs and foreign compounds is often species dependent. Human liver contains less cytochrome P-450 per gram of tissue than do the livers of other species. For example, rat liver contains approximately 30 to 50 nmol/g of Cytochrome P450, whereas human liver contains 10 to 20 nmol/g. Furthermore, human liver is 2 percent of body weight, whereas rat liver is approximately 4 percent. Different animal species may biotransform a particular xenobiotic by similar or markedly different metabolic pathways. Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway. This is a problem when a new drug is under development. A new drug application requires the developer to account for the product as it moves from the site of administration to final elimination from the body. It is difficult enough to find appropriate animal models for a disease. It is even harder to find animal models that mimic human drug metabolism.

Species variation has been observed in many oxidative biotransformation reactions. For example, metabolism of amphetamine occurs by two main pathways: oxidative deamina-tion or aromatic hydroxylation. In human, rabbit, and guinea pig, oxidative deamination appears to be the predominant pathway; in the rat, aromatic hydroxylation appears to be the more important route. Phenytoin is another drug that shows marked species differences in metabolism. In the human, phenytoin undergoes aromatic oxidation to yield primarily GS)(-)-p-hydroxyphenytoin; in the dog, oxidation occurs to give mainly (R)(+)-m-hydroxyphenytoin.496 There is a dramatic difference not only in the position (i.e., meta or para) of aromatic hydroxylation but also in which of the two phenyl rings (at C-5 of phenytoin) undergoes aromatic oxidation.

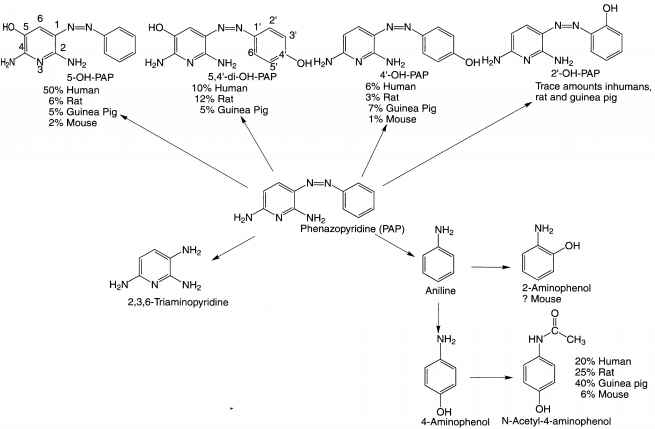
Species differences in many conjugation reactions also have been observed. Often, these differences are caused by the presence or absence of transferase enzymes involved in the conjugative process. For example, [cats](https://www.pharmacologicalsciences.us/cats.html) lack glucuronyltransferase enzymes and, therefore, tend to conjugate phenolic xenobiotics by sulfation instead. In pigs, the situation is reversed: pigs are not able to conjugate phenols with sulfate (because of lack of sulfotransferase enzymes) but appear to have good glucuronidation capability. The conjugation of aromatic acids with amino acids (e.g., glycine, glutamine) depends on the animal species as well as on the substrate. For example, [glycine conjugation](https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/info-xub.html) is a common conjugation pathway for benzoic acid in many animals. In certain birds (e.g., duck, goose, turkey), however, glycine is replaced by the amino acid ornithine.498 Phenylacetic acid is a substrate for both [glycine and glutamine](https://www.pharmacologicalsciences.us/pharmaceutical-chemistry/info-xub.html) conjugation in humans and other primates. However, nonprimates, such as rabbit and rat, excrete phenylacetic acid only as the glycine conjugate. The metabolism of the urinary antiseptic, phenazopyridine (Pyridium) depends strongly on the animal. The diazo linkage remains intact in over half of the metabolites in humans, whereas 40% of the metabolites in the guinea pig result from its cleavage. The metabolic product pattern in human or guinea pig does not correlate with that of either rat or mouse.

Strain differences in drug metabolism exist, particularly in inbred mice and rabbits. These differences apparently are caused by genetic variations in the amount of metabolizing enzyme present among the different strains. For example, in vitro studies indicate that cottontail rabbit liver microsomes metabolize hexobarbital about 10 times faster than New Zealand rabbit liver microsomes. Inter-individual differences in drug metabolism in humans are considered in the section that follows.

**Hereditary or Genetic Factors**

Marked individual differences in the metabolism of several drugs exist in humans. Many of these genetic or hereditary factors are responsible for the large differences seen in the rate of metabolism of these drugs. Genetic factors also appear to influence the rate of oxidation of drugs such as phenytoin, phenylbutazone, dicumarol, and nortriptyline. The rate of oxidation of these drugs varies widely among different individuals; however, these differences do not appear to be distributed bimodally, as in acetylation. In general, individuals who tend to oxidize one drug rapidly are also likely to oxidize other drugs rapidly. Numerous studies in twins (identical and fraternal) and in families indicate that oxidation of these drugs is under genetic control.

Many patients state that they do not respond to codeine and codeine analogs. It now is realized that their CYP2D6 isozyme does not readily O-demethylate codeine to form morphine. This genetic polymorphism is seen in about 8% of Caucasians, 4% of African Americans, and less than 1% of Asians. (Genetic polymorphism with CYP isozymes) There is limited evidence of polymorphism involving MAO-A and MAO-B. The chemical imbalances seen with some mental diseases may be the cause.



• Phenazopyridine metabolism in humans, guinea pigs, rats, and mice.

**Sex Differences**

The rate of metabolism of xenobiotics also varies according to gender in some animal species. A marked difference is observed between female and male rats. Adult male rats metabolize several foreign compounds at a much faster rate than female rats (e.g., N-demethylation of aminopyrine, hexobarbital oxidation, glucuronidation of o-aminophenol). Apparently, this sex difference also depends on the substrate, because some xenobiotics are metabolized at the same rate in both female and male rats. Differences in microsomal oxidation are under the control of sex hormones, particularly androgens; the anabolic action of androgens seems to [increase metabolism](https://www.pharmacologicalsciences.us/increase-metabolism.html).

Sex differences in drug metabolism appear to be species dependent. Rabbits and mice, for example, do not show a significant sex difference in drug metabolism. In humans, there have been a few reports of sex differences in metabolism. For instance, [nicotine](https://www.pharmacologicalsciences.us/nicotine.html) and aspirin seem to be metabolized differently in women and men. On the other hand, gender differences can become significant in terms of drug-[drug interactions](https://www.pharmacologicalsciences.us/drug-interactions.html) based on the drug's metabolism. For women, the focus is on drugs used for contraception. Note that the antibiotic rifampin, a CYP3A4 inducer, can shorten the half-life of oral contraceptives. In humans, women metabolize benzodiazepines slowly than men.

**Enzyme Induction**

The activity of hepatic microsomal enzymes, such as the CYP mixed-function oxidase system, can be increased markedly by exposure to diverse drugs, pesticides, polycyclic aromatic hydrocarbons, and environmental xenobiotics. The process by which the activity of these drug-metabolizing enzymes is increased is termed enzyme induction. The increased activity is apparently caused by an increased amount of newly synthesized enzyme. Enzyme induction often increases the rate of drug metabolism and decreases the duration of drug action.

Inducing agents may increase the rate of their own metabolism as well as those of other unrelated drugs or foreign compounds. Concomitant administration of two or more drugs often may lead to serious drug interactions as a result of enzyme induction. For instance, a clinically critical drug interaction occurs with phenobarbital and warfarin. Induction of microsomal enzymes by phenobarbital increases the metabolism of warfarin and, consequently, markedly decreases the anticoagulant effect. Therefore, if a patient is receiving warfarin anticoagulant therapy and begins taking phenobarbital, careful attention must be paid to readjustment of the warfarin dose. Dosage readjustment is also needed if a patient receiving both warfarin and phenobarbital therapy suddenly stops taking the barbiturate. The ineffectiveness of oral contraceptives in women on concurrent phenobarbital or rifampin therapy has been attributed to the enhanced metabolism of estrogens (e.g., 17a-ethinylestradiol) caused by phenobarbital513 and rifampin514 induction.

Mechanisms of enzyme induction:

* Increase in both liver size and liver blood flow
* Increase in both total and microsomal protein content
* Increased stability of enzymes
* Increased stability of cytochrome P-450
* Decreased degradation of cytochrome P-450
* Proliferation of smooth endoplasmic reticulum

Consequences of enzyme induction include:

* Decrease in pharmacological activity of drugs
* Increased activity where the metabolites are active
* Altered physiological status due to enhanced metabolism of endogenous compounds such as sex hormones. Some examples of drug induction are: Oral Contraceptive Steroids CYP3A4 Inactive, Excreted Induction 3 Rifampin

**Diseases**

While drug metabolism can occur in other organs, the primary site of drug metabolism is the liver, as the enzymes that facilitate the reactions are concentrated there. Cytochrome P450 refers to a family of liver enzymes that play an important role in drug metabolism. The activity of these enzymes varies depending on people’s age and genetic predisposition. Also, a number of cytochrome P450 mutations have been observed which can affect the rate of drug metabolism and thus affect the patient's response to treatment. Once the drug has been converted to an inactive substance through metabolism, the body must excrete it. The kidneys are the main organs of the body’s excretory system. However, small amounts of the drug can also be excreted in the bile and through minor excretion routes, such as sweat, saliva, exhalation, etc.

This implies that any damage to these organs will affect its function. Inability of the liver to metabolize drugs due to diseases such as cirrhosis or hepatitis and inability of the kidney(Nephritis) and other parts of the body to excrete said drugs following (or in the absence of) metabolism, leads to accumulation of the drug and its metabolites in the body which will have adverse effects on the body. Failure to metabolize a drug will lead to increase in the duration and intensity of drug action.

The possible cause in the effect of metabolism due to diseases may be: • Decreased enzyme activity in liver • Altered hepatic blood flow • Hypoalbuminaemia (leading to lower plasma binding of drugs). For example: glycine conjugation of salicylates, oxidation of Vitamin D and hydrolysis of procaine are impaired in kidney diseases

**Enzyme inhibition**

A decrease in the drug metabolizing ability of an enzyme is called as enzyme inhibition. The process of inhibition may be direct or indirect.

* Direct inhibition: It may result from interaction at the enzymic site, the net outcome being a change in enzyme activity. Direct enzyme inhibition can occur by one of the following mechanisms: i. Competitive inhibition: occurs when structurally similar compounds compete for the same site on an enzyme. ii. Non-competitive inhibition: occur when a structurally unrelated agent interacts with the enzyme and prevents the metabolism of drugs. iii. Product inhibition: occurs when the metabolic product competes with the substrate for the same enzyme.
* Indirect inhibition: it is caused by one of the following mechanism: i. Repression: it may be due to fall in the rate of enzyme synthesis or rise in the rate of enzyme degradation. ii. Altered physiology: it may be due to nutritional deficiency or hormonal imbalance. Some examples of enzyme inhibition are: CYP3A4 Active Antihistamine Terfenadine Inhibition Erythromycin Ketoconazole Enzyme inhibition is more important clinically than enzyme induction esp. for drugs with narrow therapeutic index. Eg: anticoagulants, antiepileptics, hypoglycemias,etc

**Hormones**

The CYP system is a constellation of enzymes responsible for most of the phase I reactions in drug metabolism. These enzymes are expressed mainly in the liver; however, they can be found in other tissues, including the kidneys, skin, intestine, lung, and brain. By definition, all proteins that contain CYP domains are enzymes. Theoretically, assorted endocrine or inflammatory conditions resulting in the oversecretion or under-secretion of a particular hormone/neuropeptide/cytokine could have potent effects on drug metabolism. Heretofore, such effects have been attributed to hormonal influences on: a) gastrointestinal drug absorption rates, b) drug binding protein systems, c) drug distribution volume, d) blood flow dynamics in drug target organs, e) renal or hepatic drugexcretion systems, or f) drug effector systems per se (e.g., the expression of receptor systems in which a drug interferes with ligand binding). The effects of endocrine or inflammatory conditions on pharmacokinetics are significant and complex, yet they remain rather poorly studied.

CYP3A4 is the predominant constitutive CYP system in the human liver. Substrates for the enzymes are both endogenous (e.g. steroids, fatty acids, eicosanoids, and retinoids) and exogenous (e.g. drugs, chemicals, and plant products). The CYP1, CYP2, and CYP3 families, particularly their members CYP1A2, CYP2C8, CYP2C18, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, CYP3A6, and CYP3A7 are responsible for the metabolism of more than 80% of the most commonly prescribed drugs.

**Effects of Thyroid Hormone Status**

The addition of triiodothyronine (T3) to primary hepatocytes significantly reduced CYP3A4 protein and mRNA. Conversely, experimental hypothyroidism in rats led to CYP3A2 induction and CYP2C11 suppression. Moreover, thyroidectomized rats exhibited a marked increase in CYP8B1 protein and mRNA levels, whereas treatment of normal rats with levothyroxine significantly decreased CYP8B1 enzyme activity and mRNA. The addition of T3 to a hepatoma cell line (HepG2) harboring a rabbit CYP2E1 transgene increased levels of CYP2E1 protein and mRNA. Treatment of the amphibian Xenopus laevis with T3 increased levels of CYP1A protein. After single oral doses of propranolol in hyperthyroid patients, the clearance of the drug has been variously reported to be increased, secondary to increased hepatic enzymatic activity, or unchanged. Similarly, clearance of metoprolol has been reported to be increased in hyperthyroid patients because it undergoes extensive hepatic metabolism to propranolol; in contrast, the oral clearance of sotalol and atenolol is not altered in hyperthyroidism because both drugs undergo mainly renal excretion.

**Effects of Ambient Levels of Glucocorticoids**

The relationship between glucocorticoids (GCs) and members of the CYP family is quite complex. On one hand, GCs are themselves partially metabolized by CYP3A enzymes; in that aspect, coadministration of CYP inhibitors, such as itraconazole, with steroids potentiates the effects of exogenous GCs, including increased suppression of the host’s hypothalamo-pituitary-adrenal axis. On the other hand, GCs are CYP enzyme inducers.

In other experimental systems, certain members of the CYP family showed a biphasic and dose dependent modulation after exposure to GCs. In human hepatocyte cultures, the expression of both CYP2C8 and CYP2C9 was increased by dexamethasone in a dose dependent manner

**Effects of Reproductive Hormones**

Gonadal steroids are among the most widely used compounds, either as oral contraceptive pills (OCPs) or as hormone replacement therapy (HRT) agents. Studies in ovariectomized rats after the administration of lindane (which has anti-estrogenic properties in rats) showed an increase in CYP1A, CYP2B1, and CYP2B2 proteins. Several human studies have shown that OCPs and HRT have a significant effect on CYP enzymes, generally inhibiting enzymatic activity. The clearance of caffeine is decreased by more than 50% with OCPs, probably secondary to CYP1A2 inhibition. Antipyrine metabolism is decreased in women on OCPs. Antipyrine is metabolized by several CYP family members, mainly CYP1A2, CYP2A6, and CYP3A.

In the treatment of Alzheimer’s disease, tacrine was more efficacious in postmenopausal subjects on HRT than in estrogen-deficient patients. The basis of the effect is the inhibition of CYP1A2-induced transformation of tacrine to its inactive metabolite 1-hydroxytacrine. Methylprednisone metabolism (mediated mainly by CYP3A4) was inhibited by OCPs. Low-dose OCPs inhibited the metabolism of certain benzodiazepines, such as alprazolam and triazolam, whereas they enhanced the metabolism of others, such as temazepam. Intake of OCPs significantly reduced CYP2C19 activity, but both HRT and OCPs decreased CYP2B6 activity. Finally, gestogen, a progestin, strongly inhibited CYP3A4 Activity. In contrast to the above findings, Gorski et al. found no difference in hepatic or intestinal CYP3A4 activity between menopausal women on HRT and matched control subjects. Similarly, no difference was noted in hepatic or renal CYP3A4 activity before and after OCP administration in premenopausal women.

Despite the generally inhibitory actions of estrogenic compounds on the CYP systems discussed above, several human studies have shown that pregnancy has minimal effects on CYP2C19 and CYP3A4 but does induce an increase in CYP2D6 levels. CYP3A1 is the major component of the CYP system in the rat placenta. Women with intrahepatic cholestasis during pregnancy exhibited significantly decreased placental P450-dependent oxygenases and P450-aromatase; these decreases might be associated with risks to the well-being of the fetus

**Effects of Growth Hormone Deficiency or Excess**

In male animals after hypophysectomy, continuous GH infusion—mimicking the female pattern of GH secretion—led to significant decreases of the initially high levels of microsomal CYP2C11 to levels typically found in normal female rats. The addition of GH to primary cultures of human hepatocytes increased CYP3A4 mRNA by 9.1-fold, yet no consistent change was noted in mRNA expression for CYP1A2, CYP2C9, or CYP2E1. GH induces the activity of hepatic CYP enzymes (probably through its mediator, IGF-1)

**EXTERNAL FACTORS**

**Diet**

The enzyme content and activity is altered by a number of dietary components.

* Low protein diet decreases and high protein diet increases the drug metabolizing ability as enzyme synthesis is promoted by protein diet and also raiss the level of amino acids for conjugation with drugs.
* Fat free diet depresses cytochrome P-450 levels since phospholipids, which are important components of microsomes become deficient.
* Grapefruit inhibits metabolism of many drugs and improve their oral bioavailability.
* Dietary deficiency of vitamins like Vitamin A, B2, B3, C and E) and minerals such as Fe, Ca, Mg, Zn retard the metabolic activity of enzymes.
* Starvation results in decreased amount of glucuronides formed than under normal conditions.

**Environmental chemicals**

Several environmental agents influence the drug metabolizing ability of enzymes through induction. For example:

* Halogenated pesticides such as DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
* Organophosphate insecticides and heavy metals such as mercury, nickel, cobalt and arsenic inhibit drug metabolizing ability of enzymes.
* Other environmental factors that may influence drug metabolism are temperature, altitude, pressure, atmosphere, etc.

**Altered physiological factors**

**Pregnancy**

Pregnancy is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alteration in drug metabolism. These include elevated concentrations of various hormones such as estrogen, progesterone, placental growth hormones and prolactin.For example: in women, the metabolism of promazine and pethidine is reduced during pregnancy. It was also confirmed by the study in animals. In pregnant Sprague-Dawley rats, hexobarbital biotransformation indicated unchanged or slightly elevated microsomal enzyme activity compared to normal rats.

Despite the generally inhibitory actions of estrogenic compounds on the CYP systems discussed above, several human studies have shown that pregnancy has minimal effects on CYP2C19 and CYP3A4 but does induce an increase in CYP2D6 levels. CYP3A1 is the major component of the CYP system in the rat placenta. Women with intrahepatic cholestasis during pregnancy exhibited significantly decreased placental P450-dependent oxygenases and P450-aromatase; these decreases might be associated with risks to the well-being of the fetus.