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QUESTIONS
1) Discuss in details the factors affecting drug metabolism

ANSWERS
1) **DRUG METABOLISM**

Drug metabolism is the metabolic breakdown of drugs by living organisms, usually through specialised enzymatic systems . The aim of drug metabolism is to convert a non polar compounds; lipid soluble to water soluble. 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. These factors range from the species of organism studied to the environment in which that organism lives.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.
NOTE: 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.

The factors affecting drug metabolism will be split into

- internal (i.e. physiological and pathological) factors
- external factors (i.e. diet and environment)

These are, of course, purely arbitrary divisions and much interaction exists between the various factors (hormonal, sex and age influences) such interactions will be pointed out where they are important.

A) **INTERNAL**

- ***SPECIES***: Species difference have been observed in both Phase I and Phase II reactions. In phase I reactions, both qualitative and quantitative variations in the enzyme and their activity have been observed. Qualitative differences among species generally result from the present or absence of specific enzymes. Quantitative differences result from variations in the amount and localisation of enzymes, the amount of natural inhibitors and the competition of enzymes for specific substrates.

  Human liver contains less city chrome P-450 per gram of tissue than do the livers of other species.
- ***GENDER:*** (strain): Young and old of animals are more susceptible to drug. Just as the difference in drug metabolising ability between

different species is attributed to genetics, the differences are observed between strains of some species also

- ***AGE***:In general, drugs are metabolised more slowly in fetal, neonatal and elderly humans and animals than in adults.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.

  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.
- ***SEX(GENDER):*** In 1932, Nicholas discovered that amobarbitol anaesthetised female rats at half of the hexobarbitone dose required to make a male to sleep .
- ***HORMONES:*** Higher level of one hormone may inhibit the activity of few enzymes while inducing that of others.
- ***DISEASE:*** Pathological factors can also influence drug metabolism including liver, kidney or heart diseases.

B) **EXTERNAL**

- ***DIET:*** The enzyme content and activity is altered by a number of dietary components. Generally:

  -) Low protein diet decreases and high protein diet increases the drug metabolising ability as enzyme synthesis is promoted by protein diet and also raise 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.

  -) 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 the decreased amount of glucoronides formed than under normal conditions.
- ***ENVIRONMENT:*** Environmental factors such as stress, pregancy and smoking also affect drug response. For example in pregnancy, it is known to affect hepatic drug metabolism. Physiological changes during pregnancy are probably responsible for the reported alterations in drug metabolism. These include elevated concentrations of various hormones such as esterogen, progesterone, placental growth hormones and prolactin. The

metabolism of promazine and pettedine is reduced during pregnancy.