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Learning Outcome of Module-1

LO	Learning Outcome	Course Outcome Code
LO1	To Understand the different terms used in Pharmacology.	BP404.1
LO2	To Understand the scope of pharmacology.	BP404.1
LO3	To Understand the Essential drug Concept and route of administration.	BP404.1
LO4	To understand the membrane transport system	BP404.1
LO5	To Understand the Pharmacokinetics	BP404.1

CONTENT TABLE

INTRODUCTION TO PHARMACOLOGY

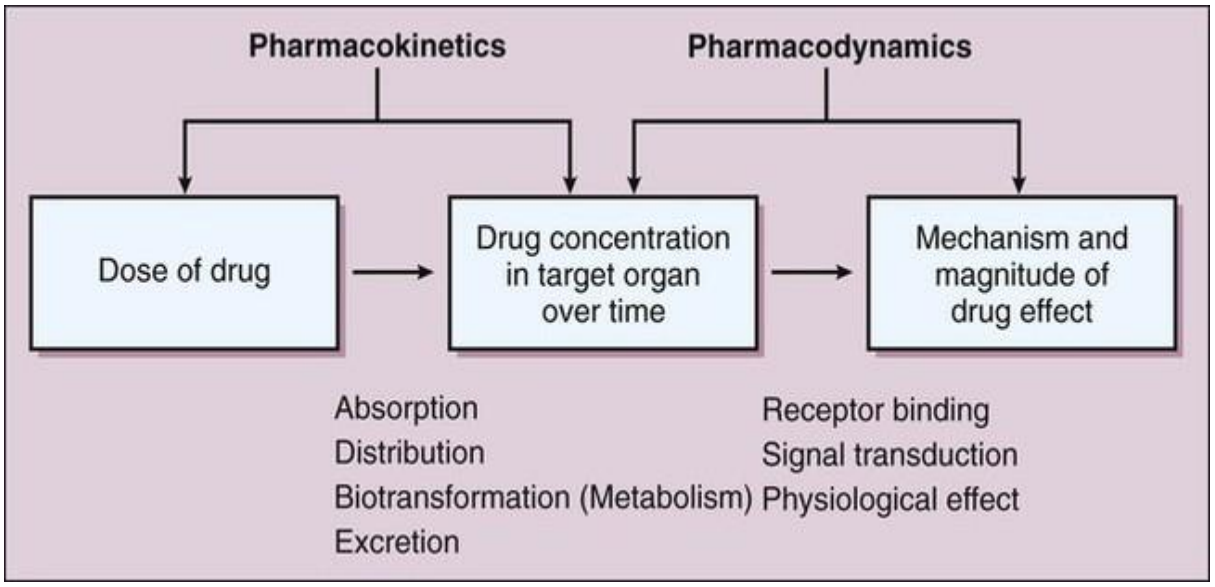
***Pharma*=Drugs, *Logos* = Knowledge (Pharmacology = study of drugs)**

Pharmacology: It is the science of drugs derived from two Greek words: Pharmakon (Greek word for drugs) and logos (the Greek word for science). It is the study of the actions of drugs on living system.

It includes physical and chemical properties, biochemical and physiological effects, mechanism of action, therapeutic uses and adverse effects of drugs.

Drug Any chemical that affects the processes of a living organism

The pharmacology from medical point of view can be further divided into Pharmacokinetics and Pharmacodynamics actions therapeutically.



Pharmacokinetics and Pharmacodynamics Pharmacology

Pharmacokinetics: It includes the study of absorption, distribution, metabolism and excretion of drug. It deals with the drug from its entry in the body, its excretion, and what happens to drug in the body is known as pharmacokinetics.

Pharmacodynamics: It is concerned with the study of mechanism of action of drugs and Pharmacological effect produced on the human body. The drugs administered are not having effectiveness only but they have also adverse effects, side effects and toxicity. The drug used for treatment should be of maximum effectiveness and with minimum toxicity and side effects. The drug is administered for one of its particular and therapeutically useful effect on the body, where as a drug does not have single effect. It has a number of effects on our body. The drug used in clinical purpose should have maximum medicinal effectiveness and minimum toxicity. The term therapeutic index is used to express safety of drug in clinical practice.

HISTORICAL LANDMARKS OF PHARMACOLOGY

Knowledge of drugs and their uses in diseases are as old as history of mankind. Primitive men gather the knowledge of healing and medicines by observing the nature, noticing the animals while ill and personal experience after consuming plants and herbs as remedies.

Ancient civilizations discovered that extracts from plants, animals, and minerals had medicinal effects on body tissue. These discoveries became the foundation of pharmacology.

Pharmacology in the present form is relatively recent branch about hundred years old.

PEN PSAO (2700 BC) It was the great herbal materia medica written in china.

Kahun Papyrus (2000 BC) is an oldest Egyptian document containing information about veterinary medicines and uterine diseases of women.

Ebers papyrus (1550 BC) also an Egyptian document containing information about number of diseases and 829 prescription where castor oil, opium like drug are being used.

Hippocrates (460-375 BC) A greek physician consider "father of Medicine". He was the first person who recognize disease as abnormal reaction of body. He introduce use of metallic salts for the treatment of disease.

Theophrastus (380-287 BC) a great philosopher called father of Pharmacognosy. He classified medicinal plants on the base of medicinal characteristics.

Dioscorides (AD 57) a greek, produced one of the first materia medica of approximately 500 plants and remedies.

Claudius Galen (AD 129–200) first attempted to consider the theoretical background of pharmacology.

Paracelsus (1493–1541) a Swiss scholar and alchemist, often considered the "grandfather of pharmacology". He introduces the use of chemicals for treatment of disease.

Valerius Cordus (1514-1544) He compiled the first pharmacopeia where he described techniques for the preparation of drugs.

MODERN PHARMACOLOGY

Conversion of old medicines into the modern pharmacology start taking shape following the introduction of animal experimentation and isolation of active ingredients from plants. *Francois Megendie (1783-1855)* a first pharmacologist established the foundation

of modern pharmacology. He developed experiment to elucidate the physiological processes and action of drugs on the body.

Rudolph Buchheim (1820–1879) German pharmacologist a key figure in the development of pharmacology, a who at the University of Dorpat, created the first pharmacological institute.

Frederich Sertürner, German pharmacist's assistant, isolated morphine—the first pure drug—in 1805

Claude Bernard (1813-1878) considered Father of experimental Medicine. He identifies the site of action of curare (arrow Poisoning).

Oswald Schmiedeberg (1838–1921) "Father of Pharmacology" established pharmacology as an independent discipline. He starts teaching Pharmacology in University of Strasbourg (France).

John Jacob Abel (1857-1938) founded first department of pharmacology in USA in the University of Michigan in 1893. In 1897 he established pharmacology department at Johns Hopkins University. Abel also co- founded the Journal of Pharmacology and Experimental Therapeutics in 1909.

L. mayer Jones (1912-2002) regarded as father of modern veterinary pharmacology. He authored first book of veterinary pharmacology therapeutics in 1954.

SCOPE OF PHARMACOLOGY

It provides the rational basis for the therapeutic use of the drug. Before the establishment of this discipline, even though many remedies were used, but doctors were reluctant to apply scientific principles to therapeutics.

In 1920s, many synthetic chemicals were first introduced and the modern pharmaceutical companies began to develop.

Scientific understanding of drugs enables us to predict the pharmacological effect of a new chemical that will produce a specified therapeutic effect.

The scope of pharmacology has expanded greatly over the last decade to incorporate many new approaches such as computer-assisted drug design, genetic screens, protein engineering and use of novel drug delivery vehicles including viruses and artificial cells.

Our society needs pharmacologists who understand the basis of modern therapeutics for careers within academic, pharmaceutical and governmental laboratories to study and develop tomorrow's drugs.

Clinical Testing Drug:

The main objectives of the clinical testing (trial) of a new drug are

(1) To determine the efficacy and safety of the new products.

(2) The optimal conditions of use of the drug.

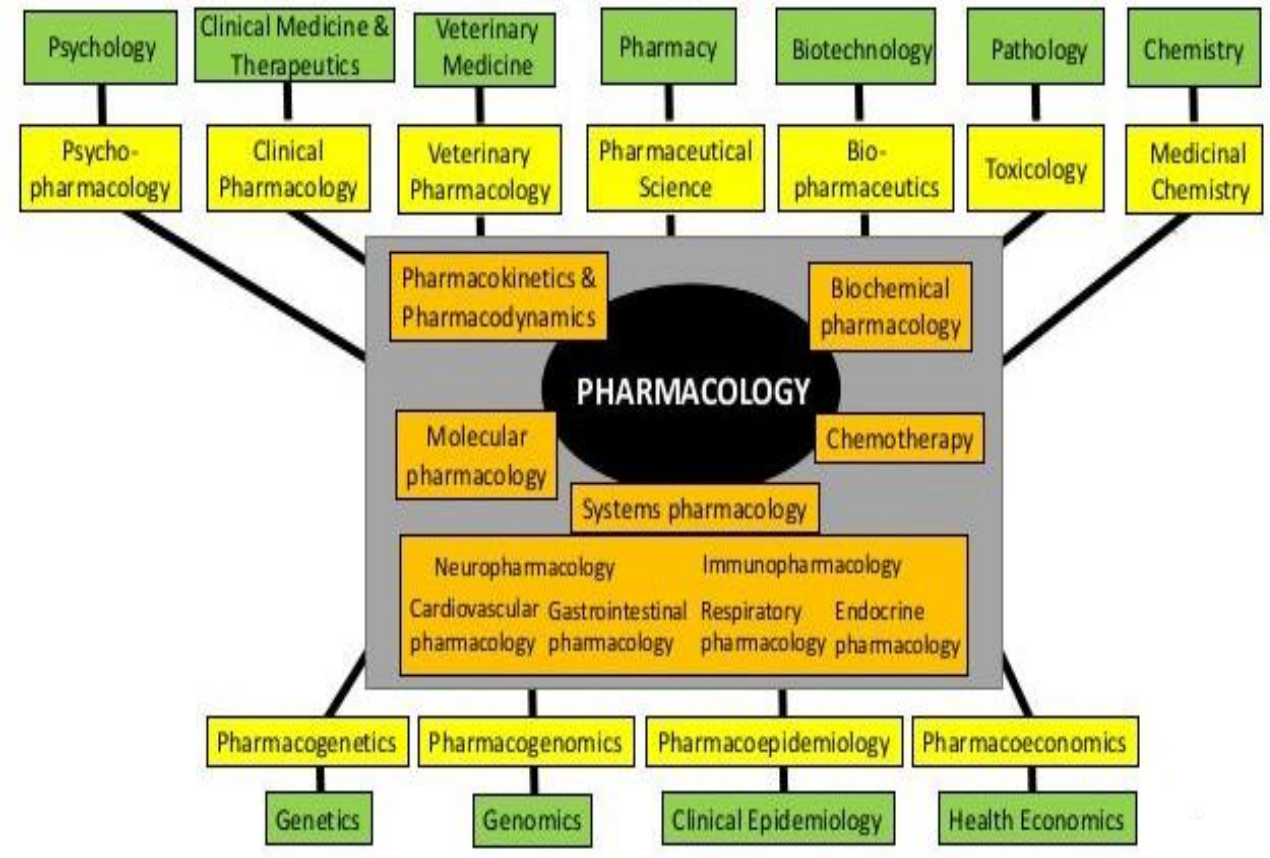
(3) To assess dosage and necessary precautions to be taken for use of drugs.

(4) Method (route) of administration of drug i.e. to be administered orally, by parenteral route or both.

(5) What precautions to be adopted to assure maximum efficacy and usefulness of the drug. While conducting any clinical trial it must be ensured that nothing to be done that may harm the concerned individual.

Evaluation

The new product synthesized or invented requires rigorous pharmacologic study and evaluation to determine its mechanism of action, therapeutic uses, toxicity etc. The study of metabolism and excretion of the drug is must to be conducted. The clinical trials are made in the laboratory on animals and on human volunteers.



A diagram representing the scope of Pharmacology

The pharmacology has two types:

(1) Clinical pharmacology: The clinical pharmacology deals with the study of actions/effects of drugs in human beings.

(2) Experimental pharmacology: The experimental pharmacology deals with the action and effect of drug on experimental animals such as action on rodents, non rodents. The experiments and clinical trials are performed in the laboratory.

Pharmacology.- Pharmacology is defined as the science of drugs. The term is derived from Greek words ***pharmakon,*** meaning a drug and ***logos,*** meaning a study. It includes knowledge about the sources of drugs, their absorption, distribution, metabolism, and excretion, their mode of action or mechanism of action and their toxicity. Pharmacology has major subdivisions, Pharmacokinetics, Pharmacodynamics, Pharmacotherapeutics, Therapeutics, Chemotherapy, Toxicology etc.

Pharmaceutical sciences Pharmacy is the study of the preparation, compounding and dispensing of medicines. It is the science and art of preparing a drug or drug combination, in a suitable dosage form, fit for administration to the patient. The pharmacist concerned primarily with preparing, compounding and dispensing medicines upon the written order of a licensed medical practitioner.

Pharmacokinetics: (Greek: ***kinesis***, means movement) is the study of the fate of drugs in the body, right from the time they enter the body until they, or their by-products, are eliminated from the body, or movement of drugs in the body. In other words this includes absorption, distribution, metabolism and excretion of drugs. These studies are done both in animals and man, and the data are essential for the safe use of drugs.

Pharmacodynamics: (Greek **dynamics** means force) is the experimental study of actions of drugs on the living organism, including their mode of action or mechanism of action.

Pharmacotherapeutics: (Greek ***therapeia*** means medical treatment) - Pharmacotherapeutics is the treatment of disease by means of drugs. It utilizes information on drugs obtained by
pharmacodynamic studies.

Therapeutics: (Greek ***therapeutike***, means medical practice) Therapeutics is the practical branch of medicine dealing with the science and art of the treatment of disease. Empirical therapeutics is therapy bases on clinical evidence that the drug is effective, although the mechanism by which it act is unknown.

Chemotherapy: according to the definition proposed by Paul Ehrlich, deals with the use of drugs capable of inhibiting or destroying invading microbes, parasites, or cancer cells, while having minimal effect on healthy living tissues.

Toxicology: (Greek ***toxikon*** means poison) Toxicology is the science of poisons, their sources, chemical composition, action, tests for detection and antidotes. It forms a major

part of forensic and environmental medicine. All drugs are potential poisons when given in high doses.

Clinical toxicology deals with the detection, diagnosis and treatment of poisoning. **Toxicodynamics** describes the harmful effects that the poison produces on the body. **Toxicokinetics** encompasses the absorption, distribution, biotransformation and elimination of the poison.

Pharmacognetics: This is a relatively new field, and deals with the study of genetically determined variation in drug response.

Clinical Pharmacology: Clinical pharmacology is the division which deals with the pharmacological effects of drugs in man. It provides information about the usefulness, potency, and toxicity of new drugs in humans. It is of great importance for the effective and safe use of drugs in man.

SOURCES OF DRUG INFORMATION

The sources of drug information is received by pharmacopeia, that is a book which contains a list of established and officially approved drug with description of their physical and chemical characteristics and tests for their identification, purity, methods of storage etc. some of the pharmacopeia's are:

•Indian Pharmacopeia. (I.P.)

•British Pharmacopeia (B.P.)

•European Pharmacopeia. (E.P)

• United states Pharmacopeia. (U.S.P).

Other sources of drug information are:

• National formulary (NF), Martindale – The extra Pharmacopeia,

• Physician desk Reference (PDR),

• American Medical Association drug Evaluation,

• Textbook & Journal of pharmacology and therapeutics, Drug bulletins, data bases like drug Micromedex, Medline, Cochrane library etc.

• Sources of drug information is also present in Formulary which provides information about available drugs – their use, dosage, adverse effect, contraindications, precautions, warnings and guidance on selecting right drugs for a range of conditions.

NATURE AND SOURCE OF DRUGS

The drug are represented by three names, which is commonly known as

1. Chemical Name

2. Non proprietary name-Generic name

3. Propitiatory name-Brand name

The use of natural products with therapeutic properties is as ancient as human civilization and, for a long time, mineral, plant and animal products were the main sources of drugs

Plant Source: The drugs are obtained from plant origin. Plants can be used as therapeutic resources in several ways. It can be used as herbal teas or other homemade remedies when they are considered as medicinal plants. They can be used as crude extracts or "standard enriched fractions" in pharmaceutical preparations, such as tinctures, fluid extracts, powder, pills and capsules, when they are considered as phytopharmaceutical preparations or herbal medicines. Finally, plants can be subjected to successive extraction and purification procedures to isolate the compounds of interest, which can themselves, be active and used directly like a drug, examples being quinine, digoxin and ergotamine.

Animal Source: Drugs obtained from an animal source. Some animal sources continue to be used to procure some modern drugs because of cumbersome and expensive procedures for the synthesis of such chemicals. For example Insulin, extracted from pork and beef pancreas, is used for the treatment of diabetes mellitus. Thyroid powder is used for treating the hypothyroidism. Heparin is used as an anticoagulant.

Mineral Sources: Drugs obtained from mineral origin Minerals or their salts are useful pharmacotherapeutic agents. For example: Ferrous sulfate is used in iron deficiency anaemia. Magnesium sulfate is employed as purgative. Kaolin (aluminum silicate) is used as an adsorbent in antidiarrheal mixtures.

Microbiological Sources: Many life-saving drugs are obtained from fungi, molds and bacteria e.g. penicillin from Penicillium notatum, chloramphenicol from Streptomyces Venezuela, grisofulvin (an anti-fungal drug) from Penicillium griseofulvum, neomycin from Streptomyces fradiae and streptomycin from Streptomyces griseous.

Semisynthetic Sources: Sometimes semi-synthetic processes are used to prepare drugs when the synthesis of drugs (complex molecules) may be difficult, expensive and uneconomical or when the natural sources may yield impure compounds. In these situation this methods play an important role. For examples are semi-synthetic human insulin and 6-aminopenicillanic acid derivatives. These are prepared by chemically modifying substances that are available from natural source improve to improve its potency, efficacy and also reduce side effects.

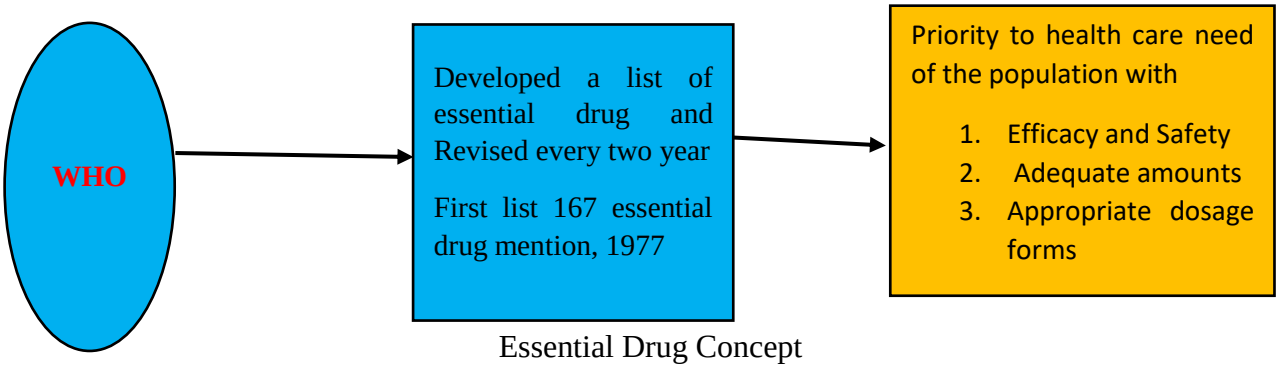
Synthetic Sources: The drugs used in clinical practice are prepared synthetically, such as aspirin, oral antidiabetics, antihistamines, amphetamine, chloroquine, chlorpromazine, general and local anesthetics, paracetamol, phenytoin, synthetic corticosteroids, sulphonamides and thiazide diuretics. Most of the synthetic drugs are prepared synthetically i.e. by chemical process (reaction) with the help of the knowledge of the phytochemical investigation.

Biosynthetic Sources: DNA Recombinant Technology This is relatively a new field which is being developed by mixing discoveries from molecular biology, recombinant DNA technology, DNA alteration, gene splicing, immunology and immunopharmacology. Some of the recent developments are genetically engineered novel vaccines (Recombinex HB- a hepatitis-B vaccine), recombinant DNA engineered insulins (Humulin- human insulin) for diabetes and interferon-alpha-2a and interferon-alpha-2b for hairy cell leukemia.

ESSENTIAL DRUGS CONCEPT

The essential drugs concept combined two emergent critical discourses regarding the role of biomedicine in public health.

Definition: Essential medicines as defined by the World Health Organization (WHO), are the medicines that "*satisfy the priority health care needs of the population*". These are the medications to which people should have access at all times in sufficient amounts. World Health Organization (WHO) introduced the concept of essential medicines in 1977. These drugs are selected in the list with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.



Essential Drug Concept

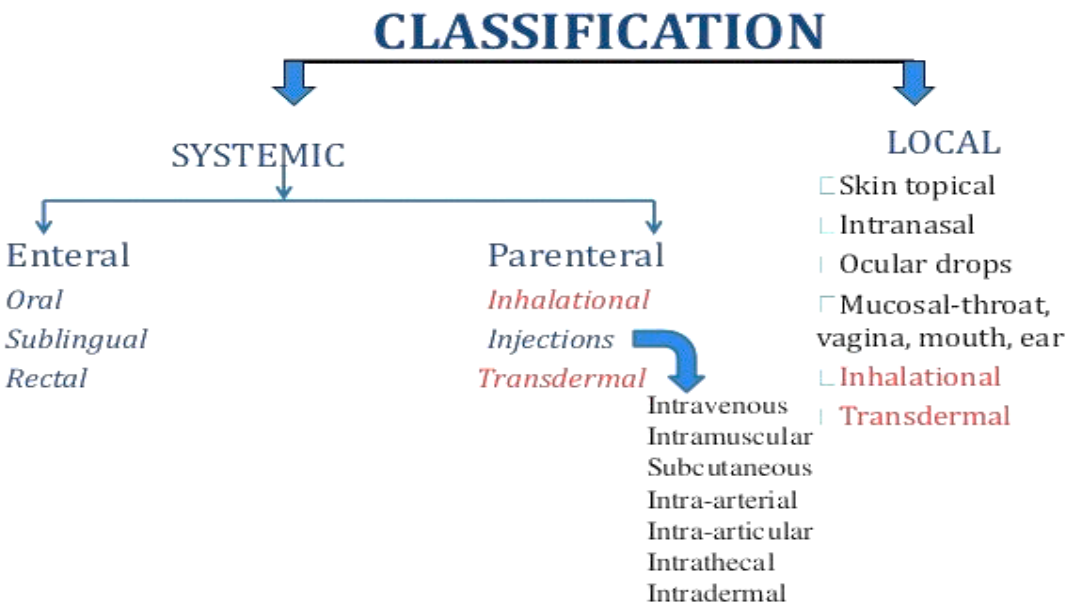
Basic concept of essential drugs

The implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential

remains a national responsibility. It has shown that careful selection of a limited range of essential medicines results in a higher quality of care, better management of medicines (including improved quality of prescribed medicines), and a more cost-effective use of available health resources.

WHO has developed the first list 167 essential medicines in 1977 and since then the list has been revised every 2 years. The current one is the 15th model list released in 2007. The essential medicine list contains limited cost-effective and safe medicines, while the open pharmaceutical market is flooded with a large number of medicines many of which are of doubtful value. The concept of essential medicines has been worldwide accepted as a powerful tool to promote health equity and its impact is remarkable as the essential medicines are proved to be one of the most cost-effective elements in health care.

ROUTES OF DRUG ADMINISTRATION



Route of administration are two main routes of administration of drugs.

(1) Enteral Route

(2) Parenteral Route

(3) Local

1. Enteral Route

The enteral route includes oral route (By mouth), nasal route, sublingual route, vaginal route and rectal route.

Oral Route (By Mouth)

This is a natural route of administration of drugs. The drugs in the form of tablets, capsules powders mixtures etc. are administered through this route.

Advantage

1. This route is the most convenient route of drug administration.
2. Patient can take the prescribed medicines himself.
3. There is no pain to the patient; this route is very convenient and economical.

Disadvantages

1. The effect of drug taken by oral route is delayed.
2. It is not an emergency route.
3. The irritant drugs cannot be given through this route.
4. This route cannot be used in case of unconscious and non-cooperative patients.
5. Certain drugs cannot be given through this route as they are destroyed by gastric enzymes.

Care should be taken that sufficient quantity of water should be given to patient with drug to prevent sticking of drug in esophagus, and to decrease irritant effect of medicines taken.

The patient has difficulty in swallowing should be given medicines in liquid form as suspensions, mixtures etc.

Nasal Route Certain drugs can produce local effect and are given in the form of nasal guttae (nasal drops) or in the form of inhalation. The drugs of imidazoline compounds like naphazoline, xylometazoline, oxymetazoline, and ephedrine are administered in the form of nasal drops.

Sub Lingual Route The tablets are placed under the tongue sucked. This route is used for administration of lingual tablets is given as male hormone. Isoprinaline is given in the treatment of Bronchial nitroglycerin tablets in the disease Angina pectoris. Methyl testosterone in the form of sub asthma.

Advantages:

(1) On set action is quick.

(2) The overdose of drug is avoided.

(3) The drug is not destroyed by stomach enzymes, metabolic destruction in the liver is avoided (prevented).

The medicines are not allowed to swallow or chew, the tablet is kept below tongue. Vaginal Route. This route is also used to produce local or systemic effect. Clotrimazole vaginal suppositories, are used in case of vulvo vaginal Candidiasis. Other medicines like Miconazole ketoconazole etc are also administered by this route.

RECTAL ROUTE

The drugs through this route in the form of suppository or enema are given to produce local or systemic effect. Glucose, Paraldehyde can be administered through this route.

Chlorpromazine suppositories are given for vomiting control. Suppositories are medicines incorporated in waxy base which melts at body temperature. The medicated suppositories are stored in refrigerator.

Indomethacin suppositories are administered for rheumatoid arthritis, aminophylline suppository for bronchial asthma. Enema is liquid preparation introduced in the colon.

Evacuation enema is used for purgation effect. Retention enema is meant for administration of drugs for systemic as well as for local use. Example cortisone is given through this route in ulcerative colitis.

Advantages of rectal route

(1) Irritation of gastric mucosa is avoided by this route.

(2) The drugs, which are destroyed by gastric enzymes gastric acidity can be administered by this route.

(3) The medicines which are destroyed during the first pass through liver can be administered through this route.

(4) This route is useful in terminal sick patients.

2. PARENTERAL ROUTE

The drug is introduced in the body with the help of a syringe and needle to produce certain physiological effect.

The types of injections are as under :-

Subcutaneous- An injection is made by inserting a hypodermic needle through the layers of the skin into areolar tissue.

Intradermal- The drug in small quantity is introduced in the upper layer of skin with the help of needle and syringe. By this route test, dose of penicillin is administered. BCG and small pox vaccines are administered by this route.

Intramuscular- The needle is introduced deeply in the deltoid muscles or gluteal muscle. The injected medicine reaches in the blood circulation and produces effect. The action of medicine administered is quicker than in oral route. if proper care is not used, there is danger of nerve injury. Total or maximum 10 ml volume of drug can be administered by this route.

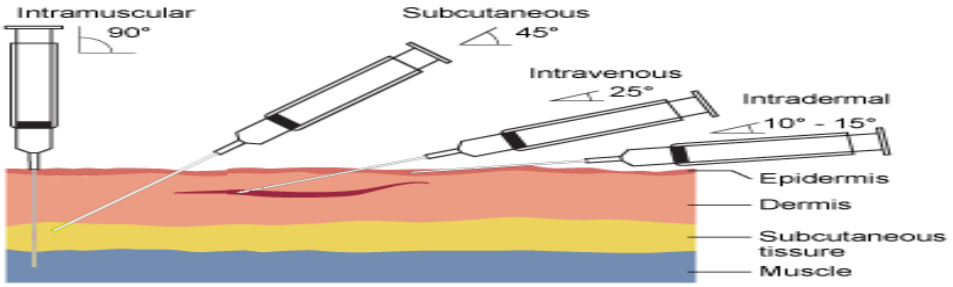
Intravenous - The drug is administered with the help of syringe and needle directly into the venous blood. Care must be taken that if excess dose is administered, the toxic effect

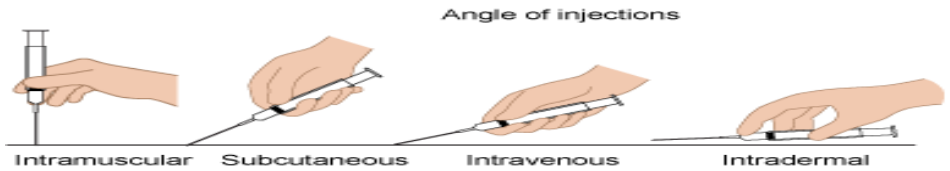
may occur. The drug introduced through this route can not be taken back. There is a danger of infection being introduced into the blood if the syringe needle and hands of person are not sterile properly.

Intrathecal. An injection is made by inserting the needle through the interspinous spaces into the spinal fluid Bone Marrow-The drug (medicine) is administered by inserting needle into the marrow of the sternum or other bones. This route is useful in case of spinal anesthesia and infections of the central nervous system.

Intraperitoneal. The drug is introduced with the help of syringe and needle in the peritoneal cavity. This route is not commonly used in clinical practice.

Intramedullary - The drug is introduced with the help of syringe and needle in the bone marrow. This route has rapid onset action. This route is used when there is difficulty in administering the drug, like blocking of veins in case of Thrombosis or circulation collapse. This route should be avoided in patients suffering from Osteomyelitis or Bacteremia





Advantages or Merits of Injections

1. There is very rapid response of drug
2. The drugs go directly into the blood, so no absorption is required.
3. This route can be used in case of a unconscious patient.
4. Less dose of drug is required by this route as compared to oral route.

Disadvantages or Demerits of Injections

1. There is a pain when needle is inserted/introduced in the body.
2. This route can be used by the trained persons only like Doctors, Pharmacists, and Nurses, which require the presence of a skilled or trained person for administration of drugs so it is an expensive route for the patient.
3. The needles and syringe are required to be properly sterilized.

4. Irritant drugs administered through this route irritate muscles and an abscess may occur. This route is not liked by patient.

5. The excess of dose if administered, cannot be taken back, the side effects of drugs are quicker.

LOCAL USE MEDICINES

Drugs or medicines are used to produce local effect or systemic effect. For local effects, ointments, lotions, pastes, sprays, tinctures, dusting powders are used.

The topical applications may be used for various body cavities or for the mucous membranes, such as irrigation and instillations of medicines in eyes, ears, nose, throat, mouth, bladder vagina etc.

The preparation for local effects be used at normal atmospheric body temperature. Droppers should be kept covered with stoppers to avoid contamination of medicines.

The preparations for local application, their appearance, expiry date, name and contents of medicine must be checked carefully before use. Nasal drops, sprays, nasal decongestants when used, avoid excess dose of drug, the drug may get aspirated.

Skin preparations: The skin should be cleaned before application of ointments, powders, tinctures, lotion and spray etc. The eye drops should be instilled carefully into the lower eyelid pouch. Similarly, while instillation ear drops use aseptic techniques. Vaginal medications be given at bed time.

AGONISTS, ANTAGONISTS (COMPETITIVE AND NON COMPETITIVE)

Agonist: Agonist is a molecule that can bind and activate a receptor to induce a biological response. The activity mediated by agonists is opposed by antagonists, which inhibit the biological response induced by an agonist. The level of agonist required to induce a desired biological response is referred to as potency.

Potency: the amount of drug required to produce an effect of given intensity. Differences in drug potency are evaluated by comparing EC50 (or ED50) values. It varies only by their potency or receptor affinity, and not in terms of their maximal response). (Fig. 1.15)

Efficacy: the ability of a drug to produce a maximum response. Differences in drug efficacy are evaluated by comparing differences in maximal response at high drug doses or concentrations. It varies only by their efficacy or maximal response, and have the same potency or EC50 values.)

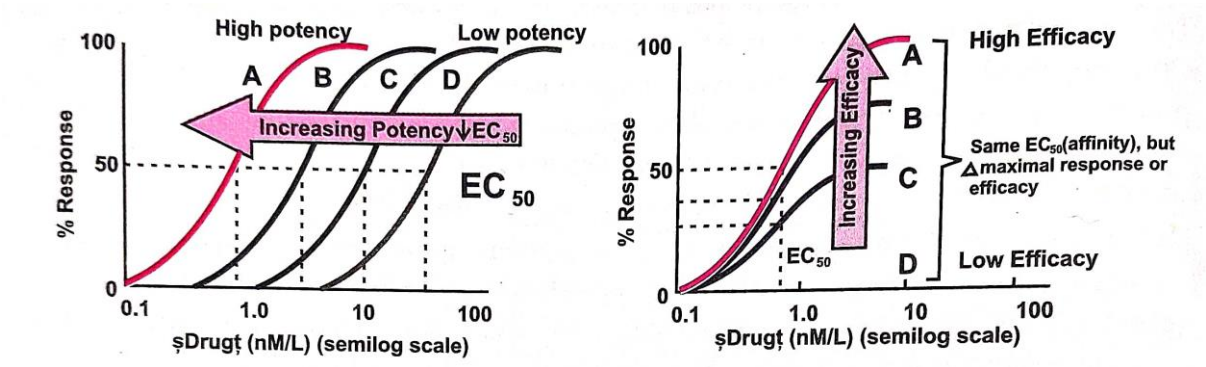
Partial agonists: agonists that produce less than a full response when they fully occupy their receptors. In contrast, full agonists produce a full or maximal response. Drug A is a full agonist, and Drugs B, C & D are partial agonists.

Two fundamental properties of agonists are affinity and efficacy. The affinity can be defined as the tenacity with which a drug binds to its receptor. In statistical terms, it can be defined as the probability that a drug molecule will bind to an available receptor at any receptor

No as response will give instant in time. The Efficacy is an inherent property of an agonist that determines its ability to produce its biological effect.

Definition, it is a property of the drug, not the or tissue. Affinity gets the drug bound to the receptor, and efficacy determines what happens once the drug is bound. typically differ from each other in terms of their affinity (potency) and/or efficacy.

The term potency is used as a comparative term for distinguishing which agonist has an affinity for a given receptor. The drug which can produce an effect at lower drug concentrations is "more potent" (in Figure-1.5 Drug A is the most potent, and Drug D is the least potent).



Schematic illustration of the dose-response curves for a series of agonists (A, B, C and D) that have the same efficacy, but differ in terms of their potency. The most potent drug (Drug A) has the lowest EC50 value, and is approximately 20-30 fold more potent than Drug D.

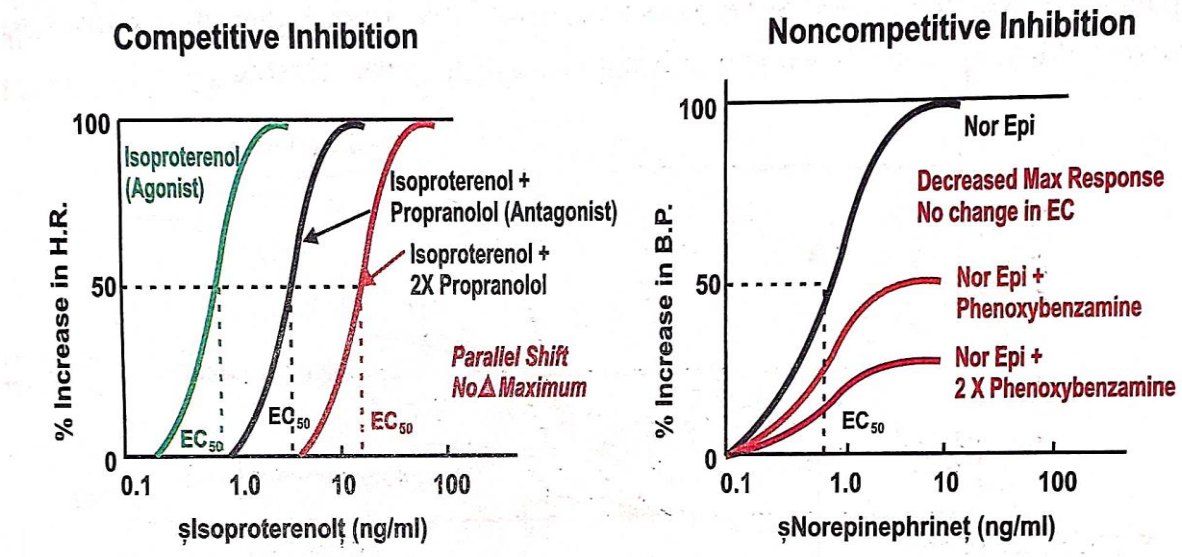
Agonists can also differ in terms of their efficacy, or maximum response. Figure shows a plot of four agonists that differ in terms of their relative efficacy. Drug A is the most efficacious, and Drug D the least. Drugs that bind to a receptor, but produce less than maximal activation (e.g. Drugs B, C & D) are referred to as partial agonists.

Antagonist: When agonist produces an action, antagonist opposes the action

Antagonists are drugs that bind to receptors (have affinity), but do not produce a substantial degree of receptor stimulation (they have very low efficacy). Antagonists are typically classified as competitive or noncompetitive.

Competitive antagonists bind reversibly to the same receptor site as the agonist. Because they bind reversibly and compete for the same binding site, their inhibitory effects can be "surmounted" by addition of a higher concentration of agonist (Figure 9A). This effect produces a rightward parallel shift of the dose-response for the agonist (towards higher concentrations). In the presence of a competitive antagonist, agonists can still produce the same (e.g. 100%) maximal effect as in the absence of an antagonist, the only difference being that higher agonist concentrations are needed to produce the same level of effect. The vast majority of clinically used drugs that act as receptor antagonists are competitive antagonists.

Noncompetitive antagonists Either bind irreversibly (e.g. by covalent bonds) to the same site as the agonist, or bind to a different site which reduces the binding of the agonist by an allosteric mechanism. The primary effect of a noncompetitive antagonist is a reduction in the maximal effect produced by the agonist. In other hand to a competitive antagonist, the effect of a noncompetitive antagonist cannot be reversed by simply increasing the concentration of the agonist, since the law of mass action does not apply.



Competitive and noncompetitive Antagonism

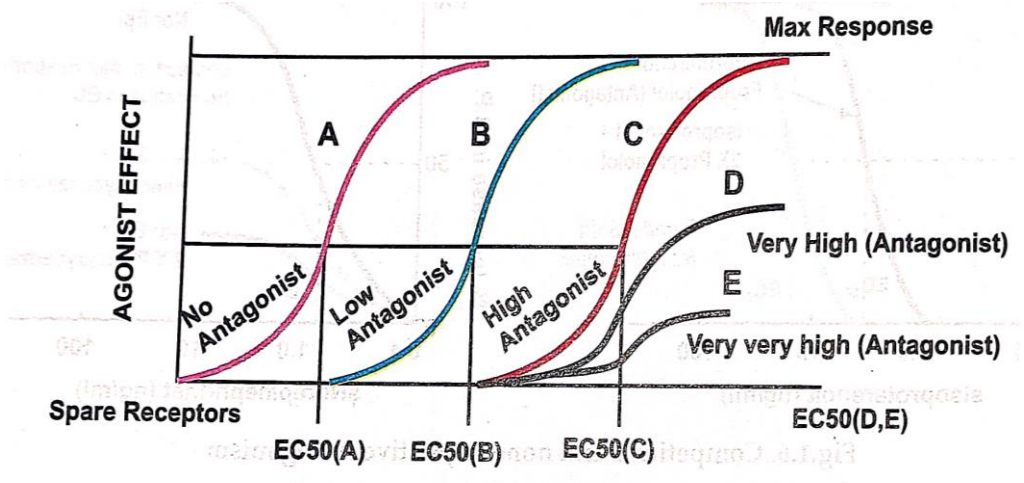
For example, competitive antagonism is where both the agonist (Isoproterenol) and antagonist (Propranolol) bind reversibly to the same receptor subtype (B-adrenoceptor). In the presence of the competitive antagonist, the dose-response curve is shifted to the right in a parallel manner. However, in non-competitive antagonism the Phenoxybenzamine is binds irreversibly (with covalent bonds) to a-adrenergic receptors. This reduces the fraction of available receptors, and reduces the maximal effect that can be produced by the agonist

Reverse Agonists: Some drugs, in some biological systems, have been shown to act as "reverse agonists". They produce a response that is opposite of that typically produced by a receptor when it is stimulated by a conventional agonist. For example, some G-protein coupled receptors appear to have a basal or "tonic" level of intrinsic activity in the absence of a hormone or neurotransmitter. This results in a tonic level of stimulation of downstream events, such as stimulation of adenylate cyclase. When a "reverse agonist" binds to this receptor, it acts similar to a conventional antagonist by binding the receptor without "stimulating it". However, in addition, the binding of the reverse agonist to the receptor alters the receptor conformation in such a way as to decrease its interaction with G-proteins, resulting in a decrease in basal stimulation of G-proteins and a reduction in the activity of adenyl cyclase.

SPARE RECEPTORS

Maximal efficacy means a state at which receptor mediated signaling is maximal and that, further increase in the drug dose does not produce any additional response. When drugs act on receptors to produce the response all the receptors are not occupied to produce the maximal response by a full agonist i.e each cell or tissue has some receptors unoccupied which may be called spare receptors.

Maximum response is produced by agonist at a concentration that does not require full occupancy of the receptor. They are not hidden or unavailable. When they are occupied, they can be coupled to response. They do not differ from the non-spare receptor.



If irreversible concentration is too high the spare receptors are occupied and maximal response is diminished. Represented in D & E

Effect of Spare receptors

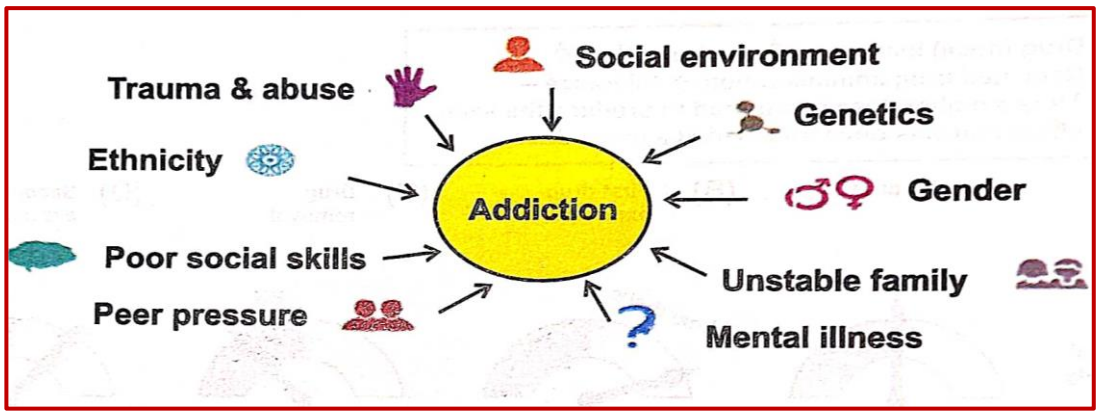
Spare receptors may be demonstrated by using irreversible antagonist, to prevent binding of an agonist to available receptors. The spare receptor concept can be shown when the

agonist can still produce an undiminished maximal response in presence of an irreversible antagonist. For example the amplitude of muscle twitch in response to Ach. Acetylcholine blocked by addition of toxin (curare).This toxin occupies at least 50% of receptors. But still max response can be demonstrated. That means, at least 50% of the receptor were spare in a sense that they were not required for a completely normal twitch of Ach.

ADDICTION

Drug addiction is a chronic disease characterized by drug seeking and use that is compulsive, or difficult to control, despite harmful consequences. Brain changes that occur over time with drug use challenge an addicted person's self-control and interfere with their ability to resist intense urges to take drugs. This is why drug addiction is also a relapsing disease. Relapse is the return to drug use after an attempt to stop. Relapse indicates the need for more or different treatment.

Most drugs affect the brain's reward circuit by flooding it with the chemical messenger dopamine. This overstimulation of the reward circuit causes the intensely pleasurable "high" that leads people to take a drug again and again. Over time, the brain adjusts to the excess dopamine, which reduces the high that the person feels compared to the high they felt when first taking the drug-an effect known as tolerance.



A major factor involves in the drug addiction

Drug addiction information indicates any type of drug can be abused or cause drug addiction. Drug addiction involves easily accessible drugs like tobacco and alcohol, as well as illegal drugs like cocaine and heroin. Some drug addictions, like alcoholism, appear to be declining, while others, like methamphetamine addiction, is on the rise.

Drug addiction info indicates the following drugs and drug types are commonly associated with drug addiction:

Alcohol - most widely abused drug with 20% of users becoming dependent on it at some point

Opiates - substances derived from the opium poppy, the most common drug addiction is that of heroin Cocaine, crack - up to 10% of users go on to heavy drug use Amphetamines - like crystal meth, use on the rise in rural communities

Hallucinogens - like PCP, LSD and marijuana, often combined with other drugs

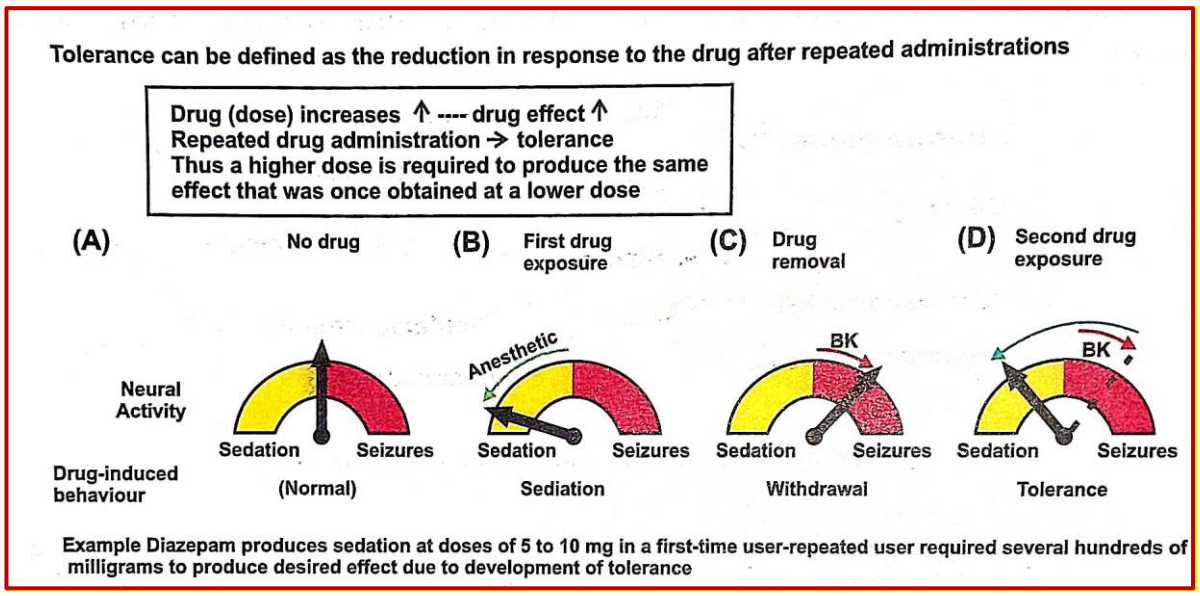
Prescription medication - such as oxycodone and morphine

Other chemicals - like tobacco, steroids and others.

TOLERANCE

The tolerance may be defined as unusual resistance to the ordinary dose of a drug. The continuous and regular use of drugs may cause tolerance. It may be acquired by constant use of drug or it may be congenital. Repeated administration of drug produces less effect. If the same effect is required, the higher dose of drug will be required to produce the required effect

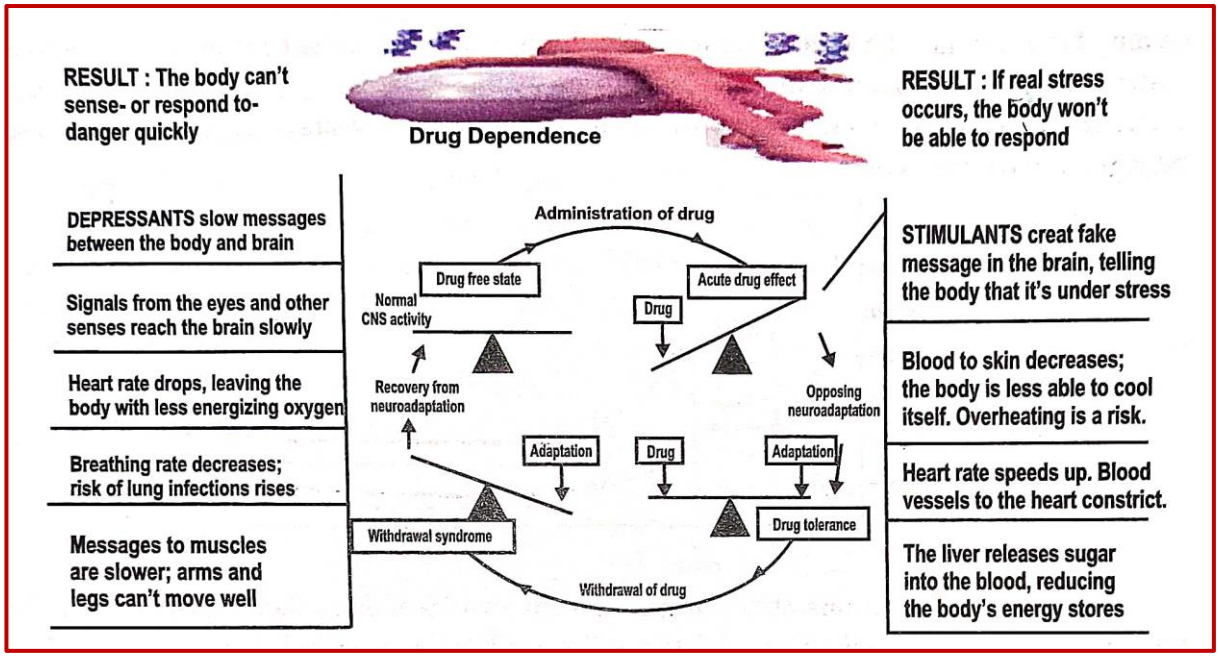
The regular intake of alcohols, opium, morphine barbiturates leads to tolerance. The tissue cells of the body may become acclimatized to the drug presence and failed to respond to drug concentrations which are ordinarily effective. The cellular acclimatization to the presence of a drug is true tolerance. When the drug is discontinued, the tolerance usually disappears after a time. The chemical Glyceryl trinitrate is used in dynamite factories. The new workers in dynamite factories when inhale, vapours of Glyceryl trinitrate cause headache. The workers of dynamite factories soon acquire a tolerance to the compound and do not suffer from a headache. When they are away from the factory for a long period of time, the acquired tolerance is lost and if they return to work, they again experience headache.



Fundamental concept of Tolerance

DRUG DEPENDENCE

Drug dependence is the body's physical need, or addiction, to a specific agent. There is therefore virtually no difference between dependency and addiction. Over the long term, this dependence results in physical harm, behavior problems, and association with people who also abuse drugs. Stopping the use of the drug can result in a specific withdrawal syndrome. With repeated use of heroin, dependence also occurs. It develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug.



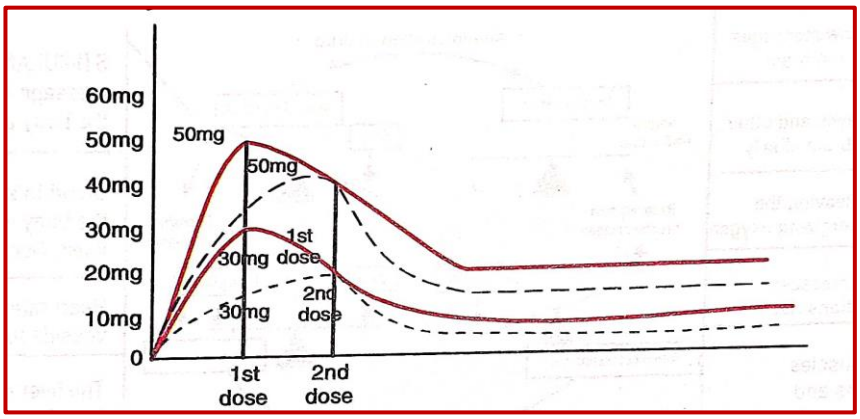
A diagram shows the effect of drug dependence

When the drug is withdrawn, several physiologic reactions occur. These can be mild (e.g., for caffeine) or even life-threatening (e.g., for alcohol). This is known as the withdrawal syndrome. In the case of heroin, withdrawal can be very serious and the abuser will use the drug again to avoid the withdrawal syndrome. The signs and symptoms displayed. Most agents cause a change in the level of consciousness usually a decrease in responsiveness. Suppression of brain activity can be so severe that the person may stop breathing, which can cause death. Alternatively, the user may be agitated, angry, anxious, and unable to sleep. Hallucinations are possible. Abnormal vital signs (temperature, pulse rate, respiratory rate, blood pressure) are possible and can be life threatening.Chest pain is possible and can be caused by heart or lung damage from drug abuse. Abdominal pain, nausea, vomiting, and diarrhea are possible. Vomiting blood, or blood in bowel movements, can be life threatening. Withdrawal syndromes are variable depending on the agent but can be life threatening.

TACCPHYLAXIS

The repeated administration of drugs at short intervals produces less effect is called taccphylaxis to The Ephedrine 50 milligram shows curve reducing curve and the same effect cannot be achieved by administration of the same dose.

The curve for the action of 50 mg and 30 mg of ephedrine administered to a patient shows like this. The same effect by administering same dose of 50 mg or 30 mg of ephedrine cannot be obtained. To obtain same effect, higher dose of ephedrine is required to be administered. The usual adult dose of ephedrine by mouth is 15 mg to 60 mg. Children upto 1 year may be given 7.5 mg, 1 to 5 years 15 milligram, 6 to 12 years 30 mg. These doses can be given three times daily.

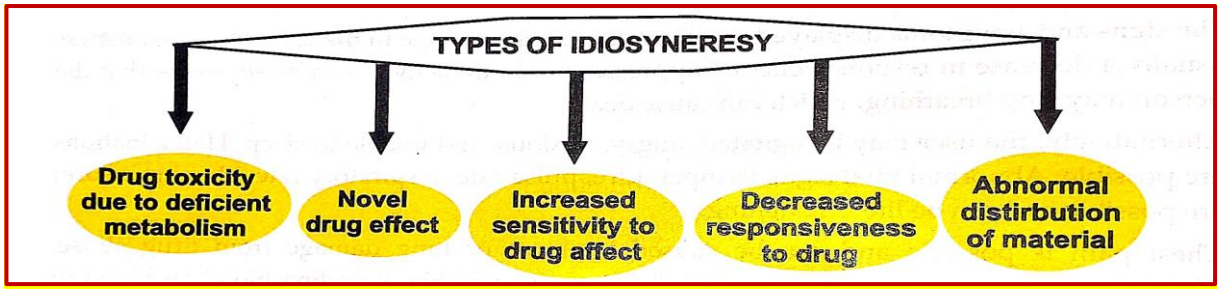


The methods of administration drugs and factors which modify their dose, our attention would be directed to mechanism of drugs action by keeping in mind the contraindications and side effects of drugs.

IDIOSYNCRASY

Drug idiosyncrasy" refers to untoward reactions to drugs that occur in a small fraction of patients and have no obvious relationship to dose or duration of therapy. The liver is a frequent target for toxicity. The idiosyncrasy induce in many way such as

TYPES OF IDIOSYNERESY



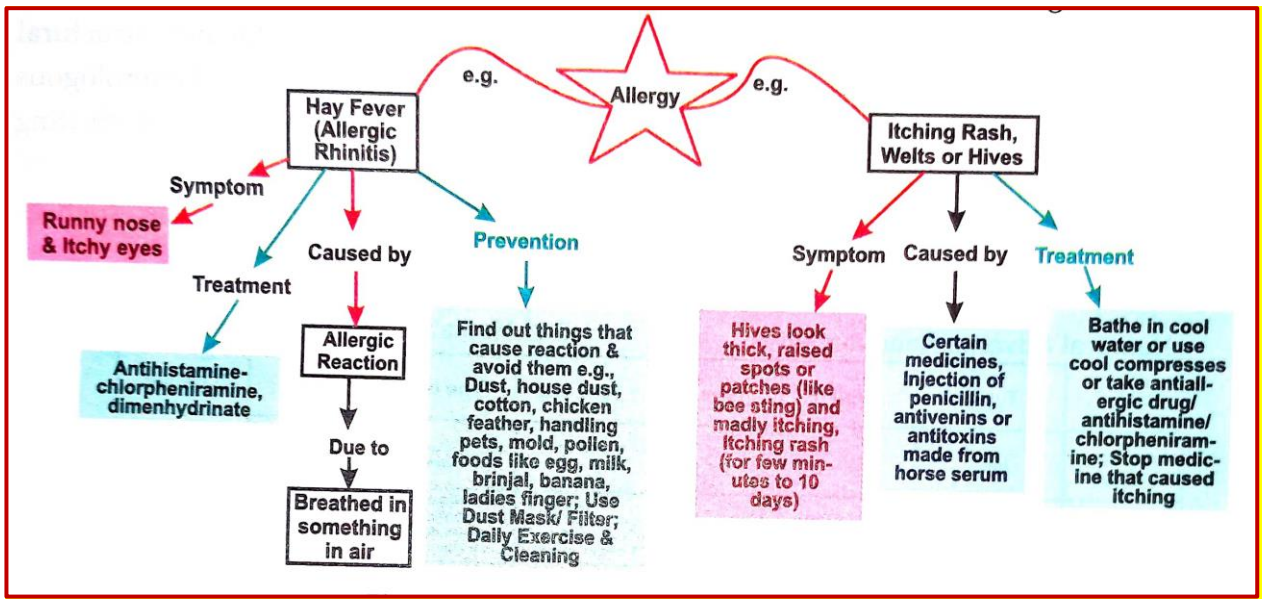
Induction of idiosyncrasy

ALLERGAY

The body system of defense is against foreign invaders, particularly pathogens (the agents of infection). The allergic reaction is misguided in that these foreign substances are usually harmless. The substances that trigger allergy are called allergen. Examples include pollens, dust mite, molds, danders, drug and certain foods. **The most common allergic conditions include hay fever (allergic rhinitis), asthma, allergic eyes (allergic conjunctivitis), allergic eczema, hives (urticaria), and allergic shock (also called anaphylaxis and anaphylactic shock). Hay fever (allergic rhinitis):** It is the most common of the allergic diseases and refers to seasonal nasal symptoms that are due to pollens. Year round or perennial allergic rhinitis is usually due to indoor allergens, such as dust mites or molds. Symptoms result from the inflammation of the tissues that line the inside of the nose (mucus lining or membranes) after allergens are inhaled. Adjacent areas, such as the ears, sinuses, and throat can also be involved. **The most common symptoms include: Such as Runny nose, Stuffy nose, Sneezing, Nasal itching (rubbing), Itchy ears and throat, Post nasal drip (throat clearing).**

Hives (urticaria) are skin reactions that appear as itchy swellings and can occur on any part of the body. It can be caused by an allergic reaction, such as to a food or medication, but they also may occur in non-allergic people. Typical hive symptoms are: Raised red welts and intense itching

Allergic eczema: It is an allergic rash that is usually not caused by skin contact with an allergen and features the following symptoms: Itching, redness, and or dryness of the skin, rash on the face, especially children, rash around the eyes, in the elbow creases, and behind the knees, especially in adults.



A diagram shows the type of allergy

Allergic shock (anaphylaxis or anaphylactic shock) : This is a life-threatening reaction that can affect a number of organs at the same time. It typically occurs when the allergen is eaten (for example, foods) or injected (for example, a bee sting). Allergic shock is caused by dilated and leaky blood vessels, which result in a drop in blood pressure. Some or all of the following symptoms may occur: Hives or reddish discoloration of the skin, Nasal congestion, swelling of the throat, stomach pain, nausea, vomiting, shortness of breath, wheezing and low blood pressure or shock

Allergic eyes (allergic conjunctivitis) is inflammation of the tissue layers (membranes) that cover the surface of the eyeball and the undersurface of the eyelid. The inflammation occurs a result of an allergic reaction and features: Redness under the lids and of the eye overall, Watery, itchy eyes and swelling of the membranes.

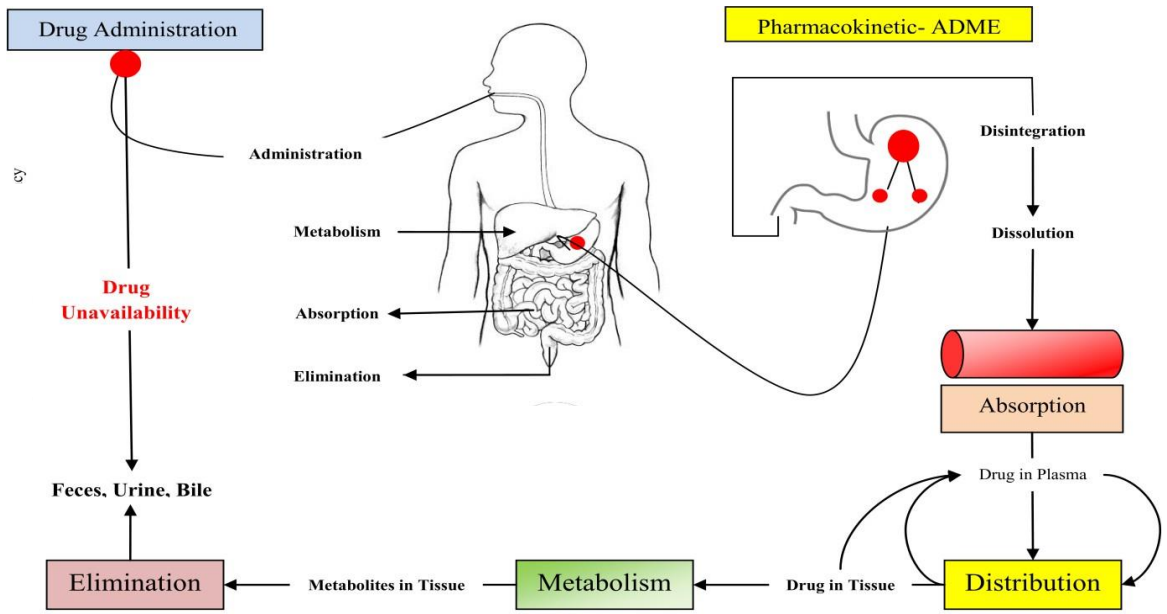
Mechanism of drug allergy: Drug hypersensitivity results from interactions between a pharmacologic agent and the human immune system. These types of reactions constitute only a small subset of all adverse drug reactions. Allergic reactions to medications represent a specific class of drug hypersensitivity reactions mediated by IgE. Immune-mediated drug reactions divided into the humoral mediated adverse reaction and cell mediated immunity. The most important drug-related risk factors for drug hypersensitivity concern the chemical properties and molecular weight of the drug. Larger drugs with greater structural complexity (e.g., nonhuman proteins) are more likely to be immunogenic. Heterologous antisera, streptokinase, and insulin are examples of complex antigens capable of eliciting hypersensitivity reactions. Most drugs have a smaller molecular weight (less than 1,000 daltons), but may still become immunogenic by coupling with carrier proteins, such as albumin, to form simple chemical-carrier complexes (hapten)

Another factor affecting the frequency of hypersensitivity drug reactions is the route of drug administration; topical, intramuscular, and intravenous administrations are more likely to cause hypersensitivity reactions. These effects are caused by the efficiency of antigen presentation in the skin, the adjuvant effects of repository drug preparations, and the high concentrations of circulating drug antigen rapidly achieved with intravenous therapy. Oral medications are less likely to result in drug hypersensitivity

PHARMACOKINETIC

Pharmacokinetic- "What does **BODY** do to the **DRUG** we have simple interchanged the BODY and DRUG to make a definition. And as per the definition our body responds to any drug by giving **ADME** effects.

1. **A** stands for - Absorption
2. **D** stand for - Distribution
3. **M** stand for - Metabolism
4. **E** stands for - Elimination or Excretion

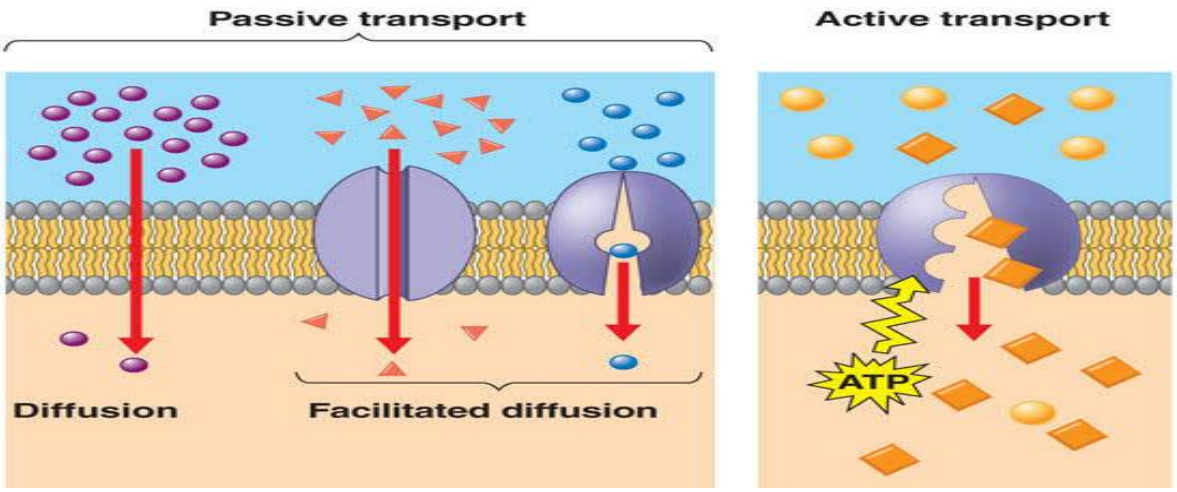


Absorption- Absorption means reaching of drug into blood vessels for further distribution. Until drug is absorbed it will not be able to produce its effect so absorption of drug is important and it is obviously done by body. Absorption has several phases and this includes- administration of drug by any of the available dosage form, here in above diagram we have taken oral route of drug administration. Once the drug reach into stomach it get disintegrated into small partials than it is get dissolved by the fluid available in stomach. Then these drug moves towards a small intestine from where they usually get absorbed into circulation. Drug given by other than oral route directly reach the systemic circulation and they don't need to get disintegrated because they are already in liquid form.

Transport Process across Cell Membrane

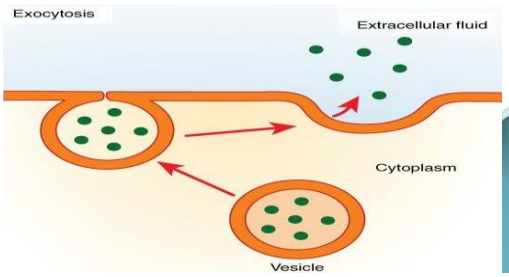
Transport of drug from small intestine to the systemic circulation takes place by many methods like-

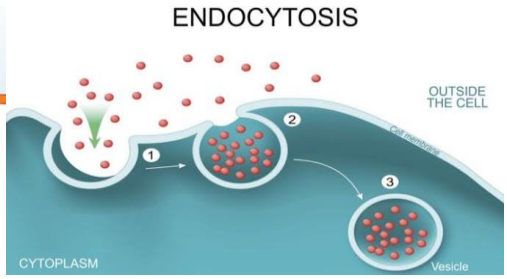
Passive Diffusion- Does not need energy for the movement till equilibrium achieved. Drugs diffuse across a cell membrane from a region of high concentration (GI fluids) to one of low concentration (blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's **lipid solubility, size, degree of ionization, and the area of absorptive surface**. Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones.

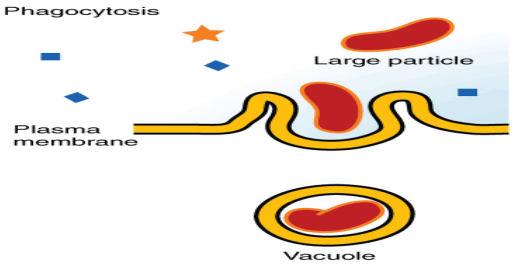


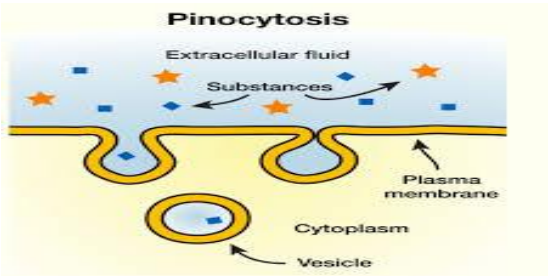
Active Transport- Need energy. Active transport is selective, requires energy expenditure, and may involve transport against a concentration gradient. Active transport seems to be limited to drugs structurally similar to endogenous substances like- **ions, vitamins, sugars, amino acids**. These drugs are usually absorbed from specific sites in the small intestine.

Endocytosis and Exocytosis- Process of engulfing either Pinocytosis or Phagocytosis. In Pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invigilates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, **except for protein drugs.**

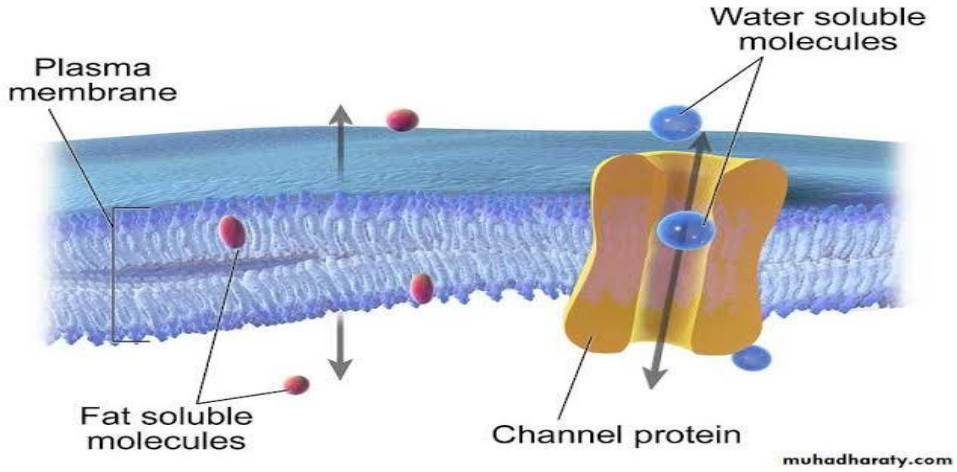


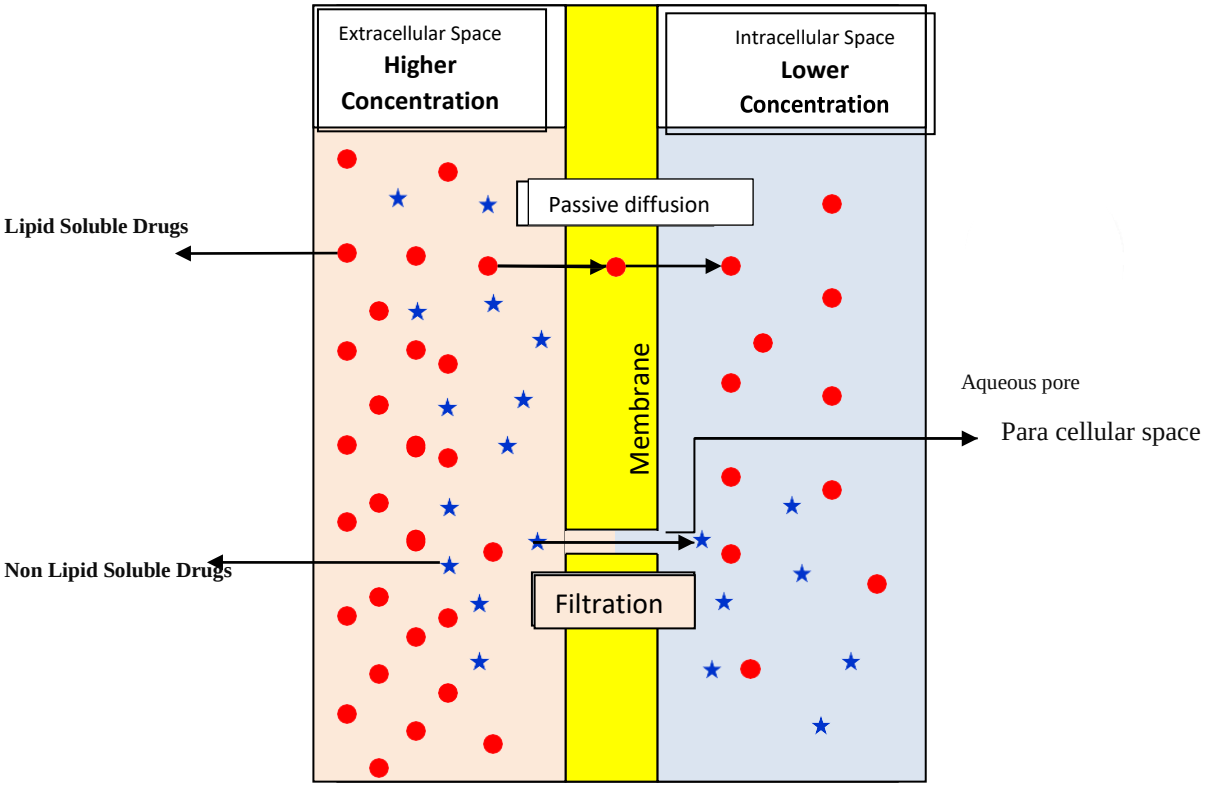




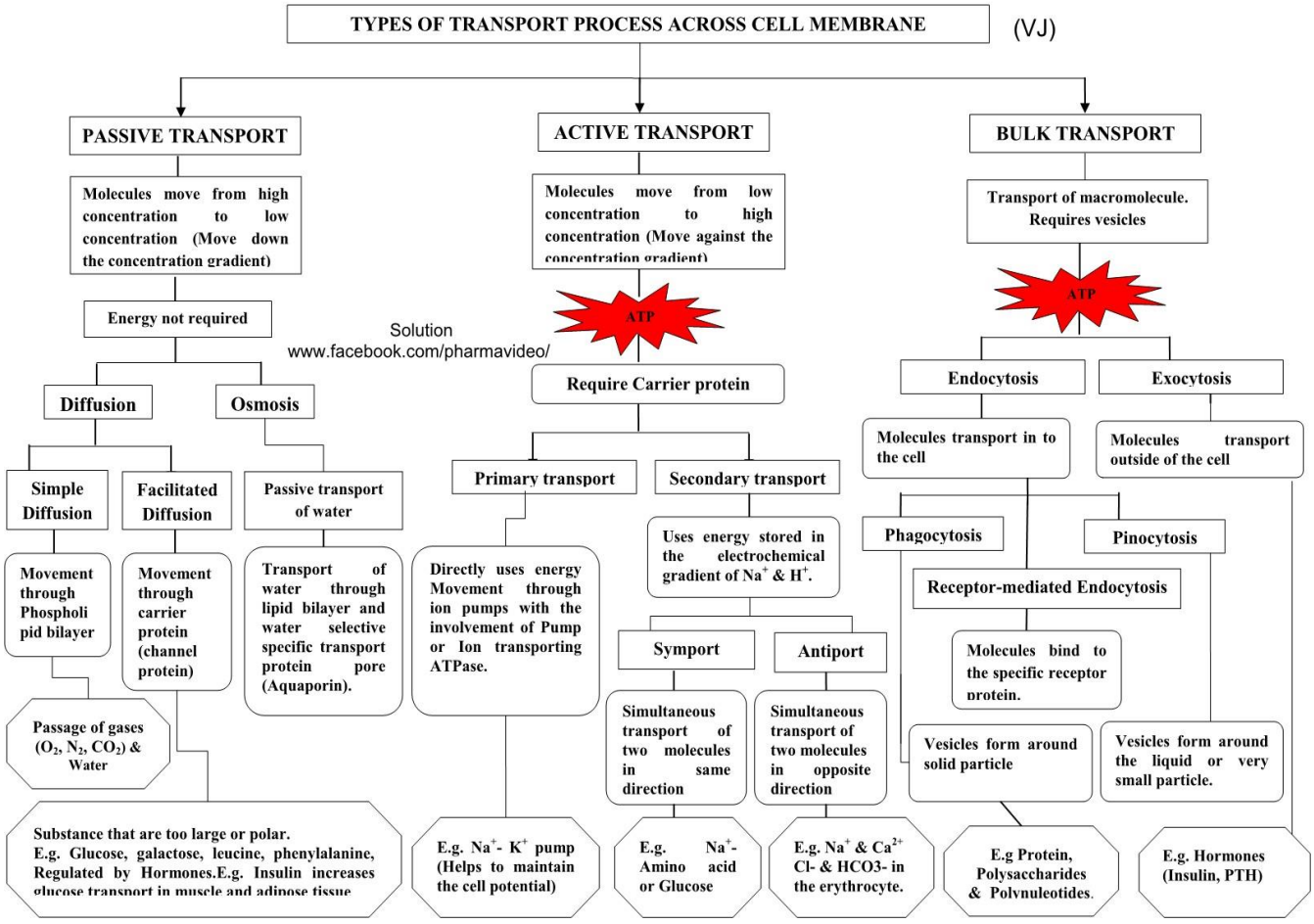


Carrier mediated transport – Need some molecule which will carry and drop the substance. Certain molecules with low lipid solubility penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process. The process does not require energy expenditure, and transport against a concentration gradient cannot occur.





Passive diffusion and filtration across the lipoid biological membrane.



BIOAVAILABILITY

Bioavailability means- **"The rate and extent of absorption of drug from its dosage form"** Bioavailability is very important for any drug for its action point of view. The more bioavailability will be more drug action and less bioavailability means less availability of drug thus less action. Bioavailability of drug given by oral route is never 100% but the drug given by Systemic route is considered to be 100%.

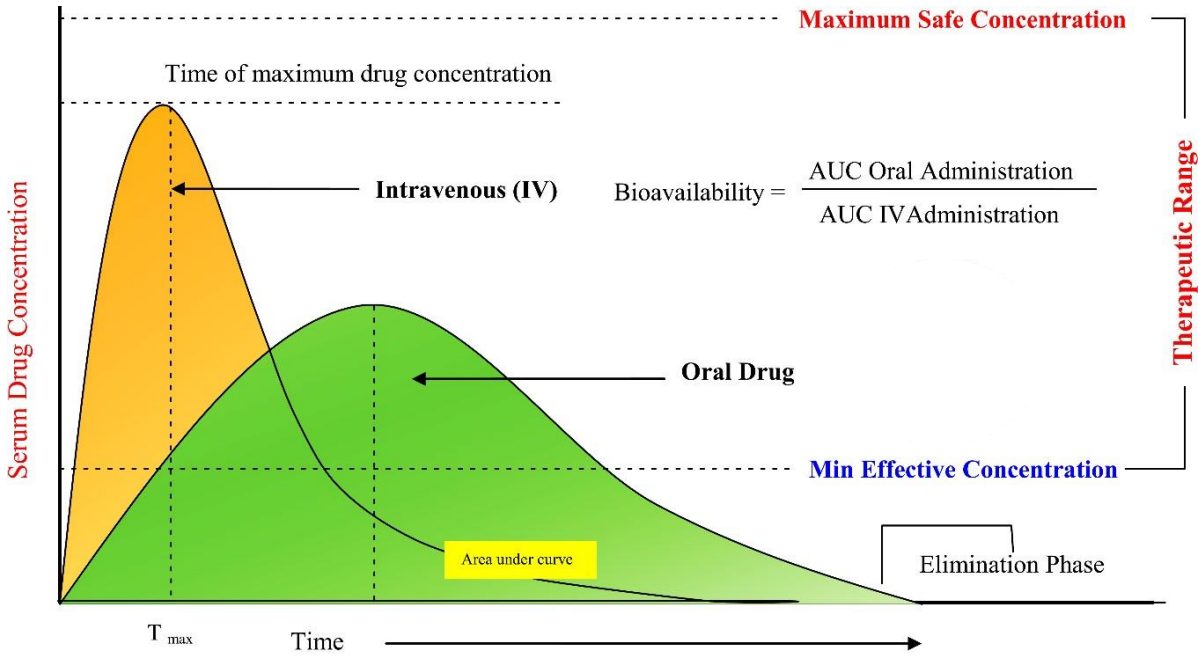


Image- Bioavailability- Plasma drug concentration Vs Time Graph, along with various indications

Factor affecting Bioavailability-

S.N	Pharmaceutical Factors	Pharmacological Factors
01	Partial Size	Gastric emptying and gastric motility
02	Salt form	Gastrointestinal disease
03	Crystal forms	Food and other substances
04	Water of hydration	First pass effects
05	Nature of Excipients	Drug-drug interaction
06	Degree of Ionization	Pharmacogenetic Factors
07	Formulation Factors	Emotional Factor (Psychological Factors)

Factors affecting Bioavailability

Pharmaceutical factors

Partial Size
Smaller the partial size the greater will be surface area and greater surface area will have more dissolution, and more dissolution will result in more bioavailability

Salt Form
Salt of weakly acidic drug are more water soluble. Free acidic drug is precipitated from this salt in a micro crystalline form so they show enhanced bioavailability

Crystal Form: Amorphous form of drug is more water soluble and hence having more bioavailability than of crystalline form. **Example- Chlourmphenicol palmitate**

Water of Hydration
Anhydrous form of caffeine, theophylline an Ampicillin has faster dissolution rate and better bioavailability than hydrous form of the drug.

Nature of Excipients
There are so many additive used in the production of tablet, capsule and many other formulation. The strength and concentration of binding agent used in tablet preparation affect its disintegration and dissolution rate, and as we have already seen that dissolution rate affect the bioavailability. More dissolution means more bioavailability. So more binding agent are of poor bioavailability

Pharmacological

Gastric Emptying
Factor that accelerate gastric emptying permit drug to reach the large absorptive surface of small intestine sooner and increase the bioavailability

GIT Disease
In gastroenteritis there is decreased absorption of drug given orally. There is much other condition which will affect the absorption of drug and hence decrease the bioavailability, like- diarrhoea

Food and other substance
In general gastrointestinal absorption of drug is favored by the empty stomach and reduced in the presence of other food materials. Absorption of tetracycline is getting reduced in the presence of milk in the stomach. Absorption of certain antifungal drug is get rapidly absorbed in the presence of fatty food.

First Pass Effect
All drug taken orally shows first pass metabolism and it means their degradation is possible thus as compare to parental administration their bioavailability is low.

Drug- Drug Interaction
Drug- drug interaction is one of the most important factors which affect bioavailability. **Example- liquid paraffin decrease the absorption of vitamin A**

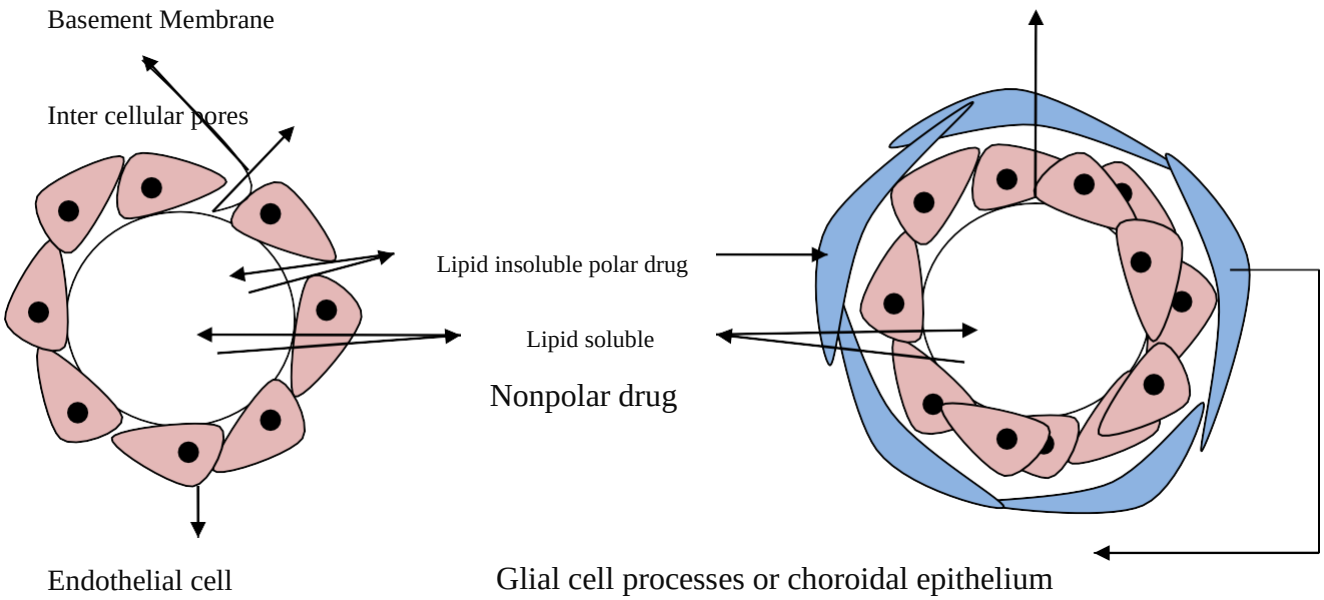
Distribution

Distribution is very important to achieve the homeostasis between all body compartments. When drug is administered into body and it reached into blood vessels, its distribution starts as per the concentration gradient. The extent of drug distribution is depends on **lipid solubility, ionization and physiological pH.** Movement of drug proceeds till the equilibrium is achieved between unbound drug in plasma and tissue fluid.

Drug distribution can be defined as the movement of drug between blood and extra vascular tissues. As drug absorption occurs, drug transfers to the blood, resulting in a concentration gradient across the capillaries, allowing filtration of drug into the interstitial fluid. The accumulated drug in the interstitial fluid drives its passive diffusion into tissues and organs.

The apparent volume of distribution (VD) is the volume of fluid in which the total drug dose would theoretically have to be diluted to produce the observed drug concentration in the blood plasma. It can be calculated as follows:

Apparent volume of distribution = amount of drug in body / drug concentration in plasma



The drug distribution is usually varied, and depends on several factors such as- blood perfusion, tissue binding, regional pH, cell membrane permeability. Additionally, the rate at which a drug enters into a tissue depends on- the flow of blood to the tissue, the mass of tissue, and the barrier existing between blood and tissues.

Redistribution – Highly lipid soluble drugs get distributed to that organ which has high blood flow like- **brain, heart kidney** etc. letter , less vascular but more bulky tissue like- **muscle, Fa**t take up the drug, plasma concentration fall and drug is withdrawn from these site. If the site of action of drug was one of the highly perused organs redistribution results in termination. Greater the lipid solubility of drug faster is the redistribution.

Binding- The distribution of a drug in the body also depends on the extent to which the drug binds to proteins and tissues in the body. ***Only drugs that are unbound to proteins and other components in the blood are free to diffuse across the cell membranes into the tissues of the body.*** The most important proteins in the blood that can affect the distribution of a drug include the plasma protein albumin, the alpha-1 acid glycoprotein, and lipoproteins. It is observed that **albumin binds acidic drugs**, in general, while more **basic drugs bind to the lipoproteins and acid glycoprotein**. Although proteins are the most common binding sites in the blood, there are other molecules in the blood to which a drug molecule may bind.

As only the unbound drug can be utilized in extra vascular and tissue sites, it is important to establish or estimate the unbound drug fraction in the blood. The following equation is used for this:

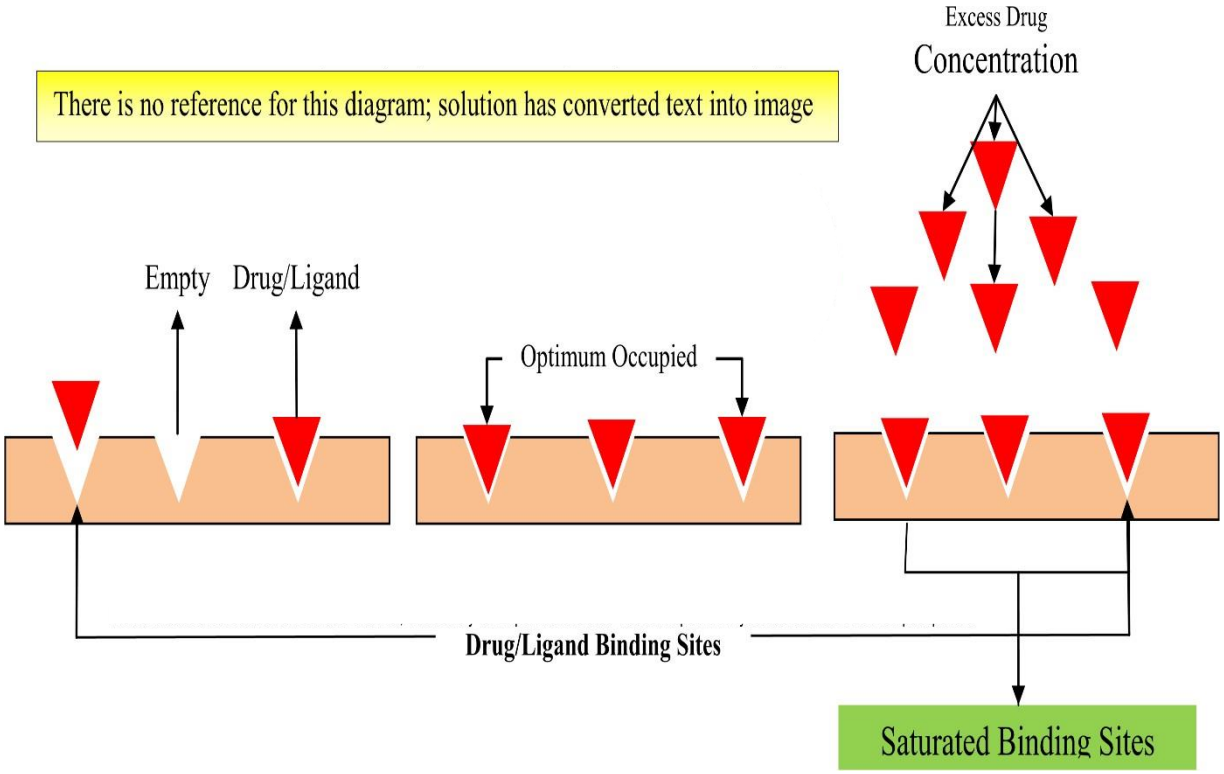
Unbound fraction = unbound drug concentration in plasma / total drug concentration in plasma

Plasma protein binding- There is some important plasma protein binding of drug-

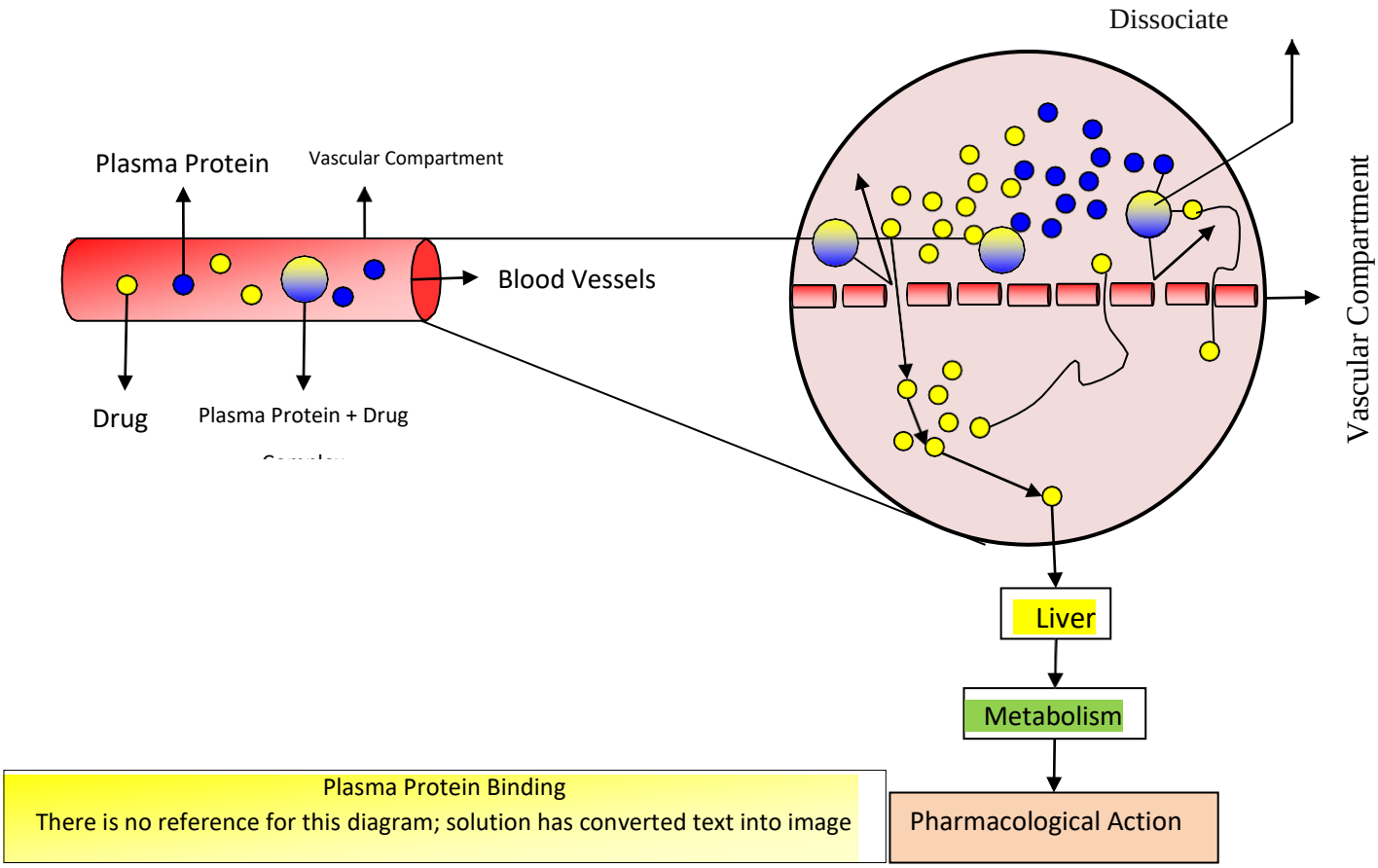
- Acidic drugs generally bind to plasma albumin
- Basic drugs bind to Alpha$_1$ acid glycoprotein
- Extent of binding of drug to the plasma protein is not on general basis, and there are no such classes. Example- (KDT) **Flurazepam- 10%, Alprazolam- 70%, Lorazepam- 90%, Diazepam- 99%**

Increasing the concentration of the drug may ultimately saturate the binding site. Saturation means the available binding site of receptor will be all most full and there will be no available free space for further binding, so no new drug molecule or Ligand can bind over the same receptor.

1. **Highly plasma protein bound drugs are mostly restricted by vascular compartment**, because protein bound drug does not cross membrane, because these protein bound drug got increase in their size and the size of pores of membrane is not that much large to allow protein bound drug. This is the reason behind their low volume of distribution.
2. The bound fraction drug is not available for the action.
3. **High degree of protein binding generally makes the drug long acting**, because bound fraction is not available for metabolism or excretion, unless it's actively extracted by liver of kidney tubules.



Drug Concentrated in tissues	
Skeletal muscle, Heart	Digoxin, Emetine (bound to muscle proteins)
Liver	Chloroquine, Tetracycline, Emetine, Digoxin
Kidney	Digoxin, Chloroquine, Emetine
Thyroid	Iodine
Brain	Chlorpromazine, Acetazolamide, Isoniazide
Retina	Chloroquine
Iris	Ephedrine, Atropine
Bone and Teeth	Tetracycline, Heavy Metals
Adipose Tissue	Thiopropionate, Ether, Minocycline, DDT,



Metabolism or Biotransformation

Biotransformation is made up of two common terms- **Bio-** in living organism and **transformation- conversion of anything *here drug from one form to another form, which is required by the body**. The liver is the principal site of drug metabolism. Although metabolism typically inactivates drugs, some drug metabolites are pharmacologically active—sometimes even more so than the parent compound. An inactive or weakly active substance that has an active metabolite is called a prodrug, especially if designed to deliver the active moiety more effectively.

Drugs can be metabolized by **oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or Isomerization**; whatever the process, the goal is to make the drug easier to excrete. The enzymes involved in metabolism are present in many tissues but generally are more concentrated in the liver. Drug metabolism rates vary among patients. Some patients metabolize a drug so rapidly that therapeutically effective blood and tissue concentrations are not reached; in others, metabolism may be so slow that usual doses have toxic effects.

Individual drug metabolism rates are influenced by genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions (especially those involving induction or inhibition of metabolism).

The primary site for drug metabolism is- liver, other are- kidney, intestine, lungs and plasma.

Biotransformation of drug many give any of this activity-

i. Inactivation of drugs
ii. Active metabolites from active drugs
iii. Activation of inactive drugs

S.No.	**Phase I Metabolism**
01	Oxidation (via cytochrome P450), reduction, and hydrolysis reactions
02	Phase I reactions convert a parent drug to more polar (water soluble) active metabolites by unmasking or inserting a polar functional group (-OH, -SH, -NH2)
03	Geriatric patients have decreased phase I metabolism
04	Drugs metabolized via phase I reactions have longer half-lives
05	Geriatric patients metabolism drugs by phase II reactions

S.No.	**Phase II Metabolism**
01	Glucuronidation, acetylating, and sulfation reactions "conjugation reactions" that increase water solubility of drug with a polar moiety
02	Glucuronate, acetate, and sulfate, respectively
03	Phase ii reactions convert a parent drug to more polar (water soluble) inactive metabolites by conjugation of subgroups to -oh, -sh, -nh2 functional groups on drug
04	Drugs metabolized via phase ii reactions are really excreted
05	Patients deficient in acetylating capacity (slow acetylators) may have prolonged or toxic responses to normal doses of certain drugs because of decreased rates of metabolism

Holfman Elimination- Holfman inhibition means inactivation of the drugs in the body fluids by the spontaneous molecular rearrangement without the agency of any enzyme like- **atracurium**

Microtonal enzyme- these are located on a smooth endoplasmic reticulum, primarily in liver, also in kidney, intestinal mucosa, and lungs. **Example-monooxygenase, cytochrome P450, glucronyl transferase** are common one.

Non-microsomal enzymes- these are present in the cytoplasm and mitochondria of hepatic cells as in other tissue including plasma.

Inhibition of drug metabolism- one drug can competitively inhibit the metabolism of another dug molecule taken at the same time or later if both drugs utilize the same enzyme or cofactors. Metabolism of drug with high hepatic extraction is dependent on liver blood flow. Propranolol reduce rate of iodine metabolism by decreasing hepatic blood flow. Some other drugs whose rate of metabolism is limited by hepatic blood flow are- morphine, propranolol, Verapamil and imipramine.

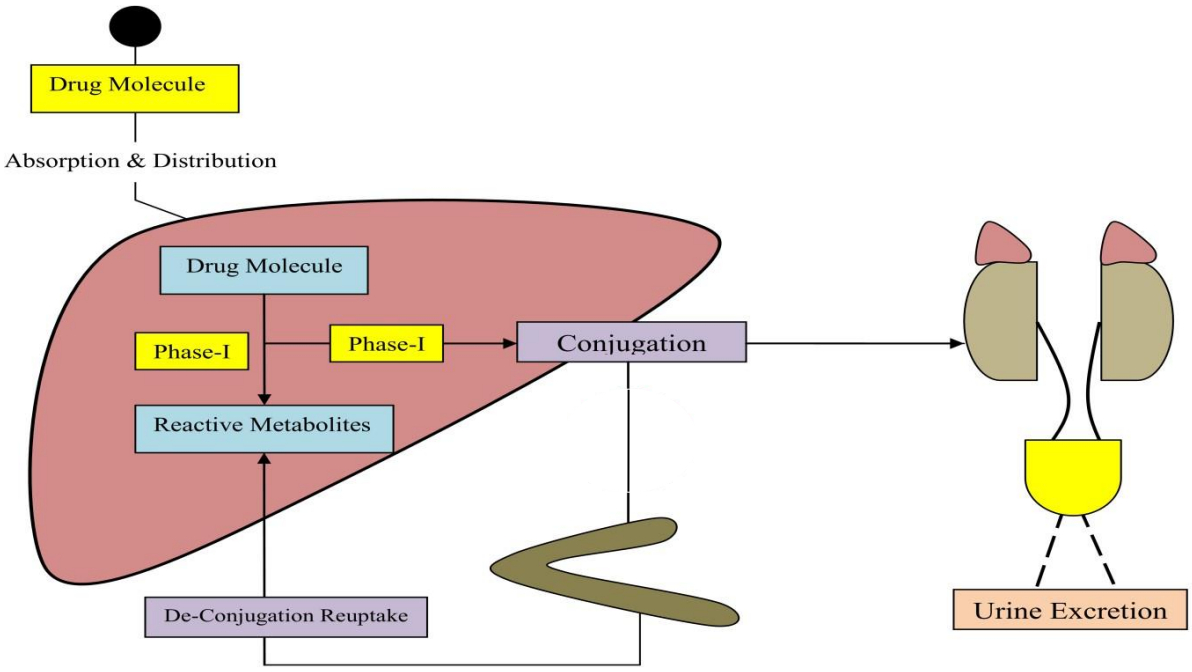


Image- Phase I and Phase II metabolism

Biotransformation Reaction

Non Synthetic
Phase-I/ Functionalization Reaction

Reduction
Converse of oxidation and involve cytochrome P-450 enzyme working in the opposite direction. Alcohols, Aldehydes, quinines, are reduced.

Exa- Chloral hydrate, Chloramphenicol, Halothane, Warfarin.

Hydrolysis
This is cleavage of drug molecule by taking up water molecule.

$Ester + H_2O \rightarrow Acid + Alcohol$

Crystallization
This is a formation of ring structure from a straight chain compound, Like- Proguanil.

Decyclization
This is opening of ring structure of cyclic drug molecule, Like- Barbiturate, Phenytoin.

Synthetic
Phase-II/Conjugation Reaction

Glucuronide conjugation
Most imp synthetic reaction carried out by group of- UDP. Example- Chloramphenicol, Aspirin, paracetamol, Lorazepam, morphine, Metronidazole.

Acetylation
Compound having amino or hydrazine, residue are conjugated with the help of acetyl co enzyme A. Exa- Sulfonamide, Isoniazide, PAS, Hydrazine etc

Methylation
The amine and phenols can be methylated. Methionine and cysteine act as a methyl donor. Exa- Adrenaline, Histamine, Nicotinic acid, methyldopa, Captopril.

Sulphate Conjugation
The phenolic compound and steroids are sulfated by sulfotransferases. Exa- Chloramphenicol, Methyldopa, adrenal and sex steroids.

Glycine Conjugation
Alicylates and other drugs having carbonic acid group are conjugated with Glycine, but this is not a major pathway of metabolism.

Glutathione Conjugation

Ribonucleotide/nucleotide synthesis

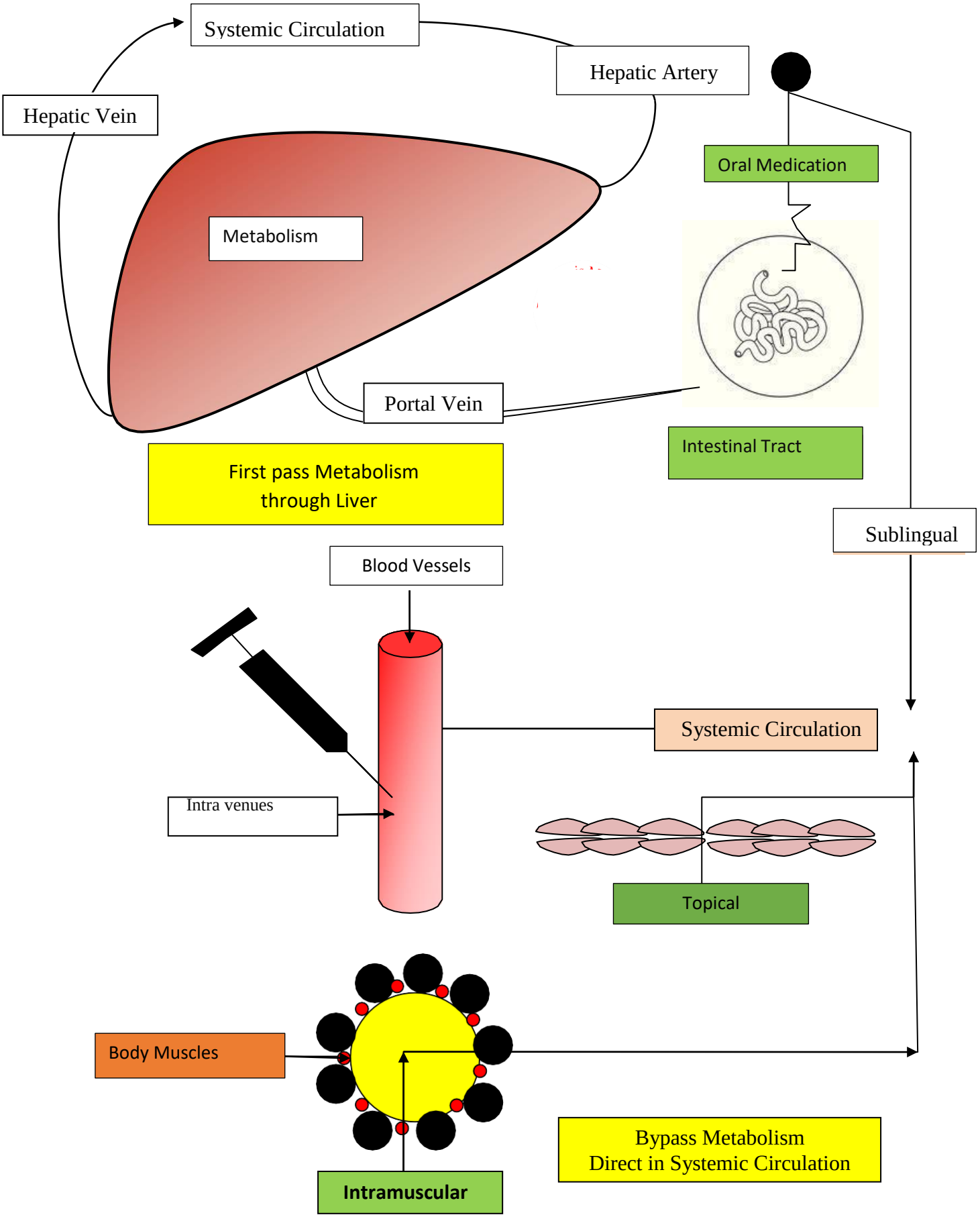


Diagram showing first passes and bypass metabolism through liver

EXCRETION OR ELIMINATION

EXCRETION- Drug excretion is the process of eliminating a drug from the body. A drug, which is either biologically active itself or a prod rug, may be excreted in its original chemical state. Alternatively, all or a portion of a drug may undergo chemical modification and be eliminated as biologically active, or inactive, metabolites. There are several routes for drug elimination from the body, he majority of drugs are eliminated by pathways that involve the kidneys or the liver. Renal excretion plays an important role in eliminating unchanged drugs or their metabolites into urine.

The kidneys are the principal organs for excreting water-soluble substances. The biliary system contributes to excretion to the degree that drug is not reabsorbed from the GI tract. Generally, the contribution of intestine, saliva, sweat, breast milk, and lungs to excretion is small, except for exhalation of volatile anesthetics. Excretion via breast milk may affect the breastfeeding infant

RENAL EXCRETION

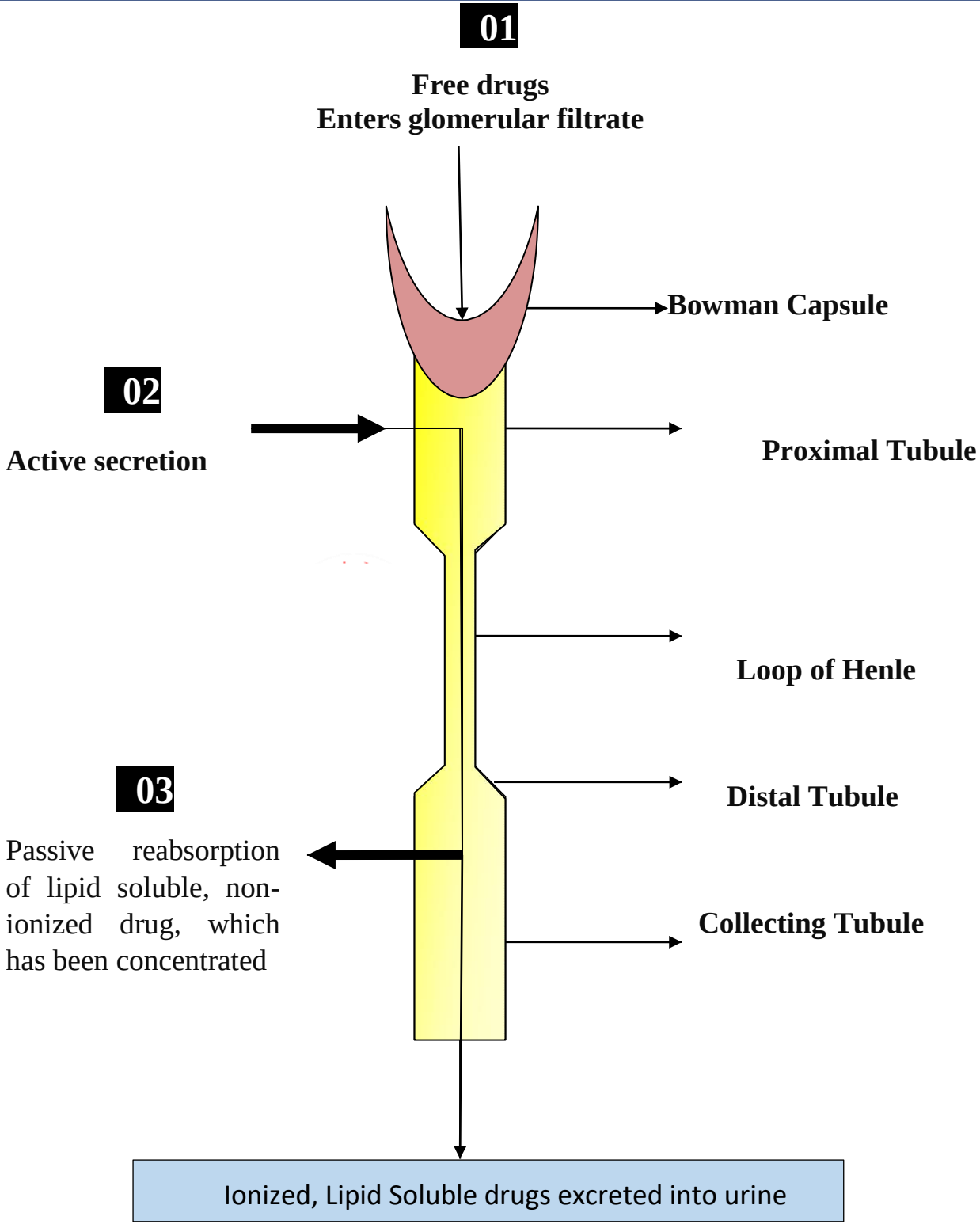
Renal filtration accounts for most drug excretion. About one fifth of the plasma reaching the glomerulus is filtered through pores in the glomerular endothelium; nearly all water and most electrolytes are passively and actively reabsorbed from the renal tubules back into the circulation. However, polar compounds, which account for most drug metabolites, cannot diffuse back into the circulation and are excreted unless a specific transport mechanism exists for their reabsorption.

Example- glucose, ascorbic acid, and B vitamins

BILIARY EXCRETION

Some drugs and their metabolites are extensively excreted in bile. Because they are transported across the biliary epithelium against a concentration gradient, active secretory transport is required. When plasma drug concentrations are high, secretory transport may approach an upper limit (transport maximum). Substances with similar physicochemical properties may compete for excretion.

Drugs with a molecular weight of > 300 g/mol and with both polar and lipophilic groups are more likely to be excreted in bile; smaller molecules are generally excreted only in negligible amounts. Conjugation, particularly with glucuronic acid, facilitates biliary excretion.



Drug Elimination by the Kidney

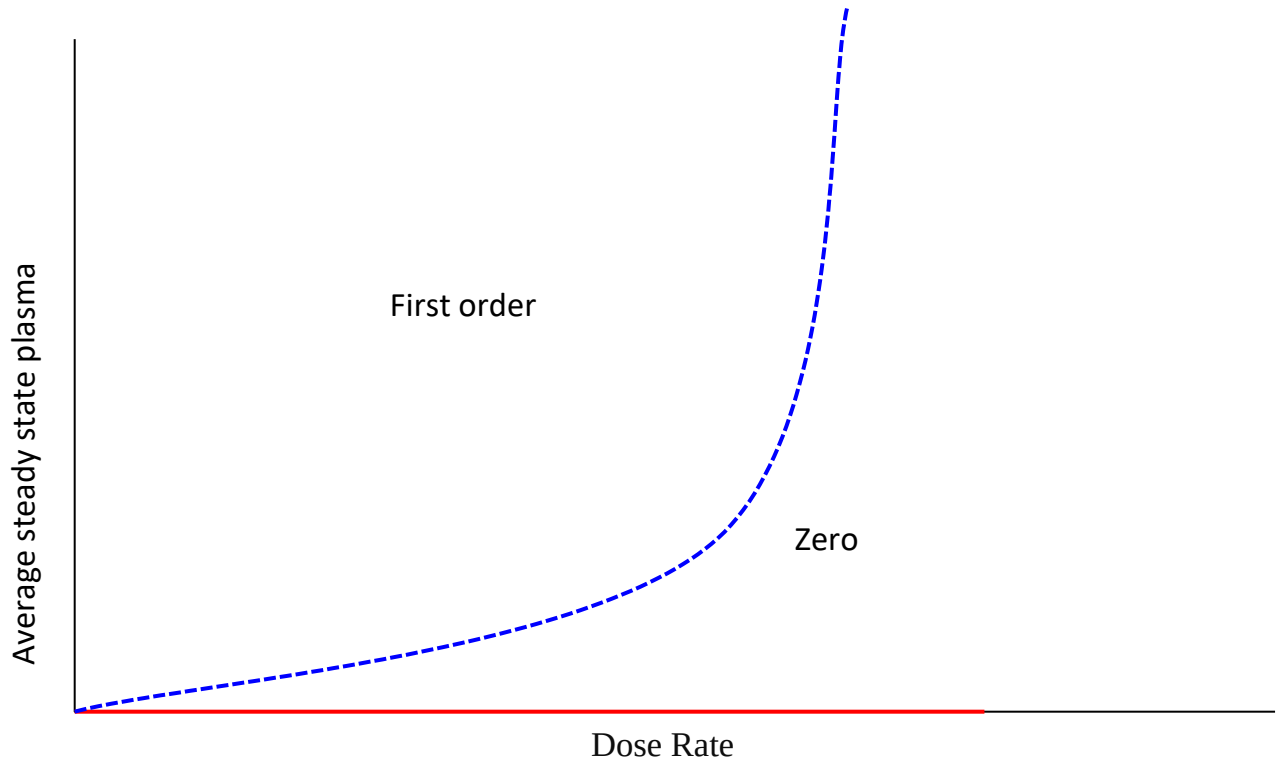
Important terms and definition

1.**Clearance-** Drugs are removed from the body by various elimination processes. *Drug elimination* refers to the irreversible removal of drug from the body by all routes of elimination.

2.**First order kinetics-** the rate of elimination of drug is directly proportional to the drug concentration, clearance remain constant or a constant fraction of drug present in the body is eliminated in unit time.

3.**Zero order kinetics-** the rate of elimination is constant irrespective of drug concentration, or a constant amount of drug is eliminated in unit time.

4.**Plasma half life-** This is the period of time required for the concentration or amount of drug in the body to be reduced by one-half. We usually consider the half life of a drug in relation to the amount of the drug in plasma. A drug's plasma half-life depends on how quickly the drug is eliminated from the plasma.



Relationship between dose rate and average Steady state plasma concentration of drug eliminated by first order and zero order kinetics.

Long answer type Questions (10 Marks)

1. Define pharmacology and explain pharmacokinetic with suitable examples. Also explain one landmark in pharmacology.
2. Explain route of drug administration. Classify various route of drug administration with their respective advantages and disadvantages.
3. Define drug. What do you understand by sources of drug? Explain with suitable example.

Short answer type questions (5Marks)

1. Explain marine source and give its importance
2. Explain tolerance and dependence
3. What do you understand by metabolism? Explain its phases in short
4. What is agonist, antagonist and inverse agonist
5. Explain idiosyncrasy and Tachyphylaxis
6. Explain enzyme induction and its clinical relevance
7. Explain cellular transport mechanism

Very Short answer type questions (2 Marks)

1. Define: Pharmacokinetics and Pharmacodynamics
2. Define First pass effect, and Therapeutic index
3. Define Bioequivalence.
4. Define enzyme induction and Inhibition.
5. Explain Child dose calculation.
6. Define tolerance with example.
7. What are the different Source of drugs.
8. Define Drug dependence & Drug abuse.
9. Explain Tachyphylaxis.
10. Define apparent volume of distribution.
11. Define Additive effects with examples.
12. Define synergistic effects with examples.
13. Define Dose response relationship.
14. Merits & Demerits of Intrathecal route of administration.
15. Define Competitive antagonism with example.
16. Define non-Competitive antagonism with example.
17. Merits & Demerits of nasal route of administration.