# 1. General Pharmacology

## INTRODUCTION TO PHARMACOLOGY

Pharmacology is divided into two main areas: Pharmacodynamics and pharmacokinetics.

The term **pharmacology** is of Greek origin and is formed from two words: *Pharmakon*, meaning "medicine," and *logia*, meaning "the study of." Pharmakon also means poison and remedy, poison because some of the early medicines were toxic enough to kill, and remedy because, at times, early medicines cured the illness. The word **drug** has a Dutch origin in which **droog** means "dry" as in the use of dry herbs.

Drugs fall into six categories of desired effects.

- **Curative**. Some drugs cure problems, as in diuretics, which help the body rid itself of excess fluid.
- **Prophylactic**. These drugs prevent problems, as in antibiotics given before surgery to prevent infection.
- **Diagnostic**. Some drugs help diagnose a disease, for example barium that patients swallow to help highlight digestive problems on a radiograph.
- **Palliative**. Other drugs, such as pain-relievers, do not cure disease, but they make patients more comfortable.
- **Replacement drugs**. These drugs "replace" missing substances. Levothyroxine sodium (synthroid), is a drug that replaces a missing thyroid hormone.
- **Destructive medications** destroy tumours and microbes. Antineoplastic (anticancer) drugs are examples of destructive and toxic drugs.

The term **pharmacodynamics** refers to the effect of a drug on the body; or more scientifically, the negative and positive biochemical or physiological changes that a drug creates.

**Pharmacokinetics** (what body does with the drug) deals with the absorption, distribution, and excretion of drugs.

- It is the quantitative study of drug movement in, through and out of the body.
- All pharmacokinetic processes involve transport of the drug across biological membrane.
- It is the quantitative study of absorption, distribution, metabolism, and excretion.

### Absorption

- Absorption is the movement of drug from its site of administration into the blood circulation.
- Absorption directly proportional to the fraction of administration dose which gets absorbed.
- Absorption is directly proportional to the rate of absorption.

### Factors affecting absorption

- State of drug.
- pH
- Physiological properties of drug
- Concentration
- Area of absorption surface
- Rate of blood flow
- Route of administration
- Biological factor
- First-pass effect.

### 1. State of drug

- Aqueous solution is better absorbed than oily solution. Liquid is absorbed faster than solid.

### 2. pH

- Change in pH affects the absorption.
- Most of the drugs are weak electrolytes.
- Acidic drug is better absorbed in acidic pH of stomach. and basic drug is better absorbed in basic pH of intestine.

### 3. Physiological properties of drug

- Shape, size and solubility affect the absorption.

### 4. Concentration

- Increase in the concentration, better the absorption.

### 5. Area of absorption surface

- Larger the surface, larger will be the absorption.
- Surface increased, absorption increased, so drugs are better absorbed from intestine than stomach.

### 6. Rate of blood flow

- Absorption from highly vascularised membrane is rapid as absorption from sublingual route is faster. Massage can increase blood flow.
- Application of heat also causes increased blood flow and increased absorption of drug.
- Decreased blood flow by vasoconstriction decreases absorption.

### 7. Route of administration

a. Oral route

- Most oral drugs are absorbed from the upper part of the small intestine, as it has a large mucosal surface area that facilitates efficient absorption.
- Presence of food affects absorption.
- Many drugs which are not absorbed orally are absorbed by injection.

b. Topical route

- Only liquid soluble drugs are absorbed from skin, e.g. nitroglycerine.
- Some insecticides absorbed from skin cause toxicity.
- Cornea is permeable to liquid soluble drugs.
- Similarly, mucous membrane of mouth, rectum, vagina absorb lipophilic drugs.

### 8. Biological factor

- Gut motility
- pH of gastrointestinal tract (GIT)
- Presence of food
- Enzyme in GIT.

### 9. First-pass effect

- Drugs administrated orally pass through liver via portal circulation is called first-pass effect.
- Drug metabolism in liver is vigorous, so less amount of drug reaches in circulation.
- In such cases, increased dosages are administered orally then by parenteral route, e.g. isoprenaline and testosterone.

## Distribution

**Drug distribution:** Transfer of drugs from the blood into various tissues is known as drug distribution. When reaches the blood, it is distributed in various parts of the body including CNS and foetal circulation. Distribution is complete when drug reaches the visible site. Some drugs concentrate in some tissue compartments which are called drug reservoirs. Factors like plasma protein binding, physicochemical properties of drug, rate and amount of drug reaching each reservoir in various body parts are extremely variable.

**Plasma protein:** In blood, drug maybe free or bound to plasma protein (albumin, globulin, etc.) only that free drug diffuses and causes action at target organ. One drug can bind to many sites.

**Tissue storage:** Drugs may accumulate in specific organ or tissue, for example, iodine in thyroid, tetracycline, heavy metal like lead in bone and teeth, and digoxin in heart.

**Adipose tissue:** Liquid soluble drug like thiopentone is stored in body fat.

Factors governing volume of drug distribution

- Liquid: Water partition coefficient of the drug.
- $pK_a$ value of the drug.
- Degree of plasma protein binding.
- Affinty of different tissues
- Fat: Lean body mass ratio
- Disease like CHF, cirrhosis, etc.

## Biotransformation

Metabolism/Biotransformation

- It means chemical alternation of the drug in body.
- Drugs in body are acted by number of enzymes resulting in structural changes, the process is called metabolism.
- By this process, drugs may get activated or can be converted into soluble and highly soluble, compound and excreted in urine.
- Liver is the main site of metabolism.

**Process of metabolism:** Reaction which bring about metabolism involves following steps:

Phase I

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

Phase II

- Glucuronide conjugation
- Acetylation
- Methylation
- Sulphate conjugation
- Glycine conjugation
- Glutathione conjugation

## Factors affecting metabolism

1. Enzyme inhibitor—many drugs inhibit drug metabolizing enzyme and decrease the drug metabolism, so they need dose reduction.
2. Enzyme induction—drugs like phenobarbital increase the synthesis of enzyme, so duration of drug action or reduced tolerance.
3. Age and sex—many enzymes are deficient in newborn making them more susceptible to many drugs.
4. Diseases present in liver and kidney affect the rate of their metabolism.

## Excretion

- Elimination is the process by which drugs or their metabolites are removed from the body. Fast-acting drugs produce their effects quickly but for a shorter duration, whereas slow-acting drugs take longer to produce effects but last for a longer period.
- Major organs involved in the excretion of drugs include the kidneys, biliary system, intestines, lungs, and mammary glands (milk).

**Kidney:** The most important organ. Products are water-soluble but lipid insoluble. Some drugs maybe reabsorbed from renal tubule. In the presence of renal damage, drug excretion is impaired, resulting in high blood levels and prolonged drug action.

**Bile:** High molecular weight drug is partially excreted into intestine through bile, is either excreted in faces or reabsorbed, e.g. erythromycin.

**Intestine:** Drugs not absorbed from GIT, are excreted in feces, e.g. sulphaguanidine.

**Lungs:** All volatile anaesthetics are excreted by lungs.

**Milk:** pH of milk is slightly acidic, so concentration of drug like morphine is higher in milk, so antithyroid, anticancer and purgative antiepileptics should be avoided in lactating mother.

# PHARMACODYNAMIC MECHANISM OF DRUG ACTION

**Pharmacodynamics** is the study of the effects of drugs on the body. It aims to explain the full sequence from drug action to resulting effects, as well as the relationship between dose and response. The interaction of one drug modifying the action of another is also a key part of pharmacodynamics.

## Principles of Drug Action

Drugs, with the exception of gene-based therapies, do not introduce new functions to any system, organ, or cell. Rather, they alter the rate of ongoing biological activity. The primary types of drug action include:

1. **Stimulation:** Refers to the selective enhancement of activity in specialized cells.
   *Examples:* Adrenaline stimulates the heart; pilocarpine stimulates salivary glands.

   However, excessive stimulation may lead to subsequent depression—for instance, high doses of picrotoxin (a CNS stimulant) can cause convulsions followed by coma and respiratory depression.
2. **Depression:** Involves selective reduction in activity of specialized cells.
   *Examples:* Barbiturates depress the central nervous system; quinidine depresses heart function.

   Some drugs stimulate certain cells while depressing others. For example, acetylcholine stimulates intestinal

smooth muscle but depresses the SA node in the heart. Hence, most drugs cannot be strictly categorized as stimulants or depressants.

3. **Irritation:** Denotes a nonselective, often harmful effect, mainly on less specialized cells like epithelial or connective tissues.

   Mild irritation may enhance function—bitters can increase salivary and gastric secretion, and counterirritants raise local blood flow.

   Strong irritation can cause inflammation, corrosion, necrosis, and damage, leading to reduced or lost function.
4. **Replacement:** Refers to supplying natural metabolites, hormones, or their analogs in cases of deficiency.

   *Examples:* Levodopa in Parkinson's disease, insulin in diabetes mellitus, iron in anemia.
5. **Cytotoxic Action:** Involves the selective destruction of harmful cells, such as cancer cells or parasites, while minimizing effects on healthy host cells.

   *Examples:* Penicillin, chloroquine, zidovudine, cyclophosphamide.

### Mechanism of Drug Action

A small number of drugs act purely through their physical or chemical properties, such as:

- **Bulk laxatives** (e.g. ispaghula)—exert effect via mass.
- **Dimethicone, petroleum jelly**—physical barrier or form.
- **Para-aminobenzoic acid**—absorbs UV rays.
- **Activated charcoal**—acts by adsorption.
- **Mannitol, magnesium sulfate**—work through osmotic activity.
- **Radioactive isotopes** (e.g. $I^{131}$)—deliver radiation.
- **Antacids**—neutralize stomach acid.
- **Potassium permanganate**—oxidizing agent.
- **Chelating agents** (e.g. EDTA, dimercaprol)—bind heavy metals.
- **Cholestyramine**—binds cholesterol in the gut.
- **Mesna**—scavenges toxic metabolites from cyclophosphamide.

Most drugs, however, produce effects by interacting with specific target biomolecules, typically proteins. This interaction provides the basis for drug selectivity. These target proteins are usually classified into four categories:

- Enzymes
- Ion channels
- Transporters
- Receptors

Some drugs also act on other proteins (like tubulin, targeted by colchicine, vinca alkaloids, and taxanes) or on nucleic acids (as seen with alkylating agents).

## FACTORS MODIFYING DRUG ACTION

Differences in how individuals respond to the same dose of a drug are common. These variations can occur between different people or even within the same person on different occasions. Several key factors contribute to these differences in drug response:

1. **Causes of Variability in Drug Response**
   - **Pharmacokinetic Differences:** Individuals process drugs differently, leading to varying concentrations in the blood or at the target site. This is especially true for drugs that are heavily metabolized (e.g. propranolol) compared to those excreted unchanged (e.g. **atenolol**).
   - **Differences in Receptor or Effector Systems:** Variation in the number, sensitivity, or function of receptors and associated proteins (e.g. G-proteins) affects how the drug exerts its action.
   - **Physiological State and Tone:** The body's neurogenic or hormonal environment can influence drug response.

     *Example:*
     - Atropine-induced tachycardia depends on vagal tone.
     - Propranolol causes more bradycardia in those with high sympathetic tone.
     - Captopril's hypotensive effect is affected by sodium balance in the body.
2. **Categories of Influencing Factors**

   These influences are broadly grouped into:
   - **Genetic Factors:** Inherited traits that affect drug metabolism, receptor structure, or immune response
   - **Nongenetic Factors:** Environmental, situational, and personal factors (e.g. diet, habits, organ function)

While not all individual variability can be predicted, understanding these factors helps in selecting the right drug and dose. However, real-time patient monitoring and adjustment remain essential.

### Types of Drug Action Modifications

Quantitative Changes: The intensity or duration of drug action is increased or decreased. Most influencing factors fall under this category and can usually be managed by adjusting the drug dosage.

Qualitative Changes: The nature of the response changes (e.g. allergic reactions, idiosyncratic responses). These are less common but often mean the drug must be permanently avoided.

#### Key Modifying Factors

1. **Body Size:** The drug concentration at its site of action is directly influenced by body size. Adult doses are usually based on a person of average build. Adjustments are needed for:
   - **Children** or **very lean/obese individuals**
   - Common calculation methods:
     - **Based on body surface area (BSA):**
       Individual dose = BW (kg)/70 × Average adult dose
     - **Based on body weight (BW):**
       Individual dose = BSA ($m^2$)/1.7 × Average adult dose
   - **BSA Calculation (Dubois Formula):**
     BSA ($m^2$) = 0.007184 × BW (kg) 0.425 Height (cm) 0.725
   - While BSA gives a more precise estimation (especially for **anticancer drugs**), dosing based on **BW** is still more widely used due to practicality and data availability.

2. **Age:** Drug dosages in children are often derived from adult doses using:
   - **Young's Formula:**
     Child dose = (Age/Age + 12) × (Adult dose)
   - **Dilling's Formula:**
     Child dose = (Age/20) × (Adult dose)
   - A more accurate method is dosing based on body weight (mg/kg) or BSA, which is often recommended by drug manufacturers.

### Infants and Children

Infants and children have significant physiological differences from adults, which can affect how drugs are processed and their response to medication. Key points include:

- **Renal Function:** Newborns have lower **glomerular filtration rate (GFR)** and immature **tubular transport**, which leads to a prolonged **half-life** (t½) for drugs eliminated by the kidneys. For example, **gentamicin** (filtered by the glomerulus) and **penicillin** (secreted by the tubules) have a t½ that is 3 to 5 times longer in neonates. GFR reaches adult levels by 5 months, while tubular secretion matures around 7 months of age.
- **Hepatic Metabolism:** The liver's ability to metabolize drugs is also underdeveloped in newborns. For example, **chloramphenicol** can cause **gray baby syndrome** in newborns due to inadequate metabolism.
- **Blood-brain Barrier:** Newborns have a more permeable **blood-brain barrier**, which means that drugs can accumulate more easily in the central nervous system (CNS). This is one reason for conditions like **kernicterus**, which is caused by the buildup of unconjugated bilirubin.
- **Absorption Differences:** Drug absorption may be altered in infants due to factors like lower **gastric acidity** and **slower intestinal transit**. However, **transdermal absorption** is faster due to the thinner and more permeable skin of infants.
- **Dosing in Infants:** Infant doses cannot be derived from adult formulas and should be learned and calculated specifically for infants based on their unique characteristics.
- **Faster Drug Metabolism in Children:** After the first year of life, children's drug metabolism often becomes faster than that of adults. For example, the **half-life** (t½) of drugs like **theophylline, phenytoin**, and **carbamazepine** is shorter in children. Also, drugs primarily excreted by the kidneys, such as **digoxin**, require higher **per kg** doses in children. For example, the daily dose for children is about **8–12 µg/kg**, compared to **3–5 µg/kg** in adults.
- **Adverse Drug Effects in Children:** Children's growth and development can make them more susceptible to certain drug side effects. For instance:
  - **Corticosteroids** may suppress growth.
  - **Androgens** can cause premature fusion of epiphyses, stunting growth.
  - **Tetracyclines** can be deposited in growing teeth, causing discoloration or deformity.
  - **Phenothiazines** may cause dystonic reactions more frequently in children.

### Elderly

In the elderly, physiological changes lead to altered drug handling, and special considerations must be made:

- **Renal Function Decline:**
  As people age, **renal function** declines due to **nephron loss**, resulting in a **GFR** of around 75% at 50 years and 50% at 75 years, compared to young adults. This necessitates dose reductions, such as:
  - The daily dose of **streptomycin** is reduced from **1 g** in young adults to **0.75 g** after 50 years, and **0.5 g** after 70 years.
- **Hepatic Function Decrease:**
  Hepatic **microsomal enzyme** activity and **liver blood flow** decrease with age. This generally results in **increased oral bioavailability** of drugs that are highly metabolized in the liver, although the overall impact on drug metabolism can vary.
- **Cumulative Toxicity:**
  Due to reduced renal and metabolic clearance, the elderly are at higher risk of **cumulative toxicity** when receiving long-term medication.
- **Absorption and Distribution Changes:**
  - **Slower absorption** occurs because of reduced intestinal motility and blood flow.
  - **Plasma protein binding** decreases due to lower plasma **albumin**, affecting drug distribution.
  - The **volume of distribution** for **lipophilic drugs** increases, while **hydrophilic drugs** have a decreased volume of distribution.
- **Digitalis Sensitivity:**
  The elderly are more likely to experience **digitalis toxicity** due to altered drug handling.
- **Reduced Beta-adrenergic Responsiveness:**
  **Beta-adrenergic receptors** become less responsive with age, which affects the response to both **agonists** and **antagonists**. Sensitivity to other drugs may also be altered.
- **Prostatism and Anticholinergic Effects:**
  **Prostatism** (enlargement of the prostate) in elderly males can cause bladder issues, and even mild **anticholinergic** effects from drugs can worsen urinary retention.
- **Polypharmacy:**
  Elderly individuals are often prescribed multiple medications for conditions like **hypertension, ischemic heart disease, diabetes,** and **arthritis,** which increase the risk of **drug interactions**.
- **Adverse Drug Reactions in the Elderly:**
  The elderly are more prone to **adverse drug reactions** (ADRs) such as **postural instability, giddiness,** and **mental confusion**.

### Sex Differences

**Females** typically have smaller body sizes than males and may require lower doses of medication. Additionally, **subjective effects** of drugs can differ between genders, potentially influencing drug responses.

Females, due to their mental and physiological makeup, may respond differently to various drugs compared to males. Some key examples include:

- **Digoxin in Heart Failure:** Maintenance treatment for heart failure with **digoxin** has been associated with higher mortality in **women** than in **men**.
- **Antihypertensive Drugs:** A number of antihypertensive drugs, such as **clonidine, methyldopa, β-blockers,** and **diuretics**, can interfere with **sexual function** in **males** but generally do not affect females in the same way.
- **Gynaecomastia: Gynaecomastia** (enlargement of breast tissue in males) is a side effect seen with drugs like **ketoconazole, metoclopramide, chlorpromazine,** and **digitalis.** This side effect only occurs in men.
- **Loss of Libido: Ketoconazole** can lead to **loss of libido** in men but not in women.
- **Hormonal Drug Therapy: Androgens** are unacceptable for women, while **estrogens** are inappropriate for men due to the differing hormonal requirements.

Additionally, in women, considerations like **menstruation, pregnancy,** and **lactation** play crucial roles in drug response and handling.

### Pregnancy and Drug Disposition

Drugs administered during pregnancy can have significant effects on the developing fetus. Pregnancy involves significant physiological changes, particularly in the third trimester, which can alter how drugs are processed in the body:

1. **Reduced Gastrointestinal Motility:** Pregnancy causes **delayed absorption** of orally administered drugs due to reduced **gastrointestinal motility**.
2. **Increased Plasma and Extracellular Fluid Volume:** The **volume of distribution** for drugs may increase due to the expansion of **plasma and extracellular fluid**.
3. **Changes in Plasma Proteins:** While **plasma albumin levels** decrease during pregnancy, **α1-acid glycoprotein** levels increase. As a result, the **unbound fraction** of **acidic drugs** increases, while that of **basic drugs** decreases.
4. **Increased Renal Blood Flow:** There is a marked increase in **renal blood flow**, which leads to **faster elimination** of **polar drugs**.
5. **Induction of Hepatic Enzymes:** Pregnancy causes the induction of **hepatic microsomal enzymes**, leading to **faster metabolism** of many drugs.

Given these complex changes, the overall impact on drug disposition during pregnancy is often difficult to predict.

### Species and Race Differences

Species Differences:

Drug responses vary widely across species. For example:

- **Rabbits** are resistant to **atropine**.
- **Rats and mice** are resistant to **digitalis**.
- **Rats** are more sensitive to **curare** than **cats**.

These species differences are important when extrapolating experimental data to humans.

Race Differences:

Certain racial groups exhibit varying responses to drugs. For example:

- **Blacks** often require higher doses of **atropine** and **ephedrine** to achieve pupil dilation compared to other racial groups.
- **Afro-Caribbean** individuals may experience less efficacy from **β-blockers** as antihypertensives.
- **Indians** tolerate **thiacetazone** better than whites.
- In **India** and **Hong Kong, chloramphenicol** use has been linked to fewer cases of **aplastic anemia** than in the West, despite widespread use.

Similarly, in **Japan, quiniochlor** has caused an epidemic of **subacute myelo-optic neuropathy (SMON),** while no such cases have been confirmed in **India**, despite similar usage.

### Genetics and Drug Response

The dosage needed for a drug to produce the same effect can vary by a factor of **4–6 times** among different individuals. Key determinants of drug response, such as **transporters, metabolizing enzymes, ion channels, receptors,** and their effectors, are genetically controlled. Thus, **genetic composition** plays a significant role in the variability of drug responses.

**Pharmacogenetics** is the study of how genetics influence drug action and how the body handles drugs. With advancements in genomic technology, large gene libraries and databases (such as the **pharmacogenetics and pharmacogenomics knowledge base and the human genome variation database**) have been created to improve precision in drug therapy.

**Pharmacogenomics** involves using genetic information to guide drug selection and dosing on an individual basis. This approach aims to identify individuals who are more or less likely to respond to a drug and those who require adjusted doses. While pharmacogenomics is still mainly applied to patients with known genetic abnormalities, the goal is to extend **personalized medicine** to a wider population. Despite significant progress, a large portion of **genetic variability** in drug response remains unaccounted for.

### Genetic Variations in Drug Response

Drugs often exhibit continuous variation in response, following a Gaussian frequency distribution. However, certain genetic defects can lead to **discontinuous variation** in drug responses. Some examples include:

1. **Atypical Pseudocholinesterase:** This genetic condition leads to **prolonged succinylcholine apnoea** (the inability to breathe due to prolonged muscle relaxation after succinylcholine administration).
2. **G-6-PD Deficiency:** Individuals with **glucose-6-phosphate dehydrogenase (G-6-PD) deficiency** may experience **hemolysis** (destruction of red blood cells) when exposed to drugs like **primaquine, sulfonamides, dapsone, quinine, nalidixic acid, nitrofurantoin,** and **menadione,** among others.

3. **CYP2C9 Variants:** Low activity **CYP2C9** variants result in **slow metabolism of warfarin**, increasing the risk of bleeding.
4. **Thiopurine Methyl Transferase (TPMT) Deficiency:** A deficiency in **TPMT** increases the risk of **severe bone marrow toxicity** with **6-mercaptopurine** and **azathioprine** treatment.
5. **Irinotecan and UGT1A1*28 Allele:** Patients with the **UGT1A1*28 allele** of **glucuronyl transferase** are more prone to **neutropenia** (low white blood cell count) and **diarrhea** when treated with irinotecan.
6. **Dihydropyrimidine Dehydrogenase (DPD) Deficiency: Severe toxicity** from **5-fluorouracil** is observed in patients with a **DPD deficiency**.
7. **P-glycoprotein (P-gp) Overexpression:** Overexpression of **P-gp** (a drug transporter protein) results in **tumour resistance** to many cancer chemotherapeutic drugs because it pumps the drug out of tumour cells.
8. **N-acetyltransferase 2 (NAT2) Polymorphism:** Polymorphism in the **NAT2 gene** leads to **rapid or slow acetylator status. Slow acetylators** are more likely to experience **neuropathy** with i**soniazid**, and **lupus** with **procainamide** and **hydralazine.**
9. **Acute Intermittent Porphyria:** This condition, which is triggered by **barbiturates,** is due to a genetic defect in the **repression of porphyrin synthesis.**
10. **CYP2D6 Abnormality:** Individuals with **CYP2D6 abnormalities** may be poor metabolizers of **metoprolol** and **debrisoquin**. This can lead to increased toxicity when taking certain antidepressants and antipsychotics, which are substrates of **CYP2D6**. Furthermore, **codeine** fails to produce **analgesia** in **CYP2D6-deficient** individuals because this enzyme is responsible for converting **codeine** to its active form, **morphine**.
11. **Malignant Hyperthermia:** This rare reaction to **halothane** anaesthesia is due to an abnormal **calcium release channel** (ryanodine receptor) in the **sarcoplasmic reticulum** of skeletal muscles.
12. **Phenytoin Hydroxylation Deficiency:** A deficiency in **phenytoin hydroxylation** leads to **toxicity** even at **standard doses**.
13. **Resistance to Coumarin Anticoagulants:** Some individuals have an **abnormal enzyme** that regenerates the reduced form of **vitamin K** with a low affinity for **coumarins**, leading to resistance to **coumarin anticoagulants**.
14. **Angle Closure Glaucoma:** This condition can be precipitated by **mydriatics** (drugs that dilate the pupil) in individuals with a narrow **iridocorneal angle**.

## Genotype-Phenotype Predictability

Predicting drug response based on genetic makeup is more reliable for monogenic traits (controlled by a single gene) such as **G-6-PD deficiency, CYP2D6 abnormalities**, and TPMT deficiency, than for multigenic traits that are influenced by multiple genes. Many genetic polymorphisms result from the substitution of a single base pair in the DNA, known as **single nucleotide polymorphisms (SNPs),** which can occur in over 1% of the population.

Gene polymorphisms are often found at varying frequencies among different **ethnic** and **geographical groups**. While significant pharmacogenomic data has accumulated, **routine patient care** has yet to fully integrate **genotyping** due to the need for **multiple drug-specific genotypic screenings**. However, simple tests for conditions like **G-6-PD deficiency** are already in clinical use.

## Route of Administration and Drug Response

The route of administration significantly affects the speed and intensity of a drug action. Parenteral administration (injection or infusion) is often used when a rapid, pronounced, and predictable response is required. A drug can also have entirely different effects depending on the route of administration. For example:

- **Magnesium sulfate** taken **orally** causes **purgation** (laxative effect), but when applied to sprained joints, it reduces swelling. Intravenous administration of magnesium sulfate produces CNS depression and hypotension.

### Environmental Factors and Time of Administration

Several environmental factors influence drug responses, including exposure to insecticides, carcinogens, tobacco smoke, and charcoal-broiled meat, all of which can induce drug metabolism. The diet and timing of drug administration also play important roles in modifying the drug effect.

This passage discusses various factors that influence the action and effectiveness of drugs, including psychological factors, pathological states, and other drugs. It also explores the concept of rational prescribing and irrational drug use. Here is a summary of the key points:

1. **Psychological Factors:**
   - The efficacy of drugs can be influenced by the patient's beliefs, expectations, and psychological state. For example, anxious patients may need more anesthetic, while alcohol can impair performance unless anxiety is introduced.
   - Placebo effects occur when an inert substance causes a response due to the patient's belief in its efficacy. Some individuals are more suggestible to placebos, which can be used in clinical trials or in certain medical settings.
   - Nocebo effects are the opposite, where negative outcomes occur due to a loss of faith in treatment or the physician.
2. **Pathological States:**
   - Diseases can alter how the body absorbs, processes, and reacts to drugs:
     - **Gastrointestinal diseases** can affect drug absorption, with certain conditions increasing or decreasing absorption.
     - **Liver diseases** can alter drug metabolism, leading to higher bioavailability or changes in the elimination of drugs.

- **Kidney diseases** reduce clearance of drugs excreted unchanged, which may require dose adjustments.
- **Congestive heart failure** affects drug absorption, distribution, and elimination, requiring careful monitoring and adjustment of drug dosages.
- **Thyroid disease** can alter drug sensitivity, such as increased sensitivity to digoxin in hypothyroidism.

3. **Drug Interactions:**
   - Drugs can interact with each other either by affecting their absorption, metabolism, or elimination, or by directly altering their pharmacodynamic effects. This includes drug interactions that enhance or diminish drug actions, leading to altered therapeutic outcomes.
4. **Drug Cumulation:**
   - Cumulation occurs when the rate of drug administration exceeds the rate of elimination, potentially leading to toxicity. This is more common with drugs that are slowly eliminated, such as chloroquine, which can cause retinal damage.
5. **Tolerance:**
   - Tolerance refers to the need for increasing doses of a drug to achieve the same effect over time. It can be natural or acquired and occurs when the body adapts to the presence of the drug. It can manifest differently depending on the drug's effects, such as developing tolerance to the sedative effects of barbiturates but not to their anticonvulsant effects.
   - Cross-tolerance occurs when tolerance to one drug extends to another drug that is pharmacologically similar.
6. **Rational Use of Medicines:**
   - The World Health Organization (WHO) defines rational use of medicines as using drugs that are appropriate for the patient's clinical needs, in the correct doses, and at the lowest possible cost.
   - Rational prescribing involves selecting the right drug, route, dose, and duration, as well as ensuring proper monitoring and communication with the patient.
   - Factors influencing prescribing include the prescriber's knowledge, attitudes, patient load, and external influences like drug promotions or unethical inducements.
7. **Irrational Prescribing:**
   - Irrational drug use includes practices like prescribing drugs that are not needed, using incorrect doses, or selecting ineffective drugs. These practices can lead to adverse outcomes, such as delayed treatment, increased morbidity and mortality, and unnecessary financial burden.
8. **Steps in Rational Prescribing:**
   - Rational prescribing involves careful consideration of the diagnosis, therapeutic goals, appropriate drug selection, dosage, route, and patient instructions. It also includes monitoring the patient's response and adjusting the treatment if necessary.

This passage highlights the importance of a holistic approach to drug therapy that considers both pharmacological and nonpharmacological factors, along with the need for rational prescribing to ensure patient safety and effectiveness of treatment.

## Drug receptor interaction

- Drug binds with receptor by weak forces like hydrogen or/and by strong force like covalent bond (nonreversible) bond, van der Waal or electrolytic bond.
- Nature of binding tells about duration of action — first the drug interacts with receptor which produces the effect ability of drug to bound with receptor is affinity and capacity to generate effect is called efficacy.

Accordingly, drugs acting through receptors:

- Agonist— drugs having affinity for receptor causing max efficacy, e.g. acetylcholine, adrenaline.
- Antagonist— drugs having affinity but no efficacy, e.g. atropine, propanol.
- Partial agonist— drugs having affinity but minimal efficacy, e.g. nalorphine.

Number of receptors are nonconstant and change according to circumstances. Receptors exposed to agonist for longtime result in their fall. This is called downregulation or desensitization and tissue is called refractory.

Chronic exposure of receptor to antagonist results in increase activity and called upregulation or supersensitivity:

- Use of propanol and beta-receptor its sudden withdrawal of propanol and beta receptor precipitate attack of angina
- Sudden withdrawal of clonidine results in hypertensive crisis.

## Routes of administration of drugs

Route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body (Fig. 1.1).

Most of the drugs can be administered by different routes. Drug and patient-related factors determine the selection of routes for drug administration. The factors are:

- Characteristics of the drug.
- Emergency/routine use.
- Site of action of the drug—local or systemic.
- Condition of the patient (unconscious, vomiting, diarrhoea).
- Age of the patient.
- Effect of gastric pH, quality of digestive enzymes and rate of first-pass metabolism.
- Patient's/doctor's choice (sometimes).

### Dosage Forms

A medicinal agent becomes a medication only after formulation suitable for therapeutic use (i.e. in an appropriate dosage form).

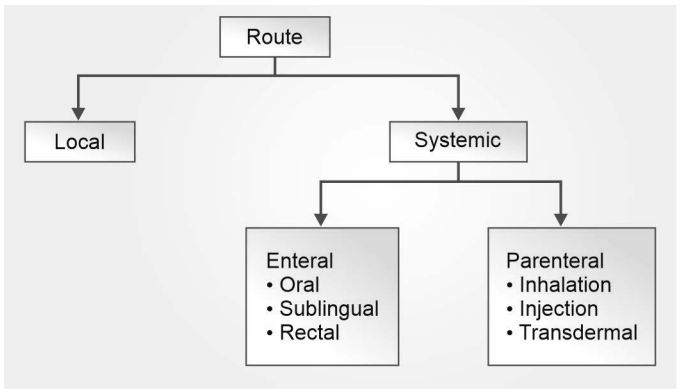


**Fig. 1.1:** Routes of drug administration

Types of Dosage Forms
- Solid
- Liquid
- Parenteral
- Pulmonary
- Rectal
- Vaginal and cutaneous application
- Transdermal drug delivery.

## PRINCIPLES OF BASIC AND CLINICAL PHARMACOKINETICS

Clinical pharmacokinetics is the science of applying pharmacokinetic principles in humans to:
1. Design individualized dosage regimens to optimize therapeutic effects.
2. Minimize adverse drug reactions.
3. Monitor medications with a narrow therapeutic index (e.g. digoxin, warfarin).
4. Assist in the development and evaluation of new drugs.

### Core Pharmacokinetic Processes (ADME)

Pharmacokinetics describes how the body absorbs, distributes, metabolizes, and excretes (ADME) drugs.

1. **Absorption**
   - Occurs when a drug enters the body via an extravascular route (oral, intramuscular, transdermal, etc.).
   - Steps involved:
     - Dissolution of the drug from its dosage form.
     - Passage through physiological barriers (e.g. GI tract lining for oral meds).
     - Entry into the vascular system (systemic circulation).
2. **Distribution**
   - After absorption, the drug is transported via the bloodstream to various tissues and organs.
   - Influenced by:
     - Blood flow
     - Drug affinity to tissues
     - Plasma protein binding
3. **Metabolism (Biotransformation)**
   - Primarily occurs in the liver (though other organs may contribute).
   - Involves enzymatic reactions converting the parent drug into metabolites.
     - Metabolites may be:
       - ♦ Active (same or different effect)
       - ♦ Inactive
       - ♦ Toxic
   - Key enzymes: Cytochrome P450 system.
4. **Excretion**
   - Irreversible removal of drug/metabolites from the body.
   - Major routes:
     - Renal (urine)
     - Biliary (feces)
     - Others: sweat, saliva, lungs

### Pharmacokinetic Principles: Steady-State Concentration (Css)

Definition of Steady State
- Steady state occurs when the rate of drug administration equals the rate of drug elimination, resulting in a constant drug concentration in the body.
- This is a dynamic equilibrium—drug is still being administered and eliminated, but the overall amount in the body remains constant.

Clinical Importance
- Steady-state concentrations (Css) are used to:
  - Evaluate patient response.
  - Adjust and optimize dosage regimens.
  - Avoid toxicity or subtherapeutic levels—especially for drugs with narrow therapeutic windows.

Time to Reach Steady State
- Generally takes about 4 to 5 half-lives (t½) of the drug to reach steady state.
  - Short half-life drugs reach Css quickly.
  - Long half-life drugs take longer (sometimes days or weeks).

Examples of Drug Administration
1. **Continuous IV Infusion:**
   - Drug concentration increases gradually.
   - Once Css is reached, the infusion rate = Rate of metabolism + Excretion.
   - Plasma level stays constant as long as infusion continues.
2. **Repeated Oral Dosing** (e.g. q12h):
   - Drug concentration fluctuates within a range (peak and trough).
   - After reaching steady state, these fluctuations are consistent for each dosing interval.

   *Example:* Theophylline Infusion
   - If given at 50 mg/h, serum levels will rise gradually.
   - Once 50 mg/h is also being removed (via liver and kidneys), the concentration stabilizes—Css is reached.

### Linear vs Nonlinear Pharmacokinetics

Linear Pharmacokinetics
- **Definition:** A proportional relationship exists between dose and steady-state concentration (Css).
- **Graph:** Plotting Css *vs* dose gives a straight line.
- **Key Feature:** If you double the dose, Css doubles.
- **Explanation:** The drug elimination mechanisms (metabolism and excretion) are not saturated—they operate under first-order kinetics.

*Example:*

- Theophylline given at 50 mg/h → Css builds until elimination = 50 mg/h
- If you increase the dose to 100 mg/h → Css doubles (assuming linear kinetics)

Nonlinear Pharmacokinetics

- **Definition:** The relationship between dose and Css is not proportional.
- **Graph:** Css *vs* dose gives a curve, not a straight line.
- Occurs when the body's capacity to metabolize or eliminate the drug becomes saturated at therapeutic or near-therapeutic doses.

Types of Nonlinearity:

1. **Css Increases More than Expected (Supraproportional Increase):**
   - Due to saturation of elimination pathways.
   - Michaelis-Menten kinetics apply.
   - Even small dose increases can lead to large increases in Css.

   *Examples:*
   - Phenytoin—narrow therapeutic index; small changes in dose = Large changes in plasma levels.
   - Salicylic acid—saturates liver metabolism at higher doses.
2. **Css Increases Less than Expected (Subproportional Increase):**

   **a. Saturable Plasma Protein Binding:**
   - At low doses, most drug is protein-bound → High total plasma levels.
   - As dose increases, binding sites saturate, and more drug remains free (unbound).
   - Total drug concentration increases less than expected, though free (active) drug may increase more.

   *Example:*
   - Valproic acid—binds to plasma proteins, and saturation leads to nonlinear increases in total serum levels.

## Therapeutic Drug Monitoring (TDM)

TDM is the **measurement of specific drug levels in blood/plasma** to maintain a therapeutic concentration and avoid toxicity—especially important for drugs with a narrow therapeutic range.

TDM is indicated when:

1. There is a known relationship between drug levels and effect.
2. Drug level affects clinical decisions (e.g. dose adjustments).
3. The drug has a narrow therapeutic window.
4. Patient compliance is questionable.
5. Clinical signs alone are insufficient to assess proper dosing.

**Common Drugs Requiring TDM**

| *Drug class* | *Examples* |
|---|---|
| Aminoglycoside antibiotics | Gentamicin, tobramycin |
| Antiepileptics | Phenytoin, carbamazepine, valproic acid |
| Mood stabilizers | Lithium |
| Antipsychotics | Clozapine, pimozide |
| Immunosuppressants | Tacrolimus, cyclosporine |

These drugs are either highly potent, have narrow therapeutic ranges, or risk serious toxicity if overdosed.

Clearance (Cl)

- Clearance is the volume of blood or plasma completely cleared of drug per unit time.
- Units: L/h, ml/min, etc.

**Importance of Clearance**

- It is a key determinant of maintenance dose needed to achieve a target steady-state concentration (Css).

**Formula:**

Maintenance dose (MD) = Css × Cl

- Ties directly into therapeutic drug monitoring: Knowing a patient's clearance allows for individualized dosing.

**Clearance Pathways**

| *Organ* | *Function* |
|---|---|
| Liver | Major site of drug metabolism, primarily via CYP450 enzymes. |
| Kidneys | Major site of excretion, via: |

- Glomerular filtration
- Tubular secretion (active)
- Tubular reabsorption (passive) || **Other organs** | GI wall, lungs, bile, skin (less common routes) |

**Hepatic Clearance and CYP Enzymes**

- Cytochrome P450 (CYP) enzymes handle the majority of drug metabolism.
- Drug interactions occur when:
  - Two drugs compete for the same enzyme (substrates).
  - One drug inhibits or induces a CYP enzyme affecting metabolism of another.

**Renal Clearance**

- Involves:
  - Glomerular filtration (passive)
  - Tubular secretion (active via transporters, mainly in proximal tubule)
  - Tubular reabsorption (passive, in distal tubule)
- Some drugs are eliminated unchanged in the urine or bile.

**Clinical Implication**

- Dose adjustments are critical in:
  - Patients with renal or hepatic impairment
  - Polypharmacy (due to risk of drug interactions)
  - Drugs with nonlinear pharmacokinetics (small dose changes → Large Css changes).

## MULTIPLE CHOICE QUESTIONS

1. **If the concentration of a drug decreases in plasma with "first-order kinetics", this means that:**
   - **A.** The drug is largely metabolized in the liver after oral administration and has low bioavailability elimination
   - **B.** The rate of elimination is always proportionate to the rate of administration
   - **C.** The half-life of the drug remains same and does not depend on plasma concentration
   - **D.** None of these

2. **The intensity of the pharmacologic action of a drug is most dependent on the:**
   - **A.** Amount of the drug present at receptor site
   - **B.** Elimination half-life (t½) of the drug
   - **C.** Minimum toxic concentration (MTC) of the drug in plasma
   - **D.** Both B and C

3. **The rate of drug bioavailability is most rapid while formulating as a:**
   - **A.** Controlled-release product
   - **B.** Solution
   - **C.** Hard gelatin capsule
   - **D.** Compressed tablet

4. **Choose one correct option for information about the changes in sensitivity of the drug in the case of population studied?**
   - **A.** Therapeutic index
   - **B.** Drug potency
   - **C.** Grade dose–response curve
   - **D.** Quantal dose–response curve

5. **Which of the following drugs may inhibit hepatic microsomal P450 ?**
   - **A.** Ethanol
   - **B.** Phenobarbital
   - **C.** Cimetidine
   - **D.** Procainamide

6. **Phocomelia is a known teratogenic effect of:**
   - **A.** Anticancer drugs
   - **B.** Antiviral drugs
   - **C.** Antiepileptic drugs
   - **D.** Thalidomide

7. **The therapeutic index of a drug measures:**
   - **A.** Safety **B.** Potency
   - **C.** Efficacy **D.** Dose variability

8. **In the following, which one is an example of colligative property?**
   - **A.** Solubility of a solute
   - **B.** Osmotic pressure
   - **C.** Concentration of hydrogen ion
   - **D.** Miscibility of the liquids

9. **The pH of a buffer system can be calculated with the:**
   - **A.** Noyes-Whitney equation
   - **B.** Henderson-Hasselbalch equation
   - **C.** Michaelis-Menten equation
   - **D.** Yong equation

10. **Active transport differs from facilitated transport in following ways, except:**
    - **A.** Carrier is involved
    - **B.** It is against concentration gradient
    - **C.** Energy is required
    - **D.** All of the above

11. **The shells of soft gelatin capsules maybe made elastic or plastic-like by the addition of:**
    - **A.** Sorbitol **B.** Povidone
    - **C.** Polyethylene glycol **D.** Lactose

12. **If a drug is administrated by oral route, it is absorbed best from the:**
    - **A.** Buccal cavity **B.** Stomach
    - **C.** Duodenum **D.** Ileum

13. **_____ is expressed in both the intestinal epithelium and the kidney.**
    - **A.** CYP2D6 **B.** CYP1A1/2
    - **C.** CYP3A4 **D.** CYP2E1

14. **Which one is the characteristic of microsomal enzyme induction?**
    - **A.** It took approx. 7 days to develop
    - **B.** Results in enhanced affinity of the enzyme for its substrate
    - **C.** It is irreversible
    - **D.** Used in the treatment of acute drug poisoning

15. **The distribution of a drug into tissue is determined mainly by the:**
    - **A.** Blood circulation rate into tissue
    - **B.** Glomerular filtration rate
    - **C.** Stomach emptying time
    - **D.** pH of the tissue

16. **Monomer units of proteins are known as:**
    - **A.** Monosaccharides **B.** Prosthetic groups
    - **C.** Amino acids **D.** Purines

17. **An antagonist:**
    - **A.** Attaches to the receptors and triggers the changes in cell function, producing maximal effect
    - **B.** Attaches to the receptors and triggers the changes in cell function, producing submaximal effect
    - **C.** Attaches to plasma proteins and does not produce any type of effect
    - **D.** Attaches to the receptors but there is no direct alteration in their functions

18. **Drug administrated through which of the following routes is most likely to be subjected to first-pass metabolism?**
    - **A.** Oral
    - **B.** Sublingual
    - **C.** Subcutaneous
    - **D.** Rectal

19. **If two drugs have similar type of effects, these can be called:**
    - **A.** Heterogenic drugs
    - **B.** Isomeric drugs
    - **C.** Homergic drugs
    - **D.** Antagonistic drugs

20. **Glucose is a carbohydrate that cannot be hydrolyzed into a simpler substance. It is best described as:**
    - **A.** A sugar
    - **B.** A monosaccharide
    - **C.** A disaccharide
    - **D.** A polysaccharide

21. **Enzymes that uncouple peptide linkage are best classified as:**
    - **A.** Hydrolases
    - **B.** Ligases
    - **C.** Oxidoreductases
    - **D.** Transferases

22. **Bacteria that grow at temperatures as high as 55°C are known as:**
    - **A.** Psychrophiles
    - **B.** Thermophiles
    - **C.** Mesophiles
    - **D.** Auxotrophs

23. **Which of the following phases is responsible for decreasing growth curve in facterial growth curve?**
    - **A.** Lag phase
    - **B.** Exponential phase
    - **C.** Death phase
    - **D.** Stationary phase

24. **Which one of the following antibodies has longest half-life in a serum? It opsonizes antigens for phagocytosis by using two different pathways ?**
    - **A.** Immunoglobulin G (IgG)
    - **B.** Immunoglobulin M (IgM)
    - **C.** Immunoglobulin A (IgA)
    - **D.** Immunoglobulin E (IgE)

25. **CD4+T cells specifically recognize antigens in which form?**
    - **A.** Bound to major histocompatibility (MHC) class I molecules on the surface of antibody
    - **B.** In free, soluble form in extracellular fluids
    - **C.** Bound to MHC class II molecules on the surface of special antigen-presenting cells (APCs)
    - **D.** None of the above

26. **Which of the following salts forms an aqueous solution that is alkaline to litmus?**
    - **A.** Sodium chloride
    - **B.** Benzalkonium chloride
    - **C.** Cefazolin sodium
    - **D.** Chlordiazepoxide hydrochloride

27. **Precipitation may occur when mixing aqueous solutions of meperidine hydrochloride with which of the following solutions?**
    - **A.** Sodium bicarbonate injection
    - **B.** Atropine sulfate injection
    - **C.** Sodium chloride injection
    - **D.** None of the above

28. **Drug of choice for anaphylactic reactions is:**
    - **A.** Clonidine
    - **B.** Isoproterenol
    - **C.** Epinephrine
    - **D.** Phenylephrine

29. **All of the following desensitizing agents are recommended for sensitive teeth, except:**
    - **A.** 10% carbamide peroxide
    - **B.** 5% potassium nitrate
    - **C.** Dibasic sodium citrate
    - **D.** 10% strontium chloride hexahydrate

30. **$pK_a$ of a compound:**
    - **A.** Is the pH of solution at which the compound is 50% ionized
    - **B.** Is the pH of compound at which it is 50% ionized
    - **C.** Is the time in which the compound is ionized
    - **D.** Is the time in which total compound is ionized

31. **Which of the following are good examples of chemical antagonism?**
    - **A.** Heparin and protamine
    - **B.** Protamine and zinc
    - **C.** Heparin and prothrombin
    - **D.** All of the above

32. **Alkalization of urine hastens the excretion of:**
    - **A.** Weakly basic drugs
    - **B.** Weakly acidic drugs
    - **C.** Strong electrolytes
    - **D.** Nonpolar drugs

33. **High plasma protein binding:**
    - **A.** Increases the volume of distribution of the drug
    - **B.** Facilitates glomerular filtration of the drug
    - **C.** Minimizes drug interactions
    - **D.** Generally, makes the drug long-acting

34. **G-protein coupled receptors span the plasma membrane as a bundle of _____ alpha helices.**
    - **A.** One
    - **B.** Three
    - **C.** Seven
    - **D.** Ten

35. **If a drug undergoes net tubular secretion, its renal clearance will be:**
    - **A.** More than the glomerular filtration rate
    - **B.** Equal to the glomerular filtration rate
    - **C.** Less than the glomerular filtration rate
    - **D.** Equal to the rate of urine formation

36. **Which is not a risk factor for hyperphosphatemia and death from sodium phosphate enemas when used in children?**
    - **A.** Renal insufficiency
    - **B.** Hirschsprung's disease
    - **C.** Anorectal malformations
    - **D.** Children between the ages of 6 and 12 years

37. **In case of constant bioavailability and first order elimination reaction rate, a drug maintenance dose rate will be directly proportional to its:**
    - **A.** Volume of distribution
    - **B.** Total body clearance
    - **C.** Plasma protein binding
    - **D.** Lipid solubility

38. **Prodrug:**
    - **A.** Facilitates absorption and distribution of drugs with poor lipid solubility
    - **B.** Increases the duration of action of drugs that are rapidly eliminated
    - **C.** Promotes site-specific delivery of drugs
    - **D.** All of the above

39. **Receptor agonists:**
    - **A.** Result in increased smooth endoplasmic reticulum
    - **B.** Result in increased rough endoplasmic reticulum
    - **C.** Result in decreased enzymes in the soluble cytoplasmic fraction
    - **D.** Require 3–4 months to reach completion

40. **'Drug efficacy' refers to:**
    - **A.** The range of diseases in which the drug is beneficial
    - **B.** The maximal intensity of response that can be produced by the drug
    - **C.** The therapeutic dose range of the drug
    - **D.** The therapeutic index of the drug

41. **A drug 'R' producing no response by itself causes the log dose–response curve of another drug 'S' to shift to the right in a parallel manner without decreasing the maximal response. Drug 'R' is a:**
    - **A.** Partial agonist
    - **B.** Inverse agonist
    - **C.** Competitive antagonist
    - **D.** Noncompetitive antagonist

42. **If gut motility increases then:**
    - **A.** Drug absorption decreases
    - **B.** Drug absorption increases
    - **C.** Drug absorption is not affected
    - **D.** None of the above

43. **Choose the best explanatory drug statement in relation to toxicity and drug poisoning:**
    - **A.** The two terms are synonymous
    - **B.** When a toxic effect requires specific treatment, it is called poisoning
    - **C.** A toxic effect which endangers life by markedly affecting vital functions is called poisoning
    - **D.** Toxicity is caused by drugs while poisoning is caused by other harmful chemicals PO

44. **Which of the following is a proven human teratogen?**
    - **A.** Chloroquine
    - **B.** Warfarin sodium
    - **C.** Dicyclomine
    - **D.** Methyldopa

45. **In presence of competitive antagonist:**
    - **A.** The maximum response of agonist can never be achieved
    - **B.** The maximum response can be achieved by increasing the concentration activity
    - **C.** Maximum response can be achieved only if the antagonist is having intrinsic activity
    - **D.** None of the above

46. **Tachyphylaxis is:**
    - **A.** A drug interaction between two similar types of drugs
    - **B.** Rapidly developing tolerance
    - **C.** A synergism between two types of drugs
    - **D.** None of the above

47. **Choose the correct option for cofactor bound to an apoenzyme.**
    - **A.** Holoenzyme
    - **B.** Coenzyme
    - **C.** Prosthetic group
    - **D.** Transferase

48. **Passage of drug across most capillary endothelial membranes is dependent upon:**
    - **A.** Lipid solubility
    - **B.** pH gradient
    - **C.** Blood flow
    - **D.** All of these

49. **The effect of enzyme induction is the greatest when the drug given is:**
    - **A.** Digoxin
    - **B.** Furosemide
    - **C.** Enalapril
    - **D.** Amrinone

50. **Drugs producing allergic reaction generally act as:**
    - **A.** Complete antigens
    - **B.** Haptens
    - **C.** Antibodies
    - **D.** Mediators

51. **The renal clearance of insulin is used as a measurement of:**
    - **A.** Effective renal blood flow
    - **B.** Intrinsic enzyme activity
    - **C.** Active renal secretion
    - **D.** Glomerular filtration rate (GFR)

**52. During liver disease the metabolism and elimination of which of the following drugs is decreased?**

**A.** Morphine **B.** Pentobarbitone
**C.** Propanolol **D.** All of these

**53. Which people are said to be the fastest acetylators because they metabolize isoniazid by the process of acetylation very quickly?**

**A.** Canadian Eskimos **B.** Indians
**C.** Asiatic Jews **D.** All of these

**54. Route of administration suitable for emergency and permits titration of the dosage as well is:**

**A.** Oral **B.** Intravenous
**C.** Intramuscular **D.** All of these

**55. Responsible organ for the metabolism of most of the drugs is:**

**A.** Skeleton system **B.** Kidney
**C.** Liver **D.** Heart

**56. Conjugation process can be defined as a:**

**A.** Process of drug hydroxylation by special hydrolyzing enzymes
**B.** Process of drug oxidation by special oxidases
**C.** Coupling of a drug with an endogenous substrate
**D.** Solubilization in lipids

**57. Which type of drugs penetrate CNS better?**

**A.** Lipid soluble **B.** Weak acids
**C.** Weak bases **D.** All equally

**58. An agonist is a substance that:**

**A.** Attaches with the receptor without producing any effect
**B.** Attaches with the receptor and initiates changes in cell function, producing various types of effects
**C.** Decreases concentration of another substance to produce effect
**D.** Attaches with plasma proteins and does not produce any effect

**59. Factor which can affect the absorption of drug is:**

**A.** Dissolution rate **B.** Particle size
**C.** Lipid solubility **D.** All of the above

**60. The mechanism of biotransformation of aspirin to salicylic acid and acetic acid is:**

**A.** Oxidation **B.** Reduction
**C.** Hydrolysis **D.** None of the above

**61. Which one of the following is a phase II drug metabolizing reaction?**

**A.** Oxidation **B.** Reduction
**C.** Acetylation **D.** All of these

**62. Bioassay is used to:**

**A.** Determine the relationship between the dose administered and the magnitude of response
**B.** Determine the potency of a new agent compared with that of an established drug
**C.** Determine the relationship between the doses producing a desired effect and those elicit in gun desirable or toxic effect
**D.** All of the above

**63. The following are excreted faster in basic urine, except:**

**A.** Weak acids **B.** Strong acids
**C.** Weak bases **D.** None of the above

**64. Which of the following therapeutic systems provides continuous, unattended, controlled drug input for a long period without gastrointestinal or hepatic drug inactivation prior to systemic circulation?**

**A.** Parenteral
**B.** Oral
**C.** Transdermal
**D.** All the above

**65. All the below mentioned drugs cause enzyme induction in man, except:**

**A.** Phenytoin
**B.** Phenobarbitone
**C.** Enalapril
**D.** Rifampicin

**66. The particle size of the dispersed solid in a suspension is usually greater than:**

**A.** 0.5 µm **B.** 0.4 µm
**C.** 0.3 µm **D.** 0.2 µm

**67. The pharmacokinetics of drugs in the neonate differs from that in adults, because their:**

**A.** Intestinal transit is fast
**B.** Glomerular filtration rate is high
**C.** Tubular transport mechanisms are not well-developed
**D.** Drug metabolizing enzymes are overactive

**68. A prodrug is:**

**A.** A type of active drug
**B.** Old class of drug
**C.** An inactive drug that is changed into an active metabolite in the body
**D.** All of the above

**69. The main mechanism of most drugs absorption in GI tract is:**

**A.** Active transport (carrier-mediated diffusion)
**B.** Filtration (aqueous diffusion)
**C.** Endocytosis and exocytosis
**D.** Passive diffusion (lipid diffusion)

**70. Agranulocytosis is:**

**A.** Virtual absence from the blood of white cells known as neutrophils
**B.** It is a life-threatening condition that results from toxic damage to the bone-marrow by some drugs
**C.** Can be treated with antibiotics and sometimes transfusion of white blood cells
**D.** All the above

**71. Competitive antagonists:**

**A.** Dissociate from receptors faster than the irrespective agonists
**B.** Alter the shape of the log dose response curve of an agonist
**C.** According to the rate theory have low dissociation rate constants
**D.** Initiate the opposite cellular response to receptor occupancy to that obtained by the agonist

**72. Theophrastus is known as:**

**A.** Father of Medicine
**B.** Father of Pharmacognosy
**C.** Father of Polypharmacy
**D.** Father of Experimental Medicine

**73. When two drugs with the same effect produce an effect greater than the sum of the effects of individual drugs (1 + 1 >2), such an effect is called:**

**A.** Additive effect **B.** Synergism
**C.** Potentiation **D.** None of these

**74. An antagonist has:**

**A.** Intrinsic activity and no affinity
**B.** Only intrinsic activity and no affinity
**C.** No intrinsic activity and no affinity
**D.** Affinity same as agonist and devoid of intrinsic activity

**75. Nitroglycerin is given in angina pectoris by sublingual route due to:**

**A.** Liver is bypassed
**B.** Can be spat after desired effect
**C.** Nonirritant and lipid soluble drug
**D.** All of the above

**76. If a drug blocks the action of epinephrine at its receptors by occupying those receptors without activating them, then which one suited the best to describe this?**

**A.** Pharmacological antagonist
**B.** Partial agonist
**C.** Physiological antagonist
**D.** Noncompetitive antagonist

**77. Receptors for _____ are DNA-binding proteins.**

**A.** Steroids **B.** Vitamin D
**C.** Retinoids **D.** All of these

**78. Which type of antagonism is found between barbiturate and amphetamine?**

**A.** Noncompetitive antagonism
**B.** Physiological antagonism
**C.** Competitive antagonism
**D.** Synergistic relationship

**79. A drug potent:**

**A.** Generates maximum response
**B.** Is required in less amount to produce a certain response
**C.** Produces no side effects
**D.** Has a rapid onset of action in body

**80. Drug metabolism occurs chiefly in:**

**A.** Liver **B.** Brain
**C.** Spleen **D.** Kidneys

**81. Idiosyncrasy reaction of a drug is:**

**A.** An example of hypersensitivity reaction
**B.** An example of drug antagonism
**C.** Qualitatively abnormal reaction of a drug which can be predictable
**D.** Quantitatively exaggerated response

**82. Which type of substances unable to permeate membranes by passive diffusion?**

**A.** Lipid-soluble
**B.** Nonionized substances
**C.** Hydrophobic substances
**D.** Hydrophilic substances

**83. Induction of drug metabolizing enzymes involves:**

**A.** A conformational change in the enzyme protein to favor binding of substrate molecules
**B.** Expression of enzyme molecules on the surface of hepatocytes
**C.** Enhanced transport of substrate molecules into hepatocytes
**D.** Increased synthesis of enzyme protein

**84. The "dominant lethal" test involves the treatment of a male adult animal with a chemical before mating; the pregnant female is later examined for fetal death and abnormalities. The dominant lethal test therefore is a test of:**

**A.** Teratogenicity
**B.** Mutagenicity
**C.** Carcinogenicity
**D.** None of these

**85. Pick out the appropriate alimentary route of administration when passage of drugs through liver is minimized.**

**A.** Oral **B.** Transdermal
**C.** Rectal **D.** Intraduodenal

**86. Biotransformation:**

**A.** Renders the drug more lipid soluble
**B.** Can be altered by drugs
**C.** Is necessary for all drugs for their elimination
**D.** Takes place only in the liver

**87. Which one is an example of parenteral route?**

**A.** Rectal **B.** Oral
**C.** Sublingual **D.** Inhalation

**88. Alcohol absorption is fast from intestine due to:**

**A.** Its lipid solubility and nonelectrolyte nature
**B.** Its lipid solubility and highly ionized nature
**C.** Its absorption by active transport method
**D.** None of the above

**89. Phenylephrine causes:**

**A.** Constriction of vessels in the nasal mucosa
**B.** Increased gastric secretion and motility
**C.** Miosis
**D.** All of the above

**90. Choose one correct statement about characteristics of a particular route of drug administration:**

**A.** Intravenous route of drug administration provides a rapid response
**B.** Intramuscular route of drug administration requires a sterile method
**C.** Inhalation route of drug administration provides slow access to the general blood circulation
**D.** Subcutaneous route of drug administration may cause local irritation reaction

**91. Which of the following is a type II (unpredictable) adverse drug reaction?**

**A.** Side effect **B.** Toxic effect
**C.** Idiosyncrasy **D.** Physical dependence

**92. Why some drugs show complicated penetration through brain–blood barrier?**

**A.** Due to high lipid solubility
**B.** Due to meningitis diseases
**C.** Due to absence of pores in the brain capillary endothelium
**D.** All of the above

**93. Receptors perform the following function(s):**

**A.** Ligand recognition
**B.** Signal transduction
**C.** Disposal of agonists and antagonists
**D.** Both A and B

**94. The volume of distribution ($V_d$) can be related to:**

**A.** Daily dose of an administrated drug
**B.** An administrated dose to a body weight
**C.** An uncharged drug reaching in blood circulation
**D.** The amount of a drug in the body to the concentration of a drug in plasma

**95. A receptor which itself has enzymatic property, is:**

**A.** Insulin receptor **B.** Progesterone receptor
**C.** Thyroxine receptor **D.** Glucagon receptor

**96. The movement of drug substance from a region of high concentration to a region of low concentration is known as:**

**A.** Active transport **B.** Bioavailability
**C.** Simple diffusion **D.** Pinocytosis

**97. Drug metabolism can be enhanced by the following factors, except:**

**A.** Smoking
**B.** Acute alcohol ingestion
**C.** Exposure to insecticides
**D.** Consumption of charcoal boiled meat

**98. Half-life (t½) is the time needed to:**

**A.** Change the amount (50%) of a drug substance in plasma during elimination
**B.** Metabolize a 75% of an introduced drug into the active metabolite
**C.** Attach 50% of drug to plasma proteins
**D.** All of the above

**99. The most important factor governing absorption of a drug from intact skin is:**

**A.** Molecular weight of the drug
**B.** Site of application
**C.** Lipid solubility of the drug
**D.** Nature of the base used in the formulation

**100. Biotransformation of the drugs is to render them:**

**A.** Less ionized
**B.** More pharmacologically active
**C.** More lipid soluble
**D.** Less lipid soluble

**101. Hippocrates is known as:**

**A.** Father of Medicine
**B.** Father of Pharmacognosy
**C.** Father of Polypharmacy
**D.** Father of Experimental Medicine

**102. The types of antagonism are:**

**A.** Summarized **B.** Potentiated
**C.** Additive **D.** Competitive

**103. Metabolism phase I is:**

**A.** The process of acetylation and methylation
**B.** The process of transformation of substances by various reactions like oxidation, reduction or hydrolysis
**C.** Glucuronide formation
**D.** Attachment to plasma proteins

**104. Intramuscular route:**

**A.** provides faster absorption as compared to oral route
**B.** Can be used to inject mild irritant type substance
**C.** In case, child is made into the gluteus maximus muscle
**D.** Can be used to inject a volume of 25 ml

**105. A process is called _____ in which a weak acid becomes less water-soluble and more lipid-soluble at low pH.**

**A.** Distribution **B.** Permeation
**C.** Protonation **D.** Elimination

**106. In case, liver disorders accompanied by a decline in microsomal enzyme activity, the duration of action of some drugs is:**

**A.** Decreased
**B.** Enlarged
**C.** Remained unchanged
**D.** Changed insignificantly

**107. Majority of drugs which are capable to cross plasma membrane are:**

**A.** Weakly basic drugs
**B.** Weakly acidic drugs
**C.** Strong electrolytes
**D.** Nonpolar drugs

**108. Two drugs binding to the same receptors is:**

**A.** Chemical antagonism
**B.** Pharmacokinetic antagonism
**C.** Competitive antagonism
**D.** Noncompetitive antagonism

**109. Elimination is best described by:**

**A.** Rate of renal tubular reabsorption
**B.** Clearance speed of some volume of blood from substance
**C.** Time required to decrease the amount of drug in plasma by one-half
**D.** Clearance of an organism from a xenobiotic

**110. The duration of action of a drug is dependent of its:**

**A.** Plasma and tissue binding
**B.** Metabolism
**C.** Tubular filtration and secretion
**D.** All of the above

**111. Pharmacodynamics involves the study of following, except:**

**A.** Therapeutic effects of drugs
**B.** Absorption and distribution of drugs
**C.** Mechanisms of drug action
**D.** Biological effects of drugs

**112. Most drugs and metabolites are excreted by:**

**A.** The kidneys
**B.** The bile
**C.** The lungs
**D.** Perspiration, saliva and tears

**113. Once the drug enters the blood, it subsequently penetrates the tissues and other body fluids depends on:**

**A.** Capillary permeability
**B.** Extent of plasma protein and tissue binding
**C.** Transport mechanism
**D.** All of the above

**114. Which one is the correct statement about most of the drug receptors?**

**A.** They are small molecules having molecular weight range between 100 and 1000
**B.** They are lipids in nature arranged in a bilayer configuration
**C.** They are proteins in nature located on cell membranes, cytosol or on nuclear membrane
**D.** DNA molecules

**115. Drugs interact with their receptor sites by forming:**

**A.** Ionic bonds
**B.** Hydrogen bonds
**C.** van der Waals bond
**D.** All of the above

**116. If an agonist can produce submaximal effects and has moderate efficacy, it is called:**

**A.** Partial agonist
**B.** Antagonist
**C.** Agonist-antagonist
**D.** Full agonist

**117. The substance binding to one receptor subtype as an agonist and to another as an antagonist is called:**

**A.** Competitive antagonist
**B.** Irreversible antagonist
**C.** Agonist-antagonist
**D.** Partial agonist

**118. When therapeutic effects decline both below and above a narrow range of doses, a drug is said to exhibit:**

**A.** Ceiling effect
**B.** Desensitization
**C.** Therapeutic window phenomenon
**D.** Nonreceptor-mediated action

**119. Choose the substance which changes the activity of an effectors element but does not belong to second messengers:**

**A.** cAMP **B.** cGMP
**C.** G-protein **D.** Calcium ions

**120. Characteristic unwanted reaction which is not related to a dose or to a pharmacodynamic property of a drug is called:**

**A.** Idiosyncrasy **B.** Hypersensitivity
**C.** Tolerance **D.** Teratogenic action

**121. Which term is used to describe a more gradual decrease in responsiveness to a drug, taking days or weeks to develop?**

**A.** Refractoriness **B.** Cumulative effect
**C.** Tolerance **D.** Tachyphylaxis

**122. Tolerance and drug resistance can be a resultant as a consequence of:**

**A.** Drug dependence
**B.** Increased metabolic degradation
**C.** Depressed renal drug excretion
**D.** Activation of a drug after hepatic first-pass

**123. The route of drug administration that gives the most rapid onset of the pharmacological effect is:**

**A.** Intramuscular injection
**B.** Intravenous injection
**C.** Intradermal injection
**D.** Peroral administration

**124. What is the type of drug-to-drug interaction which is connected with processes of absorption, biotransformation, distribution and excretion?**

**A.** Pharmacodynamic interaction
**B.** Physical and chemical interaction
**C.** Pharmaceutical interaction
**D.** Pharmacokinetic interaction

**125. The removal of oxygen or an alteration in a drug which leads to a decrease in the proportion of oxygen in the drug compound is known as:**

**A.** Oxidation **B.** Reduction
**C.** Hydrolysis **D.** All the above

**126. The absorption time of a drug can be reduced by:**

**A.** Making a more soluble salt — for oral
**B.** By using hyaluronidase — for injection
**C.** By using vasoconstrictor substances
**D.** By giving combination of drugs

**127. Definition for a therapeutic dose is:**

**A.** The amount of a substance to produce the minimal biological effect
**B.** The amount of a substance to produce side effects for an organism
**C.** The amount of a substance to produce the required effect in most patients
**D.** All of the above

**128. If two drugs with the same effect, taken together, produce an effect that is equal in magnitude to the sum of the effects of the drugs given individually, it is called:**

**A.** Antagonism
**B.** Potentiation
**C.** Additive effect
**D.** None of these

**129. Choose the best suitable statement regarding clinical trials of a new drug.**

**A.** Phase I involves the study of a small number of normal volunteers by highly trained clinical pharmacologists
**B.** Phase II involves the use of the new drug in many patients (100–5000) who have the disease to be treated
**C.** Phase III involves the determination of the drug's therapeutic index by the cautious induction of toxicity
**D.** Chemical antagonist

**130. Parenteral administration:**

**A.** Cannot be used with unconsciousness of patients
**B.** Generally, results in a less accurate dosage than oral administration
**C.** Usually produces a more rapid response than oral administration
**D.** Is too slow for emergency

## ANSWER KEY

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. C | 2. A | 3. B | 4. D | 5. C | 6. D | 7. A | 8. B | 9. B | 10. A | 11. A | 12. C | 13. C | 14. A |
| 15. A | 16. C | 17. D | 18. A | 19. C | 20. B | 21. B | 22. B | 23. C | 24. A | 25. C | 26. C | 27. A | 28. C |
| 29. A | 30. A | 31. A | 32. B | 33. D | 34. C | 35. A | 36. D | 37. B | 38. D | 39. C | 40. B | 41. C | 42. A |
| 43. C | 44. B | 45. B | 46. B | 47. C | 48. C | 49. A | 50. B | 51. D | 52. D | 53. A | 54. B | 55. C | 56. C |
| 57. A | 58. B | 59. D | 60. C | 61. C | 62. B | 63. C | 64. C | 65. C | 66. A | 67. C | 68. C | 69. D | 70. D |
| 71. C | 72. B | 73. B | 74. D | 75. D | 76. A | 77. D | 78. B | 79. B | 80. A | 81. C | 82. D | 83. D | 84. B |
| 85. C | 86. B | 87. D | 88. A | 89. A | 90. C | 91. C | 92. C | 93. D | 94. D | 95. A | 96. C | 97. B | 98. A |
| 99. C | 100. D | 101. A | 102. D | 103. B | 104. B | 105. C | 106. B | 107. A | 108. C | 109. D | 110. D | 111. B | 112. A |
| 113. D | 114. C | 115. D | 116. A | 117. C | 118. C | 119. C | 120. B | 121. C | 122. B | 123. B | 124. D | 125. B | 126. A |
| 127. C | 128. C | 129. A | 130. C | | | | | | | | | | |

# 2. Pharmacology of Peripheral Nervous System

Our body function is regulated and integrated by the two systems: (1) The endocrine system and (2) the nervous system.

- The endocrine system sends signals to target tissues by varying the levels of blood-borne hormones.
- In nervous system, more than 10 million neurons communicate with other through chemical mediators between the adjacent neurons and also exert their effects on peripheral structures by release of neurotransmitters.

The pharmacology of nervous system can be discussed as follows:

### NEURO AND PSYCHOPHARMACOLOGY DIFFERENCES

i. Neuropharmacology (peripheral autonomic nervous system):
- It deals with drugs that produce their primary therapeutic effects by mimicking or affecting the response of the autonomic nervous system, are called autonomic drugs.

ii. Psychopharmacology (the CNS):
- It deals with those drugs that affect the central nervous system (CNS) act by altering some steps in the neurotransmission process.
- "Drugs affecting the CNS" may act presynaptically by influencing the production, storage, release and termination of action of neurotransmitters (NTs).

All these NTs combine with their receptors and regulate the physiological functions, but any form of deficiency or excess can cause many diseases.