17BCU602A **DRUG BIOCHEMISTRY** **4H-4C**

Instruction hours/week: L:4 T:0 P:0 **Marks:** Internal: **40** External: **60** Total: **100**
End Semester Exam: 3 Hours

Course objectives

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

Course outcomes (CO's)

1. The goal of the paper will ensure the widespread visibility and high impact of Drugs.
2. 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

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 ClinicalPharmacology 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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KARPAGAM ACADEMY OF HIGHER EDUCATION

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Lecture Plan

Section:

S. No.	Duration of Period	Topics to be Covered	Page No.	Books referred	Web page referred
1	1	**UNIT I** Classification, routes of administration – factors influencing dosage and drug action	5-9	T1	
2	1	Absorption and distribution of drugs	9-16	T1	
3	1	binding of drugs to plasma proteins	9-16	T1	
4	1	Drug Dose relationship (LD_{50}, ED_{50}, therapeutic index)	33-34	T1	
5	1	Drug – Receptor interaction,	29-32	T1	
6	1	Drug binding forces, Receptor theories, Drug – Receptor interaction	21	T1	
7	1	Bioavailability; Pharmaco kinetics.	144	T1	
8	1	Revision of Unit I			
Total	8				
1	1	**UNIT II** Drug Biotransformation pathways	16-22	T1	
2	1	phase I – oxidation, reduction and hydroxylation	16-18	T1	
3	1	Phase II- Conjugation	18-20	T1	
4	1	Elimination of drugs from body system	18-20	T1	
5	1	Storage of drugs in adipose tissue	18-20	T1	
6	1	Revision of Unit II			
7	1	Class test			

Total	7				
1	1	**UNIT III** Drug abuse; drug dependence; drug resistance- Biological mechanism, ways to overcome	54-56	T1	
2	1	Antibacterials – Mode of action of sulfonamides, penicillin, streptomycin, tetracycline	625-633		W1
3	1	chloramphenicol, antiviral drugs	684-688	T1	
4	1	antifungal drugs	689-694	T1	
5	1	Antimetabolites of folate	807-809	T1	
6	1	purines & pyrimidines	807-809	T1	
7	1	Anti tubercular drugs	722-724	T1	
8	1	Revision of Unit III			
Total	8				
1	1	**UNIT IV** Mechanism of action drugs used in the treatment of diabetes mellitus (Acarbose, Biguanides)	861-890	T1	
2	1	AIDS (Azidophymidine, Didanosine)	722-726	T1	
3	1	cancer(Mechlorethamine, Busulfan), heart (Amrinone, Digoxin) and kidney disorder (Benzophiadiazines, furosemide);	805	T1	
4	1	antiepileptic drug(Lamictal, Tapclob), drugs for cough (Dextromethorphane Hydrobromide, Noscapine)	437-445	T1	
5	1	bronchial asthma (Salbutamol,Aminophylline)	340-345	T1	
6	1	diuretics (Manitol, Xanthine)	346-361	T1	
7	1	anti ulcer drugs (Cimetidine, Ranitidine)	535-560	T1	
8	1	drugs for fever (Paracetamol, Ibuprofen)	535-561	T1	
Total	8				
1	1	**UNIT V** Introduction, definition and		J1	

		disciplines of toxicology			
2	1	classification of toxicity and toxicants		J1	
3	1	Mechanisms of toxic effect, treatment of intoxication		J1	
4	1	methods in toxicology testing		J1	
5	1	heavy metal toxicity and chelation therpy		J1	
6	1	Environmental pollution, mycotoxins, mushroom poisons		J1	
Total	6				
Previous year end semester examinations question paper discussion					
1	1	Previous year ESE question paper Discussion			
2	1	Previous year ESE question paper Discussion			
3	1	Previous year ESE question paper Discussion			
Total	3				
Grand Total : 40					

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.

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

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

Journal

1. Minder, Daniel, Clausen.Bicket adipose tissue distribution. The journal of Pharmacy and Pharmacology 1994 (313-315)

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 (LD_{50}, ED_{50}, and therapeutic index), Drug – Receptor interaction, Drug binding forces, Receptor theories, Drug – Receptor interaction.

Introduction to drug Biochemistry:

Role of biochemistry in the search for a new therapeutic agent is reviewed. It is stated that the great importance of the various disciplines of biochemistry, including pathobiochemistry and pharmacological biochemistry, is presently recognized, and the involvement of biochemistry in drug research is increasing. Biochemistry at the present time and in the future will utilize the already known basic biological principles for the new development of new and more useful medicines. It is emphasized that the limiting factor in new drug discovery today, however, is the lack of new basic discoveries in biology. The most important concept in drug design is to understand the methods by which the active site of a receptor selectively restricts the binding of inappropriate structures. Any potential molecule that can bind to a receptor is called a *ligand*. In order for a ligand to bind, it must contain a specific combination of atoms that presents the correct size, shape, and charge composition in order to bind and interact with the receptor. In essence, the ligand must possess the molecular key that binds the receptor lock.

Drug Classifications

The vast numbers of prescribed and recreational drugs fall into certain drug classifications.

- Stimulants (amphetamines, caffeine, nicotine and cocaine)
- Depressants (opiates and opioids, alcohol, barbiturates, tranquilizers and benzodiazepines)
- Anti-Psychotics
- Anti-Depressants
- Cannabis
- Inhalants

Pharmaceutical or a drug is classified on the basis of their origin.

1. Drug from natural origin: Herbal or plant or mineral origin, some drug substances are of marine origin.
2. Drug from chemical as well as natural origin: Derived from partial herbal and partial chemical synthesis Chemical, example steroidal drugs
3. Drug derived from chemical synthesis.
4. Drug derived from animal origin: For example, hormones, and enzymes.
5. Drug derived from microbial origin: Antibiotics
6. Drug derived by biotechnology genetic-engineering, hybridoma technique for example
7. Drug derived from radioactive substances.

One of the key classifications is between traditional small molecule drugs, usually derived from chemical synthesis, and biologic medical products, which include recombinant proteins, vaccines, blood products used therapeutically (such as IVIG), gene therapy, and cell therapy (for instance, stem cell therapies).

Pharmaceutical or drug or medicines are classified in various other groups besides their origin on the basis of pharmacological properties like mode of action and their pharmacological action or activity,[7] such as by chemical properties, mode or route of administration, biological system affected, or therapeutic effects. An elaborate and widely used classification system is the Anatomical Therapeutic Chemical Classification System (ATC system). The World Health Organization keeps a list of essential medicines.

A sampling of classes of medicine includes:

1. Antipyretics: reducing fever (pyrexia/pyresis)
2. Analgesics: reducing pain (painkillers)
3. Antimalarial drugs: treating malaria
4. Antibiotics: inhibiting germ growth
5. Antiseptics: prevention of germ growth near burns, cuts and wounds
6. Mood stabilizers: lithium and valpromide
7. Hormone replacements: Premarin
8. Oral contraceptives: Enovid, "biphasic" pill, and "triphasic" pill
9. Stimulants: methylphenidate, amphetamine

10. Tranquilizers: meprobamate, chlorpromazine, reserpine, chlordiazepoxide, diazepam, and alprazolam
11. Statins: lovastatin, pravastatin, and simvastatin

Pharmaceuticals may also be described as "specialty", independent of other classifications, which is an ill-defined class of drugs that might be difficult to administer, require special handling during administration, require patient monitoring during and immediately after administration, have particular regulatory requirements restricting their use, and are generally expensive relative to other drugs.

DRUG ABSORPTION

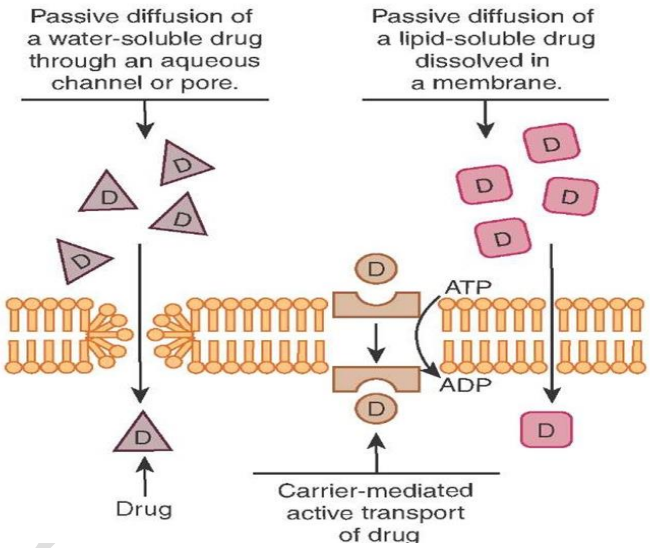
Drug absorption is determined by the drug's physicochemical properties, formulation, and route of administration. Dosage forms (eg, tablets, capsules, solutions), consisting of the drug plus other ingredients, are formulated to be given by various routes (eg, oral, buccal, sublingual, rectal, parenteral, topical, inhalational). Regardless of the route of administration, drugs must be in solution to be absorbed. Thus, solid forms (eg, tablets) must be able to disintegrate and disaggregate. Unless given IV, a drug must cross several semi permeable cell membranes before it reaches the systemic circulation. Cell membranes are biologic barriers that selectively inhibit passage of drug molecules. The membranes are composed primarily of a bimolecular lipid matrix, which determines membrane permeability characteristics. Drugs may cross cell membranes by passive diffusion, facilitated passive diffusion, active transport, or pinocytosis. Sometimes various globular proteins embedded in the matrix function as receptors and help transport molecules across the membrane.

The different modes of drug absorption are:

Passive diffusion:

Drugs diffuse across a cell membrane from a region of high concentration (eg, GI fluids) to one of low concentration (eg, blood). Diffusion rate is directly proportional to the gradient but also depends on the molecule's lipid solubility, size, degree of ionization, and the area of absorptive surface. Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly. Small molecules tend to penetrate membranes more rapidly than larger ones. Most drugs are weak organic acids or bases, existing in un-ionized and ionized forms in an aqueous environment. The un-ionized form is usually lipid soluble (lipophilic) and diffuses readily across

cell membranes. The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily. The proportion of the un-ionized form present (and thus the drug's ability to cross a membrane) is determined by the environmental pH and the drug's pK_a (acid dissociation constant). The pK_a is the pH at which concentrations of ionized and un-ionized forms are equal. When the pH is lower than the pK_a, the un-ionized form of a weak acid predominates, but the ionized form of a weak base predominates. Thus, in plasma (pH 7.4), the ratio of un-ionized to ionized forms for a weak acid (eg, with a pK_a of 4.4) is 1:1000; in gastric fluid (pH 1.4), the ratio is reversed (1000:1). Therefore, when a weak acid is given orally, most of the drug in the stomach is un-ionized, favoring diffusion through the gastric mucosa. For a weak base with a pK_a of 4.4, the outcome is reversed; most of the drug in the stomach is ionized. Theoretically, weakly acidic drugs (eg, aspirin) are more readily absorbed from an acid medium (stomach) than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable.



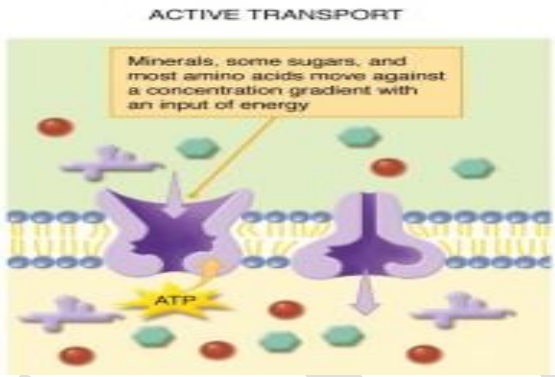
Facilitated passive diffusion:

Certain molecules with low lipid solubility (eg, glucose) penetrate membranes more rapidly than expected. One theory is facilitated passive diffusion: A carrier molecule in the membrane combines reversibly with the substrate molecule outside the cell membrane, and the carrier-substrate complex diffuses rapidly across the membrane, releasing the substrate at the

interior surface. In such cases, the membrane transports only substrates with a relatively specific molecular configuration, and the availability of carriers limits the process.

Active transport:

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



Pinocytosis:

In pinocytosis, fluid or particles are engulfed by a cell. The cell membrane invaginates, encloses the fluid or particles, then fuses again, forming a vesicle that later detaches and moves to the cell interior. Energy expenditure is required. Pinocytosis probably plays a small role in drug transport, except for protein drugs.

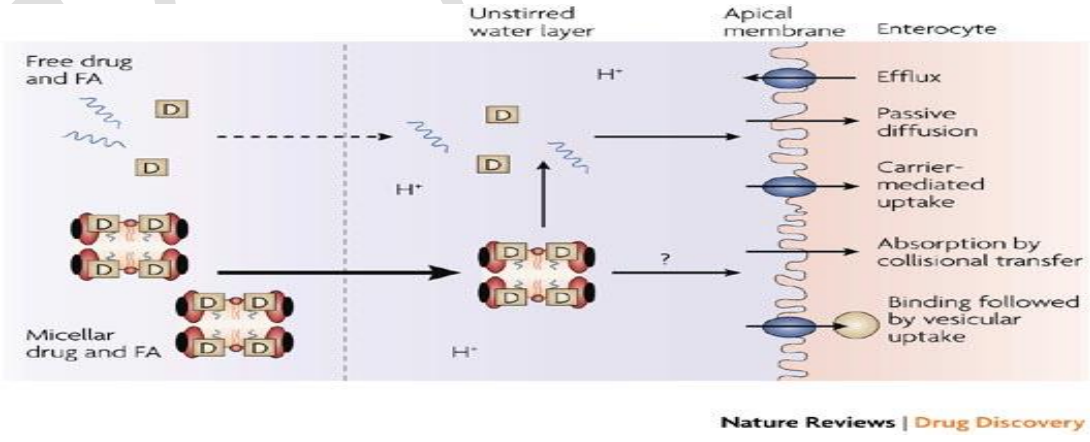


Fig: Drug absorption from intestine

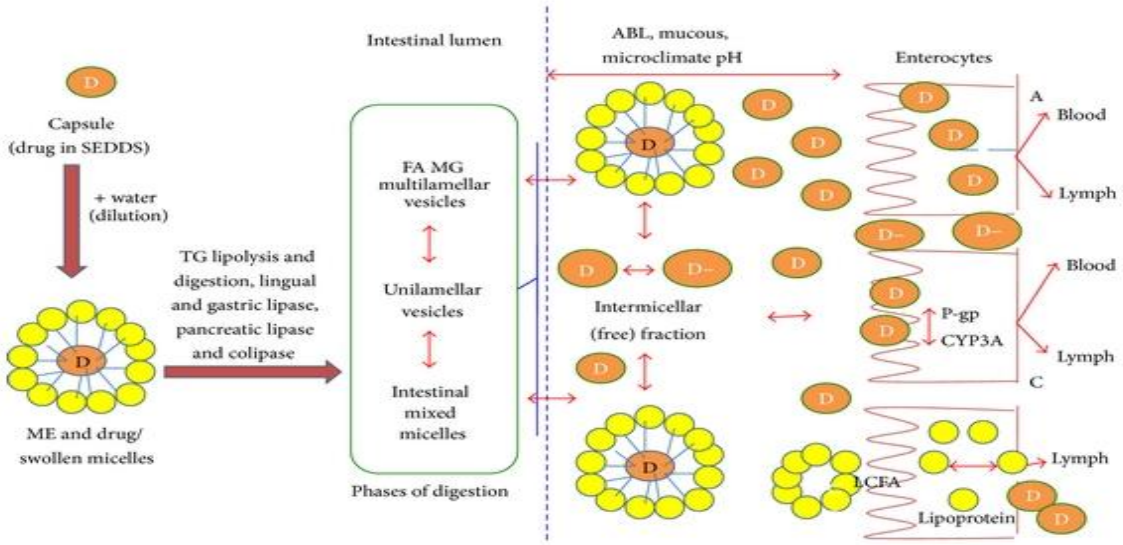


Figure : Schematic diagram of intestinal drug transport from lipid-based formulations via the portal and the mesenteric lymphatic routes.

(A) Increased membrane fluidity facilitating transcellular absorption. (B) Opening of tight junctions to allow paracellular transport. (C) Inhibition of P-gp and/or CYP450 to increase intracellular concentration and residence time. (D) Stimulation of lipoprotein/chylomicron production. ABL: aqueous boundary layer; D: drug; D−: ionized drug substance; FA: fatty acid; LCFA: long chain fatty acid; ME: microemulsion; MG: monoglyceride; SEDDS: self-emulsifying drug delivery system; TG, triglyceride; TJ, tight junction.

FACTORS AFFECTING DRUG ABSORPTION:

- **Lipid-water partition co-efficient:** Non electrolyte drug depends upon lipid solubility. More lipid soluble and less water soluble that is it has high lipid-water partition co-efficient, it will absorbed rapidly
- **Drug solubility:** drugs given in aqueous solutions are more rapidly soluble than when given in oily solution, suspension or solid form.
- **Dosage form:** Tablets and capsules, rate of disintegration and dissolution is limiting factor in their absorption. After dissolution, smaller the particle size, more efficient will be absorption
- **Circulation at the site:** Increased blood flow increase absorption.

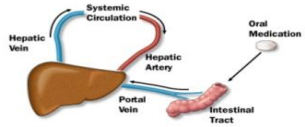
- **Area of absorbing surface :** Absorbed more from large surface areas for example intestinal mucosa
- **Effect of pH:** Most drugs are either weak acids or weak bases. Weak electrolytes, in addition to lipid solubility, depends upon its degree of ionization which is influenced by pH of the area.Weak acids become less ionized(charged) in an acidic medium and weak bases become less ionized in an alkaline medium.Unionized drug is lipid.

BIOAVAILABILITY

The fraction of unchanged drug reaching the systemic circulation following administration by any route" or The percentage of administered drug that reaches the systemic circulation in a chemically unchanged form". Thus by definition a drug that is administered by intravenous route has 100% bioavailability.

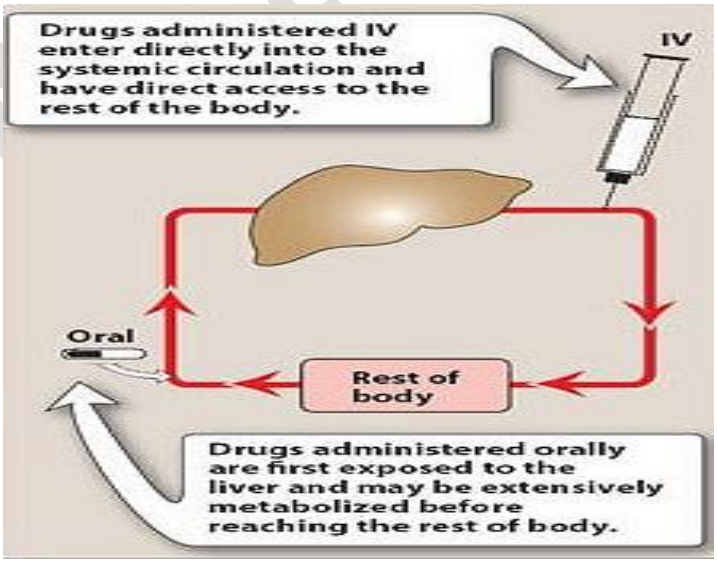
First Pass metabolism can occur with orally administered drugs

The First Pass Effect



The fraction, f, of orally administered drug that successfully passes through gut lumen and gut wall is then taken via the hepatic portal vein to the liver, where metabolism of the drug by enzymes may take place.
This extraction by the liver of orally administered drug is called the first pass effect.

Anas Bahnassi PhD 2011 12



- Specific drugs are metabolized in gut wall, skin, lungs

Factors affecting bioavailbiltiy

- First-pass hepatic metabolism: when a drug is absorbed across GIT, it enters the portal circulation before entering the systemic circulation. If the drug is rapidly metabolized by the liver, the amount of unchanged drug that gains access to the systemic circulation is decreased.
- Absorption
- Solubility of the drug: hydrophobic drug will absorb more so bioavailability will be more.
- Chemical instability: some drugs are unstable in pH of the gastric contents. Others are destroyed in GIT by degradative enzymes.
- Particle size: smaller the particle size more absorption will be there.

PLASMA HALF LIFE

- The time required for the concentration of drug in the plasma to decrease to one half of its initial value. For example if the initial conc. of drug is 100mg and if the half life is 1 hr, only 50mg will remain in the plasma at the end of 1 hr.

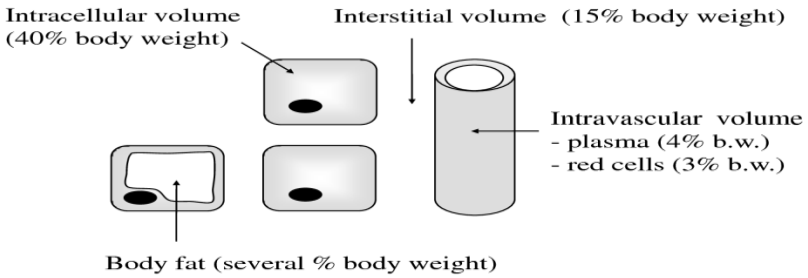
DISTRIBUTION OF DRUGS

Drug distribution means the reversible transfer of drug from one location to another within the body. Once a drug has entered the vascular system it becomes distributed throughout the various tissues and body fluids in a pattern that reflects the physiochemical nature of the drug and the ease with which it penetrates different membranes. After absorption, a drug enters or passes through the various body fluid compartments such as

- Plasma
- Interstitial fluid compartment, eg: fluids in the gastrointestinal tract, bronchi, CSF, and
- Cellular fluid compartment.

Every drug is distributed throughout the body in a characteristic maner, depending upon its physiochemical properties.

Drug distribution: Compartments



Drug distribution patterns

- The drug may remain largely within the vascular system, ex: Plasma substitutes such as dextran and drugs which are strongly bound to plasma protein
- Some are uniformly distributed throughout the body water, ex: low molecular weight water soluble compounds (ethanol) and a few sulfonamides
- A few drugs are concentrated specifically in one or more tissues that may or may not be the site of action, ex: Iodine (in the thyroid gland), chloroquine (in the liver even at conc 1000 times those present in plasma), tetracycline (irreversibly bound to bone and developing teeth) and highly lipid soluble compounds (distribute into fat tissue)
- Most drugs exhibit a non-uniform distribution in the body (largely determined by the ability to pass through membranes and their lipid/water solubility). The highest concentrations are often present in the kidney, liver, and intestine.

The apparent volume of distribution (Vd) is defined as the volume into which the total amount of a drug in the body would have to be uniformly distributed to provide the concentration of that drug actually measured in the plasma.

It is calculated as

$$Vd = \frac{\text{The total amount of drug in the body}}{\text{The concentration of the drug in the plasma at zero time.}}$$

For many drugs, (Vd) is constant over a wide dosage range.

Factors affecting drug distribution

1. Rate of distribution

i) **Membrane permeability** - Lipid soluble drugs pass through very rapidly. Water soluble compounds penetrate more slowly at a rate more dependent on their size. Low molecular weight drugs pass through by simple diffusion. For compounds with molecular diameter above 100 Å transfer is slow.

ii) **Blood perfusion** - The rate at which blood perfuses to different organs varies widely. Total blood flow is greatest to brain, kidneys, liver, and muscle with highest perfusion rates to brain, kidney, liver, and heart. It would be expected that total drug concentration would rise most rapidly in these organs. Certain organs such as the adrenals (1.2/0.2%) and thyroid (2.4/1%) also have large perfusion rates.

2. Extent of Distribution

i) Lipid Solubility

Lipid soluble drugs pass through very rapidly where as water soluble compounds penetrate more slowly at a rate more dependent on their size.

ii) pH - pKa

The rate of passage of a drug through a membrane is dependent of pH of the drugs environment and the dissociation constant (pK) of the drug, the pH at which the nonionized and ionized drug concentrations are equal. Nonionized, lipid soluble drugs (the vast majority) that readily cross membranes are distributed throughout the body; they have large volumes of distribution

iii) Plasma protein binding

- Extensive plasma protein binding will cause more drug to stay in the central blood compartment. Therefore drugs which bind strongly to plasma protein tend to have lower volumes of distribution. (5-6liters).
- Of these plasma proteins, albumin, which comprises 50 % of the total proteins, binds the widest range of drugs. Acidic drugs commonly bind to albumin, while basic drugs often bind to alpha1-acid glycoproteins and lipoproteins. Many endogenous substances, steroids, vitamins, and metal ions are bound to globulins.

iv) Intracellular binding

A drug with Vd =16 litres is likely to be distributed in ECF water, which includes plasma and interstitial fluid. Where the Vd exceeds the total volume of body water (42 L), there is substantial uptake and binding of the drug within tissues such as muscle and brain.

Plasma concentration of drugs depends upon the drugs

- Rate of absorption
- Distribution
- Metabolism
- Excretion

Factros Affecting Drug Distribution

I) Factors Related to the Drug:

1. Lipid Solubility

Greater the lipid solubility, more is the distribution and vice versa.

2. Molecular size

Larger the size, less is the distribution. Smaller sized drugs are more extensively distributed.

3. Degree of Ionization

4. Cellular binding

Drugs may exist in free or bound form. Bound form of drugs exists as reservoirs. The free and bound forms co-exist in equilibrium. Cellular binding depends on the plasma binding proteins.

Tissue binding:

Different drugs have different affinity for different cells. All cells do not bind the same drugs.

5. Duration of Action

The duration of action of drugs is prolonged by the presence of bound form while the free form is released. This leads to a longer half life and duration of action of drug.

6. Therapeutic Effects:

Bisphosphonate compounds bind with the bone matrix cells and strengthen them. They are used in the treatment of osteoporosis.

7. Toxic Effects:

Chloroquinine can be deposited in the retina. Tetracycline can bind the bone material. It may also get bound to the enamel of the teeth.

II) Factors Related to the Body:

1. Vascularity

Most of the blood passes through the highly profused organs (75%) while the remaining (25%) passes through the less profused areas. Therefore, most of the drugs go first to the highly profused areas. They may get bound to these organs. They are then redistributed to the less profused areas like the skin and the skeletal muscles. This phenomenon is common among the lipid soluble drugs.

Example includes thiopentone sodium which is used as general anesthetic. When given, it goes to the brain producing its effects. It is then redistributed to the less profused organs. Because of high lipid solubility, it is accumulated in the fatty tissue for longer duration. Thus the clearance of the drug is slow, producing prolonged period of drowsiness (up to 24 hours).

2. Transport Mechanism

Different drugs are taken up by different compartments of the body differently. Lipid soluble drug move by passive transport which is non specific. Active transport occurs only where carrier proteins are present.

3. Blood Barriers

Different blood barriers exist. Blood brain barrier is present because of the delicacy of nervous tissue to avoid chemical insult to the brain.

Structure:

Endothelial cells and pericytes and glial cells form the barrier through which drugs cannot pass easily. Only selective passage takes place.

Transporters:

Certain efflux pumps or transporters exist through which drug can be effluxed as well. Example includes p-glycoprotein.

Disruption:

Disruption of barrier may occur, e.g. by inflamed meningitis. Drugs may pass which might be toxic as well as beneficial i.e. during meningitis penicillin can pass which has beneficial effects.

4. Placental Barriers

Trophoblastic tissue separates maternal blood from fetal blood. Different transporters are present. Efflux transporters cause efflux back of the drugs from the fetus to the mother.

5. Plasma Binding Proteins

Many proteins exist in the plasma. Plasma binding proteins include:

a. Albumin

Albumin is the most abundant plasma protein. It has higher affinity for acidic drugs but the capacity is low. Only two sites are present for binding drug molecules.

However, albumin can bind a large number of basic drugs but has lower attractive forces. Its capacity for binding basic drugs is more but the affinity is less.

b. Globulins

Globulins can bind hormones, vitamins, etc.

c. Glycoproteins

Alpha glycoproteins mainly bind basic drugs. Their levels are increased during stress, trauma and surgery. It is during these times that their more amounts are required.

d. Lipoproteins

Lipoproteins also bind some drugs.

6. Free and Bound Forms of Drugs

When drug enters the body, it exists in:

- Free form
- Bound form

These two forms have certain effects on the pharmacokinetics and pharmacodynamics. Free forms are metabolized and excreted because they can cross the glomerular membrane. Free forms of drugs are therapeutically active. Bound forms of drugs act as a reservoir. They are not metabolized or excreted and do not have therapeutic or toxic effect. When the free form is used up, drug is released from the reservoirs. Thus both forms exist in equilibrium.

Significance:

Bound form acts as a reservoir, providing free form when required, Drugs having higher plasma protein binding if given in normal doses, are only used in binding plasma proteins, with the result that less free form is available for therapeutic effect. Thus drugs having higher plasma protein binding are given in larger doses at the start. This is known as loading dose. This is to ensure that enough free form of the drug is available. Higher plasma protein binding drugs include warfarin and phenytoin while those having negligible plasma protein binding include lithium, metronidazole and myxothiazol.

7. Drug Interactions

If a number of drugs are simultaneously given, or drugs interact with endogenous substances, one drug can be displaced by another. Example includes interaction of sulphonamide with bilirubin, with the result that bilirubin is displaced which may cause kernicterus in babies.

Drug interactions occur if both drugs bind to same protein and depend on:

a. Affinity

Higher the affinity of the drug, more easily can it displace the other drug.

b. Concentration

Higher concentration drug can displace the lower concentration drugs.

This phenomenon might be of consequence in the following situations:

a. Volume of Distribution:

The volume into which the drug is distributed is known as the volume of distribution. If drug can be distributed to different body compartments, it is diluted when goes to the different compartment. If the drug has a small volume of distribution, it stays in the same compartment producing toxic effects. (Explained separately)

Toxic effects are produced when more drugs is present in free form than usual.

b. Therapeutic Index

Therapeutic index is the safety margin, the range in which the drug is safe. If drug has a large therapeutic index, then large concentrations of the drug are safe. If it has a small therapeutic index, it may move out of the safe range and cause toxic effects. Thus the drug displacement phenomenon is significant in low therapeutic index drugs.

8. Disease States

Different diseases affect the distribution of drugs. Renal diseases cause hypoalbuminemia. Due to less proteins, toxic levels of free drugs may be present. Uremic by-products are also produced which compete with drugs. Hepatic diseases cause decreased synthesis of proteins causing hypoalbuminemia. Free drugs may be present in toxic levels and bilirubin by products increase as well.

Thus drug, whose doses have to be adjusted to produced desired effects (may be reduced even to half).

9. Drug Reservoirs

Drugs are stored and are released slowly which affects their pharmacokinetics and pharmacodynamics. Drug reservoirs include:

- Plasma proteins
- Liver
- Adipose
- Bone
- Placenta
- Breast milk
- Transcellular fluid reserves
- Other body tissues- eye, kidneys, skeletal muscles, skin

10. Volume of Distribution

The apparent or hypothetical volume in the body into which a drug distributes.

DRUG RECEPTOR

Types of Receptors:

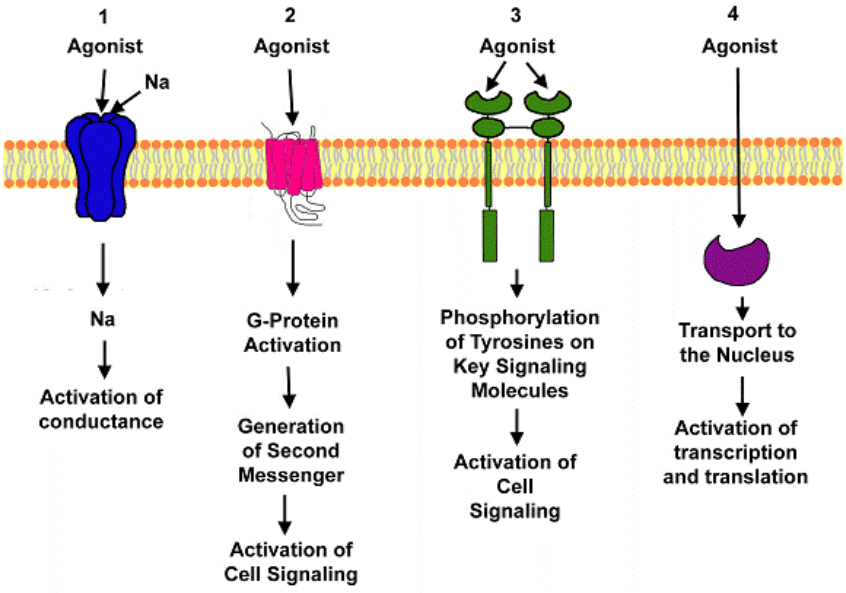
There are four receptor types

Type 1: Channel linked (Ionotropic)

Type 2: G-Protein coupled (GPCR)

Type 3: Kinase – linked

Type 4: Receptor that regulate gene transcription



Channel linked (Ionotropic)

Ion channels are cell membrane spanning proteins. Agents binding with them open a transmembrane channel and permit ions to cross the membrane phospholipids bilayer.

Coupling

Transduction process between occupancy of the receptor by agonist and response to occur is called coupling. Most agonists when bind to receptors cause activation. Most of them alter the second messenger systems in the cells.

There are three second messenger systems:

- Cyclic AMP
- Cyclic GMP
- Calcium and phosphoinositol second messenger system

The levels of these second messenger systems may increase or decrease. This may occur in three steps:

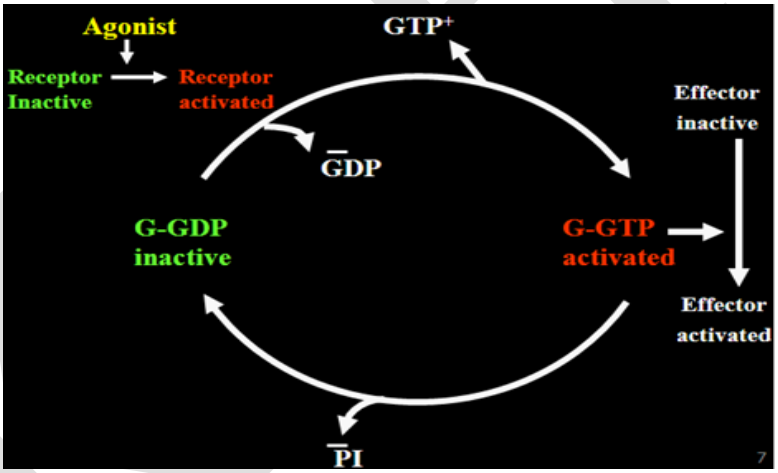
- Drug binds receptor
- Stimulation of g-regulatory protein occurs. G-regulatory protein exists in two forms; GS (stimulatory G-protein) and GI (inhibitory g-protein).
- This causes change in the effector element-enzyme or ionic channel depending on GS or GI.

Table 1.10: The main types of receptors

	Type 1	Type 2	Type 3	Type 4
Class	Channel-linked (Ionotropic)	G-protein coupled (GPCR) (Metabotropic)	Kinase linked	Acting on gene transcription
Location	Cell membrane	Cell membrane	Cell membrane	Cytosol and nucleus
Effector	Channel	Enzyme or channel	Enzyme	Gene transcription
Coupling	Direct	G-protein	Direct or indirect	Via DNA
Examples	nAChR $GABA_A$R Glycine	mAChR Beta adreno R TSH H_2R	Insulin R Growth factor R Cytokine R ANF R	Steroid / thyroid hormone R
Second messenger	None	cAMP, cGMP, Ca^{++}	None	None

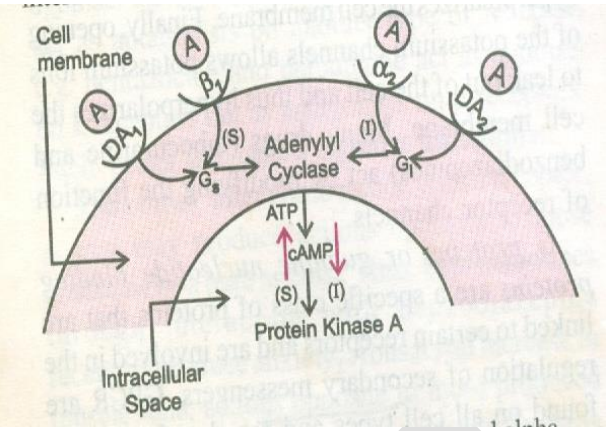
R= Receptor. ANF = Atrial Natriuretic Factor. cAMP= cyclic AMP. cGMP= cyclic GMP
N = Nicotinic. M = Muscarinic. H = Histaminic. ACh = Acetylcholine.

Drug Receptor Interactions



1. cAMP Second Messenger System

Beta 1, beta 2,alpha 2, and dopamine 1 are the receptors associated with cAMP second messenger system. Ligands include ACTH, catecholamines (beta adrenoreceptors), hCG, FSH, glucagon, histamine (H_2 receptors), LH, MSH, PTH, serotonin, etc.



2. Calcium and Phospho-inositol system

Muscarinic and alpha 1 receptors are associated with calcium phospho-inositol system. Ligands include acetylcholine (muscaranic receptors), angiotensin, serotonin, vasopressin (V1 receptors), and catecholamines (alpha 1 adrenoreceptors).

When drug binds the receptor, activation occurs, and the response gradually increases until it reaches the peak, then the response decreases, although agonist still binds. This is due to desensitization of receptors, which might be overcome by removing the agonists from the receptor. Example includes suxamethonium (succinyl choline), which produces relaxation of skeletal muscles by:

- Activation of nicotinic receptors
- Desensitization of receptors in the neuromuscular junction

The reason for desensitization is not clear. In beta blockers (which act by cAMP), ultimately phosphorylation of proteins and accumulation of phosphosilines occurs, which increases the binding of beta receptors with proteins, known as beta arrestin. This beta arrestin interferes with the activity, ultimately leading to inhibition of adenyl cyclase enzyme.

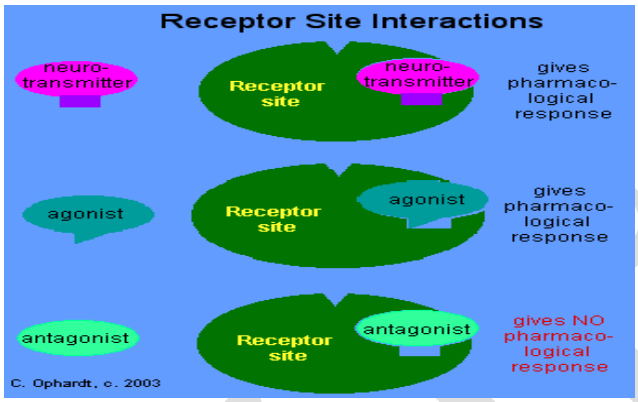
The binding of drug with receptor may by of two types:

- Reversible binding
- Irreversible binding

In reversible binding, the bond between the drug and receptor is very weak ionic, hydrogen or van der wall. This is the effect is short lived.

In irreversible binding, very strong covalent bonds are present, which prolongs the effects of drug. The effect continues until the drug is excreted or new receptor is generated.

Prolong contact of tissues with the agonists results in decreased number of receptors in the tissues called down regulation of receptors. Example includes the patients suffering from bronchial asthma, in whom by prolong usage of beta agonists down regulation occurs. This the effect is reduced.



Spare Receptors

Sometimes it is seen, especially in isolated tissues, that when various amounts of drugs are added e.g. when in intestines of rabbits acetyl choline is added, this may lead to maximum effect. Only one percent of receptors might be occupied but maximum response might be seen. This is due to the vast reserve. There are spare receptors, only very small amounts of drugs are required for maximum effect.

DRUG BINDING FORCES

Three major types of chemical forces/bonds:

Covalent- very strong

Frequently, a covalent bond is described as essentially "irreversible" under biological conditions. The term "irreversible" is in fact in quotes because all reactions are reversible. However, once a covalent bond is formed, the resulting structure is typically extremely stable and although the reverse reaction occurs its occurrence may be highly improbable.

The covalent interaction explains the drug's long duration of action. To overcome the alpha-adrenergic receptor blockade, new alpha receptor protein must be synthesized in the inhibited receptor internalized by the cell and degraded. This process may take 48 hours. Another example of drugs that interact covalently with their targets are the DNA-alkylating chemotherapy

agents. These drugs are chemically highly reactive, forming covalent bonds with DNA functional groups. Such covalently-modified DNA may be incompatible with successful tumor cell division.

Electrostatic- weaker than covalent

Electrostatic interactions tend to be much more common than the covalent bonding in drug-receptor interactions.

- The interaction strength is variable:
- Strong electrostatic interactions occur between between permanently charged ionic molecules
- Weaker interactions all are due to hydrogen bonding
- Still weaker interactions are called induced-dipole interactions, e.g. van der Waals forces

Hydrophobic interactions referred to interactions between molecules in which the interactions are less driven by molecule to molecule attraction and more by the tendency of molecules to wish to avoid the aqueous (water) environments:

- Hydrophobic interactions are generally weak, but important.
- Hydrophobic interactions are probably significant in driving interactions
- Between lipophilic drugs and the lipid component of biological membranes
- Between drugs and relatively nonpolar (not charged) receptor regions

RECEPTOR THEORIES

Receptor theory is the application of receptor models to explain drug behaviour. John Newport Langley and Paul Ehrlich introduced the concept of a receptor that would mediate drug action at the beginning of the 20th century. A J Clark was the first to quantify drug-induced biological responses (using an equation described firstly by A V Hill in 1909 and then in 1910) and propose a model to explain drug-mediated receptor activation.

Receptor occupancy model

The receptor occupancy model, which describes agonist and competitive antagonists, was built on the work of Langley, Hill and Clark. The occupancy model was the first model put forward by Clark to explain the activity of drugs at receptors and quantified the relationship between drug concentration and observed effect. It is based on mass-action kinetics and attempts

to link the action of a drug to the proportion of receptors occupied by that drug at equilibrium. In particular, the magnitude of the response is directly proportional to the amount of drug bound, and the maximum response would be elicited once all receptors were occupied at equilibrium.

Competitive inhibition models

The development of the classic theory of drug antagonism by Gaddum, Schild and Arunlakshana built on the work of Langley, Hill and Clark. Gaddum described a model for the competitive binding of two ligands to the same receptor in short communication to the Physiological Society in 1937. The description referred only to binding, it was not immediately useful for the analysis of experimental measurements of the effects of antagonists on the response to agonists. In Schild regression, the change in the dose ratio, the ratio of the EC_{50} of an agonist alone compared to the EC_{50} in the presence of a competitive antagonist as determined on a dose response curve used to determine the affinity of an antagonist for its receptor.

Agonist models

The flaw in Clark's receptor-occupancy model was that it was insufficient to explain the concept of partial agonist lead to the development of agonist models of drug action by Ariens in 1954 and by Stephenson in 1956 to account for the intrinsic activity (efficacy) of a drug (that is, its ability to induce an effect after binding).

Two-state receptor theory

The two-state model is a simple linear model to describe the interaction between a ligand and its receptor, but also the active receptor (R^*). The model uses an equilibrium dissociation constant to describe the interaction between ligand and receptor. It proposes that ligand binding results in a change in receptor state from an inactive to an active state based on the receptor's conformation. A receptor in its active state will ultimately elicit its biological response. In this model, agonists and inverse agonists are thought to have selective binding affinity for the pre-existing resting and active states or can induce a conformational change to a different receptor state. Whereas antagonists have no preference in their affinity for a receptor state. The fact that receptor conformation (state) would affect binding affinity of a ligand was used to explain a mechanism of partial agonism of receptors.

Ternary complex model

The original Ternary complex model was used to describe ligand, receptor, and G-protein interactions. It uses equilibrium dissociation constants for the interactions between the receptor and each ligand (K_a for ligand A; K_b for ligand B), as well as a cooperativity factor (α) that denotes the mutual effect of the two ligands on each other's affinity for the receptor.

Postulates of receptor theory

- Receptors must possess structural and stereo specificity.
- Receptors are saturable and finite (limited number of binding sites)
- Receptors must possess high affinity for its endogenous ligand at physiological concentrations
- Once the endogenous ligand binds to the receptor, some early recognizable chemical event must occur

Occupation theory

The central dogma of receptor pharmacology is that drug effect is directly proportional to number of receptors occupied. Furthermore, drug effect ceases as drug-receptor complex dissociates. Ariëns & Stephenson introduced the terms "affinity" & "efficacy" to describe the action of ligands bound to receptors.

- Affinity: ability of the drug to combine with receptor to create drug-receptor complex
- Efficacy: ability of the drug-receptor complex to initiate a response

Rate theory

In contrast to the accepted occupation theory, rate theory proposes that the activation of receptors is directly proportional to the total number of encounters of the drug with its receptors per unit time. Pharmacological activity is directly proportional to the rates of dissociation and association, not number of receptors occupied:

- Agonist: drug with fast association & fast dissociation
- Partial agonist: drug with intermediate association & intermediate dissociation
- Antagonist: drug with fast association & slow dissociation

Induced fit theory

As the drug approaches the receptor, the receptor alters the conformation of its binding site to produce drug-receptor complex.

Possible Questions

1. Write the pharmacological activity of drug?
2. Discuss about Phase I reactions in Metabolism of drug
3. Briefly describe the pro drug and its concept
4. Describe Phase II reactions in metabolism of drug
5. Given account of Agonist and antagonist
6. Explain the Distribution of drug
7. What is Receptor? Explain its types
8. Write account of absorption and first pass effect of drugs
9. Given account of elimination of drug in body
10. Briefly explains the G – protein coupled receptor and ion- Channel linked receptors

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Department of Biochemistry
III B,.Sc., Biochemistry
17BCU602A- Drug Biochemistry
Prepared By Dr.A. Ramakrishnan

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	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	Dichloroisopropylartere nol 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						

15	I	Irreversible interaction of an antagonist with a receptor is due to:	Ionic bonds	Hydrogen bonds	Covalent bonds	Sulphur bond	**Covalent bonds**
16	I	The second messenger of G-protein-coupled (metabotropic) receptor:	Adenylyl cyclase	Sodium ions	Phospholipase C	cAMP	**cAMP**
17	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**
18	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**
19	I	An agonist can produce submaximal effects and has moderate efficacy it's called:	Partial agonist	Antagonist	Agonist-antagonist	Full agonist	**Partial agonist**
20	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**

21	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**
22	I	What kind of substances can't permeate membranes by passive diffusion?	Lipid-soluble	Non-ionized substances	Hydrophobic substances	Hydrophilic substances	**Hydrophilic substances**
23	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**
24	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**
25	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**
26	I	The organelle that carry Cytochorome p450 MO is	Endoplasmic reticulam	Golgi complex	Mitochondria	Mitochondria	**Endoplasmic reticulam**
27	I	Conjugation of a drug includes the following EXCEPT:	Glucoronidation	Sulfate formation	Hydrolysis	Methylation	**Hydrolysis**
28	I	The phase II reaction which produce a compound with greater pharmocological actvity	Glucoronic acid conjugation	Conjugation with amino acid	Methylation	Glutathione conjugation	**Methylation**

29	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**
30	I	Acidic drug rapidly absorbed at	Stomach	GI tract	Large intestine	Mouth	**Stomach**
31	I	Coenzyme required by Cytochorome p450 MO is	NADH	NADPH	Lipoic acid	TPP	**NADPH**
32	I	Basic drugs are absorbed in	small intestine	stomach	Large intestine	Pancreas	**small intestine**
33	I	Which effect may lead to toxic reactions when a drug is taken continuously or repeatedly?	Refractoriness	Cumulative effect	Tolerance	Tachyphylaxis	**Cumulative effect**
34	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**
35	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**
36	I	Which drug that cross the lipid bilayer easily	Water soluble drug	lipid soluble drug	ionsoluble drug	Non ionsoluble drug	**lipid soluble drug**
37	I	Science that deals with drug	Pharmacy	pharmacognosy	pharmacodynamics	pharmacology	**pharmacology**

38	I	Inhibition of MAO causses an	decrease in the deamination of noradrenalin	increasse in the deamination of dopamine	increase in the deamination of noradrenalin	decrease in the deamination of dopamine	**decrease in the deamination of noradrenalin**
39	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**
40	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)**
41	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**
42	I	Aspirin is chemically	Sodium salicylate	Acetylsalicylic acid	Salicylamide	Sodium salicylamide	**Acetylsalicylic acid**
43	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**
44	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**

		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**
45	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**
46	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**
47	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**
48	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**
49	I						
		Irreversible interaction of an antagonist with a receptor is due to:	Ionic bonds	Hydrogen bonds	Covalent bonds	Weak bonds	**Covalent bonds**
50	I						

		Tick the second messenger of G-protein-coupled (metabotropic) receptor:	Adenylyl cyclase	Sodium ions	Phospholipase C	cAMP	**cAMP**
51	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**
52	I						
		Chloramphenicol is derived from	Streptomyces venezulae	Streptomyces griseus	Streptomyces kanamycin	Pencillin	**Streptomyces griseus**
53	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**
54	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**
55	I						
		Pick out the parenteral route of medicinal agent administration:	Rectal	Oral	Sublingual	Inhalation	**Inhalation**
56	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**
57	I						

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**

UNIT-II

SYLLABUS

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. The metabolism of a drug or toxin in a body is an example of a biotransformation. The body typically deals with a foreign compound by making it more water-soluble, to increase the rate of its excretion through the urine. Drugs can undergo one of four potential biotransformations: Active Drug to Inactive Metabolite, Active Drug to Active Metabolite, Inactive Drug to Active Metabolite, active Drug to Toxic Metabolite (biotoxification).

It takes place in two phases

- Phase I
- Phase II

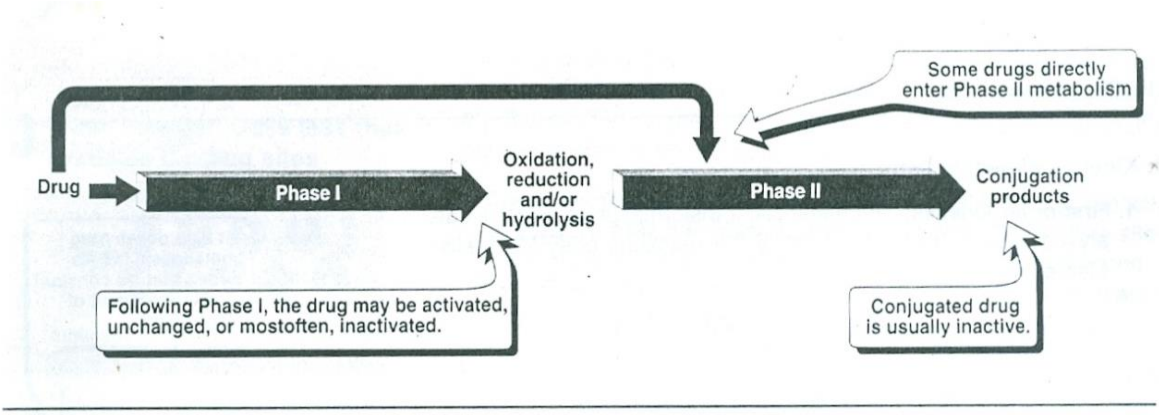


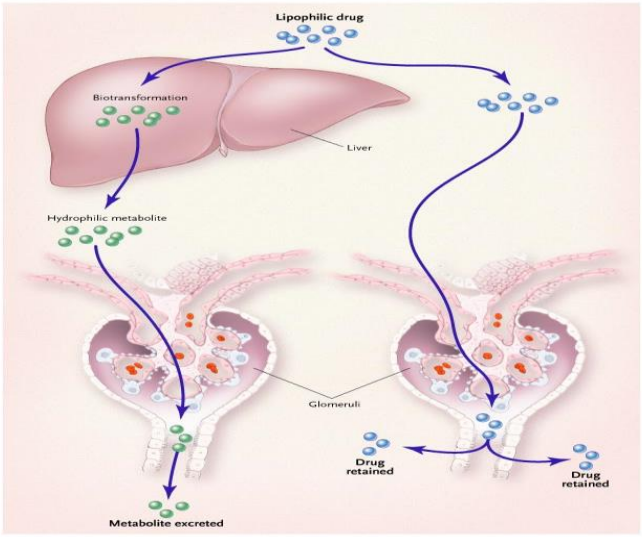
Figure 1.15
The biotransformations of drugs.

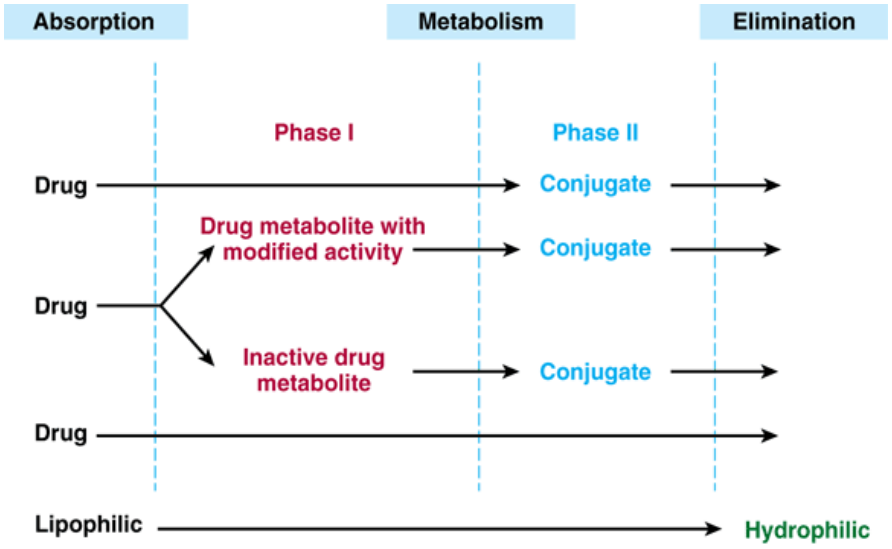
Phase I reaction

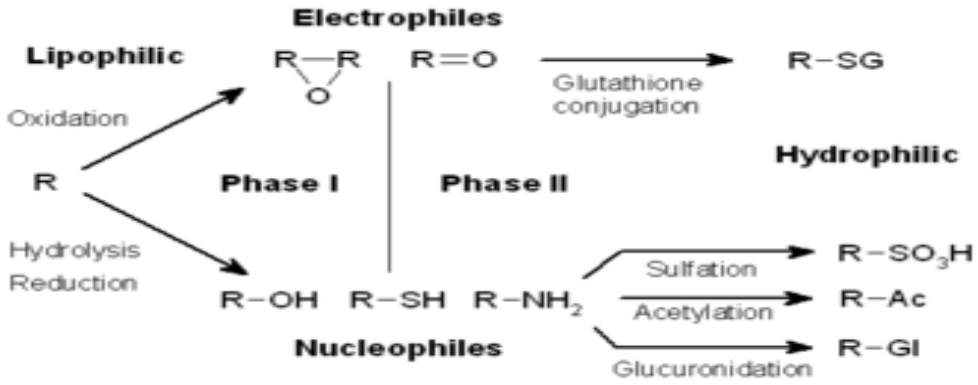
Includes oxidative, reductive, and hydrolytic reactions, In these type of reactions, a polar group is either introduced or unmasked, so the drug molecule becomes more water-soluble and can be excreted. Convert the parent drug to a more polar (water-soluble) and/ or more reactive product by unmasking or inserting a polar group such as -OH, -SH, $-NH_2$. Reactions are non-synthetic in nature and in general produce a more water-soluble and less active metabolites. The majority of metabolites are generated by a common hydroxylating enzyme system known as Cytochrome P_{450}.

Phase II reaction

These reactions involve covalent attachment of small polar endogenous molecule such as glucuronic acid, sulfate, acete, glycine and methyl groups to form water-soluble compounds. This is also known as a conjugation reaction. The final compounds have a larger molecular weight. Both types of reaction convert relatively lipid- soluble original drug molecules into more water-soluble metabolites that are more easily excreted which are illustrated with following diagrams.


Lipophilic drug
Biotransformation
Liver
Hydrophilic metabolite
Glomeruli
Drug retained
Drug retained
Metabolite excreted


Absorption
Metabolism
Elimination
Phase I
Phase II
Drug
Conjugate
Drug metabolite with modified activity
Conjugate
Drug
Inactive drug metabolite
Conjugate
Drug
Lipophilic
Hydrophilic


Electrophiles
Lipophilic
R—R
O
R=O
Glutathione conjugation
R-SG
Oxidation
Hydrophilic
R
Phase I
Phase II
Hydrolysis
Reduction
R-OH
R-SH
R-NH2
Sulfation
R-SO3H
Acetylation
R-Ac
Glucuronidation
R-Gl
Nucleophiles

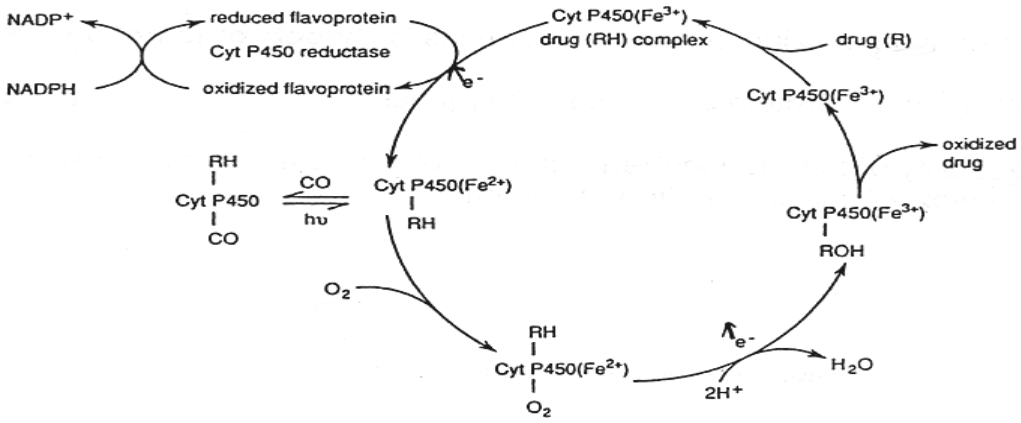
PHASE I REACTIONS

In phase I, a variety of enzymes act to introduce reactive and polar groups into their substrates. One of the most common modifications is hydroxylation catalysed by the cytochrome P-450-dependent mixed-function oxidase system. These enzyme complexes act to incorporate an atom of oxygen into nonactivated hydrocarbons, which can result in either the introduction of hydroxyl groups or N-, O- and S-dealkylation of substrates. The reaction mechanism of the P-450 oxidases proceeds through the reduction of cytochrome-bound oxygen and the generation of a highly-reactive oxyferryl species, according to the following scheme:

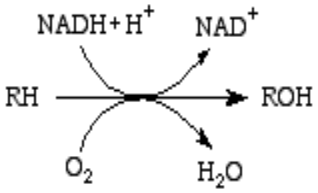
$$O_2 + NADPH + H^+ + RH \rightarrow NADP^+ + H_2O + ROH$$

Phase I reactions (also termed nonsynthetic reactions) may occur by oxidation, reduction, hydrolysis, cyclization, decyclization, and addition of oxygen or removal of hydrogen, carried out by mixed function oxidases, often in the liver. These oxidative reactions typically involve a cytochrome P_{450} monooxygenase (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 (toxification). For example, phase I metabolism converts acetonitrile to $HOCH_2CN$, which rapidly dissociates into formaldehyde and hydrogen cyanide, both of which are toxic.

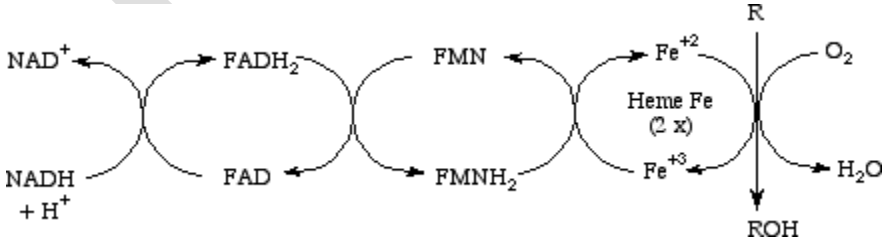
Fig: Cyt P450 catalysed hydroxylase cycle



Most phase one reactions are catalyzed by the microsomal monooxygenases (mixed function oxidases). These enzymes are localized to a large degree on the sER, though they are also found on the rER. The most common microsomal oxidases are the P_{450}s, a large family of enzymes catalyzing the same chemistry on a wide variety of mostly non-polar substrates. Different forms of the enzyme may be induced by exposure to different chemicals. Thus exposure to phenobarbital or PBB's result in P_{450}s with different specificities, though they catalyze the same reaction. Over a dozen families of P_{450} are known which catalyze the hydroxylation/epoxidation of endogenous and/or exogenous compounds. The overall reaction can be summarized as:



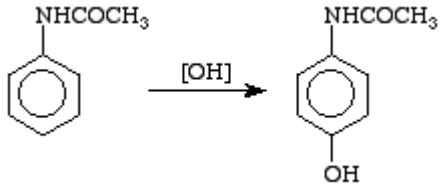
A generalized electron transport system for the P_{450} mixed-function oxidases is shown below:



Note the involvement of two reducing agents (the substrate and NADPH) to provide the total of four electrons required by molecular oxygen. The Table below summarizes some of the

common reactions catalyzed by P_{450} and illustrates the hydroxyl intermediate theme commonly occurring in these reactions.

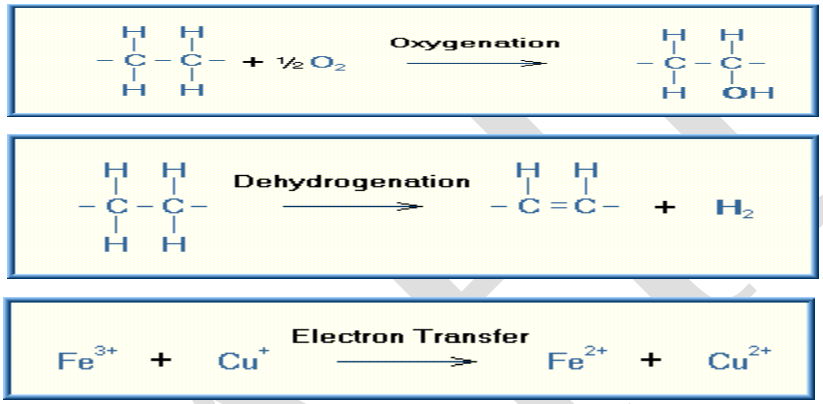
Common Cytochrome P_{450} Catalyzed Reactions

Aromatic hydroxylation	
Aliphatic hydroxylation	$R-CH_3 \xrightarrow{[OH]} R-CH_2\text{-}OH + H^+$
N-Dealkylation	$R-NH-CH_3 \xrightarrow{[OH]} [R-NH-CH_2OH] \longrightarrow RNH_2 + CH_2O$
O-Dealkylation	$R-O-CH_3 \xrightarrow{[OH]} [R-O-CH_2OH] \longrightarrow ROH + CH_2O$
Deamination	$R-CH(NH_2)-CH_3 \xrightarrow{[OH]} R-C(OH)(NH_2)-CH_3 \longrightarrow R-CO-CH_3 + NH_3$
N-Oxidation	$(CH_3)_3N \xrightarrow{[OH]} [(CH_3)_3NOH]^+ \longrightarrow (CH_3)_3NO + H^+$
Sulphoxidation	$R-S-R' \xrightarrow{[OH]} [R-SOH-R']^+ \longrightarrow R-SO-R' + H^+$

i) Oxidation

Oxidation is a chemical reaction in which a substrate loses electrons. There are a number of reactions that can achieve the removal of electrons from the substrate. Addition of oxygen was the first of these reactions discovered and thus the reaction was named oxidation. However, many of the oxidizing reactions do not involve oxygen. The simplest type of oxidation reaction is dehydrogenation, that is the removal of hydrogen from the molecule. Another example of oxidation is electron transfer that consists simply of the transfer of an electron from the substrate.

Examples of these types of oxidizing reactions are illustrated below:



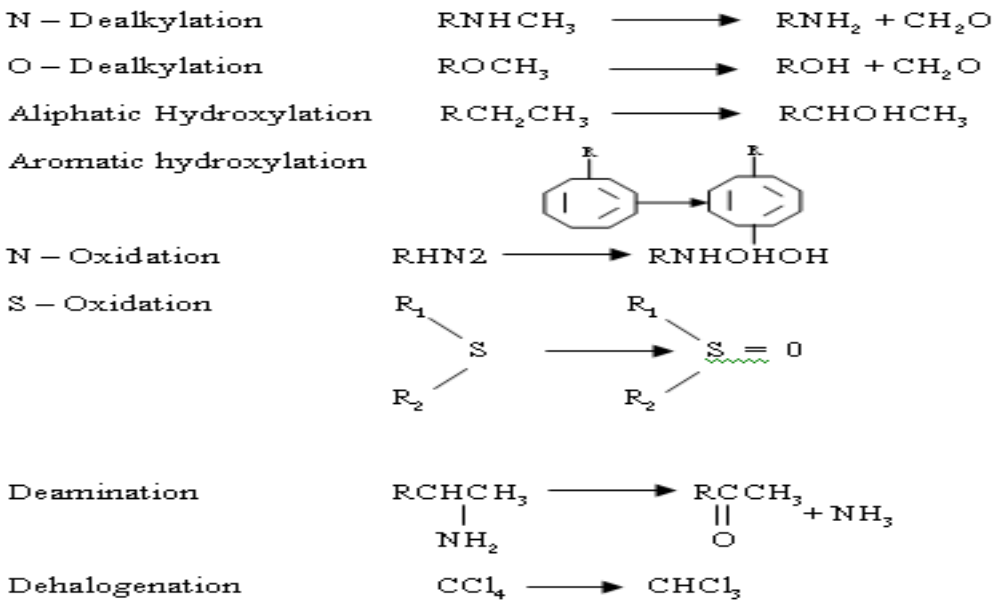
The enzymes involved are

- Cytochrome P450 monooxygenase system
- Flavin-containing monooxygenase system
- Alcohol dehydrogenase and aldehyde dehydrogenase
- Monoamine oxidase
- Co-oxidation by peroxidases

Major oxidation reactions carried out by mammalian CYPs that are involved in drug metabolism are,

- Alcohol dehydrogenation
- Aldehyde dehydrogenation
- Alkyl/acyclic hydroxylation
- Aromatic hydroxylation
- Deamination
- Desulfuration

- N-dealkylation
- N-hydroxylation
- N-oxidation
- O-dealkylation
- Sulphoxidation

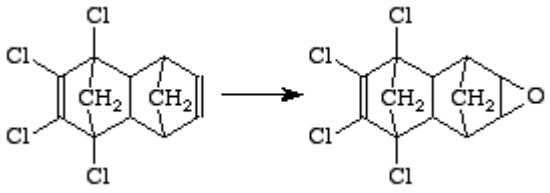


Phase One CYT P450 Monooxygenases catalysed Reactions

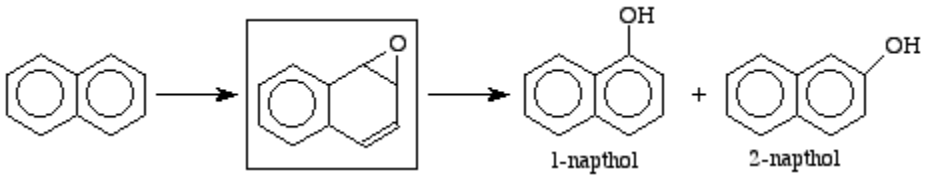
Epoxidation and Hydroxylation Reactions:

Aromatic Reactions:

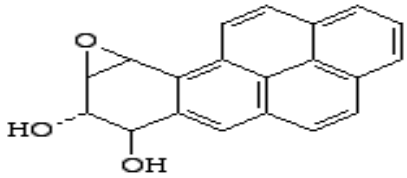
Stable epoxide intermediate - transformation of Aldrin to Dieldrin.



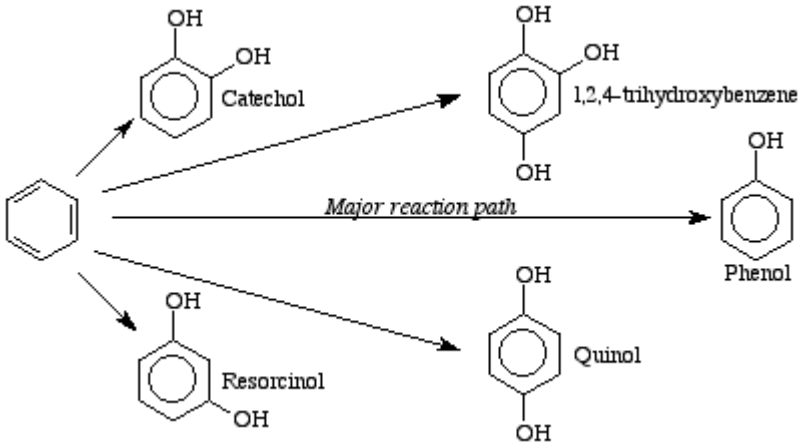
Epoxides also serve as intermediates -transformation of naphthalene to naphthol. In addition to the products shown below the 1,2-dihydroxy- and 1,2-dihydroxy-1,2-dihydro- napthols are also formed.



Can get metabolic activation, such as seen in benzopyrenes where the epoxide is a potent carcinogen (note that the epoxide can be cis or trans to the adjacent hydroxyl group, the trans isomer is shown):

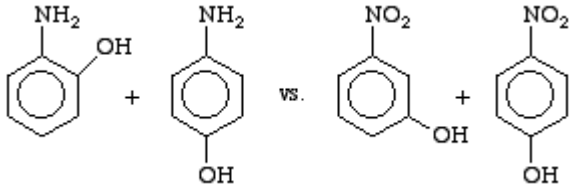


Benzene gives a variety of products:

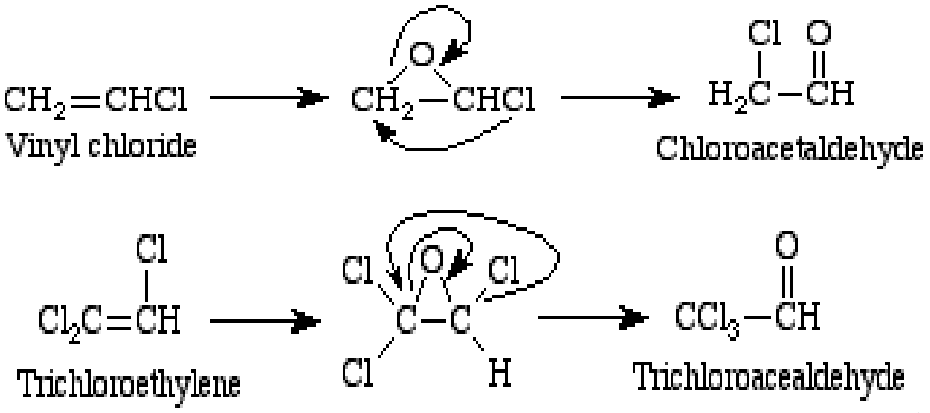


Epoxidation and Hydroxylation Reactions:

As in organic chemistry can get ortho- and meta- directing substituents:

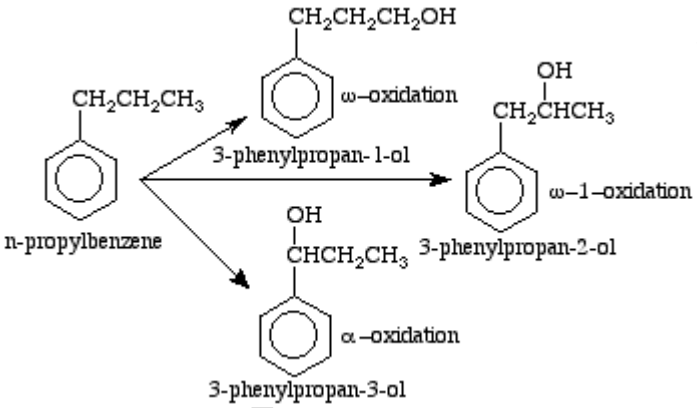


Unsaturated Aliphatic Hydroxylations:



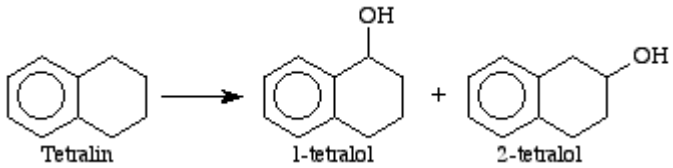
Aliphatic Hydroxylations:

Aliphatic compounds are not readily oxidized or metabolized unless there is an aromatic side chain. For aromatic substituted compounds initially get 1° & 2° alcohols:



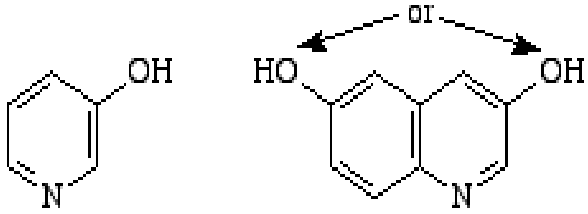
Alicyclic Hydroxylations:

Alicyclic compounds are preferentially hydroxylated on the aliphatic parts (aromatic hydroxylation occurs as a minor product and is not shown):



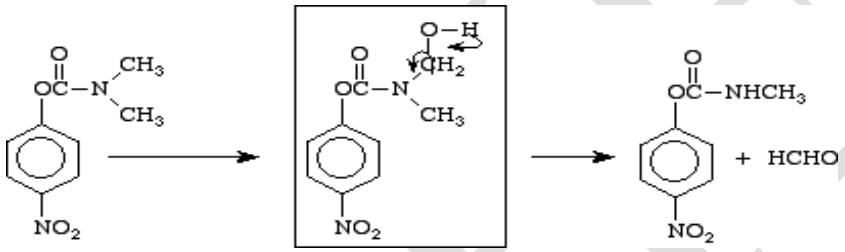
Heterocyclic Hydroxylations:

Heterocyclic compounds are hydroxylated on the three position:

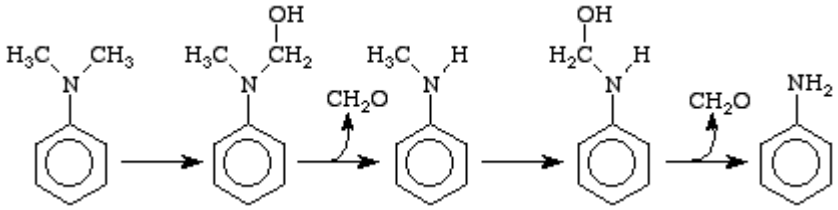


Dealkylation Reactions:

N-dealkylations: Alkyl groups are hydroxylated adjacent to nitrogen and rearrange to release an aldehyde as shown below for the dealkylation of N,N-dimethyl-p-nitrophenylcarbamate:

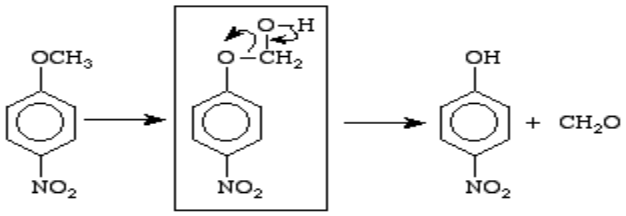


didealkylation of N,N-dimethylaniline:

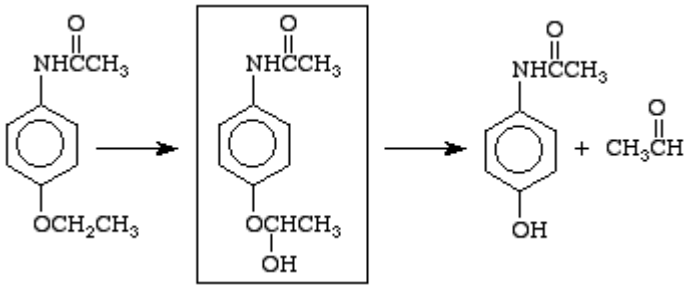


O-dealkylations:

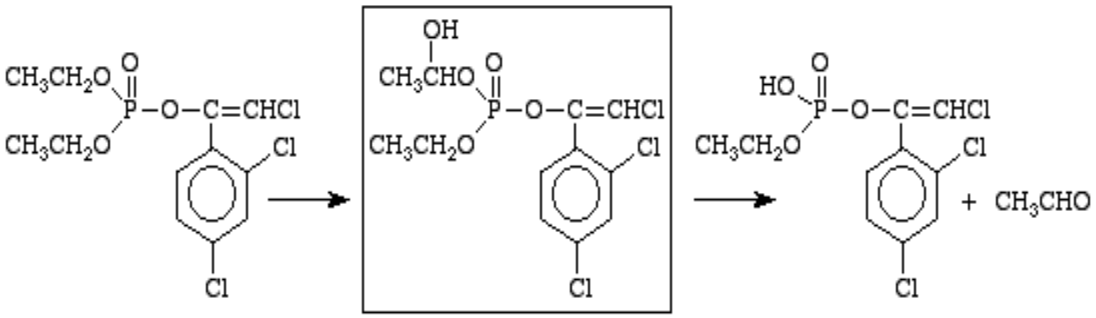
Alkyl groups are hydroxylated adjacent to oxygen and rearrange to release an aldehyde as shown below for the dealkylation of p-Nitroanisole:



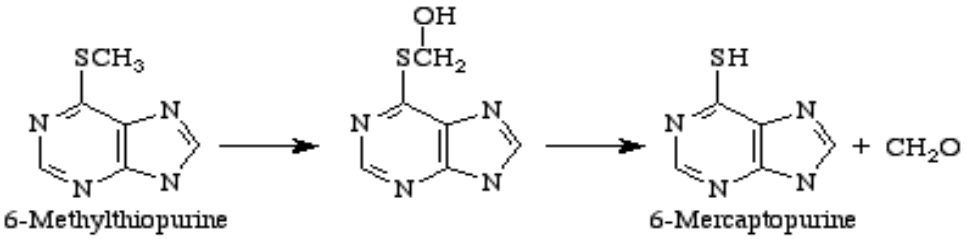
dealkylation of Phenacetin:



With organo-phospho triesters the dealkylation occurs with the ester instead of the ether as shown for Chlorfenvinphos:

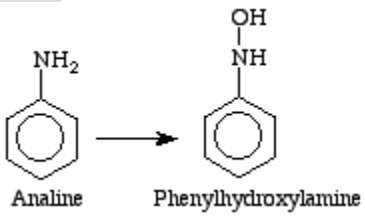


S-Dealkylation:

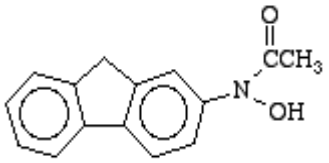


N-Oxidation

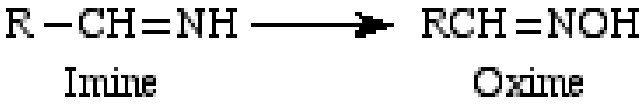
Hydroxylamine formation:



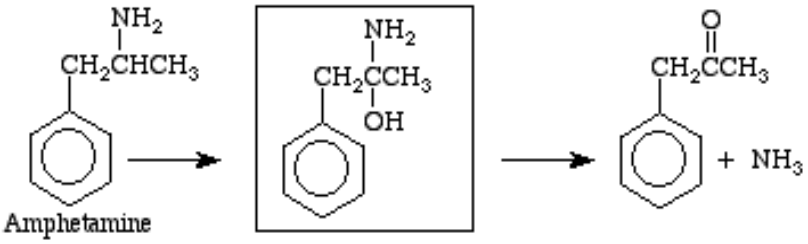
In this instance the product is thought to be responsible for the formation of methemoglobin following aniline administration. In another reaction 2-acetylaminofluorine is activated to a potent carcinogen, N-hydroxy-2-acetylaminofluorine:



Oxime formation:

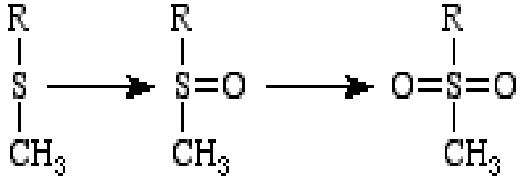


Deamination:



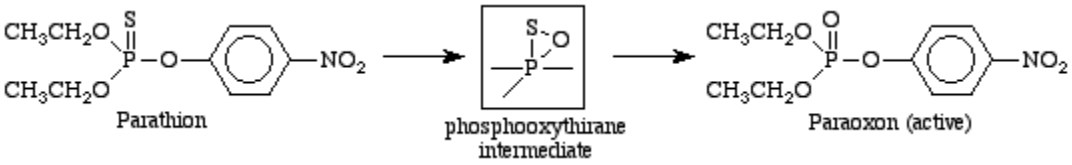
S-Oxidation

For sulfur compounds such as sulfides, thiols, thioethers (shown), etc. get a common pattern of oxidation to the sulfoxide and then further oxidation to the sulfone:



Desulfuration

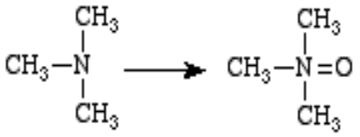
The replacement of sulfur by oxygen results in the activation of a number of insecticides, such as Parathion, below, where the Paraoxon product is the more active substance:



NON-P_{450} BASED OXIDATIONS:

i) Microsomal oxidations: (Largely sER localized enzymes)

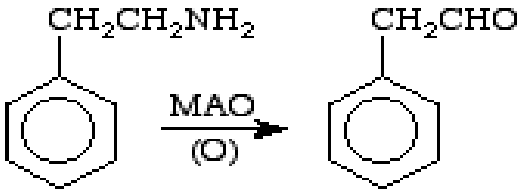
Amine oxidase:



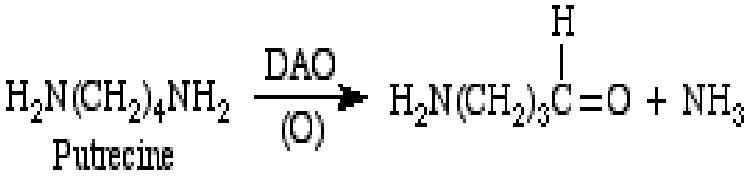
ii) Non-microsomal oxidations: (Enzymes of the mitochondrial or soluble fraction of cytosol)

Amine oxidation:

Monoamine oxidases (MAO) - flavoproteins in the mitochondria. Primary amines are preferred:



Diamine oxidases (DAO) - diamines to charectristic aldehydes

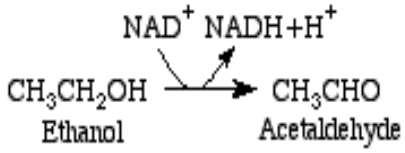


DAO oxidizes primary diamines only. The rate depends on the chain length, with a maximum at four carbons (putrecine) and five carbons (cadaverine), and going to 0 at nine or above. At nine carbons and above MAO becomes active, since the separation of the amine groups is sufficient for the substrate to look like a monoamine.

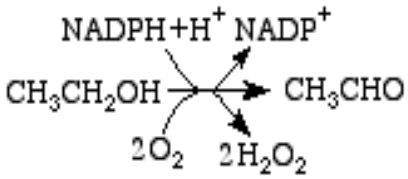
Alcohol and Aldehyde oxidation:

Regardless of ethanol consumption its metabolism is important since it is endogenously produced in the large intestine by the microbial fauna to give about 0.5 mM ethanol in the hepatic portal vein! (Compare to the concentration reached after a single drink of 2-5 mM.)

- Most ethanol metabolism takes place in the liver, with the primary pathway catalyzed by Alcohol Dehydrogenase (ADH) at low concentrations of ethanol since the K_M of ADH is low (approximately 1mM):



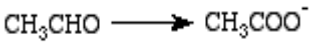
- Ethanol is also oxidized by the microsomal ethanol oxidation system (MEOS), which is P_{450} based:



This reaction may explain ethanol's competition with drug metabolism.

Ethanol can also be oxidized by Catalase:

The aldehyde produced in alcohol metabolism can be oxidized further:

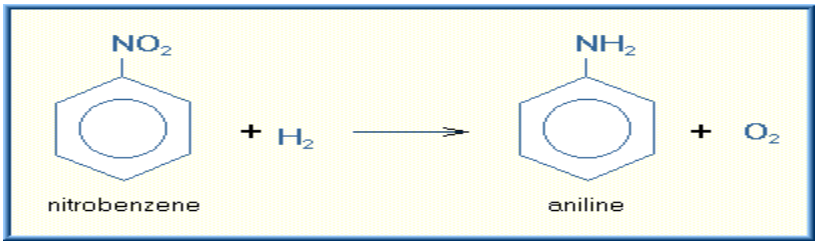


Aldehyde oxidation is mostly due to mitochondrial aldehyde dehydrogenase in liver (K_M = 0.01mM, cytosolic = 1 mM). The mitochodrial enzyme also has a greater capacity.

Some of the toxic effects of ethanol on the liver are due to NAD^+/NADH.

Reduction Reactions

Reduction is a chemical reaction in which the substrate gains electrons. Reductions are most likely to occur with xenobiotics in which oxygen content is low. Reductions can occur across nitrogen-nitrogen double bonds (azo reduction) or on nitro groups (NO_2). Frequently, the resulting amino compounds are oxidized forming toxic metabolites. Some chemicals such as carbon tetrachloride can be reduced to free radicals, which are quite reactive with biological tissues. Thus, reduction reactions frequently result in activation of a xenobiotic rather than detoxification. An example of a reduction reaction in which the nitro group is reduced is illustrated below:



There are fewer specific reduction reactions than oxidizing reactions. The nature of these reactions is also self-evident from their name. Listed are several of the reducing reactions.

- Azo reduction
- Dehalogenation
- Disulfide reduction
- Nitro reduction
- N-oxide reduction
- Sulfoxide reduction

II) Reduction

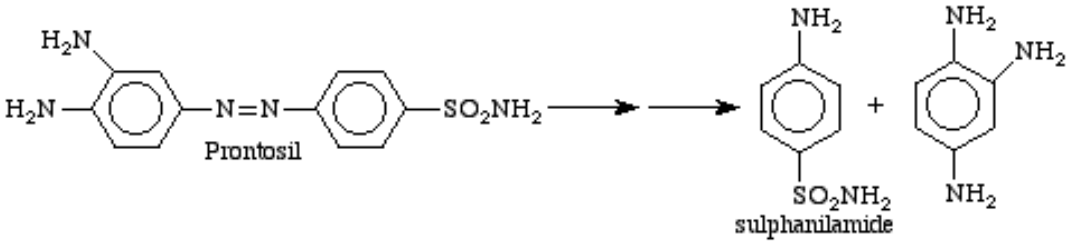
NADPH-cytochrome P_{450} reductase Cytochrome P_{450} reductase, also known as NADPH:ferrihemoprotein oxidoreductase, NADPH:hemoprotein oxidoreductase, NADPH:P_{450} oxidoreductase, P_{450} reductase, POR, CPR, CYPOR, is a membrane-bound enzyme required for electron transfer to cytochrome P_{450} in the microsome of the eukaryotic cell from a FAD- and FMN-containing enzyme NADPH: cytochrome P_{450} reductase.

The general scheme of electron flow in the POR/P450 system is:

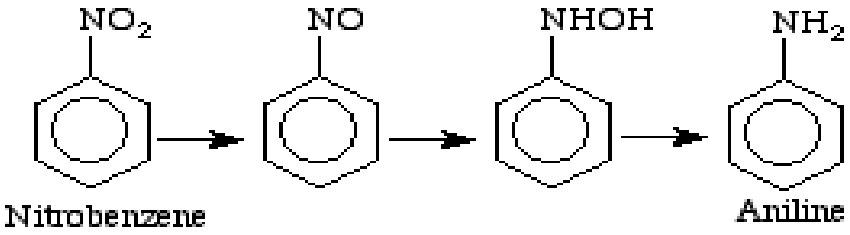
$$NADPH \rightarrow FAD \rightarrow FMN \rightarrow P450 \rightarrow O_2$$

Reduced (ferrous) cytochrome P_{450}

During reduction reactions, a chemical can enter futile cycling, in which it gains a free-radical electron, then promptly loses it to oxygen (to form a superoxide anion). Reductions take place in both the soluble and microsomal fractions under anaerobic conditions. Cytochrome P_{450} or a flavoprotein may be involved in the microsomal reactions, with NADPH as a required reductant. Important reduction reactions may also take place in the gut by bacterial P_{450} reductases. An example is the reduction of the azo dye prontosil to give the antimicrobial drug sulfanilamide:

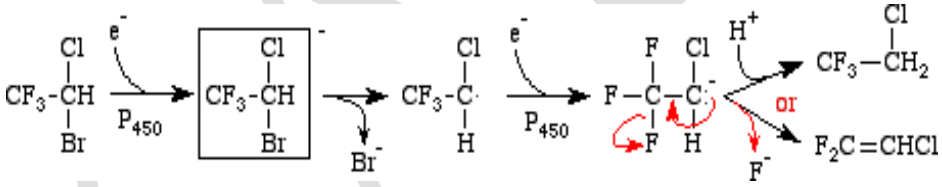


Nitrobenzene toxicity to red blood cells occurs as a result of its reduction by the microbial P_{450}/NADPH system. The nitrosobenzene and phenylhydroxylamine intermediates in this reduction are toxic to red cells:



Reductive Dehydrohalogenation

Under anerobic conditions can get dehalogenation using P_{450}/NADPH. An example is the reaction of Halothane under anaerobic conditions:

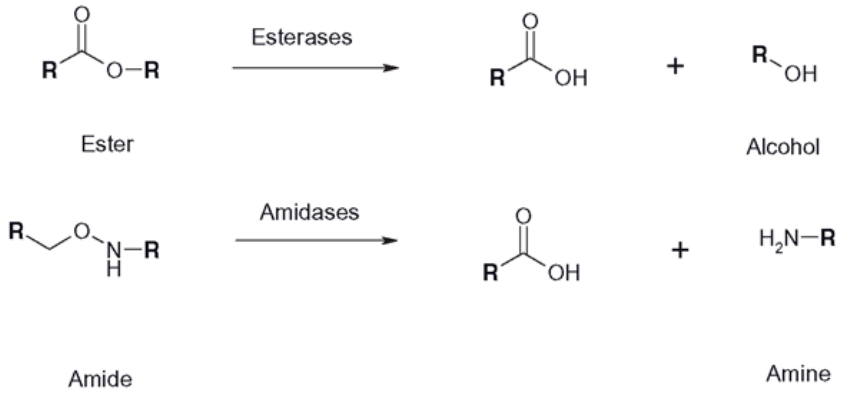


III) Hydrolysis Reactions

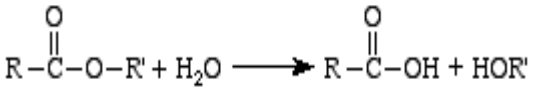
Hydrolysis is a chemical reaction in which the addition of water splits the toxicant into two fragments or smaller molecules. The hydroxyl group (OH-) is incorporated into one fragment and the hydrogen atom is incorporated into the other. Larger chemicals such as esters, amines, hydrazines, and carbamates are generally biotransformed by hydrolysis.The enzymes involved are

- Esterases and Amidase
- Epoxide hydrolase

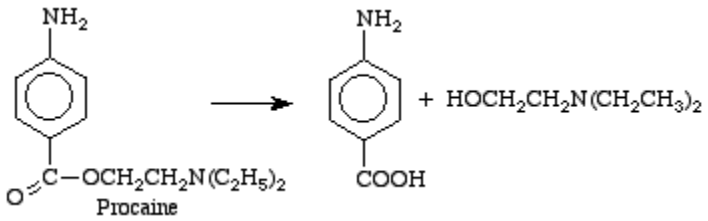
The example of the biotransformation of procaine (local anesthetic) which is hydrolyzed to two smaller chemicals is illustrated below:



Esters and amides are commonly hydrolyzed:



An example is the hydrolysis of the anesthetic, procaine, that is rapidly hydrolized by esterases in the plasma and by tissue microsomal esterases:



The analogous amide, procainamide, is hydrolyzed more slowly by amidases in the microsomal fraction of tissue. It is not hydrolyzed at all in the plasma.

Phase II Reactions

In subsequent phase II reactions, these activated xenobiotic metabolites are conjugated with charged species such as glutathione (GSH), sulfate, glycine, or glucuronic acid. Sites on drugs where conjugation reactions occur include carboxyl (-COOH), hydroxyl (-OH), amino (NH_2), and sulfhydryl (-SH) groups. Products of conjugation reactions have increased molecular weight and tend to be less active than their substrates, unlike Phase I reactions which often produce active metabolites. The addition of large anionic groups (such as GSH) detoxifies reactive electrophiles and produces more polar metabolites that cannot diffuse across membranes, and may, therefore, be actively transported.

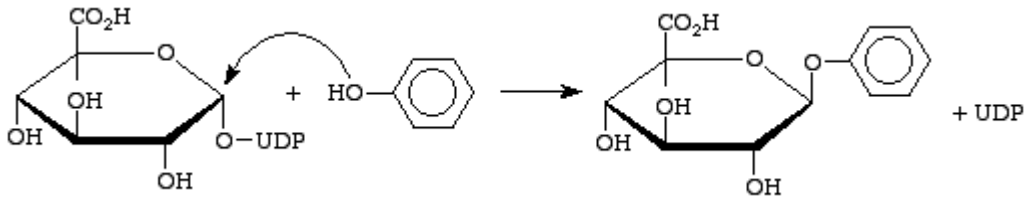
These reactions are catalysed by a large group of broad-specificity transferases, which in combination can metabolise almost any hydrophobic compound that contains nucleophilic or electrophilic groups. One of the most important classes of this group is that of the glutathione S-transferases (GSTs).

Phase II reactions are conjugation reactions, that is, a molecule normally present in the body is added to the reactive site of the Phase I metabolite. The result is a conjugated metabolite that is more water-soluble than the original xenobiotic or Phase I metabolite. Usually the Phase II metabolite is quite hydrophilic and can be readily eliminated from the body. The primary Phase II reactions are:

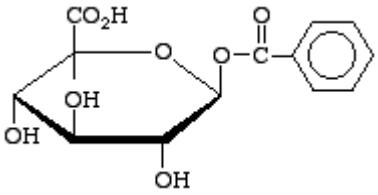
- Glucuronide conjugation - most important reaction
- Sulfate conjugation - important reaction
- Acetylation
- Amino acid conjugation
- Glutathione conjugation
- Methylation

Phase two reactions involve the attachment of a generally polar, readily available in vivo, molecule to a susceptible functional group. Reactive functional groups are often, but not necessarily a result of Phase 1 reactions). The result is to make the whole molecule more polar, and thus more readily excreted.

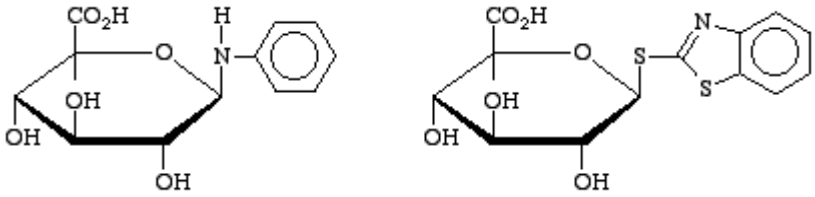
Conjugation by glucuronyl transferase now takes place on the ER, mostly via reaction with hydroxyl and carbonyl groups (but occasionally with N & S also). Example: Conjugation of phenol gives an acetal glucuronide, phenyl β-D-glucuronide:



Conjugation with benzoic acid gives an ester glucuronide, benzoyl-β-D-glucuronide:



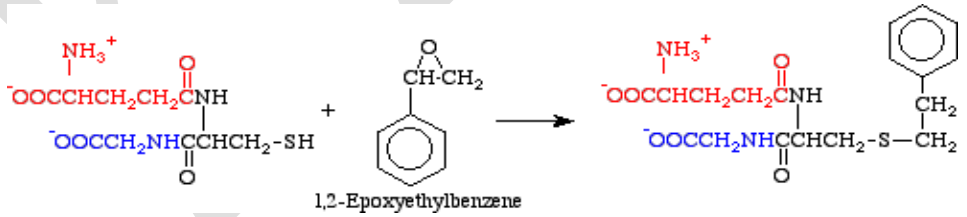
Examples with nitrogen and sulfur include the conjugation of aniline to give phenylamino-β-D-glucuronide, and conjugation with 2-mercaptobenzothiazole to give the benzothiazole-2-thio-β-D-glucuronide:



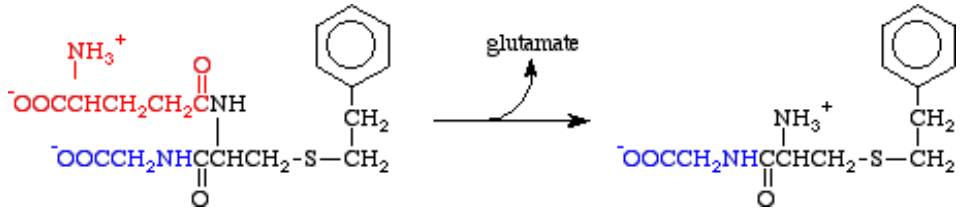
Glutathione conjugation: Glutathione is a tripeptide (γ-glutamylcyteinylglycine, with the amino acid residues color coded in the structures below). It is used in cells as a recyclable anti-oxidant as well as a conjugating agent. When used in conjugation it is initially conjugated by a glutathione-S-transferase, or sometimes as a simple chemical reaction. Generally the conjugation occurs as a nucleophilic attack by the -SH group on a reactive electrophilic center. Conjugation is often followed by metabolic cleavage of the peptide to leave only the cysteinyl residue, which may then be acetylated to give a mercapturic acid.

Example:

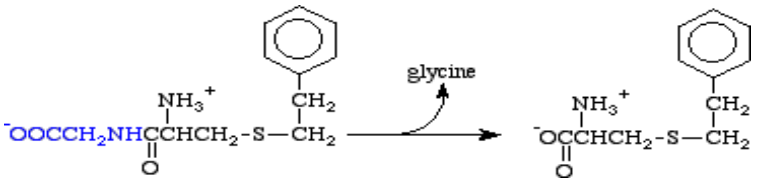
1. Glutathione S-transferase:



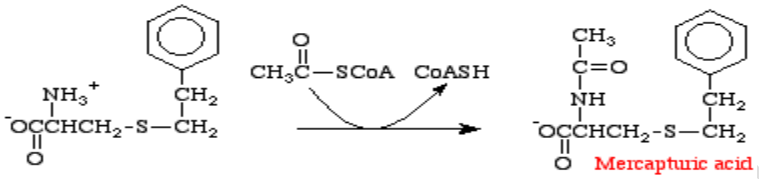
2. γ-glutamyltranspeptidase:



3. Cysteinyl glycinase:

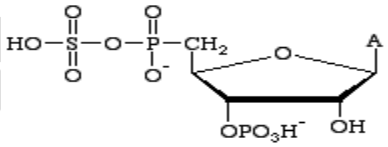


4. N-acetyl transferase:

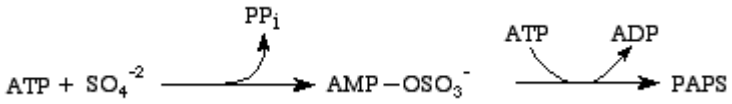


However, if the derivative is excreted via the bile, it may be metabolized by the gut fauna and the toxin may be reabsorbed.

Sulfate Conjugation: This is the major Phase two process for a variety of hydroxyl groups and for some amines. The first step is to "activate" the sulfate to give "PAPS" (Adenosine-3'-P-5'-Phosphosulfate)

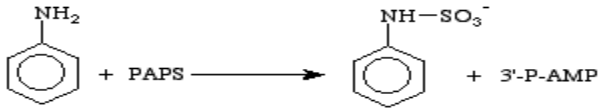


PAPS is synthesized via Kinases:



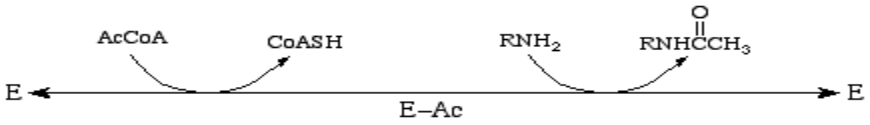
These enzymes are in the soluble fractions of a wide variety of tissues (e.g. liver, muscle, intestine, testes, etc.). Can get Aryl sulfates, Alkyl sulfates, and Sulfamates via a sulfotransferase reaction.

Example, sulfamate synthesis

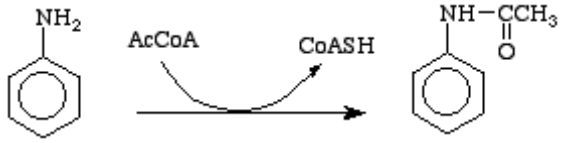


Acetylation: Acetyl transferases are found in the cytosol of hepatic endothelial cells, intestinal mucosal cells and white blood cells.

The "activated" acetyl group on acetyl CoA is used as the source of acetate, so it is readily available from normal metabolic sources. The enzyme mechanism is outlined below:

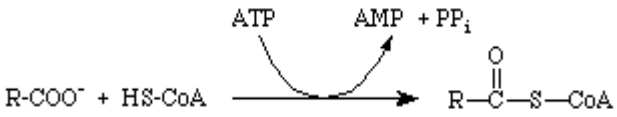


Example: acetylation of a primary aryl amine:

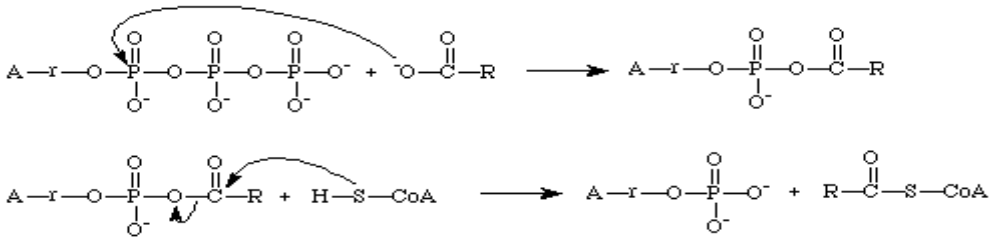


There is evidence for more than one acetylase, which provides the genetic basis for "slow" and "fast" acetylators. Apparently there is polymorphism for various acetylases (we will see again later in comparative studies). Slow acetylators are more susceptable to xenobiotics which are inactivated by acetylation. Turns out deacetylases are also present. The two processes show dominance in different organisms, varying the importance of acetylation.

Acylation: Acylation is similar to acetylation in the products excreted, but with an amino acid substituting for acetate (most commonly glycine; ornithine, taurine, and glutamine are also known). However, the synthetic strategy is "reversed" in that the xenobiotic is activated by adding coenzyme A, which then reacts with the amino acid.These reactions may be catalyzed by fatty acyl CoA synthetases:

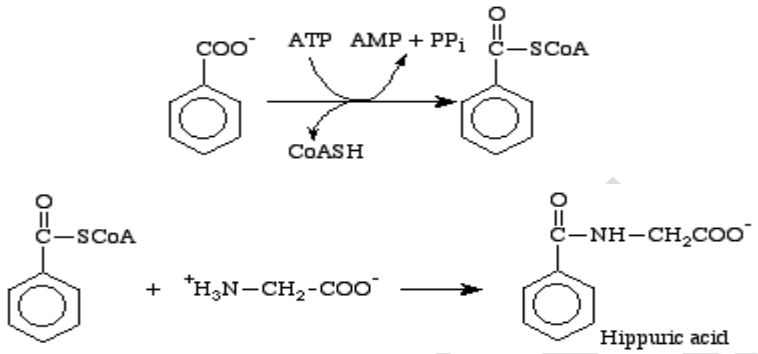


These enzyme catalyses a two part reaction:



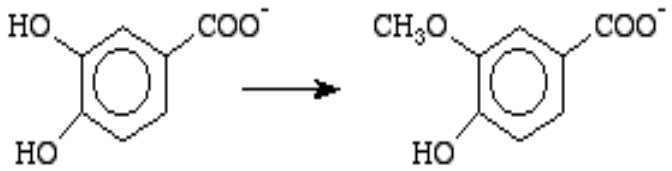
The resulting acylCoA derivative can then react with an amino acid to give the acyl excretory product.

Example: Benzoic acid is first converted to benzoyl CoA, the benzoyl CoA then reacts with glycine to give the product, Hippuric acid:

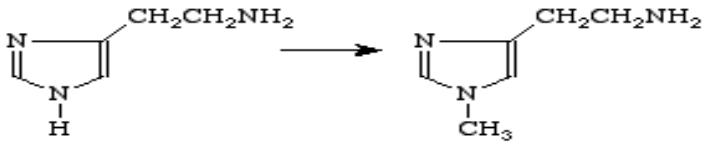


Methylation involves the transfer of an "activated" methyl group, most commonly from S Adenosyl methionine (methyl H_4 folate and methyl Vitamin B_{12} are other possibilities). The organism can then use this system to methylate amine, hydroxyl, or sulfhydral compounds. Bacteria can also methylate heavy metals, most notoriously mercury to give dimethyl mercury.

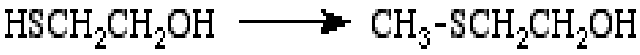
Example: Methylation of dihydroxy benzoic acid by catechol O-methyl transferase.



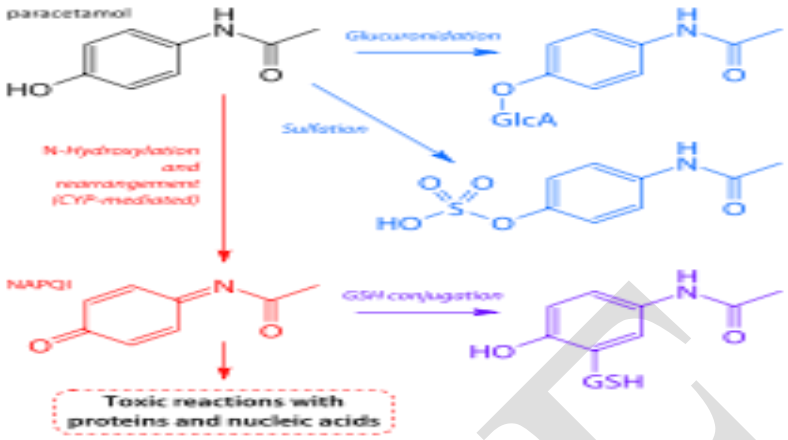
Methylation of histamine:



Methylation of mercaptoethanol:



The following is the fate of paracetamol



Factors affecting drug metabolism

- Environmental Determinants
  - Induction
  - Inhibition
- Disease Factors
- Age and Sex
- Genetic Variation

Various physiological and pathological factors can also affect drug metabolism. Physiological factors that can influence drug metabolism include age, individual variation (e.g., pharmacogenetics), enterohepatic circulation, nutrition, intestinal flora, orsex differences. In general, drugs are metabolized more slowly in fetal, neonatal and elderly humans and animals than in adults. Genetic variation (polymorphism) accounts for some of the variability in the effect of drugs. With N-acetyltransferases (involved in Phase II reactions), individual variation creates a group of people who acetylate slowly (slow acetylators) and those who acetylate quickly, split roughly 50:50 in the population of Canada. This variation may have dramatic consequences, as the slow acetylators are more prone to dose-dependent toxicity.

Cytochrome P_{450} monooxygenase system enzymes can also vary across individuals, with deficiencies occurring in 1 – 30% of people, depending on their ethnic background.

Pathological factors can also influence drug metabolism, including liver, kidney, or heart diseases.

Age:

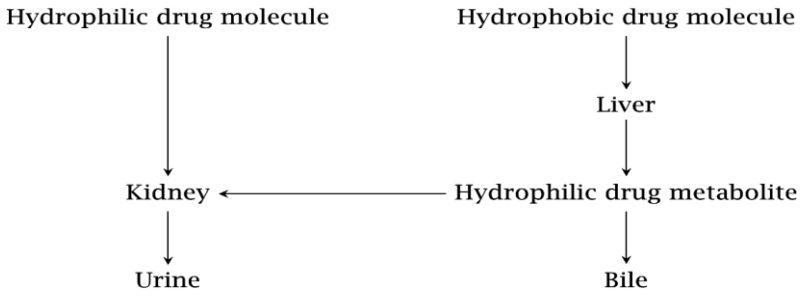
- Responsiveness to certain drugs is different for men and women
- Pregnancy – induction of certain drug metabolizing enzymes occurs in second and third trimester
- Hormonal changes during development have a profound effect on drug metabolism

Sex:

- Responsiveness to certain drugs is different for men and women
- Pregnancy – induction of certain drug metabolizing enzymes occurs in second and third trimester
- Hormonal changes during development have a profound effect on drug metabolism wide variability in the response to drugs between individuals.
- Consequences of such variation may be therapeutic failure or an adverse drug reaction. Genetic diversity is the rule rather than the exception with all proteins, including drug metabolizing enzymes.
- Allelic variants with different catalytic activities from that of the wild-type form have been identified inheritance leads to subpopulations (genetic polymorphisms) with different drug metabolizing abilities lack of activity reduction in catalytic ability enhanced activity.
- Frequency of the polymorphism often varies according to the ethnic ancestry of the individual.

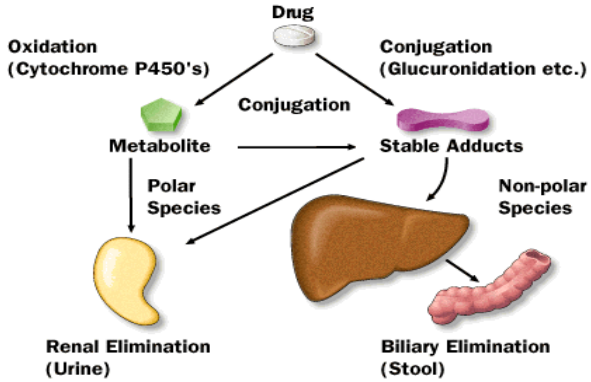
ELIMINATION OF DRUG BODY SYSTEM

Drugs are eliminated from the body either unchanged as the parent drug or as metabolites (a changed form of the drug). Organs that excrete drugs eliminate polar compounds (water soluble) more readily than components with high lipid (fat) solubility. The exception to this premise is the lungs. Lipid soluble drugs are not readily eliminated until they are metabolized to more polar compounds. The following diagram depict the same



Drug elimination from body by various routes

Drugs are excreted either unchanged (polar, lipid insoluble and water soluble drugs) or as metabolites (lipid soluble drugs and non polar drugs). Mostly excreted via urine (kidney), stool (colon) and expiration (lungs) Minor excretion via sweat, bile, milk, tears.



Possible sources of excretion include:

- Breath
- Urine
- Saliva
- Perspiration
- Feces
- Milk
- Bile
- Hair

1. Kidney

2. Lungs

Drugs like paraldehyde and alcohol excreted via lungs

3. Gastro intestinal tract

The drug orally subjected to first pass effect, which means that enzyme in GI tract breakdown drugs to some degree.

4. Biliary and fecal infection drug metabolites may be excreted in liver bile.

5. Excretion of drugs through milk this way is not crucial so much because of proportion of drug that leaves the body this way but because of dangers posed to the nursing infant. The kidney is the most important organ involved in the elimination of drugs and their metabolites.

Substances excreted in the feces usually involve orally ingested unabsorbed drugs or metabolites excreted in the bile that are not reabsorbed from the intestinal tract.

Excretion of drugs in milk is relevant because excreted drugs can produce drug toxicity in the nursing infant. Pulmonary excretion (through breathing) is important as it pertains to the elimination of anesthetic gases and vapors, as well as alcohol.

Excretion of drugs through the kidneys:

The kidneys are a pair of bean-shaped organs, each a little smaller than the fist and weighing about 0.25 pounds. They lie on the back of the abdominal cavity at the level of the lower ribs. They act as a pressure filter. On its way through the kidneys the blood is filtered. The liquid or "primary urine" consists of a considerable amount of the blood's water, together with all substances dissolved in this water (including drugs). The kidneys reabsorb most of the water and some of the dissolved substances. Components that are fat-soluble tend to diffuse back into the bloodstream.

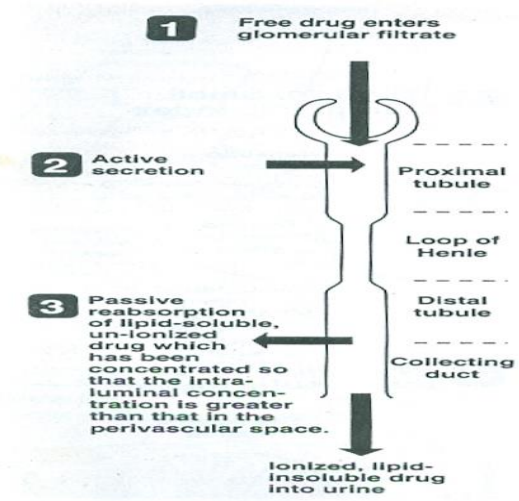


Figure 2.10
Drug elimination by the kidney.

The kidneys perform two major functions:

- They excrete most of the end-products of body metabolism (including drugs);
- They closely regulate the levels of most of the substances
- Kidneys:The processes which contribute to the elimination of a drug in the urine are:
- Passive glomerular filtration.
- Active tubular secretion;and
- Passive diffusion across the tubules.
- Passive glomerular filtration.
- Driving force for GF is hydrostatic pressure of blood flowing in capillaries.
- Hydrostatic pressure pushes a portion of blood to be filtered across a semi-permeable membrane into the Bowman's Capsule.
- Most drugs are filtered through glomerulus.

Blood cells, platelets, and plasma proteins are retained in the blood and not filtered.

- The amount of blood filtered by the glomeruli in a given time (GFR = 120-130 ml/min).
- GFR

Unionized drugs which are well absorbed are filtered at the glomerulus, but they can diffuse back from the lumen of the renal tubule into the cells lining the tubules. Thus, ultimately a very small amount of the drug appears in the urine. Ionized drugs which are poorly absorbed

are excreted almost entirely by glomerular filteration and are not reabsorbed. Many weak acids (anionic substances) and weak bases (cationic substances) are actively transports across the proximal tubules by systems that are responsible for the transport of naturally occurring substances such as uric acid ie they are secreted in the urine.

Passive diffusion

Passive diffusion is a bidirectional process and drugs may diffude across the tubules in either direction depending upon the drug concentration and the pH eg mepacrine and salicylates. In the presence of renal damage, the ability of the kidney to excrete drugs is impaired. This might result in high blood levels and prolonged drug action with normal doses. Great care must, therefore be exercised when drugs like aminoglycosides or coumarin anticoagulants are used in the presence of impaired renal function. Similarily, potassium salts may produce dangerous hyperkalemia if the kidney function is inadequate. Protein binding reduces the amount of the drug available for filteration at the glomerulus but protein bound drugs may still be available for secretion by the proximal renal tubules.eg phenyl butazone. This is because the bound form of the drug is released from its combination with plasma proteins when the plasma concentration of the free form of the drug is lowered.

Active Tubular Secretion of drugs

- Occurs mainly in proximal tubules
- It increases drug concentration in filtrate
- Drugs undergo active secretion have excretion rate values greater than normal GFR
- Secretion of K^+, H^+, ammonia; excess amino acids
- Secretion of ionized drugs into the lumen

Characters of active tubular secretion:

- Is an active process
- Needs energy
- Requires carriers (transporters)
- Can transport drugs against concentration gradients
- Saturable
- Not specific (competition may happens)

  e.g. penicillin

Two secretion mechanisms are identified

System for secretion of organic acids/anions

- Penicillin, salicylates, sulfonamides
- Probenecid, uric acid

System for organic bases / cations

- Atropine, morphine
- Catecholamines, quinine, neostigmine

Active tubulasr secretion of drug:

Therapeutic advantages of competition: Probenecid is used to block renal tubular secretion of some acidic drugs (e.g. penicillin) and thus prolong its duration. Therapeutic disadvantages of competition: probenecid inhibits renal tubular secretion of nitrofurantoin thus decreases its efficacy in urinary tract infections (UTIs).

Tubular re-absorption

- After glomerular filtration, drugs may be reabsorbed from tubular lumen into systemic circulation.
- It takes place all along the renal tubules.
- Drugs undergo tubular re-absorption have excretion rates less than the GFR. e.g. Glucose
- Re-absorption increases half life of a drug.
- Re-absorption may be active or passive.

Passive Tubular re-absorption

- In distal convoluted tubules & collecting ducts.
- Only lipid soluble drug undergoes passive tubular re-absorption from tubular lumen into systemic circulation.
- Lipophilic drugs can be passively reabsorbed back (urinary excretion will be low).
- Ionized drugs (water soluble) are poorly reabsorbed & so urinary excretion will be high.

Active tubular re-absorption

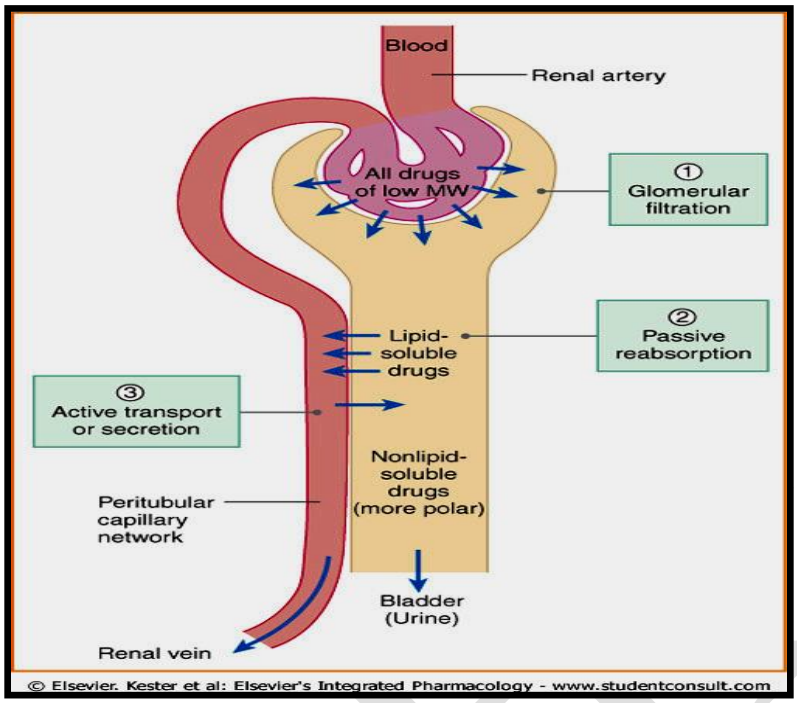
- It occurs with endogenous substances or nutrients that the body needs to conserve. e.g. glucose, electrolytes, amino acids, uric acid, vitamins.
- Probenecid acts as a uricosuric agent in treatment of gout.

- It increases excretion of uric acid in urine by inhibiting active tubular re-absorption of the endogenous metabolite uric acid.

Passive Tubular re-absorption and urinary pH trapping (Ion trapping)

- Most drugs are weak acids or weak bases thus by changing pH of urine via chemicals can inhibit the passive tubular re-absorption of drugs.
- Urine is normally slightly acidic and favors excretion of basic drugs.

Most of the acidic and the basic drugs are secreted by the renal tubules . Tubular secretion of weak organic acids such as penicillin can be blocked by probenecid and their half life can be prolonged. Secretion of weak bases by renal tubules can also be blocked but the blocking agents are too toxic for any therapeutic utility. The pH of the urine influences the excretion of certain weak acids and bases. Thus, weak acids are quickly eliminated in an alkaline urine eg: barbiturates and salicylates; while weak bases are rapidly excreted in an acidic urine eg: pethidine, mecamylamine and amphetamine. On the other hand, the action of these substances in the body can be prolonged if the urinary pH is not favourable for their excretion. The tubular reabsorption of weak acids is minimum when the urine is alkaline because a large portion of these compounds is ionized in an alkaline medium. Similar is the case with weak bases in acid urine.



Substances that must be excreted include the end-products of body metabolism, as well as sodium, potassium, and chloride, which frequently accumulate in the body in excess quantities. The kidneys must also be capable of conserving water, sugar, and the necessary quantities of sodium, potassium and chloride.

Since drugs are small particles dissolved in the blood, they too are usually filtered into the kidneys and then reabsorbed back into the bloodstream. Water is reabsorbed from the kidney into the bloodstream to a much greater extent than most drugs, so the drugs become more concentrated inside the kidney than they are in the blood. In order for the kidney to eliminate drugs from the body, the drug must somehow be prevented from being reabsorbed from the urine into the bloodstream. The drug must be chemically changed into a compound that is less fat-soluble and therefore less capable of being reabsorbed.

Conversion

This process of converting fat-soluble drugs into water soluble metabolites that can be excreted by the kidney is carried out in the liver. Usually (but not always) the process of metabolism decreases the pharmacological activity of a drug. Even though a metabolite might remain in the body (awaiting excretion), it would usually be pharmacologically inactive or less

active and would not produce the effects of the parent drug to the same extent. Many drugs can increase the rate at which an enzyme system metabolizes a variety of drugs, thereby increasing the speed with which a drug is eliminated. Certain drugs induce an increase in enzyme activity. This process can decrease the pharmacological response to certain agents metabolized in the liver. For example, phenobarbital stimulates the production of enzymes that normally metabolize the anti-coagulant warfarin. Thus phenobarbital decreases the effect of warfarin by increasing the metabolism of warfarin.

Some drugs can also stimulate their own metabolism. This is one mechanism to explain why increasing doses of a drug must be administered in order to produce the same effect that smaller doses produced earlier. Regarding the placental barrier referred to earlier, the fetus may excrete drugs through the umbilical cord back into the bloodstream of the mother. The mother can then eliminate the drug through the liver and kidneys. After delivery, however, the newborn baby is no longer attached to the mother and must deal on its own with any drug in its blood. Unfortunately, the newborn baby has few drug metabolizing enzymes in the liver and the kidneys may not yet be fully functional. This means, that the infant has great difficulty metabolizing and excreting drugs.

Factors affecting renal excretion of drug

- Physiochemical properties of drugs
  - Molecular weight
  - Lipid solubility
  - Volume of distribution
  - Binding character
  - Degree of ionization
- Blood flow to the kidney
- Urine pH
- Biological factor e.g. age
- Disease states

Drug MW:

Larger MW drugs are difficult to be excreted than smaller MW especially by glomerular filtration.

Drug lipid solubility:

Urinary excretion is inversely related to lipophilicity, increased lipid solubility increase volume of distribution of drug and decrease renal excretion.

Volume of distribution:

Clearance is inversely related to volume of distribution of drugs (Vd). A drug with large Vd is poorly excreted in urine. Drugs restricted to blood (low vd) have higher excretion rates.

Renal blood flow:

Increased perfusion leads to increased excretion; Important for drugs excreted by glomerular filtration.

Binding characteristics of the drugs

Drugs that are bound to plasma proteins behave as macromolecules and cannot be filtered through glomerulus. Only unbound or free drug appear in glomerular filtrate. Protein bound drug has long half lives.

Biological factor:

Age can affect renal clearance. Renal clearance is reduced in neonates and elderly.

Disease states:

Impairs the elimination of drugs e.g. hypertension, Diabetes, pyelonephritis

Drug renal clearance:

A rate of excretion of a drug by the kidney into urine relative to the plasma drug concentration.

$$\text{Renal Clearance (ml/min)} = \frac{\text{Excretion rate (mg/min)}}{\text{Plasma concentration (mg/ml)}}$$

Renal clearance of many drugs and their metabolites depends on adequate renal function. If renal clearance is impaired, this may increase t ½ of drugs and toxic levels of drugs may remain in the body. Renal clearance is especially important for some drugs which are: Mainly excreted by the kidney, Have narrow therapeutic index (e.g. lithium, digoxin, warfarin). Diseases like Congestive heart failure, Hemorrhage, Cardiogenic shock,Renal disease - Dose reduction of drugs is required

- Creatinine clearance and drugs excretion
- Creatinine clearance rate (CCr or CrCl) is the volume of blood that is cleared of creatinine per unit time.
- CrCl is a useful measure for approximating the GFR because creatinine is produced from muscle and freely filtered (low MW, water soluble, and is not protein bound).
- Drugs that are primarily excreted by the kidney
- (> 60%) needs dose adjustment (Dose reduction of drugs is required -when creatinine clearance is below 60 ml/min).

Biliary and fecal excretion

Many metabolites of drugs created in the liver are excreted into the intestinal tract in the bile. Hence the intestine is not only a site of absorption but it is also a site of excretion.

The net excretion by this route may be greatly reduced by subsequent reabsorption into the bloodstream of fat-soluble compounds further along the intestines. In this case drugs will undergo the process of excretion all over again and the drug effect is prolonged. This excretion/reabsorption phenomenon is called enterohepatic cycling. Metabolites may be excreted in the feces. More commonly, they are reabsorbed into the blood and ultimately excreted in the urine.

Lungs:

Volatile general anaesthetics and certain other drugs like paraldehyde and alcohol are partially excreted by the lungs. The presence of paraldehyde and alcohol can be recognized by the odour they impart to the breath.

Excretion by other routes

Minute amounts of drugs are excreted into sweat, saliva and tears. Drugs excreted into the saliva enter the mouth, where they are usually swallowed. Their fate thereafter is the same as drugs taken orally. Some drug concentrations in the saliva parallel those found in the plasma. Since breast milk is more acidic than blood plasma, basic compounds may become slightly concentrated in this location. Although excretion into hair and skin occurs in small quantities, it does have forensic significance.

STORAGE DRUGS IN ADIPOSE TISSUE

The current concept used to describe how drugs move in the body is a two compartment model. The first area is called the central compartment and is typically the blood and well perfused organs like the liver and kidneys. The second area is called the peripheral compartment and is typically poorly perfused tissues like fat and lean tissues like muscle.

Very few drugs show simple direct distribution and equilibrium through the body. Sometimes, it may take 2 or 3 (or more) doses of a drug before that drug shows up in the blood at a level that might be expected with the first dose. This means that a portion of the drug goes to other areas of the body and gets "removed" from circulation.

In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly as reversibly bound to blood components (eg, plasma proteins, blood cells). The extent of drug distribution into tissues depends on the extent of plasma protein and tissue binding. Tissue binding is a mechanism by which a drug is removed from circulation and stored in tissue such as a hair, bone, teeth, and adipose tissue. This mechanism can result in storage of significant quantities of a drug, because tissue storage sites may need to be saturated before there is sufficient free drug to be effective at receptor sites.

Only unbound drug is thought to be available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug can occur. Therefore, the unbound drug concentration in systemic circulation typically determines drug concentration at the active site and thus efficacy. Some lipid-soluble drugs (e.g., caffeine, diazepam, thiopental) have a longer half-life in the pregnant woman, whereas polar drugs (e.g., oxazepam, ampicillin) tend to have a shorter half-life. The volume of distribution for lipophilic drugs is increased during pregnancy because of the accumulation of fat, which may serve as a reservoir for some drugs via tissue binding.

When the drug is discontinued, tissue deposits may give up their stores slowly, resulting in persistent drug effects. Because lipid-soluble drugs are stored in adipose tissue, the increased adipose tissue during pregnancy can lead to a slight decrease in the amount of the free lipid-soluble drugs, such as sedatives and hypnotics, and persistence of drug effects ("hangover") after the drug has been discontinued.

The fat or adipose tissue is a "highly sluggish reservoir due to lesser blood flow; but if body fat starts depleting, as occurs during starvation, the stored drug may be mobilized and toxicity may occur." Thus, storage in fat initially shortens the drug's effect but then prolongs it. Some drugs accumulate within cells because they bind with proteins, phospholipids, or nucleic acids. For example, chloroquine concentrations in white blood cells and liver cells can be thousands of times higher than those in plasma. Phencyclidine, or PCP, is one example of a drug that remains in fat tissue for over three weeks after a single injection. THC, the active chemical in marijuana, is detectable in adipose tissue for up to four weeks after last use. Very sensitive test methods can detect THC in blood and urine for as much as two months following discontinued use. The reality is that drug storage is real and this may be why some people experience persistent effects even after having stopped their prescribed medication for some time.

Possible Questions

1. Write account of receptor interaction
2. Given account on drug allergy
3. Explain the adverse response of drugs
4. Write short notes on tachyphylaxis
5. Briefly discuss the drug tolerance
6. Explain the drug abuse
7. Discuss about drug-intolerance
8. Describe the multidrug resistance phenotypes
9. What are the different factors that modify the effect of drug?
10. Write the assay of drug potency

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17BCU602A- Drug Biochemistry
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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**

		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**
43	II	Facilitation of a pharmacological response by the concomitant use of two or more Drugs is called	antagonism	synergism	additive effect	drug intolerance	**synergism**
44	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**
45	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**
46	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**
47	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 abuse

Substance abuse, also known as **drug abuse**, refers to a maladaptive pattern of use of a substance that is not considered dependent. The term "drug abuse" does not exclude dependency, but is otherwise used in a similar manner in nonmedical contexts. The terms have a huge range of definitions related to taking a psychoactive drug orperformance enhancing drug for a non-therapeutic or non-medical effect. All of these definitions imply a negative judgment of the drug use in question (compare with the term responsible drug use for alternative views). Some of the drugs most often associated with this term include alcohol, amphetamines, barbiturates, benzodiazepines (particularly temazepam, nimetazepam, and flunitrazepam), cocaine, methaqualone, and opioids. Use of these drugs may lead to criminal penalty in addition to possible physical, social, and psychological harm, both strongly depending on local jurisdiction. Other definitions of drug abuse fall into four main categories: public health definitions, mass communication and vernacular usage, medical definitions, and political and criminal justice definitions. Substance abuse is a form of substance-related disorder.

Drug dependence

Multiple drug resistance

Multiple drug resistance or **Multidrug resistance** is a condition enabling a disease-causing organism to resist distinct drugs or chemicals of a wide variety of structure and function targeted at eradicating the organism. Organisms that display multidrug resistance can be pathologic cells, including bacterial and neoplastic (tumor) cells.

Common MultiDrug-Resistant Organisms (MDROs)

- Vancomycin Resistant Enterococci (VRE)
- Methicillin Resistant *Staphylococcus aureus* (MRSA)

- Extended spectrum ß-lactamse (ESBLs) producing Gram-negative bacteria
- *Klebsiella pneumoniae* carbapenemase (KPC) producing Gram-negatives
- Imipenem resistant or MultiDrug Resistant Organisms *Acinetobacter baumannii*
- Imipenem resistant or MultiDrug Resistant Organisms *Pseudomonas aerginosa*

Bacterial resistance to antibiotics

Various microorganisms have survived for thousands of years by their being able to adapt to antimicrobial agents. They do so via spontaneous mutation or by DNA transfer. This process enables some bacteria to oppose the assault of certain antibiotics, rendering the antibiotics ineffective. These microorganisms employ several mechanisms in attaining multidrug resistance:

- No longer relying on a glycoprotein cell wall
- Enzymatic deactivation of antibiotics
- Decreased cell wall permeability to antibiotics
- Altered target sites of antibiotic
- Efflux mechanisms to remove antibiotics
- Increased mutation rate as a stress response

Many different bacteria now exhibit multidrug resistance, including staphylococci, enterococci, gonococci, streptococci, salmonella, *Mycobacterium tuberculosis* and others. In addition, some resistant bacteria are able to transfer copies of DNA that codes for a mechanism of resistance to other bacteria, thereby conferring resistance to their neighbors, which then are also able to pass on the resistant gene. This process is called horizontal gene transfer.To limit the development of antibiotic resistance, one should:

- Use antibiotics only for bacterial infections
- Identify the causative organism if possible
- Use the right antibiotic; do not rely on broad-range antibiotics
- Not stop antibiotics as soon as symptoms improve; finish the full course
- Not use antibiotics for most colds, coughs, bronchitis, sinus infections, and eye infections, which are caused by viruses.

It is argued that government legislation will aid in educating the public on the importance of restrictive use of antibiotics, not only for human clinical use but also for treating animals

raised for human consumption. As an alternative to antibiotics, destroying the resistant bacteria can often still be archeived by using specific bacteriophage (virus that kill bacteria).

Multiple drug resistance 2

Neoplastic resistance

Cancer cells also have the ability to become resistant to multiple different drugs, and share many of the same mechanisms:

- **Increased efflux of drug** (as by P-glycoprotein, multidrug resistance-associated protein, lung resistance-related protein, and breast cancer resistance protein & reproductive cancer resistance protein)
- Enzymatic deactivation (i.e., glutathione conjugation)
- Decreased permeability (drugs cannot enter the cell)
- Altered binding-sites
- Alternate metabolic pathways (the cancer compensates for the effect of the drug).

Because efflux is a significant contributor for multidrug resistance in cancer cells, current research is aimed at blocking specific efflux mechanisms. Treatment of cancer is complicated by the fact that there is such a variety of different DNA mutations that cause or contribute to tumor formation, as well as myriad mechanisms by which cells resist drugs. There are also certain notable differences between antibiotic drugs and antineoplastic (anticancer) drugs that complicate designing antineoplastic agents. Antibiotics are designed to target sites that are specific and unique to bacteria, thereby harming bacteria without harming host cells. Cancer cells, on the other hand, are altered human cells; therefore they are much more difficult to damage without also damaging healthy cells.

Antifungal resistance

Scedosporium prolificans infections are almost uniformly fatal because of their resistance to antifungal agents and Combatting increasing resistance.

Assay

Assay is the estimation of the amount or the activity of an active principle in a unit quantity of the preparation. It can be:

- Chemical

- Biological or
- Immunological

I. Chemical assay:

In this assay the mass concentration of the active principle is estimated by means of a chemical method, e.g, the salicylates, sulfonamides, and many others. It is the most commonly used procedure. The useful techniques are spectrophotometry, flurometry, gas chromatography, mass spectrometry and high pressure liquid chromatography.

II. Bioassay:

Bioassay or biological standardization is a type of scientific experiment. A bioassay involves the use of live animal or plant (*in vivo*) or tissue or cell (*in vitro*) to determine the biological activity of a substance, such as a hormone or drug. Bioassays are typically conducted to measure the effects of a substance on a living organism and are essential in the development of new drugs and in monitoring environmental pollutants. Both are procedures by which the potency or the nature of a substance is estimated by studying its effects on living matter. A bioassay can also be used to determine the concentration of a particular constitution of a mixture that may cause harmful effects on organisms or the environment.

Types

Bioassays are of two types:

- **Quantal:** A quantal assay involves an "all or none response".
- **Graded:** Graded assays are based on the observation that there is a proportionate increase in the observed response following an increase in the concentration or dose. The parameters employed in such bioassays are based on the nature of the effect the substance is expected to produce. For example: contraction of smooth muscle preparation for assaying histamine or the study of blood pressure response in case of adrenaline.

A graded bioassay can be performed by employing any of the below-mentioned techniques. The choice of procedure depends on:

- The precision of the assay required
- The quantity of the sample substance available
- The availability of the experimental animals.

Methods of bioassay

1. Matching Bioassay
2. Interpolation Method
3. Bracketing Method
4. Multiple Point Bioassay (i.e.-Three-point, Four-point and Six Point Bioassay)
5. Divided bioassay

Matching Bioassay: It is the simplest type of the bioassay. In this type of bioassay, response of the test substance taken first and the observed response is tried to match with the standard response. Several responses of the standard drug are recorded till a close matching point to that of the test substance is observed. A corresponding concentration is thus calculated. This assay is applied when the sample size is too small. Since the assay does not involve the recording of concentration response curve, the sensitivity of the preparation is not taken into consideration. Therefore, precision and reliability is not very good.

Interpolation bioassay: Bioassays are conducted by determining the amount of preparation of unknown potency required to produce a definite effect on suitable test animals or organs or tissue under standard conditions. This effect is compared with that of a standard. Thus the amount of the test substance required to produce the same biological effect as a given quantity the unit of a standard preparation is compared and the potency of the unknown is expressed as a % of that of the standard by employing a simple formula.

Many times, a reliable result cannot be obtained using this calculation. Therefore it may be necessary to adopt more precise methods of calculating potency based upon observations of relative, but not necessarily equal effects, likewise, statistical methods may also be employed. The data (obtained from either of assay techniques used) on which bioassay are based may be classified as quantal or graded response. Both these depend ultimately on plotting or making assumption concerning the form of DRC.

Environmental bioassays: Environmental bioassays are generally a broad-range survey of toxicity. A toxicity identification evaluation is conducted to determine what the relevant toxicants are. Although bioassays are beneficial in determining the biological activity within an organism, they can often be time-consuming and laborious. Organism-specific factors may result

in data that is not applicable to others in that species. For these reasons, other biological techniques are often employed, including radioimmunoassays.

Water pollution control requirements in the United States require some industrial dischargers and municipal sewage treatment plants to conduct bioassays. These procedures, called whole effluent toxicity tests, include acute toxicity tests as well as chronic test methods. The methods involve exposing living aquatic organisms to samples of wastewater. For example the bioassay ECOTOX uses the microalgae *Euglena gracilis* to test the toxicity of water samples.

Importance of Bioassay:

Bioassays, as compared to other methods of assays (e.g. chemical or physical assay) are less accurate, less elaborate, more laborious, more troublesome and more expensive.

1. Active principle of drug is unknown or cannot be isolated, e.g. insulin, posterior pituitary extract etc.
2. Chemical method is either not available or if available, it is too complex and insensitive or requires higher dose e.g. insulin, acetylcholine.
3. Chemical composition is not known, e.g. long acting thyroid stimulants.
4. Chemical composition of drug differs but have the same pharmacological action and vice-versa, e.g. cardiac glycosides, catecholamines etc.

Moreover, even if chemical methods are available and the results of bioassay conflict with those of the chemical assay, the bioassay is relied upon and not the chemical assay, since it is the assessment on living organism. From the clinical point of view, bioassay may help in the diagnosis of various conditions, e.g. gonadotrophins for pregnancy.

III. Immuno assay:

An immunoassay is a biochemical test that measures the presence or concentration of a macromolecule in a solution through the use of an antibody or immunoglobulin. The macromolecule detected by the immunoassay is often referred to as an "analyte" and is in many cases a protein. Analytes in biological liquids such as serum or urine are frequently measured using immunoassays for medical and research purposes.

Principle:

Immunoassays rely on the ability of an antibody to recognize and bind a specific macromolecule in what might be a complex mixture of macromolecules. In immunology the

particular macromolecule bound by an antibody is referred to as an antigen and the area on an antigen to which the antibody binds is called an epitope. In some cases an immunoassay may use an antigen to detect for the presence of antibodies, which recognize that antigen, in a solution. In other words, in some immunoassays, the analyte may be an antibody rather than an antigen.

In addition to the binding of an antibody to its antigen, the other key feature of all immunoassays is a means to produce a measurable signal in response to the binding. Most, though not all, immunoassays involve chemically linking antibodies or antigens with some kind of detectable label. A large number of labels exist in modern immunoassays, and they allow for detection through different means. Many labels are detectable because they either emit radiation, produce a color change in a solution, fluoresce under light, or because they can be induced to emit light.

Methods of Immuno assay:

One of the widely used method is Radio immuno assay (RIA). Radioimmunoassay is a very sensitive in vitro assay technique used to measure concentrations of antigens (for example, hormone levels in the blood) by use of antibodies. As such, it can be seen as the inverse of a radiobinding assay, which quantifies an antibody by use of corresponding antigens. Although the RIA technique is extremely sensitive and extremely specific, requiring specialized equipment, it remains among the least expensive methods to perform such measurements. It requires special precautions and licensing, since radioactive substances are used. The RAST test (radioallergosorbent test) is an example of radioimmunoassay. It is used to detect the causative allergen for an allergy.

A radioimmunoassay, a known quantity of an antigen is made radioactive, frequently by labeling it with gamma-radioactive isotopes of iodine, such as 125-I, attached to tyrosine. This radiolabeled antigen is then mixed with a known amount of antibody for that antigen, and as a result, the two specifically bind to one another. Then, a sample of serum from a patient containing an unknown quantity of that same antigen is added. This causes the unlabeled antigen from the serum to compete with the radiolabeled antigen for antibody binding sites. As the concentration of unlabeled antigen is increased, more of it binds to the antibody, displacing the radiolabeled variant, and reducing the ratio of antibody-bound radiolabeled antigen to free radiolabeled antigen. The bound antigens are then separated from the unbound ones, and the

radioactivity of the free antigen remaining in the supernatant is measured using a gamma counter.

Chemotherapy

Chemotherapy (sometimes cancer chemotherapy) is the treatment of cancer with an antineoplastic drug or with a combination of such drugs into a standardized treatment regimen. Most commonly, chemotherapy acts by killing cells that divide rapidly, one of the main properties of most cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles; this results in the most common side effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss). Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy and is technically not chemotherapy.

ANTIMICROBIAL DRUG

SULFONAMlDES

(SULFONAMlDES are the antimicrobial compounds containing a sulfonamido ($S0_2NH_2$) group) This group is also present in other non-antibacterial compounds like the antidiabetic sulfnonylureas, diuretics like benzothiazide and their congeners furosemide and acetazolamide, and anticonvulsants like sulthiame.

The sulfonamides are white, powders, mildly acidic in character. They form water soluble salts with bases. The pH of the sodium salts, with some exception, eg., sodium sulfacetamide is very high; given 1M, their marked alkalinity causes damage to the tissues.

Classification:

The sulfonamides can be classifed according to their therapeutic utility as:

- Those employed for the treatment of systemic infections. Depending upon their duration of action, they are subdivided into:

Short acting: Sulfadiazine, Sulfadimidine Sulfacetamide, Sulfgfsrazone (sulfisoxazole), and Sulfamethizole.

Intermediate acting: Sulfamethoxazole.

Long acting like Sulfamethoxypyridazine, Sulfadimethoxine, Sui formethoxine. Their use as single agents in therapy is discouraged because of their association with severe allergic reactions

such as Stevens-Johnson syndrome. However, some of them are used ascombination drugs in malaria

- Those employed orally for the treatment of ulcerative colitis: Sulfasalazine.
- Those used topically: Mafenide; Silver sulfadiazine; Sulfacetamide.

Pharmacological actions: They are effective against a variety of Gram positive and Gram negative organisms and certain chlamydia; these are:

(a) Streptococci, Staphylococci (some strains), Gonococci, Pneumococci and Meningococci.) Streptococcus fecalis is resistant.

(b) *Clostridia, Bacillus anthracis*.

(c) *Haemoph ilus influenzae, H. ducreyi, Vibrio comma, E. coli, pastuerella pestis, Shigella, Donovania granulomatosis.*

(d) Nocardia and *Actinomyces.*

(e) Chlamydia organisms causing lympho- granuloma venereum, *psittacosis* and trachoma.

(f) In combination with drugs that inhibit folic acid synthesis, sulfonamides are effective inmalaria and in toxoplasmosis.

They are mainly but occasionally, in very high concentrations, particularly in the urinary tract, they may act as bactericidal compounds.j Their clinical efficacy and potency are much less than those of antibiotics. Thus, the minimum inhibitory concentration of sulfonamides for a highly susceptible bacterial strain. is 1 : 10,000 to 1 : 20,000, in comparison to 1: 50 million observed with penicillin. Mechanism of action: The compound sulfanilamide exhibits a structural similarity to para-aminobenzoic acid (PABA). Sulfonamides,byvirtueof their structural similarity to PABA, compete with and substitute for the latter in the bacterial metabolism Folic acid derived from PABA is important in bacterial metabolism. Sulfonamides inhibit the enzyme folic acid synthetase which is involved in the conversion of PABA to folic acidrff ig. 42.3): This causes folic acid deficiency resulting in injury to the bacterial cell. Such an injured or disruptedbacterial cellcan be easily phagocytosed. Sulfonamides are ineffective in the presence of pus and tissuebreakdown products which contain large amounts of. PABA:. The bacteriostatic actionof sulfonamides can be countered by PABA: and sulfonamide resistant microorganismsoften show enhanced PABA synthesis. This theory, however, cannot explain tne

antibacterial action of mafenide hydrochloride. The antibacterial action of this compound is not antagonized by PABA.

Sulfonamide resistance:

A variety of micro-organisms, such as *Staphylococci, Streptococci, Pneumococci, Meningococci, Gonococci* and *E. coli* can acquire resistance to sulfonamides. Resistance in all enterobacteria is now common, and in *Shigella sonnei* it is almost invariable. Resistancecan be chromosomally mediated or transferred by 'R' factors. Some of the resistant strains synthesize a folic acid synthetase with a lowered affinity for sulfonamides while some others overproduce PABA. Widespread bacterial resistance to sulfonamides now limits their clinical usefulness.

Absorption, fate and excretion:

Sulfonamides intended for systemic use are rapidly absorbed from the gastrointestinal tract, and 70 to 90 per cent of the oral dose reaches the blood stream. The main site of absorption is the small intestine. The absorption of sulfonamides from other sites like the abraded skin, respiratory tract and vagina is variable, but sufficient amounts may be absorbed from these sites to produce sensitization and even toxicity. In the blood, these drugs are loosely bound to plasma proteins, particularly albumin. The degree of binding differs among the various compounds. In general, at least 50 per cent of the compound is bound to plasma proteins.

Protein binding of sulfonamides is important for several reasons:

- The bound sulfonamide has much less of bacteriostatic activity and cannot normally pass into tissue fluids or cross the blood brain barrier.
- Since the bound form is not available for renal excretion, protein binding helps to prolong the action of sulfonamides. The long acting sulfonamides are long acting because they are extensively bound to plasma proteins and are excreted slowly.
- The highly protein bound sulfon amides are not so effective in tire treatment of acute infections.

The free form of sulfonamides is uniformly distributed throughout all the tissue fluids although the concentration in the tissue fluids is usually lower than in the plasma. Sulfadiazine, because of relatively lower degree of binding with plasma proteins, achieves a CSf concentration 50 to 80 per cent that of the plasma levels and therefore, is superior to other sulfonamides in the treatment of meningococcal meningitis. In practice, however, adequate CSF concentration is achieved with

majority of the short acting sulfonamides given orally. These drugs readily cross the placental barrier, the foetal concentrations being approximately equivalent to maternal blood levels. They are also secreted in milk.

Preparations and dosage:

Short acting (5-6 hours) Sulfisoxazole (Sulfafurazole, Gantrisin): Highly soluble;urinary concentration greatly exceeds the plasma concentration and may be bactericidal. Dose: Initial 1-2 gm, then 0.5-1 grm 12 hourly.

Intermediate acting (10-12 hours)

(i) Sulfadiazine : Good penetration into CSF. Can cause crystalluria. Tab 500 mg. Dose: 150mg/kg/ 24 hrs. in 4-6 divided doses. Injection 250 mg/rnl in 10 ml ampoules. Dose (in adults) by slow, IV injection, 100 mg/kg body weight, 2gm initially, then 30-50 mg /kg 6-8 hourly.The solution is strongly alkaline.

(ii) Sulfadimidine: Acetyl derivative relatively more soluble in urine. Dose: similar to that of oral sulfadiazine.

(iii) Sulfamethoxazole (Gantanol): Used only as a component of cotrimoxozole.

Long acting (7- 9 days) Sulformethoxine (Sulfadoxine): Plasma l2 150-200 hrs.Used only in combination in malaria.

Used in Bowel disease: Sulfalazine (Salazopyrine)

Used topically

(i) Mafenide propionate (Marfanil): Prevents colonization of burns by gram positive and gram negative bacteria. Not so effective after infection is established.Used in 1% methyl cellulose and as 10% cream.

(ii) Silver sulfadiazine: Silver released slowly is toxic to nearly all pathogens. Other properties same as those of mafenide propionate.Used as 1% cream.

(iii) Sulfacetamide (Albucid): sodium salt has almost neutral pH and better penetration into tissues.Used as 6% eye ointment and 10% eye drops.

Adverse reactions: Unfortunately, there is a tendency to exaggerate the ill-effects of sulfonamides which are still valuable in therapeutics. However, the toxic potential of these drugs should be remembered and their indiscriminate use avoided.

Allergy: This can occur at any time during the drug administration. The commonest allergic symptoms are drug fever, skin rash, usually morbilliform in type -and eosinophilia. The rash is often accompanied by conjunctivitis. Rarely, severe exfoliative dermatitis and high fever may develop. Sulfonamide drug fever usually disappears within 72 hours of discontinuation of the medication. Serum sickness, characterised by ever, joint pains, urticaria, bronchospasm and 1euopenia sometimes develops within the I st or 2nd week after commencement of therapy. The uncommon allergic mani festations include cutaneous photosensitization, a fatal necrotizing aJteritis resembling polyarteritis nodosa, acute toxic hepatitis and rarely fatal hepatic necrosis, toxic nephrosis, and acute haemolytic anemia.

A severe exudative type of erythema multifonne, associated with widespread lesions of the skin and mucous membranes, termed Stevens Johnson syndrome, has been reported with long acting sulfonamides. The syndrome, which is fortunately rare, is usually self-limiting but can occasionally be fatal. Cross sensitivity among various sulfonamides and between sulfonamides and other drugs containing the sulfonamido group such as diuretics is known. Local application of sulfonamides to skin is discouraged as it may sensitize the patient.

GI symptoms: They commonly produce nausea and vomiting, but these are rarely troublesome. In spite of their wide antibacterial range, unlike the broad spectrum antibiotics, sulfonamides do not usually produce troublesome disturbances in the gut flora. Treatment for 14 days or less with conventional doses rarely gives rise to troublesome reactions.

Renal toxicity: In the presence of acid urine, form of the drug may be precipitated, mainly in-the collecting tubules and the calyces. This causes renal irritation, obstruction to the urine flow and haerriaturia can occur, leading to the development of oliguria and anuria. These renal complications can be minimised by:

- Ensuring an adequate output (one litre or more) of urine.
- Making the urine alkaline with the use of an alkaline mixture, to increase the solubility of the conjugation products.
- Use of sulfonamides whose acetylated metabolites are soluble in acid urine. Renal damage with tubular necrosis and vasculitis can also occur as an allergic reaction.

Haemopoietic toxicity:

The haemopoietic toxicity includes agranulQcytosis, thrombo-cytopenia causing petechiae, hematuriararely aplastic 'anemia. Sulfo'i1amttlCs;-like many other drugs, tend to oxidize hemoglobin to methemoglobin. In patients with G6PD deficiency, these compounds may cause intravascular hemolysis.

Bilirubin metabolism:

Sulfonamides compete with serum bilirubin for albumin "binding sites. Adminisfered during late pregnancy, they may displace bilirubin from albumin binding sitesin -the foetus. The free bilirubin, by crossing the blood-brain barrier, which is permeable to bilirubin only in foetuses and infants, causes kernicterus. Sulfonamides may also cause Kemicterus when administered to new born and premature infants, particularly in those with G6PD deficiency. They-should not be given to neonates, and to pregnant women when there is a possibility of Rh incompatibility and premature delivery.

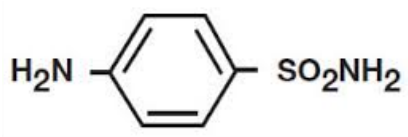
Table 42.3: Interactions of sulfonamides

Interfering drug	Result
Sulfonylureas	ID displaced from plasm protein binding, with possible
Coumarin anticogu-lants, methotrexate, phenytoin, thiopental	10 activity enhanced
Phenylbutazone, salicylate, probenecid	S displaced from plasma binding, with ment of S activity
Methenemine	Certain S are preci-pitated in urine
PABA-containing local anaesthetics (procaine)	Direct inhibition of S activity

ID = Interfering drug; S = Sulfonamide

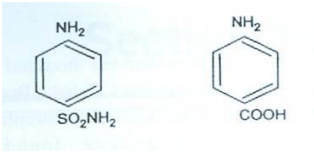
Sulfonamides

Sulfonamides are the oldest and remain among the most widely used antibacterial agents in veterinary medicine, chiefly because of low cost and their relative efficacy in some common bacterial diseases. The synergistic action of sulfonamides with specific diaminopyrimidines renders these drugs much more effective compared to sulfonamides alone.



Classes

The many available sulfonamides and sulfonamide derivatives can be categorized into several types, based mainly on their indications and duration of action in the body.



General properties

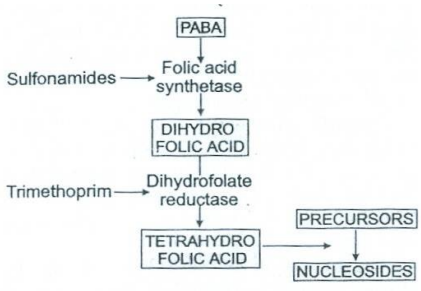
The sulfonamides are derivatives of sulfanilamide. All have the same nucleus to which various functional groups have been added to the amido group or in which various substitutions on the amino group are made. These changes produce compounds with varying physical, chemical, pharmacologic, and antibacterial properties. Although amphoteric, sulfonamides generally behave as weak organic acids and are much more soluble in an alkaline than in an acidic environment. Those of therapeutic interest have pK_a values of 4.8–8.6. Water-soluble sodium or disodium salts are used for parenteral administration. Such solutions are highly alkaline, somewhat unstable, and readily precipitate with the addition of polyionic electrolytes. In a mixture of sulfonamides (eg, the sulfa-pyrimidine group), each component drug has its own solubility; therefore, a combination of sulfonamides is more water-soluble than a single drug at the same total concentration. This is the basis of triple sulfonamide mixtures used clinically. The N-4 acetylated sulfonamides, except for the sulfapyrimidine group (sulfamethazine, sulfa-merazine, sulfadiazine), are less water-soluble than their non-acetylated forms. This has bearing in the development of sulfonamide crystalluria. The highly insoluble sulfonamides (phthalylsulfathiazole and succinylsulfathiazole) are retained in the lumen of the GI tract for prolonged periods and are known as "gut-active" sulfonamides.

Mode of Action

The sulfonamides are structural analogs of para-aminobenzoic acid (PABA) and competitively inhibit dihydropterate synthetase, an enzyme that facilitates PABA as a substrate for the synthesis of dihydrofolic acid (folic acid). Dihydrofolate is a precursor for formation of

tetrahydrofolate (folinic acid), an essential component of the coenzymes responsible for single carbon metabolism in cells. Sulfonamides are antimetabolites that substitute for PABA, resulting in blockade of several enzymes needed for the biogenesis of purine bases; for the transfer of desoxy-uridine to thymidine; and for the biosynthesis of methionine, glycine, and formylmethionyl-transfer-RNA. Protein synthesis, metabolic processes, and inhibition of growth and replication occur in organisms that cannot use preformed (eg, dietary) folate. The effect is bacteriostatic, although a bactericidal action is evident at the high concentrations that may be found in urine.

Sulfonamides are most effective in the early stages of acute infections when organisms are rapidly multiplying. They are not active against quiescent bacteria. Typically, there is a latent period before the effects of sulfonamide therapy become evident. This lag period occurs because the bacteria use existing stores of folic acid, folinic acid, purines, thymidine, and amino acids. Once these stores are depleted, bacteriostasis occurs. Bacterial growth can resume when the concentration of PABA increases or when the level of sulfonamide falls below an enzyme-inhibitory concentration. Because of the bacteriostatic nature of sulfonamides, adequate cellular and humoral defense mechanisms are critical for successful sulfonamide therapy.



The efficacy of sulfonamides can be reduced radically by excess PABA, folic acid, thymine, purine, methionine, plasma, blood, albumin, tissue autolysates, and endogenous protein-degradation products.

Bacterial Resistance

Both chromosomal and R-factor-mediated resistance to sulfonamides have been attributed to altered forms of dihydropterate synthetase (for which sulfonamides have a lowered affinity). Because sulfonamides act in a competitive fashion, overproduction of PABA can preclude inhibition of dihydropterate synthetase. Cross-resistance between sulfonamides is

common. Resistance emerges gradually and is widespread in many animal populations. Plasmid-mediated sulfonamide resistance in intestinal gram-negative bacteria is often linked with ampicillin and tetracycline resistance.

Antimicrobial Spectrum

The spectrum of all sulfonamides is generally the same. Sulfonamides inhibit both gram-positive and gram-negative bacteria, *Nocardia*, *Actinomyces spp*, and some protozoa such as coccidia and*Toxoplasma spp*. More active sulfonamides may include several species of *Streptococcus*,*Staphylococcus*, *Salmonella*, *Pasteurella*, and even *Escherichia coli* in their spectra. Strains of *Pseudomonas*, *Klebsiella*, *Proteus*, *Clostridium*, and *Leptospira spp* are most often highly resistant, as are rickettsiae, mycoplasmas, and most *Chlamydia*.

Pharmacokinetic features

There are notable differences among the many sulfonamides with respect to their pharmacokinetic fate in the various species. The standard classification of short-, medium-, and long-acting sulfonamides that is used in human therapeutics is usually inappropriate in veterinary medicine because of species differences in disposition and elimination.

Absorption

Sulfonamides may be administered PO, IV, IP, IM, intrauterine, or topically, depending on the specific preparation. Except for the poorly absorbed sulfonamides intended for intestinal use, most are rather rapidly and completely absorbed from the GI tract of monogastric animals. Absorption from the ruminoreticulum is delayed, especially if ruminal stasis is present. Therapeutic doses of sulfonamides are usually administered PO except in acute life-threatening infections when IV infusions are used to establish adequate blood concentrations as rapidly as possible. Sulfonamides are frequently added to drinking water or feed either for therapeutic purposes or to improve feed efficiency. A few highly water-soluble preparations may be injected IM (eg, sodium sulfadimethoxine) or IP (some irritation of the peritoneum can be seen). Absorption is rapid from these parenteral sites. Generally, sulfonamide solutions are too alkaline for routine parenteral use.

Distribution

Sulfonamides are distributed throughout all body tissues. The distribution pattern depends on the ionization state of the sulfonamide, the vascularity of specific tissues, the

presence of specific barriers to sulfonamide diffusion, and the fraction of the administered dose bound to plasma proteins. The unbound drug fraction is freely diffusible. Sulfonamides are bound to plasma proteins to a greater or lesser extent, and concentrations in pleural, peritoneal, synovial, and ocular fluids may be 50–90% of that in blood. Sulfadiazine is 90% or more bound to plasma proteins. Concentrations in the kidneys exceed plasma concentrations, and those in the skin, liver, and lungs are only slightly less than the corresponding plasma concentrations. Concentrations in muscle and bone are ~50% of those in the plasma, and those in the CSF may be 20–80% of blood concentrations, depending on the particular sulfonamide. Low concentrations are found in adipose tissue. After parenteral administration, sulfamethazine is found in jejunal and colonic contents at about the same concentration as in blood. Passive diffusion into milk also occurs; although the concentrations achieved are usually inadequate to control infections, sulfonamide residues may be detected in milk.

Biotransformation

Sulfonamides are usually extensively metabolized, mainly by several oxidative pathways, acetylation, and conjugation with sulfate or glucuronic acid. Species differences are marked in this regard. The acetylated, hydroxylated, and conjugated forms have little antibacterial activity. Acetylation (poorly developed in dogs) reduces the solubility of most sulfonamides except for the sulfapyrimidine group. The hydroxylated and conjugated forms are less likely to precipitate in urine.

Excretion

Most sulfonamides are excreted primarily in the urine. Bile, feces, milk, and sweat are excretory routes of lesser significance. Glomerular filtration, active tubular secretion, and tubular reabsorption are the main processes involved. The proportion reabsorbed is influenced by the inherent lipid solubility of individual sulfonamides and their metabolites and by urinary pH. Urinary pH, renal clearance, and the concentration and solubility of the respective sulfonamides and their metabolites determine whether solubilities are exceeded and crystals precipitate. This can be prevented by alkalinizing the urine, increasing fluid intake, reducing dose rates in renal insufficiency, and using triple-sulfonamide or sulfonamide-diaminopyrimidine combinations.

Therapeutic Indications and Dose Rates

The sulfonamides are commonly used to treat or prevent acute systemic or local infections. Disease syndromes treated with sulfonamides include actinobacillosis, coccidiosis, mastitis, metritis, colibacillosis, pododermatitis, polyarthritis, respiratory infections, and toxoplasmosis.

Sulfonamides are more effective when administered early in the course of a disease. Chronic infections, particularly with large amounts of exudate or tissue debris present, often are not responsive. In severe infections, the initial dose should be administered IV to reduce the lag time between dose and effect. For drugs with a long elimination half-life, the initial dose should be double the maintenance dose. Adequate drinking water should be available at all times, and urine output monitored. A course of treatment should not exceed 7 days under usual circumstances. If a favorable response is seen within 72 hr, treatment should be continued for 48 hr after remission to prevent relapse and the emergence of resistance. The ability to mount an immune response must be intact for successful sulfonamide therapy.

Adverse Effects and Toxicity

Adverse reactions to sulfonamides may be due to hypersensitivity or direct toxic effects. Possible hypersensitivity reactions include urticaria, angioedema, anaphylaxis, skin rashes, drug fever, polyarthritis, hemolytic anemia, and agranulocytosis. Crystalluria with hematuria, and even tubular obstruction, is not common in veterinary medicine. Acute toxic manifestations may be seen after too rapid IV administration or if an excessive dose is injected. Clinical signs include muscle weakness, ataxia, blindness, and collapse. GI disturbances, in addition to nausea and vomiting, may occur when sulfonamide concentrations are sufficiently high in the tract to disturb normal micro-floral balance and vitamin B synthesis. Sulfonamides depress the cellulolytic function of ruminal microflora, but the effect is usually transient (unless excessively high concentrations are reached). Several adverse effects have been reported after prolonged treatment, including bone marrow depression (aplastic anemia, granulocytopenia, thrombocytopenia), hepatitis and icterus, peripheral neuritis and myelin degeneration in the spinal cord and peripheral nerves, photosensitization, stomatitis, conjunctivitis, and keratitis sicca. Mild follicular thyroid hyperplasia may be associated with prolonged administration of sulfonamides in sensitive species such as dogs, and reversible hypothyroidism can be induced

after treatment with high doses in dogs. Several sulfonamides can lead to decreased egg production and growth. Topically, the sulfonamides retard healing of uncontaminated wounds.

Interactions

Sulfonamide solutions are incompatible with calcium- or other polyionic-containing fluids as well as many other preparations. Sulfonamides may be displaced from their plasma-protein-binding sites by other acidic drugs with higher binding affinities. Antacids tend to inhibit the GI absorption of sulfonamides. Alkalinization of the urine promotes sulfonamide excretion, and urinary acidification increases the risk of crystalluria. Some sulfonamides act as microsomal enzyme inhibitors, which may lead to toxic manifestations of concurrently administered drugs such as phenytoin.

Penicillin

In 1929 Alexander Fleming, a British biologist, inadvertently discovered penicillin. He had observed bacterial *Staphylococci* colonies disappearing in cultures that were contaminated with mold.

Fleming eventually extracted the compound from the mold that had been responsible for destruction of the bacterial colonies. The product was named penicillin, after the *Penicillium* mold from which it was derived.

Penicillin is the earliest antibiotic drug which was made to prevent bacterial infections. Originally, this drug was obtained from the Penicillium fungi. Today this is no longer just one drug but a class of drugs having many different variants in them such as penicillin G, procaine penicillin, benzathine penicillin, penicillin V and many more. Penicillins have been used for a long time and therefore there are many strains of bacteria which have become more resistant to this antibiotic. The variations in the different penicillin drugs try to combat these resistant strains of the bacteria.

Some examples of penicillins include:

- amoxicillin
- ampicillin
- bacampicillin
- oxacillin
- penicillin

Mode of Action

Structurally, penicillins are β-lactam antibiotics. Bacterial cell walls are consisting of a protective peptidoglycan layer, which is continuously undergoing remodeling. The remodelling process involves the breaking of the β-(1,4) linked N-acetylmuramic acid and N-acetylglucosamine; as well as the breaking of the cross-linking peptide chains. This cross-linking peptide chains is what provides the rigidity, to the otherwise fluid cell wall. The breaking of this peptide cross-linking is performed by an enzyme called transpeptidase. The transpeptidase also helps in reforming the peptide bonds once the restructuring of the cell wall is done. The penicillins act by inhibiting this particular enzyme. By inhibiting this enzyme the penicillin prevents the reformation of the peptide bonds and thus makes the cell wall less strong. This loss of cell wall integrity causes the bacteria to leak out its cellular contents and perish.

This beta-lactam ring of the penicillin is generally not very stable and therefore it participates in the inactivation of bacterial cell enzymes which are essential for synthesis of peptidoglycan. Transpeptidase attacks the beta-lactam ring which opens up to give a more stable compound. When this happens the drug remains bound to the transpeptidase via covalent linkage and thereby inhibits the enzyme by acylation of the active site.

The resistance to penicillin arises due to mutations in the active site of the transpeptidase enzyme. Thus there are many variants of the transpeptidase enzyme which need the use of newer penicillin antibiotics.

Penicillins, and other beta-lactam antibiotics, work by interfering with interpeptide linking of peptidoglycan, the a strong, structural molecule found specifically bacterial cell walls. Cell walls without intact peptidoglycan cross-links are structurally weak, prone to collapse and disintegrate when the bacteria attempts to divide. Since the eukaryotic cells of humans do not have cell walls, our cells are not damaged by penicillins.

Antimicrobial Spectrum of Penicillins

Penicillins have a bacteriocidal effect on Gram-positive bacteria. In Gram-positive cells, peptidoglycan makes up as much as 90% of the thick, compact cell wall, and is the outermost layer

Penicillins are not effective against Gram-negative bacteria, which have cell walls in which peptidoglycan is not the outermost layer, but that lies between the plasma membrane and a

lipopolysaccharide (LPS) outer membrane. Penicillin cannot access the peptidoglycan of Gram-negative cells.

Structure of Streptomycin:

Streptomycin is characterised chemically as an aminoglycoside antibiotic. It consists of three components linked glycosidically (by ether bonds):

(i) Streptidine (inositol with two guanido groups),

(ii) Streptose (methyl pentose), and

(iii) Streptoscamine (N-methyl-L-glycosamine) as shown in Fig. 45.9.

Both guanido groups of streptidine are essential for the antibiotic activity and removal of one group reduces antibiotic activity upto 90%.

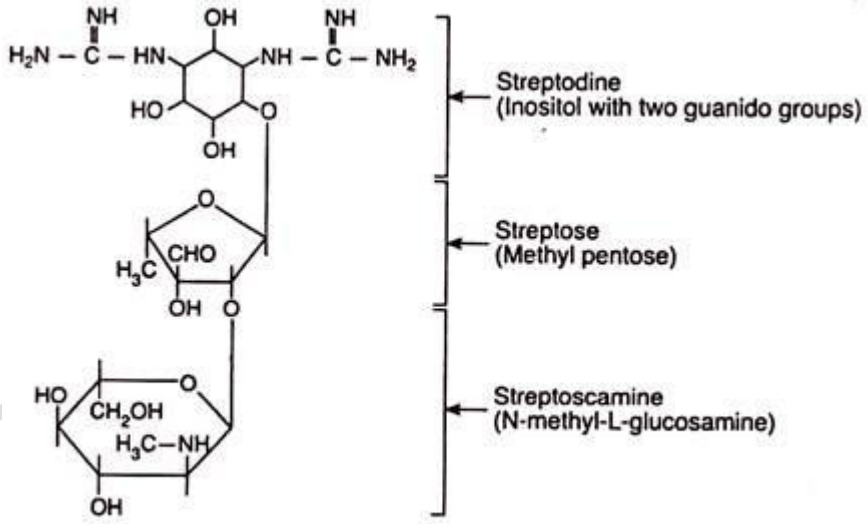


FIG. 45.9. Chemical structure of streptomycin.

Antibiotic Spectrum of Streptomycin:

Streptomycin is bactericidal and broad-spectrum antibiotic. It is active against both gram-positive and gram-negative bacteria. Streptomycin is inhibitory for several species of Mycobacterium and is an effective antibiotic for treatment of tuberculosis caused by M. tuberculosis.

Streptomycin is toxic to humans and other animals and causes side effects such as allergic responses, loss of hearing, nausea, and kidney damage. Highly purified streptomycin is nontoxic when given in small doses, but it appears to have a cumulative detrimental effect on nervous system when, given as a medication over long periods of time.

Mechanism of Action of Streptomycin:

Streptomycin, like other aminoglycosidic antibiotics (e.g., gentamycin, neomycin, kanamycin, tobramycin), inhibits protein synthesis in bacterial cells by binding to the 30S subunit of ribosomes.

By doing so, the streptomycin causes a structural change which interferes with the recognition site of codon-anticodon interaction resulting in misreading of the genetic message carried by messenger RNA (mRNA). The mechanism of inhibition of protein synthesis by streptomycin is schematically shown in Fig. 45.10.

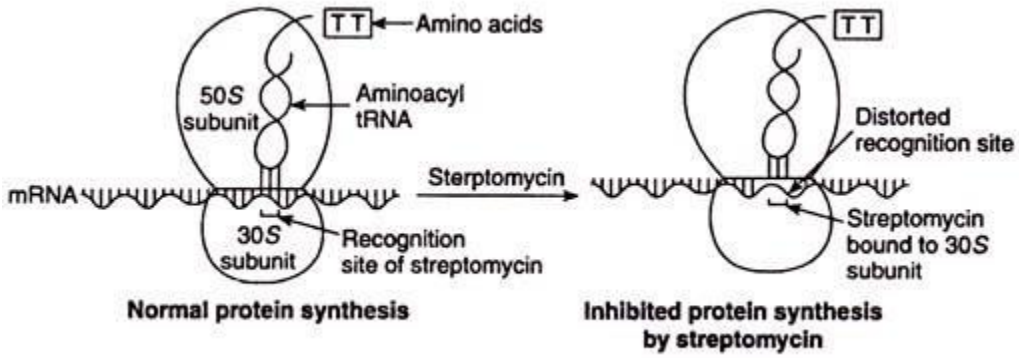


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.

Streptomycin-Dependence:

It has been found that streptomycin-susceptible bacteria may become resistant to the antibiotic by a single step mutation. Such mutation results in a structural alteration in the 30S subunit leading to a loss of affinity for streptomycin, so that the antibiotic can no longer bind its recognition site and inhibit protein synthesis.

A very interesting observation has been made in some streptomycin-resistant mutants and is called streptomycin- dependence. Streptomycin-dependence is thought to develop as a result of another mutation which causes an opposite distortion of the recognition site of the 305 subunit of ribosome.

In streptomycin-dependent mutants of bacterial pathogen, protein synthesis fails to take place in absence of streptomycin. The schematic representation of the mechanism of streptomycin dependence is shown in Fig. 45.11.

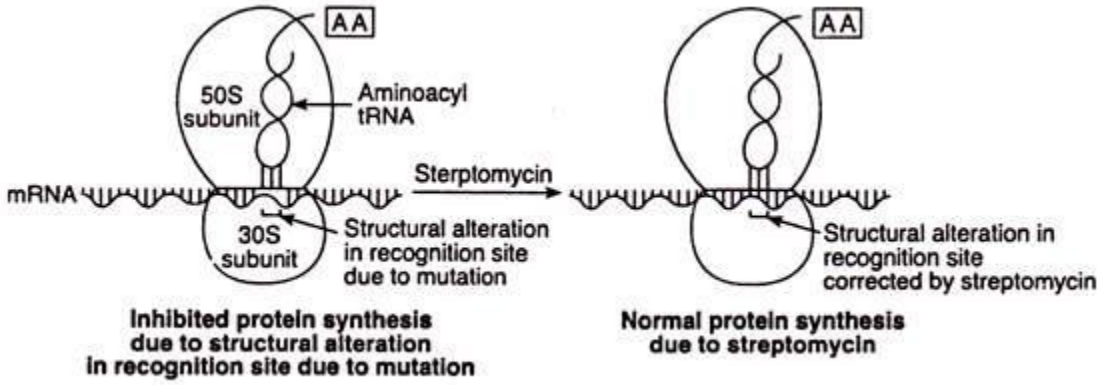


FIG. 45.11. Schematic representation of the mechanism of streptomycin-dependent protein synthesis in mutants.

Tetracycline Antibiotics

Discovered in the lat 1940s, tetracyclines are a family of broad spectrum antibiotics used to treat a wide range of bacterial infections. The original tetracyclines were derived from *Streptomyces* bacteria, but the newer derivatives are semi-synthetic.

Some representative tetracyclines include:

- tetracycline
- doxycycline
- minocycline
- panmycin
- terramycin
- trimocycline

Tetracycline Mode of Action

Tetracyclines exert their bacteriostatic effect by inhibiting protein synthesis in bacteria. This antibiotic prevents transfer-RNA (tRNA) molecules (a type of nucleic acids which transport amino acids) from binding to the 30S subunit of bacterial ribosomes.

It is possible for tetracyclines to inhibit protein synthesis in the eukaryotic cells of the host, but the drug is less likely to reach the required concentrations in humans because eukaryotic cells do not have a tetracycline uptake mechanism.

Antimicrobial Spectrum of Tetracyclines

Tetracyclines are broad spectrum antibiotics which exhibit activity against a wide range of microbes including both Gram-positive (Gram+) and Gram-negative (Gram-) bacteria,

chlamydias, mycoplasmas, rickettsiae, as well as some protozoan parasites.

Type of Infections Tetracyclines Are Used Against

Tetracycline is used to treat many different infections including respiratory tract infections caused by *Hemophilus influenzae, Streptococcus pneumoniae*, or *Mycoplasma pneumoniae*. It also is used for urinary tract infections (UTIs), Rocky Mountain spotted fever, typhus, chancroid, cholera, brucellosis, anthrax, syphilis, lyme disease, acne and may be used concomitantly with other medications against *Helicobacter pylori*, the bacteria associated with stomach ulcers.

Antibiotic Resistance

Because tetracyclines have been around for so long, bacterial resistance is common, and the presence of tetracycline-resistant pathogens limits the use of this class of antibiotic.

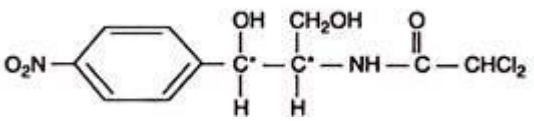
Adverse Effects of Tetracyclines

Side effects may include nausea, diarrhea, and sensitivity to light. Tetracyclines also form complexes with calcium, which can stain the developing teeth of children and affect the strength and shape of bones.Since tetracyclines are active against such a wide range of microbes, destruction of normal intestinal flora often occurs, resulting in increased secondary infections.

Chloramphenicol:

Structure of Chloramphenicol:

Chemically, chloramphenicol is a simple structure (Fig. 45.12) made up of nitrobenzene ring bonded with non-ionic chlorine. It consists of two unusual components—one nitro ($-NO_2$) group and a dichloroacetyl ($-COCHCl_2$) group. The molecule possesses two asymmetric carbon atoms (marked with asterisk in the figure). As a result, four optical isomers of chloramphenicol are possible. Of these isomers, only D (-) threo isomer is antibiotically active.



Antibiotic Spectrum of Chloramphenicol:

Chloramphenicol is bacteriostatic and a broad-spectrum antibiotic active against both gram-positive and gram-negative bacteria including rickettsia (cause of rocky-mountain spotted fever) and chlamydia. It is also found effective against Haemophilus influenzae causing

meningitis.

Chloramphenicol, as mentioned, has a broad-spectrum of activity but unfortunately is quite toxic and causes serious side effects. The most common side effect is a temporary or permanent depression of bone marrow function that results in cessation of formation of blood cells.

This antibiotic has been found to prevent incorporation of haemoglobin by the blood cells, leading to aplastic anaemia. It also causes thrombocytopenia and leucopenia (depletion of platelets and leucocytes). Other side effects are allergic responses or neurotoxic reactions. Thus, chloramphenicol is now used only in life-threatening situations when other suitable drugs are inadequate.

Mechanism of Action of Chloramphenicol:

Chloramphenicol, like many other antibiotics such as streptomycin, gentamicin, tetracycline's, erythromycin, etc. inhibits protein synthesis. It binds to the 23S rRNA on the 50S subunit of bacterial ribosome and inhibits the action of peptidyl transferase enzyme (Fig. 45.13).

Peptidyl transferase transfers the growing polypeptide from the peptidyl tRNA to the amino acid bound to the aminoacyl tRNA leading to formation of a peptide bond and thereby lenthens the polypeptide by one amino acid rest.

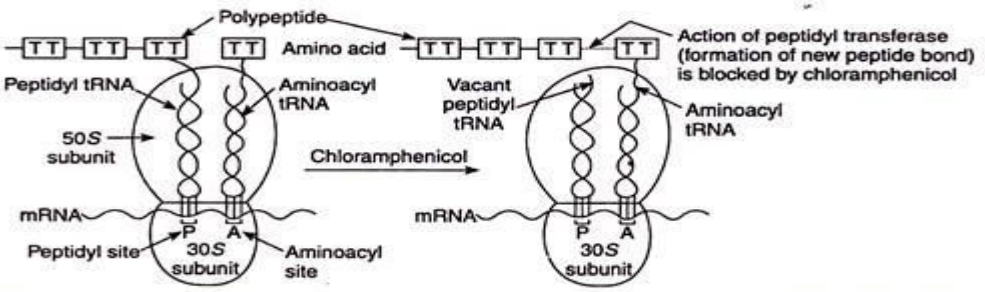


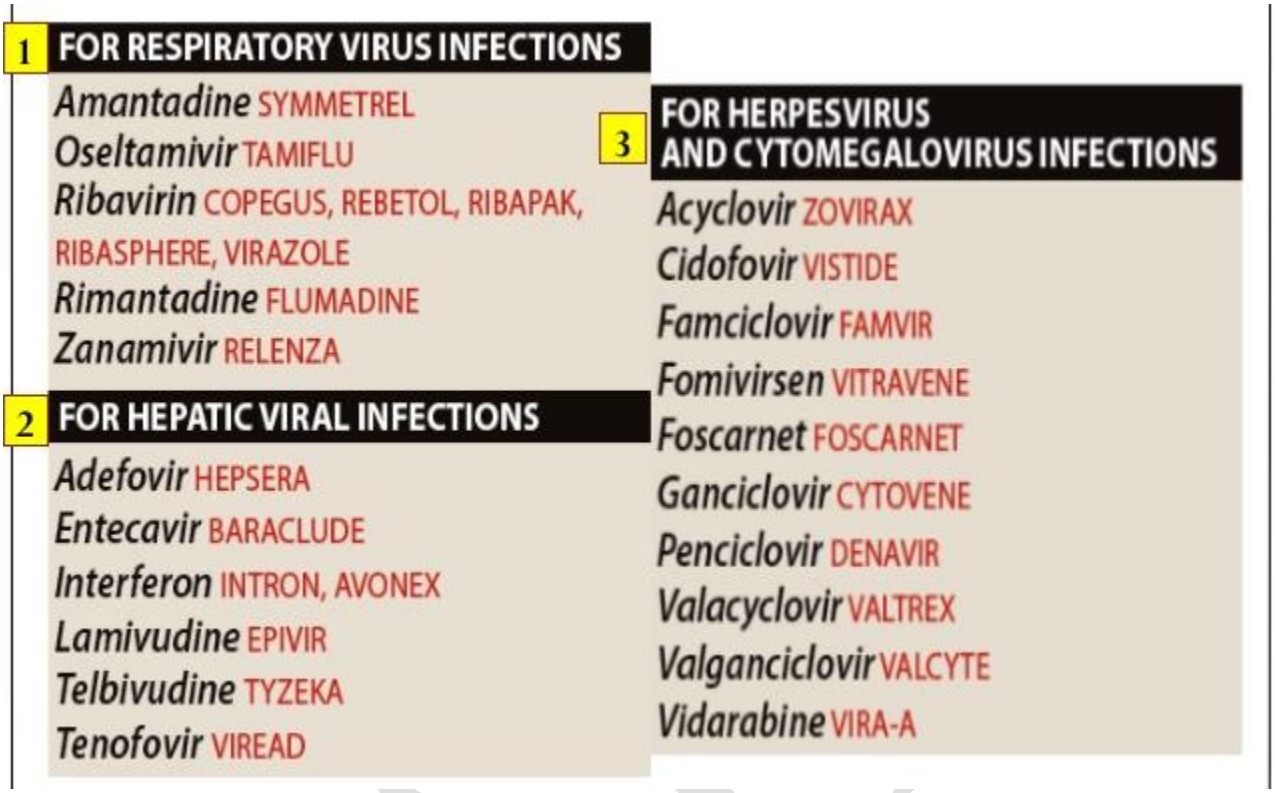
FIG. 45.13. Schematic representation of the inhibitory action of chloramphenicol. Note that the new peptide bond formation between polypeptide and newly transfered amino acid is blocked and as a result growth of polypeptide stops.

Antiviral Drugs

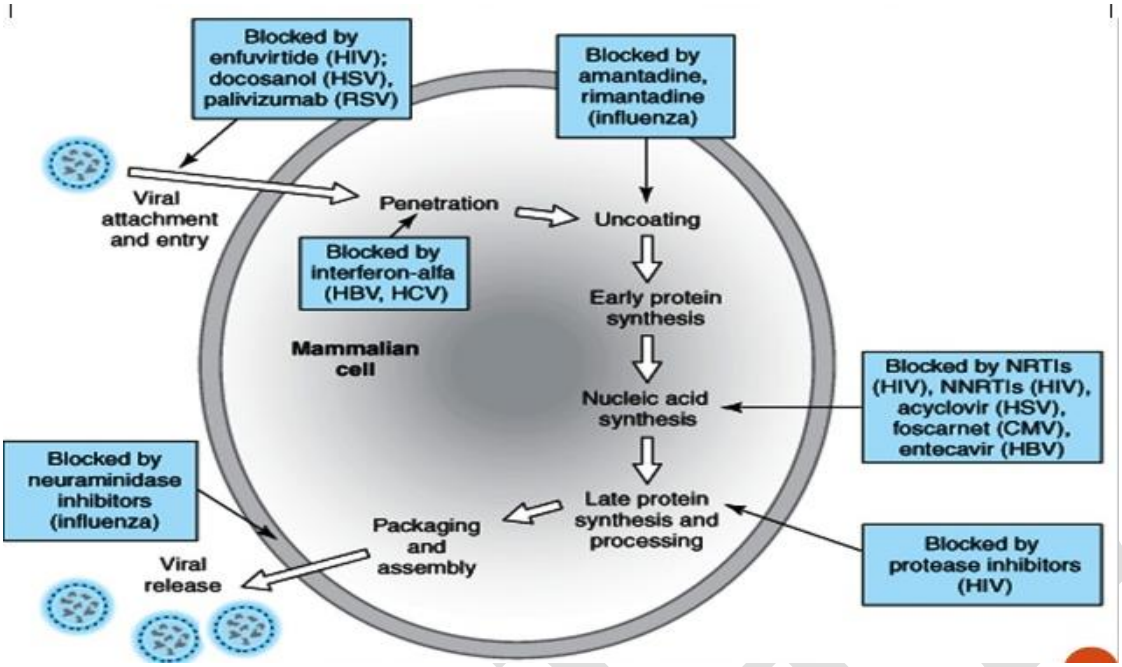
1. Characters of Virus Viruses are obligate intracellular parasites their replication depends primarily on synthetic processes of the host cell.

2.Classification of virus DNA virus RNA virus

Classification of Antiviral Drugs



Mechanism of Antiviral Drugs



Mechanism of selected Antiviral agents

Lamivudine	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1
Oseltamivir	Inhibition of viral neuramidase	Influenza A
Penciclovir	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex
Ribavirin	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with *interferon-α*) RSV in children and infants
Rimantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Valacyclovir	Same as *acyclovir*	Herpes simplex, varicella-zoster, cytomegalovirus
Vidarabine	Inhibits viral DNA synthesis	HSV-1, HSV-2, and VZV; its use is limited to treatment of immunocompromised patients with HSV keratitis
Zanamivir	Inhibition of viral neuramidase	Influenza A

Antifungal drugs

Pathogenic fungi of animals and humans are generally filamentous molds or intracellular yeasts.

• The fungal cell wall contains chitin and polysaccharides making it rigid, and acts as a barrier to drug penetration.
• The cell membrane contains ergosterol, which influences the efficacy and the risk of drug resistance.
• Most antifungal agents are fungistatic with infectionclearance largely dependent on host response.

Classification of antifungal drugs

• **Based on chemical structures:** The classes include Polyene macrolides, Imidazoles, Fluorinated pyrimidines, Benzo-furans and Iodides
• **Based on their sites of action:** Either systemic or topical antifungal drugs.
• **Miscellaneous classifications:** Organic acids and their salts and other inorganic salts.

Polyene Macrolides antifungals •

Polyene macrolides antifungals were isolated from various species of Streptomyces.
• Examples used in veterinary medicine include; Amphotericin B, Nystatin, Pimaricin (natamycin)

Mechanisms of polyene macrolides

• Polyene macrolides bind to sterols (ergosterol) in the cell membrane of susceptible fungi.
• This creates a transmembrane channel, changing membrane permeability and thus allowing leakage of intracellular components.
• In particular, amphotericin B binds to ergosterol in fungal membranes disrupting its function leading to K+ ion efflux and H+ ion influx.
• Consequently, internal acidification of fungal cell occurs and thus stopping enzymatic functions. Sugars and amino acids also leak from an arrested cell.
• For Natamycin, the binding to ergosterol in the plasma membrane, prevents ergosterol-dependent fusion of vacuoles, as well as membrane fusion and fission.
• This differs from the mechanism of amphotericin B, which alters fungal membrane permeability. 8 Spectrum of activity of polyene macrolides
• They have broad antifungal activity including filamentous fungi, saprophytic and pathogenic fungi. • Amphotericin B is effective against Coccidiomycosis, histoplasmosis, candidiasis and blastomycosis. • Nystatin is effective against candidiasis against, other yeasts and fungi.
• Pimaricin is effective against candidiasis, trichomoniasis, and mycotic keratitis (dermatophytes).

Antimetabolites

An **antimetabolite** is a chemical that inhibits the use of a metabolite, which is another chemical that is part of normal metabolism. Such substances are often similar in structure to the metabolite that they interfere with, such as the antifolates that interfere with the use of folic acid. The presence of antimetabolites can have toxic effects on cells, such as halting cell growth and cell division, so these compounds are used as chemotherapy for cancer.

Antifolates are a class of antimetabolite medications that antagonise (that is, block) the actions of folic acid (vitamin B_9). Folic acid's primary function in the body is as a cofactor to various methyltransferases involved in serine, methionine, thymidine and purine biosynthesis. Consequently, antifolates inhibit cell division, DNA/RNA synthesis and repair and protein synthesis. Some such as proguanil, pyrimethamine and trimethoprim selectively inhibit folate's

actions in microbial organisms such as bacteria, protozoa and fungi. The majority of antifolates work by inhibiting dihydrofolate reductase (DHFR).

Antimetabolites

- An antimetabolites are drugs have similar structure to normal metabolites which are required for normal biochemical reactions.
- (S-phase specific).
- Antimetabolite are classified into:

1- Folic acid Antagonists:

Methotrexate, Pemetrexed, Nolatrexed, Raltitrexed

2- Pyrimidine Antagonists:

- 5-FU
- ORALLY BIOAVAILABLE 5'-FLUOROPYRIMIDINES (Capecitabine, Ftorafur)
- Cytidine Analogues
  - Ara-C
  - Gemcitabine
  - 5-Azacytidine

3- Purine Antagonists:

- 6-Mercaptopurine
- Azathioprine

Purine and pyrimidine antagonists are phosphorelated inside the body into nucleotid form in order to be cytotoxic

Anti-Metabolites: Anti-Folates

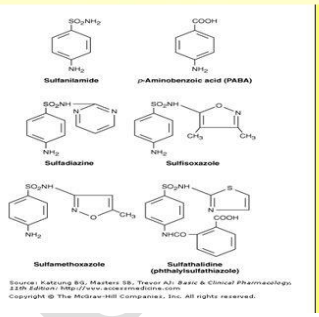
Two Classes—

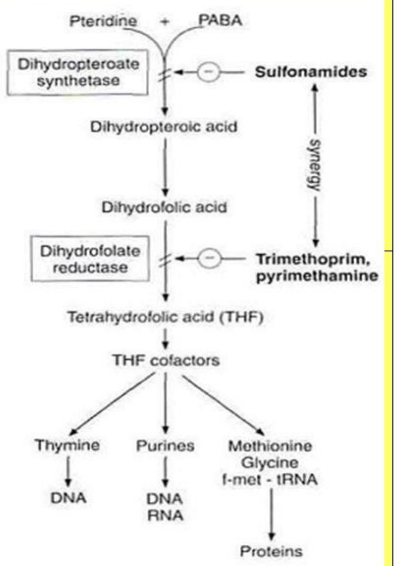
Inhibitors of folate synthesis

- **p-Aminobenzoic acid analogs (PABA)**

Inhibitors of folate use

- **dihydrofolate reductase inhibitors**
  - Trimethoprim – bacterial
  - Pyrimethamine – protozoa
  - Methotrexate - mammalian





Purine antagonist: 6-Thioguanine

- 6-Thioguanine is purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with daunorubicin and cytarabine.
- **MOA:**

Like 6-MP, 6-TG is converted intracellularly to TGMP (6-thioguanylic acid) by the enzyme **Hypoxanthine-guanine phosphoribosyltransferase** (HGPRT)

↓

TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate and thioguanosine triphosphate

↓

which *inhibits the biosynthesis of purines* and also the phosphorylation of GMP to guanosine diphosphate

Pyrimidine antagonist: 5-Fluorouracil

- In system, 5-fluorouracil is converted in to **5-fluoro-2-deoxyuridine monophosphate (5-FdUMP)**, which inhibits thymidylate synthase (**form covalent ternary complex with methyl-THFA and thymidylate synthase → irreversible inhibition of TS**) and **blocks the conversion of deoxyuridilic acid to deoxythymidylic acid**.
- *5-FU* incorporated into RNA, interferes with RNA synthesis and causing cytotoxic effect.
- *5-FU* produces the anticancer effect in the **S phase** of the cell cycle.
- *5-FU* is employed **primarily in the treatment of slowly growing solid tumors** (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas).

Anti tubercular drugs.

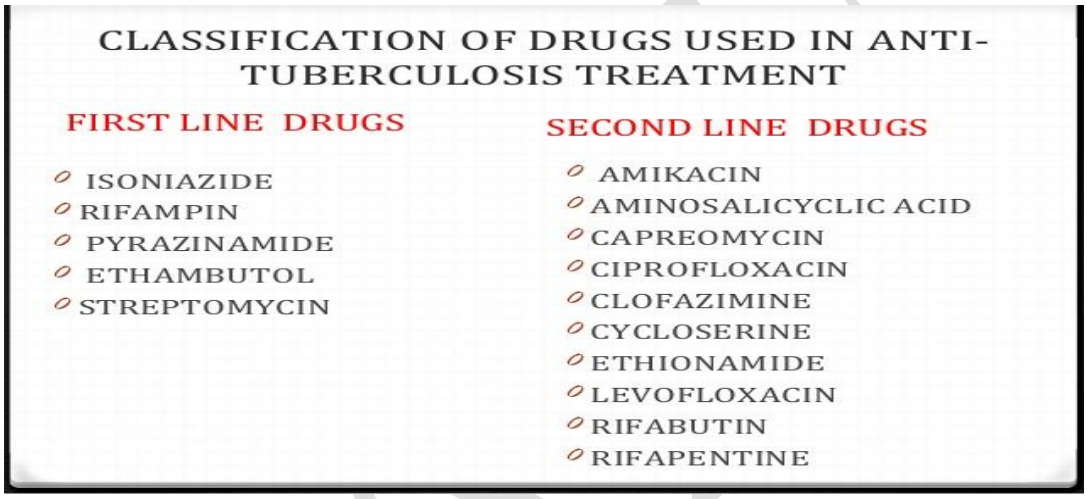
More than twenty drugs have been developed for the treatment of TB. Most of them were developed some years ago. The drugs are used in differing combinations in different circumstances. For example some TB drugs are only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs. There are other drugs that are only used for the treatment of drug resistant TB.[1] There are now starting to be some new TB drugs, but there is not very much known about them, and they are still undergoing testing.

TB drugs – the basic drugs

The five basic or "first line" TB drugs are:[2]

- Isoniazid (H/Inh)
- Rifampicin (R/Rif) (In the United States rifampicin is called rifampin)
- Pyrazinamide (Z/Pza)
- Ethambutol (E/Emb)
- and Streptomycin (S/Stm)

These are the TB drugs that generally have the greatest activity against TB bacteria. These drugs are particularly used for someone with active TB disease who has not had TB drug treatment before. All the other TB drugs are generally referred to as second line or reserve TB drugs.



Possible Questions

1. Explain genetically engineered protein
2. Write any peptide agents used as drugs
3. Discuss novel drug delivery systems
4. What are the non-conventional routes of drug administration
5. Describe the anti-AIDS drug
6. Write notes on Oncogenes as targets for drugs?
7. Discuss about cancer chemotherapy?

1	III	Colloidal drug carrier	**micellar**	vacuoles	solid crystal	Mobile vesicles	**micellar solutions**
2	III	A three-dimensional, hydrophilic, polymeric networks capable of	**Hydrogels**	Vaccum gels	Non vaccum gels	Polymeric gels	**Hydrogels**
3	III	Controlled release (CR)	Tinature	**Spansules**	tamuare	chisuare	**Spansules**
4	III	_____ is the first genetically engineered	Growth hormone	**Insulin**	HBsAg	HIB	**Insulin**
5	III	Genes for insulin peptides is incorporated	**beta galactosidase**	Synthetic vectors	pBr322	TMV	**beta galactosidase**
6	III	Genetically engineered growth hormone is used	**Dwarfism**	Gigantism	malignancies	Renal failure	**Dwarfism**
7	III	Insulin injection for the treatment of diabetes	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	ntravenously	**intra arterially**	intramuscularly	intradermally	**intra arterially**
11	III	For rhematoid arthritis	**Intra articularly**	Intramedullary	Intraperitoneally	Intrathecally	**Intra articularly**
12	III	Using galvanic current penetration of drugs to	Transmucosal method	**Iontophoresis**	Trans nasal method	Transrectal method	**Iontophoresis**
13	III	BCG vaccine is	**intradermally**	intramuscularly	intravenously	subcutaneously	**intradermally**
14	III	Sublingually taken drugs	pulmonary	hepatic	**systemic circulation**	renal circulation	**systemic**
15	III	The initial antibody secreted after immune	IgG	**IgM**	IgA	IgE	**IgM**
16	III	Toxoids are produced by adding _____to toxins of	Acetic acid	Formic acid	**Formalin**	Saline	**Formalin**
17	III	BCG vaccine is used	Typhoid	**Tuberculosis**	Tetanus	chicken pox	**Tuberculosis**
18	III	Salk vaccine is a part of	BCG vaccine	**Poliomyelitus**	MMR vaccine	Hepatitis vaccine	**Poliomyelitus**
19	III	Sabin vaccine for polimyelitus is	subcutaneously	**orally**	intramuscularly	intravenously	**orally**

20	III	OPV provides systemic immunity & induces	IgG	IgM	**IgA**	IgE	**IgA**
21	III	The usual incubation	**4-6 weeks**	1-2 weeks	7-8 weeks	8-10 weeks	**4-6 weeks**
22	III	Which vaccine is given subcutaneously on	rubella vaccine	Poliomyelitus vaccine	Anthrax vaccine	**rabies vaccine**	**rabies vaccine**
23	III	Nerve tissue vaccine is	Hepatitis B	**Rabies**	Mumps	Cholera	**Rabies**
24	III	The first vaccine prepared by rDNA	**Hepatitis B vaccine**	DPT vaccine	Hib vaccine	MMR vaccine	**Hepatitis B vaccine**
25	III	To prevent neonatal tetanus____is given	DPT	OPV	MMR	**TT**	**TT**
26	III	Anti-D (Rho) immunoglobulin is used	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	MMR vaccine	**Diptheria**	Varicella vaccine	poliomyelitis	**Diptheria**
29	III	Glycosylated erythropoietin is a	**Anemia**	Skin disorders	Muscular dystrophy	Brain disorders	**Anemia**
30	III	The mean incubation	7 years	**4.5 years**	6.5 years	2 years	**4.5 years**
31	III	Antibodies to HIV develops in_eafter	**2-8 weeks**	1-2 weeks	7-8 weeks	8-10 weeks	**2-8 weeks**
32	III	In AIDS patients opportunistic infections	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	**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	Provide synergism resulting from the use of	Provide stimulation of immune system	Provide stimulation of cell proliferation	**Provide synergism resulting from the use of**
38	III	Anticancer alkylating drug, a derivative of	Methotrexate	Cisplatin	Cyclophosphamide	Carmustine	**Cyclophosphamide**
39	III	Tick the anticancer alkylating drug, a	Mercaptopurine	Thiotepa	Chlorambucil	Procarbazine	**Thiotepa**
40	III	The group of hormonal drugs used for cancer	Mineralocorticoids and	Glucocorticoids and gonadal	Gonadal hormones and somatotropin	Insulin	**Glucocorticoids and gonadal**
41	III	The anticancer drug of	Dactinomycin	Vincristine	Methotrexate	Procarbazine	**Vincristine**
42	III	Action mechanism of alkylating agents is:	Producing carbonium ions	Producing carbonium ions	Structural antagonism against	Inhibition of DNA-dependent RNA	**Producing carbonium ions**
43	III	Methotrexate is	A purine	A folic acid	An antibiotic	An alkylating agent	**A folic acid**
44	III	The antibiotic for cancer	Cytarabine	Doxorubicin	Gentamycin	Etoposide	**Doxorubicin**
45	III	Fluorouracil belongs to	Antibiotics	Antimetabolites	Plant alkaloids	Bone marrow	**Antimetabolites**
46	III	The action mechanism of anticancer drugs	Inhibition of DNA-dependent	Cross-linking of DNA	Mitotic arrest at a metaphase	Nonselective inhibition of	**Mitotic arrest at a metaphase**
47	III	Action mechanism of methotrexate is	Inhibition of dihydrofolate	Activation of cell differentiation	Catabolic depletion of serum asparagine	Activation of cell differentiation	**Inhibition of dihydrofolate**
48	III	The anticancer drug belonging to inorganic	Dacarbazine	Cisplatin	Methotrexate	Vincristine	**Cisplatin**
49	III	The indication for estrogens in oncological	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	Carmustine	Vincristine	Lomustine	Semustine	**Vincristine**
52	III	Estrogen inhibitor:	Leuprolide	Tamoxifen	Flutamide	Anastrozole	**Tamoxifen**
53	III	The antiandrogen drug:	Flutamide	Aminoglutethimi	Tamoxifen	Testosterone	**Flutamide**
54	III	The drug belonging to	Octreotide	Anastrozole	Flutamide	Tamoxifen	**Anastrozole**

55	III	The drug belonging to gonadotropin-releasing	Leuprolide	Tamoxifen	Flutamide	Anastrozole	**Leuprolide**
56	III	Which of the following chemotherapy drug is	Adriamycin	Vinblastine	Paclitaxel	Procarbazine	**Procarbazine**
57	III	High dose chemotherapy given prior to stem cell transplant may be	Busulfan + cyclophosphamide	Cyclophosphamide + TBI	Ifosfamide +carboplatin+ Etoposide	Fludarabine + ATG	**Fludarabine + ATG**
58	III	Incidence of Gallbladder	Chile	India	United Kingdom	South Africa	**Chile**
59	III	Which of the following is least to occur as	Adenocarcinoma	Squamous cell carcinoma	Lymphoma	Carcinoid tumour	**Lymphoma**
60	III	Which of the following is less likely to be	Obesity	Use of tobacco and alcohol	Aflotoxins	Past history of enteric fever	**Aflotoxins**

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17BCU602A- Drug Biochemistry
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UNIT-IV

SYLLABUS

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).

Pharmacologic Treatment

When considering appropriate pharmacologic therapy, a major factor to consider is whether the patient is insulin deficient, insulin resistant, or both. Treatment options can be divided into noninsulin therapies—insulin sensitizers, secretagogues, alpha glucosidase inhibitors, incretins, pramlintide, bromocriptine, and sodium glucose cotransporter 2 (SGLT-2) inhibitors—and insulins (insulin and insulin analogs). Table 3 lists the noninsulin therapies available.

Diabetes mellitus (**DM**), commonly referred to as **diabetes**, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes.

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.

- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is excessive body weight and not enough exercise.

- Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease. Type 1 DM must be managed with insulin injections. Type 2 DM may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby.

Table 3: Noninsulin Therapies

Subgroup	Generic name (Brand)	Route	Comments
Insulin sensitizers			
Biguanides	Metformin (Glucophage)	Oral	Weight loss No hypoglycemia GI upset
Thiazolidinediones	Rosiglitazone (Avandia) Pioglitazone (Actos)	Oral	Weight gain Peripheral edema
Insulin secretagogues			

Sulfonylureas	Chlorpropamide (Diabinese) Glibenclamide (Glyburide) Glimepiride (Amaryl) Glipizide (Glucotrol) Tolazamide (Tolinase) Tolbutamide (Orinase)	Oral	Hypoglycemia Weight gain
Glinides	Nateglinide (Starlix) Repaglinide (Prandin)	Oral	Weight gain
Alpha-glucosidase inhibitors			
	Acarbose (Precose) Miglitol (Glyset)	Oral	GI upset No hypoglycemia
Incretins			
GLP-1 receptor agonists *Short-acting (4-6 hrs)*	Exenatide (Byetta)	SC	Weight loss GI upset
GLP-1 receptor agonists *Intermediate-acting (24 hrs)*	Liraglutide (Victoza)	SC	Weight loss Nausea
GLP-1 receptor agonists *Long-acting (7 days)*	Exenatide ER (Bydureon) Albiglutide (Tanzeum) Dulaglutide (Trulicity)	SC	Weight loss Nausea

DPP-4 inhibitors	Sitagliptin (Januvia) Saxagliptin (Onglyza) Linagliptin (Tradjenta) Alogliptin (Nesina)	Oral	No hypoglycemia Nasopharyngitis Weight neutral
Pramlintide			
	Pramlinitide (Symlin)	SC	Weight loss GI upset Adjunctive tx with insulin
Rapid-release bromocriptine			
	Bromocriptine quick-release (Cycloset)	Oral	Take within 2 hrs of awakening Nausea, stuffy nose
SGLT-2 inhibitors			
	Canagliflozin (Invokana) Dapagliflozin (Farxiga) Empagliflozin (Jardiance)	Oral	Polyuria UTIs

Abbreviations: DPP-4=dipeptidyl peptidase-4; ER=extended release; GI=gastrointestinal; GLP-1=glucagon-like peptide- 1; SGLT-2=sodium-glucose cotransporter-2; SC=subcutaneous injection; UTIs=urinary tract infections.

Insulin Sensitizers

Insulin sensitizers reduce glycemic load primarily by improving insulin actions in peripheral tissues. Two classes of these oral hypoglycemic drugs are available: biguanides and

thiazolidinediones. They have been shown through more than a decade of clinical use to have positive, durable effects in the treatment of diabetes. These drug classes can be used as monotherapy or in combination with sulfonylurea, insulin, or with each other.

Biguanides (Metformin)

Metformin was first marketed in the 1950s. Its primary mechanism of action is suppression of hepatic glucose output, but it also enhances insulin sensitivity of muscle and fat. Metformin primarily lowers fasting glycemia; however, some decreases in postprandial glucose concentrations, especially after the midday meal, are seen.

Metformin is well tolerated, with the most common side effect being gastrointestinal (GI) complaints, such as diarrhea, nausea, and abdominal discomfort, and a metallic taste. All of these symptoms improve with time and dose reduction. Metformin causes a small increase in basal and postprandial lactate concentrations in the blood, which can produce rare but life-threatening lactic acidosis (<1 in 100,000). It is best to avoid metformin use in patients with hepatic impairment. Metformin is contraindicated in males with a serum creatinine 1.5 mg/dL or higher and in females with a level 1.4 mg/dL or higher.

A major benefit of metformin is that it usually does not lead to hypoglycemia when used as monotherapy. It can lead to weight loss, and it has been shown to decrease plasma triglycerides concentration by 10% to 20%.

Dosing is typically twice daily, but it can be dosed three times daily; the extended-release formulation is dosed once daily. The typical metformin starting dose is 500 mg/day with a maximum dose of 2,550 mg/day. Gradual titration of metformin, starting at 500 mg with breakfast and increasing by 500 mg in weekly intervals until reaching a maximum dose of 1,000 mg with breakfast and dinner, helps prevent GI side effects.

Thiazolidinediones

Thiazolidinediones (TZDs) are agonists of peroxisome proliferator-activated receptor gamma. They primarily enhance sensitivity of muscle and fat, and, mildly, the liver, to exogenous and endogenous insulin. These effects lower fasting and postprandial blood glucose levels.

Major side effects include weight gain, with an increase in subcutaneous adiposity and fluid retention, which typically manifests as peripheral edema although heart failure has occurred on occasion. These effects are mostly seen at higher doses. As a result, these agents should be avoided in patients with functional class III or IV heart failure.

The PROactive trial (PROspective pioglitAzone Clinical Trial In macroVascular Events) showed that compared with placebo, pioglitazone does not increase cardiovascular risks. The TZDs have been associated with an increased risk of bone fractures, particularly in women. They do not cause hypoglycemia when used as monotherapy. Pioglitazone use leads to lowering triglycerides, increasing high-density lipoprotein (HDL), and increasing the low-density lipoprotein (LDL) particle size.

Dosing is once daily. It takes 2 to 12 weeks for TZDs to become fully effective. For rosiglitazone, the starting dose is 4 mg/day and maximum dose is 8 mg/day. For pioglitazone, the starting dose is 7.5 mg/day and the maximum dose is 45 mg/day.

Insulin Secretagogues

Insulin secretagogues stimulate secretion of insulin from the pancreas, thereby enhancing glucose uptake by muscles and fat and decreasing hepatic glucose production. Two types of secretagogues are marketed: sulfonylureas and glinides.

Sulfonylureas

Sulfonylureas lower fasting and postprandial glucose levels. The main adverse effects are weight gain (about 2 kg a few months after initiation) and hypoglycemia. Hypoglycemia episodes can be significant, leading to need for medical care, coma, or seizure, and are seen more often in the elderly. Benefits include a 25% reduction in microvascular complications with or without

insulin, as noted in the United Kingdom Prospective Diabetes Study (UKPDS). Dosing is typically once or twice daily. Caution should be used in patients with liver or kidney dysfunction or in those who often skip meals.

Glinides

Glinides work in a manner similar to sulfonylureas; however, they have a more rapid onset of action and shorter duration, so they are a good option for patients with erratic timing of meals. Also, the hypoglycemia risk is lower than with sulfonylureas, but they have a similar-to-lower risk of weight gain after initiating therapy. Caution must be used in patients with liver dysfunction. Dosing is before meals

Alpha-Glucosidase Inhibitors

Alpha-glucosidase inhibitors competitively block the enzyme alpha glucosidase in the brush borders of the small intestine, which delays absorption of carbohydrates (absorbed in the mid and distal portions of the small intestine instead). They primarily target postprandial hyperglycemia but do it without causing hypoglycemia. GI complaints, such as bloating, abdominal cramps, flatulence, and diarrhea, are the main side effects. Use should be avoided in patients with severe hepatic or renal impairment. Dosing must occur before carbohydrate-containing meals.

Incretins

Incretin-based therapies are available as injections (GLP-1 analogs) or oral formulations (DPP-4 inhibitors). These therapies differ slightly in their mechanisms of actions, as described in the following sections. All incretin-based medications carry an increased risk of acute pancreatitis. Patients must be warned about this risk and be advised to stop taking these medications and to seek medical evaluation if acute abdominal pain develops.

These medications should not be given to individuals who have a history of medullary thyroid carcinomas or have multiple endocrine neoplasia type 2. This restriction is based on increased incidences of thyroid C-cell tumors observed with these medications in murine models. So far,

no increased risk in humans has been observed. Nevertheless, the above groups of individuals should not use these medications.

GLP-1 Receptor Agonists

Short-Acting (4-6 hrs)

Exenatide is a synthetic form of exendin 4, a hormone found in the saliva of the Gila monster, which mimics glucagon-like peptide-1 (GLP-1). GLP-1 is produced in the small intestine. It stimulates insulin secretion and inhibits glucagon secretion and hepatic glucose production in a glucose-dependent manner. It also delays gastric emptying and suppresses appetite through central pathways. It primarily decreases postprandial blood glucose levels; however, a moderate reduction in fasting blood glucose levels also can be seen.

Due to its delaying effects on gastric emptying, the major side effects are GI complaints of nausea, vomiting, and diarrhea. Hypoglycemia does not occur when exenatide is used as monotherapy or with metformin, but it does occur when exenatide is combined with a sulfonylurea. Benefits include weight loss up to 2 to 3 kg in the first 6 months and up to 5.5 kg in the first 2 years.

Dosing is twice daily by subcutaneous injection. The initial starting dose is 5 µg. If this dose is tolerated, titrate after 1 month to 10 µg.

Intermediate-Acting (24 hrs)

Liraglutide is a GLP-1 analog derived from human GLP-1. It is administered once a day as a subcutaneous injection from its pen device. Timing is independent of meals. Half-life is about 13 hours. Its beneficial effects and side effects are similar to those of exenatide, but it may be slightly more powerful in its actions.

The initial dose is 0.6 mg/day for a week. If there are no side effects, the dose is increased to 1.2 mg/day (the dose at which most clinical benefits are seen). For most patients, dose will be increased to 1.8 mg/day after another week if there are no side effects.

Long-Acting (7 days)

Exenatide also is available as a once per week injection, supplied as a kit containing 2 mg of extended-release exenatide. If a dose is missed, it should be administered as soon as noticed provided that next dose is scheduled 3 or more days later. Albiglutide is a newer GLP-1 analog that has a half-life of 4 to 7 days. It is given as 30 or 50 mg weekly injections. Dulaglutide is another long-acting GLP-1 analog. It is given as 0.75 and 1.5 mg weekly injections.

DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) is a cell membrane protein that rapidly degrades GLP-1 and glucose-dependent insulinotropic polypeptide. Suppression of DPP-4 leads to higher levels of insulin secretion and suppression of glucagon secretion in a glucose-dependent manner.

The DPP-4 inhibitors act primarily on postprandial blood glucose levels, but reductions in fasting glycemia are also seen. These agents are generally well tolerated, with the most common side effect being headache. An increase in nasopharyngitis also has been seen. Benefits include that it is weight neutral and does not cause hypoglycemia as monotherapy or when combined with metformin or thiazolidinediones. When combined with sulfonylurea or insulin, it increases the risk of hypoglycemia.

Four DPP-4 inhibitors are approved by the US Food and Drug Administration (FDA) for use in type 2 DM: sitagliptin, saxagliptin, linagliptin, and alogliptin. These agents are indicated for use as monotherapy or in combination with other agents such as metformin, sulfonylureas, thiazolidinediones, or insulin.

Sitagliptin dosing is 100 mg orally once daily with or without meals. Dose reduction is needed in patients with renal impairment. For patients with a creatinine clearance of 30 to 50 mL/min, dosing is 50 mg once daily. For patients with a creatinine clearance less than 30 mL/min, dosing is 25 mg once daily.

Saxagliptin dosing is 2.5 or 5 mg orally once daily with or without meals. The 2.5 mg daily dose is used in patients whose estimated glomerular filtration rate (eGFR) is <50 mg/mL and those using the strong inhibitors of P450 3A4/5 (eg, ketoconazole, ritonavir).

Linagliptin dosing is 5 mg orally once daily with or without meals. Dose reduction is not needed in renal impairment.

Alogliptin dosing is 25 mg orally once daily with or without meals. Dose reduction is needed in renal impairment. In patients with a creatinine clearance 30 to 60 mL/min, dosing is 12.5 mg once daily. In patients with a creatinine clearance below 30 mL/min, dosing is 6.25 mg once daily.

Pramlintide

Pramlintide is a synthetic form of amylin, a hormone secreted by beta cells that acts to suppress glucagon secretion, slow gastric emptying, and suppress appetite through central pathways. It acts primarily on postprandial blood glucose levels. Efficacy data from well-conducted studies are lacking. Dosage varies in different patients.

The major side effects are GI complaints, especially nausea and hypoglycemia. Benefits of therapy include weight loss of 1 to 1.5 kg over 6 months and up to 4.5 kg after chronic therapy.

Pramlintide is FDA approved only as adjunctive therapy with insulin, but it is used off-label in patients with either type 1 DM or type 2 DM. Pramlintide can reduce insulin requirements by up to 50%. The starting dose for patients with type 2 DM is generally 60 µg subcutaneously before meals. In patients with type 1 DM, the starting dose is 15 µg before each meal. Pramlintide can be used by patients taking insulin, metformin, or sulfonylureas.

Bromocriptine

Fast release bromocriptine improves glycemic control in patients with type 2 DM when taken within the 2 hours of waking up. Mechanism of action is not known. Improvement in Hba1c is 0.6-0.7%. It is sold as 0.8 mg tablet and therapeutic dose varies from 1.6-4.8 mg. Nausea is main side effect.

SGLT-2 Inhibitors

The SGLT-2 inhibitors are the newest group of FDA-approved medications for type 2 DM. SGLT-2 is a protein acting as sodium-glucose cotransporter in the kidney's proximal tubules whose main function is reabsorption of the filtered glucose from the urine back into the circulation. It is responsible for about 90% of total glucose reabsorption. Inhibition of this protein leads to the excretion of glucose in the urine at much lower blood glucose levels than normal (at approximately 120 mg/dL instead of 180 mg/dL).

The most common side effects of SGLT-2 inhibitors are vaginal yeast infections and urinary tract infections. The greatest risk is seen in female patients and in uncircumcised males. Polyuria also may occur.

Additional benefits are weight loss (two-thirds of weight loss is related to loss of fat tissue and one-third is related to loss of water) and lower blood pressure.

These medications are not indicated in children, in patients with type 1 DM, frequent ketones in their blood or urine, or severe renal impairment. Patients should be advised to expect glucose to be in the urine and, thus, urine glucose strips will usually have a positive reading.

Three SGLT-2 inhibitors are currently available: canagliflozin, dapagliflozin, and empagliflozin.

Canagliflozin is dosed at 100 mg/day before the first meal of the day and can be increased to 300 mg/day, if tolerated. Canagliflozin should not be used in patients with eGFR less than 45 mL/min/1.73m^2 and should be limited to 100 mg in those with eGFR 45 to 60 mL/min/1.73m^2.

Dapagliflozin is dosed at 5 mg/day and can be increased to 10 mg/day, if tolerated. It should not be used if eGFR is less than 60 mL/min/1.73m^2.

Empagliflozin is dosed at 10 or 25 mg once a day. It should not be started if eGFR is less than 60 mL/min/1.73m^2. If eGFR decreases below 60 mL/min/1.73m^2 while patient takes this medication, it should be continued at 10 mg/day and stopped if eGFR decreases below 45 mL/min/1.73m^2. At this time, empagliflozin is the only antidiabetic medication shown to decrease cardiovascular risk in patients with type 2 DM.

Insulin

Insulin was the first treatment for diabetes. It was discovered in 1921, and clinical testing in humans started in 1922.

Insulin therapy remains the most effective method of reducing hyperglycemia. There is no upper limit in dosing for therapeutic effect, so it can be used to bring any elevated HbA1c level down to near normal. Other benefits of insulin include its effects on reducing triglycerides levels and increasing HDL.

Hypoglycemia is a concern, although the actual risk of severe episodes is small. Studies have shown that insulin-induced hypoglycemic episodes requiring therapy occur in 1 to 3 per 100,000 patient-years. Weight gain can occur after initiation and is typically about 2 to 4 kg.

Most brands of insulin are available in both vial and pen form for delivery.

Acarbose

Acarbose is a pseudotetrasaccharide, a natural microbial product derived from culture broths of *Actinoplanes* strain SE 50. The unsaturated cyclitol component of the molecule has been identified as essential for *a*-glucosidase inhibitory activity.

Acarbose binds reversibly, competitively and in a dose-dependent manner to the oligosaccharide binding site of *a*-glucosidase enzymes in the brush border of the small intestinal mucosa. As a consequence, hydrolysis is prevented. This effect lasts for 4 to 6 hours provided that acarbose is present at the site of enzymatic action at the same time as the oligosaccharides. Thus acarbose must be administered with the first bite of a main meal.

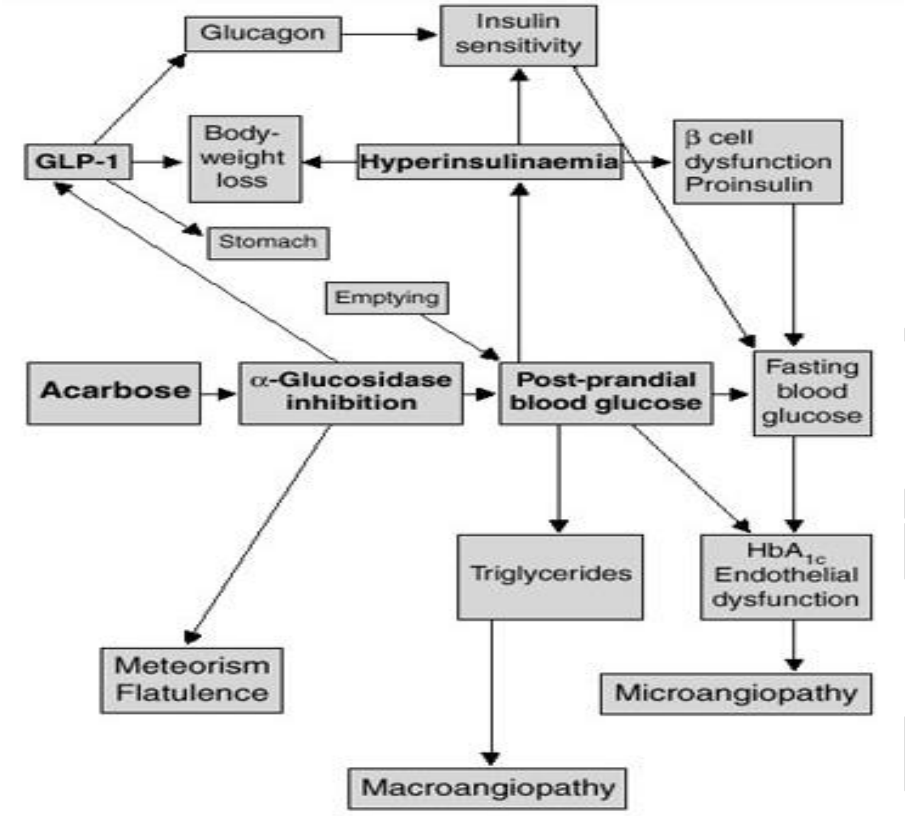
Acarbose binds to intestinal sucrase with a 10^4 - to 10^5 - fold greater affinity than sucrose. The drug delays the intestinal hydrolysis of oligo-and disaccharides by *a*-glucosidases, mainly in the upper half of the small intestine. Consequently, the absorption of monosaccharides after a meal is delayed and transport through the mucosal surfaces into the circulation is interrupted. The suppression of *a*-glucosidase is reversible, although pharmacological activity is reliable and persistent with long-term use. Effects with continued use can be maintained over years and no

reportsof acarbose failure are present in the available literature. There is no need for dosage adjustment in slight renal insufficiency; however, acarbose should be withdrawn in case of severe progressive renal insufficiency.

Acarbose (INN) is an anti-diabetic drug used to treat diabetes mellitus type 2 and, in some countries, prediabetes. However, a recent large study concludes "acarbose is effective, safe and well tolerated in a large cohort of Asian patients with type 2 diabetes." A possible explanation for the differing opinions is an observation that acarbose is significantly more effective in patients eating a relatively high carbohydrate Eastern diet It is a starch blocker, and inhibits alpha glucosidase, an intestinal enzyme that releases glucose from larger carbohydrates. It is composed of an acarviosin moiety with a maltose at the reducing terminus.

Mechanism of action

Acarbose inhibits enzymes (glycoside hydrolases) needed to digest carbohydrates, specifically, alpha-glucosidase enzymes in the brush border of the small intestines, and pancreatic alpha-amylase. Pancreatic alpha-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the small intestine, whereas the membrane-bound intestinal alpha-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine. Inhibition of these enzyme systems reduces the rate of digestion of complex carbohydrates. Less glucose is absorbed because the carbohydrates are not broken down into glucose molecules. In diabetic patients, the short-term effect of these drug therapies is to decrease current blood glucose levels; the long-term effect is a reduction in HbA_{1c} level. This reduction averages an absolute decrease of 0.7%, which is a decrease of about 10% in typical HbA_{1c} values in diabetes studies.



Biguanide

Biguanide is the organic compound with the formula $HN(C(NH)NH_2)_2$. It is a colorless solid that dissolves in water to give highly basic solution. These solutions slowly hydrolyse to ammonia and urea. The term "biguanidine" often refers specifically to a class of drugs that function as oral antihyperglycemic drugs used for diabetes mellitus or prediabetes treatment.

Examples include:

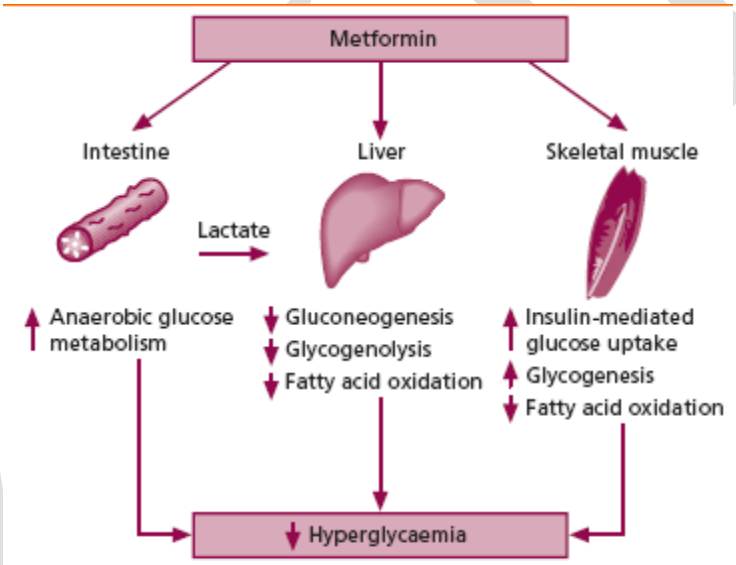
- Metformin - widely used in treatment of diabetes mellitus type 2
- Phenformin - withdrawn from the market in most countries due to toxic effects
- Buformin - withdrawn from the market due to toxic effects

Mechanism of action

Biguanides do not affect the output of insulin, unlike other hypoglycemic agents such as sulfonylureas and meglitinides. Therefore, they are effective in Type 2 diabetics; and in Type 1 diabetes when used in conjunction with insulin therapy.

The mechanism of action of biguanides is not fully understood, and many mechanisms have been proposed for metformin. Mainly used in Type II diabetes, metformin is considered to increase insulin sensitivity in vivo, resulting in reduced plasma glucose concentrations, increased glucose uptake, and decreased gluconeogenesis.

However, in hyperinsulinemia, biguanides can lower fasting levels of insulin in plasma. Their therapeutic uses derive from their tendency to reduce gluconeogenesis in the liver, and, as a result, reduce the level of glucose in the blood. Biguanides also tend to make the cells of the body more willing to absorb glucose already present in the blood stream, and there again reducing the level of glucose in the plasma.



Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004

AIDS

Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is a spectrum of conditions caused by infection with the human immunodeficiency virus (HIV). Following initial infection, a person may not notice any

symptoms or may experience a brief period of influenza-like illness. Typically, this is followed by a prolonged period with no symptoms. As the infection progresses, it interferes more with the immune system, increasing the risk of common infections like tuberculosis, as well as other opportunistic infections, and tumors that rarely affect people who have working immune systems. These late symptoms of infection are referred to as AIDS. This stage is often also associated with weight loss.

HIV is spread primarily by unprotected sex (including anal and oral sex), contaminated blood transfusions, hypodermic needles, and from mother to child during pregnancy, delivery, or breastfeeding. Some bodily fluids, such as saliva and tears, do not transmit HIV. Methods of prevention include safe sex, needle exchange programs, treating those who are infected, and male circumcision. Disease in a baby can often be prevented by giving both the mother and child antiretroviral medication. There is no cure or vaccine; however, antiretroviral treatment can slow the course of the disease and may lead to a near-normal life expectancy. Treatment is recommended as soon as the diagnosis is made. Without treatment, the average survival time after infection is 11 years.

Azidothymidine (AZT)

Azidothymidine (AZT), is an antiretroviral medication used to prevent and treat HIV/AIDS. It is generally recommended for use with other antiretrovirals. It may be used to prevent mother-to-child spread during birth or after a needlestick injury or other potential exposure. It is sold both by itself and together as lamivudine/zidovudine and abacavir/lamivudine/zidovudine. It can be used by mouth or by slow injection into a vein.

Common side effects include headaches, fever, and nausea. Serious side effects include liver problems, muscle damage, and high blood lactate levels. It is commonly used in pregnancy and appears to be safe for the baby. ZDV is of the nucleoside analog reverse-transcriptase inhibitor (NRTI) class. It works by inhibiting the enzyme reverse transcriptase that HIV uses to make DNA and therefore decreases replication of the virus.

Mechanism of action

AZT is a thymidine analogue. AZT works by selectively inhibiting HIV's reverse transcriptase, the enzyme that the virus uses to make a DNA copy of its RNA. Reverse transcription is necessary for production of HIV's double-stranded DNA, which would be subsequently integrated into the genetic material of the infected cell (where it is called a provirus). Cellular enzymes convert AZT into the effective 5'-triphosphate form. Studies have shown that the termination of HIV's forming DNA chains is the specific factor in the inhibitory effect.

At very high doses, AZT's triphosphate form may also inhibit DNA polymerase used by human cells to undergo cell division, but regardless of dosage AZT has an approximately 100-fold greater affinity for HIV's reverse transcriptase. The selectivity has been proven to be due to the cell's ability to quickly repair its own DNA chain if it is broken by AZT during its formation, whereas the HIV virus lacks that ability. Thus AZT inhibits HIV replication without affecting the function of uninfected cells. At sufficiently high dosages, AZT begins to inhibit the cellular DNA polymerase used by mitochondria to replicate, accounting for its potentially toxic but reversible effects on cardiac and skeletal muscles, causing myositis.

Didanosine

Didanosine (ddI, DDI), marketed under the trade names Videx, is an medication used to treat HIV/AIDS. It is used in combination with other medications as part of highly active antiretroviral therapy (HAART). It is of the reverse transcriptase inhibitor class. It is on the World Health Organization's List of Essential Medicines, a list of the most important medication needed in a basic health system.

Mechanism of action

Didanosine (ddI) is a nucleoside analogue of adenosine. It differs from other nucleoside analogues, because it does not have any of the regular bases, instead it has hypoxanthine attached

to the sugar ring. Within the cell, ddI is phosphorylated to the active metabolite of dideoxyadenosine triphosphate, ddATP, by cellular enzymes. Like other anti-HIV nucleoside analogs, it acts as a chain terminator by incorporation and inhibits viral reverse transcriptase by competing with natural dATP.

Cancer

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. Not all tumors are cancerous; benign tumors do not spread to other parts of the body. Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. While these symptoms may indicate cancer, they may have other causes. Over 100 types of cancers affect humans.

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body. They form a subset of neoplasms. A neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely.

All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor. They include:

- Cell growth and division absent the proper signals
- Continuous growth and division even given contrary signals
- Avoidance of programmed cell death
- Limitless number of cell divisions
- Promoting blood vessel construction
- Invasion of tissue and formation of metastases

The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression

Mechlorethamine

Chemocare.com uses generic names in all descriptions of drugs. Mustargen is the trade name for Mechlorethamine. Nitrogen Mustard, Mustine, and Mechlorethamine Hydrochloride are other names for Mechlorethamine. In some cases, health care professionals may use the trade

name Mustargen or other names Nitrogen Mustard, Mustine, and Mechlorethamine Hydrochloride when referring to the generic drug name Mechlorethamine.

Mechlorethamine Uses:

- As part of combination regimens in treatment of Hodgkin's disease, non-Hodgkin's lymphoma.
- As palliative chemotherapy in lung and breast cancers.
- As a lotion to skin lesions of mycosis fungoides (cutaneous T-cell lymphoma).

Cancerous tumors are characterized by cell division, which is no longer controlled as it is in normal tissue. "Normal" cells stop dividing when they come into contact with like cells, a mechanism known as contact inhibition. Cancerous cells lose this ability. Cancer cells no longer have the normal checks and balances in place that control and limit cell division. The process of cell division, whether normal or cancerous cells, is through the cell cycle. The cell cycle goes from the resting phase, through active growing phases, and then to mitosis (division).

The ability of chemotherapy to kill cancer cells depends on its ability to halt cell division. Usually, the drugs work by damaging the RNA or DNA that tells the cell how to copy itself in division. If the cells are unable to divide, they die. The faster the cells are dividing, the more likely it is that chemotherapy will kill the cells, causing the tumor to shrink. They also induce cell suicide (self-death or apoptosis).

Chemotherapy drugs that affect cells only when they are dividing are called cell-cycle specific. Chemotherapy drugs that affect cells when they are at rest are called cell-cycle non-specific. The scheduling of chemotherapy is set based on the type of cells, rate at which they divide, and the time at which a given drug is likely to be effective. This is why chemotherapy is typically given in cycles.

Chemotherapy is most effective at killing cells that are rapidly dividing. Unfortunately, chemotherapy does not know the difference between the cancerous cells and the normal cells. The "normal" cells will grow back and be healthy but in the meantime, side effects occur. The "normal" cells most commonly affected by chemotherapy are the blood cells, the cells in the mouth, stomach and bowel, and the hair follicles; resulting in low blood counts, mouth sores, nausea, diarrhea, and/or hair loss. Different drugs may affect different parts of the body.

Mechlorethamine is classified as an alkylating agent. Alkylating agents are most active in the resting phase of the cell. These drugs are cell cycle non-specific. There are several types of alkylating agents.

- Mustard gas derivatives: Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, and Ifosfamide.
- Ethylenimines: Thiotepa and Hexamethylmelamine.
- Alkylsulfonates: Busulfan.
- Hydrazines and Triazines: Altretamine, Procarbazine, Dacarbazine and Temozolomide.
- Nitrosureas: Carmustine, Lomustine and Streptozocin. Nitrosureas are unique because, unlike most chemotherapy, they can cross the blood-brain barrier. They can be useful in treating brain tumors.
- Metal salts: Carboplatin, Cisplatin, and Oxaliplatin.

Busulfan

Busulfan is a bifunctional alkylating agent, having a selective immunosuppressive effect on bone marrow. It is not a structural analog of the nitrogen mustards. It has been used in the palliative treatment of chronic myeloid leukemia (myeloid leukemia, chronic), but although symptomatic relief is provided, no permanent remission is brought about. According to the Fourth Annual Report on Carcinogens (NTP 85-002, 1985), busulfan is listed as a known carcinogen.

Mechanism of action of busulfan

Busulfan is an antineoplastic in the class of alkylating agents and is used to treat various forms of cancer. Alkylating agents are so named because of their ability to add alkyl groups to many electronegative groups under conditions present in cells. They stop tumor growth by cross-linking guanine bases in DNA double-helix strands - directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide. In addition, these drugs add methyl or other alkyl groups onto molecules where they do not belong which in turn leads to a miscoding of DNA. Alkylating agents are cell cycle-nonspecific and work by three different mechanisms, all of which achieve the same end result -

disruption of DNA function and cell death. Overexpression of MGST2, a glutathione s-transferase, is thought to confer resistance to busulfan. The role of MGST2 in the metabolism of busulfan is unknown however.

Busulfan is an alkylating agent that contains 2 labile methanesulfonate groups attached to opposite ends of a 4-carbon alkyl chain. Once busulfan is hydrolyzed, the methanesulfonate groups are released and carbonium ions are produced. These carbonium ions alkylate DNA, which results in the interference of DNA replication and RNA transcription, ultimately leading to the disruption of nucleic acid function. Specifically, its mechanism of action through alkylation produces guanine-adenine intrastrand crosslinks. This occurs through an SN2 reaction in which the relatively nucleophilic guanine N7 attacks the carbon adjacent to the mesylate leaving group. This kind of damage cannot be repaired by cellular machinery and thus the cell undergoes apoptosis.

Heart

The heart is a muscular organ in humans and other animals, which pumps blood through the blood vessels of the circulatory system. Blood provides the body with oxygen and nutrients, as well as assists in the removal of metabolic wastes. In humans, the heart is located between the lungs, in the middle compartment of the chest.

The heart pumps blood with a rhythm determined by a group of pacemaking cells in the sinoatrial node. These generate a current that causes contraction of the heart, traveling through the atrioventricular node and along the conduction system of the heart. The heart receives blood low in oxygen from the systemic circulation, which enters the right atrium from the superior and inferior venae cavae and passes to the right ventricle. From here it is pumped into the pulmonary circulation, through the lungs where it receives oxygen and gives off carbon dioxide. Oxygenated blood then returns to the left atrium, passes through the left ventricle and is pumped out through the aorta to the systemic circulation−where the oxygen is used and metabolized to carbon dioxide. The heart beats at a resting rate close to 72 beats per minute. Exercise temporarily increases the rate, but lowers resting heart rate in the long term, and is good for heart health.

Cardiovascular diseases (CVD) are the most common cause of death globally as of 2008, accounting for 30% of deaths. Of these more than three quarters are a result of coronary artery disease and stroke. Risk factors include: smoking, being overweight, little exercise, high cholesterol, high blood pressure, and poorly controlled diabetes, among others. Cardiovascular diseases frequently have no symptoms or may cause chest pain or shortness of breath. Diagnosis of heart disease is often done by the taking of a medical history, listening to the heart-sounds with a stethoscope, ECG, and ultrasound. Specialists who focus on diseases of the heart are called cardiologists, although many specialties of medicine may be involved in treatment.

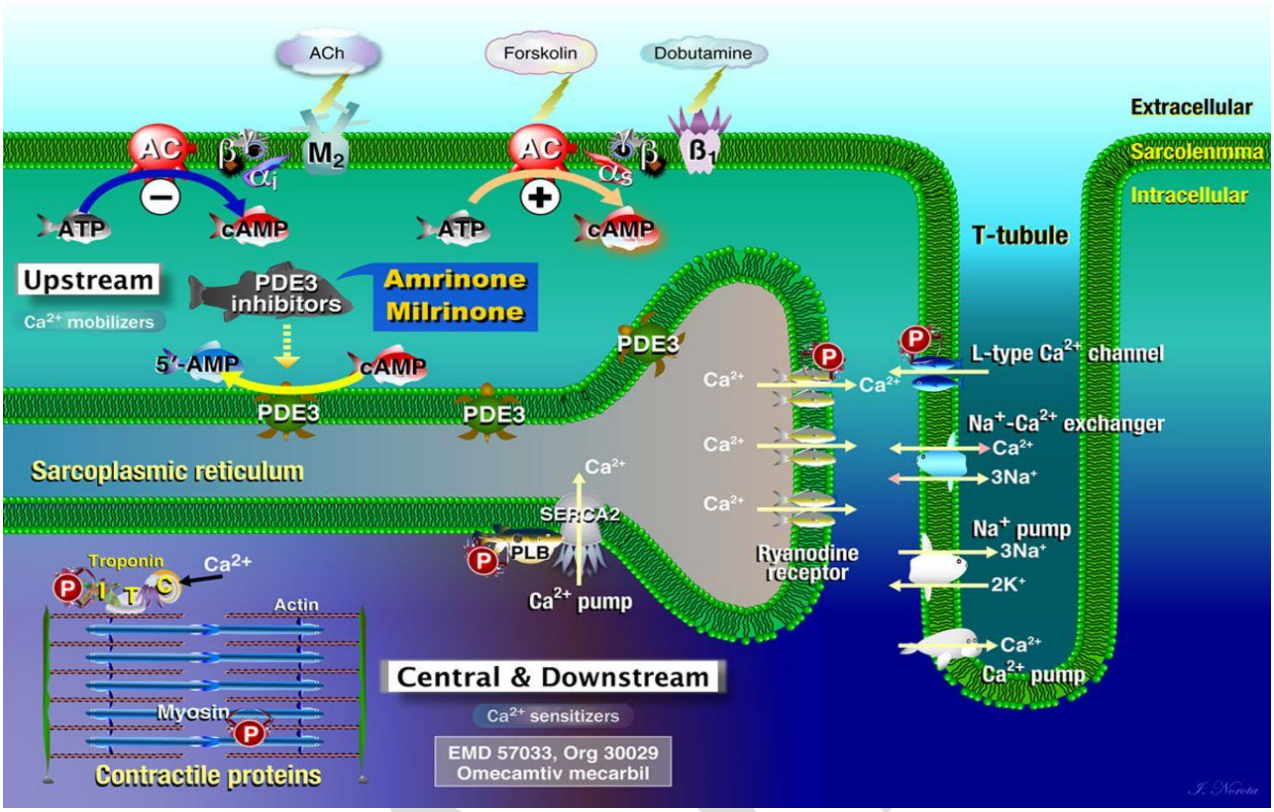
Amrinone

Amrinone (or inamrinone) is a type 3 pyridine phosphodiesterase inhibitor. It is used in the treatment of congestive heart failure.

Mechanism of action

Amrinone is a positive inotropic cardiotonic with vasodilator properties, phosphodiesterase inhibitory activity, and the ability to stimulate calcium ion influx into the cardiac cell. Amrinone is a phosphodiesterase inhibitor (PDE3), resulting in increased cAMP and cGMP which leads to an increase in the calcium influx like that caused by beta-agonists resulting in increased inotropic effect.

Increases cardiac contractility, vasodilator. Acts by inhibiting the breakdown of both cAMP and cGMP by the phosphodiesterase (PDE3) enzyme. There is a long-standing controversy regarding whether the drug actually increases cardiac contractility in diseased myocardium (and therefore whether it is of any clinical use).



Digoxin

A cardiotonic glycoside obtained mainly from Digitalis lanata; it consists of three sugars and the aglycone digoxigenin. Digoxin has positive inotropic and negative chronotropic activity. It is used to control ventricular rate in atrial fibrillation and in the management of congestive heart failure with atrial fibrillation. Its use in congestive heart failure and sinus rhythm is less certain. The margin between toxic and therapeutic doses is small. Digoxin, a cardiac glycoside similar to digitoxin, is used to treat congestive heart failure and supraventricular arrhythmias due to reentry mechanisms, and to control ventricular rate in the treatment of chronic atrial fibrillation.

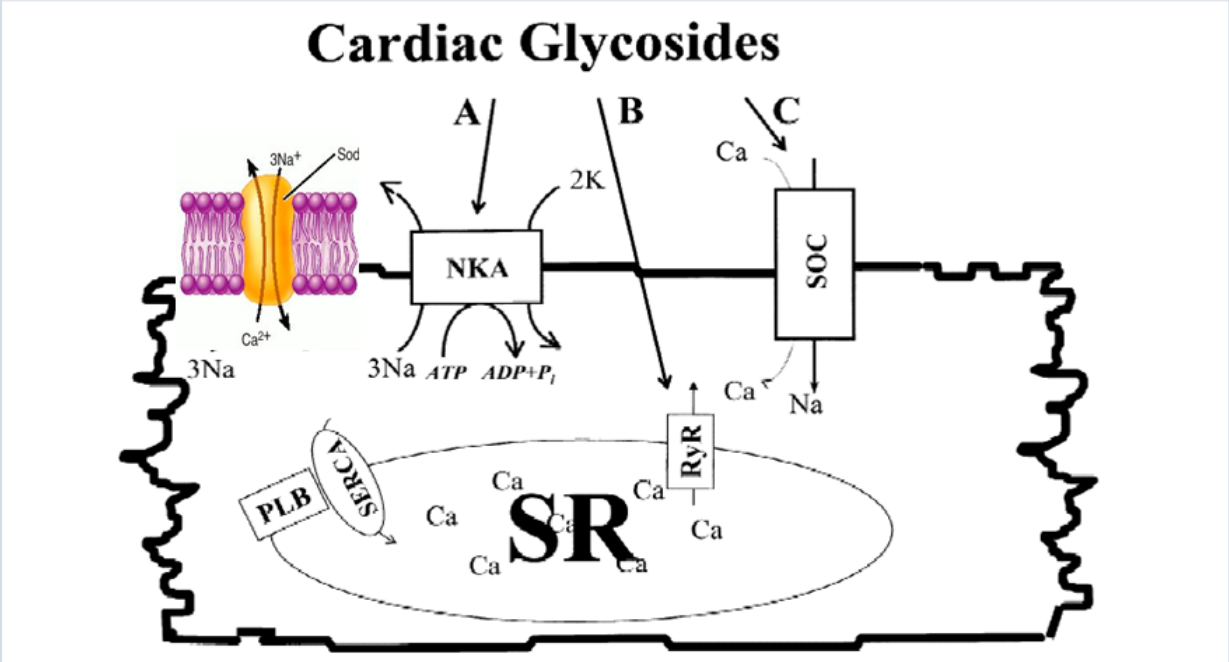
Mechanism of action

Digoxin inhibits the Na-K-ATPase membrane pump, resulting in an increase in intracellular sodium. The sodium calcium exchanger (NCX)in turn tries to extrude the sodium and in so doing, pumps in more calcium. Increased intracellular concentrations of calcium may

promote activation of contractile proteins (e.g., actin, myosin). Digoxin also acts on the electrical activity of the heart, increasing the slope of phase 4 depolarization, shortening the action potential duration, and decreasing the maximal diastolic potential.

Mechanism of Action of Digoxin:

Blockade of Na^+/K^+-ATPase Reduces Activity of Na^+–Ca^{2+} Exchanger, which leads to increased intracellular Ca^{2+}



ADP=adenosine diphosphate; ATPase=adenosine triphosphatase; Ca=calcium; Na=sodium; NKA= sodium-potassium-ATPase; Pi =phosphate; PLB=phospholamban; RyR= ryanodine receptors; SERCA=sarcoplasmic reticulum calcium transport ATPase; SOC= sodium-calcium exchanger; SR=sarcoplasmic reticulum.

In order to optimize dosing and hence the benefits of digoxin, we need to consider the mechanism of action of digoxin. Therefore this presentation begins with a review of the scientific background explaining why, as a medication, digoxin can act as a double-edged sword. The fundamental action of digoxin is to affect the activity of intracellular sodium–potassium adenosine triphosphatase (Na^+/K^+-ATPase). But the mechanism of action of digoxin is more complicated, as inhibition of Na^+/K^+-ATPase affects the sodium–calcium (Na^+–Ca^{2+}) exchanger, with a resulting build-up of sodium inside the cell and preventing calcium from being

extruded. It is the combination of those two effects that leads to increased calcium within the cell.

Kidney disorder

Kidney disease, also known as nephropathy or renal disease, is damage to or disease of a kidney. Nephritis is inflammatory kidney disease. Nephrosis is noninflammatory kidney disease. Kidney disease usually causes kidney failure to some degree, with the amount depending on the type of disease. In precise usage, disease denotes the structural and causal disease entity whereas failure denotes the impaired kidney function. In common usage these meanings overlap; for example, the terms chronic kidney disease and chronic renal failure are usually considered synonymous. Acute kidney disease has often been called acute renal failure, although nephrologists now often tend to call it acute kidney injury. About 1 in 8 Americans suffer from chronic kidney disease

Benzodiazepines

Benzodiazepines (BZD, BZs), sometimes called "benzos", are a class of psychoactive drugs whose core chemical structure is the fusion of a benzene ring and a diazepine ring. Benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the $GABA_A$ receptor, resulting in sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties. High doses of many shorter-acting benzodiazepines may also cause anterograde amnesia and dissociation. These properties make benzodiazepines useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. Benzodiazepines are categorized as either short-, intermediate-, or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety.

Mechanism of action

Benzodiazepines work by increasing the efficiency of a natural brain chemical, GABA, to decrease the excitability of neurons. This reduces the communication between neurons and, therefore, has a calming effect on many of the functions of the brain.

GABA controls the excitability of neurons by binding to the $GABA_A$ receptor. The $GABA_A$ receptor is a protein complex located in the synapses of neurons. All $GABA_A$ receptors contain an ion channel that conducts chloride ions across neuronal cell membranes and two binding sites for the neurotransmitter gamma-aminobutyric acid (GABA), while a subset of $GABA_A$ receptor complexes also contain a single binding site for benzodiazepines. Binding of benzodiazepines to this receptor complex does not alter binding of GABA. Unlike other positive allosteric modulators that increases ligand binding, benzodiazepine binding acts as a positive allosteric modulator by increasing the total conduction of chloride ions across the neuronal cell membrane when GABA is already bound to its receptor. This increased chloride ion influx hyperpolarizes the neuron's membrane potential. As a result, the difference between resting potential and threshold potential is increased and firing is less likely. Different $GABA_A$ receptor subtypes have varying distributions within different regions of the brain and, therefore, control distinct neuronal circuits. Hence, activation of different $GABA_A$ receptor subtypes by benzodiazepines may result in distinct pharmacological actions. In terms of the mechanism of action of benzodiazepines, their similarities are too great to separate them into individual categories such as anxiolytic or hypnotic. For example, a hypnotic administered in low doses produces anxiety-relieving effects, whereas a benzodiazepine marketed as an anti-anxiety drug at higher doses induces sleep.

The subset of $GABA_A$ receptors that also bind benzodiazepines are referred to as benzodiazepine receptors (BzR). The $GABA_A$ receptor is a heteromer composed of five subunits, the most common ones being two αs, two βs, and one γ ($\alpha_2\beta_2\gamma$). For each subunit, many subtypes exist (α_{1-6}, β_{1-3}, and γ_{1-3}). $GABA_A$ receptors that are made up of different combinations of subunit subtypes have different properties, different distributions in the brain and different activities relative to pharmacological and clinical effects.[149] Benzodiazepines bind at the interface of the α and γ subunits on the $GABA_A$ receptor. Binding also requires that alpha subunits contain a histidine amino acid residue, (*i.e.*, α_1, α_2, α_3, and $\alpha_5$containing $GABA_A$ receptors). For this

reason, benzodiazepines show no affinity for $GABA_A$ receptors containing α_4 and α_6 subunits with an arginine instead of a histidine residue. Once bound to the benzodiazepine receptor, the benzodiazepine ligand locks the benzodiazepine receptor into a conformation in which it has a greater affinity for the GABA neurotransmitter. This increases the frequency of the opening of the associated chloride ion channel and hyperpolarizes the membrane of the associated neuron. The inhibitory effect of the available GABA is potentiated, leading to sedatory and anxiolytic effects. For instance, those ligands with high activity at the α_1 are associated with stronger hypnotic effects, whereas those with higher affinity for $GABA_A$ receptors containing α_2 and/or α_3 subunits have good anti-anxiety activity.

The benzodiazepine class of drugs also interact with peripheral benzodiazepine receptors. Peripheral benzodiazepine receptors are present in peripheral nervous system tissues, glial cells, and to a lesser extent the central nervous system. These peripheral receptors are not structurally related or coupled to $GABA_A$ receptors. They modulate the immune system and are involved in the body response to injury. Benzodiazepines also function as weak adenosine reuptake inhibitors. It has been suggested that some of their anticonvulsant, anxiolytic, and muscle relaxant effects may be in part mediated by this action

Furosemide

Furosemide, sold under the brand name Lasix among others, is a medication used to treat fluid build-up due to heart failure, liver scarring, or kidney disease. It may also be used for the treatment of high blood pressure. The amount of medication required depends on the person in question. It can be taken intravenously or by mouth. When taken by mouth it typically begins working within an hour while intravenously it typically begins working within five minutes.

Common side effects include low blood pressure with standing, ringing in the ears, and sensitivity to the sun. Potentially serious side effects include electrolyte abnormalities, low blood pressure, and hearing loss. Blood tests are recommended regularly for those on treatment. Furosemide is a type of loop diuretic that works by decreasing the reabsorption of sodium by the kidneys.

Mechanism of action

Furosemide, like other loop diuretics, acts by inhibiting NKCC2, the luminal Na-K-Cl cotransporter in the thick ascending limb of the loop of Henle. The action on the distal tubules is independent of any inhibitory effect on carbonic anhydrase or aldosterone; it also abolishes the corticomedullary osmotic gradient and blocks negative, as well as positive, free water clearance.Because of the large NaCl absorptive capacity of the loop of Henle, diuresis is not limited by development of acidosis, as it is with the carbonic anhydrase inhibitors. Additionally, furosemide is a noncompetitive subtype-specific blocker of GABA-A receptors. Furosemide has been reported to reversibly antagonize GABA-evoked currents of $\alpha_6\beta_2\gamma_2$ receptors at μM concentrations, but not $\alpha_1\beta_2\gamma_2$ receptors. During development, the $\alpha_6\beta_2\gamma_2$ receptor increases in expression in cerebellar granule neurons, corresponding to increased sensitivity to furosemide.

Antiepileptic drugs

Anticonvulsants (also commonly known as antiepileptic drugs or as antiseizure drugs) are a diverse group of pharmacological agents used in the treatment of epilepticseizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorderand borderline personality disorder since many seem to act as mood stabilizers, and for the treatment of neuropathic pain. Anticonvulsants suppress the rapid and excessive firing of neurons during seizures. Anticonvulsants also prevent the spread of the seizure within the brain. Some investigators have observed that anticonvulsants themselves may cause reduced IQ in children. However these adverse effects must be balanced against the significant risk epileptic seizures pose to children and the distinct possibility of death and devastating neurological sequelae secondary to seizures. Anticonvulsants are more accurately called antiepileptic drugs (abbreviated "AEDs"), and are often referred to as antiseizure drugs because they provide symptomatic treatment only and have not been demonstrated to alter the course of epilepsy.

Lamictal

Lamotrigine, originally marketed as Lamictal and available under many brands worldwide, is an anticonvulsant drug used in the treatment of epilepsy and bipolar disorder. It is

also used off-label as an adjunct in treating clinical depression. For epilepsy, it is used to treat focal seizures, primary and secondary tonic-clonic seizures, and seizures associated with Lennox-Gastaut syndrome. Like many other anticonvulsant medications, lamotrigine also seems to act as an effective mood stabilizer, and was the first U.S. Food and Drug Administration (FDA)-approved drug for this purpose since lithium, a drug approved almost 30 years earlier. It is approved for the maintenance treatment of bipolar type II.

Lamictal (lamotrigine) is an anti-epileptic medication, also called an anticonvulsant. Lamictal is used either alone or in combination with other medications to treat epileptic seizures in adults and children. Lamotrigine is also used to delay mood episodes in adults with bipolar disorder (manic depression).The immediate-release form of Lamictal (regular tablet and orally disintegrating tablet) can be used in children as young as 2 years old when it is given as part of a combination of seizure medications. However, this form should not be used as a single medication in a child or teenager who is younger than 16 years old.The extended-release form of lamotrigine (Lamictal XR) is for use only in adults and children who are at least 13 years old.

Mechanism of action

Lamotrigine is a member of the sodium channel blocking class of antiepileptic drugs. It is a triazine derivate that inhibits voltage-sensitive sodium channels, leading to stabilization of neuronal membranes. It also blocks L-, N-, and P-type calcium channels and has weak 5-hydroxytryptamine-3 (5-HT3) receptor inhibition. These actions are thought to inhibit release of glutamate at cortical projections in the ventral striatum limbic areas, and its neuroprotective and antiglutamatergic effects have been pointed out as promising contributors to its mood stabilizing activity. Observations that lamotrigine reduced γ-aminobutyric acid (GABA) A receptor-mediated neurotransmission in rat amygdala, suggest that a GABAergic mechanism may also be involved, although this concept is controversial.

Lamotrigine does not have pronounced effects on any of the usual neurotransmitter receptors (adrenergic, dopamine D1 and D2, muscarinic, GABA, histaminergic H1, serotonin 5-HT2, and N-methyl-D-asparate). Inhibitory effects on 5-HT, norepinephrine, and dopamine

transporters are weak. Lamotrigine is a weak inhibitor of dihydrofolate reductase, but whether this effect is sufficient to contribute to a mechanism of action or increases risk to the fetus during pregnancy is not known. Early studies of lamotrigine's mechanism of action examined its effects on the release of endogenous amino acids from rat cerebral cortex slices in vitro. As is the case for antiepileptic drugs that act on voltage-dependent sodium channels, lamotrigine inhibited the release of glutamate and aspartate evoked by the sodium-channel activator veratrine and was less effective in the inhibition of acetylcholine or GABA release. At high concentrations, it had no effect on spontaneous or potassium evoked amino acid release.

These studies suggested that lamotrigine acts presynaptically on voltage-gated sodium channels to decrease glutamate release. Several electrophysiological studies have investigated the effects of lamotrigine on voltage-dependent sodium channels. For example, lamotrigine blocked sustained repetitive firing in cultured mouse spinal cord neurons in a concentration-dependent manner, at concentrations that are therapeutically relevant in the treatment of human seizures. In cultured hippocampal neurons, lamotrigine reduced sodium currents in a voltage-dependent manner, and at depolarised potentials showed a small frequency-dependent inhibition. These and a variety of other results indicate that the antiepileptic effect of lamotrigine, like that of phenytoin and carbamazepine, is at least in part due to use- and voltage-dependent modulation of fast voltage-dependent sodium currents. However, lamotrigine has a broader clinical spectrum of activity than phenytoin and carbamazepine and is recognised to be protective against generalised absence epilepsy and other generalised epilepsy syndromes, including primary generalised tonic–clonic seizures, juvenile myoclonic epilepsy, and Lennox-Gastaut syndrome.

The basis for this broader spectrum of activity of lamotrigine is unknown, but could relate to actions of the drug on voltage-activated calcium channels. Lamotrigine blocks T-type calcium channels weakly, if at all. However, it does inhibit native and recombinant high-voltage–activated calcium channels (N- and P/Q/R-types) at therapeutic concentrations. Whether this activity on calcium channels accounts for lamotrigine's broader clinical spectrum of activity in comparison with phenytoin and carbamazepine remains to be determined.

Tapclob

Tapclob Oral Suspension is used for Adjunctive treatment of seizures associated with lennox-gastaut syndrome in patients 2 years of age or older and other conditions. Tapclob Oral Suspension contains Clobazam as an active ingredient. Tapclob Oral Suspension works by binding at the benzodiazepine site of the GABA-A receptor to potentiate GABAergic neurotransmission.

Mechanism of action

Tapclob Oral Suspension improves the patient's condition by performing the following functions:

- Binding at the benzodiazepine site of the GABA-A receptor to potentiate GABAergic neurotransmission.

Before using this drug, inform your doctor about your current list of medications, over the counter products (e.g. vitamins, herbal supplements, etc.), allergies, pre-existing diseases, and current health conditions (e.g. pregnancy, upcoming surgery, etc.). Some health conditions may make you more susceptible to the side-effects of the drug. Take as directed by your doctor or follow the direction printed on the product insert. Dosage is based on your condition. Tell your doctor if your condition persists or worsens. Important counseling points are listed below.

- Abrupt withdrawal may increase your risk of seizure
- Avoid alcohol and other central nervous system depressants
- Avoid driving
- Concomitant use with central nervous system depressants
- Physical and psychological dependence
- Report to doctor immediately if experiencing serious skin reactions

Cough

A cough is a sudden and often repetitively occurring, protective reflex, which helps to clear the large breathing passages from fluids, irritants, foreign particles and microbes. The cough reflex consists of three phases: an inhalation, a forced exhalation against a closed glottis, and a violent release of air from the lungs following opening of the glottis, usually accompanied by a distinctive sound. Coughing is either voluntary or involuntary.

Frequent coughing usually indicates the presence of a disease. Many viruses and bacteria benefit, from an evolutionary perspective, by causing the host to cough, which helps to spread the disease to new hosts. Most of the time, irregular coughing is caused by a respiratory tract infection but can also be triggered by choking, smoking, air pollution, asthma, gastroesophageal reflux disease, post-nasal drip, chronic bronchitis, lung tumors, heart failure and medications such as ACE inhibitors.Treatment should target the cause; for example, smoking cessation or discontinuing ACE inhibitors. Cough suppressants such as codeine or dextromethorphan are frequently prescribed, but have been demonstrated to have little effect. Other treatment options may target airway inflammation or may promote mucus expectoration. As it is a natural protective reflex, suppressing the cough reflex might have damaging effects, especially if the cough is productive

Dextromethorphane Hydrobromide

Dextromethorphan (DXM or DM) is a drug of the morphinan class with sedative, Promethazine HCl and **Dextromethorphan Hydrobromide** Syrup is a combination of an antihistamine and a cough suppressant used to treat cough, itching, runny nose, sneezing, and itchy or watery eyes caused by colds or allergies. Promethazine HCl and **dextromethorphan hydrobromide** syrup is available in generic form.dissociative, and stimulant properties (at higher doses).

It is a cough suppressant in many over-the-counter cold and cough medicines including generic labels and store brands, Benylin DM, Mucinex DM, Camydex-20 tablets, Robitussin, NyQuil, Dimetapp, Vicks, Coricidin, Delsym, TheraFlu, Cheracol D, and others. Dextromethorphan has also found numerous other uses in medicine, ranging from pain relief (as either the primary analgesic, or an opioid potentiator) over psychological applications to the treatment of addiction. It is sold in syrup, tablet, spray, and lozenge forms. In its pure form, dextromethorphan occurs as a white powder.[3]

DXM is also used recreationally. When exceeding approved dosages, dextromethorphan acts as a dissociative anesthetic. Its mechanism of action is via multiple effects, including actions as a nonselective serotonin reuptake inhibitor[4] and a sigma-1 receptor agonist.[5][6] DXM and its major metabolite, dextrorphan, also act as an NMDA receptor antagonist at high doses, which

produces effects similar to, yet distinct from, the dissociative states created by other dissociative anesthetics such as ketamine and phencyclidine.

Dextromethorphan suppresses the cough reflex by a direct action on the cough center in the medulla of the brain. Dextromethorphan shows high affinity binding to several regions of the brain, including the medullary cough center. This compound is an NMDA receptor antagonist and acts as a non-competitive channel blocker. It is one of the widely used antitussives, and is also used to study the involvement of glutamate receptors in neurotoxicity.

Mechanism of action

Dextromethorphan is an opioid-like drug that binds to and acts as antagonist to the NMDA glutamatergic receptor, it is an agonist to the opioid sigma 1 and sigma 2 receptors, it is also an alpha3/beta4 nicotinic receptor antagonist and targets the serotonin reuptake pump. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, where it enters the bloodstream and crosses the blood-brain barrier. The first-pass through the hepatic portal vein results in some of the drug being metabolized into an active metabolite of dextromethorphan, dextrorphan, the 3-hydroxy derivative of dextromethorphan.

Noscapine

Noscapine (also known as Narcotine, Nectodon, Nospen, Anarcotine and (archaic) Opiane) is a benzylisoquinoline alkaloid from plants of the poppy family, without painkilling properties. This agent is primarily used for its antitussive (cough-suppressing) effects.

Mechanism of action

Noscapine's antitussive effects appear to be primarily mediated by its σ–receptor agonist activity. Evidence for this mechanism is suggested by experimental evidence in rats. Pretreatment with rimcazole, a σ-specific antagonist, causes a dose-dependent reduction in antitussive activity of noscapine. Noscapine, and its synthetic derivatives called noscapinoids, are known to interact with microtubules and inhibit cancer cell proliferation

Bronchial asthma

Ever hear the term "bronchial asthma" and wonder what it means? When people talk about bronchial asthma, they are really talking about asthma, a chronic inflammatory disease of the airways that causes periodic "attacks" of coughing, wheezing, shortness of breath, and chest

tightness.According to the CDC, more than 25 million Americans, including 6.8 million children under age 18, suffer with asthma today.

Allergies are strongly linked to asthma and to other respiratory diseases such as chronic sinusitis, middle ear infections, and nasal polyps. Most interestingly, a recent analysis of people with asthma showed that those who had both allergies and asthma were much more likely to have nighttime awakening due to asthma, miss work because of asthma, and require more powerful medications to control their symptoms.

Asthma is associated with mast cells, eosinophils, and T lymphocytes. Mast cells are the allergy-causing cells that release chemicals like histamine. Histamine is the substance that causes nasal stuffiness and dripping in a cold or hay fever, constriction of airways in asthma, and itchy areas in a skin allergy. Eosinophils are a type of white blood cell associated with allergic disease. T lymphocytes are also white blood cells associated with allergy and inflammation.

Salbutamol

Salbutamol, also known as albuterol and marketed as Ventolin among other names, is a medication that opens up the medium and large airways in the lungs. It is used to treat asthma, exercise-induced bronchoconstriction, and chronic obstructive pulmonary disease (COPD). It may also be used to treat high blood potassium levels. It is usually used by inhaler or nebulizer but is also available as a pill and intravenous solution. Onset of action of the inhaled version is typically within 15 minutes and lasts for two to six hours.

Common side effects include shakiness, headache, fast heart rate, dizziness, and feeling anxious. Serious side effects may include worsening bronchospasm, irregular heartbeat, and low blood potassium levels. It can be used during pregnancy and breastfeeding, but safety is not entirely clear. Salbutamol is a short-acting β_2 adrenergic receptor agonist which works by causing airway smooth muscles to relax.

Salbutamol is a short-acting, selective beta2-adrenergic receptor agonist used in the treatment of asthma and COPD. It is 29 times more selective for beta2 receptors than beta1 receptors giving it higher specificity for pulmonary beta receptors versus beta1-adrenergic receptors located in the heart. Salbutamol is formulated as a racemic mixture of the R- and S-isomers. The R-isomer has 150 times greater affinity for the beta2-receptor than the S-isomer and the S-isomer has been associated with toxicity. This lead to the development of levalbuterol,

the single R-isomer of salbutamol. However, the high cost of levalbuterol compared to salbutamol has deterred wide-spread use of this enantiomerically pure version of the drug. Salbutamol is generally used for acute episodes of bronchospasm caused by bronchial asthma, chronic bronchitis and other chronic bronchopulmonary disorders such as chronic obstructive pulmonary disorder (COPD). It is also used prophylactically for exercise-induced asthma.

Salbutamol (INN) or albuterol (USAN), a moderately selective beta(2)-receptor agonist similar in structure to terbutaline, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. The R-isomer, levalbuterol, is responsible for bronchodilation while the S-isomer increases bronchial reactivity. The R-enantiomer is sold in its pure form as Levalbuterol. The manufacturer of levalbuterol, Sepracor, has implied (although not directly claimed) that the presence of only the R-enantiomer produces fewer side-effects.

Mechanism of action

Salbutamol is a beta(2)-adrenergic agonist and thus it stimulates beta(2)-adrenergic receptors. Binding of albuterol to beta(2)-receptors in the lungs results in relaxation of bronchial smooth muscles. It is believed that salbutamol increases cAMP production by activating adenylate cyclase, and the actions of salbutamol are mediated by cAMP. Increased intracellular cyclic AMP increases the activity of cAMP-dependent protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular calcium concentrations. A lowered intracellular calcium concentration leads to a smooth muscle relaxation and bronchodilation. In addition to bronchodilation, salbutamol inhibits the release of bronchoconstricting agents from mast cells, inhibits microvascular leakage, and enhances mucociliary clearance.

Aminophylline

Aminophylline is a drug combination that contains theophylline and ethylenediamine in a 2:1 ratio. Once in the body, theophylline is released and acts as a phosphodiesterase inhibitor, adenosine receptor blocker, and histone deacetylase activator. Similar to other theophyllines, aminophylline is indicated for the treatment of lung diseases such as asthma, chronic bronchitis, and COPD. The majority of aminophylline medications are discontinued and the remaining medications on the market are in short supply.Aminophylline is the ethylenediamine salt of theophylline. Theophylline stimulates the CNS, skeletal muscles, and cardiac muscle. It relaxes

certain smooth muscles in the bronchi, produces diuresis, and causes an increase in gastric secretion.

Mechanism of action

Aminophylline is the ethylenediamine salt of theophylline. After ingestion, theophylline is released from aminophylline, and theophylline relaxes the smooth muscle of the bronchial airways and pulmonary blood vessels and reduces airway responsiveness to histamine, methacholine, adenosine, and allergen. Theophylline competitively inhibits type III and type IV phosphodiesterase (PDE), the enzyme responsible for breaking down cyclic AMP in smooth muscle cells, possibly resulting in bronchodilation. Theophylline also binds to the adenosine A2B receptor and blocks adenosine mediated bronchoconstriction. In inflammatory states, theophylline activates histone deacetylase to prevent transcription of inflammatory genes that require the acetylation of histones for transcription to begin.

Diuretic

A **diuretic** is any substance that promotes diuresis, that is, the increased production of urine. This includes forced diuresis. There are several categories of diuretics. All diuretics increase the excretion of water from bodies, although each class does so in a distinct way. Alternatively, an antidiuretic such as vasopressin, or antidiuretic hormone, is an agent or drug which reduces the excretion of water in urine.

Medical uses

In medicine, diuretics are used to treat heart failure, liver cirrhosis, hypertension, influenza, water poisoning, and certain kidney diseases. Some diuretics, such as acetazolamide, help to make the urine more alkaline and are helpful in increasing excretion of substances such as aspirin in cases of overdose or poisoning. Diuretics are often abused by those with eating disorders, especially bulimics, in attempts to lose weight.

The antihypertensive actions of some diuretics (thiazides and loop diuretics in particular) are independent of their diuretic effect.[citation needed] That is, the reduction in blood pressure is not due to decreased blood volume resulting from increased urine production, but occurs through other mechanisms and at lower doses than that required to produce diuresis.

Indapamide was specifically designed with this in mind, and has a larger therapeutic window for hypertension (without pronounced diuresis) than most other diuretics.

Mechanism of action

Diuretics are tools of considerable therapeutic importance. First, they effectively reduce blood pressure. Loop and thiazide diuretics are secreted from the proximal tubule via the organic anion transporter-1 and exert their diuretic action by binding to the Na(+)-K(+)-2Cl(-) co-transporter type 2 in the thick ascending limb and the Na(+)-Cl(-) co-transporter in the distal convoluted tubule, respectively. Classification of common diuretics and their mechanisms of action.

Mannitol

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 may also be used for the promotion of diuresis before irreversible renal failure becomes established; the promotion of urinary excretion of toxic substances; as an Antiglaucoma agent; and as a renal function diagnostic aid.

Chemically, mannitol is an alcohol and a sugar, or a polyol; it is similar to xylitol or sorbitol. However, mannitol has a tendency to lose a hydrogen ion in aqueous solutions, which causes the solution to become acidic. For this reason, it is not uncommon to add a substance to adjust its pH, such as sodium bicarbonate. Mannitol is commonly used to increase urine production (diuretic). It is also used to treat or prevent medical conditions that are caused by an increase in body fluids/water (e.g., cerebral edema, glaucoma, kidney failure). Mannitol is frequently given along with other diuretics (e.g., furosemide, chlorothiazide) and/or IV fluid replacement.

Mechanism of action

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. As a diurectic mannitol induces diuresis because it is not reabsorbed in the renal tubule, thereby increasing the osmolality of the glomerular filtrate, facilitating excretion of water, and inhibiting the renal tubular reabsorption of sodium, chloride, and other solutes. Mannitol promotes the urinary excretion of toxic materials and protects against nephrotoxicity by preventing the concentration of toxic substances in the tubular fluid. As an Antiglaucoma agent mannitol levates blood plasma osmolarity, resulting in enhanced flow of water from the eye into plasma and a consequent reduction in intraocular pressure. As a renal function diagnostic aid mannitol is freely filtered by the glomeruli with less than 10% tubular reabsorption. Therefore, its urinary excretion rate may serve as a measurement of glomerular filtration rate (GFR).

Xanthine

Xanthine (3,7-dihydropurine-2,6-dione), is a purine base found in most human body tissues and fluids and in other organisms. A number of stimulants are derived from xanthine, including caffeine and theobromine.

Xanthine is a product on the pathway of purine degradation.

- It is created from guanine by guanine deaminase.
- It is created from hypoxanthine by xanthine oxidoreductase.
- It is also created from xanthosine by purine nucleoside phosphorylase (PNP).

Xanthine is subsequently converted to uric acid by the action of the xanthine oxidase enzyme.

Studies reported in 2008, based on $^{12}C/^{13}C$ isotopic ratios of organic compounds found in the Murchison meteorite, suggested that xanthine and related chemicals, including the RNA component uracil, were formed extraterrestrially. In August 2011, a report, based on NASA studies with meteorites found on Earth, was published suggesting xanthine and related organic molecules, including the DNA and RNA components adenine and guanine, were found in outer space.

Mechanism of action

Xanthines are effective in the treatment of asthma, but the mechanism of action remains unclear. Pulmonary effects of seven xanthines, exhibiting a range of potencies as cyclic nucleotide phosphodiesterase (PDE) inhibitors and as adenosine antagonists, were investigated in anesthetized and ventilated guinea pigs. The bronchodilator effects of xanthines, determined from reversal of bronchoconstriction induced by aerosols of histamine and carbachol, correlated with their relative potencies as cyclic AMP-PDE inhibitors. The hypotensive effects of xanthines at bronchodilator doses were also consistent with PDE inhibition. Prophylactic effects of xanthines against bronchoconstriction induced by an aerosol of ovalbumin in sensitized guinea pigs, or by aerosols of leukotriene D4 and platelet-activating factor (PAF) in normal guinea pigs, occurred by a mechanism unrelated to bronchodilation and could not be readily attributed to PDE inhibition or adenosine A1/A2 receptor antagonism. There was a close association between inhibition of the responses to antigen and leukotriene D4, suggesting a common mechanism of action, but these effects gave a different profile from inhibition of the response to PAF. In addition, PAF-induced hypotension was unaffected in animals in which PAF-induced bronchoconstriction was inhibited, suggesting a mechanism other than PAF receptor antagonism. These results indicate that the bronchodilator, antiallergic and anti-inflammatory effects of xanthines occur through multiple molecular mechanisms of action, including at least one unknown mechanism. Furthermore, 8-phenyltheophylline produces these prophylactic effects at a dose that does not produce the cardiovascular or emetic side effects associated with xanthines, thereby exhibiting unique characteristics of potential therapeutic importance.

Anti Ulcer Drugs

Anti Ulcer Drugs are medicines used to treat ulcers in the stomach and the upper part of the small intestine.

Purpose

The Anti Ulcer Drugs are used as part of the treatment for ulcers. Ulcers are sores or raw areas that form in the lining of the stomach or the duodenum (the upper part of the intestine). Those that form in the stomach are called Gastric Ulcers; in the duodenum, they are called

Duodenal Ulcers. Both types are referred to as Peptic Ulcers. For a long time, physicians thought that stress and certain foods caused ulcers.

Cimetidine

A histamine congener, it competitively inhibits histamine binding to histamine H2 receptors. Cimetidine has a range of pharmacological actions. It inhibits gastric acid secretion, as well as pepsin and gastrins output. It also blocks the activity of cytochrome P-450 which might explain proposals for use in neoadjuvant therapy.Cimetidine is a histamine H2-receptor antagonist. It reduces basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin. It is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Cimetidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of Cimetidine include an increase in gastric bacterial flora such as nitrate-reducing organisms.

Mechanism of action

Cimetidine binds to an H2-receptor located on the basolateral membrane of the gastric parietal cell, blocking histamine effects. This competitive inhibition results in reduced gastric acid secretion and a reduction in gastric volume and acidity. **Cimetidine** is a drug that blocks the production of acid by acid-producing cells in the stomach and can be administered orally, IM or IV. It belongs to a class of drugs called H2 (histamine-2) blockers that also includes ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid).

Histamine is a naturally-occurring chemical that stimulates cells in the stomach (parietal cells) to produce acid. H2-blockers inhibit the action of histamine on the cells, thus reducing the production of acid by the stomach. Since excessive stomach acid can damage the esophagus, stomach, and duodenum by reflux and lead to inflammation and ulceration, reducing stomach acid prevents and allows acid-induced inflammation and ulcers to heal.

Ranitidine

Ranitidine, sold under the trade name Zantac among others, is a medication that decreases stomach acid production. It is commonly used in treatment of peptic ulcer disease, gastroesophageal reflux disease, and Zollinger–Ellison syndrome. There is also tentative evidence of benefit for hives. It can be taken by mouth, by injection into a muscle, or into a vein.

Common side effects include headaches and pain or burning if given by injection. Serious side effects may include liver problems, a slow heart rate, pneumonia, and the potential of masking stomach cancer. It is also linked to an increased risk of Clostridium difficile colitis. It is generally safe in pregnancy. Ranitidine is an H_2 histamine receptor antagonist that works by blocking histamine and thus decreasing the amount of acid released by cells of the stomach.

Mechanism of action

Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H2 receptors found in gastric parietal cells. This results in decreased gastric acid secretion and gastric volume, and reduced hydrogen ion concentration.Ranitidine is a histamine H2-receptor antagonist similar to cimetidine and famotidine. An H2-receptor antagonist, often shortened to H2 antagonist, is a drug used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia, however their use has waned since the advent of the more effective proton pump inhibitors. Like the H1-antihistamines, the H2 antagonists are inverse agonists rather than true receptor antagonists.The H2 antagonists are competitive inhibitors of histamine at the parietal cell H2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked.

Fever

Fever, also known as pyrexia and febrile response, is defined as having a temperature above the normal range due to an increase in the body's temperature set-point. There is not a single agreed-upon upper limit for normal temperature with sources using values between 37.5 and 38.3 °C (99.5 and 100.9 °F). The increase in set-point triggers increased muscle contractions and causes a feeling of cold. This results in greater heat production and efforts to conserve heat. When the set-point temperature returns to normal, a person feels hot, becomes flushed, and may begin to sweat. Rarely a fever may trigger a febrile seizure. This is more common in young children. Fevers do not typically go higher than 41 to 42 °C (105.8 to 107.6 °F). A fever can be caused by many medical conditions ranging from not serious to potentially serious. This includes viral, bacterial and parasitic infections such as the common cold, urinary tract infections, meningitis, malaria and appendicitis among others. Non-infectious causes include vasculitis, deep vein thrombosis, side effects of medication, and cancer among others. It differs from hyperthermia, in that hyperthermia is an increase in body temperature over the temperature set-point, due to either too much heat production or not enough heat loss.

Treatment to reduce fever is generally not required. Treatment of associated pain and inflammation, however, may be useful and help a person rest. Medications such as ibuprofen or paracetamol (acetaminophen) may help with this as well as lower temperature. Measures such as putting a cool damp cloth on the forehead and having a slightly warm bath are not useful and may simply make a person more uncomfortable. Children younger than three months require medical attention, as might people with serious medical problems such as a compromised immune system or people with other symptoms. Hyperthermia does require treatment.Fever is one of the most common medical signs. It is part of about 30% of healthcare visits by children[1] and occurs in up to 75% of adults who are seriously sick. While fever is a useful defense mechanism, treating fever does not appear to worsen outcomes. Fever is viewed with greater concern by parents and healthcare professionals than it usually deserves, a phenomenon known as fever phobia.

Paracetamol

Paracetamol, also known as acetaminophen or APAP, is a medication used to treat pain and fever. It is typically used for mild to moderate pain. The quality of the evidence regarding the use for fever relief in children is poor. It is often sold in combination with other ingredients such as in many cold medications. In combination with opioid pain medication, paracetamol is used for more severe pain such as cancer pain and after surgery. It is typically used either by mouth or rectally but is also available intravenously. Effects last between two and four hours.

Paracetamol is generally safe at recommended doses. Serious skin rashes may rarely occur, and too high a dose can result in liver failure. It appears to be safe during pregnancy and when breastfeeding. In those with liver disease, it may still be used, but in lower doses. Paracetamol is classified as a mild analgesic. It does not have significant anti-inflammatory activity and how it works is not entirely clear

Mechanism of action

The mechanism of action of paracetamol is not completely understood. Unlike NSAIDs such as aspirin, paracetamol does not appear to inhibit the function of any cyclooxygenase (COX) enzyme outside the central nervous system, and this appears to be the reason why it is not useful as an anti-inflammatory. It does appear to selectively inhibit COX activities in the brain, which may contribute to its ability to treat fever and pain. This activity does not appear to be direct inhibition by blocking an active site, but rather by reducing COX, which must be oxidized in order to function.

It also appears that paracetamol might modulate the endogenous cannabinoid system in the brain through paracetamol's metabolite, AM404 AM404 appears to inhibit the reuptake of the endogenous cannabinoid/vanilloid anandamide by neurons, making it more available to reduce pain. AM404 also appears to be able to directly activate the TRPV1 (older name: vanilloid receptor), which also inhibits pain signals in the brain.

Ibuprofen

Ibuprofen is a medication in the nonsteroidal anti-inflammatory drug (NSAID) class that is used for treating pain, fever, and inflammation. This includes painful menstrual periods, migraines, and rheumatoid arthritis. About 60% of people improve with any given NSAID, and it is recommended that if one does not work then another should be tried. It may also be used to close a patent ductus arteriosus in a premature baby. It can be used by mouth or intravenously. It typically begins working within an hour.

Common side effects include heartburn and a rash. Compared to other NSAIDs it may have fewer side effects such as gastrointestinal bleedingIt increases the risk of heart failure, kidney failure, and liver failure. At low doses, it does not appear to increase the risk of myocardial infarction; however, at higher doses it may. Ibuprofen can also result in worsened asthma. While it is unclear if it is safe in early pregnancy, it appears to be harmful in later pregnancy and therefore is not recommended. Like other NSAIDs, it works by inhibiting the production of prostaglandins by decreasing the activity of the enzyme cyclooxygenase. Ibuprofen might be a weaker anti-inflammatory than other NSAIDs

Mechanism of action

Nonsteroidal anti-inflammatory drugs such as ibuprofen work by inhibiting the cyclooxygenase (COX) enzymes, which convert arachidonic acid to prostaglandin H_2 (PGH_2). PGH_2, in turn, is converted by other enzymes to several other prostaglandins (which are mediators of pain, inflammation, and fever) and to thromboxane A_2 (which stimulates platelet aggregation, leading to the formation of blood clots).

Like aspirin and indometacin, ibuprofen is a nonselective COX inhibitor, in that it inhibits two isoforms of cyclooxygenase, COX-1 and COX-2. The analgesic, antipyretic, and anti-inflammatory activity of NSAIDs appears to operate mainly through inhibition of COX-2, which decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling. Antipyretic effects may be due to action on the hypothalamus, resulting in an increased peripheral blood flow, vasodilation, and subsequent heat dissipation. Inhibition of

COX-1 instead would be responsible for unwanted effects on the gastrointestinal tract. However, the role of the individual COX isoforms in the analgesic, anti-inflammatory, and gastric damage effects of NSAIDs is uncertain and different compounds cause different degrees of analgesia and gastric damage.

Ibuprofen is administered as a racemic mixture. The R-enantiomer undergoes extensive interconversion to the S-enantiomer *in vivo*. The S-enantiomer is believed to be the more pharmacologically active enantiomer. The R-enantiomer is converted through a series of three main enzymes. These enzymes include acyl-CoA-synthetase, which converts the R-enantiomer to (-)-R-ibuprofen I-CoA; 2-arylpropionyl-CoA epimerase, which converts (-)-R-ibuprofen I-CoA to (+)-S-Ibuprofen I-CoA; and hydrolase, which converts (+)-S-ibuprofen I-CoA to the S-enantiomer. In addition to the conversion of ibuprofen to the S-enantiomer, the body can metabolize ibuprofen to several other compounds, including numerous hydroxyl, carboxyl and glucuronyl metabolites. Virtually all of these have no pharmacological effects.

Possible Questions

1. Discuss used in therapy for bronchial asthma
2. Discuss mechanism of action, adverse reactions and therapeutic uses of antithyroid drugs
3. Describe the management of pulmonary tuberulosis
4. Describe the pharmacotherapy of diabetes mellitus
5. How sulfonamides act as antimicrobial drug? Explain the mechanism of action.
6. Discuss pharmacotherapy of peptic ulcer disease.
7. What are all the drugs which can act as digestants?
8. Discuss about anti fertility drugs.
9. Explain (i) emitics (ii) Antiemitics drugs
10. Write pharmacological actions and adverse reactions of ovulation inducing drugs.

1	IV	The main mechanism of most drugs absorption in	Active transport (carrier-	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	The reflex mechanism	The mixed mechanism	Active transport	**The reflex mechanism**
3	IV	What kind of substances can't permeate membranes	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	Dry cough and respiratory	**Sedative and hypnotic effects**
5	IV	The tissues most sensitive to atropine are:	The salivary, bronchial and	The gastric parietal cells	Smooth muscle and autonomic	The heart	**The salivary, bronchial and**
6	IV	Compared with atropine, scopolamine has all of the following properties	More marked central effect	Less potent in decreasing bronchial, salivary	More potent in producing mydriasis and	Lower effects on the heart, bronchial muscle	**Less potent in decreasing bronchial,**
7	IV	Contraindications to the use of antimuscarinic drugs are all of the	Glaucoma	Myasthenia	Bronchial asthma	Paralytic ileus and atony of the urinary bladder	**Bronchial asthma**
8	IV	A bronchial smooth	Alfa$_1$ receptor	Alfa$_2$ receptor	Beta $_1$ receptor	Beta $_2$ receptor	**Beta $_2$ receptor**
9	IV	Which of the following sympathomimetics is used	Formoterol	Norepinephrine	Methoxamine	Dobutamine	**Formoterol**
10	IV	Pick out the bronchodilator drug	Atropine	Orciprenaline	Adrenaline	Theophylline.	**Theophylline**
11	IV	Pick out the bronchodilator drug	Isoprenaline	Ephedrine	Atropine	Salbutamol	**Ephedrine**
12	IV	Propranolol is used in the treatment all of the	Cardiovascular diseases	Hyperthyroidism	Migraine headache	Bronchial asthma	**Bronchial asthma**
13	IV	This drug is contraindicated in patients	Propranolol	Clonidine	Enalapril	Nifedipine	**Propranolol**
14	IV	Which of the following vitamins is given along with isoniazide in	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	**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 of 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

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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

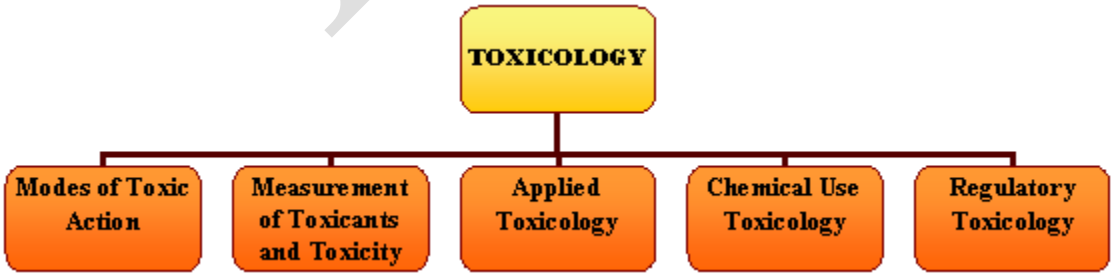
Toxicology

It is a branch of biology, chemistry, and medicine (morespecifically pharmacology) concerned with the study of the adverse effects of chemicals on living organisms. It also studies the harmful effects of chemical, biological and physical agents in biological systems that establishes the extent of damage in living organisms. 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); the route of exposure, the species, age, sex and environment.

Disciplines of Toxicology

Toxicology addresses a variety of questions. For example, in agriculture, toxicology determines the possible health effects from exposure to pesticides or herbicides, or the effect of animal feed additives, such as growth factors, on people. Toxicology is used in laboratory experiments on animals to establish dose-response relationships, agriculture, forensic, environmental etc. Toxicology also deals with the way chemicals and waste products affect the health of an individual

The field of toxicology can be further divided in to following sub-discipline on various basis



- **Mode of Toxic Action:** This includes the consideration, at the fundamental level of organ, cell and molecular function, of all events leading to toxicity in vivo: uptake, distribution, metabolism, mode of action, and excretion.

Biochemical and molecular toxicology consider events at the biochemical and molecular levels, including enzymes that metabolize Toxins, generation of reactive intermediates, interaction of Toxins or their metabolites with macromolecules, gene expression in metabolism and modes of action.

Behavioral toxicology deals with the effects of toxicants on animal and human behavior. This involves both the peripheral and central nervous systems.

Nutritional toxicology deals with the effects of diet on the expression of toxicity and with the mechanisms of these effects.

Carcinogenesis includes the chemical, biochemical, and molecular events that lead to the large number of effects on cell growth collectively known as cancer.

Mutagenesis is concerned with toxic effects on the genetic material and the inheritance of these effects.

Organ toxicity considers effects at the level of organ function (neurotoxicity, hepatotoxicity, nephrotoxicity, etc.).

- **Measurement of Toxicants and Toxicity.** These important aspects deal primarily with analytical chemistry, bioassay, and applied mathematic

Analytical toxicology is a branch of analytical chemistry concerned with the identification and assay of toxic chemicals and their metabolites in biological and environmental materials.

Toxicity testing involves the use of living systems to estimate toxic effects.

Toxicologic pathology is the branch of pathology that deals with the effects of toxic agents manifested as changes in sub cellular, cellular, tissue, or organ morphology.

Epidemiology as it applies to toxicology is of great importance as it deals with the relationship between chemical exposure and human disease in actual populations rather than in experimental settings.

- **Applied Toxicology.** This includes the various aspects of toxicology as they apply in the field or the development of new methodology or new selective toxicants for early application in the field setting.

Clinical Toxicology is concerned with diseases and illnesses associated with short term or long term exposure to toxic chemicals. Clinical toxicologists include emergency room physicians who must be familiar with the symptoms associated with exposure to a wide variety of toxic substances in order to administer the appropriate treatment.

Forensic Toxicology is used to help establish cause and effect relationships between exposure to a drug or chemical and the toxic or lethal effects that result from that exposure.

Occupational (Industrial) Toxicology is concerned with health effects from exposure to chemicals in the workplace. This field grew out of a need to protect workers from toxic substances and to make their work environment safe.

Environmental Toxicology is concerned with the study of chemicals that contaminate food, water, soil, or the atmosphere. It also deals with toxic substances that enter bodies of waters such as lakes, streams, rivers, and oceans.

Veterinary toxicology is the diagnosis and treatment of poisoning in animals other than humans, particularly livestock and companion animals, but not excluding feral species.

- **Chemical Use Classes.** This includes the toxicology aspects of the development of new chemicals for commercial use. In some of these use classes, toxicity, at least to some organisms, is a desirable trait; in others, it is an undesirable side effect. Use classes are not composed entirely of synthetic chemicals; many natural products are isolated and used for commercial and other purposes and must be subjected to

the same toxicity testing as that required for synthetic chemicals.

Agricultural chemicals include many compounds, such as insecticides, herbicides, fungicides, and rodenticides, in which toxicity to the target organism is a desired quality whereas toxicity to 'nontarget species' is to be avoided.

Clinical drugs are properly the province of pharmaceutical chemistry and pharmacology.

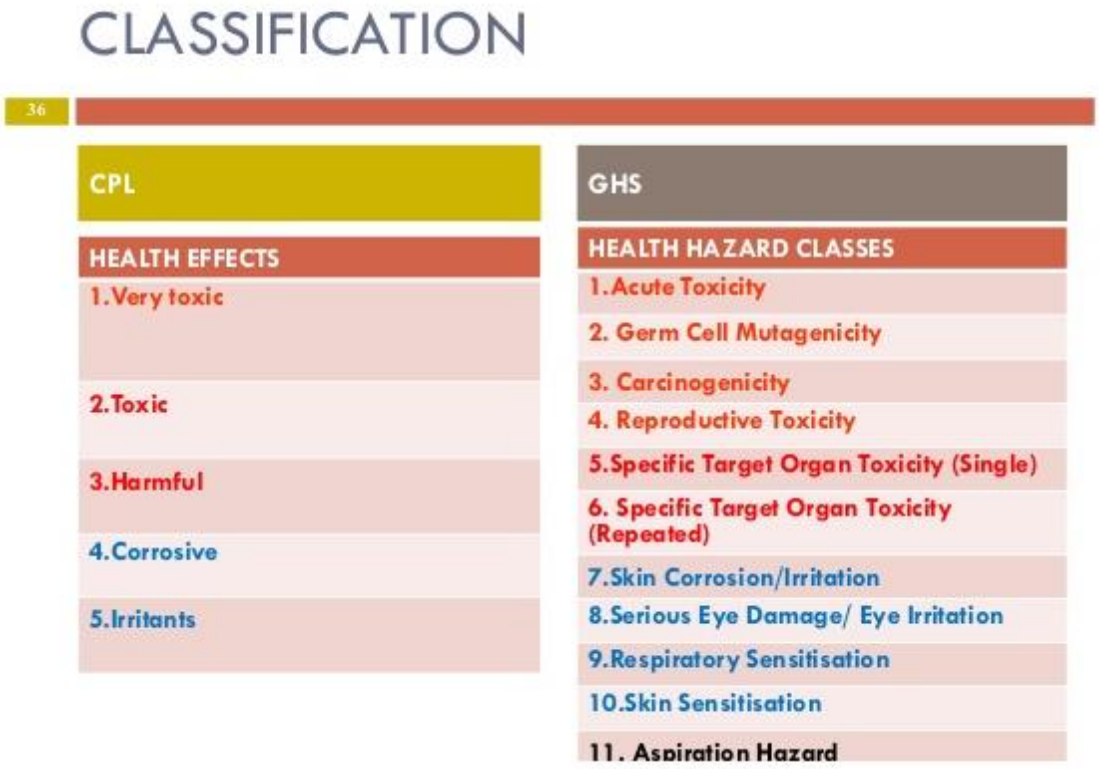
Drugs of abuse are chemicals taken for psychological or other effects and may cause dependence and toxicity.

- **Regulatory Toxicology** concerned with the formulation of laws, and regulations authorized by laws, are intended to minimize the effect of toxic chemicals on human health and the environment.

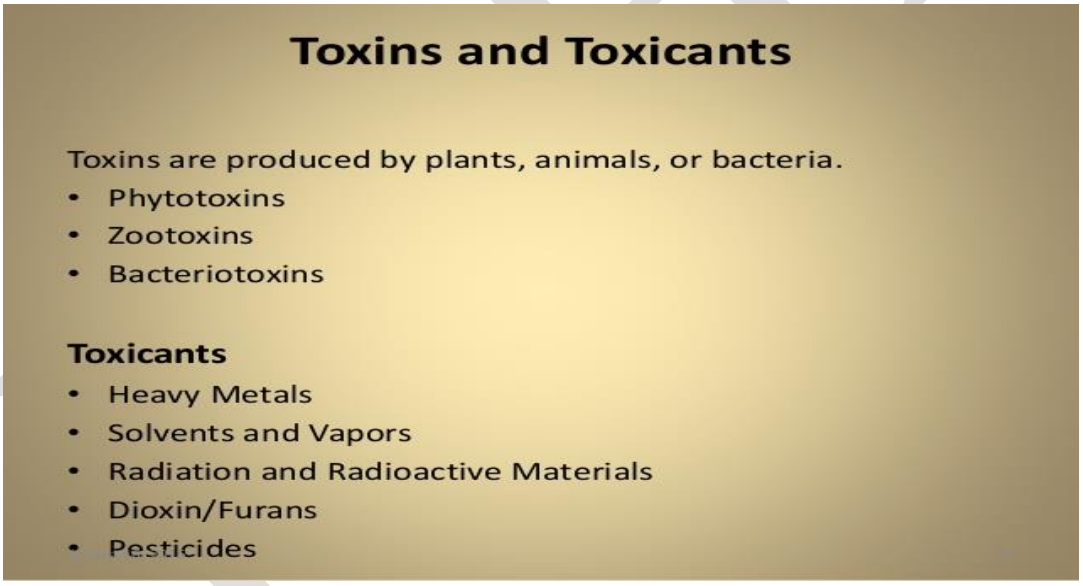
Legal aspects are the formulation of laws and regulations and their enforcement.

Risk assessment is the definition of risks, potential risks, and the risk-benefit equations necessary for the regulation of toxic substances.

Classification of toxicity and toxicants

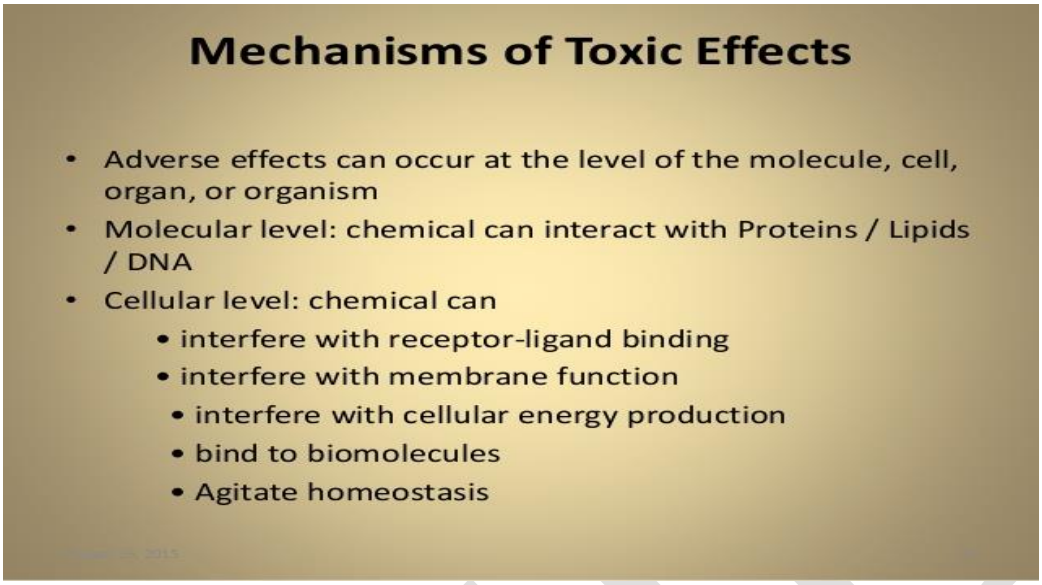


Class of toxicant	Examples
Toxic gases or vapours	Carbon monoxide, hydrogen sulphide, diethyl ether, chloroform
Volatile liquid poisons	Benzene, toluene, aromatic hydrocarbons, glycols, aldehydes, essential oils of some plants
Acids and strong bases	Hydrochloric or sulphuric acid, sodium or potassium hydroxide
Inorganic anions	Permanganates, chromates
Metals or salts of heavy metals	Arsenic, mercury, lead
Acidic, basic or neutral non-volatile organic chemicals and drugs	Most man-made drugs, alkaloids, illicit drugs, insecticides



Mechanisms of toxic effect

Mechanistic toxicology is the study of how chemical or physical agents interact with living organisms to cause toxicity. Knowledge of the mechanism of toxicity of a substance enhances the ability to prevent toxicity and design more desirable chemicals; it constitutes the basis for therapy upon overexposure, and frequently enables a further understanding of fundamental biological processes



Intoxication — or poisoning, especially by an alcoholic or narcotic substance — may refer to:

Each person responds differently to the effects of alcohol based on mood, setting, physical health, and tolerance.

- Intoxication is the point at which alcohol depresses the central nervous system so that mood and physical and mental abilities are noticeably changed.
- The legal definition of intoxication is a Blood Alcohol Content (BAC) of .08.

Tolerance is completely unrelated to a person's BAC. BAC is the amount of alcohol in one's system based on weight, number of drinks, and the period of time during which alcohol is consumed. Tolerance, on the other hand, refers to the experience of lesser effects of alcohol at the same BAC and can be highly dangerous.

It is suggested that a person not exceed a BAC of .056, as this is the point where the positive, relaxed, euphoric effects of alcohol are experienced. When a BAC of .056 is exceeded, the negative, depressant effects of alcohol take place.

A BAC of .06 - .10 is considered the point of diminishing returns. Typically a person at this BAC will experience the following:

- Impaired judgment, inappropriate behavior (such as drinking competitively or annoying others)
- Impaired coordination (stumbling, swaying, staggering, or loss of fine motor skills, distance acuity, or glare recovery)

- Slurred speech
- Diminished senses (speaks louder, cannot hear as well as normal, vision is not as clear, glassy, unfocused eyes)
- Slowed mental processing (can only do one task at a time, forgetting things, lighting more than one cigarette at a time, or losing their train of thought, cannot listen well, follow conversations well, or understand what others are saying)
- Intensified emotions (overly friendly, laughing intensely, displaying mood swings)
- Lowered inhibitions

Some people may become significantly more affected at lower BACs, whereas others at similar BACs may not appear to show symptoms due to developed tolerance

Substance intoxication:

- Alcohol intoxication
- Toxidrome
- Effects of cannabis
- Cocaine intoxication
- Caffeine#Caffeine intoxication
- Stimulant#Effects
- Water intoxication
- Drug overdose
- Inhalant abuse#Administration and effects

Treatment

Alcohol poisoning treatment usually involves supportive care while your body rids itself of the alcohol. This typically includes:

- Careful monitoring
- Prevention of breathing or choking problems
- Oxygen therapy
- Fluids given through a vein (intravenously) to prevent dehydration
- Use of vitamins and glucose to help prevent serious complications of alcohol poisoning

Adults and children who have accidentally consumed methanol or isopropyl alcohol may need hemodialysis — a mechanical way of filtering waste and toxins from your system — to speed the removal of alcohol from their bloodstream.

Mild intoxication may remain asymptomatic and require only fluid restriction. In more severe cases, treatment consists of:

- Diuretics to increase urination, which are most effective for excess blood volume. Such as furosamide (lasix)
- Vasopressin receptor antagonists. Lixivaptan Mozavaptan Satavaptan Tolvaptan

Methods in toxicology testing

THE PURPOSE OF THIS CHAPTER is to familiarize the reader with the testing that is currently conducted by a manufacturer prior to and during the process of submitting a petition to register a pesticide. Codified toxicologic evaluation of potential pesticides has been a requirement in the United States for approximately 50 years. The testing requirements and guidelines continue to evolve based on new science. This chapter identifies the current testing that is pertinent to the young animal and young human as well as aspects of testing that are needed to fill the data gaps to better ensure the protection of infants and children. The current testing guidelines can be found in *Pesticide Assessment Guidelines* issued by the Environmental Protection Agency (EPA, 1991a,b).

Toxicity testing methods

- **Acute toxicity testing**
- **Subchronic toxicity testing (repeated dose =/ >90 day)**
- **Chronic toxicity testing (repeated dose <90 day)**

- Mutagenicity testing
- Carcinogenicity testing
- One-generation reproduction toxicity testing
- Two-generation reproduction toxicity studies
- Developmental toxicity/embryotoxicity studies
- Genetic toxicity testing

Toxicity studies are required to assess potential hazards to humans through the acute, subchronic, and chronic exposure of laboratory animals to pesticides. The more specific types of toxicity that are determined include carcinogenicity; developmental (including teratogenicity in offspring) and reproductive toxicity; mutagenicity; and neurotoxicity.

ACUTE TOXICITY STUDIES

General Description

Acute toxicity studies provide information on the potential for health hazards that may arise as result of short-term exposure. Determination of acute oral, dermal, and inhalation toxicity is usually the initial step in evaluating the toxic characteristics of a pesticide. In each of these tests the animal is exposed to the test material only once on 1 day. Together with information derived from primary eye and primary dermal irritation studies (also 1 dose on 1 day), which assess possible hazards resulting from pesticide contact with eyes and skin, these data provide a basis for precautionary labeling and may influence the classification of a pesticide for restricted use. Acute toxicity data also provide information used to determine the need for child-resistant packaging, for protective clothing requirements for applicator, and for calculation of farm worker reentry intervals. A minimum number of animals, usually adults, are used in these studies and only the end points of concern are monitored, i.e., mortality, observable skin or eye effects, dermal sensitization, and observable neurotoxic behavioral changes. One exception

is the inclusion of microscopic examination of neural tissues in the newly required acute neurotoxicity study.

EPA's Proposed Changes

Guideline number 81-1 (EPA, 1984), acute oral study in the rat, would be revised to include special visual system testing, which would be required for all organophosphate pesticide and other pesticides known to affect the visual system. (https://www.nap.edu/read/2126/chapter/6#133)

SUBCHRONIC TOXICITY STUDIES

General Description

Subchronic exposures do not elicit effects that have a long latency period (e.g., carcinogenicity). However, they do provide information on health hazards that may result from repeated exposures to a pesticide over a period up to approximately 30% of the lifetime of a rodent. Subchronic tests also provide information necessary to select proper dose levels for chronic studies, especially for carcinogenicity studies for which an MTD must be selected. According to EPA (1984), rats selected for these studies should be started on the test material shortly after weaning, "ideally before the rats are 6 and, in any case, not more than 8 weeks old." For dogs, dosing should begin when they are 4 to 6 months of age and "not later than 9 months of age."

Most subchronic toxicity studies monitor clinical or behavioral (neurological) signs of toxicity, body weight, food consumption, eye effects, certain plasma or serum and urine parameters, organ weights, and gross and microscopic pathology. Clinical and behavioral signs of toxicity are observed and recorded daily. They can consist of activity, gait, excreta, hair coat, and feeding and drinking patterns. Body weight and food consumption data are routinely recorded throughout the study at intervals (usually weekly) determined by the length of the study. Ophthalmoscopic examinations are conducted at the beginning of the study and, typically, just before it terminates. The results of hematology testing indicate whether, for example, the chemical affects blood cell formation and survival, clotting factors, and platelets. Clinical chemistry and urinalysis results can indicate possible kidney, liver, pancreas, and cardiac function or toxicity as well as any electrolyte imbalance. Urinalysis results can indicate adequacy of kidney, liver, and pancreas function.

After necropsy, the weights of certain organs are also recorded. These organs generally include brain, gonads, liver, and kidneys, which are the four required according to EPA testing guidelines (EPA, 1984). If toxicity is known to occur in another organ from previous testing, the weight of this organ should also be reported. For thyroid toxicity, for example, the weight of the thyroids should be recorded. Changes from untreated control animals are generally an indication of potential toxicity in this organ.

A complete necropsy is performed after sacrifice or death of the test animal. Generally all tissues are examined, and those saved for microscopic examination are aorta, jejunum, peripheral nerve, eyes, bone marrow, kidneys, cecum, liver, esophagus, colon, lung, ovaries, duodenum

CHRONIC TOXICITY STUDIES

General Description

Information derived from chronic studies is used to assess potential hazards resulting from prolonged and repeated exposure to a pesticide over a large portion of the human life span. These studies usually last 12 to 24 months. Of particular importance are long-term carcinogenicity studies, the purpose of which is to observe the test animals for the development of neoplastic lesions after a lifetime of exposure at dose levels up to and including the MTD determined from subchronic testing.

The emphasis of the carcinogenicity study is the detection of tumors in animals. For these studies, both concurrent and historical control data are used to evaluate the relevance of tumors. Historical control data should be derived from studies in the same species and strain and, preferably, in the same laboratory as used in the study under consideration. Carcinogenicity studies should be 24 months long in rats and 18 months long in mice. The age of test animals in carcinogenicity (rat and mouse) studies and other chronic (rat and dog) studies is determined by the same criteria as for subchronic toxicity studies. The parameters to be examined in carcinogenicity studies are also generally the same as those discussed above for subchronic and chronic studies, except that clinical chemistry and urine parameters are not required and only limited hematology data are required.

EPA's Proposed Changes

Modifications to chronic feeding studies in two species (rodent and nonrodent; Guideline 83-1; EPA, 1984) may be required to include additional end points for neurotoxicity or

immunotoxicity or special visual system toxicity (for organophosphates) if these were not tested in other studies.

Range-finding studies of at least 90 days duration in rats and mice will generally be required to determine dose levels that are adequate to test the carcinogenicity (Guideline 83-2; EPA, 1984) of a pesticide. Studies conducted to satisfy the requirement for Guideline 82-1 (EPA, 1984) will also be acceptable to satisfy this 90-day study requirement.

DEVELOPMENTAL TOXICITY STUDIES

General Description

Developmental toxicity studies are designed to assess the potential of developmental effects in offspring resulting from the mother's exposure to the test substance during pregnancy. These effects include death of the developing organism, structural abnormalities, altered growth, and functional deficiencies. In addition to the classic teratology (now called developmental toxicity) study, a postnatal study is required by the EPA on a case-by-case basis. It is in this study that functional deficiencies are best studied.

The EPA prefers that the rat and the rabbit be used in these studies; however, hamster and mouse are also acceptable. Doses should be administered over the period of major organogenesis (major visceral and skeletal formation) in the fetus. The maternal animals only are dosed in this study and only for specified periods. When day 0 is the day that evidence of mating was observed, the rat and mouse are dosed on days 6 through 15; the rabbit, days 6 through 18; and the hamster, days 6 through 14.Dosing is usually administered by gavage (oral bolus dose). The pregnant animal should be observed daily for signs of toxicity. Maternal body weight should be monitored at least every 2 to 3 days during gestation. At sacrifice, the maternal animals should be examined for any abnormalities or pathological changes that may have influenced the pregnancy. The uterus is then removed and examined. The number of corpora lutea and live and dead fetuses should be recorded. The sex of the fetuses should be determined. Each fetus is then weighed and examined externally and malformations recorded by litter along with weight and sex. A certain percentage (depending on the animal species used) of the fetuses are then prepared for visceral examination and the remainder for examination of skeletal anomalies. Although the litter is considered the most relevant unit for statistical analysis, data should also be presented and assessed for each fetus.

Historical control data are also useful for determining the biological importance of visceral or skeletal anomalies that are elevated to a statistically significant level by treatment. Again, only historical control data from studies on the same species and strain of animal should be used for comparison purposes.

EPA's Proposed Changes

At least one developmental toxicity (formerly teratogenicity) study (Guideline 83-3; EPA, 1984) would now be required for all nonfood uses. In the past it was required only if there was expected exposure of women of childbearing age. A second study could be required if concerns are raised from the results of the first study. For food use EUPs accompanied by a temporary tolerance request, a second study could also be required, depending on the results of the first study.

A postnatal development toxicity study (Guideline 83-6; EPA, 1984) is proposed as a conditional requirement. This study could be required to more fully assess the manifestations of developmental toxicity, especially potential deficits in function or developmental neurotoxicity.

The parameters that need to be studied in a postnatal study depend on the effects seen in the prenatal study. Guidelines are presently being developed by EPA.

REPRODUCTION STUDIES

General Description

Multigeneration reproduction studies are designed to provide information concerning the general effects of a test substance on overall reproductive capability. Such studies may also provide information about the effects of the test substance on neonatal morbidity and mortality and about the meaning of preliminary data for developmental toxicity. EPA requires that the study include a minimum of two generations and that one litter be produced each generation. Dosing of both parents should begin when they are 8 weeks old and continue for 8 weeks prior to mating. Dosing of parental males should continue at least until mating is completed. Dosing of parental females continues through a 3-week mating period and pregnancy and up to the time of weaning 3 weeks after delivery of the pups. Dosing of pups selected for mating to produce the second generation should begin at weaning and continue as discussed above. Parental animals should be observed daily for signs of toxicity. This is especially important for females during pregnancy in order to detect signs of difficult or prolonged parturition. Weights of parental

animals are recorded weekly. The duration of pregnancy should be determined from the time evidence of mating was first observed. Each litter should be examined for the number of dead and live pups and for gross abnormalities. Live pups should be individually weighed on days 0 (optional), 4, 7 (optional), 14, and 21 after birth. A complete gross necropsy should be performed on all parental animals, all pups found dead prior to day 21 (weaning), and all weanlings not selected as parental animals for a next generation. Pups culled on day 4 do not have to undergo gross necropsy. Histopathology is required for reproductive and target organs (those known from previous studies to be adversely affected by the test material) for all control and high-dose parental animals and should be conducted on weanling animals (except for those selected as parental animals in the next generation) as described for parental animals (EPA, 1988).

EPA's Proposed Changes

The addition of a fertility assessment of parental males is recommended by EPA if fertility or reproductive parameters are found to be affected by the test chemical. The parameters to be examined or reported in this assessment include weight of reproductive organs, spermatid count, total cauda epididymal sperm count, assessment of sperm morphology and motility, examination of epididymal fluid for debris and unexpected cell types, and additional histopathology of the testes. A reproduction study (Guideline 83-4; EPA, 1984) could also be required to support nonfood uses if adverse effects on the reproductive system or developmental toxicity are observed in other studies.

MUTAGENICITY STUDIES

General Description

A battery of mutagenicity tests is required to assess the potential of each test chemical to affect genetic material. The test selection criteria focus on the test's ability to detect, with appropriate assay methods, the capacity of the chemical to alter genetic material in cells. When mutagenic potential is demonstrated, these findings are considered in the assessment of potential heritable effects in humans, in the weight-of-the-evidence evaluation for carcinogenicity, and in the decision to require submission of a carcinogenicity study if otherwise conditionally required. Mutagenicity results per se are not used by themselves for risk assessment purposes, even when results suggest possible heritable genetic effects in humans.

EPA's Proposed Changes

EPA has already published changes to the 40 CFR Part 158 data requirements for mutagenicity (EPA, 1984).

As described in *Pesticide Assessment Guidelines: Subdivision F* (EPA, 1984), the original mutagenicity test battery consisted of three assays: one for gene mutations, one for structural chromosome aberrations, and one for other genotoxic effects. Other testing included DNA damage and repair. The revised guidelines would require an initial battery of tests consisting of:

- *Salmonella typhimurium* reverse mutation assay;
- mammalian cells in culture forward gene mutation assay allowing detection of point mutations, large deletions, and chromosome rearrangements; and
- *in vivo* cytogenetics.

Results derived from these assays could trigger the requirement for further mutagenicity testing. The type of additional required testing would depend on the observed results from the initial battery and other toxicity testing results. For example, testing could involve cytogenetic testing in spermatozoa if other test results suggest that they are targets.

GENERAL METABOLISM STUDIES

General Description

Data from studies on the absorption, distribution, bioaccumulation, excretion, and metabolism of a pesticide may also allow more meaningful evaluation of test results and more appropriate risk assessment (as a result of more meaningful extrapolation from data on animals to humans). Suchdata may also aid in designing more relevant toxicology studies. Information on metabolites formed in laboratory animals is also used to determine whether further toxicity testing is required on plant metabolites. If a major metabolite forms in the plant but not in the test animal, separate toxicity testing on the plant metabolite could be necessary. The extent of testing required depends on the level of concern raised by the initial battery of toxicity tests (acute and subchronic studies, one teratology study, and a battery of mutagenicity tests).

As presently designed, the metabolism study consists of four separate parts: a single low, intravenous dose of radiolabeled test material (not required if the test material is insoluble in water or normal saline solution); a single low, oral dose of radiolabeled test material; 14 consecutive daily low, oral doses of unlabeled test material followed by a single low dose of

radiolabeled material; and single high, oral dose of radiolabeled test material. Selection of the low dose is based on the NOEL. The high dose should elicit some signs of toxicity but not be so high that it results in mortality. The test species of choice is the rat.

Urine, feces, and expired air are collected for 7 days after administration of the radiolabeled material or until >90% of the radioactivity is recovered. Bone, brain, fat, testes, heart, kidney, liver, lung, blood, muscle, spleen, residual carcass, and tissues showing pathology in this or prior tests should be examined for radioactivity for all animals except those given the intravenous dose. This is done to determine if the test material or radiolabeled metabolite accumulates in any particular organ and to relate this information to the findings in toxicity studies. In addition, quantities of radiolabeled material in feces, urine, and expired air must be monitored for all dose groups at appropriate intervals up to 7 days after dosing. Furthermore, urinary and fecal metabolites must be identified.

EPA's Proposed Changes

A metabolism study would also be required when significant adverse effects are observed in toxicology studies, including reproduction and developmental studies (Guideline 85-1; EPA, 1984). EPA is currently rewriting to guidelines for conducting metabolism studies and is including a tiered approach for study design and conduct.

NEUROTOXICITY STUDIES

General Description

Neurotoxicity studies are required to evaluate the potential of each pesticide to adversely affect the structure or function of the nervous system. The objectives of these studies are to detect and characterize the following:

- effects on the incidence and severity of clinical signs, the alteration of motor activity, and histopathology in the nervous system following acute, subchronic, and chronic exposures;
- the potential of cholinesterase inhibiting pesticides and related substances to cause a specific organophosphate-pesticide-type induced delayed neurotoxicity;
- other neurotoxic effects based on screening studies on certain chemical classes; and
- effects on organisms exposed prior to birth or weaning.

Results from these studies may be used for qualitative and quantitative risk assessment. The guidelines for these studies were published in March 1991 as addendum 10 to the EPA guidelines (EPA, 1991a).

EPA's Proposed Changes

The changes in the requirements for neurotoxicity testing were described above under "Acute Toxicity" and "Subchronic Toxicity."

SPECIAL TESTING

EPA intends to develop better definitions of the conditions under which domestic animal safety (Guideline 85-2; EPA, 1984) testing and visual system studies (Guideline 85-4; EPA, 1984) would be required for all organophosphates and other pesticides shown to affect the visual system. These studies could be of acute, subchronic, or chronic duration, whichever is deemed appropriate for the pesticide under study. Since guidelines have not been formulated for these studies, they will be designed in conjunction with EPA scientists.

Heavy metal toxicity

Some debate exists as to exactly what constitutes a "heavy metal" and which elements should properly be classified as such. Some authors have based the definition on atomic weight; others, on a specific gravity of greater than 4.0, or greater than 5.0. The actinides may or may not be included. Most recently, the term "heavy metal" has been used as a general term for those metals and semimetals with potential human or environmental toxicity. This definition includes a broad section of the periodic table under the rubric of interest.

Regardless of how one chooses to define the category, heavy metal toxicity is an uncommon diagnosis. With the possible exceptions of acute iron toxicity from intentional or unintentional ingestion and suspected lead toxicity, emergency physicians will rarely be alerted to the possibility of metal exposure. Yet, if unrecognized or inappropriately treated, heavy metal exposure can result in significant morbidity and mortality.

Many of the elements that can be considered heavy metals have no known benefit for human physiology. Lead, mercury, and cadmium are prime examples of such "toxic metals." Yet, other metals are essential to human biochemical processes. For example, zinc is an important cofactor for several enzymatic reactions in the human body, vitamin B-12 has a cobalt atom at its core, and hemoglobin contains iron. Likewise, copper, manganese, selenium,

chromium, and molybdenum are all trace elements that are important in the human diet. Another subset of metals includes those used therapeutically in medicine; aluminum, bismuth, gold, gallium, lithium, and silver are all part of the medical armamentarium. Any of these elements may have pernicious effects if taken in quantity or if the usual mechanisms of elimination are impaired.

The toxicity of heavy metals depends on a number of factors. Specific symptomatology varies according to the metal in question, the total dose absorbed, and whether the exposure was acute or chronic. The age of the person can also influence toxicity. For example, young children are more susceptible to the effects of lead exposure because they absorb several times the percent ingested compared with adults and because their brains are more plastic and even brief exposures may influence developmental processes. The route of exposure is also important. Elemental mercury is relatively inert in the gastrointestinal tract and also poorly absorbed through intact skin, yet inhaled or injected elemental mercury may have disastrous effects.

Some elements may have very different toxic profiles depending on their chemical form. For example, barium sulfate is basically nontoxic, whereas barium salts are rapidly absorbed and cause profound, potentially fatal hypokalemia. The toxicity of radioactive metals like polonium, which was discovered by Marie Curie but only recently brought to public attention after the 2006 murder of Russian dissident Alexander Litvinenko, relates more to their ability to emit particles than to their ability to bind cell proteins.

Exposure to metals may occur through the diet, from medications, from the environment, or in the course of work or play. Where heavy metal toxicity is suspected, time taken to perform a thorough dietary, occupational, and recreational history is time well spent, since identification and removal of the source of exposure is frequently the only therapy required.

A full dietary and lifestyle history may reveal hidden sources of metal exposure. Metals may be contaminants in dietary supplements, or they may leech into food and drink stores in metal containers like lead decanters. Persons intentionally taking colloidal metals for their purported health benefits may ultimately develop toxicity. Metal toxicity may complicate some forms of drug abuse. Beer drinker's cardiomyopathy was diagnosed in alcoholics in Quebec, and later Minnesota, during a brief period in the 1970s when cobalt was added to beer on tap to

stabilize the head. More recently, a parkinsonian syndrome among Latvian injection drug users of methcathinone has been linked to manganese toxicity.

Classification of naturally occuring metals by toxicity and hydrologic availability

[Metals that normally do not exist as dissolved species in natural waters or are very rare in crustal rocks are in italics]

Nontoxic		Low toxicity		Moderate to high toxicity			
Aluminum	Magnesium	Barium	*Praseodymium*	*Actinium*	Indium	Polonium	Uranium
Bismuth	Manganese	*Cerium*	*Promethium*	Antimony	*Iridium*	*Radium*	Vanadium
Calcium	Molybdenum	*Dysprosium*	*Rhenium*	Beryllium	Lead	*Ruthenium*	Zinc
Cesium	Potassium	*Erbium*	*Rhodium*	Boron	Mercury	Silver	*Zirconium*
Iron	Strontium	*Europium*	*Samarium*	Cadmium	Nickel	*Tantalum*	
Lithium	Rubidium	*Gadolinium*	Scandium	Chromium	*Niobium*	Thallium	
	Sodium	*Gallium*	*Terbium*	Cobalt	*Osmium*	Thorium	
		Germanium	Thulium	Copper	Palladium	*Titanium*	
		Gold	*Tin*	*Hafnium*	Platinum	*Tungsten*	
		Holmium	*Ytterbium*				
		Neodymium	Yttrium				

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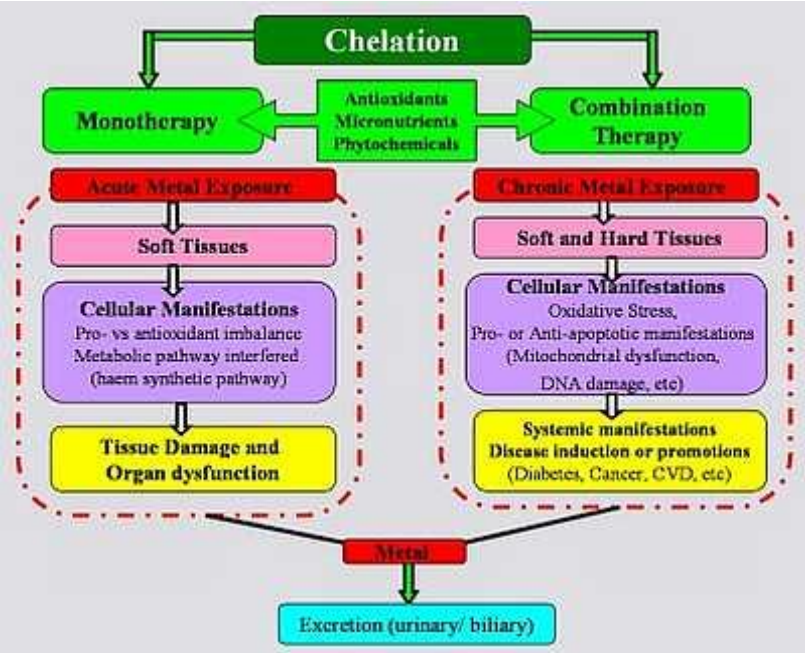
Chelation therapy

Chelation therapy is a chemical process in which a synthetic solution-EDTA (ethylenediaminetetraacetic acid)-is injected into the bloodstream to remove heavy metals and/or minerals from the body. Chelation means "to grab" or "to bind." When EDTA is injected into the veins, it "grabs" heavy metals and minerals such as lead, mercury, copper, iron, arsenic, aluminum, and calcium and removes them from the body. Except as a treatment for lead poisoning, chelation therapy is controversial and unproved. Chelation therapy is performed on an outpatient basis.



Chelation therapy uses

Chelation is a very effective way to treat heavy-metal poisoning. The U.S. Food and Drug Administration (FDA) has approved prescription chelation therapy for the treatment of lead poisoning. Injected EDTA binds with the harmful metal and both are then eliminated from the body through the kidneys. Some health professionals have also used chelation therapy to treat atherosclerosis and/or coronary artery disease, although there is not enough scientific evidence to prove that this treatment is effective. Some people believe that EDTA binds with calcium deposits (the part of plaque that obstructs the flow of blood to the heart) in the arteries, and then EDTA "cleans out" the calcium deposits from the arteries, reducing the risk of heart problems. Research results have been inconsistent. Chelation therapy should not replace lifestyle changes or standard treatments for coronary artery disease.

Some health professionals also suspect that EDTA may act as an antioxidant by removing metals that combine with LDL cholesterol, which can damage arteries. The theory is that when you remove metals that flow freely through arteries (such as copper or calcium), you may slow down diseases such as atherosclerosis. Research has not proved this theory. Some experts believe that EDTA could remove calcium from healthy bones, muscles, and other tissues, as well as from diseased arteries.Many people report less pain from chronic inflammatory diseases such as arthritis, lupus, and scleroderma after chelation therapy. The theory is that EDTA acts as an

antioxidant, which protects the body from inflammation and protects blood vessels. Again, this idea has not been proved by scientific research.

Environmental pollution

Environmental pollution has existed for centuries but only started to be significant following the industrial revolution in the 19th century. Pollution occurs when the natural environment cannot destroy an element without creating harm or damage to itself. The elements involved are not produced by nature, and the destroying process can vary from a few days to thousands of years (that is, for instance, the case for radioactive pollutants). In other words, pollution takes place when nature does not know how to decompose an element that has been brought to it in an unnatural way.

Environmental pollution is "the **contamination** of the physical and biological components of the earth/atmosphere system to such an extent that normal **environmental processes** are adversely **affected**". (Ref. 1)

"**Pollution** is the introduction of **contaminants** into the environment that cause **harm** or **discomfort** to humans or other living organisms, or that damage the environment" which can come "in the form of chemical substances, or energy such as noise, heat or light". "**Pollutants** can be naturally occurring substances or energies, but are considered contaminants when **in excess of natural levels**."

Pollution is "the **addition** of any substance or form of energy (e.g., heat, sound, radioactivity) **to the environment** at a rate **faster** than the environment can accommodate it by dispersion, breakdown, recycling, or storage in some harmless form".

"**Pollution** is a special case of habitat destruction; it is **chemical destruction** rather than the more obvious physical destruction. Pollution occurs in all habitats—land, sea, and fresh water—and in the atmosphere."

"Much of what we have come to call **pollution** is in reality the nonrecoverable matter resources and waste heat."

"Any use of natural resources at a rate higher than nature's capacity to restore itself can result in **pollution** of air, water, and land.

"**Pollution** is habitat contamination".

Biological Decomposition of Environmental Pollutants

Santos divides environmental pollutants into *biodegradable* and *non-biodegradable* ones, and describes them as follows.

Biodegradable Pollutants

Fruit peel is **biodegradable**

Biodegradable pollutants are the ones that can be **broken down** and **processed** by *living organisms*, including organic waste products, phosphates, and inorganic salts. For example, if a pollutant is organic, it can be used by a living organism to obtain energy and other material from carbohydrates, proteins etc. Therefore, biodegradable pollutants are only "temporary nuisances" that can be neutralised and converted into harmless compounds. However, it is important to remember that they can become serious pollutants if released in large amounts in small areas, thus exceeding the natural capacity of the environment to "assimilate" them.

Non-Biodegradable Pollutants

Plastic may look beautiful but it is **not biodegradable**

Non-biodegradable pollutants are the ones that **cannot** be **decomposed** by *living organisms* and therefore persist in the ecosphere for extremely long periods of time. They include plastics, metal, glass, some pesticides and herbicides, and radioactive isotopes. In addition to that, **fat soluble** (but not water soluble) non-biodegradable pollutants, ex. mercury and some hydrocarbons, are not excreted with urine but are accumulated in the fat of living organisms and **cannot** be metabolised. Non-Biological Decomposition of Environmental Pollutants.Non-biological decomposition of non-biodegradable pollutants requires a combination of many

factors, such as wind, water and climate to work together to achieve neutralisation of pollutants. Some of the most dangerous pollutants such as radioactive isotopes can decompose by themselves but it will take them thousands of years.

Removal of Air Pollutants from the Atmosphere. Air pollutants, as opposed to solid and liquid pollutants found on land and in water, may be removed from the atmosphere through ***wet deposition*** or ***dry deposition***. In case of **wet** deposition pollutants make way into clouds or other precipitation and then get deposited onto the surface of the Earth by way of rain. In case of **dry** deposition, pollutants are deposited directly onto the planet's surface and vegetation, such as plants and trees of tropical rainforests. We may assume that once air pollution has been deposited onto the planet's surface, the normal rules of biological and non-biological decomposition for other types of pollutants will apply.

Types of Environmental Pollution

Generally speaking, there are many **types of environmental pollution** but the most important ones are:

- **Air** pollution
- **Water** pollution
- **Soil** pollution (contamination)

Some of the most notable **air pollutants** are sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone, volatile organic compounds (VOCs) and airborne particles, with radioactive pollutants probably among the most destructive ones (specifically when produced by nuclear explosions).

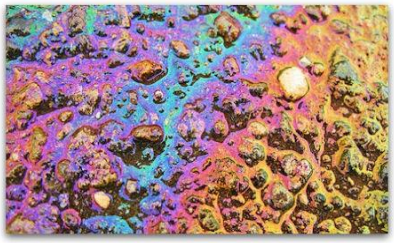
Our **Air Pollutants** article provides a clear overview of sources and effects of these air pollutants.

Water pollutants include insecticides and herbicides, food processing waste, pollutants from livestock operations, volatile organic compounds (VOCs), heavy metals, chemical waste and others.

Some **soil pollutants** are: hydrocarbons, solvents and heavy metals.

Sources of Environmental Pollution

Fossil Fuel Sources of Environmental Pollution



Oil Pollution

In modern industrialized societies, **fossil fuels** (oil, gas, coal) transcended virtually all imaginable barriers and firmly established themselves in our everyday lives.

Not only do we use fossil fuels for our obvious everyday needs (such as filling a car), as well as in the power-generating industry, they (specifically oil) are also present in such products as all sorts of plastics, solvents, detergents, asphalt, lubricating oils, a wide range of chemicals for industrial use, etc.

Combustion of fossil fuels produces extremely high levels of ***air pollution*** and is widely recognized as one of the most important "target" areas for reduction and control of environmental pollution. Fossil fuels also contribute to ***soil contamination*** and ***water pollution***. For example, when oil is transported from the point of its production to further destinations by pipelines, an oil leak from the pipeline may occur and pollute soil and subsequently groundwater. When oil is transported by tankers by ocean, an oil spill may occur and pollute ocean water. Of course, there are **other natural resources** whose exploitation is a cause of serious pollution; for example, the use of *uranium* for *nuclear power generation* produces extremely dangerous waste that would take thousands of years to neutralize. But there is no reasonable doubt that **fossil fuels** are among the **most** serious sources of environmental pollution. Power-generating plants and transport are probably the biggest sources of fossil fuel pollution.

Common **sources** of fossil fuel pollution are:

Industry:

- Power-generating plants
- Petroleum refineries
- Petrochemical plants
- Production and distribution of fossil fuels
- Other manufacturing facilities

Transport:

- Road transport (motor vehicles)
- Shipping industry
- Aircraft

Fossil fuel combustion is also a major source of **carbon dioxide** (CO_2) emissions and perhaps the most important cause of global warming. Learn more about the causes and effects of global warming here.

Environmental Pollution Effects

Environmental pollution **effects** can be truly damaging.

Some of the effects of ***air pollution*** include asthma, reduced energy levels, irritation of eyes, disruption of the immune system, malfunction of the central nervous system, cancer.

Water pollution can cause skin rashes & allergies, all sorts of water-borne infections, vomiting & stomach aches, malfunction of the central nervous system and so on.

Soil pollution is, in a way, connected to water pollution and may cause cancer, headaches, fatigue, skin rashes and so on.

Causes of Environmental Pollution

Let us first take a look at the causes of environmental pollution:

1. Industries: Industries have been polluting our environment especially since the beginning of the industrial revolution, as mentioned above, notably due to the increasing use of fossil fuels. In the 19^{th} century and for a significant part of the 20^{th}century, coal has been use to make machines work faster, replacing human force. Though pollution by industries mainly causes air pollution, soil and water contamination can also occur. This is particularly the case for power-generating industries, such as plants producing electricity (May they be a dam, a nuclear reactor or some other type of plant). Also, the transportation of this energy can be harmful to the environment. We can take as an example the transportation of petrol through pipelines; if there is a leak in the pipeline, soil will automatically be polluted. At the same time, if the tanker transporting the petrol from its production plant to the place where it will be consumed leaks or sinks, the water will get contaminated.

2. Transportation: Ever since men abandoned animal power to travel, pollution of the environment has become higher and higher. Its levels have only been increasing until now. Similarly to industries, pollution caused by transport can mainly be attributed to fossil fuels. Indeed, humans went from horse carriages to cars, trains (which, before electricity, used to be propelled by coal), and airplanes. As the traffic is increasing every day, pollution follows that evolution.

3. Agricultural Activities: Agriculture is mainly responsible for the contamination of water and soil. This is caused by the increased use of pesticides, as well as by the intensive character of its production. Almost all pesticides are made from chemical substances and are meant to keep diseases and threatening animals away from the crops. However, by keeping these forms of life away, harm is almost always made to the surrounding environment as well.

Furthermore, as agriculture gets more and more intensive to feed the increasing world population, more environments and ecosystems are destroyed to make space for the crops. Some of them, like rapeseed –used to make oil – demand a lot of space for a relatively small output.

4. Trading Activities: Trading activities including the production and exchange of goods and services. Concerning goods, pollution can be caused by packaging (which often involves the use of plastic, which is made from fossil fuels) or transport, mainly.

5. Residences: Finally, residential areas provide their fair share of pollution as well. First, to be able to build homes, natural environment has to be destroyed in one way or another. Wildlife and plants are driven away and replaced by human constructions. As it requires the work of industries, construction itself is also a source of contamination of the environment. Then, when people settle in, they will produce waste every day, including a part that cannot be processed by the environment without harm yet.

Effects of Environmental Pollution

Now that we have identified the main causes of environmental pollution, let us study the negative effects it has:

1. Effects on Humans: The effects of environmental pollution on humans are mainly physical, but can also turn into neuro-affections in the long term. The best-known troubles to us are respiratory, in the form of allergies, asthma, irritation of the eyes and nasal passages, or other forms of respiratory infections. Notably, these well spread affections can be observed when air

pollution is high in cities, when the weather gets hot, for instance. On top of that, environmental pollution has been proven to be a major factor in the development of cancer. This can happen for example when we eat reminiscences of pollutants used in the production of processed foods, or pesticides from the crops. Other, rarer, diseases include hepatitis, typhoid affections, diarrhoea and hormonal disruptions.

2. Effects on Animals: Environmental pollution mainly affects animal by causing harm to their living environment, making it toxic for them to live in. Acid rains can change the composition of rivers and seas, making them toxic for fishes, an important quantity of ozone in the lower parts of the atmosphere can cause lung problems to all animals. Nitrogen and phosphates in water will cause overgrowth of toxic algae, preventing other forms of life to follow their normal course. Eventually, soil pollution will cause harm and sometimes even the destruction of microorganisms, which can have the dramatic effect of killing the first layers of the primary food chain.

3. Effects on Plants: As for animals, plants, and especially trees, can be destroyed by acid rains (and this will also have a negative effect on animals as well, as their natural environment will be modified), ozone in the lower atmosphere block the plant respiration, and harmful pollutants can be absorbed from the water or soil.

4. Effects on the Ecosystem: In short, environmental pollution, almost exclusively created by human activities, has a negative effect on the ecosystem, destroying crucial layers of it and causing an even more negative effect on the upper layers.

Mycotoxin

A mycotoxin is a toxic secondary metabolite produced by organisms of the fungus kingdom and is capable of causing disease and death in both humans and animals. The term 'mycotoxin' is usually reserved for the toxic chemical products produced by fungi that readily colonize crops. One mold species may produce many different mycotoxins, and several species may produce the same mycotoxin.

Production

Most fungi are aerobic (use oxygen) and are found almost everywhere in extremely small quantities due to the minute size of their spores. They consume organic

matter wherever humidity and temperature are sufficient. Where conditions are right, fungi proliferate into colonies and mycotoxin levels become high. The reason for the production of mycotoxins is not yet known; they are not necessary for the growth or the development of the fungi. Because mycotoxins weaken the receiving host, the fungus may use them as a strategy to better the environment for further fungal proliferation. The production of toxins depends on the surrounding intrinsic and extrinsic environments and these substances vary greatly in their toxicity, depending on the organism infected and its susceptibility, metabolism, and defense mechanisms.

Major groups

Aflatoxins are a type of mycotoxin produced by *Aspergillus* species of fungi, such as *A. flavus* and *A. parasiticus*. The umbrella term aflatoxin refers to four different types of mycotoxins produced, which are B_1, B_2, G_1, and G_2. Aflatoxin B_1, the most toxic, is a potent carcinogen and has been directly correlated to adverse health effects, such as liver cancer, in many animal species. Aflatoxins are largely associated with commodities produced in the tropics and subtropics, such as cotton, peanuts, spices, pistachios, and maize.

Ochratoxin is a mycotoxin that comes in three secondary metabolite forms, A, B, and C. All are produced by *Penicillium* and *Aspergillus* species. The three forms differ in that Ochratoxin B (OTB) is a nonchlorinated form of Ochratoxin A (OTA) and that Ochratoxin C (OTC) is an ethyl ester form Ochratoxin A. *Aspergillus ochraceus* is found as a contaminant of a wide range of commodities including beverages such as beer and wine. *Aspergillus carbonarius* is the main species found on vine fruit, which releases its toxin during the juice making process. OTA has been labeled as a carcinogen and a nephrotoxin, and has been linked to tumors in the human urinary tract, although research in humans is limited by confounding factors.

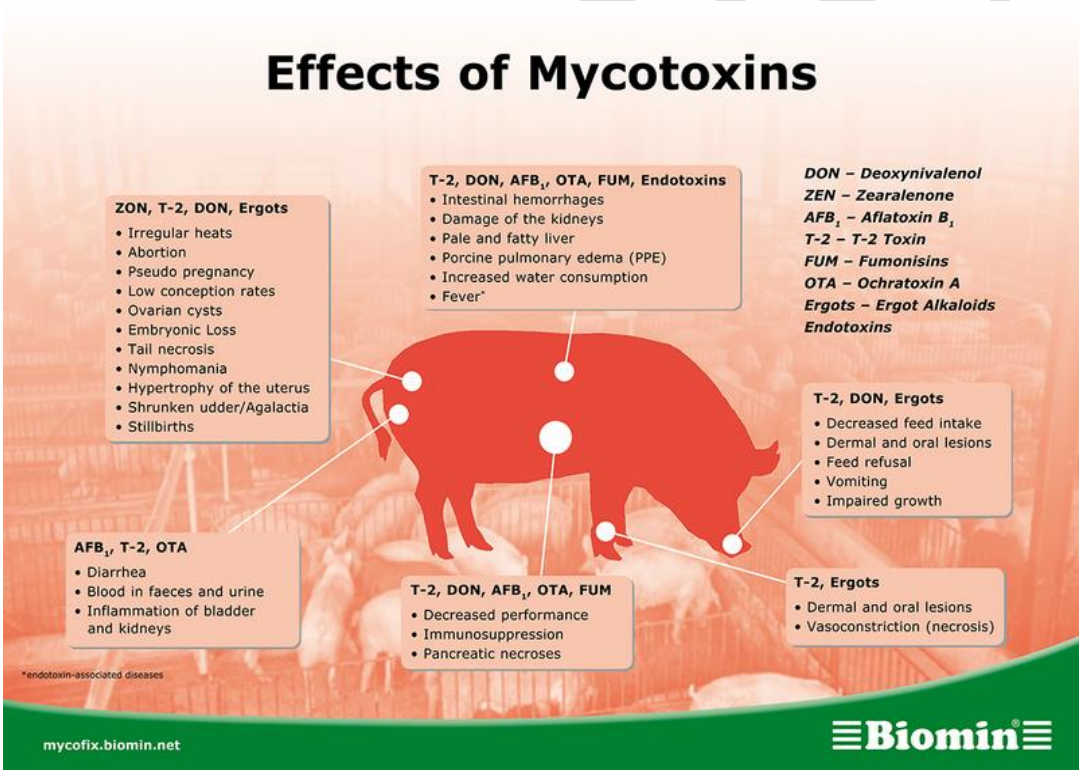
Citrinin is a toxin that was first isolated from *Penicillium citrinum*, but has been identified in over a dozen species of *Penicillium* and several species of *Aspergillus*. Some of these species are used to produce human foodstuffs such as cheese (*Penicillium camemberti*), sake, miso, and soy sauce (*Aspergillus oryzae*). Citrinin is associated with yellowed rice disease in Japan and acts as a nephrotoxin in all animal species tested. Although it is associated with many human foods (wheat, rice, corn, barley, oats, rye, and food colored with Monascus pigment) its full

significance for human health is unknown. Citrinin can also act synergistically with Ochratoxin A to depress RNA synthesis in murine kidneys.

Ergot Alkaloids are compounds produced as a toxic mixture of alkaloids in the sclerotia of species of *Claviceps*, which are common pathogens of various grass species. The ingestion of ergot sclerotia from infected cereals, commonly in the form of bread produced from contaminated flour, cause ergotism, the human disease historically known as St. Anthony's Fire. There are two forms of ergotism: gangrenous, affecting blood supply to extremities, and convulsive, affecting the central nervous system. Modern methods of grain cleaning have significantly reduced ergotism as a human disease, however it is still an important veterinary problem. Ergot alkaloids have been used pharmaceutically.

Patulin is a toxin produced by the *P. expansum*, *Aspergillus*, *Penicillium*, and *Paecilomyces* fungal species. *P. expansum* is especially associated with a range of moldy fruits and vegetables, in particular rotting apples and figs. It is destroyed by the fermentation process and so is not found in apple beverages, such as cider. Although patulin has not been shown to be carcinogenic, it has been reported to damage the immune system in animals. In 2004, the European Community set limits to the concentrations of patulin in food products. They currently stand at 50 μg/kg in all fruit juice concentrations, at 25 μg/kg in solid apple products used for direct consumption, and at 10 μg/kg for children's apple products, including apple juice.

Fusarium toxins are produced by over 50 species of *Fusarium* and have a history of infecting the grain of developing cereals such as wheat and maize. They include a range of mycotoxins, such as: the **fumonisins**, which affect the nervous systems of horses and may cause cancer in rodents; the **trichothecenes**, which are most strongly associated with chronic and fatal toxic effects in animals and humans; and **zearalenone**, which is not correlated to any fatal toxic effects in animals or humans. Some of the other major types of *Fusarium* toxins include: beauvercin and enniatins, butenolide, equisetin, and fusarins.



Mushroom poisoning

Mushroom poisoning (also known as mycetism or mycetismus) refers to harmful effects from ingestion of toxic substances present in a mushroom. 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.To prevent mushroom poisoning, mushroom gatherers familiarize themselves with the mushrooms they intend to collect as well as with any similar-looking toxic species. In addition, edibility of mushrooms may depend on methods of preparation for cooking. The edibility or toxicity of some species varies with geographic location.

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.

No simple rule exists for distinguishing edible mushrooms from poisonous mushrooms. In more than 95% of mushroom toxicity cases, poisoning occurs as a result of misidentification of the mushroom by an amateur mushroom hunter. In less than 5% of the cases, poisoning occurs after the mushroom is consumed for its mind-altering properties.

The severity of mushroom poisoning may vary, depending on the geographic location where the mushroom is grown, growth conditions, the amount of toxin delivered, and the genetic characteristics of the mushroom. Boiling, cooking, freezing, or processing may not alter the toxicity of some mushrooms.

Variations in clinical effects may depend on an individual's susceptibility and on the presence of confounding factors such as contamination or co-ingestion. In general, children are often exposed to nontoxic mushrooms, while older persons are at greater risk for the development of serious complications with mushroom poisoning than are healthy young adults.

Mushroom exposure in children is an infrequent but perennial problem for parents and clinicians. Parental anxiety is generally high because of fears of unknown or untoward effects. The

challenges for clinicians are to identify such poisonings, to discern whether poisoning has taken place, to order appropriate diagnostic studies, and to prescribe reasonable therapy. The varied nature of mushroom toxicities, their ubiquitous distribution, and the relative infrequency of the ingestions make these challenges difficult to meet.

Mushroom Poisoning Syndromes

There are many different types of mycotoxins. Of 14 distinctive types of mushroom poisoning found worldwide, so far about 10 distinctive patterns of reactions to mycotoxins have been observed in North America. However, since most mushroom species are rarely eaten, many toxins are poorly documented and syndromes not yet observed in North America may turn up as more and more people experiment with eating wild mushrooms. NAMA maintains a case registry where you may report instances of mushroom poisoning.

The following list is not exhaustive. It is presented here for informational purposes, and should not be considered an aid to diagnosis. The images are shown as examples only and should not be used for identification. For emergency identification, please consult

It is important to file a report, even if the outcome was only a gastrointestinal upset. NAMA tracks ALL mushroom poisonings.

- Gastrointestinal Irritants
- Muscarine
- Isoxazole Derivatives (Muscimol, Ibotenic Acid, and relatives)
- Amanitin (Amatoxins)
- Gyromitrin
- Delayed Kidney Damage: Orellanine
- Psilocybin, Psilocin, and other Indole Derivatives
- Prompt Kidney Damage
- Coprine and other Alcohol Induced Syndromes
- Miscellaneous and Unknown Toxins

Possible Questions

1. Explain about anti-inflammatory drugs.
2. How to manage shock?
3. Discuss mechanism of action, adverse reactions and therapeutic uses of catecholamines
4. Explain pharmacotherapy of Gout.
5. Write about the pharmacotherapy of cardiac failure
6. Describe diuretic and antidiuretic drugs?
7. How to manage hypertension?
8. Explain pharmacotherapy of Rhumatoid arthriris
9. How are vasodilators used as drugs for angina pectoris?
10. Give an account of immuno therapy- (i) immunosuppresents (ii) immunostimulants.

1	V	The protein fraction with	Albumin	alpha globulin	beta globulin	gamma globulin	**gamma globulin**
2	V	Human normal Ig is also called	Histafine	immuneserum	hyperimmuneserum	human specific Ig	**Histafine**
		_____ is used	muromab	infliximab	daclizumab	rituximab	**infliximab**
3	V	intreatment of Rhematoid					
4	V	Cyclosporin is a cyclic	undecapeptid	hexapeptide	octapeptide	nonapeptide	**undecapeptide**
		_____is a T cell growth	IL-4	IL-2	IL-6	IL-8	**IL-2**
5	V	differentiation factor					
6	V	Tacrolimus is obtained from	Aspergillus	Beauveria	E.coli	Streptomyces	**Beauveria nivea**
7	V	Cyclosporin is produced by	Aspergillus	Beauveria	E.coli	Streptomyces	**Aspergillus niger**
		Thalidomide is a selective	TNF-alpha	TNF-beta	TNF-gamma	TNF-delta	**TNF-alpha**
8	V	_____inhibitor					
		Daclizumab is a geneticall	IgG	IgA	IgD	IgE	**IgG**
9	V	engineered human_____					
10	V	_____ is an	Interferon	glatiramer	lavamisole	Sirolimus	**glatiramer acetate**
		_____restore cutaneous	amantadine	tilorane	levamisole	BCG	**levamisole**
11	V	delayed hypersensitive					
		____&_____ stimulate	Amantidine&	tilorane&levam	BCG&clofazimine	amantidine&tilora	**amantidine&tilora**
12	V	humoral immune system	levamisole	isole		ne	**ne**
		Drugs which increase the rate	Anti-diuretics	Vasopressin	osmotic diuretics	diuretics	**Anti-diuretics**
13	V	of urine formation together					
14	V	Which of the following is a	furosemide	chlorthalidone	bumetamide	mannitol &	**mannitol &**
15	V	Extravasation of mannitol may	intracranial	pulmonary	confusion	thrombophlebitis	**thrombophlebitis**
		_____ present in the	electrolytes	carbonic	xanthine	sucrose	**carbonic**
		cilia which is improtant in the		anhydrase			**anhydrase**
16	V	production of aqeuous humour					
		_____ should be	dexamethaso	nifedipine	dexamethason and	sedative hypnotics	**sedative hypnotics**
17	V	avoided for fear of causing	n		nifedipine		
		Excessive renal loss of Na and	hyponatremia	hyponatremic	hypokalemic	weak diuretics	**hypokalemic**
18	V	chloride with potassium loss		hypochloremia	hypocloremic		**hypocloremic**
		_____ is an anti-	osmotic	potassium	benzothiadiazine	high ceiling	**benzothiadiazine**
19	V	bacterial drug possessing mild	diuretic	sparing diuretic	diuretic	diuretic	**diuretic**

20	V	Diabetes insipidus treated with _____ decrease the urine volume	mannitol	furosemide	aminophylline	benzothiadiazine	**benzothiadiazine**
21	V	_____ acts as a competitive aldosterone antagonist	thiazides	mannitol	spironolactone	weak diuretics	**spironolactone**
22	V	Absense of _____ may cause diabetes insipidus	Desmopressin	arginine vasopressin	high ceiling diuretics	osmotic diuretics	**arginine vasopressin**
23	V	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**
24	V	colichicine is used for the treatment of ----------	chronic gout	acute gout	RA	Anaemia	**acute gout**
25	V	Lesch-Nyhan syndrome leads to----------gout	chronic gout	acute gout	chronic and acute gout	RA	**chronic gout**
26	V	uricosuric drugs are employed in the treatment of ----------	chronic gout	acute gout	RA	Epilepsy	**chronic gout**
27	V	The colichicine is rapidly absorbed from ----------	GI tract	duodenum	intestine	stomach	**GI tract**
28	V	Myopathy is caused by the chronic administration of --------	colichicine	allopurinol	probenecid	stomach	**colichicine**
29	V	The derivative of phenylbutazone which is used as uricosuric agent is	probenecid	sulfinpyrazone	Azapropazone	benzbromarone	**sulfinpyrazone**
30	V	The drug used in the treatment of RA	muromab	infliximab	daclizumab	rituximab	**infliximab**

		cyclophosphamide used in the treatment of RA is a ----------	analgesic	NSAID	daclizumab	DMARD	**daclizumab**
31	V						
		Which of the following is used for the treatment of patients with severe RA who have'nt responded to NSAID&slow acting agents	methotrexate	cyclophosphamide	daclizumab	Ibuprofen	**methotrexate**
32	V						
		Enzyme used in the treatment of gastrointestinal distribution is _____	urokinase	bibrinolysin	pepsin	hyaluronidase	**pepsin**
33	V						
		Cretain snake and bee venum contains	hyaluroonidase	disastase	trypsin	streptokinase	**hyaluroonidase**
34	V						
		_____ in highly purified form is used in opthalmic surgical procedures	potassium hyaluronidase	sodium hyaluronidase	chymotrypsin	collagenase	**sodium hyaluronidase**
35	V						
		Streptokinase is produced by certain strains of_____	stephylococci	bacilli	pneumococci	beta hemolytic streptococci	**beta hemolytic streptococci**
36	V						
		Trypsin is obtained from	bovine pancreas	ox pancreas	horse pancreas	bacterial strains	**ox pancreas**
37	V						
		The activity of collagenase is optimal at_____	pH 6-8	pH 5-8	pH 3-5	pH 7	**pH 6-8**
38	V						
		The concentrated protease enzyme bromelains obtained from	carcia papaya	pineapple	ox pancreas	bacterial strains	**pineapple**
39	V						
		Collagenase enzyme is derived from fermentation of	cl.bromelains	cl.histolyticum	cl.papase	cl.botulinum	**cl.histolyticum**
40	V						
		_____ used to liquefy excessive bronchial secretions	aerosal trypsin	bovine pancreas	chymoral	collagenase	**aerosal trypsin**
41	V						
		Streptokinase has its maximum activity between	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						

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**
46	V	NSAID repress the sensatoin of pain by decreasing ---------- synthesis	PGE2	PGI2	PGF2 alpha	PGF2 beta	**PGE2**
47	V	Aspirin ---------- thromboxane production.	reversibly inhibit	irreversibly inhibit	reversibly activate	irreversibly activate	**irreversibly inhibit**
48	V	Hyperkalemia is the increase of ----------	sodium	Magnesium	Calcium	Potassium	**Potassium**
49	V	Therapeutic action of aspirin is ------- -----	Anti inflammation	anti tumour	diuretic	antiemitic	**Anti inflammation**
50	V	A cyclooxigenase inhibitor used in the long term treatment of RA, osteo arthritis and .angkylosing spondilitis is	Diclofenac	Ketorolac	Tolmetin	Ibuprofen	**Diclofenac**
51	V	The inactive prodrug closely related to indomethacin which is used as NSAID is ---------- -	Diclofenac	Sulindac	Etodolac	Fenamates	**Sulindac**
52	V	Orally administered aspirin is usually absorbed from --------	GI tract	Intestine	Stomach	Liver	**Stomach**
53	V	---------- is the competitive block of alpha 1 and alpha 2 receptor	Prazosin	Perazosin	Phentolamine	Propranolol	**Phentolamine**
54	V	All beta blockers are competitive ----------	Agonist	Antagonist	Agonst and Antagonist	beta blocker	**Agonist**

55	V	Labetalol is a ---------	alpha blocker	beta blocker	alpha and beta blocker	gamma blocker	**alpha and beta blocker**
56	V	All of them are competitive blockers of alpha 1 receptor except	Prazosin	Terazosin	Daxazosin	Propranolol	**Propranolol**
57	V	---------- drug related to nitrogen mustard	Phenoxybenzamine	Propramolol	Labetalol	Esmolol	**Phenoxybenzamine**
58	V	Drug used in the treatment of pheochromocytoma is	Phenoxybenzamine	Propramolol	Labetalol	Acebutolol	**Phenoxybenzamine**
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**

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