1.0 Introduction

1.0.1 Objectives

1.1 Development of new drugs

1.2 Procedures followed in drug design.

1.3 Concept of lead compound and lead modification.

1.4 Concept of prodrugs and soft drugs

1.5 Structure

1.5.1 Activity relationship (SAR), factors affecting bioactivity resonance, inductive effect.

1.5.2 Isosterism, bio-isosterism, spacial considerations

1.5.3 Theories of drug activity

1.5.4 Occupancy theory, rate theory, induced fit theory.

1.5.5 Quantitative structure activity relationship & History and development of QSAR.

1.6 Concepts of drug receptors

1.6.1 Elementary treatment of drug receptor interactions.

1.7 Physicochemical parameters: Lipophilicity

1.7.1 Partition coefficient

1.7.2 Electronic ionization constants

1.7.3 Steric, Shelton and surface activity parameters & redox potentials

1.7.4 Free-Wilson analysis

1.7.5 Hansch analysis

1.7.6 Relationship between Free-Wilson and Hansch analysis

1.7.7 LD-50, ED-50 (Mathematical deviations of equations excluded)

1.7.8 Let us sum up

1.7.9 Check your progress, the key

1.8 References

1.0 Introduction:

The drug term is derived from drogue—a dry herb, a French word. Drug is present in medicine i.e. used to prevent and cure of different diseases by treatment. According to WHO (1966), "Drug is any substance or product i.e. used or intended to be used to explore physiological systems for the benefit of the recipient.

Essential drugs satisfy the priority of healthcare needs of the public, are intended to be available of functioning Health systems at all times in excess amounts. Essential drugs is changing priorities of public health, epidemiological conditions and also the availability of better drugs, formulations and progress in pharmacology. Adequate data on its safety and efficacy should be determined by clinical studies. Quality of drug, bioavailability and stability on storage, safety and price can be assured.

Brand names of drugs are different in different countries. Local action of drug is shown by tropical route (skin and mucous membranes, deep tissue route and by arterial router). There are some categories of systemic action, the drug is administered by systemic routes and absorbed by blood and distributed all over the desired site of areas.

Oral route of drug is safer, convenient, cheaper, painless. In sublingual route drug is kept under tongue in mouth and spread by buccal mucosa. Rectal route is used when the patient has vomiting, cutaneous route drug is used as an ointment and applied on specific area of skin. Others ways are inhalation of drug, nasal route and parental route (subcutaneous injection, intramuscular, intravenous and intradermal injection).
Adverse effects of drugs, any unintended consequence of drug is called adverse effect, include all types of noxious effects as serious or fatal. All drugs are capable to produce adverse effects Minimization of adverse effects as injection of aminophylline must intravenously given slowly, rule out possibility of drug interaction when more than one drug is prescribed, elicit history of drug diseases and exercise caution, considering previous history of drug reactions, use appropriate dose, frequency and route of drug administration according to patient's clinical conditions.

Drug design for our purpose is constituted as the process of envisioning and preparing specific new molecules that can lead more efficiently to useful drug discovery. Not only did the rapid development of organic & medicinal chemistry make it possible to determine the structure of natural drugs.

New drug discovery may be considered broadly in terms of two kinds of investigational activities "exploration and exploitations" of leads. The former involves the search for a new lead: the latter the assessment, improvement and extension of the lead & rational approaches to drug design have been productive. The smaller the expenditure of human and material resources required to generate a new drug of a particular value, the more efficient the design of the program. Contributing factors include not only the compounds it was necessary to prepare before the most satisfactory was found, the medicinal chemists can contribute to the efficiency of developing or exploiting a lead by making fewest unsatisfactory compounds. The discovery of useful new drug or lead involves an element of luck. However, the probability of a favorably manifestation of luck can be improved by taking into consideration the potential for interaction with living systems through involvement of steric and electronic features of the designed molecules and of possible biochemical target moieties.

1.0.1 Objectives:
- The main aim of this unit is to study the development and procedure of new drugs with lead compound and modification
- We also get knowledge about prodrugs & soft drugs.
- The knowledge of structure activity relationship (SAR) and factors is important.
- Stereochemistry of drugs i.e. isosterism, bio-isosterism with spacial considerations.
- The theory of drug activities including occupancy, rate theory & induced fit theory, Drug receptors, physicochemical parameters. Free Wilson and Hansch analysis & its relationship
- We also shall know about doses of drugs LD-50 ED-50 i.e. Lithal and essential doses.

1.1 Development of New Drugs
Hippocrates postulated that, "A disease is pathological process, containing a cause and nature, and its treatment with medicine is not a magic", based on science, observations, analysis and deductions. Before this study, it was believed that the cure of disease was mainly based on the combination of guess work and experience.

In eleventh century Persian scientists Rhazes and Avrienna introduced for cold and cough and extract of wild autumn crocus (Colchicum) seed for the treatment of gout pain. Both of these medicines are still used in modern medicine.

The era of synthetic drugs had to wait till the process and techniques of synthetis organic chemistry became quite advanced and physiology of human body systems was well studied.

During the first half of nineteenth century, ether and chloroform were introduced as anaesthesia, for the first time as synthetic or organic chemicals.
In 1899, aspirin was prepared, it was a result from an experiment to reduce the nausea which was caused by the salicylates. Phenacetin was discovered during this time, its preparation was resulted from observations of the hydroxylation and conjugation of aniline.

Antipyrine was introduced from investigations of the chemistry of quinine.

Poul Ehrlich (1854-1915), who was called Father of Chemotherapy. He gave original ideas about the models of action of drugs. At the age of 45, he was appointed director of the Institute for experimental therapy in Frankfurt (Germany) in 1899.

In 1891, Ehrlich discovered the antimalarial activity of methylene blue. He further developed an antibacterial compound acriflavine. Ehrlich also proposed that union between the alkaloid and the chemoreceptor is labile and reversible and not firmly bound. His further work with dyes resulted in the discovery of trypanocidal action of trypan red and trypanflavin.

In 1891, the antimalarial activity of Plasmoquine (1926) and Atabrine (932) were discovered by Ehrlich.

Theory of drug action and the discovery of the sulfonamides and antibiotics were characterized by increasing knowledge of the chemistry of natural substances specifically enzymes.

The science of enzymology developed rapidly during post-Ehrlich period. In 1897, Buchner firstly observed fermentative capacity of cell-free-yeast broth. In 1926, Summer had crystallized urease enzyme.

**Factors affecting development of new drugs:**

(a) Ability of the Chemist: Knowledge about biology of the diseased state of which therapies are being considered. Ability of organize and plan the research project to get maximum success.

(b) Screening Facility Drugs: Capacity of the screening to evaluate a large number of compounds. The test system which is able to detect potentially and clinically useful drugs.

(c) Development facility: To develop a new drug, there should be a healthy environment with all physico-chemical facilities, including electron microscope etc. To investigate the modes of action of bioactive compounds.

(d) Cost of drug development: If the compound is prepared by an expensive process then the cost of manufacturing may also increase dramatically, hence the cost of drug into market may rise. The number of compounds synthesized in 1958 were 14600, out of them 94 compounds found their way into the market (1 in 332 compounds). Similarly in 1964 1,50,000 compounds were synthesized as new drugs, but only 17 could be marketed.

1.2 Procedure followed in Drug Design:

The development and search of new, safe and effective drugs has become expensive and costly. A drug does not have and leave any adverse effect on the health as well as on genetic material affecting the offspring. The drug scientist must create a degree of efficiency in the synthesis, testing and clinical trial, which will improve the chances for finding new drugs and also will preserve the resource at their disposal. The information found during this process describes a structure activity relationship (SAR). For a particular study, there are two steps to a search for an SAR:

- A relationship can be obtained between a systemic structural change in a series of molecules and the observed changes in the biologic activity through the series.
- The development of a useful SAR from chemical and biological work is an intellectual exercise. The search for an SAR is a non-experimental part of drug design and study. This is a theoretical aspect of the drug design process.
1.3 Concept of Lead compound:
The drugs used in medicine are developed from so-called lead compounds are also called Tailor made compounds. "A lead compound is the starting point from which a clinically useful compound can be developed" or it is starting point when designing a new drug. Lead compounds are often unsuitable for clinical use because they may be either toxic or have some side effects. Sources of lead compound is flora (plant) and fauna (animal) e.g. Artemisinin, Venom and toxins. Micro-organism eg. antibiotics asperlicin, Lovastatin, marine chemistry eg. Curacin-A & Biochemistry-Epinephrine and histamine.

The search of Lead compound: Suitable tests are required to search for lead compound i.e. physiological and cellular effect, or the binding of compound & pharmacologically active.

1.4 Concepts of Pro drugs and Soft drugs:
These drugs require a conversion in the body to one or more active metabolites. Such a drug is called a prodrug.

The prodrugs are more stable, having better bioavailability, less side effects and toxicity, as well as better other desirable pharmacokinetic properties.

Phases in Prodrug Action
(1) Pharmaceutical
(2) Pharmacokinetics
(3) Pharmacodynamics

Pharmaceutical Phase
(a) Esthetic Problems: This is a problem of foul odour, appears due to chemical composition of drug. Ethylmercaptan is a useful medicine as antitubercular and antilepral drug.
(b) Physicochemical Problems: Few drugs some physicochemical problems, e.g. sodium salt of ampicillin in concentrated solution forms polymer of degraded ampicillin.

Pharmacokinetics Phase:
In this phase the formation of a prodrug undergoes following problems:
- Absorption: The drug is poorly absorbed by gastrointestinal tract and other membranes. Elimination: A drug is eliminated from human body at rapid rate that it can not have the physiological action in the body over a longer period of time. Metabolism: The drug is metabolised fastly and converted into inactive metabolites. Toxicity may effect at the site of administration of the drug.

Pharmacodynamics Phase:
Formation of Prodrugs containing various chemical groups:
(a) Mercaptans: Similar to the alcohols, mercaptans may be formulated as the ester prodrugs. Mercaptans are more reactive than alcohols, because sulphur atom of mercaptan is more chemically active than oxygen of alcohols.
(b) The following two types of compounds were prepared as insect repellants, in which the idea was to liberate the insect propellant known as undecylenic acid \( \text{CH}_2 = \text{CH}-(\text{CH}_2)_8 - \text{COOH} \)
   (a) The quaternary ammonium group was introduced to act as an "anchoring group". Anchoring group assists to fixing of the molecule onto dermal tissue.
   (b) The alkyl group, present in the above compounds would help in binding to dermal tissues and also would assist in the hydrolysis of esters.
Configurational Properties:
In an acids reacts with a racemic alcohol, forms an ester, which would be a mixture of 50% of the (+) isomer and 50% of the (-) isomer. When this Easter is hydrolysed by enzyme esterases gives:
(a) Fast release of the acid, if ester is formed with the (+) alcohol.
(b) Slow release of the acid, if ester is formed with the (-) alcohol.

Formation of Amines from Amino Acids:
Levodopa is an amino acid, which is converted into dopamine in the brain by decarboxylase enzyme. L-dopa is a prodrug while dopamine is its active form.

Double Prodrug:
In the prodrug, there are two potential disadvantages:
(a) The bond between the drug and the carrier portion of the prodrug may be too unstable under storage conditions and also in vivo.
(b) The carrier portion of the prodrug may be inadequate to release the prodrug at the site of action.

Sitespecific delivery of a double prodrug:

\[
\text{Double prodrug} \xrightarrow{\text{movement to site}} \text{Prodrug} \xrightarrow{\text{specific cleavage}} \text{drug}
\]

Triple Prodrugs:
In the formation of a triple prodrug, the length of action is increased, since there is a release of the drug from both the double prodrug and prodrug, cephalosporin was require, and in particular, the compound should be water soluble.
1.4 Soft Drugs

The term 'soft drug' has been derived from the concept of hard and soft acids and bases. A compound which is easily metabolised, whereas a hard drug means a compound which is hard to metabolize or is non-metabolisable.

(a) The compound of soft drug is physiologically active.
(b) The main aim of preparing soft drugs is not to increase potency, but to increase the therapeutic indices.
(c) Soft drug avoids the pharmacologically active metabolites.
(d) Elimination the drug interactions resulting from metabolite indication of enzymes, and

\[
\text{T.I.} = \frac{\text{TD}_{50}}{\text{ED}_{50}}
\]

where, \(\text{T.I.}\) = Therapeutic index
\(\text{TD}_{50}\) = Median toxic dose
\(\text{ED}_{50}\) = Median effective dose

Soft Analogs:

Soft analogs are the bioactive compounds. They are specifically designed that a portion of the molecule undergoes a checked one stage metabolite process. The metabolism process is to be encouraged by the hydrolysis process. In the alcohol is released, which decomposed to formaldehyde and a tertiary amine.

This ester decomposed rapidly. The duration of action was a minute at a concentration of 10-8 M in human plasma. It is absorbed rapidly and then it will be hydrolyzed in vivo. The structure of this ester resembles to a drug, glycopyrolate.

Activated Soft Compounds:

Activated soft compounds are not traditional analogs of bioactive compounds. Their design start with a known non-toxic inactive metabolite. An activated group is placed to the non-toxic inactive molecule, so that in vivo the activated group is released and shows its pharmacological activity.

Many traditional N-chloramines are very unstable, whereas these compounds liberate \(\text{Cl}^+\) both inside and outside of the bacterial cell.

1.5 Relationship of Structure and Activity (SAR)

In the nineteenth century, several natural products were isolated and investigated for their structure and pharmacological activity. It was found that the physiological activity of a compound is associated with a specific structural group or unit. If such it also contains biological activity. The part of the compound which is responsible for the actual physiological activity is known as pharmacophore group.

Factors

1. Effect of Alkyl Groups:

If an alkyl group is introduced in a compound in place of active hydrogen atom,

\[
\begin{align*}
\text{HCN} & \rightarrow \text{RCN} \\
\text{ArOH} & \rightarrow \text{ArOR} \\
\text{RNH}_2 & \rightarrow \text{RNHR} \\
\text{R} & = \text{alkyl group}
\end{align*}
\]

(a) Antipyrine is a strong antipyretic, while reduction of a methyl group shows its inactivity.
2. **Effect of Hydroxyl Group**:

   Introduction of hydroxyl group into aliphatic compounds generally decreases their biological and physiological activity which is almost proportional to the number of the hydroxyl groups.

   (a) Hexanol is more physiologically active than sorbitol.
   (b) Butyraldehyde is more active than its β-hydroxy derivative.
   (c) Propanol is much more active than glycerol.
   (d) Hexaldehyde is a toxic compound while its hydroxyl derivative glucose is physiologically inert.
   (e) The physiological action of caffeine is lost in hydroxy-caffeine.
   (f) Among the alcohols possessing the same number of carbon atoms, tertiary alcohol is much more physiologically active than primary alcohol. The order of their activity is tertiary > secondary > primary.
   (g) Salicylic acid consists of antiseptic and antirheumatic properties as compared to that of inert parent compound, benzoic acid.
   (h) Phenol is an antiseptic compound and contains strong toxicity than benzene.
   (i) Polyphenols are more toxic in nature than phenol.

3. **Effect of Aldehydes and Ketones**:

   Aldehydes are more reactive than ketones. Their physiological effect is also much more intense. For example, formaldehyde is an antiseptic compound and it exerts the hardening effect on tissues. Ketones consist of narcotic action. Their pharmacological properties are similar to that of secondary alcohols. Aliphatic ketones having alkyl groups, possess the hypnotic activity while mixed ketones.

4. **Effect of Acidic Groups**:

   Introduction of acidic group in a compound either decreases or totally remove the biological action of the parent compound. For example:

   (a) Nitrobenzene is a poisonous compound whereas its acid derivative nitrobenzoic acid is harmless.
   (b) Phenol is poisonous, but benzene sulphonic acid is harmless.
   (c) Morphine consists of strong physiological activity, but morphine sulphuric acid is completely inactive.
   (d) Aniline is toxic while meta-amino benzoic acid has no harms.
   (e) Amines are toxic compounds whereas amino acids are used as food-stuffs.

   The sequence of various acyl derivatives in the decreasing order of their solubility are as follows: Lactyl > Acetyl > Benzoyl > Slicyl.

   Acetyl derivatives are cheap and can be easily hydrolysed, therefore these are generally more convenient. The benzoyl derivatives are hydrolysed very slowly. The presence of benzoyl group is of great importance to the physiological activity of ester compounds. The poisoning effect of tyrosine can be restored by esterification.

   ![Tyrosine](image)

   The acylation of the compound decreases its basicity. Action of the acylated derivative is then of immense importance after hydrolysis in the body and thus exerts its physiological action.
5. **Effects of Halogens:**
   (a) Positive Halogens: The presence of 'positive halogen' atom in the compound decreases the toxicity as well as other useful properties.
   (b) Negative Halogens: The presence of 'negative halogen' atom generally increases both the useful and toxic properties. Negative halogen is present at the non-conjugated position of the compound. It is important to note that increase in toxicity by the halogenation process is very negligible. It is observed that the aliphatic fluorocarbons are much less physiologically active than the other halogens and even less than the corresponding non fluorinated compounds.

6. **Effect of Nitro and Nitrite Groups:**
   (a) Nitro Groups: The introduction of nitrogroup into an aromatic compound makes it more toxic.
   (b) Nitrite Groups: Physiological activity increases.

7. **Effect of Amino Group:**
   Amino group is toxic in nature. Alkylation reduces their toxicity. Acylation also decreases the physiological action of parent compound. For example, aniline is physiologically toxic while acylated derivative, acetanilide is an important fabricute. However, aromatic amines and hydrazines are the compounds possessing analgesic and antipyretic properties.

8. **Effect of Nitrile Group:**
   For KCNS (potassium thiocyanate) is a weak poison while Na₂Fe(CN)₅ - No (sodium nitro prusside) is strong poison and even causes death.

9. **Effect of Unsaturation:**
   The toxicity of the compound increases with increasing unsaturation. Alkyl alcohol (CH₂ = CH – CH₂OH) consists of strong poisonous properties whereas saturated compound, propanol (CH₃CH₂CH₂OH).

10. **Effect of Isomerism:**
    The isomerism also plays an important role in the field of physiological action of drugs. For example, the ordinary cocaine is a well known anaesthetic compound while its structural isomer α-cocaine does not have this property. Similarly, sulphanilamide is a very active sulpha drug, whereas its other two isomers are inactive in nature.
    (a) The natural l-adrenaline is twelve times active than its dextro isomer.
    (b) l-nicotine is two times more poisonous than d-nicotine.
    (c) dl-hyoscyamine (atropine) is more active than l-hyocycamine.

1.5.2 **Isosterism**
   The concept of isosterism is credited to Langmuir in 1919. He stated that the atoms, groups, radicals and molecules which have similar physicochemical properties and similar electronic structure, are known as 'Isosters' and this phenomenon is called "isosterism". Such similarities occurred in atoms which are in the same vertical column of the periodic table, where the outer shell of the electrons are identical or almost identical.

   In a horizontal row of periodic table, recognized for contiguous atoms. Chemical properties of chlorine and bromine are more similar than those of carbon and chlorine or chlorine and iodine. Chlorine consists to 35.46 atomic weight and 1.80 A radii, while iodine have 126.91 and 2.15 A.
### Physical Properties

<table>
<thead>
<tr>
<th></th>
<th>N₂O</th>
<th>CO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Viscosity (at 20°C)</td>
<td>148 x 10^-6</td>
<td>148 x 10^-6</td>
</tr>
<tr>
<td>2. Density (at 10°C)</td>
<td>0.856</td>
<td>0.858</td>
</tr>
<tr>
<td>3. Refractive index of liquid, D line 16°</td>
<td>1.193</td>
<td>1.190</td>
</tr>
<tr>
<td>4. Dielectric constant at 0°</td>
<td>1.593</td>
<td>1.582</td>
</tr>
<tr>
<td>5. Solubility in alcohol at 15°</td>
<td>3.250</td>
<td>3.130</td>
</tr>
</tbody>
</table>

In 1925, Grimn has given a set of hydride displacement rules. He formulated that the vertical columns of isosteric groups were formed by displacing one place to the right the elements of a horizontal row and adding a hydrogen atom i.e., a hydride ion and continuing this process. The example is illustrated below where each vertical column represented a group of isosteres and the process is continued with the next horizontal row of elements.

#### 1.5.2 Bioisosterism

Bioisosteres are the isosteric compounds which have the same type of biological activity. In 1951, Friedman coined the term biosterism and since then the meaning of the term has gradually broadened.

(a) **Classical Bioisosteres**
   - (i) Monovalent atoms and groups
   - (ii) Divalent atoms and groups
   - (iii) Trivalent atoms and groups
   - (iv) Tetra substituted atoms
   - (v) Ring equivalents

(b) **Non-classical bioisosteres**
   - (i) Exchangeable groups
   - (ii) Rings versus noncyclic structures

The monovalent bioisoteres consist of the halogens and the group-XHₙ, where n=C, N, O and S.

The divalent atoms and groups included the R-O-R', R-NH-R, R-CH₂-R', and R-Si-R'.

The trivalent bioisoteres comprise C and N in the formation of trivalent groups, e.g., R-N=N=R' and R-CH=H=R'.

The tetrasubstituted atoms are limited to three elements = C = C = N =, and = P =.

1. **True bio isosteres**:
   Such types of bio sciences have the same type of bioactivity as the analog and in addition have the same magnitude of the biological response.

2. **Partial bio isoterse**:
   The partial bio isosteres have the same type of bioactivity but has different magnitude of response. The partial bio isotere are useful if desired bioactivity is retained and reducing the magnitude of undesired side effects, the modification of some ethylenediamines.

**Application of Recent Bioisosterism**:

Sulfonamido isosteres of the catecholamines is an excellent example of exchangeable groups. An alkyl sulfonamido group may be substituted for the phenolic hydroxy group of some catecholamines. Few of the resulting compounds possess agonist activity, while others are antagonists. Between catecholamine and alkyl sulfonamido phen ethanol amines, there may be some analogies.
Alkyl sulfonamidophene ethanotamine & phonylephrine. Above compounds consist of the same bioactivity when administered intravenously, 0.004 mg/kg of the alkyl sulfonamido compound and 0.002 mg/kg of phenylephrine cause a 20% increase in blood pressure.

Electro negativity, polarizability, vander wall's radii, bond angles, charge, number of substituents, acidity and basicity of the atom can highly influence the physiochemical characteristics of the molecule. The drug molecules exert their effect by affecting receptor sites in living system, via their physicochemical properties. It is also notable that change the physico chemical properties of the molecule, and thus causes the biologic response to it.

1.5.3 Theories of Drug Activity
The drug action is either due to their physiochemical properties, as in the case of structurally non specific drugs or from their chemical structure, as in the structurally specific drugs. The structurally specific drugs act in very small doses, and their activity arises from complexation with specific receptors localized in molecules of the organism. The structural non specific drugs aliphatic alcohols, act in large doses by forming a monomolecular layer over the whole area of certain cells of the organism.

1.5.4 Occupancy Theory:
This theory was developed by Clark and Gaddum, and also called template theory which states that the intensity of certain pharmacological effect has been directly proportional to the number of receptors occupied by the drug. According to occupancy theory, drug receptor interactions, comply with the law of mass action, may be shown by the following equation.

where R = receptor and D = a molecule of the drug

\[ \frac{K_1}{K_2} \]

RD = drug-receptor complex
E = pharmacological effect and \( k_1 \), \( k_2 \) are rate constants of absorption and desorption respectively.

The number of occupied receptors depend on the concentration of the drug in the compartment of the receptors and also on the total number of receptors in the unit area or volume.

Affinity and Intrinsic activity:
In opposite to the occupancy theory not all agonist of a given class of drugs elicit the same maximal response an example is the alkyltrimethyl ammonium series of acetylcholine congeners. This theory fails to explain some drugs act. They stated that drug-receptor interaction involves two stages:
(a) Complexation of the drug with its receptors.
(b) Production of effect.

Localization of some drug-receptors or acceptors has been determined. Most of them is either active sites or allosteric sites of enzymes or parts of DNA or RNA. Certain drugs act either by intercalation between DNA base pairs, as in the case of chloroquine or by alkylating or cross-linking of DNA strands as in the example of mitomycin.

1.5.4 Rate Theory:
The rate theory depends on the basis that a drug is efficient only at the moment of encounter with its receptor.
Paton stated that activation of receptors is proportional not to the number of occupied receptors but to the total number of encounters of the drug with its receptor per unit time. The rate theory does not need formation of a stable Michaelis-Menten complex for activation of the receptor by a drug. According to this theory, pharmacological activity has been a function only of the rate of association and dissociation between molecules of drug and receptor and not of formation of a stable drug-receptor complex. Each association forms a quantum of stimulus for the biological interaction.

In the example of agonists, the rate of association and dissociation is faster and produce many impulses in unit of time.

The rate theory is not able to explain various experimentally given facts. For example, the agonist has characteristics that favour the formation of a complex which does not quickly dissociate.

The rate theory as well as the occupancy theory have been widely criticized because these fail to explain the interpretation of phenomena which found at the molecular level, why a drug acts as an agonist or antagonist.

Paton and Rang gave an alternative to dissociation theory. In their efforts, the dissociation rate constant has been a function not of the intensity of the binding forces but of the extent to which the drug molecule disturbs the secondary protein structure. The dissociation theory has not been formally different from the occupancy theory in relating stimulus to rate of dissociation, and this rate being proportional to the occupation of receptors.

1.5.4 Induced Fit Theory:

The induced-fit theory is based on hypothesis, for which recent evidence is being accumulated of induced conformational changes in enzymes. Koshland postulated that the active site of an isolated crystalline enzyme does not have a morphology which is complementary to that of the substrate as a kind negative to it. It acquires such morphology only after interacting with the substrate, which induces a conformational change. The active sites of the enzyme is flexible, and not rigid, i.e. not only it can be deformed or change but it also consists of the ability to return to the original form. The induced-fit theory states that the biological effect produced by drugs arises due to activation or deactivation of enzymes, or of non catalytic proteins, through a reversible perturbation or alter in tertiary structure of enzymes or proteins. Conformational change does not get restricted to proteins. Drugs having flexible structure can also undergo conformational change as they approach the site of action or the receptor site. Drug receptors interaction can be seen as a dynamic, and reversible, which gives rise to the biological effect.

Koshland et al. have modified the induced fit theory to explain co-operative effects. Binds one ligand molecule accelerates binding of subsequent ones.

1.5.5 Quantum Mechanical Approaches: History & Development of QSAR

Quantum mechanics or wave mechanics explains a description of matter which is based on fundamental assumptions of natural phenomena.

Matter is composed of atoms, molecules, protons, neutrons and electrons. Quantum mechanics must successfully describe properties of these fundamental particles. Electrons of molecules are involved in the chemical changes, therefore, these are most important particles to a drug scientist. This theory is a natural extension of the notion of atomic orbitals.

Chemical reactions are governed by the probabilities of finding an electron in a particular place in the molecule and by the energy of that electron. Molecular orbital theory provides the calculations on drug molecules, electron location probabilities and energies.

The introduction of the Hansch Model in 1964 was a starting point of QSAR.

(1) In 1968 Crum-Brown and Fraster examined the neuromuscular blocking effects of a variety of simple quaternary ammonium salts and quarternized alkaloids in animals.
From these studies they concluded that the physiological action of a molecular was a function of its chemical constitution.

Richardson noted that the hypnotic activity of aliphatic alcohol was a function of their molecular weight.

These observation were the basic of QSAR.

Quantitative Structure Activity (QSAR) represents an attempt to correlate structural or property descriptors of compound with activities. These physico-chemical descriptors, which include parameters to account for hydrophobicity topology, electronic parameters and steric effects are determined empirically or more recently by computational methods.

QSAR is defined by physical properties Intrinsic properties and Biological properties.

The introduction of Hansch method in 1964 enabled chemists to describe SAR studies in quantitative terms. Methods used in QSAR analysis can be summarised follows :-

(a) Hansch Method : linear free energy relationship
(b) Free Wilson model

1.6 Drug Receptors

Nature of Drug Receptors :
Consist of biological activity even in much less concentrations. These drugs are termed as structurally specific drugs. A chemical must first with semi-rigid macromolecule, which performs a biological function. This macromolecule may be an enzyme or may contain a 'receptor'.

(a) A receptor is a macromolecule bearing sites. It possesses chemorecognitive properties for a specific natural endogenous molecule or for specific drugs.
(b) The specificity of the sites on the receptor macromolecule and the function for a particular endogenous molecule is genetically determined.
(c) Binding of agonists, either the endogenous molecule or a drug, causes a specific perturbation or change in state of the receptor macromolecule.
(d) The initiation of a response by binding at a receptor sites does not depend on the making or breaking of covalent bonds in the agonist.
(e) The destructive toxins develop their injurious action on the cell by the fact that they are absorbed by certain specific component parts of the cell side chains, which I have characterized as 'receptors'.

a. **High Potency** : Many drugs act at very low concentration, i.e. \( 10^{-9} \) M and \( 10^{-11} \) M.

b. **Chemical Specificity** : The differences in effects produced by optical isomers. Only one of the four isomers of chloramphenicol has been active.

c. **Biological specificity** : Epinephrine which has marked effect on heart muscle but very weak action on striated muscle.

That receptors are localized in macromolecules most of which have protein like properties and have the specific ability to interact with natural substrates at their active sites. Nature has been probably similar to the active site of enzymes, and they approximate equal in size the drug molecule which is able to form a complex with them. A drug converted to a receptor depend on the structural, configurational and conformational characteristics of both drug and receptor.

1.6.1 Receptor Interaction :
One of the most useful bits of information that can be obtained from SAR studies is the types of atoms and functional groups that are important in binding a drug to its target binding site. There are various forms of bonding that can take place. Usually these are intermolecular bonding
interactions such as ionic bonds, hydrogen bonds, van der waals interactions and dipole-dipole interactions. However, some drugs may form covalent bonds to their targets.

**Direct Method:**
In the direct method, the functional groups of a receptor with substance able to bind irreversibly, i.e. by covalent bonding, and then to isolate the resultant drug-receptor complex. Among the chemical reagents used, can react with the serine hydroxyl group, phosphorylating agents, sulfonyl fluorides, carbamylating agents, alkylating agent, and N-alkyl maleimides as given below:

**Indirect Method:**
In the indirect method the macromolecule has the receptor through the use of substances able to complex with it reversibly.

1.7 Physico-chemical parameters:
It seemed that the compound was effective in man only when potentiated with anesthetics & the trend to do without deep anesthesia appeared to make the compound impractical as a drug. As an interesting sidelight, it was conjectured that the presence of two lipophilic groups in the molecule might result in bonding of the agent to lipophilic sites of loss in the body, and that prior administration of lipophilic aesthetics might potentiate the blocker by masking these sites of loss.

In a drug series with an ionizable functional group there is some relationship between biological activity and ionization. Optimum range in pka values for eliciting the biological activity. Quaternous ammonium salts may be completely ionized, the electron or charge distribution can vary among different structures and materially alter activity. Phenolic, mercapto and enolic gps with H-bondig may be more significant.

Change or electron transfer complex formation has attracted attention as a possibly important biochemical and drug bonding. By Resonance delocalized, IT-electron cloud in aromatic & hetero aromatic ring systems molecules that are favorable to a receptor. It may be quite common for drug molecules to induce conformational changes at receptor areas.

1.7.1 Molecular Orbital Indices: Molecular orbital calculations provide useful information and can give numerical indices which reflect the probable position of an electron and its energy in a molecular orbital.

**Charge:** In a molecular orbital, a wave function \( \Psi \), is stated to contain a three-dimensional coordinates of an electron. The wave function of the molecular orbital is assumed to be a linear combination of \( \Psi \) values from the contributing atoms in a molecule. The contributions are designed by coefficient, \( C \). It gives an expression for a molecular orbital of a molecule of \( n \) atoms.

\[
\Psi = C_a \Psi_{a+} + C_b \Psi_{b+} + \ldots + C_n \Psi_{n+}
\]

As there are only two electrons in a molecular orbital, there must be many molecular orbitals in a drug molecule to accommodate the large number of electrons. By summing the individual \( 2C^2 \) values of each molecular orbital to obtain electron probability or electron density in any part of the molecule.

\[
q_i = \sum 2C_i^2
\]

The value of \( q \) may deviate due to the nature of atom, \( i \), and a simple count of the number of electrons contributed by atom \( i \), to the molecular orbital.

Ionization energy \( E \), is related to the wave function \( \Psi \), of the molecular orbital.

According to Schrodinger equation:

\[
H \Psi = E \Psi
\]

where \( H \) = Hamiltonian operator
A SAR method was developed by Kier and Hall. This method is much less complex than quantum mechanics, and known as molecular connectivity, which is useful in structural description.

1.7.2 **Electronic Ionization constants**

When ionization of a molecule takes place the hydrophilicity also increases and hence true partition coefficient of molecule may be determined by assuming that the ion is found exclusively in the aqueous phase.

\[ P = \frac{C_{\text{octanol}}}{C_{\text{water}}} (1-\alpha) \]

\( P \) = partition coefficient, \( C_{\text{octanol}} \) concentration of the compound is 1-octanol, \( C_{\text{water}} \) = conc. of compound in water. \( \alpha \) = degree of ionization of compound.

1.7.3 **Steric factors**

Taft steric parameters: Meyer 1895, postulated that the Atomic weight of o-substituent determined the ease of esterification of o-substituent of aromatic acids, Taft defined numerically the steric constant \( E_s \) as an equation:

\[ E_s = \log \left( \frac{k_x}{k_H} \right) A \]

\( k \) = rate constant for acid hydrolysis of esters of type \( X-\text{CH}_2\text{COOR} \)

1.7.3 The redox potential of a system may be calculated from the equation:

\[ E = E' - \frac{0.06 \text{ conc. of reductant}}{n \text{ concn. of oxidant}} \]

\( E \) = redox potential studied

\( E' \) = standard potential at given pH

\( n \) = number of electrons transferred

Surface activity: for surface active agents, while they exist as manomers in dilute solution. They form polymers as the conc. increases and the concentration at which polymers form is called Critical Micelle Concentration (CMC), since the polymers are micelles. Advantage of using surface active agents is that the polymers can solubilizes of water insoluble compounds e.g. lipophilic phenols. Thus in evaluating the antimicrobial activity of 4-benzylphenol in the presence of sodium lauryl sulphate, 3 zones of antibacterials are noted, Antibacterial activity enhances the antibacterial activity of 4-benzylphenol.

1.7.4 **Empirical Fragment Evaluation : Free and Wilson Analysis**

Free and Wilson developed an approach to structure-activity relationship. In this approach, changes in biologic activity within a series of related molecules can give numerical values on a logarithmic scale.

Ban and Fujita studied the action of a series of phenethylamines on the isolated heart.

If \( A_0 = \) activity of the parent skeleton

and \( A = \) activity of any particular molecule in a series,

the model can be expressed as:

\[ \log \left( \frac{A}{A_0} \right) = \sum G_i X_i \]

where \( X = 1 \) or 0, according to the feature or substituent,

\( G_i \) is absent or present. Substituent may be present in ring or chain and compound may be optically active or racemic.

\[ \log a = \sum G_i X_i + k \]

Thus for ± Noradrenaline, the equation is in the form:
The 'best-fit' value for all G2 and k are solve by computer. The G value represent the contribution of a particular feature or substituent to activity. Comparison of G values allows one to discern important features. A more potent molecule may be designed by using substituents with large positive G values.

1.7.5 Hansch Analysis

This method seeks relationships between biological activity and common physical properties e.g. degree of ionization, molecular size or lipid solubility. In this method biologic activity are explained in terms of physical model. Correlations can be made between biologic activity and a linear combination of indices (parameters).

The activity of a drug molecule can be related to the probability p. A drug going through the three above steps, a, b, c thus related to the probability of its going through the individual steps:

\[ p = p_a p_b p_c \]

If \( k \) = proportionality constant and
\( c \) = molar concentration then,
Activity = \( k \cdot c \cdot p \)

\[ = k \cdot c \cdot p_a p_b p_c \]

\[ \log \frac{1}{c} = \log p_a + \log p_b + \log p_c + k \]

DOSE, C → \( |k| \) → → → Response
random walk receptor

\[ \log \frac{1}{c} = k_1 \log p_a + k_2 \log k + k_3 \]

Here, we have expressed.

Intrinsic activity and linear free energy relationship: If a drug is \( \log p_a = 0 \). As a model the equation is:
\( \log \frac{1}{c} = k_1 \log k + k_2 \)

Sulfonanilides: Antibacterial Effect: In sulfonamide drugs, the effect of the substituents \( R \) was parameterized by \( \sigma \). Between \( \sigma \) and potency, a good relationship was found.

\[
\begin{align*}
\text{NH}_2 & \quad \text{SO}_2\text{NH} & \quad \text{R} \\
\log \frac{1}{c} & = 1.05 \sigma - 1.28 \\
r & = 0.97, N = 17
\end{align*}
\]

Expanding above equation to include hydrophobic bonding, a general model equation in vitro can be written as:
\( \log \frac{1}{c} = k_1 \pi + k_2 \sigma + k_3 \)

1.7.6 Relationship between Free Wilson and Hansch Analysis (Mixed approach):

Kubinyi has presented the combination of Hansch and Free-Wilson models as mixed approach. The mixed approach can be written as \( \log \frac{1}{c} = \Sigma a i j + \Sigma k j \phi j + k \) parameters. In this equation \( \Sigma a i j \) is the Free-Wilson part for the substituents and \( \phi j = \pi, \alpha \) and Es contribution of the present skeleton. The mixed approach was developed to find possible interactions between Free-
Wilson parameters and physicochemical properties of the substituents used. Another advantage of this equation is that the symmetry equations need not to be develop. The reduction of the matrix is done by setting the increments of the substituents of one chosen reference compound equal to zero.

The basic assumptions for the use of the Free-Wilson approach are:

(a) The approach can be applied to a congenic series having a common skeleton.
(b) Various derivatives must have been prepared by using different substituents at the same distinct positions of the parent skeleton.
(c) When choosing derivatives for the synthesis, care has to be taken that every substituent appears at least twice at the same position.
(d) It is stated that number of derivatives for the solutions of the regression analysis must be at least ten, equal to the number of increments. To reduce the number of compounds to be synthesized, Free and Wilson have proposed a symmetry condition where the sum of increments in a substitution position was considered equals to zero.

### 1.7.7 LD$_{50}$ and ED$_{50}$:

The medicinal value of the drugs is generally represented by 'therapeutic index' or 'safety margin'. Therapeutic index is described as the ratio of the amount necessary to kill the patient [i.e., median lethal dose (LD$_{50}$)] to that required for a median effective dose (ED$_{50}$). In experimental animals, therapeutic index is calculated as:

$$\text{Therapeutic Index} = \frac{\text{Median Lethal dose}}{\text{Median Effective dose}}$$

LD$_{50}$

$$= \frac{\text{LD50}}{\text{ED50}}$$

A therapeutic index often means that ten times a dose used for effective purpose would kill the patient as well as parasite.

The minimum dose to cause death of 50 percent animals is called LD$_{50}$. This dose in general is also known as tolerance or threshold dose.

Similarly, the minimum concentration required to have positive response from 50 percent of animals is known as ED$_{50}$, i.e., the effective dose for 50 percent with standard.

### LET US SUM UP

After going through this unit, you would have achieved the objectives and learnt about these stated earlier in the unit. Let us remind/recall what we have discussed so far.

- Drug is present in medicine i.e. used to prevent and cure of different diseases by treatment. Essential drugs satisfy the priority of healthcare needs of the public. Brand names of drugs are differ in different countries.
- Oral route of drug is safer, convenient, cheaper and painless than inhalation by nasal route & parental route.
- New drug discovery may be considered broadly in term of exploration sand exploitation. The discovery of useful new drug or lead involves an element of luck. In a drug series with an ionizable functional group there is some relationship between biological activity sand ionization.
- Theory of drug action and the discovery of the sulfonamides and antibiotics were characterized by increasing of chemistry of natural products specially enzymes.
The development and search of new, safe and effective drugs has become expensive and costly.

- Structure Activity Relationship (SAR) is information found during the process. Computers are used in drug designing and development.
- Prodrugs and derivatives of bioactive molecules which are inactive and converted in vivo to the drug. The term soft drugs is taken from the concept of Hard and Soft acids and bases. Thus a hard drug is hard to metabolise and is non-metabolisable while soft drug is easily metabolised.
- Free and Wilson analysis used for structure activity relationship and in Hansch analysis we came to know relationships between biological activity and common physical properties i.e. degree of ionization, molecular size or lipid solubility. Quantitative Structure Activity (QSAR) represents an attempt to correlate structural or property descriptions of compound with activities.
- The concept of receptor is most useful information that is obtained from SAR studies, is the types of atoms and functional groups that bind a drug to its target binding sites.
- Occupation theory : shows that different agonists action on the same receptor system do not give identical maximum effects. This theory lead to the introduction of the terms like intrinsic activity sand affinity as two different parameters from drug action unlike that just affinity as proposed in clark's view.
  Biological effect = intrinsic activity x drug receptor complex
- Induced fit theory postulated that the active site of the enzyme is flexible or better, plastic or elastic and not rigid.
- Lipophilicity of a drug can be measured readily by distribution of the compound between an aqueous and non-aqueous, water immissible solvent. The non-aqueous solvent used is l-octanol.
- The Hansch term indicates the contribution of a substituent to the hydrophobicity and hydrophilicity for different bioactive compounds.
  \[ \pi = \log \left( \frac{P_x}{P_u} \right) \]
- Steric factors (Taft steric parameters : Es), Meyer postulated that atomic weight of O-substituent determined the ease of esterification of O-substituted aromatic acids.
  \[ Es = \log \left( \frac{K_s}{K_H} \right) \]
  Ions are found in Aqueous phase.
- When surface active compounds is placed in water, it will align itself so that polar group in water & the non-polar functions is placed vertically above water. The surface active agents, exists as monomers in dil solution. They form polymers as the concentration increase & form the polymers at concentration is the critical Micelle concentration (CMC), since the polymers are micelles.
CHECK YOUR PROGRESS: THE KEY

1. (a) Development of new drugs
   (b) Drug design
   (c) Concept of lead compounds
   (d) Activity relationship (SAR)
   (e) Isosterism
   (f) Spacial considerations

2. (a) Theories of drug activity
   (b) Occupancy theory
   (c) Rate theory
   (d) Induced Fit theory
   (e) Free & Wilson analysis
   (f) Hansch analysis
   (g) Concept of Pro & Soft drugs

3. (a) Applications of bioisosterism
   (b) How the drug activity increased
   (c) LD$_{50}$ and ED$_{50}$ - Lethal dose & effective dose
   (d) How the esterification & chlorination affect the activity of drug?
   (e) Lack of literature & knowledge of drugs.

1.8 References:

- M.L. Gangwal & S. Baghel, Drug design & synthetic drugs, Student publishing house, Old Palasia, Indore.
UNIT-2
PHARMACOKINETICS & PHARMACODYNAMICS

2.0 Pharmacokinetics
2.0.1 Objectives

2.1 Introduction to drug absorption,

2.2 Disposition
2.2.1 Elimination
2.2.2 Pharmacokinetics of elimination

2.3 Important pharmacokinetic parameters in defining drug disposition and in therapeutics.

2.4 Mention of uses of pharmacokinetics in drug development process.

2.5 Introduction of pharmacodynamics.
2.5.1 Elementary treatment of enzyme stimulation.
2.5.2 Enzyme inhibition.
2.5.3 Sulphonamides.
2.5.4 Membrane active drugs.
2.5.5 Drug metabolism.
2.5.6 Xenobiotics.
2.5.7 Biotransformation
2.5.8 Significance of drug metabolism in medicinal chemistry.

2.6 Let us sum up

2.7 Check your progress: the key

2.7 Reference

2.0 Pharmacokinetics
2.0.1 Objectives:
The aim of this unit is to study the drug movement inside the outside the body. We also get knowledge about Pharmacokinetics, the quantitative study of drug movement inside, through and outside of the body is done. We also studied drug absorption by different ways, Distribution & disposition of drugs, excretion and elimination of drugs & pharmacokinetics of elimination and different pharmacokinetics in drugs development process has also studied.

We will get knowledge of Pharmacodynamics that deals enzyme stimulation, enzyme inhibition, sulphonamides, membrane active drugs, drug metabolism, xenobiotics & significances of drug metabolism in medicinal chemistry.

2.1 Introduction
Pharmacokinetics is the quantitative study of drug movement inside, through and outside of the body. Therefore, pharmacokinetic considerations determine the routes of drug administration, dose, time of peak action duration of action and frequency of administration of drug. drug movement occurs through the membranes. Biological membrane is a bilayer, 100 A in thickness made up of phospholipid, cholesterol, polar groups such as glycercyl phosphate attached to ethanol amine/choline or hydroxyl group of cholesterol. Polymeric sugars, amino sugars and sialic acids are attached on the surface and formed glycoprotein or glycolipids. The protein molecules are able to freely float through the membrane and some proteins are fixed and present in the full thickness of the biological membrane, which are also surrounded by fine aqueous pores. The movement of drugs across the membranes occur by following processes

(A) passive diffusion
(B) filtration
(C) Specialized transport

The drug diffuses across the biological membrane in the direction of its concentration gradient. The drugs which are soluble in lipids, diffused by dissolving in the lipoidal matrix of the
biological membrane. Highly lipid soluble drug attains higher concentration in the membrane and diffuses quickly.

Generally most of the drugs are weak electrolytes and their rate of ionization depend on pH of drugs. They in the following manner:

1. Acidic drugs, e.g., aspirin, whose pka value is 3.5, are pH of gastric juices. These drugs are absorbed by stomach.
2. Basic drugs, e.g., atropine, whose pka value is 10, are largely ionized. These are absorbed only when they reach in the intestine.
3. Unionized form of acidic drugs cross the surface membrane of gastric mucosal cell. These drugs also revert to the ionized form within the cell (pH 7.0) than slowly pass to the extracellular fluid. This is called ion trapping of drug.
4. Basic drugs attain higher concentration intracellularly.
5. Acidic drugs are rapidly ionized in alkaline urine. They do not diffuse back in the kidney tubules and are excreted quickly.
6. If urine is acidified, basic drugs are excreted faster.

(B) Filtration: Drugs filtration occur through aqueous pores of the membrane or through paracellular spaces. It is faster when osmotic pressure gradient is available. Most of the cells, e.g., RBC, intestinal mucosa etc. consist of very small pore size, i.e., 4 Å, and drugs with molecular weight more than 100 or 200 are not able to penetrate them. Drugs of larger molecular wt. e.g. albumin can filter through capillaries depend on rate of blood flow.

(C) Specialized transport: This is of two types:

(a) Carrier transport
(b) Pinacytosis

(a) Carrier transport:
In the carrier transport system, a drug combines with a carrier which is present in the biological membrane and forms a complex.

(i) Active transport: This transport system need energy and occurs against the concentration gradient. It gets inhibited by metabolic poisons.

DRUG ABSORPTION

Absorption of drug is the movement from its site of administration into the circulation. When given intravenously, the drug has to cross the biological membrane. The absorption of drugs is governed by the above described principles. The factors affecting the absorption are as follows:

(a) Aqueous solubility: If drug is solid, it is necessary to dissolve it in aqueous biophase before absorption. A drug given as watery solution is absorbed faster than when the same is given in solid form or as oily solution.
(b) Concentration: Drug given as concentrated solution is absorbed faster than from dilute solution.
(c) Surface area: if surface area of drug absorption is larger, it means faster absorption.
(d) Vascularity of the absorbing surface: circulation of blood removes the drug from the site of absorption and maintains concentration gradient across the biological membrane.
**Route of Administration**: Route of administration affects the absorption of drug.

(a) **Oral route**: Drug which are taken orally, absorb in the following manner:

(i) Nonionized lipid-soluble drugs: are quickly absorbed by stomach and intestine.

(ii) Acidic drugs: salicylates and barbiturates etc. are acidic drugs which are unionized in gastric juices. These drugs are readily absorbed by stomach.

(iii) Basic drugs: Quinine, morphine etc. are highly ionized drugs. These are absorbed only in duodenum.

(iv) Solid drugs: Drugs which are given in the form of solid dosage are governed by rate of dissolution and rate of abortion.

(v) Absorption in presence of food: Presence of food reduces the absorption of drugs. Some drugs form an complex compound with food constituents, e.g., an antibiotic "tetracycline", form a complex with a calcium which is present in milk. These most of the drugs absorbed better when taken in empty stomach condition.

(vi) Ionized drugs: Drugs e.g. neostigmine, streptomycin etc. are highly ionized in nature and are poorly absorbed when given orally.

(vii) Degradation of drugs by gastric juices: Insulin is a drug which is degraded by peptidasa enzyme of gastrointestinal tract, if taken orally. Therefore, it is administered intramuscularly. Similarly, penicillin G is degraded by acid, and is also ineffective orally.

(viii) Luminal effect of drugs: If two drugs are taken together, they may form an insoluble complex, this known as Luminal effect of drugs. Hence, to minimize this effect, two drugs must be taken at 2-3 hour intervals. Example of such drugs are phenytoin with sucralfate and tetracycline with antacid and iron preparations.

(ix) Gut–flora changing drugs:

(x) Gut wall effects

(b) **Subcutaneous and Intramuscular**:

Absorption of drugs from subcutaneous site is slower than from intramuscular site, but routes are generally faster and consistent than oral absorption. Application of heat and muscular exercise accelerate drug absorption by increasing blood flow.

By these routes the drug deposited directly in the capillaries. The capillaries are highly porous and they do not obstruct absorption of large lipid–insoluble molecules or ions. Extremely large molecules are absorbed through lymphatics.

(c) **Topical sites administration**:

This type of drug administration occurs though skin, cornea and mucous membranes and depends on lipid-solubility of drugs. Only few drugs such as estradiol, hyoscine, clonidine and nitroglycerine can significantly penetrate intact skin.

Cornea is permeable to lipid–soluble, unionized physostigmine but not to highly ionized neostigmine.

Abraded surface of skin quickly absorbs drugs. If tannic acid is applied over burnt skin surface, causes a side effect, 'hepatic necrosis'. Similarly, corticosteroids applied over skin can produce systemic effects and pituitary–adrenal suppression. Organophosphate insecticides coming in contact of skin can cause systemic toxicity effect.
2.3 Distribution And Disposition Of Drugs

After administering the drug in the blood stream, it is ready to distribute to other tissues. Distribution of drugs depend upon its (a) solubility in lipid; (b) differences in regional blood flow (c) binding to plasma and tissue proteins (d) ionization at physiological pH.

The distribution of drug continues till an equilibrium occurs between unbound drug.

Apparent volume of distribution (V) : If the body is homogenous single compartment of volume v, where drug gets immediately and uniformly distributed,

\[
V = \frac{{\text{Intravenous dose administered}}}{{\text{Plasma concentration}}}
\]

"V is the volume which would accommodate all the drug in the body if its concentration is same as in plasma."

Penetration of drug into brain and cerebro spinal fluid: In the brain blood capillaries do not contain large inercellular pores and have tight junctions. Neural tissues cover the capillaries of endothelial cells in brain. Thus they form a 'blood-brain barrier'. Choroidal epithelium tissues also line the capillaries and form a similar 'blood-cerebro spinal fluid barrier'.

Efflux carrier such as P-glycoprotein present in brain capillary endothelial cells, extrude several drugs which enter in brain by other processes. Dopamine doses not enter into brain but its precursor levodopa can penetrate. In the capillary walls or cells lining of brain monoamine oxidase, cholinesterage and some other enzymes are present, they also form an 'enzymatic blood brain barrier, this barrier does not permit acetylcholine, catecholamines, 5-hydroxy tryptamine to enter into brain in active form.

Passage across placenta: Placental membranes are lipoidal and permit free passage only to lipid-soluble drugs. But when non lipid soluble drugs are taken in high concentration and/or for long periods by mother, it is gained by foetus. Thus it is an incomplete barrier and almost any drug administered by the mother can affect the new born.

Plasma protein binding: Acidic drugs bind to plasma albumin and basic drugs bind to α1 acid glycoproteins. Extent of binding dependson the individual compound e.g., sulphamethaxine binds 30% sulphadiazine, 50% sulphamethoxazole 60% and sulfisoxazole binds 90%.

The clinical importance of plasma proteins binding are as follows:

- The bound fraction of drugs is not available for action. This fraction is in equilibrium with free drug in plasma nad dissociates when the concentration of the latter is decreased due to elimination.
- If protein and drug binding is very high, then it makes the drug long acting,
- One drug can bind to many sites of the protein albumin Opposite to it more than one drug can bind to the same site.

Tissue storage: Drugs may also accumulate in specific organs or get bound to specific tissue constituents. Some drugs may also bind to specific intracellular organelle, e.g., tetracycline to mitochondria and chloroquine to nucleus. Certain drugs possess high toxicity because of chloroquine on retina, emetine on heart and skeletal muscle, and tetracycline on bone and teeth.

2.2.1 Excretion and elimination

After absorption of drugs, they undergo the process of biotransformation, i.e., altered chemically in the body, and thus form their metabolites which are excreted in the following way:

- Urine :
- Faeces :
- Exhaled air : Gases and volatile liquids such as alcohol, general anaesthetics and paraldehyde etc. are eliminated by lungs.
Saliva and sweat: In the excretion of drugs, the importance of sweat and saliva is negligible. However, potassium iodide, lithium, rifampin, heavy metals and thiocyanates are excreted through this way.

Milk: Most of the drugs enter in breast milk by passive diffusion, such as more lipid soluble and less protein bound the drugs.

Renal excretion: All water soluble drugs are excreted by kidney.

Glomerular filtration: In the capillaries of glomerular, larger pores are found which are able to filter all non protein bound drugs. In renal failure of after the age of 50 glomerular filtration rate decreases progressively.

Tubular reabsorption: Lipid soluble drugs filtered at the glomerulus diffuse back in the tubules, because 99% of glomerular filtrate is reabsorbed, but non lipid soluble and highly ionized drugs are not able to do so. This occur by following way.

(a) Weak acids ionize more and are less reabsorbed in alkaline urine.
(b) Weak bases ionize more and are less reabsorbed in acidic urine.

This principle is important to utilize for elimination of poisonous drugs.

Tubular secretion: This is the active transfer of organic acids and bases. Tubular transport mechanisms are not well developed at birth. Duration of action in many drugs, e.g. penicillin, aspirin cephalosporins etc. is longer in neonates. These systems mature during infancy.

2.2.2 Pharmacokinetics Of Elimination

Drug elimination is sum total of metabolic inactivation and excretion. The pharmacokinetics of elimination of drug gives an idea to devise rational dosage regimens and to modify them according to individual needs. There are three pharmacokinetic parameters, such as:

(a) Clearance
(b) Bio availability
(c) Volume of distribution

(a) Clearance: The clearance of a drug is the theoretical volume of plasma from which the drug removed completely in unit time. Clearance (CL) can be expressed as

\[
\text{CL} = \frac{\text{Rate of elimination of drug}}{\text{Plasma concentration (c)}}
\]

(i) First order Kinetics: The rate of elimination of drug is directly proportional to drug concentration while clearance remains constant, or a constant fraction of the drug present in the body is eliminated in unit time.

(ii) Kinetics of drugs alter from first order to zero order at higher doses.

Plasma half-life: The plasma half-life of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

A drug which has one compartment distribution and first order of elimination, is plot is drawn between plasma concentration and time, which shows two slopes:

(a) Due to distribution, initially declining an a-phase.

Half-life, of the drugs. Plasma concentration: Time plot of a drug eliminated by first order kinetics after intravenous injection elimination t_1/2 is:

where \( \ln 2 = \text{natural logarithm of 2 or 0.693} \)

\( k = \) elimination rate constant of the drug i.e. the fractions of total amount of drug in the body which are removed in per unit of time.

\[
K = \frac{\text{Clearance (CL)}}{\text{Volume of distribution (V)}}
\]
\( t_{\frac{1}{2}} = 0.693 \times \frac{C}{L} \)

Hence

For example, if 2g of a drug is present in the body and 0.1 g of it is eliminated every hour then,

\[ K = \frac{0.1}{2} = 0.05 \]

The drugs can be eliminated from the body as:
1. -50% drug is eliminated from body
2. -75% (50+25) drug is eliminated
3. -87% (50+25+12.5) drug is eliminated
4. -93.75% (50+25+12.5+6.25) drug is eliminated

**Repeated drug administration:**

If the therapeutic plasma concentration of the drug has been worked out and its clearance is known the dose rate can be obtained as:

Dose rate = target Cpss $\times$ Clearance
dose rate = target Cpss $\times$ clearance

\[ \text{Dose rate} = \frac{\text{Fraction}}{\frac{\text{Target level strategy}}{\frac{\text{Loading dose}}{\frac{\text{Maintenance dose rate}}{\text{Bioavailability of drug is 100% which is administered intravenously, but is low when taken orally because:}}}}}} \]

(i) The drug may be absorbed partially.
(ii) The absorbed drug may undergo first pass metabolism in intestinal wall, liver of to be excreted in bile.

Oral formulation of a drug from different manufacturers of different batches from the same manufacturer may have the same quantity of drug (chemically equivalent) but may not yield same blood level, i.e. biologically inequivalent.

When a drug is taken in solid form, it must break into particles of the active drug, before its absorption.

Tablets and capsules consist of a number of different materials such as binders, lubricants, diluents, stabilizing agents etc. The nature of these and details of the manufacture
The rate of dissolution is governed by the particle size, solubility, crystal form etc. of the physical properties of drug. Difference in bioavailability may be due to the change in dissolution and disintegration rate.

2.4 Pharmacokinetics In Drug Development Process

To use a drug for longer time, it is generally advantageous to modify a drug by following manner:

(i) **By prolonging absorption from site of administration:**
   (a) Oral: Drug particles are coated with resins, plastic materials etc. which disperse release of the active ingredients in gastrointestinal tract. A semipermeable membrane is used to control the release of drug from the bable of capsule.
   (b) Parenteral: The subcutaneous and intramuscular injection of drug in insoluble form or as oily solution pallet implantation and biodegradable implants may develop a drug action.
   (c) Transdermal drug delivery: The drug which is used as ointment, in adhesive patches, or strips applied on skin is becoming popular.

(ii) **By increasing plasma protein binding:** Development of drugs have been made by increasing plasma proteins binding which may be slowly released in the free active form e.g. sulphadoxine.

(iii) **By retarding renal excretion:** The tubular secretion of drug being an active process which can be reduced by a competing substance, for instance, probenecid prolongs time of action of penicillin and ampicillin.

2.5 Introduction

Pharmacodynamics is the study of drug effects, attempts to elucidate the complete effect of action, sequence and the dose effect relationship.

Modification of the effects of one drug by another drug and by other factors is also a part of pharmacodynamics.

**Drug Action:**
(a) Stimulatio:
(b) Depression:
(c) Irritation:
(d) Replacement:
(e) Cytotoxic Action:

**Mechanism of Drug Action:** Drug Action mechanism is classified into four parts:
(a) Physical Action:
(b) Chemical Action:
(c) Through Enzymes:

2.5.1 enzyme stimulation

Drugs are truly foreign substances. Stimulation of enzymes by drugs is unusual. The endogenous mediators and modulators stimulate the enzymes, e.g., pyridoxine acts as a cofactor and increase decarboxylase activity similarly adrenaline stimulates adenylyl cyclase. Stimulation of an enzyme enhances its affinity for the substrate, thus rate constant (Km) of the enzyme reaction decreases.

Many drugs induce the microsomal enzymes e.g., enzyme penicillinase is obtained from a mould, and is induced by methicillin.

Many insecticides, carcinogens, and drugs interact with DNA and increase the synthesis of microsomal enzyme protein, particularly glucuronyl transferase and cytochrome P-450.
2.5.2 Enzyme Inhibition

Enzymes are inhibited generally by drugs. Inhibition is of two types:

(a) Non specific inhibition: Strong acids, heavy metal salts, phenols, alcohol, formaldehyde and alkalies inhibit enzymes non specifically. The chemicals and drugs change the tertiary structure of enzymes and denature their protein portion and thus inhibit them.

(b) Specific inhibition: Many drugs inhibit a specific enzyme without affecting others. This type of inhibition is categorised in two parts:
   (i) Competitive Inhibition (Equilibrium Type)
   (ii) Non competitive Inhibition

In this type, the drug competes with the normal substrate or coenzyme to get a new equilibrium. substrate concentration is increased sufficiently, it can displace the drug and the same maximal reaction velocity can be obtained.

(A) Sulfonamides compete with para aminobenzoic acid (PABA) for bacterial folate synthetase.

(B) Carbidopa and methyldopa compete with levodopa for dopa decarboxylase.

(C) Neostigmine and phystostigmine compete with acetylcholine for cholinesterase.

(D) A drug may also compete with coenzyme e.g., Warfarin competes with vitamin k which acts as a coenzyme for enzyme which synthesize clotting factors in the liver.

(iii) Noncompetitive inhibition: In noncompetitive inhibition, the inhibitors react with an adjacent site but not with the catalytic site of enzymes. Inhibitor also changes the enzyme in such a way that it loses its catalytic property. In such type of inhibition Km remains unchanged.

2.5.3 Sulphonamides :

In 1935, the daughter of Gerhand Domagk, a doctor working in a German dye factory, suffered from severe streptococcal infection contracted from a pin prick. Domagk gave her an oral dose of a dye called prontosil which had shown to inhibit the growth of streptococci in mice. Ernest fourneau in 1936 demonstrated that prontosil breaks down to produce sulphanilamide in human body which is the actual active agent specifically lethal to streptococci.

2.5.4 Membrane Active Drugs

Membrane active drugs are volatile anesthetics and also known as general anesthetics. General anesthetics are depressant drugs which produce partial or total loss of sense of pain, and may be accompanied by loss of consciousness. This state of insensibility is known as anesthesia. Membrane active drugs or general anesthetics act by depressing nervous function.

To administer gas or volatile liquid anesthetics, various equipment and techniques have been used such as open drop method in which liquid anesthetic is dropped on a gauze of other absorbent material supported on the patient's nose and mouth by a wire frame During the intake of an anesthetic, its concentration in the blood quickly increases when the anesthetic moves towards tissues, this concentration reaches in the arterial blood supply and thus the brain rapidly acquires high concentration of anesthetic.
Types of membrane active drugs: A number of membrane active drugs are described below.

Cyclopropane is also a currently used membrane active drug, but due to explosive nature its use has declined now a days.

Ethers: Alkane, alkene, alkyne and alicyclic ethers are potent membrane active drugs, but only vinyl-substituted and ethyl-substituted ethers have been investigated as anesthetic drugs. Chain length increases, the anesthetic activity of low-molecular-weight hydrocarbon ethers increase. Divinyl ether and its analogs are not much important as anesthetic.

(2) Halogenated anesthetic agents: Introduction of halogen atoms (Cl,Br,F) in membrane active ethers increases anesthetic potency and decreases flammability. These drugs are as follows:

Fluorinated hydrocarbons: Fluorinated hydrocarbons such as fluorene, methoxyflurane, isoflurane, and sevoflurane are developed as perfect anesthetic.

(3) Nitrous oxide: Nitrous oxide is a least potent and least toxic membrane active drug.

(4) Ketamine hydrochloride: Ketamine hydrochloride e.g., 2-(o-chlorophenyl)-2-methylaminocyclohexanone hydrochloride is a rapid-acting, potent, and a short duration membrane active drug. Accidental inhalation of trichloroethylene and 1, 1,1-trichloroethane has been associated with brain damage.

2.5.5 Drug Metabolism

After the pharmacological response, the drugs are required then excreted from the body. By enzymes of liver and various other tissue, the drugs may undergo a variety of chemical changes.

2.5.6 The study of drug-metabolism and other xenobiotics,

Drug metabolism usually leads to detoxication, oxidation, reduction and other enzyme catalyzed reactions, therefore, may form a metabolite having toxic or therapeutic effects. Thus drugs and other chemicals such as some natural products, food additives, insecticides, preservatives, environmental and agrochemicals etc, undergo enzymic transformation in the body, which generally cause the loss of pharmacological activity.

Although liver is the major site of drug metabolism, however, some drug metabolizing enzymes are also found in kidney, lung, plasma, nervous tissue and the gastrointestinal tract.

Liver disease should have an important effect on the metabolism of drugs. The capacity of drug metabolism is greatly affected in damaged or chronic diseased liver.

The ability of the liver to metabolize a substance in one pass is called 'first-pass effect or presystemic hepatic elimination.

The liver can remove chemicals from the blood after their absorption from the gastrointestinal tract.

The principal route of drugs and their metabolites excretion occurs in the urine. If drugs and other compounds are not metabolized.

Urine is not the only route for excreting drugs and their metabolites from the animal body. The other routes for excretion are:

(a) Bile
(b) Saliva
(c) Lungs
(d) Sweat and
(e) Milk

The bile has been recognized as a major route of excretion for various exogenous and endogenous substances.
Pathways Of Drug Metabolism

(1) **Phase 1 Reaction**: This is a biotransformation process and consists of oxidation, hydroxylation, reduction, and hydrolysis-enzymatic reactions. In phase 1 reactions, either a new functional group is introduced into the drug molecule or an preexisting functional group undergoes modification. Hence, drug becomes more polar and therefore it can be excreted more readily.

(2) **Phase 2 Reaction**: The phase 2 reactions are conjugation reactions. These are enzymatic synthesis in which a functional group is masked by the addition of a new group. Such groups are glucuronic acid, certain amino acids, acetyl of sulfate groups. These groups increase the polarity of the drug and caused rapid excretion.

(3) **Dealkylation of Ether and Thioether**: By a hydroxylation of the sulphur and oxygen alkyl groups, an acetal or thio-acetal are formed.

**Microsomal Reductions**: For the metabolism of drugs, some enzymes are capable of reducing azo and nitro groups of the drugs. These enzymes are found in microsomal systems. For example, the nitro group of hypnotic benzodiazepine, nitrazepam, gets reduced into the 7-amino derivative.

The most important of these has been alcohol dehydrogenase which catalyses the oxidation of ethanol to acetaldehyde.

**Hydrolysis**: In the brain, Kidney, blood liver microsomes and many other tissues esters and amides get hydrolysed by enzymes. The bulky esters get slowly hydrolysed and may often get excreted unchanged or unhydrolysed.

**Phase 2 Reactions-Conjugation**

The added group helps in blocking the functional group as well as decreasing the lipophility of the molecule, hence facilitating its excretion. Formation of glucuronide is a most common encountered conjugation reaction. Alcohols and phenols form ether type glucuronides, acids form acid-type glucuronide, amines form N-glucuronides, while thiols give S-glucuronides. These glucuronides are more soluble in water and are more acidic than the starting drug, hence at normal pH they are more likely to be ionised and consequently even less lipophilic. Most of the elimination into the urine occurs via kidney. Glycine conjugation, acetylation and mercapturic acid formation are other types of conjugations of lesser importance.

2.5.7 **Biotransformation**

Chemical changes of the drug in the body is called biotransformation. It is important to convert non-polar, i.e., lipid soluble compounds into polar, i.e., lipid insoluble, so that they may not be reabsorbed in the renal tubules and are excreted from the body. Many of the hydrophilec drugs, for example, neostigmine, decamethonium and streptomyci etc. can not be biotransformed and are excreted unchanged.

**Types Of Biotransformation Reactions**

(i) Non synthetic reactions
(ii) Synthetic reactions

(i) **Non Synthetic Reactions**

Non synthetic reactions form metabolite which may be either active of inactive. These are phase 1 reactions and can be classified as:
A) **Oxidation**: Oxidation is the most important drug metabolizing reaction. This reaction involves addition of oxygen or removal of hydrogen. The examples are oxygenation at C, N or S atoms, hydroxylation, N- or O-dealkylation, oxidative deamination etc.

Generally oxidative reactions are occurred by a group of monooxygenases in the liver. Phenothiazines, barbiturates, steroids, paracetamol, benzodiazepines, phenytoin, theophylline and many other drugs are oxidized in this way. Rate of metabolism of drugs.

(1) CyP 3A 4/5: About 50% drugs are biotransformed by this isoenzyme. It is available in liver, kidney and intestine.

_Inhibitors_: This is inhibited by many compounds such as clarithromycin, erythromycin, itraconazole, verapamil etc.

(2) CYP 2D6: About 20% drugs get transformed by this isoenzyme.

(3) CYP 2C8/9: Nearly > 15 commonly used drugs including narrow safety margin drugs such as warfarin and phenytoin etc. are metabolized by this enzyme.

(4) CYP 2C19: This enzyme metabolizes about >12 frequently used drugs such as lansoprazole and omeprazole etc.

(ii) **SYNTHETIC REACTIONS**

These are phase 2 conjugation reactions. The metabolites formed by this biotransformations are mostly inactive. Synthetic reactions have high energy requirement. These involve conjugation of drug or its phase 1, metabolite with an endogenous substrate such as amino acids, of carbohydrate.

(a) **Glucuronide Conjugation**: This is a most important synthetic reaction where a compound which contains hydroxyl or carboxylic acid group can be easily conjugated with glucuronic acid.

(b) **Acetylation**: Compounds containing amino or hydrazine residues are conjugated with the help of acetyl coenzyme-A and show acetylation reaction e.g. sulfonamides, hydralazine, p-amino sulfanilamide, isoniazid etc.

**2.5.8 Significance Of Drug-Metabolism In Medicinal Chemistry**

The metabolic changed drugs have been of considerable interest and of great practical value in the search for new and improved medicines.

The azodye, prontosil, which is inactive in vitro, is converted in the body to the active sulphanilamide by metabolic reduction process.

The metabolic acetylation of the sulphonamides served in the development of compounds which are acetylated to a lesser extent and whose acetylated derivatives are more soluble, hence reduce kidney damage to crystallization in the renal tubules.

Other significance of drug development related to metabolism is analgesic properties of phenacetin, i.e., p-ethoxy acetanilide which depends on its conversion by O-dealkylation to produce an active metabolite, acetaminophen i.e., p-hydroxyacetanilide.

The antidepressant properties of imipramine and amitriptyline, both tertiary amines are to be mediated by their secondary amine metabolites, called desipramine and noritriptyline.

Chloroguanide (paludrine), 1(p-chlorophenyl)-5-isopropylbiguanide, shows its antimalarial activity only when it is converted into 1-(p-chlorophenyl)-2, 4-diamino-6-dimethyl-dihydro-1, 3, 5-triazine by the human body.

Arsine-oxide is a therapeutically useful compound resulted from arseno compound-As=As-, when it undergoes oxidation reaction. Arsine-oxide is although more toxic but a superior therapeutic compound developed by drug metabolism process. The introduction of mandelic acid as a genito- urinary antisepctic drug showed the observation that it gets excreted unchanged and in the acidic pH of urine, it has significant bactericidal properties.

After metabolism process, the drugs may lead to the following way:
(a) **Inactivation**: Most drugs and their active metabolites are rendered inactive or less active. For example, chloramphenicol, morphine etc.

(b) **Active metabolite from an active drug**: Many drugs are found to be partially transformed to one or more active metabolites by metabolism reactions. They also exhibit better bioavailability and other desirable pharmacokinetic properties.

**Prodrug** | **Active Form**
--- | ---
Sulindac | Sulfide metabolite.

### 2.5.9 Let us sum up:

After going through this unit, you would have achieved the objectives stated earlier. Let us recall what we have discussed so far:

- Pharmacokinetics is the study of action and metabolism on drugs in the body. It deals with different aspects of absorption, distribution, biotransformation and elimination of drugs.
- Drug elimination through lungs is important for gaseous anesthetics. The rate of elimination of drugs from the lungs is based on blood/air partition coefficient.
- The transport mechanisms for acids & bases in the kidney have some characteristics of active transport for drugs.
- The description of drug distribution & elimination is often termed drug disposition.
- Clearance (CL) of a drug is theoretical volume of plasma from which the drug is completely removed in unit time.
- The pharmacokinetic parameters consists of items like the determination of biological half-life, the apparent volume distribution, the rate constants for absorption and elimination for a drug. These parameters can be investigated by compartmental analysis includes the blood and urine.
- Pharmacodynamics is the study of drug effects and attempts to elucidate the complete action - effect sequence and the dose effect relationship.
- The stimulation of enzymes by drugs, that are truly foreign substances, is unusual. Enzyme stimulation is relevant to many endogenous meditation and modulators. Stimulation of an enzyme increases its affinity for the substrate see that rate constant of the reaction decreases.
- Inhibition of enzyme is a common mode of drug action, these are non specific and specific.
- The prontosil breaks down to produce sulphanilamide in human body. The sulpha drugs are derivatives of sulphanilamide & these were the first synthetic compounds found to be effective against pathogenic organisms.
- Drug which inhibits cell wall synthesis is called membrane active drug e.g. antibiotics.
- Xenobiotics word is derived from greek 'xenos' word, means foreign and 'bios' means life. Any foreign substance to living systems is called xenobiotics. It include drugs, pesticides and carcinogens. Detoxification of such substances occur mainly in liver.
- Biotransformation means chemical alteration of the drug is the body. The primary site for drug metabolism is liver, kidney intestine, lungs & plasms. Metabolic enzymes exist mainly is liver.
2.6 Check you progress: the key
Pharmacokinetics
- Filtration
- Carrier transport
- Drug absorption
- Route of administration
- Distribution and disposition of drugs
- Sulphonamide
- Biotransformation & its types
UNIT-3
ANTINEOPLASTIC AGENTS & CARDIOVASCULAR DRUGS.

3.0 Introduction
3.0.1 Objectives
3.1 Cancer chemotherapy, special problem.
3.1.1 Role of alkylating agents antimetabolites in treatment of Cancer
3.1.2 Mention of carcinolytic antibiotics and mitotic inhibitors.
3.3.3 Synthesis of mechlorethamine, cyclophosphamide, melphalan, Uracil, mustards and 6–mercaptopurine.
3.1.4 Recent development in cancer chemotherapy.
3.5.5 Hormones and Natural products.
3.6 Cardiovascular drugs: Introduction
3.6.1 Cardiovascular diseases,
3.6.2 Drug inhibitors of periphereral sympathetic function, central intervention of cardiovascular output.
3.6.3 Direct acting arteriolar dilators.
3.6.4 Synthesis of amyl nitrate, sorbitrate, diltiazerm, quinidine, verapamil, methyldopa, atenol, oxyprenolol.
3.6.5 Let us sum up
3.6.6 Check your progress: The key

3.0 Introduction
The medical term for 'tumor' or 'cancer' is neoplasm, which means, 'a relatively autonomous growth of body tissue.' Tumor is a general term for any abnormal mass of growth of tissue, which is not necessarily life-threatening.

(a) **Malignant tumor**: It is a "cancerous tumor", which is known as malignant neoplasm with potential danger.

(b) **Non-malignant tumor or benign tumor**: It is a "non-cancerous tumor and known as non-malignant or benign tumor which does not metastasize. Metastasis is secondary growth originating from the primary tumor and may grow elsewhere in the body.

Cancer is feared more than any other disease. Only in the 20th century, the cancer of lung, alimentary tract, and breast account for at least 50% for all malignancies. Lung cancer in particular has increased rapidly due to the long –term effects of air pollution especially from smoking tobacco.

According to the embryologic origin the name for cancers is divided into two general categories

(1) **Sarcoma**: Before organs begin to develop from the early embryo of a multicellular organism.

   Sarcoma is a cancer which arises from the abnormal growth of mesodermal tissue.

(2) **Carcinoma**: Ectodermal cells form skin, its appendages and nerve tissue.

A cancer that arises from ecto-or endodermal cells is called a carcinoma.

**Carcinosarcoma**: A highly malignant tumor with the appearance of both a carcinoma and a sarcoma is termed as a carcinosarcoma.

**Teratoma**: A tumor derived from all three embryonic layers is termed as a teratoma.
Blastoma: The suffix-blastoma is used to indicate certain types of tumors that have a primitive appearance resembling to embryonic structures e.g. neuroblastoma of nerve tissue and the myoblastoma of muscle tissue.

Lymphma is an exception, being a tumor of lymph tissue which may be malignant and dangerous.

Blood cancer: A cancer of the blood involving abnormal increase of Leukocytes is called 'Leukemia'. In a normal person, the W.B.C. count about 7500/mm3. With leukemia, the number may increase to 105 to 106 mm3.

Tumors can develop anywhere on the surface or in the interior part of the body. The unlimited and uncontrolled repeated divisions of cells occur usually after the age of 35-40 years but it may also occur at a younger age.

3.0.1 Objectives:
Antineoplastic agents are used in tumor or cancer treatment. In the present chapter study of cancer chemotherapy, role of alkylating agents, antimetabolites, carcinolytic antibiotics, mitotic inhibitors and synthesis of mechlorethamine, cyclophosphamide, melphalan, Uracil, mustard and 6-mercaptopurine with recent development of cancer chemotherapy, hormones & Natural products.

Introduction of cardiovascular drugs & diseases, drug inhibitors, and synthesis of cardiovascular drugs e.g. amyl sitrate, sorbitrate, diltiazem, guinidine, verapamil, methyedopa, aterolo & oxyprenolol are given in next step.

3.1 Chemotherapy:
In this treatment antineoplastic drugs are allowed permeate in the body which act on clumps of cells that may have lodged in other organs, the anti cancer drugs have great difficulty in destroying all cell in a large tumor. A large cells, weighing 100 g and containing 10^11 cells, after a 99.9% kill, would still leave 10^8 cells, often too much for the patient's immune response to control. Chemotherapy results in the common side effects like nausea, hair loss, and increased susceptibility to infection etc. Fast dividing normal body cells e.g. hair follicles, cells lining in the gastrointestinal tract and bone marrow cells which involve in the immune defense system, are also destroyed by antineoplastic drugs.

Anticancer drugs are actually palliative not curative, but some exceptions are there. Cancer chemotherapy has been under development for the past 30 years resulting in cures of certain types of disseminated cancers which were previously fatal in nature.

Antineoplastic Drugs
(a) They can react with the nuclei of cells as well as with the cell membrane and other cell organelles.
(b) Antitumor drugs can act at all phases of the cell cycle by inhibiting cellular processes;
(c) They act by disrupting DNA-dependent enzymes such as DNA or RNA polymerases, which are essential for replication and transcription of the cellular DNA.

Types Of Chemotherapy
The type of chemotherapy is described below:
(1) Combination chemotherapy: In cancer chemotherapy, a combination of drugs are necessary to inhibit the cell division. A single drug may reduce the growth of tumor but it does not destroy all cells because the reservoir regrows the tumor soon after the chemotherapy is completed. In killing cells during DNA synthesis or mitosis, most of the anticancer drugs have different secondary killing capacity
for cells in other stages of cell cycle, but it must be given relatively long periods. For example in leukemia, the cell, which is impervious to drug 6-mercaptopurine might still succumb to methotrexate.

(2) **Adjuvant chemotherapy**: Adjuvant chemotherapy is also known as combined modality treatment. It is the combination of chemotherapy with surgery and radiation, which causes the removal of old part of tumor growth. Chemotherapy kills the two types of tumor cells often left behind following local removal (a) the microscopic nest of cells in the tissue planes adjacent to the primary tumor left outside the surgical margin and (b) clinically in apparent distant metastases. Both types of cells are in the infancy of their cycle and are highly susceptible to drugs given after surgery.

Adjuvant chemotherapy is also applied to the cancer of the breast, which has spread to the axillary lymph nodes under the arm and cancer of the large bowel which has spread to the lymph nodes in the bowel wall.

### 3.1.1 Role of Alkylating Agents in Treatment of Cancer

These are called as polyfunctional alkylating agents and characterized by containing at least one and usually two or more reactive alkyl groups in the molecule which perform important cellular functions.

Alkylating agents act upon DNA, RNA and certain enzymes. These compounds produce highly reactive carbonium ion intermediates which transfer alkyl groups to cellular macromolecules by forming covalent bonds. Alkylating agents can damage bone marrow and lymphoid tissues, therefore these chemicals were decided to use cautiously in the treatment of cancers of lymphoid tissues, such as lymphosarcoma and Hodgkin's diseases. The drugs were successful in shrinking tumor masses, but also destroy normal bone marrow.

The alkylating agents are thought to react with the 7 position of guanine in each of the double strands of DNA causing cross linking. This interferes in the separation of the strands and prevents mitosis.

### Role Of Antimetabolites In Treatment Of Cancer

**Antimetabolites**: The cancerous growth might be induced by some compounds which are being produced by abnormal metabolism of some organic compounds. e.g., methyl cholantherene is produced by metabolic reactions of cholesterol, cholic acid etc. The use of certain compounds may check the production of these carcinogenic compounds and thus may be useful in the treatment of cancer. Such compounds are called antimetabolites.

Antimetabolites inhibit a metabolic pathway which is essential for survival or reproduction of cancer cells through inhibition of folate, uracil, pyrimidine, and pyrimidine nucleoside which are also required for DNA synthesis.

The main examples of antimetabolites are - methotrexate, mercaptopurine, fluorouracil, thioguanine, cytarabine, azathioprine etc.

Methotrexate is an antimetabolite of folic acid. In the cell, folic acid is first of all reduced to dihydrofolinic acid and then to tetrahydrofolinic acid. Methotrexate is able to inhibit the enzyme dihydrofolate reductase and does not allow the formation of tetrahydrofolate which has been essential for synthesis of purine and pyrimidine and thereby check the formation of DNA and RNA.

Dihydrofolinic Acid \[\xrightarrow{\text{reductase}}\] Tetrahydrofolinic acid.

Methotrexate \[\xrightarrow{\text{reductase}}\] No reaction.
(e) **6-Mercaptopurine**: It is an analogue of naturally occurring purine, which is an essential component of DNA called adenine. Chemically it is purine 6-thiol. After the intercellular conversion of mercaptopurine to active nucleosides, it gets interfered with nucleic acid synthesis.

Physical properties: It is yellow, crystalline, odourless, tasteless powder and is insoluble in water. When exposed to air it gets darkended, therefore it is stored in well-closed containers.

*Side effects:* It causes bone-marrow depression, and orogastro intestinal damage.

![Mercaptopurine](image)

**Uses:** 6- Mercaptopurine is effective in choriocarcinoma, leukemias, and chronic myelocytic leukemia.

(f) **Thioguanine**: It is an analogue of naturally occurring purine called guanine, which is a component of DNA. Chemically it is 6-amino purine-6 (1H) thione.

![6-Thioguanine](image)

*Administration:* it is administered orally, and is given intravenously as thioguanine-sodium salt.

*Uses:* Thioguanine actually incorporated into the DNA of normal and cancerous cell.
(g) **Cytarabine**: It is pyrimidine analogue. It is 1-B-D arabinofuranosyl cytosine.

![Cytarabine](image)

(h) **5-Fluouracil**: It is a pyrimidine analogue. Chemically it is 6=5-fluoropyrimidine 2,4(1H, 3H) dione. A fluorine atom is substituted for hydrogen in the 5 position of the pyrimidine of uracil.

   **Administration**: Some 5 fluorouracil is absorbed after oral administration, therefore, it should be used intravenously.

   **Uses**: This is a most active drug available for colorectal cancer and has modest activity in pancreatic and other gastrointestinal tumors, 5 fluorouracil has also been used intra-arterially for treatment of hepatic metastases from colorectal cancer, but it has remarkable toxicity.

(i) **Azathioprine**: Azathioprine is a derivative of mercaptopurine. Chemically it is 6-(1 methyl-4-nitroimidazol-5-ythio) purine.

   **Uses**: Its main use is as an immunosuppressant to facilitate the survival of organ and tissue transplants. It is also used in lupus erythematosus, rheumatoid arthritis renal disorders, chronic active hepatitis and in severe skin disorders which are regarded to be autoimmune in character.

![Azathioprine](image)

3.1.2 **Carcinolytic Antibiotics**

(a) **Actinomycin D (Dactinomycin)**: Actinomycins are obtained on growth of certain species of streptomycyes parvullus, it is the most active of a series of cyclic pentapeptides. It was first discovered in 1940 as a most powerful bacteriostatic and cytostatic agent. Actinomycin binds strongly but reversibly to DNA interfering with synthesis of RNA and consequently with protein synthesis. Actinomycin binds with DNA with intercalation insertion between base pairs as in a sandwich, and perpendicular to the main axis of the
helix, as are the base pairs. Because of its rigid flat aromatic structure, the oxazine portion of actinomycin can bind non covalently between two successive bases in DNA, thus elongating the DNA molecule. This process is considered a point mutation.

The chemical structure of actinomycin is composed of a tricyclic, phenoxazin 3-one chromophore and two identical penta peptide lactone groups. A and B attached to the chromophore.

(b) **Bleomycin**: Bleomycin is the name of a group glycopeptides, which was isolated from *streptomyces verticillus*. Its clinical preparation is a mixture of bleomycin A2, A2 I, B1-4 etc. It causes strand scission and fragmentation of DNA. It acts in the form of a cupric complex, which inhibits DNA ligase. Bleomycin A2 is a predominant component.

*Bleomycin A2*

Bleomycin produces single and double strand breaks in DNA. Fe++ ion, bound to imidazole and pyrimidine under goes oxidation to Fe+++ . Electrons are liberated from superoxides and OH radicals through reaction with oxygen, these radicals attack phosphodiester bond between the G-C or G-T sequence, leading to strand breaks.

*Uses*: Bleomycin is active in lymphomas and testicular cancer and provides the basis of new combinations, especially it lacks bone marrow toxicity and immune suppression. It has
modest activity in a variety of squamous cell cancers of skin, head, neck, genitourinary tract and esophagus. It is also useful in Hodgkin's lymphoma.

**Administration**: It is given as a running infusion, which crosses the blood–brain barrier and shows marked bone marrow toxicity.

**Side effects**:

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**Mitotic Inhibitors**

These are a family of alkaloids obtained from the Vinca roseas Linn. The examples of these alkaloids are:

1. **Vincristine** and
2. **Vinblastine**

These are mitotic inhibitors, and bind to microtubular protein –tubulin', which prevents its polymerization, causes disruption of mitotic spindle and interfere with cytoskeletal function.

**Vincristine**: This drug is given intravenously. It is a rapidly acting drug, and useful against childhood acute leukemia, the lymphomas, breast cancer, sarcomas and the various childhood neoplasm. In combination with other antineoplastic agents, Vincristine sulphate finds use for the treatment of Hodgkin's disease, Burkitt's disease and Wilm's tumors.
3.1.3 **Synthesis of mechlorethamine, cyclophosphamide, melphalan, Uracil, mustards and 6-mercaptopurine.**

(a) **Mechlorethamine**: It is the first nitrogen mustard drug and also known as mustine hydrochloride. Its chemical name is N,N-bis (2-chloroethyl)-methyl amine and it finds use as the hydrochloride.

![Chemical structure of mechlorethamine](image)

**Uses**: The principal use of mechlorethamine is in combination chemotherapy of Hodgkin's disease and the non-Hodgkin's lymphomas. It has veterinary use, including treatment of lymphosarcoma and mast cell sarcoma in dogs and leukosis in chickens.

**Synthesis**: The mechlorethamine can be synthesised with the reaction of 2,2(methamino) diethanol and thionyl chloride.

![Synthesis reaction of mechlorethamine](image)

(b) **Cyclophosphamide**: Cyclophosphamide consists of a nitrogen and phosphoramidic moiety in its structure. Its chemical name is 2-bis (2-chlorethyl) amino per hydro-1,2,3-oxaza phosphorinane-2-oxide.

![Chemical structure of cyclophosphamide](image)

**Administration**: It may be given by mouth, even though the absorption is incomplete, however, it is often used intravenously to ensure maximum effectiveness.
Synthesis: Cyclophosphamide can be synthesised with the reaction of bis-(2-chloroethyl) phosphoramidem dichloride and propanolamine in the following manner.

(c) Melphalan: Melphalan is 4-bis-(2-chloromethyl) amino L-phenyl alanine and has nitrogen mustard moiety which is attached at para-position of L-phenylalanine.

Synthesis: It can be synthesized from L-N-phthalimido p7aminophenylalanine ethyl ester which yields an intermediate on reaction with ethylene oxide. This compound further reacts with phosphorus oxychloride and gives 4-bis (2-chloroethyl)–amino-L-phenylalanine etyl ester. On hydrolysis, it forms melphalan.

(d) Uracil: Uracil is a 2, 4-di hydroxy pyrimidine. It is a hydrolysis product of nucleic acid. It can be synthesized in the following ways.

(i) Fisher and Roeder (1901)
Several types of treatment are available for cancer management. Some are given below.

Cancer gene therapy is explained in the earlier chapter.

1. **Chemotherapy**: Compounds that block replication of cells and antimetabolites that block nucleotide biosynthesis are used as anti-cancer agents or in chemotherapy of cancer.

   (a) **Mercapto purine**: It is a purine analog used in the treatment of leukaemia. It is converted into nucleotide *in vivo* and incorporated into nucleic acids and interferes with replication.

   (b) **Fluoro uracil**: It is a pyrimidine analog and used in the treatment of colorectal cancer, *in vivo* it is converted to fluorodeoxy uridine phosphate and inhibits replication.
Methotrexate: It is a folic acid analog and used in the treatment of chorio carcinoma.

Azaserine: It is a glutamine analog used in cancer treatment. It blocks nucleic acid biosynthesis (replication), by inhibiting glutamine dependent metabolic reactions.

Acivicin: Another glutamine analog used as anti cancer agent. It is a competitive inhibitor of glutamine utilizing enzyme.

Methotrexate, azaserine and acivicin are anti metabolites used in cancer treatment. They are called anti metabolites because they block nucleic acid synthesis by antagonising the metabolic role of glutamine.

2. Radiotherapy: Radiation can break phosphodiester linkages of DNA, and interfere with the replication process. As a result, growth of cancer cells can come down. Based on this principle radiation is used to treat tumours.

3. Photochemotherapy: It is a newly introduced treatment of cancer. It uses a photosensitive drug and laser light to destroy cancer cells.

Gene Therapy:
Some inherited diseases due to deficiency of particular gene or gene product are fatal and generally proper treatment is not available. Gene therapy offers a chance of a correcting such fatal disease. Gene therapy is the use of genes to correct genetic diseases or use of genes as therapeutic agents.

Vectors used in gene therapy:
Retroviruses particularly in urine leukaemia virus (MLV) is used as a gene carrier. When virus infects the host cell, the recombinant retroviral RNA is reverse transcribed and integrated randomly into the host cell DNA.

Even though the gene therapy was initially developed for the treatment of inherited diseases, not it is used in the treatment of cancer, neurological diseases and infectious diseases.

Cystic fibrosis, severe combined immunodeficiency disease (SCID), familial hypercholesterolemia, hemophilia and Duchenne muscular dystrophy (DMD) are genetic diseases treated by using gene therapy.

Acquired diseases treated with gene therapy are cancer, cardiovascular diseases, Alzheimer's disease, Parkinson's disease and AIDS.

Steps of Familial hyper Cholesteroloma Gene Therapy
1. Preparation of the retroviral vector carrying LDL receptor gene.
2. Hepatocytes are isolated from the patients liver.
3. Transfection of hepatocytes with virus carrying LDL receptor gene.
4. Introduction of modified hepatocytes into portal blood of the patient.

Cystic fibrosis gene therapy protocol differs from the above examples. It involves direct introduction of viral vectors containing a cystic fibrosis transmembrane regulator (CFTR) gene, into the nasal or bronchial epithelium, where it is expressed after integration into the host DNA.

Cancer gene therapy involves introduction of tumor cells containing genes for cytokines into the patients. An alternative cancer gene therapy involves introduction of a tumor suppressor gene into the patient.

3.1.5 Hormones:
The steroid hormones which comprises estrogens, androgens, progestin as well as glucocorticoids have been described to respond favourably in human cancer. The hormones in general are said to act on the appropriate target tissue at the level of transcription. On the
contrary, glucocorticoids are reported to interfere with glucose uptake and protein synthesis in the lymphatic tissue.

The cytoplasm of the target cells contain specific protein receptors which have very high affinities for the hormones. The hormones bind to receptor sites and cause a transformation in the receptors structure. The complex thus formed migrates into the nucleus where it interacts with an acceptor site to modify the transcription stage.

Some neoplastic cells are hormone dependent and therefore respond to hormone therapy whereas others are independent and do not respond to hormones.

Another androgenic compound used in the palliative treatment of metastatic breast carcinoma in postmenopausal women is dromostandolone.

A progesterone derivative namely 17-methylpregna-4, 6-diene-3, 20-dione (Megestrol), Merace, XXVIII) is recommended for the treatment of advanced breast or endometrial carcinoma.

A non-steroidal compound known as tamoxifen is (Nalvadex, XXIX; (Z)-2[4-(1,2-diphenyl-1-butenyl)]-N, N-dimethyl ethanamine citrate. The drug is useful for treatment of advanced breast cancer in postmenopausal women. The side effects are nausea, vomiting but no severe. The usual dose is 10 to 20 mg tablets twice daily.

A non-steroidal anticancer agent used for treating inoperable adrenal cortical carcinoma is mitotan [ploysodren R; 1,1-dichloro-2-(O-chlorophenyl) ethane. The side effects are G.I. disturbances and the dose is 8-10 mg daily.

3.1.5 Hormones

Hormones are chiefly used in the treatment of prostate and breast cancer. The growth of metastatic prostrate cancer is flavoured by androgens but it is reduced by oestrogens. Hence, in the prostrate cancer, oestrogen therapy is used as a substitute for orchiectomy and after the surgical procedure. The mechanism of action of oestrogen therapy is not known.

The common oestrogenic compounds used in breast cancer are ethinyl oestradiol, dimestrol, oestradiol propionate, diethylstilbestrol, and conjugated oestrogenic substances.

Glucocorticoids :They have marked lymphocytic action and are primarily used in acute childhood leukemia and lymphomas. They induce remission, but relapses occur after variable intervals and gradually and gradually the responsiveness is lost.

Estrogens : Estrogens produce gratifying results in carcinoma prostate, which is an androgen dependent tumour. When hormones dependence is gradually lost, relapses eventually occur, but prolonged the life. Estrogens have been used in the palliative treatment of carcinoma of male breast. Some breast cancer have estrogen receptors in their cells. These respond to estrogen and antiestrogens.

Hormone therapy is used only in advance case, where surgery or radiotherapy is not possible. Estrogens should be employed only in women who are >5 years postmenopausal and have become non-responsive to tamoxiphen.

Tamoxfen (Antiestrogen) : Chemically, tamoxifen has been (z) 2 [4.(1, 2-diphenyl but-1-enyl) phenoxy]-N-N-dimethy ethyl amine. It is given orally and its citrate form is found officially as :

It is effective in estrogen receptor positive as well as negative breast cancer in both pre and post menopausal women. It is a first line drug for palliative treatment of carcinoma breast and after mastectomy.
Antiandrogen: Flutamides antagonises androgen action on prostrate carcinoma and has palliative effect in advance and metastatic cases.

Progestins: These bring about temporary remission in some cases of advanced, recurrent (after surgery and radiotherapy) and metastatic endometrial carcinoma. They have also been used in treatment of metastatic breast that has become unresponsive to tamoxifen.

5-a reductase Inhibitor: Finasteride inhibits conversion of testosterone to dihydrotestosterone in prostrate and other tissues. It shows effect in advanced carcinoma prostrate.

3.1.5 Natural Products

Asparaginase: It is a natural product, isolated from Escherichia coli or other sources. This is an enzyme. Administration of a large dose of asparaginase, which removes amino group from asparagine, circulating in the blood plasma and the leukemic cells.

This therapy has produced complete remissions in about 50% children with acute leukemia. Asparaginase is given intravenously to induce remissions in acute lymphatic leukemia.

Toxicity: Although bone marrow depression, hair loss, and effects on gastrointestinal mucosa are not seen with asparagine but it has many other serious toxicities in man, specially on organs which synthesize large amounts of proteins.

Interferons: It is a natural product of a small class of proteins and released by cells which have been invaded by a virus. A source of interferons has been the human white blood cell ingredient leukocyte, but recently, a DNA recombinant technique has been applied to supplement their rare source of supply.

Natural killer cells and lymphokines: Lymphokines are glycoproteins which are formed by white blood cells in trace amounts. Lymphokines regale the body's natural immune responses. Few lymphokines either suppress or induce the growth of cells, known as B-cells or T-cells.

B-cells are supposed to generate antibodies, which recognized foreign and invading cells. T-cell are believed to have the potential to promote production of cytotoxic or killer cells which attack on foreign cells of body.

<table>
<thead>
<tr>
<th>Name</th>
<th>Uses in the treatment of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Vinblastin sulphate</td>
<td>Hodgkin's disease, chorio carcinoma</td>
</tr>
<tr>
<td>(2) Vincristin Sulfate</td>
<td>Acute leukemia in children</td>
</tr>
<tr>
<td>(3) Podophyllum peltatum</td>
<td>Testicular carcinoma</td>
</tr>
<tr>
<td>(4) Colchicine</td>
<td>Anti-tumor action</td>
</tr>
</tbody>
</table>

**HARMONES:**

(1) Estrogens and Androgens  | In the treatment mammary carcinoma                                  |
(2) Ethinyl Estradiol        | Breast Cancer                                                       |
(3) Testosterone             | Breast Cancer                                                       |
(4) Progestrone              | Advanced Breast cancer or endometrial carcinoma                      |
(5) Tamoxifen [non-steriod compound] | Breast Cancer                                                   |
3.6 **Dardiovascular Drugs**

Cardiovascular drugs are a group of drugs, which have major action on the heart or blood vessels, or those used primarily for cardiovascular disorder, so that they check the total output of the heart as well as the distribution of blood to certain parts of the circulatory system.

Cardiovascular drugs are classified into the following types:

(a) Cardiac glycosides
(b) Antianginal drugs
(c) Calcium channel blockers
(d) B-Adrenergic blocking agents
(e) Vasodilators
(f) Antiarrythmic agents
(g) Anti hypercholesterolemic drugs
(h) Sclerosing agents

(a) **Cardiac Glycosides**

Cardiac glycosides are an important class of naturally occurring drugs whose action include both toxic effects and cardiotonic effects.

Cardiac glycosides can be obtained from both plants like, Digitalis and Strophanthus and certain animals, e.g. poisonous toad.

Cardiac glycosides have been used as medicinals as well as poisons.

<table>
<thead>
<tr>
<th>Source</th>
<th>Glycoside</th>
<th>Aglycone</th>
<th>General Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digitalis lanata (from leaf)</td>
<td>Lanatoside-A</td>
<td>Digitoxigenin</td>
<td>Glucose-3-acetyldigitoxyose-digitoxyose2-aglycone</td>
</tr>
<tr>
<td></td>
<td>Lanatoside-B</td>
<td>Gitoxigenin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lanatoside-C</td>
<td>Digitoxigenin</td>
<td></td>
</tr>
<tr>
<td>Digitalis purpurea (from leaf)</td>
<td>Purpurea glycoside-A</td>
<td>Digitoxigenin</td>
<td>Glucose-digitoxose3-glycone</td>
</tr>
<tr>
<td></td>
<td>Purpurea glycoside-B</td>
<td>Gitoxigenin</td>
<td></td>
</tr>
<tr>
<td>Strophanthus gratus (from leaf)</td>
<td>g-Strophanthin</td>
<td>Quabagenin</td>
<td>Rhamnose-aglycone</td>
</tr>
<tr>
<td>Strophanthus kombe (from seed)</td>
<td>k-Strophanthosi de</td>
<td>Strophanthidin</td>
<td>Glucose-glucose-cymarose-aglycone</td>
</tr>
</tbody>
</table>
Some major aglycones are given below:

**Toxicity:** The toxicity of cardiac glycosides is due to inhibition of the Na⁺,K⁺-ATPase pump, which results in increased intracellular levels of Ca++. The high levels of Ca++ are responsible for the observed cardiac arrhythmias, characteristics of glycoside toxicity.

**Antianginal Drugs**

Angina pectoris is a sudden, severe pain originating in the chest, often radiating to the left shoulder and down the left arm. The cause of such pain is believed to be transient myocardial ischemia resulting from a decrease in coronary blood flow and an increase in myocardial oxygen demand.
**Antianginal Drugs**

All of the organic nitrated have rapid first-pass metabolism, not only in the liver by the action of glutathione-nitrate reductase enzyme, but also in extra hepatic tissues like blood vessels.

Glyceryl nitrate is most frequently used in the treatment of acute anginal pain. This is rapidly absorbed from the lingual, sublingual and buccal mucosa and provides relief within two minutes.

To prevent recurring anginal pain, long-acting organic nitrate drugs are used, e.g., orally administered ososorbide dinitrate, pentaerythritol tetranitrate and erythrityl tetranitrate. oral sustained release forms, glyceryl trinitrate ointment, buccal tablets, and transdermal patches.

(c) **Calcium Channel Blockers**

There are a number of calcium channel blockers which may play a critical role in the treatment of myocardial insufficiency. The inhibition of calcium ion(Ca++) influx into myocardial cells may be advantageous in preventing anginal pain. Physiologic calcium is found in both intracellular and extracellular location. Many of the drugs are found to influence the calcium movement and availability. When therapeutic agents show their effect by inhibiting calcium—dependent events, they often achieve this blockade by decreasing the amounts of free calcium in the cytoplasm.

![Calcium channel blockers](image)

(d) **β-Adrenergic Blocking Agents**

β-adrenergic blocking agents are used in the treatment of exertion-induced angina. Although these drugs may be used alone, they are often used in combination therapy with nitrates, calcium channel blockers or both. A prototype drug of this class is propranolol.

The adrenergic nervous system plays an important role in regulating heart rate, blood pressure, bronchial tone, and gastrointestinal motility.

Norepinephrine is synthesized and stored inside the nerve endings in granules. It is liberated into the synapse in quantum amounts during nerve depolarization.

An interaction with B-receptor causes myocardial contraction, increased blood flow through vasodilation, relaxation of the bronchi, and increased glycolysis.

The principal effect of β-adrenergic blocking agent is to reduce cardiac activity by decreasing or preventing beta-adrenergic receptor stimulation. They find use in the treatment of cardiac arrhythmia and angina pectoris for reducing the oxygen consumption and for increasing the exercise tolerance of the heart.
Vasodilators represent a group of drugs which act on the vascular system. Their therapeutic action is due to their ability to dilate coronary vessels and are used for treating coronary artery diseases particularly in angina pain.

Adenosine is a natural vasodilatory substance released by the myocardium during hypoxic episodes.

Dipyridamole causes its long acting and selective coronary vasodilation, presumably, through inhibition of adenosine uptake by the red blood cells and vasculature.
(f) **Antiarrythmic Agents**

Antiarrythmic agents are useful in the treatment of cardiac arrhythmias. Cardiac arrhythmias is a disturbance in the conduction of impulses through the myocardium by disorders of impulse formation.

(a) **Class I drugs**: Class I antiarrythmic agents are usually local anaesthetic drugs which work on myocardial membrane and nerve to decrease the conduction. These drugs also reduce the rate of depolarization without changing the resting potential. Quinidine is the example of this class:

**Quinidine**: For acute and chronic treatment of ventricular and supra ventricular arrhythmias, particularly supra ventricular tachycardia, quinidine is a widely used drug.

It is a member of a family of alkaloids found in cinchona bark. It is closely related with quinine.

(b) **Class II drugs**: Class II antiarrythmic agents are B-adrenergic receptor blocking agents.

(i) they depress adrenergically enhanced phase 4 depolarization through B receptor blockade.
(ii) these drugs decrease neurologically induced automaticity at normal therapeutic doses.

(iii) at higher doses, these drugs cause excitability.

The example

Propranolol: Propranolol is a B-asrenergic receptor blocker.

Class III drugs: Class III antiarrhythmic agents cause homogeneous prolongation of the duration of the action potential.

Class IV drugs: Class IV antiarrhythmic drugs block the slow inward current carried by calcium.

The above effects block the conduction of premature impulses at the AV-node and are very effective in treating supr ventricular arrhythmias.

**Verapamil**: Verapamil is a calcium channel blocker and is used in the treatment of angina pectoris and supraventricular arrhythmias.

### Classification Of Antiarrhythmic Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Pharmacological Effects</th>
<th>Antiarrhythmic Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Decrease maximal rate of depolarization, decreases duration of action potential</td>
<td>Quinidine, procainamide, Disopyramide</td>
</tr>
<tr>
<td>IB</td>
<td>Decreases maximal rate of depolarization, decreases duration of action potential</td>
<td>Lidocaine, Phenytoin, tocainide, Mexilitine</td>
</tr>
<tr>
<td>IC</td>
<td>Decreases maximal rate of depolarisation, no change in duration of action potential</td>
<td>Flecainide</td>
</tr>
</tbody>
</table>
Inhibition of sympathetic activity  | Propranolol
---|---
Prolongation of duration of action potential.  | Bretylium, Amiodarone
Inhibition of slow inward calcium current  | Verapamil

(g) *Antihypercholesteromic Drugs*

In the development of atherosclerosis, cholesterol plays an important role. Atherosclerosis is deposition of fat in the inner of arteries in human beings. Deposition of cholesterol in arteries may interfere in the supply of blood, and causing high blood pressure and heart attack. The cholesterol level can be regulated by using following antihypercholesterolicmic agents:

- Aluminium Nicotinate (Niclex):
- Clofibrate (Atromid-S):
- D-Thiroxine Sodium:

(h) *Sclerosing Agents*

Sclerosing agents irritate the intimal layer of the vessel wall and start a thrombus. It causes adhesion of the endothelium and occlude the vessels. These drugs are used in obliteration of varicose (dilated veins).

3.6.1 *Cardiovascular Diseases*

Cardiovascular diseases are related to the heart and other parts of vascular system. The following trypes of cardiovascular discussed here:

(1) *Cardiac Failure*

In cardiac failure or congestive heart failure, the contractility of the ventricles gets reduced, and thus causing a decreased cardiac output which is not sufficient to fulfil the metabolic demands of the body. As the degree of cardiac failure increases, blood volume, end-diastolic volume and venous return are all increased, which systemic blood pressure gets decreased. In responses of these changes, a normal heart would try to increases its force of contraction. therefore, it results in an increases in heart rate, systemic vascular resistance (after load), and venous load (preload). Myocardial contractility may also be increased when sympathetic tone is increased. Since the cardiac failure becomes more severe, the heart becomes dilated, thus edema and ascites in lung may occur.

(2) *Ischemic Heart Disease*

Ischemic heart diseases generally the result of advanced atherosclerosis. It frequently produces angina pectoris. Angina pectoris characterized by a sudden, severe pain originating in the chest, often radiating to the left shoulder and down the left arm. Angina may be of two types:

(1) Typical
(2) Variant

This classification depends upon the precipitating factors and electro physiologic changes observed during the attack. Regardless of anginal type, the underlying cause is due to the
myocardial ischemia resulting from a decrease in coronary blood flow and an increase in myocardial oxygen demand.

The organic nitrates, calcium channel blockers, and B-adrenergic blocking agents are used in the treatment of acute angina pain.

The oxygen requirement of the myocardial tissues are according to the work load of the heart which includes a function of the heart rat, the systolic pressure, the thickness of the ventricular heart muscle, and the diameter of the heart. Myocardial ischemia occurs when oxygen is not sufficient to meet the myocardial work load. This can occur due to atherosclerotic narrowing of the coronary circulation or by vasospasms of the coronary vessels.

In some patients, the cause of angina pain is atherosclerotic narrowing of the coronary blood vessels. In these patients, the relief of ischemia occurs as a result of a nitrate-induced decreased myocardial O2 demand, which is a direct result of alteration in the systemic circulation. Administration of nitrates to these individuals causes dilation of both resistance and capacitance vessels.

(3) Cardiac Arrhythmias

Cardiac arrhythmias can be caused by a disturbance in the conduction of impulses through the myocardium, by disorders of impulse formation, or by a combination of these factors. Many factors influence the normal rhythm of electrical activity in heart. Arrhythmias may occur due to two reasons:

(a) Pacemaker cells fail to function properly.
(b) A blockage in transmission through the AV-node.

Sometimes lung disease, hyperthyroidism, and atherosclerosis may also initiate arrhythmias.

Some of the more common arrhythmias are called ectopic. Ectopic occurs when electrical signals spontaneously arise in regions other than the pacemaker and then compete with the normal impulses. Ectopic foci is also stimulated by myocardial

One more cause of arrhythmias generation is from a phenomenon called re-entry. This occurs when the electrical impulse does not die out after firing, but continues to circulate and re-excite resting heart cells into depolarizing.

(4) Thrombosis

Under cardiovascular diseases, various forms of thrombosis, such as coronary, embolic, venous, and traumatic thromboses, account for a large number of deaths per year.

The thrombosis (intravascular clotting) can be caused by vascular injury, blood stasis of blood hypercoagulability.

When an injury to the subendothelial cells of a blood vessel or to tissue occurs, an immediate vasoconstrictive reflex reduces the volume of blood flow, and the platelets start to adhere to the injured cells of tissue. The platelets then release ADP and prostaglandin peroxide molecules and come to one another to form a plug like structure.

These processes are known as platelets release’ and 'platelets aggregation', respectively. The release of biochemicals from the platelets can lead to thromboxane A2, synthesized by the platelets (induces platelet aggregation) or to prostacyclin (PGI2), synthesized by the blood vessel cells, which inhibits platelet aggregation.

(5) Platelet Aggregation

Platelet aggregation is implicated in thrombus formation, particularly in the arterial system; and in general in the pathogenesis of atherosclerosis. Aggregation of platelet causes atherosclerotic disease.

Aspirin acts as an antiplatelet drug by inhibiting platelet aggregation by acetylating cyclo-oxygenase a platelet enzyme. This inhibits the synthesis of thromboxane A2, which is a
powerful vasoconstrictor and inducer of the platelet release reaction and platelet aggregation. The irreversible effect lasts for the life of the acetylated platelet i.e., 4 to 7 days.

Recent clinical studies by the food and drug administration that one aspirin tablet a day (0.324g=5gr) reduces by 20% the risk of a second heart attack in those who have had one attack already.

![Diagram of Arachidonic Acid metabolism](image)

(6) Kawasaki Disease
Kawasaki disease is a disorder in children (6 months to 4 years) which produces a coronary aneurysms and also leading to heart attack and death. Recent clinical study shows that aspirin may be effective in high doses in treating the complications of kawasaki disease.

(7) Atherosclerosis
Atherosclerosis is the deposition of fat in the inner linings of arteries. Cholesterol plays and important role in the development of atherosclerosis in human beings. This may interfere in the supply of blood and causing high blood pressure and heart attack. In normal man, the range of serum cholesterol is 190 to 250 mg percent with about 70% as cholesterol esters and 30% in the free state. To bring the serum cholesterol level within the range, there are following methods:
(a) By inhibiting the synthesis of cholesterol within the liver.
(b) By increasing the metabolism and biliary excretion of cholesterol.
(c) By diminishing the absorption of cholesterol from the gastrointestinal tracts.

The prime source of the precursor of cholesterol formation in human body is the fat. Thus the synthesis of serum cholesterol can be reduced by decreasing the fat content in the diet. The use of unsaturated fats from vegetable sources also appears to lead to a decreased serum cholesterol accumulation in arteries.

3.6.4 Synthesis Of Cardiovascular Drugs
(1) Amyl Nitrate:
Amyl nitrate have been found effective in both relieving and preventing the painful anginal attacks.

The most prominent action of this drug is exerted on vascular smooth muscle. Nitrate dilates veins more than arteries which causes peripheral pooling of blood, this reduces the preload on heart and diastolic size and pressure, therefore, decreases cardiac work load.

**Synthesis:** The amyl nitrate can be prepared by esterification of simple amyl alcohol with nitric acid or sodium nitrite in concentrated sulphuric acid as given below:

(2) Diltiazem:
Diltiazem is a calcium channel blocker. For the treatment of myocardial insufficiency and angina pain, Ca ++ (calcium ion) is inhibited to influx into myocordial cells. Since 1960, calcium ions are known to play a critical role in many physiological functions. Physiologic calcium is found in a variety of location, such as extracellular and intracellular, both. Diltiazem interferes the movement of Ca++ ions into the cell.

**Synthesis:** Diltiazem can be prepared in the following way:
Verapamil: Verapamil was developed in Germany in 1962 as a coronary dilator. It is a calcium channel blocker which is used in the treatment of angina. Verapamil is also effective and widely used for the treatment of supraventricular arrhythmias chemically, it is a derivative of papaverine and was originally conceived as vasodilator for angina.

Synthesis: Verapamil can be prepared as follows:
Methyldopa: It is the a methyl analogue of dopa, which is a precursor of dopamine. It has been one of the oldest and most widely used antihypertensive agents. It is alpha methyl derivative of dopa (3, 4-dihydroxyphenyl)-2-methyl-L-alanine sesqui hydrate.

When the blood transfers from arteries to the tissue capillaries and veins, it results in excessive stimulation of sympathetic nervous system (CNS). This may cause arteriole contraction and increased peripheral resistance to the flow of blood.

**Synthesis:** Methyldopa can be prepared as given below:
Atenolol is an antiarrhythmic agent and known as beta-adrenoceptor blocking agent. Its half life is 6-9 hours.

**Uses:** Its principal effect has been to reduce cardiac activity by decreasing of preventing beta-adrenoceptor stimulation. This drug also find use in the treatment of angina pectoris for reducing the oxygen consumption and for increasing the exercise tolerance of the heart. Atenolol is also useful in the longterm treatment of hypertension.

**Synthesis:** Atenolol can be prepared in the following manner:

(5) **Sorbitrate:** This drug is also known as isosorbide dinitrate. Sorbitrate is used for both treatment and prevention of painful anginal attacks. It is a long-acting antianginal agent. This drug can be administered sub lingually i.e., transdermal and buccal administration
routes. The action of sorbitrate may last for 4 to 6 hours. Sorbitrate is metabolized primarily in the liver by glutathione-nitrate reductase.

**Synthesis:** Sorbitrate can be prepared as follows:

(7) **Quinidine:** Quinidine is an alkaloid, found in cinchona bark (Cinchona officinalis L) and is a close relative of quinine. In fact, quinidine and quinine are diastereomers of one another.

Structurally quinidine and quinine are similar, and quinidine is dextro isomer of quinine.

Quinidine consists of a quinoline ring and the bicyclic quinuclidine ring system with a hydroxy methylene bridge connecting these two components.

Quinidine is metabolized mainly in liver. Its renal excretion is also significant.

Quinidine is not tolerated by a significant percentage of patients, and it cannot be given further than the test dose.

**Synthesis:** Quinidine can be prepared in the following manner:
Oxyprenolol: Oxyprenolol is a B-adrenergic blocking drug. The branch of the autonomic nervous system in which norepinephrine is the neurotransmitter between the nerve ending and the effector muscle is known as the adrenergic nervous system.

The adrenergic nervous system plays an important role in regulating many physiological functions, including blood pressure, heart rate and force, bronchial tone and gastrointestinal motility.

3.6.5 Let us sum up

- Antineoplastic agents are used in tumor, cancer or neoplasm. Tumor indicates any abnormal mass or growth of tissues. Cancerous tumor is a malignant neoplasm with potential danger. The tumors have a rapid growth of cells but the rate of cell death is less.
- Cancer chemotherapy compounds that block replication of cells and antimetabolites that block nucleotide biosynthesis are used as anti cancer agents or in chemotherapy of cancer.
- Miotic inhibitors (plant products and hormones miotic inhibitors). Natural products vinblastin sulfate, colchicine & hormones. Ethynyl estradiol, testosterone, progesterone are used in treatment of cancer.
- Cardiovascular drugs affects the heart or blood vessels or circulatory system director or indirectly. Generally those drugs that affect the cardiac system are called cardiovascular drugs. Cardiovascular diseases are hypertension, coronary artery disease in angina.
- Central intervention of cardiovascular output. The aim of drug therapy in CHF is to restore cardiac performance, reduce congestive and low output symptoms and improve survival, reduces peripheral needs, but advised to compensation, it may lower myocardial reserve.
- Synthesis of different cardiovascular drugs e.g. amyl nitrate, diltiazem, verapamil, methyldopa, sorbitrate, quinidine etc. are studied.

3.6.6 Check your progress: the key
- Cancer chemotherapy
- Antineoplastic digents
- Hormones and natural products used in cancer chemotherapy
- Cardiovascular drug
- Synthesis of drugs
UNIT-4
LOCAL ANTIINFECTIVE DRUGS AND PSYCHOACTIVE DRUGS

4.0 Introduction
4.0.1 Objectives

4.1 Synthesis of antiinfective drugs
4.1.1 Antifungal drugs
4.1.2 Antiviral drugs
4.1.3 Antimalarial drugs - Antiamoebic, antiyiadiasis, antiritichomoniasis
4.1.4 Anthelmintics
4.1.5 Antibacterial drugs, General mode of action
4.1.6 Synthesis of Dapsone
4.1.7 p-Amino Salicyclic Acid (PAS)
4.1.8 Ethambutol
4.1.9 Fluconazole

4.2 Econazole
4.2.1 Griseofulvin
4.2.2 Chloroquine
4.2.3 Ethionamide
4.2.4 Isoniazid
4.2.5 Nalidixic acid

4.3 Psychoactive drugs : Introduction
4.3.1 Neurotransmitters
4.3.2 CNS depressants : Barbiturates
4.3.3 Sedatives, hypnotics
4.3.4 Benzodiazepines
4.3.5 General anaesthetics
4.3.6 Antianxiety drugs
4.3.7 Let us sum up
4.3.8 Check your progress : The key

4.0 Introduction
The antiinfective drugs act against the infections by bacteria, fungus, protozoan, virus and helminths etc. Drugs of this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no or minimal effect on the recipient or host.

Local antiinfective drugs can be classified in many ways:

4.0.1 Objectives : 
The aim of this unit is to study the antiinfective drugs i.e. antifungal, antiviral, antimalarial, anthelmintics, antibacterial drugs. Synthesis of Dapsone, p-amino osalicyclic acid, Ethambutal, fluconazole, Econazole, Griseofulvin, Chloroquine, Ethionamide, Isoniazid, Nalidixic acid and their uses.

The knowledge about psychoactive drugs, CNS depressants, Barbituralis, sedatives, hypnotics, Benzodiazepines & General anaesthetics are also studied.

1. Antifungal Drugs
These drugs are used for deep systemic and superficial fungal infections. Fungal infection is due to fungi, which are plant-like, non photosynthetic eukaryotes growing either in colonies of single cell (yeasts) or in filamentous multicellular aggregates (molds). Most of the fungi live as saprophytes in soil or dead plants material and are very important in the mineralization of organic
matters. Some species of fungi produce disease in humans and animals. Mycotic (fungus) illness in human beings are divided into 3 groups:

(a) Contagious skin and hair infections.
(b) Non contagious soilborne or airborne systemic infections.
(c) Non contagious food-borne toxemias.

Classification:
Antifungal drugs are divided in following ways:
(i) Antibiotics:
   (A) Polyenes: e.g., Amphotericin, Nystatin, Hamycin, Natamycin.
   (B) Heterocyclic benzofuran: e.g., Griseofulvin.
(ii) Antimetabolite: e.g., flucytosine
(iii) Azoles:
   (A) Imidazoles: e.g., clotrimazole, econazole, Miconazole (all are topical)
       Ketoconazole (systemic)
   (B) Triazoles: e.g., Fluconazole, Itraconazole (systemic)
(iv) Allylamine: e.g., Terbinafine
(v) Other topical agents: e.g., Benzoic acid, sod. thiosulfate, etc.

2. Antiviral Drugs
Antiviral drugs act against the infection causes due to virus. Viruses are microscopic organisms which can infect all living cells. They are the ultimate expression of parasitism.

Viruses are smallest microorganisms, sized 0.02 to 0.4 micrometer (μm), filtrable through porcelain filters and can be seen with the help of an electron microscope. Basically, viruses consist of a nucleic acid core containing either deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) which constitutes genetic material and provides a basis of classification of viruses.

Classification
(i) Anti-herpes virus: Idoxuridine, Acyclovir, Foscarnet, Famciclovir, Ganciclovir.
(ii) Anti-Retrovirus:
   (a) Nucleoside reverse transcriptase inhibitors: e.g., Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir.
   (b) Nonnucleoside reverse transcriptase inhibitors: e.g., Nevirapine, Efavirenz, Delavirdine.
   (c) Protease inhibitors: e.g., Ritonavir, Indinavir, Nelfinavir, Saquinavir, Amprenavir, Lopinavir.
   (iii) Anti-influenza virus: e.g., Amantadine, Rimantadine.
   (iv) Non selective antiviral drugs: e.g., Ribavirin, Lamivudine, Interferon a.

4.1 Antimalarial Drugs
These are the drugs used for prophylaxis, treatment and prevention of relapses and malaria. Malaria caused by 4 species of the protozoal parasite Plasmodium, is endemic in most parts of India and other tropical countries.

Classification
(i) 4-Aminoquinolines: e.g., Chloroquine, Amodiaquine.
(ii) Quinoline-methanol: e.g., Mefloquine.
(iii) Acriflavine: e.g., Mefloquine.
(iv) Cinchona Alkaloid: e.g., Quinine.
(v) Biguanides: e.g., Proguanil.
(vi) Diaminopyrimidines: e.g., Pyrimethamine. (vii) S-Aminoquinoline: e.g., Primaquine, Bulaquine.
(viii) Sulfonamides and sulfones e.g., Sulfadoxine, dapsone, sulfamethopyrazine.
(ix) Tetracyclines: e.g., Tetracycline, Doxycycline.
(x) Sesquiterpene lactones: e.g., Artesunate, Artemether, Arteether.
(xi) Phenanthrene methanol: e.g., Halofantrine.
(xii) Naphthoquinone: e.g., Atovaquone.

4. Antiamoebic Drugs

These drugs are useful in infection caused by the protozoa Entamoeba histolytica. Amoebiasis has a worldwide distribution.

Classification

(1) Tissue Amoebicides:
   (a) For both intestinal and extraintestinal amoebiasis: Nitroimidazoles: Examples are metronidazole, tinidazole, satranidazole.
   (b) For extraintestinal amoebiasis only: e.g., chloroquine.

(ii) Luminal amoebicides:
   (a) Amide: Diloxanide furoate.
   (b) S-hydroxy quinoline: Quinidochlor, Diiodohydroxyquin.
   (c) Antibiotics: Tetracyclines.

5. Antigiardiasis Drugs

Giardia Lamblia is a flagellate protozoon which mostly lives as a commensal in the intestine. It sometimes invades the mucosa and causes diarrhoea. Many drugs which are useful in amoebiasis are also used in the treatment of giardiasis. The drugs are:

(i) Metronidazole
(ii) Mepacrine
(iii) Quinodochlor
(iv) Furazolidone

6. Antitrichomoniasis Drugs

Trichomonas vagina lis is another flagellate protozoon which causes vulvovaginitis. A large number of effective drugs are used for vaginal application such as:

(i) Drugs used orally: e.g., Metronidazole, Nimorazole.
(ii) Drugs used intravaginally: e.g., Diiodo hydroquin, Quiniodochlor, Clotrimazole, Hamycin, Natamycin, Povidone-iodine.

7. Antileishmaniasis Drugs

Visceral leishmaniasis (kalazar) caused by Leishmania donovani occurs in tropical and subtropical region of the world. Mucocutaneous and dermal leishmaniasis are caused respectively by L. braziliensis and L. tropica. Drugs used in the treatment of leishmaniasis are:

(i) Antimonials: Sodium stibio gluconate, meglumine antimonate.
(ii) Diamidine: Pentamidine.
(iii) Others: Amphotericin B, Ketoconazole, Mitefosine, Allopurinol.

8. Anthelmintics

Anthelmintics are drugs which either kill (vermicide) or expel (vermifuge) infesting helminth. Helminthiasis is found globally, but is more common in developing countries with poorer personal and environmental hygiene. In the human body, gastrointestinal tract is the abode
of many helminths, but some also live in tissues or their larvae migrate into tissues. The drugs which are useful against helminth are:

(i) Mebendazole (For round worm and hook worm, whip worm, thread worm, Guinea worm, Tapeworm, and Hydatid disease).
(ii) Albendazole
(iii) Thiabendazole
(iv) Ivermectin
(v) Pyrantel
(vi) Metronidazole
(vii) Praziquantel

9. Antibacterial Drugs
Antituberculosis drugs: These drugs act against the infections by Mycobacterium tuberculosis causing tuberculosis disease. It is a chronic disease which affects the respiratory tracts, but also may involve the lymphatic, urogenital, nervous system or gastrointestinal tract. The disease is a destructive process which replaces normal tissues with tubercles.

The antituberculosis drugs are divided according to their clinical utility.
(i) First line drugs: These drugs have high antitubercular efficacy as well as low toxicity, are used routinely e.g., Isoniazid, Rifampin, pyrazinamide, ethambutol, streptomycin.
(ii) Second line drugs: These drugs have either low antitubercular efficacy or high toxicity or both, and are used in special circumstances only e.g., Ethionamide, p-amino salicylic acid, capreomycin, kanamycin, thiacetazone, cycloserine, ciprofloxacin, ofloxacin, rifabutin.

10. Antileprotic Drugs
These drugs act against Mycobacterium laprae, causing leprosy disease. These drugs are:
(i) Sulfone: e.g., Dapsone
(ii) Phenazine derivative: e.g., clofazimine
(iii) Antitubercular Drugs: e.g., Ethionamide, Rifampin.
(iv) Other antibiotics: Ofloxacin, minocycline, clarithromycin.

11. Antimicrobial Agents
These are the drugs acting as antibacterial agents which are as follows:
(i) Sulphonamides
(a) Short acting: Sulfadiazine
(b) Intermediate acting: Sulfamethoxazole, sulfamoxole.
(c) Long acting: Sulfadoxine, Sulfamethopyrazine.
(d) Special purpose sulphonamides: e.g., Sulfaacetamide. Sulfasalazine, Mafenide, Silver Sulfadiazine.

General Mode of Action
(1) In Antifungal Drugs
(a) Polyene antibiotics: The polyene contains a macrocyclic ring, which is highly lipophilic in nature and possesses several conjugate double bonds. This ring consists of many OH groups in other side. This side is hydrophilic in nature. A polar amino sugar and a carboxylic acid group are present at one end in ring; which are all insoluble in water and unstable in aqueous medium.

In fungal cell membrane, ergosterol is found. The polyene combine with it and form a 'micropore'. The hydrophilic side forms the interior of the pore, through which ions, amino acids and other water soluble substances move out. The micropore is stabilized by membrane sterols...
which fill up the spaces between the polyene drug molecules on the lipophilic side and constituting the outer surface of pore. Thus cell permeability is increased by several times.

(b) Heterocyclic Benzofuran: These compounds interfere with mitosis. Multinucleated and stunted fungal hyphae result from its action. It also causes abnormal metaphase configuration. It does not cause metaphase arrest, rather the daughter nuclei fail to move apart or move only a short distance. It also disorient the microtubules of fungi.

(c) Imidazoles and Triazoles: These drugs inhibit the fungal cytochrome P 450 enzyme lanosterol 14-demethylase and thus prevent ergosterol synthesis in the fungus.

(2) **Antiviral Drugs**

(a) Anti-herpes virus: Antiherpes drugs get incorporated in DNA so that faulty DNA is formed which breaks down easily. This DNA directs the synthesis of wrong viral proteins and thus viral components collect in the host cells, but infective viruses do not arise.

(b) Anti-retrovirus: These are drugs which act against human immuno deficiency virus (HIV), this is a retrovirus: After phosphorylation in the host cell, these drugs inhibit viral reverse transcriptase (RNA dependent DNA polymerase) in preference to cellular DNA polymerase.

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Single Stranded viral RNA
Virus directed reverse transcriptase
Double stranded viral DNA
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On the template of single stranded RNA genome of HIV a double stranded DNA copy is produced by viral reverse transcriptase. This DNA relocates to the nucleus and is integrated with chromosomal DNA of the host cell, which starts transcribing viral genomic RNA and also mRNA. Under the direction of viral mRNA, structural proteins are formed.

(c) Anti-influenza virus: These drugs unrelated to any nucleic acid precursor, but inhibit, replication of influenza A virus. It appears to act at any early stage (uncoating) and at a late stage (viral aggregation) in viral replication. A protein which is designated ‘M2’ acts as an ion channel, has been reported as its targets of action. Resistance to anti-influenza virus drug develops by mutation causing amino acid substitutions in the M2 protein.

(3) **Antimalarial Drugs**

Antimalarial drugs attack the parasite at its various stages of life cycle in the human host. Antimalarials which act on erythrocytic schizogony are called erythrocytic schizontocides, those which act on preerythrocytic and also exoerythrocytic stages in liver are called tissue schizontocides, whereas those which kill gametocytes in blood are called gametocides.

(4) **Antiamoebiasis Drugs**

The mode of action of these drugs is that they are selectively toxic to anaerobic microorganisms. After entering into the cell by diffusion the drug gets reduced by some redox proteins which operate only in anaerobic microbes and exerts cytotoxicity by damaging DNA and other critical biomolecules.

(5) **Antileishmaniasis Drugs**

(a) Antimonials: These drugs inhibited. SH-dependent enzymes and thus bioenergetics of the parasite is interfered. It has been shown to block glycolytic and fatty acid oxidation pathways.

(b) Diamidine: Diamidine probably interacts with kinetoplast DNA and inhibits topoisomerase II or interferes with aerobic glycolysis.
(6) **Anthelmintics**
These drugs act probably by blocking glucose uptake in the parasite and depletion of its glycogen stores. Intracellular microtubules in the cells of the worm get gradually lost. The drug binds to microtubular protein "3-tubulin" of the susceptible worms with high affinity and inhibits its polymerization.

(7) **Antitubercular Drugs**
(a) Isoniazid: The mode of action of this drug is inhibition of synthesis of mycolic acids which are essential fatty acid component in mycobacterial cell wall. The lipid content which exposed against drug gets reduced. The sensitive mycobacteria concentrate the drug and convert it by a catalase peroxidase enzyme into an active metabolite which appears to interact with the gene.
(b) Ethambutol: This drug inhibits arabinogalactan synthesis and to interfere with mycolic acid incorporation in mycobacterial cell wall.

(8) **Antileprotic Drugs**
Inhibition of para amino benzoic acid (PABA) incorporation into folic acid. Its antibacterial action is antagonized by PABA.

4.1.1 **Synthesis of Antiinfective Drugs**
**Sulphonamides**
SulPhonamide is an antimicrobial drug, which was discovered in 1930. It was established by Domagk in 1935 he suggested that the activity of sulphonamide is due to its metabolic product 4-aminobenzene sulphonamide (sulfanilamide).
The antimicrobial activity of sulphonamides extends to many microbial species having a folic acid pathway which consists of many gram (+) and gram (-) cocci and bacilli, fungi, mycobacteria, some large viruses, and protozoa.
On the basis of their half-life and absorption, the sulphonamides are divided into the following groups:
(a) Sulphonamides of one group remain largely unabsorbed after oral administration, hence are useful for gastrointestinal infections.
(b) Sulphonamides of another group are highly soluble have, quick absorption and rapid excretion (half-life upto 10 hours) mainly in the unchanged form and are generally used for urinary tract infections.
(c) The another group sulphonamides are absorbed quickly but excreted slowly, they require less frequent administration and are useful for chronic infections for prophylaxis.

**Synthesis**: Some important sulphonamides can be prepared in the following
1. Sulphanilamide (para-amino benzene sulphonamide): In 1908 Glemo prepared this compound by the conversion of sodium para acetamidobenzene sulphonate to p-acetyl sulphanilyl chloride, followed by amination at 40-50°C. The yield undergoes hydrolysis and produces sulphanilamide.

**Dapsone**
This compound is used for the treatment of leprosy. Leprosy, caused by Mycobacterium leprae, which has been considered an incurable disease since ages and bears a social stigma. For past centuries, caulmoogra oil has been used as weak antileprotic agent in Indian medicine.
After the demonstration of antibacterial property of sulfones and sulphonamides, congeners were tested and dapsone, the parent sulfone, was found to be active antileprotic agent. None of the sulfones tested is useful in the treatment of common bacterial infections, however,
interest in this group increased when they were shown to be active against tubercle bacillus infections.

Dapsone is 4, 4'-diaminodiphenyl sulfone. It is also known by the name DDS.

Synthesis: It is synthesized from aceto amino benzene parasodium sulfinate. This is reacted with 1-chloro-4-nitro benzene in a mixture of ethylene glycol and ethanol. The 4-nitro-4'-acetyl amino diphenyl sulfone so obtained is then filtered and dried. Now the nitro group of this sulfone is reduced with stannous chloride in HCL to -NH₂ group. Simultaneously deacetylation is also performed.

Another method of preparation of dapsone is from 4-chloronitro benzene with sodium sulphide followed by oxidation and reduction process in the following manner:

**p-Amino Salicylic Acid (PAS)**

p-Amino salicylic acid was introduced in 1946 as antimycobacterium tuberculosis. Tubercle bacilli have been found to effect any order or tissue in the body but the most common is tuberculosis of the lungs. As tubercle bacilli may survive and multiply within mononuclear cells, the antitubercular agent must be able to penetrate the cell membrane.

p-Amino salicylic cid is widely used compound both alone and with antibiotics in the treatment of tuberculosis.
**Synthesis**: p-Amino Salicylic Acid may be synthesized by nitrating the benzene, followed by sulphonation. The sodium salt of yield is fused with caustic soda and treated with potassium carbonate followed by treatment with CO$_2$ (Kolbe reaction) and careful acidification.

In another method, p-amino salicylic acid can be prepared by nitrating the anthranilic acid, followed by diazotisation, and reduction.

**Ethambutol**

Ethambutol is chemically named (+) -2-2- (ethylenediiimino) -di-1-butanol. It is an antitycobacterial agent.

Ethambutol is well absorbed by intestinal tract after oral administration and blood levels reached a peak after 24 hours.

Ethambutol checks the synthesis of protein, DNA and RNA. It has been found that it complexes with divalent cations and inhibits the function of amines, e.g. spermine and spermidine.

**Synthesis**: Ethambutol is synthesized from nitropropane treated with formaldehyde in the presence of sodium hydroxide. Now it is reduced with iron and sulphuric acid followed by reduction.
treatment with calcium hydroxide, forms 2-nitrobutanol. This alcoholic compound when treated with ethylene dichloride yields ethambutol.

\[
\begin{align*}
\text{Nitropropane} & \xrightarrow{\text{HCHO}} \text{CH}_3\text{CH}_2\text{CH} \cdots \text{CH}_2\text{OH} \xrightarrow{\text{(1) Fe/H}_2\text{SO}_4} \text{CH}_3\text{CH}_2\text{CH} \cdots \text{CH}_2\text{OH} & \xrightarrow{\text{(2) Ca(OH)}_2} \text{NO}_2 \\
\text{NO}_2 & + \text{CICH}_2\cdots\text{CH}_2\text{Cl} & \text{2-aminobutanol} \\
\text{NO}_2 & + \text{CH}_3\cdots\text{CH}_2\cdots\text{CH}_2\text{OH} & \text{HCl} \\
\text{CH}_2\text{OH} & | \\
\text{C}_2\text{H}_5 \cdots \text{CH} \cdots \text{NH} \cdots \text{CH}_2 \cdots \text{NH} \cdots \text{CH} & \text{C}_2\text{H}_5 \\
& & \text{Ethambutol}
\end{align*}
\]

**Use**: Ethambutol is commonly given along with other antitubercular drug for the treatment of pulmonary tuberculosis.

**Fluconazole**

Fluconazole is a drug for superficial and deep (systemic) antifungal infections. It is a newer water soluble triazole having a wider range of activity.

Fluconazole is 94% absorbed. Its oral bioavailability is not affected by food or gastric pH. It is primarily excreted unchanged in the urine. Its funginal concentrations are achieved in nails, vagina and saliva.

This triazole (fluconazole) inhibit the fungal cytochrome p 450 enzyme lanosterol 14-demethylase and thus impair ergosterol synthesis. The lower toxicity of triazole has correlated with their lower affinity for mammalian cytochrome p 450 and lesser propensity to inhibit mammalian sterol synthesis.

Fluconazole produces vomiting, nausea, rash, abdominal pain and headache. It does not inhibit steroid synthesis in man.

Fluconazole can be administered orally as well as intravenously in severe infections. It is a longer acting, safer and more efficacious drug.

A single 150 mg oral dose can cure vaginal candidiasis with few relapses. It is the preferred drug for fungal meningitis. In fungal keratitis, an eye drop is useful.
Econazole

Econazole is an antifungal drug. It is active in vitro against dermatophytes, yeasts, and dimorphic fungi. Its clinical use is confined mainly to topical treatment for dermatophytic and superficial candidal infections.

It is poorly absorbed by oral route, its intravenous administration is accompanied by undesirable complications.

General mechanism of action: At lower concentrations the econazole inhibits ergosterol synthesis by suppressing C-14 de methylation of lanosterol. At 0.01 mm this compound suppress cytochrome P 450 of yeast microsomes.

At concentrations above those achievable in patients, the drug can combine with free fatty acids in the membrane to cause cell death.

Several mechanism of action of the imidazoles have been proposed.

Use: It is a most extensively used antifungal drug. It has broad spectrum antifungal activity covering dermatophytes, Candida, other fungi involved in deep mycosis, Nocardia, some gram positive and anaerobic bacteria, e.g. Staph. aureus, Strep. faecalis, Bac. fragilis and Leishmania.

Econazole effectively penetrates superficial layers of the skin and is highly effective in otomycosis, oral thrush, and in vaginitis.

Synthesis In the preparation of econazole, bromination of 2, 4-dichloroacetophenone provides the a-bromoketone, which is the key to the synthesis of a number of conazoles. The corresponding a-imidazo derivative is obtained by displacement of halogen by imidazole, the carbonyl function is then typically reduced to the alcohol with sodium borohydride. Displacement of chlorine from a-4-dichlorotoluene with the alkoxide from alcoholic compound affords the antifungal agent econazole.
Griseofulvin

Griseofulvin is a natural product first obtained from Penicillium griseofulvin in 1939, known as an antibiotic and has been used against plant fungal pathogens since 1951 and also against dermatophytes since 1958. Now this drug is produced commercially by large scale fermentation.

Griseofulvin is used topically, but it is more effective when administered orally. Because of poor absorption, only a small portion of the drug becomes biologically available. The reason of irregular absorption by gastro-intestinal tract is due to its very low water solubility. It can be improved by taking along with fats and by micro fining the drug particles.

Griseofulvin gets deposited in keratin forming the cells of skin, hair and nails.

Use: Griseofulvin is used systemically only for dermatophytosis. It is ineffective topically. Griseofulvin is generally reserved for cases with nail, hair or large body surface involvement. It is effective in athletes foot, but not in pityriasis versicolor.

Synthesis: A concise synthesis of griseofulvin has been developed but one drawback to its practical use is the fact that it produces racemic material while the natural product is chiral.

Methoxyacetylene and crotonaldehyde reacts with a lithium reagent followed by oxidation manganese dioxide gives the Michael double acceptor enone. Preparation of the dihydrobenzofuran fragment begins with acylation of the highly substituted phenol with chloroacetyl chloride in the presence of aluminium chloride. Treatment of the intermediate chloroketone with sodium acetate leads to cyclization. This cyclic product add with enone in presence of potassium tert-butoxide. Thus, the formed product from this reaction is $\pm$ griseofulvin.
**Chloroquine**

This is a drug used for prophylaxis, treatment, and prevention of relapses of malaria. Malaria constitutes one of the most widespread infectious diseases in humans. The causative protozoan of malaria disease is *Plasmodium*, which comprises largely of the species falciparum and vivax. These species undergo a complex life history cycling between mosquitoes and vertebrates as hosts. In spite of the fact that it is one of the earliest recorded human diseases, the role of the *Anopheles* mosquito as the infecting agent was not recognized until 1898. In the early seventeenth century, the first and still widely used drug for treating this disease comes from the adventitious finding of the antimalarial activity of cinchona bark.

Chloroquine was produced in the USA as a less toxic drug. It had already been synthesized and used by Germans in 1934 as 'Resochin'.

Chloroquine is a rapidly acting erythrocytic schizontocide against all species of *Plasmodium*. It controls most of the clinical attacks in 1-2 days with disappearance of parasites from peripheral blood.

Chloroquine is active against *Entamoeba histolytica* and *Giardia lamblia* also. It has anti-inflammatory, local irritant, and local anaesthetic (on injection), antihistamine, antiarrhythmic and weak smooth muscle relaxant properties.

**Synthesis**: Chloroquine can be synthesized by the reaction of enol tautomer of diethyl 2-ketoglutarate with 3-chloroaniline, leads to the imine. Heating imine in a high-boiling solvent leads to displacement of an ethoxyl fragment from the ester with consequent cyclization. Saponification of product leads to an acid. By heating this acid leads to loss of the carboxyl group. The enol group at the 4-position is then converted to the chloride by the reaction with phosphorus oxychloride. Displacement of halogen by the primary amine with 2-amino-S-(di ethyl amino) pentane leads to chloroquine.
Ethionamide

Ethionamide is a tuberculostatic drug of moderate efficacy introduced in 1956. This compound is poor in vitro action. It acts on both extra and intracellular organisms. Ethionamide inhibits peptide synthesis in mycobacteria by blocking the incorporation of amino acids containing sulfur, e.g. cysteine and methionine.

Ethionamide is rapidly absorbed and distributed throughout the body. Peak blood levels are obtained about 3 hours after oral administration. Ethionamide is rapidly excreted in the urine and contains sulfoxide with the major metabolite.

Synthesis: Synthesis of ethionamide begins with the aldol condensation of diethyl oxalate and 2-butanone to give the diketoester. Condensation of this diketoester with cyanoacetamide leads to the pyridone, which is depicted as its unconjugated tautomer. The reaction can be visualized as involving initial conjugate addition of the cyanoacetamide anion to diketoester, followed by the elimination of hydroxide. Now internal imine formation closes the ring. Hydrolysis of the intermediate leads to p-keto acid which loses CO2 under the reaction conditions to afford the pyridone acid. Treatment of pyridone acid with phosphorus oxychloride converts the amide to its amino chloride; the carboxyl group is converted to the acid chloride under reaction conditions. Exposure of the first formed product to ethanol then gives the ester. The ring chlorine is then removed by catalytic hydrogenation and the ester is exchanged to an amide with ammonia. The two-step sequence used originally to convert this function to a thioamide would now be accomplished directly with phosphorus pentasulfide to give ethionamide.
Isoniazid

(pyridine-4-carboxylic acid hydrazide): It is a very simple derivative of pyridine, showed antibacterial activity against tuberculosis in western society. Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited. It acts on extracellular as well as on intracellular TB and equally active in acidic and alkaline medium. It is one of the cheapest antitubercular drugs.

Nalidixic acid

Nalidixic acid was introduced in 1962 as a chemotherapeutic agent. It is highly active against gram-negative organisms specially coliforms, e.g., E. coli, Proteus, Klebsiella, Enterobacter, Shigella but not Pseudomonas. It has shown good activity against urinary tract infections.

Nalidixic acid is used against urinary tract infection. It has also been employed against diarrhoea caused by Proteus, E. coli, Shigella or Salmonella, and has a special place in ampicillin resistant Shigella enteritis.

Synthesis: Nalidixic acid is actually a naphthyridine rather than a quinoline. It can be prepared by addition-elimination of aminopicoline to EMME gives the corresponding enamino ester. Thermal cyclization of this compound leads to the hydroxyquinoline. Reaction of the ambident anion from this compound leads to alkylation via the keto tautomer and thus formation of the N-alkylated derivative. Saponification of the ester than gives nalidixic acid.
Furazolidone
It is a nitrofuran compound which is active against several gram negative bacilli including Salmonella, and Shigella also Giardia and Trichomonas.

Giardia lamblia is flagellate protozoon which mostly lives as a commensal in the intestine. It sometimes invades the mucosa and causes diarrhoea. This drug has also been used in diarrhoea, bacillary dysentery, food poisoning and bacterial enteritis.

Furazolidone is partly absorbed by intestine and excreted in urine.

Norfloxacin
Norfloxacin is active against Gram negative bacteria. It attains lower concentration in tissues. It is metabolized as well as excreted unchanged in urine.

Norfloxacin is primarily used by urinary and genital tract infections. It is also good for bacterial diarrhoeas, because high concentrations are present in gut and anaerobic flora is not disturbed. Norfloxacin is not recommended for respiratory and other systemic infections, particularly where Gram positive cocci are involved.

This drug inhibits the enzyme bacterial DNA gyrase; which nicks double stranded DNA, introduces negative super coils and then reseals the nicked ends. This is important to check excessive positive super coiling of the strands when they separate to permit replication or transcription.

4.3 Psychoactive drugs
The Psychoactive drugs are those agents which have primary effect on psyche (mental processes) and are used for treatment of psychiatric disorders.

On the basis of clinical usefulness, the drugs primarily affecting the mental processes, can be divided into three major categories; neuroleptics (called antipsychotic agents), antidepressants and mood stabilizers, and anxiolytics (also called antianxiety agents).

In 1952, the introduction of chlorpromazine transforms the life of schizophrenic patients. Soon after reserpine was discovered, it was a powerful drug, but its clinical use in psychiatry lasted a few years. Many psychoactive and antidepressant drugs have been introduced now.

(1) Antipsychotic Drugs or Neuroleptics: Antipsychotic drugs are useful in all types of psychosis, particularly schizophrenia.
(2) Antianxiety Drugs: Antianxiety drugs are used for anxiety and phobic states.
(3) Antidepressants: Such types of drugs are used for phobic states, obsessive compulsive behaviour, minor as well as major depressive illness and some anxiety disorders.
(4) Antimanic or Mood stabilizer drugs: These drugs used for mania and to break cyclic effective disorders.
(5) Psychotomimetics: These drugs also known as psychedelic, psychodisleptic and hallucinogens. They are rarely used therapeutically, because majority of these drugs are abused.

Psychoses
These are severe psychiatric illness. They consist of serious distortion of thought, behaviour, capacity to recognise reality and of perception (delusions and hallucinations). Psychoses means following illnesses:

(a) Acute and chronic organic brain syndromes
Prominent features of these syndromes are confusion, disorientation, disorganized behaviour and defective memory.

(b) Functional disorder: They are of two types: (i) Schizophrenia (split mind)
Schizophrenia is splitting of perception and interpretation from reality i.e., hallucinations and inability to think coherently.

(ii) Paranoid states
These are false beliefs (kinds of fixed delusions) and loss of insight resulting into the abnormality.

Neuroses
Neuroses are less serious mental illness. These may be manifested as:

(a) Anxiety: It is an unpleasant emotional state which is associated with uneasiness and concern for the future.

(b) Hysterical: Dramatic symptoms of hysterical patient resemble with the serious physical illness; but are situational and always occur in the presence of others.

(c) Obsessive, compulsive disorder: It is abnormality of thought and behaviours e.g., rituals like, the patient is not able to overcome this type of disorder even on voluntary efforts.

(d) Phobic states: These are the fear of person, situations or some unknown and specific objects.

(e) Reactive depression: It is due to physical illness, loss, blow to self-esteem or bereavement.

4.3.1 Neurotransmitters
Nerves transmit their message across synapses and neuroeffector junctions by the release of chemical messengers, these are known as neurotransmitters.

It was thought that junctional transmission is electrical, but in 1905, Elliot suggested that sympathetic nerves functioned by the release of an adrenaline like chemical.

Today many chemical transmitters are known e.g., dopamine, GABA (y-amino butyric acid), 5-HT, peptides, purines and noradrenaline etc.

The chemical, released by neurotransmission, must possess following properties:

(a) It should be present in the presynaptic neuron.

(b) It should be released in the medium following nerve stimulation.

(c) Its applications should produce responses similar to those produced by nerve stimulation.

(d) Its effects should be antagonized by other chemical which change the effects of nerve stimulation.

Various steps in nerve transmission
The following steps are found in the entire process of nerve transmission -

(1) Impulse conduction
(2) Transmitter Release
(3) Transmitter action on post-junctional membrane
(4) Postjunctional Activity
(5) Termination of Transmitter Action

Cyclic nucleotides, catabolizing enzymes, petptide hormones of the endocrine and neuroendocrine system, prostaglandin specially PGE₁ and PGE₂ are present in central nervous system and can function as either neurotransmitter/neuromodulators/neuroregulators.

(a) Neurotransmitters attach to specialized receptor sites on the surface of the cell.

(b) They influence membrane intracellular biochemical processes from the outside.
A transmitter, once bound with a receptor, transmits its message to the interior of the cells. Various neurotransmitters e.g. dopamine, acetylcholine, norepinephrine etc. as well as hormone such as cortisone and the sex hormones, for which different kind of cells have different receptors. Any given neurotransmitter or hormone increase the level of cyclic AMP in its target cells, but not in other cells. It is believed that the cyclic AMP produced by adenylate cyclase in response to the binding of neurotransmitter to the receptor acts as 'second messenger' to relay the message of the neurotransmitter (the first messenger) from the membrane to the cell interior.

Those drugs which act as 'antagonists' of the dopamine receptor, e.g., phenothiazine, chlorpromazine and butyrophenones such as haloperidol, are useful therapeutic drugs in cure of psychoses and some neurological disorders, which may involve excess dopaminergic function.

4.3.2 CNS Depressants

Sedatives

Hypnotics

Barbiturates

Barbiturates have been popular hypnotics and sedatives of the last century upto 1960s but are not preferred now.

Hypnotic class :

(1) 5, 5-disubstituted barbituric acid.
(2) 5, 5-disubs. thiobarbituric acid.
(3) 1, 5, 5-Trisubsti. barbituric acid.

Mode of action

In sufficient concentrations barbiturate changes the permeability of the cell membrane, thus causes reduction in excitability of the postsynaptic cell.

Barbiturate appears to act on the central synaptic transmission process of the reticular activating system, and hence cerebral cortex becomes deactivated. Barbiturates are antidepolarizing blocking agents because they prevent the generation of excitatory postsynaptic potential.

The cerebral electrical activity of a normal man increases with anxiety, emotional tension or consumption of a central nervous system stimulant such as : caffeine, lysergic acid, diethylamide or amphetamine. The increased cerebral electrical activity is caused by intensified reticular activation of the cortex.

GABA (γ-aminobutyric acid) is present in all portions of the brain and it inhibits all central nervous system neurons by increasing the cell permeability to chloride ions, thus, stabilizing resting membrane potential to remain in a depolarized state.

In sufficient concentrations of barbiturates the GABA-mediated pre and post synaptic inhibition is enhanced. In large concentrations, barbiturates activate GABA receptors and thus changing transmission action; which produces a marked shift in the balance between inhibitory and excitatory synapses.

Synthesis: Condensation reactions are generally used in the preparation of barbiturates. These reactions may take place in acidic, alkaline or neutral media.

4.3.4 Benzodiazepines

Benzodiazepines are CNS depressant drugs and used as day time sedatives, tranquilizers, sleep inducers, anaesthetics, anticonvulsants and muscle relaxants.

If Benzodiazepines are given intravenously, its sedative activity occurs rapidly, i.e., with in range of 15-30 seconds to a few minutes, depending on dose "ize and patient's sensitivity.
Many benzodiazepines are used for the treatment of insomnia; e.g., flurazepam (absorbed most rapidly), triazolam (absorbed little slowly), and temazepam (absorbed slowly). These drugs are given one to two hours before bedtime.

Mode of action: In the CNS, the benzodiazepines interact with a macromolecular membrane complex which also has a recognition site for GABA (y-aminobutyric acid) and a chloride ionophore.

Benzodiazepines have gained popularity over barbiturates as hypnotic and sedative agents because:

(a) Benzodiazepines have a high therapeutic index, i.e., ingestion of even SO doses does not endanger life.
(b) Benzodiazepines do not affect respiration or cardiovascular functions.
(c) Benzodiazepines have no side effect on other body functions. Only on intravenous injection, blood pressure fall is seen with little cardiac contractility.
(d) Benzodiazepines cause less distortion of sleep.
(e) These hypnotics do not change disposition of other drugs by microsomal enzyme induction.
(f) They have lower abuse liability, tolerance is mild, psychological and physical dependence are less marked.

Diazepam: On occasional use, diazepam is free of residual effects. With regular use, accumulation occurs, and prolonged anxiolytic effects may be seen. On discontinuation of chronic use, it is less likely to cause rebound insomnia. The withdrawal phenomena of diazepam are mild.

Oral administration of diazepam is much less effective because tolerance to the anticonvulsant effects of diazepam develops with in a short period of time. Intravenous administration of diazepam enters into the central nervous system with great rapidity, because it is highly soluble in lipids.

Synthesis: Diazepam can be synthesized by acetylation of the aminobenzophenone with chloro acetyl chloride, which give an amide. By heating this amide with ammonia or its latent equivalent, hexamethylenetetramine (HMTA), chlorine is displaced and glycineamide is formed. Its cyclization gives diazepam in the following manner:
4.3.5 General Anaesthetics

In 1846, Morton another dentist and medical student of Boston, gave a demonstration of ether anaesthesia, chloroform became a very popular anaesthetic. In 1929, cyclopropane was discovered and the new generation of anaesthetics was introduced by halothane in 1956. The first intravenous anaesthetic was thiopentone, which was discovered in 1935.

"General anaesthetics are drugs which produce reversible loss of all sensation and consciousness." The important features of general anaesthesia are:

(a) Loss of all sensation, specially pain
(b) Sleep and amnesia,
(c) Immobility and muscle relaxation and
(d) Abolition of reflexes.

These modalities can be obtained by using a combination of drugs, because each drug is specialized for a specific purpose only.

The mechanism of action of general anaesthesia is not clearly known. It is suggested that it depends on physiochemical property of the drugs. In 1901, mayer and overton gave a correlation between lipid/water partition coefficient of the general anaesthesia and their anaesthetic potency.

In 50% individuals, minimal alveolar concentration is the lowest concentration of the anaesthetic.

Minimal alveolar concentration of several general anaesthesia shows a relation with their oil/gas partition coefficient, which only reflects the capacity of anaesthetic to enter into central nervous system and attain sufficient concentration in neuronal membrane.

The GABA<sub>A</sub>, receptor gated Cl<sup>-</sup> channel is the most important of these. Various inhalation anaesthetics such as, barbiturates, benzodiazepines, and propofol potentiate the action of inhibitory transmitter in GABA to open Cl- channels. Each of the above anaesthetic interact with its own specific binding site on the GABAA, receptor-Cl<sup>-</sup> channel complex, but none binds to the GABA binding site as such.

Another inhibitory transmitter is glycine, which also activates Cl<sup>-</sup> channels in the spinal cord and medulla is augmented by barbiturates, propofol and other inhalational anaesthetics. This action may block responsiveness to painful stimuli resulting in immobility of the anaesthetic state.

In 1920, Guedel has described following four stages with ether anaesthesia.
(1) Stage of Analgesia: This stage starts from beginning of anaesthetic inhalation and lasts upto the loss of consciousness. During this stage pain is gradually abolished, patient remains conscious and can hear, see, reflexes and respiration also become normal.

(2) Stage of Delirium: This stage starts from loss of consciousness and up to beginning of regular respiration. During this stage patient may shout, struggle and hold his breath, jaws are tightly closed, breathing may be jerky, vomiting and involuntary micturition or defecation may occur.

(3) Surgical anaesthesia: This stage is divided into following 4 planes:
   Plane 1: This plane ends when eyes become fixed.
   Plane 2: This plane lasts when laryngeal reflexes and corneal become lost.
   Plane 3: In this plane pupils of eyes begin dilating and light reflex is lost.
   Plane 4: In plane 4, intercostal paralysis, shallow abdominal respiration and dilation in pupil occur.
   When anaesthesia moves to deeper planes, then muscle tone decreases, blood pressure falls, respiration decreases in depth, and heart rate increases with weak pulse rate.

(4) Medullary Paralysis: In this stage, cessation of breathing and failure of circulation with death occurs.

4.3.3 Anti-Anxiety Drugs
Types of Anti-Anxiety Drugs
(1) Benzodiazepines
   (a) Diazepam
   (b) Chlordiazepoxide
   (c) Oxazepam
   (d) Lorazepam
   (e) Alprazolam

(2) Azapirones
   (a) Buspirone
   (b) Gepirone
   (c) Ispapirone

(3) Sedative Antihistamine
   (a) Hydroxyzine

(4) β-Blocker
   (a) Propranolol

(1) Benzodiazepines: Without producing global CNS depression, benzodiazepines have a slow and prolonged action and give relief from anxiety at low doses. They suppress the induced aggression. They are much better in quality and quantity than barbiturates. Benzodiazepines have proven more clinically improved in anxiety and stress related symptoms.
   These drugs are relatively safe even in gross overdosage; their withdrawal syndrome is milder, and have little effect on other body systems.

Adverse effects
(1) On regular use of these drugs, some women fail to ovulate.
(2) Sedation, psychomotor, confusional state, light headedness, cognitive impairment, weight gain, change ir. sexual function, and increased appetite are some side effects of these drugs which occur in their use to relieve anxiety. Various types of benzodiazepines are:

(a) Chlordiazepoxide: Chlordiazepoxide is the first benzodiazepine, which was used clinically. This drug is preferred in the treatment of chronic anxiety. For the cure of
psychosomatic diseases, this drug is often used with other drugs. Its oral absorption is slow and produces a smooth long lasting effect. It has poor anticonvulsant action.

\[ \text{Chlordiazepoxide} \]

(b) **Diazepam**: This drug is mainly preferred in acute panic states and anxiety, which is associated with organic disease. It is a rapidly absorbed drug and produces a brief initial phase of strong action.

\[ \text{Diazepam} \]

(c) **Lorazepam**: Lorazepam is recommended for short lived anxiety states, psychosomatic diseases, obsessive compulsive neurosis, and tension syndrome. It is a good sedative. When given intravenously, it produces marked amnesia. Lorazepam is the only benzodiazepine which is recommended for intramuscular use. It has slow absorption, when administered orally. It is less lipid soluble drug. Its rate of entry in brain is slower.

\[ \text{Lorazepam} \]

(d) **Oxazepam**: Oxazepam is a slowly absorbed drug and its rate of entry in brain is also slow. It has been used mainly in short lasting anxiety states. Its hepatic

(2) **Buspirone**

Treatment of Anxiety

Benzodiazepines should be used in the smallest possible dose. The quantity of dose must be found out for each patient by titration. Acute anxiety states generally respond better. The drug should be withdrawn as soon as it is no longer required, but when large quantity of doses have been used for the treatment for longer periods, then they should be withdrawn gradually. Buspirone is a non sedative drug which is an alternative to benzodiazepines. It is given in less severe forms of anxiety.
Mode of Action of Antianxiety Drugs
(1) Benzodiazepines
(2) Buspirone

Antipsychotic Drugs
Antipsychotic drugs are used in the treatment of all types of psychoses, specially in the therapy of schizophrenia, organic psychoses, the manic phase of manic-depressive illness and other acute or chronic idiopathic psychotic illness.

The occasional use of antipsychotic drugs may be indicated in depression or in severe anxiety. In fact this expression is not correct because antipsychotic drugs are used for symptomatic treatment of psychoses without curing the underlying disease states.

"Pharmacologically, the essential effects of these agents are to reduce dopaminergic activity in the central nervous system (CNS)".

Mechanism of Action
Antipsychotic or Neuroleptic drugs classification
1. Phenothiazines
2. Butyrophenones
3. Thioxanthenes
4. Other Heterocyclics
5. Atypical Neuroleptics
6. Miscellaneous

Thiopental Sodium (Pentothal Sodium)
It is one of the most volatile general anaesthetic agents. It can be synthesized by diethyl malonate. This is treated with sodium ethoxide and ethylidide to get monoethyl derivative. Then it is treated with sodium ethoxide and 2-iodopentane, thus diethylisopentyl malonate is formed. In the presence of thiourea, and sodium ethoxide this compound gives thiopental sodium.

Properties: It is a white to yellowish powder. Its solution is unstable, therefore stored in a dry state in the sealed ampule and prepared freshly before use. It is soluble in water. It is administered intravenously.

Ethosuximide: It is a hypnotic sedative drug, and can be prepared by heating of a-ethylsuccinic acid with methyl amine in the following manner:
Glutethimide (C$_{13}$H$_{15}$NO$_2$)

It is 2-ethyl-2-phenylglutarimide. It is a short-acting central nervous system depressants. It is prepared by Michael condensation of phenyl ethyl acetonitrile with acrylonitrile followed by saponification. After closing the ring glutethimide is obtained.

Trimethadione

It is prepared by the reaction of ethylacetae with guanidine. The first step probably involves interchange of the ester to an acylated guanidine derivative. Addition of alkoxide to the imine followed by loss ammonia leads to formation of the iminoazolidone. The amino group then hydrolysis to a carbonyl and the resulting imide is methylated by means of base and methyl iodide to give the oxazolidinedione. Further alkylation of this intermediate leads to a number of anticonvulsants. For example, treatment of the carbanion from oxazolidinedione and sodiumethoxide with methyl iodide gives trimethadione.

Phenytoin

Phenytoin is an anticonvulsant drug. It is prepared by the reaction of hydantoin with benzophenone, resulting phenytoin. This compound is often formulated as its sodium salt.
4.3.7 Let us sum up:

- Man harbours many harmless microbes & also become an unwilling host to harmful pathogenic microbes that result in disease. They may be bacteria, fungi & viruses. Obvious answer is to have drugs which suppress or kill these microbes. They grow multiply quite fast & tend to overwhelm body defence, if pathogenic.

- Sulpha drugs are among the most powerful bacteriostatic drugs and very widely used in medicine. Sulpha drugs is sulphanilamide or aminobenzene sulphonamide which active against cocci infections.

- Antifungal drugs used for superficial and deep fungal infections.

- Heterocyclic benzofuran are Griseofulvin, they have mode of action & side effects described in this unit.

- Psychoactive drugs (Chemotherapy of mind), the drugs which are used for psychiatric disorders are called psychoactive drugs. Treatment of disorders is known as the chemotherapy of mind.

- Barbiturals are substituted derivatives of barbituric acid stereochemical aspects of chiral drugs, neurotransmitters are studied.

4.3.8

- Antiinfective drugs
- Antimalarial drugs
- Antibacterial drugs
- Anthelmintics
- Dapsone
- Psychoactive drugs
- Neurotransmitters
- CNS depressants
- Antianxiety drugs
UNIT-5
ANTIBIOTICS

5.0 Antibiotics: Cell Wall biosynthesis

5.1 Inhibitors
5.1.1 B-lactam rings
5.1.2 Antibiotics inhibiting protein synthesis
5.1.3 Synthesis of Penicillin G,
5.1.4 Penicillin V
5.1.5 Ampicillin
5.1.6 Amoxicillin
5.1.7 Chlorampheric
5.1.8 Cephalosporin
5.1.9 Tetracycline

5.2 Streptomycin

5.3 Let us sum up

5.4 Check your progress: the key

5.5 References

5.0 Cell Wall Biosynthesis:

A cell wall is found in plant cells while it is absent in animal cells. Cell wall is a rigid, and rather porous structure. A corresponding structure is present outside the plasma membrane of animal cells also. This structure making the outer most boundary of the cell, both in animal and plants and is known as extracellular matrix (ECM). Therefore, the cell wall in higher plants actually represents an unique type of extracellular matrix, having both structural and growth regulating functions.

Biosynthesis Of Cell Wall Polysaccharide

Biosynthesis of carbohydrates in green plants and in some other living organisms (e.g. purple bacteria) have been proved synthetically in such manner:

\[ \text{CO}_2 + 2\text{H}_2\text{O}^{18} \xrightarrow{\text{light}} \text{chlorophyll} \xrightarrow{\text{carbohydrate}} \left[ \text{CH}_2\text{O} \right] + \text{O}_2^{18} + \text{H}_2\text{O} \]

By absorbing a quantum of light, the chlorophyll molecule gets excited and splits water molecule into molecular oxygen and active hydrogen. The active hydrogen reduces NADP⁺ to NADPH which will reduce CO₂ in the next step. Simultaneously, during the light reaction the ADP (adenosine diphosphate) and inorganic phosphate (Pi) combines in the chloroplast and form ATP (adenosine triphosphate). it is important to understand that ATP and NADPH are the energetic cofactors and transfer their energy during the reduction of carbon dioxide.

By absorbing a quantum of light, the chlorophyll molecule gets excited and splits water molecule into molecular oxygen and active hydrogen. The active hydrogen reduces NADP⁺ to NADPH which will reduce CO₂ in the next step. Simultaneously, during the light reaction the ADP (adenosine diphosphate) and inorganic phosphate (Pi) combines in the chloroplast and form ATP (adenosine triphosphate). it is important to understand that ATP and NADPH are the energetic cofactors and transfer their energy during the reduction of carbon dioxide.

\[ \text{Ch} \xrightarrow{\text{hv}} \text{Ch}^* \]

\[ \text{4H}_2\text{O} \xrightarrow{\text{Ch}^*} 4\text{H} \downarrow \text{2NADP}^+ \downarrow \text{4OH} \]

\[ 2\text{NADPH} + 2\text{H}^+ \downarrow 2\text{H}_2\text{O} + \text{O}_2 \]

2ADP + 2Pi \xrightarrow{\text{Mg}^{2+}} 2\text{ATP}

So the overall reaction may be defined as:

\[ 2\text{ADP} + 2\text{Pi} + 2\text{NADP}^+ + 2\text{H}_2\text{O} \xrightarrow{\text{light}} 2\text{ATP} + 2\text{NADPH} + 2\text{H}^+ + \text{O}_2 \]
In plants, biosynthesis of polysaccharides are observed on a general pattern in which a molecule of sugar substituted at the anomeric centre by a group X (G1 -OX) acts as a substrate for the enzyme system to form an enzyme complex (G1 -enzyme). This enzyme complex then transfers the sugar unit to a carbohydrate acceptor molecule (G 2 -OH) to form a higher saccharide (G1 -O-G 2 ).

\[
G_1 -OX + \text{Enzyme} \rightarrow HOX \rightarrow G_1 -\text{Enzyme} \rightarrow G_2 -OH \rightarrow G_1 -O-G_2 + \text{Enzyme}
\]

This general pattern can be explained by taking starch as an example of polysaccharide.

**Biosynthesis Of Proteins**

Proteins are polymer, that are produced by the repeated addition of a subunit called monomer, onto one end of growing chain. The condensation step on each case depends on energy from nucleoside triphosphate hydrolysis. The mode of synthesis of protein is outlined below:

\[\text{Protein} \rightarrow \text{Amino acid} \rightarrow \text{Protein} \]

\[-H_2O \quad \text{Energy from nucleoside tri phosphate}\]

**β-Lactam-Rings**

Some antibiotics consist of a β-lactam rings. The two major groups are, penicillins and cephalosporins. Monobactams and carbapenems are the newer addition in this series.

**Penicillins:** Since 1941, penicillin was the first antibiotic to be used clinically. It was originally obtained from a fungus Penicillium notatum, but nowadays it is produced from a high yielding source mutant, Penicillium chrysogenum.

**Chemistry and Properties:** In the penicillin nucleus, a fused thiazolidine and a β-lactam ring is present to which side chains are attached with an amide linkage.

\[\text{Chemical Structure of Penicillin :}
\]

(a) = Thiazolidine ring 
(b) = β-lactam ring 
(c) = Bond which is broken by penicillinase

Penicillin G is the original penicillin used clinically. It consists of a benzyl side chain at position R.

The early commercial penicillin was a yellow, red or brown amorphous powder which was unstable at room temperature and to maintain its potency even for a short time, refrigeration
was required. By an improved purification method, white, crystalline and stable penicillin is manufactured which can remain active without refrigeration.

The sodium and potassium salts of most of the penicillins are water soluble and readily absorbed when given by injection or orally.

**Cephalosporin**

Cephalosporin was discovered by Brotzu. It was produced by a strain of fungus Cephalosporium. The identification of the antibiotics from this microorganism was done by Abraham and Newton.

Cephalosporins have high potency against Gram-positive bacteria and moderate activity against Gram-negative organisms. Cepalothin and cephaloridine are given by injection, because they have limited stability in acid medium and are less absorbed by intestine. Cephaloglycin and cephalexin are administered orally. On continuous use of cephalosporins, resistant bacteria have been found which produce an enzyme hydrolyzing the β-lactam ring.

Cephalosporins are bactericidal. Their mode of action is similar to penicillin, i.e., inhibition of bacterial cell wall synthesis. However, cephalosporins bind different protein molecules than those which bind penicillin. This is due to the difference in spectrum, potency and lack of cross resistance.

**Structures of some cephalosporins**

![Structures of some cephalosporins](image)

**Antibiotic inhibiting protein synthesis**

There are many specific inhibitors which have played a major role in separating the steps in the synthesis of nucleic acids and proteins. Some of these protein-synthesis inhibitors are synthetic compounds and others were first isolated from the fermented culture filtrates of various organisms as antibiotics. These antibiotics control the infectious diseases or to inhibit the growth of malignant tissues.

In cellular physiology, protein synthesis plays an important role. Protein is a primary target of a number of naturally occurring antibiotics. Most of these antibiotics inhibit protein synthesis in bacteria, i.e., prokaryotes and are harmless to eukaryotes.

Some known inhibitors of protein synthesis are given below:

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Organisms</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>Prokaryotic cells</td>
<td>Inhibits movement of initiation complex causes misreading of mRNA.</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Prokaryotic cells</td>
<td>Blocks recognition site and inhibits binding of aminoacyl t-RNA.</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Prokaryotic cells</td>
<td>Inhibits peptidyl transferase activity on 70 S ribosomes.</td>
</tr>
<tr>
<td>Drug</td>
<td>Organism</td>
<td>Effect</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cycloheximide</td>
<td>Eukaryotic cells</td>
<td>Inhibits peptidyl transferase activity on 80S ribosomes.</td>
</tr>
<tr>
<td>Erthyromycin</td>
<td>Prokaryotic cells</td>
<td>Inhibits translocation reaction on ribosomes.</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Prokaryotic cells</td>
<td>Blocks the release of EF-G and GDP during elongation cycle.</td>
</tr>
<tr>
<td>Puromycin</td>
<td>Prokaryotic cells</td>
<td>Causes premature chain termination by acting as analogue of aminoacyl-tRNA.</td>
</tr>
<tr>
<td>Puromycin</td>
<td>Eukaryotic cells</td>
<td></td>
</tr>
<tr>
<td>Rifapmycin</td>
<td>Prokaryotes</td>
<td>Blocks initiation of RNA chains by binding to RNA polymerase.</td>
</tr>
<tr>
<td>Streptoligandin</td>
<td>Prokaryotes</td>
<td>Inhibits elongation of peptide chains.</td>
</tr>
<tr>
<td>Antinomycin D</td>
<td>Prokaryotic cells</td>
<td>Binds DNA and blocks RNA polymerase movement.</td>
</tr>
<tr>
<td>Antinomycin D</td>
<td>Eukaryotic cells</td>
<td></td>
</tr>
<tr>
<td>Anisomycin</td>
<td>Eukaryotes</td>
<td>Blocks peptidyl transferase reaction on ribosomes.</td>
</tr>
<tr>
<td>β-amanitin</td>
<td>Eukaryotes</td>
<td>Blocks m-RNA synthesis</td>
</tr>
</tbody>
</table>

**Streptomycin**

Streptomycin discovered by S. Wakes-man in (1944). It is a highly basic trisaccharide, which is known as amino glycoside. It inhibits prokaryotic ribosomes in various manners. At higher concentrations, it interferes with the binding of f-Met-tRNA to ribosomes and thus prevents the initiation of protein synthesis.

At low concentrations, streptomycin leads to a misreading of the genetic code on the m-RNA and inhibits the initiation of polypeptide chain.

![Streptomycin](image)

**Tetracycline**

Tetracycline and its derivatives are broad-spectrum antibiotics, which inhibit protein synthesis by blocking A site on the ribosome thus the binding of aminoacyl t-RNA is inhibited. The nascent polypeptide chain remain at site P which can react with another antibiotic inhibitor, puromycin.

![Tetracycline](image)
**Chloramphenicol**

Chloromycetin: Chloramphenicol is the first 'broad-spectrum' antibiotic. It inhibits peptidyl transferase activity on the large subunit of prokaryotic ribosomes. Chloramphenicol is a classic inhibitor of protein synthesis in bacteria. It acts at low concentrations on bacterial interactions of ribosomes with A site-bound aminoacyl t-RNAs, but does not affect on cytoplasmic protein synthesis in eukaryotic cells.

The clinical uses of chloramphenicol are limited, i.e., up to only severe infections, because it possesses toxic side effects.

![Chloramphenicol](image)

**Cycloheximide**

Actidione: Cyloheximide is a strong fungicide antibiotic. It blocks the peptidyl transferase of 80 S eukaryotic ribosomes but not that of 70 S bacterial ribosomes. Cycloheximide affects only ribosomes in cytosol.

![Cycloheximide](image)

**Synthesis of Penicillin G**

Penicillin is a generic term which refers to a class of compounds of the molecular formula C\(_9\)H\(_{11}\)N\(_2\)O\(_{4}\)SR, produced by various strains of Penicillium notatum, Penicillium chrysogenum and some other fermented moulds.

Penicillin G or benzyl penicillin is the most important commercial penicillin. It is a narrow spectrum antibiotic and its activity is limited primarily to Gram-positive bacteria and few others.

Penicillin G is one of the most nontoxic antibiotics, upto 100 Mu (60 g) has been injected in a day without any direct toxicity. It is acid labile and destroyed by gastric acid.

Synthesis: By D. vigneaud et. al. (1946)

Penicillin-G is obtained in small quantities by condensing D-penicillamine (I) with 2-benzyl-4-methoxymethylene oxazolone (II), in pyridine at 70°C. The benzyl penicillin was isolated as the crystalline triethyl amine salt. The starting material (II) was prepared by methyl phenaceturate in the following way:
**Synthesis of Penicillin-V**

Penicillin-V is acid stable antibiotic. Its antibacterial spectrum is identical to penicillin-G; but it is about 1/5 as active against Nisseria, other Gram negative bacteria and anaerobes. It cannot be depended upon for more serious infections and is used only for sinusitis, otitis media, prophylaxis of rheumatic fever, trench mouth, less serious pneumococcal infections, and streptococcal pharyngitis.

The chemical name of penicillin-V is phenoxy methyl penicillin.

**Synthesis of Ampicillin**

Ampicillin is a semisynthetic penicillin. It is active against all organisms sensitive to penicillin G, and in addition of many Gram-negative bacilli, e.g., H. influenzae, E-coli, Proteus, Salmonella and Shigella are inhibited. Due to wide spread use, many of these antibiotics have developed resistance, therefore, usefulness of the ampicillin has decreased.

Ampicillin has an amino group in its side chain.

Ampicillin is not degraded by gastric acid. Its oral absorption is incomplete. Food interferes with absorption of ampicillin.

**Use:** Ampicillin has been used for most acute infections of urinary tract. Respiratory tract infections including bronchitis, Otitis media, sinusitis etc. are generally treated with ampicillin. It is also a first line drug for meningitis and gonorrhoea. With combination of other antibiotics, it is used for the treatment of septicaemias, and mixed infections.
**Adverse effects**: Diarrhoea is frequent adverse effect after oral administration of ampicillin. It produces a high incidence of rashes, particularly, in AIDS, lymphatic leukemia and EB virus infections. Sometimes rashes may be of toxic nature.

**Synthesis**: It is prepared with the acylation of 6-aminopenicillanic acid (6-APA) with acid chloride from D-2-azidophenylacetic acid followed by a catalytic reduction.

**Synthesis of Amoxycillin**

Amoxycillin is semisynthetic penicillin has an amino and hydroxy substitution in side chain. It is active against all organisms sensitive to penicillin G, in addition of many gram negative bacilli. It is a close congener of ampicillin, similar to it in all respects except: in amoxycillin, oral absorption is better and food does not interfere in absorption. Incidence of diarrhoea by this drug is less. Amoxycillin is less active against H. irifluenzae, Shigella. Many physicians prefer it over ampicillin for urinary infections, typhoid, gonorrhoea, bronchitis and subacute bacterial endocarditis.

**Synthesis**: 
Synthesis Of Chloramphenicol

Chloramphenicol was initially synthesized from streptomyces Venezuelae in 1947. It was soon synthesized chemically. The commercial product available now is all synthetic.

Chloramphenicol consists of a nitrobenzene substitution, which is probably responsible for its antibacterial activity and its intensely bitter taste. Chloramphenicol is yellowish white crystalline solid antibiotic. Its aqueous solution is quite stable, stands on boiling but it needs protection from light.

Chloramphenicol is broad spectrum antibiotic, i.e., active against Gram-positive and Gram-negative bacteria, Rickettsiae, Mycoplasma and Chlamydia. It is inactive against Pseudomonas, many Proteus, viruses and fungi. It is highly active against Salmonella including S.typhi. Chloramphenicol is less active against Gram-positive cocci, spirochetes and certain enterobacteriaceae. It is inactive on Entamoeba and Plasmodia.

Chloramphenicol is rapidly and completely absorbed after oral administration. 

Adverse effects: Chloramphenicol causes bone marrow depression, rashes, fever, angioedema, atrophic glossitis, nausea, vomiting, diarrhoea, pain, and aplastic anaemia.

Use: It is a drug of choice for typhoid fever. It is also used in intraocular infections, H. influenzae meningitis, anaerobic infections caused by Bact. fagilis and others. It is highly effective topically e.g., in external ear infections. It has been extensively used in urinary tract infections.

Synthesis: Chloramphenicol is synthesized by nitro-propanediol. This is reduced catalytically to the mixture of aminodiols. The threo isomer is then separated by crystallization and resolved as a diastereomeric salt to give the D (-) isomer. On acylation with dichloroacetyl chloride it initially gives the triacetate. Its saponification gives a new product. The free hydroxyl groups are then converted to the acetates by means of acetic anhydride and the resulting product is then nitrated with nitric-sulfuric acid mixture. Its saponification removes the acetate protecting groups and affords chloramphenicol.
Tetracyclines

Tetracyclines are obtained from soil actinomycetes. The first tetracycline to be introduced was chlortetracycline in 1947, it was obtained from S. aureofaciens under the name aureomycin. Tetracyclines being active orally and affecting a broad range of microorganisms, hence are called 'broad spectrum antibiotics'. Oxytetracycline (Terramycin) was produced 2 years later in 1949, from a mutant strain, Streptomyces rimosus.

Tetracyclines are a class of antibiotics having a nucleus containing four cyclic rings.

Tetracycline: \( R_1 = H, R_2 = OH, R_3 = CH_3, R_4 = H \)
Chlortetracycline: \( R_1 = H, R_2 = OH, R_3 = CH_3, R_4 = Cl \)
Oxytetracycline: \( R_1 \) and \( R_2 = OH, R_1 = CH_3, R_4 = H \)

All tetracyclines are solid, bitter in taste and weak water soluble antibiotics. Their aqueous solutions are unstable. All have almost same antimicrobial activity. On the basis of chronological order of development, tetracyclines are divided into 3 following groups

<table>
<thead>
<tr>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracycline</td>
<td>Demeclocycline</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Chlortetracycline</td>
<td>Methacycline</td>
<td>Minocycline</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>Lymecycline</td>
<td></td>
</tr>
</tbody>
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Mechanisms of action: Primarily, tetracyclines are bacteriostatic, and inhibit protein synthesis by binding to 30 S ribosomes in infected organisms. Due to such binding, attachment of
amino acyl-t-RNA to the moRNA-ribosome complex is interfered. As a result, the peptide chain fails to grow.

**Antimicrobial spectrum**: Tetracycline inhibit practically all types of pathogenic microorganisms except fungi and viruses, hence the name 'broad spectrum antibiotic'.

**Administration**: Most commonly tetracyclines are administered in the oral dosage form. The capsule should be taken 112 hour before or 2 hours after food. Tetracyclines are not recommended by intra muscular route because it is painful and absorption from the injection site is poor. In severe cases, slow intravenous injection may be given, but nowadays it is rarely required.

**Adverse effects**: Sometimes liver damage, kidney damage, phototoxicity, diabetes insipidus, teeth and bone chelation by calcium, and antianabolic effects are seen as dose related toxicity.

**Streptomycin**

It is a member of aminoglycoside antibiotics, obtained naturally and semisynthetically, having polybasic amino groups linked glycosidically to two or more amino sugars (streptidine, 2-deoxy streptamine, garosamine) residues.

Streptomycin was first discovered in 1944 by Waksman et. al. from Streptomyces giseus. Unlike penicillin (which was a chance discovery) streptomycin was a product of deliberate search for drugs effective against Gram-negative bacteria. Neomycin was next drug (1949) to be isolated, but could not be used systemically.

All aminoglycosides are produced from soil actinomycetes and have many common properties.

Streptomycin assumed great importance because this antibiotic is active against tubercle bacilli, but now practically restricted to treatment of tuberculosis.

**Mechanism of action**: The mode of action of this antibiotic is in 2 steps:
(a) Transport of the streptomycin through the bacterial cell wall and cytoplasmic membrane.
(b) Binding to ribosomes resulting in inhibition of protein synthesis.

**Pharmacokinetics**: Streptomycin is highly ionized in nature. It is neither absorbed nor destroyed in the gastrointestinal tract. Its absorption from intramuscular injection is rapid.

**Adverse effects**: By streptomycin, rashes, eosinophilia, fever, exfoliative dermatitis, anphylaxis, scotoma, paresthesias, pain at injection site, auditory disturbances are found as adverse effects.

**Use**: It is used in tuberculosis, urinary tract infections, peritonitis, septicaemia, subacute endocarditis, tularemia and plague.

**Structure**

[Chemical structure of streptomycin]
5.3 Let us sum up

- Antibiotics are defined as chemical substances produced by various species of micro-organisms (fungi, actinomycetes, bacteria, yeast and moulds) that suppress the growth of other organisms and may destroy them. These agents are either bacteriostatic or bactericidal. Antibiotics are agents developed from various microorganisms therefore they may develop bacterial resistance or patients may be hypersensitive to these drugs.

- Classification:
  - Narrow spectrum antibiotics: are penicillin, streptomycin, Erythromycin.
  - Broad spectrum antibiotics: are chloramphenical, tetracyclines, cephalosporins.
  - According to mode of action they classified as bacterial cell wall synthesis inhibitors: Penicillin, cephalosporins, Bacitracin, ioniazid.
  - Protein synthesis inhibitors: Tetracycline, chloramphenicol, aminoglycosides.
  - Bacterial cell membrane inhibitors:
  - Different synthesis of antibiotics are given in this unit.
  - Cell wall is a peptidolycan structure.
  - Antifungal drugs are Griseofulvin, Dapsone, Imidazole (Miconazole, Econazole, Ketoconazole).

5.4 Check you progress: the key

- Antibiotics
  - Penicillin, Streptomycin
  - Chloramphenical, Tetracyclines, Cephalosporins
  - Griseofulvin
  - Dapsone
  - Econazole
  - Ketoconazole