Chapter
1

General Pharmacology

- Scope of pharmacology
- Absorption of drugs
- Distribution of drug in the body
- Excretion/disposition of drugs (elimination of drugs)
- Routes of administration of drugs
- Bioavailability
- Biotransformation/metabolism of drugs
- Factors modifying drug action

Q 1. Define pharmacology. Explain scope of pharmacology.

Pharmacology

Pharmacology is the science, which deals with the study of drugs and their actions on human body or animals.

Pharmacology has two branches:

1. **Clinical pharmacology:** It deals with the study of action or effects of drugs in human being.
2. **Experimental pharmacology:** It deals with the action or effects of a drug on experimental animals.

Scope of Pharmacology

1. The knowledge of pharmacology is needed for the purpose of regular screening and testing of new drugs to determine their therapeutic uses, harmful effects, safety and efficacy on humans and animals.
2. The pharmacology has made its position in the medical field and in medicines of greater importance.
3. The scope of pharmacology includes the cultivation of medicinal plants which serves as drugs, the synthesis of chemical compounds of medicinal use.
4. Pharmacy is the allied branch of pharmacology, which is concerned with the collection, preparation and standardization of drugs.
5. The various branches of pharmacology provides knowledge of drugs to the world especially to the persons of medical, paramedical and nursing field category.
6. The knowledge of pharmacological principles is essential for maintenance of optimal health of the humanity and animals.
7. The allied fields/branches/subdivisions of pharmacology are:
   a. **Pharmacy:** It deals with the science and art of analysing standardising, compounding and dispensing of drugs, so as to make them fit for administration.

b. **Pharmacognosy:** It is a branch of pharmacy which deals with identification of drugs based on the study of physical, chemical botanical and some aspects of biological properties.
c. **Pharmacodynamics:** It deals with the site and mode of action of drugs on living organisms.
d. **Pharmacokinetics:** It deals with the study of absorption, distribution, metabolism and excretion of drugs and their relationship to the pharmacological response.
e. **Pharmacotherapeutics:** It means various methods and systems that are used in prevention and treatment of diseases.
f. **Toxicology:** It is the science which deals with the adverse effects of the drugs and study of poisons.
g. **Posology:** It deals with the study of doses of the drugs.
h. **Chemotherapy:** It is defined as the use of chemical compounds in the treatment of infectious diseases so as to destroy the microorganisms without damaging host tissues.
i. **Clinical pharmacology:** It involves the principles of clinical drug evaluation that apply to medicine.
j. **Therapeutics:** It is a general term describing the use of drugs in the treatment of disease.
k. **Pharmacogenetics:** This area of pharmacology examines relation of genetic factors to variations in response to drugs.
l. **Pharmacoeconomics:** It deals with the study of the analysis of cost of drug therapy to the health care system and the society.
m. **Clinical pharmacy:** It involves co-operation of the pharmacist with the physician in educating the patient about compliance and counselling him on how to take the medication and monitoring the errors in taking the drugs.

Q 2. Define 'pharmacology'. Give the classification of drugs on the basis of source, nature and active constituent present in it.

Pharmacology

Pharmacology is defined as the study of effect of drugs on the living organism and its organs along with mechanism of action, adverse effects, and doses of the drugs.

The word pharmacology is derived from two Greek words, *pharmacon* → a drug, *logus* → to treat or science.

Classification of Drugs

a. As per Source of Drugs

1. Plants, e.g. morphine, digoxin, reserpine, vinblastin.
2. Animals, e.g. insulin, heparin, thyroid extract.

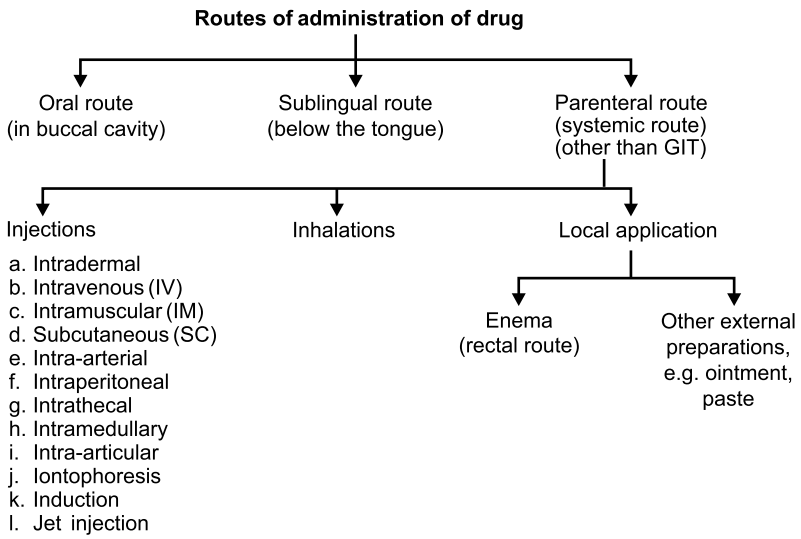
3. Minerals, e.g. liquid paraffin, magnesium sulphate, kaolin.
4. Synthetic, e.g. aspirin, sulphonamides, corticosteroids.
5. Microorganisms, e.g. penicillins, tetracyclines, rifampicin, cephalosporins, l-asparaginase.

b. As per Nature of Drugs

The drugs from plant origin contain pharmacologically active constituents such as:

1. Alkaloids, e.g. reserpine, morphine, emetine, atropine.
2. Glycosides, e.g. digoxin, strophanthin.
3. Oils:
   a. Fixed oils, e.g. olive oil, castor oil, cod-liver oil,
   b. Volatile oil, e.g. clove oil, eucalyptus oil, turpentine oil.
4. Resins, e.g. podophyllum resin.
5. Gums, e.g. agar, acacia, tragacanth.
6. Tannins, e.g. catechu, tannic acid.
7. Hormones, e.g. insulin, sex hormones.

Q 3. Give the classification of routes of administration of drugs.



Q 4. Give the advantages and disadvantages of oral route of drug administration.

Oral Route

In this route, the drug is placed in oral cavity and is swallowed along with water or milk, etc.

Advantages

1. It is a common and safe route of drug administration.
2. No special skill is required for administration of drug.
3. It is very convenient route.
4. Sterilisation is not required for the preparations taken orally.
5. There are low possibilities of adverse reactions.
6. This route is applicable from infants up to aged patients.
7. The large quantity of drug can be administered by this route.
8. Preparations like syrup, mixture, tablet, capsule, pills are administered by this route.

Disadvantages

1. Onset of action is slow.
2. Absorption of certain drugs is irregular and negligible.
3. This route is not useful in clinical emergencies.
4. The irritant and unpalatable drugs cannot be administered by this route.
5. This route is not useful in cases of unconscious and incooperative patients.
6. This route is not useful in prevomiting and diarrhoea patients.
7. The drugs which are destroyed in alimentary canal are not given by this route, e.g. insulin.
8. The presence of food in GIT may interfere with absorption of drug.
9. Oral administration of some drugs may disturb the microflora of GIT.
10. Accurate blood levels of the drug cannot be maintained by this route.

Q 5. What is sublingual route? Give advantages and disadvantages of sublingual route.

Sublingual Route

In this route, tablet is placed below the tongue and allowed to dissolve in mouth cavity. The active drug gets absorbed through the sublingual mucus membrane directly into blood circulation.

Examples of Drugs

i. Isoprenaline tablet in the treatment of bronchial asthma.
ii. Glyceryl trinitrite in the treatment of angina pectoris.

Advantages

1. Rapid onset of action.
2. Degradation of drug is avoided in stomach.
3. Inactivation of drug in the liver is avoided.
4. If tablet is found to be toxic, it can be spit out easily.
5. Presence of food in GIT does not affect the absorption of drug.

Disadvantages

1. Not suitable for large doses and frequent use of drug.
2. Some drugs may cause irritation to buccal mucosa.
3. Excessive salivation may cause swallowing of drug.
4. The drugs having direct or toxic effects should be administered carefully to avoid side effects on heart.

Q 6. What is parenteral route? Give advantages and disadvantages of parenteral route.

Parenteral Route

The routes of administration of drug other than alimentary canal are called parenteral routes.

- In this case, the drug in the form of solution or suspension is injected in the body with the help of hollow needle and syringe.
- In some cases, drugs in the form of vapour or fine droplets are inhaled in respiratory tract or sometimes pastes are rubbed over the skin.

Advantages

1. Rapid onset of action.
2. The drugs which irritate the GIT, can be given by this route.
3. Accurate dose and accurate blood level of drug can be possible.
4. This route is useful in cases of vomiting and diarrhoea.
5. This route is useful in unconscious and uncooperative patients.
6. The drugs which are destroyed in GIT can be given by this route.
7. The smaller quantity of drugs is required by this route.
8. This route is useful in clinical emergencies.
9. The large quantities of drug are also administered by this route, e.g. saline solution.
10. 100% bioavailability is possible by IV route.

Disadvantages

1. This route is inconvenient to the patient and for frequent administration of drugs.
2. Skilled person is necessary for administration of drugs.
3. Strict aseptic technique is to be followed during drug administration.
4. The possibility of pain and edema at the site of application.
5. Self-medication is difficult.
6. The sterilization of syringe and needle is necessary.
7. The possibility of nerve damage.
8. Once the drug is absorbed in blood circulation, the adverse effects cannot be reversed or controlled.

Q 7. Explain various types of parenteral routes. Give their advantages and disadvantages.

a. Intradermal Route

In this route, the drug is injected in the dermis layer of the skin. Only a small quantity of drug can be administered by this route and the injection is painful.

Importance

i. This route is used for the detection of drug allergy, e.g. penicillin is injected intradermally to observe allergic reactions to it.
ii. Vaccines such as BCG, smallpox are administered by this route.

b. Intramuscular Route

In this route, drug is administered directly into the muscular tissue.

Advantages

1. Mild irritants, suspensions, colloids and injections with insoluble oily bases can be administered by this route.
2. The absorption of water-soluble drugs is rapid than subcutaneous or oral route.
3. Massaging and application of heat at the site of injection by IM route may increase the drug absorption.
4. The drugs administered by this route form tissue depots from where drug is slowly released and this provides prolonged duration of action.

Disadvantages

1. Sterilization of syringe and needle is essential.
2. Skilled person is required for drug administration.
3. Some drugs may cause tissue irritation and pains by intramuscular route.
4. If proper care is not taken there is an injury to the nerves.
5. Total volume of drug injected by IM route is restricted up to 10 ml.
6. Certain intramuscular injections require more time for absorption as compared to oral route.

c. Inhalation Route

In this route, the drug in the form of gas or in vapour form can be inhaled, e.g.

i. Isoprenaline spray is used in bronchial asthma.
ii. Volatile general anaesthetics are also given by this route.

Advantages

1. The absorption of drug by this route is very rapid.
2. The drug given by this route produces local as well as systemic effects.
3. Blood levels of volatile substances such as general anaesthetics can be conveniently controlled.

Disadvantages

1. The drug directly enters the left side of the heart, hence there is a danger of cardiac toxicity.
2. Certain drugs produce local irritation, may increase respiratory secretions.
3. Special apparatus such as automizer or nebuliser is needed for administration of drug.

d. Intravenous Route (IV Route)

In this route, the drug is injected directly into the lumen of vein. The drug produces rapid action and desired blood concentration can be achieved by a definite dose of a drug.

Advantages

1. The onset of drug action is very rapid.
2. This route is effective in clinical emergencies.
3. 100% absorption of drug is possible by this route.
4. Large quantity of drug can be administered by this route, e.g. normal saline solution.
5. The drug which produces irritation and pains by IM route can be given by this route.
6. The hypertonic solutions can be administered intravenously because the drug is diluted by bloodstream.
7. The accurate blood concentration of drug can be achieved by this route.
8. Only minimum quantity of drug is required to get a particular effect as compared to other routes.
9. Adjustment of additional dose and control on the rate of administration is possible by IV route.
10. Complete bioavailability of drug can be assured by IV route.

Disadvantages

1. Self-medication is difficult.
2. Sometimes, leakage of drug outside the vein produces severe irritation and abscess formation.
3. Sterilization of needle and syringe is essential.
4. Skilled person is essential for drug administration.
5. Speed of drug entering through IV set should be slow and constant supervision is necessary.
6. Once the drug is absorbed in the systemic circulation, the adverse effects of drug cannot be reversed or controlled.

e. Intra-arterial Route

- In this route the drug is administered directly into the artery.

- The drug produces a sudden high concentration in arterial blood and hence may be harmful locally or damaging to tissues supplied by the artery.
- This route has no advantages except in diagnostic studies, such as angiograms and in embolization therapy.
- Certain anti-malignancy compounds are administered by regional intra-arterial perfusing in localized malignancies.

f. Intraperitoneal Route

- This route has been sometimes used in infants for giving fluids like glucose, saline, as the peritoneum offers a large surface for absorption.
- This route is also used for peritoneal dialysis.

g. Intrathecal Route

- In this route involves introduction of drugs such as spinal anaesthetics into the subarachnoid space.
- The drugs act directly on the central nervous system.
- This route is also convenient for producing high local concentrations in the subarachnoid space.
- Examples:
  1. Certain antibiotics and antimalignancy drugs are given by this route.
  2. Lignocaine is now used extradurally to produce anaesthesia for pelvic surgery.

h. Intramedullary Route

It involves the introduction of a drug into the bone marrow and is now rarely used.

i. Intra-articular Route

- In this case the drugs are administered directly into a joint for treatment of local conditions.
- This ensures a high local concentration of the drug, e.g. hydrocortisone acetate in the treatment of rheumatoid arthritis.

j. Iontophoresis

- In this procedure, galvanic current is used for bringing about the penetration of drugs into the deeper tissues where they may act upon the tissues in the neighbourhood of the point of application.
- Anode iontophoresis is used for compounds bearing positive charge and cathode iontophoresis for the negatively charged compounds.
- The force of repulsion between similar charges drives the drug into the deeper tissues. salicylates have been used by this method.

k. Inuction

- Certain drugs when rubbed into the skin (inuction) can get absorbed and produces systemic effects.
- For example: Nitroglycerin ointment in angina pectoris.

l. Jet Injection (Dermojet)

- This method involves the transcutaneous introduction of a drug by means of a high velocity jet produced through a micro-fine orifice.
- This method does not require the use of a needle and is therefore painless.

m. Subcutaneous (SC) Route

In this route the drug is injected into the subcutaneous tissues of the thigh, abdomen and arm, e.g. adrenaline, insulin, etc.

Advantages of SC route	*Disadvantages of SC route*
• Actions of the drugs are sustained and uniform • Useful in diarrhoea and vomiting patients • Useful in unconscious patient • First pass effect is avoided • Self-medication is possible (e.g. insulin) • Depot preparations can be inserted	• Only non-irritant drugs can be given • Absorption of drug is slow than IM route • Expensive • Sterilization technique must be followed • Large volume of drug cannot be administered

Q 8. What is local/topical route? Give its advantages and disadvantages.

Local Route/Local Application/Topical Route

- In this route, the drugs are applied or administered to the localized or specific areas of the body.
- These preparations are to be meant for their action at the site of application, e.g. paste, ointment, drops, lotions.

Advantages

1. This route provides an easy administration of drug.
2. Local application is useful when prolonged effect of drug is required.
3. There is a low possibility of systemic absorption of the medicament.
4. No special skill or apparatus is required for administration.

Disadvantages

1. The drugs in the form of watery solution are sometimes absorbed into the blood and may produce undesirable effects.
2. The drugs like eyedrops may penetrate into the anterior chamber and affect ciliary muscles, e.g. cocaine.
3. Some drugs may show toxic effect at the site of application.

Q 9. What is rectal route of drug administration? Give its advantages and disadvantages. OR Write a note on 'rectal route'.

Rectal Route

The route of administration in which the drug in the form of solution is introduced into the rectum is called rectal route, e.g. enema preparation, suppository.

Advantages

1. When the drug produces irritation by oral route, this route may be used.
2. When patient does not swallow the drug, this route is preferred.
3. The children who do not cooperate in taking medicines by oral route, the rectal route may be recommended.
4. This route is used when local effects in the rectum are required.

Disadvantages

1. The absorption of drug is not complete because less surface area is available for absorption as compared to oral route.
2. This route is not liked by the patients.
3. A few drugs may produce local irritation of nasal mucosa.
4. Possibility of absorption of drug into blood and drug may be metabolized in the liver before reaching the target organ.

Q 10. Define the terms.

- **Agonist:** A drug which combines with receptor and gives a pharmacological response is called agonist.
- **Antagonist:** A drug which combines with receptor but does not produce pharmacological action and only blocks the receptor is called antagonist.
- **Affinity:** The ability of a drug to get bound to the receptor is called affinity of a drug for the receptor.
- **Efficacy or intrinsic activity:** The ability of a drug to give a pharmacological action after combination with receptor is called efficacy of a drug.
- **Receptor:** A receptor is a specific functional cellular component which when combines with drug produces a pharmacological action.

Q 11. What is absorption? Explain various mechanisms of absorption of drugs.

Absorption of Drugs

The passage of drug from route of administration into blood circulation is known as absorption.

Types/Process/Mechanism/Ways of Absorption

Absorption of drug may be either directly or indirectly but absorption involves the passage of drug dose across the cell membrane. This passage is governed by lipid carriers present at the permeable membrane. The membrane contains small pores and only water-soluble molecules can pass through them.

The absorption of drug through membrane occurs by following ways:

a. Simple Diffusion (Passive Diffusion)

- This is a bidirectional process where the rate of transfer across the membrane is proportional to the concentration ingredient of the cell membrane.
- A water-soluble drug of low molecular weight such as alcohol, urea, water itself diffuses passively through aqueous pores of the membrane.
- The drugs which are lipid soluble are mainly transferred by simple or passive diffusion after dissolution.

b. Active Transport Process

- This is a specialised process requiring energy and is independent on physical property of the membrane.
- In this process, the carrier molecule combines with drug molecule and forms a drug carrier complex on one side of the membrane.
- This complex then diffuses through the membrane and dissociates into carrier and drug molecule when reaches other side of the membrane.
- After that carrier molecule returns to the original surface to repeat the process.
- The ions which are transported by active transport process include Na^+, K^+, I^-, amino acids, some drugs, strong acids, strong bases and weak electrolytes in ionised form, glucose, pyrimidines and some antimetabolites are also transported by this process.
- This transport process is rapid than simple diffusion.

c. Pinocytosis

In this process, the cell takes up the fluid or micromolecule from its surrounding. This process is important for unicellular organisms like amoeba.

In this process, cell forms a cavity like pseudopodium and particles are taken inside the cell.

d. Filtration

The passage of drug molecule through the channels is called filtration. Small, soluble and polar drugs are absorbed by this phenomenon.

e. Facilitated Diffusion

Like passive transfer this process is also not energy-dependant. The movement of drug is from high concentration to low concentration. There is no involvement of carrier system in this process. The process is rapid than passive transport process.

Q 12. Define bioavailability. Give types of bioavailability. Give the importance or object of studying bioavailability.

Bioavailability

"It is defined as the rate and extent at which active concentration of drug is available at the desired site of action".

Types of Bioavailability

1. **Relative bioavailability:** The relative bioavailability is the bioavailability in comparison with reference standard.
2. **Absolute bioavailability:** The absolute bioavailability is the bioavailability in which whole quantity of administered drug reaches the blood circulation. It is possible only by IV route.

Study of Bioavailability is Necessary

1. To avoid toxic and side effects of the drugs.
2. To adjust the dosage regimen.
3. To study pharmacological action of drug.
4. For pre-formulation study.
5. To judge about the clinical responses of drugs.
6. To avoid wastage of drugs.
7. To decide the dose and dosage forms.

Q 13. Enumerate different factors that affect/influence the bioavailability of a drug.

Factors affecting bioavailability of drug		
a. *Pharmaceutical factors*	b. *Physiological factors*	c. *Physicochemical factors*
Dosage form	Anatomy of GIT	Particle size
Dissolution rate	Gastric emptying rate	Stability
	Gastric pH	Complex formation
	Food	Viscosity
Manufacturing variables	Interaction with GI components	Surfactants P^{KA} and P^{KB}
	First pass effect	Partition coefficient
	Diseased condition	Salt form
	Drug–drug interaction	Particle state
		Molecular weight
	GIT flora	Route of administration of drug

Q 14. Discuss physiological factors affecting (influencing) the absorption of drug (bioavailability) from the GIT or gut.

1. **Physical state of drug:** The liquids are better absorbed than solid medicaments. Aqueous solutions are more rapidly absorbed than colloids.

2. **Particle size:** Smaller the particle size, greater is the absorption of drugs from gut. Smaller particle size provides greater surface area for absorption. Thus, the dose required to produce an action is reduced due to smaller particle size.
3. **Concentration of drug:** Higher the cencentration of drug, better is the absorption of drug from intestine.
4. **Area of absorbing surface:** Larger the absorbing surface area, greater is the absorption. Thus, in small intestine the absorption of drug is greater than the stomach.
5. **Physical and mental state of the patient:** Disturbed physiological conditions such as infection, fever affect the absorption of drug. Emotional upset condition also affects absorption of drug adversely.
6. **Functional integrity of GIT:** Increased peristalsis of GIT decreases absorption of drug, e.g. in diarrhoea condition, absorption of drug decreases.
7. **pH of drug:** Acidic drugs are rapidly absorbed in stomach while basic drugs are rapidly absorbed in intestine due to respective pH ranges.
8. **Formulation:** Calcium and magnesium ions reduce the absorption of tetracyclines because tetracycline forms complexes with Ca^{++} and Mg^{++}. Hence, such formulation should not be made.
9. **Presence of other agent:** Vitamin C increases the absorption of drug from GIT. The absorption of fat-soluble vitamins increases in presence of liquid paraffin.
10. **Presence of food in GIT:** The presence of food in GIT may reduce absorption of drug from GIT because there is no direct contact with walls of GIT. But gastric irritation will not occur.
11. **First pass effect:** It is the time required for the drug to pass through hepatic portal system. The drugs are inactivated, therefore bioavailability of such drugs is reduced.

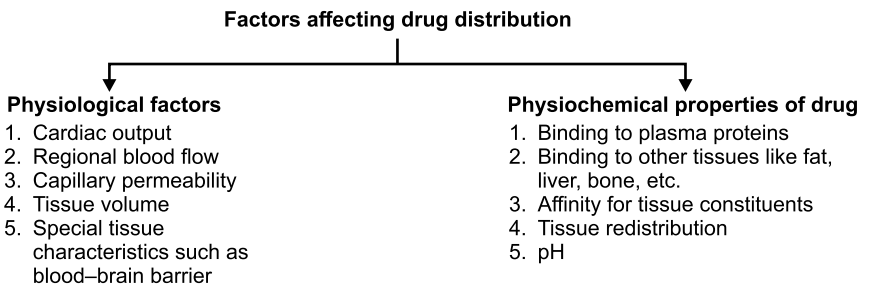
Q 15. What do you mean by distribution of drugs? Enlist various compartments in which drug is distributed. OR Write a note on 'distribution of drug in the body'.

Distribution of Drug in the Body

Distribution of drug involves transport of drug to the tissues. The body fluids act as solvents and carriers for the majority of drugs for distribution in the body. Drugs may be distributed into body as follows:

i. Extracellular fluid
ii. In blood
iii. Adipose tissue (fat)
iv. Other body tissues (organs)
v. Transcellular fluid compartments, e.g. fluids in GIT, bronchi, CSF.

- In blood, the majority of drugs are simply dissolved in serum water but some of them are bound to blood proteins such as albumin, globulin, etc.
- The plasma protein binding of drugs acts as a storage site in the blood. Thus, plasma protein binding of drug can increase the duration of action of drugs.
- Distribution of drugs into the brain and CSF depends upon the lipid soluble properties of drugs. Lipid soluble drugs enter in the brain more easily. Similarly, lipid soluble compounds cross the placental barrier and show similar pharmacological effects in both mother and foetus.
- The enterohepatic circulation is another site of drug distribution. Some drugs are extracted from the body by liver and then excreted into the small intestine via bile. Further they are reabsorbed across the mucosa back into the blood.
- Factors affecting distribution of drug in the body are:



The Distribution of Drugs in Specific Compartments

These are some specific compartments in the body that are characterized by barriers and they restrict entry of some drugs.

a. Blood–brain and blood–CSF barrier
b. Placental barrier.

a. Blood–Brain Barrier (BBB)

Nature has offered special protection to brain from drugs. The passage of drug in the brain is different from all organs. This is facilitated by different structure of capillaries in the CNS. Therefore only lipid soluble drugs can cross this barrier and enter inside.

Clinical significance of blood–brain barrier:

- The blood–brain barrier protects the brain from the toxic effects of lipid non-soluble drugs and poisons.
- During inflammation of meninges, permeability of BBB for drugs like penicillins or aminoglycosides is increased and they are effective.

b. Placental Barrier

Similar to BBB if also allows lipid soluble drugs but it is a weak barrier and almost all drugs can ultimately cross this barrier increases as pregnancy advances.

Distribution of Drugs in Different Body Compartments

Body compartment	*Types of drugs distributed*
1. Total body water	Small water-soluble molecules such as alcohol and antipyrine
2. Extracellular space	Large water-soluble molecules such as mannitol
3. Intracellular space	Very large, strongly protein-bound molecules such as heparin
4. Body fat	Highly lipid soluble molecules such as DDT and thiopentone
5. Bones	Fluoride and lead

Q 16. What is protein binding of drugs? Give its importance and its effects. OR Write a note on 'protein binding' of drugs.

Protein Binding of Drugs

After absorption, the drug circulates in the blood and binds with plasma proteins which is known as protein binding of drugs.

Explanation

- Due to protein binding of drug, it is not available for diffusion into extracellular compartment. Thus, there is no excretion of drug and prolongs the during of action of a drug.
- After absorption, the drug circulates in the blood either in free form or bound to plasma proteins either albumin or alpha-acid-glycoprotein.
- The fraction bound to protein usually falls as the total concentration of the drug increases and binding sites becomes saturated.
- Binding of drugs to plasma proteins assists absorption.
- Protein binding acts as a temporary 'store' of drug and tends to prevent large fluctuations in concentration of unbound drug in the body fluids.
- Protein binding reduces diffusion of the drug into the cell and thereby delays its metabolic degradation.
- Protein binding also reduces the amount of drug available for filtration at the glomeruli and hence delays its excretion.
- Protein binding reduces drug clearance.
- The extent of drug binding depends on the binding protein concentration in the plasma.

Importance of Protein Binding

1. Protein binding makes the drug inactive.
2. The drug becomes impermeable to membrane after protein.
3. Protein binding acts as a temporary storage of drugs.
4. Protein binding also reduces the amount of drug available for filtration at the glomeruli and hence reduces its excretion.
5. Protein binding reduces drug clearance.

Effects of Protein Binding on Drugs

1. Assists enteral absorption of a drug.
2. Acts as a temporary store for it and thereby prolongs drug action.
3. Causes prolonged, low levels of free drug.
4. Delays its metabolic degradation.
5. Delays its excretion.
6. Diminishes its penetration into the CNS.

Q 17. Write a note on 'biotransformation/metabolism of drugs'.

Biotransformation/Metabolism of Drugs

The alteration of drug within a living organism so as to modify its activity or its nature, is known as biotransformation or metabolism.

- The enzymes involved in the biotransformation of drugs are called microsomal enzymes.
- Some drugs are biotransformed into more active compounds, e.g.
  i. Levodopa (inactive) is converted to dopamine (active) in brain.
  ii. Conversion of diazepam to oxazepam which is more active.
  iii. Conversion of phenylbutazone to oxyphenbutazone which is more active.
- The important pathways of biotransformation of drugs are:
  i. **Oxidation:** Microsomal oxidation may involve the introduction of a hydroxyl group into the drug molecule, e.g. conversion of salicylic acid into gentisic acid.
  ii. **Reduction:** Many halogenated compounds and nitrated aromatic compounds are reduced by the microsomal enzymes, e.g. halothane, chloramphenicol.
  iii. **Hydrolysis:** Hydrolysis is usually carried out by enzymes esterases that hydrolyse the esters.
  Drugs like pethidine, procaine, acetylcholine are hydrolysed by esterase.
  iv. **Conjugation:** This is a synthetic process by which a drug or its metabolite is combined with an endogenous substance, resulting in various conjugates such as glucuronides, etheral sulphates and amino acid conjugates, e.g. phenobarbitone is oxidised to its hydroxy derivative which is conjugated with glucuronic acid.

Factors Affecting Drug Metabolism/Biotransformation

1. Animal species and strains
2. Age and sex
3. Genetic determinants
4. Nutritional status
5. Altitude and temperature
6. Route and duration of drug administration
7. Environmental determinants such as air solution

8. Simultaneous administration of other drugs
9. Presence of disease (hepatic/renal damage)

Q 18. Define metabolism/biotransformation. Mention the enzymes responsible for metabolism of drugs. Explain types of biotransformation reactions.

Metabolism /Biotransformation

The alteration of drug within a living organism so as to modify its activity or nature, is known as biotransformation or metabolism.

Enzymes for Biotransformation

a. **Microsomal enzymes:** They are present in the smooth endoplasmic reticulum of the liver, kidney and GIT, e.g. glucuronyl transferase, dehydrogenase, hydroxylase and cytochrome P450.
b. **Non-microsomal enzymes:** They are present in the cytoplasm, mitochondria of different organs, e.g. esterases, amidase, hydrolase.

Types of Biotransformation Reactions

1. Phase 1 Reactions (Non-synthetic Reactions)

- In this phase, the enzymes carryout oxidation, reduction and hydrolysis reactions.
- The phase 1 reactions introduce functional groups such as –OH, –COOH, –SH, –O–, $–NH_2$, etc.
- The phase 1 reactions leads to inactivation of active drug.
- The phase 1 reaction is reffered as functionalisation phase of drug metabolism.
- Phase 1 reactions are carried out by CYPs (cytochrome P450 isoenzyme), flavin-containing monooxygenases (FMO) and epoxide hydrolases (EH).

a. **Oxidation:** Microsomal oxidation involves the introduction of an oxygen or removal of hydrogen atom.
b. **Reduction:** The reduction reaction will take place by the enzyme reductase which catalyze the reduction of azo and nitro compounds, e.g. prontosil converted to sulfonamide.
c. **Hydrolysis:** Hydrolysis is usually carried out by the enzymes esterases that hydrolyse the esters, e.g. drugs like pethidine, procaine, acetylcholine are hydrolysed by esterase.

2. Phase 2 Reactions (Synthetic Reactions/Conjugation Reactions)

This is a synthetic process by which a drug or its metabolite is combined with an endogenous substance, resulting in various conjugates such as glucuronides, etheral sulphates and amino acid conjugates.

The active enzymes in this phase 2 reaction include UDP-glucuronosyltransferases (UGT), sulfotransferases, glutathione-S transferases (GST), e.g. phenobarbitone is oxidised to its hydroxy derivative which is conjugated with glucuronic acid.

Q 19. What is 'disposition/excretion' of drugs? Explain different routes/channels/ways of excretion of drugs from the body. OR Write a note on 'disposition/excretion of drugs'.

Excretion/Disposition of Drugs (Elimination of Drugs)

It means removal of a drug from the body through various routes.
The important channels of excretion of drugs are as follows:

1. **Kidney:** The kidneys act as a primary organ for the excretion of most of the drugs. The rate of glomerular filtrate, tubular reabsorption and tubular secretion influences the rate of excretion of drugs, e.g. weak acids are quickly eliminated in an alkaline urine while weak bases are rapidly excreted in an acidic urine.
2. **Lungs:** Volatile general anaesthetics and certain other drugs like paraldehyde and alcohol are partially excreted by the lungs.
3. **Skin:** Some metals like arsenic and mercury may be partly excreted through the skin. Arsenic gets deposited in the hair follicles on prolonged administration. This phenomenon is useful for detecting arsenic poisoning.
4. **Bile:** The drugs such as erythromycin are excreted in the urine only in small amounts but appear in high concentration in bile and are partially excreted into the intestine through the bile.
5. **Intestine:** Some substances which are not fully absorbed from the GIT are excreted in the faeces, e.g. purgatives like senna.
6. **Milk:** Antibiotics are deposited in the milk. Drugs like chloramphenicol, chlorpromazine, diazepam are deposited in milk and excreted via milk.
7. **Saliva:** Certain drugs like iodides and metallic salts are excreted in the saliva. Lead compounds deposited as lead sulphide produce blue line on gums.

Q 20. Define pharmacodynamics. Explain various general mechanisms of action of a drug.

Pharmacodynamics

It is the study of mechanism of action of drug and the pharmacological effects produced on the human body.

General Mechanisms of Action of a Drug/Types of Drug Actions

The drug may produce their effects by following different mechanisms:

1. By stimulation
2. By depression
3. By irritation
4. By replacement of a deficient hormone.
5. As anti-infective agents
6. By modification of the immune status.

1. By Stimulation

- Increase in activity of specialized cells is called stimulation.
- Excess stimulation produces changes in the protoplasm of the cell which may ultimately leads to depression.
- A drug may specifically stimulate certain portion of a particular system but depress others, e.g. morphine stimulates the vagus and the oculomotor nuclei and chemoreceptor trigger zone but depresses the respiratory and cough centres.

2. By Depression

- Decrease in the activity of specialized cells is called depression.
- Quinine depresses the myocardium while barbiturate depresses the central nervous system.

3. By Irritation

- The term irritation indicates that a drug produces adverse effects on the growth, nutrition and morphology of living tissues.
- Irritation is thus a phenomenon not restricted to specialized cells but can occur in all the body tissues.
- Irritation produces changes in the cellular structure and is capable of producing inflammation, corrosion and necrosis of cells.

a. Astringent effect (precipitation of proteins)
b. Dehydration
c. Action on cellular enzymes, usually inhibition
d. Cytotoxic action
e. Counter irritant action (e.g. like turpentine oil)

4. By Replacement of a Deficient Hormone

- In this case drugs may be used as replacement when the production of endogenous substance is reduced.
- Replacement finds an important application in the treatment of hormonal deficiencies, e.g. insulin in diabetes mellitus.

5. As Anti-infective Agents

The drugs are used for prevention, arrest and eradication of infections, they act specifically on the causative organisms.

6. Modification of Immune Status

Vaccine, sera and certain other agents act by altering the immune status.

Q 21. Enlist various factors modifying drug action.

1. Body weight
2. Age
3. Sex
4. Route of administration
5. Time of administration
6. Diet and environmental factor
7. Genetic factor
8. Emotional factor
9. Presence of disease
10. Metabolic disturbances
11. Cumulative effect
12. Additive effect
13. Synergism (potentiation)
14. Antagonism
15. Tolerance
16. Dependance.

Q 22. Explain the factors modifying drug action.

1. **Body weight:** The dose of a drug is related to body weight. The dose of drug is usually expressed as mg/kg of body weight.
2. **Age:** Infants and old patients need dose different from adults. In infants, the metabolising enzymes and excretory process are not fully developed. Hence, doses of children should be smaller than adults.
3. **Sex:** Some drugs which cross the placental barrier and depress foetal respiration are avoided in pregnant women, e.g. morphine.
4. **Route of administration of drug:** As the route of administration changes, the dose required for same pharmacological action varies. Hence, IV dose is smaller than SC dose which is smaller than oral dose.

   IV dose < SC dose < oral dose.
5. **Time of administration of drugs:** When the drugs are taken before meals, the absorption is greater, but there is irritation to GIT due to direct contact of drug with walls of GIT.

   When the drugs are taken after meals, the absorption is poor but there is not irritation to GIT. This is because drug is mixed with food material hence direct contact of drug with walls of GIT is avoided.
6. **Diet and environmental factor:** In the presence of diet, the absorption of drug is poor. Environmental factor also affects the variations in the doses of drugs, e.g.
   i. The alcohol is well tolerated in cold environment than in summer.
   ii. The dose of phenobarbitone required to produce a sleep during day-time is much more than the dose required during night.
7. **Genetic factor:** The patients with hereditary metabolic disorders rarely show a disturbance in the metabolism of drugs. This is because of microsomal enzyme systems involved in the metabolism of drugs. Thus, the genetic factor gives individual variations in response to drugs. Some drugs pass through genes and modify drug response from generation to generation, e.g. diabetes mellitus.

8. **Emotional factor:** The personality of the physician may influence the drug effect particularly in psychic patients. Hence, nervous patients require smaller doses of drugs as compared to normal patients.
9. **Presence of disease:** In diseased conditions, some drugs may produce unusually prolonged effects in cirrhotic patients. Thus, drugs like barbiturates and chlorpromazine may produce unusually prolonged effects in cirrhotic patients.
10. **Metabolic disturbances:** The changes in water balance, electrolyte balance and acid–base balance, body temperature and other physiological factors may modify the effects of drugs, e.g. the absorption of iron from the GIT is maximum if the individual has an iron deficiency anaemia.
11. **Cumulation (cumulative effect):** When excretion of drug is slow, repeated administration of drug accumulates in the body and may lead to toxicity. This is known as cumulation. The phenomenon is known as cumulative effect, e.g. digitalis, emetine, heavy metals, chloramphenicol show cumulation.

    Cumulation can be avoided by following ways:
    i. Stop the administration of drug at the appearance of first warning symptom.
    ii. It must be known that the drug is eliminated slowly or rapidly.
    iii. Carefully select the dosage form in which the drug is to be administered.
    iv. Check the liver and kidney function before and during drug administration.
12. **Additive effect:** When total pharmacological action of two or more drugs administered together is equivalent to their individual pharmacological actions, the phenomenon is known as additive effect, i.e.

    $$1 + 1 = 2$$

    For example, combination of ephedrine and aminophylline shows additive effect in the treatment of bronchial asthma.
13. **Synergistic effect (synergism):** The increase in pharmacological response by the use of two or more drugs at the same time is called synergism. The effect is known as synergistic effect, i.e.

    $$1 + 1 = 3$$

    For example:
    a. Aspirin and codeine as analgesic
    b. Sulphamethoxazole and trimethoprim as antibacterial
    c. Aspirin, phenacetin and caffeine as analgesic.
14. **Antagonism:** The opposite actions of two drugs on the same physiological system are termed antagonism.

- *Classification/types of antagonism*
  i. **Chemical antagonism:** When the biological activity of drug is totally reduced by a chemical reaction with another agent, the phenomenon is known as chemical antagonism, e.g. acid and alkali react with each other for neutralization.

ii. **Competitive/reversible antagonism:** In competitive antagonism, the agonist and antagonist compete for the same receptor. Hence, in such cases, the extent to which the antagonist opposes the pharmacological action of agonist depends on the relative number of receptors occupied by two compounds, e.g. acetylcholine and atropine compete for each other at the receptor sites.

If concentration of acetylcholine is increased, the blockade produced by atropine can be overcome. Hence, antagonism is also termed reversible antagonism.

iii. **Noncompetitive irreversible antagonism:** In this type of antagonism, the antagonist inactivates the receptor by some mechanism in such a way that the effective complex with agonist cannot be formed. Hence, though the concentration of agonist is increased at the receptor site, the receptor is inactive to produce any combination with agonist. Hence, there is no any pharmacological action with agonist. Thus, it is called irreversible antagonism, e.g. acetylcholine and papaverine on smooth muscles produce noncompetitive antagonism.

iv. **Physiological antagonism:** When a drug is administered, it reverses the effects of another drug by acting on different receptors. This phenomenon is known as physiological antagonism, e.g. adrenaline and histamine reactions are of this type.

v. **Functional antagonism:** When interaction of two agonists which act independently of each other but give opposite effects take place, the reaction is known as functional antagonism, e.g. acetylcholine and adrenaline show functional antagonism.

• Importance of antagonism

i. Antagonism is useful in poisoning cases to block the actions of poisons.

ii. Antagonism is useful to control the adverse effects of the drugs.

iii. Antagonism is useful to adjust the doses of the drugs combined.

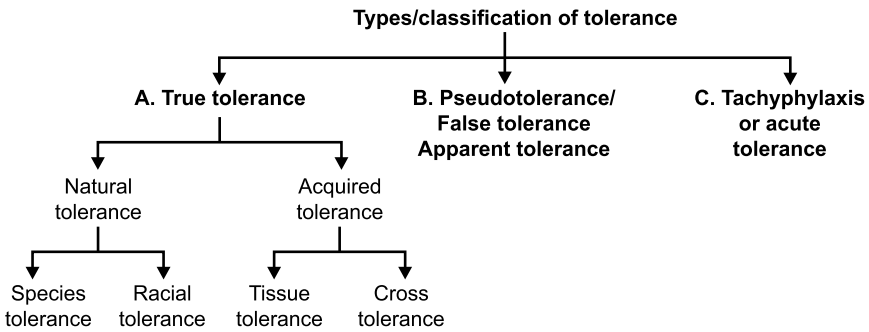
15. **Drug tolerance:** When large dose of a drug is required to get an effect, produced by the normal therapeutic dose of a drug, the phenomenon is known as drug tolerance.

• Types/classification of tolerance

A. **True tolerance:** It is seen on both oral and parenteral administration.

a. ***Natural tolerance:*** It results in difference between species and races.

i. *Species tolerance:* Some animal species can tolerate large amount of particular drug which may prove to be lethal (toxic) to man, e.g. some rabbits can tolerate large amount of belladonna. This is because of enzyme atropine esterase present in the rabbits' liver and plasma which rapidly detoxify the belladonna.



ii. *Racial tolerance:* When solution of ephedrine is instilled into the conjunctival sac of the Caucasians, it produces prompt dilation of pupils but in Negroes ephedrine does not produce any dilation at all.

b. ***Acquired tolerance:*** Repeated administration of drug produce a tendency to produce a tolerance. This is known as acquired tolerance, e.g. the drugs like barbiturates, opiates, alcohol, xanthines, produce acquired type of tolerance. Acquired tolerance is of two types:

i. *Tissue tolerance:* In this type, development of tolerance is related to certain pharmacological action and certain tissues, organs or systems, e.g. morphine produces tolerance for its euphoriant effect but pupils and GIT never become tolerated. Thus, same dose of morphine invariably produces constipation but may fail to "euphoria".

ii. *Cross tolerance:* When an individual develops tolerance to a drug belonging to a particular group, it also shows tolerance to other drugs belonging to the same grouping, it is known as cross tolerance, e.g. tolerance to vasodialator effect of 'glyceryl trinitrite' in an individual shows tolerance to 'pentaerythritol tetranitrite' which belongs to same group.

B. **Pseudotolerance/false/apparent tolerance:** It is observed only by oral route. When small dose of poison is taken orally, tolerance is developed to that poison by the GIT. This is possible after repeated administration of small quantity by oral route in the individual immune to such poison.

This tolerance to the oral administration of drug is probably due to local changes developed by GIT which prevent poison from getting absorbed into the systemic circulation.

C. **Tachyphylaxis/acute tolerance:** The repeated administration of drug within a short interval of time decreases the pharmacological response progressively. This phenomenon is known as tachyphylaxis or acute tolerance.

Tachyphylaxis probably can occur if the drug dissociates only slowly from its combination with receptor and thus continuing receptor blockade, while

loosing its intrinsic activity, i.e. looses its pharmacological effects, e.g. repeated administration of ephedrine in the treatment of bronchial asthma decreases the response to ephedrine.

Difference between true tolerance and pseudotolerance

True tolerance	*Pseudotolerance*
1. It is seen on both oral and parenteral administration of drug	It is seen only on oral administration of drug
2. It is observed naturally due to presence of certain enzyme system to tolerate certain drugs	It is observed probably due to local changes developed by GIT
3. It is further divided into: i. Natural tolerance, ii. Acquired tolerance	It has no further types
4. Example, morphine produces tolerance for its euphoriant effect but pupils and GIT are not affected	Example, if small quantity of poison is taken orally, poisoning will not occur

16. **Drug dependance:** It is a psychic or physical condition of the person due to interaction between living organism and drug, which includes a compulsion to take the drug and tendency to increase the dose at the cost of health, e.g. morphine, heroin, alcohol, tobacco.

• Dependance is of two types:

i. *Physical dependance:* It is the condition in which the body shows dependant stage on the drug. If the drug is withdrawn, the intense physical disturbances occur.

ii. *Psychic dependance:* A condition in which a drug produces a feeling of satisfaction and a psychic drive that requires periodic or continuous administration of the drug to produce pleasure and to avoid discomfort is called psychic dependance.

Q 23. Give the formulae for calculating doses in children.

a. Age-based Formulae

1. Young's formula $$\text{Child dose} = \frac{\text{Age in years}}{\text{Age in years} + 12} \times \text{Adult dose}$$
2. WJ Dilling formula $$\text{Child dose} = \frac{\text{Age in years}}{20} \times \text{Adult dose}$$
3. Fried's rule for infant $$\text{Infant dose} = \frac{\text{Age in months}}{150} \times \text{Adult dose}$$

b. Body Weight-based Formulae

1. Clark's formula $$\text{Child dose} = \frac{\text{Wt of child in kg}}{70} \times \text{Adult dose}$$
2. Clark's rule for infants $$\text{Dose of infant} = \frac{\text{Wt in pound}}{150} \times \text{Adult dose}$$

c. As per Surface Area $\dfrac{\text{Surface area of child } (m^2)}{\text{Surface area of adult } (m^2) \; (1.73\,m^2)} \times 100 = \%$ of adult dose

Q 24. Give the difference between 'drug tolerance and tachyphylaxis'.

Drug tolerance	*Tachyphylaxis*
1. It develops slowly	It develops rapidly
2. It takes a time-in days to months	It develops within a few minutes
3. The higher dose causes tolerance	It does not depend on dose
4. The effects are seen when dose is increased	The effects are not seen even when dose is increased
5. Seen routinely in clinical practice	Not seen routinely in clinical practice
6. For example: Opium, barbiturates, ethanol, etc.	Frequent administration of ephedrine in bronchial asthma

Q 25. Define 'therapeutic index' (TI). Give the reasons 'why a drug with larger therapeutic index is safer than one with smaller therapeutic index'. OR 'Drugs having lesser therapeutic index should be administered cautiously'. OR 'Why therapeutic index shows margin of safety of drug'?

Therapeutic Index

Therapeutic index is the ratio of median lethal dose (LD_{50}) and median effective dose (ED_{50}).

$$\text{Therapeutic index (TI)} = \frac{LD_{50}}{ED_{50}}$$

Reason

1. Therapeutic index indicates the relative margin of safety of a drug.
2. A dose of the drug which produces the stated effect in 50% of individuals within the population is called median dose.
3. Depending upon the stated effect it can be designated as 'median effective dose (ED_{50}) and median lethal dose (LD_{50})'.
4. The therapeutic index indicates how close the effective dose is to the lethal dose for 50% of the test population. Thus, therapeutic index gives an idea about the 'margin of safety'.
5. As the ED_{50} approaches the ED_{50}, the danger of the drug toxicity increases significantly.
6. Therefore, a drug with larger therapeutic index is safer than one with smaller therapeutic index. Hence, drug with lesser therapeutic index should be administered cautiously.
7. Therefore therapeutic index shows margin of safety of drug.
8. Drugs with a therapeutic index of 10 or more are almost sure to be safe.

Objective Questions with Answers in Bold Letters

1. **Pharmacology** is the science, which deals with the drugs and their actions on human body or animals.
2. **Pharmacodynamics** is concerned with study of mechanism of action of drugs and pharmacological effects produced on the human body.
3. **Pharmacokinetic** includes the study of absorption, distribution, metabolism and excretion of drugs.
4. **Toxicology** is the science deals with study of poisons.
5. **Posology** deals with the study of doses of drugs.
6. **Teratology** is a branch of science which concern with the harmful effects of drugs on foetus.
7. Pharmacokinetics decides the **fate of drug** in the body.
8. In **sublingual** route tablets are placed under the tongue.
9. Maximum **10 ml** volume of drug can be administered by intramuscular (IM) route.
10. Accurate blood levels of drug can be achieved only by **intravenous route**.
11. The routes of administration of drugs other than alimentary canal are called **parenteral routes**.
12. 100% bioavailability is possible only by **intravenous route**.
13. **Intradermal route** is useful for the detection of drug allergy.
14. Injections with oily bases can be given by **intramuscular route**.
15. In **iontophoresis**, the galvanic current is used for penetration of drug into the deeper tissues.
16. Certain drugs are rubbed into the skin to get absorbed and produce systemic effect, the route is known as **innuction**.
17. Enema preparations, suppositories are administered by **rectal route**.
18. A drug which combines with receptor and produces a pharmacological response is called **agonist**.
19. A drug which combines with receptor is called **antagonist**.
20. The ability of a drug to combine with receptor is known as **affinity** of a drug for the receptor.
21. The ability of a drug to give a pharmacological action after combination with the receptor is called **efficacy (instrinsic activity)**.
22. The **absorption** means passage of drug from route or administration into the blood circulation.
23. Simple diffusion (passive diffusion) is a **bidirectional** process.
24. The energy is required for **active transport process** of absorption of drug.
25. In **pinocytosis**, the drug molecules/particles are taken inside the cell in cavity like pseudopodium.
26. In **first pass effect**, the drugs go to liver first and then into the blood circulation.

27. **Bioavailability** means the rate and extent at which the active concentration of drug reaches in blood and is available at the desired site of action.
28. **Distribution** of drug involves the transport of drug to the tissues.
29. Distribution of drugs in the brain and CSF depends upon the **lipid soluble** properties of drug.
30. BBB means **blood–brain barrier**.
31. **Protein binding** acts as a temporary storage of drug.
32. Protein binding makes the drug **inactive**.
33. Protein binding produced **prolonged** drug actions.
34. **Biotransformation/metabolism** involves modification of activity or nature of drug.
35. The enzymes involved in the biotransformation of drugs are called **microsomal enzymes**.
36. **Disposition/elimination** means removal of drug from the body through various routes.
37. The accumulation/deposition of drug in the body producing toxicity is known as **cumulation**.
38. When total pharmacological action of two or more drugs administered together is equivalent to their individual pharmacological actions, the phenomenon is known as **additive effect**.
39. **Synergism/synergistic** effect means increase in pharmacological effect by the use of two or more drugs at the same time.
40. The opposite actions of two drugs on the same physiological system, the phenomenon is known as **antagonism**.
41. **Theapeutic index** indicates the relative 'margin of safety' of a drug.
42. The drugs with **larger** therapeutic index are safer.
43. The drugs having **lesser** therapeutic index should be administered cautiously.
44. Only up to **2 ml** quantity of drug can be injected by subcutaneous route.
45. Total volume of drug injected by intramuscular route is restricted up to **10 ml**.
46. In **intramedullary injection route** the drugs are directly injected into the bone marrow.
47. **Enteral route** means the drug is placed directly in the gastrointestinal tract (GIT).
48. The effect produced by the drug after being effectively where it is absorbed in blood stream is known as **systemic effect**.
49. The effect produced by the drug in a localized area where it is applied is known as **local effect**.
50. A **receptor** is a specific functional cellular component which when combines with drug produces a pharmacological action.
51. **Phase 1 reaction** of biotransformation is known as non-synthetic reaction.
52. **Cytochrome P450** is a microsomal enzyme involved in biotransformation reactions.

53. The phase 1 reaction of biotransformation leads to **inactivation** of active drug.
54. The phase 1 reaction is reffered as **functionalisation** phase of drug metabolism/biotransformation.
55. The phase 2 reaction is also known as **synthetic reaction/conjugation reaction**.
56. **UDP–glucuronosyltransferases (UGT)** is active enzyme involved in phase 2 reaction of biotransformation.
57. **Pharmacokinetics** is the movement or passage of drug across the body.
58. The process which refers to the passage of a drug dose over cell membrane from the point of delivery to the bloodstream is called **absorption**.
59. The primary site of drug metabolism is **liver**.
60. Simple diffusion is also called **passive diffusion**.
61. The macromolecules with which medicines bind to elicit their specific biological effects are called **receptors**.
62. The phenomenon of two medications being used at the same time to facilitate pharmacological action is called **synergism**.