Semester VI

17BCU603A **DRUG BIOCHEMISTRY** **4H-4C**

SCOPE

The goal of the paper will ensure the widespread visibility and high impact of Drugs, thereby promoting on emerging research, pointing the way for the establishment of new medicines – from the identification of targets, through to the synthesis and evaluation of putative therapeutic entities.

OBJECTIVES

This paper gives an insight knowledge about the emerging themes, and provides an in depth analysis of specific drug classes, its metabolism and therapeutic approaches.

Unit 1

Introduction to drug Biochemistry: Classification, routes of administration – factors influencing dosage and drug action, Absorption and distribution of drugs, binding of drugs to plasma proteins, Drug Dose relationship (LD_{50}, ED_{50}, therapeutic index), Drug – Receptor interaction, Drug binding forces, Receptor theories, Drug – Receptor interaction. Bioavailability; Pharmaco kinetics.

Unit 2

Drug metabolism: Drug Biotransformation pathways - phase I – oxidation, reduction and hydroxylation. Phase II- Conjugation, Elimination of drugs from body system. Storage of drugs in adipose tissue.

Unit 3

Drug abuse; drug dependence; drug resistance- Biological mechanism, ways to overcome.

Chemotherapy: Antibacterials – Mode of action of sulfonamides, penicillin, streptomycin, tetracycline, chloramphenicol, antiviral drugs, antifungal drugs; Antimetabolites of folate, purines & pyrimidines, Anti tubercular drugs.

Unit 4

Mechanism of action drugs used in the treatment of diabetes mellitus (Acarbose, Biguanides), AIDS (Azidophymidine, Didanosine), cancer(Mechlorethamine, Busulfan), heart (Amrinone, Digoxin) and kidney disorder (Benzophiadiazines, furosemide); antiepileptic drug(Lamictal, Tapclob), drugs for cough (Dextromethorphane Hydrobromide, Noscapine) and bronchial asthma (Salbutamol,Aminophylline), diuretics (Manitol, Xanthine), anti ulcer drugs (Cimetidine, Ranitidine) and drugs for fever (Paracetamol, Ibuprofen).

Unit 5

Toxicology- Introduction, definition and disciplines of toxicology, classification of toxicity and toxicants, Mechanisms of toxic effect, treatment of intoxication, methods in toxicology testing, heavy metal toxicity and chelation therpy. Environmental pollution, mycotoxins, mushroom poisons

TEXTBOOKS

Satoskar, R.S., Bhandarkar, S.P., and Ainapuri, S.S., (2003). Pharmacology and Pharmacotherapeutic, 18th edition,Popular Prakashan, Mumbai.

REFERENCE BOOKS

Hamilton, D., Philips, R.J., and Scott, D., (2004). Occupational, Industrial and Environmental Toxicology, Moshy Inc Publishers.

Berg, G., Hendrickson, R.G., and Morocco, A., (2005). Medical Toxicology Review. McGraw Hill Mical Publishing Company**.**

Foye, W., (2012). Principles of Medicinal Chemistry, 7th edition, B.I. Wanerly Pvt. Ltd, New Delhi.

Grahame-Smith, D.G., and Aronson, J.K., (2002). Oxford textbook of Clinical Pharmacology and Drug Therapy: 3rd edition. Oxford University Press.

Tripathy, K.D., (2009). Essentials of Medical Pharmacology, Jaypee brothers medical publishers, New Delhi.

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LESSON PLAN

DRUG BIOCHEMISTRY

UNIT I

S.No	Lecture Duration	Topics	Support Materials
1.	1	Classification, routes of administration of drugs	R5: 5-7 R5: 5-9
2.	1	Factors influencing dosage and drug action	R5: 62-70
3.	1	Absorption and distribution of drugs	R5: 10-20
4.	1	Binding of drugs to plasma proteins	R5: 19-21
5.	1	Drug Dose relationship (LD_{50}, ED_{50}, therapeutic index	R5: 898
6.	1	Drug – Receptor interaction	R5: 49-52
7.	1	Drug binding forces	R5: 19-21
8.	1	Receptor theories	T1: 29-31
9.	1	Drug – Receptor interaction	T1: 29-31
10.	1	Bioavailability	R5: 16-17
11.	1	Pharmaco kinetics.	R3: 84-87

UNIT II

S.No	Lecture Duration	Topics to be covered	Support Materials
1.	1	Drug Biotransformation pathways	R5: 22-26
2.	1	Phase I- Oxidation	R5: 55
3.	1	Phase 1- Reduction	T1: 16-17
4.	1	Phase 1- Hydroxylation	T1: 16-17
5.	1	Phase 2- Conjugation	T1: 17-18
6.	1	Elimination of drugs from body system	R5: 30-31
7.	1	Storage of drugs in adipose tissue.	R5: 30-31

UNIT III-

S.No	Lecture Duration	Topics to be covered	Support Materials
1.	1	Drug abuse	R5: 88
2.	1	Drug dependence	R5: 87-88
3.	1	Drug resistance- Biological mechanism	R5: 691-693
4.	1	Antibacterials – Mode of action of sulfonamides	R5: 704-706
5.	1	Antibacterials – Mode of action of penicillin and streptomycin	R5: 716-720 R5: 748-749
6.	1	Antibacterials – Mode of action of tetracycline and chloramphenicol	R5: 733-742
7.	1	Antiviral drugs, antifungal drugs	R5: 787-805
8.	1	Antimetabolites of folate, purines & pyrimidines	R5: 862-865
9.	1	Anti tubercular drugs.	T1: 735-741

UNIT IV

S.No	Lecture Duration	Topics to be covered	Support Materials
1.	1	Mechanism of action drugs used in the treatment of diabetes mellitus (Acarbose, Biguanides)	R5: 275-277
2.	1	Mechanism of action drugs used in the treatment of cancer(Mechlorethamine, Busulfan)	R5: 860-861; 873
3.	1	Mechanism of action drugs used in the treatment of heart (Amrinone, Digoxin)	R5: 524-527, R5: 515-523
4.	1	Mechanism of action drugs used in the treatment of kidney disorder (Benzophiadiazines, furosemide)	R5: 578-583
5.	1	Mechanism of action drugs used in the treatment of AIDS (Azidophymidine, Didanosine)	R5: 807-809
6.	1	Mechanism of action drugs used in the treatment of antiepileptic drug(Lamictal, Tapclob)	R5: 411-413
7.	1	Mechanism of action drugs used in the treatment of drugs for cough (Dextromethorphane Hydrobromide, Noscapine) and bronchial asthma (Salbutamol,Aminophylline)	R5: 218- 224
8.	1	Mechanism of action drugs used in the treatment of diuretics (Manitol, Xanthine), anti ulcer drugs (Cimetidine, Ranitidine)	R5: 579-586 R5: 647-658
9.	1	Mechanism of action drugs used in the treatment of drugs for fever (Paracetamol, Ibuprofen).	R5: 206-207, 199-200

UNIT V

S.No	Lecture Duration	Topics to be covered	Support Materials
1.	1	Introduction, definition and disciplines of toxicology	R5: 2-5
2.	1	Classification of toxicity and toxicants	R3: 707-709
3.	1	Mechanisms of toxic effect	R3: 707-709
4.	1	Treatment of intoxication	R3:723
5.	1	Methods in toxicology testing	R3: 708-709
6.	1	Heavy metal toxicity	R5: 907
7.	1	Chelation therapy	R5: 907
8.	1	Environmental pollution	R1: 588
9.	1	Mycotoxins, mushroom poisons	R3: 142

TEXTBOOKS

T1: Satoskar, R.S., Bhandarkar, S.P., and Ainapuri, S.S., (2003). Pharmacology and Pharmacotherapeutics, 18th edition,Popular Prakashan, Mumbai.

REFERENCE BOOKS

R1: Hamilton, D., Philips, R.J., and Scott, D., (2004). Occupational, Industrial and Environmental Toxicology, Moshy Inc Publishers.

R2: Berg, G., Hendrickson, R.G., and Morocco, A., (2005). Medical Toxicology Review. McGraw Hill Mical Publishing Company**.**

R3: Foye, W., (2012). Principles of Medicinal Chemistry, 7th edition, B.I. Wanerly Pvt. Ltd, New Delhi.

R4: Grahame -Smith, D.G., and Aronson, J.K., (2002). Oxford textbook of Clinical Pharmacology and Drug Therapy: 3rd edition. Oxford University Press.

R5: Tripathy, K.D., (2009). Essentials of Medical Pharmacology, Jaypee brothers medical publishers, New Delhi.

UNIT-I-SYLLABUS

Introduction to drug Biochemistry:

Classification, routes of administration – factors influencing dosage and drug action, Absorption and distribution of drugs, binding of drugs to plasma proteins, Drug Dose relationship (LD50, ED50, therapeutic index), Drug – Receptor interaction, Drug binding forces, Receptor theories, Drug – Receptor interaction. Bioavailability; Pharmaco kinetics.

Drug:

A medicine or other substance which has a physiological effect when ingested or otherwise introduced into the body.

Classification of drugs:

A drug classification system represents a common language for describing the drug assortment in a country or region and is a prerequisite for national and international comparisons of drug utilization data, which have to be collected and aggregated in a uniform way.

Drugs can be classified in different ways according to:

* their mode of action.
* their indications.
* their chemical structure.

Drugs are classified chemically according to how they affect the brain and the body. Common classifications include stimulants, depressants, hallucinogens, and opioids. Additionally, the DEA legally classifies drugs into schedules (I, II, III, IV, and V) based on their medical use and potential for abuse and dependence.

Depressants. Drugs that suppress or slow the activity of the brain and nerves, acting directly on the central nervous system to create a calming or sedating effect. This category includes barbiturates (phenobarbital, thiopental, butalbital), benzodiazepines (alprazolam, diazepam, clonazepam, lorazepam, midazolam), alcohol, and gamma hydroxybutyrate (GHB). Depressants are taken to relieve anxiety, promote sleep and manage seizure activity.

Stimulants. Drugs that accelerate the activity of the central nervous system. Stimulants can make you feel energetic, focused, and alert. This class of drugs can also make you feel edgy, angry, or paranoid. Stimulants include drugs such as cocaine, crack cocaine, amphetamine, and methamphetamine. According to the recent World Drug Report published by the United Nations Office on Drugs and Crime, amphetamine-derived stimulants like ecstasy and methamphetamine are the most commonly abused drugs around the world after marijuana.

Hallucinogens. Also known as psychedelics, these drugs act on the central nervous system to alter your perception of reality, time, and space. Hallucinogens may cause you to hear or see things that don't exist or imagine situations that aren't real. Hallucinogenic drugs include psilocybin (found in magic mushrooms), lysergic acid diethylamide (LSD), peyote, and dimethyltryptamine (DMT).

Opioids. These are the drugs that act through the opioid receptors. Opioids are one of the most commonly prescribed medicines worldwide and are commonly used to treat pain and cough. These include drugs such as heroin, codeine, morphine, fentanyl, hydrocodone, oxycodone, buprenorphine, and methadone.

Inhalants. These are a broad class of drugs with the shared trait of being primarily consumed through inhalation. Most of the substances in this class can exist in vapor form at room temperature. As many of these substances can be found as household items, inhalants are frequently abused by children and adolescents. These include substances such as paint, glue, paint thinners, gasoline, marker or pen ink, and others. Though ultimately all of these substances cross through the lungs into the bloodstream, their precise method of abuse may vary but can include sniffing, spraying, huffing, bagging, and inhaling, among other delivery routes.

Cannabis. Cannabis is a plant-derived drug that is the most commonly used illicit drug worldwide. It acts through the cannabinoid receptors in the brain. Cannabis is abused in various forms including bhang, ganja, charas, and hashish oil.

New psychoactive substances (NPS). These are drugs designed to evade the existing drug laws. Drugs such as synthetic cannabinoids, synthetic cathinones, ketamine, piperazines, and some plant-based drugs such as khat and kratom are examples of NPS.

Each classification system will have its advantages and limitations and its usefulness will depend on the purpose, the setting used and the user's knowledge of the methodology.

ROUTES OF DRUG ADMINISTRATION:

- Most drugs can be administered by a variety of routes. The choice of appropriate route in a given situation depends both on drug as well as patient related factors. Mostly common sense considerations, feasibility and convenience dictate the route to be used.
- Routes can be broadly divided into two types
  - (*a*) Local action
  - (*b*) Systemic action.

LOCAL ROUTES:

- These routes can only be used for localized lesions at accessible sites and for drugs whose systemic absorption from these sites are minimal or absent.
- Thus, high concentrations are attained at the desired site without exposing the rest of the body. Systemic side effects or toxicity are consequently absent or minimal. The local routes are:

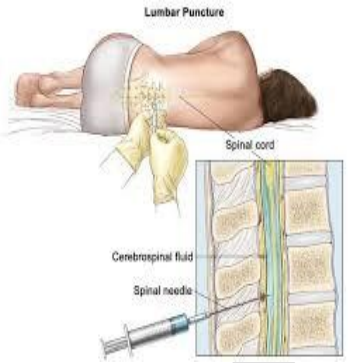
1. Topical

- This refers to external application of the drug to the surface for localized action. It is often more convenient as well as encouraging to the patient.
- Drugs can be efficiently delivered to the localized lesions on skin, oropharyngeal/ nasal mucosa, eyes, ear canal, anal canal or vagina in the form of lotion, ointment, cream, powder, rinse, paints, drops, spray, lozengens, suppositories or pesseries.
- Non absorbable drugs given orally for action on g.i. mucosa (sucralfate, vancomycin), inhalation of drugs for action on bronchi (salbutamol, cromolyn sodium) and irrigating solutions/jellys (povidone iodine, lidocaine) applied to urethra are other forms of topical medication.



2. Deeper tissues

- Certain deep areas can be approached by using a syringe and needle, but the drug should be in such a form that systemic absorption is slow.
- For example, intra-articular injection (hydrocortisone acetate in knee joint), infiltration around a nerve or intrathecal injection (lidocaine), retrobulbar injection (hydrocortisone acetate behind the eyeball).



Intra-articular injection Intrathecal injection Retrobulbar injection

1. Arterial supply

- Close intra-arterial injection is used for contrast media in angiography; anticancer drugs can be infused in femoral or brachial artery to localise the effect for limb malignancies.

SYSTEMIC ROUTES:

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

1. Oral

- Oral ingestion is the oldest and commonest mode of drug administration. It is safer, more convenient, does not need assistance, noninvasive, often painless, the medicament need not be sterile.
- Both solid dosage forms (powders, tablets, capsules, spansules, dragees, moulded tablets, gastrointestinal therapeutic systems— GITs) and liquid dosage forms (elixirs, syrups, emulsions, mixtures) can be given orally.

2. Sublingual (s.l.) or buccal

- The tablet or pellet containing the drug is placed under the tongue or crushed in the mouth and spread over the buccal mucosa.
- Only lipid soluble and non-irritating drugs can be so administered. Absorption is relatively rapid—action can be produced in minutes.
- Though it is somewhat inconvenient, one can spit the drug after the desired assed and drugs with high first pass metabolism can be absorbed directly into systemic circulation. Drugs given sublingually are—GTN, buprenorphine, desamino-oxytocin.

3. Rectal

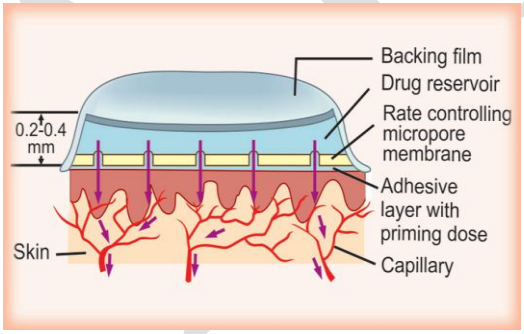
- Certain irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect.
- This route can also be used when the patient is having recurrent vomiting or is unconscious.
- However, it is rather inconvenient and embarrassing; absorption is slower, irregular and often unpredictable, though diazepam solution and paracetamol suppository are rapidly and dependably absorbed from the rectum in children.
- Drug absorbed into external haemorrhoidal veins (about 50%) bypasses liver, but not that absorbed into internal haemorrhoidal veins.
- Rectal inflammation can result from irritant drugs. Diazepam, indomethacin, paracetamol, ergotamine and few other drugs are some times given rectally.

2. Cutaneous

- Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. The liver is also bypassed.
- The drug can be incorporated in an ointment and applied over specified area of skin.
- Absorption of the drug can be enhanced by rubbing the preparation, by using an oily base and by an occlusive dressing.

Transdermal therapeutic systems (TTS)

- These are devices in the form of adhesive patches of various shapes and sizes (5–20 cm2) which deliver the contained drug at a constant rate into systemic circulation via the stratum corneum .
- The drug (in solution or bound to a polymer) is held in a reservoir between an occlusive backing film and a rate controlling micropore membrane, the under surface of which is smeared with an adhesive impregnated with priming dose of the drug.
- The adhesive layer is protected by another film that is to be peeled off just before application.
- The drug is delivered at the skin surface by diffusion for percutaneous absorption into circulation. Transdermal patches of GTN, fentanyl, nicotine and estradiol are available in india.



5. Inhalation

- Volatile liquids and gases are given by inhalation for systemic action, e.g. general anaesthetics. 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 with moment to moment adjustment. Irritant vapours (ether) cause inflammation of respiratory tract and increase secretion.

6. Nasal

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

7. Parenteral

- Conventionally, parenteral refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the enteral mucosa.
- Drug action is faster and surer. Gastric irritation and vomiting are not provoked. Parenteral routes can be employed even in unconscious, uncooperative or vomiting patient.

- There are no chances of interference by food or digestive juices. Liver is bypassed. The important parenteral routes are:

i. Subcutaneous (s.c.)

ii. Intramuscular (i.m.)

iii. Intravenous (i.v.)

iv. Intradermal injection

1. Subcutaneous (s.c.)

- The drug is deposited in the loose subcutaneous tissue which is richly supplied by nerves (irritant drugs cannot be injected) but is less vascular (absorption is slower than intramuscular).
- Only small volumes can be injected s.c. Self-injection is possible because deep penetration is not needed. This route should be avoided in shock patients who are vasoconstricted— absorption will be delayed.
- Some special forms of this route are:

(a) *Dermojet*

– In this method needle is not used; a high velocity jet of drug solution is projected from a microfine orifice using a gun like implement.

– The solution passes through the superficial layers and gets deposited in the subcutaneous tissue.

(b) *Pellet implantation*

– The drug in the form of a solid pellet is introduced with a trochar and cannula.

– This provides sustained release of the drug over weeks and months, e.g. DOCA, testosterone.

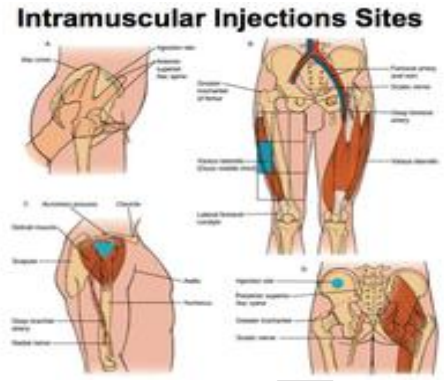
(ii) Intramuscular (i.m.)

– The drug is injected in one of the large skeletal muscles—deltoid, triceps, gluteus maximus, rectus femoris, etc.

– Muscle is less richly supplied with sensory nerves (mild irritants can be injected) and is more vascular (absorption of drugs in aqueous solution is faster).

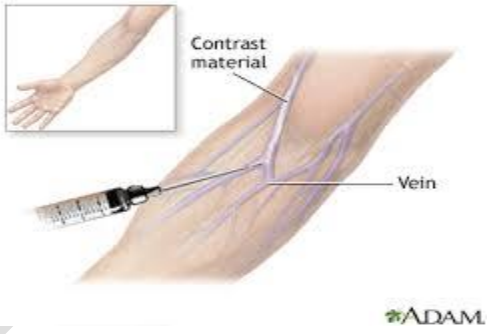
– It is less painful, but self injection is often impracticable because deep penetration is needed. Depot preparations (oily solutions, aqueous suspensions) can be injected by this route.

- Intramuscular injections should be avoided in anticoagulant treated patients, because it can produce local haematoma.



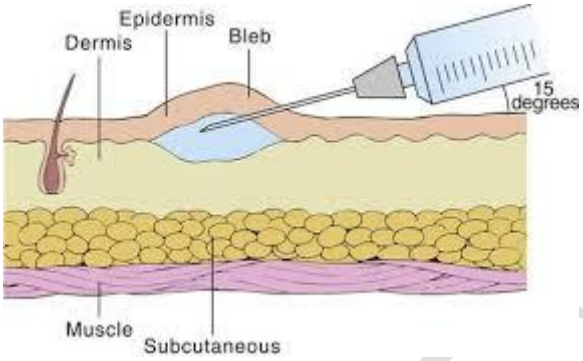
(iii) Intravenous (i.v.)

- The drug is injected into the veins and drug reaches directly into the blood stream and effects are produced immediately (great value in emergency).
- The intima of veins is insensitive and drug gets diluted with blood, therefore, even highly irritant drugs can be injected i.v.,
- Chances of causing air embolism is another risk. The dose of the drug required is smallest (bioavailability is 100%) and even large volumes can be infused.



(iv) Intradermal injection

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



ABSORPTION OF DRUGS

Absorption of Drugs:

- Absorption is the transfer of a drug from the site of administration to the bloodstream. The rate and extent of absorption depend on the environment where the drug is absorbed, chemical characteristics of the drug, and the route of administration (which influences bioavailability).
- Routes of administration other than intravenous may result in partial absorption and lower bioavailability.

Mechanisms of absorption of drugs from the GI tract:

❖ Depending on their chemical properties, drugs may be absorbed from the GI tract by several ways. Like

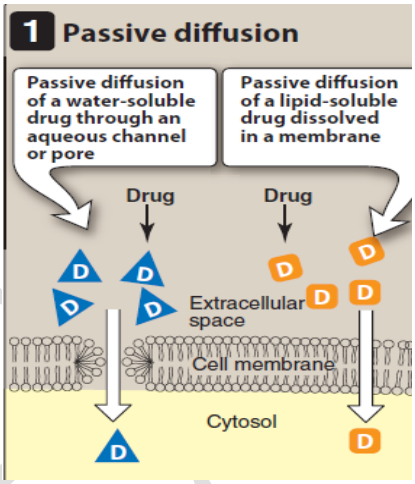
- passive diffusion,
- facilitated diffusion
- active transport
- endocytosis

Passive diffusion:

- The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments; that is, the drug moves

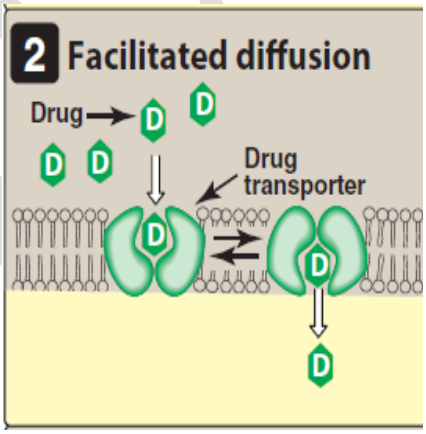
from a region of high concentration to one of lower concentration.

- Lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane bilayers. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores.



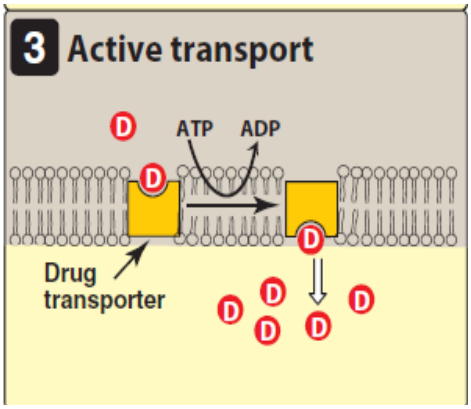
Facilitated diffusion:

- Molecules enter the cell through specialized trans membrane carrier proteins that facilitate the passage of large molecules.
- These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration.
- This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier.



Active transport:

- This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins.
- Active transport is energy-dependent and is driven by the hydrolysis of adenosine triphosphate . It is capable of moving drugs against a concentration gradient that is, from a region of low drug concentration to one of higher drug concentration.



Endocytosis and exocytosis:

- This type of absorption is used to transport drugs of exceptionally large size across the cell membrane. Endocytosis involves engulfment of a drug by the cell membrane and transport into the cell by pinching off the drug filled vesicle.
- Exocytosis is the reverse of endocytosis. Many cells use exocytosis to secrete substances out of the cell through a similar process of vesicle formation.

B. Factors influencing absorption

1. Effect of pH on drug absorption:

- Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H+), causing a charged anion (A−) to form:

$$HA \rightleftharpoons H^+ + A^-$$

- Weak bases (BH+) can also release an H+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B):

$$BH^+ \rightleftharpoons B + H^+$$

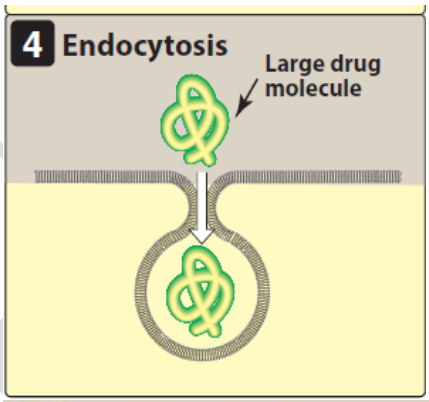
- A drug passes through membranes more readily if it is uncharged. Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and A− cannot.
- For a weak base, the uncharged form B penetrates through the cell membrane, but the protonated form BH+ does not.
- Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms.

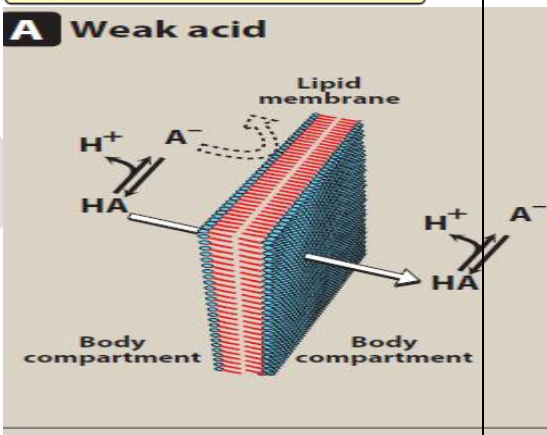
2. Blood flow to the absorption site:

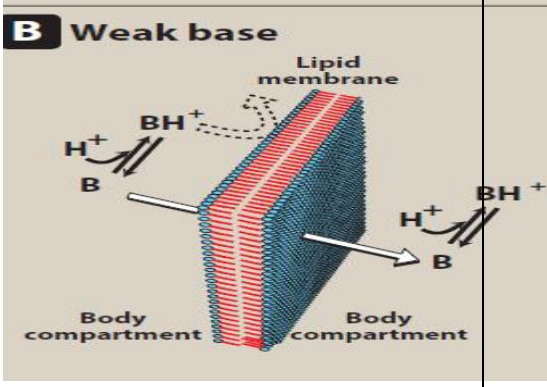
The intestines receive much more blood flow than the stomach, so absorption from the intestine is favored over the stomach.

3. Total surface area available for absorption:

With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient.





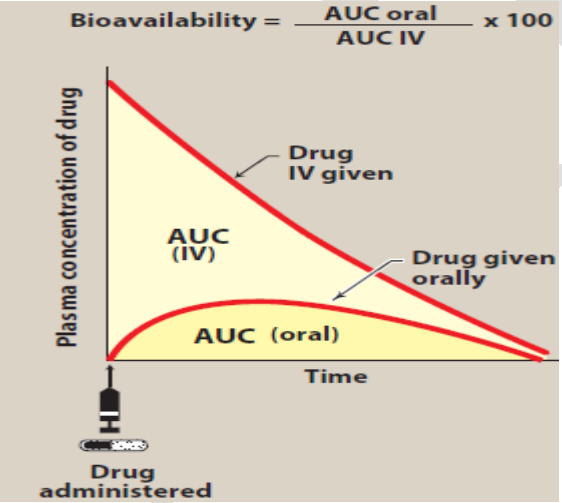


C. Bioavailability

- Bioavailability is the rate and extent to which an administered drug reaches the systemic circulation. For example, if 100 mg of a drug is administered orally and 70 mg is absorbed unchanged, the bioavailability is 0.7 or 70%.
- Determining bioavailability is important for calculating drug dosages for non intravenous routes of administration.

1. Determination of bioavailability:

Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with levels achieved by IV administration.



Factors that influence bioavailability:

1.First-pass hepatic metabolism:

- When a drug is absorbed from the GI tract, it enters the portal circulation before entering the systemic circulation .
- If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug entering the systemic circulation is decreased.

2. Solubility of the drug:

- Very hydrophilic drugs are poorly absorbed because of their inability to cross lipid-rich cell membranes.
- Paradoxically, drugs that are extremely lipophilic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells.

3. **Chemical instability:**
   - Some drugs, such as *penicillin G,* are unstable in the pH of the gastric contents. Others, such as *insulin,* are destroyed in the GI tract by degradative enzymes.

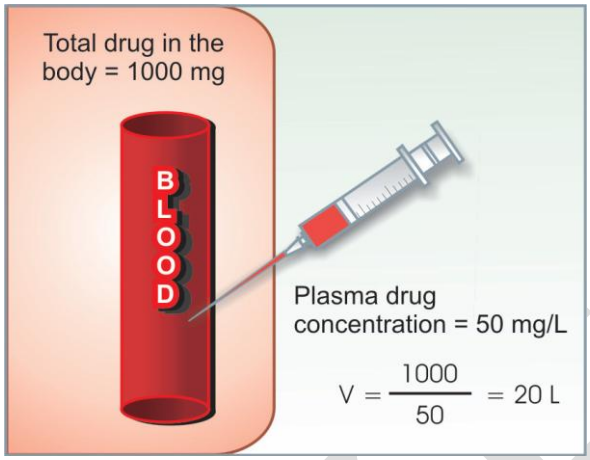
4. **Nature of the drug formulation:**
   - Drug absorption may be altered by factors unrelated to the chemistry of the drug.
   - For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients can influence the ease of dissolution and, therefore, alter the rate of absorption.

DISTRIBUTION OF DRUGS

- Once a drug has gained access to the blood stream, it gets distributed to other tissues that initially had no drug, concentration gradient being in the direction of plasma to tissues. The extent and pattern of distribution of a drug depends on its:
  - lipid solubility
  - ionization at physiological pH (a function of its pKa)
  - extent of binding to plasma and tissue proteins
  - presence of tissue-specific transporters
  - differences in regional blood flow.
- Movement of drug proceeds until an equilibrium is established between unbound drug in the plasma and the tissue fluids. Subsequently, there is a parallel decline in both due to elimination.

Apparent volume of distribution (V) Presuming that the body behaves as a single homogeneous compartment with volume *V* into which the drug gets immediately and uniformly distributed.

$$V = \frac{\text{dose administered i.v.}}{\text{plasma concentration}}$$



- The drug does not actually distribute into 20 L of body water, with the exclusion of the rest of it, this is only an apparent volume of distribution which can be defined as "the volume that would accommodate all the drug in the body, if the concentration throughout was the same as in plasma".
- Thus, it describes the amount of drug present in the body as a multiple of that contained in a unit volume of plasma. Considered together with drug clearance, this is a very useful pharmacokinetic concept.
- Lipid-insoluble drugs do not enter cells— *V* approximates extracellular fluid volume, e.g. streptomycin, gentamicin 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 the vascular compartment and have low values, e.g. diclofenac and warfarin (99% bound) *V* = 0.15 L/kg.
- Pathological states, e.g. congestive heart failure, uraemia, cirrhosis of liver, etc. can alter the *V* of many drugs by altering distribution of body water, permeability of membranes, binding proteins or by accumulation of metabolites that displace the drug from binding sites.

- More precise multiple compartment models for drug distribution have been worked out, but the single compartment model, described above, is simple and fairly accurate for many drugs.

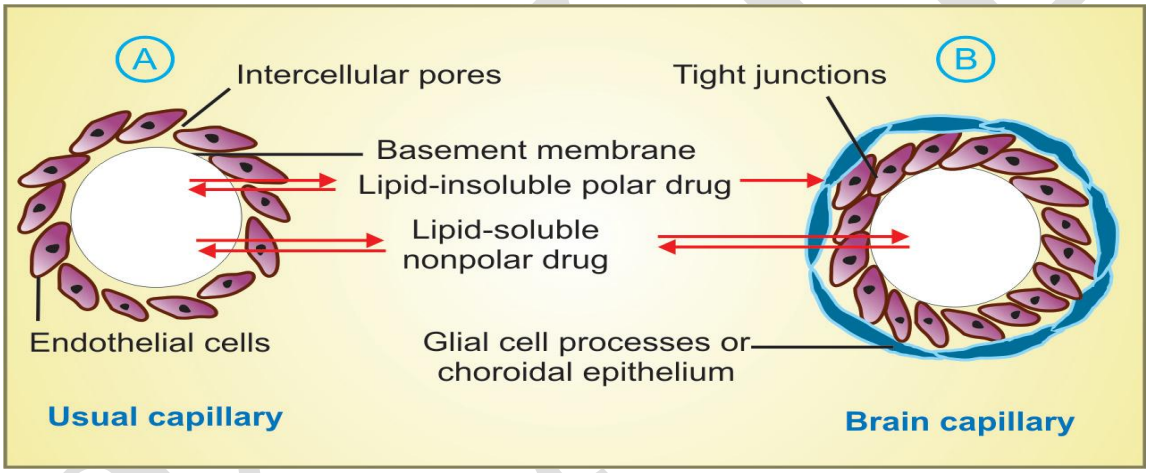
Redistribution:

- Highly lipid-soluble drugs get initially distributed to organs with high blood flow, i.e. 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 the highly perfused sites.

- If the site of action of the drug was in one of the highly perfused organs, redistribution results in termination of drug action. Greater the lipid solubility of the drug, faster is its redistribution.

Penetration into brain and CSF:

- The capillary endothelial cells in brain have tight junctions and lack large paracellular spaces. Further, an investment of neural tissue covers the capillaries. Together they constitute the so called *blood-brain barrier (BBB).*
- A similar *blood-CSF barrier* is located in the choroid plexus: capillaries are lined by choroidal barriers are lipoidal and limit the entry of nonlipidsoluble drugs, e.g. streptomycin, neostigmine, etc.
- Only lipid-soluble drugs, therefore, are able to penetrate and have action on the central nervous system.



Passage across placenta:

- Placental membranes are lipoidal and allow free passage of lipophilic drugs, while restricting hydrophilic drugs.
- The placental efflux P-gp and other transporters like BCRP, MRP3 also serve to limit foetal exposure to maternally administered drugs.
- Placenta is a site for drug metabolism as well, which may lower/modify exposure of the foetus to the administered drug. However, restricted amounts of nonlipid-soluble drugs, when present in high concentration or for long periods in maternal circulation, gain access to the foetus.

Binding of drugs to plasma proteins and tissues

1. **Binding to plasma proteins:**

- Reversible binding to plasma proteins sequesters drugs in a non diffusible form and slows their transfer out of the vascular compartment.
- Albumin is the major drug-binding protein and may act as a drug reservoir (as the concentration of free drug decreases due to elimination, the bound drug dissociates from the protein). This maintains the free drug concentration as a constant fraction of the total drug in the plasma.

2. Binding to tissue proteins:

- Many drugs accumulate in tissues, leading to higher concentrations in tissues than in the extracellular fluid and blood.
- Drugs may accumulate as a result of bindingto lipids, proteins, or nucleic acids. Drugs may also be actively transported into tissues.
- Tissue reservoirs may serve as a major source of the drug and prolong its actions or cause local drug toxicity.

Binding of drugs to plasma proteins

- Most drugs possess physicochemical affinity for plasma proteins and get reversibly bound to these. Acidic drugs generally bind to plasma albumin and basic drugs to α1 acid glycoprotein. Binding to albumin is quantitatively more important.
- Extent of binding depends on the individual compound; no generalization for a pharmacological or chemical class can be made (even small chemical change can markedly alter protein binding), for example the binding percentage of some benzodiazepines is:

Flurazepam 10% Alprazolam 70%
Lorazepam 90% Diazepam 99%

- Increasing concentrations of the drug can progressively saturate the binding sites: fractional binding may be lower when large amounts of the drug are given. The generally expressed percentage binding refers to the usual therapeutic plasma concentrations of a drug.

Drugs highly bound to plasma protein	
To albumin	*To α_1-acid glycoprotein*
Barbiturates	β-blockers
Benzodiazepines	Bupivacaine
NSAIDs	Lidocaine
Valproic acid	Disopyramide
Phenytoin	Imipramine
Penicillins	Methadone
Sulfonamides	Prazosin
Tetracyclines	Quinidine
Tolbutamide	Verapamil
Warfarin	

The clinically significant implications of plasma protein binding are:

(i) Highly plasma protein bound drugs are largely restricted to the vascular compartment because protein bound drug does not cross membranes (except through large paracellular spaces, such as in capillaries). They tend to have smaller volumes of distribution.

(ii) The bound fraction is not available for action. However, it is in equilibrium with the free drug in plasma and dissociates when the concentration of the latter is reduced due to elimination. Plasma protein binding thus tantamounts to temporary storage of the drug.

(iii) High degree of protein binding generally makes the drug long acting, because bound fraction is not available for metabolism or excretion, unless it is actively extracted by liver or by kidney tubules. Glomerular filtration does not reduce the concentration of the free form in the efferent vessels, because water is also filtered. Active tubular secretion, however, removes the drug without the attendant solvent → concentration of free drug falls → bound drug dissociates and is eliminated resulting in a higher renal clearance value of the drug than the total renal blood flow.

(iv) The generally expressed plasma concentrations of the drug refer to bound as well as free drug. Degree of protein binding should be taken into account while relating these to concentrations of the drug that are active *in vitro,* e.g. MIC of an antimicrobial.

v) One drug can bind to many sites on the albumin molecule. Conversely, more than one drug can bind to the same site. This can give rise to displacement interactions among drugs

bound to the same site(s). The drug bound with higher affinity will displace that bound with lower affinity.

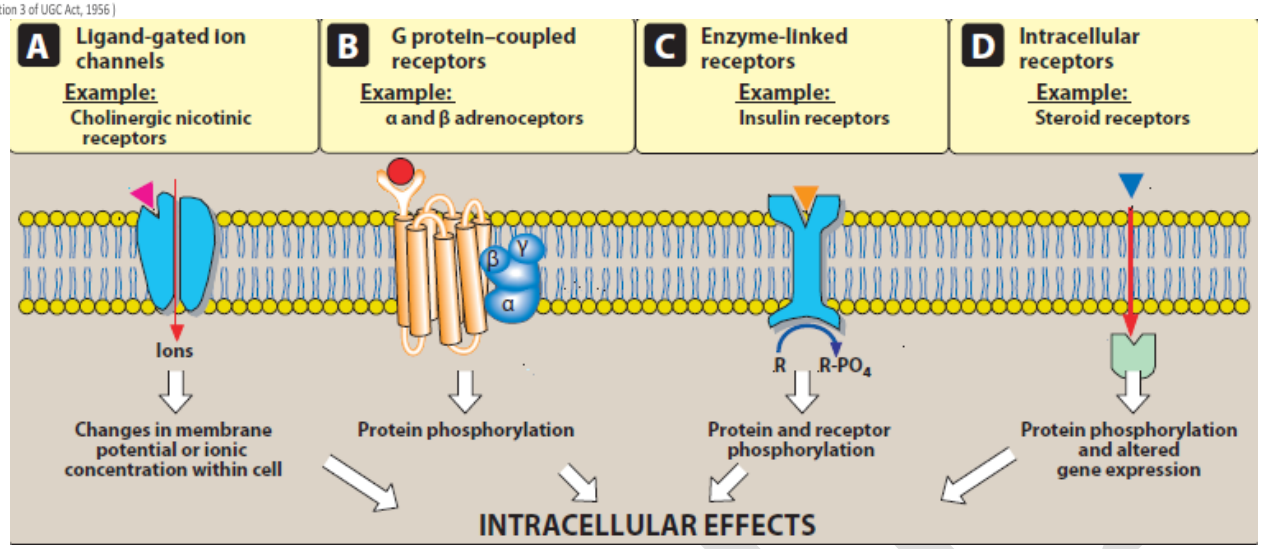
(vi) In hypoalbuminemia, binding may be reduced and high concentrations of free drug may be attained, e.g. phenytoin and furosemide. Other diseases may also alter drug binding, e.g. phenytoin and pethidine binding is reduced in uraemia; propranolol binding is increased in pregnant women and in patients with inflammatory disease

Drug – Receptor interaction

- Drugs act as signals, and their receptors act as signal detectors. Receptors transduce their recognition of a bound agonist by initiating a series of reactions that ultimately result in a specific intracellular response.
- Second messenger" or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

The drug–receptor complex

- Cells have many different types of receptor, each of which is specific for a particular agonist and produces a unique response. Cardiac cell membranes, for example, contain β receptors that bind and respond to epinephrine or norepinephrine, as well as muscarinic receptors specificfor acetylcholine.
- These different receptor populations dynamically interact to control the heart's vital functions.
- The magnitude of the response is proportional to the number of drug– receptor complexes. This concept is closely related to the formation of complexes between enzyme and substrate or antigen and antibody.
- These interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given agonist.
- Most receptors are named for the type of agonist that interacts best with it. For example, the receptor for histamine is called a histamine receptor.
- Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response.
- The richest sources of therapeutically relevant pharmacologic receptors are proteins that transduce extracellular signals into intracellular responses. These receptors may be divided into four families:
  - **1) ligand-gated ion channels,**
  - **2) G protein– coupled receptors,**
  - **3) enzyme-linked receptors, and**
  - **4) intracellular receptors**

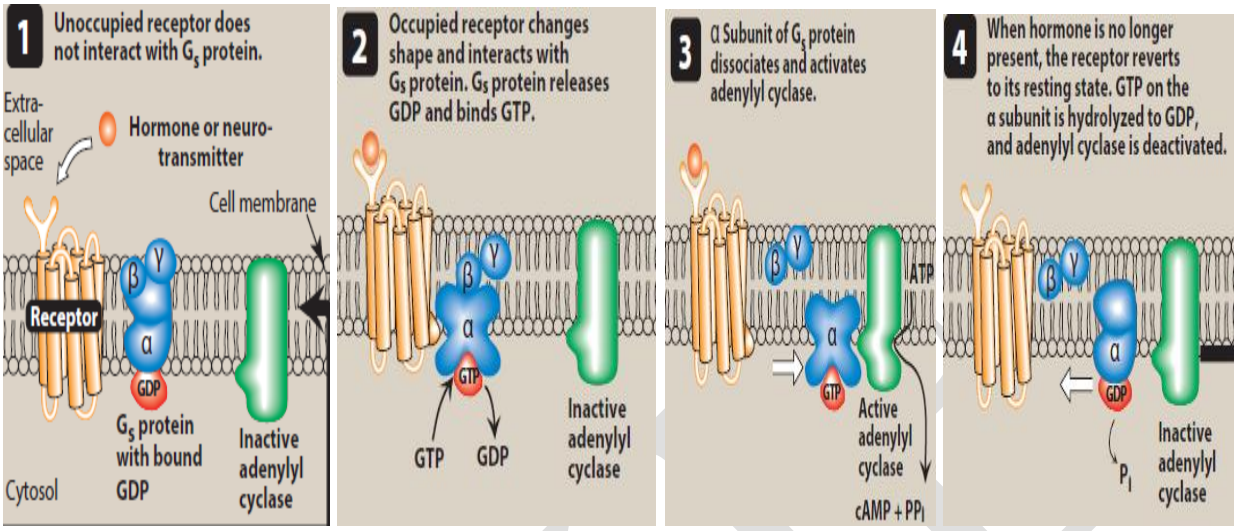


Transmembrane ligand-gated ion channels:

- The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes.
- The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction.
- For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium out flux, generating an action potential in a neuron or contraction in skeletal muscle.

3. Transmembrane G protein–coupled receptors:

- The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule.
- There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all are composed of three protein subunits.
- The α subunit binds guanosine triphosphate (GTP), and the β and γ subunits anchor the G protein in the cell membrane.
- Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex.
- These two complexes can then interact with other cellular effectors, usually an enzyme, a protein, or an ion channel, that are responsible for further actions within the cell.



4. **Enzyme-linked receptors:**
   - This family of receptors consists of a protein that may form dimers or multisubunit complexes. When activated, these receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function.
   - The most common enzymelinked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) possess tyrosine kinase activity as part of their structure.
5. **Intracellular receptors:**
   - The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor. In order to move across the target cell membrane, the ligand must have sufficient lipid solubility.

- The primary targets of these ligand– receptor complexes are transcription factors in the cell nucleus. Binding of the ligand with its receptor generally activates the receptor via dissociation from a variety of binding proteins.
- The activated ligand–receptor complex then translocates to the nucleus, where it often dimerizes before binding to transcription factors that regulate gene expression.
- The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins.
- For example, steroid hormones exert their action on target cells via intracellular receptors. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes.

Therapeutic index

- The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD50) to the dose that produces a clinically desired or effective response (ED50) in half the population:

$$TI = TD_{50} / ED_{50}$$

- The TI is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

Clinical usefulness of the therapeutic index

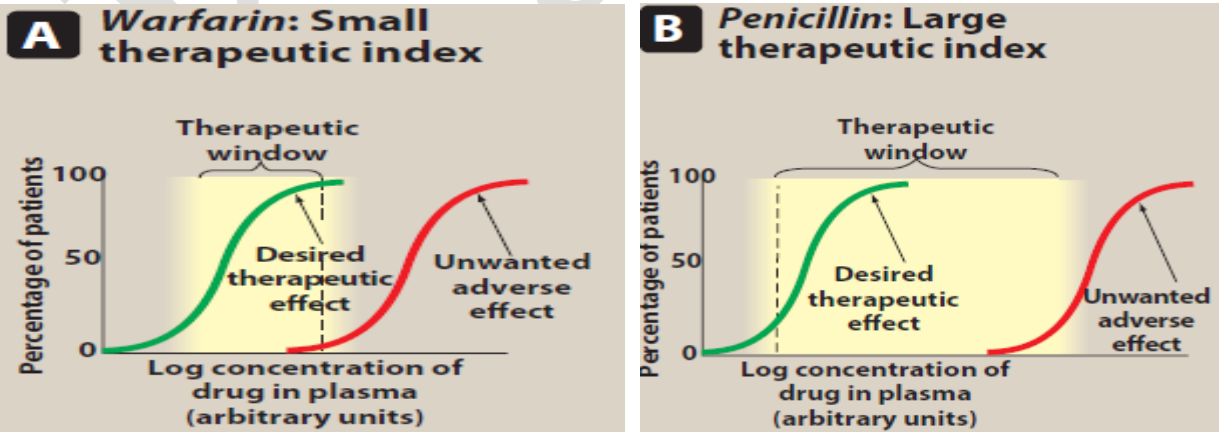
- The TI of a drug is determined using drug trials and accumulated clinical experience. These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses.
- Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases.
- In these cases, the risk of experiencing side effects is not as great as the risk of leaving the disease untreated.

1. Warfarin (example of a drug with a small therapeutic index):

- As the dose of *warfarin* is increased, a greater fraction of the patients respond until, eventually, all patients respond.
- However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percent of patients. Agents with a low TI are those drugs for which bioavailability critically alters the therapeutic effects .

3. Penicillin (example of a drug with a large therapeutic index):

- For drugs such as *penicillin* , it is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse side effects. In this case, bioavailability does not critically alter the therapeutic or clinical effects.



Pharmacokinetics

- Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics describes what the drug does to the body. Four pharmacokinetic properties determine the onset, intensity, and the duration of drug action:

• **Absorption:**

First, absorption from the site of administration permits entry of the drug (either directly or indirectly) into plasma.

• **Distribution:**

Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids.

• **Metabolism:**

Third, the drug may be biotransformed by metabolism by the liver or other tissues.

• **Elimination:**

Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces.

- Using knowledge of pharmacokinetic parameters, clinicians can design optimal drug regimens, including the route of administration, the dose, the frequency, and the duration of treatment.

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16BCU603A- Drug Biochemistry
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S.No	Unit	Questions	Option 1	Option 2	Option 3	Option 4	Answer
1	I	Pharmacokinetics is:	The study of biological and therapeutic effects of drugs	The study of absorption, distribution, metabolism and excretion of drugs	The study of mechanisms of drug action	The study of methods of new drug development	**The study of absorption, distribution, metabolism and excretion of drugs**
2	I	The main mechanism of drugs absorption in GI tract :	Active transport (carrier-mediated diffusion)	Filtration (aqueous diffusion)	Endocytosis and exocytosis	Passive diffusion (lipid diffusion)	**Passive diffusion (lipid diffusion)**
3	I	What does the term "bioavailability" mean?	Plasma protein binding degree of substance	Permeability through the brain-blood barrier	Fraction of an uncharged drug reaching the systemic circulation following any route administration	Amount of a substance in urine relative to the initial dose	**Fraction of an uncharged drug reaching the systemic circulation following any route administration**
4	I	Which route of drug administration is most likely to lead to the first-pass effect?	Sublingual	Oral	Intravenous	Intramuscular	**Oral**
5	I	The volume of distribution (Vd) relates:	Single to a daily dose of an administrated drug	An administrated dose to a body weight	An uncharged drug reaching the systemic circulation	The amount of a drug in the body to the concentration of a drug in plasma	**The amount of a drug in the body to the concentration of a drug in plasma**
6	I	Metabolic transformation (phase 1) is:	Acetylation and methylation of substances	Transformation of substances due to oxidation, reduction or hydrolysis	Glucuronide formation	Binding to plasma proteins	**Transformation of substances due to oxidation, reduction or hydrolysis**
7	I	Which organ involved in first pass effect?	Heart	Kidney	Brain	Liver	**Liver**
8	I	Which one of the following is not a route of administration?	Intravenous	Oral	Topical	Dissolution	**Dissolution**
9	I	Which of the following processes proceeds in the second phase of biotransformation?	Acetylation	Reduction	Oxidation	Hydrolysis	**Acetylation**
10	I	Which enzyme is involved in phase I metabolism	Catalase	Polyphenol oxidase	Cytochorome p450 MO	Oxygenase	**Cytochorome p450 MO**
11	I	Cytochorome p450 MO is found mainly in	Heart	Liver	Brain	Kidney	**Liver**
12	I	Dichloroisopropylarterenol blocks	Alpha adrenergic receptors	Beta adrenergic receptors	Both alpha and beta receptors	Gamma adrenergic receptors	**Beta adrenergic receptors**
13	I	Half life (t ½) is the time required to:	Change the amount of a drug in plasma by half during elimination	Metabolize a half of an introduced drug into the active metabolite	Absorb a half of an introduced drug	Bind a half of an introduced drug to plasma proteins	**Change the amount of a drug in plasma by half during elimination**
14	I	Irreversible interaction of an antagonist with a receptor is due to:	Ionic bonds	Hydrogen bonds	Covalent bonds	Sulphur bond	**Covalent bonds**
15	I	The second messenger of G-protein-coupled (metabotropic) receptor:	Adenylyl cyclase	Sodium ions	Phospholipase C	cAMP	**cAMP**
16	I	Give the definition for a therapeutical dose:	The amount of a substance to produce the minimal biological effect	The amount of a substance to produce effects hazardous for an organism	The amount of a substance to produce the required effect in most patients	The amount of a substance to accelerate an increase of concentration of medicine in an organism	**The amount of a substance to produce the required effect in most patients**
17	I	The substance which changes the activity of an effector element but doesn't belong to second messengers:	cAMP	cGMP	G–protein	Calcium ions	**G–protein**
18	I	An agonist can produce submaximal effects and has moderate efficacy it's called:	Partial agonist	Antagonist	Agonist-antagonist	Full agonist	**Partial agonist**
19	I	Conjugation is:	Process of drug reduction by special enzymes	Process of drug oxidation by special oxidases	Coupling of a drug with an endogenous substrate	Solubilization in lipids	**Coupling of a drug with an endogenous substrate**
20	I	What is implied by "active transport"?	Transport of drugs trough a membrane by means of diffusion	Transport without energy consumption	Engulf of drug by a cell membrane with a new vesicle formation	Transport against concentration gradient	**Transport against concentration gradient**
21	I	What kind of substances can't permeate membranes by passive diffusion?	Lipid-soluble	Non-ionized substances	Hydrophobic substances	Hydrophilic substances	**Hydrophilic substances**
22	I	The reasons determining bioavailability are:	Rheological parameters of blood	Amount of a substance obtained orally and quantity of intakes	Extent of absorption and hepatic first-pass effect	Glomerular filtration rate	**Extent of absorption and hepatic first-pass effect**
23	I	For the calculation of the volume of distribution (Vd) one must take into account:	Concentration of a substance in plasma	Concentration of substance in urine	Therapeutical width of drug action	A daily dose of drug	**Concentration of a substance in plasma**
24	I	Biotransformation of a medicinal substance results in:	Faster urinary excretion	Slower urinary excretion	Easier distribution in organism	Higher binding to membranes	**Faster urinary excretion**
25	I	The organelle that carry Cytochorome p450 MO is	Endoplasmic reticulam	Golgi complex	Mitochondria	Mitochondria	**Endoplasmic reticulam**
26	I	Conjugation of a drug includes the following EXCEPT:	Glucoronidation	Sulfate formation	Hydrolysis	Methylation	**Hydrolysis**
27	I	The phase II reaction which produce a compound with greater pharmocological actvity	Glucoronic acid conjugation	Conjugation with amino acid	Methylation	Glutathione conjugation	**Methylation**
28	I	Elimination is expressed as follows:	Rate of renal tubular reabsorption	Clearance speed of some volume of blood from substance	Time required to decrease the amount of drug in plasma by one-half	Clearance of an organism from a xenobiotic	**Clearance of an organism from a xenobiotic**
29	I	Acidic drug rapidly absorbed at	Stomach	GI tract	Large intestine	Mouth	**Stomach**
30	I	Coenzyme required by Cytochorome p450 MO is	NADH	NADPH	Lipoic acid	TPP	**NADPH**
31	I	Basic drugs are absorbed in	small intestine	stomach	Large intestine	Pancreas	**small intestine**
32	I	Which effect may lead to toxic reactions when a drug is taken continuously or repeatedly?	Refractoriness	Cumulative effect	Tolerance	Tachyphylaxis	**Cumulative effect**
33	I	What term is used to describe a more gradual decrease in responsiveness to a drug, taking days or weeks to develop?	Refractoriness	Cumulative effect	Tolerance	Tachyphylaxis	**Tolerance**
34	I	What term is used to describe a decrease in responsiveness to a drug which develops in a few minutes?	Refractoriness	Cumulative effect	Tolerance	Tachyphylaxis	**Tachyphylaxis**
35	I	Which drug that cross the lipid bilayer easily	Water soluble drug	lipid soluble drug	ionsoluble drug	Non ionsoluble drug	**lipid soluble drug**
36	I	Science that deals with drug	Pharmacy	pharmacognosy	pharmacodynamics	pharmacology	**pharmacology**
37	I	Inhibition of MAO causses an	decrease in the deamination of noradrenalin	increase in the deamination of dopamine	increase in the deamination of noradrenalin	decrease in the deamination of dopamine	**decrease in the deamination of noradrenalin**
38	I	Systemic clearance (CLs) is related with:	Only the concentration of substances in plasma	Only the elimination rate constant	Volume of distribution, half life and elimination rate constant	Bioavailability and half life	**Volume of distribution, half life and elimination rate constant**
39	I	Elimination rate constant (Kelim) is defined by the following parameter:	Rate of absorption	Maximal concentration of a substance in plasma	Highest single dose	Half life (t ½)	**Half life (t ½)**
40	I	Half life (t ½) is the time required to:	Change the amount of a drug in plasma by half during elimination	Metabolize a half of an introduced drug into the active metabolite	Absorb a half of an introduced drug	Bind a half of an introduced drug to plasma proteins	**Change the amount of a drug in plasma by half during elimination**
41	I	Aspirin is chemically	Sodium salicylate	Acetylsalicylic acid	Salicylamide	Sodium salicylamide	**Acetylsalicylic acid**
42	I	Which is the most appropriate to the term "receptor"	All types of ion channels modulated by a drug	Enzymes of oxidizing-reducing reactions activated by a drug	Active macromolecular components of a cell or an organism which a drug molecule has to combine with in order to elicit its specific effect	Carriers activated by a drug	**Active macromolecular components of a cell or an organism which a drug molecule has to combine with in order to elicit its specific effect**
43	I	What does "affinity" mean?	A measure of how tightly a drug binds to plasma proteins	A measure of how tightly a drug binds to a receptor	A measure of inhibiting potency of a drug	A measure of bioavailability of a drug	**A measure of how tightly a drug binds to a receptor**
44	I						

45	I	A measure of bioavailability of a drug	A measure of how tightly a drug binds to a receptor	An agonist is a substance that:	Interacts with the receptor without producing any effect	Interacts with the receptor and initiates changes in cell function, producing various effects	**Increases concentration of another substance to produce effect**
46	I	An agonist is a substance that:	Interacts with the receptor without producing any effect	Interacts with the receptor and initiates changes in cell function, producing various effects	Increases concentration of another substance to produce effect	Interacts with plasma proteins and doesn't produce any effect	**Interacts with the receptor and initiates changes in cell function, producing various effects**
47	I	An antagonist is a substance that:	Binds to the receptors and initiates changes in cell function, producing maximal effect	Binds to the receptors and initiates changes in cell function, producing submaximal effect	Interacts with plasma proteins and doesn't produce any effect	Binds to the receptors without directly altering their functions	**Binds to the receptors without directly altering their functions**
48	I	A competitive antagonist is a substance that:	Interacts with receptors and produces sub maximal effect	Binds to the same receptor site and progressively inhibits the agonist response	Binds to the nonspecific sites of tissue	Binds to one receptor subtype as an agonist and to another as an antagonist	**Binds to the same receptor site and progressively inhibits the agonist response**
49	I	The substance binding to one receptor subtype as an agonist and to another as an antagonist is called:	Competitive antagonist	Irreversible antagonist	Agonist-antagonist	Partial agonist	**Agonist-antagonist**
50	I	Irreversible interaction of an antagonist with a receptor is due to:	Ionic bonds	Hydrogen bonds	Covalent bonds	Weak bonds	**Covalent bonds**
51	I	Tick the second messenger of G-protein-coupled (metabotropic) receptor:	Adenylyl cyclase	Sodium ions	Phospholipase C	cAMP	**cAMP**
52	I	What is the type of drug-to-drug interaction which is connected with processes of absorption, biotransformation, distribution and excretion?	Pharmacodynamic interaction	Physical and chemical interaction	Pharmaceutical interaction	Pharmacokinetic interaction	**Pharmacokinetic interaction**
53	I	Chloramphenicol is derived from	Streptomyces venezulae	Streptomyces griseus	Streptomyces kanamycin	Pencillin	**Streptomyces griseus**
54	I	A hydrophilic medicinal agent has the following property:	Low ability to penetrate through the cell membrane lipids	Penetrate through membranes by means of endocytosis	Easy permeation through the blood-brain barrier	High reabsorption in renal tubules	**Low ability to penetrate through the cell membrane lipids**
55	I	The feature of the sublingual route:	Pretty fast absorption	A drug is exposed to gastric secretion	A drug is exposed more prominent liver metabolism	A drug can be administrated in a variety of doses	**Pretty fast absorption**
56	I	Pick out the parenteral route of medicinal agent administration:	Rectal	Oral	Sublingual	Inhalation	**Inhalation**
57	I	Parenteral administration:	Cannot be used with unconsciousness patients	Generally results in a less accurate dosage than oral administration	Usually produces a more rapid response than oral administration	Is too slow for emergency use	**Usually produces a more rapid response than oral administration**
58	I	Volume of distribution (Vd) one must take into _____	Concentration of a substance in plasma	Concentration of substance in urine	Therapeutical width of drug action	A daily dose of drug	**Concentration of a substance in plasma**
59	I	Biotransformation of the drugs is to render them:	Less ionized	More pharmacologically active	More lipid soluble	Less lipid soluble	**Less lipid soluble**
60	I	Tick the drug type for which microsomal oxidation is the most prominent:	Lipid soluble	Water soluble	Low molecular weight	High molecular weight	**Lipid soluble**

Drug metabolism:

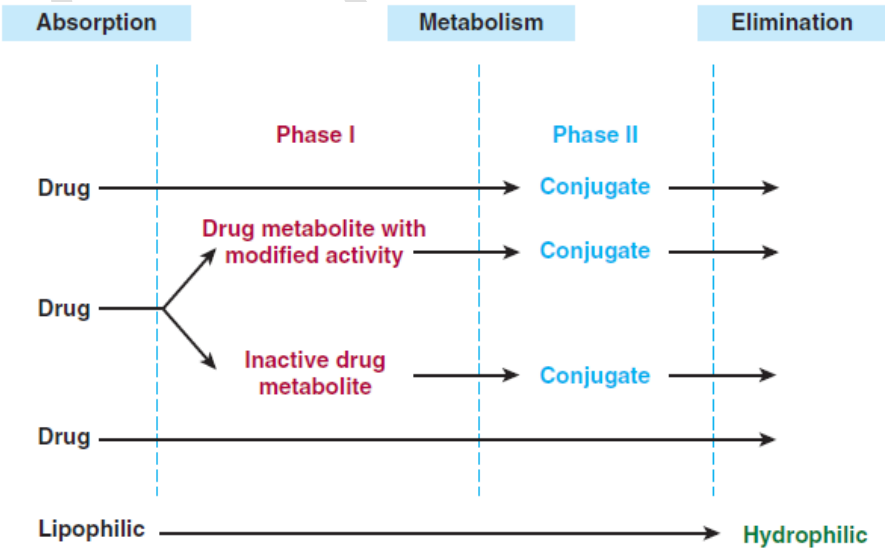
Drug Biotransformation pathways - phase I – oxidation, reduction and hydroxylation. Phase II- Conjugation, Elimination of drugs from body system. Storage of drugs in adipose tissue.

Drug metabolism

- Drug metabolism is the biochemical modification of pharmaceutical substances by living organisms, usually through specialized enzymatic systems. This is a form of xenobiotic metabolism.
- Drug metabolism often converts lipophilic chemical compounds into more readily excreted polar products. Its rate is an important determinant of the duration and intensity of the pharmacological action of drugs.
- Drug metabolism can result in toxication or detoxication - the activation or deactivation of the chemical. While both occur, the major metabolites of most drugs are detoxication products.
- Drugs are almost all xenobiotics. Other commonly used organic chemicals are also xenobiotics, and are metabolized by the same enzymes as drugs. This provides the opportunity for *drug-drug* and *drug-chemical* interactions or reactions.

Phase I metabolism

Phase II metabolism



Where do drug biotransformations occur?

- Although every tissue has some ability to metabolize drugs, the liver is the principal organ of drug metabolism.
- Other tissues that display considerable activity include the gastrointestinal tract, the lungs, the skin, the kidneys, and the brain.
- After oral administration, many drugs (eg, isoproterenol, meperidine, pentazocine, morphine) are absorbed intact from the small intestine and transported first via the portal system to the liver, where they undergo extensive metabolism.
- This process is called the **first-pass effect.**
- Some orally administered drugs (eg, clonazepam, chlorpromazine, cyclosporine) are more extensively metabolized in the intestine than in the liver, while others (eg, midazolam) undergo significant (≈ 50%) intestinal metabolism.
- Thus, intestinal metabolism can contribute to the overall first-pass effect, and individuals with compromised liver function may rely increasingly on such intestinal metabolism for drug elimination.

Phase I metabolism:

❖ Phase I reactions usually convert the parent drug to a more polar metabolite by introducing or unmasking a functional group (−OH, −NH 2 , −SH). Often these metabolites are inactive, although in some instances activity is only modified or even enhanced.

❖ Phase I reactions (also termed nonsynthetic reactions) may occur by oxidation, reduction, hydrolysis, cyclization, and decyclization addition of oxygen or removal of hydrogen, carried out by mixed function oxidases, often in the liver.

❖ These oxidative reactions typically involve a cytochrome P450monooxygenase (often abbreviated CYP), NADPH and oxygen.

❖ The classes of pharmaceutical drugs that utilize this method for their metabolism include phenothiazines, paracetamol, and steroids.

❖ If the metabolites of phase I reactions are sufficiently polar, they may be readily excreted at this point. However, many phase I products are not eliminated rapidly and undergo a subsequent reaction in which an endogenous substrate combines with the newly incorporated functional group to form a highly polar conjugate.

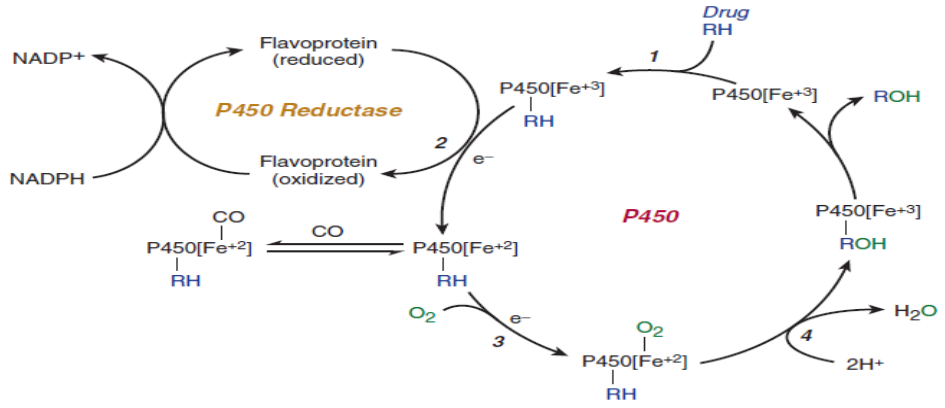
- A common Phase I oxidation involves conversion of a C-H bond to a C-OH. This reaction sometimes converts a pharmacologically inactive compound (a prodrug) to a pharmacologically active one.

- By the same token, Phase I can turn a nontoxic molecule into a poisonous one. Simple hydrolysis in the stomach transforms. Which are comparatively innocuous.

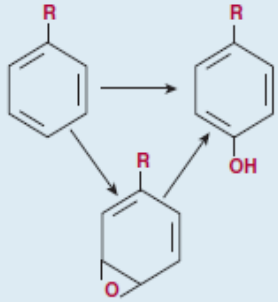
- Phase I metabolism of drug candidates can be simulated in the laboratory using non-enzyme catalysts. This example of a biomimetic reaction tends to give products that often contains the Phase I metabolites.

Microsomal mixed function oxidase system & phase i reactions:

- Many drug-metabolizing enzymes are located in the lipophilic endoplasmic reticulum membranes of the liver and other tissues.
- They contain the important class of enzymes known as the **mixed function oxidases** (MFOs), or **monooxygenases.**
- The activity of these enzymes requires both a reducing agent (nicotinamide adenine dinucleotide phosphate [NADPH]) and molecular oxygen; in a typical reaction, one molecule of oxygen is consumed (reduced) per substrate molecule, with one oxygen atom appearing in the product and the other in the form of water.
- In this oxidation-reduction process, two microsomal enzymes play a key role. The first of these is a flavoprotein, **NADPHcytochrome P450 oxidoreductase** (POR) .
- One mole of this enzyme contains 1 mol each of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD).
- The second microsomal enzyme is a hemoprotein called **cytochrome P450,** which serves as the terminal oxidase.
- Microsomal drug oxidations require P450, P450 reductase, NADPH, and molecular oxygen.



Phase I reactions:

Reaction Class	Structural Change	Drug Substrates
Oxidations		
Cytochrome P450-dependent oxidations:		
Aromatic hydroxylations		Acetanilide, propranolol, phenobarbital, phenytoin, phenylbutazone, amphetamine, warfarin, 17α-ethinyl estradiol, naphthalene, benzpyrene
Aliphatic hydroxylations	$RCH_2CH_3 \longrightarrow RCH_2CH_2OH$ $RCH_2CH_3 \longrightarrow RCHCH_3$ (OH)	Amobarbital, pentobarbital, secobarbital, chlorpropamide, ibuprofen, meprobamate, glutethimide, phenylbutazone, digitoxin
Epoxidation	$RCH{=}CHR \longrightarrow R{-}C(H)(O){-}C(H){-}R$	Aldrin
Oxidative dealkylation		
N-Dealkylation	$RNHCH_3 \longrightarrow RNH_2 + CH_2O$	Morphine, ethylmorphine, benzphetamine, aminopyrine, caffeine, theophylline
O-Dealkylation	$ROCH_3 \longrightarrow ROH + CH_2O$	Codeine, *p*-nitroanisole
S-Dealkylation	$RSCH_3 \longrightarrow RSH + CH_2O$	6-Methylthiopurine, methitural
***N*-Oxidation**		
Primary amines	$RNH_2 \longrightarrow RNHOH$	Aniline, chlorphentermine
Secondary amines	$R_1R_2NH \longrightarrow R_1R_2N{-}OH$	2-Acetylaminofluorene, acetaminophen
Deamination	$RCHCH_3(NH_2) \longrightarrow R{-}C(OH)(NH_2){-}CH_3 \longrightarrow R{-}C(=O){-}CH_3 + NH_3$	Amphetamine, diazepam
Desulfuration	$R_1R_2C{=}S \longrightarrow R_1R_2C{=}O$	Thiopental

Reductions		
Azo reductions	$RN{=}NR_1 \longrightarrow RNH{-}NHR_1 \longrightarrow RNH_2 + R_1NH_2$	Prontosil, tartrazine
Nitro reductions	$RNO_2 \longrightarrow RNO \longrightarrow RNHOH \longrightarrow RNH_2$	Nitrobenzene, chloramphenicol, clonazepam, dantrolene
Carbonyl reductions	$RCR' \longrightarrow RCHR'$ (O, OH)	Metyrapone, methadone, naloxone
Hydrolyses		
Esters	$R_1COOR_2 \longrightarrow R_1COOH + R_2OH$	Procaine, succinylcholine, aspirin, clofibrate, methylphenidate
Amides	$RCONHR_1 \longrightarrow RCOOH + R_1NH_2$	Procainamide, lidocaine, indomethacin

Phase II Metabolism

- Parent drugs or their phase I metabolites that contain suitable chemical groups often undergo coupling or conjugation reactions with an endogenous substance to yield **drug conjugates**. In general, conjugates are polar molecules that are readily excreted and often inactive.
- Conjugate formation involves high-energy intermediates and specific transfer enzymes. Such enzymes (**transferases**) may be located in microsomes or in the cytosol. Of these, uridine 5′-diphosphate (UDP)-glucuronosyl transferases **(UGTs)** are the most dominant enzymes.
- These microsomal enzymes catalyze the coupling of an activated endogenous substance (such as the UDP derivative of glucuronic acid) with a drug (or endogenous compound such as bilirubin, the end product of heme metabolism).
- Similarly, 11 human sulfotransferases (**SULTs**) catalyze the sulfation of substrates using 3′- phosphoadenosine 5′-phosphosulfate (**PAPS**) as the endogenous sulfate donor. Cytosolic and microsomal glutathione (**GSH**) transferases (**GSTs**) are also engaged in the metabolism of drugs and xenobiotics, and in that of leukotrienes and prostaglandins, respectively.
- Chemicals containing an aromatic amine or a hydrazine moiety (eg, isoniazid) are substrates of cytosolic *N* -acetyltransferases **(NATs**), encoded by *NAT1* and *NAT2* genes, which utilize **acetyl-CoA** as the endogenous cofactor.

- *S* -Adenosyl-L-methionine (**SAMe** ; AdoMet)-mediated *O* -, *N* -, and *S* -methylation of drugs and xenobiotics by methyltransferases (**MTs)** also occurs.
- Finally, endobiotic, drug, and xenobiotics epoxides generated via P450-catalyzed oxidations can also be hydrolyzed by microsomal or cytosolic epoxide hydrolases (**EHs**).
- Conjugation of an activated drug such as the *S*-CoA derivative of benzoic acid, with an endogenous substrate, such as glycine, also occurs.
- Because the endogenous substrates originate in the diet, nutrition plays a critical role in the regulation of drug conjugations.
- Phase II reactions are relatively faster than P450-catalyzed reactions, thus effectively accelerating drug biotransformation.
- Drug conjugations were once believed to represent terminal inactivation events and as such have been viewed as "true detoxification" reactions. However, this concept must be modified, because it is now known that certain conjugation reactions (acyl glucuronidation of nonsteroidal anti-inflammatory drugs, *O* -sulfation of *N* -hydroxyacetylaminofluorene, and *N* –acetylation of isoniazid) may lead to the formation of reactive species responsible for the toxicity of the drugs.

Type of Conjugation	Endogenous Reactant	Transferase (Location)	Types of Substrates	Examples
Glucuronidation	UDP glucuronic acid	UDP glucuronosyltransferase (microsomes)	Phenols, alcohols, carboxylic acids, hydroxylamines, sulfonamides	Nitrophenol, morphine, acetaminophen, diazepam, *N*-hydroxydapsone, sulfathiazole, meprobamate, digitoxin, digoxin
Acetylation	Acetyl-CoA	*N*–Acetyltransferase (cytosol)	Amines	Sulfonamides, isoniazid, clonazepam, dapsone, mescaline
Glutathione conjugation	Glutathione (GSH)	GSH-*S*-transferase (cytosol, microsomes)	Epoxides, arene oxides, nitro groups, hydroxylamines	Acetaminophen, ethacrynic acid, bromobenzene
Glycine conjugation	Glycine	Acyl-CoA glycinetransferase (mitochondria)	Acyl-CoA derivatives of carboxylic acids	Salicylic acid, benzoic acid, nicotinic acid, cinnamic acid, cholic acid, deoxycholic acid
Sulfation	Phosphoadenosyl phosphosulfate	Sulfotransferase (cytosol)	Phenols, alcohols, aromatic amines	Estrone, aniline, phenol, 3-hydroxycoumarin, acetaminophen, methyldopa
Methylation	S-Adenosylmethionine	Transmethylases (cytosol)	Catecholamines, phenols, amines	Dopamine, epinephrine, pyridine, histamine, thiouracil
Water conjugation	Water	Epoxide hydrolase (microsomes)	Arene oxides, *cis*-disubstituted and monosubstituted oxiranes	Benzopyrene 7,8-epoxide, styrene 1,2-oxide, carbamazepine epoxide
		(cytosol)	Alkene oxides, fatty acid epoxides	Leukotriene A_4

Clinical relevance of drug metabolism:

- The dose and frequency of administration required to achieve effective therapeutic blood and tissue levels vary in different patients because of individual differences in drug distribution and rates of drug metabolism and elimination.
- These differences are determined by genetic factors and nongenetic variables, such as **age, sex, liver size, liver function, circadian rhythm, body temperature, and nutritional and environmental factors** such as concomitant exposure to inducers or inhibitors of drug metabolism.

Individual Differences:

- Individual differences in metabolic rate depend on the nature of the drug itself. Thus, within the same population, steady-state plasma levels may reflect a 30-fold variation in the metabolism of one drug and only a two-fold variation in the metabolism of another.

Genetic Factors

- Genetic factors that influence enzyme levels account for some of these differences, giving rise to "genetic polymorphisms" in drug metabolism.
- The first examples of drugs found to be subject to genetic polymorphisms were the muscle relaxant succinylcholine, the anti-tuberculosis drug isoniazid, and the anticoagulant warfarin.
- Well-defined and clinically relevant genetic polymorphisms in both phase I and phase II drug-metabolizing enzymes exist that result in altered efficacy of drug therapy or adverse drug reactions (**ADRs**).

Diet & Environmental Factors

- Diet and environmental factors contribute to individual variations in drug metabolism. Charcoal-broiled foods and cruciferous vegetables are known to induce CYP1A enzymes, whereas grapefruit juice is known to inhibit the CYP3A metabolism of co-administered drug substrates .
- Cigarette smokers metabolize some drugs more rapidly than nonsmokers because of enzyme induction.
- Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than unexposed individuals. Such differences make it difficult to determine effective and safe doses of drugs that have narrow therapeutic indices.

Age & Sex

- Increased susceptibility to the pharmacologic or toxic activity of drugs has been reported in very young and very old patients compared with young adults. Although this may reflect differences in absorption, distribution, and elimination, differences in drug metabolism also play a role.
- Slower metabolism could be due to reduced activity of metabolic enzymes or reduced availability of essential endogenous cofactors.
- Sex-dependent variations in drug metabolism have been well documented in rats but not in other rodents. Young adult male rats metabolize drugs much faster than mature female rats or prepubertal male rats.

- These differences in drug metabolism have been clearly associated with androgenic hormones. Clinical reports suggest that similar sex-dependent differences in drug metabolism also exist in humans for ethanol, propranolol, some benzodiazepines, estrogens, and salicylates.

Elimination of drugs from body system

EXCRETION

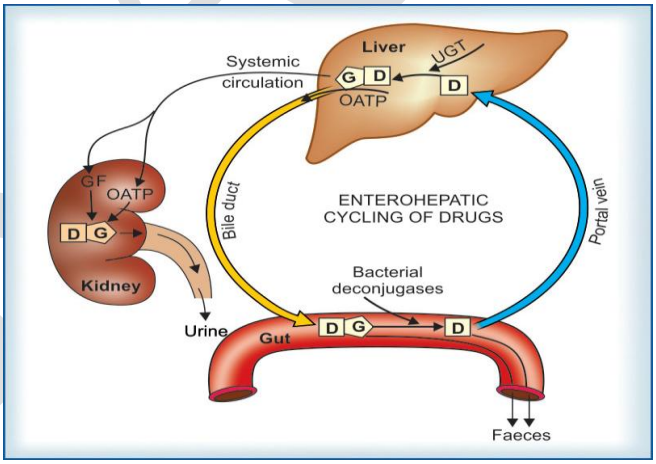
Excretion is the passage out of systemically absorbed drug. Drugs and their metabolites are excreted in:

1. Urine

Through the kidney. It is the most important channel of excretion for majority of drugs .

2. Faeces

- Apart from the unabsorbed fraction, most of the drug present in faeces is derived from bile. Liver actively transports into bile organic acids (especially drug glucuronides by OATP and MRP2), organic bases (by OCT), other lipophilic drugs (by P-gp) and steroids by distinct nonspecific active transport mechanisms.
- Relatively larger molecules (MW > 300) are preferentially eliminated in the bile. Most of the free drug in the gut, including that released by deconjugation of glucuronides by enteric bacteria is reabsorbed (enterohepatic cycling) and ultimate excretion occurs in urine . Only the remaining is excreted in the faeces.
- Enterohepatic cycling contributes to longer stay of the drug in the body. Drugs that attain high concentrations in bile are erythromycin, ampicillin, rifampin, tetracycline, oral contraceptives, vecuronium, phenolphthalein. Certain drugs are excreted directly in colon, e.g. anthracene purgatives, heavy metals.



3. Exhaled air

- Gases and volatile liquids (general anaesthetics, alcohol) are eliminated by lungs, irrespective of their lipid solubility.
- Alveolar transfer of the gas/vapour depends on its partial pressure in the blood. Lungs also serve to trap and extrude any particulate matter that enters circulation.

4. Saliva and sweat

- These are of minor importance for drug excretion. Lithium, pot. iodide, rifampin and heavy metals are present in these secretions in significant amounts.
- Most of the saliva along with the drug in it, is swallowed and meets the same fate as orally taken drug.

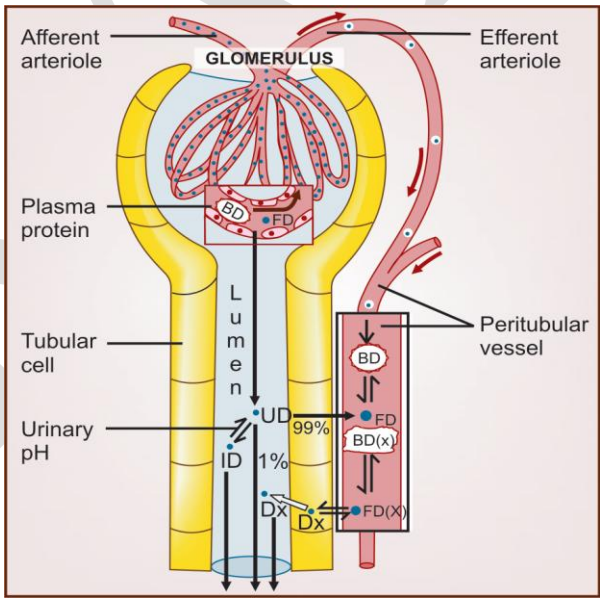
5. Milk

- The excretion of drug in milk is not important for the mother, but the suckling infant inadvertently receives the drug. Most drugs enter breast milk by passive diffusion. As such, more lipid soluble and less protein bound drugs cross better.
- Milk has a lower pH (7.0) than plasma, basic drugs are somewhat more concentrated in it. However, the total amount of drug reaching the infant through breast feeding is generally small and majority of drugs can be given to lactating mothers without ill effects on the infant.
- Nevertheless, it is advisable to administer any drug to a lactating woman only when essential.

RENAL EXCRETION:

The kidney is responsible for excreting all water soluble substances. The amount of drug or its metabolites ultimately present in urine is the sum total of glomerular filtration, tubular reabsorption and tubular secretion.

Net renal excretion = (Glomerular filtration + tubular secretion) – tubular reabsorption



Glomerular filtration

- Glomerular capillaries have pores larger than usual; all nonprotein bound drug (whether lipid-soluble or insoluble) presented to the glomerulus is filtered.
- Thus, glomerular filtration of a drug depends on its plasma protein binding and renal blood flow. Glomerular filtration rate (g.f.r.), normally ~ 120 ml/min, declines progressively after the age of 50, and is low in renal failure.

Tubular reabsorption

- This occurs by passive diffusion and depends on lipid solubility and ionization of the drug at the existing urinary pH.
- Lipid-soluble drugs filtered at the glomerulus back diffuse in the tubules because 99% of glomerular filtrate is reabsorbed, but nonlipid-soluble and highly ionized drugs are unable to do so.
- Thus, rate of excretion of such drugs, e.g. aminoglycoside antibiotics, quaternary ammonium compounds parallels g.f.r. (or creatinine clearance). Changes in urinary pH affect tubular reabsorption of drugs that are partially ionized—
  - Weak bases ionize more and are less reabsorbed in acidic urine.
  - Weak acids ionize more and are less reabsorbed in alkaline urine.

Tubular secretion

- This is the active transfer of organic acids and bases by two separate classes of relatively nonspecific transporters (OAT and OCT) which operate in the proximal tubules.
- In addition, efflux transporters P-gp and MRP2 are located in the luminal membrane of proximal tubular cells. If renal clearance of a drug is greaterthan 120 mL/min (g.f.r.), additional tubular secretion can be assumed to be occurring.
- Active transport of the drug across tubules reduces concentration of its free form in the tubular vessels and promotes dissociation of protein bound drug, which then becomes available for secretion.

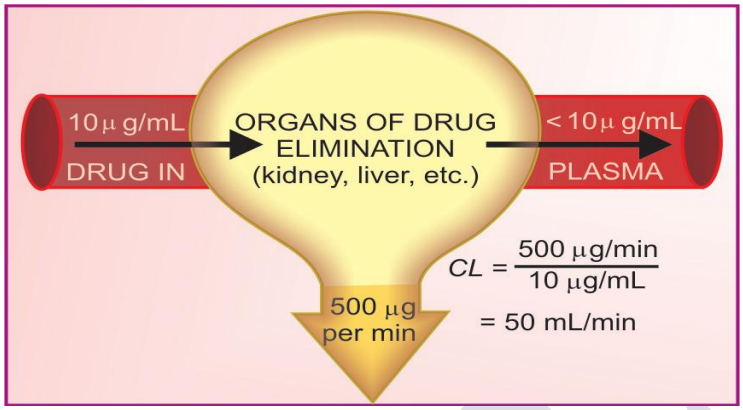
Kinetics of elimination:

- The knowledge of kinetics of elimination of a drug provides the basis for, as well as serves to devise rational dosage regimens and to modify them according to individual needs.
- There are three fundamental pharmacokinetic parameters, *viz.* bioavailability (*F*), volume of distribution (*V*) and clearance (*CL*) which must be understood.

Clearance (CL) - The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time (analogy creatinine clearance). It can be calculated as

$$CL = \text{Rate of elimination}/C$$

where *C* is the plasma concentration.



First order kinetics:

- The rate of elimination is directly proportional to the drug concentration, *CL* remains constant; or a constant *fraction* of the drug present in the body is eliminated in unit time.
- This applies to majority of drugs which do not saturate the elimination processes (transporters, enzymes, blood flow, etc.) over the therapeutic concentration range.

Zero order kinetics

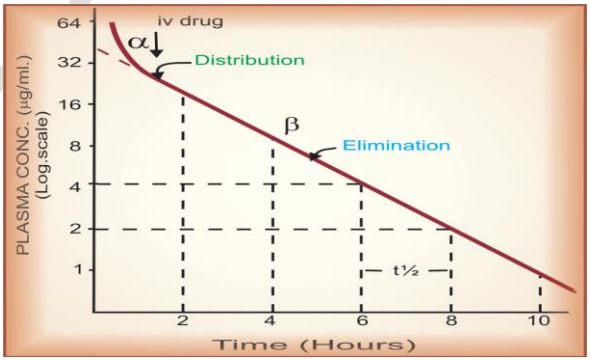
- The rate of elimination remains constant irrespective of drug concentration, *CL* decreases with increase in concentration; or a constant *amount* of the drug is eliminated in unit time, e.g. ethyl alcohol.
- This is also called *capacity limited elimination* or *Michaelis-Menten elimination.*

Plasma half-life

The Plasma half-life (t½) of a drug is the time taken for its plasma concentration to be reduced to half of its original value. Taking the simplest case of a drug which has rapid one compartment distribution and first order elimination, and is given i.v. a semilog plasma concentration-time plot . The plot has two slopes.

- initial rapidly declining (α) phase—due to distribution.
- later less declined (β) phase—due to elimination.

At least two half-lives (distribution t½ and elimination t½) can be calculated from the two slopes. The elimination half life derived from the β slope is simply called the 'half life' of the drug.



Karpagam Academy of Higher Education
Department of Biochemistry
III B,.Sc., Biochemistry
16BCU603A- Drug Biochemistry
Prepared By Dr.M. SRIDHAR MUTHUSAMI

1	II	Cell surface receptors are	C protein coupled receptors	G-protein coupled receptors	Protein A tyrosine kinases	Protein A B tyrosine kinase	**G-protein coupled receptors**
2	II	The receptor serves as	Recognition molecule	Non recognition molecule	Target sites	Active sites	**Recognition molecule**
3	II	Which one of the following not bound to membrane?	Tyrosine linked receptors	Steroid receptors	ion channel linked receptors	G- protein coupled receptors	**steroid receptors**
4	II	When the person remains well only when he is taking the drug is termed as the State of	psychic dependence	physical dependence	withdrawal syndrome	Non Psychic dependence	**physical dependence**
5	II	If the abusing drug is withdrawn the person develops	Abstinence	physical dependence	Tolerance	psychic dependence	**Abstinence**
6	II	If a greaster dose of the drug is required to elicit the normal pharmachological Effect the state is known as	dependence	abstinence	tolerance	intolerance	**tolerance**
7	II	Th 1 cells	enhance CMI	enhance humoral immunity	inhibit CMI	inhibit humoral immunity	**enhance CMI**
8	II	If the drug is disposed more speedily the state is known as	pharmacokinetic tolerance	pharmacodynamic tolerance	psychic tolerance	drug intolerance	**pharmacokinetic tolerance**
9	II	A repeated injection of egg albumin in such an animalcauses a violent reaction Called	cytotoxic type reaction	cell mediated reaction	immune complex mediated reaction	anaphylaxis	**anaphylaxis**
10	II	A state where some changes develop in the tissue leading to less pharmacological Effect of the drug is known as	pharmacokinetic tolerance	pharmacodynamic tolerance	psychic tolerance	drug intolerance	**pharmacodynamic tolerance**
11	II	Best example of psychic dependence is	cigarette smoking	barbiturates	sulphonamides	salicylates	**cigarette smoking**
12	II	The state when the person seeks drugs purely for psychological pleasure is	drug dependence	physical dependence	psychic dependence	pathological equilibrium	**psychic dependence**
13	II	bstances like lead can remain deposited in bones without producing toxic effects Which is called	passive immunization	additive effect	antagonism	synergism	**passive immunization**
14	II	Inflammatory reactions initiated by mononuclear lymphocytes and not by Antibody alone are called	type I hypersensitivity	type II hypersensitivity	delayed hypersensitivity	type III hypersensitivity	**delayed hypersensitivity**
15	II	Methadone is	agonist of opioid receptors	antagonist of opioid receptors	agonist of μ receptors	antagonist of μ receptors	**agonist of opioid receptors**
16	II	Opioids used for abusing are by themselves	CNS stimulants	CNS depressants	CVS stimulants	CVS depressants	**CNS depressants**
17	II	The drug naltrexone is	agonist of opioid receptors	antagonist of opioid receptors	agonist of μ receptors	antagonist of μ receptors	**antagonist of opioid receptors**
18	II	The drugs used to treat abusing of opioids is	Ibu brufen	methadone	Diclofenac	Analgesic	**methadone**
19	II	If the opioid abusers are doctors,nurses and other health workers The choice of drug used for treatment is	methadone	methadyl acetate	naltrexone	pethidine	**pethidine**
20	II	Amphetamine is an	antifatigue agent	fatigue agent	nausea inducer	heroin	**antifatigue agent**
21	II	Polydrug abuse common in USA is	cocaine and heroin	heroin and amphetamine	amphetamine and cocaine	nicotine	**cocaine and heroin**
22	II	The half life of cocaine is	2 hrs	3 hrs	15 hrs	1hr	**1hr**
23	II	Drug used for the treatment of acute cocaine overdose is	Naproxen	amphetamine	diazepam	Ibu brufen	**diazepam**
24	II	The mechanism of action of labetalol used for acute cocaine overdose is	blocking of Ca^{2+} channel	blocking of α and β receptor	blocking of K^{+} channel	blocking of P^{+} channel	**blocking of α and β receptor**
25	II	The mechanism of action of nifedipine used for acute cocaine overdose is	blocking of Ca^{2+} channel	blocking of α and β receptor	blocking of K^{+} channel	blocking of P^{+} channel	**blocking of Ca^{2+} channel**
26	II	The drug of choice for CNS complications due to acute cocaine overdose is	labetalol	nifedipine	diazepam	sulphonamides	**diazepam**
27	II	The craving of cocaine is reduced by	labetalol	nifedipine	desipramine	diazepam	**desipramine**
28	II	LSD causes ---------- of seratoninergic neurons	hyper activity	hypo activity	normal activity	less activity	**hypo activity**
29	II	The half life of LSD is	1 hr	2 hrs	3 hrs	4 hrs	**3 hrs**
30	II	The active principle of cannabis is	diazepam	nifedipine	cannabinol	Ibu brufen	**cannabinol**
31	II	A repeated injection of egg albumin in such an animal causes a violent reaction called	Cytotoxic type reaction	Cell mediated reaction	Immune complex mediated reaction	Anaphylaxis	**Anaphylaxis**
32	II	The drug naltrexone is	Agonist of opioid receptors	Antagonist of opioid receptors	Agonist of morphine receptors	Antagonist of morphine receptors	**Antagonist of opioid receptors**
33	II	The average dose of drug is mentioned in terms of	mg per kg body weight	μg per kg body weight	kg per kg body weight	Cal per kg body weight	**mg per kg body weight**
34	II	The pharmacokinetics of drug changes with	sex	height	weight	age	**age**
35	II	The body surface area is calculated from	height and age	height and weight	weight and age	weight alone	**height and weight**
36	II	What type of drugs should be avoided during menstruation	drugs likely to produce pelvic congestion	drugs which may stimulate uterine smooth muscle	nephrotoxic drugs	neurotoxic drugs	**drugs likely to produce pelvic congestion**
37	II	Consumption of alcohol enhances the effect of	CNS depressants	CNS stimulants	PNS depressants	PNS stimulants	**CNS depressants**
38	II	The chances of drug toxicity is enhanced by administration of drug through	IV route	orally	IM route	Rectal route	**IV route**
39	II	Aspirin reduces body temperature only in the presence of	pyrexia	angina pectoris	bronchial asthma	congestive cardiac failure	**pyrexia**
40	II	The vasoconstrictor effect of noradrenaline is reduced in the presence of	metabolic ketosis	metabolic acidosis	myxedema	pyrexia	**metabolic acidosis**
41	II	In myxedema, morphine acts for a much longer time because of the low rate of	acylation	reduction	oxidation	hydration	**oxidation**
42	II	Both tobacco smoke and alcohol consumption induce	renal enzymes	cardiac enzymes	liver enzymes	Kidney enzymes	**liver enzymes**
43	II	The phenomenon of the total pharmacological action of two or more drugs Administered together is equivalent to the sum of their individual Pharmacological actions is termed as	an synergism	an antagonism	a drug intolerance	an addictive effect	**an addictive effect**
44	II	Facilitation of a pharmacological response by the concomitant use of two or more Drugs is called	antagonism	synergism	additive effect	drug intolerance	**synergism**
45	II	The phenomenon of opposing actions of two drugs on the same physiological System is termed as	drug antagonism	synergism	additive effect	drug intolerance	**drug antagonism**
46	II	The phenomenon of an unusually large dose of a drug is required to elicit an Effect ordinarily producedby the normal therapeutic dose of the drug is termed as drug	tolerance	drug tolerance	antagonism	synergism	**drug tolerance**
47	II	The development of tolerance is confined to certain effects or to certain systems is called	cross tolerance	racial tolerance	tissue tolerance	species tolerance	**tissue tolerance**
48	II	Functional tolerance is otherwise known as	pharmacodynamic tolerance	pharmacogenetic tolerance	acquired tolerance	tachyphylaxis	**pharmacodynamic tolerance**
49	II	If drugs like ephedrine, tyramine etc are administered repeatedly as very short Intervals, the pharmacological response elicited decrease progressively, this Phenomenon is known as	true tolerance	functional tolerance	antagonism	tachyphylaxis	**tachyphylaxis**
50	II	chyphylaxis is otherwise known as	acquired tolerance	acute tolerance	tissue tolerance	true tolerance	**acute tolerance**
51	II	Determination of the amount of biological activity in a unit quantity of the Preparation is known as	chemical assay	immunological assay	bioassay	Radioassay	**bioassay**

52	II	Radio immuno assay is	physico-chemical assay	chemical assay	biological assay	Radioassay	**physico-chemical assay**
53	II	ELISA	Enzyme linked Immunosorbent assay	Enzyme linked innate assay	Enzyme linked immune assay	Enzyme linked immune soluble assay	**Enzyme linked Immunosorbent assay**
54	II	Any response to a drug that is noxious and unintended and that occurs at doses Used in man for prophylaxis, diagnosis or therapy is called an	adverse drug reactions	drug intolerance	drug allergy	idiosyncracy	**adverse drug reactions**
55	II	Inability of the individuals to tolerate a drug is called	Idiosyncracy	drug intolerance	adverse drug reactions	drug allergy	**drug intolerance**
56	II	Qualitative intolerance due to other than immune mechanism is known as	tachyphylaxis	drug intolerance	adverse effects	idiosyncracy	**idiosyncracy**
57	II	The innate immune system are	macrophages and NKcells	lymphocytes	macrophages and lymphocytes	NKcells and mast cells	**macrophages and NKcells**
58	II	Origin of T-lymphocytes is	bursa of fabricus	thymus	thyroid	T cells	**Thymus**
59	II	What type of T-cells are mainly responsible for the helper function	T-cells bearing on CD_4 antigen	T-cells bearing on CD_8 antigen	B cells	K cells	**T-cells bearing on CD_4 antigen**
60	II	When does tachyphylaxis occur	When there is a decreased receptor mediated response to a drug	When there is an increased risk of side effect occurring	When smaller doses cause an increased response to a drug	When the drug causes a faster heart rate	**When there is a decreased receptor mediated response to a drug**
61	II	What term is used to describe a decrease in responsiveness to a drug which develops in a few minutes?	Refractoriness	Cumulative effect	Tolerance	Tachyphylaxis	**Tachyphylaxis**
62	II	If two drugs with the same effect, taken together, produce an effect that is equal in magnitude to the sum of the effects of the drugs given individually, it is called as:	Antagonism	Potentiation	Additive effect	Agonism	**Additive effect**
63	II	What phenomenon can occur in case of using a combination of drugs?	Tolerance	Tachyphylaxis	Accumulation	Synergism	**Synergism**
64	II	Inflammatory reactions initiated by mononuclear lymphocytes and not by Antibody alone are called	Type I hypersensitivity	Type II hypersensitivity	Delayed hypersensitivity	Type III hypersensitivity	**Delayed hypersensitivity**
65	II	What type of drugs should be avoided during menstruation?	Drugs likely to produce pelvic congestion	Drugs which may stimulate uterine smooth muscle	Nephrotoxic drugs	Neurotoxic drugs	**Drugs likely to produce pelvic congestion**
66	II	The development of tolerance is confined to certain effects or to certain systems is called	Cross tolerance	Racial tolerance	Tissue tolerance	Species tolerance	**Tissue tolerance**
67	II	Enzymes used in ELISA are	Acid phosphatase and penicillinase	Acid phosphatase and peptidase	Alkaline phosphatase and penicillanase	Zinc phosphate	**Alkaline phosphatase and penicillanase**
68	II	Cells of the innate immune system are	Macrophages and NK cells	Lymphocytes	Macrophages and lymphocytes	NK cells and mast cells	**Macrophages and NK cells**
69	II	Origin of T-lymphocytes is	Bursa of fabricus	Thymus	Thyroid	T cells	**Thymus**
70	II	Idiosyncratic reaction of a drug is:	A type of hypersensitivity reaction	A type of drug antagonism	Unpredictable, inherent, qualitatively abnormal reaction to a drug	Quantitatively exaggerated response	**Unpredictable, inherent, qualitatively abnormal reaction to a drug**
71	II	Tachyphylaxis is:	A drug interaction between two similar types of drugs	Very rapidly developing tolerance	A decrease in responsiveness to a drug, taking days or weeks to develop	A drug interaction between similar types of drugs	**Very rapidly developing tolerance**
72	II	What type of T-cells is mainly responsible for the helper function?	T-cells bearing on CD_4 antigen	T-cells bearing on CD_8 antigen	B cells bearing on CD_8 antigen	NK cells	**T-cells bearing on CD_4 antigen**
73	II	Radio immuno assay is	Physico-chemical assay	Chemical assay	Biological assay	Radioassay	**Physico-chemical assay**
74	II	The drugs used to treat abusing of opioids is	Ibu brufen	Methadone	Diclofenac	Analgesic	**Methadone**
75	II	The average dose of drug is mentioned in terms of	mg per kg body weight	µg per kg body weight	kg per kg body weight	cal per kg body weight	**mg per kg body weight**
76	II	Consumption of alcohol enhances the effect of	CNS depressants	CNS stimulants	CSF depressants	CSF stimulants	**CNS depressants**
77	II	The phenomenon of an unusually large dose of a drug is required to elicit an effect ordinarily produced by the normal therapeutic dose of the drug is termed as drug	Tolerance	Drug tolerance	Antagonism	Synergism	**Drug tolerance**

UNIT-III-SYLLABUS

Drug abuse; drug dependence; drug resistance- Biological mechanism, ways to overcome. **Chemotherapy**: Antibacterials – Mode of action of sulfonamides, penicillin, streptomycin, tetracycline, chloramphenicol, antiviral drugs, antifungal drugs; Antimetabolites of folate, purines & pyrimidines, Anti tubercular drugs.

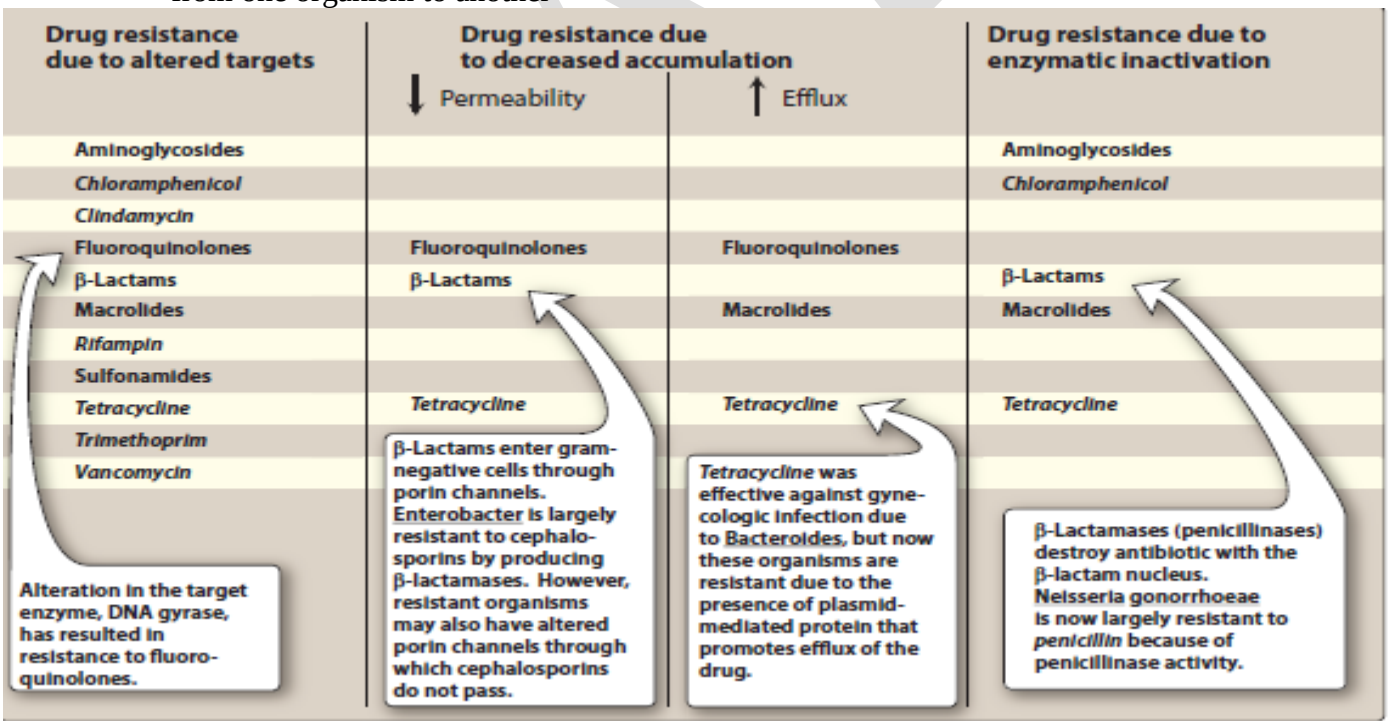
Drug resistance:

- ♣ Bacteria are considered resistant to an antibiotic if the maximal level of that antibiotic that can be tolerated by the host does not halt their growth. Some organisms are inherently resistant to an antibiotic.
- ♣ For example, most gram-negative organisms are inherently resistant to *vancomycin*.
- ♣ However, microbial species that are normally responsive to a particular drug may develop more virulent or resistant strains through spontaneous mutation or acquired resistance and selection.

A. Genetic alterations leading to drug resistance

– Acquired antibiotic resistance requires the temporary or permanent gain or alteration of bacterial genetic information.

– Resistance develops due to the ability of DNA to undergo spontaneous mutation or to move from one organism to another



B. Altered expression of proteins in drug-resistant organisms

Drug resistance is mediated by a variety of mechanisms, such as an alteration in an antibiotic target site, lowered penetrability of the drug due to decreased permeability, increased efflux of the drug, or presence of antibiotic-inactivating enzymes

1. **Modification of target sites:**
   - ♣ Alteration of an antibiotic's target site through mutation can confer resistance to one or more related antibiotics.
   - ♣ For example, S. pneumoniae resistance to β-lactam antibiotics involves alterations in one or more of the major bacterial penicillin-binding proteins, resulting in decreased binding of the antibiotic to its target.
2. **Decreased accumulation:**
   - ♣ Decreased uptake or increased efflux of an antibiotic can confer resistance because the drug is unable to attain access to the site of its action in sufficient concentrations to injure or kill the organism.
   - ♣ For example, gram-negative organisms can limit the penetration of certain agents, including β-lactam antibiotics, as a result of an alteration in the number and structure of porins (channels) in the outer membrane.
3. **Enzymatic inactivation:**
   - ♣ The ability to destroy or inactivate the antimicrobial agent can also confer resistance on microorganisms. Examples of antibiotic-inactivating enzymes include

1) β-lactamases ("penicillinases") that hydrolytically inactivate the β-lactam ring of penicillins, cephalosporins, and related drugs;
2) acetyltransferases that transfer an acetyl group to the antibiotic, inactivating *chloramphenicol* or aminoglycosides; and
3) esterases that hydrolyze the lactone ring of macrolides.

Drug abuse

- ♣ Drug abuse/ Substance abuse: using chemicals for nontherapeutic effects on the body or mind .
- ♣ Excessive use or misuse of drugs or alcohol for} intoxicating or mind altering effects.

Examples on commonly abused substance:

- Amphetamines
- Cocaine
- MDMA
- Synthetic cathiones (Bath salts)
- Marijuana
- Synthetic cannabinoids
- Ethanol
- Prescription drugs (particularly opioids)

- Substances have become more potent, and their routes of administration have become increasingly effective, resulting in greater risks of addiction and toxicity.

Sympathomimetics:

- Sympathomimetics are stimulants that mimic the sympathetic nervous system, producing "fightor-flight" responses Sympathomimetics produce a relative increase of adrenergic neurotransmitters at their sites of action causing tachycardia, hypertension, hyperthermia, and tachypnea Many have a remarkable ability to produce} pleasure with high addictive potential.
  - ❖ Amphetamines
  - ❖ Cocaine
  - ❖ Methylenedioxymethamphetamine (MDMA)}
  - ❖ Synthetic cathiones (Bath salts)}

Cocaine:

- Derived from the erythroxylon coca shrub Causes CNS) stimulation by inhibiting the reuptake of NE The profound ability of cocaine to stimulate the pleasure.
- center of the human brain is thought to result from inhibition of reuptake of dopamine and serotonin Minimal bioavailability when taken by the oral route.
- Cocaine hydrochloride powder is snorted, or solubilized and injected Crack cocaine, an alkaloidal form, can be smoked.
- Smoking is an extremely effective route of administration, as the drug reaches the brain within seconds" that is followed rapidly by an intense dysphoria or "crash" It is this immediate positive reinforcement, followed rapidly by the negative reinforcement, that makes the drug so addictive.
- Common reasons for cocaine users to come to the emergency department include psychiatric complaints (depression precipitated by cocaine dysphoria, agitation/paranoia), convulsions, hyperthermia, and chest pain.
- Hyperthermia is a major causes of cocaine fatalities.
- Commonly, cocaine is consumed with alcohol, which} creates a cardiotoxic metabolite called cocaethylene.

Ethanol:

- ❖ Clear colorless hydroxylated hydrocarbon that is the product of fermentation of fruits, grains, or vegetables.
- ❖ It is a major cause of fatal automobile accidents,} drownings, and fatal falls and is a related factor in many hospital admissions Alcoholism decreases life expectancy by 10 to 15 years}.
- ❖ It is thought that ethanol exerts its desired and toxic} effects through several mechanisms

◦ Enhancing the effects of the inhibitory neurotransmitter GABA

- Inducing the release of endogenous opioids
- Altering levels of serotonin and dopamine

❖ At high doses, it is a general CNS depressant, which} can result in coma and respiratory depression.

Chemotherapy

♣ Drugs in this class differ from all others in that they are designed to inhibit/kill the infecting organism and to have no/minimal effect on the recipient.

♣ This type of therapy is generally called *chemotherapy* which has come to mean 'treatment of systemic infections with specific drugs that selectively suppress the infecting microorganism without significantly affecting the host.'

♣ The basis of selective microbial toxicity is the action of the drug on a component of the microbe (e.g. bacterial cell wall) or metabolic processes (e.g. folate synthesis) that is not found in the host, or high affinity for certain microbial biomolecules (e.g. trimethoprim for bacterial dihydrofolate reductase).

Antibiotics:

- *Antibiotics* These are substances produced by microorganisms, which selectively suppress the growth of or kill other microorganisms at very low concentrations.
- This definition excludes other natural substances which also inhibit microorganisms but are produced by higher forms (e.g. antibodies) or even those produced by microbes but are needed in high concentrations (ethanol, lactic acid, H2O2).

A. Narrow-spectrum antibiotics

❖ Chemotherapeutic agents acting only on a single or a limited group of microorganisms are said to have a narrow spectrum. For example, *isoniazid* is active only against Mycobacterium tuberculosis .

B. Extended-spectrum antibiotics

❖ Extended spectrum is the term applied to antibiotics that are modified to be effective against gram-positive organisms and also against a significant number of gram-negative bacteria.

❖ For example, *ampicillin* is considered to have an extended spectrum because it acts against gram-positive and some gram-negative bacteria .

C. Broad-spectrum antibiotics

❖ Drugs such as *tetracycline*, fluoroquinolones and carbapenems affect a wide variety of microbial species and are referred to as broad-spectrum antibiotics .

CLASSIFICATION:

Antimicrobial drugs can be classified in many ways:

A. Chemical structure

1. *Sulfonamides and related drugs*:

Sulfadiazine and others, Sulfones—Dapsone (DDS), Paraaminosalicylic acid (PAS).

2. *Diaminopyrimidines:*

Trimethoprim, Pyrimethamine.

3. *Quinolones:*

Nalidixic acid, Norfloxacin, Ciprofloxacin, Prulifloxacin, etc.

4. β-*Lactam antibiotics:*

Penicillins, Cephalosporins, Monobactams, Carbapenems.

5. *Tetracyclines:*

Oxytetracycline, Doxycycline, etc.

6. *Nitrobenzene derivative:*

Chloramphenicol.

7. *Aminoglycosides:*

Streptomycin, Gentamicin, Amikacin, Neomycin, etc.

8. *Macrolide antibiotics:*

Erythromycin, Clarithromycin, Azithromycin, etc.

9. *Lincosamide antibiotics:*

Lincomycin, Clindamycin.

10. *Glycopeptide antibiotics:*

Vancomycin, Teicoplanin.

11. *Oxazolidinone:*

Linezolid.

12. *Polypeptide antibiotics:*

Polymyxin-B, Colistin, Bacitracin, Tyrothricin.

13. *Nitrofuran derivatives:*

Nitrofurantoin, Furazolidone.

14. *Nitroimidazoles:*

Metronidazole, Tinidazole, etc.

15. *Nicotinic acid derivatives:*

Isoniazid, Pyrazinamide, Ethionamide.

16. *Polyene antibiotics:*

Nystatin, Amphotericin- B, Hamycin.

17. *Azole derivatives:*

Miconazole, Clotrimazole, Ketoconazole, Fluconazole.

18. *Others:*

Rifampin, Spectinomycin, Sod. fusidate, Cycloserine, Viomycin, Ethambutol, Thiacetazone, Clofazimine, Griseofulvin.

B. Mechanism of action

1. *Inhibit cell wall synthesis*:

Penicillins, Cephalosporins, Cycloserine, Vancomycin, Bacitracin.

2. *Cause leakage from cell membranes*:

Polypeptides—Polymyxins, Colistin, Bacitracin. Polyenes-Amphotericin B, Nystatin, Hamycin.

3. *Inhibit protein synthesis:*

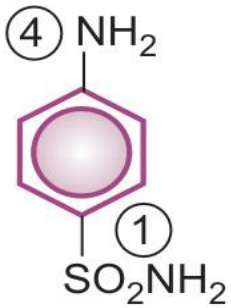
Tetracyclines, Chloramphenicol, Erythromycin, Clindamycin, Linezolid.

4. *Cause misreading of m-RNA code and affect permeability:*

Aminoglycosides— Streptomycin, Gentamicin, etc.

SULFONAMIDES

- Sulfonamides were the first antimicrobial agents (AMAs) effective against pyogenic bacterial infections.
- Sulfonamido-chrysoidine (Prontosil Red) was one of the dyes included by Domagk to treat experimental streptococcal infection in mice and found it to be highly effective.
- Subsequently an infant was cured of staphylococcal septicaemia (which was 100% fatal at that time) by prontosil. By 1937, it became clear that prontosil was broken down in the body to release sulfanilamide which was the active antibacterial agent.



SULFANILAMIDE

Sulfonamides that are still of clinical interest are:

1. Short acting (4–8 hr): Sulfadiazine
2. Intermediate acting (8–12 hr): Sulfamethoxazole
3. Long acting (~7 days): Sulfadoxine, Sulfamethopyrazine
4. Special purpose sulfonamides: Sulfacetamide sod., Mafenide, Silver sulfadiazine, Sulfasalazine

Antibacterial spectrum:

- Sulfonamides are primarily bacteriostatic against many gram-positive and gram-negative bacteria. However, bactericidal concentrations may be attained in urine.
- Sensitivity patterns among microorganisms have changed from time-to-time and place-to-place.
- Those still sensitive are: many *Strepto. pyogenes, Haemophilus influenzae, H. ducreyi, Calymmatobacterium granulomatis, Vibrio cholerae. Only a* few *Staph. aureus,* gonococci, meningococci, pneumococci, *Escherichia coli,* and *Shigella* respond, but majority are resistant.
- Anaerobic bacteria are not susceptible.

Mechanism of action

- Many bacteria synthesize their own folic acid (FA) of which p-aminobenzoic acid (PABA) is a constituent, and is taken up from the medium.
- Woods and Fildes (1940) proposed the hypothesis that sulfonamides, being structural analogues of PABA, inhibit bacterial folate synthase → FA is not formed and a number of essential metabolic reactions suffer.
- Sulfonamides competitively inhibit the union of PABA with pteridine residue to form dihydropteroic acid which conjugates with glutamic acid to produce dihydrofolic acid. Also, being chemically similar to PABA, the sulfonamide may itself get incorporated to form an altered folate which is metabolically injurious.
- Human cells also require FA, but they utilize preformed FA supplied in diet and are unaffected by sulfonamides.
- Evidences in favour of this mechanism of action of sulfonamides are:
  (a) PABA, in small quantities, antagonizes the antibacterial action of sulfonamides.
  (b) Only those microbes which synthesize their own FA, and cannot take it from the medium are susceptible to sulfonamides.
- Pus and tissue extracts contain purines and thymidine which decrease bacterial requirement for FA and antagonize sulfonamide action. Pus is also rich in PABA.

Resistance to sulfonamides

- Most bacteria are capable of developing resistance to sulfonamides. Prominent among these are gonococci, pneumococci, *Staph. aureus*, meningococci, *E. coli*, *Shigella* and some *Strep. pyogenes*, *Strep. viridans* and anaerobes.
- The resistant mutants either:
  (a) produce increased amounts of PABA, or
  (b) their folate synthase enzyme has low affinity for sulfonamides, or
  (c) adopt an alternative pathway in folate metabolism.

Pharmacokinetics

- Sulfonamides are rapidly and nearly completely absorbed from g.i.t. Extent of plasma protein binding differs considerably (10–95%) among different members.
- The highly protein bound members are longer acting. Sulfonamides are widely distributed in the body—enter serous cavities easily.
- The free form of sulfadiazine attains the same concentration in CSF as in plasma. They cross placenta freely. drug—may precipitate and cause crystalluria.
- Sulfonamides are excreted mainly by the kidney through glomerular filtration. Both renal tubular secretion and reabsorption occur.
- The more lipid-soluble members are highly reabsorbed in the tubule, therefore are longer acting.

Adverse effects

Adverse effects to sulfonamides are relatively common. These are:

- Nausea, vomiting and epigastric pain.
- Crystalluria is dose related, but infrequent now. Precipitation in urine can be minimized by taking plenty of fluids and by alkalinizing the urine in which sulfonamides and their acetylated derivatives are more soluble.
- Hypersensitivity reactions occur in 2–5% patients. These are mostly in the form of rashes, urticaria and drug fever. Photosensitization is reported.
- Hepatitis, unrelated to dose, occurs in 0.1% patients. Topical use of sulfonamides is not allowed, because of risk of contact sensitization. However, ocular use is permitted.
- Haemolysis can occur in G-6-PD deficient individuals with high doses of sulfonamides. Neutropenia and other blood dyscrasias are rare.

PENICILLINS

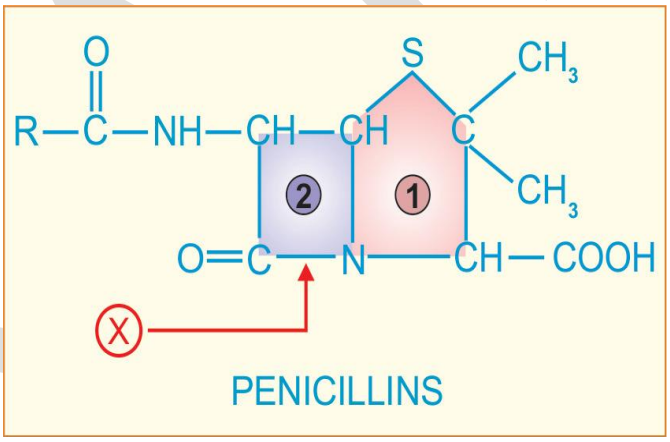
Prepared by Dr. M. Sridhar Muthusami, Department of Biochemistry, KAHE

- Beta-Lactam Antibiotics

- Penicillin was the first antibiotic to be used clinically in 1941. It is a miracle that the least toxic drug of its kind was the first to be discovered. It was originally obtained from the fungus *Penicillium notatum*, but the present source is a high yielding mutant of *P. chrysogenum*.
- These are antibiotics having a β-lactam ring. The two major groups are penicillins and cephalosporins.

Chemistry and properties

- The penicillin nucleus consists of fused thiazolidine and β-lactam rings to which side chains are attached through an amide linkage .
- Penicillin G (PnG), having a benzyl side chain at R (benzyl penicillin), is the original penicillin used clinically.
- The side chain of natural penicillin can be split off by an amidase to produce 6-aminopenicillanic acid.
- Other side chains can then be attached to it resulting in different semisynthetic penicillins with unique antibacterial activities and different pharmacokinetic profiles.



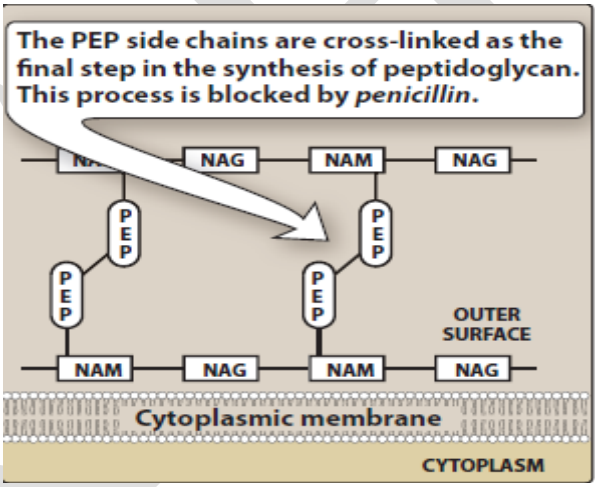
(1) Thiazolidine ring; (2) β-lactam ring; (X) Bond which is broken by penicillinase.

Mechanism of action

- All β-lactam antibiotics interfere with the synthesis of bacterial cell wall. The bacteria

synthesize UDP-N-acetylmuramic acid pentapeptide, called 'Park nucleotide' (because Park in 1957 found it to accumulate when susceptible *Staphylococcus* was grown in the presence of penicillin) and UDP-N-acetyl glucosamine.

- The peptidoglycan residues are linked together forming long strands and UDP is split off. The final step is cleavage of the terminal D-alanine of the peptide chains by transpeptidases; the energy so released is utilized for establishment of cross linkages between peptide chains of the neighbouring strands .
- This cross linking provides stability and rigidity to the cell wall.
- The β-lactam antibiotics inhibit the transpeptidases so that cross linking (which maintains the close knit structure of the cell wall) does not take place.
- These enzymes and related proteins constitute the *penicillin binding proteins (PBPs)* which have been located in the bacterial cell membrane.



Bacterial cell wall of gram-positive bacteria. (NAM = *N*-acetylmuramic acid; NAG = *N*-acetylglucosamine; PEP = cross-linking peptide.)

Bacterial resistance

- Many bacteria are inherently insensitive to PnG because in them the target enzymes and PBPs are located deeper under lipoprotein barrier where PnG is unable to penetrate or have low affinity for PnG. The primary mechanism of acquired resistance is production of penicillinase.
- *Penicillinase:* It is a narrow spectrum β-lactamase which opens the β-lactam ring and inactivates PnG and some closely related congeners.
- Majority of *Staphylococci* and some strains of gonococci, *B. subtilis, E. coli, H. influenza* and few other bacteria produce penicillinase.

Pharmacokinetics

- Penicillin G is acid labile, therefore destroyed by gastric acid. As such, less than 1/3rd of an oral dose is absorbed in the active form.
- Absorption of sod. PnG from i.m. site is rapid and complete; peak plasma level is attained in 30 min. It is distributed mainly extracellularly; reaches most body fluids, but penetration in serous cavities and CSF is poor.
- However, in the presence of inflammation (sinovitis, meningitis, etc.) adequate amounts may reach these sites. About 60% is plasma protein bound.
- It is little metabolized because of rapid excretion.
- The pharmacokinetics of PnG is dominated by very rapid renal excretion; about 10% by glomerular filtration and the rest by tubular secretion.
- Penicillinase has been successfully used to destroy PnG in patient's blood sample so that it does not interfere with bacterial growth when such blood is cultured.
- Some resistant bacteria become *penicillin tolerant* and not penicillin destroying.
- Their target enzymes are altered to have low affinity for penicillin, e.g. highly resistant pneumococci isolated in some areas have altered PBPs.

Adverse reactions

Penicillins are among the safest drugs, and blood levels are not monitored. However, adverse reactions may occur.

1. **Hypersensitivity:**

Approximately 5% percent of patients have some kind of reaction, ranging

from rashes to angioedema (marked swelling of the lips, tongue, and periorbital area) and anaphylaxis. Cross-allergic reactions occur among the β-lactam antibiotics.

2. **Diarrhea:**

   Diarrhea is a common problem that is caused by a disruption of the normal balance of intestinal microorganisms. It occurs to a greater extent with those agents that are incompletely absorbed and have an extended antibacterial spectrum. seudomembranous colitis from Clostridium difficile and other organisms may occur with penicillin use.

3. **Nephritis:**

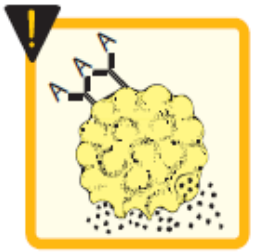
   Penicillins, particularly *methicillin*, have the potential to cause acute interstitial nephritis.

4. **Neurotoxicity:**

   The penicillins are irritating to neuronal tissue, and they can provoke seizures if injected intrathecally or if very high blood levels are reached. Epileptic patients are particularly at risk due to the ability of penicillins to cause GABAergic inhibition.

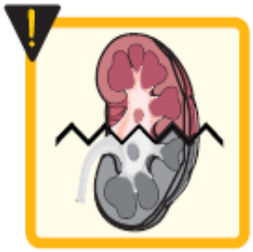
5. **Hematologic toxicities:**

   Decreased coagulation may be observed with high doses of *piperacillin*, *ticarcillin*, and *nafcillin* (and, to some extent, with *penicillin G*). Cytopenias have been associated with therapy of greater than 2 weeks, and therefore, blood counts should be monitored weekly for such patients.



Hypersensitivit

Diarrhea



Nephritis

Neurotoxicity

Hematologic toxicities

Uses

Penicillin G is the drug of choice for infections caused by organisms susceptible to it, unless the patient is allergic to this antibiotic. However, use has declined very much due to fear of causing anaphylaxis.

- *Streptococcal infections* Like pharyngitis, otitis media, scarlet fever, rheumatic fever respond to ordinary doses of PnG because *Strep. pyogenes* has not developed significant resistance.
- *Pneumococcal infections* PnG is not used now for empirical therapy of pneumococcal (lobar) pneumonia and meningitis because many strains have become highly penicillin resistant.
- *Meningococcal infections* are still mostly responsive; meningitis and other infections may be treated with intravenous injection of high doses.
- *Gonorrhoea* PnG has become unreliable for treatment of gonorrhoea due to spread of resistant strains.
- *Diphtheria* Antitoxin therapy is of prime importance. Procaine penicillin 1–2 MU daily for 10 days is used to prevent carrier state.
- *Tetanus and gas gangrene* Antitoxin and other measures are more important; PnG 6–12 MU/day is used to kill the causative organism and has adjuvant value.
- Penicillin G is the drug of choice for rare infections like anthrax, actinomycosis, rat bite fever and those caused by *Listeria monocytogenes, Pasteurella multocida.*

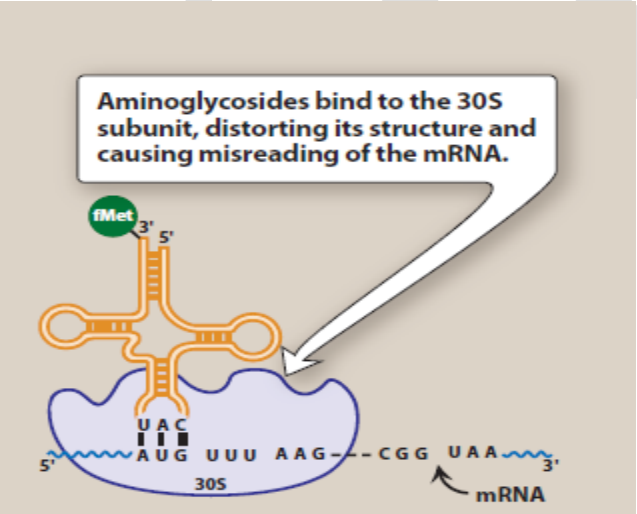
Streptomycin

- It is the oldest aminoglycoside antibiotic obtained from *Streptomyces griseus*; which was used extensively in the past, but is now practically restricted to treatment of tuberculosis.
- It is less potent (MICs are higher) than many other aminoglycosides.
- The antimicrobial spectrum of streptomycin is relatively narrow: primarily covers aerobic gram-negative bacilli. Sensitive organisms are—*H. ducreyi, Brucella, Yersinia pestis, Francisella tularensis, Nocardia, Calym. granulomatis, M. tuberculosis*.
- Only few strains of *E. coli, H. influenzae, V. cholerae, Shigella, Klebsiella*, enterococci and some gram-positive cocci are now inhibited, that too at higher concentrations.
- All other organisms including *Pseudomonas* are unaffected. *Resistance* Many organisms rapidly develop resistance to streptomycin, either by one-step mutation or by acquisition of plasmid which codes for inactivating enzymes.

- In the intestinal and urinary tracts, resistant organisms may emerge within 2 days of therapy. *E. coli, H. influenzae, Str. pneumoniae, Str. pyogenes, Staph. Aureus* have become largely resistant.

A. Mechanism of action

- Aminoglycosides diffuse through porin channels in the outer membrane of susceptible organisms. These organisms also have an oxygen-dependent system that transports the drug across the cytoplasmic membrane.
- Inside the cell, they bind the 30S ribosomal subunit, where they interfere with assembly of the functional ribosomal apparatus and/or cause the 30S subunit of the completed ribosome to misread the genetic code .
- Antibiotics that disrupt protein synthesis are generally bacteriostatic; however, aminoglycosides are unique in that they are bactericidal.



Antibacterial spectrum

- The aminoglycosides are effective for the majority of aerobic gram negative bacilli, including those that may be multidrug resistant, such as Pseudomonas aeruginosa, Klebsiella pneumoniae, and Enterobacter sp. Additionally, aminoglycosides are often combined with a β-lactam antibiotic to employ a synergistic effect, particularly in the treatment of Enterococcus faecalis and Enterococcus faecium infective endocarditis.

Pharmacokinetics

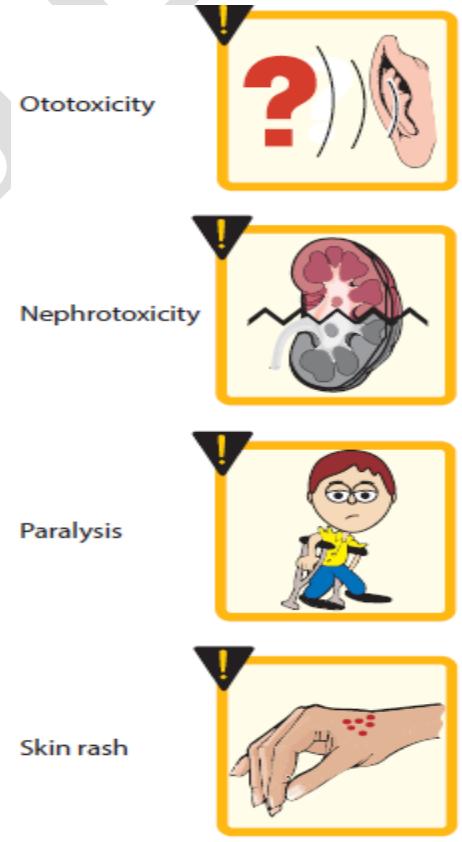
1. **Absorption:** The highly polar, polycationic structure of the aminoglycosides prevents adequate absorption after oral administration. Therefore, all aminoglycosides (except *neomycin* [nee-oh-MYEsin]) must be given parenterally to achieve adequate serum levels.

2. Distribution: All the aminoglycosides have similar pharmacokinetic properties. Due to their hydrophilicity, tissue concentrations may be subtherapeutic, and penetration into most body fluids is variable.

3. Elimination: More than 90% of the parenteral aminoglycosides are excreted unchanged in the urine. Accumulation occurs in patients with renal dysfunction, and dose adjustments are required.

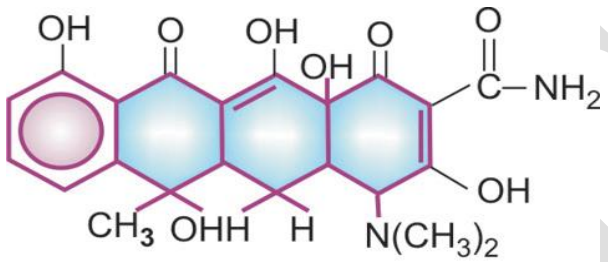
Adverse effects

- About 1/5 patients given streptomycin 1 g BD i.m. experience vestibular disturbances. Auditory disturbances are less common.
- Streptomycin has the lowest nephrotoxicity among aminoglycosides; probably because it is not concentrated in the renal cortex.
- Hypersensitivity reactions are rare; rashes, eosinophilia, fever and exfoliative dermatitis have been reported. Anaphylaxis is very rare.
- Topical use is contraindicated for fear of contact sensitization. Super infections are not significant. Pain at injection site is common.
- Paraesthesias and scotoma are occasional. It is contraindicated during pregnancy due to risk of foetal ototoxicity.
- Ototoxicity (vestibular and auditory)-antibiotic accumulates in the endolymph and perilymph of the inner ear.
- Deafness may be irreversible and has been known to affect developing fetuses.



TETRACYCLINES

❖ These are a class of antibiotics having a nucleus of four cyclic rings.



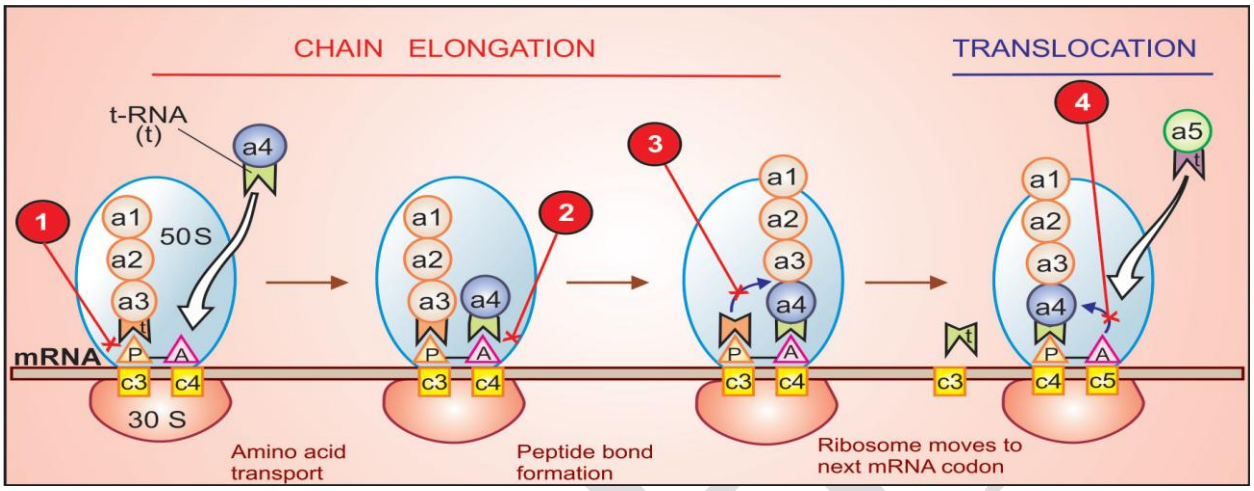
TETRACYCLINE

- ❖ All are obtained from soil actinomycetes. The first to be introduced was chlortetracycline in 1948 under the name *aureomycin* (because of the golden yellow colour of *S. aureofaciens* colonies producing it).
- ❖ All tetracyclines are slightly bitter solids which are slightly water soluble, but their hydrochlorides are more soluble.
- ❖ Aqueous solutions are unstable. All have practically the same antimicrobial activity (with minor differences).
- ❖ The subsequently developed members have high lipid solubility, greater potency and some other differences.
- ❖ The tetracyclines still available in India for clinical use are:
  - Tetracycline
  - Doxycycline
  - Oxytetracycline
  - Minocycline and Demeclocycline

Mechanism of action:

- ❖ The tetracyclines are primarily bacteriostatic; inhibit protein synthesis by binding to 30S ribosomes in susceptible organism. Subsequent to such binding, attachment of aminoacyl-t-RNA to the acceptor (A) site of mRNA-ribosome complex is interferred with.
- ❖ As a result, the peptide chain fails to grow. The sensitive organisms have an energy dependent active transport process which concentrates tetracyclines intracellularly.
- ❖ In gram-negative bacteria tetracyclines diffuse through porin channels as well. The more lipid-soluble members (doxycycline, minocycline) enter by passive diffusion also (this is partly responsible for their higher potency).

❖ The carrier involved in active transport of tetracyclines is absent in the host cells. Moreover, protein synthesizing apparatus of host cells is less susceptible to tetracyclines. These two factors are responsible for the selective toxicity of tetracyclines for the microbes.



Bacterial protein synthesis and the site of action of antibiotics

The messenger RNA (mRNA) attaches to the 30S ribosome. The initiation complex of mRNA starts protein synthesis and polysome formation. The nacent peptide chain is attached to the peptidyl (P) site of the 50S ribosome. The next amino acid (a) is transported to the acceptor (A) site of the ribosome by its specific tRNA which is complementary to the base sequence of the next mRNA codon (C). The nascent peptide chain is transferred to the newly attached amino acid by peptide bond formation. The elongated peptide chain is shifted back from the 'A' to the 'P' site and the ribosome moves along the mRNA to expose the next codon for amino acid attachment. Finally the process is terminated by the termination complex and the protein is released.

(1) Aminoglycosides bind to several sites at 30S and 50S subunits as well as to their interface—freeze initiation, interfere with polysome formation and cause misreading of mRNA code.

(2) Tetracyclines bind to 30S ribosome and inhibit aminoacyl tRNA attachment to the 'A' site.

(3) Chloramphenicol binds to 50S subunit—interferes with peptide bond formation and transfer of peptide chain from 'P' site.

(4) Erythromycin and clindamycin also bind to 50S ribosome and hinder translocation of the elongated peptide chain back from 'A' site to 'P' site and the ribosome does not move along the mRNA to expose the next codon. Peptide synthesis may be prematurely terminated.

Antibacterial spectrum

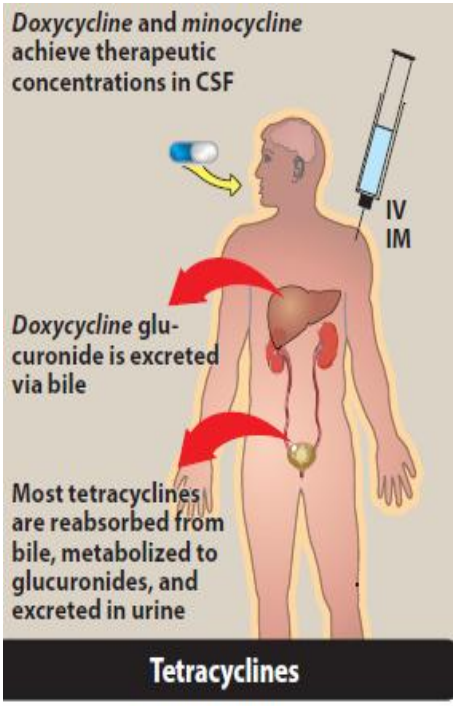
- The tetracyclines are bacteriostatic antibiotics effective against a wide variety of organisms, including gram-positive and gram-negative bacteria, protozoa, spirochetes, mycobacteria, and atypical species . They are commonly used in the treatment of acne and Chlamydia infections (*doxycycline).*

Resistance

- Resistance to tetracyclines develops slowly in a graded manner. In such bacteria, usually the tetracycline concentrating mechanism becomes less efficient or the bacteria acquire capacity to pump it out.
- Another mechanism is plasmid mediated synthesis of a 'protection' protein which protects the ribosomal binding site from tetracycline.
- Elaboration of tetracycline inactivating enzymes is an unimportant mechanism of the tetracycline resistance. Due to widespread use, tetracycline resistance has become common among grampositive cocci, *E. coli*, *Enterobacter* and many others.
- Incomplete cross resistance is seen among different members of the tetracycline group. Some organisms not responding to other tetracyclines may be inhibited by therapeutically attained concentrations of doxycycline and minocycline (the most potent agent).
- Partial cross resistance between tetracyclines and chloramphenicol has been noted.

Pharmacokinetics

1. Absorption: Tetracyclines are adequately absorbed after oral ingestion . Administration with dairy products or other substances that contain divalent and trivalent cations (for example, magnesium and aluminum antacids or iron supplements) decreases absorption, particularly for *tetracycline* , due to the formation of nonabsorbable chelates



2. Distribution: The tetracyclines concentrate well in the bile, liver, kidney, gingival fluid, and skin. Moreover, they bind to tissues undergoing calcification (for example, teeth and bones) or to tumors that have a high calcium content. Penetration into most body fluids is adequate. Only *minocycline* and *doxycycline* achieve therapeutic levels in the cerebrospinal fluid (CSF).

3. Elimination: *Tetracycline* and *doxycycline* are not hepatically metabolized. *Tetracycline* is primarily eliminated unchanged in the urine, whereas *minocycline* undergoes hepatic metabolism and is eliminated to a lesser extent via the kidney. In renally compromised patients, *doxycycline* is preferred, as it is primarily eliminated via the bile into the feces.

Adverse effects

1. Gastric discomfort: Epigastric distress commonly results from irritation of the gastric mucosa and is often responsible for noncompliance with tetracyclines. *Tetracycline* should be taken on an empty stomach

2. Effects on calcified tissues: Deposition in the bone and primary dentition occurs during the calcification process in growing children. This may cause discoloration and hypoplasia of teeth and a temporary stunting of growth.

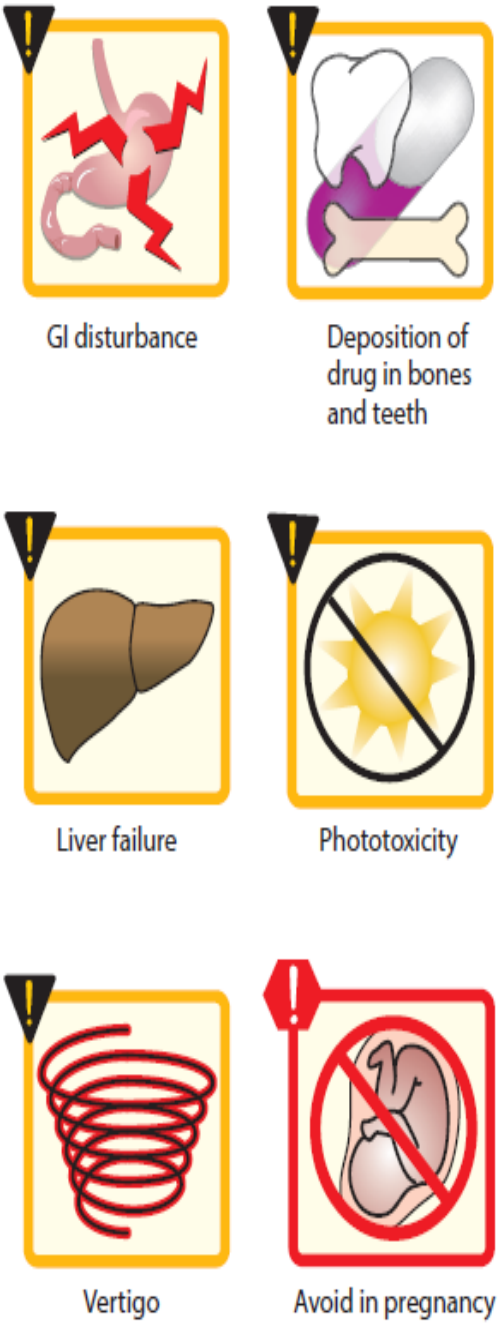
3. Hepatotoxicity: Rarely hepatotoxicity may occur with high doses, particularly in pregnant women and those with preexisting hepatic dysfunction or renal impairment.

4. Phototoxicity: Severe sunburn may occur in patients receiving a tetracycline who are exposed to sun or ultraviolet rays. This toxicity is encountered with any tetracycline, but more frequently with *tetracycline* and *demeclocycline*. Patients should be advised to wear adequate sun protection.

5. Vestibular dysfunction: Dizziness, vertigo, and tinnitus may occur particularly with *minocycline*, which concentrates in the endolymph of the ear and affects function. *Doxycycline* may also cause vestibular dysfunction.

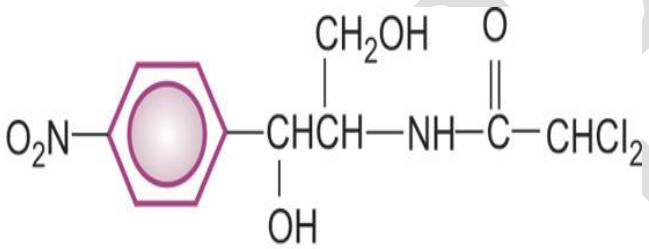
6. Pseudotumor cerebri: Benign, intracranial hypertension characterized by headache and blurred vision may occur rarely in adults. Although discontinuation of the drug reverses this condition, it is not clear whether permanent sequelae may occur.

7. Contraindications: The tetracyclines should not be used in pregnant or breast-feeding women or in children less than 8 years of age.



CHLORAMPHENICOL

- Chloramphenicol was initially obtained from *Streptomyces venezuelae* in 1947. It was soon synthesized chemically and the commercial product now is all synthetic.
- It is a yellowish white crystalline solid, aqueous solution is quite stable, stands boiling, but needs protection from light.
- The nitrobenzene moiety of chloramphenicol is probably responsible for the antibacterial activity as well as its intensely bitter taste**.**



CHLORAMPHENICOL

Mechanism of action

- Chloramphenicol inhibits bacterial protein synthesis by interfering with 'transfer' of the elongating peptide chain to the newly attached aminoacyl-tRNA at the ribosome-mRNA complex.
- It specifically attaches to the 50S ribosome near the acceptor (A) site and prevents peptide bond formation between the newly attached aminoacid and the nascent peptide chain without interfering with the aminoacyl-tRNA attachment to the 30S ribosome (the step blocked by tetracycline).
- At high doses, it can inhibit mammalian mitochondrial protein synthesis as well. Bone marrow cells are especially susceptible.

Antimicrobial spectrum

- Chloramphenicol is primarily bacteriostatic, though high concentrations have been shown to exert cidal effect on some bacteria, e.g. *H. influenzae* and *N. meningitidis*.
- It is a broad-spectrum antibiotic, active against nearly the same range of organisms (gram-positive and negative cocci and bacilli, rickettsiae, mycoplasma) as tetracyclines.
- Notable differences between these two are:

  (a) Chloramphenicol was highly active against *Salmonella* including *S. typhi*, but resistant strains are now rampant.

(b) It is more active than tetracyclines against *H. influenzae* (though some have now developed resistance), *B. pertussis, Klebsiella, N. meningitidis* and anaerobes including *Bact. fragilis.*

(c) It is less active against gram-positive cocci, spirochetes, certain Enterobacteriaceae and *Chlamydia. Entamoeba* and *Plasmodia* are not inhibited.

- Like tetracyclines, it is ineffective against *Mycobacteria*, *Pseudomonas*, many *Proteus*, viruses and fungi.

Resistance

- Resistance is conferred by the presence of enzymes that inactivate *chloramphenicol.* Other mechanisms include decreased ability to penetrate the organism and ribosomal binding site alterations.

Pharmacokinetics

- *Chloramphenicol* is administered intravenously and is widely distributed throughout the body. It reaches therapeutic concentrations in the CSF.
- *Chloramphenicol* primarily undergoes hepatic metabolism to an inactive glucuronide, which is secreted by the renal tubule and eliminated in the urine.
- Dose reductions are necessary in patients with liver dysfunction or cirrhosis. It is also secreted into breast milk and should be avoided in breastfeeding mothers.

Adverse effects

1. Anemias:

- Patients may experience dose-related anemia, hemolytic anemia (seen in patients with glucose-6-phosphate dehydrogenase deficiency), and aplastic anemia.

2. Gray baby syndrome:

- Neonates have a low capacity to glucuronidate the antibiotic, and they have underdeveloped renal function. Therefore, neonates have a decreased ability to excrete the drug, which accumulates to levels that interfere with the function of mitochondrial ribosomes.
- This leads to poor feeding, depressed breathing, cardiovascular collapse, cyanosis (hence the term "gray baby"), and death. Adults who have received very high doses of the drug can also exhibit this toxicity.

3. Drug interactions:

- *Chloramphenicol* inhibits some of the hepatic mixed-function oxidases and, thus, blocks the metabolism of drugs such as *warfarin* and *phenytoin,* thereby elevating their concentrations and potentiating their effects.

Uses

Clinical use of chloramphenicol for systemic infections is now highly restricted due to fear of fatal toxicity. Because of risk of serious (though rare) bone marrow aplasia:

(a) Never use chloramphenicol for minor infections or those of undefined etiology.

(b) Do not use chloramphenicol for infections treatable by other safer antimicrobials.

(c) Avoid repeated courses.

(d) Daily dose not to exceed 2–3 g; duration of therapy to be < 2 weeks, total dose in a course < 28 g.

(e) Regular blood counts (especially reticulocyte count) may detect dose-related bone marrow toxicity but not the idiosyncratic type.

(f) Combined formulation of chloramphenicol with any drug meant for internal use is banned in India.

Antiviral drugs

- Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- Viruses use much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the infected hostcells.
- Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated.
- At this stage of viral infection, administration of drugs that block viral replication has limited effectiveness. However, some antiviral agents are useful as prophylactic agents.

CLASSIFICATION

1. Anti-Herpes virus

Idoxuridine, Trifluridine, Acyclovir, Valacyclovir, Famciclovir, Ganciclovir, Valganciclovir, Cidofovir, Foscarnet, Fomivirsen

2. Anti-Influenza virus

Amantadine, Rimantadine, Oseltamivir, Zanamivir

3. Anti-Hepatitis virus/Nonselective antiviral drugs

Primarily for hepatitis B: Lamivudine, Adefovir dipivoxil, Tenofovir

Primarily for hepatitis C: Ribavirin, Interferon α

4. Anti-Retrovirus

(a) Nucleoside reverse transcriptase inhibitors (NRTIs): Zidovudine (AZT).

ANTI-HERPES VIRUS DRUGS

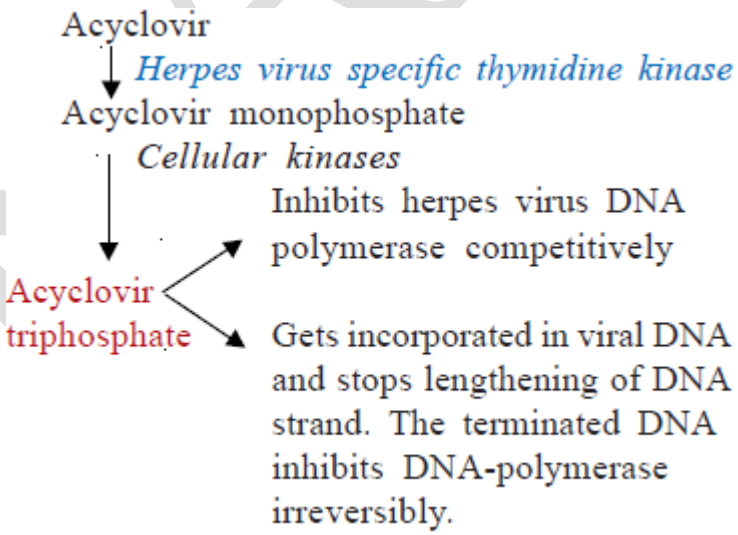
These are drugs active against the Herpes group of DNA viruses which include *Herpes simplex virus-1* (HSV-1), *Herpes simplex virus-2* (HSV2), *Varicella-Zoster virus* (VZV), *Epstein-Barr virus* (EBV), and *Cytomegalovirus* (CMV).

Idoxuridine

- It is 5-iodo-2-deoxyuridine (IUDR), which acts as a thymidine analogue. It was the first pyrimidine antimetabolite to be used as antiviral drug.
- It competes with thymidine, gets incorporated in DNA so that faulty DNA is formed which breaks down easily. It is effective only against DNA viruses and clinical utility is limited to topical treatment of *Herpes simplex* keratitis.
- Because of low virus selectivity, higher local toxicity and rapid development of viral resistance, use of idoxuridine is restricted to superficial dendritic keratitis when rapid action is required.
- Idoxuridine eye drops act faster than acyclovir eye ointment, which is more effective when there is stromal involvement of the cornea.
- Ocular irritation occurs with idoxuridine eye drops.
- *Dose*: 0.1% eye drops to be instilled hourly, then 2 hourly and 4 hourly; apply 0.1% eye ointment at night. IDURIN, TOXIL 0.1% eye drops and eye oint.

Acyclovir

- This deoxiguanosine analogue antiviral drug requires a virus specific enzyme for conversion to the active metabolite that inhibits DNA synthesis and viral replication.



- Acyclovir is preferentially taken up by the virus infected cells.
- Because of selective generation of the active inhibitor in the virus infected cell and its greater inhibitory effect on viral DNA synthesis, acyclovir has low toxicity for host cells: a several hundred-fold chemotherapeutic index has been noted.

Pharmacokinetics

- Only about 20% of an oral dose of acyclovir is absorbed. It is little plasma protein bound and is widely distributed attaining CSF concentration that is 50% of plasma concentration.
- After topical application, it penetrates cornea well. Acyclovir is primarily excreted unchanged in urine, both by glomerular filtration and tubular secretion; plasma t½ is 2–3 hours. Renal impairment necessitates dose reduction.

ANTI-INFLUENZA VIRUS DRUGS

Amantadine

- Chemically, it is a unique tricyclic amine unrelated to any nucleic acid precursor, but inhibits replication of influenza A virus (a myxovirus).
- The antiviral activity of amantadine is strain specific; influenza B is not affected. Moreover, H5N1 (avian influenza/bird flu) and H1N1 (swine flu) strains of influenza A are resistant in most areas.
- It appears to act at an early step (possibly uncoating) as well as at a late step (viral assembly) in viral replication. A protein designated ‘M2’ which acts as an ion channel has been identified as one of its targets of action.
- Resistance to amantadine develops by mutation causing amino acid substitutions in the M2 protein. Amantadine is well absorbed orally and excreted unchanged in urine over 2–3 days (t½ 16 hr).

Adverse effects

- Generally well tolerated; nausea, anorexia, insomnia, dizziness, nightmares, lack of mental concentration, rarely hallucinations have been reported. Ankle edema occurs due to local vasoconstriction.

USES

1. Prophylaxis of influenza A2 during an epidemic or seasonal influenza, especially in high risk patients. Influenza season and epidemics generally last ~ 2 months, and only this period needs to be covered by prophylaxis.
2. Treatment of influenzal (A2) illness: a modest therapeutic effect (reduction in fever, congestion, cough and quicker recovery) occurs if the drug is given immediately after the symptoms appear. A 5 day treatment is advised.

Oseltamivir

- This newer anti-influenza virus drug is a sialic acid analogue with broad spectrum activity covering influenza A (amantadine sensitive as well as resistant), H5N1 (bird flu), nH1N1 (swine flu) strains and influenza B.
- It is an ester prodrug that is rapidly and nearly completely hydrolysed during absorption in intestine and by liver to the active form *oseltamivir carboxylate* with an oral bioavailability of ~ 80%.
- The active metabolite is not further metabolized and is excreted by the kidney with a t½ of 6–10 hours.
- It acts by inhibiting influenza virus neuraminidase enzyme which is needed for release of progeny virions from the infected cell.
- Spread of the virus in the body is thus checked. Resistance can develop by mutation of the viral neuraminidase enzyme.
- In many areas oseltamivir-resistant H1N1 (seasonal influenza) and H5N1 have been encountered, though swine flu (nH1N1) is still mostly sensitive. Some oseltamivir-resistant strains remain susceptible to zanamivir and *vice versa*.
- Oseltamivir is indicated both for prophylaxis as well as treatment of influenza A, swine flu, bird flu and influenza B. Started at the onset of symptoms, it is the most effective drug; reduces the severity, duration and complications of the illness.
- Prophylactic use for 5–10 days prevents illness in contacts of influenza patients.

ANTI-HEPATITIS VIRUS/NONSELECTIVE - ANTIVIRAL DRUGS

- Several antiviral drugs are relatively virus nonselective and inhibit viruses belonging to different classes; even cover both DNA and RNA viruses.
- While hepatitis B virus (HBV) is a DNA virus which, like retroviruses, can integrate into host chromosomal DNA to establish permanent infection, the hepatitis C virus (HCV) is a RNA virus, which does not integrate into chromosomal DNA, does not establish noncurable infection, but frequently causes chronic hepatitis.

Interferon α

- Interferons (IFNs)are low molecular weight glycoprotein cytokines produced by host cells in response to viral infections, TNFα, IL-1 and some other inducers. They have nonspecific antiviral as well as other complex effects on immunity and cell proliferation.
- Interferons bind to specific cell surface receptors and affect viral replication at multiple steps, *viz.* viral penetration, synthesis of viral mRNA, assembly of viral particles and their release, but the most widespread effect is direct or indirect suppression of viral protein synthesis, i.e. inhibition of translation.

- Interferon receptors are JAK-STAT tyrosine protein kinase receptors which on activation phosphorylate cellular proteins. These then migrate to the nucleus and induce transcription of 'interferon-inducedproteins' which exert antiviral effects.
- Interferons inhibit many RNA and DNA viruses, but they are host specific: those produced by another species have poor activity in man.
- Three types of human IFNs (α, β and γ) are known to have antiviral activity. Only IFNα2A and IFNα2B produced by recombinant technology are available and are clinically used.
- Both are nonglycosylated low MW proteins administered by i.m. or s.c. injection. Their pegylated forms are meant for s.c. injection at weekly intervals.
- Plasma levels of pegIFNα2A are sustained twice longer than those of pegIFNα2B.

Uses

1. *Chronic hepatitis B:* IFNα2A 2.5−5 MU/m2 or IFNα2B 5−10 MU given 3 times per week for 4–6 months causes disappearance of HBV DNA from plasma and improvement in liver function tests/histology in nearly half of the patients.
2. *Chronic hepatitis C:* IFNα2B 3MU 3 times weekly for 6–12 months has produced remission in 50–70% patients. Viral RNA becomes undetectable and liver function tests return to normal.
3. *AIDS-related Kaposi's sarcoma:* IFN is used to treat AIDS related Kaposi's sarcoma, but not to treat HIV as such. However, interferon accentuates haematological toxicity of zidovudine.
4. *Condyloma acuminata:* caused by papilloma virus is usually treated with topical podophyllin. Intralesional interferon injection may be used in refractory cases.

Adverse effects

• Flu-like symptoms—fatigue, aches and pains, malaise, fever, dizziness, anorexia, nausea, taste and visual disturbances develop few hours after each injection, but become milder later.
• Neurotoxicity—numbness, neuropathy, altered behaviour, mental depression, tremor, sleepiness, rarely convulsions.
• Myelosuppression: dose dependent neutropenia, thrombocytopenia. • Thyroid dysfunction (hypo as well as hyper).
• Hypotension, transient arrhythmias, alopecia and liver dysfunction.

Ribavirin

- This purine nucleoside analogue has broad-spectrum antiviral activity, including that against influenza A and B, respiratory syncytial virus and many other DNA and double stranded RNA viruses.
- Its mono- and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA synthesis and have other sites of action as well. Viral resistance to ribavirin is rare. Oral bioavailability of ribavirin is ~50%.

- It is partly metabolized and eliminated in a multiexponential manner; accumulates in the body on daily dosing and persists months after discontinuation; long term t½ is > 10 days.
- Administered orally or i.v. ribavirin has been used in severe influenza A/B and measles in immunosuppressed patients as well as for herpes virus infections, acute hepatitis, but is not a first line drug for any of these.
- The most common therapeutic use of oral ribavirin is in chronic hepatitis C. Though ribavirin monotherapy may produce a response, it is incomplete.
- As per current recommendation, the first line treatment of chronic hepatitis C is oral ribavirin combined with injected peginterferon for 6–12 months.
- Recurrent cases are treated in the same way. Nebulized ribavirin is used for respiratory syncytial virus bronchiolitis in infants and children, particularly those with congenital heart disease, prematurity or other high risk conditions.
- It has also shown efficacy in some rare viral infections.

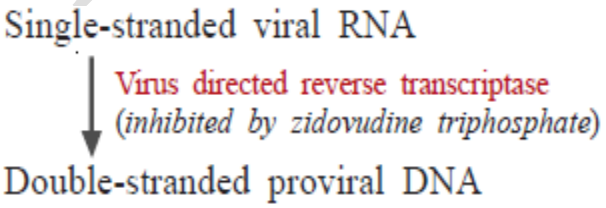
ANTI-RETROVIRUS DRUGS

- These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDSrelated complex (ARC), but do not cure the infection.
- The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

Nucleoside reverse transcriptase inhibitors (NRTIs):

Zidovudine

- It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudine triphosphate selectively inhibits viral reverse transcriptase in preference to cellular DNA polymerase.



- On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase.

- This proviral DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell (by viral integrase enzyme) which then starts transcribing viral genomic RNA as well as viral mRNA.
- Under the direction of viral mRNA, viral regulatory and structural proteins are produced in the form of a polyprotein. Finally, viral particles are assembled and matured after fractionation of the polyprotein by viral protease.
- Zidovudine thus prevents infection of new cells by HIV, but has no effect on proviral DNA that has already integrated into the host chromosome.
- It is effective only against retroviruses. Zidovudine itself gets incorporated into the proviral DNA and terminates chain elongation.
- Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme.

Pharmacokinetics

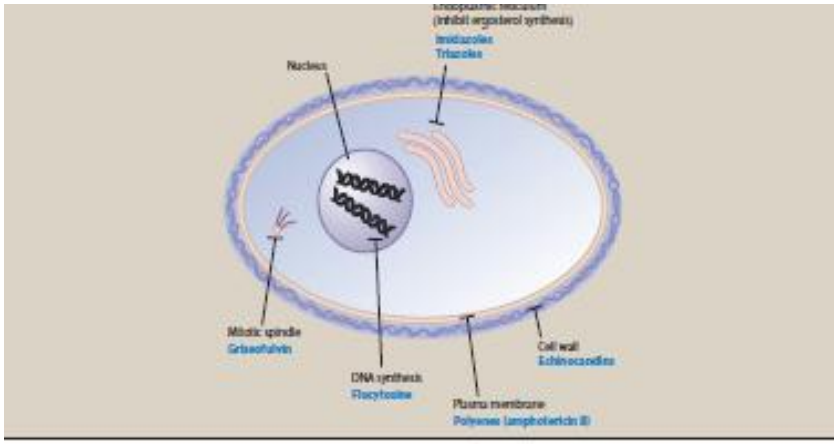
- The oral absorption of AZT is rapid, but bioavailability is ~65%. It is quickly cleared by hepatic glucuronidation (t½ 1 hr); 15–20% of the unchanged drug along with the metabolite is excreted in urine
- Plasma protein binding is 30% and CSF level is ~50% of that in plasma. It crosses placenta and is found in milk.

Adverse effects

- Toxicity is mainly due to partial inhibition of cellular mitochondrial DNA polymerase γ which has higher affinity for zidovudine triphosphate than chromosomal DNA polymerase.
- Anaemia and neutropenia are the most important and dose-related adverse effects. Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy, but diminish later.

Antifungal Drugs

- These are drugs used for superficial and deep (systemic) fungal infections. A disquietening trend after 1950s is the rising prevalence of more sinister type of fungal infections which are, to a large extent, iatrogenic.
- Fungal infections are mostly associated with the use of broad-spectrum antibiotics, corticosteroids, anticancer/immunosuppressant drugs, dentures, indwelling catheters and implants, and emergence of AIDS.
- As a result of breakdown of host defence mechanisms by the above agents, saprophytic fungi easily invade living tissue.

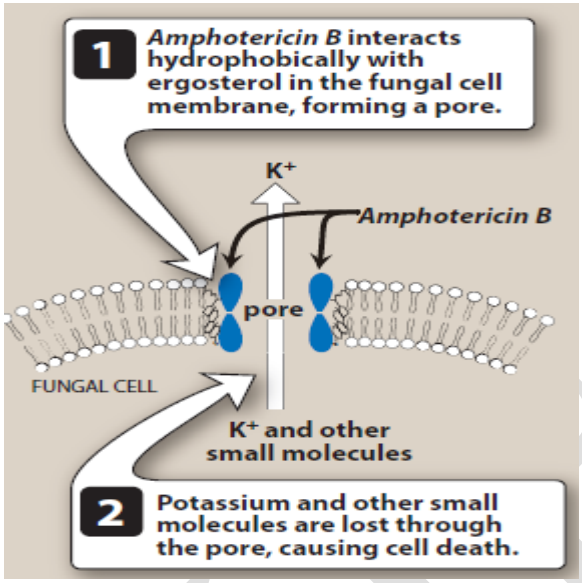


Amphotericin B (AMB)

- It is obtained from *Streptomyces nodosus*. *Chemistry and mechanism of action* The polyenes possess a macrocyclic ring, one side of which has several conjugated double bonds and is highly lipophilic, while the other side is hydrophilic with many OH groups.
- A polar amino sugar and a carboxylic acid group are present at one end in some. They are all insoluble in water and unstable in aqueous medium. The polyenes have high affinity for ergosterol present in fungal cell membrane.
- They combine with it, get inserted into the membrane and several polyene molecules together orient themselves in such a way as to form a 'micropore'.
- The hydrophilic side forms the interior of the pore through which ions, amino acids and other water-soluble substances move out.
- The micropore is stabilized by membrane sterols which fill up the spaces between the AMB molecules on the lipophilic side—constituting the outer surface of the pore. Thus, cell permeability is markedly increased.

1. Mechanism of action:

- *Amphotericin B* binds to ergosterol in the plasma membranes of sensitive fungal cells. There, it forms pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antifungal and the sterol .
- The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.



2. Antifungal spectrum:

- *Amphotericin B* is either fungicidal or fungistatic, depending on the organism and the concentration of the drug.
- It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus.

3. Resistance:

- Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane.

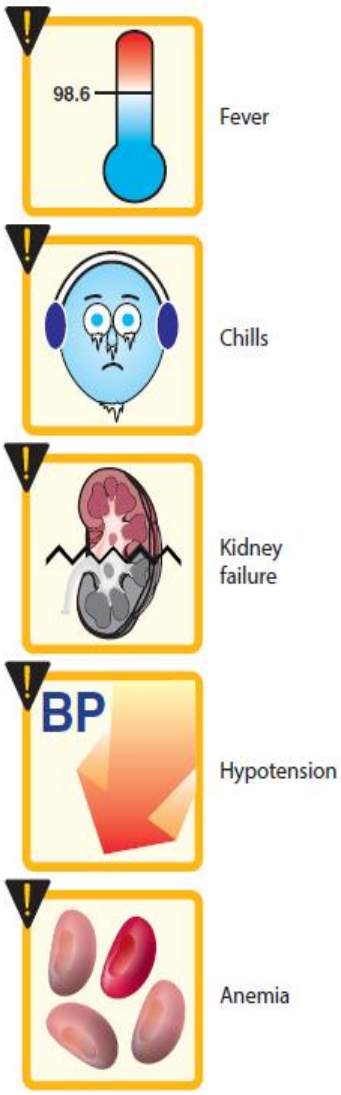
4. Pharmacokinetics:

- *Amphotericin B* is administered by slow, intravenous (IV) infusion . *Amphotericin B* is insoluble in water and must be coformulated with either sodium deoxycholate (conventional) or a variety of artificial lipids to form liposomes.
- The liposomal preparations have the primary advantage of reduced renal and infusion toxicity. However, due to high cost, liposomal preparations are reserved mainly as salvage therapy for patients who cannot tolerate conventional *amphotericin B.*
- *Amphotericin B* is extensively bound to plasma proteins and is distributed throughout the body.
- Inflammation favors penetration into various body fluids, but little of the drug is found in the CSF, vitreous humor, or amniotic fluid. However, *amphotericin B* does cross the placenta.
  Low levels of the drug and its metabolites appear in the urine over a long period of time, and some are also eliminated via the bile.

5. Adverse effects:

Amphotericin B has a low therapeutic index. The total adult daily dose of the conventional formulation should not exceed 1.5 mg/kg/d, whereas lipid formulations have been given

safely in doses up to 10 mg/kg/d. Toxic manifestations are outlined below.



a. Fever and chills:

These occur most commonly 1 to 3 hours after starting the IV administration but usually subside with repeated administration of the drug.

Premedication with a corticosteroid or an antipyretic helps to prevent this problem.

b. Renal impairment:

Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function.

Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost.

c. Hypotension:

A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation.

Care must be exercised in patients taking *digoxin* and other drugs that can cause potassium fluctuations.

d. Thrombophlebitis:

Adding *heparin* to the infusion can alleviate this problem.

Nystatin

- Obtained from *S. noursei*, it is similar to AMB in antifungal action and other properties.

However, because of higher systemic toxicity, it is used only locally in superficial candidiasis. Nystatin is effective (but less than azoles) in monilial vaginitis—1 lac U tab inserted twice daily.

- For oral thrush, the vaginal tab may be crushed and suspended in glycerine for application

in mouth. Corticosteroid aerosols (e.g. beclomethasone) can cause oral candidiasis: nystatin is effective in preventing as well as treating it. Similarly, it is used for corneal, conjunctival and cutaneous candidiasis in the form of an ointment.

- No irritation or other side effect is ordinarily seen. Candidal resistance to nystatin is not a clinical problem. It is ineffective in dermatophytosis.

Antitubercular Drugs

Isoniazid

- Isoniazid is an excellent antitubercular drug, and an essential component of all antitubercular regimens, unless the patient is not able to tolerate it or bacilli are resistant. It is primarily tuberculocidal.
- Fast multiplying organisms are rapidly killed, but quiescent ones are only inhibited. It acts on extracellular as well as on intracellular TB (bacilli present within macrophages), and is equally active in acidic or alkaline medium.
- It is one of the cheapest antitubercular drugs. However, most nontubercular mycobacteria are not inhibited by INH.

Pharmacokinetics

- INH is completely absorbed orally and penetrates all body tissues, tubercular cavities, placenta and meninges. It is extensively metabolized in liver; most important pathway being N-acetylation by NAT2.
- The acetylated metabolite is excreted in urine. The rate of INH acetylation shows genetic variation. There are either:
- Fast acetylators
  (30–40% of Indians) t½ of INH 1 hr.
- Slow acetylators
  (60–70% of Indians) t½ of INH 3 hr.
- The proportion of fast and slow acetylators differs in different parts of the world. However, acetylator status does not matter if INH is taken daily, but biweekly regimens are less effective in fast acetylators.

- Isoniazid induced peripheral neuritis is more common in slow acetylators. A hepatotoxic minor metabolite is produced by CYP2E1 from acetylhydrazine.

Adverse effects:

- INH is well tolerated by most patients. Peripheral neuritis and a variety of neurological manifestations (paresthesias, numbness, mental disturbances, rarely convulsions) are the most important dose-dependent toxic effects.
- These are due to interference with production of the active coenzyme pyridoxal phosphate from pyridoxine, and its increased excretion in urine.

Rifampin (Rifampicin, R)

- It is a semisynthetic derivative of rifamycin B obtained from *Streptomyces mediterranei*.

Rifampin is bactericidal to *M. tuberculosis* and many other gram-positive and gram-negative bacteria like *Staph. aureus*, *N. meningitidis*, *H. influenzae*, *E. coli*, *Klebsiella*, *Pseudomonas*, *Proteus* and *Legionella*.

- Against TB bacilli, it is as efficacious as INH and better than all other drugs. The bactericidal action covers all subpopulations of TB bacilli, but acts best on slowly or intermittently dividing ones (spurters).
- *M. leprae* is highly sensitive, while MAC and some other mycobacteria, but not *M. fortuitum*, are moderately susceptible. Both extra- and intracellular organisms are affected. It has good sterilizing and resistance preventing actions.
- Rifampin interrupts RNA synthesis by binding to β subunit of mycobacterial DNA-dependent RNA polymerase (encoded by *rpoB* gene and blocking its polymerizing function.
- The basis of selective toxicity is that mammalian RNA polymerase does not avidly bind rifampin.

Pharmacokinetics

- It is well absorbed orally, (bioavailability is ~ 70%), but food decreases absorption; rifampin is to be taken in empty stomach. It is widely distributed in the body: penetrates intracellularly, enters tubercular cavities, caseous masses and placenta.
- Though it crosses meninges, it is largely pumped out from CNS by P-glycoprotein. It is metabolized in liver to an active deacetylated metabolite which is excreted mainly in bile, some in urine also.
- Rifampin and its desacetyl derivative undergo enterohepatic circulation. The t½ of rifampin is variable (2–5 hours).

Adverse effects

- The incidence of adverse effects is similar to INH. Hepatitis, a major adverse effect, generally occurs in patients with preexisting liver disease and is dose-related; infrequent with < 600 mg/ day dose.

- Development of jaundice requires discontinuation of the drug—then it is reversible.
- Cutaneous syndrome: flushing, pruritus + rash (especially on face and scalp), redness and watering of eyes.
- Flu syndrome: with chills, fever, headache, malaise and bone pain.
- Abdominal syndrome: nausea, vomiting, abdominal cramps with or without diarrhoea.

Streptomycin (S)

- It was the first clinically useful antitubercular drug. It is tuberculocidal, but less effective than INH or rifampin; acts only on extracellular bacilli (because of poor penetration into cells).
- Thus, other drugs and host defence mechanisms are needed to eradicate the disease. It penetrates tubercular cavities, but does not cross to the CSF, and has poor action in acidic medium.
- Resistance developed rapidly when streptomycin was used alone in tuberculosis—most patients had a relapse. Recent studies indicate worldwide increase in resistance to S.
- In case of S-resistant infection, it must be stopped at the earliest because of risk of S-dependence,in which case the infection flourishes when the drug is continued.
- Most nontubercular mycobacteria are unaffected by S. Because of need for i.m. injections and lower margin of safety (ototoxicity and nephrotoxicity, especially in the elderly and in those with impaired renal function) S is used only as an alternative to or in addition to other 1st line anti- TB drugs.
- Use is restricted to a maximum of 2 months. It is thus also labelled as a 'supplemental' 1st line drug.

Antimetabolites

- Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis.
- Their maximal cytotoxic effects are in S-phase and are, therefore, cell cycle specific.

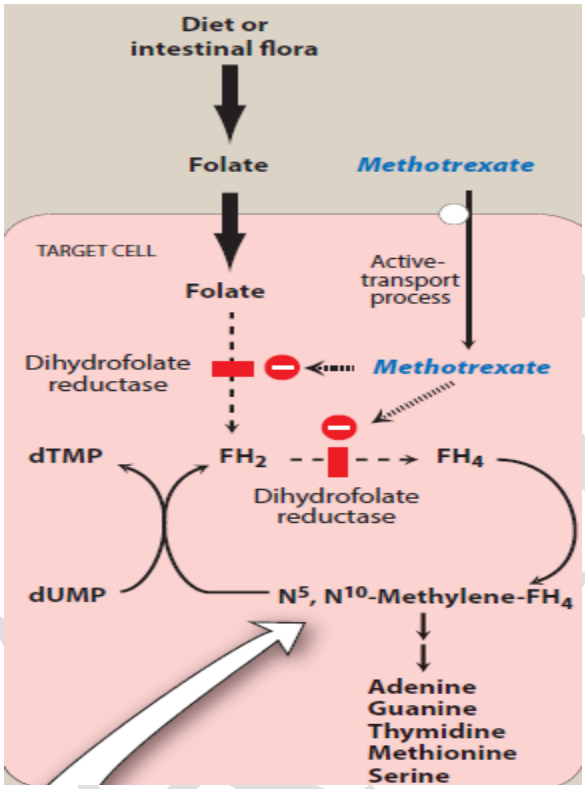
Methotrexate

- The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication. Folic acid is obtained mainly from dietary sources and from that produced by intestinal flora.

1. **Mechanism of action:**

- *MTX* is structurally related to folic acid and acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4) .

- The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH2), or by administration of *leucovorin*, which bypasses the blocked enzyme and replenishes the folate pool.



Resistance:

- Nonproliferating cells are resistant to *MTX*, probably because of a relative lack of DHFR, thymidylate synthase, and/ or the glutamylating enzyme. Decreased levels of the *MTX* polyglutamate have been reported in resistant cells and may be due to its decreased formation or increased breakdown.
- Resistance in neoplastic cells can be due to amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme.

Pharmacokinetics:

- *MTX* is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes.
- Because *MTX* does not easily penetrate the blood–brain barrier, it can be administered intrathecally to destroy neoplastic cells that are thriving in the sanctuary of the CNS.
- High concentrations of the drug are found in the intestinal epithelium, liver, and kidney, as well as in ascites and pleural effusions. *MTX is* also distributed to the skin.

Adverse effects:

- *Pemetrexed* should be given with folic acid and vitamin B12 supplements to reduce hematologic and GI toxicities.
- It is also recommended to pretreat with corticosteroids to prevent cutaneousreactions. One of the more common side effects of *pralatrexate* is mucositis.
- Doses must be adjusted or withheld based on the severity of mucositis. *Pralatrexate* also requires supplementation with folic acid and vitamin B12.

6-Mercaptopurine

- *6-Mercaptopurine* (*6-MP*) is the thiol analog of hypoxanthine. *6-MP* and *6-thioguanine* were the first purine analogs to prove beneficial for treating neoplastic disease. *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia.

1. Mechanism of action:

a. Nucleotide formation:

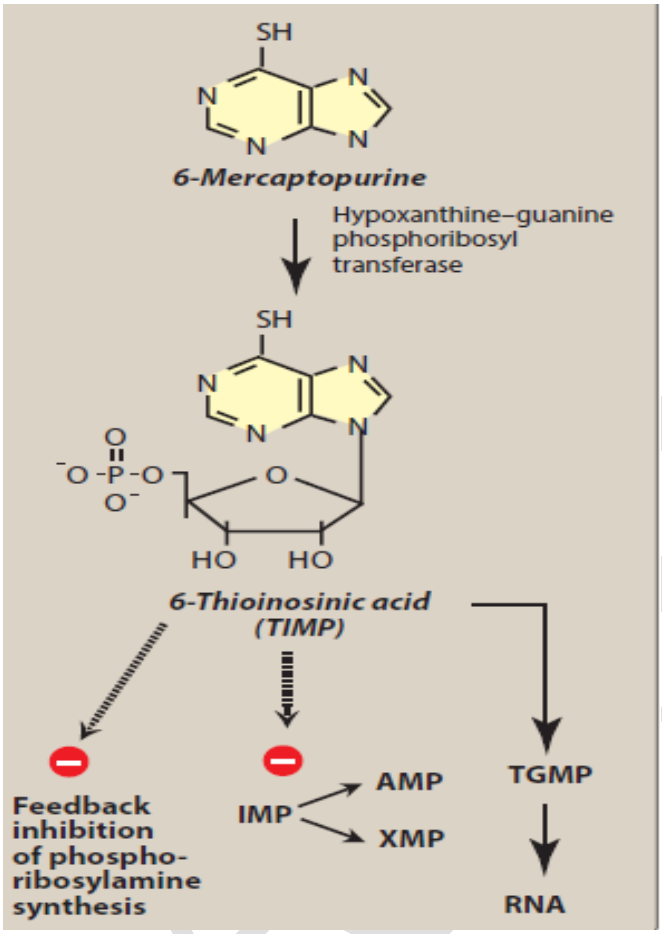
- To exert its antileukemic effect, *6-MP* must penetrate target cells and be converted to the nucleotide analog, 6-MP-ribose phosphate (better known as 6-thioinosinic acid or TIMP;
- The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine– guanine phosphoribosyltransferase (HGPRT).

b. Inhibition of purine synthesis:

- A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP. Similar to nucleotide monophosphates, TIMP can inhibit the first step of de novo purine ring biosynthesis (catalyzed by glutamine phosphoribosyl pyrophosphate amidotransferase).
- TIMP also blocks the formation of adenosine monophosphate and xanthinuric acid from inosinic acid.

c. Incorporation into nucleic acids:

- TIMP is converted to thioguanine monophosphate, which after phosphorylation to di- and triphosphates can be incorporated into RNA.
- The deoxyribonucleotide analogs that are also formed are incorporated into DNA. This results in nonfunctional RNA and DNA.



2. Resistance:

Resistance is associated with

1) an inability to biotransform *6-MP* to the corresponding nucleotide because of decreased levels of HGPRT,
2) increased dephosphorylation, or
3) increased metabolism of the drug to thiouric acid or other metabolites.

3. Pharmacokinetics:

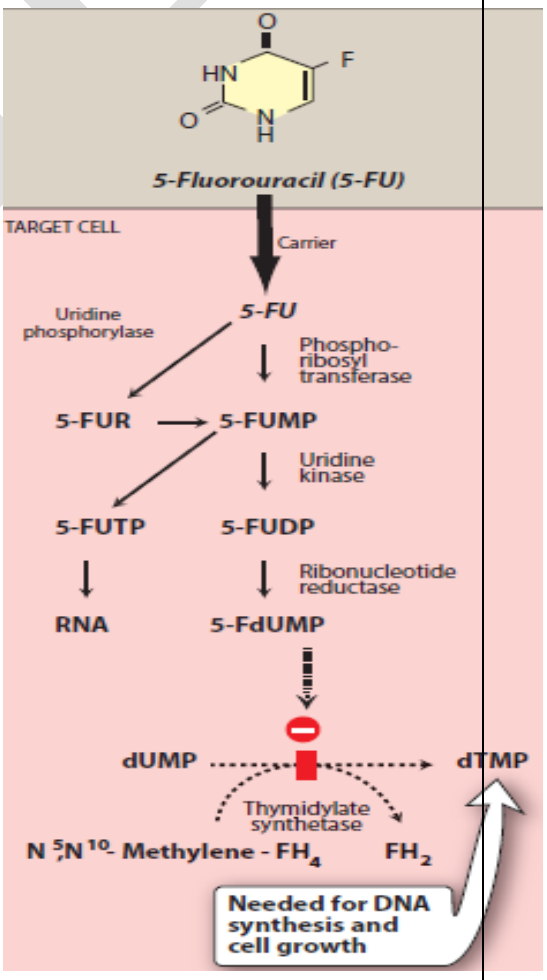
- Oral absorption is erratic and incomplete. Once it enters the blood circulation, the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF).
- The bioavailability of *6-MP* can be reduced by first-pass metabolism in the liver. *6-MP* is converted in the liver to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite.
- The parent drug and its metabolites are excreted by the kidney.

5-Fluorouracil [flure-oh-YOOR-ah-sil] (*5-FU*), a pyrimidine analog, has

5-Fluorouracil

- *5-Fluorouracil* (*5-FU*), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring.
- The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis.
- *5-FU* is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas).
- When applied topically, *5-FU* is also effective for the treatment of superficial basal cell carcinomas.

1. Mechanism of action:



- *5-FU* itself is devoid of antineoplastic activity.
- It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]; which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action.
- DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine-less death" of rapidly dividing cells.
- *5-FU* is also incorporated into RNA, and low levels have been detected in DNA.
- In the latter case, a glycosylase excises the *5-FU,* damaging the DNA. *5-FU* produces the anticancer effect in the S-phase of the cell cycle.
- For example, a standard regimen for advanced colorectal cancer is *irinotecan* plus *5-FU/leucovorin*.] *5-FU* is also incorporated into RNA, and low levels have been detected in DNA.

2. Resistance:

- Resistance is encountered when the cells have lost their ability to convert *5-FU* into its active form (5-FdUMP) or when they have altered or increased thymidylate synthase levels.

3. Pharmacokinetics:

- Because of its severe toxicity to the GI tract, *5-FU* is given IV or, in the case of skin cancer, topically. The drug penetrates well into all tissues, including the CNS.
- *5-FU* is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine. The dose of *5-FU* must be adjusted in impaired hepatic function.
- Elevated levels of dihydropyrimidine dehydrogenase (DPD) can increase the rate of *5-FU* catabolism and decrease its bioavailability.
- The DPD level varies from individual to individual and may differ by as much as sixfold in the general population.

1	III	Colloidal drug carrier systems are	**micellar solutions**	vacuoles	solid crystal dispersions	Mobile vesicles	**micellar solutions**
2	III	A three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids.	**Hydrogels**	Vaccum gels	Non vaccum gels	Polymeric gels	**Hydrogels**
3	III	Controlled release (CR) drugs are called	Tinature	**Spansules**	tamuare	chisuare	**Spansules**
4	III	_____ is the first genetically engineered protein	Growth hormone	**Insulin**	HBsAg	HIB	**Insulin**
5	III	Genes for insulin peptides is incorporated into____during synthesis	**beta galactosidase gene**	Synthetic vectors	pBr322	TMV	**beta galactosidase gene**
6	III	Genetically engineered growth hormone is used to treat	**Dwarfism**	Gigantism	malignancies	Renal failure	**Dwarfism**
7	III	Insulin injection for the treatment of diabetes mellitus is given	intramuscularly	intradermally	**subcutaneously**	intravenously	**subcutaneously**
8	III	Which of the following method has slower action	**intradermal injection**	IM injection	IV injection	Intrathecal injection	**intradermal injection**
9	III	Which of the following method is rapid in action	intradermal injection	IM injection	**IV injection**	subcutaneous injection	**IV injection**
10	III	Diagnostic studies such as angiogram is done	ntravenously	**intra arterially**	intramuscularly	intradermally	**intra arterially**
11	III	For rhematoid arthritis drug is given	**Intra articularly**	Intramedullary	Intraperitoneally	Intrathecally	**Intra articularly**
12	III	Using galvanic current penetration of drugs to skin into tissues is	Transmucosal method	**Iontophoresis**	Trans nasal method	Transrectal method	**Iontophoresis**
13	III	BCG vaccine is administred	**intradermally**	intramuscularly	intravenously	subcutaneously	**intradermally**
14	III	Sublingually taken drugs are absorbed into	pulmonary circulation	hepatic circulation	**systemic circulation**	renal circulation	**systemic circulation**
15	III	The initial antibody secreted after immune response is	IgG	**IgM**	IgA	IgE	**IgM**
16	III	Toxoids are produced by adding _____to toxins of microorganism	Acetic acid	Formic acid	**Formalin**	Saline	**Formalin**
17	III	BCG vaccine is used against	Typhoid	**Tuberculosis**	Tetanus	chicken pox	**Tuberculosis**
18	III	Salk vaccine is a part of	BCG vaccine	**Poliomyelitus vaccine**	MMR vaccine	Hepatitis vaccine	**Poliomyelitus vaccine**
19	III	Sabin vaccine for polimyelitus is administered	subcutaneously	**orally**	intramuscularly	intravenously	**orally**
20	III	OPV provides systemic immunity & induces mucosal secretion of	IgG	IgM	**IgA**	IgE	**IgA**
21	III	The usual incubation period of rabies virus is	**4-6 weeks**	1-2 weeks	7-8 weeks	8-10 weeks	**4-6 weeks**
22	III	Which vaccine is given subcutaneously on abdominal wall	rubella vaccine	Poliomyelitus vaccine	Anthrax vaccine	**rabies vaccine**	**rabies vaccine**
23	III	Nerve tissue vaccine is used for	Hepatitis B	**Rabies**	Mumps	Cholera	**Rabies**
24	III	The first vaccine prepared by rDNA technology is	**Hepatitis B vaccine**	DPT vaccine	Hib vaccine	MMR vaccine	**Hepatitis B vaccine**
25	III	To prevent neonatal tetanus____is given during pregnancy	DPT	OPV	MMR	**TT**	**TT**
26	III	Anti-D (Rho) immunoglobulin is used to prevent	yellow fever	Encephalitis	**Erythroblastosis foetalis**	Plague	**Erythroblastosis foetalis**
27	III	Which of the following is not a bacterial vaccine	**Rabies vaccine**	Plague vaccine	BCG vaccine	Anthrax vaccine	**Rabies vaccine**
28	III	Which of the following is not a viral vaccine	MMR vaccine	**Diptheria vaccine**	Varicella vaccine	poliomyelitis vaccine	**Diptheria vaccine**
29	III	Glycosylated erythropoietin is a glycoprotein drug for	**Anemia**	Skin disorders	Muscular dystrophy	Brain disorders	**Anemia**
30	III	The mean incubation period of HIV is	7 years	**4.5 years**	6.5 years	2 years	**4.5 years**
31	III	Antibodies to HIV develops in_eafter infection	**2-8 weeks**	1-2 weeks	7-8 weeks	8-10 weeks	**2-8 weeks**
32	III	In AIDS patients opportunistic infections caused are	Renal failure	Anti Candidiasis	**Pneumonia**	NSAID	**Pneumonia**
33	III	Drugs for AIDS is still in infancy stage because	HIV infects T cells	**available drugs are toxic**	virus develops Antiresistance	antiviruses	**available drugs are toxic**
34	III	Which of the following is a drug used for AIDS	**Abacavir**	Saquinavir	diazepam	Ibubrufen	**Abacavir**
35	III	Azidothymidine is a_____used for AIDS	**NRTI**	NNRTI	Protease inhibitor	Fusion inhibitor	**NRTI**
36	III	Advantages of anticancer drugs	Low selectivity to cancer cells	Depression of bone marrow	Depression of angiogenesis	Depression of immune system	**Depression of angiogenesis**
37	III	Rational combination of anticancer drugs is used to	Provide synergism resulting from the use of anticancer drugs with different mechanisms combination	Provide synergism resulting from the use of anticancer drugs with the same mechanisms combination	Provide stimulation of immune system	Provide stimulation of cell proliferation	**Provide synergism resulting from the use of anticancer drugs with different mechanisms combination**
38	III	Anticancer alkylating drug, a derivative of chloroethylamine:	Methotrexate	Cisplatin	Cyclophosphamide	Carmustine	**Cyclophosphamide**
39	III	Tick the anticancer alkylating drug, a derivative of ethylenimine	Mercaptopurine	Thiotepa	Chlorambucil	Procarbazine	**Thiotepa**
40	III	The group of hormonal drugs used for cancer treatment:	Mineralocorticoids and glucocorticoids	Glucocorticoids and gonadal hormones	Gonadal hormones and somatotropin	Insulin	**Glucocorticoids and gonadal hormones**
41	III	The anticancer drug of plant origin:	Dactinomycin	Vincristine	Methotrexate	Procarbazine	**Vincristine**
42	III	Action mechanism of alkylating agents is:	Producing carbonium ions altering protein structure	Producing carbonium ions altering DNA structure	Structural antagonism against purine and pyrimidine	Inhibition of DNA-dependent RNA synthesis	**Producing carbonium ions altering DNA structure**
43	III	Methotrexate is	A purine antagonist	A folic acid antagonist	An antibiotic	An alkylating agent	**A folic acid antagonist**
44	III	The antibiotic for cancer chemotherapy	Cytarabine	Doxorubicin	Gentamycin	Etoposide	**Doxorubicin**
45	III	Fluorouracil belongs to	Antibiotics	Antimetabolites	Plant alkaloids	Bone marrow growth factor	**Antimetabolites**
46	III	The action mechanism of anticancer drugs belonging to plant alkaloids	Inhibition of DNA-dependent RNA synthesis	Cross-linking of DNA	Mitotic arrest at a metaphase	Nonselective inhibition of aromatases	**Mitotic arrest at a metaphase**
47	III	Action mechanism of methotrexate is	Inhibition of dihydrofolate reductase	Activation of cell differentiation	Catabolic depletion of serum asparagine	Activation of cell differentiation	**Inhibition of dihydrofolate reductase**
48	III	The anticancer drug belonging to inorganic metal complexes	Dacarbazine	Cisplatin	Methotrexate	Vincristine	**Cisplatin**
49	III	The indication for estrogens in oncological practice	Leukemia	Cancer of prostate	Endometrial cancer	Brain tumors	**Cancer of prostate**
50	III	Enzyme drug used for acute leukemia treatment	Dihydrofolate reductase	Asparaginase	Aromatase	DNA gyrase	**Dihydrofolate reductase**
51	III	Which one of the following drug is not the derivative of nitrosoureas	Carmustine	Vincristine	Lomustine	Semustine	**Vincristine**
52	III	Estrogen inhibitor:	Leuprolide	Tamoxifen	Flutamide	Anastrozole	**Tamoxifen**
53	III	The antiandrogen drug:	Flutamide	Aminoglutethimide	Tamoxifen	Testosterone	**Flutamide**
54	III	The drug belonging to aromatase inhibitors	Octreotide	Anastrozole	Flutamide	Tamoxifen	**Anastrozole**
55	III	The drug belonging to gonadotropin-releasing hormone agonists	Leuprolide	Tamoxifen	Flutamide	Anastrozole	**Leuprolide**
56	III	Which of the following chemotherapy drug is likely to be toxic to gonads?	Adriamycin	Vinblastine	Paclitaxel	Procarbazine	**Procarbazine**
57	III	High dose chemotherapy given prior to stem cell transplant may be associated with gonadal failure. Risk is least with the use of	Busulfan + cyclophosphamide	Cyclophosphamide + TBI	Ifosfamide +carboplatin+ Etoposide	Fludarabine + ATG	**Fludarabine + ATG**
58	III	Incidence of Gallbladder cancer is highest in	Chile	India	United Kingdom	South Africa	**Chile**
59	III	Which of the following is least to occur as Gallbladder primary?	Adenocarcinoma	Squamous cell carcinoma	Lymphoma	Carcinoid tumour	**Lymphoma**
60	III	Which of the following is less likely to be associated with Gallbladder cancer?	Obesity	Use of tobacco and alcohol	Aflotoxins	Past history of enteric fever	**Aflotoxins**

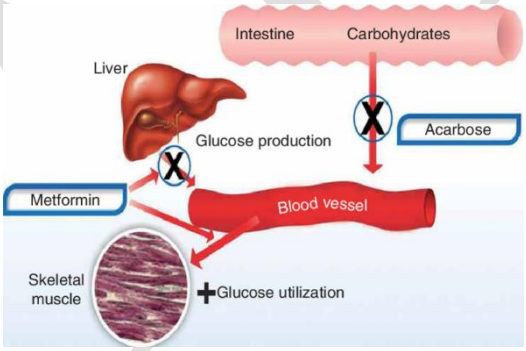
UNIT IV

Mechanism of action drugs used in the treatment of diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia.

αGlucosidase inhibitors

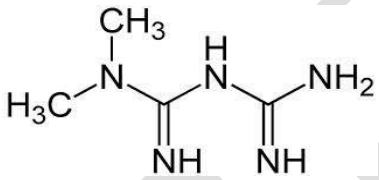
Acarbose It is a complex oligosaccharide which reversibly inhibits α-glucosidases, the final enzymes for the digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose. In addition, GLP-1 release is promoted which may contribute to the effect. Postprandial glycaemia is reduced without significant increase in insulin levels. Regular use lowers HbA1c modestly (by 0.4–0.8%), but change in body weight and lipid levels is minimal. The stop-NIDDM trial (2002) has shown that long-term acarbose treatment in prediabetics reduces occurrence of type 2 DM as well as hypertension and cardiac disease. In diabetics, it reduces cardiovascular events.



Acarbose is a mild antihyperglycaemic and not a hypoglycaemic; may be used as an adjuvant to diet (with or without metformin/SU) in obese diabetics. Dose 50–100 mg TDS is taken at the beginning of each major meal. Only a small fraction of the dose is absorbed. Flatulence, abdominal discomfort and loose stool are produced in about 50% patients due to fermentation of unabsorbed carbohydrates. Patient acceptability of α-glucosidase inhibitors is poor due to uncomfortable g.i. symptoms. Hepatic transaminases may rise, but liver damage is rare.

Biguanide (AMPK activator)

Two biguanideantidiabetics, phenformin and metformin were introduced in the 1950s. Because of higher risk of lactic acidosis, phenformin was withdrawn and has been banned in India since 2003. Metformin It differs markedly from SUs: causes little or no hypoglycaemia in nondiabetic subjects, and even in diabetics, episodes of hypoglycaemia are rare. It does not stimulate pancreatic β cells. Metformin is reported to improve lipid profile as well in type 2 diabetics.

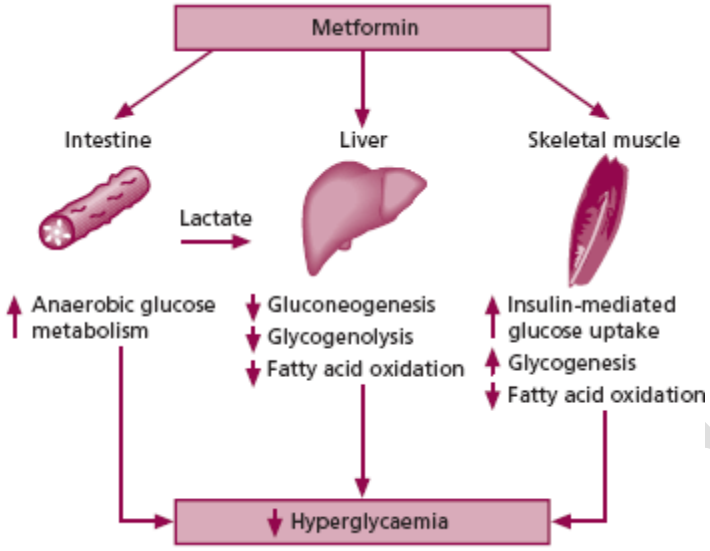


Mechanism of actionBiguanides do not cause insulin release, but presence of insulin is essential for their action. Metformin is not effective in pancreatectomized animals and in type 1 diabetics. Though the details are not clear, recent studies have recognized activation of AMPdependent protein kinase (AMPK) to play a crucial role in mediating the actions of metformin, the key features of which are:

1. Suppresses hepatic gluconeogenesis and glucose output from liver. This is the major action responsible for lowering of blood glucose in diabetics.

2. Enhances insulin-mediated glucose uptake and disposal in skeletal muscle and fat. Insulin resistance exhibited by type-2 diabetics is thus overcome. This translates into— glycogen storage in skeletal muscle reduced lipogenesis in adipose tissue and enhanced fatty acid oxidation.

3. Interferes with mitochondrial respiratory chain and promotes peripheral glucose utilization through anaerobic glycolysis. AMPK activation by metformin appears to be an indirect consequence of interference with cellular respiration and lowering of intracellular ATP and other energy sources. Metformin also retards intestinal absorption of glucose, other hexoses, amino acids and Vit B_{12}.



Pharmacokinetics

Clearance of metformin approximates g.f.r. It accumulates in renal failure and increases the risk of lactic acidosis. Adverse effects Side effects with metformin are frequent, but generally not serious. Abdominal pain, anorexia, bloating, nausea, metallic taste, mild diarrhoea and tiredness are the usual complaints, which tend to subside with time. Metformin does not cause hypoglycaemia except in overdose. Lactic acidosis Small increase in blood lactate occurs with metformin, but lactic acidosis is rare (<1 per 10,000 patient years) because it is poorly concentrated in hepatic cells. Alcohol ingestion can precipitate lactic acidosis. Vit B_{12} deficiency due to interference with its absorption can occur with high dose of metformin. In addition to general restrictions for use of oral hypoglycaemics, metformin is contraindicated in hypotensive states, heart failure, severe respiratory, hepatic and renal disease, as well as in alcoholics because of increased risk of lactic acidosis. Drugs like cimetidine, furosemide may compete with metformin excretion and enhance its toxicity. Uses Metformin is now established as a first choice drug for all type 2 DM patients, except when not tolerated or contraindicated. Advantages of metformin are:

- Non-hypoglycaemic
- Weight loss promoting

- Has potential to prevent macro vascular as well as microvascular complications of diabetes no acceleration of β cell exhaustion/ failure in type 2 dm.
- Antihyperglycaemic efficacy (hba1c reduction by 0.8–1.2%) equivalent to other oral drugs.
- Can be combined with any other oral or injectable antidiabetic, if one drug is no adequate.

The limiting feature is g.i. intolerance, especially at higher doses, but lack of serious toxicity is well established by decades of use.

Infertility:

Metformin has been found to improve ovulation and fertility in some infertile women with polycystic ovary. This benefit is observed irrespective of the glycaemic status of the woman. It may be due to mitigation of insulin resistance and lowering of circulating insulin levels.

Mechanism of action drugs used in the treatment of AIDS

These are drugs active against human immunodeficiency virus (HIV) which is a retrovirus. They are useful in prolonging and improving the quality of life and postponing complications of acquired immunodeficiency syndrome (AIDS) or AIDS related complex (ARC), but do not cure the infection. The clinical efficacy of antiretrovirus drugs is monitored primarily by plasma HIV-RNA assays and CD4 lymphocyte count carried out at regular intervals.

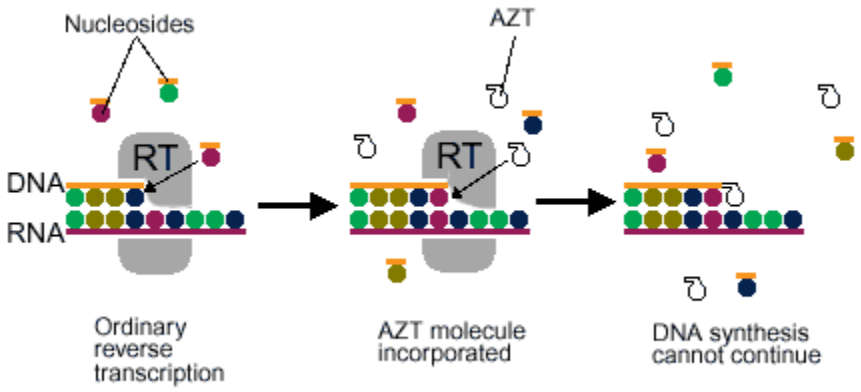
HIV is a single stranded RNA retrovirus which uniquely carries out reverse transcription of proviral DNA from viral RNA (normally RNA is transcripted from DNA) with the help of a viral RNA-dependent DNA polymerase (reverse transcriptase). The primary cell type attacked by HIV is the CD4+ helper T-lymphocyte, but later macrophages and some other cell types may also be infected. When population of CD4 cells declines markedly (<200 cells/μL), cell mediated immunity (CMI) is lost and opportunistic infections abound, to which the victim ultimately succumbs, unless treated. Because the HIV genome integrates with the host DNA, eradication of the virus from the body of the victim appears impossible at present. The aim of anti-HIV therapy is to cause maximal suppression of viral replication for the maximal period of time that is

possible. For this, ARV drugs are always used in combination of at least 3 drugs and regimens have to be changed over time due to development of resistance. Life long therapy is required.

Zidovudine

It is a thymidine analogue (azidothymidine, AZT), the prototype NRTI. After phosphorylation in the host cell—zidovudinetriphosphate selectively inhibits viral reverse transcriptase in preference to cellular DNA polymerase. Single-stranded viral RNA Virus directed reverse transcriptase (inhibited by zidovudine triphosphate) Double-stranded proviral DNA On the template of single-stranded RNA genome of HIV, a double-stranded DNA copy is produced by viral reverse transcriptase. This proviral DNA translocates to the nucleus and is integrated with chromosomal DNA of the host cell (by viral integrase enzyme) which then starts transcribing

viral genomic RNA as well as viral mRNA. Underthe direction of viral mRNA, viral regulatory and structural proteins are produced in the form of a polyprotein. Finally, viral particles are assembled and matured after fractionation of the polyprotein by viral protease. Zidovudine thus prevents infection of new cells by HIV, but has no effect on proviral DNA that has already integratedinto the host chromosome. It is effective only against retroviruses. Zidovudineitself gets incorporated into the proviral DNA and terminates chain elongation. Resistance to AZT occurs by point mutations which alter reverse transcriptase enzyme. In the past, when AZT was used alone, >50% patients became nonresponsive to AZT within 1–2 years therapy due to growth of resistant mutants.



Pharmacokinetics

The oral absorption of AZTis rapid, but bioavailability is ~65%. It is quickly 15–20% of the unchanged drug along with the metabolite is excreted in urine. Plasma protein binding is 30% and CSF level is ~50% of that in plasma. It crosses placenta and is found in milk.

Dose Adults 300 mg BD; Children 180 mg/m2 (max 200 mg) 6–8 hourly.

RETROVIR, ZIDOVIR 100 mg cap, 300 mg tab, 50 mg/5 ml syrVIRO-Z, ZIDOMAX, ZYDOWIN 100 mg cap, 300 mg tab. (to be taken with plenty of water).

Adverse effects

Toxicity is mainly due topartial inhibition of cellular mitochondrial DNA polymerase γ which has higher affinity for zidovudine triphosphate than chromosomal DNA polymerase. Anaemia and neutropenia are the most important and dose-related adverse effects. Nausea, anorexia, abdominal pain, headache, insomnia and myalgia are common at the start of therapy, but diminish later. Myopathy, pigmentation of nails, lactic acidosis, hepatomegaly, convulsions and encephalopathy are infrequent. Interactions Paracetamol increases AZT toxicity, probably by competing for glucuronidation. Azole antifungals also inhibit AZT metabolism. Other nephrotoxic and myelosuppressive drugs and probenecidenhance toxicity. Stavudine and zidovudine exhibit mutual antagonism by competing for the same activation pathway.

Use

Zidovudine is used in HIV infected patientsonly in combination with at least 2 other ARV drugs. It is one of the two optional NRTIs used by NACO for its first line triple drug ARV regimen. Its efficacy as mono therapy in AIDS was confirmed in the past. HIV-RNA titer is reduced to undetectable levels and CD4 count increasesprogressively. Immune status is improved andopportunistic infections become less common. There is a sense of well-being and patients gain weight. AZT also reduces neurological manifestations of AIDS and new Kaposi's lesions do not appear. Mortality among AIDS patients is reduced. However, beneficial effects are limited from a few months to a couple of years after which progressively non-responsiveness develops.

Didanosine(ddI)

It is a purine nucleoside analogue which after intracellular conversion to didanosine triphosphate competes with ATP for incorporation into viral DNA, inhibits HIV reverse transcriptase and terminates proviralDNA. Antiretroviral activity of didanosine is equivalent to AZT. Mutational resistance develops, but only few AZT resistant mutants are nonresponsive to didanosine also. Its use has declined due to higher toxicity than other NRTIs. Dose: 400 mg/day (for > 60 kg BW), 250 mg/day (< 50 kg BW) 1 hour before or 2 hour after meals.

DINEX EC, DDRETRO, VIROSINE DR 250 mg, 400 mg tabs.

Oral absorption of didanosineis somewhat erratic due to acid lability. It is metabolized as well as excreted unchanged; t½ 1 to 1.5 hr. In contrast to AZT, it does not cause myelosuppression.

The major dose-related toxicity is peripheral (stocking and glove) neuropathy, which may be irreversible, and rarely acute pancreatitis.Diarrhoea, abdominal pain, dry mouth and nausea are the side effects.

Mechanism of action drugs used in the treatment of Cancer

Mechlorethamine (MustineHCl) It is the first nitrogen mustard; highly reactive and local vesicant—can be given only by i.v. route. It produces many acute effects like nausea, vomiting and haemodynamic changes. Extravasation during i.v. injection may cause sloughing. Hodgkin and non-Hodgkin lymphomas are the main indications. It has been a component of erstwhile MOPP regimen.

Dose: 0.1 mg/kg i.v. daily × 4 days; courses may be repeated at suitable intervals.

Busulfan It is highly specific for myeloid elements; granulocyte precursors being the most sensitive, followed by those of platelets and RBC. It produces little effect on lymphoid tissue and g.i.t. Hyperuricaemia is common; pulmonary fibrosis and skin pigmentation are the specific adverse effects. Sterility also occurs. It is the drug of choice for chronic myeloid leukaemia. Dose: 2–6 mg/day (0.06 mg/kg/day) orally. MYLERAN, BUSUPHAN 2 mg tab.

Drugs for Heart

Inamrinone(amrinone) It is chemically and pharmacologically distinct from digitalis and catecholamines. This bipyridine derivative is a selective phosphodiesterase 3 (PDE3) inhibitor. The PDE3 isoenzyme is specific for intracellular degradation of cAMP in heart, blood vessels and bronchial smooth muscles. Amrinone increases myocardial cAMP and transmembrane influx

of Ca^{2+}. It does not inhibit $Na^{+}K^{+}$ATPase, and its action is independent of tissue catecholamines as well as adrenergic receptors.

The two most important actions of amrinone are positive inotropy and direct vasodilatation: has been called an 'inodilator'. Both preload and afterload on the heart is reduced. Compared to dobutamine, proportionately greater decrease in systemic vascular resistance is noted. In CHF patients i.v.amrinone action starts in 5 min and lasts 2–3 hours; elimination t½ is 2–4 hours. It increases cardiac index, left ventricular ejection fraction and decreases peripheral vascular resistance, CVP, left ventricular end diastolic volume and pressure accompanied by mild tachycardia and slight fall in BP. Adverse effects Thrombocytopenia is the most prominent and dose related side effect, but is mostly transient and asymptomatic. Nausea, diarrhoea, abdominal pain, liver damage, fever and arrhythmias are the other adverse effects.

Use Thoughamrinone is active orally, its oral use in maintenance therapy of CHF has been abandoned, because efficacy was lost and mortality was increased in comparison to placebo. It is indicated only for short-term i.v. use in severe and refractory CHF, as an additional drug to conventional therapy with digitalis, diuretics and vasodilators.

Dose: 0.5 mg/kg bolus injection followed by 5–10 μg/kg/ min i.v. infusion (max. 10 mg/kg in 24 hours). AMICOR, CARDIOTONE 5 mg/ml (as lactate) 20 ml amp.

Digoxin

Cardiac glycosides are found in several plants and in toad skin (Bufotoxin). Digitalis lanata is the source of Digoxin, the only glycoside that is currently in use. Others like Digitoxin (from *Digitalis purpurea*) and Ouabain (from Strophan thus gratus), etc. are no longer clinically used or marketed. By convention the term, 'Digitalis' has come to mean 'a cardiac glycoside'. Chemistry The cardiac glycosides consist of an aglycone (genin) to which are attached one or more sugar (glucose or digitoxose) moieties.

Pharmacological Actions

All digitalis glycosides have qualitatively similar action. Digoxin is described as prototype.

1. Heart Digitalis has direct effects on myocardial contractility and electrophysiological properties. In addition, it has vagomimetic action, reflex effects due to alteration in haemodynamics and direct CNS effects altering sympathetic activity. Force of contraction

Digitalis causes a dose dependent increase in force of contraction of heart—a positive inotropic action. This is especially seen in the failing heart which is exquisitely sensitive. There is increased velocity of tension development and higher peak tension can be generated. Systole is shortened, diastole is prolonged. When a normal heart is subjected to increased impedance to outflow, it generates increased tension so that stroke volume is maintained upto considerably higher values of impedance (Fig. 37.1), while the failing heart is not able to do so and the stroke volume progressively decreases. The digitalized failing heart regains some of its capacity to contract more forcefully when subjected to increased resistance to ejection. There is more complete emptying of failing and dilated ventricles—cardiac output is increased and end-diastolic volume is reduced.

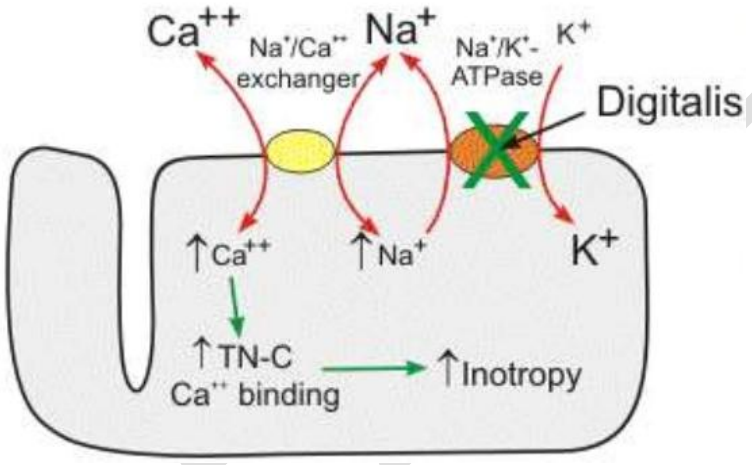
However, therapeutic doses of digoxin do not increase resting tension (tone) in myocardial

fibres. Rate Heart rate is decreased by digitalis. Bradycardia is more marked in CHF patients because improved circulation (due to positive inotropic action) restores the diminished vagal tone and abolishes sympathetic overactivity. In addition, digitalis slows the heart by vagal and extravagal actions. Vagal tone is increased reflexly by sensitization of baroreceptors, as well as by stimulation of vagal centre. Extravagal A direct depressant action on SA and A-V nodes. This component of bradycardia is not reversed by atropine.

Mechanism of action

Digitalis increases force of cardiac contraction by a direct action independent of innervation. It selectively binds to extracellular face of the membrane associated Na^+K^+ ATPase of myocardial fibres and inhibitis this enzyme. Inhibition of this cation pump results in progressive accumulation of Na^+intracellularly. This indirectly results in intracellular Ca^{2+} accumulation. During depolarization Ca^{2+} ions enter the cell driven by the steep Ca^{2+} gradient (>1 mM extracellular to < 100 nM cytosolic during diastole) through voltage sensitive L type Ca2+ channels. This triggers release of larger amount of Ca^{2+} stored in sarcoplasmic reticulum (SR) through Ryanodine calcium channel 2 (RYR2) → cytosolic Ca^{2+} increases transiently to about 500 nM (calcium transients) → triggers contraction by activating troponin C on myofibrils. The sarcoplasmic-endoplasmic reticular Cal. ATPase 2 (SERCA2) is then activated which

pumps Ca^{2+} back into the SR. A fraction (equal to that which entered from outside during depolarization) is extruded mainly by 3Na+/1Ca2+ exchange transporter (NCX-antiporter) and to a lesser extent by sarcolemmal Ca2+ pump (Ca2+ ATPase). During phase 3 of AP, membrane Na+K+ATPase moves 3 intracellular Na^+ ions for 2 extracellular K^+ ions. The slight (1–1.5 mM) increase in cytosolic Na+ over normal (8–10 mM) due to partial inhibition of Na+K+ATPase by digitalis reduces transmembrane gradient of Na^+ which drives the extrusion of Ca2+. The excess Ca2+ remaining in cytosol is taken up into SR which progressively get loaded with more Ca^{2+} → subsequent calcium transients are augmented Bioavailability of digoxin tablets from different manufacturers may differ. Presence of food in stomach delays absorption of digoxin.

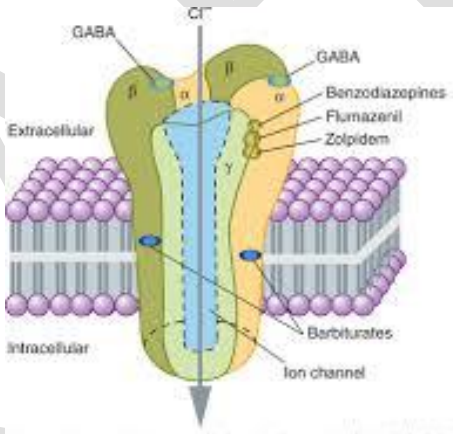


The volume of distribution of digoxin is large (6–8 L/Kg). It is concentrated in the heart (~20 times than plasma), skeletal muscle, liver and kidney. Digoxin is primarily excreted unchanged by the kidney: mainly by glomerular filtration; rate of excretion is altered parallel to creatinine clearance. Its t½ is prolonged in elderly patients and in those with renal insufficiency: dose has to be reduced. Digoxin is a cumulative drug. When maintenance doses are given from the beginning, steady state levels and full therapeutic effect are attained after 4 × t½, i.e. 6–7 days.

Drugs for kidney disorder

Benzodiazepines (BZDs) In addition to preanaesthetic medication, BZDs are nowfrequently used for inducing, maintaining and supplementing anaesthesia as well as for 'conscious sedation'. Relatively large doses (diazepam 0.2–0.3 mg/kg or equivalent) injected i.v.

produce sedation, amnesia and then unconsciousness in 5–10 min. If no other anaesthetic or opioid is given, the patient becomes responsive in 1 hr or so due to redistribution of the drug (distribution t½ of diazepam is 15 min), but amnesia persists for 2–3 hr and sedation for 6 hr or more. Recovery is further delayed if larger doses are given. BZDs are poor analgesics : an opioid or N_2O is usually added if the procedure is painful. By themselves, BZDs donot markedly depress respiration, cardiac contractility or BP, but when opioids are also given these functions are considerably compromised. BZDs decrease muscle tone by central action, but require neuromuscular blocking drugs for muscle relaxation of surgical grade. They do not provoke postoperative nausea or vomiting. Involuntary movements are not stimulated. BZDs are now the preferred drugs for endoscopies, cardiac catheterization, angiographies, conscious sedation during local/regional anaesthesia, fracture setting, ECT, etc. They are a frequent component of balanced anaesthesiaemploying several drugs. The anaesthetic actionof BZDs can be rapidly reversed by flumazenil0.5–2 mg i.v.



Diazepam0.2–0.5 mg/kg by slow undiluted injection in a running i.v. drip: this technique reduces the burning sensation in the vein and incidence of thrombophlebitis.

VALIUM, CALMPOSE 10 mg/2 ml inj.

Lorazepam Three times more potent, slower acting and less irritating than diazepam. It distributes more gradually—awakening may be delayed. Amnesia is more profound.

Dose: 2–4 mg (0.04 mg/kg) i.v. CALMESE 4 mg/2 ml inj.

Midazolam This BZD is water soluble, nonirritating to veins, faster and shorter acting (t½ 2 hours) and 3 times more potent than diazepam. Fall in BP is somewhat greater than with

diazepam. It is being preferred over diazepam foranaesthetic use: 1–2.5 mg i.v.followed by 1/4th supplemental doses. Also used for sedation of intubated and mechanically ventilated patients and in other critical care anaesthesiaas 0.02–0.1 mg/kg/hr continuous i.v.infusion.

FULSED, MEZOLAM, SHORTAL 1 mg/ml, 5 mg/ml inj.

Furosemide (20–80 mg oral or i.v.) It may be given as an adjunct with any of the above drugs if there is volume overload (acute LVF, pulmonary edema, CHF) or cerebral edema (in encephalopathy), but should be avoided when patient may be hypovolemic due to pressure induced natriuresis (especially in eclampsia, pheochromocytoma).

Drugs for antiepileptic drug

These are a group of disorders ofthe CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena.

Lamotrigine A new anticonvulsant having carbamazepine-like action profile: modifies maximal electroshock and decreases electrically evoked as well as photic after-discharge duration. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate. This may account for its broader-spectrum of antiseizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors. Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS,it has now been shown effective as monotherapy as well. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated. Reduction in seizure frequency or complete control is obtained as frequently as with carbamazepine. Lamotrigine is well absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hr in patients receiving phenytoin, carbamazepine or phenobarbitone. On the contrary valproate inhibits glucuronidation of lamotrigine and doubles its blood level, but valproate levels are lowered by lamotrigine. Reduce the dose of lamotrigine to

half in patients taking valproate. However, metabolism of other anticonvulsants and oral contraceptives is not altered.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting. In some comparative trials lamotrigine has been found to be better tolerated than carbamazepine or phenytoin. Negative effect on cognitive function is not reported. Rash may be a severe reaction, particularly in children, requiring withdrawal.

Dose: 50 mg/day initially, increase upto 300 mg/day as needed; not to be used in children.

LAMETEC, LAMITOR, LAMIDUS 25, 50, 100 mg tabs.

Clobazam It is a 1,5 benzodiazepine (diazepam and others are 1,4 benzodiazepines) introduced first as anxiolytic and later found to possess useful antiepileptic efficacy in partial, secondarily generalized tonic-clonic as well as absence and atonic seizures, including some refractory cases. Sedation and psychomotor retardation are less prominent, but side effect profile is similar to other BZDs. It appears to act by facilitating GABA action. Oral bioavailability of clobazam is ~90% and elimination t½ 18 hrs, but an active metabolite is produced which has longer t½ (>35 hr). It is generally used as adjuvant to other antiepileptic drugs like phenytoin, carbamazepine or valproate in refractory epilepsy.

Dose: start with 10–20 mg at bedtime, can be increased upto 60 mg/day; FRISIUM, LOBAZAM, CLOZAM, 5, 10, 20 mg cap.

Drugs for cough

DextromethorphanHydrobromide A synthetic central NMDA (N-methyl D-aspartate) receptor antagonist; the d-isomer has antitussive action while l-isomer is analgesic. Dextromethorphan does not depress mucociliary function of the airway mucosa and is practically devoid of constipating action. Though considered nonaddicting, some drug abusers indulge in it. The antitussive action of dextromethorphan has been rated equivalent to codeine, but some clinical studies have found it to be no better than placebo.

Side effect: Dizziness, nausea, drowsiness; at high doses hallucinations and ataxia may occur.

Dose: 10–20 mg, children 2–6 years 2.5–5 mg, 6–12 years 5–10 mg. It is a common ingredient of many proprietary cough formulations.

Noscapine (Narcotine) An opium alkaloid ofthe benzoisoquinoline series (see Ch. 34). It depressescough but has no narcotic, analgesic or dependenceinducing properties. It is nearly equipotentantitussive as codeine, especially useful inspasmodic cough. Headache and nausea occuroccasionally as side effect. It can release histamineand produce bronchoconstriction in asthmatics.

Dose: 15–30 mg, children 2–6 years 7.5 mg, 6–12 years 15 mg.

COSCOPIN 7 mg/5 ml syrup, COSCOTABS 25 mg tab.

Drugs used for Bronchialasthma

Salbutamol (Albuterol) A highly selective β2agonist; cardiac side effects are less prominent.Selectivity is further increased by inhaling thedrug. Inhaled salbutamol delivered mostly frompressurized metered dose inhaler (pMDI) producesbronchodilatation within 5 min and the actionlasts for 2–4 hours. It is, therefore, used to abortand terminate attacks of asthma, but is not suitablefor round-the-clock prophylaxis. Muscle tremorsare the dose related side effect. Palpitation,restlessness, nervousness, throat irritation andankle edema can also occur. Hypokalaemia is apossible complication. Salbutamol undergoespresystemic metabolism in the gut wall, oralbioavailability is 50%. Oral salbutamol acts for4–6 hours, is longer acting and safer than isoprenaline,but not superior in bronchodilator efficacy.

Because of more frequent side effects, oralβ2 agonist therapy is reserved for patients whocannot correctly use inhalers or as alternative/adjuvant drugs in severe asthma.

Dose: 2–4 mg oral, 0.25–0.5 mg i.m./s.c., 100–200 µg byinhalation.

ASTHALIN 2, 4 mg tab., 8 mg SR tab., 2 mg/5 ml syrup, 100µg metered dose inhaler; 5 mg/ml respirator soln., 200 µgrotacaps; CROYSAL 0.5 mg/ml inj, SALOL 2.5 mg/3 ml inj;

VENTORLIN 2 mg/5 ml syr, 4 mg, 8 mg CR caps;DERIHALER 100 µg metered dose inhaler.

Single enantiomer preparation of R(–) salbutamol has alsobeen marketed, because it is the active β2 agonist and morepotent bronchodilator which may produce fewer side effectsthan the racemate.

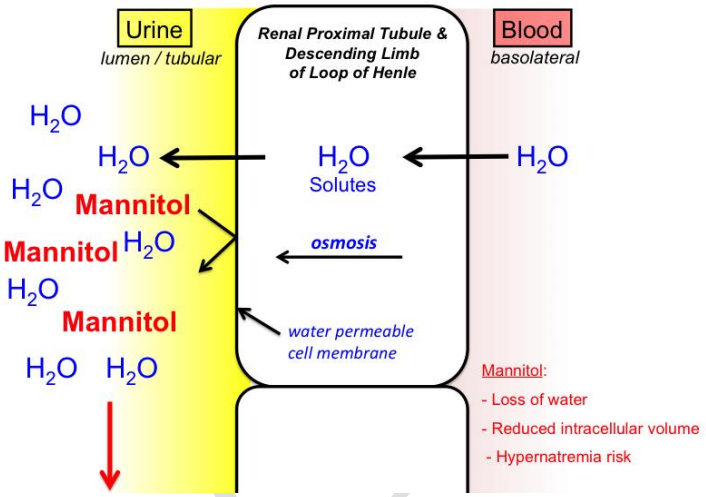
Aminophylline (Theophylline-ethylenediamine; 85%theophylline) water soluble, can be injected i.v. but noti.m. or s.c.—highly irritating. 250–500 mg oral or slow i.v.injection; children 7.5 mg/kg i.v.; AMINOPHYLLINE 100mg tab, 250 mg/10 ml inj. Aminophylline 250–500 mg

diluted in 20–50 ml glucose(5%) solution injected i.v. over 20–30 min had been routinelyused, but recent evidence shows that it does not affordadditional benefit; may even produce.

Drugs used for diuretics

Antidiuretics (more precisely 'anti-aquaretics', because they inhibit water excretion withoutaffecting salt excretion) are drugs that reduce urine volume, particularly in diabetes insipidus (DI) which is their primary indication. Drugs are:

1. Antidiuretic hormone (ADH, Vasopressin), Desmopressin, Lypressin, Terlipressin
2. Thiazide diuretics, Amiloride.
3. Miscellaneous: Indomethacin, Chlorpropamide, Carbamazepine.



Mannitol is an osmotic diuretic that is metabolically inert in humans and occurs naturally, as a sugar or sugar alcohol, in fruits and vegetables. Mannitol elevates blood plasma osmolality, resulting in enhanced flow of water from tissues, including the brain and cerebrospinal fluid, into interstitial fluid and plasma. As a result, cerebral edema, elevated intracranial pressure, and cerebrospinal fluid volume and pressure may be reduced.

Mannitol is a nonelectrolyte of low molecularweight (182) that is pharmacologically inert— can be given in large quantities sufficient to raise osmolarity of plasma and tubular fluid. It is minimally metabolized in the body; freely filtered at the glomerulus and undergoes limited reabsorption: therefore excellently suited to be used as osmotic diuretic. Mannitol appears to limittubular water and electrolyte reabsorption in a variety of ways:

1. Retains water isoosmotically in PT—dilutes luminal fluid which opposes NaCl reabsorption.

2. Inhibits transport processes in the thick AscLH by an unknown mechanism. Quantitatively this appears to be the largest contributor to the diuresis.e promotion of urinary excretion of toxic substances; as an Antiglaucoma agent; and as a renal function diagnostic aid. Expands extracellular fluid volume (because it does not enter cells, mannitol draws water from the intracellular compartment)—increases g.f.r. and inhibits renin release.

4. Increases renal blood flow, especially to the medulla—medullary hypertonicity is reduced (due to washing off)—corticomedullaryosmotic gradient is dissipated—passive salt reabsorption is reduced. Though the primary action of mannitol is to increase urinary volume, excretion of all cations(Na+, K+, Ca2+, Mg2+) and anions (Cl^-, $HCO3^-$, $PO43^-$) is also enhanced.

Administration Mannitol is not absorbed orally; has to be giveni.v. as 10–20% solution. It is excreted with a t½ of 0.5–1.5 hour. MANNITOL 10%, 20%, in 100, 350 and 500 ml vac. Uses Mannitolis never used for the treatment of chronic edema or as a natriuretic. Its indications are:

1. Increased intracranial or intraocular tension (acute congestive glaucoma, head injury, stroke, etc.): by osmotic action it encourages movement of water from brain parenchyma, CSF and aqueous humour; 1–1.5 g/kg is infused over 1 hour as 20% solution to transiently raise plasma osmolarity. It is also used before and after ocular/brain surgery to prevent acute rise in intraocular/intracranial pressure.To maintain g.f.r. and urine flow in impending acute renal failure, e.g. in shock, severe trauma, cardiac surgery, haemolytic reactions: 500–1000 ml of the solution may be infused over 24 hours. However, prognostic benefits in conditions other than cardiac surgery are still unproven. If acute renal failure has already set in, kidney is incapable of forming urine even after an osmotic load; mannitol is contraindicated: it will then expand plasma volume pulmonary edemaand heart failure may develop.

To counteract low osmolality of plasma/e.c.f. due to rapid haemodialysis or peritoneal dialysis (dialysis disequilibrium). Mannitol along with large volumes of saline was infused i.v. to produce ‘forced diuresis’ in acute poisonings in the hope of enhancing excretion of the poison. However, this has been found to be ineffective and to produce electrolyte imbalances. Mannitol is contraindicated in acute tubular necrosis, anuria, pulmonary edema; acute left ventricular failure, CHF, cerebral haemorrhage. The most common side effect is headache. Nausea and vomiting may occur; hypersensitivity reactions are rare.

Xanthine

Derivatives of xanthine (known collectively as xanthines) are a group of alkaloids commonly used for their effects as mild stimulants and as bronchodilators, notably in the treatment of asthma symptoms. In contrast to other, more potent stimulants like sympathomimetic amines, xanthines mainly act to oppose the actions of the sleepiness-inducing adenosine, and increase alertness in the central nervous system. They also stimulate the respiratory centre, and are used for treatment of infantile apnea. Due to widespread effects, the therapeutic range of xanthines is narrow, making them merely a second-line asthma treatment. The therapeutic level is 10-20 micrograms/mL blood; signs of toxicity include tremor, nausea, nervousness, and tachycardia/arrhythmia.

Methylated xanthines (methylxanthines), which include caffeine, aminophylline, IBMX, paraxanthine, pentoxifylline,theobromine, and theophylline, affect not only the airways but stimulate heart rate, force of contraction, and cardiac arrhythmias at high concentrations. In high doses they can lead to convulsions that are resistant to anticonvulsants.

Drugs used for anti-ulcer drugs

These are the first class of highly effective drugs for acid-peptic disease, but have been surpassed by proton pump inhibitors (PPIs). Four H_2antagonists cimetidine, ranitidine, famotidine and roxatidine are available in India; many others are marketed elsewhere. Their interaction with H2 receptors has been found to be competitive in case of cimetidine, ranitidine and roxatidine, but competitive-noncompetitive in case of famotidine.

Cimetidine was the first H_2 blocker to be introduced clinically and is described as the prototype, though other H_2 blockers are more commonly used now.

Pharmacological actions

H_2 blockade Cimetidine and all other H_2antagonists block histamine-induced gastric secretion, cardiac stimulation (prominent in isolated preparations, especially in guinea pig), uterine relaxation (in rat) and bronchial relaxation (H_2 blockers potentiate histamine induced bronchospasm). They attenuate fall in BP due to histamine, especially the late phase response seen with high doses. They are highly selective: have no effect on H1 mediated responses or on the action of other transmitters/autacoids. Pharmacokinetics Cimetidine is adequately absorbed

orally, though bioavailability is 60–80% due to first pass hepatic metabolism. Absorption is not interfered by presence of food in stomach. It crosses placenta and reaches milk, but penetration in brain is poor because of its hydrophilic nature. About 2/3 of a dose is excreted unchanged in urine and bile, the rest as oxidized metabolites. The elimination t½ is 2–3 hr. Dose reduction is needed in renal failure.

Adverse effects

Cimetidine is well tolerated by most patients:adverse effects occur in < 5%. These are generally mild.

- Headache, dizziness, bowel upset, dry mouth, rashes.
- Cimetidine (but not other H2 blockers) has antiandrogenicaction (displaces dihydrotestosterone from its cytoplasmic receptor), increases plasma prolactin and inhibits degradation of estradiol by liver.
- High doses given for long periods have producedgynaecomastia, loss of libido, impotence and temporary decrease in sperm count.
- Transient elevation of plasma aminotransferases; but hepatotoxicity is rare.

Interactions

Cimetidine inhibits several cytochrome P-450 isoenzymesand reduces hepatic blood flow. Itinhibits the metabolism of many drugs so that they can accumulate to toxic levels, e.g. theophylline, phenytoin, carbamazepine, phenobarbitone, sulfonylureas, metronidazole, warfarin, imipramine, lidocaine, nifedipine, quinidine. Metabolism of propranolol and diazepam is also retarded, but this may not be clinically significant. Antacids reduce absorption of all H2 blockers. When used concurrently a gap of 2 hr should be allowed. Ketoconazole absorption is decreased by H_2 blockers due to reduced gastric acidity.

Dose: For ulcer healing—400 mg BD or 800 mg at bed time orally; maintenance—400 mg at bed time.

For stress ulcer—50 mg/hri.v. infusion. Rapid or higher dose i.v. injection can cause confusional state, hallucinations, convulsions, bradycardia, arrhythmias, coma or cardiac arrest.

CIMETIDINE 200 mg, 400 mg, 800 mg tabs, 200 mg/2 ml inj., LOCK-2 200 mg tab.

Ranitidine

A nonimidazole (has a furan ring) H_2 blocker, it has several desirable features compared to cimetidine:

- About 5 times more potent than cimetidine. Though its pharmacokinetic profile and t½ of 2–3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.
- No antiandrogenic action, does not increase prolactin secretion or spare estradiol from hepatic metabolism—no effect on male sexual function or gynaecomastia.
- Lesser permeability into the brain: lower propensity to cause CNS effects. In fact, little effect outside g.i.t. has been observed.
- Less marked inhibition of hepatic metabolism of other drugs; drug interactions mostly have no clinical relevance.
- Overall incidence of side effects is lower: headache, diarrhoea/constipation, dizziness have an incidence similar to placebo.

Dose: for ulcer healing 300 mg at bed time or 150 mg BD; for maintenance 150 mg at bed time. Parenteral dose—50 mg i.m. or slow i.v. inj. every 6–8 hr (rapid i.v. injection can cause hypotension), 0.1–0.25 mg/kg/hr by i.v. infusion has been used for prophylaxis of stress ulcers. For gastrinoma 300 mg 3–4 times a day.

ULTAC, ZINETAC 150 mg, 300 mg tabs; HISTAC, RANITIN,

ACILOC, RANTAC 150 mg, 300 mg tabs, 50 mg/2 ml inj.

PARA-AMINO PHENOL DERIVATIVES

Phenacetin introduced in 1887 was extensively used as analgesic-antipyretic, but is now banned because it was implicated in analgesic abuse nephropathy. Paracetamol (acetaminophen) the deethylated active metabolite of phenacetin, was also introduced in the last century but has come into common use only since 1950.

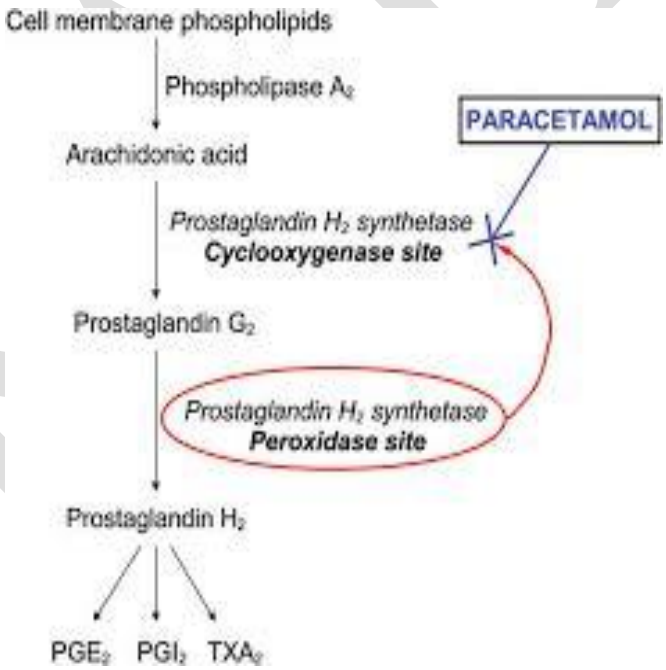
Actions

The central analgesic action of paracetamol is like aspirin, i.e. it raises pain threshold, but has weak peripheral antiinflammatory component. Analgesic action of aspirin and paracetamol is additive. Paracetamol is a good and promptly acting antipyretic. Paracetamol has negligible anti-inflammatory action. It is a poor inhibitor of PG synthesis in peripheral tissues,

but more active on COX in the brain. One explanation offered for the discrepancy between its analgesic-antipyretic and antiinflammatory actions is its inability to inhibit COX in the presence of peroxides which are generated at sites of inflammation, but are not present in the brain. The ability of paracetamol to inhibit COX-3 (an isoenzyme so far located in dog brain) could also account for its analgesicantipyretic action.

In contrast to aspirin, paracetamol does not stimulate respiration or affect acid-base balance; does not increase cellular metabolism. It has no effect on CVS. Gastric irritation is insignificant— mucosal erosion and bleeding occur rarely only in overdose. It does not affect platelet function or clotting factors and is not uricosuric. Pharmacokinetics Paracetamol is well absorbed orally, only about 1/4th is protein bound in plasma and it is uniformly distributed in the body.

Metabolism occurs mainly by conjugation with glucuronic acid and sulfate: conjugates are excreted rapidly in urine. Plasma t½ is 2–3 hours. Effects after an oral dose last for 3–5 hours.



Adverse effects

In isolated antipyretic doses paracetamol is safe and well tolerated. Nausea and rashes occur occasionally, leukopenia is rare. Acute paracetamol poisoning It occurs especially in small

children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in an adult) is taken, serious toxicity can occur. Fatality is common with > 250 mg/kg. Paracetamol is not recommended in premature infants (< 2 kg) for fear of hepatotoxicity. Uses Paracetamol is one of the most commonly used 'over-the-counter' analgesic for headache, mild migraine, musculoskeletal pain, dysmenorrhoea, etc. but is relatively ineffective when inflammation is prominent as in rheumatoid arthritis. Paracetamol is recommended as first choice analgesic for osteoarthritis by many professional bodies. It is one of the best drugs to be used as antipyretic, especially in children (no risk of Reye's syndrome). Dose to dose it is equally efficacious as aspirin for non-inflammatory conditions. It is much safer than aspirin in terms of gastric irritation, ulceration and bleeding (can be given to ulcer patients), does not prolong bleeding time. Hypersensitivity reactions are rare; no metabolic effects or acid base disturbances; can be used in all age groups (infants to elderly), pregnant/lactating women, in presence of other disease states and in patients in whom aspirin is contraindicated. It does not have significant drug interactions. Thus, it may be preferred over aspirin for most minor conditions.

Dose: 325–650 mg (children 10–15 mg/kg) 3–5 times a day.

CROCIN 0.5, 1.0 g tabs; METACIN, PARACIN 500 mg tab, 125 mg/5 ml syrup, 150 mg/ml paed. drops, ULTRAGIN, PYRIGESIC, CALPOL 500 mg tab, 125 mg/5 ml syrup, NEOMOL, FEVASTIN, FEBRINIL 300 mg/2 ml inj., CROCIN PAIN RELIEF: 650 mg + Caffeine 50 mg tab. JUNIMOL-RDS 80, 170, 250 mg suppository (for children), PARACETAMOL RECTAL SUPPOSITORY 80, 170 mg.

IBUPROFEN

Ibuprofen was the first member of this class to be introduced in 1969 as a better tolerated alternative to aspirin. Many others have followed. All have similar pharmacodynamic properties but differ considerably in potency and to some extent in duration of action The analgesic, antipyretic and anti-inflammatory efficacy is rated somewhat lower than high dose of aspirin. All members inhibit PG synthesis, naproxen being the most potent; but their in vitro potency to inhibit COX does not closely parallel in vivo antiinflammatory potency. Inhibition of platelet aggregation is short-lasting with ibuprofen, but longer lasting with naproxen.

Adverse effects Ibuprofen and all its congeners are better tolerated than aspirin. Side effects are milder and their incidence is lower. Gastric discomfort, nausea and vomiting, though less than aspirin or indomethacin, are still the most common side effects. Gastric erosion and occult blood loss are rare. CNS side effects include headache, dizziness, blurring of vision, tinnitus and depression. Rashes, itching and other hypersensitivity phenomena are infrequent. However, these drugs precipitate aspirin-induced asthma. Fluid retention is less marked. They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient.

Pharmacokineticsand interactions

All are well absorbed orally, highly bound to plasma proteins (90–99%), but displacement interactions are not clinically significant—dose of oral anticoagulants and oral hypoglycaemics need not be altered. Because they inhibit platelet function, use with anticoagulants should, nevertheless, be avoided. Similar to other NSAIDs, they are likely to decrease diuretic and antihypertensive action of thiazides, furosemide and β blockers.All propionic acid derivatives enter brain, synovial fluid and cross placenta. They are largely metabolized in liver by hydroxylation and glucuronide conjugation and excreted in urine as well as bile.

Uses

1. Ibuprofen is used as a simple analgesic and antipyretic in the same way as low dose of aspirin. It is particularly effective in dysmenorrhoea in which the action is clearly due to PG synthesis inhibition. It is available as an ‘over-the-counter’ drug.

2. Ibuprofen and its congeners are widely used in rheumatoid arthritis, osteoarthritis and other musculoskeletal disorders, especially where pain is more prominent than inflammation.

3. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation. Ibuprofen it has been rated as the safest

traditional NSAID by the spontaneous adverse drug reaction reporting system in U.K. Ibuprofen (400 mg) has been found equally or more efficacious than a combination of aspirin (650 mg) + codeine (60 mg) in relieving dental surgery pain, but is a weaker anti-inflammatory; not suitable for acute gout and other similar conditions. Concurrent treatment with ibuprofen has been found to prevent irreversible COX inhibition by low dose aspirin by reversibly occupying the active serine residue of COX-1 and protecting it from irreversible acetylation by aspirin. Thus, the antiplatelet action of ibuprofen is short lasting and it antagonizes the antiplatelet and cardioprotective effect of low dose aspirin.

1	IV	The main mechanism of most drugs absorption in GI tract is:	Active transport (carrier-mediated diffusion)	Filtration (aqueous diffusion)	Endocytosis and exocytosis	Passive diffusion (lipid diffusion)	**Passive diffusion (lipid diffusion)**
2	IV	The mechanism of Cytiton action is	Direct activation of the respiratory center	The reflex mechanism	The mixed mechanism	Active transport	**The reflex mechanism**
3	IV	What kind of substances can't permeate membranes by passive diffusion?	Lipid-soluble	Non-ionized substances	Hydrophobic substances	Hydrophilic substances	**Hydrophilic substances**
4	IV	Choose the unwanted effects of clonidine:	Parkinson's syndrome	Sedative and hypnotic effects	Agranulocytosis and aplastic anemia	Dry cough and respiratory depression	**Sedative and hypnotic effects**
5	IV	The tissues most sensitive to atropine are:	The salivary, bronchial and sweat glands	The gastric parietal cells	Smooth muscle and autonomic effectors	The heart	**The salivary, bronchial and sweat glands**
6	IV	Compared with atropine, scopolamine has all of the following properties EXCEPT:	More marked central effect	Less potent in decreasing bronchial, salivary and sweat gland secretion	More potent in producing mydriasis and cycloplegia	Lower effects on the heart, bronchial muscle and intestines	**Less potent in decreasing bronchial, salivary and sweat gland secretion**
7	IV	Contraindications to the use of antimuscarinic drugs are all of the following except:	Glaucoma	Myasthenia	Bronchial asthma	Paralytic ileus and atony of the urinary bladder	**Bronchial asthma**
8	IV	A bronchial smooth muscle contains:	Alfa$_1$ receptor	Alfa$_2$ receptor	Beta $_1$ receptor	Beta $_2$ receptor	**Beta $_2$ receptor**
9	IV	Which of the following sympathomimetics is used in the therapy of bronchial asthma?	Formoterol	Norepinephrine	Methoxamine	Dobutamine	**Formoterol**
10	IV	Pick out the bronchodilator drug related to xanthine:	Atropine	Orciprenaline	Adrenaline	Theophylline.	**Theophylline**
11	IV	Pick out the bronchodilator drug belonging to sympathomimics	Isoprenaline	Ephedrine	Atropine	Salbutamol	**Ephedrine**
12	IV	Propranolol is used in the treatment all of the following diseases EXCEPT:	Cardiovascular diseases	Hyperthyroidism	Migraine headache	Bronchial asthma	**Bronchial asthma**
13	IV	This drug is contraindicated in patients with bronchial asthma:	Propranolol	Clonidine	Enalapril	Nifedipine	**Propranolol**
14	IV	Which of the following vitamins is given along with isoniazide in treatment of tuberculosis?	Nicotinic acid	Riboflavin	Pyridoxine	Ascorbic acid	**Pyridoxine**
15	IV	Combined chemotherapy of tuberculosis is used to:	Decrease mycobacterium drug-resistance	Increase mycobacterium drug-resistance	Decrease the antimicrobal activity	Decrease the onset of antimycobacterial drugs biotransformation	**Decrease mycobacterium drug-resistance**
16	IV	Which of the following enzymes improves GIT functions (replacement therapy):	Pepsin	Urokinase	L-asparaginase	Lydaze	**Pepsin**
17	IV	All of the following drugs stimulate appetite EXCEPT:	Vitamins	Bitters	Fepranone	Insulin	**Fepranone**
18	IV	Serious side effects of glucocorticoids include the following, EXCEPT:	Acute peptic ulcers	Iatrogenic Cushing's syndrome (rounding, puffiness, fat deposition and plethora alter the appearance of the face – moon faces)	Salicylism (vomiting, tinnitus, decreased hearing, and vertigo)	Hypomania or acute psychosis	**Salicylism (vomiting, tinnitus, decreased hearing, and vertigo)**
19	IV	Gastric acid secretion is under the control of the following agents EXCEPT:	Histamine	Acetylcholine	Serotonin	Gastrin	**Serotonin**
20	IV	Indicate the drug belonging to proton pump inhibitors:	Pirenzepine	Ranitidine	Omeprazole	Trimethaphan	**Omeprazole**
21	IV	All of the following agents intensify the secretion of gastric glands EXCEPT:	Pepsin	Gastrin	Histamine	Carbonate mineral waters	**Pepsin**
22	IV	Which of the following drugs is an agent of substitution therapy?	Gastrin	Hydrochloric acid	Hystamine	Carbonate mineral waters	**Hydrochloric acid**
23	IV	An adverse effect of oral iron therapy is:	Anemia	Thrombocytopenia	Headache	Constipation	**Constipation**
24	IV	Mental confusion and hallucinations, peripheral atropine-like toxicity (e.g. Cycloplegia, tachycardia, urinary retention, and constipation) are possible adverse effects of	Sinemet	Benztropine	Tolkapone	Bromocriptine	**Benztropine**
25	IV	Adverse peripheral effects, such as loss of accommodation, dry mouth, tachycardia, urinary retention, constipation are related to	Alpha adrenoreceptor blockade	Muscarinic cholinoreceptor blockade	Supersesitivity of the dopamine receptor	Dopamine receptor blockade	**Muscarinic cholinoreceptor blockade**
26	IV	Sedation, peripheral atropine-like toxicity (e.g. Cycloplegia, tachycardia, urinary retention, and constipation), orthostatic hypotension, arrhythmias, weight gain and sexual disturbances are possible adverse effects of	Sertaline	Amitriptyline	Phenelsine	Bupropion	**Amitriptyline**
27	IV	Choose the drug that causes constipation	Sodium bicarbonate	Aluminium hydroxide	Calcium carbonate	Magnesium oxide	**Aluminium hydroxide**
28	IV	Which of histamine H1 antagonists is noted for the ulcerogenic effect?	Diazoline	Loratadine	Suprastine	Dimedrol	**Diazoline**
29	IV	Combination of sulfonamides with trimethoprim	Decreases the unwanted effects of sulfonamides	Increases the antimicrobial activity	Decreases the antimicrobial activity	Increases the elimination of sulfonamides	**Increases the antimicrobial activity**
30	IV	Indicate a beta-blocker, which is particularly efficacious in thyroid storm	Pindolol	Sotalol	Phentolamine	Propranolol	**Propranolol**
31	IV	Which of the following hormones is produced by the thyroid gland?	Thyroxine	Thyroid-stimulating hormone	Thyrotropin-releasing hormone	Thyroglobulin.	**Thyroxine**
32	IV	Thyroid hormones produce various pharmacological effects. Indicate the wrong statement(s).	Decline of the basal metabolic rate in the body	Increase in the rate and force of contraction of the heart	Increase in the blood cholestrol level	Increase in the heat production	**Decline of the basal metabolic rate in the body**
33	IV	Currently used antithyroid drugs include the following, EXCEPT	Propylthiouracil (PTU)	Diatrizoate sodium (Hypaque)	Methimazole (Tapazole)	Potassium perchlorate	**Potassium perchlorate**
34	IV	Secretory products of pancreatic β-cells are	Glucagon, proglucagon	Insulin, C-peptide, proinsulin, islet amyloid polypeptide (IAPP)	Somatostatin	Pancreatic polypeptide (PP)	**Insulin, C-peptide, proinsulin, islet amyloid polypeptide (IAPP)**
35	IV	Insulin cannot be administered by	Oral route	Intravenous route	Subcutaneous route	Intramuscular route	**Oral route**
36	IV	Diabetic coma is treated by the administration of	Lente insulin	Glucose	Crystalline insulin	Oral anti-diabetic drugs	**Crystalline insulin**
37	IV	Which of the following oral hypoglycaemic drugs stimulates both synthesis and release of insulin from beta islet cells	Glibenclamide	Phenformin	Buformine	Metformin	**Glibenclamide**
38	IV	The action of insulin is potentiated by	Sulphonylureas	Glucagon	Biguanides	Glibenclamide	**Biguanides**
39	IV	Insulin causes reduction in blood sugar level by the following mechanisms, EXCEPT	Increased glucose uptake in the peripheral tissue	Reduction of breakdown of glycogen	Diminished gluconeogenesis	Decreased glucose absorption from the gut	**Decreased glucose absorption from the gut**
40	IV	Sulphonylureas act by	Reducing the absorption of carbohydrate from the gut	Increasing the uptake of glucose in peripheral tissues	Reducing the hepatic gluconeogenesis	Stimulating the beta islet cells of pancreas to produce insulin	**Stimulating the beta islet cells of pancreas to produce insulin**
41	IV	The primary reason for a physician to prescribe human insulin is that	It has a faster onset of action than other insulins	It has a shorter duration of action than other insulins	It can be given to patients who have an allergy to animal insulins	It is more effective in preventing the complications of diabetes than animal insulins	**It can be given to patients who have an allergy to animal insulins**
42	IV	Mechanism of sulfonamides' antibacterial effect is	Inhibition of dihydropteroate reductase	Inhibition of dihydropteroate synthase	Inhibition of cyclooxygenase	Activation of DNA gyrase	**Inhibition of dihydropteroate synthase**
43	IV	Mechanism of Rifampin action is	Inhibition of mycolic acids synthesis	Inhibition of DNA dependent RNA polymerase	Inhibition of topoisomerase II	Inhibition of cAMP synthesis	**Inhibition of DNA dependent RNA polymerase**
44	IV	Choose the drug which is a H2-receptor antagonist	Omeprazole	Pirenzepine	Carbenoxolone	Ranitidine	**Ranitidine**
45	IV	All of the following drugs are proton pump inhibitors EXCEPT	Pantoprozole	Omeprazole	Famotidine	Rabeprazole	**Famotidine**
46	IV	Indicate the drug belonging to M1-cholinoblockers:	Cimetidine	Ranitidine	Pirenzepin	Omeprazole	**Pirenzepin**
47	IV	Which of the following drugs may cause reversible gynecomastia?	Omeprazole	Pirenzepine	Cimetidine	Sucralfate	**Cimetidine**

48	IV	Select an endocrine drug which is an amino acid derivative	Insulin	Hydrocortisone	Calcitonin	Thyroxine	**Thyroxine**
49	IV	Thiazolidinediones act by	Diminishing insulin resistance by increasing glucose uptake and metabolism in muscle and adipose tissues	Reducing the absorption of carbohydrate from the gut	Stimulating the beta islet cells of pancreas to produce insulin	Stimulating the alpha islet cells of pancreas to produce glucagon	**Diminishing insulin resistance by increasing glucose uptake and metabolism in muscle and adipose tissues**
50	IV	Tamoxifen is	Antiprogestin	Antiandrogen	Antiestrogen	Androgen	**Antiestrogen**
51	IV	The major natural progestin is	Estradiol	Estron	Progesterone	Estriol	**Progesterone**
52	IV	Progesterone is secreted by	Ovarian follicles	Corpus luteum	Granulosa cells	Theca cells	**Corpus luteum**
53	IV	Mifepristone (RU-486) is	Antiprogestin	Antiandrogen	Antiestrogen	Androgen	**Antiprogestin**
54	IV	An endogenous vasoconstrictor that can stimulate aldosterone release from suprarenal glands:	Angiotensinogen	Angiotensin I	Angiotensin II	Angiotensin-converting enzyme	**Angiotensin II**
55	IV	Choose the vasodilator which releases NO	Nifedipine	Hydralazine	Minoxidil	Sodium nitroprusside	**Sodium nitroprusside**
56	IV	Tick the drug belonging to non-selective beta2-adrenomimics:	Salbutamol	Isoprenaline	Salmeterol	Terbutaline	**Isoprenaline**
57	IV	The mechanism of methylxanthines action is	Inhibition of the enzyme phosphodiesterase	Beta2 -adrenoreceptor stimulation	Inhibition of the production of inflammatory cytokines	Inhibition of M-cholinoreceptors	**Inhibition of the enzyme phosphodiesterase**
58	IV	Choose an emetic drug of central action:	Ipecacuanha derivatives	Promethazine	Tropisetron	Apomorphine hydrochloride	**Apomorphine hydrochloride**
59	IV	Indicate an antiemetic agent which is related to neuroleptics	Metoclopramide	Nabilone	Tropisetron	Prochlorperazine	Prochlorperazine
60	IV	The mechanism of stimulant purgatives is	Increasing the volume of non-absorbable solid residue	Increasing motility and secretion	Altering the consistency of the feces	Increasing the water content	Increasing motility and secretion

UNIT-V-SYLLABUS

Toxicology- Introduction, definition and disciplines of toxicology, classification of toxicity and toxicants, Mechanisms of toxic effect, treatment of intoxication, methods in toxicology testing, heavy metal toxicity and chelation therpy. Environmental pollution, mycotoxins, mushroom poisons.

Toxicology

- Toxicology is a discipline, overlapping with **biology, chemistry, pharmacology, and medicine,** that involves the study of the adverse effects of chemical substances on living organisms and the practice of diagnosing and treating exposures to toxins and toxicants.
- The relationship between dose and its effects on the exposed organism is of high significance in toxicology. Factors that influence chemical toxicity include the dosage (and whether it is acute or chronic), route of exposure, species, age, sex, and environment. Toxicologists are experts on poisons and poisoning.
- The goal of toxicity assessment is to identify adverse effects of a substance. Adverse effects depend on two main factors:

  i) routes of exposure (oral, inhalation, or dermal) and

  ii) dose (duration and concentration of exposure).
- To explore dose, substances are tested in both acute and chronic models.[10] Generally, different sets of experiments are conducted to determine whether a substance causes cancer and to examine other forms of toxicity.

Factors that influence chemical toxicity

* Dosage
* Both large single exposures (acute) and continuous small exposures (chronic) are studied.
* Route of exposure
* Ingestion, inhalation or skin absorption
* Other factors
* Species

* Age
* Sex
* Health
* Environment

Medical toxicology

- Medical toxicology is the discipline that requires physician status (MD or DO degree plus specialty education and experience).

Clinical toxicology

- Clinical toxicology is the discipline that can be practiced not only by physicians but also other health professionals with a master's degree in clinical toxicology: physician extenders (physician assistants, nurse practitioners), nurses, pharmacists, and allied health professionals.

Computational toxicology

- Computational toxicology is a discipline that develops mathematical and computer-based models to better understand and predict adverse health effects caused by chemicals, such as environmental pollutants and pharmaceuticals.

- Within the Toxicology in the 21st Century project, the best predictive models were identified to be Deep Neural Networks, Random Forest, and Support Vector Machines, which can reach the performance of in vitro experiments

There are generally four types of toxic entities; chemical, biological, physical and radiation:

- Chemical toxicants include inorganic substances such as, lead, mercury, hydrofluoric acid, and chlorine gas, and organic compounds such as methyl alcohol, most medications, and poisons from living things.

- While some weakly radioactive substances, such as uranium, are also chemical toxicants, more strongly radioactive materials like radium are not, their harmful effects (radiation poisoning) being caused by the ionizing radiation produced by the substance rather than chemical interactions with the substance itself.

- Disease-causing microorganisms and parasites are toxic in a broad sense, but are generally called pathogens rather than toxicants.

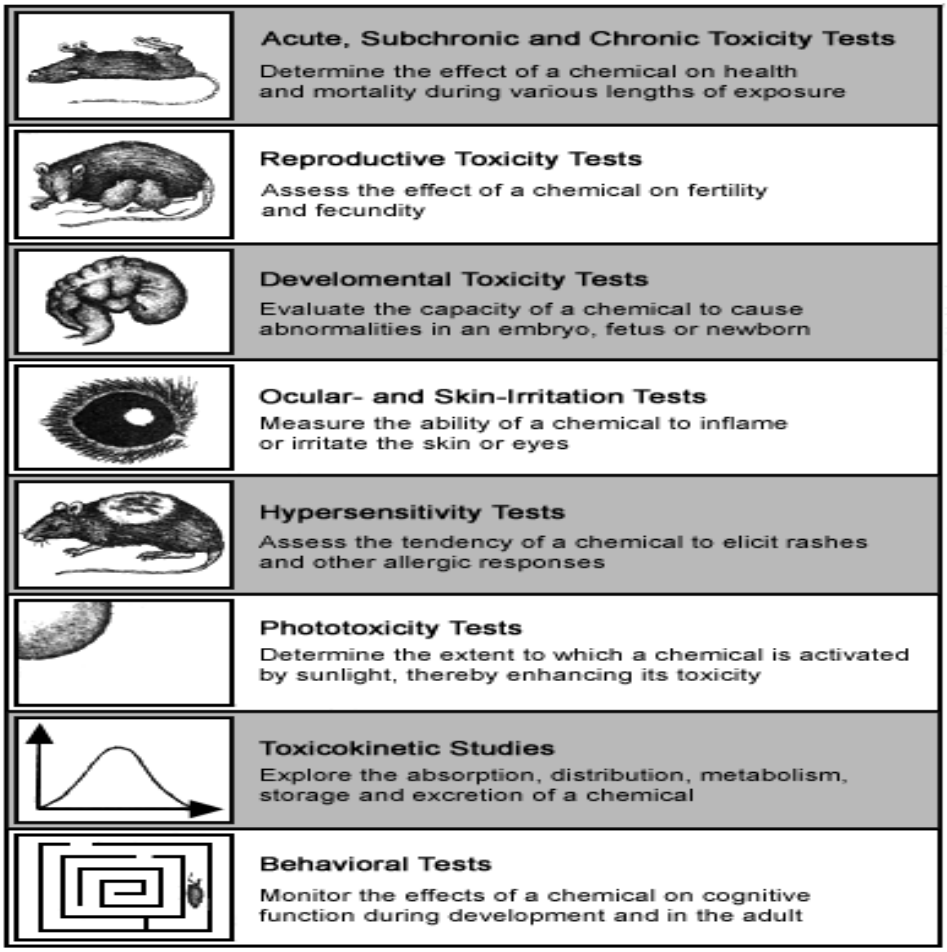
- The biological toxicity of pathogens can be difficult to measure because the "threshold dose" may be a single organism. Theoretically one virus, bacterium or worm can reproduce to cause a serious infection.
- However, in a host with an intact immune system the inherent toxicity of the organism is balanced by the host's ability to fight back; the effective toxicity is then a combination of both parts of the relationship.
- In some cases, e.g. cholera, the disease is chiefly caused by a nonliving substance secreted by the organism, rather than the organism itself.
- Such nonliving biological toxicants are generally called toxins if produced by a microorganism, plant, or fungus, and venoms if produced by an animal.
- Physical toxicants are substances that, due to their physical nature, interfere with biological processes.
- Examples include coal dust, asbestos fibers or finely divided silicon dioxide, all of which can ultimately be fatal if inhaled.
- Corrosive chemicals possess physical toxicity because they destroy tissues, but they're not directly poisonous unless they interfere directly with biological activity.
- Water can act as a physical toxicant if taken in extremely high doses because the concentration of vital ions decreases dramatically if there's too much water in the body.
- Asphyxiant gases can be considered physical toxicants because they act by displacing oxygen in the environment but they are inert, not chemically toxic gases.Radiation can have a toxic effect on organisms

Methods of toxicology:

- Humans and animals can be exposed to both naturally occurring and man-made chemicals in a variety of ways -- by mouth, skin contact, or inhalation.
- Toxicological tests measure the effects of a limited exposure of an animal to a substance (acute toxicity) as well as repeated, long-term exposure (chronic toxicity).
- Substances are also tested for more specific endpoints such as cytotoxicity (ability to damage cells), mutagenicity (ability to cause changes in genetic material),

carcinogenicity (ability to cause cancer), and teratogenicity (ability to cause birth defects).

Toxicity Testing



Toxicity Testing

- ***Acute toxicity***
- ***Subacute toxicity***
- ***Chronic toxicity***
- ***Reproductive toxicity***
- ***Genotoxicity***
- ***Neurotoxicity***
- ***Immunotoxicity***

Heavy metal toxicity:

- Accumulating too much of certain metals in the body can lead to dangerous symptoms.
- Heavy metal poisoning is caused by the accumulation of certain metals in the body due to exposure through food, water, industrial chemicals, or other sources.
- While our bodies need small amounts of some heavy metals — such as zinc, copper, chromium, iron, and manganese — toxic amounts are harmful.
- soft tissues accumulate too much of heavy metals, the resulting poisoning can cause serious damage. Lead, mercury, arsenic, and cadmium are the metals most commonly associated with heavy metal poisoning in the United States.
- Men and women are equally susceptible to heavy metal poisoning if they're exposed in the same ways.Mercury poisoning is very rare in children.

Causes of Heavy Metal Poisoning

Heavy metal poisoning can be caused by:

- Industrial exposure
- Air or water pollution
- Foods
- Medicines
- Improperly coated food containers, plates, and cookware
- Ingestion of lead-based paints.

Heavy Metal Poisoning Symptoms

Symptoms of heavy metal poisoning depend on the type of metal causing toxicity.

If you have acute heavy metal poisoning — meaning you were exposed to a large amount of metal at once (for example, by swallowing a toy) — your symptoms may include:

- Confusion
- Numbness
- Nausea

- Vomiting
- Falling into a coma

Long-term or chronic exposure to heavy metals may cause the following symptoms:

- Headache
- Weakness
- Tiredness
- Muscle pain
- Joint pain
- Constipation

Heavy Metal Poisoning Treatment

Other forms of treatment may include:

- Chelating agents such as Chemet (succimer), which bind to the metal and are then excreted in your urine
- Suctioning of the stomach to remove some ingested metals
- A diuretic called mannitol (Aridol, Osmitrol), corticosteroid drugs, or intracranial monitoring for swelling of the brain
- Hemodialysis and/or other special treatments if kidney failure occurs.

Heavy Metal Poisoning Prevention

The following tips may help you prevent heavy metal poisoning:

- Wear masks and protective clothing if you work around heavy metals
- Since many metals accumulate in dust and dirt, keep these out of your home as much as possible
- Pay attention to local fish advisories regarding mercury levels
- Be aware of potential sources of lead exposure.

Chelation therapy is a medical procedure that involves the administration of chelating agents to remove heavy metals from the body.

Environmental pollution:

* Environmental pollution is increasing with each passing year and inflicting grave and irreparable injury to the world. Environmental pollution is of different types namely air, water, soil, noise and light-weight.

* These cause damage to the living system. How pollution interacts with public health, environmental medicine and the environment has undergone dramatic change.

* Environmental and occupational medicine are however more commonly viewed as an integrated subject, with emphasis given to industrial issues. Certainly, pollution problems have been recognized in the distant past but were more easily mitigated by nature due to the limited complexity of the pollutant, its degradability (e.g. biodegradable organics) and lower industrialization.

Sources and Causes of Environmental Pollution

The sources and causes of environmental pollution includes the following:

Industrial activities: The industries all over the world that brought prosperity and affluence, made inroads in the biosphere and disturbed the ecological balances. The pall of smoke, the swirling gases, industrial effluents and the fall-out of scientific experiments became constant health hazards, polluting and contaminating both air and water. The improper disposal of industrial wastes are the sources of soil and water pollution. Chemical waste resulting from industry can pollute lakes, rivers and seas and soil too as well as releasing fumes.

Dumping solid waste: Household and commercial waste pollutes the environment when not disposed of properly.

Vehicles: The smoke emitted by vehicles using petrol and diesel and the cooking coal also pollutes the environment. The multiplication of vehicles, emitting black smoke that, being free and unfettered, spreads out and mixes with the air we breathe. The harmful smoke of these vehicles causes air pollution. Further, the sounds produced by these vehicles produces causes noise-pollution.

Rapid urbanization and industrialization: The urbanization and the rapid growth of industrialization are causing through environmental pollution the greatest harm to the plant life, which in turn causing harm to the animal kingdom and the human lives.

Population overgrowth: Due to the increase in population, particularly in developing countries, there has been surge in demand for basic food, occupation and shelter. The world has witnessed massive deforestation to expand absorb the growing population and their demands.

Combustion of fossil fuels: The combustion of fossil fuels pollutes the air, the soil and the water with noxious gases such as CO2 and CO.

Agricultural waste: Fertilizers and pesticides used in agriculture are key causes of environmental pollution.

Effects of Pollution:

Environment Degradation: Environment is the first casualty for increase in pollution weather in air or water. The increase in the amount of CO2 in the atmosphere leads to smog which can restrict sunlight from reaching the earth. Thus, preventing plants in the process of photosynthesis. Gases like Sulfur dioxide and nitrogen oxide can cause acid rain. Water pollution in terms of Oil spill may lead to death of several wildlife species.

Human Health: The decrease in quality of air leads to several respiratory problems including asthma or lung cancer. Chest pain, congestion, throat inflammation, cardiovascular disease, respiratory disease are some of diseases that can be causes by air pollution. Water pollution occurs due to contamination of water and may pose skin related problems including skin irritations and rashes. Similarly, Noise pollution leads to hearing loss, stress and sleep disturbance.

Global Warming: The emission of greenhouse gases particularly CO2 is leading to global warming. Every other day new industries are being set up, new vehicles come on roads and trees are cut to make way for new homes. All of them, in direct or indirect way lead to increase in CO2 in the environment. The increase in CO_2 leads to melting of polar ice caps which increases the sea level and pose danger for the people living near coastal areas.

Depletion of the Ozone Layer: Ozone layer stops ultra violet rays from reaching the earth. UV exposure in excess can lead to skin cancer. Due to release of CFCs & aerosols in the atmosphere which contributed to the depletion of ozone layer. This removes the sheet that protects us from the harmful UV-rays which is more than just threatening.

Infertile Land:Constant use of pesticides, insecticides & other chemicals causes the soil to become infertile. Soil is the major and in some cases the only source of nutrition for plants & vegetables. Importance of these can never be overstated. But due to infertile soil, plants will not be able to grow properly. Industrial waste also affects the fertility of the soil.

Pollution not only affect humans by destroying their respiratory, cardiovascular and neurological systems; it also affects the nature, plants, fruits, vegetables, rivers, ponds, forests, animals, etc, on which they are highly dependent for survival. It is crucial to control pollution as the nature, wildlife and human life are precious gifts to the mankind.

Solutions to Environmental Pollution

- Gas emission pollution is being mitigated in a variety of ways with car emission control, **electric and hybrid vehicles and public transportation systems**. Not all major cities have successful implementation and decent public transportation in place, but the world is working on this issue constantly and we have managed to reduce emissions profoundly over the last decade. There is much catching up to do.
- The cost of radioactive power plants is becoming apparent and the days of coal power plants are nearly dead. The radiation is a serious issue. Radioactive leakage from power plants and nuclear testing have already contaminated oceanic life to such a degree that it will take hundreds of years to return to normal. More radiation solutions are in the works with various **ecologically friendly power technologies**being built every day.
- **Solar power is a fantastic solution**. Now that solar radiation is at a climactic peak, we can reap power from the sun using solar panel systems. These range from home systems to larger scale systems powering entire communities and cities.
- **Wind power is coming into play**. This may not seem like much at first, but when you get about 100 feet off the ground, there is a great deal of wind up there. By building wind turbines to harvest natural wind energy, electricity is produced. Wind turbine power and solar power are both powerful forces against fossil fuel power and radioactive power.
- **Electromagnetic radiation (ER) reduction**. Once major manufacturers of computers and electronic devices realized the blatant potential for huge ER emissions directly into the eyes and brains of users, they started to implement hardware protocols to minimize risks and reduce ER production significantly. Newer devices are in the lead to knock this problem out and, fortunately, this is working.

Mycotoxins

- Mycotoxins are toxic compounds that are naturally produced by certain types of moulds (fungi). Moulds that can produce mycotoxins grow on numerous foodstuffs such as cereals, dried fruits, nuts and spices.
- Mould growth can occur either before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions. Most mycotoxins are chemically stable and survive food processing.

- Several hundred different mycotoxins have been identified, but the most commonly observed mycotoxins that present a concern to human health and livestock include aflatoxins, ochratoxin A, patulin, fumonisins, zearalenone and nivalenol/deoxynivalenol.
- Mycotoxins appear in the food chain as a result of mould infection of crops both before and after harvest. Exposure to mycotoxins can happen either directly by eating infected food or indirectly from animals that are fed contaminated feed, in particular from milk.

Mycotoxins commonly found in food and why they are of concern

- The effects of some food-borne mycotoxins are acute with symptoms of severe illness appearing quickly after consumption of food products contaminated with mycotoxins.
- Other mycotoxins occurring in food have been linked to long-term effects on health, including the induction of cancers and immune deficiency. Of the several hundred mycotoxins identified so far, about a dozen have gained the most attention due to their severe effects on human health and their occurrences in food.
- **Aflatoxins** are amongst the most poisonous mycotoxins and are produced by certain moulds (*Aspergillus flavus* and *Aspergillus parasiticus*) which grow in soil, decaying vegetation, hay, and grains.
- Crops that are frequently affected by *Aspergillus* spp. include cereals (corn, sorghum, wheat and rice), oilseeds (soybean, peanut, sunflower and cotton seeds), spices (chili peppers, black pepper, coriander, turmeric and ginger) and tree nuts (pistachio, almond, walnut, coconut and Brazil nut).
- Large doses of aflatoxins can lead to acute poisoning (aflatoxicosis) and can be life threatening, usually through damage to the liver. Aflatoxins have also been shown to be genotoxic, meaning they can damage DNA and cause cancer in animal species. There is also evidence that they can cause liver cancer in humans.
- **Ochratoxin A** is produced by several species *Aspergillus* and *Penicillium* and is a common food-contaminating mycotoxin. Contamination of food commodities, such as cereals and cereal products, coffee beans, dry vine fruits, wine and grape juice, spices and liquorice, occurs worldwide.
- Ochratoxin A is formed during the storage of crops and is known to cause a number of toxic effects in animal species. The most sensitive and notable effect is kidney damage, but the toxin may also have effects on fetal development and on the immune system.

- **Patulin** is a mycotoxin produced by a variety of moulds, particularly *Aspergillus*, *Penicillium*and *Byssochlamys*. Often found in rotting apples and apple products, patulin can also occur in various mouldy fruits, grains and other foods. Major human dietary sources of patulin are apples and apple juice made from affected fruit.
- The acute symptoms in animals include liver, spleen and kidney damage and toxicity to the immune system. For humans, nausea, gastrointestinal disturbances and vomiting have been reported.

To minimize the health risk from mycotoxins, people are advised to:

- inspect whole grains (especially corn, sorghum, wheat, rice), dried figs and nuts such as peanuts, pistachio, almond, walnut, coconut, Brazil nuts and hazelnuts which are all regularly contaminated with aflatoxins for evidence of mould, and discard any that look mouldy, discoloured, or shrivelled;
- avoid damage of grains before and during drying, and in storage, as damaged grain is more prone to invasion of moulds and therefore mycotoxin contamination;
- buy grains and nuts as fresh as possible;
- make sure that foods are stored properly – kept free of insects, dry, and not too warm;
- not keep foods for extended periods of time before being used; and
- ensure a diverse diet – this not only helps to reduce mycotoxins exposure, but also improves nutrition.

Mushroom poisons

- Mushroom poisoning (mushroom toxicity) occurs after the ingestion of mushrooms that contain toxins, often in the context of foraging for nontoxic, similarly appearing mushrooms. Mushrooms are the fruiting bodies of a group of higher fungi that have evolved contemporaneously with plants for millions of years. They are widely distributed throughout the world.

- There are thousands of species of mushrooms, but only about 100 species of mushrooms cause symptoms when eaten by humans, and only 15-20 mushroom species are potentially lethal when ingested.

- These symptoms can vary from slight gastrointestinal discomfort to death. The toxins present are secondary metabolites produced by the fungus. Mushroom poisoning is usually the result of ingestion of wild mushrooms after misidentification of a toxic mushroom as an edible species. The most common reason for this misidentification is close resemblance in terms of colour and general morphology of the toxic mushrooms species with edible species.

Toxin	Toxicity	Effects
Alpha-amanitin	Deadly	Causes often fatal liver damage 1–3 days after ingestion. Principal toxin in the death cap.
Phallotoxin	Non-lethal	Causes extreme gastrointestinal upset. Found in various mushrooms.
Orellanine	Deadly	Redox cycler similar to paraquat. Causes kidney failure within 3 weeks after ingestion. Principal toxin in genus *Cortinarius*.
Muscarine	Potentially deadly	Causes SLUDGE syndrome. Found in various mushrooms. Antidote is atropine
Monomethylhydrazine(MMH)	Deadly	Causes brain damage, seizures, gastrointestinal upset, and hemolysis. Metabolic poison. Principal toxin in genus *Gyromitra*. Antidote is large doses of intravenous pyridoxine hydrochloride[22]
Coprine	Non-lethal	Causes illness when consumed with alcohol. Principal toxin in genus *Coprinus*.
Ibotenic acid	Potentially deadly	Excitotoxin. Principal toxin in *Amanita muscaria*, *A. pantherina*, and *A. gemmata*.
Muscimol	Psychoactive	Causes CNS depression and hallucinations. Principal toxin in *Amanita muscaria*, *A. pantherina*, and *A. gemmata*.

Psilocybin and psilocin	Psychoactive	Causes CNS arousal and hallucinations. Principal Effects in psilocybin mushrooms, many of which belonging to the genus *Psilocybe* (often used recreationally).
Arabitol	Non-lethal	Causes diarrhea in some people.
Bolesatine	Non-lethal	Causes gastrointestinal irritation, vomiting, nausea.
Ergotamine	Deadly	Affects the vascular system and can lead to loss of limbs and/or cardiac arrest. Found in genus *Claviceps*.

1	V	The protein fraction with immuno antibodies	Albumin	alpha globulin	beta globulin	gamma globulin	**gamma globulin**
2	V	Human normal Ig is also called as _____	Histafine	immuneserum	hyperimmuneserum	human specific Ig	**Histafine**
		_____ is used intreatment of	muromab	infliximab	daclizumab	rituximab	**infliximab**
3	V	Rhematoid arthiritis					
4	V	Cyclosporin is a cyclic _____	undecapeptide	hexapeptide	octapeptide	nonapeptide	**undecapeptide**
		_____is a T cell growth differentiation	IL-4	IL-2	IL-6	IL-8	**IL-2**
5	V	factor					
6	V	Tacrolimus is obtained from	Aspergillus niger	Beauveria nivea	E.coli	Streptomyces tsukubaensis	**Beauveria nivea**
7	V	Cyclosporin is produced by	Aspergillus niger	Beauveria nivea	E.coli	Streptomyces tsukubaensis	**Aspergillus niger**
		Thalidomide is a selective	TNF-alpha	TNF-beta	TNF-gamma	TNF-delta	**TNF-alpha**
8	V	_____inhibitor					
		Daclizumab is a geneticall engineered	IgG	IgA	IgD	IgE	**IgG**
9	V	human_____ mAb					
10	V	_____ is an immunomodulator	Interferon	glatiramer acetate	lavamisole	Sirolimus	**glatiramer acetate**
		_____restore cutaneous delayed	amantadine	tilorane	levamisole	BCG	**levamisole**
11	V	hypersensitive reactions					
		____&_____ stimulate humoral immune	Amantidine&levamisole	tilorane&levamisole	BCG&clofazimine	amantidine&tilorane	**amantidine&tilorane**
12	V	system					
		Drugs which increase the rate of urine	Anti-diuretics	Vasopressin	osmotic diuretics	diuretics	**Anti-diuretics**
13	V	formation together with natriuresis are called					
14	V	Which of the following is a osmotic diuretic	furosemide	chlorthalidone	bumetamide	mannitol & sucrose	**mannitol & sucrose**
15	V	Extravasation of mannitol may cause	intracranial tension	pulmonary edema	confusion	thrombophlebitis	**thrombophlebitis**
		_____ present in the cilia which is	electrolytes	carbonic anhydrase	xanthine	sucrose	**carbonic anhydrase**
16	V	improtant in the production of aqeuous humour					
		_____ should be avoided for fear of	dexamethason	nifedipine	dexamethason and nifedipine	sedative hypnotics	**sedative hypnotics**
17	V	causing respiratory depression					
		Excessive renal loss of Na and chloride with	hyponatremia	hyponatremic hypochloremia	hypokalemic hypocloremic	weak diuretics	**hypokalemic hypocloremic**
18	V	potassium loss can cause			alkalosis		**alkalosis**
		_____ is an anti-bacterial drug	osmotic diuretic	potassium sparing diuretic	benzothiadiazine diuretic	high ceiling diuretic	**benzothiadiazine diuretic**
19	V	possessing mild diuretic activity					
		Diabetes insipidus treated with _____	mannitol	furosemide	aminophylline	benzothiadiazine	**benzothiadiazine**
20	V	decrease the urine volume					
		_____ acts as a competitive	thiazides	mannitol	spironolactone	weak diuretics	**spironolactone**
21	V	aldosterone antagonist					
		Absense of _____ may cause diabetes	Desmopressin	arginine vasopressin	high ceiling diuretics	osmotic diuretics	**arginine vasopressin**
22	V	insipidus					
		In gout plasma level of uric acid is----------	2 to 7 mg/dl	10 to 15 mg/dl	below 7mg/dl	above 7mg/dl	**above 7mg/dl**
23	V						
		colichicine is used for the treatment of ----------	chronic gout	acute gout	RA	Anaemia	**acute gout**
24	V	----------					
		Lesch-Nyhan syndrome leads to----------	chronic gout	acute gout	chronic and acute gout	RA	**chronic gout**
25	V	gout					
		uricosuric drugs are employed in the treatment	chronic gout	acute gout	RA	Epilepsy	**chronic gout**
26	V	of ----------					
		The colichicine is rapidly absorbed from --------	GI tract	duodenum	intestine	stomach	**GI tract**
27	V	----------					
		Myopathy is caused by the chronic	colichicine	allopurinol	probenecid	stomach	**colichicine**
28	V	administration of ----------					
		The derivative of phenylbutazone which is	probenecid	sulfinpyrazone	Azapropazone	benzbromarone	**sulfinpyrazone**
29	V	used as uricosuric agent is					
30	V	The drug used in the treatment of RA	muromab	infliximab	daclizumab	rituximab	**infliximab**
		cyclophosphamide used in the treatment of RA	analgesic	NSAID	daclizumab	DMARD	**daclizumab**
31	V	is a ----------					
		Which of the following is used for the treatment of patients with severe RA who have'nt responded to NSAID&slow acting	methotrexate	cyclophosphamide	daclizumab	Ibuprofen	**methotrexate**
32	V	agents					
		Enzyme used in the treatment of	urokinase	bibrinolysin	pepsin	hyaluronidase	**pepsin**
33	V	gastrointestinal distribution is _____					
34	V	Cretain snake and bee venum contains	hyaluroonidase	disastase	trypsin	streptokinase	**hyaluroonidase**
		_____ in highly purified form is used in	potassium hyaluronidase	sodium hyaluronidase	chymotrypsin	collagenase	**sodium hyaluronidase**
35	V	opthalmic surgical procedures					
		Streptokinase is produced by certain strains	stephylococci	bacilli	pneumococci	beta hemolytic streptococci	**beta hemolytic streptococci**
36	V	of_____					
37	V	Trypsin is obtained from	bovine pancreas	ox pancreas	horse pancreas	bacterial strains	**ox pancreas**
		The activity of collagenase is optimal	pH 6-8	pH 5-8	pH 3-5	pH 7	**pH 6-8**
38	V	at_____					
		The concentrated protease enzyme bromelains	carcia papaya	pineapple	ox pancreas	bacterial strains	**pineapple**
39	V	obtained from					
		Collagenase enzyme is derived from	cl.bromelains	cl.histolyticum	cl.papase	cl.botulinum	**cl.histolyticum**
40	V	fermentation of					
		_____ used to liquefy excessive bronchial	aerosal trypsin	bovine pancreas	chymoral	collagenase	**aerosal trypsin**
41	V	secretions					
		Streptokinase has its maximum activity	pH 6.0-7.0	pH 7.3-7.6	pH 2.5-6.2	pH 5-7	**pH 7.3-7.6**
42	V	between					
43	V	Aspirin is chemically ----------	sodium salicylate	salicylamide	acetyl salicylic acid	salicylate	**acetyl salicylic acid**
44	V	Aspirin is an example for ----------	NSAID	Adrenergic drug	Cholinergic drug	Emitic drug	**NSAID**
45	V	Aspirin inhibit ---------- activity	Cyclooxygenase	Esterase	Xanthine oxidase	Oxidase	**Cyclooxygenase**
		NSAID repress the sensatoin of pain by	PGE2	PGI2	PGF2 alpha	PGF2 beta	**PGE2**
46	V	decreasing ----------synthesis					
		Aspirin ----------thromboxane production.	reversibly inhibit	irreversibly inhibit	reversibly activate	irreversibly activate	**irreversibly inhibit**
47	V						
		Hyperkalemia is the increase of ----------	sodium	Magnesium	Calcium	Potassium	**Potassium**
48	V						
49	V	Therapeutic action of aspirin is ------- -----	Anti inflammation	anti tumour	diuretic	antiemitic	**Anti inflammation**
		A cyclooxigenase inhibitor used in the long	Diclofenac	Ketorolac	Tolmetin	Ibuprofen	**Diclofenac**
50	V	term treatment of RA, osteo arthritis and .angkylosing spondilitis is					
		The inactive prodrug closely related to	Diclofenac	Sulindac	Etodolac	Fenamates	**Sulindac**
		indomethacin which is used as NSAID is ------					
51	V	--------					
		Orally administered aspirin is usually	GI tract	Intestine	Stomach	Liver	**Stomach**
52	V	absorbed from --------					
		---------- is the competitive block of alpha	Prazosin	Perazosin	Phentolamine	Propranolol	**Phentolamine**
53	V	1 and alpha 2 receptor					
		All beta blockers are competitive ----------	Agonist	Antagonist	Agonst and Antagonist	beta blocker	**Agonist**
54	V						
55	V	Labetalol is a ---------	alpha blocker	beta blocker	alpha and beta blocker	gamma blocker	**alpha and beta blocker**
		All of them are competitive blockers of alpha	Prazosin	Terazosin	Daxazosin	Propranolol	**Propranolol**
56	V	1 receptor except					
57	V	---------- drug related to nitrogen mustard	Phenoxybenzamine	Propramolol	Labetalol	Esmolol	**Phenoxybenzamine**
		Drug used in the treatment of	Phenoxybenzamine	Propramolol	Labetalol	Acebutolol	**Phenoxybenzamine**
58	V	pheochromocytoma is					
59	V	The other name of anticholinergic drug is	anti adregenic	anti muscuranic	anti inflammatory	anti emitic	**anti muscuranic**
60	V	Which one is not anticholinergic drugs?	Atrophin	scopalamine	dicyclomine	labetalol	**labetalol**