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COURSE BCH313 assignment

1.Discuss in details the factors affecting drug metabolism.

**Drug metabolism** is the [metabolic breakdown](https://en.m.wikipedia.org/wiki/Metabolism) of [drugs](https://en.m.wikipedia.org/wiki/Drug) by living [organisms](https://en.m.wikipedia.org/wiki/Organism), usually through specialized [enzymatic](https://en.m.wikipedia.org/wiki/Enzyme) systems.

 The duration and intensity of pharmacological action of most lipophilic drugs are determined by the rate they are metabolized to inactive products.

 Many substances (such as drugs and foods) affect the cytochrome P-450 enzymes. If these substances decrease the ability of the enzymes to break down a drug, then that drug's effects (including side effects) are increased. If the substances increase the ability of the enzymes to break down a drug, then that drug's effects are decreased. Most drugs must pass through the liver, which is the primary site for drug metabolism. Once in the liver, enzymes convert prodrugs to active metabolites or convert active drugs to inactive forms. The liver’s primary mechanism for metabolizing drugs is via a specific group of cytochrome P-450 enzymes.

 Some drugs are chemically altered by the body (metabolized). The substances that result from metabolism (metabolites) may be inactive, or they may be similar to or different from the original drug in therapeutic activity or toxicity. Some drugs, called prodrugs, are administered in an inactive form, which is metabolized into an active form. The resulting active metabolites produce the desired therapeutic effects. Metabolites may be metabolized further instead of being excreted from the body. The subsequent metabolites are then excreted. Excretion involves [elimination of the drug](https://www.merckmanuals.com/home/drugs/administration-and-kinetics-of-drugs/drug-elimination) from the body, for example, in the urine or bile.

 The rate of metabolism determines the duration and intensity of a drug's pharmacologic action. Drug metabolism also affects [multidrug resistance](https://en.m.wikipedia.org/wiki/Multidrug_resistance) in [infectious diseases](https://en.m.wikipedia.org/wiki/Infectious_disease), [chemotherapy](https://en.m.wikipedia.org/wiki/Chemotherapy) for [cancer](https://en.m.wikipedia.org/wiki/Cancer), and the actions of some drugs as [substrates](https://en.m.wikipedia.org/wiki/Substrate_%28chemistry%29) or [inhibitors](https://en.m.wikipedia.org/wiki/Enzyme_inhibitor) of enzymes involved in xenobiotic metabolism are a common reason for hazardous [drug interactions](https://en.m.wikipedia.org/wiki/Drug_interaction). Drug metabolism is divided into three phases. In phase I, enzymes such as [cytochrome P450 oxidases](https://en.m.wikipedia.org/wiki/Cytochrome_P450_oxidase) introduce reactive or polar groups into xenobiotics. These modified compounds are then conjugated to polar compounds in phase II reactions. These reactions are catalysed by [transferase](https://en.m.wikipedia.org/wiki/Transferase) enzymes. Finally, in phase III, the conjugated xenobiotics may be further processed, before being recognised by [efflux transporters](https://en.m.wikipedia.org/wiki/Efflux_%28microbiology%29) and pumped out of cells. Drug metabolism often converts [lipophilic](https://en.m.wikipedia.org/wiki/Lipophilic) compounds into [hydrophilic](https://en.m.wikipedia.org/wiki/Hydrophile) products that are more readily [excreted](https://en.m.wikipedia.org/wiki/Excretion).

 Drug metabolism also varies based on several ongoing factors that has to do with the human body. Anything that increases the rate of metabolism of a pharmacologically active metabolite will decrease the duration and intensity of the action of the drug.

An example of this is the fact drugs are also metabolized more slowly in [fetal](https://en.m.wikipedia.org/wiki/Fetal), [neonatal](https://en.m.wikipedia.org/wiki/Neonatal) and [elderly](https://en.m.wikipedia.org/wiki/Elderly) [humans](https://en.m.wikipedia.org/wiki/Human) and [animals](https://en.m.wikipedia.org/wiki/Animal) than in [adults](https://en.m.wikipedia.org/wiki/Adult).

Various physiological and pathological factors can also affect drug metabolism.

Physiological factors that can influence drug metabolism include age, individual variation e.g.  [enterohepatic circulation](https://en.m.wikipedia.org/wiki/Enterohepatic_circulation), [nutrition](https://en.m.wikipedia.org/wiki/Nutrition), [intestinal flora](https://en.m.wikipedia.org/wiki/Intestinal_flora), or [sex differences](https://en.m.wikipedia.org/wiki/Sex_difference).

* **Age-** Because metabolic enzyme systems are only partially developed at birth, newborns have difficulty metabolizing certain drugs. As people age, enzymatic activity decreases, so that older people, like newborns, cannot metabolize drugs as well as younger adults and children do (see [Aging and Drugs](https://www.merckmanuals.com/home/older-people%E2%80%99s-health-issues/aging-and-drugs)). Consequently, newborns and Older people often need smaller doses per pound of body weight than do young or middle-aged adults.
* **Genetic variation (**[**polymorphism**](https://en.m.wikipedia.org/wiki/Polymorphism_%28biology%29)**)-** accounts for some of the variability in the effect of drugs. With N-acetyltransferases (involved in *Phase II* reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly. This variation may have dramatic consequences, as the [slow acetylators](https://en.m.wikipedia.org/w/index.php?title=Slow_acetylators&action=edit&redlink=1) are more prone to dose-dependent toxicity.
* **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.
* [**Cytochrome P450 monooxygenase system**](https://en.m.wikipedia.org/wiki/Cytochrome_P450_monooxygenase_system)**-** enzymes can also vary across individuals, with deficiencies occurring in 1 – 30% of people, depending on their ethnic background. Dose, frequency, route of administration, tissue distribution and protein binding of the drug affect its metabolism.

 Pathologicalfactors can also influence drug metabolism, including [liver](https://en.m.wikipedia.org/wiki/Liver), [kidney](https://en.m.wikipedia.org/wiki/Kidney), or [heart](https://en.m.wikipedia.org/wiki/Heart) dIseases.

* **Disease states-**There are many disease states that affect the metabolism of drugs. Some of them are cirrhosis of the liver, alcohol liver disease, cholestatic jaundice, diabetes mellitus, acromegaly, malaria, various viral and bacterial diseases. It can be seen that many of these diseases which affect the liver also affect the rate at which a drug is metabolized due to the fact that the liver is the primary organ for metabolism.

The possible cause in the effect of metabolism due to diseases may be due to the following:

-Decreased enzyme activity in the liver

-Altered hepatic blood flow

-Hypoalbuminaemia

* **Hormonal imbalance-** Higher level of one hormonemay inhibit the activity of few enzymes while inducing that of others. Adrenolectomy, thyroidectomy and alloxan induced diabetes in animals showed impairment in the enzyme activity with subsequent fall in the rate of metabolism. A similar effect was also observed in the pituitary growth hormone and stress related changes in ACTH levels.
* **Physiochemical properties of the drug-** Molecular size and shape,acidity/basicity,steric and electronic characteristics of a drug influence in the interaction with the active sites of enzymes and the metabolism to which it is subjected.