SUBJECT- PHARMACOLOGY - Ist
YEAR- IIIrd : SEM- Vth

UNIT- Ist

INTRODUCTION TO PHARMACOLOGY

Pharmacology is the science of drugs (greek: pharmacon- drug, logos- discourse in), it means it deals with interaction of exogenously administered chemical molecule (drug) with living system.

Pharmacology as an experimental science was introduced by RUDOLF BUCHHEIM, who founded the first institute of Pharmacology in 1847 in Germany. OSWALD SCHMIEDEBERG, regarded as the FATHER OF PHARMACOLOGY propounded some of the fundamental concepts in Pharmacology.

PHARMACOLOGY IN INDIA:

The credit for initiating, promoting and establishing Pharmacology as a teaching and research goes to SIR RAMNATH CHOPRA (1882-1973).

He was acclaimed as a FATHER OF PHARMACOLOGY IN INDIA. He was a FIRST PROFESSOR OF PHARMACOLOGY IN INDIA in the newly established CALCUTTA SCHOOL OF TROPICAL MEDICINE and simultaneously HEAD OF DEPARTMENT OF PHARMACOLOGY at the CALCUTTA MEDICAL COLLEGE.

In the past independence era, Chopra was establishing 'the first National drug research institute at Lucknow (NDRI, in present known as CDRI at Lucknow), in collaboration with student and colleague Dr. B. Mukherjee.

The credit for initiating and establishing CLINICAL PHARMACOLOGY in India goes to Prof. U.K.Seth(Mumbai).

The two main division of Pharmacology are Pharmacodynamics and Pharmacokinetics.

DRUG:

The word drug is derived from the French word **Drogue**- means **A DRY HERB**, so the drug is defined as **single active chemical entity present in medicine that is used for diagnosis, prevention, treatment and cure of a disease or for the relief of its symptoms in human or animals.**

Action of drugs on cell employes the interaction of the cell and the drug. The term 'drug and medicine' are the often used as synonyms, however,' the drug is a single entity that may be one of the constituents of a medicine.

A medicine may contain one or more active constituents (drug) together with additives to facilitate administration.

BRANCHES OF PHARMACOLOGY:

1) Pharmacodynamics
2) Pharmacokinetics
3) Pharmacotherapeutics
4) Clinical pharmacology
5) Chemotherapy
6) Toxicology
7) Pharmacometrics

PHARMACODYNAMICS: (GREEK: DYNAMIS- POWER):

'WHAT THE DRUG DOES TO THE BODY/ FOR THE DRUGS TO THE BODY/ ACTION OF DRUG ON THE BODY'

This includes physiological and biochemical effects of drugs and their mechanism of action at organ system/ subcellular/ macro molecular levels.

Adrenaline

↓

Interaction with adrenoceptors

↓

G- protein mediated stimulation of cell membrane bound Adenylyl cyclase

↓

Increased intracellular cyclic 3,5 AMP

↓

Cardiac stimulation, hepatic glycogenolysis and hyperglycaemia etc.

PHARMACOKINETICS: (GREEK: KINESIS- MOVEMENT):

'WHAT THE BODY DOES TO THE DRUG/ FOR THE BODY DOES TO THE DRUG/ ACTION OF BODY ON THE DRUG'

This refers the movement of the drug in an alteration of the drug by the body.

It is the part of Pharmacology, deals with the study of ABSORPTION, DISTRIBUTION, METABOLISM(BIOTRANSFORMATION) AND EXCRETION of the drugs.

Thus, it deals with all process involves in the changes of concentration of the drug in the body.

Example: PCM(paracetamol) is rapidly and almost completely absorbed orally attaining peak blood levels at 30-60 minute; 25 % bound to plasma proteins; widely and almost uniformly distributed in the body (Vd=1 L/Kg) mainly metabolized in the liver and excreted through urine.

PHARMACOTHERAPEUTICS

It is the application of pharmacological information together with knowledge of disease for its prevention or cure, selection of the most appropriate drug doses and duration of treatment taking into account the specific features of a patient are a part of pharmacotherapeutics.

CLINICAL PHARMACOLOGY

It is the scientific study of drug in human. It includes Pharmacodynamics and Pharmacokinetics investigation in healthy volunteers and in patient. The aim of clinical Pharmacology is generate data for optimum use of drug.

CHEMOTHERAPY

It is the use of clinical compound in the treatment of infectious disease, so as to destroy pathogenic microorganism without damaging the host tissues. A drug should be ideally parasitotropic (having affinity for parasites) nonorganotropic.

TOXICOLOGY

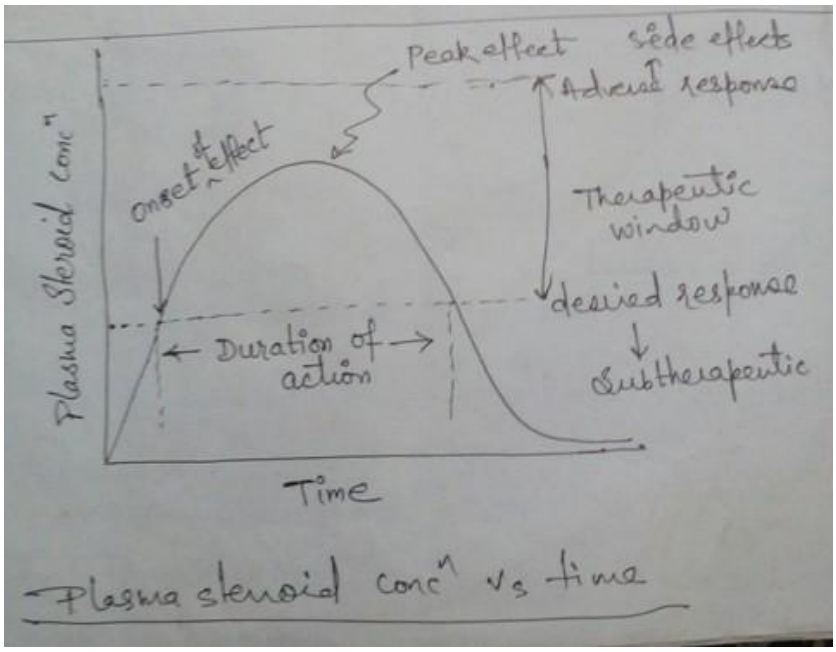
It is the study of poisonous effect of drugs and other chemicals (households, environmental pollutant, industrial, agricultural) with emphasis on detection, prevention and treatment of poisonings.

It is the science dealing with the adverse effect or a study of poison. Poison are harmful substances which are dangerous or fatal to living organism. As such it difficult to differentiate a drug and poison, since any drug may be poisonous, if not used properly, act as toxic doses.

PHARMACOMETRICS (drug+ measurement)

It is the branch of Pharmacology, dealing with identification (screening) and competitive evaluation (qualitative and quantitative) of drugs.

PHARMACY- it is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs to human or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medical substances.



ROUTES OF DRUG ADMINISTRATION

Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drugs as well as patient related factors.

FACTORS GOVERNING CHOICE OF ROUTE

1) Physical and chemical properties of the drug (solubility, stability, pH, irritancy, state of drug).
2) Rate and extent of absorption of the drug from different routes.
3) Effect of digestive juice and first pass metabolism of the drug.
4) Emergency cases.
5) Accuracy of doses required.
6) Condition of the patient (unconscious, vomiting).
7) Site of desired action- local and approachable or generalized and not approachable.

There are three main routes of the drug administration:

(A) LOCAL ROUTE
   a. TOPICAL ROUTE
   b. DEEPER TISSUE
   c. ARTERIAL SUPPLY

(B) SYSTEMIC ROUTE
   a. Oral/ internal route
   b. Parenteral / injectional route

(A) LOCAL ROUTE

(1) TOPICAL ROUTE

Local application is the simplest mode of drug administration of drug at the site where effect is desired.

This method is used for topical effect on the skin or mucous membrane or deeper tissues.

Generally the action of drug is limited to the area of application. Thus the optimum concentration can be attaining with the minimum quantity of the drug and in general without any systemic effects.

The doses forms depend on the site:

1) Mouth and pharynx- mouthwash, paints, gargales, lozengens
2) Eye, ear, nose- eyedrop, ointment, nasal, spray
3) G.I.T.- non absorbable drug given only

   Example: $Mg(OH)_2$ – antacids

   Sucralfate – ulcer protective

   Neomycin – antibiotic for H.Pylori
4) Anal canal – ointment and suppositories
5) Vagina – creams, vaginal tablets, powder, pessaries

Application of the drug on the skin may be:

(a) ENEPIDERMIC: applied to the skin without friction.

(b) INUNCTION: application of medicaments by rubbing.

(c) IONTOPHORESIS: this is a special method of applying drug to pushing it through the skin to reach the blood vessels and surrounding deeper tissue by electric transmission.

The drug is soaked in a wet pack and kept at the site of absorption, electrode having the same polarity with drug therefore free drug escaped above it and enters through the skin.

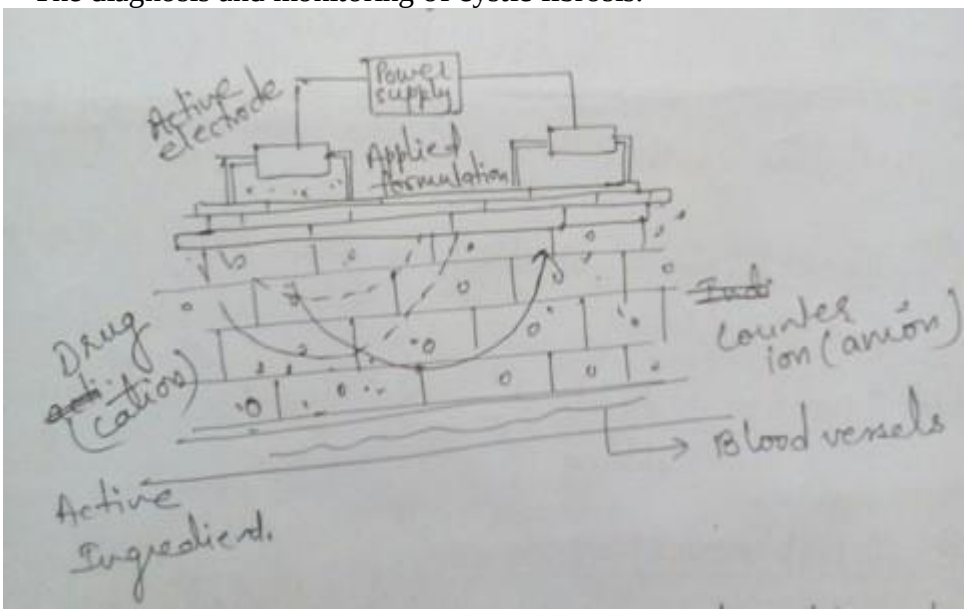
Example: (1) in case of arthritis that is joint inflammation, methyl salicylates are administered by iontophoresis method.

(2) Treatment of excessive sweating (hyperhydrosis) by obstructing the sweat gland.

(3) Delivery of iron/ titanium oxide for tattoo removal.

(4) Delivery of histamine in allergy testing.

(5) The diagnosis and monitoring of cystic fibrosis.



(2) DEEPER TISSUE:

Certain deep areas can be approached by using a syringe and needle, but the drug should be such that systemic absorption is slow.

Example- i) intra-articular injection (hydrocortisone acetate)

ii) Infiltration around a nerve or intrathecal injection (lidocaine)

(3) ARTERIAL SUPPLY: close intra- arterial injection used in angiography, anticancer drugs infused in femoral or brachial artery to realize the effect of limb malignancies.

(B) SYSTEMIC ROUTES:

The drug administered through systemic routes is intended to be absorbed into the blood stream and distributed all over, including the site of action, through circulation.

1) Internal/ intestinal/ oral route
2) Sublingual (s.l.)/ buccal route
3) Rectal route
4) Cutaneous route
5) Inhalation route
6) Nasal route
7) Parenteral route-
   (a) Subcutaneous/ hypodermic
   (b) Intramuscular
   (c) intravenous
   (d) Intradermal
   (e) Intracardiac
   (f) Intra-arterial
   (g) Intraarticular

1) INTERNAL/ INTESTINAL/ ORAL ROUTE

This is the most ancient, convenient, and suitable and commonly used route of administration of drugs. Drugs administered by oral route have as follows-

a) LOCAL ACTION-

kaolin (in diarrhea) as a local absorbent, streptomycin for local antibiotic action on intestine and glycerin tannic acid are astringent action on gums. Such action is called as Topical agents.

b) REFLEX ACTION-

Gentian as a bitter reflex (increased saliva and gastric juice).

NH_4Cl is a reflex expectorant (expel cough outside, decreased viscosity of cough) find as large emetic in large doses.

c) SYSTEMIC ACTION-

Drug like Aspirin used as analgesic and antipyretic, barbiturate as hypnotics, anthracene group of drug as purgative. Drugs are either destroy or altered absorption in the G.I.T. or liver (biotransformation), this is known as FIRST PASS METABOLISM (effect).

Irritant and unpalatable drugs cannot be administered since they will be vomited out.

If larger doses of drugs should be required then it given by injectional route.

NOTE: Emytoin is an exception of oral route required smaller dose than parenteral route.

Acid sensitive drug does not be given.

1. Ex: Penicillin
2. Adrenaline and noradrenalin
3. Ephedrine
4. Insulin etc.

Some drugs may form complexes with food like Tetracycline with milk.

ADVANTAGES OF ORAL ROUTE

1. It is economical
2. Convenient for the patient
3. Safe, self medication is possible, does not need assistance.
4. Often painless
5. No need of sterilization
6. Withdrawal of drug possible in case of toxicity.

DISADVANTAGES

1. Onset of action is slow, so not useful in emergency
2. Absorption is irregular, due to presence or absence of food in G.I.T.
3. It is not possible during vomiting and severe diarrhea
4. Cannot be used in unconscious patient
5. Some drugs like insulin and oxytocin are destroyed by G.I.T. fluids and drugs like Streptomycin not absorbed by G.I.T.
6. Chlormphenicol is unpalatable, give in the form of capsule.

2) SUBLINGUAL (s.l.)/ BUCCAL ROUTE

The drug in the form of tablet is put under tongue, the drug is thus absorbed in the systemic circulation through the sublingual route without passing through the liver

Eg: GTN in Angina pectoris

Isoprenaline in Asthma

DISADVANTAGE:

If the drug is being used in large amount and frequently then this route is not suitable.

Only lipid soluble and non- irritating drugs can be administered.

3) RECTAL ROUTE

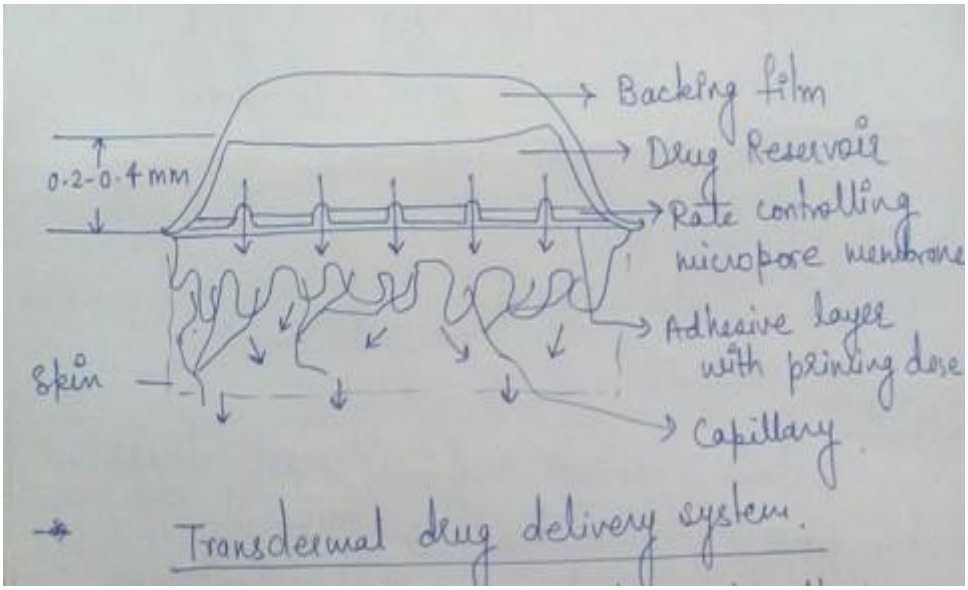
Certain irritant and unpleasant drugs can be put into rectum as suppositories. This route can also be used when the patient is unconscious or recurrent vomiting.

Eg: Diazepam, Indometacin etc.

4) CUTANEOUS

Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. Eg: if ointment is applied over specified area of skin, absorption enhanced by rubbing, by using oily base etc.

TRANSDERMAL THERAPEUTIC SYSTEM



These are devices in the form of adhesive patches of various shapes and size i.e. 5-20 cm^2, which deliver the contained drug at a constant rate into systemic circulation via the STRATUM CORNEUM.

Drug is held in a reservoir between an occlusive backing film (protective layer) and a rate controlling micropore membrane, the under surface of which is smeared with an adhesive impregnated with priming dose of the drug. The adhesive layer is protected by another film that is to be pealed off just before application.

ADVANTAGES:

1. Patient compliance is better.
2. It prevents the first pass metabolism of drug.
3. Constant rate absorption.

Eg: GTN, fentanyl, nicotine, estradiol etc.

5) INHALATION

Volatile liquid and gases are given by inhalation for systemic action.

Eg: general anaesthetic

Absorption takes place from the vast surface of alveoli and action is very rapid.

6) NASAL ROUTE

The mucous membrane of the nose can readily absorb many drugs. Digestive juices and liver are bypassed however only certain drugs like GnRH agonist and DESMOPRESSIN applied as a spray or nebulizer solution have been used by this route.

7) PARENTERAL ROUTE (Par- beyond, enteral- intestinal)

1. This refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa.

2. Drug action is faster, quick onset of action and surer (valuable in emergencies).
3. This route employed in unconscious, uncooperative or vomiting patients.
4. Liver is bypassed
5. Smaller dose are required for the effect.

DISADVANTAGES

1. This is painful and expensive and needs surgical sterility.
2. It needs proper technology used in its administration.
3. Self medication is not possible.
4. There are chances of local tissue injury and in general parenteral route is more risky than oral route.

The important parenteral routes are-

(a) Subcutaneous/ hypodermic
(b) Intramuscular
(c) intravenous
(d) Intradermal
(e) Intracardiac
(f) Intra-arterial
(g) Intraarticular

SUBCUTANEOUS ROUTE (s.c.)/ HYPODERMIC ROUTE

1. The drugs are injected under the skin means below the dermis.
2. The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves.
3. Only non irritant drugs can be given by this route.
4. Due to less vascular supply, absorption is slower than intramuscular.
5. Volume of drug should be **LESS THAN 1 ml.**
6. Sometimes drug pellet are used as depot therapy for prolonged action.

There are three different methods for subcutaneous route for drug administration:
DERMOJET
PELLET IMPLANTATION
SIALISTIC (nonbiodegradable) and biodegradable implants.
DERMOJET
In this method needle is not used, high velocity jet of drug solution is projected from a microfine orifice using gun like implement.
The solution passes through the superficial layers and gets deposited in the subcutaneous tissue.
IMPLANTS
This is the new technology of implanting a tablet or porous capsule into the loose tissue by incision of skin which is then stitched up.
The tablet or porous capsule so introduced slowly released the drug and the action continuous for a weak to 12 months.
Certain hormonal drug implanted by this route.
(i) PELLET IMPLANTATION
The drug in the form of a solid pellet is introduced with a trochar and cannula, this provide sustained release of the drug. Eg: TESTOSTERONE, DOCA.
(ii) BIODEGRADABLE/ NONBIODEGRADABLE IMPLANTS
Crystalline drug is packed tubes or capsule made of suitable material and implanted under the skin.
Slow and uniform leaching of the drug occurs over months providing constant blood levels.

The nonbiodegradable implants have to be removed later on but not the biodegradable one.
Eg: hormones and contraceptives.

INTRAMUSCULAR ROUTE

This is the most common route of administration of injectable drug.
The muscle has rich lymph and vascular absorption of drug is faster.
Less nerve supply, mild irritant can be injected.
The drug is injected in one of the large skeletal muscles- deltoid, triceps,gluteus maximus, rectus femora etc.
Depot preparation (oily solution, aqueous suspension) can be injected by this route.
Eg: Irondextran, penicillin.

CARE FOR THE I.M. INJECTION

The drug should be given as safe site, eg: lower part of the deltoid region (shoulder), the site of injection should be away from nerves and joint otherwise there is risk of nerve damage.
THE VOLUME OF FLUID GIVEN SHOULD NOT BE MORE THAN 10 ml.
Ordinary injection should be given in superficial part of the muscle, whereas irritating drug are painful given deeply.
Eg: injection of Quinine.

DISADVANTAGE

Irritant drug may cause opsist and pain.
Risk of injecting drug into the blood vessels which can be harmful.
Self medication is not possible.

INTRAVENOUS ROUTE

Drug injected as a bolus or infused slowly over hours in one of the superficial vein. This is the quickest route for fastest action of drug. It goes directly into the blood circulation hence desired drug action concentration can be achieved. Irritant substances can be given by this route.

CARE

For i.v. injection, the superficial vein is selected, area sterilized and injection is administered and speed of administration regulated.
Air bubble should not find entry in vein.

ADVANTAGE

1. The drug have Very rapid onset of action and thus useful in emergency and unconscious patient.
2. The drug gain very accurate concentration in blood.
3. Large volume of solution can be injected over a period of hours.
4. By this route small doses of drugs are effective.

DISADVANTAGE

1. It is not suitable for oily and insoluble drugs.
2. Sometimes it causes thrombosis and tissue necrosis.
3. It is not suitable for drugs which causes haemolysis and precipitate drug.
4. This is the most risky route, vital organs like heart, brain etc. get exposed to high concentration of drug.

INTRADERMAL ROUTE

The drug is given within the skin layer between epidermis and dermis.
This route is used for testing sensitivity to drug. Eg: Penicillin, ATS (antitetanus serum) and BCG vaccines.
Highly diluted and small quantity of drug administered.
Drug should be **LESS THAN 0.2 ml.**

INTRACARDIAC ROUTE

It is given quickly and directly in the cardiac muscle. Eg: adrenaline

INTRAARTERIAL ROUTE

This route is rarely used by surgeon or reliving certain arterial disease.

The procedure is very risky.

Eg: anticancer drug

INTRAARTICULAR ROUTE

Drugs like Hydrocortisone is injected into joints, this route is used for treatment of local condition.

DRUG DISCOVERY:

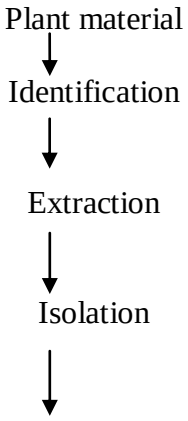
Drug discovery can be done by two ways:
1. Drug discovery without a lead compound.
2. Drug discovery with the help of lead compound.

The lead is a prototype compound that has desired biological or pharmacological activity, but may have many other undesirable activities.
For eg: high toxicity, other pharmacological activities, insolubility or metabolic problem.
Thus a new drug discovery involves the following steps-
1. The search for suitable lead compound.
2. Lead optimization by chemical modification to get better drug.

Search for leads:

The lead compound can be found by following approaches:-
1. Search for a lead compound from a nature.
2. Drug metabolism study.
3. Study of side effects of drug.
4. Testing of intermediate products used in the synthesis of drugs.
5. Random screening of chemicals or pharmacological activities.
6. From Ayurveda and Siddha that is-

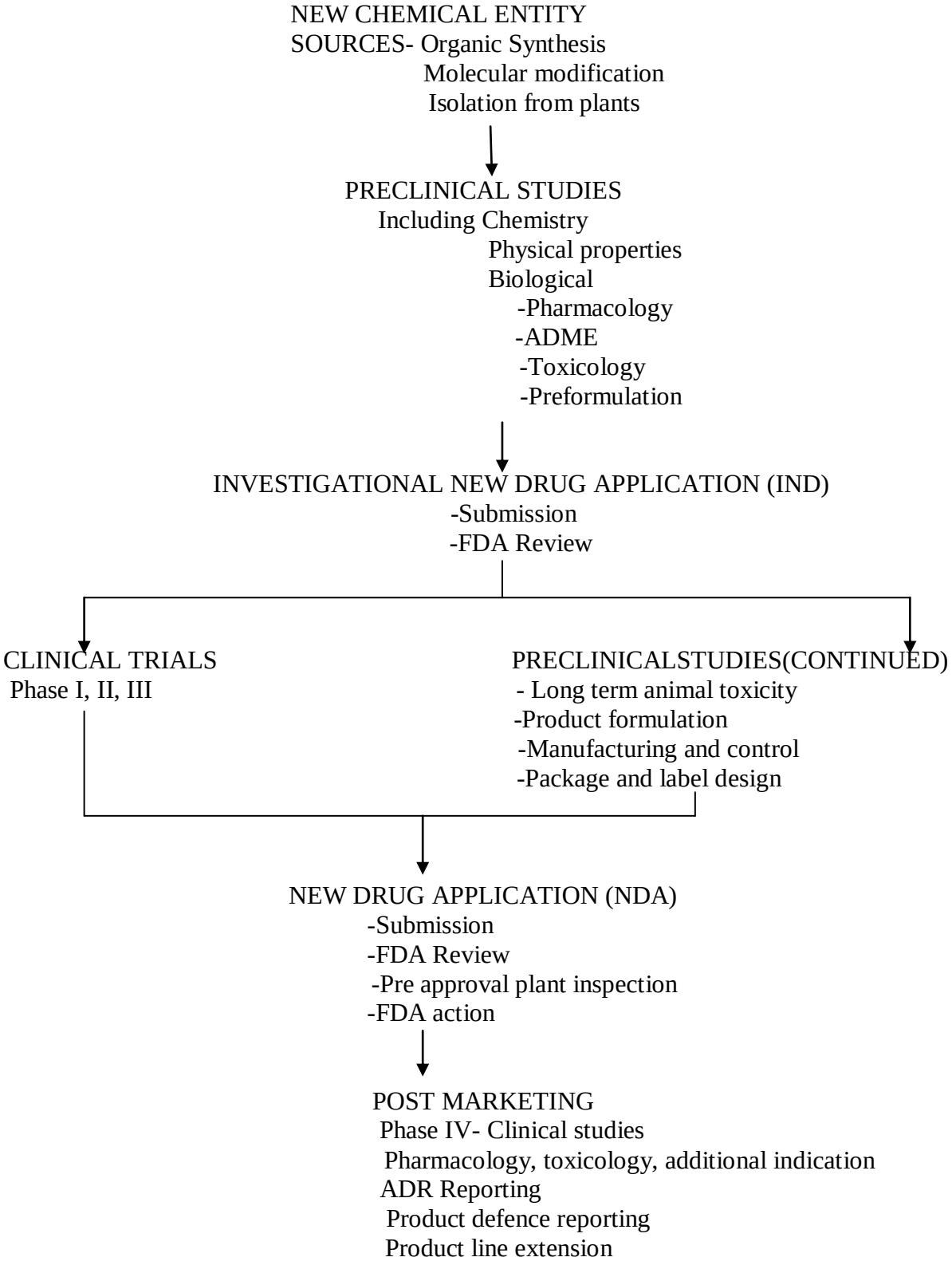
Which plants is responsible for the Pharmacological effects:



7. This study followed by determination of the chemical structure of the compound.
8. Now this compound can be used as lead and used in development of better drug.

After identification of lead compound, the next step in New drug discovery-
To synthesize compound which have related structure to the lead compound and testing their Pharmacological activity? This process is called' lead modification or lead manipulation or lead optimization'.
Lead modification is carried out with one or more of the following objectives:
1. To increase the potency of lead compound to get better drug
2. To decrease or eliminate toxic effects.
3. To isolate the singular pharmacological effect from the lead compound.
4. To make a resistant with metabolic enzymes.
5. To prevent the entry of the drug to the BRAIN by making it more polar or ionic, so that it will not cross the BBB.

NEW DRUG DEVELOPMENT PROCESS



PRECLINICAL STUDIES

A) PHARMACOLOGICAL STUDIES/ TOXICOLOGY STUDY

B) TOXICITY STUDY

i) Acute toxicity
ii) Sub acute/ chronic toxicity
Teratogenicity
Carcinogenicity
Mechanism of toxicity
Drug metabolism

2- 4 weeks= sub acute
6- 24 months= chronic

PHASES OF CLINICAL TRIALS

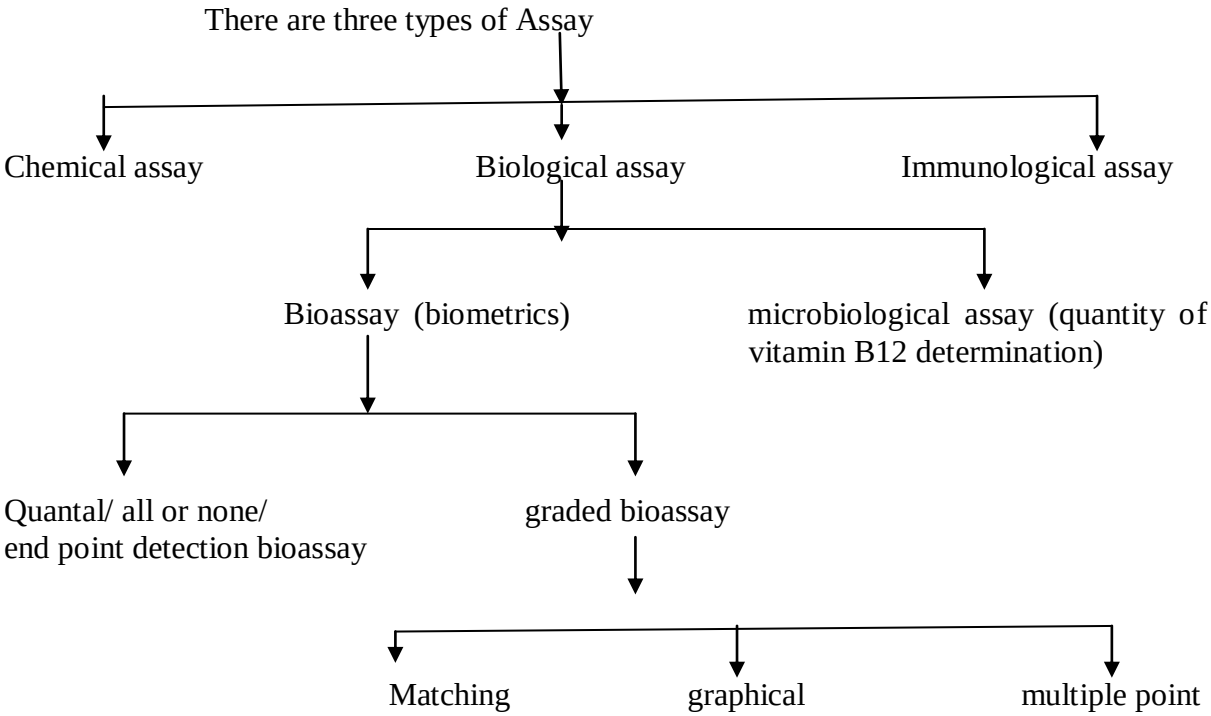
TRIALS	NUMBER OF PATIENT	LENGTH	PURPOSE	SUCCESS
PHASE I	20-100	SEVERAL MONTHS	MAINLY SAFETY IN VOLUNTEERS	67%
PHASE II	100-500	MONTHS TO YEARS	SHORT TERM SAFETY, EFFECTIVENESS	45%
PHASE III	1000-5000	1-4 YEARS	SHORT TERM SAFETY, EFFECTIVENESS IN LARGER NUMBER OF PATIENTS POPULATION	5- 10 %
PHASE IV	-	-	DETECT ADR	-

BIOASSAY:

Assay is the

1) Estimation of POTENCY of an active principle.
2) Determination of the QUANTITY present in the sample.
3) Determination of the PURITY of the sample.

TYPES OF ASSAY



Types of bioassay

Bioassay is of two types on the basis of response.

Quantal and

Graded

Quantal or all or none bioassay

The Quantal bioassay is a all or none phenomena.

Eg: convulsion, cardiac arrest in pigeons and guinea pig

Either convulsion / or no convulsion

Graded response

it is dose dependent response, assays are based on the observations that there is proportionate increased in the observed response with a subsequent increase in the concentration or dose.

Types of graded bioassay

1) Matching
2) Bracketing
3) Graphical/interpolation
4) Multiple points

Application of bioassay

1) Standardization of drugs.
2) Estimation of biologically active substances in body fluid and tissue extract.
3) Screening of new compound for biological activity.
4) Diagnosis of clinical research.

5) Estimation of the dose of a drug required to produce a therapeutic or toxic response.

RECEPTORS

There are four types of receptors.

1) G-protein coupled receptors (GPCR)

A) Adenylyl cyclase: c- AMP pathway

B) Phospholipase: IP3- DAG pathway

C) Channel regulation

2) Receptor with intrinsic ion channel/ ionotropic/ ligand gated ion channel

3) Enzyme linked receptor

A) Intrinsic Enzyme receptor

B) JAK-STAT kinase binding receptor

4) Receptor regulating gene expression/ nuclear or steroidal receptor/ cytoplasmic intracellular receptor.

G- PROTEIN COUPLED RECEPTOR

These are a large family of cell membrane receptor consist of G Protein Coupled Receptor.

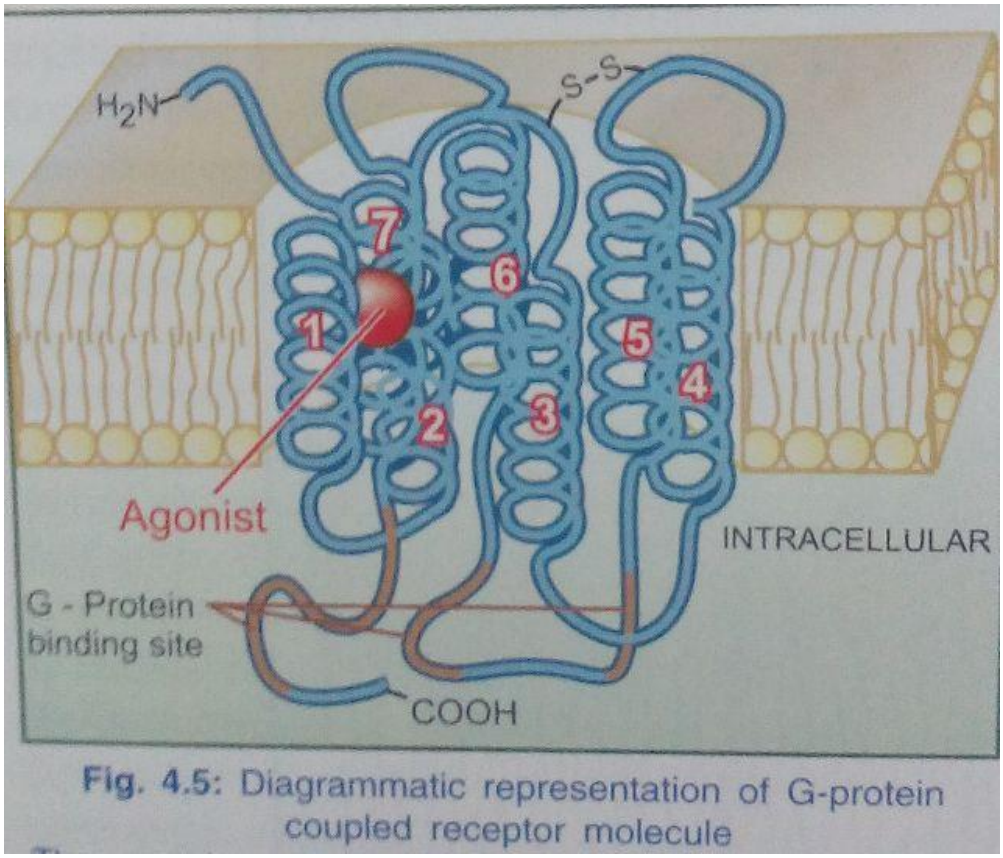


Fig. 4.5: Diagrammatic representation of G-protein coupled receptor molecule

There are three major effectors pathways through which GPCRs functions-

<u>Adenylyl cyclase: c- AMP pathway</u>

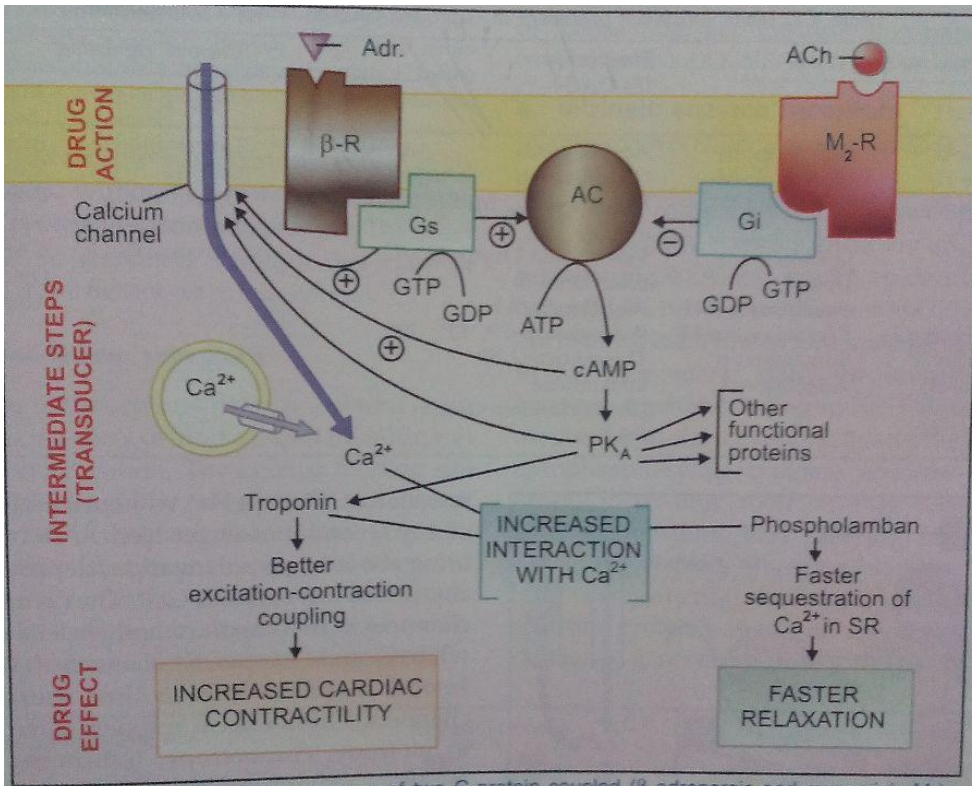


Fig. 4.6: The action-effect sequence of two G-protein coupled (β adrenergic and muscarinic M_2) receptor activation in myocardial cell

The agonist binding site is located somewhere between the helices on the extracellular faces, while another binding site in the cytosolic segment binds the coupling G- protein.

<u>Phospholipase C: IP3- DAG pathway</u>

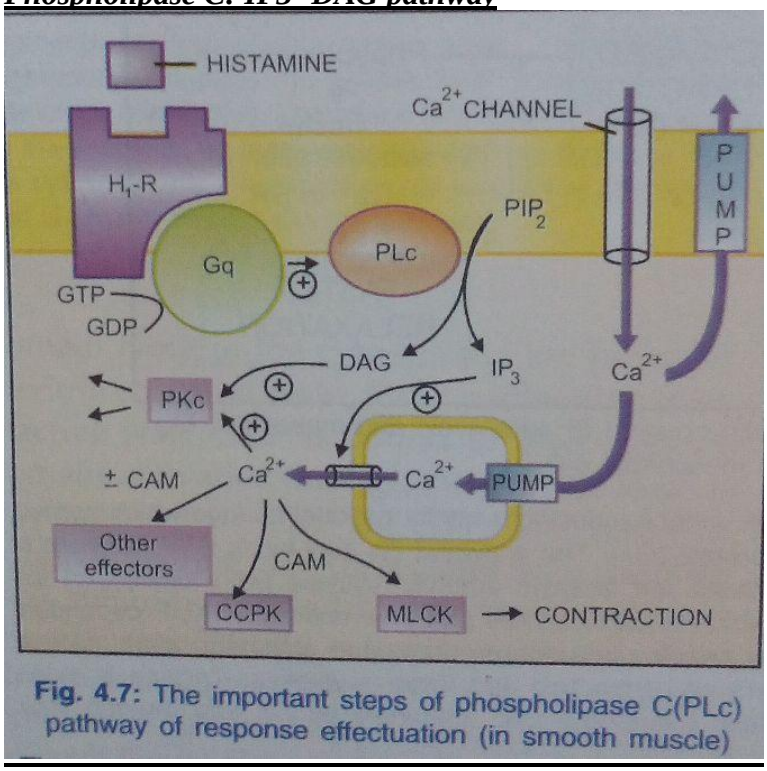
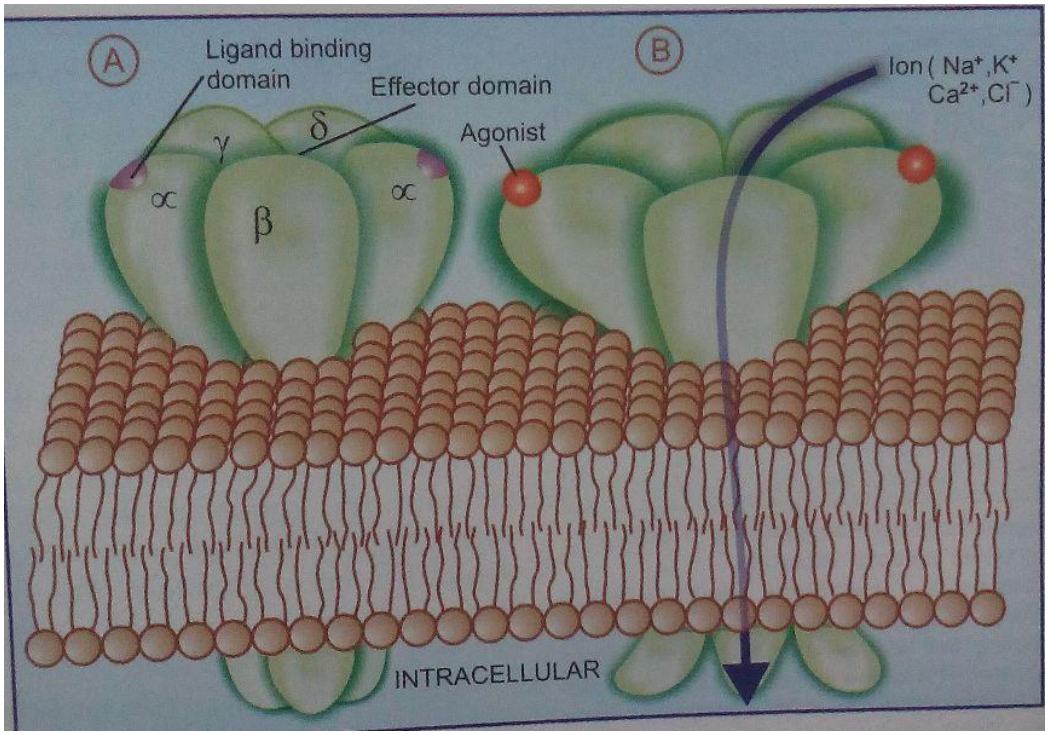


Fig. 4.7: The important steps of phospholipase C(PLc) pathway of response effectuation (in smooth muscle)

RECEPTOR WITH INTRINSIC ION CHANNEL

These cell surface receptor, also called LIGAND GATED ION CHANNELS, encloses ion selective channels (for Na^+, K^+, Ca^+, or Cl^+) within their molecules.



ENZYME LINKED RECEPTOR

There are two major subgroups of such receptors.-

a)those that have intrinsic enzymatic activity.

b)those that lack intrinsic enzymatic activity but bind a JAK- STAT kinase on activation.

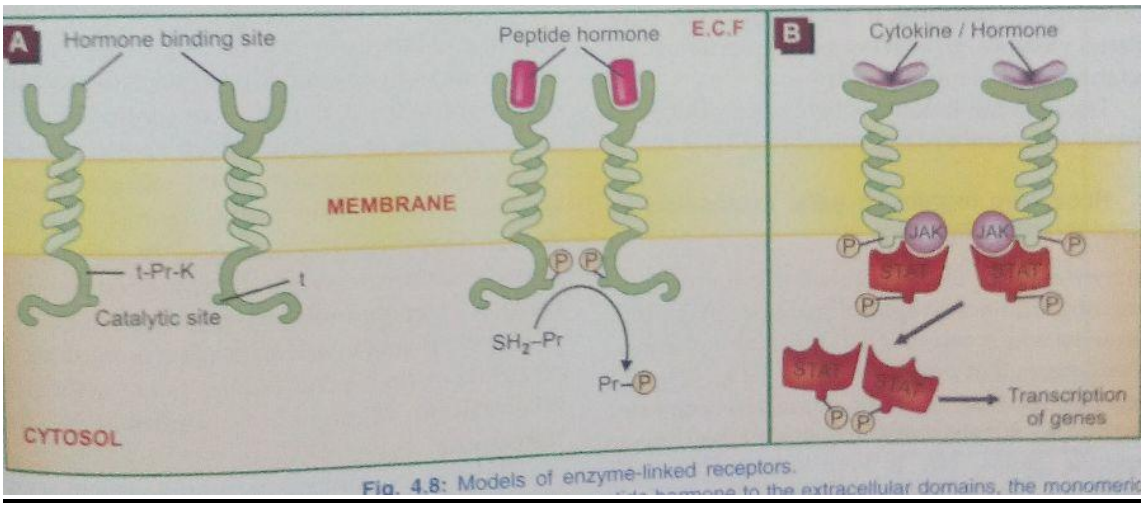


Fig. 4.8: Models of enzyme-linked receptors.

RECEPTOR REGULATING GENE EXPRESSION

There are intracellular (cytoplasmic or nuclear) soluble proteins which respond to lipid soluble chemical messenger that penetrate the cell.

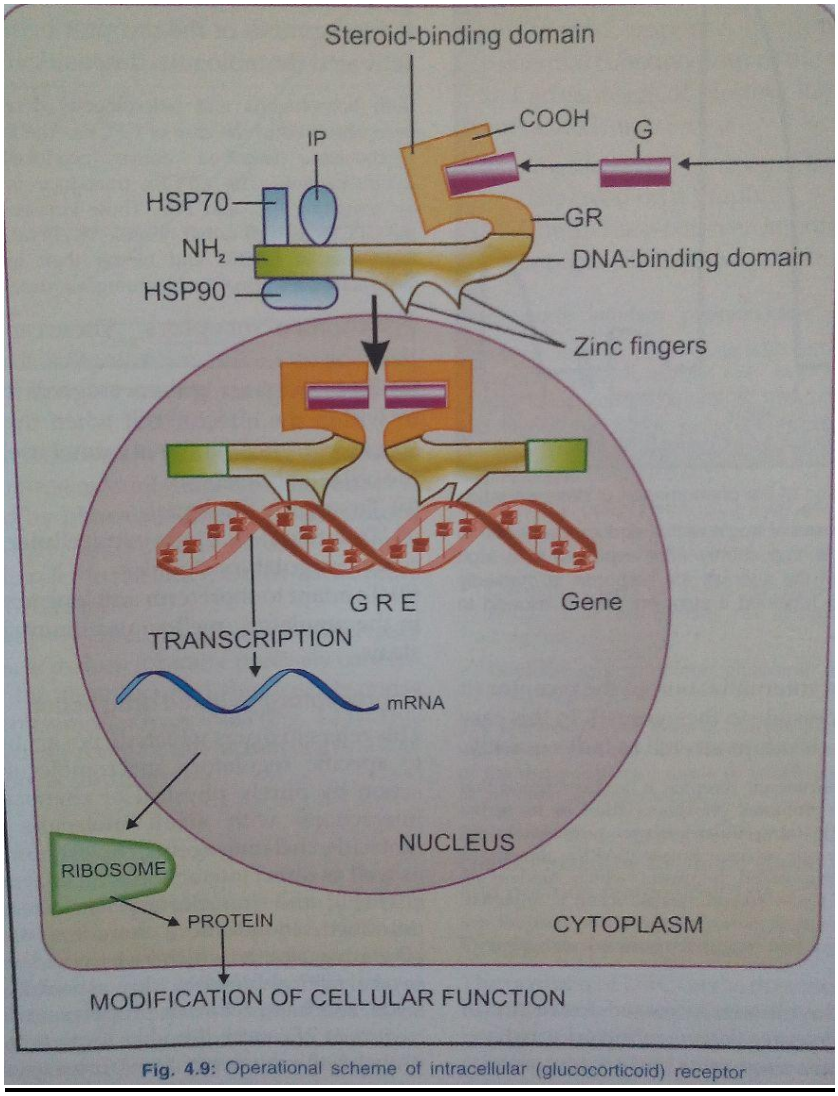


Fig. 4.9: Operational scheme of intracellular (glucocorticoid) receptor

COMBINED EFFECT OF NEW DRUGS

When two or more drugs given simultaneously or in quick succession, they may be either indifferent to each other or exhibit Synergism or Antagonism.

The interaction may be take place at Pharmacolokinetic level or at Pharmacodynamics level.

SYNERGISM:

When the action of one drug is facilitated or increased by the other, they are said to be Synergistic. Synergism can be:

ADDIITIVE

SUPRADDITIVE

ANTAGONISM:

When one drug decreases or abolishes(block) the action of another, they are said to be Antagonist. Depending on the mechanism involved antagonism may be:

A) Physical antagonism

B) Chemically antagonism

c) Physiological/ Functional antagonism
D) Receptor antagonism

RECEPTOR ANTAGONISM

COMPETITIVE — NON- COMPETITIVE

EQUILIBRIUM — NON-EQUILIBRIUM

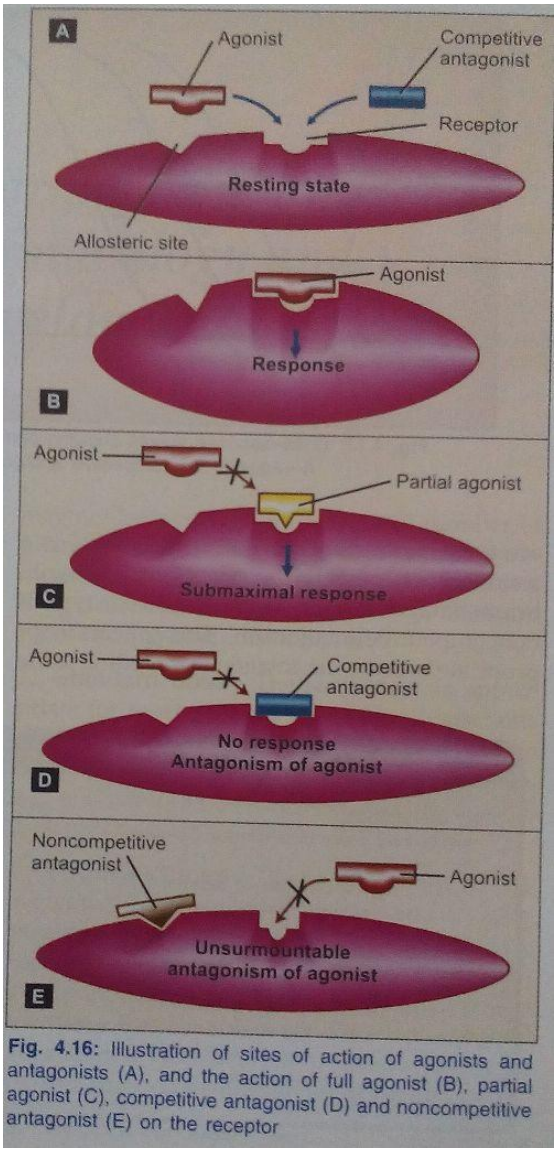


Fig. 4.16: Illustration of sites of action of agonists and antagonists (A), and the action of full agonist (B), partial agonist (C), competitive antagonist (D) and noncompetitive antagonist (E) on the receptor

FACTORS MODIFYING DRUG ACTION

The factor modifying drug action either:

QUANTITATIVELY-

The plasma concentration and// or the action of the drug is increased or decreased. This problem overcomes by adjustment of drug doses.

QUALITATIVELY-

The type of response is altered, eg: drug allergy or idiosyncracy.

There are following factors that modify drug action:

1) Physiological factor
2) Pathological factor
3) Psychological factor
4) Genetic factor
5) Environmental factor
6) Interaction with other drugs.

1) PHYSIOLOGICAL FACTOR
- AGE
- BODY SIZE
- GENDER
- PREGNANCY
- LACTATION
- FOOD
- ALLERGY
- DRUG DEPENDENCE

2) PATHOLOGICAL FACTORS
- LIVER DISEASES
- RENAL DISEASES
- GIT DISEASES
- CHF DISEASES
- THYROID DISEASES

3) GENETIC FACTORS
-IDIOSYNCRACY
-DEFICIENCY OF G-6-PD
-SPECIES AND RACE

4) ENVIRONMENTAL FACTORS
- ROUTES OF DRUG ADMINISTRATION
- TIME OF ADMINISTRATION
- EFFECT OF CLIMATE
- RACIAL DIFFERENCE
- PREPARATION OF DRUG
-AGE OF DRUG
-ACID OR BASIC MEDIUM
-EFFECT OF DISEASE
-HYPERSUSCEPTIBILITY OF DRUG
-HYPERSENSITIVITY
-TOLERANCE

-TACHYPHYLAXIS
-CUMULATION
-DRUG RESISTANCE
6) PSYCHOLOGICAL FACTORS
-PLACEBO
-NOCEBO
7) INTERACTION OF DRUGS
-SYNERGISM
-ANTAGONISM

ABSORPTION

Pharmacokinetic is the quantitative study of drug movement in through and out of the body.

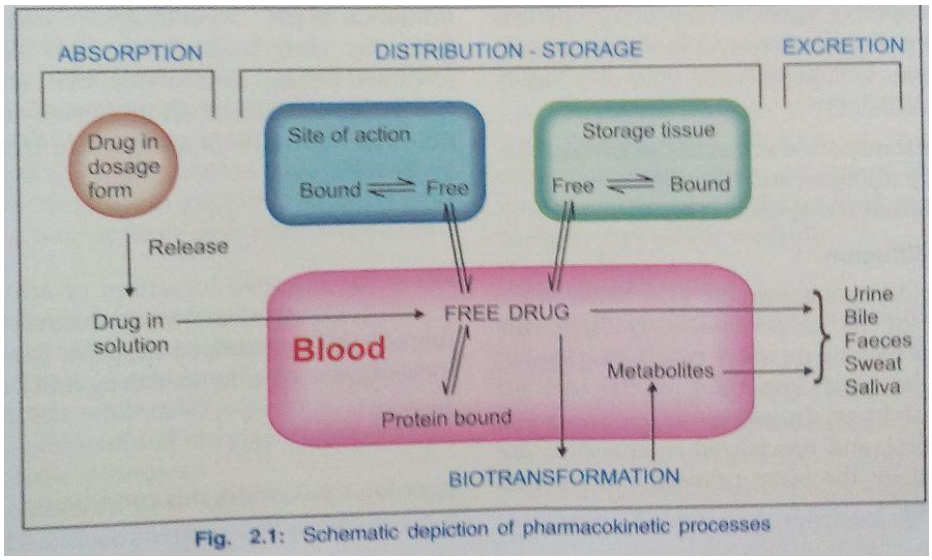


Fig. 2.1: Schematic depiction of pharmacokinetic processes

Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation.

BIOLOGICAL MEMBRANE

This is a bilayer (about 100 A thick) of phospholipid and cholesterol molecules.their hydrocarbon chain are oriented inwards to form the hydrophobic or lipophilic phase and their polar heads oriented to form the outer and inner hydrophilic layer of the cellular membrane that face the surrounding aqueous environment.

The hydrophobic core of the membrane is responsible for the relative impermeability of polar molecules.

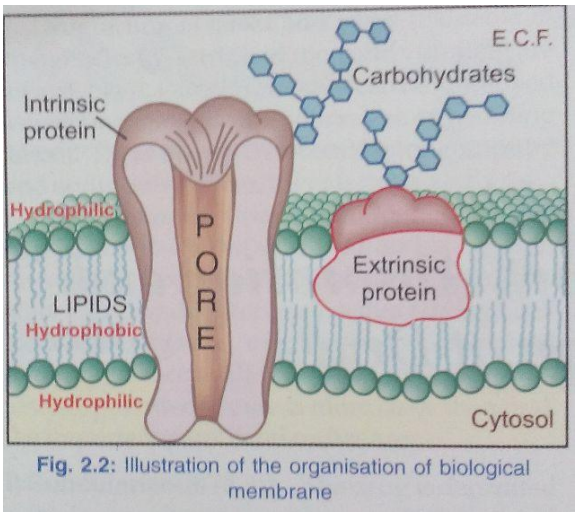


Fig. 2.2: Illustration of the organisation of biological membrane

MECHANISM OF DRUG ABSORPTION

The two broad categories of drug transport mechanism involved in absorption are:-

1) PASSIVE TRANSPORT PROCESS

-PASSIVE DIFFUSION

-PORE TRANSPORT

-ION PAIR TRANSPORT

-FACILITATED OR MEDIATED DIFFUSION

2) ACTIVE TRANSPORT

-PRIMARY ACTIVE TRANSPORT

-SECONDARY ACTIVE TRANSPORT

A) Symport (co- transport)

B) Antiport (counter transport)

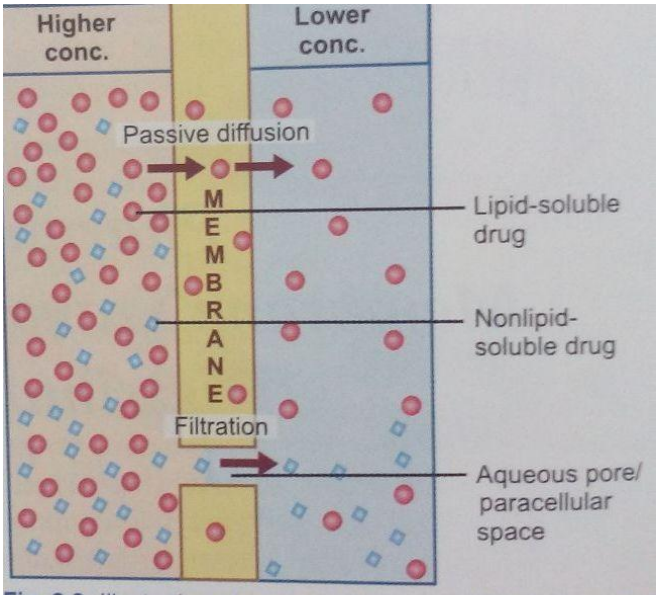


Fig. 2.3: Illustration of passive diffusion and filtration across the lipoidal biological membrane with aqueous pores

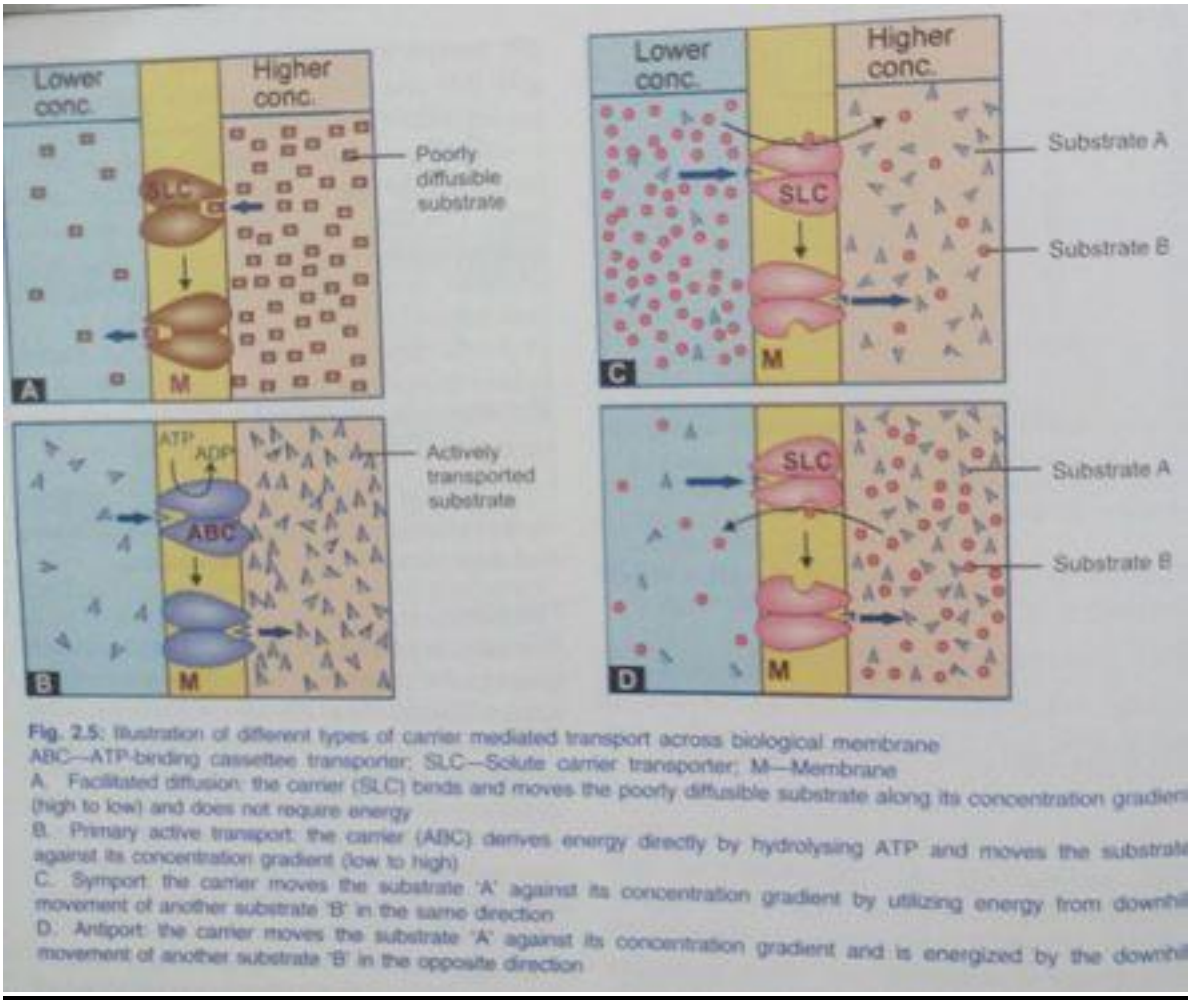


Fig. 2.5: Illustration of different types of carrier mediated transport across biological membrane
ABC—ATP-binding cassettee transporter; SLC—Solute carrier transporter; M—Membrane
A. Facilitated diffusion: the carrier (SLC) binds and moves the poorly diffusible substrate along its concentration gradien (high to low) and does not require energy
B. Primary active transport: the carrier (ABC) derives energy directly by hydrolysing ATP and moves the substrat against its concentration gradient (low to high)
C. Symport: the carrier moves the substrate 'A' against its concentration gradient by utilizing energy from downhil movement of another substrate 'B' in the same direction
D. Antiport: the carrier moves the substrate 'A' against its concentration gradient and is energized by the downhil movement of another substrate 'B' in the opposite direction

BIOAVAILABILITY

Bioavailability refers to the rate and extent of absorption of a drug from a dosage form as determined by its concentration- time curve in blood or by its excretion in urine.
It is denoted by F
The therapeutic effect or Pharmacological effect of the drug is depends upon the bioavailability of the drug.

BIOAVAILABILITY= AUC (ORAL)*100/AUC (I.V.)

FACTORS AFFECTING DRUG ABSORPTION
-aqueous solubility of the drug
-concentration
-area of absorbing surface
-vascularity of absorbing surface
-route of drug administration
-dosage form
-patient factor like age, disease states, etc.

DISTRIBUTION OF DRUG

Distribution is a passive process for which the driving force is concentration gradient between the blood stream and the extravascular tissues.

Steps of drug distribution-
1) Permeation of free or unbound drug present in the blood through capillary wall and entry into the extracellular fluid (ECF).
2) Permeation of drug present in the ECF through the membrane of tissue cells and into the intracellular fluid.

FACTORS AFFECTING DRUG DISTRIBUTION

1) Tissue permeability of the drug.
-Physicochemical properties of the drug like molecular size, partition coefficient etc.
-physiological barrier of diffusion of the drug
2) Binding of drug to tissue components
-binding of drugs to blood component
-binding of drugs to extravascular tissue protein
3) Other factors
-age, pregnancy, obesity, diet, disease states, drug interaction.

VOLUME OF DISTRIBUTION

Presuming that the body behaves as a single homogenous compartment with volume V into which drug gets immediately and uniformly distributed.

V= DOSE ADMINISTERED I.V. / PLASMA CONCENTRATION

BIOTRANSFORMATION/ METABOLISM

Biotransformation or metabolism or detoxification of drugs or removal of pharmacological effect of drug from the body.
Biotransformation means chemical alteration of drug in the body. It changes nonpolar or lipid soluble compound to polar or lipid insoluble compound so that they are not reabsorbed in the renal tubules and are excreted.
Biotransformation of drugs may lead to the following:

1) INACTIVATION
Most drugs and their active metabolite are changed in inactive or less active form. E.g. - ibuprofen, paracetamol etc.

2) ACTIVE METABOLITE FROM AN ACTIVE DRUG
Drug partially converted to one or more active metabolite, the effect observed are the sumtotal of that due to parent drug and its active metabolite.
E.g. - digitoxin converted in digoxin.

Biotransformation reaction can be classified into-
A) Nonsynthetic/ phase I/ fictionalization reaction
A functional group is generated or exposed- metabolite may be active or inactive.
- Oxidation
-reduction
-hydrolysis
-cyclization
-decyclization
B) Synthetic/ conjugation/ phase II reaction
Metabolite is mostly inactive, except few drugs.
- glucuronide conjugation
-acetylation

-methylation
-sulfate conjugation
-glycine conjugation
-glutathione conjugation
-ribonucleoside/ nucleotide synthesis

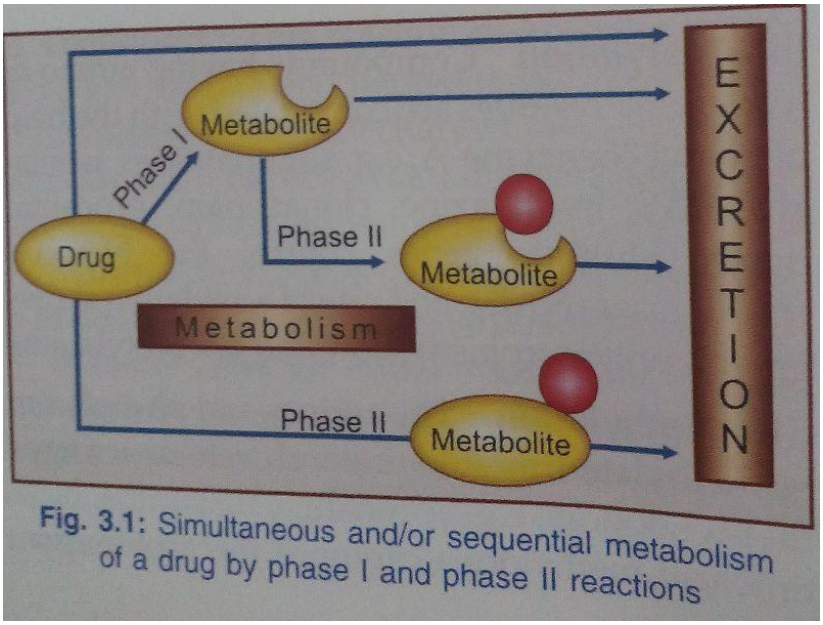


Fig. 3.1: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

EXCRETION

Excretion is defined as the process whereby drugs and their metabolites are irreversibly transferred from internal to external environment. The principal organs of excretion are kidneys. Excretion of drugs by kidney is called as renal excretion.

Drugs and their metabolites are excreted in-
Urine
Faeces
Exhaled air
Saliva and sweat
Milk

RENAL EXCRETION OF DRUGS

Almost all drugs and their metabolites are excreted by the kidneys to some extent or the others.

Agents that are excreted in urine are-
1) Water soluble
2) Non- volatile
3) Small in molecular size(less than 500 Dalton)
4) The ones that are metabolized slowly

Principal processes that determine the urinary excretion of a drug are-
1) Glomerular filtration
2) Active tubular secretion
3) Active or passive tubular reabsorption

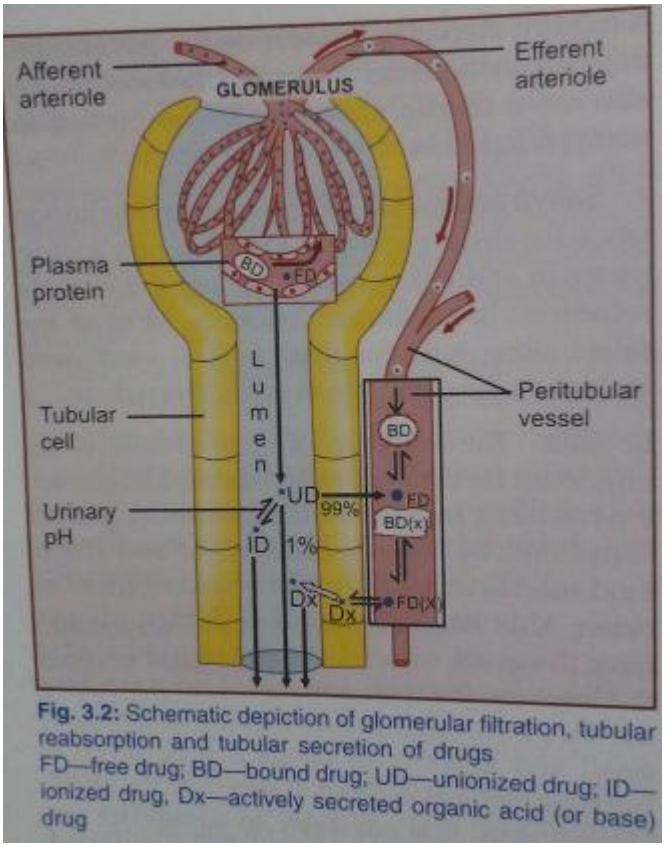


Fig. 3.2: Schematic depiction of glomerular filtration, tubular reabsorption and tubular secretion of drugs
FD—free drug; BD—bound drug; UD—unionized drug; ID—ionized drug, Dx—actively secreted organic acid (or base) drug

CONCEPT OF CLEARANCE

The clearance concept was first introduced to describe renal excretion of endogenous compound in order to measure kidney function.

The term is now applied to all organs involved in drug elimination such as liver, lungs, the biliary system, and reffered to as hepatic clearance, pulmonary clearance, biliary clearance and so on.

The sum of individual clearance by all eliminating organs is called as 'TOTAL BODY CLEARANCE' or 'TOTAL SYSTEMIC CLEARANCE'.

CLEARANCE= RENAL CLEARANCE+ HEPATIC CLEARANCE+ PULMONARY CLEARANCE +BILIARY CLEARANCE+…….

CLEARANCE

Clearance is defined as the hypothetical volume of body fluids containing drug from which the drug is removed or cleared completely in a specific period of time. It is expressed in ml/min.

CLEARANCE(Cl) = elimination rate/ plasma drug concentration

RENAL CLEARANCE (Cl_R)

It can be defined as the volume of blood or plasma which is completely cleared of unchanged drug by the kidney per unit time.

$Cl_{R=}$ Rate Of Urinary Excretion/ Plasma Drug Concentration

Cl_R = Rate Of Filtration+Rate Of Secretion-Rate Of Reabsorption/C (Plasma Drug Concentration)

FACTORS AFFECTING RENAL EXCRETION OR RENAL CLEARANCE

1) Physicochemical properties of the drug.
2) Plasma concentration of the drug.
3) Distribution and binding characteristics of the drug.
4) Urine pH
5) Blood flow to the kidneys
6) Biological factors
7) Drug interaction
8) Disease states