Lecture Notes on

General Pharmacology

(Unit I)

[As per VCI MSVE 2016 Syllabus]

Compiled by

Dr. Nirbhay Kumar

Asstt. Professor & Head
Department of Veterinary Pharmacology & Toxicology
Bihar Veterinary College, Bihar Animal Sciences University
Patna – 800 014, Bihar

Unit I

GENERAL PHARMACOLOGY

Syllabus

Chapter 1: Introduction, historical development, branches and scope of Pharmacology. Sources and nature of drugs. Pharmacological terms and definitions, nomenclature of drugs.

Chapter 2: Principles of drug activity: Pharmacokinetics - Routes of drug administration, absorption, distribution, biotransformation and excretion of drugs.

Chapter 3: Pharmacodynamics - Concept of drug and receptor, dose-response relationship, terms related to drug activity and factors modifying the drug effect and dosage. Adverse drug reactions, drug interactions.

⌖ ⌖ ⌖ ⌖ ⌖

Suggested Text books of Pharmacology:

1. Veterinary Pharmacology & Therapeutics (10th Edn.-2018) – Jim E. Riviere and Mark G. Papich
2. Essentials of Medical Pharmacology (8th Edn.-2019) – K.D. Tripathi
3. Rang & Dale's Pharmacology (9th Edn.- 2019) – James M. Ritter, Rod Flower, Graeme Henderson, Yoon Kong Loke, David MacEwan & Humphrey P. Rang.
4. Goodman & Gilman's The Pharmacological Basis of Therapeutics (13th Edn.-2018) – Laurence L. Brunton, Randa Hilal-Dandan & Björn C. Knollmann.

Chapter - 1

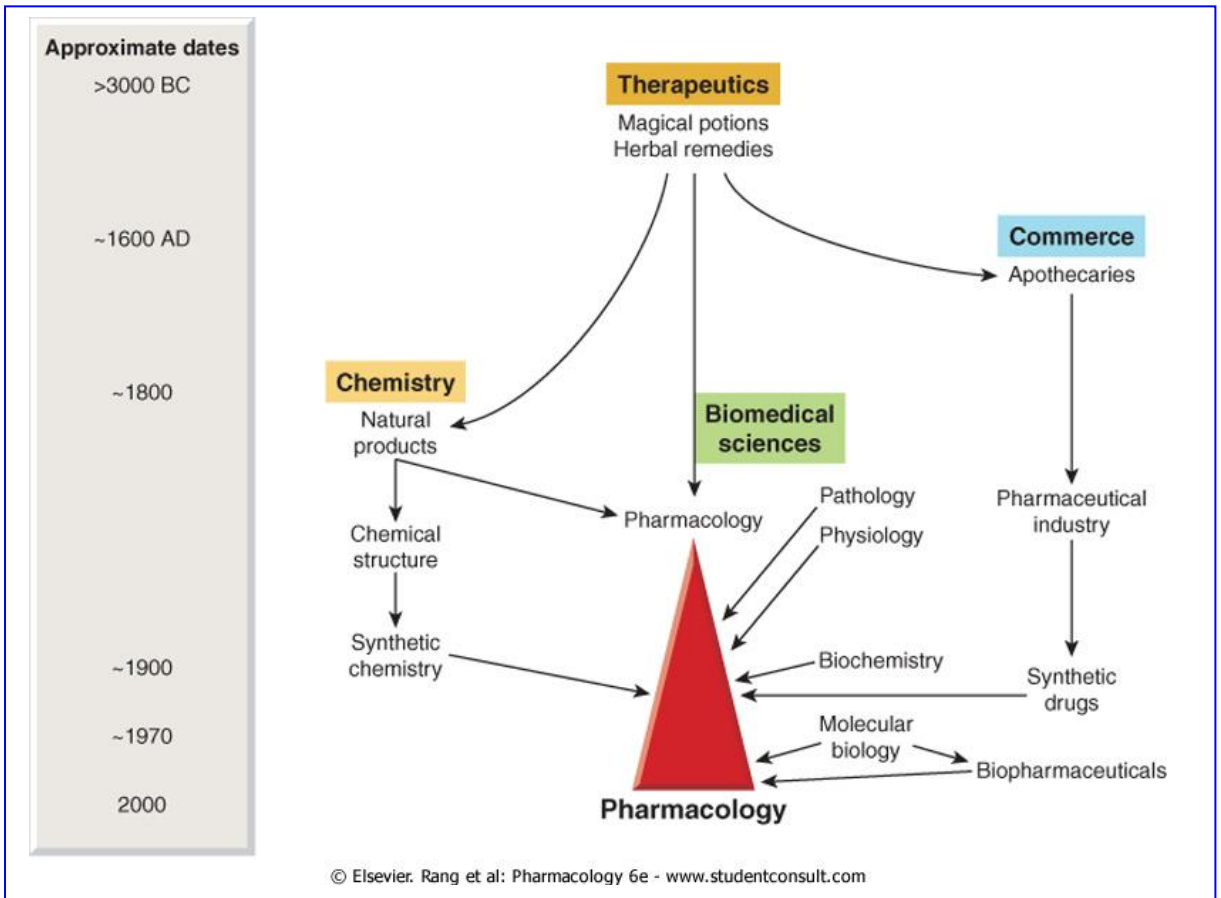
Introduction to Pharmacology

INTRODUCTION TO PHARMACOLOGY

HISTORICAL DEVELOPMENTS:

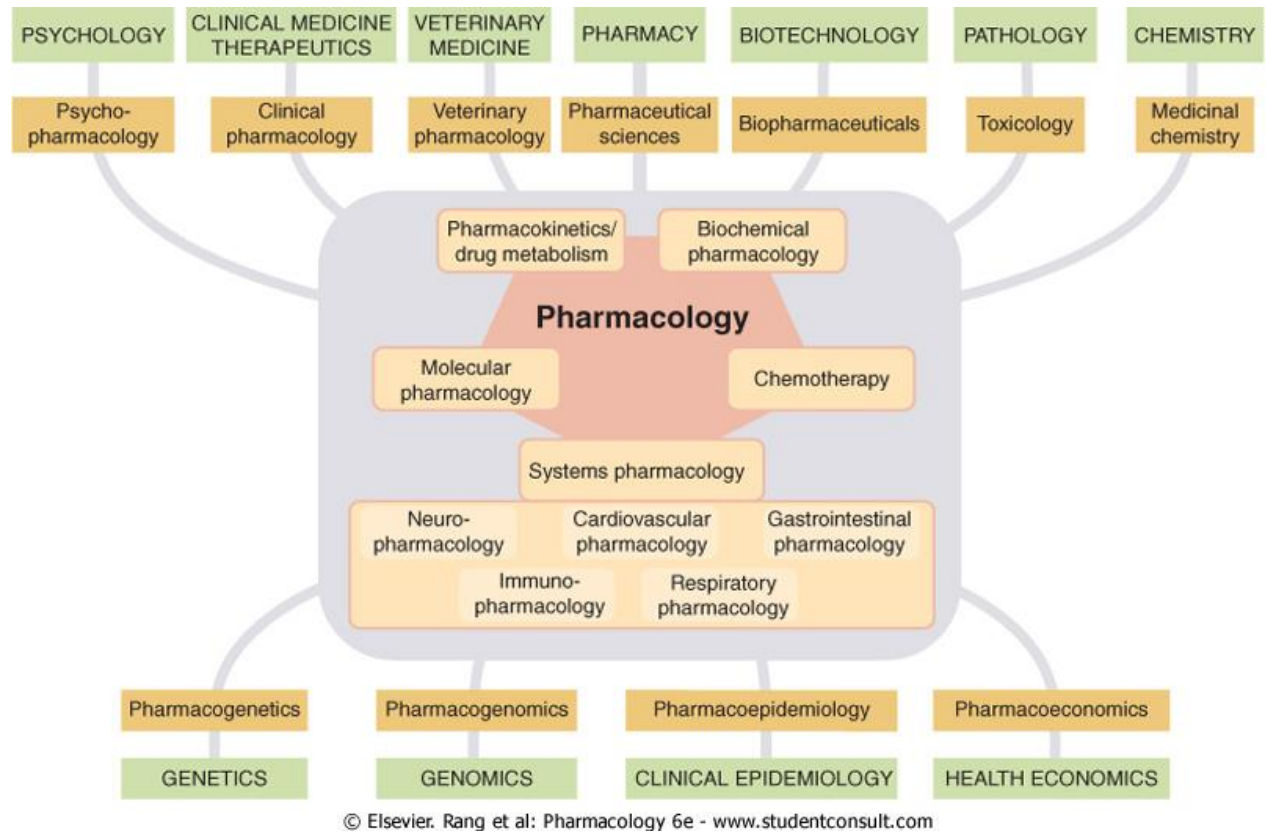
- The oldest writings of medicinal agents belonged to Ancient India, closely followed by Chinese and Egyptian literatures.
- Rigveda, the oldest records of civilization (3000 BC) describes the value of medicinal herbs.
- Ayurveda, the oldest system of medicine, which is very popular in these days also, recommends herbal remedies and animal origin products for treatment of disease in man and animals. Charaka, Sushruta and Vaghbata pioneered in Ayurveda. Nakula, one of the Pandavas followed sound principles of animal husbandry and veterinary science.
- The earliest written compilation of drugs is the Chinese Herbal Formulary (Materia Medica) "**Pen Tsao**" which was written by **Emperor Shen Nung** (2700 BC). It contains many vegetables, metallic and animal products as remedies.
- The oldest record of **Egyptian drug codification** is the **Kahun Papyrus** (2000 BC). It deals with veterinary medicine and uterine disease of women and contains a number of prescriptions. The **Ebers Papyrus** (1550 BC) is a compilation of number of disease conditions and 829 prescriptions for medicaments employed in Egyptian medicine.
- **Hippocrates** (460 – 375 BC), a Greek physician and a great teacher of medicine advocated little use of drugs, maintained very high ethical standards of practice ("Above all, do no harm") and attempted to treat diseases based on four elements of nature i.e. water, fire, air and earth. Combination of these elements gave rise to four humours of the body related to a scale of life from most alive to dead. They are – Blood (Sanguine temperament), Phlegm (Phlegmatic), Yellow Bile or Urine (Bilious) and Black Bile (Melancholic). Treatment consisted of attempting to balance these humours by replenishment of deficiencies or removing excesses. Thus arose the practices of bleeding, purging and sweating.
- **Aristotle** (384 – 322 BC) gave scientific basis for medicine who recorded numerous observations on animals.
- **Theophrastus** (380 – 287 BC), a pupil of Aristotle, classified systematically medicinal herbs on the basis of their individual characteristics rather than their recommended use in treatment.
- **Dioscorides** (77), a surgeon, compiled and improved the work of Theophrastus and wrote the **First Materia Medica** which consisted of **6 volumes** and described 600 plants. Drugs were discussed from the standpoint of name, source, identification, test for adulteration, preparation of dosage form, what it would do and for what conditions it would be used.

- Following the fall of Roman Empire, Europe entered the dark ages, during which time there was little advancement in intellectual development. Custodian of knowledge and medical thought during this period were found in Muslims. An intellectual Persian writer, **Geber Ibn Hajar** (702 - 765) classified drugs and poisons of his time and stated that difference between a drug and a poison was just a matter of dosage. Any drug can be toxic if given in large enough amounts.
- The spirit of enquiry was reestablished in Europe during Renaissance. A German person **Valerius Cordus** (1514 - 1544) compiled **First Pharmacopoeia**.
- During 17^{th} and 18^{th} centuries, drug trade flourished and medical experimentation began. Drugs like cinchona (Quinine), coffee, tea, cocoa (methylxanthines), curare, digitalis and a variety of alkaloids were discovered.
- **William Withering** (1741 - 1799) worked on digitalis in the treatment of dropsy (due to congestive heart failure, CHF).
- **Edward Jenner** (1749 - 1823) gave principle of prophylactic immunization against small pox and first described anaphylaxis.
- **William Harvey** (1578 - 1657) discovered circulation of blood and indicated that drugs were distributed to various body parts via blood.
- **Christopher Wren** (1632 - 1723) made first intravenous injection in a dog.
- **Alexander Wood** (1817 - 1884) devised hypodermic syringe and needle.
- **Friedrich Surtner** (1783 - 1841) isolated morphine from opium and named it after the Roman God of sleep, “Morpheus”.
- **Claude Bernard** (1813 - 1878) and **James Blake** (1814 - 1893) established the foundations of modern pharmacology. They worked on dose response relationship, drug disposition in the body, mechanism of action of drugs and structure activity relationship (SAR).
- **Rudolph Buchheim** (1820 - 1879) established the first laboratory for pharmacology at University of Dorpat, Estonia.
- **John J. Abel** (1857 - 1938) who is regarded as the Father of Pharmacology in USA, established Departments of Pharmacology at University of Michigan and at John Hopkins University. He also founded reputed journals like Journal of Biological Chemistry and Journal of Pharmacology and Experimental Therapeutics.
- During 20^{th} Century, the science of Pharmacology flourished in the medical and pharmacy schools, and focus of leadership shifted from Europe to USA (due to two world wars and emergence of USA as industrial power). The science of Pharmacology developed exponentially thereafter due to emergence of Organic Chemistry.



Source: Rang & Dale's Pharmacology, Elsevier

Figure : The Development of Pharmacology



Source: Rang & Dale's Pharmacology, Elsevier

Figure : Pharmacology today with its various subdivisions. Interface disciplines (brown boxes) link pharmacology to other mainstream biomedical disciplines (green boxes).

DEFINITIONS & BRANCHES OF PHARMACOLOGY

Pharmacology: It is an experimental science dealing with the properties of drugs and their effects on living systems.

Pharmacognosy: It deals with the study of sources and identification (origin) of drugs.

Pharmacodynamics: It refers to the study of response of an organism to the action of drugs in absence of disease.

Pharmacokinetics: It is defined as the mathematical description of temporal changes in concentration of drugs and/ or their metabolites within the body.

Pharmacometrics: It deals with the study of qualitative and quantitative aspects of drug effects in laboratory animals. It deals with measurement of drug responses.

Pharmacotherapy: It refers to use of drugs in treatment of diseases.

Therapeutics: It is a term describing treatment of disease in general and includes use of drugs, surgery, radiation, behavioural modification and other modalities.

Clinical Pharmacology: Much of our knowledge of pharmacodynamics, pharmacokinetics and pharmacometrics come from and continues to come from experiments performed on healthy lab animals. The difficulty of transposing this information with reliability into the realm of diseased domesticated patients gave rise to clinical pharmacology.

In this, the appropriate pharmacodynamic, pharmacometric and pharmacokinetic studies are repeated in healthy and diseased domesticated target species with resultant gain in the precision of use of remedies.

Chemotherapy: It is a branch of pharmacology dealing with drugs that selectively inhibit or destroy specific agents or disease such as bacteria, viruses, fungi and other parasites.

Toxicology: Classically, it is defined as the study of poisons. It includes study of toxicity or adverse effects of drugs or chemical, physical or biological agents in man and animals.

It is a science that defines the limits of safety of chemical agents for human and animal population.

Posology: It is the study of medicine dosage.

Dose: A dose is the quantity of medication to be administered at one time.

Dosage: It refers to determination and regulation of doses.

Loading dose: It is one or series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly.

Maintenance dose: It is a series of relatively small doses that follow the loading dose in order to maintain an effective concentration in the bio-phase.

Metrology: It is the study of weights and measures as applied to preparation and administration of drugs.

Pharmacy: It is the art and science of compounding and dispensing drugs or preparing suitable dosage forms for administration of drugs in man or animals. It includes collection, identification, purification, isolation, synthesis, standardization and quality control of medicinal substances. The large scale manufacture of drugs is called Pharmaceutics. It is primarily a technological science.

Materia medica: It is an obsolete didactic (instructive) subject that was concerned with pharmacy, posology, pharmacognosy and indications for therapeutic use of drugs. This subject was purely descriptive in nature and has been replaced in the modern veterinary medical curriculum by the science of comparative pharmacology.

Comparative pharmacology: It deals with the study of variation in drug effects in different species of animals.

Neutraceuticals: These are nutritional products which allegedly have some therapeutic value in addition to their scientifically recognized nutritional content.

Biotechnology: Originally, this was the production of drugs or other useful products by biological means (e.g. antibiotic production from microorganisms or production of monoclonal antibodies). Currently in the biomedical sphere, biotechnology refers mainly to the use of recombinant DNA technology for a wide variety of purposes, including the manufacture of therapeutic proteins, diagnostics, genotyping, production of transgenic animals, etc. The many non-medical applications include agriculture, forensics, environmental sciences, etc.

Pharmacogenetics: This is the study of genetic influences on responses to drugs. Originally, pharmacogenetics focused on familial idiosyncratic drug reactions, where affected individuals show an abnormal-usually adverse-response to a class of drug. It now covers broader variations in drug response, where the genetic basis is more complex.

Pharmacogenomics: This recent term overlaps with pharmacogenetics, describing the use of genetic information to guide the choice of drug therapy on an individual basis. The underlying principle is that differences between individuals in their response to therapeutic drugs can be predicted from their genetic make-up.

Pharmacoepidemiology: This is the study of drug effects at the population level. It is concerned with the variability of drug effects between individuals in a population, and between populations.

Pharmacoeconomics: This branch of health economics aims to quantify in economic terms the cost and benefit of drugs used therapeutically.

Nanotechnology: Nanotechnology is the study and use of structures between 1 nanometer (nm) and 100 nanometers in size. Nanotechnology is the study of phenomena and fine-tuning of materials at atomic, molecular and macromolecular scales, where properties differ significantly from those at a larger scale.

The applications of nanotechnology to pharmacology are biochips, nanosensors, bioreactors, neural stem cells, immune nanoparticles, biodegradable polymers, and convection-enhanced drug delivery in the diagnostics and treatment of diseases.

OTHER DEFINITIONS:

Drug: A drug can be defined as a chemical substance of known structure, other than a nutrient or an essential dietary ingredient, which when administered to a living organism, produces a biological effect. Drugs may be synthetic chemicals, chemicals obtained from plants or animals or products of genetic engineering.

According to WHO, “Drug is any substance or product other than food that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient”.

(To use the word ‘drug’ intending only a harmful, dangerous or addictive substance is to abuse a respectable and useful word.)

Medicine: A medicine is a chemical preparation which usually but not necessarily contains one or more drugs, administered with the intention of producing a therapeutic effect. Medicines usually contain other substances (excipients, stabilizers, solvents etc.) besides the active drug to make them more convenient to use.

Over the counter drugs: These are those preparations that can be sold without any restriction because they can be adequately labeled for layman use.

Prescription drugs: Drugs that can be used only on the order of a licensed veterinarian/ physician/ dentist/ surgeon. They are also known as legend drugs.

Essential drugs: Drugs that satisfy the healthcare needs of majority of the population. They should therefore be available at all times in adequate amounts and in appropriate dosage forms.

Pro-drugs: Drugs that are inactive or have a low order of activity in the form administered and are metabolized to the active form in the body.

Hard drugs: Drugs used for non-medical purposes that are liable to disable the individual seriously as a functioning member of the society by inducing severe psychological and/or physical dependence. Example - Heroin.

Soft drugs: Drugs used for non-medical purposes that are less dependence producing. There may be psychological dependence but not physical dependence, except with heavy dose. Example - Amphetamine.

Nootropic drugs: Drugs that affect the intellect. These drugs are claimed to enhance learning, increase brain resistance to stress including hypoxia and stimulate brain metabolism especially in senile patients. Example – Piracetam

Orphan drugs: Orphan drugs are drugs or biological products for diagnosis/ treatment/ prevention of a rare disease condition for which there is no reasonable expectation that the cost of developing and marketing it will be recovered from sales of that drug. Examples – Acetylcysteine. These drugs may be life saving for some patients, but are not commercially available.

Empirical therapy: It is the use of certain agents that prove successful in a series of cases of the same disease, although, it is not possible to explain their actions. Their value has been demonstrated by experience.

Rational therapy: It is the term used with reference to the application of remedial measures which can clearly explain the reasons for their application. Rational therapy is based on a thorough knowledge of the normal physiology, changes in physiology due to pathological conditions and the pharmacological basis for use of the drug. This implies a precise diagnosis and knowledge of the etiology of affection, so that we can act directly or indirectly on the causes which produce it and an intimate knowledge of the actions of the drugs which we employ.

Curative therapy: It is the therapy aimed at bringing about a cure in the patient, like the use of antimicrobials in a bacterial infection.

Prophylactic or preventive therapy: It is the therapy aimed at preventing the occurrence of a disease, like the use of vaccines for preventing bacterial and viral infections.

Symptomatic or palliative therapy: It aims at treating the condition based on the symptoms and providing relief to the patient without actually spending time on finding the cause of the disease, like the use of anti-convulsants in epilepsy.

Replacement therapy: It aims at replacing the constituents to the normal level when there is a reduction in the level of the constituent due to some pathological condition, like fluid and electrolyte replacement in dehydration.

Additive therapy: It is the therapy given to add on the existing level of the normal constituent even though there may not be a reduction in the level of that constituent, like the use of anabolic steroid to build up body mass.

Iatrogenic disease: It means physician caused disease i.e. disease consequent upon following medical advice or intervention. Iatrogenic was first applied to disorder induced in the patient by auto suggestion based on physical examination or manner of examination or discussion by the doctor.

DRUG NOMENCLATURE

When a new drug is synthesized, it is first assigned a code or number (usually identifying with its inventor, manufacturer/ pharmaceutical company). If it is found promising after clinical evaluation, the manufacturer wants to put it in the market; the new drug is given a generic name to designate its pharmacological class (non-proprietary name). If the new drug gets official recognition by drug regulatory authority, its manufacturer gives it a proprietary or trade name.

Chemical name: IUPAC name, generally long and hard to remember.

Generic, Official, Approved or Trivial name:

- The chemical is entered in pharmacopoeias under this name.
- The chemical compound is known throughout the world by this generic name.
- Approved names are generally used by researchers and non-clinical teachers.

Proprietary, Brand or Trade name:

- One chemical compound can have several proprietary names.
- Even one proprietary name may not contain single chemical.
- Manufacturers and clinicians prefer to use brand names.

Examples:

Chemical name	*Generic name*	*Trade name*
3,4-dihydroxyphenylethanolmethylamine	Epinephrine	Adrenaline
Acetylsalicylic acid	Aspirin	Ecosprin

PHARMACOPOEIA

- It is a drug compendium consisting of officially recognized drug preparations/ formulations.
- It gives the information on source, properties, purity, potency of recognized drugs and tests for their identity.
- A pharmacopoeia is the official publication of drug standards.
- It is revised regularly. The different pharmacopoeias are:-

IP	The International or Indian Pharmacopoeia
USP	The United States Pharmacopoeia
BP	The British Pharmacopoeia
BPC	The British Pharmaceutical Codex
EP	European Pharmacopoeia
I.Vet.P	The Indian Veterinary Pharmacopoeia
B.Vet.C.	The British Veterinary Codex
NF	The National Formulary (USA)
NF	The National Formulary of India
BNF	The British National Formulary
ADR	The Accepted Dental Remedies

NB: The abbreviation of the pharmacopoeia is mentioned after the name of the drug. For example, Tr. Benzoin Co. I.P. i.e. the tincture of benzoin corresponding to the standard tincture of benzoin mentioned in the Indian Pharmacopoeia.

SOURCES OF DRUGS

(1) Drugs from plant sources:

The ancient or original sources of drugs are the plants collectively known as medicinal plants. All parts of the medicinal plants have therapeutic values.

Root	:	Sarpgandha
Rhizome	:	Ginger, Haldi
Bark	:	Cinchona, Catechu, Acacia
Leaves	:	Atropine, Cocaine, Physostigmine
Flowers	:	Digitalis, Chrysenthemum
Fruits	:	Papaya, Anise
Seeds	:	Nux vomica, Kali mirchi, Methi

(2) Drugs from animal sources:

Hormones	:	Oxytocin, Insulin, Thyroxine, Gonadotrophins
Vitamins	:	Cod or shark liver oil (Rich sources of Vitamin A & D)
Antisera	:	Antisnake venom, Canine distemper antiserum etc.
Others	:	Heparin, Liver extract, Immunoglobulins, Blood/Plasma.

(3) Drugs from microbial sources:

Fungi/ Actinomycetes and Bacteria	:	Sources of antibiotics (penicillin, streptomycin, gentamicin, neomycin etc.)
Viruses/ Bacteria	:	Preparation of vaccines
Yeasts	:	Dried yeast as source of Vitamin B-complex

(4) Drugs from mineral sources: (Inorganic salts)

Antacid	:	Magnesium oxide, Sodium bicarbonate
Purgative	:	Magnesium sulphate
Expectorant	:	Potassium iodide
Diuretic	:	Potassium nitrate
Haematinic	:	Ferrous sulphate
Hypothyroidism	:	Iodine
Mineral oils	:	Liquid paraffin (Laxative effect) – Long term administration interferes with Vitamin A & D, Calcium and Phosphorus absorption.

(5) Synthetic drugs:

Majority of the current day dugs are from synthetic source. Examples are –

- Antipyretics
- Barbiturates
- Tranquillizers
- Anti-inflammatory drugs
- Anaesthetics
- Antiseptics
- Antiprotozoals
- Antihistamines etc.

(6) Semi-synthetic drugs: Examples are –

- Agonists and antagonists of morphine
- Dihydrostreptomycin – from streptomycin
- Semi-synthetic penicillins – from penicillin.

(7) Gene therapy:

- ✓ It means prevention or treatment of disease through manipulation of gene function.
- ✓ It is insertion of specific genes (therapeutic genes) exogenously into the animal cells.
- ✓ The concept of gene therapy has its origin from the fact that manipulation of gene expression could change the function of abnormal genes or supplementation of a non-functional gene or suppression of an abnormal gene.
- ✓ Gene therapy refers to introduction of functional genetic material into target cells to replace or supplement defective genes, or to modify target cells so as to achieve therapeutic goals.
- ✓ In contrast to all other drugs, this kind of therapy can impart new functions to a cell.
- ✓ Gene therapy holds a great promise for curing a number of diseases which at present can at best be only palliated or controlled.
- ✓ Gene defects result in failure to synthesize a functional protein or in the synthesis of a dysfunctional protein. Equipping the cell (specially the one which physiologically expresses it) with a normal copy of the defective gene would overcome the deficiency at the site where it is needed on a long term (may be permanent) basis.
- ✓ Recombinant DNA technology forms the basis of synthesis of therapeutic genes.

Technique of gene delivery into host:

It is highly complicated and different from that of conventional drug delivery systems. The technique involves inserting a therapeutic gene first into a vector. The vector may be either viral (Retro or Adenovirus) or non-viral vector (plasmid DNA, liposomes, microsomes). A vector with a gene is then introduced into the patient through either *in vivo* or *ex vivo* means.

In vivo gene transfer: The vector, usually a retrovirus carrying the gene is injected systemically or directly into the concerned organ.

Ex vivo gene transfer: The patient's tissue cells (blood/ bone marrow) are isolated and maintained in tissue culture. These are then transfected with vector carrying the relevant gene and injected back into the patient.

Applications of gene therapy:

- Cystic fibrosis
- Severe combined immunodeficiency disease (SCID)
- Growth hormone deficiency
- Parkinsonism
- HIV infection
- Alzheimer's disease
- Huntington's chorea
- Cancers
- Hypertension
- Haemophilia
- Insulin dependent diabetes etc.

8) Biopharmaceuticals:

- ✓ These are therapeutic agents produced through biotechnological means, but not by conventional laboratory (chemical) synthesis.
- ✓ The principle of biopharmaceuticals and the process of their development have origin from the advancement in the knowledge of molecular cell biology and biotechnology.
- ✓ Therefore, biopharmaceuticals popularly known as **Designer Proteins** are the promising therapeutic tools of the future.

Examples are –

Functional human peptides:		ADH, Oxytocin, GnRH, ACTH, TSH/TRH, Calcitonin, Insulin, Somatostatin, Growth hormone, Cyclosporin etc.
Enzymes/ Peptides	:	Streptokinase, Asparaginase, DNAase, Erythropoietin, Clotting factors, Interferons, Monoclonal antibodies, Vaccines etc.

* * * * *

ACTIVE PRINCIPLES OF MEDICINAL PLANTS

The medicinal value of plants or crude preparations of medicinal plants is due to presence of a variety of pharmacologically active principles, such as alkaloids, glycosides, oils, resins, oleoresins, gums, saponins, tannins etc.

(1) Alkaloids:

- ✓ Basic, nitrogenous substances.
- ✓ Insoluble in water, less soluble in alcohol, soluble in ether, chloroform and oils.
- ✓ Form water soluble crystalline salts with acids.
- ✓ **Alkaloids consisting of oxygen are solids.** (e.g. Atropine, reserpine, emetine, morphine, strychnine, quinine etc.)
- ✓ **Alkaloids without oxygen are liquids.** (e.g. Nicotine, pilocarpine, lobeline etc.)
- ✓ Mostly derived from plants. Exception – Epinephrine (obtained from adrenal medulla).

Alkaloid	Source	Action
Atropine	*Atropa belladonna*	Anticholinergic
Arecholine	*Areca catechu*	Cholinergic
Caffeine	*Coffea arabica*	Cortical & CVS stimulant
Cocaine	*Erythroxylon cocoa*	Local anaesthetic & CNS stimulant
Emetine	*Cephalis ipecacuanha*	Reflex emetic
Morphine	*Papaver somniferum*	Narcotic analgesic
Nicotine	*Nicotiana tabacum*	Ganglionic stimulant/ blocker
Physostigmine	*Physostigma venenosum*	Anti-AChE
Reserpine	*Rauwolfia serpentina*	Antihypertensive
Strychnine	*Strychnos nuxvomica*	Spinal stimulant/ convulsant

(2) Glycosides:

- ✓ Compounds containing a sugar (glycone) and a non-sugar (aglycone or genin) part joined together through an ester linkage. So, these are **sugar esters.**
- ✓ The pharmacological action resides in the aglycone/ genin.
- ✓ Glycone part determines solubility, tissue permeability and duration of action of aglycone.
- ✓ Glycosides do not form salt with acids. On acid, alkali or enzyme hydrolysis, the glycosides break into two parts i.e. glycone and aglycone.

Examples –

Category	Glycoside	Source
Cardiac glycosides	Digitoxin, Gitoxin, Digoxin & Gitalin	*Digitalis lanata/ purpurea* (leaves)
	Strophanthin	*Strophanthus gratus* (seeds)
	Ouabain	*Urginea maritima* (bulb)

Cyanogenic glycosides	Amygdalin	*Prunus amygdalus*
	Dhurrin	*Sorghum vulgare*
	Linamarin	*Linum usitatissimum*
Miscellaneous glycosides	Mangeferin (Hepatoprotective/ Antioxidant)	*Manfifera indica* (Leaves, fruit)
	Swertiamarin (Cardiotonic/ Hepatoprotective)	*Swertia chirata* (Stem, leaves)

(3) Oils:

These are of two types: Fixed oils and Volatile oils.

Fixed oils:

- ✓ These are glycerides of oleic, palmitic and stearic acids.
- ✓ Many fixed oils have food value (i.e. cooking oils). e.g. corn, ground nut, sunflower, mustard, soybean, coconut, palm oils etc.
- ✓ Cooking oils are pharmacologically inert and serve as vehicle for fat soluble vitamins.
- ✓ Some others have pharmacological actions. Examples –

Fixed oils	**Source**	**Pharmacological action**
Castor oil	*Ricinus communis*	Purgative
Linseed oil	*Linum usitatissimum*	Demulcent, vehicle, purgative
Croton oil	*Croton tiglium*	Drastic purgative

Volatile oils:

- ✓ Also known as **Aromatic, Essential, Ethereal** or **Flavouring oils**.
- ✓ These have no food value.
- ✓ These are volatile and emit characteristic odour while evaporation.
- ✓ Most of these have medicinal values. Examples are –

Volatile oils	**Source**	**Pharmacological action**
Eucalyptus oil	*Eucalyptus globulus*	Expectorant, Rubefacient
Ginger oil	*Zingiber officinale*	Stomachic, Carminative
Turpentine oil	*Cedrus deodara*	Counterirritant, Astringent
Clove oil	*Eugenia caryophyllus*	Analgesic, Antiseptic
Pippermint oil	*Mentha piperata*	Antiseptic, Antiemetic
Asafoetida oil	*Ferula foetida*	Carminative, Anthelmintic

(4) Resins:

- ✓ These are brittle, amorphous compounds formed from oxidation or polymerization of terpene components of volatile oils.
- ✓ These are insoluble in water, soluble in alcohol and other organic solvents.
- ✓ Form soap with alkali.

Examples -

Resin	**Source**	**Pharmacological action**
Colophonium	Residue left after distillation of crude turpentine	Antiseptic, styptic, astringent
Podophylline	Dried rhizome & root of *Podophyllum emodi*	Purgative, sialic, cholagogue, antimitotic (anticancer).

Oleoresins:

- ✓ These are mixtures of volatile oils, gums and resins. Example –

Oleoresin	Source	Pharmacological action
Asafoetida	Secretion from root of *Ferula foetida*	Carminative, antispasmodic

- ✓ **Balsams** are also considered as oleoresins. These contain an aromatic acid, resin and volatile oil. Examples –

Balsam	Source	Pharmacological action
Balsam of Tolu	Secretion from trunk of *Myroxylon toluiferum*	Expectorant, antiseptic
Balsam of Peru	Secretion from trunk of *Myroxylon pereoie*	Antiseptic, acaricide

(5) Gums:

- ✓ These are polysaccharide secretory products of plants capable of forming thick mucilaginous colloids when mixed with water.
- ✓ Gums are pharmacologically inert with no systemic effects, but exert demulcent action on surfaces and are mainly used as suspending or emulsifying agents in pharmacy.

Gums	Source	Pharmacological action
Agar	Colloidal carbohydrate from sea weeds	Bulk purgative
Gum acacia	*Acacia senegal*	Demulcent, emulsifier
Gum arabica	*Acacia arabica*	Demulcent, emulsifier
Gum tragacanth	*Astragalus gummifier*	Demulcent, emulsifier

(6) Saponins:

- ✓ These are non-nitrogenous substances soluble in water which form foam or froth when shaken with water.
- ✓ Saponins upon hydrolysis, split into a sugar and a non-sugar (sapogenin), hence considered as a sub-class of glycosides.
- ✓ Saponins cause haemolysis of blood.
  Examples – Quillaris, Senega etc.

(7) Tannins:

- ✓ These are water soluble, non-nitrogenous plant constituents having characteristic astringent action (precipitation of protein) upon mucous membrane.
- ✓ These exert a protective action on the mucosa (GI) against irritants.
- ✓ Tannins also inactivate alkaloidal poisons.

Tannins	Source	Pharmacological action
Catechu	*Uncaria gambier*	Astringent, Precipitates alkaloids
Kino	*Pterocarpus marsupium*	Astringent, Precipitates alkaloids
Galla (Galls)	*Quercus infectoria*	Astringent, Antiseptic, Antisialic.

Chapter - 2

Pharmacokinetics

PHARMACOKINETICS

Pharmacokinetics is the quantitative study of drug movement in, through and out of the body. It studies the processes of absorption, distribution, metabolism and excretion of drugs (how the body affects the drugs; movement or disposition of drugs in the body). It quantifies the fate of a drug by measurement of its concentration and metabolites in blood and urine over a period of time after its administration.

Intensity of response of a drug is related to its concentration at the site of action, which in turn is dependent on its pharmacokinetic properties. Pharmacokinetic considerations, therefore, determine the route (s) of administration, dose, latency of onset, time of peak action, duration of action – frequency of administration of a drug.

ABSORPTION OF DRUGS:

- ✓ **Dosage form:** The term describes the pharmaceutical preparation in which the active principle is introduced into or onto the body. Whether this is solid, liquid, gaseous or any state in between, the prime requisite for pharmacological activity is that the drug leaves the dosage form and goes into solution in the immediately adjacent body water: insoluble drugs are pharmacologically inert.
- ✓ Body water (which is approximately 70% of the body by weight) is found to exist in several compartments like intracellular fluid (ICF) and extra cellular fluid (ECF). Clearly, drugs have to cross these boundaries (biological membranes) if they are to penetrate throughout the body water.

PASSAGE OF DRUGS ACROSS BIOLOGICAL MEMBRANES:

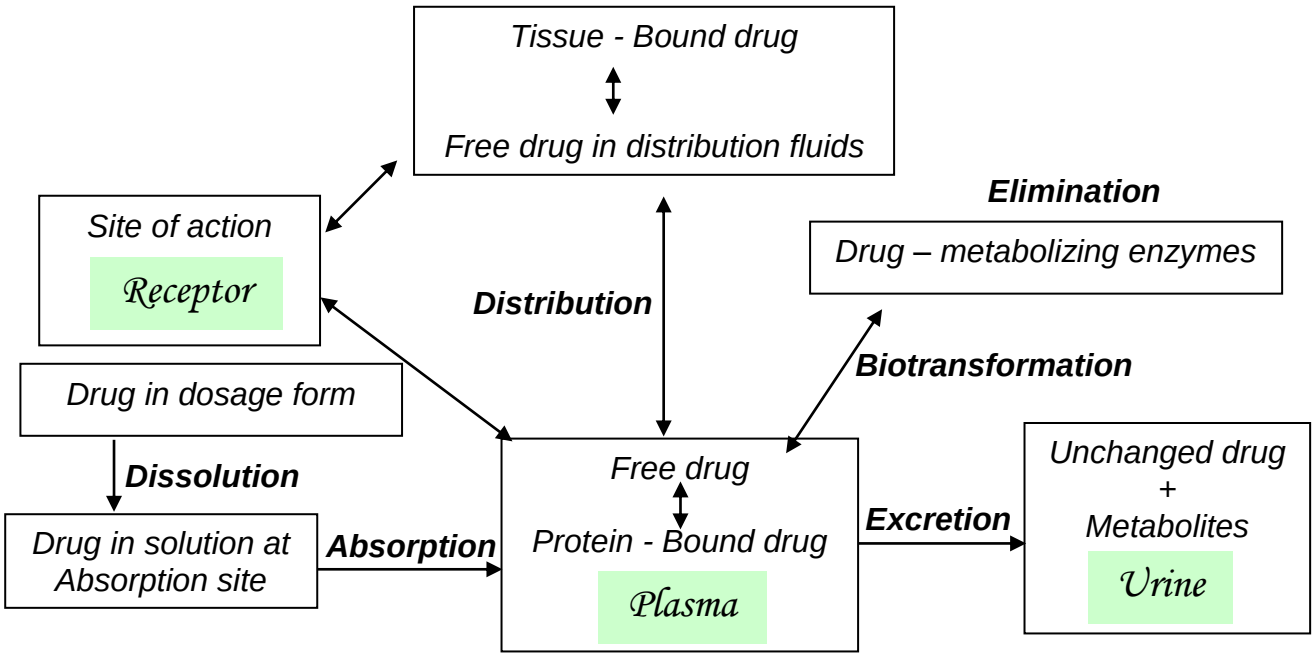


Figure : *Schematic representation of various processes that determine duration of drug action.*

Nature of Biological membranes:

- ✓ These functionally important components (comprising organelle, cytoplasmic and plasma membranes) account for about 80% of the dry weight of a cell.
- ✓ The plasma membrane, which is the interface between a cell and the ECF, possesses features and properties which allow movement of solutes into and out of the cell.
- ✓ The membrane is now visualized as a cholesterol-containing, double layer of phospholipids molecules arranged perpendicular to the surfaces. The outer layer has its polar groups directed to the ECF while the inner layer presents its polar groups towards the ICF. Individual lipids can move laterally, endowing the membrane with fluidity, flexibility, imperviousness to polar molecules, and high electrical resistance. The lipid molecules can even flip from one bilayer of the membrane to the other.
- ✓ In this model (fluid mosaic model), proteins integral to the membrane are a heterogenous set of globular molecules, each arranged in an amphipathic structure, i.e. with their ionic and highly polar groups located largely on membrane surfaces in contact with the extra- and intra-cellular aqueous media and with their non-polar residues sequestered from contact with water in the membrane interior. These proteins are partially embedded in a discontinuous, fluid bilayer of phospholipids that forms the matrix of the mosaic.
- ✓ Aqueous channels appear to be present in the core of the globular intrinsic (integral) proteins and may be gated (i.e. channels may open and close) by conformational changes in the proteins.
- ✓ Biological membranes behave as if they were lipoids punctured by aqueous pores and allow drugs and physiological materials to cross by passive or carrier mediated processes.

Drug Passage across Membranes:

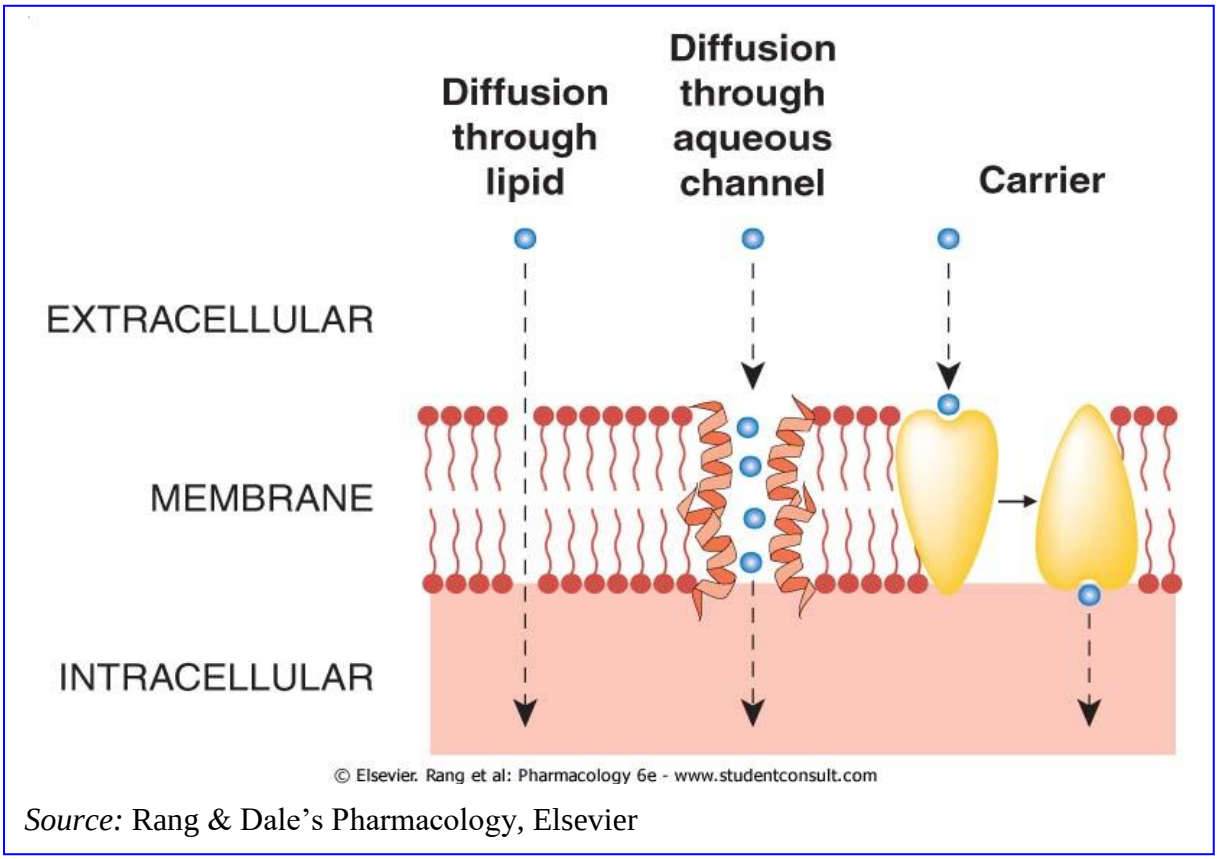
1. **<u>Passive Diffusion</u>:**

   The drug diffuses across the membrane in the direction of its concentration gradient, the membrane playing no active role in the process. This is the most important mechanism for majority of the drugs.

   Lipid soluble drugs diffuse by dissolving in the lipoidal matrix of the membrane, the rate of transport being proportional to lipid**:**water partition coefficient of the drug. A more lipid soluble drug attains higher concentration in the membrane and diffuses quickly. Also, greater the difference in the concentration of the drug on two sides of the membrane, faster is its diffusion.

2. **<u>Filtration</u>:**

   Filtration is passage of drugs through aqueous pores in the membrane or through paracellular spaces. This can be accelerated if hydrodynamic flow of the solvent is occurring under hydrostatic or osmotic pressure gradient, e.g. in most capillaries including glomeruli. Lipid insoluble drugs cross biological membranes by filtration if their molecular size is smaller than the diameter of the pores. Majority of cells (intestinal mucosa, RBC etc.) have very small pores (4 Å) and drugs with MW>100 or 200 are not able to penetrate. However, capillaries (except those in brain) have larger pores (40 Å) and most drugs (even albumin can filter through these).



Source: Rang & Dale's Pharmacology, Elsevier

Figure : Routes by which solutes can traverse cell membranes (Molecules can also cross cellular barriers by pinocytosis)

3. Specialized Transport (Carrier - Mediated Transport):

When the rate of movement of molecules across a membrane is greater than can be accounted for by the operation of conventional laws of diffusion, the existence of a carrier-mediated transport system can be suspected. Such systems are well known in physiology, e.g. in glucose uptake into erythrocytes and sodium ion expulsion from erythrocytes.

Carrier-mediated transport across membranes implies a rapidly reversible interaction between components of the membrane and the transported substance. The drug combines with a carrier present in the membrane and the complex then translocates from one face of the membrane to the other. This kind of transport shows relative selectivity toward the chemical nature of the substance moved across the membrane. Since a carrier (membrane component) is involved in transport, the process is saturable, and substances of a similar chemical nature may compete for the carrier. Competitive inhibition is a characteristic of carrier-mediated transport.

The carriers for polar molecules appear to form a hydrophobic coating over the hydrophilic groups and thus facilitate passage through the membrane. Substances permitting transit of ions across membranes are called *ionophores*. Carrier-mediated transport is of two types i.e. active transport and facilitated diffusion.

(i) Active transport:

Movement occurs against the concentration gradient, needs energy and is inhibited by metabolic poisons. It results in selective accumulation of the substance on one side of the membrane. Drugs related to normal metabolites, e.g. levadopa and methyldopa are actively absorbed from the gut by aromatic amino acid transport process. The rapid transfer into urine and bile of drugs that are strongly acidic or basic as well as most drug metabolites takes place by active transport. It is also responsible for removal of certain drugs (e.g. penicillins) from the central nervous system (CNS) at the choroids plexus. This is now believed to be accomplished through reverse transport from the CSF back into the bloodstream by the *p*-glycoprotein pump. Generation of pH gradient across a biological membrane is also an active process.

(ii) Facilitated diffusion:

It is neither an energy-dependent process nor does it move substances against a concentration gradient. Transport is facilitated, however, by attachment to a carrier and is more rapid than simple diffusion and translocates even non-diffusible substrates. Entry of glucose into most cells takes place by facilitated diffusion (enhanced by insulin), but its passage across the GI mucosa and excretion by renal tubular cells are active processes.

Phagocytosis and Pinocytosis of drugs:

Cells have the ability to engulf either particles (phagocytosis) or droplets (pinocytosis). If the engulfed material is not susceptible to enzyme degradation it will persist, e.g. particles of talc or droplets of liquid paraffin. In relation to drugs, this possibility is of more histopathological than pharmacological interest at present.

The absorption of immunoglobulins through the gut mucosa of young calves depends on pinocytosis.

The pH Partition Hypothesis:

- ✓ Most drugs are weak organic acids or bases and exist in solution as both non-ionized and ionized forms. The non-ionized form is usually more lipid soluble and can more readily diffuse across the cell membrane to achieve the same equilibrium concentration on either side. In contrast, the ionized moiety is often virtually excluded from transmembrane diffusion because of its low lipid solubility.
- ✓ The degree of ionization of an organic electrolyte depends on its pK_a value and the pH of the environment.

For an acid, this is

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog}(pKa - pH)}$$

For a base,

$$\% \text{ ionized} = \frac{100}{1 + \text{antilog}(pH - pKa)}$$

- ✓ The pK_a value, the negative logarithm of acidic ionization (or dissociation) constant is a constant for an acid or a base. The majority of therapeutic agents have pK_a values between 3 and 11 and exist accordingly as both non-ionized and ionized forms within the range of physiological pH. (Strong electrolytes are nearly completely ionized at acidic as well as alkaline pH).
- ✓ The ratio of non-ionized to ionized drug at a given pH can be calculated from the Henderson-Hasselbalch equation. For an acid, this is

$$pH - pK_a = \log \frac{\text{(conc. ionized)}}{\text{(conc. non-ionized)}}$$

and for a base,

$$pH - pK_a = \log \frac{\text{(conc. non-ionized)}}{\text{(conc. ionized)}}$$

- Thus, pK_a is numerically equal to the pH at which the drug is 50% ionized and 50% non-ionized.
- 1 scale change in pH will cause 10 fold change in ionization.

- ✓ Weakly acidic drugs, which form salts with cations, e.g. sod. phenobarbitone, sod. sulfathiazine, pot. penicillin V etc. ionize more at alkaline pH and one scale change in pH causes 10 fold change in ionization.
- ✓ Weakly basic drugs, which form salts with anions, e.g. atropine sulphate, ephedrine HCl, chloroquine phosphate etc. conversely ionize more at acidic pH. Ions being lipid insoluble do not diffuse and a pH difference across a membrane can cause differential distribution of weakly acidic and weakly basic drugs on the two sides of the membrane.
- ✓ Implications of the above considerations include the following:

1) Acidic drugs, e.g. aspirin (pK_a 3.5) are largely unionized at gastric pH and are absorbed from stomach, while bases, e.g. atropine (pK_a 10) are largely ionized and are absorbed only when they reach the intestines.
2) *Ion Trapping:* The unionized form of acidic drugs which crosses the surface membrane of gastric mucosal cell, reverts to the ionized form within the cell (pH 7.0) and then only slowly passes to the extracellular fluid. This is called *ion trapping*, i.e. a weak electrolyte crossing a membrane to encounter a pH from which it is not able to escape easily. This may contribute to gastric mucosal cell damage caused by aspirin.
3) Basic drugs attain higher concentration intracellularly (pH 7.0 versus 7.4 of plasma).
4) Acidic drugs are ionized more in alkaline urine – do not back diffuse in the kidney tubules and are excreted faster. Accordingly, basic drugs are excreted faster if urine is acidified.

ROUTES OF DRUG ADMINISTRATION:

Factors governing choice of route of administration of drugs:

(i) Physical and chemical properties of drugs (solid/ liquid/ gas; solubility, stability, pH, irritancy).
(ii) Site of desired action – localized and approachable or generalized or not approachable.
(iii) Rate and extent of absorption of the drug from different routes.
(iv) Effect of digestive juices and first pass metabolism on the drug.
(v) Rapidity with which the response is desired (routine treatment or emergency).
(vi) Accuracy of dosage required (i.v. and inhalational can provide fine tuning).
(vii) Condition of the patient (unconscious, vomiting) etc.

LOCAL ROUTE **:**

- ✓ Systemic absorption from these routes is minimal.
- ✓ Systemic side effect is minimized.
- ✓ Desired localized action.

Topical Route:

(a) Skin: Ointment, cream, lotion, paste, powder, dressings, spray etc.
(b) Mucous membranes:
  (i) Mouth & Pharynx – Paint, mouth wash, gargles etc.
  (ii) Eye, ear, nose – Drops, ointment, nasal spray etc.
  (iii) GI tract – As non-absorbable drugs given orally, e.g. $Mg(OH)_2$, sucralfate, neomycin etc.
  (iv) Bronchi and lungs – As inhalations, aerosols (nebulized solution or fine powder), e.g. salbutamol, cromolyn sodium.
  (v) Urethra – As jellys e.g lidocaine; irrigating solutions.
  (vi) Vagina – As pessaries (vaginal suppositories), vaginal tablets, inserts, cream, powders, douches.
  (vii) Anal canal – As ointment, suppositories.

SYSTEMIC ROUTES **:**

- ✓ Intended to be absorbed into blood and distributed all over through systemic circulation.

1. Oral route:

- ✓ Oldest and commonest mode of drug administration.
- ✓ Safer and more convenient.
- ✓ Medicament need not be sterile, so cheaper.

Solid dosage forms: Powders, tablets, boluses, capsules

Liquid dosage forms: Elixirs, syrups, emulsions, mixtures etc.

Limitations of Oral Route administration:

(i) Action is slower – not suitable for emergencies.

(ii) Unpalatable drugs are difficult to administer. Drugs may be filled in capsules to circumvent this.

(iii) May cause nausea (tendency to vomit) and vomition.

(iv) Can't be used for uncooperative, unconscious or vomiting patient.

(v) Certain drugs are not absorbed by oral route (e.g. streptomycin).

(vi) Some drugs are destroyed by gastric juices (e.g. Penicillin G).

2. Sublingual or buccal route:

- ✓ Only lipid soluble and non-irritating drugs can be used.
- ✓ Absorption – rapid.
- ✓ The chief advantage is that the liver is bypassed and drugs with high first pass effect can be absorbed into systemic circulation directly. For example, Nitroglycerine, isoprenaline, clonidine, methyltestosterone.

3. Rectal route:

- ✓ Certain irritant and unpleasant drugs can be put into rectum as suppositories for systemic effect.
- ✓ This route is used when the patient is having recurrent vomiting.
- ✓ Route is inconvenient and embarrassing.
- ✓ Absorption is slower, irregular and often unpredictable.
- ✓ Rectal inflammation can result from irritant drugs.

  Examples: Aminophylline, endomethacin, paraldehyde, diazepam etc. are sometimes given rectally.

4. Cutaneous route:

- ✓ Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption.
- ✓ Liver is also bypassed.

  Example: Ointments.

5. Inhalational route:

- ✓ Absorption takes place from the vast surface of alveoli – action is very rapid.
- ✓ When administration is discontinued, the drug diffuses back and is rapidly eliminated in expired air. Thus, controlled administration is possible.
  Examples: Volatile liquids and gases (General anaesthetics).

6. Nasal route:

- ✓ The mucous membrane of the nose can readily absorb many drugs; digestive juices and liver are bypassed.
- ✓ Only certain drugs like GnRH agonists and desmopressin applied as spray or nebulized solution have been used by this route.

7. Parenteral route: (*par* – beyond, *enteral* - intestinal)

- ✓ It refers to injection of drug directly into tissue fluid or blood without having to cross the intestinal mucosa.
- ✓ The limitations of oral administration are circumvented.
- ✓ Action is faster and surer (valuable in emergencies).
- ✓ Liver is bypassed.
- ✓ *Disadvantage*: The preparation has to be sterilized, so costlier. The technique is invasive and painful, so assistance of other persons is required.

(i) Subcutaneous (s.c.):

- The drug is deposited into the loose subcutaneous connective tissue which is richly supplied by nerves (so, irritant drugs can't be injected) but is less vascular (absorption is slower).
- Repository (depot) preparations – oily solutions (like vaccines) or aqueous suspensions can be injected for prolonged action.

(ii) Intramuscular (i.m.):

- The drug is injected in one of the large skeletal muscles (like deltoid, triceps, gluteus maximus, rectus femoris etc.).
- Muscle is less richly supplied with sensory nerves (mild irritants can be injected) and more vascular (absorption is faster).
- It is less painful. Deep injection is needed.
- Depot preparations can be injected by this route.

(iii) Intravenous (i.v.):

- The drug is injected as a bolus or infused slowly after hours in one of the superficial veins.
- The drug directly reaches into the blood stream and effects are produced immediately (great value in emergencies).
- The intima of veins is insensitive and drug gets diluted with blood, therefore even highly irritant drugs can be injected i.v., but hazards are – thrombophlebitis of the injected vein and necrosis of adjoining tissues if extravasation occurs.
- Only aqueous solutions are injected (not suspensions).
- Dose of the drug is smallest in this route and bioavailability is 100%.
- Response of the drug can be accurately measured.
- It is the most risky route – vital organs like heart, brain etc. get exposed to high concentrations of the drug.

(iv) Intradermal:

- The drug is injected into the skin by raising a bleb (e.g. BCG vaccine, sensitivity testing) or *scarring*/ *multiple puncture* of the epidermis through a drop of the drug (small pox vaccine) is done.
- This route is employed for specific purposes only.

(v) Intraperitoneal (i.p.):

- This route is of importance in large animal practice for the administration of large volumes, because of great absorbing surface of the peritoneum and because the absorption rate is rapid.
- The injection is made via the sub-lumbar fossa, care being taken to avoid delivering the solution into an abdominal organ.
- The risk of causing peritoneal adhesions should also be borne in mind.

(vi) Other parenteral routes are:

- Intrathoracic and intracardiac injections.
- Intrathecal injection.
- Epidural injection.
- Intra-articular injection.

Order of absorption through various routes: i.v. > inhalation > i.m. > i.p. > s.c. > oral

BIOAVAILABILITY:

- It refers to the rate and extent of absorption of a drug from dosage form. It is a measure of the fraction (F) of administered dose of a drug that reaches the systemic circulation in the unchanged form.
- Bioavailability of drug injected i.v. is 100%, but is frequently lower after oral ingestion because –
  (a) the drug may not be completely absorbed.
  (b) the absorbed drug may undergo first pass metabolism in intestinal wall/ liver or be excreted in bile.
- The fraction of dose which is absorbed (F) following non-intravascular dosing can be found by relating the area under the curve (AUC) to that obtained when the same size dose is administered intravenously.

$$\text{Bioavailability, } F = \frac{AUC_{oral}}{AUC_{i.v.}}$$

BIOEQUIVALENCE:

- ✓ Two drug products are considered to be bioequivalent when the rates and extents of absorption of active ingredient in the two products are statistically equivalent to each other according to predetermined criteria under controlled test conditions.
- ✓ Bioequivalence assessment relies on the concept that pharmaceutically equivalent drug products provide essentially equivalent plasma concentration profiles, in terms of rate and extent of absorption, will produce the same pharmacologic response (therapeutic effect).

DISTRIBUTION OF DRUGS:

- ✓ Drugs are conveyed throughout the body in the circulating blood, and reach tissues of each organ in an amount determined by blood flow and blood concentration to the organ.
- ✓ Concentrations attained in the tissues depend upon its ability of the drug to penetrate capillary endothelium (influenced mainly by binding to plasma proteins) and diffuse across cell membranes.
- ✓ Kinetics of drug distribution to several tissues depends on the following:
  (i) Dose and route of administration
  (ii) Lipid solubility of the drug
  (iii) Ionization at physiological pH (dependent on pKa)
  (iv) Extent of binding to plasma & tissue proteins
  (v) Blood flow rates through tissues and organs, e.g. thiopental sodium is redistributed to poorly perfused tissues (fat and muscles) after attaining high concentration in well perfused tissues (brain, liver and kidneys).

Plasma protein binding of drugs:

- ✓ A variable and often significant amount of absorbed drug may become reversibly bound to plasma proteins.
- ✓ The most important plasma protein in relation to drug binding is albumin, which binds mainly acidic drugs (e.g. warfarin, NSAIDs, sulfonamides) and a smaller no. of basic drugs (e.g. tricyclic antidepressants & chlorpromazine). Other plasma proteins including β-globulin and an acid glycoprotein (α_1-acid glycoprotein) that increases in inflammatory disease, have also been implicated in the binding of certain basic drugs, such as quinine.
- ✓ Approximately 2 molecules of drug bind to one molecule of albumin.
- ✓ Binding of a drug to proteins restricts its distribution, thereby limiting its receptor availability, and can influence the elimination of the drug from the body.
- ✓ The active concentration of the drug is that part which is not bound, because it is only this fraction which is free to leave the plasma and enter the site of action.
- ✓ There is a dynamic equilibrium between bound and free drug fractions.
- ✓ When free drug leaves the circulation bound drug is released to restore the balance (Equilibrium, ⇆).
- ✓ In this way, bound drug can be regarded as a storage depot.
- ✓ Plasma protein binding does also reduce the rate of loss of drug in the kidneys, as only free drug is filtered.
- ✓ *Toxicity and activity of drugs:* A practical consequence of binding of plasma proteins is that the toxicity and activity of drugs which are normally highly bound is greatly increased in hypoproteinemia.

  Similarly, the free concentration of a highly bound drug can be increased by administering a second drug which has a greater affinity for the same binding

sites. This is one mechanism by which drug interaction toxicity can occur, especially when displaced drug is highly protein bound. For example, displacement of warfarin by phenylbutazone.

- ✓ The amount of drug bound can exceed 99%. For example, phenylbutazone; or even nil e.g. aminoantipyrine.
- ✓ Drugs that are extensively (>80%) plasma protein bound are – phenylbutazone, warfarin, furosemide, digitoxin, ceftiofur, propranolol, quinidine, phenytoin, diazepam, valproate etc.

Clinically significant implications of Plasma protein binding:

1. High plasma protein bound drugs are largely restricted to the vascular compartment and tend to have lower volumes of distribution.
2. The bound fraction is not available for action. (Bound form – Temporary storage of drug).
3. High degree of plasma protein binding generally makes the drug long acting, because the bound fraction is not available for metabolism or excretion.
   (NB: Highly protein bound drugs are not removed even by haemodialysis).
4. Competition between drugs for protein binding can lead, rarely, to clinically important drug interactions.

Accumulation and storage of drugs in the body:

Drugs may accumulate in specific organs by binding to specific tissue structures (sequestration).

The examples are –

Digitoxin and emetine	-	Skeletal muscles
Iodine	-	Thyroid
Chloroquine	-	Retina
Tetracyclines and heavy metals	-	Bone and teeth
Thiopentone, DDT, ether etc.	-	Adipose tissue
Chlorpromazine	-	Brain
Calcium	-	Collagen
Griseofulvin	-	Skin, nails and hair roots.

Drug dilution in body water:

- ✓ *Volume of distribution:* It refers to that portion of total body water which it is capable of entering. (By no means, all drugs diffuse throughout the total body water).
- ✓ *Apparent volume of distribution:* Since, the drug does not actually distribute into all body water (approx 20 L in man) with the exclusion of rest of it, this is only an apparent volume of distribution that would accommodate all the drug in the body, if the concentration throughout was the same as in the plasma.

$$V, \text{Apparent volume of distribution} = \frac{\text{Dose administered i.v.}}{\text{Plasma concentration}}$$

- ✓ Approximately, 70% of body weight is water, out of which 2/3rd account for intracellular fluid and remaining 1/3rd remain in the form of extra cellular fluids (Plasma, interstitial fluid and trans-cellular fluid).
- ✓ Lipid insoluble drugs do not enter cells – V approximates extracellular fluid volume, e.g. streptomycin, gentamicin (V = 0.25 L/Kg).
- ✓ Distribution is not only a matter of dilution but also binding and sequestration. Drugs extensively bound to plasma proteins are largely restricted to vascular compartment and have low values. e.g. Phenylbutazone and warfarin (99% plasma protein bound; V= 0.1 L/Kg).
- ✓ Drugs sequestrated in other tissues may have V much more than total body water or even body mass, e.g. digoxin 6 L/Kg, propranolol 4 L/Kg, morphine 3.5 L/Kg because most of the drug is present in other tissues and plasma concentration is low. Therefore, in case of poisoning, drugs with large volumes of distribution are not easily removed by haemodialysis.
- ✓ Pathological states like congestive heart failure (CHF), uraemia, cirrhosis of liver etc. can alter the apparent volume of distribution of many drugs by altering distribution of body water, permeability of membrane binding proteins, accumulation of metabolites that displace the drug from binding sites.

Redistribution:

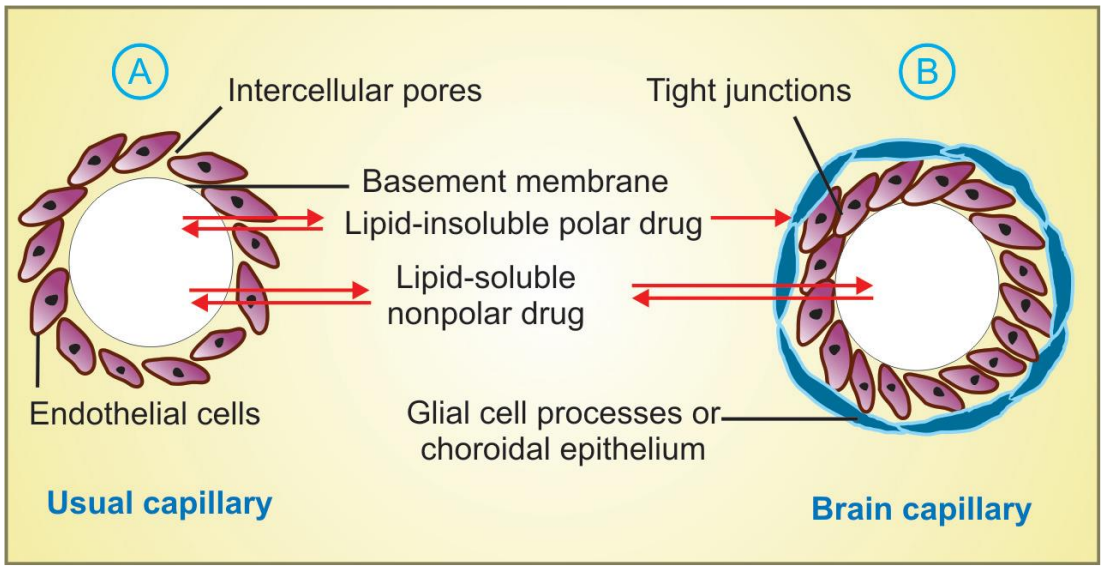
Highly lipid soluble drugs given i.v. or by inhalation initially get distributed to organs with high blood flow, e.g. brain, heart, kidney etc. Later, less vascular but more bulky tissues (muscle, fat) take up the drug – plasma concentration falls and the drug is withdrawn from these sites. If the site of action of the drug was in more of the highly perfused organs, redistribution results in termination of drug action. Greater the lipid solubility of the drug, faster is its redistribution. Anaesthetic action of **thiopentone** is terminated in few minutes due to redistribution. However, when the same drug is given repeatedly or continuously over long periods, the low perfusion high capacity sites get progressively filled up and the drug becomes longer acting.

Morphine, although quite lipid soluble enough to cross blood-brain barrier, has a lipid – water partition coefficient of 0.4, so sequestration of the drug by body fat is of little importance. Thiopentone, by comparison (fat: water partition coefficient, approx. 10) accumulates substantially in body fat. This has important consequences that limit its usefulness as an intravenous anaesthetic to short term initiation (induction) of anaesthesia.

Specialized Barriers:

Blood - Brain Barrier:

- ✓ It exists between plasma and extra-cellular space of the brain. Blood – CSF barrier exists in the choroids plexus.
- ✓ These barriers can be regarded as protective in function as nutrients usually penetrate with ease assisted by carrier mediated systems.
- ✓ In general, lipid insoluble and highly ionized drugs penetrate the brain very slowly, while lipid soluble agents (e.g. volatile anaesthetics) enter very rapidly.
- ✓ *Capillaries in the brain lack the pores which elsewhere in the body enable them to be rather leaky. The endothelial cells are joined by tight junctions in the substance of the brain, not the customary gap junctions. Furthermore, capillaries in the brain are tightly invested with glial cells.*
- ✓ During inflammation, the epithelia are disrupted, the barrier becomes temporarily permeable to ionized drugs (e.g. penicillin & streptomycin can then attain therapeutic concentrations).



Source: Essentials of Medical Pharmacology by K.D. Tripathi, Jaypee Publishers

Figure : Passage of drugs across capillaries

A Usual capillary with large intercellular pores through which even large lipid insoluble molecules diffuse.

B Capillary constituting blood brain or blood-CSF barrier. Tight junctions between capillary endothelial cells and investment of glial cell processes or choroids epithelium

Placental Barrier:

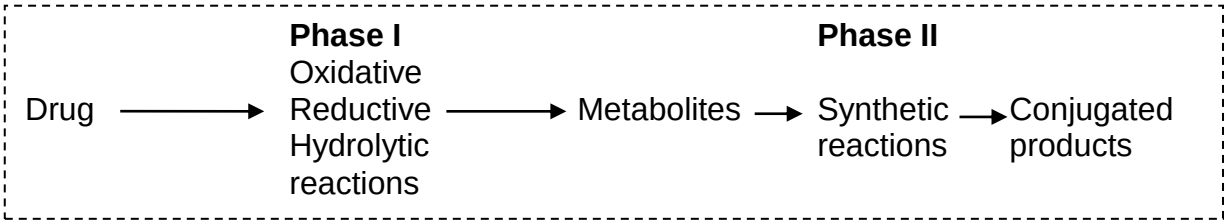
- ✓ Lipid soluble drugs cross the placenta with ease.
- ✓ So, most anaesthetics therefore, cause some respiratory depression in the newborn.
- ✓ Highly ionized drugs are among those to which the placenta does present a barrier to diffusion.
- ✓ Placenta is an effective barrier to very few drugs.

MECHANISMS OF DRUG ELIMINATION:

- ✓ Mechanisms of drug elimination are biotransformation (metabolism) and excretion.
- ✓ The fate of a drug is largely determined by certain of its physicochemical properties, specifically **lipid solubility** and **degree of ionization**.
- ✓ Lipid solubility appears to be a prerequisite for biotransformation of drugs by the hepatic microsomal enzyme system.
- ✓ **Polar drugs** and many drug metabolites are excreted by the kidneys.
- ✓ Apart from **liver**, metabolism of drugs takes place in blood **plasma** and lumen of the **gut**, where hydrolytic and reductive reactions may occur, as well as in other tissues (**intestinal mucosa, kidney & lung**).
- ✓ An ester linkage is a feature of drugs that undergo hydrolysis. These include acetylcholine, succinylcholine, atropine, procaine, meperidine, aspirin to salicylate, ceftiofur to desfuroylceftiofur and hetacillin to ampicillin.

DRUG METABOLISM (Biotransformation):

- ✓ Drugs undergo metabolic changes in the body that are directed primarily toward formation of metabolites that have physicochemical properties favourable for their excretion.
- ✓ **Products of biotransformation** are generally **less lipid soluble** and **more polar** in nature. These properties help excretion of drugs.
- ✓ Mostly hydrophilic drugs are not biotransformed. Example – Streptomycin, Neostigmine etc.
- ✓ Drug metabolism has been generally divided into two types of reactions, termed phase I and phase II reactions.



- ✓ The initial phase consists of reactions that can be classified as oxidative, reductive, and hydrolytic while the second phase includes the synthetic reactions (conjugations).
- ✓ Phase I biotransformations usually unmask or introduce into the drug molecule **polar groups** such as – OH, –SH, –COOH, and $–NH_2$. These functional groups enable the compound to undergo conjugation with endogenous substances such as glucuronic acid, acetate (acetylation), sulphate (sulphuric acid ester formation) and various amino acids (primarily glutathione, cysteine and glycine). The drug conjugates formed are water soluble and almost invariably inactive pharmacologically.
- ✓ Metabolites of phase I biotransformation reactions may be pharmacologically active or inactive, but phase II metabolites are mostly inactive.

Biotransformation reactions may lead to the following:

(i) Inactivation: Most drugs and their active metabolites are rendered inactive or less active. For example, phenobarbitone, morphine, chloramphenicol etc.

(ii) Active metabolite from an active drug: Many drugs have been found to be partially converted to one or more active metabolite, the effects observed are the sum total of that due to the parent drug and its active metabolite (s).

(iii)Activation of the inactive drug: Few drugs are inactive as such and need conversion in the body to one or more active metabolites. Such a drug is called a **'Prodrug'**. The prodrug may offer advantages over the active form in being more stable, having better bioavailability, or other desirable pharmacokinetic properties or less side effects and toxicity.

Examples:

Prodrug	***Active form***
Enalpril	Enalaprilat
Levadopa	Dopamine
Prontosil	Sulfanilamide
Hetacillin	Ampicillin

PHASE - I BIOTRANSFORMATION REACTIONS (Non-synthetic reactions):

Metabolites may be active or inactive.

(1) Oxidation:

- ✓ It involves addition of oxygen or negatively charged radical or removal of hydrogen or positively charged radical.
- ✓ Oxidation reactions are the **most important** drug metabolizing reactions.
- ✓ Oxidation reactions are mostly carried out by a group of monoxygenases in the liver, which in the final step involve a cytochrome P-450 haemoprotein, NADPH, cytochrome P-450 reductase and O_2. These enzymes are also known as microsomal oxidases or mixed function oxidases.

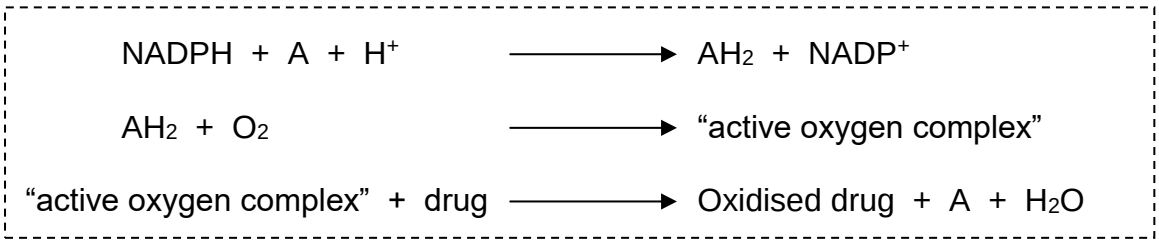


Fig.: Hepatic microsomal drug oxidizing system. The oxidative mechanism requires that equivalent amounts of NADPH, oxygen and drug substrate be utilized in the reaction. "A" represents the oxidized form and "AH_2" is the reduced form of cytochrome P-450.

- ✓ Various oxidative reactions of drugs are as follow:

Oxidative reaction	*Drug*	*Metabolite*
Aromatic hydroxylation	Phenylbutazone* Phenobarbital*	Oxyphenbutazone* p-hydroxyphenobarbital
Aliphatic oxidation	Pentobarbital*	Pentobarbital alcohol
O-dealkylation	Phenacetin*	Acetaminophen*
N-dealkylation	Diazepam*	N-desmethyldiazepam*
Oxidative deamination	Amphetamine*	Phenylacetone
Desulfuration	Parathion	Paraxon*
Sulfoxidation	Phenothiazine tranquilizers*	Corresponding sulfoxide

* *Pharmacologically active compound.*

(2) Reduction:

- ✓ Microsomal reductions occur less frequently than oxidations, but can take place in drugs which contain – **disulphide (S=S), azo (N=N),** or **nitro (–NO_2)** groups.
- ✓ These reactions are converse of oxidations and involve cytochrome P-450 enzymes working in opposite direction. The enzymes involved are reductases.
- ✓ Various reductive biotransformation reactions are as follow:

Drug	*Metabolite*
Prontosil	Sulfanilamide*
Chloramphenicol*	Inactive amine metabolites

[Chloramphenicol is inactivated by ruminal microbes. For this reason, the oral route is unsuitable for administration in ruminants**]**.

* *Pharmacologically active compound.*

(3) Hydrolysis:

- ✓ Hydrolysis is an important metabolic pathway for compounds with an **ester linkage** (**–COO–**) or an **amide (–CONH–)** bond.
- ✓ Hydrolytic cleavage reactions can take place in <u>liver</u>, <u>intestines</u>, <u>plasma</u> and <u>other tissues</u>.

Examples: Hydrolysis of –

(i) Acetylcholine (ACh) by acetylchonesterase (AChE)

(ii) Suxamethonium (plasma) by plasma pseudocholinesterase

(iii) Atropine (plasma) by atropinase – Rabbits are able to consume deadly nightshade (*Atropa belladonna*) without danger because atropine, an ester of tropic acid and tropine is hydrolyzed in its plasma.

(iv) Procaine (plasma) by plasma cholinesterase.

(v) Lignocaine (liver) by non-microsomal hepatic amidase.

(vi) Digitalis glycosides.

(vii) Gut acting sulphonamides.

PHASE - II BIOTRANSFORMATION REACTIONS:

(Synthetic/ Conjugation reactions)

- ✓ Synthetic reactions may take place when a drug or phase I metabolite contains a chemical group such as **hydroxyl (–OH), carboxyl (–COOH), amino (–NH_2)** or **sulfhydryl (–SH)** and is suitable for combining with a natural compound provided by the body to form readily excreted water soluble polar metabolites.
- ✓ Conjugating agents include –

  Glucuronic acid, glutathione, glycine, cysteine, methionine (for methylation), sulphate and acetate.
- ✓ These conjugating agents do not, however, react directly with the drug or phase I metabolite but do so either in an activated form or with an activated form of the drug (as an example, acetyl CoA rather than acetate).
- ✓ Conjugation reactions have high energy requirement.

(1) Glucuronide conjuagation: (In liver, by microsomal enzyme glucuronyl transferase**)**

- ✓ The **cat** synthesizes glucuronide conjugates at a slow rate, as this species is deficient in the transferring enzyme, glucuronyl transferase .
- ✓ Glucuronide conjugation reactions are important metabolic pathway for drugs and certain endogenous compounds (steroid hormones, thyroxine, bilirubin etc.).
- ✓ The activated form of glucuronic acid is the nucleotide – Uridine diphosphate glucuronic acid (UDPGA).
- ✓ Examples – Morphine, salicylates, acetaminophen, chloramphenicol, sulphadimethine and phase-1 metabolites of diazepam (oxazepam), phenylbutazone (oxyphenbutazone).
- ✓ The glucuronyl conjugates are extensively excreted in the **bile.**

(2) Sulphate conjuagation: (In liver, soluble fraction of liver**)**

- ✓ Capacity for sulphate conjugation in the **pig** is limited.
- ✓ Examples – Phenol, aliphatic alcohols, isoproterenol, ascorbic acid etc. and endogenous compounds like chondroitin, heparin etc.

(3) Acetylation: (Reticuloendothelial cells rather than parenchymal cells of liver, spleen, lungs and intestinal mucosa**)**

- ✓ **Dogs** and **foxes** do not acetylate.
- ✓ Examples – Sulphonamide compounds etc.
- ✓ Acetylation reaction takes place in two stages – (i) formation of Acetyl CoA (ii) nucleophilic attack by the amino – containing compound on the acetylated enzyme.
- ✓ Acetylation decreases water solubility as well as lipid solubility of metabolites. e.g. Acetylation of sulphonamides lead to chances of crystalluria.

Table: Domestic animals with defects in certain conjugation reactions

Species	Conjugation reaction	Major target groups	State of synthetic reaction
Cat	Glucuronide synthesis	–OH, –COOH, $–NH_2$, =NH, –SH	Present but slow rate
Dog & Foxes	Acetylation	Ar. $–NH_2$	Absent
Pig	Sulphate conjugation	Ar. –OH, Ar. $–NH_2$	Present but low extent

FIRST PASS EFFECT:

- ✓ From the gut, absorbed drug is conducted by hepatic portal system to the liver and so is exposed to drug metabolizing enzymes before entering the systemic circulation (**presystolic metabolism**).
- ✓ When a large proportion of the drug becomes biotransformed during this transit, it is said to be subject to the first pass effect.
- ✓ This, plus inactivation of drug in the lumen and/ or wall of the gut contribute to the problem of bioavailability.
- ✓ For some drugs, this problem is such as to render oral administration ineffective. e.g. Chloramphenicol in ruminants, morphine, pethidine, isoprenaline, testosterone etc.

EXCRETION OF DRUGS:

(1) Renal Excretion:

- ✓ In general, compounds that have low lipid solubility and those that are predominantly ionized in blood plasma are rapidly excreted by the kidneys.
- ✓ Carrier mediated excretion of drugs: Probenecid decreases the rate of elimination of Penicillin G and ceftiofur by reducing tubular secretion of the antibiotic.
- ✓ pH of the urine is also an important determinant of drug excretion. Acidic drugs are excreted more in alkaline urine whereas alkaline drugs are eliminated fast in acidic urine.
- ✓ Smaller molecular weight and ionized drugs are excreted unchanged in urine. Examples – Penicillin, cephalosporins, aminoglycosides, oxytetracyclines and most diuretics etc.

(2) Biliary Excretion:

- ✓ Apart from kidneys, liver also eliminates few drugs via bile.
- ✓ High molecular weight compounds and presence of polar groups are the properties of compounds excreted by the liver via bile. Examples – Nafcillin, erythromycin, digitoxin, certain indigenous compounds like steroid hormones and conjugates of chloramphenicol, morphine and bilirubin are excreted via bile.
- ✓ ***Enterohepatic circulation:*** Delays elimination of drugs. e.g. Tetracycline etc.

(3) Excretion into milk:

- ✓ Cows milk is slightly acidic (pH 6.5 – 6.9) relative to plasma (pH 7.2 – 7.4) and therefore tends to concentrate basic fat soluble drugs.

(4) Excretion from lungs:

- ✓ Volatile anaesthetics.

(5) Saliva and sweat:

- ✓ These routes of excretion are of minor importance. e.g. Potassium iodide, lithium iodide etc.

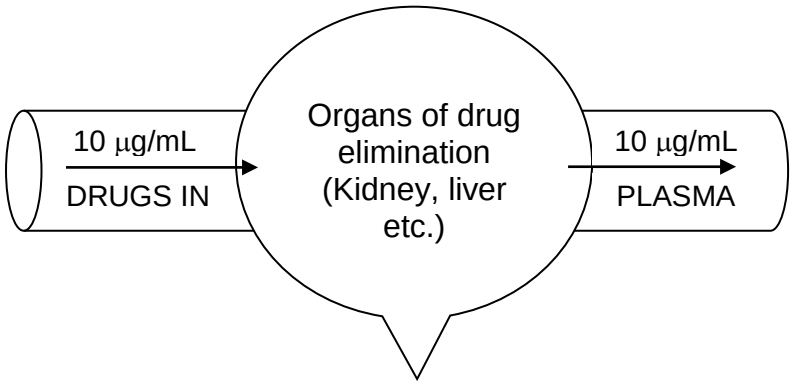
KINETICS OF ELIMINATION:

Knowledge of kinetics of elimination helps to devise rational dosage regimens and to modify them according to individual needs. There are three fundamental pharmacokinetic parameters :-

(i) Bioavailability (F)
(ii) Volume of distribution (V), and
(iii) Clearance (CL)

Clearance: It is the theoretical volume of plasma from which the drug is completely removed in unit time.

CL = Rate of elimination/ C, where, C is plasma concentration.



$$CL = \frac{500\ \mu g/min}{10\ \mu g/mL}$$

$$= 50\ ml/min$$

FIRST ORDER (Exponential) KINETICS:

- Rate of elimination is directly proportional to drug concentration.
- CL remains a constant.
- A constant fraction of drug is eliminated in unit time.
- Majority of drugs follow first order kinetics.

ZERO ORDER (Linear) KINETICS:

- Rate of elimination remains constant irrespective of drug concentration.
- CL decreases with increase in concentration.
- A constant amount of drug is eliminated in unit time.
- Few drugs follow zero order kinetics. e.g. Ethyl alcohol.

Plasma half life ($t_{1/2}$): The plasma half life of a drug is the time taken for its plasma concentration to be reduced to half of its original value.

$t_{1/2}$ = ln 2/k = 0.693/k, and k=CL/V (k, elimination rate constant)

1 $t_{1/2}$ = 50% drug is eliminated
2 $t_{1/2}$ = 75% (50+25) drug is eliminated
3 $t_{1/2}$ = 87.5% (50+25+12.5) drug is eliminated
4 $t_{1/2}$ = 93.75% (50+25+12.5+6.25) drug is eliminated.

Thus, nearly complete drug elimination occurs in 4-5 half lives.

For drugs eliminated by first order kinetics, $t_{1/2}$ remains constant whereas for zero order kinetics $t_{1/2}$ increases with dose.

Methods of prolongation of drug action:

1. **By prolonging absorption from site of action:**
   (a) *Oral* – Sustained release tablets/ boluses, drug particles coated with resins.
   (b) *Parenteral* – Depot injections for s.c. or i.m. routes, inclusion of vasoconstrictor with the drug (e.g. adrenaline with local anaesthetic).
2. **By increasing plasma protein binding:** Use of congeners which are highly bound to plasma protein. e.g. Sulfadoxine.
3. **By retarding rate of metabolism:**
   - By small chemical alteration in the molecule without affecting its biological value, but metabolism is markedly affected. Example – Addition of ethinyl group to Estradiol makes it longer acting and suitable for use as oral contraceptive.
   - Inhibition of specific enzymes by one drug can prolong the action of another. Example – Physostigmine prolongs the action of acetylcholine.
4. **By retarding renal excretion:** The tubular secretion of drug is an active process which can be suppressed by competing substances. Example – Probenecid prolongs duration of action of penicillins.

Chapter - 3

Pharmacodynamics

PHARMACODYNAMICS

Pharmacodynamics is the study of physiological and biochemical effects of drugs and how these effects relate to a drug's mechanism of action. It focuses on the action and the effects of drugs within the body. In general, pharmacodynamics characterizes what a drug does to a patient. In contrast, the study of pharmacokinetics addresses what the patients body does to a drug. Effective use of a drug requires knowledge of the drug's pharmacokinetic and pharmacodynamic properties.

PRINCIPLES OF DRUG ACTION:

Drugs (except those gene based) do not impart new functions to any system, organ or cell. They only alter the pace of ongoing activity. The basic types of drug action can be broadly classed as follows:

1. Stimulation: It is a selective enhancement of the level of activity of specialized cells. Example – adrenaline stimulates heart, pilocarpine stimulates salivary glands. However, excessive stimulation is often followed by depression of that function. Example – High dose of picrotoxin, a CNS stimulant produces convulsions followed by coma and respiratory depression.
2. Depression: It is a selective diminution of activity of specialized cells. Example – Barbiturates depress CNS, quinidine depresses heart. Certain drugs stimulate one type of cells but depress the other. Example – acetylcholine stimulates intestinal smooth muscles but depress the SA node in the heart. Most drugs can not be just classed as stimulants or depressants.
3. Irritation: This connotes a non-selective, often noxious effect and is particularly applied to specialized cells like epithelium, connective tissue etc. Mild irritation may stimulate associated function like bitters increase salivary and gastric secretions and counterirritants increase blood flow to the site. But strong irritation results in inflammation, corrosion, necrosis and morphological damage. This may result in diminution or loss of function.
4. Replacement: This refers to the use of natural metabolites, hormones or their congeners in deficiency states like insulin in diabetes and fluids in dehydration.
5. Cytotoxic effect: Selective cytotoxic action for invading parasites or cancer cells, attenuating them without significantly affecting the host cells is utilized for cure or palliation of infections and neoplasms.

BASIC MECHANISMS OF DRUG ACTION:

Mechanisms of drug action can be grouped as non-cellular mechanisms of drug action and cellular mechanisms of drug action.

Non-cellular mechanisms of drug action: Drug reactions that occur extracellularly and that involve non-cellular constituents include the following:-

1. *Physical effects:* Examples include protective, adsorbent and lubricant properties of locally active agents that are applied to cutaneous and membrane surfaces.
2. *Chemical reactions*: A number of drugs produce their effects through a chemical union with an endogenous or foreign substance. Examples include the inactivation of heparin (an organic acid) by protamine (an organic base), the chelation of lead by calcium disodium edentate, neutralization of hydrochloric acid in the stomach by antacids such as aluminum hydroxide or sodium bicarbonate, treatment of alkali poisoning with weak acids, conversion of haemoglobin to methaemoglobin by nitrites, precipitation of proteins by astringents and oxidation reactions initiated by certain antiseptics and disinfectants.
3. *Physicochemical mechanisms:* Certain drugs act by altering the physicochemical or biophysical properties of specific fluids or even components of cells. Examples of the former include the surface-active agents or surfactants. Surfactants reduce the surface tension of the interface between two immiscible phases because their molecules contain two localized regions, one being hydrophilic in nature and the other hydrophobic. Detergents, emulsifiers, antifoaming agents and several antiseptics and disinfectants possess surfactant properties.
4. *Modifications of the composition of body fluids:* Several therapeutic manipulations involve the administration of substances that exert osmotic effects across particular cell membranes. Examples of osmotically active agents include magnesium sulphate as a purgative, mannitol as a diuretic, hypertonic poultices applied to the skin and use of dextran as plasma volume expander. In addition, acid-base electrolyte derangements which occur in the extracellular fluid in many diseases can be corrected by the appropriate and judicious use of various electrolyte solutions. Also acidifying and alkalinizing salts may be administered to alter the pH of the urine for specific therapeutic purposes.

Cellular mechanisms of drug action: Most of the responses elicited by drugs occur at cellular level and involve either functional constituents or more commonly, specific biochemical reactions.

1. *Physicochemical and biophysical mechanisms*: Certain drugs appear to act by altering the physicochemical or biophysical characteristics of specific components of cells. Examples include the effect of general inhalant anaesthetics on the lipid matrix and perhaps the hydrophobic proteins in neuronal membranes within the CNS.

2. *Modification of cell membrane structure and function*: Various drugs may influence either the structure or specific functional components of cell membranes and thereby initiate their characteristic effects. These mechanisms of action may also involve enzyme stsyems or receptor mediated reactions. A few examples include, local anaesthetics that bind to components of the sodium channels in excitable membranes and prevent depolarization, calcium channel blockers that inhibit the entry of calcium into cells, insulin that facilitates the transport of glucose, neurotransmitters that increase or decrease sodium ion permeability and antifungal antibiotics that disrupt the sterol component of fungal cell membrane.
3. *Mechanisms associated with neurohumoural transmission*: A number of drugs interfere with the synthesis, release, effects or re-uptake of neurotransmitters. Once again enzyme and/or receptor mediated effects may be responsible. For example, reserpine blocks the transport system of adrenergic storage granules, while amphetamine displaces norepinephrine from axonal terminals. Botulinum toxin prevents the release of acetylcholine from cholinergic terminals and bretylium inhibits the release of norepinephrine from adrenergic terminals.
4. *Enzyme inhibition*: Certain enzymes exert their effects by inhibiting the activity of specific enzyme systems either in the host animal or the invading pathogens. This inhibition may be competitive or non-competitive. Non-competitive inhibition may be reversible or irreversible.

PROTEIN TARGETS FOR DRUG BINDING:

Four main kinds of regulatory proteins are commonly involved as primary drug targets, namely:

- Receptors
- Enzymes
- Carrier molecules (transporters)
- Ion channels

RECEPTORS:

J.N. Langley (1878) introduced the concept of receptor while he was studying about the actions of atropine and pilocarpine on salivary flow. He used the term receptive substance. The term receptor was first used by Paul Ehrlich (1913) to describe the hypothetical specific chemical groupings of “side chains” on cells upon which the chemotherapeutic agents were postulated to act.

Receptors are sensing elements in the system of chemical communications that coordinates the function of different cells in the body, the chemical messengers being hormones, transmitter substances or other mediators. Many therapeutically useful synthetic drugs act as agonists or antagonists on receptors for known endogenous mediators. Receptors are macromolecular structures with which a drug interacts to initiate its pharmacologic effects. Receptors elicit many different types of

cellular effect, some of which may be rapid, such as those involved in synaptic transmission. A receptor is often defined in terms of the endogenous substance or ligand that produces a given effect upon interaction with a given biological substrate. A number of binding sites exist in biological tissues for drugs and toxins for which there is no known endogenous ligand.

Binding of drugs to receptors necessarily obeys the Laws of Mass Action. At equilibrium, receptor occupancy is related to drug concentration. The higher the affinity of the drug for the receptor, the lower is the concentration at which it produces a given level of occupancy. The same principles apply when two or more drugs compete for the same receptors; each of which has the effect of reducing the apparent affinity for the other.

Properties of receptors: To define a receptor, three criteria should be satisfied namely saturability, specificity and reversibility.

- *Saturability*: A finite number of receptors per cell should be present as revealed by a saturable binding curve. By adding increasing amounts of the drug, the number of drug molecules bound should form a plateau at the number of binding sites present.
- *Specificity*: The drug should be structurally complementary to the receptor. This can be demonstrated by a series of drugs that vary slightly in chemical structure and showing that affinity is affected by chemical structure. Also, if the drug is optically active, then the two isomers should have markedly different affinities.
- *Reversibility*: The drug should bind to the receptor and then dissociate in its non-metabolized form. This property distinguishes receptor-drug interactions from enzyme-substrate interactions.

Types of receptors:

1. Type 1: **Ligand-gated ion channels** (also known as **ionotropic receptors**)**:** These are membrane receptors that are coupled directly to ion channels and are the receptors on which fast neurotransmitters act. Examples include the nicotinic acetylcholine receptor; $GABA_A$ receptor; and glutamate receptors.
2. Type 2: **G-protein-coupled receptors** (GPCRs)**:** These are also known as **metabotropic receptors** or **7-transmembrane-spanning (heptahelical) receptors**. They are membrane receptors that are coupled to intracellular effector systems via a G-protein. This class includes receptors for many hormones and slow transmitters, for example the muscarinic acetylcholine receptor and adrenergic receptors.
3. Type 3: **Kinase-linked and related receptors:** These are membrane receptors that incorporate an intracellular protein kinase domain within their structure. They include receptors for insulin, various cytokines and growth factors.
4. Type 4: **Nuclear receptors:** These are receptors that regulate gene transcription. The term *nuclear receptor* is something of a misnomer, because some are actually located in the cytosol and migrate to the nuclear compartment when a ligand is present. They include receptors for steroid hormones, thyroid hormone, and other agents such as retinoic acid and vitamin D.

Function of receptors:

- To propagate regulatory signals from outside to within the effector cell when the molecular species carrying the signal can not itself penetrate the cell membrane.
- To amplify the signal.
- To integrate various extra cellular and intracellular regulatory signals.
- To adopt short term and long term changes in the regulatory milieu and maintain homeostasis.

Structure activity relationships (SAR): The ability of a drug to combine with a receptor to produce an effect is dependent on the three dimensional chemical structure of the drug. Relatively minor modifications in the drug molecule may result in major changes in pharmacological properties. Changes in structure can change the activity of the drug, some actions may be affected while others are not, drug may have lesser toxic side effects with better pharmacokinetic characteristics.

Non-receptor mediated reactions: Some drugs produce an effect without combining with receptors. Some important examples are given below:-

- Mannitol is used as a diuretic. Mannitol molecules circulate in the blood and are excreted in the urine. These molecules drag water from the body into the urine by osmosis. Mannitol does not bring about this effect by combining with any receptor.
- Chelators are also examples of non-receptor mediated actions. They physically combine with ions or other selected compounds in the environment to produce their effects. For example, chelators like BAL are used to facilitate removal of lead from the body by chelation. EDTA, an anticoagulant also acts by chelation.
- Antacids also form another group of drugs whose action is not mediated through receptors. Calcium, magnesium or aluminium in the antacid drug combines with the strong hydrochloric acid in the stomach thereby reducing stomach irritation.

ION CHANNELS:

Some ion channels (known as ligand gated channels) are directly linked to a receptor and they open only when the receptor is occupied by an agonist. However, many other types of ion channels also serve as targets for drug action. The simplest type of interaction involves the physical blocking action of local anaesthetics on the voltage-gated sodium channels. Ion channel modulation by drugs, acting directly on the channel or indirectly is one of the most important mechanisms by which pharmacological effects are produced at the cellular level.

ENZYMES:

Many drugs are targeted on enzymes. Most commonly the drug molecule is a substrate analogue that acts as a competitive inhibitor of the enzyme either reversibly or irreversibly.

CARRIER MOLECULES:

The transport of ions and small organic molecules across cell membranes generally requires a carrier protein, since the permeating molecules are often polar, to penetrate lipid membranes on their own.

SOME DEFINITIONS:

1. **Affinity and Efficacy:** Affinity describes the tendency of a drug to combine with a particular kind of a receptor whereas **efficacy (or intrinsic activity)** of a drug refers to the maximal effect the drug can produce. That is why; a partial agonist has less intrinsic activity/ efficacy than a full agonist.

2. **Potency:** It refers to the dose of a drug that must be administered to produce a particular effect of given intensity. It is influenced by the affinity of a drug. It varies inversely with dose. It is a relative rather than an absolute expression of drug activity. Potency of a drug is not necessarily correlated with its efficacy or safety and the most potent drug within a series is not necessarily clinically superior. Low potency is a disadvantage only if the effective dose is so large that it is too costly to produce or too cumbersome to administer.

3. **Selectivity:** It depends on the capacity of a drug to preferentially produce a particular effect. The characteristic effect of the drug is produced at lower doses than those required to elicit other responses. For instance, clenbuterol has a high degree of selectivity for β_2 receptors (in lungs). At higher doses, β_1 receptors (in heart) are also activated.

4. **Specificity:** When all the effects produced by a drug are due to a single mechanism of action, the drug is said to be specific. A specific drug acts at only one type of receptor, but may produce multiple pharmacological effects because of location of receptors in various organs. For instance, atropine is a specific drug in that its varied effects can be attributed to its antimuscarinic action.

   Effects of a non-specific drug results from several mechanisms of action. For instance, the potential effects of phenothiazine tranquilizers (e.g. acepromazine) include **sedation** (due to increased rate of dopamine turnover in brain), an **antiemetic action** (due to depressed activity of CTZ), **hypotension** (due to α-adrenergic receptor blockade), an **antispasmodic effect** on GI smooth muscles (due to anticholinergic action) and **hypothermia** (due to interference with hypothalamic control of temperature regulation).

5. **Agonist:** An agonist is a drug that possesses affinity for a particular receptor and causes a change in the receptor that result in an observable effect. Agonists are further categorized as:

   Full agonist: Produces a maximal response by occupying all or a fraction of receptors. (Affinity=1, Efficacy=1)

   Partial agonist: Produces less than a maximal response even when the drug occupies all of the receptors. A partial agonist has less intrinsic activity than a full agonist. (Affinity=1, Efficacy= 0 to 1)

   Inverse agonist: Activates a receptor to produce an effect in the opposite direction to that of the well recognized agonist. (Affinity=1, Efficacy= –1 to 0)

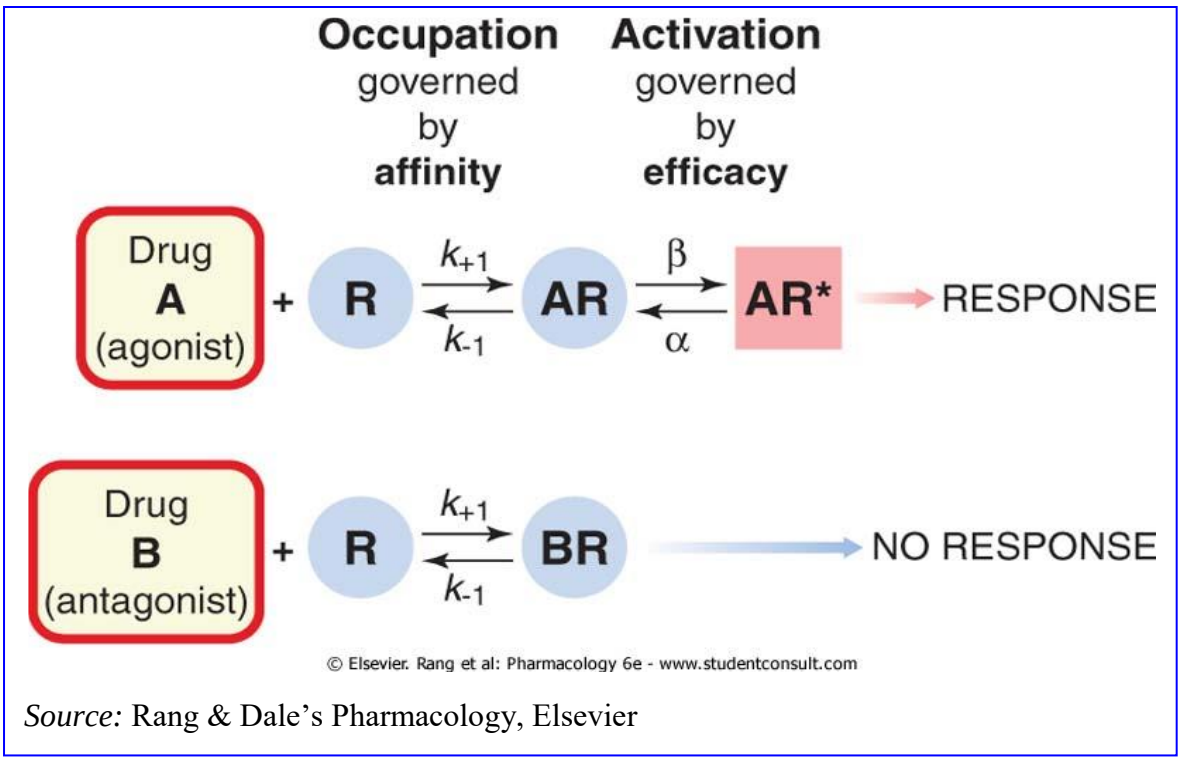
6. **Antagonist:** An antagonist is a drug that blocks the response produced by an agonist. Antagonists interact with the receptor or other components of the effector mechanism, but **antagonists are devoid of intrinsic activity** (Affinity=1, Efficacy=0). Antagonism can be classified as:-

(i) **Competitive Antagonism:** It is completely reversible; an increase in the concentration of the agonist in the immediate vicinity of its site of action or bio-phase will overcome the effect of the antagonist.
Example: Atropine (Antimuscarinic agent)
Diphenhydramine (H_1 receptor blocker)
Propranolol (β-adrenergic blocker)
Spironolactone (Aldosterone antagonist)

(ii) **Non-competitive antagonism:** A non-competitive antagonist conceptually removes the receptor or response potential from the system. Addition of more agonist to the bio-phase of inhibited receptor will not overcome the antagonism achieved by a non-competitive antagonist. Thus, the agonist has no influence upon the degree of antagonism or its reversibility.
Example: Platelet inhibiting action of aspirin (The thromboxane synthase enzyme of platelets is irreversibly inhibited by aspirin, a process that is reversed only by production of new platelets).

7. **Drug action:** It is the initial combination of the drug with its receptor resulting in conformational change in the latter (in case of agonist), or prevention of conformational change through exclusion of the agonist (in case of antagonists).
8. **Drug effect:** It is the ultimate change in biological function brought about as a consequence of drug action, through a series of intermediate steps.

DRUG-RECEPTOR INTERACTIONS:



Source: Rang & Dale's Pharmacology, Elsevier

Figure : **The distinction between drug binding and receptor activation**. The rate constants k_{+1}, k_{-1}, β and α, which apply to the binding and activation reactions, respectively. Ligand A is an agonist, because it leads to activation of the receptor (R), whereas ligand B is an antagonist.

Occupation of a receptor by a drug molecule may or may not result in *activation* of the receptor. By activation, we mean that the receptor is affected by the bound molecule in such a way as to elicit a tissue response. Binding and activation represent two distinct steps in the generation of the receptor-mediated response by an agonist (Fig. 3.1). If a drug binds to the receptor without causing activation and thereby prevents the agonist from binding, it is termed a *receptor antagonist*. The tendency of a drug to bind to the receptors is governed by its *affinity*, whereas the tendency for it, once bound, to activate the receptor is denoted by its *efficacy*. Drugs of high potency will generally have a high affinity for the receptors and thus occupy a significant proportion of the receptors even at low concentrations. Agonists will also possess high efficacy, whereas antagonists will, in the simplest case, have zero efficacy. Drugs with intermediate levels of efficacy, such that even when 100% of the receptors are occupied the tissue response is submaximal, are known as *partial agonists*, to distinguish them from *full agonists*, the efficacy of which is sufficient that they can elicit a maximal tissue response.

Receptor drug binding can be measured by radioactive tracers, injection of isotope into animal, *in vitro* radio-labeled drug binding, autoradiographic localization of isotope, spectroscopic techniques, NMR (Nuclear Magnetic Resonance) spectroscopy, ESR (Electron Spine Resonance) spectroscopy, fluorescence and optical absorption and enzyme linked assay.

The forces that determine whether or not a drug will interact significantly with a receptor are thermodynamic and involve enthalpy (the absorption or production of heat associated with binding interaction). Five types of chemical bonds can be formed between a receptor and a drug. They are covalent, electrostatic, hydrogen, Van der Waals and hydrophobic.

(i) Covalent bond – Strongest chemical bond and is commonly associated with a drug that interacts irreversibly with a receptor. Most drugs do not form covalent bonds.

(ii) Electrostatic bond – This type of bonding is very common type of bond between a receptor and a drug. Electrostatic interactions include a simple attraction between oppositely charged groups on the receptor and drug as well as more complex interactions between uncharged or polar groups.

(iii) Hydrogen bond – A hydrogen bond represents a strong interaction between drug and receptor arises from a sharing of the hydrogen atom between an acidic group and a basic group.

(iv) Van der Waals bond – A van der Waals interaction is a weak attraction between either polar or non-polar molecules. It is essentially electrostatic in nature and varies with distance.

(v) Hydrophobic bond – This can be a major driving force for a binding interaction of the drug and/or binding site if non-polar. The basis of this effect is that the interaction of non-polar with water is unfavourable and that by removing two non-polar surfaces from an interaction with water a net attractive force is produced.

DOSE RESPONSE RELATIONSHIP:

The response to a drug varies according to its dosage i.e. the magnitude of the drug effect is a function of the dose administered. The relation between the response produced by different dosage is expressed by graphical representation called **Dose Response Curve** (DRCs). These are of two types:

(i) Graded dose response curve, and
(ii) Quantal dose response curve.

Graded Dose Response Curve:

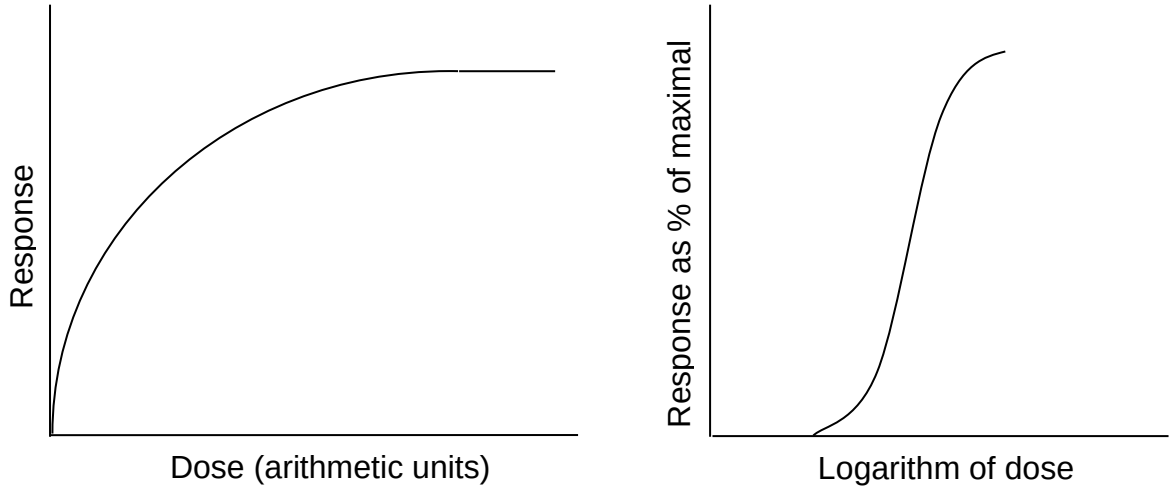


Fig. 1(a) **Fig. 1(b)**

Figure : Logarithmic transformation of the dose data is used to convert the hyperbolic curve characteristic of an arithmetic graded response (a) into the sigmoid form (b).

It gives the relation between dose of a drug and the intensity of response in a single biological unit. The curve depicts that when the dose exceeds a critical level (threshold dose), the response also increases progressively until it reaches a steady level (ceiling effect-ceiling dose). The **threshold dose** may be defined as the minimum dose required to produce an observable response. The dose producing ceiling effect may be called as **ceiling dose**, which may be defined as the minimum dose producing the maximum response. Any further increase in the dose above the ceiling dose will not increase the level of response. The graded dose response represents the relationship between dose and response in a single unit or animal, but it does not indicate the normal biological individual variation on a population basis.

When the graded response is plotted as a graph, a hyperbolic curve is obtained. When the response is expressed as a % of maximum instead of in absolute units, and is plotted against the logarithm of the dose, the curve adopts a sigmoid shape characteristic of a log-dose-percent response curve. The central portion of such curves is more or less linear. When two or more different dilutions of the same drug are applied in sequence to the same test tissue in increasing volumes to obtain for each response the minimal to maximal range, the curves resulting from

each dilution are parallel. In such a quantitative bioassay, the separation between the curves gives the ratio of the concentrations of the dilutions tested.

Quantal Dose Response Curve:

It represents the percent response of animals in a group of population to the doses of a drug. Each animal receiving a dosage is characterized as responding or non-responding. The percentages responding to each dose are recorded (i.e. 0% dead, 0% alive, % responded or % not responded etc.). The relation is based on **all-or-non** phenomenon, which cannot be quantitatively measured such as occurrence of death, convulsions, emesis, oestrous etc. These quantal responses (%) when plotted against log doses do not show a linear regression. However, when the percent is transformed into probits (probabilities), the relationship becomes linear. This type of curve is used for estimating ED_{50} or LD_{50} values of a drug. For a quantal response, both the dose response and the log dose response curves are sigmoid.

LD_{50}: It is called median lethal dose, which is defined as the dose which would be expected to kill 50% of the exposed population.

ED_{50}: It is called median effective dose, which is defined as the dose which would be expected to produce a desired therapeutic response among 50% of the exposed population.

Both the two estimates are used for the assessment of safety of a drug by determining the **therapeutic index** which is the ratio of LD_{50}/ED_{50}. Wider the ratio, safer will be the drug. Expression of safety of a drug by the therapeutic index will be valid when both the median dose curves are parallel. The **therapeutic ratio** is an index of safety which includes consideration of curve steepness and so preferable to therapeutic index. It may be obtained by dividing LD_{25} by the ED_{75}. The division of LD_1 by ED_{99} would give an even better index of safety, but the difficulty of determining such values with accuracy excludes this possibility.

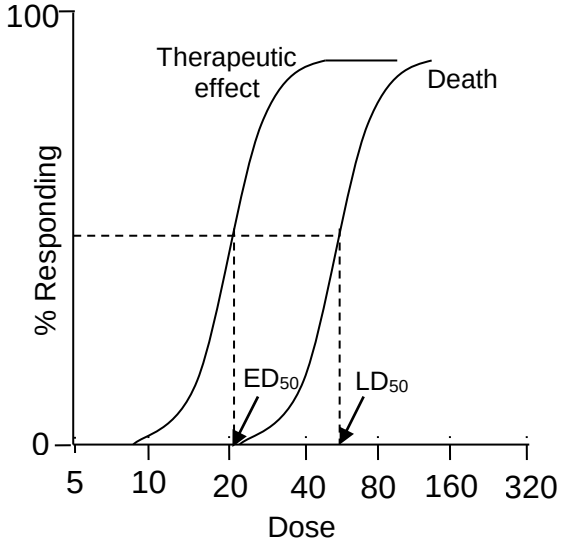


Figure : In this hypothetical and extreme case, the effective dose in only 50% of the population (ED_{50}) will cause death in the most sensitive individual in the population. The dose of the drug sufficient to be effective in almost all the individuals in the population (ED_{99}) is also the LD_{50} and therefore sufficient to kill half of the population. The margin of safety of this drug is unacceptable.

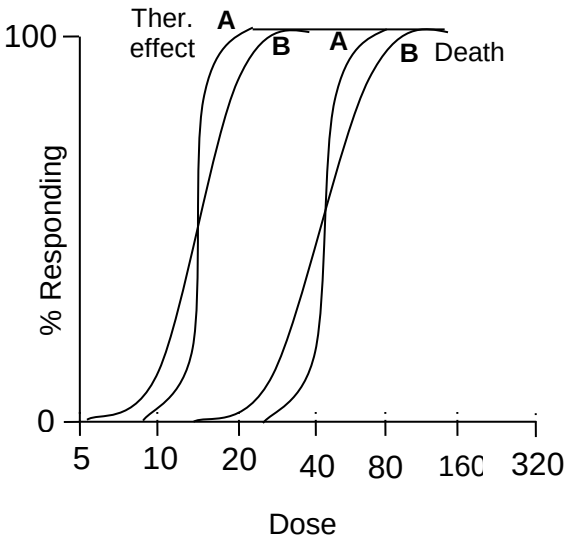


Figure : Shows the dose response curves for two drugs A & B, that have identical ED_{50} and Ld_{50} but different slopes to the dose response curves. Drug A with a steeper dose response curve can be used effectively on the whole without causing death, while drug B with the shallower curves, can not be used in this way. The dose of drug B that yields a therapeutic effect in the majority of the patient population will also be lethal to a significant no. of patients.

COMBINED EFFECT OF DRUGS:

When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit synergism or antagonism. The interaction may take place at pharmacokinetic level or at pharmacodynamic level.

I. SYNERGISM: (Greek words “Syn” = together, “ergon “= work)

When the action of one drug is facilitated or increased by the other, they are said to be synergistic. In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together. Synergism can be Additive or Supra-additive.

(1) **Additive:** The effect of two drugs are in the same direction and simply add up i.e.
Effect of drug A + B = Effect of drug A + Effect of drug B.
Examples are -
Aspirin + Paracetamol = As analgesic antipyretic
Nitrous oxide + Ether = As general anaesthetic.

(2) **Supra-additive (Potentiation):** The effect of the combination is greater than the individual effects of the components, i.e.
Effect of drug A + B > Effect of drug A + Effect of drug B.
Examples are -
Acetylcholine (ACh) + Physostigmine = Inhibition of ACh breakdown
Levadopa + Carbidopa = Inhibition of peripheral metabolism
Sulfonamide + Trimethoprim = Sequential blocking

II. ANTAGONISM:

When one drug decreases or inhibits the action of another, they are said to be antagonistic, i.e. Effect of drugs A + B < Effect of drug A + Effect of drug B.

Depending upon the mechanism involved, antagonism may be of following types –

1. **Physical antagonism:** Antagonism is based on physical property of drugs. i.e. charcoal adsorbs alkaloids and can prevent their absorption. This phenomenon is employed in alkaloidal poisonings.
2. **Chemical antagonism:** The two drugs react chemically and form an inactive product. Examples-
   $KMnO_4$ oxidizes alkaloids (used for gastric lavage of drugs)
   Chelating agents (like BAL, $CaNa_2EDTA$) complex with metals (like As, Pb etc.).
   Drugs may react when mixed in the same syringe or infusion bottle. Example – Thiopentone Na + Succinylcholine chloride.
3. **Physiological/ Functional antagonism:** Two drugs act on different receptors, or by different mechanisms, have opposite overt effects on the same physiological function i.e. have pharmacological effects in opposite direction.
   Examples –
   Histamine and adrenaline on bronchial muscles and blood pressure,
   Glucagon and Insulin on blood sugar level.
4. **Antagonism by Receptor Block:** The antagonist interferes with binding of the agonist with its receptor or inhibits the generation of response consequent to such binding. It may be competitive or non-competitive.

   (a) Competitive antagonism:

   1. *Reversible, competitive antagonism:* Agonist and antagonist compete with each other, because the receptor can bind only one drug molecule at a time. At a given agonist concentration, the agonist occupancy will be reduced in the presence of the antagonist. However, because the two are in competition, raising the agonist concentration can restore the agonist occupancy (and hence the tissue response).

      Reversible competitive antagonism is the commonest and most important type of antagonism.

      Examples – ACh + Atropine, Morphine + Naloxone.
   2. *Irreversible, non-equilibrium, competitive antagonism:* It occurs when the antagonist dissociates very slowly, or not at all, from the receptors, with the result that no change in the antagonist occupancy takes place when the agonist is applied. This kind of antagonism occurs with drugs which possess reactive groups that form covalent bonds with the receptor.

      Examples – Irreversible enzyme inhibitors that act similarly like aspirin, omeprazole, monoamine oxidase inhibitors etc.

   (b) Non-competitive antagonism: This kind of antagonism describes the situation where the antagonist blocks at some point the chain of events that leads to the production of a response by the agonist.

   Example – Drugs such as verapamil and nifedipine prevent the influx of Ca^{2+} through the cell membrane and thus block non-specifically the contraction of smooth muscle produced by other drugs.

FACTORS MODIFYING DRUG ACTION:

A variety of factors either singly or in combination influence the magnitude of response observed following the administration of a drug. They are discussed as follow.

(1) Species variation: The response of a drug is not uniform among different species. Example –

- ✓ Morphine produces CNS depression in man and dog but excitation in cat.
- ✓ Rabbits can thrive on Belladona leaves which are too toxic to other species.

(2) Individual variation: A drug at equal doses in similar animals will not produce identical magnitude of the response. This is due to normal biological variation between the individuals in a population, as determined by genetic factors. This is known as **Idiosyncracy**. There may be some specific genetic defects which lead to discontinuous variation in drug responses.

(3) Age of the animal: Very young (new born) and very old animals are more sensitive to the drug effects than the normal adults. In the former, the organs of biotransformation (liver) and excretion (kidneys) are not functionally developed to full capacity. These mechanisms are defective in very old animals. The renal clearance of drugs in these animals is also poor (low GFR i.e. glomerular filtration rate). Young and old animals need relatively low doses of a drug as compared to the adults.

(4) Sex of the animal: Generally female animals are more sensitive to the effects of drugs than the males. This is also true for effects of toxic substances. The relative resistance of males is due to presence of high concentrations of testosterone.

- ✓ Gynaecomastia is a side effect (of ketoconazole, metoclopramide, chlorpromazine, digitalis etc.) that can occur only in men.
- ✓ Ketoconazole causes loss of libido in men, not in women.

(5) Body weight of the animal: It indicates the extent of tissues that are exposed to the action of drugs. Therefore, the dose of a drug is based on the body weight of the animal. While computing dose rates of drugs in ruminants, the weight of rumen contents should be taken in consideration. The other conditions such as pregnancy (weight of foetus), oedema (fluid) and fat deposits (obese pigs) also need to be considered.

(6) Route of administration: Route of administration governs the speed and intensity of drug response. The onset of action following administration of drugs by different routes is in the order – **I.V. > I.M. > I.P. >S.C. > I.D. > oral**. A drug may have entirely different uses through different routes. For instance, $MgSO_4$ given orally causes purgation, applied on inflamed areas decreases swelling, while intravenously it may produce CNS depression and hypotension.

(7) Time of administration: Subjective effect of a drug may be markedly affected by the setup in which it is taken. Hypnotics taken at night and in quiet, familiar surroundings may work more easily. It has been shown that corticosteroids taken as a single morning dose cause less pituitary-adrenal suppression.

(8) Psychological factor: Efficacy of a drug can be affected by patients belief's, attitudes and expectations.

"Placebo" – A Latin word meaning "I shall please".

Placebo is an inert substance which is given in the garb of a medicine. It works by psychological rather than by pharmacological means and often produces responses equivalent to the active drug. A patient responds to the whole therapeutic setting; placebo effect largely depends on the physician – patient relationship.

(9) Drug Interactions: Drugs may modify the response of each other by pharmacokinetic or pharmacodynamic interaction between them.

Pharmacokinetic interactions: It refers to interactions between the drugs during absorption, distribution, metabolism and excretion processes, resulting in either increase or decrease in the concentration of the drug at the site of action.

Absorption: Examples:

1. Tetracyclines are not absorbed when given orally with metallic antacids (due to formation of insoluble chelates).
2. Adrenaline along with local anaesthetics prolongs the duration of local anaesthesia by causing capillary constriction (delays absorption).

Distribution: Examples:

Phenylbutazone, frusemide, digoxin, propranolol, diazepam and quinidine are extensively bound to plasma proteins. If their displacement from protein binding occurs they show intense effects.

Metabolism: Examples:

Barbiturates stimulate the metabolism of oral anticoagulant coumarin; and that of DDT and griseofulvin.

Excretion: Examples:

Probenecid inhibits renal excretion of penicillin G.

Pharmacodynamic interactions: These interactions occur due to the action of drugs at a common receptor site or at different sites, resulting in increase or decrease in response of a drug. For example, α-adrenergic receptor antagonism by phenoxybenzamine.

(10) General state of health of animal: Generally weak and debilitated animals are more sensitive to drug effects than the normal healthy animals. The reason being low hepatic glycogen stores in the former, contributing to reduced metabolic capacity of the organ. Drugs having high fat affinity may cause toxic effects in lean animals. Similarly, fatty and obese animals (pigs) require more doses of a fat soluble drug than that is required for a lean animal in producing identical therapeutic effect. Hepatic and renal diseases increase the intensity and prolong the effects of drugs.

(11) Drug tolerance: It means requirement of higher dose of a drug to produce a given response. Tolerance is widely occurring adaptive biological phenomenon. Drug tolerance may be natural or acquired.

Natural drug tolerance: The individual/ species is inherently less sensitive to the drug.

Examples:

- ✓ Rabbits are tolerant to atropine (due to the presence of atropinase enzyme).
- ✓ Chicks are tolerant to strychnine (due to underdevelopment of spinal cord in chicken).

Acquired drug tolerance: It occurs by repeated use of a drug in an individual who was initially responsive. Body is capable of developing tolerance to most drugs, but the phenomenon is very recognized in the case of CNS depressants (e.g. morphine, barbiturate, tranquilizers etc.).

Tolerance need not develop equally to all actions of a drug.

Examples are –

- ✓ Tolerance develops to sedative action of chlorpromazine but not to its antipsychotic action.
- ✓ Tolerance occurs to the sedative action of phenobarbitone but not to its antiepileptic action.

Cross tolerance: It is the development of tolerance to pharmacologically related drugs. Closer the two drugs are, the more complete is the cross tolerance between them. For example, there is partial cross tolerance between morphine and barbiturates but complete cross tolerance between morphine and pethidine.

Tachyphylaxis: (tachy = fast, phylaxis = protection) When certain drugs are administered at the same dose at frequent short intervals, the response will decrease progressively. This is called as tachyphylaxis. However, the response returns to normal magnitude if sufficient gap is given in between two consecutive doses. This kind of tolerance is usually seen with **indirectly acting drugs**, e.g. ephedrine, tyramine, nicotine etc which act by liberating catecholamines in the body, synthesis of which is unable to match release because stores get depleted.

Drug Resistance: It refers to tolerance of micro-organisms to inhibitory action of antimicrobials. e.g. Staphylococci to penicillin etc.

Mechanism of drug tolerance: It may be –

1. Pharmacokinetic/ Drug disposition tolerance: Effective concentration of the drug at the active site is decreased, mostly by enhancement of drug elimination on chronic use. For example, barbiturates etc.
2. Pharmacodynamic/ Cellular tolerance: Drug action is lessened, cells of the target organ become less responsive, e.g. morphine, barbiturates, nitrates etc. This may be due to down regulation of receptors (destruction of receptors), weakening of response effectuation or other compensatory homeostatic mechanisms (e.g. antihypertensives).