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DRUG DISTRIBUTION

❖ **Drug distribution**

- It refers to the reversible transfer of a drug between the blood and the extra vascular fluids and tissues of the body (for example, fat, muscle, and brain tissue).

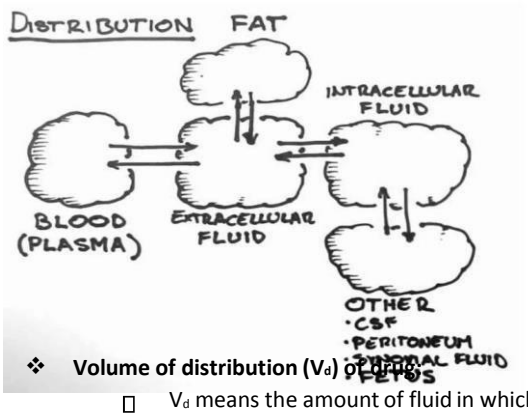
Drugs come into the circulation after absorption

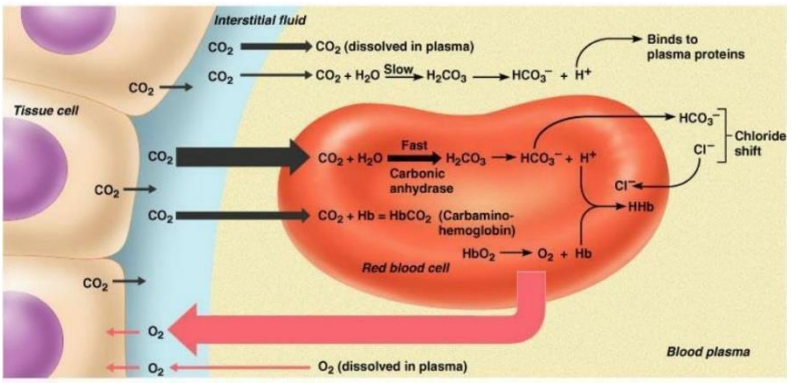
↓

From plasma, drugs have to cross the capillary membrane to come to interstitial space

↓

And then need cross the cell-membrane to enter into the intracellular fluid.

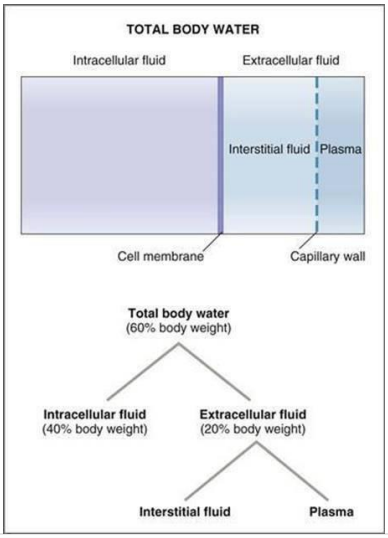


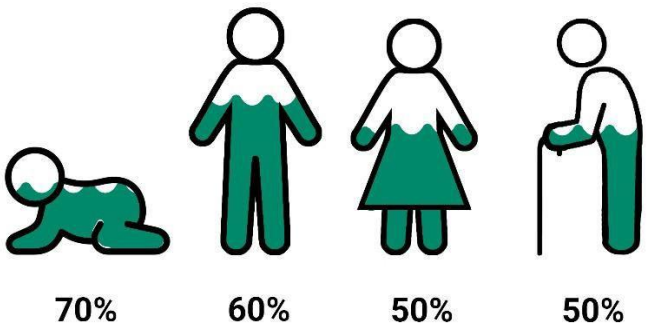


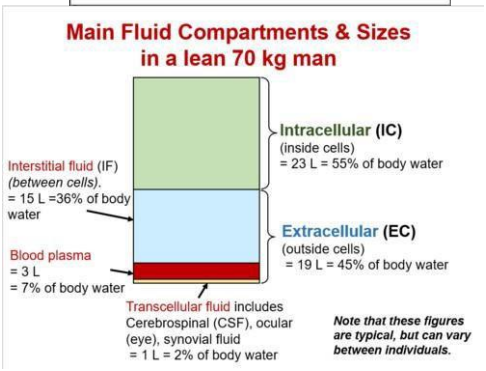
❖ **Volume of distribution (V_d) of drug:**

- V_d means the amount of fluid in which the administered drug is distributed.
- The Volume of distribution (VD), also known as Apparent volume of distribution, is used to quantify the distribution of a drug between plasma and the rest of the body after oral or parenteral dosing.
- It is called as Apparent Volume because all parts of the body equilibrated with the drug do not have equal concentration.

$$V_d = \frac{amount\ of\ drug\ in\ the\ body}{concentration\ of\ drugs\ in\ the\ plasma}$$







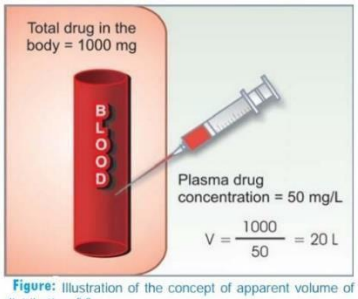


Figure: Illustration of the concept of apparent volume of distribution (V).
In this example, 1000 mg of drug injected i.v. produces steady-state plasma concentration of 50 mg/L, apparent volume of distribution is 20 L

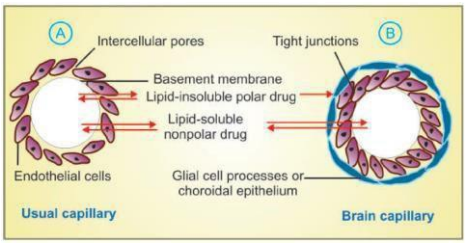
❖ **Redistribution of drugs**

- Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. brain, heart, kidney, etc.
- Later, less vascular but more bulky tissues (muscle, fat) take up the drug—plasma concentration falls and the drug is withdrawn from the highly perfused sites.
- If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action.
- Greater the lipid solubility of the drug, faster is its redistribution.
- Anaesthetic action of thiopentone sod. injected i.v. is terminated in few minutes due to redistribution. However, when the same drug is given repeatedly or continuously over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

❖ **Penetration into brain and CSF**

- The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, a layer of neural tissue covers the capillaries. Together they form blood-brain barrier (BBB).

- A similar blood- CSF barrier is located in the choroid plexus: capillaries are lined by choroidal epithelium having tight junctions.



- Both these barriers are lipoidal and limit the entry of nonlipid-soluble drugs, e.g. streptomycin, eostigmine, etc.
- Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system.
- In addition, efflux transporters like P-gp and anion transporter (OATP) present in brain and choroidal vessels extrude many drugs that enter brain by other processes and serve to augment the protective barrier against potentially harmful xenobiotics

❖ **Passage across placenta**

- Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs.
- The placental efflux P-gp and other transporters like BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs.
- Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to the administered drug.
- However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus.
- Some influx transporters also operate at the placenta. Thus, it is an incomplete barrier and almost any drug taken by the mother can affect the foetus or the new born (drug taken just before delivery, e.g. morphine).

❖ **Plasma protein binding**

- Most drugs possess physicochemical affinity for plasma proteins and get reversibly bound to these.
- Acidic drugs generally bind to plasma albumin and basic drugs to α1 acid glycoprotein.
- Extent of binding depends on the individual compound;
- **The clinically significant implications of plasma protein binding are:**
  - i) Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membranes. They tend to have smaller volumes of distribution(V_d).
  - ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination.
  - iii) Plasma protein binding thus behave as temporary storage of the drug.
  - iv) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or by kidney.
  - v) The generally expressed plasma concentrations of the drug refer to bound as well as free drug.
  - vi) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs bound to the same site(s). The drug bound with higher affinity will displace that bound with lower affinity and tend to increase the concentration of its free form.
  - vii) In hypoalbuminemia, binding may be reduced and high concentrations of free drug is attained. Some disease may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia

❖ **Tissue storage**

- Drugs may also accumulate in specific organs by active transport or get bound to specific tissue constituents.
- Drugs sequestrated in various tissues are unequally distributed, and have larger volume of distribution and longer duration of action.

- Some drugs may exert local toxicity due to high concentration, e.g. tetracyclines on bone and teeth, chloroquine on retina, streptomycin on vestibular apparatus, emetine on heart and skeletal muscle.
- Drugs may also selectively bind to specific intracellular organelle, e.g. tetracycline to mitochondria, chloroquine to nuclei.

❖ **Factors affecting drug distribution**

1. Tissue Permeability of Drugs

a. Physicochemical Properties of drug like: Molecular size, pKa, o/w Partition Coefficient

b. Physiological barriers to diffusion of drugs

2. Organ/tissue size and perfusion rate
3. Binding of drugs to tissue components.

a. Binding of drug to blood components

b. binding of drug to extra cellular components

4. Miscellaneous

a. Age

b. Pregnancy

c. Obesity

d. Diet

e. Disease states

f. Drug interactions

1. **TISSUE PERMEABILITY OF DRUGS**

 The tissue permeability of a drug depends upon the physicochemical properties of the drug as well as the physiologic barriers that restrict diffusion of drug into tissues.

a) **Physicochemical Properties of drugs of the drug**- Important physicochemical properties that influence its distribution are molecular size, degree of ionization, partition coefficient

i) Molecular size-

→ Almost all drugs having molecular weight less than 500 to 600 Daltons easily cross the capillary membrane to diffuse into the extracellular interstitial fluids

→ penetration of drugs from the extracellular fluid into the cells is a function of molecular size, ionization constant(K_a) and lipophilicity of the drug. Only small, water-soluble molecules and ions of size below 50 Daltons enter the cell through aqueous filled channels whereas those of larger size are restricted unless a specialized transport system exists for them.

ii) Degree of ionisation(pK_a) –

→ Most drugs are either weak acids or weak bases and their degree of ionization at plasma or ECF pH depends upon their pKa. All drugs that ionise at plasma pH (i.e. polar, hydrophilic drugs), cannot penetrate the lipoidal cell membrane and tissue permeability is the rate-imiting step in the

distribution of such drugs. Only unionized drugs which are generally lipophilicity, rapidly cross the cell membrane.

iii) $K_{o/w}$ Partition Co-efficient-

→ In drug discovery and development, lipophilicity is usually expressed by the partition between water and octan-1-ol.

→ A sample of the drug is shaken with a mixture of octan-1-ol and water and its concentration in each layer is determined.

→ The partition coefficient is the measure of the lipophilicity of a drug and an indication of its ability to cross the cell membrane. Higher the partition coefficient, the higher the permeability of the membrane to that particular substance.

b) Physiological barriers to Distribution of Drugs

i) Simple Capillary Endothelial Barrier

- All drugs, ionised or unionised, with a molecular size less than 600 Daltons, diffuse through the capillary endothelium and into the interstitial fluid.
- Only drugs that bound to that blood components can't pass through this barrier Because of larger size of complex.

ii) Simple Cell Membrane Barrier

- Simple cell Membrane is similar to the lipoidal barrier (absorption) Non polar & hydrophillic drugs will passes through it (passively).
- Lipophilic drugs with 50-600 Dalton molecular size & Hydrophilic, Polar drugs with < 50 dalton will pass this membrane

iii) Blood Brain Barrier

- A solute may cross to brain via only one of the two pathway:
  1) Passive diffusion through the lipoidal barrier: Which restricted to smaller molecules (with a molecular weight less than 700 Daltons) having high o/w partition coefficient.
  2) Active transport of essential nutrients such as sugars and amino acid. Thus structurally similar foreign molecules can also penetrate the BBB by the same mechanism.
- Approaches of BBB Three different approaches have been utilized successfully to promote crossing the BBB by drugs:
  1) Use of permeation enhancer: Dimethyl sulphoxide (DMSO)
  2) Osmotic disruption of the BBB by infusing internal carotid artery (main blood vessels that **carry blood and oxygen to the brain**)with mannitol.
  3) Use of dihydropyridine redox system as drug carriers to the brain.

iv) Blood – CSF Barrier-

- Blood- CSF barrier which has permeability characteristics similar to that of the BBB.
- But For any given drug, its concentration in the brain will always be higher than in the CSF. v) Blood Placental Barrier
- Many drugs having molecular weight less than l000 daltons and moderate to high lipid solubility e.g. ethanol, sulfonamides, barbiturates, gaseous anaesthetics, steroids, narcotic analgesics, anticonvulsants and some antibiotics, cross the barrier by simple diffusion quite rapidly

- An agent that causes toxic effect on foetus is called as teratogen. Teratogenicity is defined as foetal abnormalities caused by administration of drug during pregnancy

vi) Blood Testis Barrier

- This barrier is located at Sertoli Sertoli cell junction.
- It is the tight junctions between the neighbouring Sertoli cells that act as the blood- testis barrier. This barrier restricts the passage of drugs to spermatocytes and spermatids.

2. **ORGAN/TISSUE PERFUSION RATE**

- Under perfusion-rate diffusion of the highly lipophilic drug from the systemic circulation to a specific tissue/organ is primarily dependent on the blood flow within an organ or tissue.
- Organs like the liver and the heart are highly perfused with blood. By contrast, the bone and the adipose tissues experience less blood perfusion. Therefore, drugs are likely to distribute more rapidly to tissues/organs that are more richly perfused with blood.

3. **BINDING OF DRUGS TO TISSUE COMPONENTS**

a) Binding of drugs to blood components

i) Plasma proteins

- Human serum albumin:-all types drug
- ά1- acid glycoprotein :-basic drugs(impr)
- Lipoproteins :-basic, lipophilic drugs(chlorpromazin)
- ά1-Globuline :-steroids like corticosterone ,vit-B12 ά2-Globuline :-vit-A,D,E,K, cupric ions.
- Haemoglobin :-Phenytoin, phenothiazines
- The binding of drug to plasma protein is reversible –The extent or order of binding of drugs to various plasma proteins is:

  Albumin > α1-Acid Glycoprotein > Lipoproteins > Globulins > Human Serum Albumin (HSA)

ii) Blood cells

- RBC : 40% of blood comprise of blood cells out of that 95% cells are RBC (RBC comprise of haemoglobin), drugs like, phenytoin, phenobarbitone binds with Hb imipramine, chlorpromazine binds with RBC Cell wall
- The RBC comprises of 3 components each of which can bind to drugs:

a) Haemoglobin

b) Carbonic Anhydrase

c) Cell Membrane

b) Binding of drugs to extra vascular tissues

- Tissue-drug binding result in localization of drug at specific site in body and serve as reservoir As binding increases it also increase bio-logical half life.
- Irreversible binding leads to drug toxicity
- Liver > kidney > lungs > muscle > skin > eye > bone > Hair, nail

4. **Miscellaneous Factors**

Difference in distribution pattern of a drug in different age groups are mainly due to differences in:

i) Age:

a) Total body water-(both Intracellular & Extracellular) greater in infants lower in older

b) Fat content - It is also higher in infants & in elderly

c) Skeletal muscles- It is also higher in infants & in elderly

d) Organ composition- BBB is poorly developed in infants & myelin content is low & cerebral blood flow is high, hence greater penetration of drug in brain

e) Plasma protein content- low albumin content in both infants & in elderly ii) Pregnancy

- During Pregnancy, due to growth of UTERUS, PLECENTA and FETUS increases the volume available for distribution drug.
- The plasma & ECF Volume also increase but albumin content is low

iii) Obesity –

- In obese persons, high adipose (fatty acid) tissue so high distribution of lipophilic drugs.

iv) Diet

- A diet high in fats will increases free fatty acid levels in circulation thereby affecting binding of acidic drugs v) Disease states- disease state change the following conditions

→ Altered albumin & other drug-binding protein concentration.
→ Alteration or reduced perfusion to organ or tissue → Altered tissue pH.

→ Alteration of permeability of physiological barrier (BBB) EX- BBB (in meningitis & encephalitis)

vi) Drug interaction:-

 Drug interaction that affect distribution are mainly due to difference in plasma protein or tissue binding of drugs.

Ex:- Warfarin (Displaced Drug) & Phenylbutazone (Displacer)HSA

Biotransformation

❖ **Definition**

- **Biotransformation** of drugs is defined as the chemical conversion of one form to another.
- The term is used synonymously with **metabolism**.
- The chemical changes are usually affected enzymatically in the body and thus, the definition excludes chemical instability of a drug within the body; for e.g. conversion of penicillin to penicilloic acid by the bacterial penicillinase and mammalian enzymes is metabolism but its degradation by the stomach acid to penicillenic acid is chemical instability.

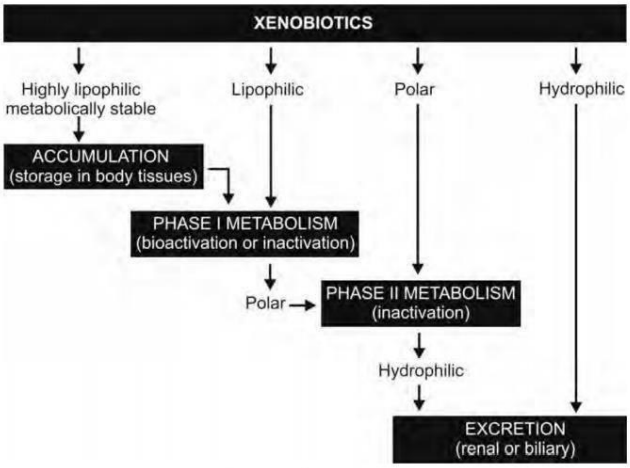
❖ **Need for Drug Biotransformation**

- All chemical substances that are not nutrients for the body and enter the body through, ingestion, inhalation or absorption are called as **xenobiotics** (Greek: xenos = foreign) or **exogenous compounds**.
- Substances foreign(xenobiotics) to body include-

i) Drugs, Processed food, Food additives, Cosmetic products, Environmental pollutants, Agrochemicals, ii) Phytoallexins (dietary plant toxins)

Biotransformation needed for detoxification & protect the body from ingested toxins.

- Drugs are also xenobiotics which enter the body by virtue of their lipophilicity.
- It is interesting to note that only water-soluble agents undergo renal excretion (major route for exit of drugs from the body) whereas lipid soluble substances are passively reabsorbed from the renal tubules into the blood after glomerular filtration.
- Drugs are lipid soluble and are passively reabsorbed from the renal tubule therefore may accumulate in the body and precipitate toxic reactions.
- However, to prevent such a consequence, the body is armed with the metabolic system which transforms the water insoluble, lipophilic, nonpolar drugs into polar and water-soluble products that can be easily excreted by the kidneys and are poorly reabsorbed; for instance, hippuric acid, the metabolite of benzoic acid, is 2.5 times more water-soluble.
- Drug biotransformation is thus a **detoxification process**. However, exceptions are there when biotransformation leads to products with decreased water solubility. The N-acetyl derivatives of sulphonamides are less water-soluble than the parent drug and thus have a tendency to cause crystalluria.



❖ **Effect of Biotransformation –**

- **Normally biotransformation** results in pharmacological inactivation of drugs, i.e. it results in formation of metabolites with little or no pharmacological activity; e.g. conversion of phenytoin to p-hydroxy phenytoin.
- **Occasionally biotransformation** yields metabolites with equal activity; e.g. conversion of phenylbutazone to oxyphenbutazone.
- **Rarely biotransformation** leads to toxicological activation of drugs, i.e. it results in formation of metabolites with high tissue reactivity; e.g. conversion of paracetamol to reactive metabolites that cause hepatic necrosis.

- Inactive drugs (prodrugs) also depend upon biotransformation for activation, the process being called as **pharmacological activation**; e.g. conversion of enalapril to enalaprilat.
- In comparison with xenobiotics, the natural endogenous substances such as neurotransmitters (dopamine, GABA, epinephrine, norepinephrine, etc.), steroids (testosterone, progesterone, cortisol, etc.) and insulin which are also used as therapeutic agents, are inactivated rapidly because of the body's well developed system for metabolising such agents. These substances are therefore called as **soft drugs**. Such soft drugs do not precipitate unexpected toxicity when used in concentrations close to their normal levels.

❖ **Drug metabolising organ**

- Liver is the primary site for metabolism of almost all drugs (and other xenobiotics) because of its relative richness in possessing a large variety of enzymes in large amounts.
- Metabolism by organs other than liver (called as **extrahepatic metabolism**) is of minor importance since lower level of drug metabolising enzymes are present in such tissues. The decreasing order of drug metabolising ability of various organs is:

  Liver > Lungs > Kidneys > Intestine > Placenta > Adrenals > Skin Brain, testes, muscles, spleen, etc.

❖ **Drug Metabolising Enzymes**

 The enzymes that biotransform xenobiotics differ from those that metabolise food materials. The enzymes are broadly divided into two categories:

i) **Microsomal enzymes**

- These are located on smooth endoplasmic reticulum, primarily in liver, also in kidney, intestinal mucosa and lungs.
- The monooxygenases, cytochrome P450, UGTs, epoxide hydrolases, etc. are microsomal enzymes.
- They catalyse most of the oxidations, reductions, hydrolysis and glucuronide conjugation.

- Microsomal enzymes are inducible by drugs, certain dietary constituents, and other agencies.

ii) **Non-microsomal enzymes**.

- These are present in the cytoplasm and mitochondria of hepatic cells as well as in other tissues including plasma.
- The esterases, amidases, some flavoprotein oxidases and most conjugases are nonmicrosomal.
- Reactions catalysed are: Some oxidations and reductions, many hydrolytic reactions and all conjugations except glucuronidation.

Note-Both microsomal and nonmicrosomal enzymes are deficient in the newborn, especially premature, making them more susceptible to many drugs, e.g. chloramphenicol, opioids

❖ **Types of biotransformation reaction**- Biotransformation reactions can be classified into:

(a) **Nonsynthetic/Phasel/Functionalization reactions**:

- a functional group (-OH, -COOH, -CHO, -NH_2, -SH) is generated or exposed-
- metabolite produce may be active or inactive.
- Lipophilic substance become polar **(b) Synthetic/Conjugation/ Phase II reactions:**
- an endogenous radical is conjugated to the drug-
- metabolite is mostly inactive; except few drugs, e.g. glucuronide conjugate of morphine and sulfate conjugate of minoxidil are active.
- Polar substance become hydrophilic

1. Phase-I Reactions (a) Oxidation

(b) Reduction

(c) Hydrolysis

(d) Cyclization (e) Decyclization

i) Oxidation

- This reaction involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical.
- Oxidations are the most important drug metabolizing reactions. Various oxidation reactions are:-
  - → hydroxylation;
  - → oxygenation at C, N or S atoms;
  - → N or O-dealkylation,
  - → oxidative deamination, etc

- Oxidative reactions are mostly carried out by a group of monooxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and molecular O2.
- The CYP isoenzymes important for drug metabolism in humans.
- **Cytochrome P450** (CYP) enzymes are a group of enzymes encoded by P450 genes and are expressed as membrane bound proteins mostly found in the endoplasmic reticulum of the liver.

ii) Reduction

- This reaction is the converse of oxidation and involves cytochrome P-450 enzymes working in the opposite direction.
- Alcohols, aldehydes, quinones are reduced. Drugs primarily reduced are chloralhydrate, chloramphenicol, halothane, warfarin.

iii) Hydrolysis

- This is cleavage of drug molecule by taking up a molecule of water.

- Similarly, amides and polypeptides are hydrolysed by amidases and peptidases.
- Hydrolysis occurs in liver, intestines, plasma and other tissues.
- Examples of hydrolysed drugs are choline esters, procaine, lidocaine, procainamide, aspirin, indomethacin, carbamazepine-epoxide, pethidine, oxytocin

iv) Cyclization

This is formation of ring structure from a straight chain compound, e.g. cycloguanil from proguanil.

v) Decyclization

This implies opening up of ring structure of the cyclic drug molecule, such as barbiturates, phenytoin. This is generally a minor pathway.

2. Phase-II reaction

- These reactions involve conjugation of the drug or its phase I metabolite with an endogenous substrate, usually derived from carbohydrate or amino acid, to form a polar highly ionized organic acid, which is easily excreted in urine or bile.
- Conjugation reactions have high energy requirement and are generally faster than phase I reactions.

***i)* Glucuronide conjugation**

- This is the most important Phase-II reaction carried out by a group of **uridine diphosphate** (UDP)- glucuronosyl transferases (UGTs).
- Compounds with a hydroxyl or carboxylic acid group are easily conjugated with glucuronic acid which is derived from glucose.
- Examples are—chloramphenicol, aspirin, paracetamol, diazepam, lorazepam, morphine, metronidazole.
- Not only drugs but endogenous substrates like bilirubin, steroidal hormones and thyroxine utilize this pathway.
- Glucuronidation increases the molecular weight of the drug which favours its excretion in bile.
- Drug glucuronides excreted in bile can be hydrolysed by bacteria in the gut—the liberated drug is reabsorbed and undergoes the same fate.
- This enterohepatic cycling of the drug prolongs its action, e.g. phenolphthalein, oral contraceptives

***ii)* Acetylation**

 Compounds having amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A
e.g. sulfonamides, isoniazid, PAS, dapsone, hydralazine, clonazepam, procainamide.

***iii)* Methylation**

- The amines and phenols can be methylated by methyl transferases (MT); methionine and cysteine acting as methyl donors,
- e.g. adrenaline, histamine, nicotinic acid, methyldopa, captopril, mercaptopurine.

***iv)* Sulfate conjugation**

- The phenolic compounds and steroids are sulfated by sulfotransferases (SULTs)
  e.g. chloramphenicol, methyldopa, adrenal and sex steroids.

v) **Glycine conjugation**

- Salicylates, nicotinic acid and other drugs having carboxylic acid group are conjugated with glycine, but this is not a major pathway of metabolism.

vi) **Glutathione conjugation**

- This is carried out by glutathione-S-transferase (GST) forming a mercapturate.
- It is normally a minor pathway.
- However, it serves to inactivate highly reactive quinone or epoxide intermediates formed during metabolism of certain drugs, e.g. paracetamol.

vii) **Ribonucleoside/nucleotide synthesis**

- This pathway is important for the activation of many purine and pyrimidine antimetabolites used in cancer chemotherapy.

❖ **Hofmann elimination-**

- This refers to inactivation of the drug in the body fluids by spontaneous molecular rearrangement without the agency of any enzyme, e.g. atracurium.

❖ **Factors influencing drug metabolism**

- 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.
- Many factors may affect drug metabolism like age, species and strain, genetic or hereditary factors, sex, enzyme induction, and enzyme inhibition.

1. Age Differences

- Age-related differences in drug metabolism are generally quite apparent in the new born.
- In most foetal and new born animals, undeveloped or deficient oxidative and conjugative enzymes are chiefly responsible for the reduced metabolic capability.
- In general, the ability to carry out metabolic reactions increases rapidly after birth and approaches adult levels in about 1 to 2 months.

2. Species and Strain Differences

- The metabolism of many drugs and foreign compounds is often species dependent. Different animal species may biotransform a particular xenobiotic by similar or different metabolic pathways.
- Even within the same species, individual variations (strain differences) may result in significant differences in a specific metabolic pathway.

3. Hereditary or Genetic Factors

- 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.

4. 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).

5. Enzyme Induction

- Many drugs, insecticides and carcinogens interact with DNA and increase the synthesis of microsomal enzyme protein, especially cytochrome P-450 and UGTs.
- As a result the rate of metabolism of inducing drug itself (autoinduction) and/or some other coadministered drugs is accelerated.

6. Enzyme Inhibition-

- Azole antifungal drugs, macrolide antibiotics and some other drugs bind to the heme iron in CYP450 and inhibit the metabolism of many drugs, as well as some endogenous substances like steroids, bilirubin.
- One drug can competitively inhibit the metabolism of another if it utilizes the same enzyme or cofactors.

7. First-pass(presystemic) metabolism

- It is the metabolism of a drug during its passage from the site of absorption into the systemic circulation.
- All orally administered drugs are exposed to drug metabolizing enzymes in the intestinal wall and liver (where they first reach through the portal vein).
- Presystemic metabolism in the gut and liver can be avoided by administering the drug through sublingual, transdermal or parenteral routes.
- The extent of first pass metabolism differs for different drugs and is an important determinant of oral bioavailability.
- A drug can also be excreted as such into bile. The hepatic extraction ratio (ER_{Liver}) of a drug is the fraction of the absorbed drug prevented by the liver from reaching systemic circulation. Both presystemic metabolism as well as direct excretion into bile determine ER_{Liver},

8. Disease

- Many disease states alter drug metabolism especially those affecting the liver.
- e.g amlodipine clearance decreased with hepatic disease

9. Extrahepatic metabolism

- Other tissues also possess significant drug metabolising activity.
- Extrahepatic tissues may contain different isozymes.
- Tissues include: Lung, kidney, intestinal mucosa, skin, brain
- Some drugs are given via different routes. i.e. skin – therefore there must be drug metabolising enzymes here.
- Examples of these isozymes:

  i) FMO and CYP 1A1 in lung ii) Xanthine oxidase, CYP3A4, glucuronosyl transferase in intestine

EXCRETION OF DRUGS

❖ **Definition**

- Excretion is defined as a process whereby drugs or metabolites are irreversibly transferred from internal to external environment through renal or non-renal route.
- Excretion, along with metabolism and tissue redistribution, is important in determining both the duration of drug action and the rate of drug elimination.
- **Clearance (CL)-**

  → The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time.

  → It can be calculated as:

$$CL = \frac{rate\ of\ elemination}{C}$$

  where C is the plasma concentration.

- **Plasma half-life -** The Plasma half-life (t½) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
- **Principal organs involved**:

  i) Kidneys (Renal Excretion) ii) Bile (Biliary Excretion) iii) Lungs (Pulmonary Excretion) iv) Saliva (Salivary Excretion)

  v) Milk (Mammary Excretion) vi) Sweat (Skin Excretion)

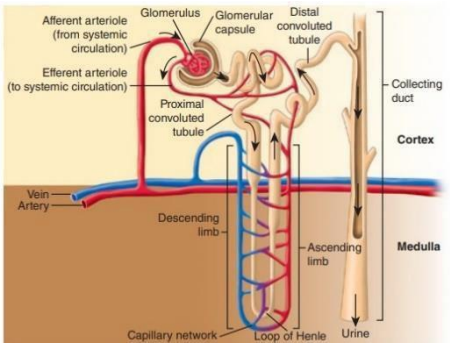
1. Kidney

- Drugs are eliminated from the body primarily by the kidneys.
- The principal renal mechanisms that are involved in the excretion of drugs are:

(a) Glomerular filtration

(b) Active tubular secretion

(c) Passive tubular reabsorption



i) Glomerular filtration

- The ultrastructure of the glomerular capillary wall is such that it permits a high degree of fluid filtration while restricting the passage of compounds having relatively large molecular weights.
- This selective filtration is important in that it prevents the filtration of plasma proteins (e.g., albumin) that are important for maintaining an osmotic gradient
- Several factors, including molecular size, charge, and shape, influence the glomerular filtration of large molecules.
- As the ultrafiltrate is formed, any drug that is free in the plasma water, i.e not bound to plasma proteins or RBC will be filtered as a result of the driving force provided by cardiac pumping.

- All unbound drugs will be filtered as long as their molecular size, charge, and shape are not excessively large.
- Compounds with 20 Å to 42Å may undergo glomerular filtration.

ii) Active Tubular secretion

- Tubular secretion is **the transfer of materials from peritubular capillaries to the renal tubular lumen** ⇨ The tubular secretion which is carried out at the level of the proximal tubule is an active process.
- It is carrier mediated process which requires energy for transportation of compounds against conc. gradient ⇨ Two secretion mechanisms are identified.
  - (a) System for secretion of organic acids/anions e.g. Penicillin, salicylates etc
  - (b) System for organic base / cations e.g. morphine, mecamylamine hexamethonium

iii) Passive tubular reabsorption

- Tubular reabsorption is **the process that moves solutes and water out of the filtrate and back into your bloodstream** ⇨ Drugs which are present in the glomerular filtrate can be reabsorbed in the tubules.
- Only un-ionized molecules are available for reabsorption.
- Many drugs are either weak bases or acids and therefore the pH of the filtrate can greatly influence the extent of tubular re-absorption for many drugs. When urine is acidic, weak acid drugs tend to be reabsorbed. Alternatively when urine is more alkaline, weak bases are more extensively reabsorbed.
- Making the urine more acidic can cause less reabsorption of weak bases or enhanced excretion.
- In the case of a drug overdose it is possible to increase the excretion of some drugs by suitable adjustment of urine pH. For example, in the case of pentobarbital (a weak acid) overdose it may be possible to increase drug excretion by making the urine more alkaline with sodium bicarbonate injection.

2. Biliary Excretion

- Biliary excretion involves **active secretion of drug molecules or their metabolites from hepatocytes into the bile**
- Transporters are present in the canalicular membrane of the hepatocyte, and these actively secrete drugs and metabolites into bile. e.g. the organic anion transporting polypeptides (OATPs), the P- glycoprotein transport system and the multidrug resistance-associated proteins (Mrps).
- Drug in bile enters the gastrointestinal tract after storage in the gallbladder. It may then be excreted from the body by the stools.
- A drug excreted in bile may be reabsorbed from the gastrointestinal tract or a drug conjugate may be hydrolyzed by gut bacteria, liberating original drug which can be returned to the general circulation. Such recycling may continue (enterohepatic cycle or circulation) until the drug either undergoes metabolic changes in the liver, is excreted by the kidneys, or both.
- Such enterohepatic recycling, if extensive, may prolong significantly the presence of a drug (or toxin) and its effects within the body prior to elimination by other pathways.
- Orally administered activated charcoal and/or anion exchange resins have been used clinically to interrupt enterohepatic cycling and trap drugs in the gastrointestinal tract.
- Cholestatic disease states, in which normal bile flow is reduced, will influence drug elimination by this route resulting in increased risk of drug toxicity.

3. Pulmonary excretion

- Gases and other volatile substances such as general anaesthetics that enter the body primarily through the respiratory tract can be expected to be excreted by this route.
- No specialized transport systems are involved in the loss of substances in expired air; simple diffusion across cell membranes is predominant.

- The rate of loss of gases is not constant; it depends on the rate of respiration and pulmonary blood flow.
- The degree of solubility of a gas in blood also will affect the rate of gas loss.
- Gases such as nitrous oxide, which are not very soluble in blood, will be excreted rapidly.
- Ethanol, which has a relatively high blood gas solubility, is excreted very slowly by the lungs.

4. Salivary excretion

- The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively.
- The bitter taste in the mouth of a patient is indication of drug excreted.
- Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.

5. Mammary excretion

- Milk consists of lactic secretions which is rich in fats and proteins.
- Excretion of drug in milk is important as it gains entry in breast feeding infants.
- pH of milk varies from 6.4 to 7.6. Free un-ionized and lipid soluble drugs diffuse passively.
- Highly plasma bound drug like Diazepam is less secreted in milk.
- Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects.
- Some potent drugs like barbiturates and morphine may induce toxicity.

6. Skin excretion

- Drugs excreted through skin via sweat follows pH partition hypothesis.
- Excretion of drugs through skin may lead to urticaria and dermatitis.
- Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

Excretory route	Mechanism	Drug Excreted
Urine	GF, ATS, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 300
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat	Passive diffusion	Free, unionized lipophilic drugs