PHARMACOLOGY

(Subject Code: 18UZOEC51)

Semester: V **ECC: 5** **Credits: 2**

Course coordinator: Dr. S. Mabel Parimala

Objective: To provide necessary information on the properties, dose, effects, metabolism and benefits of drugs.

Course Outcomes: At the end of the course the students will be able to

1. gain knowledge on the therapeutic uses of the commonly available drugs for various ailments.
2. know the impact of drugs on nervous system
3. know the impact of drugs on organs
4. understand hormones and hormone antagonists
5. understand chemotherapy

Unit I: General Pharmacology

Definition, categories of drugs, routes of drug administration; absorption, distribution and excretion of drugs; factors modifying drug effects.

Unit II: Drugs acting on nervous system

Hypnotics and sedatives, anti-convulsants, analgesic-antipyretics, antidepressants, local anaesthetics, cholinergic and adrenergic drugs and their side effects.

Unit III: Drugs acting on organs

Gastrointestinal - appetizers, emetics, antiulcer drugs; Respiratory organ -bronchial asthma, expectorants, antitussives; Heart -anti-arrhythmic, anti-hypertensive agents; and their side effects.

Unit IV: Hormones and hormone antagonists

Adrenocortical steroids, androgen and anabolic steroids, estrogens and progestins, thyroid and antithyroid drugs, oral antidiabetic drugs and their side effects.

Unit V: Chemotherapy

Synthetic antimicrobial agents; Common Antibiotics-penicillins, cephalosporins, tetracyclins; Chemotherapy of urinary tract infections, malaria, typhoid, tuberculosis, amoebiasis; Diabetics and hypoglycaemic drugs, Disinfectants and antiseptics.

Text Books:

1. Murugesh N., 2004. A Concise Textbook of Pharmacology. Sathya Publishers.
2. Tripathi K..., 2000. Essentials of Medical Pharmacology. Jaypee Brothers.

Reference Books:

1. Panda, U.N., 2005. Handbook of Pharmacology. AITBS Publishers.
2. Uma, Bhandari, 2012. A Textbook of Pharmacology. Biotech Pharma Publications.
3. Das, 2001. Pharmacology. Books and Allied Pvt. Ltd.
4. Chunawalla, S.A., 1998. Essentials of Pharmacology. Himalaya Publishing House.
5. Budhiraja, R.D., 1993. Elementary Pharmacology and Toxicology. Popular Prakashan.

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UNIT I: GENERAL PHARMACOLOGY

Definitions

Pharmacology: Pharmacology is a science that deals with drugs. It includes a detailed study of the history, properties, physiological effects, mechanism of action, absorption, distribution, metabolism, excretion and uses of a drug.

Drug: A drug is defined as any substance which is used to cure, diagnose or prevent a disease.

Main divisions of pharmacology: The subject matter of pharmacology includes the following main divisions:

1. Materia medica which deals with sources, description and preparation of drugs. It is an old branch of pharmacology.
2. Pharmacodynamics which deals with biochemical and physiological effects of drugs and also their mechanism of action.
3. Pharmacokinetics which deals with the absorption, distribution, metabolism and excretion of drugs.
4. Therapeutics which is concerned with the use of a drug for curing diseases and relieving their symptoms.
5. Clinical pharmacology which is the scientific study of drugs in man. The efficacy and safety of a drug is studied in patients and healthy volunteers.
6. Chemotherapy which deals with the effects of drugs on micro-organisms and parasites which occur in a living organism. It also includes the treatment of cancer.
7. Toxicology which deals with poisonous effects of drugs, detection of poisoning and its treatment.

Drug standards: The governments of most of the countries have established legal standards for all important drugs. These standards are published in Pharmacopoeia which is an official code containing a list of established drugs along with their standards. The following are some well known Pharmacopoeias:

1. The Indian Pharmacopoeia (I.P)
2. The British Pharmacopoeia (B.P)
3. The United States Pharmacopoeia (U.S.P)

Categories of drugs

Drugs used in the treatment of human diseases can be categorized as follows:

- Drugs acting on the central nervous system
- Local anaesthetics
- Drugs acting on autonomic nervous system

- Drugs acting on eye
- Drugs acting on respiratory system
- Autacoids
- Cardiovascular drugs
- Drugs acting on blood and blood forming organs
- Drugs acting on kidney
- Hormones and hormone antagonists
- Drugs acting on the gastrointestinal tract
- Drugs acting on the uterus
- Antimicrobial agents
- Chemotherapy of caner

Administration and Kinetics of Drugs

Drug administration is the giving of a drug by one of several means (routes). Drug kinetics (pharmacokinetics) describes how the body handles a drug and accounts for the processes of absorption, distribution, metabolism, and elimination.

Drug treatment requires getting a drug to its specific target site or sites in tissues where the drug performs its action. Typically, the drug is introduced into the body (the process of administration), sometimes far from this target site. The drug must move into the bloodstream (the process of absorption) and be transported to the target sites where the drug is needed (the process of distribution). Some drugs are chemically altered (the process of metabolism) by the body before they perform their action, others are metabolized afterward, and still others are not metabolized at all. The final step is the removal of the drug and its metabolites from the body (the process of elimination). Many factors, including a person's weight, genetic makeup, and kidney or liver function, can influence these kinetic processes. Changes due to aging also affect how the body processes drugs.

Routes of drug administration

A route of administration in pharmacology and toxicology is the path by which a drug, fluid, poison, or other substance is taken into the body. Route of administration is an important factor which influences the absorption of a drug. The interval between administration and onset of action is determined by the route of administration. Biological lag is the interval between administration of a drug and development of response.

Drugs are introduced into the body by several routes. They may be:

- Taken by mouth (orally)
- Given by injection into a vein (intravenously, IV), into a muscle (intramuscularly, IM), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously, sc)

- Placed under the tongue (sublingually) or between the gums and cheek (buccally)
- Inserted in the rectum (rectally) or vagina (vaginally)
- Placed in the eye (by the ocular route) or the ear (by the otic route)
- Sprayed into the nose and absorbed through the nasal membranes (nasally)
- Breathed into the lungs, usually through the mouth (by inhalation) or mouth and nose (by nebulization)
- Applied to the skin (cutaneously) for a local (topical) or bodywide (systemic) effect
- Delivered through the skin by a patch (transdermally) for a systemic effect

Each route has specific purposes, advantages, and disadvantages.

Oral route

Many drugs can be administered orally as liquids, capsules, tablets, or chewable tablets. Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. However, most drugs are usually absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before being transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount of drug reaching the bloodstream. Consequently, these drugs are often given in smaller doses when injected intravenously to produce the same effect.

When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract. For example, aspirin and most other nonsteroidal anti-inflammatory drugs (NSAIDs) can harm the lining of the stomach and small intestine to potentially cause or aggravate preexisting ulcers. Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Other routes of administration are required when the oral route cannot be used, for example:

- When a person cannot take anything by mouth
- When a drug must be administered rapidly or in a precise or very high dose
- When a drug is poorly or erratically absorbed from the digestive tract

Injection routes

Administration by injection (parenteral administration) includes the following routes:

- Subcutaneous (under the skin)
- Intramuscular (in a muscle)

- Intravenous (in a vein)
- Intrathecal (around the spinal cord)

A drug product can be prepared or manufactured in ways that prolong drug absorption from the injection site for hours, days, or longer. Such products do not need to be administered as often as drug products with more rapid absorption.

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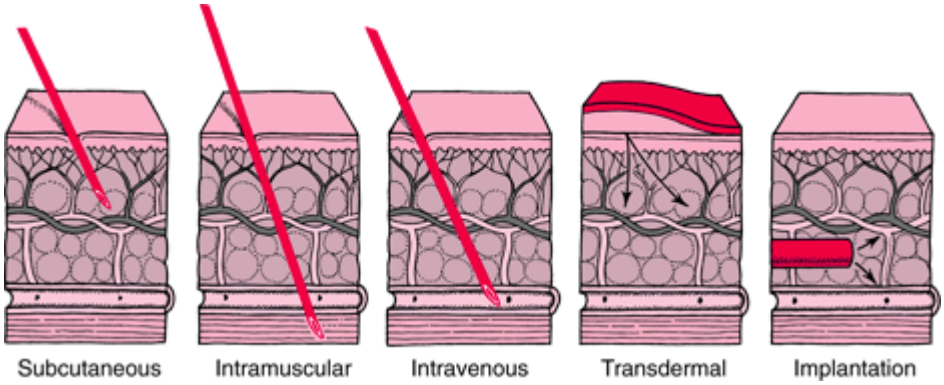
Through the Skin

Sometimes a drug is given through the skin—by needle (subcutaneous, intramuscular, or intravenous route), by patch (transdermal route), or by implantation



For the **subcutaneous route,** a needle is inserted into fatty tissue just beneath the skin. After a drug is injected, it then moves into small blood vessels (capillaries) and is carried away by the bloodstream. Alternatively, a drug reaches the bloodstream through the lymphatic vessels (see Figure: Lymphatic System: Helping Defend Against Infection). Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be destroyed in the digestive tract if they were taken orally. Certain drugs (such as progestins used for hormonal birth control) may be given by inserting plastic capsules under the skin (implantation). Although this route of administration is rarely used, its main advantage is to provide a long-term therapeutic effect (for example, etonogestrel that is implanted for contraception may last up to 3 years).

The **intramuscular route** is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into the muscle of the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer it takes for the drug to be absorbed.

For the **intravenous route,** a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the

solution is moved by gravity (from a collapsible plastic bag) or, more commonly, by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. It is also used for irritating solutions, which would cause pain and damage tissues if given by subcutaneous or intramuscular injection. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection because inserting a needle or catheter into a vein may be difficult, especially if the person is obese. When given intravenously, a drug is delivered immediately to the bloodstream and tends to take effect more quickly than when given by any other route. Consequently, health care practitioners closely monitor people who receive an intravenous injection for signs that the drug is working or is causing undesired side effects. Also, the effect of a drug given by this route tends to last for a shorter time. Therefore, some drugs must be given by continuous infusion to keep their effect constant.

For the **intrathecal route,** a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)—for example, to treat infections of these structures. Anesthetics and analgesics (such as morphine) are sometimes given this way.

Sublingual and buccal routes

A few drugs are placed under the tongue (taken sublingually) or between the gums and teeth (bucally) so that they can dissolve and be absorbed directly into the small blood vessels that lie beneath the tongue. These drugs are not swallowed. The sublingual route is especially good for nitroglycerin, which is used to relieve angina, because absorption is rapid and the drug immediately enters the bloodstream without first passing through the intestinal wall and liver. However, most drugs cannot be taken this way because they may be absorbed incompletely or erratically.

Rectal route

Many drugs that are administered orally can also be administered rectally as a suppository. In this form, a drug is mixed with a waxy substance that dissolves or liquefies after it is inserted into the rectum. Because the rectum's wall is thin and its blood supply rich, the drug is readily absorbed. A suppository is prescribed for people who cannot take a drug orally because they have nausea, cannot swallow, or have restrictions on eating, as is required before and after many surgical operations. Drugs that can be administered rectally include acetaminophen (for fever), diazepam (for seizures), and laxatives (for constipation). Drugs that are irritating in suppository form may have to be given by injection.

Vaginal route

Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, suppository, or ring. The drug is slowly absorbed through the vaginal wall. This route is often

used to give estrogen to women during menopause to relieve vaginal symptoms such as dryness, soreness, and redness.

Ocular route

Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer, but they may blur vision. Solid inserts, which release the drug continuously and slowly, are also available, but they may be hard to put in and keep in place.
Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other drugs (for example, those used to treat glaucoma [see Table: Drugs Used to Treat Glaucoma], such as acetazolamide and betaxolol, and those used to dilate pupils, such as phenylephrine and tropicamide) produce a local effect (acting directly on the eyes) after they are absorbed through the cornea and conjunctiva. Some of these drugs then enter the bloodstream and may cause unwanted side effects on other parts of the body.

Otic route

Drugs used to treat ear inflammation and infection can be applied directly to the affected ears. Ear drops containing solutions or suspensions are typically applied only to the outer ear canal. Before applying ear drops, people should thoroughly clean the ear with a moist cloth and dry it. Unless the drugs are used for a long time or used too much, little of the drugs enter the bloodstream, so bodywide side effects are absent or minimal. Drugs that can be given by the otic route include hydrocortisone (to relieve inflammation), ciprofloxacin (to treat infection), and benzocaine (to numb the ear).

Nasal route

If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs administered by this route generally work quickly. Some of them irritate the nasal passages. Drugs that can be administered by the nasal route include nicotine (for smoking cessation), calcitonin (for osteoporosis), sumatriptan (for migraine headaches), and corticosteroids (for allergies).

Inhalation route

Drugs administered by inhalation through the mouth must be atomized into smaller droplets than those administered by the nasal route, so that the drugs can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets. Smaller droplets go deeper, which increases the amount of drug absorbed. Inside the lungs, they are absorbed into the bloodstream. Relatively few drugs are administered this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. In addition, specialized equipment may be needed to give the drug by this route. Usually, this method is used to administer drugs

that act specifically on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers (called inhalers), and to administer gases used for general anesthesia.

Nebulization route

Similar to the inhalation route, drugs given by nebulization must be aerosolized into small particles to reach the lungs. Nebulization requires the use of special devices, most commonly ultrasonic or jet nebulizer systems. Using the devices properly helps maximize the amount of drug delivered to the lungs. Drugs that are nebulized include tobramycin (for cystic fibrosis), pentamidine (for pneumonia caused by *Pneumocystis jirovecii*), and albuterol (for asthma attacks). Side effects can include those that occur when the drug is deposited directly in the lungs (such as cough, wheezing, shortness of breath, and lung irritation), spread of the drug into the environment (possibly affecting people other than the one taking the drug), and contamination of the device used for nebulization (particularly when the device is reused and inadequately cleaned). Using the device properly helps prevent side effects.

Cutaneous route

Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, such as psoriasis, eczema, skin infections (viral, bacterial, and fungal), itching, and dry skin. The drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an ointment, cream, lotion, solution, powder, or gel.

Transdermal route

Some drugs are delivered body-wide through a patch on the skin. These drugs are sometimes mixed with a chemical (such as alcohol) that enhances penetration through the skin into the bloodstream without any injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people. In addition, patches are limited by how quickly the drug can penetrate the skin. Only drugs to be given in relatively small daily doses can be given through patches. Examples of such drugs include nitroglycerin (for chest pain), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), and fentanyl (for pain relief).

Absorption of drugs

A drug can enter into circulation and reach the site of action only after absorption. The absorption of a drug involves its passage across cell membrane. As a rule, lipid insoluble and water insoluble drugs are not absorbed from the gut.

Passage of drugs across cell membrane: Drugs can pass through cell membrane by two processes. They are:

a. Passive transfer – simple diffusion, filtration
b. Specialised transport – active transport, facilitated diffusion, pinocytosis

1. Simple diffusion: It is a bidirectional process. Polar water-soluble and non polar lipid-soluble substances can be transported by this process.
2. Filtration: Only water soluble substances can be transported by this process. It involves passage through pores present in the cell membrane.
3. Active transport: It is a selective process which requires energy. Also it requires a carrier and so is called as carrier transport.
4. Facilitated diffusion: It is very similar to carrier transport, but it does not require energy.
5. Pinocytosis: Proteins and macromolecules are transported by this process. It is similar to phagocytosis where cells engulf fluids or macromolecules from the surroundings.

Factors modifying drug absorption: The absorption of a drug can be influenced by the following factors:

1. Physical state: Drugs in the form of liquids are well absorbed than solids. Gases are quickly absorbed through lungs.
2. Particle size: Smaller the particle size, better is the absorption of a drug. If the particle size is large, the drug is slowly absorbed and hence the action is delayed.
3. Solubility: An easily soluble drug is quickly absorbed. Also drugs in the form of solutions are quickly absorbed than solids.
4. Concentration: Concentrated forms of drugs are quickly absorbed than dilute solutions.
5. Area of absorbing surface: greater the area of absorbing surface, quicker is the absorption of a drug. For example, lungs and peritoneal cavity are large surface areas from where drugs can be quickly absorbed.
6. Circulation to site of absorption: Increased blood flow to the area of absorption can increase the absorption of a drug. This can be achieved by massage or local application of heat. Vasoconstrictors decrease blood flow and so decrease the absorption of a drug.
7. Route of administration: This is a very important factor which determines drug absorption. Some drugs are absorbed only on parenteral administration and they fail to get absorbed on oral administration. So it is necessary to carefully choose the route of administration of a drug.

Bioavailability: It is defined as the quantity of the drug that is absorbed and reaches systemic circulation after non-vascular administration. The bioavailability is 100% after intravenous injection. But it is less after oral administration. Bioavailability is affected by physical properties, dosage form and physiological factors.

Distribution of drugs

After a drug is absorbed, it is distributed to various body tissues and fluids. Drugs which easily pass through cell membrane achieve wide distribution. Drugs which do not pass through cell membrane are limited in their distribution.

Entry into central nervous system: Entry of drugs into central nervous system is limited by blood-brain barrier. It is a hypothetical barrier which exists between plasma and extracellular surface of brain. This barrier is constituted by glial cells and capillary endothelium in the brain. Only lipid-soluble, non-ionised drugs readily pass through this barrier.

Entry into foetal circulation: Entry of drugs into foetal circulation is restricted by blood-placental barrier. It is also a hypothetical barrier which exists between maternal and foetal circulation. It permits the entry of only lipid-soluble and non-ionised forms of drugs.

Storage depots: A drug can get stored at different areas of the body. Slow release of the drug from these areas can produce prolonged effects. The following are major storage sites where drugs can be stored.

1. Plasma proteins like albumin e.g. phenylbutazone and sulphonamides
2. Connective tissues like bone e.g. heavy metals and tetracyclines
3. Cells like liver cells e.g. quinacrine an antimalarial drug
4. Fat, if the drug is highly lipid-soluble e.g. thiopental a lipid-soluble barbiturate

After a drug is absorbed into the blood, it rapidly circulates through the body. The average circulation time of blood is 1 minute. As the blood recirculates, the drug moves from the bloodstream into the body's tissues.

Once absorbed, most drugs do not spread evenly throughout the body. Drugs that dissolve in water (water-soluble drugs), such as the antihypertensive drug atenolol, tend to stay within the blood and the fluid that surrounds cells (interstitial space). Drugs that dissolve in fat (fat-soluble drugs), such as the antianxiety drug clorazepate, tend to concentrate in fatty tissues. Other drugs concentrate mainly in only one small part of the body (for example, iodine concentrates mainly in the thyroid gland) because the tissues there have a special attraction for (affinity) and ability to retain that drug.

Drugs penetrate different tissues at different speeds, depending on the drug's ability to cross membranes. For example, the antibiotic rifampin, a highly fat-soluble drug, rapidly enters the brain, but the antibiotic penicillin, a water-soluble drug, does not. In general, fat-soluble drugs can cross cell membranes more quickly than water-soluble drugs can. For some drugs, transport mechanisms aid movement into or out of the tissues.

Some drugs leave the bloodstream very slowly because they bind tightly to proteins circulating in the blood. Others quickly leave the bloodstream and enter other tissues because they are less tightly bound to blood proteins. Some or virtually all molecules of a drug in the

blood may be bound to blood proteins. The protein-bound part is generally inactive. As unbound drug is distributed to tissues and its level in the bloodstream decreases, blood proteins gradually release the drug bound to them. Thus, the bound drug in the bloodstream may act as a reservoir for the drug.

Some drugs accumulate in certain tissues (for example, digoxin accumulates in heart and skeletal muscles), which can also act as reservoirs of extra drug. These tissues slowly release the drug into the bloodstream, keeping blood levels of the drug from decreasing rapidly and thereby prolonging the effect of the drug. Some drugs, such as those that accumulate in fatty tissues, leave the tissues so slowly that they circulate in the bloodstream for days after a person has stopped taking the drug.

Distribution of a drug may also vary from person to person. For instance, obese people may store large amounts of fat-soluble drugs, whereas very thin people may store relatively little. Older people, even when thin, may store large amounts of fat-soluble drugs because the proportion of body fat increases with age.

Biotransformation of drugs

Alteration of a drug in a living organism is known as biotransformation. By this process, a drug may either be inactivated or converted into a more active compound. Biotransformation is sometimes called drug metabolism or detoxication. By means of biotransformation, the duration of action of a drug is decreased. Hence the toxicity is also decreased.

Methods of biotransformation: The reactions which bring about biotransformation of drugs can be classified as:

a. Non-synthetic reactions (Phase I reactions)
b. Synthetic reactions (Phase II reactions)

a. Non-synthetic reactions: Non-synthetic reactions lead either to activation or inactivation of a drug. These reactions are further classified as:

1. Oxidation: Oxidation occurs mainly in the liver. A typical example is the oxidation of ethyl alcohol to acetyl CoA.
2. Reduction: It is a less common process. Drugs like prontosil and chloralhydrate are metabolised by reduction.
3. Hydrolysis: This is brought about by enzymes called esterases which produce cleavage of the ester linkage e.g. acetylcholine is hydrolysed by cholinesterase and converted into choline and acetic acid.

b. Synthetic reactions: Synthetic reactions also called as conjugation reactions lead only to inactivation of a drug. The following are the various synthetic reactions:

1. Glucuronide formation – e.g. morphine

2. Sulphate formation – e.g. phenols
3. Acetylation – e.g. sulphanilamide
4. Methylation – e.g. adrenaline and noradrenaline
5. Glycine conjugation – e.g. salicylic acid

Sites of biotransformation: Biotransformation of drugs occurs primarily in the liver. Other minor sites of biotransformation are kidney, plasma and testis. In the liver, drug metabolising enzymes are present in microsomes. So these enzymes are called as hepatic microsomal drug metabolizing enzymes.

Factors modifying biotransformation: Biotransformation of a drug may be modified by the following factors:

1. Inhibitors: Drug metabolising enzymes can be inhibited by certain other drugs e.g. cimetidine, omeprazole, ciprofloxacin. Such drugs increase the metabolism of a drug. This in turn increases the duration of action.
2. Stimulators: The activity of drug metabolising enzymes can be increased by certain drugs e.g. phenobarbitone and rifampicin. They increase the metabolism of drugs like phenytoin and warfarin.
3. Age: Metabolism of drugs is poor in young children because of poor development of drug metabolising enzymes e.g. lack of glucuronyl transferase for the inactivation of chloramphenicol in the new born.
4. Sex: Females have less ability to metabolise drugs.
5. Species: Rabbits metabolise atropine due to the presence of atropinase. Humans lack this enzyme. So atropine is toxic to humans but non-toxic to rabbits.
6. Genetic: Deficiencies in drug metabolising enzymes can be inherited e.g. primaquine produces haemolysis in genetic deficiency of the enzyme glucose-6-phosphate dehydrogenase.
7. Body temperature: Increase in body temperature increases drug metabolism, whereas decrease in body temperature has the opposite effect.

Excretion of drugs

Excretion of a drug decreases its duration of action. This in turn decreases the toxicity. Drugs may be excreted in an active or inactive form. The various routes through which drugs can be eliminated are:

1. Kidneys: Drugs may be eliminated through the kidney by:
    i. Passive glomerular filtration – most of the drugs are eliminated by this mechanism.
    ii. Active tubular secretion e.g. penicillin.
    iii. Passive tubular diffusion e.g. salicylates and mepacrine.

    In case of renal damage, excretion of drugs is decreased and so the toxicity is increased.

2. Lungs: Drugs like volatile general anaesthetics, alcohol and paraldehyde are excreted through lungs.
3. Skin: Heavy metals like arsenic and mercury are excreted through skin.
4. Intestine: Purgatives like senna and cascara are absorbed in small intestine and later get excreted in large intestine.
5. Bile: Drugs like diphenylhydantoin and phenolphthalein are excreted into small intestine through bile. These drugs may be absorbed again, carried to the liver and again excreted into small intestine through bile. This process called as enterohepatic circulation prolongs the duration of action of such drugs.
6. Milk: Milk is more acidic than plasma and hence basic drugs like pethidine are eliminated through it.
7. Saliva: Drugs like iodides and metallic salts are excreted through saliva. Lead is eliminated through saliva and its deposition produces black lining of teeth.

Factors modifying drug effects

The response to a drug varies from one individual to the other. The following are the factors which are responsible for variation in drug effects.

1. **Age:** Children are hyper reactive to certain drugs. The reasons are immaturity of renal functions or poor development of enzymes needed for inactivation. So a lesser dose must be given for children than for adults. The dose for children can be calculated by making use of the following formulae:
2. **Body weight:** Body weight has a definite influence on the concentration of the drug at the site of action. So the dose of a drug must be suitably adjusted in case of lean or obese individuals.
3. **Sex:** Women are more susceptible to the effects of certain drugs e.g. morphine produces more excitation in women than in men.
4. **Route of administration:** The rate of absorption of a drug differs with the route of administration. The dose also varies with the route of administration e.g. intravenous dose of a drug is less than subcutaneous dose.
5. **Time of administration:** This factor has a definite effect on drug absorption and hence on its effect e.g. drugs which produce nausea and vomiting should be taken after food. But anthelmintics should be taken in empty stomach.
6. **Physiological factors:** Body temperature and acid-base status are some factors which modify drug effects, e.g. salicylates lower body temperature only in fever but not in normal individuals.
7. **Psychological factors:** The effect of a drug may be modified by psychogenic response of the patient. Sometimes it is necessary to please the patient by psychological means. Placebo which is a dummy medication is used for this purpose.
8. **Pathological state:** The effect of a drug may be modified in pathological conditions e.g. hyperthyroid individuals require a large dose of morphine.
9. **Genetic factors:** The effect of a drug may vary due to genetic factors like inherited enzyme deficiencies e.g. primaquine produces hemolysis in individuals with a deficiency of glucose-6-phosphate dehydrogenase.

10. **Cumulation:** Drugs like digitalis are excreted slowly. So repeated administration leads to accumulation in the body so as to produce toxicity. This phenomenon is called cumulation.
11. **Tolerance:** It is the unusual resistance to normal therapeutic dose of a drug. So a large dose is required to produce and effect. Tolerance can be classified into:
    i. True tolerance: It can be produced on both oral and parenteral administration of a drug. When it occurs by nature, it is called as natural tolerance e.g. tolerance for atropine in rabbits. This can occur even without previous exposure to the drug. Acquired tolerance is produced on repeated administration e.g. tolerance for the euphoriant effect of morphine.
    ii. Tachyphylaxis: It is an acute type of tolerance. It occurs on repeated administration of the drug at short intervals. For example, tyramine produces decreased rise in blood pressure on repeated administration. This decreased response is due to depletion of noradrenaline stores from sympathetic nerves.
12. **Drug interaction:** The effects of a drug may be modified by the prior or simultaneous administration of another drug. The effects produced by drug combinations can be classified as:
    i. Additive effect: The total pharmacological response produced by two drugs is equal to the sum of the individual effects e.g. the effects of ephedrine and aminophylline in bronchial asthma.
    ii. Synergism: The total effect produced by two drugs is greater than the sum of individual effects e.g. ammonium chloride synergises the effect of mercurial diuretics.
    iii. Antagonism: Two drugs act on the same physiological system and produce opposite effects. Antagonism can be classified as:
        a. Chemical antagonism: This occurs as a result of chemical interaction between two drugs e.g. BAL in arsenic poisoning.
        b. Competitive or reversible antagonism: This occurs due to competition between two drugs for the same receptor. The drug having a greater concentration at the receptor produces its effect e.g. antagonism of acetylcholine by atropine at muscarinic receptor.
        c. Non-competitive antagonism: This occurs due to inactivation of the receptor by the antagonist e.g. antagonism of acetylcholine by decamethonium at the neuromuscular junction.
        d. Physiological antagonism: The drug and its antagonist act at different receptors to produce an opposite effect e.g. adrenaline in histamine anaphylaxis.

UNIT II: DRUGS ACTING ON NERVOUS SYSTEM

Hypnotics and sedatives

Hypnotics are drugs which produce sleep resembling natural sleep. Sedatives are drugs which reduce excitement without producing sleep. Qualitatively hypnotics and sedatives produce depression of central nervous system and the difference between them is mainly quantitative.

Classification of sedative – hypnotics:

Barbiturates	Phenobarbitone Mephobarbitone Butobarbitone Secobarbitone Pentobarbitone Thiopentone Hexobarbitone Methohexitone
Benzodiazepines	Diazepam Flurazepam Nitrazepam
Newer non-benzo diazepines	Zopiclone Zolpidem

BARBITURATES: Barbiturates are derivatives of barbituric acid which is obtained by the condensation of urea and malonic acid. Barbituric acid itself does not possess hypnotic activity but hypnotic activity is produced if the hydrogen atoms at position 5 are replaced by alkyl or aryl groups.

Pharmacological actions:

1. Central nervous system: Barbiturates produce all degrees of CNS depression like mild sedation, hypnosis and general anaesthesia.
    a. Sleep: Barbiturate-induced sleep resembles natural sleep. But it decreases the time spent on rapid eye movement sleep. Also there is hangover effect after awakening.
    b. Analgesic effect: Barbiturates do not relieve pain without producing unconsciousness. But they enhance the analgesic effect of salicylates and para-armino phenol derivatives.
    c. Anaesthetic effect: Thiobarbiturates and some ultra short acting oxybarbiturates produce anaesthesia on intravenous administration.
    d. Anticonvulsant effect: Barbiturates like phenobarbitone which have a phenyl group at the 5^{th} carbon atom have anticonvulsant effect.

e. Respiration: Respiration is not affected at sedative or hypnotic dose. Large dose administered intravenously may produce death due to central respiratory paralysis.

2. Gastrointestinal tract: Intestinal motility is not affected at a normal dose, but gastric secretion may be depressed.
3. Uterus: Force and frequency of uterine contractions are depressed at toxic dose.
4. Kidney: No effect at normal dose, but anaesthetic dose decreases urinary output due to decrease in glomerular filtration and release of ADH.
5. Liver: No effect at normal dose but anaesthetic dose may produce hepatic dysfunction.

Absorption, fate and excretion: Barbiturates can be administered by oral and parenteral routes. They are distributed in all tissues and body fluids. They cross placental barrier and also are excreted in milk. They are chiefly metabolized in the liver and to a small extent in kidney and brain. Excretion is through urine both in free form and as glucuronic acid conjugate.

Adverse reactions:

1. Intolerance like nausea, headache and diarrhoea.
2. Foetal respiratory depression if administered during labour.
3. Drug automatism due to repeatedly taking the drug owing to forgetfulness.
4. Tolerance because of increased inactivation in the liver.
5. Dependence and withdrawal symptoms.

Therapeutic uses:

1. Sedation in case of anxiety or tension.
2. Hypnosis to relieve insomnia.
3. Anticonvulsant effect in case of tetanus or status epilepticus.
4. Pre-anaesthetic medication and to produce basal anaesthesia.
5. Potentiation of analgesics like salicylates.
6. In psychiatric practice and in neonatal jaundice.

BENZODIAZEPINES: Diazepam, nitrozepam and flurazepam are the important benzodiazepines. Diazepam is the commonly used drug. The benzodiazepines have anxiolytic, hypnotic, anti-convulsant and muscle relaxant effects. All the benzodiazepines have a hypnotic effect. They produce less unconsciousness and respiratory depression. So these compounds are relatively non-toxic.

NEWER NON-BENZODIAZEPINES:

Zopiclone: It is a non-benzodiazepine sedative. It is a cyclopyrrolone derivative. It shortens sleep latency and increases total sleep time. It does not affect REM sleep and also there is no hangover. Tolerance or rebound insomnia does not occur.

Zolpidem: It is an imidazopyridine derivative. It decreases sleep latency and increases sleep duration. It has a weak anti-convulsant effect. Advantages: no tolerance or physical dependence, low abuse potential, no rebound insomnia and safety with overdosage.

Anti-convulsants

Epilepsy: Epilepsy is a collective term applied for a group of convulsive disorders. The common features of epilepsy are:

1. Loss or disturbance of consciousness.
2. Characteristic body movements.
3. Autonomic hyperactivity.

The different types of epilepsy are grand mal epilepsy, petit mal epilepsy, psychomotor epilepsy, myoclonic epilepsy, etc.

Classification of anti-epileptic drugs:

Hydantoins	Phenytoin
Barbiturates	Phenobarbitone Primidone
Iminostilbenes	Carbamazepine
Succinimides	Ethosuximide
Aliphatic carboxylic acids	Sodium valproate
Benzodiazepines	Clonazepam Clobazam Diazepam
Newer antiepileptics	Lamotrigine Gabapentine Vigabatrin
Miscellaneous	Trimethadione Phenacemide Acetazolamide

Hydantoin derivatives: Diphenylhydantoin is the most important derivative. It acts by:

1. Normalizing the lowered threshold for seizures.
2. Reducing sodium concentration in brain cells which leads to decrease in post-tectanic potentiation.

It is well absorbed after oral administration. The onset of action is slow. But the duration of action is long. Its is metabolised by parahydroxylation of the phenolic ring. The metabolites are subjected to enterohepatic circulation. It is almost completely excreted in urine within 48 hours.

Adverse reaction:

- CNS sysmptoms: Giddiness, tremors, headache, insomnia and drowsiness.
- Gastrointestinal effects: Nausea, vomiting and anorexia.
- Rashes: Urticarial, scarlantiform and measles-like rashes.
- Gums: Swelling of gums, bleeding and gingivitis.
- Foetal hydantoin syndrome: When used in pregnancy, it causes cleft palate, hair lip and microcephaly in the foetus.

- Miscellaneous: Blood dyscrasias, hepatitis, jaundice, megaloblastic anemia and lymphadenopathy.

Dose: 100 mg three times daily by oral route and it is gradually increased to 500 mg.
Use: Grand mal epilepsy, psychomotor epilepsy and cardiac arrhythmias.

BARBITURATES: The most important anti-convulsant barbiturate is phenobarbitone. It is effective in grand mal, focal cortical and psychomotor epilepsy. It should not be used in petit mal epilepsy. Sudden withdrawal of phenobarbitone increases the frequency of convulsions. So it must be gradually substituted by phenytoin. The toxicities are drowsiness, depression and lethargy. Dose: 60 to 180 mg daily in divided doses.

CARBAMAZEPINE: It is a tricyclic compound. It has a structural similarity to imipramine, and anti-depressant drug.

1. It is more effective in temporal lobe epilepsy. It is also effective in grand mal epilepsy.
2. It improves the personality, attention and concentration of epileptic patient.
3. It is remarkably effective in trigeminal neuralgia and glassopharyngeal neuralgia.
4. It is slowly absorbed on oral administration. But the overall bioavailability is 90%.
5. Adverse reactions: anorexia, nausea, vomiting, giddiness, skin rashes, diplopia, blurred vision, agranulocytosis, obstructive jaundice, peripheral neuritis and aplastic anemia.
6. Dose: Initial 100 mg twice a day as tablets. Gradually increased to 600 to 1200 mg per day for temporal lobe epilepsy.

SUCCINIMIDES: Ethosuximide is an important member of this group. It is effective only in petit mal epilepsy. It is effective on oral administration. Adverse effects are anorexia, nausea, vomiting and drowsiness. It is available as capsules and syrup. Dose: initial 250 mg per day. Gradually increased by 250 mg each week to a maximum of 750 to 1000 mg daily.

SODIUM VALPORATE:

1. It is highly effective in petit mal epilepsy. It is ineffective in focal cortical epilepsy and temporal lobe epilepsy.
2. Mechanism: Inhibition of gamma aminobutyrate transaminase and potentiation of post-synaptic GABA activity.
3. It is completely absorbed after oral administration. It is extensively bound to plasma proteins. It is metabolised in liver.
4. Adverse reactions: Nausea, vomiting, hepatic damage, sedation, ataxia and in co-ordination. Spina bifida when used in pregnancy.
5. Dose: 600 mg to 1600 mg per day orally.

CLONAZEPAM: it is a benzodiazepine compound. It is effective in petit mal epilepsy and myoclonic seizures. It can be used with phenytoin or phenobarbitone for treating grand mal epilepsy. It acts by increasing the effect of GABA in CNS. Adverse reactions: Drowsiness,

ataxia, personality changes, tremor, vertigo and confusion. Sometimes anemia, leucopenia, skin eruption,s cardiovascular and gastrointestinal effects.

DIAZEPAM: It is the drug of choice for emergency control of convulsions like status epilepticus and tetanus. For this purpose, it is given intravenously.

LAMOTRIGINE: It is a phenyltriazine compound. It acts by blocking sodium channels and preventing the release of glutamate. This stabilises pre-synaptic membrane. It is used as an add-on treatment in patients resistant to other anti-epileptic drugs. Adverse reactions: Sleepiness, dizziness, diplopia, ataxia and vomiting.

GABAPENTINE: It is a centrally active GABA agonist. It has a high lipid solubility. It does not act on GABA receptors. But it acts by releasing GABA. Gabapentine is well absorbed orally. It is excreted unchanged in urine.
Adverse reactions: Mild sedation, tiredness and dizziness.
Use: Partial seizures resistant to other drugs.

VIGABATRIN: It is a GABA transaminase inhibitor. It acts by increasing synaptic GABA concentration. It is well absorbed orally and excreted unchanged in urine. It is useful in refractory epilepsy not controlled by other drugs. Adverse effects are weight gain, drowsiness, depression and diplopia.

PHENACEMIDE: It is an acetylurea derivative. Due to high incidence of toxicity it use is restricted only to psychomotor epilepsy refractory to other drugs.

ACETAZOLAMIDE: It is a carbonic anhydrase inhibitor. It is used in petit mal epilepsy. It also has a diuretic effect.

Analgesic antipyretics

Analgesic-antipyretics are drugs which produce relief of pain and lowering of body temperature. These drugs relieve pain of lesser intensity like tooth-ache and muscle pain. But they do not relieve severe pain like visceral pain which is relieved by opioid analgesics. Also these drugs do not produce addiction. All these drugs produce an anti-inflammatory effect. So they are called as non-steroidal anti-inflammatory drugs (NSAID). Since they act without interacting with opioid receptors, they are called as non-opioid analgesics.

NSAID and prostaglandin synthesis:

The three major actions of NSAID (analgesic, antipyretic and anti-inflammatory) are mediated through inhibition of prostaglandin synthesis.

1. During pain, fever and inflammation, arachidonic acid is liberated from phospholipid fraction of cell membrane.
2. The enzyme cyclooxygenase (COX) converts arachidonic acid to prostaglandins. The prostaglandins formed are responsible for inflammation.

3. There are two forms of the enzyme COX viz. COX-1 and COX-2. COX-1 is always present and it is found in blood vessels, stomach and kidney. But COX-2 is induced only during inflammation.
4. Drugs like aspirin are non-selective COX inhibitors and they inhibit both COX-1 and COX-2. Aspirin inhibits COX irreversibly by acetylation of this enzyme.
5. Certain drugs inhibit COX-2 selectively e.g. celecoxib, rofecoxib and valdecoxib.

Classification of drugs

Non-selective COX inhibitors	
Salicylates and congeners	Aspirin Salicylic acid Sodium salicylate Methyl salicylate
Para-aminophenol derivatives	Paracetamol
Pyrazolon derivatives	Aminopyrine Antipyrine Phenylbutazone Oxyphenbutazone
Miscellaneous	Indomethacin Ibuprofen Mefenamic acid Piroxicam Diclofenac Ketorolac Nimesulide
B. Selective COX-2 inhibitors	Celecoxib Rofecoxib Valdecoxib Nemesulido

SALICYLATES (aspirin as the prototype)

Pharmacological actions:

The pharmacological actions mentioned are those of salicylates in general and those of aspirin in particular.

- Analgesic effect: Salicylates are effective only in dull-aching pain of low intensity. They do not relieve severe pain like visceral pain. They act by preventing the integration of pain sensation in the thalamus. But they do not alter the emotional reaction to pain.
- Antipyretic effect: Salicylates do not lower normal body temperature. Only the elevated temperature is lowered. Mechanism: a) The hypothalamic heat regulating center is set for a higher temperature in fever. This is reset for a lower temperature by salicylates b) The salicylates produce sweating which also lowers body temperature.

- Respiration: Salicylates stimulate respiration directly by stimulating the respiratory center and indirectly through carbondioxide produced by increased oxygen utilisation of skeletal muscles.
- Gastrointestinal tract: Salicylates produce nausea and vomiting due to direct irritation and stimulation of chemoreceptor trigger zone. Salicylates can also cause gastric ulceration and hemorrhage.
- Anti-inflammatory and anti-rheumatic effect: Salicylates have powerful anti-rheumatic effect. This effect is produced by reducing pain and inflammation of the joints.
- Immunological effect: Salicylates inhibit antigen-antibody reaction and so prevent the release of histamine.
- Uricosuric effect: Salicylates promote the excretion of uric acid. This effect is produced by inhibiting the reabsorption of uric acid in the proximal tubule.
- Cardiovascular system: No effect at normal dose. Toxic doses produce paralysis of vasomotor center.
- Blood: Salicylates lower erythrocytic sedimentation rate (ESR) which is high in rheumatic fever. They also decrease prothrombin level of plasma.
- Endocrines: Salicylates stimulate the release of adrenaline from adrenal medulla. They also stimulate the release of adrenocorticotrophic hormone (ACTH). They interfere with the binding of thyroxine with plasma proteins. This free thyroxine depresses the secretion of thyroid stimulating hormone (TSH).
- Metabolic effects: Salicylates produce uncoupling of oxidative phosphorylation. They produce hyperglycemia and glycosuria. They inhibit the synthesis but enhance the breakdown of fatty acids.
- Local actions: Salicylates have antiseptic, fungistatic and keratolytic effects.

Absorption, fate and excretion: Salicylates are absorbed from the stomach and intestine. They are bound to plasma proteins. They are mainly concentrated in the liver, heart, muscle and brain. They are metabolised in liver by conjugation with glycine and glucuronic acid. The metabolic products are mainly excreted through urine.

Adverse reactions:

1. Gastrointestinal disturbances like nausea, vomiting and diarrhoea. Also ulceration, perforation and hemorrhage are produced.
2. Intolerance leading to skin rashes of various types.
3. Bone marrow depression leading to agranulocytosis, thrombocytopenia and aplastic anemia.
4. Fatty infiltration of liver and kidney.
5. Salicylism characterised by headache, tinnitus, difficulty in hearing, drowsiness, lethargy and confusion.

PARACETAMOL: It is a para-amino phenol derivative. It has analgesic and antipyretic effects like salicylates. But it does not have anti-inflammatory and uricosuric effects. Also it does not produce gastrointestinal irritation. Paracetamol is well absorbed on oral administration. It is metabolised in liver and excreted in urine in a conjugated form. Dose: 300 to 600 mg as tablets. Maximum dose of 2.5 g.

AMINOPYRINE AND ANTIPYRINE: Both are pyrazolon derivatives. They have analgesic, anti-pyretic and anti-inflammatory effects. The use of these drugs is limited due to their toxicity.

PHENYLBUTAZONE: Phenylbutazone belongs to the group of pyrazolon derivatives. It has less analgesic and antipyretic activity. But the anti-inflammatory effect is more than that produced by salicylates. It also has an uricosuric effect. It is well absorbed on oral and parenteral administration. It is extensively bound to plasma proteins. It is completely metabolised in the liver. Oxyphenbutazone is a metabolic product of phenylbutazone. Dose: 200 to 400 mg daily in divided doses as tablets.

OXYPHENBUTAZONE: It is a metabolic product of phenylbutazone. Its actions, toxicities and uses are similar to phenylbutazone.

INDOMETHACIN: It is a derivative of indole acetic acid. It has an analgesic, anti-pyretic and anti-inflammatory activity. It is much effective in the treatment of rheumatoid arthritis and gout. It is administered at a dose of 50 to 150 mg daily in divided doses. It is commonly used for medical closure of patent ductus arteriosus. Sulindoc is a fluorinated derivative of indomethacin.

IBUPROFEN (BRUFEN): It is a synthetic compound having analgesic and mild anti-inflammatory effect. It produces less gastric irritation than aspirin. Dose: 0.4 to 0.6 g three times daily by oral route.

MEFENAMIC ACID: It is derivative of anthranilic acid. It has a weak analgesic effect. It produces toxicities like gastrointestinal disturbances, skin rashes and blood dyscrasias.

PIROXICAM: It belongs to the group of oxicams. It has an analgesic, antipyretic and anti-inflammatory effect. But it does not produce gastric irritation. It is well absorbed on oral administration. Also it has a prolonged effect. It is used in rheumatoid arthritis and acute gout. Dose: 20 mg once daily.

DICLOFENAC: It is an aryl acetic acid derivative. It is an analgesic antipyretic and anti-inflammatory drug. It inhibits prostaglandin synthesis. Also, it has a short anti-platelet action. Since it accumulates in synovial fluid it has a longer action. It is used in rheumatoid arthritis and osteoarthritis.

KETOROLAC: It is a pyrrolo-pyrrole derivative. It has a potent analgesic and moderate anti-inflammatory activity. it inhibits prostaglandin synthesis. Also it inhibits platelet aggregation for short periods. It is useful in post-operative pain and acute musculo-skeletal pain.

CELECOXIB: It is a selective COX-2 inhibitor. It has anti-inflammatory, analgesic and anti-pyretic effects. But ulcerogenic effect is less. Also it does not have anti-platelet action. It is metabolised in liver. Hepatic impairment increases its plasma concentration. it has a plasma life of hours. Adverse effects: hypertension, oedema, abdominal pain, dyspepsia and mild diarrhoea. Use: osteoarthritis, rheumatoid arthritis, dysmenorrhea, dental and post-operative pain.

ROFECOXIB: It is a more potent COX-2 inhibitor than celecoxib. Similar to celecoxib it has no anti-platelet action. Like celecoxib, it is useful in osteoarthritis, rheumatoid arthritis, dysmenorrhea, dental and post-operative pain. It has a plasma life of 17 hours. Adverse effects: headache, dizziness, gastrointestinal disturbances, oedema and hypertension.

VALDECOXIB: It is a newer selective COX-2 inhibitor. Its efficacy is similar to rofecoxib. It has a plasma half life of 8 to 11 hours. It is useful in osteoarthritis, rheumatoid arthritis, dysmenorrhea and post-operative pain.

NIMESULIDE: It is a NSAID with less COX-2 inhibiting effect. It has analgesic, antipyretic and anti-inflammatory effect. Also it has mild anti-histaminic and anti-platelet actions. It can cause gastrointestinal disturbances. Advantage: It can be used in patients allergic to aspirin or other NSAIDs. Dose: 200 to 300 mg daily in divided doses.

Anti-depressant drugs

These are drugs used for the treatment of mental depression. They are also called as 'psychoanaleptics' or 'mood elevators'.

Classification of drugs:

Monoamine oxidase inhibitors (MAOI)	
a. Hydrazine derivatives	Isocarboxazid Iproniazid Nialamide Phenelzine
b. Non-hydrazine derivatives	Tranylcypromine
Tricyclic compounds	Imipramine Desipramine Amitriptyline Nortriptyline
Serotonin re-uptake inhibitors	Fluoxetine Paroxetine Fluvoxamine Sertaline
Lithium compounds	Lithium carbonate

MONOAMINE OXIDASE INHIBITORS (MAOI)

Mechanism of action: Biogenic amines like 5-hydroxy tryptamine, noradrenaline and dopamine are inactivated by the enzyme monoamine oxidase (MAO). MAOI inhibit the enzyme MAO. This leads to accumulation of these amines in brain. This produces anti-depressant effect.

Pharmacological actions:

- Behaviour: In case of mental depression, these compounds elevate the mood. The patient feels more energetic and fresh.
- Reserpine reversal: In animals pretreated with MAOI, reserpine does not produce dorwsiness. Instead, it produces agitation and excitement.
- Cardiovascular system: No effect on heart or circulation at normal dose.
- Potentiation of sympathomimetic amines: These compounds potentiate the action of sympathomimetic amines like amphetamine and tyramine.

Absorption, fate and excretion: These compounds are well absorbed after oral administration. They are uickly metabolised. But they produce long lasting effects.

Adverse reactions:

- Behavioural effects: headache, excitement and disturbed sleep.
- CNS effects: twitching, ataxia and tremors.
- ANS effects: dry mouth, constipation and blurred vision.
- Hypertensive crisis: in the presence of MAOI, tyramine is not metabolised that results in rise in blood pressure by releasing noradrenaline.

TRICYCLIC COMPOUNDS: Imipramine is the commonly used drug.

Mechanism of action: Imipramine acts by inhibiting the reuptake of noradrenaline. This produces increase in its concentration at the receptor sites. This contributes for the anti-depressant action.

Pharmacological actions:

- Behaviour: same as MAOI.
- Reserpine reversal: same as MAOI.
- Cardiovascular system: no effect at normal dose. But toxic doses may produce cardiac arrhythmias.
- Autonomic nervous system: imipramine produces anti-cholinergic effects like dry mouth, constipation, palpitation and blurred vision.

Absorption, fate and excretion: Imipramine is well absorbed on oral administration. Its actions are mediated through desmethylimipramine which is a metabolic product.

Adverse reactions:

- CNS effects: lethargy, headache and drowsiness.
- ANS effects: dry mouth, constipation and tachycardia.
- CVS effects: cardiac arrhythmia and hypotension.
- Allergic reactions: skin rashes and photosensitivity

Therapeutic uses: Mental depression and nocturnal enuresis.

SEROTONIN REUPTAKE INHIBITORS: Drugs which belong to this group are fluoxetine, fluvoxamine and sertaline. They selectively inhibit serotonin reuptake. They have less anti-muscarinic and less sedative effects. Also, they are safer than tricyclic anti-depressants. Adverse effects: nausea, anxiety, insomnia, headache and sexual dysfunction.

LITHIUM CARBONATE: It is used in the treatment of manic depressive psychosis. Also it is used prophylactically in bipolar depression. Mechanism: a) interference with Na+/K+ ATPase b) interference with AMP formation c) interference with inositol-triphosphate formation. Adverse effects: nausea, vomiting and mild diarrhoea, thirst and polyuria, fine tremors and rarely seizures, CNS effects like tremors, giddiness, ataxia, nystagmus and confusion, teratogenic effects such as foetal goitre and cardiac abnormalities.

Local anaesthetics

Local anaesthetics are agents which block conduction of impulses in nerves. When applied locally, they produce loss of sensation in the desired area.

Classification of drugs:

Injectable	
a. Low potency	Procaine Chlorprocaine
b. Intermediate potency	Lignocaine Prilocaine Mepivancaine
c. High potency	Tetracaine Bupivacaine Ropivacaine Dibucaine
Surface anaesthetics	Cocaine Lignocaine Tetracaine Benzocaine Oxethazine

Mechanism of action: Local anaesthetics prevent the generation and conduction of impulses. This is produced by blocking voltage dependent sodium channels. So they decrease the permeability of cell membrane to sodium (membrane stabilizing effect). This prevents depolarisation. As a result rise of action potential declines, impulse conduction slows and nerve conduction fails.

Pharmacological actions:

- Effect on sensation: Initially the local anaesthetics block the sensation of pain and temperature. Later they produce loss of sensation for touch and pressure. They produce blockade of smaller nerve fibers initially followed by large nerve fibers. Recovery occurs in the reverse order.
- Central nervous system: Local anaesthetics produce stimulation of CNS. This manifests as euphoria, restlessness and tremors. Addiction to cocaine occurs mainly due to its euphoric effects.
- Cardiovascular system: All local anaesthetics except cocaine produce vasodilation and so hypotension. But cocaine produces vasoconstriction and so a hypertensive effect. All local anaesthetics produce a depressant effect on the myocardium.
- Other actions: They produce relaxant effect on smooth muscles and neuromuscular blockade.

Absorption, fate and excretion: Local anaesthetics are not absorbed from unbroken skin. But absorption can occur through mucous membranes. They are usually administered by subcutaneous infiltration. Vasoconstrictors like adrenaline prolong their duration of action. The local anaesthetics are metabolised in the liver and plasma by hydrolysis.

Adverse reactions:

- Intolerance like dermatitis, asthmatic attack and anaphylactic reactions.
- Cardiovascular symptoms like hypotension and cardiac arrest.
- Central effects like euphoria, excitation, restlessness, tremors and convulsions.

Therapeutic uses:

- Surface anaesthesia for pain due to burns, fissures and ulcers.
- Infiltration anaesthesia to anaesthetise nerve endings by subcutaneous infiltration.
- Nerve block anaesthesia where it is injected close to a specific nerve.
- Spinal anaesthesia where it is injected into the subarachnoid space
- Systemic use for anti-arrhythmic effect.

Cholinergic drugs

Cholinergic drugs (also called as parasympathomimetics) act on organs innervated by potganglionic parasympathetic nerves. They produce an effect similar to the stimulation of parasympathetic nervous system.

Classification of cholinergic drugs:

Esters of choline	Acetylcholine Methacholine Carbachol Bethanechol
Cholinomimetic alkaloids	Pilocarpine Arecholine Muscarine
Anti-cholinesterases	Physostigmine Neostigmine Di-isopropyl fluropohate Tetraethyl pyrophosphate Octamethyl pyrophosphotetramide

ACETYLCHOLINE: It is an ester of choline with acetic acid.

Pharmacological actions:

- Muscarinic action produced on organs innervated by postganglionic parasympathetic nerves. This action is blocked by atropine.
- Nicotinic action produced as stimulation of both sympathetic and parasympathetic ganglia. This action is blocked by pentamethonium or hexamethonium. The other action is contraction of skeletal muscles and this effect is blocked by d-tubocurarine.

Muscarinic actions:

- Heart: The effect of acetylcholine on heart is similar to that produced by stimulation of the vagus. It decreases heart rate and may produce cardiac arrest.
- Blood vessels: Acetylcholine dilates a variety of blood vessels and produces a fall in blood pressure.
- Smooth muscles: Acetylcholine produces contraction of smooth muscles like those of gastrointestinal tract, bronchi, urinary bladder and ureters.
- Secretions: Acetylcholine increases gastric, intestinal, pancreatic, bronchial, lacrimal and salivary secretions.
- Eye: Instillation into the eye has no effect. But injection of acetylcholine in the carotid artery produces miosis, spasm of accommodation and decrease in intraocular tension.

Nicotinic actions:

- Rise in blood pressure
- Contraction of skeletal muscle

ANTICHOLINESTERASE DRUGS: Acetylcholine is inactivated by the enzyme acetylcholinesterase. Anti-cholinesterase drugs also called as cholinesterase inhibitors act by inhibiting the enzyme acetylcholinesterase. This produces accumulation of acetylcholine at cholinergic sites.

Pharmacological actions:

- Eye: On the eye, the anticholinesterase agents produce miosis, spasm of accommodation and decrease in intraocular tension.
- Gastrointestinal tract: The effect of anticholinesterases on gastrointestinal tract are identical. They produce increase in motility and also secretions of gastrointestinal tract.
- Skeletal muscle: These drugs produce stimulation followed by depression.
- Secretions: Bronchial, lacrimal, salivary, gastric and pancreatic secretions are increased.
- Smooth muscles: Bronchioles and ureters are contracted.

Therapeutic uses:

- For reducing intraocular tension in glaucoma.
- For the diagnosis and treatment of myasthenia gravis.
- For the treatment of curare and atropine poisoning.
- For the treatment of post-operative paralytic ileus.
- For the treatment of paroxysmal atrial and supraventricular tachycardia.

Adrenergic drugs

Adrenergic drugs (sympathomimetic drugs) are agents which produce an effect similar to the stimulation of postganglionic sympathetic nerves. Most of these compounds have an intact or partially substituted amino group. So they are called as sympathomimetic amines.

Classification of drugs:

Based on the presence or absence of catechol nucleus, the sympathomimetic amines can be classified as:

Catecholamines	Adrenaline Noradrenaline Dopamine Isoprenaline
Non-catecholamines	Ephedrine Amphetamine Methylamphetamine Hydroxyamphetamine Mephentermine Metaraminol Phenylephrine

CATECHOLAMINES: Are compounds which contain catechol nucleus.
Adrenaline: Is synthesised in the adrenal medulla. The parent compound for the synthesis of adrenaline is phenylalanine.

Pharmacological actions:

- Heart: acts on beta receptors of heart and produces an increase in rate of contraction, force of contraction and cardiac output.
- Blood vessels: constricts the blood vessels of skin and mucous membranes but dilates the blood vessels of skeletal muscles.
- Blood pressure: produces biphasic effect. There is an initial rise due to stimulation of alpha receptors. Later there is a fall due to an effect on beta receptors.
- Smooth muscles: relaxes the smooth muscles of intestine and decreases motility, relaxes bronchial smooth muscle and relieves spasm, relaxes uterus, releases more erythrocytes from splenic capsule, contracts pilomotor muscle of hair follicle, producing erection of hair.
- Eye: produces mydriasis and reduction in intraocular tension.
- Respiration: produces a weak stimulation of respoiration.
- Skeletal muscles: improves neuromuscular transmission and relieves fatigue of skeletal muscles.
- Metabolic effect: increases blood sugar level and increases free fatty acid level of plasma.

Absorption, fate and excretion: Adrenaline is inactivated in the gastrointestinal tract. So it is administered by injection or inhalation. Adrenaline is metabolised by catechol orthomethyl transferase (which converts adrenaline to metanephrine) and monoamine oxidase (which converts adrenaline to 3-methoxy-4-hydroxy mandelic acid). This product is excreted in urine.

Therapeutic uses:

- In the syncopal attacks of Stokes-Adams syndrome.
- For resuscitation of failing heart.
- In allergic disorders, as a physiological antidote to histamine.
- As a bronchodilator, in bronchial asthma.
- To prolong the effect of local anaesthetics.
- To control hemorrhage by producing vasoconstriction.

NON-CATECHOLAMINES: Are symapthomimetic amines and they are devoid of catechol nucleus. They act directly by stimulating alpha and beta adrenergic receptors and indirectly by releasing noradrenaline and dopamine from chromaffin granules of sympathetic nerves.

EPHEDRINE: It is an alkaloid obtained from plants belonging to the genus ephedra. It acts directly on both alpha and beta adrenergic receptors and also by releasing noradrenaline from sympathetic nerve ending.

Actions:

- It increase blood pressure by peripheral vasoconstriction and by increasing cardiac output.
- It also has a relaxant effect on bronchial and uterine smooth muscles.
- It also produces CNS stimulant effect characterized by restlessness, insomnia, anxiety and increased mental activity.
- It produces mydriasis without affecting accommodation and intraocular tension.

Uses:

- Useful for bronchial asthma.
- Used as a nasal decongestant and also for the treatment of narcolepsy.
- Used in nocturnal enuresis.

UNIT III: DRUGS ACTING ON ORGANS

Drugs acting on the gastrointestinal tract

Appetizers

These are drugs used for the treatment of anorexia (loss of appetite). The appetizers induce appetite by increasing gastric secretion. The agents used in the treatment of anorexia are:

1. Bitters: These agents stimulate the taste buds and this produces reflex secretion of gastric juice. Chirate, quassia, aristolochia and gentian are the commonly used bitters.
2. Alcohol: Alcohol induces gastric secretion by a direct action and also by reflex stimulation of taste buds.
3. Miscellaneous compounds: The miscellaneous compounds which induce appetite are: insulin which increases gastric secretion by producing hypoglycaemia and histamine which produces direct stimulation of gastric glands. But these drugs have no therapeutic application.

Emetics

Emetics are drugs which produce vomiting.

Mechanism of vomiting: Vomiting often starts with nausea in which case there is increased secretion of saliva, bronchial fluid and sweat. Vomiting is a complicated, co-ordinated act which is controlled by vomiting centre present in the reticular formation of the medulla oblongata. Vomiting centre is sensitised by another centre in the medulla called the chemoreceptor trigger zone (CTZ). CTZ has neuronal connections with the vomiting centre. Stimulation of CTZ cannot produce vomiting in the absence of vomiting centre. But direct stimulation of vomiting centre can induce vomiting.

Classification of emetics:

Stimulants of CTZ	Apomorphine Morphine Hydergine
Irritants of gastrointestinal mucosa	Mustard Copper sulphate Sodium chloride
Both by stimulation of CTZ and irritation of gastrointestinal mucosa	Digitalis Emetine

APOMORPHINE: It is obtained by treating morphine with concentrated hydrochloric acid. It acts by stimulating CTZ. Vomiting induced by apomorphine is blocked by

chlorpromazine. Apomorphine produces vomiting within 15 minutes after subcutaneous injection. Dose: 2 to 8 mg by subcutaneous injection.

MUSTARD: Mustard is a household remedy. It liberates a volatile oil in the gastrointestinal tract which produces irritation. Dose: teaspoonful with water.

COPPER SULPHATE: It produce vomiting due to irritation of gastrointestinal tract. It also has an astringent effect. Dose: 200 ml of 0.15% solution. If vomiting does not occur within 15 minutes, a second dose can be given. If this also fails, a stomach wash should be given to prevent the poisonous effect.

HYPERTONIC SODIUM CHLORIDE: It produces irritation due to dehydration of the stomach wall. This produces reflex emesis.

DIGITALIS AND EMETINE: These drugs act by direct irritation of gastrointestinal mucosa and stimulation of CTZ. Since they are too toxic they are not used as emetics.

Antiulcer drugs

These drugs act by inhibiting gastric acid secretion of by promoting ulcer healing.

Classification of antiulcer drugs:

Inhibitors of gastric acid secretion	
a. Anticholinergics	Belladoma alkaloids Pirenzepine
b. H2 receptor antagonists	Cimetidine Ranitidine Fomotidine
c. Proton pump inhibitors	Omeprazole
Ulcer protectives	Sucralfate
Ulcer healing agents	Carbenoxolone sodium

Inhibitors of gastric acid secretion

ANTICHOLINERGIC DRUGS: Belladoma alkaloids like atropine act by a) inhibiting gastric acid secretion b) inhibiting gastric motility which increases the stay of antacid in the stomach. But they produce adverse effects like dryness of mouth.

PIRENZEPINE: It has a selective anticholinergic action on muscarinic receptors in the stomach. It is 10 times more potent than cimetidine in ulcer healing. Adverse reactions: dry mouth and blurred vision.

CIMETIDINE: It is a H2 receptor antagonist. It inhibits gastric acid secretion induced by histamine, insulin and pentagastrin. It decreases both volume and acid content of gastric juice without any effect on pepsin secretion. It crosses the placenta and is secreted in milk. It is used in the treatment of duodenal ulcer, multiple peptic ulcers and sress-induced ulcer. Adverse reactions: gynecomastia, impotence and mental confusion. Dose: 400 mg two times daily or 800 mg at bed time.

RANITIDINE: It is a H2 receptor antagonist 5 times more potent than cimetidine. It has a selective and prolonged effect. A single dose of 150 mg is effective for 12 hours. It is a safer drug than cimetidine. Adverse reactions: nausea, vomiting, diarrhoea, tiredness and skin rashes. It does not produce gynecomastia or sexual impotence.

FOMOTIDINE: It is a thiazole compound. It is an effective H2 receptor antagonist. It is more potent than cimetidine and ranitidine in inhibiting gastric acid secretion. It also produces healing of duodenal ulcer. It does not inhibit drug metabolising enzymes of liver. Adverse effects: head ache, dizziness and gastrointestinal symptoms.

OMEPERAZOLE: It is a substituted benzimidazole. It acts by inhibiting proton pump which is the final common step in gastric acid secretion. It has a dose dependent suppression of gastric acid secretion. It does not have anticholinergic or H2 receptor blocking action. It is a powerful inhibitor of gastric acid secretion which can totally abolish HCl secretion. Adverse reactions: nausea, headache, GI disturbances and dizziness.

Ulcer protective and healing agents:

SUCRALFATE: It is a complex of sulphated sucrose and aluminium hydroxide. It acts by forming a gel which coats ulcer sites. The coating lasts for 6 hrs and it is impermeable to gastric acid. Also it is not disturbed by food. It is more effective in healing duodenal ulcer. Dose: 1 g tablets before a meal and at bed time for 4 to 8 weeks. An antacid should be taken 30 minutes before or after taking sucralfate.

CARBENOXOLONE SODIUM: It is prepared from glycyrrhetemic acid which is a liquorice glucoside. It promotes healing of gastric ulcer. It acts by stimulating mucous secretion which in turn protects ulcer site from gastric acid. It also has an anti-inflammatory effect like corticosteroids. It is rapidly absorbed from stomach and is excreted in bile. Adverse reactions: water and sodium retention, potassium depletion, headache, heatburn and hypertension. Dose: 50 to 100 mg thrice daily after meals as tablets for 4 to 8 weeks.

Drugs acting on respiratory system

Bronchial asthma

Bronchial asthma is characterized by periodic spasm of bronchial smooth muscles, increased secretion and oedema of bronchial mucosa. Because of the spasm, large volume of air remains locked in the alveoli. This decreases tidal air and vital capacity leading to dyspnea.

Classification of drugs: Drugs used for the treatement of bronchial asthma can be classified as:

Bronchodilators	
a. Sympathomimetics	Adrenaline Ephedrine Isoprenaline Orciprenaline Salbutamol
b. Methyl xanthenes	Theophylline
c. Anti-cholinergics	Atropine Ipratropium bromide
Mast cell stabilizers	Disodium chromoglycate Ketotifen
Corticosteroids	Beclomethasone dipropionate

ADRENALINE: It is a potent drug which acts by stimulating beta receptors in the bronchial smooth muscle. It relieves an acute attack and also relieves pulmonary congestion by constricting pulmonary arteries. Prolonged use of adrenaline bronchial asthma may produce resistance. Also it produces side effects like ventricular tachycardia and ventricular fibrillation. Adrenaline should not be given to patients with cardia asthma, hypertension and hyperthyroidism. Dose: 0.2 to 0.5 ml of 1 in 1000 solution administered by subcutaneous injection.

EPHEDRINE: It is a symapathomimetic drug which acts on both alpha and beta adrenergic receptors. It is a weaker bronchodilator. Also it produces sleeplessness. This can be prevented by combining with phenobarbitone.

ISOPRENALINE: It acts on beta receptors of bronchi. It is administered sublingually at a dose of 10 to 20 mg. It can also be administered by inhalation. The only risk of isoprenaline is cardiac stimulation.

THEOPHYLLINE: It is a relative weak bronchodilator. It acts synergistically with beta adrenergic agonists. It is effective when adrenaline fails to relieve an acute attack or if the patient is resistant to adrenaline. It produces a direct relaxant effect on bronchial smooth

muscle. Repeated use of theophylline in children may produce disturbance in learning and sleep.

KETOTIFEN: It has similar actions as disodium chromoglycate. It acts by inhibiting airway inflammation induced by platelet activating factor. It also has an antihistamine effect. Side effects: drowsiness and dry mouth. Dose: 1 to 2 mg twice daily.

BECLOMETHASONE DIPROPIONATE: It is a corticosteroid which is effective in chronic asthma. It is administered as an aerosol. It has a topical action in bronchial asthma. So it does not produce any systemic effects. In chronic asthma it is preferred over glucocorticoids. Sometimes it produces local infections of candida in the mouth and throat.

Expectorants and antitussives

Drugs used in the treatment of cough are pharyngeal demulcents, expectorants and antitussives (central cough suppressants). They act at different sits and by different mechanisms.

Classification of drugs:

Pharyngeal demulcents	Syrups Linctuses Lozenges Liquorice
Expectorants	
a. Direct expectorants	Guaiacol Guaiphenesin Balsum of Tolu Vasaka
b. Reflex expectorants	Ammonium chloride Potassium iodide
c. Mucolytics	Acetylcysteine Carbocysteine Bromohexine Ambroxol
Antitussives	
a. Opioids	Codeine Pholcodeine
b. Nonopioids	Noscapine Dextromethorphan
c. Antihistamines	Chlorpheniramine Diphenhydramine Promethazine

Pharyngeal demulcents: They are syrups, linctuses, lozenges and liquorice. They produce a smooth coating over the pharyngeal mucosa. This effect is produced directly or by increasing the flow of saliva. So they reduce the afferent impulses arising from the irritated pharyngeal mucosa. They are useful in the symptomatic relief of dry cough.

Expectorants (Mucokinetics): Expectorants are drugs which increase respiratory tract secretions or liquify them. This helps in their easy expulsion.

Direct expectorants: They are guaiacol, Tolu balsam and vasaka. They are administered orally. They act directly and increase bronchial secretion. Also, they increase mucociliary action.

Reflex expectorants: These are emetics which in subemetic doses act as expectorants. These drugs produce mild irritation of the gastric mucosa which stimulates gastric reflexes. This helps to increase the respiratory secretions. In large doses, they produce nausea and vomiting. Drugs used as reflex expectorants are:

- Ammonium salts like ammonium chloride and ammonium bicarbonate.
- Potassium salts like potassium iodide.

All these drugs are potential emetics and hence produce nausea and vomiting. Potassium iodide can produce iodism characterised by conjunctival swelling, edema of eyelids and lacrimation. It can also produce goitre and hypothyroidism.

Mucolytic agents: These are drugs which decrease the viscosity of the sputum. This helps in easy expectoration.

- Acetylcysteine acts by opening disulfide bonds of mucoproteins present in sputum. This makes the sputum less viscid and has to be directly administered into the respiratory tract.
- Carbocysteine acts in the same way and administered orally. Side effects: GI irritation and rashes.
- Bromohexine obtained from the plant Adhathoda vasica decreases the viscosity of the sputum by dissolving the mucopolysaccharide fibres.

Antitussives: These drugs act on the CNS. They reduce the tussal impulses by raising the threshold of cough centre. Antitussives are used only in dry unproductive cough. Antitussives are classified as:

CODEINE: It is an opium alkaloid of phenanthrene group. It is a narcotic antitussive. Its actions are similar but less potent when compared to morphine. It suppresses cough for 6 hrs. analgesic and constipating effects are less. It does not produce tolerance or addiction. It is administered as syrup of codeine phosphate. Dose: 4 to 8 ml by mouth.

PHOLCODEINE: Its antitussive potency is similar to codeine. But it is longer acting. It has no analgesic or addicting property. Dose: 10 to 15 mg.

NOSCAPINE: It is an opium alkaloid of benzylisoquinoline group. It is equivalent to codeine in antitussive effect. But it has no analgesic effect. Also it has no narcotic or addicting property. So it is grouped as a nonopioid antitussive. Adverse effects: headache and nausea.

DEXTROMETHORPHAN: It is a synthetic compound. Only the d-isomer has antitussive action. Adverse effects: nausea, drowsiness, dizziness and ataxia.

ANTIHISTAMINES: Relieve cough by their sedative and anticholinergic actions. They do not act on cough centre. Also they do not have an expectorant action. They reduce secretions by anti-cholinergic effect.

Cardiovascular drugs

Antiarrhythmic drugs

Antiarrhythmic drugs are used to correct cardiac arrhythmias. Cardiac arrhythmias occur as a result of defective impulse formation or defective impulse conduction.

Classification of drugs:

Myocardial depressants	Quinidine Procainamide Disopyramide Lignocaine Phenytoin
Sympathetic blockers	Propranolol
Calcium channel blockers	Verapamil
Miscellaneous	Potassium Amiodorone Aprindine

QUINIDINE: It is an isomer of quinine. It is a natural alkaloid occurring in cinchona bark.

Pharmacological actions:

- Depolarisation: Quinidine slows the rate of depolarisation. This is produced by depressing the entry of sodium into the cell. So it prolongs the depolarisation repolarisation cycle. So the rate at which cardiac contractions occur is decreased.
- Impulse formation: Quinidine by a direct effect, depresses or slows the production of impulses from the sinoauricular node or pace maker.
- Excitability: Quinidine decreases the excitability of the cardiac muscle. So the threshold of an impulse to initiate cardiac activity is increased. So a weak impulse becomes ineffective.

- Refractory period: Quinidine prolongs repolarisation of the cardiac tissue. This is produced by depressing potassium efflux during repolarisation. This increases the refractory period bringing down the rate of heart.
- Conduction velocity: Quinidine slows the rate of conduction in the heart muscle. This along with decreased excitability and increased refractory period brings down the rate of heart.
- Cardiac contractility: Cardiac contractility is decreased by decrease in the entry of calcium into cardiac muscle cells.
- Blood pressure: Quinidine produces a fall in blood pressure on oral or parenteral administration. This is due to decreased sympathetic activity and direct dilatation of arteries.
- Cardiac output: Quinidine returns cardiac output to normal if it is low. No change is produced, if it is normal.
- Relaxant effect: Quinidine produces a relaxant effect on skeletal muscles. It also has antimalarial, antipyretic and oxytocic actions.

Absorption, fate and excretion: Quinidine is slowly but completely absorbed from gastrointestinal tract and also after intramuscular injection. In plasma, it is partly bound to albumin. It is metabolised in the liver by hydroxylation. These metabolites are excreted in urine along with unchanged Quinidine.

Adverse reactions:

- Gastrointestinal: nausea, vomiting and diarrhoea due to local irritant effects.
- Cinchonism: characterised by giddiness, light-headedness, tinnitus, impaired hearing and blurred vision.
- Cerebral: convulsions due to an effect on central nervous system.
- Hypotension: this is produced on intravenous administration.
- Cardiac: arrhythmias like ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation.

Preparations and dose:

- Quinidine sulphate tablets and capsules 200 to 400 mg every 6 hours.
- Quinidine gluconate injection 200 mg by intramuscular or slow intravenous injection.

Therapeutic uses: Cardiac arrhythmias like paroxysmal ventricular tachycardia and atrial fibrillation.

Antihypertensive agents

Hypertension is a disease characterised by abnormally high blood pressure. Hypertension is classified as: primary hypertension (for which the exact cause is not known) and secondary hypertension (which may be due to renal, endocrine or vascular lesions). Irrespective of the cause, hypertension is harmful. It may lead to degenerative changes in

cerebral, coronary, renal and retinal tissues. Antihypertensive drugs are helpful in the treatment of hypertension.

Classification of antihypertensive drugs:

ACE inhibitors	Captopril Enalapril Lisinopril Ramipril
Angiotensin antagonist	Losartan
Calcium channel blockers	Nifedipine Felodipine Amlodipine Verapamil Diltiazem
Diuretics	Chlorothiazide Frusemide Spironolactone Triameterene Amiloride
Beta adrenergic blockers	Propranolol Metoprolol Atenolol
Alpha adrenergic blockers	Prazocin Terazocin Phentolamine
Central sympatholytics	Clonidine Methyldopa
Vasodilators	Hydralazine Minoxidil Diazoxide Sodium nitroprusside Pinacidil

Adverse reactions:

- Captopril: renal damage, hyperkalemia, impairment of immune response, loss of taste sensation, neutropenia and proteinuria.
- Enalapril: hypotension, hyperkalemia, fetal toxicity, weakness and dizziness.
- Nifedipine: palpitation, flushing, ankle edema, hypotension, headache, drowsiness and nausea.
- Prazosin: giddiness, drowsiness, tiredness, weakness, nausea, diarrhoea, fluid retention and nervousness.
- Clonidine: dry mouth, constipation, vertigo, impotence, drowsiness and depression.

- Methyldopa: sedation, headache, weakness, mental depression, changes in sleep rhythm and night mares, lactation in females, retention of sodium and water.
- Hydralazine: headache, nausea, weakness, palpitation, flushing and tachycardia. Also neuropathy which is reversed by pyridoxine. It also produces priopism.

UNIT IV: HORMONES AND HORMONE ANTAGONISTS

Adrenocortical steroids

The cortex of adrenal glands secretes mineralocorticoids (influence water and mineral metabolism), glucocorticoids (influence carbohydrate metabolism) and androgenic steroids. These adrenocortical hormones are steroids with a basic structure, namely cyclopentanophenanthrene ring. Hypofunction of the adrenal cortex produces Addison's disease. Hyperfunction produces Cushing's syndrome.

GLUCOCORTICOIDS: The glucocorticoids are hydrocortisone, cortisone and corticosterone. Hydrocortisone is the important glucocorticoid secreted in man.

Pharmacological actions:

- Carbohydrate metabolism: The glucocorticoids promote gluconeogenesis and deposition of glycogen in the liver. But utilisation of glucose is inhibited.
- Protein metabolism: It increases the breakdown of protein. The aminoacids so produced support gluconeogenesis.
- Fat metabolism: It increases the mobilisation of fat from peripheral fat depots. On prolonged administration, they produce a redistribution of fat in the body. There is loss of fat from extremities and is deposited in the neck, face, etc.
- Electrolyte and water metabolism: Hydrocortisone increases sodium retention and potassium excretion. Sodium retention leads to water retention and edema. This may produce rise in blood pressure.
- Calcium metabolism: It increases calcium excretion. Also absorption of calcium from the gut is decreased. They also stimulate breakdown of the protein matrix of bone. All these effects lead to osteoporosis.
- Haematological actions: It decreases production of eosinophils and lymphocytes. But they stimulate erythropoiesis and production of polymorphonuclear leucocytes.
- Muscle: Muscle weakness seen in Addison's disease is corrected by glucocorticoids.
- GI tract: It stimulates the secretion of pepsin and hydrochloric acid of gastric juice.
- Anti-inflammatory effect: It inhibits inflammatory response caused by bacterial, chemical or immunological factors.
- CNS: It has an effect on psyche. Large doses can produce elevation of mood, euphoria and restlessness.

Adverse reactions:

- Cushing's syndrome characterised by rounding of face.
- Sodium retention and edema.
- Muscular weakness due to potassium loss.
- Gain in weight due to fluid retention and fat deposition.
- Glycosuria and aggravation of diabetes.
- Hypertension and congestive cardiac failure.

- Androgenic effects like hirsutism and amenorrhea.
- Psychological effects like euphoria and excitation.
- Osteoporosis and spontaneous fracture of bones.
- Peptic ulcer, perforation and haemorrhage.
- Increased susceptibility to infections.

MINERALOCORTICOIDS: Are aldosterone and deoxycorticosterone. Actions of these two compounds are almost similar. But aldosterone is thirty times more potent than deoxycorticosterone. Fludrocortisone is a synthetic mineralocorticoid.

Pharmacological actions:

- Induce reabsorption of sodium by the renal tubules.
- Increase urinary loss of potassium.
- Induce sodium reabsorption in the sweat and salivary glands.
- Excessive levels of aldosterone leads to hypernatremia, hypokalemia, increased plasma volume and hypertension.
- In case of aldosterone deficiency, there is hyperkalemia, decrease in blood volume and collapse.

Adrenocortical antagonists

AMPHENONE B: It inhibits the synthesis of adrenocortical steroids including aldosterone. It also has an antithyroid effect. The adverse reactions are CNS depression, gastrointestinal disturbances, liver damage and neurological symptoms.

METYRAPONE: It inhibits the synthesis of hydrocortisone and corticosterone. It also inhibits the synthesis of aldosterone. This leads to dieresis. Inhibition of the synthesis of adrenocortical steroids induces the liberation of ACTH. This in turn stimulates the production of mineralocorticoids. This produces sodium retention and nullifies the diuretic effect. Adverse reactions are dizziness and gastrointestinal disturbances.

AMINOGLUTETHIMIDE: It blocks the early steps in the pathway of the synthesis of adrenocortical steroids. So it inhibits the synthesis of adrenocortical steroids. It may be useful in reducing steroid secretion in patients with adrenocortical malignancy. Lethargy is a common side effect.

Androgens and anabolic steroids

The endocrine activity of the testes is carried out by cells known as interstitial cells or Leydig cells. They occur in groups in the connective tissues between the seminiferous tubules. The hormones secreted by these cells are known as androgens. The most important androgen is testosterone.

Physiological actions: Androgen is formed in the fetal testes under the influence of maternal gonadotropin. This causes descent of the testes. Later, no androgen is formed until puberty. At puberty, the hypophysial cells stimulate the Leydig cells to produce androgen. This leads to the development of testes and secondary sex characters. In adult male the effects of androgens are:

- Induction of spermatogenesis, growth of prostate and seminal vesicles.
- Changes in skin like appearance of pubic hair, axillary hair and beard hair.
- Growth promoting effect on body tissues including penile and scrotal growth.
- Growth of larynx and thickening of vocal cord such that the voice becomes low pitched.
- Skeletal growth and epiphyseal closure.
- Psychological and behavioural changes.

Adverse reactions:

- Enlargement of clitoris, deepening of voice, baldness, hirsutism, acne and masculinisation in females.
- Early closure of epiphysis and blockade of its growth.
- Suppression of spermatogenesis and degeneration of seminiferous tubules produced at large doses.
- Retention of sodium and edema.

ANABOLIC STEROIDS: Anabolic steroids were synthesized in an attempt to produce compounds with more anabolic effects and less androgenic effects. Anabolic steroids can be classified as:

Derivatives of testosterone	Nandrolone phenylpropionate Nandrolone decanoate
Derivatives of methyltestosterone	Oxymethalone Oxandralon Oxymesterone

Pharmacological actions:

- Protein anabolism: Promote protein anabolism. This manifests as increase in muscle mass and body weight.
- Anticatabolic effect: Catabolic effect of glucocorticoids are counteracted and a positive nitrogen balance is produced.
- Miscellaneous: Progestational activity and decrease in bone resorption which prevents osteoporosis.

Adverse reactions:

- Virilisation of foetus when given in pregnancy.
- Cholestatic jaundice and liver damage.
- Sodium and water retention of prolonged use.

Therapeutic uses:

- In chronic illness, to accelerate rebuilding of tissues.
- To promote growth in hypogonadal children and pituitary dwarfs.
- Carcinoma of the breast in females.

Estrogens and progestins

ESTROGENS: Are produced mainly in the ovary. Small amounts are produced by the placenta, adrenals and testes.

Classification of estrogens:

Natural estrogens	Estradiol Estrone Estriol
Semisynthetic estrogens	Ethinyl estradiol
Synthetic estrogens	Stilbesterol Mestranol Hexoesterol Chlorotrianesene

Actions:

- Growth and development of vagina, uterus, fallopian tube and also secondary sex characters.
- Growth of ducts in the mammary gland.
- Growth of axillary and pubic hair.
- Distribution of body fat and accumulation around hip and breasts. This produces typical femal body contour.
- Development of endometrial lining.
- Metabolic changes like retention of sodium, nitrogen and fluid in tissues.

Adverse reactions:

- Nausea, vomiting, diarrhoea and anorexia.
- General malaise and dizziness.
- Sodium and water retention leading to edema and breast engorgement.
- Development of endometrial carcinoma.

Therapeutic uses:

- To control menopausal symptoms.
- In atrophic vaginitis.
- In postpartum breast engorgement.
- Amenorrhea, dysmenorrhea and menorrhagia.
- Substitution therapy in ovarian dwarfism.
- Acne and hirsutism.

PROGESTINS: Progesterone is the natural progestin. It is secreted by the ovary. It is also synthesized by placenta, adrenals and testes.

Classification of progestins:

Progesterone and its derivatives	Progesterone Hydroxy progesterone caproate Medroxy progesterone acetate Chlormadinone acetate
Derivatives of testosterone	Ethisterone Dimethisterone
Derivatives of 19-nor testosterone	Norethisterone Norethynodrel Norgestrel Lynesterol

Physiological functions:

- Maturation and secretory changes of endometrium.
- Development of alveolar system of breast.
- Preparation of the endometrium for implantation of fertilised ovum.
- Metabolic changes like increase in body temperature.

Therapeutic uses of progestins:

- Treatment of threatened and habitual abortion.
- To relieve pre-menstrual tension.
- Treatment of dysfunctional uterine bleeding.
- To induce menstruation in amenorrhea.
- As oral contraceptives.

Thyroid and antithyroid drugs

THYROID HORMONES: Secretion of thyroid hormones is controlled by thyroid stimulating hormone secreted by anterior pituitary. They are stored in the thyroid gland as thyroglobulin. About 80 micrograms of thyroid hormones are secreted by day.

Pharmacological actions: Thyroid hormones produce major effects on growth and metabolism. These effects are:

- Increase in oxygen consumption and heat production in most tissues.
- Increase in basal metabolic rate.
- Intra-uterine and extra-uterine growth as also tissue differentiation.
- Anabolic effects like promotion of growth and protein synthesis.
- Increase in the absorption and utilisation of glucose.
- Increase in the rate of cholesterol synthesis in the liver.
- Myelination of central nervous sytem.

Therapeutic uses:

- In hypothyroid states like cretinism and myxoedema.
- In the treatment of non-toxic goitres.
- In the treatment of obesity.
- To lower cholesterol content of blood.

ANTITHYROID DRUGS: Are those which are used in the treatment of hyperthyroidism. These drugs control the over production of thyroid hormones.

Classification of drugs:

Thiourea derivatives	Propylthiouracil Methiamazole Carbimazole
Ionic inhibitors	Potassium thiocyanate Potassium perchlorate
Iodides	Sodium iodide Potassium iodide Lugol's iodine
Radioactive iodine	I^{131}

THIOUREA DERIVATIVES:

Mechanism of action: The thiourea compounds act by:

- Inhibiting the oxidation of iodide to iodine.
- Inhibiting the incorporation of iodine into tyrosyl residues of thyroglobulin.

Absorption, fate and excretion: These drugs are well absorbed within 20 to 30 minutes after oral administration. Only a fraction is metabolised in the body. The rest is excreted unchanged. They cross placental barrier and also are secreted in milk.

Adverse reactions:

- Drug fever, skin rashes and arthralgia.
- Leucopenia, agranulocytosis and thrombocytopenia.
- Hypothyroidism and goitre.

Therapeutic uses:

- Treatment of hyperthyroidism
- In the preparation of patients for thyroid surgery.

IONIC INHIBITORS: These drugs competitively inhibit the trapping of iodide by the thyroid gland. This effect can be countered by an excess of iodide ions

IODIDES: The iodides act by decreasing the response of thyroid gland to TSH. Iodides shut off the release of preformed thyroid hormones. This effect is called as thyroid constipation. Actions: a) the secretion of thyroid hormones is decreased, b) there is a fall in basal metabolic rate, c) the gland becomes less vascular and firm, d) the acinar cells become small in size and colloid content increases. Adverse reactions: iodism characterised by skin rashes, lacrimation and increased salivary secretion.

RADIOACTIVE IODINE: I^{131} is the isotope of iodine that has a half-life of 8 days. It is trapped in the thyroid gland. It is incorporated into thyroid hormones and stored in the colloid. It emits beta and gamma rays. The beta rays destroy the overactive thyroid tissue and inhibit their replication. Radioactive iodine reuires no hospitalisation. Also it is useful in patients who cannot undergo surgery. Adverse reactions: febrile reactions, decrease in leucocyte count, neoplastic changes in the thyroid, damage to foetal thyroid and hypothyroidism.

Oral antidiabetic drugs

Insulin is ineffective orally and so it has be injected. But the oral antidiabetic drugs lower blood glucose level on oral administration.

Classification of drugs:

Sulfonylureas	
a. First generation	Tolbutamide Chlorpropamide
b. Second generation	Glibenclamide Glipizide Glyclazide Glymepiride
Biguanides	Phenformin Metformin

SULFONYLUREAS: These compounds are chemically related to sulphonamides. They have the following basic structure:
R1 – SO2NH – CONH – R2

Pharmacological actions:

- Lowers blood sugar level on oral and parenteral administration.
- Lowers blood sugar level in some of the diabetic and in all non-diabetic individuals.
- Effective only in presence of functional pancreas.
- Produce increase in body weight like insulin.

Mechanism of action:

- Stimulation of the synthesis and release of insulin from the beta cells of islets of Langerhans.
- Increase in the number of beta cells.
- Inhibition of glycogenolysis and gluconeogenesis.
- Decrease in the rate of insulin degradation.

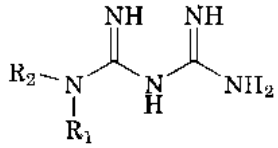
Absorption, fate and excretion: Sulfonylureas are rapidly absorbed from gastrointestinal tract. They are partly bound to plasma proteins. They are metabolised in liver and excreted in urine.

Adverse reactions:

- Hypoglycaemia and this effect is potentiated by phenylbutazones and salicylates.
- Allergic reactions leading to skin rashes.
- Bone marrow changes like leucopenia and thrombocytopenia.
- Hypothyroidism and goitre.
- Potentiating of barbiturates and other sedative hypnotics.

Therapeutic uses: In the treatment of maturity onset diabetes, insulin resistant diabetes and diabetes insipidus.

BIGUANIDES: Biguanides have the following general chemical structure



Pharmacological actions:

- Lowers blood sugar level only in a diabetic individual but not in a normal individual.
- Potentiate the hypoglycaemic action of insulin and sulfonylureas.
- Inhibit lipogenesis in adipose tissue.
- Increase fibrinolytic activity of plasma.

Mechanism of action:

- Presence of exogenous or endogenous insulin is necessary for the action of biguanides. But insulin release from pancreas is not stimulated.
- Peripheral utilisation of glucose is stimulated.
- Absorption of glucose from intestine is inhibited.

Absorption, fate and excretion: Biguanides are well absorbed from gastrointestinal tract. Maximum activity occurs in 4 hrs. They are eliminated through urine within 24 hrs.

Adverse reactions:

- Unpleasant, bitter or metallic taste.
- Abdominal discomfort, anorexia and nausea.
- Lethargy and muscle weakness.
- Decrease in body weight.

Therapeutic uses:

- Obese mild diabetics.
- Non-diabetic obese patients.
- In patients allergic to sulfonylureas.

Alpha-glucosidase inhibitors:

ACARBOSE: It is an alpha-glucosidase inhibitor. By reversibly binding with this enzyme, it prevents the absorption of glucose. This effect occurs in the brush border of small intestine. It can be used with insulin, sulfonylureas or biguanides.

MEGLITOL: It is another alpha-glucosidase inhibitor. It acts by similar mechanism as acarbose.

UNIT V: CHEMOTHERAPY

Chemotherapy is defined as the treatment of specific infections with chemical agenst. It includes therapy with antibiotics and also conditions where infection is not involved e.g. malignancy. A chemotherapeutic agent may be:

- Bacteriostatic if it inhibits the growth of bacteria.
- Bactericidal if it destroys and kills the bacteria.

Chemotherapeutic agents include synthetic substances e.g. sulphonamides and antibiotics e.g. penicillin.

Synthetic antimicrobial agents

SULPHONAMIDES: Are antimicrobial agents which contain a sulphonamide group. They are derivatives of the parent compound, para aminobenzene sulphonamide. Sulphonamides inhibit the growth of gram-positive and gram-negative bacteria, actinomyces and *Nocardia*, *Chlamydia* organisms causing lymphogranuloma venerum and psittacosis. Sulphonamides are mainly bacteriostatic. But at very high concentrations they may have bactericidal effEct. Sulphonamides compete with PABA for incorporation into folic acid and inhibit the enzyme folic acid synthetase. So folic acid which is essential for bacterial growth is not synthesised.

Therapeutic uses:

- Acute bacillary dysentery.
- Ulcerative colitis.
- Urinary tract infection and chancroid.
- Meningococcal meningitis.
- Trachoma and inclusion conjunctivitis.

NITROFURANS: Are synthetic antimicrobial agents. They include nitrofurantoin, furazolidone, nitrofurazone and nifuroxime. They are bacteriostatic in low concentrations and bactericidal in high concentrations. They are effective against a variety of gram-positive and gram-negative organisms, protozoa like *Trichomonas vaginalis* and fungi like *Candida albicans. By acting on DNA, nitrofurans produce various changes in microorganisms.*

FLUOROUINOLONES: They contain fluorine in their structure and are chemically related to nalidixic acid. The important drugs are ciprofloxacin, norfloxacin, ofloxacin and pefloxacin. They are bactericidal. They inhibit the enzyme DNA gyrase. This prevents DNA replication. They are highly effective against *Enterobacteriaceae*, *H. influenza*, and *Pseudomonas aeruginosa.*

Therapeutic uses:

- Urinary tract infections.
- Severe GI infections like gastroenteritis.
- Invasive external otitis due to *Pseudomonas.*
- Chronic gram negative osteomyelitis.
- First choice in typhoid fever.

Antibiotics

Antibiotics are chemical substances synthesized by various species of microorganisms and produce suppression of growth and destruction of other rmicroorganisms.

Classification of antibiotics:

Broad spectrum antibiotics	Tetracyclines Chloramphenicol Cycloserine
Narrow spectrum antibiotics	
Effective against gram-positive bacteria	Penicillins Erythromycin Lincomycin Vancomycin Novobiocin
Effective against gram-negative bacteria	Streptomycin Kanamycin Gentamicin Cycloserine
Antiprotozoal antibiotics	Paramomycin Fumagillin
Antifungal antibiotics	Nystatin Amphotericin B Griseofulvin Hamycin Pimaricin
Antimalignant antibiotics	Actinomycin D

PENICILLINS: The most important of the antibiotics are obtained from *Penicillium notatum* and *Penicillium chrysogenum*. It is a narrow spectrum antibiotic very effective against gram-positive organisms like *Gonococci, Pneumococci, Meningococci, Treponema pallidum, Bacillus anthracis, Corynebacterium diphtheria, Clostridium welchii*, etc.

Classification:

Acid resistant	Potassium phenoxymethyl penicillin Potassium phenoxyethyl penicillin
Penicillinase resistance penicillins	Methicillin Cloxacillin Dicloxacillin Nafcillin
Broad spectrum penicillins	Ampicillin Talampicillin Amoxicillin

Mechanism of action: Penicillin is a bactericidal drug. It acts by inhibiting the synthesis of bacterial cell wall. This action is produced by inhibiting the synthesis and cross linkage of peptidoglycans.

Absorption, fate and excretion: On oral administration, benzyl penicillin is inactivated by gastric acid. Also food interferes with its absorption. It is rapidly absorbed after subcutaneous or intramuscular injection. About 60% is bound to plasma proteins. It is distributed in kidneys, liver, plasma and intestine. Normally it is not taken up by CSF. But high concentrations are present in CSF during meningeal inflammation. It is eliminated through urine by tubular secretion.

Adverse reactions: Intolerance which includes allergic and anaphylactic reactions. Allergy is the major problem which may occur in the form of skin rashes, renal disturbances and haemolytic anemia. The manifestations of anaphylaxis are cardiovascular collapse, bronchospasm and angioedema.

Therapeutic uses: Used against streptococcal, pneumococcal and meningococcal infections, veneral diseases like gonorrhoea and syphilis, diphtheria, tentanus and gas gangrene, actinomycosis and anthrax, in the prophylaxis of rheumatic fever and streptococcal infections.

CEPHALOSPORINS: Are derived from *Cephalosporium acremonium* and have a structural resemblance to 6-APA nucleus of penicillins. They are effective against both gram-positive and gram-negative bacteria.

Classification:

1st generation	Cephalexin, Cephalothin, Cefazolin
2nd generation	Cefoxitin, Cefuroxime, Cefaclor
3rd generation	Cefotoxime, Ceftazidime, Ceftizoxime
4th generation	Cefepime, Cefpirome

Mechanism of action: The cephalosporins are bactericidal. They act by the same mechanism as penicillin by inhibiting cell wall synthesis of bacteria. But they bind to a different protein of the cell wall.

Absorption, fate and excretion: Cephalosporins are administered orally or intravenously. Intramuscular injection is painful. They bind to plasma proteins. The extent of protein binding varies with individual cephalosporins. Penetration into CSF is poor. Most of them are eliminated by tubular secretion. Their elimination is decreased by probenecid.

Adverse reactions: The cephalosporins produce skin rashes, fever and serum sickness, eosinophilia, neutropenia and splenomegaly, azotemia and anaphylactoid reaction, renal damage.

Therapeutic uses: Used in infections resistant to penicillin, patients allergic to penicillin, urinary tract infections produced by *E. coli* and *Aerobacter*.

TETRACYCLINES: Are broad spectrum antibiotics. They are effective against gram-positive organisms, gram-negative organisms, actinomyces, rickettsiae and Chlamydia organisms. It is obtained from *Streptomyces aureofaciens*. They are bacteriostatic. They act by inhibition of enzyme systems and protein synthesis, chelation of cations like calcium and magnesium and interference with phosphorylation of glucose.

Absorption, fate and excretion: Tetracyclines are adequately absorbed from GI tract. They chelate cations. Hence cations in milk and antacids prevent absorption of tetracyclines. They are widely distributed in body tissues and fluids including CSF. They are excreted mainly in urine by glomerular filtration.

Adverse reactions: Intolerance like skin rashes and photosensitivity, GI disturbances, liver damage, renal disturbances, dental effects like yellow staining of teeth, bone changes like decrease in linear growth, superinfection and deficiency of vitamin K due to inhibition of intestinal microflora.

Therapeutic uses: Used against rickettsial infections, Chlamydia infections, bacillary and amoebic dysentery, venereal diseases like gonorrhoea and syphilis.

Chemotherapy of urinary tract infections

Urinary tract infection (UTI) occurs in both sexes. These infections may be acute or chronic. Most of the UTI occur due to gram-negative bacilli. The causative organisms are *E. coli, Aerobacter, P. aeruginosa, P. mirabilis, Klebsiella*, *Streptococci* and *Staphylococci.*

Classification of drugs:

Synthetic drugs	Sulphonamides Nitrofurantoin Cotrimoxazole Methenamine mandalate Nalidixic acid
Antibiotics	Ampicillin Cephalothin Streptomycin Kanamycin Gentamicin Fluoroquinalones Cycloserine Polymyxin B

Chemotherapy of malaria

Malaria is caused by a parasitic protozoan which belongs to the genus *Plasmodium*. The symptoms of malaria are fever, rigor and splenomegaly.

Classification of drugs:

Cinchona alkaloids	Quinine
4-aminoquinolines	Chloroquine Hydroxychloroquine Amodiaquine
8-aminoquinolines	Pamaquine Primaquine Pentaquine
Acridines	Mepacrine
Biguanides	Proguanil Chlorproguanil Cycloguanil
Diamidopyrimidines	Pyrimethamine
Miscellaneous	Mefloquine Halofantrine Qinghaosu

Chemotherapy of tuberculosis

Tuberculosis is an infectious disease caused by the mycobacteria, *M. tuberculosis* and *M. bovis*. It was once considered to be an incurable disease. But now effective chemotherapeutic agents are available for its treatment.

Classification of drugs:

Primary or standard drugs	
Bactericidal	Isonicotinic acid hydrazide Rifampicin Streptomycin Pyrazinamide
Bacteriostatic	Ethambutol Para aminosalicylic acid Thiacetazone
Secondary or reserve drugs	
Bactericidal	Capreomycin Kanamycin
Bacteriostatic	Ethionamide Cycloserine

Chemotherapy of amoebiasis

Amoebiasis is a protozoal disease caused by *Entamoeba histolytica*. Amoebiasis can be classified as: a) intestinal amoebiasis with symptoms of dysentery, amoeboma, etc. b) extraintestinal amoebiasis which may affect liver, lungs or brain.

Classification of drugs:

Tissue amoebicides	
a. For both intestinal and extraintestinal amoebiasis	Metronidazole Tinidazole Secnidazole Emetine Dehydroemetine
b. For extraintestinal amoebiasis only	Chloroquine
Luminal amoebicides	Diloxanide furoate Halogenated hydroxy quinolines Tetracycline

Disinfectants and antiseptics

A disinfectant or germicide is a substance which kills microorganism in the inanimate environment.

An antiseptic is a chemical disinfectant that can be safely applied to skin or mucous membranes.

Classification:

Acids	Benzoic acid, salicylic acid and boric acid
Alkalies	Sodium and potassium hydroxide
Aldehydes	Formaldehyde and gluteraldehyde
Alcohols	Ethyl alcohol
Surfactants	Soaps and benzalkonium
Halogens	Chlorine and iodine
Phenols	Phenol and cresol
Oxidising agents	Hydrogen peroxide and potassium permanganate
Dyes	Crystal violet and acriflavine
Heavy metals	Silver, zinc and mercurial compounds

Acids:

- Benzoic acid: It is used as a preservative and for treating fungal infections.
- Salicylic acid: It has bacteriostatic, fungicidal and keratolytic properties. Whitefield's ointment contains salicylic acid and benzoic acid. It is widely used in fungal infections.
- Boric acid: It is a bacteriostatic and fungistatic agent. It is used as an aqueous solution, drops or lotion.

Alkalies: Alkalies like sodium and potassium hydroxides are highly irritant. So they are used only for disinfecting excreta.

Aldehydes: Formaldehyde is highly irritant. It is used for disinfecting surgical gloves, instruments and excreta. Gluteraldehyde is less irritant. It is used for sterilizing rubber, plastic and metal appliances.

Alcohols: 70% solution of ethyl alcohol is used as antiseptic. It is also used for sterilisation of surgical instruments.

Surfactants: Surfactants are chemical compounds which lower the surface tension of solutions. They are also called as detergents. Soap is an anionic surfactant. It is effective against gram-positive and acid-fast organisms. Benzlkonium is a cationic surfactant. It is useful for cleaning and disinfecting burns, wounds, surgical instruments, etc.

Halogens: Chlorine is used for purification of water. Chloramine acts by releasing chlorine. It is used for disinfection. Iodine has a bactericidal, fungicidal, amoebicidal and sporicidal effects. Iodine is used for the treatment of wounds and abrasions.

Phenols: Phenol and cresol have bactericidal and fungicidal effects. Both have corrosive effect on GI tract.

Oxidising agents: Hydrogen peroxide produces antiseptic effect due to release of nascent oxygen. It is used for cleaning wounds and abscess. Potassium permanganate has oxidising and astringent properties. It is used as a gargle and mouth wash.

Dyes: Crystal vioet is a potent antiseptic. It is applied topically for the treatment of burns, boils, impetigo and mycotic infections of the skin. Acriflavine, an acridine dye is an antiseptic. It is used for the treatment of infected burns and wounds.

Heavy metals: Silver nitrate has antiseptic and astringent properties. It is used as eye drops in conjunctivitis. Zinc sulphate is used as an astringent lotion. It is used for indolent ulcers and to assist granulation. Mercury compounds act by inhibiting SH enzymes of bacteria. Mercuric oxide is used as an ointment in the treatment of conjunctivitis.