**Pharmacology:** A study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules and activating or inhibiting normal body processes or (is the study of the therapeutic value and/or potential toxicity of chemical agents on biological systems. It targets every aspect of the mechanisms for the chemical actions of both traditional and novel therapeutic agents).

- **Systemic Pharmacology:** studying the effect of drug or group of drugs on a determined system of living organism. Ex, Neuropharmacology, Cardiovascular pharmacology,…..etc.
- **Molecular pharmacology** deals with the biochemical and biophysical characteristics of interactions between drug molecules and those of the cell.
- **Clinical pharmacology** is the application of pharmacodynamics and pharmacokinetics to patients with diseases.

*Pharmacokinetics:* the manner in which the body handles a drug, or (what the body does to the drug).

*Pharmacodynamic:* the relationship between the drug concentration and effect (what the drug does to the body).

- **Veterinary pharmacology** concerns the use of drugs for diseases and health problems unique to animals.
- **Toxicology:** is that branch of pharmacology which deals with the undesirable effects of chemicals (poisons) or toxins on living systems.

**Note:** Often confused with pharmacology, pharmacy is a separate field in the health sciences. It is the profession responsible for the preparation, dispensing and appropriate use of medication, and provides services to achieve optimal therapeutic outcomes.

**Routes of drug administration:**

- Enteral (Oral) like Tablets, Solutions, Suspensions,
- Parenteral by injections

And it’s classified according to the speed of stimulation to the drug in to four ways those are:-

- Intravenous injection (i.v.).
- Intraperitonial injection (i.p.).
- Intramuscular injection (i.m.).
Subcutaneous injection (s/c).

- Topical administration or (local)

And includes:-

- On skin.
- In the eye.
- Intravaginal.

Other special routes include:-

- Inhalation (Respiratory system).
- Intrathecal (epidural anesthesia in spinal cord).
- Sublingual.

Methods of transport of drug across cell membrane:

1. Passive diffusion (simple diffusion)
   depend on lipid solubility, example (weak acids, weak basis).
3. Carrier mediated transport (facilitated diffusion) example Amino acids.
4. Active transport, example (excretion of penicillin through the proximal convoluted tubules).

The Pharmacokinetics: the manner in which the body handles a drug or Examines the rate at which drug concentrations change in the body by observing

- Input processes
  - Absorption: movement of drug into the body from the site of administration
  - Output processes: responsible for drug delivery and removal from the body
- Distribution: movement of drug from intravascular to extravascular compartment
- Metabolism: chemical transformation of drug
- Elimination: removal of drug from the body

Absorption

Most drugs are absorbed into the systemic circulation via passive diffusion

Other mechanisms of absorption include: active transport, facilitated diffusion

Absorption rate and amount depends on
• local blood flow at administration site
  (e.g. sublingual vessels provide significant blood flow therefore rapid absorption)
• Lipid solubility: greater lipid solubility = increased rate of diffusion through membranes
  • E.g. anesthetics are very lipid soluble therefore have a rapid onset of action
  • Molecular size: small size, water soluble drugs can pass through channels in membranes, Large molecules cannot
  • e.g. aminoglycosides are large molecules and are not absorbed through intestinal mucosa and are therefore not orally active
• local pH and drug ionization: charged molecules do not cross membranes e.g. lactulose ionizes ammonia to ammonium and keeps it in the bowel
• total surface area for absorption: the small intestine has villi which increase the surface area for absorption, and hence is the primary site of absorption for most oral drugs.

**Henderson-Hesselbach Equation:**

The proportion of the total drug concentration that is present in either ionized or un-ionized form is dictated by the drug’s dissociation or ionization constant (K) and the local pH of the solution in which the drug is dissolved.

The dissociation of a weak acid, RH, and a weak base, B, is described by the following equations:

\[
RH \rightleftharpoons H^+ + R^- \quad \text{(acid)}
\]
\[
B + H^+ \rightleftharpoons BH^+ \quad \text{(base)}
\]

If these equations are rewritten in terms of their dissociation constants (using Ka for both weak acids and weak bases), we obtain:

\[
K_a = \frac{[R^-][H^+]}{[RH]} \quad \text{(acid)}
\]
\[
K_a = \frac{[H^+][B]}{[BH^+]} \quad \text{(base)}
\]
By taking logarithms and then substituting the terms $pK$ and $pH$ for the negative logarithms of $K_a$ and $[H^+]$, respectively, we arrive at the Henderson-Hasselbach equations:

\[ \text{For acid: } pH = pK_a + \log \frac{[R^-]}{[RH]} \]  
and \[ \text{For base: } pH = pK_a + \log \frac{[B]}{[BH^+]} \]

And we can simplify these two formulas to:

- for weak acids drugs: \[ PH - Pka = \log \frac{\text{Ionized}}{\text{Unionized}} \]
- for weak bases drugs: \[ PH - Pka = \log \frac{\text{Unionized}}{\text{Ionized}} \]

Factors which affect drug absorption:

1. The chemical nature of drug.
2. Pharmaceutical form of the drug.
3. Dissociation constant $P_K$ of the drug.
4. PH of the medium.
5. Presence or absence of food.
7. Nature of the food.
8. Species of animal.

**Bioavailability** ($F$): A fraction of the drug which reach to the circulation after administration from any route other than the (i.v.) route, for example if 100mg of drug administrated orally and 70mg of this drug is absorbed unchanged, the bioavailability is 70%.

\[
\text{Bioavailability} (F) = \frac{\text{Amount drug in any route of administration}}{\text{Amount of drug after intravenous administration}} \times 100\%
\]
**First pass effect**: Metabolism of orally administered drug in the liver before it reaches the systemic circulation. That’s to say if a drug with high first pass effect it means low bioavailability and vise versa (inverse proportion). Drugs with a high first-pass effect include: chlorpromazine, levodopa, morphine, propranolol, lidocaine, hydralazine, nortriptyline, and organic nitrates, drugs with low hepatic extraction (little or no first pass effect) include: diazepam, digoxin, phenylbutazone, phenytoin, theophylline, tolbutamide, warfarin.

**Distribution:**

Movement of drug from intravascular to extravascular compartment or process by which drugs are carried throughout the body to reach target sites of action.

**Factors effect on the drug distribution:**

1. **Blood flow**: Drug molecules are highly distributed to the highly vascularized tissues like brain, liver, and kidney.
2. **Capillary permeability**: Capillaries of some organs (Brain, Testes, Placenta) have tight pores there for only lipid soluble materials can pass by simple diffusion.
3. **Chemical nature of the drug**: Its play an important role in drug distribution, so the non-polar drugs are well distributed across tissues while polar drugs are not well distributed across tissues.
4. **Binding of drug to plasma proteins**: Drugs with high affinity to bind to plasma proteins have low distribution, and this binding will slow there transfer out the vascular compartment, Albumine tends to bind to the acidic drugs while Globuline tends to bind with basic drugs.

**Volume of Distribution (Vd)**: The volume of distribution (Vd) relates the amount of drug in the body to the concentration of drug (C) in the blood. This volume does not necessarily refer to an identifiable physiological volume but rather to the fluid volume that would be required to contain the entire drug in the body at the same concentration measured in the blood:
Dose (mg/kg)  = \frac{\text{Concentration mg/liter}}{(V_d)} \text{ liter/kg}

**Actual volume of distribution (V_d):** the anatomic volume that is accessible to drug, e.g. total body water of 40 L.

**Apparent volume of distribution (V_d):** is a calculated value that does not correspond to an anatomical space, a drug with a large Vd (larger than 40 L) must distribute in other tissues besides body water.

**Metabolism or Biotransformation:** chemical transformation of drug, Alteration of drugs by the liver. Drugs can be metabolized from active to inactive or from inactive to active. Generally drugs are made more hydrophilic by the process. Liver is the principal organ of drug metabolism. Other tissues that display considerable activity include the gastrointestinal tract, the lungs, the skin, and the kidneys.

**Significance of Biotransformation:**
1. Change the pharmacological activity of the drug.
2. Lead to change the solubility of the drugs, so that the lipid soluble drugs will become more water soluble, and this change will enhance the excretion of drug from the body.
3. It will minimize the time of presence of the drug in the body.

**Metabolism pathways:** - drug metabolism is biphasic process, drugs undergo phase I then phase II or directly phase II according to the chemical nature of the drug.

*(Phase I) Oxidation, Reduction, and Hydroxylation:*

Mixed-Function Oxidases, formed by microsomes made out of SER folded over on itself.
- introduce or unmask polar chemical groups therefore increase water solubility
- mediated by cytochrome P450 enzymes
- P450’s are found in the endoplasmic reticulum or cell cytoplasm

**Cytochrome-P450 Enzyme Complex:** Has four required components in order to work.
- Cytochrome-P450 Enzyme
- Cytochrome-P450 Reductase
- \( \text{O}_2 \)
- NADPH: NADPH is the only energy source. No ATP is required.
Phase I enzymes perform multiple types of reactions:

1. **OXIDATIVE REACTIONS**: on drugs, such as Aromatic hydroxylation, aliphatic hydroxylation, N-dealkylation, O-dealkylation, S-dealkylation, N-Oxidation, S-Oxidation, Desulfuration.

2. **REDUCTIVE REACTIONS**: Carbamyl

3. **HYDROLYTIC REACTIONS**: Ester hydrolysis, Amide hydrolysis.

**Phase II Conjugation**:
- Conjugation with polar endogenous substrates e.g. glucoronic acid, glutathione
- Increases water solubility and renal elimination

Factors which affect Biotransformation:

1. Enzyme induction: some chemicals or drugs tends to increase amount of metabolic enzymes which lead to increase biotransformation rate (Phenobarbitone, Glucocorticoids and Alcohol).

2. Enzyme inhibition: other chemicals or drugs tends to decrease amount of metabolic enzymes which lead to decrease biotransformation rate (Cimitidine, chloramphenicol and carbon tetrachloride).

3. Age: in young animals slow metabolism due to slow metabolic enzymes in the liver, also in the old animals.

4. Liver diseases: also slowing the metabolism, e.g. Liver cirrhosis, parasitic infestation of liver.

5. Species variation: Equine have high rate of oxidation, also glucourimdation, Ruminants have high acetylation, Cats, Geese and Fish have low Glucourimdation, dog has low acetylation.
### Major Reactions Involved in Drug Metabolism

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. Oxidative reactions</strong></td>
<td></td>
</tr>
<tr>
<td>N-Dealkylation</td>
<td>Imipramine, diazepam, codeine, erythromycin, morphine, tamoxifen, theophylline, caffeine</td>
</tr>
<tr>
<td>O-Dealkylation</td>
<td>Codeine, indomethacin, dextromethorphan</td>
</tr>
<tr>
<td>Aliphatic hydroxylation</td>
<td>Tolbutamide, ibuprofen, phenobarbital, meprobamate, cyclosporine, midazolam</td>
</tr>
<tr>
<td>Aromatic hydroxylation</td>
<td>Phenytoin, phenobarbital, propranolol, ethinyl estradiol, amphetamine, warfarin</td>
</tr>
<tr>
<td>N-Oxidation</td>
<td>Chlorpheniramine, dapsone, meperidine</td>
</tr>
<tr>
<td>S-Oxidation</td>
<td>Cimetidine, chlorpromazine, thioridazine, omeprazole</td>
</tr>
<tr>
<td>Deamination</td>
<td>Diazepam, amphetamine</td>
</tr>
</tbody>
</table>

### II. Hydrolysis reactions

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Procaine, aspirin, clofibrate, meperidine, enalapril, cocaine</td>
</tr>
<tr>
<td></td>
<td>Lidocaine, procainamide, indomethacin</td>
</tr>
</tbody>
</table>

### III. Conjugation reactions

#### Glucuronidation

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen, morphine, oxazepam, lorazepam</th>
</tr>
</thead>
</table>

#### Sulfation

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen, steroids, methyldopa</th>
</tr>
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</table>

#### Acetylation

<table>
<thead>
<tr>
<th></th>
<th>Sulfonamides, isoniazid, dapsone, clonazepam (see Table 3–3)</th>
</tr>
</thead>
</table>

#### Methylation

| | L-Dopa, methyldopa, mercaptopurine, captopril |

#### Glutathione conjugation

| | Adriamycin, fosfomycin, bosulfan |

*UNREVISED EDITION*
Elimination:
Removal of drug from the body

* Routes of elimination include:
  - Urine most drugs are eliminated through this route
  - stool (e.g. corticosteroids from biliary system)
  - lungs (e.g. general anesthetics eliminated by expiration)
  - skin and mucous membranes (e.g. rifampin in tears)

Amount of excreted drug = Amount of filtered drug + amount of active secreted drug – amount of absorbed drug.

Clearance of drug: volume of blood which cleared from drug per unit of time

\[ CL = \text{rate of elimination} / C \]

Half life (\( t_{1/2} \)): time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

\[ t_{1/2} = \frac{0.693}{K_e} \]

0.693: inverse natural log. of 2.

Ke (1/minute): constant of drug elimination, In case of drug follow the first order of excretion

FIRST-ORDER EXCRETION: The rate of excretion of a drug is directly proportional to its concentration.

ZERO-ORDER EXCRETION: The rate of excretion of a drug is independent of its concentration.
The Pharmacodynamic: the relationship between the drug concentration and effect (what the drug does to the body).

Receptor: it’s a macromolecule component of cell when bound to low concentration of drug will produce action.

Nature of receptors:
Receptors in nature may be:
1. proteins\nicotinic receptor
2. enzymes\Na\(^+\)K\(^+\) ATPase
3. DNA
4. RNA
5. Ribosomes

Types of receptors:
1. Ligand - gated ion channels: this type of receptors is responsible or regulation of flow of ions across cell membrane. The duration of action of these receptors is very rapid (a few milliseconds), E.g. GABA - receptor, nicotinic receptor.

2. G protein coupled receptors: a single peptide linked to the G protein complex this receptor work when a drug molecule link with this complex lead to promotion of second messengers inside the cell (cAMP, phospholipase then Inositol triphosphate IP\(_3\) and diacylglycerol DAG) which responsible of regulation of calcium concentration within cell. E.g. norepinephrin, dopamine, serotonin and Acetylcholine receptors. The duration of action of these receptors is between several seconds to minutes.

3. Enzyme linked receptors: receptors consist of those of that have a cytosolic enzyme activity as an integral component of their structure or function, binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. The duration of action of these receptors is extended from minutes to hours. E.g. insulin hormone receptor.

4. Intracellular receptors: this type of receptors is differs from the other previous in that the receptor is entirely intracellular and, therefore, the ligand must diffuse in to the cell to interact with the receptor, e.g. steroid hormones which must inter to the cell and bind to DNA to exert its effect, The duration of action of these receptors is extend from hours to days.
**Characteristic features of receptor:**
1. specific chemical structure
2. ability of saturation
3. irreversibility
4. blocking by specific antagonist

**Types of drug response:**
- Graded response: the response following the dose of the drug
- Quantal response (all or non response).

**Potency:** A potent drug induces the same response at a lower concentration.

**Efficacy:** The biologic response resulting from the binding of a drug to its receptor.

- **ED50:** The drug-dosage at which 50% of the population attains the desired characteristic.
- **LD50:** Lethal-Dose-50. The drug-dosage at which 50% of the population is killed from a drug.

- **THERAPEUTIC INDEX = LD50 / ED50**
  - The ratio of median lethal dose to median effective dose.
  - The higher the therapeutic index, the better. That means that a higher dose is required for lethality, compared to the dose required to be effective.

- **MARGIN OF SAFETY = LD1 / ED99**
  - The ratio of the dosage required to kill 1% of population, compared to the dosage that is effective in 99% of population.
  - The higher the margin of safety, the better.
Agonists Have Two Main Properties

- **Affinity**: the ability of the agonist to “bind to” the receptor
- **Efficacy**: the ability to cause a response via the receptor interaction

  e.g. the β2-agonist (salbutamol) bind to β2-receptors (i.e. has affinity) and result in activation of smooth muscle relaxation (i.e. has efficacy)

**Antagonists**

- have affinity (can bind to a receptor) but no efficacy

  - **Chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist binding to receptor
  - e.g. chelator agents for removal of heavy metals

  - **Functional antagonism**: interaction of 2 agonists that act at different receptors independent of each other but have opposite physiological effects
    - e.g. acetylcholine at the muscurinic receptor decreases HR, constricts pupil, stimulates intestinal motility
    - epinephrine at the adrenergic receptor increases HR, dilates pupil, decreases intestinal motility

    - **Competitive antagonism** (most common in clinical practice)
      - antagonist acts at same receptor (i.e. binds) displacing agonist
      - antagonist binding is reversible and can be overcome
      - non-competitive antagonism
        - irreversible binding of antagonist to receptor
        - allosteric effect: changes ability of the agonist to bind to the receptor through various mechanisms such as changing the conformation of the receptor
        - increasing concentrations of agonist cannot reverse the antagonism.

**Tolerance**: decrease the action of the drug due to long persistent use.

**Tachyphylaxis**: sudden decrease in the response after use of one dose.

**Idiosyncrasy**: unusual response to the drug.
Neuropharmacology

Nervous system is divided into two anatomical parts:

1. The central nervous system (CNS) which is composed of brain and spinal cord.
2. The peripheral nervous system (PNS) which includes neurons located outside the brain and the spinal cord. PNS is subdivided into:
   - The efferent division: includes the neurons which carry the signals away from the brain and the spinal cord to the peripheral tissues. This division is also divided into:
     A- The somatic efferent neurons: they are involved in the voluntary control function such as contraction of skeletal muscles.
     B- The autonomic efferent neurons (Autonomic nervous system ANS): they regulate the daily involuntary needs and the requirements of the vital body functions without the conscious participation of mind.
   - The afferent division: includes the neurons which bring the information from periphery to the CNS.

Autonomic nervous system

The autonomic nervous system consists of two large divisions:

- Parasympathetic (craniosacral) outflow, which include the motor roots of the {oculomotor (III), facial (VII), glossopharyngeal (IX) and vagus (X)} cranial nerves and the 2nd, 3rd, and 4th.
- Sympathetic (thoracolumbar) outflow, which include the motor roots of 1-12 thoracic, 1-5 lumber and 1 sacral nerves.

According to the Neurotransmitters (endogenous chemical substances which transmit the impulses through the nerve) we can classify the efferent nerve fibers to:

1. Cholinergic N.: include the somatic and parasympathetic nerves
2. Adrenergic N.: include the sympathetic nerves.

- Functions of ANS are attributed to presence of specific receptors on affected cells or tissues which either classified to:
  1- Cholinoceptors.
  2- Adrenoceptors.

Tissues which contain these receptors and sensitive to Acetylcholine (Ach) are called
cholinoceptive, while nerves that are sensitive to the Noradrenaline (NA) are called adrenoceptive.

The Parasympathetic Nervous System

The Parasympathetic Nervous System is a part of the autonomic nervous system; it helps in conserving of body energy and is partly responsible for activities such as slowing of the heart rate, food digestion processes, and elimination of body waste.

The Parasympathetic Nervous System has two neurohormones (neurotransmitters): Acetylcholine (ACh) and acetylcholinesterase (AChE).

ACh is a neurotransmitter responsible for the transmission of nerve impulses to effector cells of the parasympathetic nervous system. ACh plays an important role in the transmission of nerve impulses at synapses and myoneural junctions. ACh is quickly destroyed by the enzyme AChE, thereby allowing the nerve impulse to pass, but not remain in an excited state.
Acetylcholine acts on two types of receptors:

1. **Muscarinic receptors**: on which the pharmacological effect of acetylcholine is seems to those of the alkaloid "Muscarine" e.g. stimulation of secretion of exocrine glands like salivary and lachrymal glands, contract plain muscle, slow and weaken heart beat, dilate arteriols.

2. **Nicotinic receptors**: which the pharmacological effect of acetylcholine is seems to those of the alkaloid "Nicotine" these cholinceptors are exist in the neurons of sympathetic and parasympathetic ganglia, motor end palate of voluntary muscles and adrenal medulla.

**Parasympathomimetics (Cholinergic agonists)**

Drugs with Ach like activity and its divided to two types:

1. Direct acting: this type of the drugs is mimic to the effect of the Ach buy binding directly to the cholinceptors this group includes:

   - **Acetylcholine**: is a quaternary amine compound that cannot penetrate the membranes therapeutically it has no benefits due to its unspecified action and its sensitivity to hydrolyzed by the AchE.
   - Ach has both mscainic and nicotinic activity.
   - It decreases the cardiac output and the heart rate due to its mimic effect on the Ach on the vagal stimulation.
   - Its decrease blood pressure although no innervation of the vasculature by the parasympathetic system, there are cholinceptors on the blood vessels that respond to cause vasodilatation.
   - GIT: Ach increase salivary secretion and stimulate intestinal secretion and motility, bronchiolar secretions also are enhanced.
   - Genitourinary tract: the tone of the (detrusor urinae) muscle will increase
   - The eye: Ach stimulates ciliary muscle contraction for near vision also cause miosis (marked constriction of the pupil).

   - **Pilocarpine**: it’s a tertiary amine alkaloid and its stable to hydrolysis of by AchE, pilocarpine exhibit the muscarinic receptor and its used primarily in ophthalmology.

   - **Carbachol**: its carbamylcholine has strong nicotinic and weak muscarnic activates, a single administration can last as long as one hour. Therapeutically it used only as
mioric agent and in cases of glaucoma.

II- Indirect acting: this group of cholinomimetic drugs has no direct effect on the cholinoreceptors and its effect is represented by inhibition of AchE and this effect lead to increase the level of Ach. This group is divided to two subtypes those are:

**Reversible anticholinesterase:** this group will inhibit AchE but reversibly and it include:

- Physostigmine (Eserine): physostigmine is an alkaloid (a nitrogenous compound found in the plant) and a tertiary amine which reversibly inhibits AchE and the result is potentiation of cholinergic activity throughout the body.

Physostigmine has a wide range of effects as a result its action and its effect is extend to the nicotinic receptor of the neuromuscular junction in addition to its effects on the muscarinic and nicotinic sites of the ANS its duration of action is about 2 - 4 hrs. physostigmine can enter and stimulate cholinergic sites of the CNS.

**Therapeutic uses of Physostigmine**

1- Physostigmine increases the intestinal and urinary bladder motility which serve as its therapeutic action in atony of each organ.

2- In the eye physostigmine produce miosis as well as lowering of the intraocular Pressure so that it’s used to treat glaucoma but pilocarpine is more effective.

3- Physostigmine is also used in treatment of overdoses of drugs with anticholinergic effects like atropine.

**Adverse effects:**

1- physostigmine can cause convulsions with high doses.

2- Bradycardia and fall in cardiac output.

3- Paralysis of skeletal muscle due to accumulation of Ach.

- Neostigmine (Prostigmine) synthetic analogue of physostigmine but cannot pass to the CNS (quaternary amine)

- Pyridostigmine (Mestinone) its similar to neostigmine but with longer duration of

- Edrophonium (Tensilon) rapid effect with short duration of action. )

Irreversible anticholinesterase: this group will inhibit AchE irreversibly and this type of chemicals are non-specific AchE inhibitors, leading to increase all sites were its released almost of these chemicals are extremely toxic and used as chemical warfare agents like
(Tupan, Sarine) some of these chemicals are used as pesticides or insecticides like diazenone and chloridine while a little types of these chemicals are used as medicines specially in ophthalmologic purpose like Echothiophate and Isoflurophate.

**Parasympatholytic or Anticholinergic (Blockers):**

This class of drugs is bind to the cholinoceptors but they do not trigger the usual receptor mediated intracellular effect and the effect distributed among muscarinic blocking agent or nicotinic (Neuromuscular blocking agents) or dual effect on the ganglia of sympathetic and parasympathetic systems.

1- Antimuscarinic agents: these agents block muscarinic receptors causing inhibition of all muscarinic functions. Antimuscarinic agents are beneficial in a variety of clinical cases because they are don't close nicotinic receptors. Also antimuscarinic have little or no action on skeletal neuromuscular junctions or autonomic ganglia.

**Atropine:** an alkaloid derived from *Atropa belladonna* this plant contain two alkaloids those are L- hyoscine and L- hyocyamine (Atropine) where it:

1- binding competitively preventing Ach from binding to these sites.
2- atropine acts both centrally and peripherally.
3- Its general action last about 4 hrs. except when placed topically in the eye where the action may last for days.

**Actions and therapeutic uses of atropine:**

- Ophthalmic: in the eye topical atropine exerts the mydriatic effect (Mydriasis: marked dilatation of the pupil). Atropine is contraindicated in glaucoma patients.
- Antispasmodic agent: its used as antispasmodic agent to relax the GIT and urinary bladder.
- Antidote for treatment overdose of AchE inhibitors like insecticides and poisoning with some types of mushroom.
- Antisecretary agent: atropine is used as pre-surgical operations drug in order to reduce (minimizing) secretion of upper and lower respiratory tracts.

**Adverse effect:** depending on the dose atropine may cause:

1- Dry mouth.
2- Blurred vision (sand fly).
3- Tachycardia.
4- Constipation.
5- CNS disturbances include: restlessness, confusion, hallucinations and delirium which may progress to depression, collapse of the circulatory and respiratory system then death.

Scopolamine: is another Atropa belladonna (Hyoscine) produce peripheral effects similar to those of atropine.

Scopolamine has greater action on the CNS. It has larger duration of action in comparison to those of atropine. Therapeutically scopolamine is used to treatment of motion sickness.

Ipratropium: A quaternary amine derivative of atropine, Inhaled ipratropium is useful to treat asthma in patients who are unable to take adrenergic agonists. It's also beneficial in the management of chronic obstructive pulmonary diseases.

II- Ganglionic blockers:

These groups of the drugs act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia.

Nicotine: its an alkaloid derived from tobacco.
- Nicotine has many undesirable actions, its with out therapeutic benefits and its deleterious to health.
- depending on the dose, nicotine depolarize ganglia resulting first in stimulation and then paralysis of all ganglia the stimulatory effect includes:
  * Increased blood pressure and cardiac rate.
  ** Increased peristalsis and secretions.
  *** At high doses the blood pressure falls because of the ganglionic and activity both in GIT and urinary bladder (atony).

Trimethophane:
- Short acting competitive nicotinic ganglionic blocker.
- It used in emergency lowering blood pressure via i.v. route only.

Mecamylamine:
- produce competitive nicotinic blockade of the ganglia.
- Duration of action is about one hour after single administration.
- It can be uptakes via oral route in contrast to trimethophane due to its good absorption.
III- Neuromuscular blocking drugs:

- These drugs block cholinergic transmission between/motor nerve ending and the nicotinic receptors on the neuro-muscular end palate of skeletal muscle.
- These neuro-muscular blocking blockers are structural analogs of Ach.
- These drugs are act as antagonists (non-depolarizing type) or agonists.

\[\text{Non-depolarizing competitive blockers:}\]
- Not effect on neural permeability to ions.
- First agent has been discovered was the curare which was used from the native tribes of Africa and south America as a tip of arrow to paralyze the victim.
- These drugs are combining with nicotinic receptor and prevent the binding of Ach lead to preventing of muscular contraction.
- Example: D-tubocurarine, Galamine and pancuronium.
- These agents are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscles.

\[\text{Depolarizing agents:-}\]
- Attach to the nicotinic receptors and act like Ach, (but they resist hydrolyzing by AchE) to depolarize the neuro-muscular junction instead of released Ach.
- The resultant effect is the paralysis but not necessarily relaxation.
- They are very useful agents when rapid endotracheal intubation is required during the induction of anesthesia.
- Ex. Succinylcholine.
Sympathetic nervous system:

- Sympathetic nervous system is the second compartment of the autonomic nervous system.
- The chemical neurotransmitter which responsible of transmitting the impulses through the adrenergic nerves is the Norepinephrine (a catecholamine synthesized in the nerve endings of the adrenergic nerves and in the adrenal medulla).

  ![Diagram of the sympathetic nervous system](image)

- The chemical substances which responsible of norepinephrine degradation are:
  - Catechol O–methyltransferase (COMT) which responsible of norepinephrine methylation.
  - Then norepinephrine will be oxidized by Monoamine oxidase (MAO).
- Norepinephrine has shown his effect via two types of receptors (Adrenoceptors)
  A- \( \alpha \)-adrenoceptor which divided to two subunits those are:
1- $\alpha_1$ receptor (post synaptic):
   - Blood vessels: vasoconstriction (arterioles of skin viscera and mucosa) which increase peripheral resistance leading to increase blood pressure.
   - Eye: dilatation of pupil (Mydriasis).
   - Sphincters smooth muscles: contraction, no digestion.

2- $\alpha_2$ (mostly presynaptic):
   - Decrease norepinephrine release (feedback mechanism).
   - Decrease Insulin release.

B- $\beta$- adrenoceptor which divided to two subunits those are:

1- $\beta_1$ receptor:
   - Heart: increase contractability (+ inotropic) and increase heart rate (+ chronotropic)
   - Metabolism: lipolysis, increase free fatty acids in the blood.
   - Glands: increase rennin secretion from juxtaglomerular system.

2- $\beta_2$ receptor:
   - Blood vessels: dilatation of coronary arteries and the vessels of skeletal muscles.
   - Smooth muscles: relaxation of bronchioles, GIT, urinary bladder and uterus.
   - Metabolism: cause glycogenolysis leading to hyperglycemia.

Adrenergic agonists (sympathomimetics): drugs with norepinephrine like effects, and it’s divided to:-

A- Direct acting agonists: these drugs act directly on the receptor and include:-

- Epinephrine (Adrenaline): one of naturally existing catecholamines in the body. Affects all types of adrenergic receptors.

- Therapeutic uses of Adrenaline:
  1. Asthma: in emergency cases of asthmatic attracts, adrenaline rapidly relieves the dyspnea and increase tidal volume.
  2. Glaucoma: adrenaline can be used to decrease aqueous humor formation through constriction of ciliary blood vessels.
3. Anaphylactic shock: it’s used in treatment of hypersensitivity (type I) in response to allergen.

4. Local anesthesia: it’s combined with local anesthetics in order to cause local vasoconstriction to slowing the absorption of local anesthetics and to control the oozing of the blood.

- **Adverse effects:**
  1. CNS: anxiety, fear, tension, headache, tremor and cerebral hemorrhage.
  2. Heart: it can cause arrhythmias in patients who receive digitalis.

Norepinephrine:
- One of the natural catecholamines analogous to epinephrine in its action.
- Its effect on $\alpha$ more than $\beta$ receptor
- Therapeutically norepinephrine is not satisfactory because it has many adverse effects, sometimes its used in treating of shock.

Dopamine:
- Another natural catecholamine
- It has general effect on both adrenergic receptors. Also on the dopaminic receptors ($D_1$, $D_2$).
- Therapeutically its considered the drug of choice in treatment of shock (shock, is a serious, life-threatening medical condition where insufficient blood flow reaches the body tissues).

Phenylephrine:
- Direct acting on $\alpha_1$ receptor.
- It is not a catechole derivative therefore it’s not a substrate for COMT.
- Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressure.
- Pharmacological uses of this drug include nasal decongestant, producing prolonged vasoconstriction and also it’s used to raise blood pressure.
- Large doses can cause hypertensive headache and cardiac irregularities.

Clonidine:
- Direct acting on $\alpha_2$ receptor. (Not a catechol derivative).
- Clonidine acts centrally to produce inhibition of sympathetic vasomotor center, therefore it’s used as central antihypertensive.
- Is used to minimize the symptoms that accompany withdrawal from opiate or benzodiazepines.

**Dubutamine**:
- Synthetic direct acting catecholamine that is a $\beta_1$ receptor agonist.
- Therapeutically, dubutamine is used to increase cardiac output in congestive heart failure.
- The main adverse effect represented by arterial fibrillation due to increase atrioventricular conduction.

**Salbutamol (Ventoline), Albuterol**:
- Direct acting $\beta_2$ agonist. (Not a catechole derivative).
- These drugs are very beneficial in treating the broncho-constriction and the cases of asthma.

**B- Indirect acting agonists**: these drugs are not act directly on the receptor and they are act on the neurotransmitter like:-

**Amphetamine**:
- This drug has CNS stimulation action.
- It increases blood pressure through $\alpha_1$ and $\beta_1$ receptors.
- It has abused CNS effect but it is useful in cases of depression, hyperactivity of children, sleeping sickness also termed by Narcolepsy (neurological condition most characterized by Excessive Daytime Sleepiness (EDS), in which a person falls asleep during the day at inappropriate times).and in treatment of obesity (appetite controller).

**C- Mixed action**: these drugs have dual effect and they work on releasing of stored norepinephrine and in the same time they effect directly on the adrenoceptors.

**Ephedrine**: alkaloid, cause release of stored catecholamines and in the same time it effect on $\alpha$ and $\beta$ receptors.
- Less potent than epinephrine.
- It is poor substrate for COMT and MAO (long duration of action).
- Pharmacologically it’s used for prevent attacks of asthma, also in treatment of Myasthenia gravis with ChE. Inhibitors, also in CNS stimulator and produce
alertness, decrease fatigue and prevent sleep, improve athletic performance and it is used in as decongestant.
Adrenergic antagonists (also called blockers or sympatholytic agents):

Adrenergic receptor antagonists inhibit the interaction of norepinephrine, epinephrine, and other sympathomimetic drugs with α and β receptors.

- **α - adrenergic blockers:**
  
  + phenoxybenzamine:
    - Its non selective α receptor blocker (effect on α₁ and α₂ receptor)
    - Its effect is irreversible and noncompetitive and only mechanism of reactivation of the adrenergic effect is by re-synthesis of adrenoceptors.
    - Action of phenoxybenzamine last about 24 hrs. After a single dose of administration.
    - The most therapeutic use of this medicine in treatment of phenocytochrma (a catecholamine – secreting tumor of cells derived from adrenal medulla.)
    - Side effects include: hypotension, nasal stiffness, nausea and vomition.
  
  + prazosin, terazosin, doxazosin and tamsulosin:
    - selective competitive blockers of α₁ receptor
    - decrease peripheral vascular resistance (relax the smooth muscles of arterioles and veins) leading to decrease in arterial blood pressure.
    - Tamsulosin is more potent inhibitor of α₁(subtype A) which exist in the smooth muscles of prostate therefore its used in the treatment of benign prostatic hyperplasia.

- **β - adrenergic blockers:**
  
  + Non- selective β adrenergic blocker propranolol (Inderal):
    - its non- selective β adrenergic blocker (effect on β₁ and β₂ both)
    - it has both negative inotropic (force of heart contraction) and chronotropic (heart rate) therefore it cause bradycardia and hypotension.
    - Another pharmacological uses are, treatment of angina pectoris, myocardial infarction and treatment of migraine.
    - The main side effect of propranolol is the bronchoconstriction due alteration of drug with β₂ receptors which mainly exist in the bronchial ramification of the lung.
- Other side effects are cardiac arrhythmias and metabolism disturbances.

**Selective β₁ blockers:**
- This group of drugs has an important role in treatment of chronic hypertension
- This group of drugs has less effect on the bronchial ramification due to its selective blocking of β₁ receptors only.
- This group includes: Acebutolol, atenolol (tenormine), esmolol and practolol (Eralidin).

**Drugs affecting neurotransmitter release or uptake:**

**+ Reserpine:**
- A plant alkaloid inhibits the mechanism transport of monoamines from the cytoplasm of the nerve cell and chromaffin cells to the storage vesicles.
- In consequence lead to depletion of norepinephrin levels in the adrenergic neuron.
- The only therapeutic use of reserpine in treatment of hypertension that fails to respond to treatment with other drugs.

**+ Cocaine:**
- Has the ability to block the mechanism of norepinephrine uptake across the cell membrane of adrenergic neuron.
- Consequently norepinephrine accumulates in the synaptic cleft resulting in enhancement of sympathetic activity and potentiation of catecholamine effects.
Central nervous system pharmacology:

The CNS is very important compartment of nervous system because it is considered as a coordinator of body organs activities because its control on vital centers, this control is occur via electrochemical substances termed (Neurotransmitters).

These neurotransmitters are divided to two types according to the postsynaptic effect these transmitters:-

1- **Excitatory neurotransmitters**: act by depolarizing the nerve cells. And include:-
   - Acetylcholine: acts on two types of receptors in the spinal cord, nicotinic receptors and muscarinic receptors. Acetylcholine effects on arousal, short term memory and learning.
   - Glutamic and aspartic acids: excite motor neurons in the CNS.
   - Substance P: mediate the nociception (pain) within spinal cord
   - Norepinephrine: acts on two types of receptors (α and β). Norepinephrine effects on arousal, wakefulness, mood and cardiovascular regulation.
   - Dopamine: its effects on emotion and reward system.
   - Serotonin: effect on the feeding behavior, control of body temperature, modulation of sensory pathways (including: nociception (pain), regulation of emotion and mood and sleep and wakefulness.

2- **Inhibitory neurotransmitters**: act by hyperpolarization of the nerve cell.
   - GABA (γ - amino butyric acid) is the major inhibitory neurotransmitter in the mammalian CNS, its inhibits the presynaptic neuron.
   - Glycine: is another inhibitory CNS neurotransmitter whereas GABA is located primarily in the brain glycine is found predominantly in the ventral horn of the spinal cord.
   - Encephalins and Endorphins: they are having morphine like effect in controlling pain and producing addiction.

**CNS drugs is either depressant or stimulant:**

- **CNS stimulants**: are drugs that increase behavioral activity, thought processes, and alertness or elevate the mood of an individual. Its also called analeptics and are classified as:
1. **Medullary stimulants:**
   - They stimulate centers in the medulla oblongata
   - The main therapeutic use of these drugs is to neutralize the depressing effect of CNS depressants like anesthesia, or in treatment of antiepileptic agents abuse.
   - E.g. Leptazole, Nickthamide, Bemigride, Doxapram Ethamivan, Amiphenazole, Picrotoxin and Camphor.

2. **Central stimulants:**
   + Drugs stimulate the cerebral cortex therefore they called central stimulants, the most important group are xanthine derivatives which characterized by the following:
     - Stimulate heart and blood vessels directly and indirectly increase blood flow in the brain and kidney causing increasing urine production (diuresis).
     - Promote prothrombine production in the liver (Vit. K like action).
     - The most commonly used agents of this group are caffeine derivatives (coffee, tea, and cocoa).
     - Another xanthine derivatives is theophylline which has similar in action of caffeine and its more potent cardiac stimulant and diuretic, it’s used mainly as bronchodilator.

3. **Spinal stimulants:**
   This type of stimulants affects the spinal cord, the most used drug for this purpose is strychnine (an alkaloid derived from Strychnos nux vomica seeds, which are still used in homeopathic medicine. It is a colorless crystalline alkaloid and is extremely bitter in taste. It is also a very toxic substance having a median lethal dose (LD$_{50}$) of approximately 10mg, and its cause the following clinical signs:-

   - Awful, bitter taste
   - Clonic-tonic convulsions
   - Dilated pupils
   - Hyperreflexia
   - Mind and consciousness are maintained
   - Death results due to asphyxia or exhaustion.
CNS depressants:

Central nervous system depressants are medications that suppress the transmission of information throughout the central nervous system. The degrees of CNS depression are graduating from mild depression (sedative – hypnosis) to complete CNS depression (general anesthesia), and this degree depends on:-

1- The used drug.
2- the dose
3- animal species
4- Combination.

1. **Sedative-hypnotics**: are commonly referred to as sedatives and is the mildest form of central nervous system depressant.
   - Sedative-hypnotics are given in low doses to diminish the patient’s physical and mental responses without affecting the patient’s consciousness.
   - With increased doses, the patient experiences a hypnotic effect causing the patient to fall a sleep.
   - Even higher doses of sedative-hypnotics anesthetize the patient. Such is the case of the ultra-short-acting barbiturate thiopental sodium (Pentothal) that produces anesthesia.

2. **Benzodiazepines**: All benzodiazepines in clinical use have the capacity to promote the binding of the major inhibitory neurotransmitter γ-amino butyric acid (GABA) to GABA receptors (GABA potentiators).
   - This group of drugs is widely used in induction of the state of hypnosis and when given by high doses it can promote other degrees of CNS depression like tranquilization and anticonvulsion.
   - The most clinically used members of this group are Diazepam (Valium), Nitrozepeam (Mogadon) and Clonazepam (Rivotril).

3. **Barbiturates**: derivatives of 2, 4, 6-trioxohexahydropyrimidine that reversibly depress the activity of all excitable tissues. This Group of drugs is effect on the CNS by the following ways:-
   1. Its minimize O₂ utilization by the brain.
   2. Preventing the synthesis of Ach. (Block the conversion of pyruvate to acetate).
3. potentiating the inhibitory neurotransmitter GABA (similar to mechanism of action benzodiazepines).

- **Barbiturates can be classified according to the duration of action to:-**
  - **Ultrashort-acting barbiturates** such as thiopental sodium (Pentothal) are a commonly used anesthetic.
  - **Short-acting barbiturates** such as Secobarbital (Seconal) and pentobarbital (Nembutal) are short-acting barbiturates that induce sleep. For longer periods of sleep, patients are prescribed
  - **Intermediate acting barbiturates** such as amobarbital (Amytal), aprobarbital (Alurate) and bubatabarbital (Butisol). For longer periods of sleep.
  - **Long-acting barbiturates** such as Phenobarbital and mephobarbital are used for controlling epileptic seizures.

- Barbiturates are Controlled Substances and should be prescribed for no more than two weeks because of the adverse side effect. Barbiturates increase CNS depression in the elderly and should not be used for sleep.

- Side effects of barbiturates include: Drowsiness may last for only a few hours after a hypnotic dose of barbiturate, but residual CNS depression sometimes is evident the following day, and slight distortions of mood and impairment of judgment. Residual effects also may take the form of vertigo, nausea, vomiting, or diarrhea or sometimes may be manifested as overt excitement. The user may awaken slightly intoxicated and feel euphoric and energetic; later, as the demands of daytime activities challenge possibly impaired faculties, the user may display irritability and temper. Overdose of barbiturates can cause respiratory failure due to depression of respiratory centers.

2. **Tranquilizers**: drugs which produce in an animal a state of indifference to its surrounding.

- Tranquilizers are used to:-
  - Facilitate the control of difficult animals of all species.
  - Pre-anesthetic drug to reduce the amount of required anesthesia in order to minimize risk of toxicity, and to help in induction of anesthesia.
Phenothiazine derivatives:

- The phenothiazines block post-synaptic dopamine receptors in the CNS and may also inhibit the release of, and increase the turnover rate of dopamine.
- They are thought to depress portions of the CTZ (chemoreceptor trigger zone) which assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness. Additionally, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects.
- The main drugs of this group are: chlorpromazine, trimeprazine, methotrimeprazine, acepromazine, promazine, and promethazine.

Butyrophenones:

- They have similar pharmacological effects to phenothiazines with rapid onset of action (10 min.).
- They have hypothermic and α blocking actions with powerful antiemetic action.
- E.g., droperidol, haloperidol, and azaperone.

Benzodiazepines:

- According to the used dose, benzodiazepines can use as tranquilizers.
- There mode of action was discussed previously.
- The most used drugs from this group are diazepam which given with morphine and its derivatives to avoid excitation and zolazepam which mixed with Tiletamine (an injectable anesthesia chemically related to ketamine) to control the exotic animals especially during transport.

3. Anticonvulsants (antiepileptic):

Epilepsy: is a common neurological abnormality. Epilepsy is a chronic, usually life-long disorder characterized by recurrent seizures or convulsions and usually, episodes of unconsciousness and/or amnesia. Patients often exhibit more than one type. In most instances, the cause of the seizure disorder is not known (idiopathic epilepsy), although trauma during birth is suspected of being one cause. Head trauma, meningitis, childhood fevers, brain tumors, and degenerative diseases of the cerebral circulation are conditions often
associated with the appearance of recurrent seizures that may require treatment with anticonvulsant drugs. Which are:-

- **Barbiturates**: long acting barbiturates are very useful in controlling of these seizures like Phenobarbital; overdoses can cause death due to respiratory failure.

- **Phentoin**: a hydantoins- derivative it depress the CNS through increasing the ionic efflux (Na⁺) from neurons.

- **Primidone**:
  - An analog of Phenobarbital.
  - Its indicated for seizures.
  - Its safer than Phenobarbital because it’s less hepatotoxic.
  - Its used to control convulsion in foals.

- **Valproates**: salts of valproic acid. They prevent degradation of GABA. and they are very important anticonvulsants.

- **Benzodiazepines**: they are very useful agents in treating deferent forms of epileptiform convulsions, and they are used as alternative medicines to barbiturates.
Anesthesia

**A - General Anesthesia:**
A state that render the patients analgesic, amnesic, and unconscious while causing muscle relaxation and suppression of undesirable reflexes.

**Stages of general anesthesia**

Stage one: analgesia: The patient experiences analgesia (a loss of pain sensation) but remains conscious.

Stage two: excitement: The patient may experience delirium or become violent. Blood pressure rises and becomes irregular and breathing rate increases.

Stage three: surgical anesthesia: Skeletal muscles relax. Breathing becomes regular. Eye movement slows then stops. It is at this point when surgery begins.

Stage four: medullary paralysis: Breathing and other vital functions cease to function because the respiratory center (medulla oblongata) is paralyzed. Death results if the patient is not revived quickly. Careful administration of the anesthesia prevents reaching this stage.

**TYPES OF GENERAL ANESTHETIC AGENTS**
There are two broad types of general anesthetics: The inhalation agents and the intravenous agents:-

A - Inhalation Agents: Inhalation anesthetic agents are gases or volatile liquids. These substances are often mixed with oxygen and the patient is allowed to breathe the mixture. After a period, a sufficient level of the anesthetic agent is obtained in the blood and anesthesia is produced. In general, anesthesia can be well controlled with these agents because the concentration of the agent in the blood can be increased or decreased easily by either increasing or decreasing the concentration of the agent in the air the patient is breathing. It is relatively uncommon for a patient to have an allergic reaction to one of the inhalation general anesthetic agents. However, the side effects of some of these agents can be quite serious. There is rapid recovery for the patient when this type of agent is used. That is, when the patient is no longer allowed to breathe the agent, the depression of the central nervous system quickly disappears.

- **Nitrous oxide.** Nitrous oxide is commonly referred to as laughing gas. Although nitrous oxide is a safe general anesthetic, it is relatively weak in terms of
producing anesthesia and muscle relaxation. Consequently, nitrous oxide is often used in conjunction with other agents. Nitrous oxide is often used in dental surgery and in obstetrical practice during delivery.

- **Halothane (Fluothane®)**. Halothane is a volatile liquid inhalation anesthetic. It is one of the most widely used general anesthetics. Since halothane does not produce potent analgesia and muscle relaxation, other agents are sometimes administered with halothane on an as-needed basis. Halothane has popularity because it is nonexplosive, rapid acting, pleasant smelling, and is compatible with other drugs.

- **Enflurane (Erthrane®)**. Enflurane is a volatile liquid inhalation anesthetic with many of the properties of halothane. It produces greater muscle relaxation than halothane, but like halothane, it is a poor analgesic.

**B- Intravenous Agents.** Intravenous general anesthetics are sterile solutions intended to be administered into the patient's circulatory system. Intravenous anesthetic agents do produce loss of consciousness; however, most of these agents lack the ability to produce complete analgesia. In general, the level of anesthesia is more difficult to control with intravenous anesthetics than with inhalation anesthetics.

- **Thiopental sodium (Pentothal®)** Thiopental sodium is an ultrashort acting barbiturate. That is, this agent acts very quickly to produce anesthesia. Sometimes this agent is used alone for minor surgical procedures. In other cases, the drug is used to initiate anesthesia. Then, other anesthetic agents are used to maintain the anesthesia. Thiopental sodium is a controlled substance.

- **Ketamine (Ketalar®)** is a non-barbiturate anesthetic that can be administered either intravenously or intramuscularly. Ketamine produces a dissociative type anesthesia in which the patient becomes detached mentally from the environment. Ketamine may be used for induction anesthesia or for diagnostic or minor surgical procedures in children.

**OTHER AGENTS USED DURING SURGERY:**

No single anesthetic agent is capable of producing the deep levels of analgesia and skeletal muscle relaxation required during all types of surgery. Consequently, other drugs...
that have certain desired effects are administered along with the general anesthetic being used. They are:

1. **ANALGESIC AGENTS:**
   Analgesic agents relieve pain. Although a general anesthetic agent will produce Unconsciousness, the patient might still be able to feel some pain. In these cases, a Pre-anesthetic medication might be administered to the patient in order to relieve the pain. A variety of analgesic agents are available to achieve this purpose. Following are some commonly used agents:
   a. Meperidine (Demerol©).
   b. Morphine.

2. **DRYING AGENTS:**
   It is sometimes advantageous during an operation to have the patient's mucous membranes (that is, nose, throat) dry. Drying agents are administered for just this reason. You are probably familiar with the use of drying agents in certain over-the-counter (O.T.C.) cold medications. Like: Atropine sulfate.

3. **NEUROMUSCULAR BLOCKING AGENTS:**
   In some types of surgery (for example, abdominal surgery) it is highly advantageous to have the patient's skeletal muscles (for example, abdominal surgery) in a state of relaxation. Most general anesthetic agents do not produce a sufficient level of skeletal muscle relaxation. Therefore, neuromuscular blocking agents are administered to achieve the desired muscle relaxation effects. Two commonly used neuromuscular blocking agents:
   a. Vecuronium (Norcuron©).
   b. Succinylcholine (Anectine®).

4. **SEDATIVE AND HYPNOTIC AGENTS:**
   Patients are sometimes administered either a sedative or a hypnotic agent. Agents commonly used for this purpose are:
   a. Pentobarbital (Nembutal®).
   b. Secobarbital (Seconal®).
5. ANTIANXIETY AGENTS:
Some surgical cases are highly anxious, such increased anxiety interferes with the functioning of the patient (interferes with rest and decreases appetite). Anti-anxiety agents help to control this anxiety. Diazepam (Valium®) is sometimes used to control anxiety.

LOCAL ANESTHTICS:-
A local anesthetic is an agent that interrupts pain impulses in a specific region of the body without a loss of patient consciousness. Normally, the process is completely reversible the agent does not produce any residual effect on the nerve fiber.

Mechanism of action:
Local anesthetics block depolarization of the nerve membrane. That is, to make the conduction of the nerve impulse impossible.

Clinical techniques of local anesthesia include:

- Surface anesthesia - application of local anesthetic spray, solution or cream to the skin or a mucous membrane. The effect is short lasting and is limited to the area of contact.
- Infiltration anesthesia - injection of local anesthetic into the tissue to be anesthetized. Surface and infiltration anesthesia are collectively topical anesthesia.
- Epidural anesthesia - a local anesthetic is injected into the epidural space where it acts primarily on the spinal nerve roots. Depending on the site of injection and the volume injected, the anesthetized area varies from limited areas of the abdomen or chest to large regions of the body.
- Spinal anesthesia - a local anesthetic is injected into the cerebrospinal fluid, usually at the lumbar spine (in the lower back), where it acts on spinal nerve roots and part of the spinal cord. The resulting anesthesia usually extends from the legs to the abdomen or chest.
- Peripheral nerve block - injection of local anesthetic in the vicinity of a peripheral nerve to anesthetize that nerve's area of innervation
PROPERTIES OF IDIAL LOCAL ANESTHESIA:
- Non-irritating to nerve
- Low systemic toxicity
- Short induction period
- Adequate duration of action
- No post anesthetic side effects

There are two chemical substances have been added to local anesthetic preparation those are:-

1- Adrenaline: is added to the local anesthetic to prolong its action by minimizing its absorption by vasoconstriction.

2- Hyaluronidase enzyme is added to the local anesthesia solution to facilitate spread and penetration of local anesthetics at the site of injection.

Example of local anesthetic agents:

- **Lidocaine Hydrochloride (Xylocaine®).**
  Lidocaine is used as a local anesthetic for infiltrations, nerve blocks, spinal anesthesia, topical anesthesia, and for caudal and epidural anesthesia. It has a rapid onset of action and its effects last from 75 to 150 minutes. It has also been used as a cardiac depressant (anti arrhythmic). Lidocaine is available in injection form (various percentage concentrations), jelly form, and in cream form.

- **Procaine (Novocaine®).**
  Procaine is used for infiltration, nerve block, and spinal anesthesia. Procaine is not applied topically. Its duration of action is approximately 1 hour. It is a fairly safe local anesthetic to use since it is metabolized quickly. Procaine is available in injection form.

- **Cocaine.**
  Cocaine is applied to produce local anesthesia with intensive vasoconstriction on mucous membranes. It is applied to procedure anesthesia in the nose, throat, ear, and in bronchoscopy (a procedure in which an instrument is used to inspect the bronchi). Cocaine is supplied in the form of a white powder, Cocaine solution must be compounded. It is a controlled substance.
Benzocaine (Americaine®).  
Benzocaine is used for topical anesthesia of the mucous membranes and skin. It is used in many over-the-counter spray preparations for the treatment of sunburn and itching. Benzocaine is available in solution, ointment, and spray forms.

Dichlorotetrafluoroethane (Freon®)  
Dichlorotetrafluoroethane is a nonflammable and non-explosive agent for topical anesthesia of the skin. It is especially useful for localized minor surgical procedures. This agent should not be sprayed on the skin for a period that exceeds 45 seconds. Dichlorotetrafluoroethane is available in a spray form.

Ethyl Chloride.  
This agent is used for topical anesthesia of the skin. Ethyl chloride is available in a spray form.
PHARMACOLOGY OF CARDIOVASCULAR SYSTEM

Introduction
The cardiovascular system is a collection of interacting structures designed to supply oxygen and nutrients to living cells and to remove carbon dioxide and other wastes. Its major components are the:

a. Blood, is the vehicle for oxygen, nutrients, and wastes.

b. Blood Vessels Are the conduits, or channels, through which the blood is moved.

c. Heart. The heart is the pump that provides the primary motive force.

d. Capillaries. The capillaries, minute (very small) vessels, provide exchange areas.

For example, in the capillaries of the lungs, oxygen is added and carbon dioxide is removed from the blood.

v CONGESTIVE HEART FAILURE:- (CHF)

Congestive heart failure may be defined as non-efficient pumping of the heart. This inefficiency in pumping the heart leads to an increase in the size of the heart and an increase in the heart rate. This increase in heart size and heart rate result because of the heart’s attempt to compensate for the poor efficiency in pumping blood to other parts of the body. Consequently, the kidneys improperly function. Improperly functioning kidneys result in edema of the extremities due to improper excretion (removal) of sodium and waste products in the urine. In cases of acute CHF, Pulmonary edema will be developed due to poor kidney function.

Treatment of congestive heart failure:
There are many categories used for treatment of CHF. Like:

1. Inhibitors of rennin – angiotensin system: - this group of drugs acts by two ways those are:-

   A- Angiotensin-converting enzyme inhibitors (ACE. Inhibitors):
   • ACE inhibitors block a specific enzyme (angiotensin converting enzyme) that converts angiotensin I to angiotensin II. Angiotensin II is one of the most potent vasoconstrictor in the body.
   • ACE inhibitors also decrease the secretion of aldosterone resulting in decreased sodium and water retention. Consequently decrease edema
• Agents included in this class include captopril (Capoten®), enalapril (Vasotec®), lisinopril (Prinivil®, Zestril®), and ramipril (Altace®)

B- Angiotensin receptor blockers:
• This group acts by blocking the specific receptor of angiotensin; the resultant effect will be seems to the previous group
• Example; Losartan, valsartan.

2- β₁ receptor blockers:
Beta adrenergic blocking agents work by blocking:-
• Block β₁-receptors on heart: Reduce heart rate and inotropic state.
• Block β₁-receptors on kidneys: Reduce renin secretion.
• Block β₁-receptors in CNS: Reduce sympathetic outflow leading to reduce vasomotor tone.
• Example; carvedilol (Coreg®) and metoprolol (Lopressor®).

3- Diuretics: A diuretic is any drug that elevates the rate of urination and thus provides a means of forced diuresis, The general uses of diuretics include the treatment of congestive heart failure, hypertension, glaucoma, ascites, toxemia of pregnancy, and diabetes insipidus. In the case of CHF the diuretics relieve pulmonary congestion and peripheral edema. Example; furosemide, bumetanide and Thiazide diuretics (e.g. hydrochlorothiazide, chlorthalidone and chlorthiazide).

4- Digitalis Products: (Digoxin and Digitoxin) they are purified cardiac glycoside extracted from the foxglove plant, Digitalis lanata they are widely used in the treatment of various heart conditions, namely atrial fibrillation, atrial flutter and sometimes congestive heart failure that cannot be controlled by other medication.
• They have positive inotropic activity on the cardiac muscle (increase contraction force).
• Mechanism of action include: Inhibition of Na⁺/K⁺-ATPase Pump leading to increase intracellular Na⁺ in myocardium causing decreased expulsion of Ca²⁺ in myocardium then tonically higher levels of intracellular Ca²⁺ lead to increase myocardial contractility.
• Digitalis products have very narrow margin of safety. And therefore they must used under control.
ANTIDYSRHYTHMIC AGENTS:
The term antidysrhythmic drugs refer to the agents that suppress abnormal beats or restore normal cardiac rhythm by depressing various properties of the myocardium (heart muscle). This is a general mechanism of action for all these drugs.

Quinidine (Quiniglute®, Quinidex®).
- Quinidine is an antiarrhythmic agent used in the treatment of atrial fibrillation and ventricular arrhythmias.
- From plant origin known by Cinchona.
- The side effects associated with quinidine include hypersensitivity reactions, gastrointestinal (GI) disturbances (nausea, vomiting, and diarrhea) and a group of symptoms known as cinchonism. Some symptoms associated with cinchonism are tinnitus (ringing in the ears), vertigo (dizziness), and headaches.

Procainamide (Pronestyl®).
- Procainamide is used in the treatment of atrial and ventricular arrhythmias.
- Procainamide is similar in chemical structure to procaine.
- It retains the quinidine like actions of procaine, but it is not rapidly hydrolyzed and its action persists long enough so that it is active even after oral as well as parenteral administration.
- Pharmacologically, procainamide is equivalent to quinidine. Procainamide may cause anorexia, nausea and vomiting, and drug hypersensitivity.

Lidocaine (Xylocaine®).
- Lidocaine is an agent that may be given intravenously in the treatment of ventricular arrhythmias. (Similar to quinidine).
- Large intravenous doses may produce convulsions, coma, and respiratory depression.

Phenytoin (Dilantin®).
- Phenytoin is an agent that may be administered intravenously to reverse digitalis-induced arrhythmias.
- Rapid intravenous administration may cause bradycardia, hypotension, and cardiac arrest (rarely).
VASODILATORS:
A vasodilator is a drug that dilates blood vessels with a resultant increase in blood flow, this type of drugs are used mainly for treatment of hypertension and angina pectoris.

Glyceryl Trinitrate (Nitroglycerin).
- It is the most common smooth muscle relaxant vasodilator used in the treatment of acute angina pectoris.
- Side effects associated with this drug include headache, dizziness, and orthostatic hypotension.
- The vasodilating effect of the drug may be so sudden that circulating blood pools in vascular (vessel) beds. This may cause the patient to become unconscious because of a lack of blood to the brain. Falling to the floor in a faint allows the immediate return of that blood flow to the brain and consciousness returns.

Isosorbide Dinitrate (Isordil®, Sorbitrate®).
- Isosorbide dinitrate is thought to be effective in the prophylactic treatment of angina pectoris, as well as the treatment of acute angina attacks.
- The side effects associated with this drug are headache and dizziness.

Hydralazine (Apresoline®) and Minoxidil (Loniten®).
- Hydralazine and minoxidil are direct acting peripheral vasodilators used in the treatment of hypertension.
- Hydralazine may be prescribed in combination with an oral nitrate in the treatment of congestive heart failure.
- Minoxidil is a powerful arterial vasodilator, given orally for severe hypertension, duration of action is about 72 Hrs.

Prazac.
- Selective competitive blocker of $\alpha_1$ receptor.
- Decrease peripheral vascular resistance (relax the smooth muscles of arterioles and veins) leading to decrease in arterial blood pressure.

ANTIANGINAL DRUGS:
Angina Pectoris. It is a condition manifested by severe chest pain sometimes radiating down the left arm. The pain probably arises from ischemia (lack of oxygen) in the heart caused by the increased demand for or decreased supply of oxygen. The strategy of
treatment of this case depends on dilation of coronary blood vessels in order to relieve the pain and reduce oxygen requirement of the cardiac muscle.

The mainly used Antianginal drugs are:

- **Nitrates and nitrites**: like; glycerile trinitrate, Isosorbide dinitrate and sodium nitroprusside.
- **Ca\(^{2+}\) channel blockers**: they inhibit entrance of Ca\(^{2+}\) to the cardiac muscle and the arteriolar coronary smooth muscle. Example; Niphedipine (Adalat), verapamil and diltiazem.
- **\(\beta_1\) receptor blockers**: they decrease cardiac output. Example; propranolol, atenolol.
Digestive system:
A group of organs designed to take in foods; initially process foods, digest the foods, and eliminate unused materials of food items. It is a hollow tubular system from one end of the body to the other end.

Agents used to treatment of digestive system disorders include:

A - Antacids:
- They are drugs which neutralize part of the hydrochloric acid in the stomach.
- They are indicated in ulcer therapy, minor stomach irritations, and other conditions depending on the type of antacid prescribed.

**Sodium Bicarbonate (NaHCO₃).**
- it is used as a gastric antacid, urinary alkalizing agent, and an agent used to counteract the lowering of the pH of the blood in heart failure.
- Side effects associated with this agent include systemic alkalization (raising the pH of the blood) and acid rebound. The patient receiving sodium bicarbonate for antacid purposes should be told that it should not be used frequently and that it should not be used for prolonged periods.
- Sodium bicarbonate is available in tablets of various strengths and in powder form.

**Magnesium Hydroxide (Milk of Magnesia).**
- it is used both as an antacid and as a cathartic (laxative).
- Patients taking this product should be cautioned that they can obtain the laxative effect if they take too large a dose or if they take the antacid dose too often.
- A side effect associated with magnesium hydroxide is diarrhea.

**Aluminum Hydroxide and Magnesium Hydroxide (Maalox®).**
- Maalox® is used as a gastric antacid and as an agent in ulcer therapy.
- This product is available in both a suspension form (225 milligrams of aluminum hydroxide and 200 milligrams of magnesium hydroxide per teaspoonful) and in tablet form (200 milligrams of aluminum hydroxide and 200 milligrams of magnesium hydroxide per tablet).
- Depending on the amount of the preparation taken, diarrhea and constipation are side effects associated with the drug.

B- Emetics:

- Chemical agent that will cause the patient to vomit (i.e., to produce emesis).
- The clinician may administer an emetic to a patient who has ingested a certain type of chemical substance.
- Emetics are not indicated for all poisonings.
- Emetics can divided in to two classes according to the mechanism of action; they are:
  1- Central emetics: agents which stimulates the vomiting center in the medulla oblongata directly or indirectly through stimulation of the CTZ. Like Apomorphine.
  2- Peripheral emetics: the agents that stimulate the sensory nerve ending of the vagal nerves in the stomach, duodenum and other organs. Like Ipecacuanha, a plant alkaloid produces emesis with in 15 – 30 min.

C- Antiemetics: agents which prevent or alleviate nausea and vomiting. Anti-emetics are typically used to treat motion sickness and the side effects of opioid analgesics, general anesthetics and chemotherapy directed against cancer.

Antiemetics include:

- 5-HT₃ receptor antagonists - these block serotonin receptors in the central nervous system and gastrointestinal tract. As such, they can be used to treat post-operative and cytotoxic drug nausea & vomiting. Examples (Dolasetron, Granisetron, Ondansetron, Tropisetron and Palonosetron (Aloxi, a new 5HT3 antagonist)
- Dopamine antagonists act in the brain and are used to treat nausea and vomiting associated with neoplastic disease, radiation sickness, opioids, cytotoxic drugs and general anaesthetics.

  Drperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine. Some of these drugs are limited in their usefulness by their extra-pyramidal and sedative side-effects.
  Metoclopramide (Reglan) also acts on the GI tract as a pro-kinetic, and is thus useful in gastrointestinal disease; however, it is poor in cytotoxic or post-op vomiting.
• Antiacetylcholine drugs: like: hyoscine or hyosciamin.
• Antihistamine drugs: (H₁ histamine receptor antagonists), effective in many conditions, including motion sickness and severe morning sickness in pregnancy.
  Examples: promethazine and diphenhydramine.

D- The purgatives (Laxatives): are foods, compounds, or drugs taken to induce bowel movements or to loosen the stool, most often taken to treat constipation.
  - Certain stimulant, lubricant, and saline laxatives are used to evacuate the colon for rectal and bowel examinations, and may be supplemented by enemas in that circumstance.
  - Sufficiently high doses of laxatives will cause diarrhea.
  - Laxatives only work to hasten the elimination of undigested remains of food in the large intestine and colon.

Types of the purgatives: there are several kinds of purgatives as listed below:

  ✓ Vegetables and foods: Some vegetables and foods can be eaten to cure constipation and act as laxatives, although the effectiveness may vary. Like: Aloe Vera, dates, chocolate, coffee, banana and orange.

  ✓ Bulk – producing agents: they act on the intestine generally, these include dietary fiber. Bulk-producing agents cause the stool to be bulkier and to retain more water, as well as forming an emollient gel, making it easier for peristaltic action to move it along. They should be taken with plenty of water. Bulk-producing agents have the gentlest of effects among laxatives and can be taken just for maintaining regular bowel movements.

  ✓ Lubricants (Emollients): they act on the large intestine (in particular on the colon) simply make the stool slippery, so that it slides through the intestine more easily. An example is mineral oils like paraffin, which also retards colonic absorption of water, softening the stool. Mineral oil may decrease the absorption of fat-soluble vitamins and minerals.

  ✓ Stimulants (Irritants): act on colon too, Stimulant laxatives act on the intestinal mucosa, or nerve plexus; they also alter water and electrolyte secretion. They are the most severe among laxatives and should be used only in extreme conditions. Castor
oil may be preferred when more complete evacuation is required. Other agents include; senna and bisacodyl.

5- **Antidiarrheal agents**: is any medication which provides symptomatic relief for diarrhea. and they are several types like:-

- Electrolyte solutions are used to replace lost fluids and salts in acute cases.

- Bulking agents like methylcellulose, guar gum or plant fiber (bran) are used for diarrhea in functional bowel disease.

- Absorbents absorb toxic substances that cause infective diarrhea; methylcellulose is an absorbent as well.

- Opioids classical use besides pain relief is use as an anti-diarrhea drug. Opioids have agonist actions on the intestinal opioid receptors, which when activated cause constipation, drugs such as morphine or codeine can be used to relief of diarrhea this way. A notable opioid for the purpose of relief of diarrhea is Loperamide which only is an agonist of the opioid receptors in the large intestine and does not have opioid affects in the central nervous system as it doesn't cross the blood brain barrier in significant amounts. This enables loperamide it to be used to the same benefit as other opioid drugs but without the CNS side effects or potential for abuse.
**RESPIRATORY SYSTEM**

Respiration is the exchange of gases between the surrounding and the cells of the body. It is a physiological process. There are two types of respiration-external and internal. External respiration is the exchange of gases between the air in the lungs and blood. Internal respiration is the exchange of gases between the blood and the individual cells of the body.

Drugs affecting the respiratory system have been in use for years. In the first part of this century, for example, various members of the morphine family were used in the treatment of coughs. At certain times of the year you will see many prescriptions for cough medicines and expectorants. We have probably seen such increases when winter arrives.

In this lecture we shall divide the drugs that effect on the respiratory system to categories and these are:-

1- **Expectorants**: the drugs that loosen and clear mucus and phlegm from the respiratory tract.

   - Most of the expectorants are act reflexively by irritating the gastric mucosa. (Reflex stimulation of vagal nerve endings in the stomach and duodenum) This, in turn, stimulates secretions in the respiratory tract. Expectorants remove bronchial secretions which are purulent (containing pus), viscid (thick), or excessive. The loosened material is then moved toward the pharynx through ciliary motion and coughing. Like: Guaifenesin, ammonia salts, Ipecacuanha and senega.

   - Some types of expectorants act as stimulators of bronchial glands secretion (diuretics like effect) by irritation of them like potassium iodide.

   - Other type of the expectorants is the inhalatory expectorants, which includes in most the volatile oils like; pine oil, turpentine oil and eucalyptus oil.

2- **Mucolytics**: is any agent which dissolves thick mucus usually used to help relieve respiratory difficulties.

   - **Acetylcysteine**: This drug reacts with mucus resulting in liquefaction of it.

   - This is a mucolytic given by inhalation or nebulization. (Nebulization is treatment by spray).
- Mucomyst® solution is nebulized into a face mask or mouth piece because of Acetylcysteine has an unpleasant (like rotten eggs) smell.
- Side effects associated with this agent include nausea and vomiting and broncho-spasms with higher concentrations.

**Bromhexine: (bisolv®)**

- Bromhexine supports the body’s own natural mechanisms for clearing mucus from the respiratory tract.
- It is secretolytic: that is, it increases the production of serous mucus in the respiratory tract and makes the phlegm thinner and less sticky. This contributes to a secretomotoric effect: it helps the cilia - tiny hairs that line the respiratory tract - to transport the phlegm out of the lungs. For this reason it is often added to some antitussive (cough) syrups.
- Sometimes it is replaced by its metabolite ambroxol, as in Mucosolvan or Mucoangin.

**Sodium Chloride Solution (U.S.P.) (0.9 % solution)**

- This agent is used alone or in combination with other mucolytic agents.
- Sodium chloride solution increases the respiratory fluid volume by osmosis, which tends to decrease the viscosity of the respiratory fluid. It is also administered by inhalation in a nebulized form as a dense mist in a tent or delivered through a face mask or mouth piece.
- The main side effect seen with sodium chloride solution occurs after prolonged inhalation. This will cause localized irritation of the bronchial mucosa.

3- **Antitussives**: agents that relieve or prevent coughing. These agents, in general, act on the central nervous system to depress the cough reflex center in the medulla of the brain. Antitussives are used to reduce respiratory irritation. Such reduction of respiratory irritation results in the patient’s being able to rest better at night because he is not kept awake by his coughing.

**Antitussives divided to:**

A- Direct acting antitussives: they act directly on the respiratory tract mucosa reducing their irritation like: Demulcients( honey and syrup) .
B- Central acting antitussives: this subdivision acts by depress the cough center in the medulla oblongata.

**Codeine:**
- Codeine is considered to be the most useful narcotic antitussive agent.
- Codeine aids in relieving the pain (that is, producing analgesia) associated with a hacking cough.
- The main side effects associated with codeine include drowsiness, nausea, vomiting, and constipation.

**Benzonatate (Tessalon®):**
- Benzonatate is a nonnarcotic antitussive that produces its effect through a CNS depressant effect similar to codeine.
- Furthermore, it produces a local anesthetic effect on the stretch receptors in the lower respiratory tract, which control coughing.
- This drug has few side effects except that it will numb the mouth, tongue, and pharynx if the capsules are chewed (this is because of its topical anesthetic effect).

**Dextromethorphan (Pertussin CS®):**
- Dextromethorphan is another non-narcotic antitussive.
- It is found alone or in combination—usually with expectorants.
- The most common side effect associated with this drug is gastrointestinal (G.I.) upset.

C- Miscellaneous drugs: this item of antitussive drugs includes:

1- **Histamine receptor blockers:** this group acts by blocking H₁ receptor in order to get rid from the cough which arises from histamine release. Example: promethazine and diphenhydramine.

2- **Corticosteroids:** they are effective in treating of chronic cough. Example: Prednisolone.

4- **Anti asthmatic agents:**

**Asthma:** a condition usually caused by allergic reactions to substances in the environment, affects many people. The allergic reactions cause the bronchioles to spasm. Hence, the flow of air into and out of the lungs becomes impaired.
Pathogenesis of asthma:
IgE-mediated sensitization of mast cells leading to degranulation of histamine in bronchioles consequently causing bronchoconstriction and increased secretions.

Drugs used for treatment of asthma:

1. Bronchodilators: Sympathomimetic bronchodilators act by relaxing contractions of the smooth muscle of the bronchioles, and they are according to their mechanism of action to:
   1. β receptor agonists:
      - These drugs have a β2 agonist effect so that they cause bronchodilation, like: albuterol and salmeterol.
      - Other β receptor agonists act without selectivity (also they act with different mechanisms) like, epinephrine, ephedrine, metaproterenol and Isoproterenol.

2. Xanthines:
   - They have long duration of action, making them useful in treatment of nocturnal asthma.
   - There are many mechanisms which explain how the xanthiens work on the bronchial smooth muscle but the most acceptable one that’s to says that xanthenis induce production of high amount of cAMP and consequently which increase norepinephrine release, and production of bronchodilation.
   - The main adverse effect of the xanthines is the narrow margin of safety.
   - Example: Aminophylline and Theophilline.

3. Anticholinergic agents:
   - They are very useful in case of exercise-induced asthma.
   - The most predominant drug for this purpose is Ipratropium.

4. Anti-inflammatory agents: agents or drugs which prevent or minimize the inflammatory reaction in the bronchi.
   1. Corticosteroids:
      - Inhibit all arachidonic acid derivatives (specially: Prostaglandins and Leukotrienes) which act as inflammatory mediators.
      - Corticosteroids are very useful in treatment of asthma and prevention of recurrent attacks
Corticosteroids have many serious side effects and these side effects appear with long usage. Include: Primary insufficiency (Addison's disease) upon withdrawal, Osteoporosis, cataracts, growth retardation in children, Diabetes, Hypokalemia, Cushing's Syndrome, behavioral affects and Susceptibility to infections.

- Example: dexamethasone, betamethasone, and prednisolone.

2- Cromolyn (Intal®).
- Cromolyn is a unique product that works by inhibiting the release of histamine and other spasm-causing compounds from mast cells located in the lungs and prevent bronchoconstriction.
- It is used mainly for the treatment or prevention of mild bronchospasms associated with asthma.
- It is available as an inhalation aerosol and nebulization solution.

3- Anti-leukotrienes:
- These drugs decrease inflammatory reaction in the bronchi by decrease production of leukotrienes and the capability of them to bind to their receptors in the lung.
- Anti-leukotrienes are used in treating of the exercise induced asthma.
- Example: Zileuton and Zafirlukast.

Calcium channel blockers:
- prevent bronchial muscles constriction by blocking the Ca\(^{+}\) cannels
- they used to treat exercise induced asthma.
- Example: Niphidipine (Adalat®).

5- Respiratory stimulants: the agents which used to treat respiratory failure. They are divide to:-

- Physiological stimulants:
  1- \(\text{CO}_2\): a direct and potent respiratory stimulant
    - \(\text{CO}_2\) works by two ways; those are :
      a- Directly, by stimulation of respiratory center.
      b- Indirectly, by reflex and stimulation of carotid and aortic sinuses.
    - \(\text{CO}_2\) used to treat the respiratory failure in small animals.
II- O₂:-
- O₂ used by inhalation and it’s mixed with 5% CO₂.
- The mechanism of stimulation depends on the sensation of CO₂.

- **Analeptics (CNS stimulants):** they act indirectly by stimulating of respiratory center in the medulla oblongata. Examples: Leptazole, Nickthamide, Bemigride, Doxapram Ethamivan, Amiphenazole, Picrotoxin and Camphor.

- **Local irritants:** act by reflex stimulation of respiratory and vasomotor center to improve respiration and ventilation. Like Ammonia.
Skin Pharmacology

**Dermatological agents:** the drugs that exert either a chemical or physical action on the skin to aid in the correction of a disorder of the skin.

**GENERAL CONSIDERATIONS INVOLVING DERMATOLOGICAL AGENTS:-**

a. The vehicles (creams, lotions, ointments, and so forth.) in which therapeutic ingredients are incorporated and diluted have been found to have pharmacological properties of their own.

b. There is a great variation in the manner in which vehicles hold, release, or assist in the absorption of their therapeutic ingredients. Therefore, it is important that the vehicle selected to contain a therapeutic ingredient be suitable for use on the portion of skin on which it will be applied.

c. The distribution of the therapeutic ingredient(s) throughout a vehicle is an important factor in the determination of a dermatological's effectiveness.

**The used agents for treating dermatological disorders are:-**

**Topical anti-infective agents:**

Localized skin infections may require the use of a topical anti-infective. The topical anti-infectives include:-

**A- Topical Antibiotic agents:-**

- Topical antibiotics exert a direct local effect on specific microorganisms and may be bactericidal or bacteriostatic.

- These drugs are used to prevent superficial infections in minor cuts, wounds, skin abrasions, and minor burns. Bacitracin, gentamicin erythromycin, and neomycin are examples of topical antibiotics. Erythromycin is also indicated for treatment of acne.

**B- Topical antifungal agents:-**

- Antifungal drugs exert a local effect by inhibiting growth of the fungi. Examples of antifungal drugs and their uses are:

  - **Amphotericin B:** used for treatment of mycotic infections (fungal)

  - **Miconazole, ciclopirox, and econazole:** used for treatment of ringworm (a skin infection, characterized by a reddish to brownish raised or bumpy patch of skin that may be lighter in the centre, giving the appearance of a “ring.” Ringworm can
occur anywhere on the body. Depending on its location, it is also known as tinea pedis or "athlete's foot" when on the feet, tinea cruris or "jock itch" when on the groin area, tinea corporis when on the body (where it is most commonly referred to as ringworm), or tinea capitis when on the scalp. Contrary to its name, ringworm is caused not by a worm but by a parasitic fungus and is medically classified as a dermatophytosis.) and superficial candidiasis.

- **Clioquinol**: used for eczema, athlete’s foot, and other fungal infections.
- **Nystatin**: used for treatment of various mycotic infections.

**C. Topical antiviral agents:**

- **Acyclovir** (Zovirax) and penciclovir (Denavir) are the only topical antiviral drugs currently available. These drugs inhibit viral replication.
  - **Acyclovir** is used in the treatment of initial episodes of genital herpes, as well as herpes simplex virus infections in immune-compromised patients (patients with an immune system incapable of fighting infection).
  - **Penciclovir** is used for the treatment of recurrent herpes labialis (cold sores).

**Keratolytics:** The agents that induce sloughing of cornified epithelium (horny or hard layer of the skin). They used to remove warts and corns. They are also used in the treatment of severe acne.

**N. B.** when the keratolytic agent has a mild sloughing and softening effect, it termed by Keratoplastic, the Keratoplastic agent is used in treatment of acne, eczema, psoriasis, and seborrheic dermatitis.

- **Coal tar** (chemical name). This agent is used as a keratoplastic in the treatment of eczema, psoriasis, and seborrheic dermatitis.
- **Salicylic acid** (chemical name). It is used as a keratolytic when present in concentrations of from 5% to 20%. It is used as a keratoplastic when present in concentrations of from 1% to 2%.
- **Sulfur** (chemical name). Sulfur is used as a keratoplastic in the treatment of acne and seborrheic dermatitis.
- **Diclofeniac**: also used as keratolytic agent.

**Antiseborrheics**: are used in the management of seborrheic dermatitis. Seborrheic dermatitis is characterized by a yellowish and greasy scaling of the scalp and/or mid-
parts of the face (around eyebrows and nose) and ears. Examples: chloroxine and selenium sulfide.

**Astringents:** An astringent is an agent that dries mucous secretions, shrinks skin, and causes blanching (whitening). Astringents are used to reduce inflammation of mucous membranes, to promote healing, and to toughen skin.

- **Aluminum acetate tablets (Domeboro®, Burow’s solution).**
  - When these tablets are added to water, aluminum acetate solution is prepared.
  - This product is used as an astringent for inflammatory skin conditions such as insect bites, poison ivy, and athlete’s foot.
  - The patient receiving these tablets should be warned that they are for external use only.

- **Calamine lotion (calamine and zinc oxide lotion).**
  - This product is used as an astringent and as a protectant (used to cover and protect epithelial surfaces).
  - Calamine is a very beneficial agent in reducing inflammation associated with insect bites, poison ivy, and sunburn.
  - The patient receiving this product should be told that the preparation is for external use only and that he should shake the product well before using it.

**Ectoparasiticides:** an agent that applied to the host in order to get rid from the ectoparasites like lice, flies, ticks and scabies.

- **Permethrin**
  - For the treatment of scabies, it is toxic to *Pediculus Spp.* and *Sarcoptes scabiei*.
  - Adverse reactions to permethrin include transient burning, stinging, and Cross-sensitization to pyrethrins may occur.
  - Residual drug persists up to 10 days following application.

- **Lindane:**
  - Lindane is available as a shampoo or lotion, for pediculosis.and as scabicide.
  - Concerns about neurotoxicity and hematotoxicity have resulted in warnings that lindane should be used with precautions.

- **Sulfur:**
  - Has a long history of use as a scabicide.
- Although it is nonirritating, it has an unpleasant odor, is staining, and is thus disagreeable to use, but it remains a possible alternative drug for use in infants and in pregnancy case. The usual formulation is 5% precipitated sulfur in petrolatum.

Malathion:
- It is an organophosphate cholinesterase inhibitor that is hydrolyzed by plasma carboxylesterases much faster in human and animals than in insects.
- It's used for remove nits, lice, ticks and flies.
Renal Pharmacology

The structures of the urinary system include paired kidneys, paired ureters, a single urinary bladder, and a single urethra.

Inside each kidney are millions of individual structures, called nephrons that do the actual work of the kidney.

A nephron consists of a glomerulus, Bowman’s capsule, proximal convoluted tubule, loop of Henle, distal convoluted tubule, and a collecting duct.

The main drug categories of Urinary system that involved in Veterinary practice are:

Diuretics

- Agents that increase the volume of urine excreted by the kidneys and promote release of water from tissues.
- They are therapeutically used to decrease edema, lower blood pressure, reduce udder edema in cattle and promote voiding to enhance removal of toxins from the body.

Diuretics are categorized in:

- Thiazides:
  - Act directly on the renal tubules to block sodium reabsorption and promote chloride ion excretion.
  - Side effects include hypokalemia and cardiac dysfunction.
  - Examples include Hydrochlorothiazide, Chlorothiazide, Hydroflumethiazide, and Bendroflumethiazide.

- Loop diuretics:
  - Influence the reabsorption action at the loop of Henle, resulting in tremendous diuresis.
  - Side effects include electrolyte imbalances, especially hypokalemia.
  - An example is Furosemide.

- Potassium-sparing diuretics:
  - Act on the distal convoluted tubules to promote sodium and water excretion and potassium retention (interfere with the Na⁺\K⁺ pump that are controlled by aldosterone).
  - Main side effect is hyperkalemia
  - Examples include Spironolactone, Triamterene, and Amiloride.
Carbonic anhydrase inhibitors.
- Block the action of the enzyme carbonic anhydrase, which is used by the body to maintain acid-base balance.
- Main side effect is metabolic acidosis.
- Examples; Acetazolamide and Dichlorphenamide.

Osmotic diuretics:
- Increase the osmolality (concentration) of the urine filtrate in the renal tubules, resulting in the excretion of chloride, potassium, and water.
- Used to prevent kidney failure and to decrease intracranial and intraocular pressure.
- Side effects include fluid and electrolyte imbalance and vomiting.
- Examples include Mannitol and Glycerin.

Urolith treatment
- Uroliths are abnormal mineral masses in the urinary system
- Types of uroliths include: struvite, calcium oxalate, calcium phosphate, urate, cystine, and mixed.
- Each type of urolith may be treated differently and may include dietary management as well as drug treatment

Drug categories used to treat uroliths include:

Urinary acidifiers:
- Are used clinically to produce acid urine, which dissolves and helps prevent formation of struvite uroliths. Their use has declined with the use of urinary acidifying diets.
- Examples include Methionine and Ammonium chloride.

Urinary alkalinizers:
- Are used clinically to treat calcium oxalate, cystine, and ammonium urate uroliths.
- An example is Potassium citrate.

Xanthine oxidase inhibitors:
- Decrease the production of uric acid, which helps decrease the formation of ammonium urate uroliths.
- An example is Allopurinol.
Pharmacology of Autocoids

Autocoids or Autacoids are the substances released from the cells in response to various types of stimulation to elicit normal physiological responses locally.

Any imbalance in autocoids synthesis, release or in the transduction system contributes significantly to pathological conditions such as inflammation, allergy, hypersensitivity and ischemia-reperfusion.

There are many autacoids which secreted in the body of animals like Histamine, Serotonin, Kinins and Ecosinids (Prostaglandins and leukotrienes) and others.

In our present lecture we shall focus individually on each previously listed autacoids and their origins, also the pharmacological effect of each one, in addition to their agonists and antagonists.

A - Histamine: is a biogenic amine (synthesized from histidine and stored in mast cells “tissue phagocytes” and basophils) throughout the body involved in local immune responses as well as regulating physiological function in the gut and acting as a neurotransmitter.

- There are at least four receptor populations, H₁, H₂, H₃, and H₄, and their distribution and their functions have been illustrated in the table below:

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₁</td>
<td>Brain, smooth muscle, heart, endothelium</td>
<td>Causes vasodilation, bronchoconstriction, bronchial smooth muscle contraction, separation of endothelial cells (responsible for hives), and pain and itching due to insect stings; the primary receptors involved in allergic rhinitis symptoms and motion sickness.</td>
</tr>
<tr>
<td>H₂</td>
<td>Chiefly on the parietal cells in stomach, Brain smooth muscle, heart, mast cells</td>
<td>Primarily stimulate gastric acid secretion.</td>
</tr>
</tbody>
</table>
Histamine agonists:

- **Histamine**: histamine injection is used to diagnose skin allergy (positive control).
- **Betazole** (histamine analog) is used to stimulate gastric acid secretion for diagnosis of hypochlorhydria.

Histamine antagonists:

- **Diphenhydramine (Allrmine® or Benadryl®)**:
  - It is H₁ receptor antagonist.
  - It is administrated orally or as injections.
  - It used for allergies and insect bites/stings; motion sickness and travel anxiety, organophosphate or carbamate poisoning; sedation, cough.
  - Side effects: lethargy, dry mouth, urinary retention. Less commonly emesis, diarrhea, and lack of appetite.
  - Overdose: excitement or seizure, lethargy, coma, respiratory depression, and death.

Other H₁ receptor blockers drugs include:

- Cyproheptadine.
- Chlorpheniramine
- Dimenhydrinate
- Loratidine
- Meclazine
Cimetidine (Tagamet®), Ranitidine (Zantac®) and Famotidine.
- They are H₂ receptor blockers.
- They used for treatment of duodenal and gastric ulcers (in adult horses; ranitidine is also used in foals). Also they used as pre-anesthetic drugs for prophylaxis against aspiration of gastric juice.

Thioperamide
- Is a potent and selective H₃ and H₄ receptors blocker.
- Its uses are not exceed the limitations of empirical purposes.

Cromolyn sodium
- It prevents the release of histamine, by preventing the degranulation of histamine from mast cell and basophil. (Unspecified histamine receptors blocker).
- It used for treatment of allergic rhinitis, preventive management of asthma, allergic conjunctivitis, urticaria and ulcerative colitis.

B - Serotonin:

- Serotonin (5-hydroxytryptamine or 5-HT) is synthesized from dietary tryptophan.
- It is stored in the intestine (enterochromaffin cells), the CNS, and mast cells (rodents). It is also found concentrated in blood platelets.
- It does not cross the blood-brain barrier. However, since serotonin is synthesized in the CNS, it is also considered as a central neurotransmitter.

Physiological and pharmacological activities of Serotonin:
- Serotonin has a vasodilator effect on the vascular bed of skeletal muscles; it also stimulates bronchi and intestinal muscles. It has inotropic and chronotropic effects.
- Its CNS action is known to influence sleep-wake cycle, mood and behavior, intestinal motility, thermoregulation, platelet aggregation.

Serotonin agonists:
- Buspirone:
  - Is used to stop inappropriate urination in cats and to treat “social” anxiety (e.g., changes in the family pack) in dogs

Serotonin antagonists
- Ondansetron, Alosetron and Cilansetron
  - They are used in treatment of irritable bowel syndrome.
- Also they are used in the prevention and treatment of nausea and vomiting. They are particularly effective in controlling the nausea and vomiting produced by cancer chemotherapy.

**Serotonin reuptake inhibitors:**

These drugs regulate serotonin turnover.

- **Clomipramine:**
  - It is a tricyclic antidepressant is thought to act by blocking serotonin re-uptake by neurons and hence increasing serotonin levels in the brain and decreasing the level of fear and anxiety.

- **Imipramine**
  - It used to inhibit urinary incontinence in dogs and narcolepsy and ejaculatory dysfunction in horses.

3- **Kinins:** A (kinin) is any of various structurally related polypeptides, such as bradykinin and kallikrein. They are members of the autacoid family.

**Physiological activities of Kinins:**

- Influence smooth muscle contractions.
- Increase blood flow throughout the body.
- Increase the permeability of small capillaries.
- Stimulate pain receptors.

**Pharmacological uses of kinins inhibitors**

The recent studies show promises to use kinins inhibitors in treatment of pancreatitis, sepsis and brain edema, while in human a new studies on new experimental kinins inhibitors may create a new pharmacological agents to treat acute attacks of hereditary angioedema.

4- **Eicosanoids:**

The Eicosanoids, {prostaglandins, thromboxane, prostacyclin, and leukotrienes}, are formed in the organism from arachidonic acid, a $C_{20}$ fatty acid with four double bonds (eicosatetraenoic acid).

- Synthesis of prostaglandins (PG), prostacyclin, and thromboxane proceeds via intermediary cyclic endoperoxides.
The letters following PG (D, E, F, G, H, or I) indicate differences in substitution with hydroxyl or keto groups; the number subscripts refer to the number of double bonds, and the Greek letter designates the position of the hydroxyl group at C9 (the substance shown is PGF2α).

PG are primarily inactivated by the enzyme {15-hydroxyprostaglandin dehydrogenase}. Inactivation in plasma is very rapid; during one passage through the lung, 90% of PG circulating in plasma are degraded. PG are local mediators that attain biologically effective concentrations only at their site of formation.

**Physiological activities of Eicosanoids:**

- **Nociceptors**: PG increase sensitivity of sensory nerve fibers towards ordinary pain stimuli, i.e., at a given stimulus strength there is an increased rate of evoked action potentials.

- **Thermoregulation**: PG raise the set point of hypothalamic (preoptic) thermoregulatory neurons; body temperature increases (fever).

- **Vascular smooth muscle**: PGE2 and PGI2 produce arteriolar vasodilation; PGF2α, venoconstriction.

- **Gastric secretion**: PG promote the production of gastric mucus and reduce the formation of gastric acid.

- **Menstruation**: PGF2α is believed to be responsible for the ischemic necrosis of the endometrium preceding menstruation. The relative proportions of individual PG are said to be altered in dysmenorrheal and excessive menstrual bleeding. Uterine muscle. PG stimulate labor contractions.

- **Bronchial muscle**: PGE2 and PGI2 induce bronchodilation; PGF2α causes constriction.

- **Renal blood flow**: when renal blood flow is lowered, vasodilating PG are released that act to restore blood flow.

- **Thromboxane and prostacyclin**: play a role in regulating the aggregability of platelets and vascular diameter.

- **Leukotrienes**: increase capillary permeability and serve as chemotactic factors for neutrophil granulocytes. As “slow-reacting
substances of anaphylaxis,” they are involved in allergic reactions; together with PG, they evoke the spectrum of characteristic inflammatory symptoms: redness, heat, swelling, and pain.

**Therapeutic applications of Prostaglandins:**

- PG derivatives are used to: induce labor or to interrupt gestation.
- In the therapy of peptic ulcer.
- PG derivatives are used in peripheral arterial disease.

**Eicosanoids antagonists:**

- **Prostaglandins Inhibitors:**

Generally, prostaglandins can be inhibiting via preventing their synthesis from the sources, and we can follow the synthesis of the prostaglandins by this simple sketch:-

From the sketch above we can divide prostaglandins inhibitors to:

1. **Phospholipase A₂ inhibitors:** - these drugs are inhibit the turning of the phospholipids in the cell wall to arachidonic acid via inhibition of Phospholipase A₂ whom responsible of this conversion. Example: Corticosteroids.
2- Cyclooxygenase (COX) inhibitors: these drugs are inhibit the turning of the arachidonic acid to prostaglandins through inhibition of cyclooxygenase (COX) whom responsible of this conversion. Example: Non steroidal anti-inflammatory drugs (NSAIDs). So that we can say that the NSAIDs can inhibit the synthesis of thromboxane and prostacyclins.
Analgesia and Analgesics

- Analgesics are drugs that relieve pain without causing loss of consciousness.
- Analgesics fall into two categories:

A - Opiate (Narcotics) analgesics:

- Narcotic analgesics (also known by Narcotic agonists) are used for moderate to severe pain; they refer to opioid (natural) or opioid-like (synthetic) products.
- They appear their action through binding to specific receptors which known by “Opiate receptors”
- The Opiate receptors can be divided to three kinds, as appear in the following table:

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
</table>
| Delta (δ) | Brain | - Analgesia.  
- Anti-depressant  
- Physical dependence. |
| Kappa (κ) | Brain and spinal cord | - Spinal analgesia.  
- Miosis  
- Sedation  
- Inhibition of ADH release. |
| Mu (μ) | Brain and spinal cord | - Supraspinal analgesia.  
- Physical dependence.  
- Respiratory depression  
- Miosis  
- Euphoria  
- Reduced GIT motility |

- Morphine:  
  - Morphine is the prototype natural alkaloid narcotic drug and is the standard against which all other opioids are tested.  
  - The predominant effects of morphine are at the μ -opioid receptor, although it interacts with other opioid receptors as well.  
  - Morphine is indicated for the treatment of moderate to severe and chronic pain (Cancer). It is useful preoperatively for sedation, anxiolytic effects, and to reduce the dose of anesthetics.  
  - Side effects includes: Respiratory disorders, constipation and physical dependence.
Meperidine (Demerol, Pethidine)
- Meperidine (Demerol) is a phenylpiperidine derivative of morphine.
- Pethidine exerts its analgesic effects by the same mechanism as morphine, by acting as an agonist at the μ-opioid receptor. In addition to its strong opioidergic and anticholinergic effects, it has local anesthetic activity related to its interactions with sodium ion channels.
- This agent has been used as an analgesic in several different species. It has been used as sedative/analgesic in small animals for both post-operative pain and for medical conditions such as acute pancreatitis and thermal burns. It is occasionally used in equine medicine in the treatment of colic and in other large animal species for pain control.
- In addition to the adverse effects common to all opioids, such as constipation, dry mouth, muscular twitches, and nausea, the repeated administration of pethidine can lead to neurotoxic effects. Pethidine should ideally not be administered by the intravenous route as there is a serious risk of triggering histamine release.

Codeine:
- It is methyl morphine natural opiate agonist too.
- It is used to produce mild analgesic effect.
- Widely used as an opioid antitussive because at antitussive doses it has few side effects and has excellent oral bioavailability. Also codeine has another uses like anti diarrheal agent and in management of Irritable Bowel Syndrome.
- Side effects are similar to morphine side effects.

**Other opiates examples include:**
- Methadone (Dolophine).
- Heroin.
- Fentanyl.

**Opioid Receptors antagonists:** drugs that bind with high affinity to opioid receptors but fail to activate the receptor mediated response.

Naloxone:
- Naloxone is a pure opioid antagonist.
- Naloxone has very wide margin of safety.
- It used most frequently for the reversal of opioid overdose.
- Also it used to treat the respiratory depression in neonates which induced by maternal opioids.

Naltrexone:
- Similar to Naloxone But with long duration (48 hrs.) of action and potent as 3-5 times than Naloxone.

B- Non-opiate (Non narcotic) Analgesics:
- In general, pain is first treated with the non-opioid analgesics or known by (Analgesic Non-Steroidal Anti-Inflammatory Drugs “ANSAIDs” too). These drugs are useful for treatment of pain, fever, and inflammation and for reduction of platelet aggregation. Although the NSAIDs are less effective than the opioids in providing pain relief, they do not produce tolerance and physical dependence, as do the opioids.
- The mechanism of action of traditional NSAIDs involves blockade of the production of prostaglandins by inhibition of the enzyme cyclooxygenase (COX) at the site of injury in the periphery, thus decreasing the formation of mediators of pain in the peripheral nervous system.
- To avoid the repetition we shall cover this group (ANSAIDs) in the next section

Anti-Inflammatory Drugs

- Inflammation is a useful and normal process that consists of a series of events, including vascular changes and release of chemicals that help destroy harmful agents at the injury site and repair damaged tissue.
- Severe inflammation must be reduced to avoid additional damage to the body.
- The most involved autacoids in the inflammation process are the Arachidonic acid derivatives.
- According to the diagram below, we can classify the agent that interact with ecosanoids synthesis to:-

![Diagram of eicosanoids synthesis](image)
1- **Steroidal Anti-Inflammatory Drugs** (Corticosteroids):

- Corticosteroids are hormones produced by the adrenal cortex.
- Corticosteroids inhibit the turning of the phospholipids in the cell wall to arachidonic acid via inhibition of Phospholipase A2 whom responsible of this conversion.
- Corticosteroids also can be classified according to the duration of action to:
  - Short-acting (duration of action less than 12 hours) Cortisone and hydrocortisone.
  - Intermediate-acting (duration of action 12–36 hours) Prednisone, prednisolone, prednisolone sodium succinate, methylprednisolone, methylprednisolone acetate, and triamcinolone.
  - Long-acting (duration of action more than 36 hours) Dexamethasone, betamethasone, and fluocinolone.

**Therapeutic uses of corticosteroids:**

1- Treatment of allergic conditions in particular asthma and some conditions that related with autoimmune diseases.

2- To treat the metabolic disorders like: hypokalemia (low potassium levels in the blood), hypernatremia (high sodium levels in the blood) without causing peripheral edema, metabolic alkalosis, Ketosis and pregnancy toxemia (nutritional disorder affects ewes and does in the trimester of pregnancy due to sudden extra nutritional demands of fetus and that leads to release of Keton bodies….etc.).

3- Also corticosteroids are used in the treatment of several types of inflammations like; joint pain or inflammation especially Rheumatic arthritis, local inflammations like skin inflammations and eye inflammations. Hepatitis, inflammatory bowel diseases and others.

4- Corticosteroids also used as replacement source for the endogenous corticosteroids in case of adrenal cortex insufficiency (Addison disease).

**Adverse effects**

1- Suppression of endogenous glucocorticoid synthesis: High levels of steroids negatively feed back on the pituitary to decrease the release of ACTH from the anterior pituitary. ACTH, So if we try to remove steroid treatment, we often get symptoms similar to a withdrawal effect, e.g. fever, muscle pain.
2- Suppression of the response to infection or injury: These drugs are immunosuppressants and also suppress wound repair due to the reduction in protein synthesis.

3- Sometimes a combination of steroid treatment with NSAIDs is given. NSAIDs may cause gastric ulceration and GIT disorders, but the steroids only exacerbate the adverse effects of NSAIDs because they suppress the repair of the ulcers.

4- Cataract, glaucoma: An increase in intraocular pressure is the normal response to steroidal treatment.

5- Fluid and electrolyte disturbances: Similarity to aldosterone or cortisol, corticosteroids increased reabsorption of Na also increased secretion of K.

6- Corticosteroids are highly contraindicated in:
   a- Diabetes mellitus.
   b- Eye cataract.
   c- Late stages of pregnancy.

2- **Non Steroidal Anti-Inflammatory Drugs (NSAIDs or ANSAIDs):**
   ÿ These drugs are inhibit the turning of the arachidonic acid to prostaglandins through inhibition of cyclooxygenase (COX) whom responsible of this conversion.
   ÿ Cyclooxygenase has two types, they are:-
     I- Cox-1 whom helps to maintain the lining of the stomach.
     II- Cox-2 whom triggers the inflammation and pain.
   ÿ NSAIDs have fewer side effects than corticosteroids.
   ÿ Therapeutic uses and general adverse effects of NSAIDs have been listed in the following tables :-
<table>
<thead>
<tr>
<th>Group</th>
<th>Examples</th>
<th>Therapeutic uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylate Derivatives</td>
<td>Acetyl Salicylic Acid (Aspirin®), diflunisal and related salicylate products.</td>
<td>Mild to moderate pain, anti-clot, antipyretic and for rheumatoid arthritis.</td>
</tr>
<tr>
<td>Fenamates Derivatives</td>
<td>Meclofenamate (Meclomen®) and mefenamic acid (Ponstel®). And Diclofenac (Voltaren®)</td>
<td>Mild to moderate pain, rheumatoid arthritis and osteoarthritis, ankylosing spondylitis.</td>
</tr>
<tr>
<td>Acetic Acid Derivatives</td>
<td>Indomethacin (Indocin®)</td>
<td>Rheumatoid arthritis, moderate to severe osteoarthritis, ankylosing spondylitis, gouty arthritis.</td>
</tr>
<tr>
<td>Enolic acid Derivatives</td>
<td>Piroxicam (Feledin®) and Meloxicam (Mobic®)</td>
<td>Mild to moderate pain, Rheumatoid arthritis and osteoarthritis</td>
</tr>
<tr>
<td>Propionic Acid Derivatives</td>
<td>Ibuprofen (Advil®), fenoprofen (Nalfon®), ketoprofen (Orudis®), and naproxen (Naprosyn®).</td>
<td>Long term management of mild to moderate pain, rheumatoid arthritis and osteoarthritis</td>
</tr>
<tr>
<td>Para-aminophenol Derivatives</td>
<td>Para-acetaminophen (Paracetmol®)</td>
<td>Mild to moderate pain antipyretic and for rheumatoid arthritis.</td>
</tr>
<tr>
<td>Selective COX-2 inhibitors</td>
<td>Celecoxib (Celebrex®) and rofecoxib (Vioxx®)</td>
<td>Acute \ long term treatment of rheumatic arthritis, osteoarthritis and management of acute pain</td>
</tr>
</tbody>
</table>

NSAIDs classification with therapeutic uses of each.
**Common and Shared Adverse Reactions of NSAIDs**

<table>
<thead>
<tr>
<th>System</th>
<th>Manifestations</th>
</tr>
</thead>
</table>
| GI (adverse effects decreased with COX-2-selective drugs) | Abdominal pain  
Nausea  
Anorexia  
Gastric erosions/ulcers  
Anemia  
GI hemorrhage  
Perforation  
Diarrhea |
| Renal           | Salt and water retention  
Edema, worsening of renal function in renal/cardiac and cirrhotic patients  
Decreased effectiveness of antihypertensive medications  
Decreased effectiveness of diuretic medications  
Decreased urate excretion (especially with aspirin)  
Hyperkalemia |
| CNS             | Headache  
Vertigo  
Dizziness  
Confusion  
Depression  
Lowering of seizure threshold  
Hyperventilation (salicylates) |
| Platelets (adverse effects decreased with COX-2-selective drugs) | Inhibited platelet activation  
Propensity for bruising  
Increased risk of hemorrhage |
| Uterus          | Prolongation of gestation  
Possible prolongation of labor |
| Hypersensitivity| Vasomotor rhinitis  
Angioedema  
Asthma  
Urticaria  
Flush  
Hypotension  
Shock |
| Vascular        | Closure of ductus arteriosus |

Common and shared adverse effects of NSAIDs
Endocrine And Reproductive system Pharmacology

I- Endocrine Pharmacology

✓ The endocrine system is composed of ductless glands that secrete chemical messengers called hormones into the blood. Hormones are chemical substances produced by cells in one part of the body and transported to another part of the body where they influence cellular activity.

✓ The endocrine system is controlled by a feedback mechanism that includes the hypothalamus, pituitary gland, and the other endocrine glands.

✓ Feedback mechanism may be either negative or positive. The Negative feedback mechanism are more common and work in response to low or high levels of hormone in the body, while Positive feedback mechanism occur when hormone levels continue to rise in response to stimuli.
A- Pituitary Gland Hormones: The pituitary gland is divided into two parts: anterior (cranial) and posterior (caudal).

- Anterior pituitary hormones used in veterinary practice include:

  § Thyroid stimulating hormone (TSH) Dermathycin®: TSH is used for temporary supportive therapy in hypothyroidism in dogs. In actuality however, TSH is used in veterinary medicine principally as a diagnostic agent in the TSH stimulation test to diagnose primary hypothyroidism.

  § Adrenocorticotropic hormone (ACTH) Adrenomone®: ACTH is approved for use in dogs, cats, and beef or dairy cattle for stimulation of the adrenal cortex when there is a deficiency of ACTH, and as a therapeutic agent in primary bovine ketosis (rising of ketone bodies level in blood due to hypoglycemia). In practice however, it tends to be used most often in the diagnosis of hyper- or hypoadrenocorticism (ACTH stimulation test) and to monitor the response to mitotane therapy in Cushing syndrome (Hypercortisolism). ACTH has been used for several purposes in human medicine for its corticosteroid stimulating properties, but as it must be injected, it is not commonly employed.

  § Follicle stimulating hormone (FSH) and Luteinizing hormone (LH): will be discussed latterly.

  § Growth hormone (GH). GH is used to increase growth rate and feed use efficiency in livestock and increase milk production in dairy cows.

- Posterior pituitary hormones used in veterinary practice include:

  § Antidiuretic hormone (ADH) or Vasopressin: Vasopressin is used in veterinary medicine as a diagnostic agent and in the treatment of diabetes insipidus (disease characterized by the inability to concentrate urine due to insufficient amounts of ADH). In small animals.

  § Oxytocin: In veterinary medicine, oxytocin has been used for induction or enhancement of uterine contractions at parturition, treatment of postpartum retained placenta and metritis, uterine involution after manual correction of prolapsed uterus in dogs, and in treating agalactia.

B- Pancreas Hormones: The pancreas secretes two hormones that help regulate blood glucose:-

*UNREvised EDITION 75
- **Insulin** (secreted from β cells of pancreas) responds to a rise in blood glucose and promotes the uptake and use of glucose for energy in cells. While **Glucagon** (secreted from α cells of pancreas) increases blood glucose levels by promoting the breakdown of glycogen into glucose.

- **Diabetes mellitus** is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia).

  **Insulin** is used to treat diabetes mellitus by keeping blood glucose in the proper range
  - Sources of insulin include pork, synthetic, and recombinant forms
  - Onset and duration of insulin action are controlled by modifying the regular insulin structure
    - Short-acting is used for initial treatment of diabetic ketoacidosis and keep blood glucose stable (regular crystalline insulin, semilente)
    - Intermediate-acting is used to control blood glucose in uncomplicated cases of diabetes mellitus (NPH and lente)
    - Long-acting is used to control blood glucose for longer periods of time, especially in cats (protamine zinc insulin and ultralente).

  **Oral hypoglycemic agents** have been used with some success in animals
  - Work by stimulating pancreatic beta cells to secrete insulin; therefore some pancreatic function is needed.
  - Has been more successful in cats.
  - An example of an oral hypoglycemic agent is glipizide

C- **Thyroid gland hormones:** The thyroid gland secretes two hormones involved in metabolism:
  a. **Thyroxine** or T₄.
  b. **Tri-iodothyronine** or T₃, (the active form of thyroxin).

- **Hyperthyroidism** is characterized by an increased production of thyroid hormone.
- Signs of hyperthyroidism include increased thirst, weight loss, increased stool production, restlessness, and tachycardia
- Diagnosed by measuring serum total T₄ and T₃.
- Hyperthyroid animals are treated with anti-thyroid drugs or surgical removal.
Radioactive isotopes of iodine ($^{131}$I): destroy the thyroid gland.

Methimazole: Methimazole is considered by most clinicians to be the agent of choice when using drugs to treat feline hyperthyroidism. It interferes with the incorporation of iodine in the molecules of T4 and T3.

Propylthiouracil (PTU): this agent acts by two mechanisms:-
- PTU inhibits the enzyme thyroperoxidase, which normally acts in thyroid hormone synthesis to add iodide to the tyrosine residues on the hormone precursor thyroglobulin, thus forming thyroxine.
- PTU also acts by inhibiting the enzyme 5'-deiodinase (tetraiodothyronine 5' deiodinase), which converts $T_4$ to the active form $T_3$.

D- Adrenal cortex hormones: The adrenal cortex is the outer part of the adrenal gland, it produce two types of hormones those are:

a. Mineralocorticosteroids (Aldosterone) increase the reabsorption of sodium and water and the release (secretion) of potassium in the kidneys.

b. Glucocorticoids (Cortisol) regulate nutrient levels in blood (increase blood glucose levels).

- The hypothalamus regulates the adrenal cortex by secreting releasing hormones for ACTH, which stimulates the adrenal cortex.

Adrenocortical insufficiency (Addison’s disease) is a progressive condition associated with adrenal atrophyis in which the adrenal gland produces insufficient amounts of steroid hormones (glucocorticoids and often mineralocorticoids).

- Treatment involves a long-acting mineralocorticoid and corticosteroids

Fludrocortisone:

- Fludrocortisone is used in small animal medicine for the treatment of Addison’s disease.

- It has also been suggested to be used as adjunctive therapy in hyperkalemia.

- Additionally in humans, fludrocortisone has been used in salt-losing congenital adrenogenital syndrome and in patients with severe postural hypotension.

Hyperadrenocorticism (Cushing’s disease): is characterized by excessive glucocorticoid production due to prolonged administration of adrenocortical hormones, adrenocortical tumors, or pituitary disorders.
Treatment involves destroying part of the adrenal cortex.

**Mitotane:**
- An adrenal cytotoxic agent, also it inhibits adrenocortical function without causing cell destruction.
- In veterinary medicine, mitotane is used primarily for the medical treatment of pituitary-dependent hyperadrenocorticism (PDH) principally in the dog.
- It has also been used for the painkilling treatment of adrenal carcinoma in humans and dogs.

**Ketoconazole:**
- An imidazole antifungal agent, but it also blocks the enzymes needed to produce steroid compounds.
- It used clinically for the medical treatment of hyperadrenocorticism in dogs (and sometimes cats).

**Selegiline:**
- Monoamine oxidase inhibitor (MAO inhibitor).
- It approved for use in dogs only for the treatment of Cushing’s disease.
- In Canada it is also approved for the treatment of Canine Cognitive Dysfunction (so-called old dog dementia).
- In humans, selegiline’s primary indication is for the adjunctive treatment of Parkinson’s disease.

**II- Reproductive Pharmacology**

- Reproductive system is responsible for the process of producing offspring, consequently maintenance of species.

- Male reproductive system, and composed from:-
  - Testes, epididymis, ductus deferens, accessory sex glands, urethra, penis.
  - Sperm are produced in the seminiferous tubules of the testes.

- Female reproductive system, and composed from:-
  - Ovaries, uterine tubes, uterus, cervix, vagina, and vulva.
  - Ova are produced in the Graafian follicle of the ovary.

So that the drugs of reproductive system are divided to:-
I- Gonadotropines: Gonadotropins are hormones that stimulate the gonads they are glycoprotines in their nature, and they secreted from pituitary gland and from placenta too (in case of pregnancy).

Gonadotropins include:-

1- Follicular stimulating hormone (FSH): is a hormone synthesized and secreted by the anterior pituitary gland. FSH regulates the development, growth, pubertal maturation, and reproductive processes of the animal body.

Effects of FSH in females:-
- FSH stimulates the growth and recruitment of immature ovarian follicles in the ovary. As the follicle matures, one becomes dominant.

Effects of FSH in males:-
- FSH enhances the production of androgen-binding protein by the Sertoli cells of the testes, and is critical for spermatogenesis.

Pharmacological Uses of FSH:-
- The exogenous FSH used as a supplemental source of FSH when there is a general deficiency in cattle, horses, swine, sheep and dogs.
- Its primary use in veterinary medicine has been to induce follicular growth for the purposes of super-ovulation and out-of-season breeding.

FSH effect is simulated by the use of Pregnant Mare Serum Gonadotropin (PMSG).

Pregnant mare serum gonadotropin (PMSG) is produced by endometrium of the mare during pregnancy and
- Usually obtained from serum obtained from serum of pregnant mare at 50-80 days of gestation
- The most predominant hormone in PMSG is FSH. So that it used to get the effect of FSH.
- It used to produce estrus and ovulation in mares and as a follicle stimulant in many species.

2- Luteinizing hormone (LH): is another gonadotropin which synthesized and secreted by the anterior pituitary gland, and its effects on Reproductive system include:-

Effects of LH in females:-
- In the female, an acute rise of LH (the LH surge) triggers ovulation.
Effects of LH in Males:-

- In the male, where LH had also been called Interstitial Cell Stimulating Hormone (ICSH), it stimulates Leydig cell production of testosterone.

Pharmacological Uses of LH analogs:-

- In females:-
  - It used to treat inactive ovaries.
  - Also LH used in treatment of Nymphomania (Cystic ovaries).

- In males:-
  - LH analogs are used to stimulate releasing of testosterone from testis.
  
Also they used to diagnose or treating of cryptochidism (failure of the testis to move, or "descend," during fetal development from an abdominal position).

LH effect is simulated by the use of Human Chorionic Gonadotropin (HCG).

*Human chorionic gonadotropin (HCG): A gonad-stimulating polypeptide secreted by the placenta, chorionic gonadotropin is obtained from the urine of pregnant women. HCG mimics quite closely the effects of luteinizing hormone (LH), but also has a little FSH-like activity.*

- It used to treat cystic ovaries in cattle.
- To detect cryptorchidism in dogs.
- To get infertile bitches to cycle.
- And to induce ovulation in breeding mares.

Ø Gonadotropin-releasing hormone (GnRH), is a tropic peptide hormone responsible for the release of FSH and LH from the anterior pituitary. GnRH is synthesized and released from neurons within the hypothalamus.

- GnRH is used to treat follicular cysts in cattle.
- Also for estrus synchronization in cattle.
- And to induce estrus in small animals.

II- Sex Hormones or Sex Steroids:- Sex steroids, also known as gonadal steroids, they are steroid hormones which made by the gonads (ovaries or testes), by adrenal glands, or by conversion from other sex steroids in other tissue such as liver or fat. Sex steroids play important roles in inducing the body changes known as primary sex characteristics and secondary sex characteristics.
1- **Androgens:** Steroid hormones that are secreted primarily by the testis, and testosterone is the principal androgen secreted. Its primary function is to regulate the differentiation and secretory function of male sex accessory organs. Androgens also possess protein anabolic activity that is manifested in skeletal muscle, bone, and kidneys. As a class, androgens are reasonably safe drugs, having limited and relatively predictable side effects.

*Testosterone (testosterone cypionante, enanthate, and propionate):*
- Made in the interstitial cells of the testes
- Used to treat conditions such as infertility and hypogonadism, produce estrus detectors, and for testosterone-responsive urinary incontinence in dogs.
- High and long periods of usage cause oligospermia and sterility in males.

*Anti-androgens:*
- Compounds those are capable of preventing or inhibiting the biologic effects of androgens.
- They used as an antineoplastic agent and palliative, adjuvant hormonal therapy in prostate cancer.
- Example: Spironolacton, Ketoclonazole and finasteride.

2- **Estrogens:** Steroid hormones that are secreted primarily by the Ovary. They promote female sex characteristics and stimulate and maintain the reproductive tract.

*Estradiol:* Estradiol is a naturally occurring steroidal estrogen. the indications for the use of estradiol include:-
- Induction of estrus during the non-breeding or breeding seasons and to enhance the mare’s uterine defense mechanism.
- Estradiol cypionate has also been used as an abortifacient agent in cattle, cats and dogs.
- To correct anestrus (absence of heat period) in the absence of follicular cysts in some cases.
- To treat cattle having persistent corpus luteum due to certain causes.
- To expel purulent material from the uterus in pyometra of cows.
- To stimulate uterine expulsion of retained placentas and mummified fetuses.
Main side effects include: prolonged estrus, genital irritation, decreased milk flow, precocious development and follicular cysts may develop after estrogen therapy.

- **Anti-estrogens:**
  - Substances that block the activity of estrogens.
  - Antiestrogens may stop some cancer cells from growing and are used to prevent and treat breast cancer. They are also being studied in the treatment of other types of cancer.
  - Example: Tamoxifen.

3- **Progesterone:** Steroid hormone that secreted primarily by the Ovary (Corpus luteum), placenta and adrenal glands. It decreases uterine activity when a female is in estrus or pregnant.

- **Medroxyprogesterone Acetate (MPA):**
  - Synthetic Progestins. (A group of compounds similar in effect to progesterone).
  - Decreases uterine activity when a female is in estrus or pregnant.
  - Progestins are used in dogs to block estrus.
  - Progestins are used in cattle to synchronize breeding and birth cycles.
  - Progestins may be used to treat behavior problems and some forms of dermatitis.
  - Other similar drugs are: Megestrol acetate, Altrenogest and Melengestrol.
  - Side effects include: Increased appetite and/or thirst, depression, lethargy, personality changes, adrenocortical depression, mammary changes (including enlargement, milk production, and neoplasms), diabetes mellitus, pyometra and temporary inhibition of spermatogenesis.

- **Anti-progesterones (Anti-progestins):**
  - Substances that prevent cells from making or using progesterone.
  - Antiprogestins are used for contraception, labour induction, and treatment of endometriosis and breast cancer.
  - Example: Mifepristone.
Drugs Affecting uterine Motility:
We can divide the drugs which effect on the uterine muscle motility to stimulants or relaxants:-

**Uterine Muscles Stimulants:**

**Oxytocin:**
- Stimulates uterine smooth muscle contraction, effect is Ca\(^{+2}\) dependent.
- It used for Induction of labor, augmentation of labor and therapeutic abortion.
- Side Effects include:-
  b. Fetus: Hypoxia, acidosis.

**Prostaglandins (PGs):**
- Also they increase Ca\(^{+2}\) ion concentration, and that leads to increase uterine muscle contractions.
- PGE\(_2\) and PGf\(_{2\alpha}\) are the two PGs whom used for increase uterine muscle contractions.
- PGf\(_{2\alpha}\) causes lysis of the corpus luteum, which initiates a new estrus cycle (Naturally).
- In small animals, prostaglandins are used to treat pyometra, cause abortion, and induce parturition
- In cattle, prostaglandins are used for estrus synchronization and inducing uterine contractions to facilitate emptying of the uterus (pus or fetus)
- In horses, prostaglandins are used for estrus synchronization too.
- Side effects include: Uterine hyper tonus sweating, increased respiration, mild abdominal discomfort, uneasiness and defecation may be seen after PGs injection.

**Ergot alkaloids (Ergonovine, M ethyl ergonovine):**
- Alpha-adrenergic agonists
- Increase uterine smooth muscle contraction.
- It has a medical use in obstetrics to facilitate delivery of the placenta and to prevent bleeding after parturition by causing smooth muscle tissue in the blood vessel walls to narrow, thereby reducing blood flow.
**Uterine Muscles Relaxants:**

- **Β2- adrenergic agonists (Albuterol, Salbutamol):**
  - To Arrest premature labor.
  - Side effects include: Tachycardia and hypotension in mother and fetus, nausea and vomiting, Hyperglycemia.

- **Magnesium Sulfate:**
  - Antagonizes the action of Ca, results in smooth muscle relaxation consequently it Delay or prevent premature parturition.
  - Side effects include: Skin flushing, nausea, headache, palpitation, decreased reflexes. Higher doses: respiratory depression and cardiac arrest CNS depression in fetus (rare).

- **Cyclooxygenase (COX) Inhibitors (In particular Endomethacin):**
  - Prevent synthesis and release of PGs, which are endogenous stimulants.
  - They Delay or prevent premature parturition.
  - Side effects include: Anorexia, nausea, headache, confusion, bone marrow depression. In fetus may cause premature closure of the ductus arteriosus, and pulmonary hypertension.

- **Calcium Channel Blockers (Niphedipine):**
  - They close Ca\(^{2+}\) channels leading to decrease uterine muscles contractions.

- **Ethanol:**
  - Inhibits both ADH and Oxytocin release. Also has a beta-adrenergic stimulating effect as well as direct inhibitory action on uterine muscle. Might seem an ideal agent. However, because it can cause CNS depression in fetus, is not used much any more.
Chemotherapy

I. History and Introduction

Chemotherapy: this term refers to treatment of disease by chemicals that kill cells, specifically those of micro-organisms (virus, bacteria, fungi, protozoa, and parasites) or cancer.

1877: Antibiosis was first described in bacteria when Louis Pasteur and Robert Koch observed that an airborne bacillus could inhibit the growth of Bacillus anthracis.

1875: The antibiotic properties of Penicillium sp. were first described in England by John Tyndall in 1875. However, his work went by without much notice from the scientific community.

1909: Modern research on antibiotic therapy began in Germany with the development of the narrow-spectrum antibiotic Salvarsan by Paul Ehrlich.

1928: Alexander Fleming. Discover penicillin.

1939: Ernst Chain and Howard Florey became interested in Alexander Fleming work, and came up with the purified form of penicillin.

1939: Rene Dubos isolated gramicidin, one of the first commercially manufactured antibiotics in use during World War II to prove highly effective in treating wounds and ulcers.

1939: Gerhard Domagk developed the Prontosil, from red tissue dye (the first commercially available antibacterial antibiotic) at the Bayer Laboratories of the IG Farben conglomerate in Germany.

The relationship among the microorganism, host and the chemotherapeutic agent can be illustrated through the chemotherapeutic triangle: (see the figure).
Antibiotic: is a substance or compound (made from a living source) that kills or inhibits the growth of bacteria.

Antibacterial: is a substance or compound that kills or inhibits the growth of bacteria. According to the two definitions above we can say that the antibacterial agents have a wide understood more than the antibiotics. (Can you see why?).

Classification of Antibacterials:

There are three ways to classify the antibacterials, they are:

1. According to the effectiveness:
   I. **Bactericidal** (agent that destroys or kills bacteria).
   II. **Bacteriostatic** (agent that slows or retards the multiplication of bacteria).

2. According to the spectrum:
   I. **Narrow spectrum** (agent acting only on a single or a limited group of microorganisms).
   II. **Extended spectrum** (agent that effective against gram-positive bacteria also against significant number of gram-negative and vire versa.
   III. **Broad spectrum** (agent that effects on a wide range Varity of microorganisms).

3. According to the mechanism of action:
   a. Inhibitors of cell wall synthesis.
   b. Inhibitors of protein synthesis.
   c. Inhibitors of cell membrane functions.
   d. Metabolism inhibitors.
   e. Inhibitors of nucleic acid synthesis or function.

In our lecture we shall follow the 3rd classification because of its inclusive understood.
Inhibitors of Cell Wall Synthesis

Penicillins

- Discovered by Felming in 1928.
- Produced by *Penicillium* spp. (mainly *natatum*).
- Contain β-lactum ring (6-amino penicillinic acid).
- The mechanism of action includes:
  - Inhibition of cell wall synthesis in bacterial cell wall. The β-lactam moiety (functional group) of penicillin binds to the enzyme transpeptidase that links the peptidoglycan molecules in bacteria, which weakens the cell wall of the bacterium (in other words, the antibiotic causes cytolysis or death due to osmotic pressure).
  - In addition, the build-up of peptidoglycan precursors triggers the activation of bacterial cell wall hydrolases and autolysins, which further digest the bacteria's existing peptidoglycan.
- Penicillins can be divided into four groups they are:
  I. Natural (Basic) Penicillins:
  - They are narrow spectrum, bactericidal, and penicillinase sensitive (Penicillinase is a specific type of β-lactamase, affect the penicillins by hydrolysing the β-lactam ring).
  - There are two types of natural penicillins they are:
    - **Penicillin G**: (Benzyl penicillin, Procain penicillin, Benzathine penicillin):
      - It was the first of the penicillins, and remains an important and useful antibiotic.
      - It is particularly active against Gram-positive bacteria; Sensitive micro-organisms include Gram-positive streptococci, Gram-positive Bacilli, Gram-negative cocci (*Neisseria*), most anaerobic bacteria including *Clostridium* and *Spirochetes* (*Treponema*).
      - Staphylococcus aureus resist natural penicillins because of its ability to produce penicillinase (β-lactamase).
      - Penicillin G is inactivated by gastric juice (Acid labile) so that it not administrated orally but used via other routes like Intravenous and Intramuscular.
    - **Penicillin V**: (Phenoxyethyl penicillin)
      - Semi synthetic penicillin, it has similar bacterial effect to Penicillin G.
- Penicillin V is acid stable in contrast to Penicillin G therefore it can be administrated orally.

II- Antistaphylococcal (penicillinase resistant) Penicillins:
- They are semi-synthetic, narrow spectrum, acid stable (can be administrated orally) and penicillinase resistant penicillins.
- These antibiotics are effective against streptococci and most community-acquired penicillinase-producing staphylococci (drug of choice).
- Examples; Nafcillin, oxacillin, cloxacillin, and dicloxacillin

III- Aminopenicillins (Extended spectrum penicillins):
- Semi-synthetic, Extended spectrum, acid stable and penicillinase sensitive penicillins.
- This group has slightly less activity than natural penicillins against Gram-positive bacteria and obligates anaerobes but considerably greater activity against Gram-negative bacteria, although their action is poor against Klebsiella, some Proteus spp., and Pseudomonas spp.
- Examples; Ampicillin, Amoxicillin and Pivampicillin.

IV- Antipseudomonal Penicillins:
- Semi-synthetic, broad spectrum, acid labile and penicillinase sensitive penicillins.
- The antipseudomonal penicillins have comparable spectra of activity against many gram-positive and gram-negative pathogens, including most anaerobes. and (as appear from their nomination) they are the drug of choice against Pseudomonas aeruginosa infections
- Examples; Carbencillin, Mezlocillin, piperacillin, and ticarcillin.

Clinical problems with penicillins :
- Narrow spectrum: it corrected by administration of extended or broad spectrum penicillins instead of narrow spectrum penicillins
- Acid lability: it corrected by administration of acid stable penicillins
- Short Half- life: it corrected by increase the half life of penicillins by using of Probenecid which blocks the tubular secretion of penicillin, thereby prolonging its half-life.
- Penicillinase sensitivity: it solved by using of Clavulanic-suitable penicillin mixture whereas clavulanic acid has a potent penicillinase inhibitory effect.
Pharmacokinetic profile of Penicillins:

- **Absorption**: all acid stable penicillins can be absorbed well (about 70%) in contrast to acid labile penicillins (about 30%).
- **Distribution**: penicillins are well distributed throughout the body, the plasma-protein binding ratio arrange between (30-90%).
- **Metabolism**: usually the metabolism in penicillins is not significant.
- **Excretion**: all penicillins are excreted through kidney (except Naficillin which excreted through the bile), penicillins have been excreted via active tubular secretion (80%), and glomerular infiltration (20%).

General side effects of Penicillins

1- Hyper sensitivity. Skin Rashes (Type I, III), Anaphylactic Shock (Type I)
2- GIT disturbances. They are cause imbalance in microflora of the GIT.
3- Nephrotoxicity. They are cause interstitial nephritis.
4- Neurotoxicity. Penicillins irritant to the neural tissues so that they induce seizures.

Cephalosporins

- The cephalosporins are semi-synthetic antibiotics derived from products of various microorganisms, including Cephalosporium and Streptomyces.
- All cephalosporins have a 7-aminocephalosporanic acid composed of a dihydrothiazine ring fused to a β-lactam ring.
- The cephalosporin β-lactam ring is the chemical group associated with antibacterial activity.
- Like the penicillins, Cephalosporins are bactericidal and relatively non-toxic (although less so than the penicillins), and less likely to cause allergic reactions.
- Cephalosporins can be divided into four generations, they are:-

1- 1st generation of Cephalosporins:

- The first generation drugs are active against a range of both Gram-positive and Gram-negative organisms comprising staphylococci (including beta-lactamase- producing strains), Pasteurella, E. coli, Actinobacillus, Actinomycetes, Haemophilus,
Erysipelothrix, Clostridium, and Salmonella spp. However Pseudomonas and many Proteus spp. are resistant.

- Examples: Cefadroxil Oral, Cefazolin IM, IV, Cephalexin Oral, Cephapirin IM, IV and Cephradine Oral

II- 2nd generation of Cephalosporins:
- Second generation cephalosporins have good activity against Gram-positive organisms and the Enterobacteriaceae but are not effective against the most intractable Gram-negative organisms such as Klebsiella spp. or Pseudomonas aeruginosa.

III- 3rd generation of cephalosporins:
- Third-generation cephalosporins generally are less active than first-generation agents against gram-positive cocci but are much more active against the Enterobacteriaceae, including β-lactamase producing strains. A subset of third generation agents (e.g., ceftazidime and cefoperazone) also is active against P. aeruginosa but less active than other third-generation agents against gram-positive cocci.

IV- 4th generation of Cephalosporins:
- They are extremely broad-spectrum being highly active against Enterobacteriaceae, staphylococci, and enterococci. In addition, they are not destroyed by the most common β-lactamase of Klebsiella spp. And Pseudomonas aeruginosa. Example: Cefepime IV.

Pharmacokinetic profile of Cefalosporins:
The pharmacokinetical profile of Cefalosporins is similar to that in Penicillins.

Side effects of Cefalosporins
1- Hypersensitivity: Those who are allergic to penicillin may also be allergic to Cephalosporins (10-15%).
2- Renal Toxicity: Interstitial nephritis, tubular necrosis. Effect can be synergistic with the aminoglycosides.

3- Thrombophlebitis, after IV administration.

4- Superinfection: 3rd generation agents may show superinfection of gram-positive organisms (Staphylococcal Enterocolitis).

5- Disulfiram: they increase toxicity of alcohol by blocking the mechanism of metabolism.

Other cell wall synthesis inhibitors: and include:-

- Bacitracin:
  - Bacitracin is a mixture of polypeptide antibiotics produced by Bacillus subtilis.
  - The mechanism of action includes inhibition of the carrier “lipid pyrophosphate” that transports cell wall precursors to the growing cell wall.
  - Bacitracin inhibits gram-positive cocci, including Staphylococcus aureus, streptococci, a few gram-negative organisms, and one anaerobe, Clostridium difficile.
  - Side effects include: ototoxicity, nausea, vomition and nephrotoxicity.

- Vancomycin and Teicoplanin.
  - Vancomycin (Vancocin) is a glycopeptide antibiotic produced by Streptomyces orientalis, while Teicoplanin (Targocid) is derived from Actinomyces teichomyceticus.
  - They inhibit cell wall synthesis by preventing the polymerization of the linear peptidoglycan by peptidoglycan synthase.
  - They are Bacteriostatic and narrow-spectrum agents that are active against gram-positive organisms. Teicoplanin is active against staphylococci, streptococci, and enterococci. Gram-positive rods, such as Bacillus anthracis, Corynebacterium diphtheriae, Clostridium tetani, and Clostridium perfringens, are also sensitive to the glycopeptides. The glycopeptides are not effective against gram-negative rods, mycobacteria, or fungi.
  - Major side effects include: Nephrotoxicity and ototoxicity may be seen with the administration of these drugs. Additional adverse reactions include nausea, chills, fever, urticaria, sudden fall in blood pressure with parenteral administration, and skin rashes.
Inhibitors of cell membrane functions.

- This group of antibiotics will alter with cell membrane permeability (cationic detergents) and this action will lead to loss the integrity of bacterial cell membrane, consequently causing death of bacteria.

Polymyxines

- The polymyxins are a group of antibiotics produced by Bacillus polymyxa. Polymyxin B (Aerosporin) and polymyxin E (Colistin) are used in the treatment of bacterial diseases.
- Their mechanism of action has been explained above.
- The polymyxins are active against gram-negative bacteria, Pseudomonas aeruginosa in particular.
- Polymyxins are not well absorbed from the gastrointestinal tract. Parenteral administration of polymyxins results in high drug concentrations in the liver and kidneys, the polymyxins are slowly excreted by glomerular filtration; the slow elimination rate is due to binding in tissues. Elimination is decreased in patients with renal disease, and drug accumulation can lead to toxicity. Therefore polymyxins are used topically only with few exceptions.
- Side effects: Polymyxins can cause extreme nephrotoxicity when used parenterally, and any preexisting renal insufficiency will potentiate the nephrotoxicity caused by these antibiotics.

Protein Synthesis Inhibitors

- This group of antibiotics has been exerting their effect by inhibition of synthesis of bacterial protein by interfering with ribosomal subunits (30S or 50S) of bacteria.
- This inhibition may be either reversible (Bacteriostatic) or irreversible (Bactericidal).
- This group includes:-

Aminoglycosides:

- They are hydrophilic, polycationic, amine containing carbohydrates.
- The major clinically important aminoglycosides are:-
- Gentamicin \ derived from Micromonosporium Spp.
- Streptomycin.
- Kanamycin
- Neomycin \ Derived from Streptomycis Spp.
- Tobramycin
- Amikacin \ Semi-synthetic from Kanamycin.
- Netilmicin \ Semi-synthetic from Gentamicin.

Ø The mechanism of action of aminoglycosides includes irreversible binding to various sites on bacterial 30S ribosomal subunit, thereby disrupting the initiation of protein synthesis, consequently misreading of genetic code and production of false protein.

Ø All aminoglycosides are bactericidal and active against Gram-negative organisms and some Gram-positive organisms, but not streptococci. Amikacin, gentamicin, and tobramycin are active against *Pseudomonas aeruginosa*.

Ø Pharmacokinetics of aminoglycosides include:
- Absorption: Poor oral absorption. There for they administrated usually IM. And occasionally IV.
- Low distribution in most tissues.
- Half-life 2-3 hrs. Excreted by passive glomerular filtration.

Ø The important side-effects of aminoglycosides are vestibular or auditory ototoxicity, and nephrotoxicity. Risk of toxicity following systemic administration varies with different members of the group. Neomycin is particularly toxic to the auditory and renal systems. Streptomycin is ototoxic and gentamicin is ototoxic and nephrotoxic.

**Tetracyclines**

Ø They are broad-spectrum and Bacteriostatic polyketide (Secondary metabolite of the microorganism) antibiotic. Produced Streptomycis Spp.

Ø The mechanism of action of Tetracyclines includes reversible binding to bacterial 30S ribosomal subunit.

Ø Tetracyclines are active against *Mycoplasma*, *Chlamydia*, and *Rickettsia* in addition to bacteria. They are active against a range of Gram-positive and Gram-negative...
bacteria but have little useful activity against E. coli, Salmonella, Proteus, or Pseudomonas spp.

뺴 Tertacyclines are classifies according to the duration of action to:-

β Short acting ($t_{1/2} = 6 – 12$ hrs.) Tetracyclines. examples
- Tetracycline.
- Chlorotertacycline.
- Oxytetracycline.

β Intermediate acting ($t_{1/2} = 10 – 17$ hrs.) Tetracyclines. examples:
- Demclocycline.
- Methacycline.

β Long acting ($t_{1/2} = 20 – 24$ hrs.) Tetracyclines. examples:
- Doxycycline.
- Minocycline.

ประเภ�파 Pharmacokinetics of Tetracyclines:
- Absorption: Tetracyclines are partially absorbed from the stomach and upper gastrointestinal tract. But the absorption will decrease in case of presence of calcium, iron magnesium and aluminum. Due to chelating nature of Tetracyclines.
- Distribution: tetracyclins are well distributed throughout the body (depending on degree of lipid solubility of each individual agent) even in CNS and placenta.
- Metabolism: they are metabolized in the liver and concentrated in the bile due to enterohepatic circulation.
- Excretion: They are excreted unchanged, in both the kidneys (passive filtration) and feces.

ประเภ�파 Side effects of Tetracyclins:
- Metal Chelation: Tetracyclines chelate calcium, as well as $Mg^{2+}$, $Fe^{2+}$, $Al^{3+}$. so that they may cause discoloration of teeth and dysplasia of bones.
- GIT: Direct irritation to GI tract (nausea, vomiting, and anorexia)
- Photosensitivity: Tetracyclines are broken down by sunlight. Outdated, deteriorated samples can cause a Fanconi-like syndrome (renal tubular acidosis).
Chloramphenicol

- It is a broad-spectrum and Bacteriostatic Nitrobenzene Derivative antibiotic. Produced Streptomycis Venezuela.
- The mechanism of action of Chloramphenicol includes reversible binding to bacterial 50S ribosomal subunit and inhibition of protein synthesis.
- It is active against rickettsial and chlamydial infections, the majority of obligate anaerobes, most Gram-positive aerobes, and non-enteric aerobes including Actinobacillus, Bordetella, Haemophilus, Pasteurella multocida, and Mannheimia haemolytica. Enterobacteriaceae including Escherichia and Salmonella spp. are Chloramphenicol has activity against Mycoplasma and Proteus spp. but is unreliable. It is inactive against Pseudomonas spp.
- Pharmacokinetics of Chloramphenicol:
  - Absorption: Chloramphenicol is rapidly and completely absorbed from the gastrointestinal tract and is not affected by food ingestion or metal ions.
  - Distribution: Although up to 60% of Chloramphenicol is bound to serum albumin, it penetrates the brain and CSF and crosses the placental barrier.
  - Metabolism: Chloramphenicol is extensively metabolized (glucuronidated) by the liver.
  - Excretion: through the kidney by tubular secretion and glomerular filtration.
- Side effects of Chloramphenicol:
  - Anemias:
    1- Anemia (Dose-related): Chloramphenicol inhibits mitochondrial protein synthesis in RBC's in the bone marrow, causing a dose-dependent anemia.
    2- Aplastic Anemia (Idiosyncratic): Dose-independent, rare (1/40000), aplastic anemia. Usually fatal.
  - Gray-Baby Syndrome (in Human): Happens in babies because they are deficient in glucuronyl-transferase. Gray color, flaccidity, hypothermia, vomiting, shock.
  - Inhibits P450 synthesis, potentiating the effects of warfarin, phenytoin, and other drugs metabolized by P450 enzymes.
  - Diarrhea: due to Fungal Super-infections in GIT.
Macrolides

- They are broad-spectrum and Bacteriostatic antibiotics consist from a large macrocyclic lactone ring to which one or more deoxy sugars may be attached.
- The mechanism of action of Macrolides includes reversible binding to bacterial 50S ribosomal subunit and inhibition of protein synthesis.
- The macrolides include Erythromycin, Josamycin, Spiramycin, Tilmicosin, Tylosin, Clarithromycin, Azithromycin and Oleandomycin
- The macrolides are effective against a number of organisms, including Mycoplasma spp., Haemophilus influenzae, Streptococcus spp. (including S. pyogenes and S. pneumoniae), staphylococci, gonococci, Legionella pneumophila, and other Legionella spp., Clarithromycin is very active against H. influenzae, Legionella, and Mycobacterium avium-intracellulare, whereas azithromycin is superior against Branhamella, Neisseria, and H. influenzae but less active against mycobacterial species.
- Pharmacokinetics of Macrolides:
  - Absorption: Macrolides are well absorbed orally, but the problem represented by their acid lability. To solve this problem they administrated within acid resistant capsule or as an acid-resistant ester. Or given via IV or IM routes.
  - Distribution: Macrolides are well distributed through the body except the CNS.
  - Metabolism: occur in the liver.
  - Excretion: Bilary excretion.
- Side effects of Macrolides:
  - GIT: Distress, nausea, vomiting, diarrhea.
  - Hepatotoxicity: found particularly with erythromycin. May be a hypersensitivity reaction.
  - Inhibiting of P450, altering the metabolism of Digoxin and Warfarin.

Lincosamides

- They are broad-spectrum and Bacteriostatic antibiotics derived from Streptomyces lincolnensis.
Like Macrolides, Lincosamides inhibit protein synthesis in bacteria through binding to 50S ribosomal subunit of bacteria reversely.

Lincosamides group include Clindamycin, Pirlimycin and Lincomycin.

They are normally used to treat staphylococci and streptococci, and have proved useful in treating Bacteroides fragilis and some other anaerobes.

Pharmacokinetics of Lincosamides is extremely similar to that of Macrolids.

Side effects of Lincosamides:
- Hypersensitivity (rashes).
- Gastrointestinal intolerance with abdominal pain, nausea, and vomiting occurs infrequently.
- Hepatotoxicity and Bone marrow suppression has been noted.

**Bacterial Metabolism Inhibitors**

This group of antibacterials are exert their effect by inhibition of folic acid which endogenously synthesized in the bacteria, while this particularity is absent in the animals, there for they get their demands of folic acid exogenously.

Folic acid is involved in the synthesis of precursors of nucleic acids and other necessary compounds for bacterial growth and replication.

**Sulfanamides:**

Sulfanamides are a bactriostatic and synthetic antibacterials which act reversely by blocking the synthesis of folic acid.

The sulfonamides, as structural analogues, competitively block Para Amino Benzoic Acid (PABA) incorporation; sulfonamides inhibit the enzyme dihydropteroate synthase, which is necessary for PABA to be incorporated into dihydropteroic acid, an intermediate compound in the formation of folinic acid.
Antibacterial spectrum: The sulfanamides are broad-spectrum antimicrobials that are effective against gram-positive and some gram-negative organisms of the Enterobacteriaceae. There are good activity against Escherichia coli, moderate activity against Proteus mirabilis and Enterobacter spp.; poor activity against indole-positive Proteus and Klebsiella spp., and no inhibitory activity against Pseudomonas aeruginosa and Serratia spp. They are also effective against Chlamydia spp and Toxoplasma gondii and Eimeria spp.

The Sulfanamides are located in two groups they are:

1- Absorbable Sulfanamide: which divided according to the dose interval to:
   A- Short acting Sulfanamides (6 hours dose interval):
      - Sulfanamide
      - Sulfasoxazol
      - Sulfadiazine
      - Sulfamerazine
      - Sulfamethazine

   B- Intermediate Sulfanamides (12 hours dose interval):
      - Sulfamethoxazol

   C- Long acting Sulfanamides (1-2days dose interval):
      - Sulfamethoxypyridazine

   D- Extra long acting Sulfanamides (2-3 days dose interval):
      - Sulfamethylphenazole

2- Non-absorbable sulfanamides (Intestinal Sulfanamides): they are non absorbable and they used in treatment of bacterial or protozoal enteritis:
   - Sulfaguanidine
   - Succinyle sulfathiazole.

Pharmacokinetics of Sulfanamides:
   - Absorption: well oral absorbed orally (in case of absorbable sulfafanamides).
   - Distribution: well distribution including CNS.
   - Metabolism: in the liver mainly by acetylation.
   - Excretion: through the kidney.
Side effects of Sulfanamides:
- Hypersensitivity: is common and it graduates from mild rashes to severe hypersensitivity (Steven-Johnson syndrome).
- Crystal urea: Sulfanamides can precipitate in the urinary tract at acidic pH. So that we must maintain adequate hydration to prevent this side effect.
- Hemolytic anemia.
- Hepatotoxicity.

Trimethoprim

Trimethoprim is a structural analogue of the pteridine portion of dihydrofolic acid. It differs from the sulfonamides in that it acts at a second step in the folic acid synthetic pathway competitively inhibits dihydrofolate reductase. This is the enzyme that catalyzes the reduction of dihydrofolic acid to tetrahydrofolic acid, the active form of folate. Dihydrofolate reductase is present in both mammalian tissues and bacteria, but 20,000 to 60,000 times more drug is required to inhibit the mammalian enzyme; this accounts for its selective toxicity against bacteria.

Trimethoprim is bacteriostatic broad spectrum antibacterial and it is predominantly used in a combination with intermediate sulfanamides especially Sulfamethaxazol due to approximation in their $t_{1/2}$, for Trimethoprim is 11 hrs. While for Sulfamethaxazol is 10 hrs. (In veterinary medicine the combination is between Trimethoprim and short-acting Sulfanamides like Sulfadiazine because of the half life of Trimethoprim in animals is arranged 2-6 hrs.); this combination is active against most gram-positive and gram-negative organisms, especially the Enterobacteriaceae.
There is little activity against anaerobic bacteria; *Pseudomonas aeruginosa*, enterococci.

Pharmacokinetics of Trimethoprim:
- Absorption: Trimethoprim is well absorbed orally.
- Distribution: well and it can enter to the CSF in cases of inflammations.
- Metabolism: in the Liver mainly.
- Excretion: it excreted within kidney.

Side effects of Trimethoprim:
- Anti-folate effects: Megaloblastic anemia, leukopenia, granulocytopenia. These effects can result from the drug's inhibition of the mammalian dihydrofolate reductase enzyme. These side effects can be treated with folinic Acid which given as ajucant in order to prevent these side effects.

**Inhibitors of nucleic acid synthesis or function**
- This group of antibacterials acts by inhibition of nucleic acids synthesis or by interaction with their functions.

**Nitrofurans**
- They are a number of 5-nitro-2-furaldehyde derivatives, which are relatively broad-spectrum, bactericidal and synthetic antibacterials.
- The mechanism of action of Nitrofurans illustrated in that the sensitive bacteria to this group will reduce the pro-drug (nitrofuran) to active form of Nitrofuran by Nitrofuran reductase, consequently this active form will modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis).
- Nitrofurans are two types:
  - Non absorbable Nitrofurans: including; Furazalidone and Nitrofurazon
  - Absorbable Nitrofurans: including; Furaltidone and Nitrofurantoin.
- Antibacterial spectrum of Nitrofurans includes; gram-positive (including *Staphylococcus Spp.*), and gram-negative like *Salmonella spp.*, coliforms, also *Mycoplasma spp.*, *Eimeria spp.*, and some other protozoa.
Pharmacokinetics of Nitrofurans:
- Absorption: well and rapidly absorbed orally (For absorbable Nitrofurans).
- Distribution: Nitrofurans have low distribution because they are metabolized rapidly.
- Metabolism and Excretion: Nitrofurans have a rapid metabolism followed by rapid excretion too via kidney.

Side effects of Nitrofurans:
- GIT disturbances.
- Hepatotoxicity.
- Hemolytic anemia.

Rifampicin:
- Rifampicin is a broad spectrum and bactericidal antibiotic derived from Streptomycis Spp.
- It acts by inhibition of RNA synthesis
- The ability of Rifampicin to penetrate into cells makes it an ideal drug for treating intracellular infections. It is used in the treatment of tuberculosis in humans and has been suggested for use in treating atypical mycobacterial infections in cats. Rifampicin is frequently used in combination with erythromycin for the treatment of some pneumonic conditions in foals, particularly those caused by Rhodococcus equi infection.

Pharmacokinetics of Rifampicin:
- Absorption: Adequate absorption from the GIT.
- Distribution: adequate levels are attained in the CSF.
- Metabolism: by liver and the drug undergoes the enterohepatic circulation.
- Excretion: through bile also through kidney too.

Side effects of Rifampicin:
- Enzyme induction: Rifampicin induces P450 in the liver and increases the metabolism of many drugs like Anticonvulsants and anticoagulants.
- GIT disturbances.
Fluroquinolones

- They are broad spectrum, bactericidal and synthetic (4-quinolone) antibacterials.
- Fluroquinolones inhibit DNA replication by inhibiting of DNA gyrase (is an enzyme that unwinds DNA).
- Fluroquinolones are classified in to four generations according to their antibacterial spectrum:
  1- 1st generation: including Nalidixic acid and Cinoxacin: this generation is active against gram-negatives rods.
  2- 2nd generation: including Norfloxacin, Ciprofloxacin, Ofloxacin, Enrofloxacin, and Lomefloxacin: this generation is active against gram-positive cocci, gram-negative rods, Chlamydia and Mycoplasma.
  3- 3rd generation: including Levofloxacin, Sparfloxacin, Gatifloxacin: this generation has a similar antibacterial activity of the 2nd generation
  4- 4th generation: including Trovafloxacin and Moxifloxacin: this generation posses an antibacterial effect against gram-positive cocci, gram positive bacilli, gram-negative rods and anaerobic microorganisms.

- Pharmacokinetics of Fluroquinolones:
  - Absorption: the Fluroquinilones are rapidly and completely absorbed after oral administration in all species.
  - Distribution: they are widely distributed among all the body.
  - Metabolism: in the liver by oxidation.
  - Excretion: via kidney by glomerular filtration and tubular secretion.

- Side effects of Fluroquinolones:
  - GIT disturbances.
  - Inhibition of articular cartilages growth: Fluroquinolones may inhibit the growth of articular cartilage and therefore should not be administered to growing dogs or cats.
  - Xanthines toxicity: Fluroquinolones inhibit the excecration of Xanthines thereby increasing their toxicity.
Metronidazole

- It is a Bactericidal, antibacterial and antiprotozoal agent; works by disrupting DNA and nucleic acid synthesis.
- Metronidazole has activity against most obligate anaerobes including Bacteroides sp. (including B. fragilis), Fusobacterium, Veillonella, Clostridium sp., peptococcus, and peptostreptococcus. Metronidazole is also Trichomonacidal and Amebicidal in action. It has therapeutic activity against Entamoeba histolytica, Trichomonas, Giardia, and Balantidium coli.
- Pharmacokinetics of Metronidazole: Metronidazole is relatively well absorbed after oral administration, with good distribution even in the CNS, metabolized in the liver and excreted within urine and feces.
- Side effects of Metronidazole:
  - Neurologic disorders.
  - GIT disturbances.
  - Hematuria.

Basis of Antibacterial combinations:

Although in principle the use of antibacterial mixtures is not recommended, in some cases antibacterials may be used in combination for the following causes:

- To treat mixed infections.
- Prevention of resistance.
- Reducing toxicity.
- For empiric purposes.

Types of Antibacterial combinations are:

1- Synergistic combination: this type of combination happens when the antibacterials in combination exert a greater antibacterial effect than either one alone. \(1 + 1 > 2\)

Examples:-

- Penicillins + Aminoglycosides.
- Amoxicillin + Clavulanic acid.
- Sulfa + Trimethoprim.
2- Additive combination: this type of combination occurs when the antibacterials in combination exert an equal antibacterial effect for each one of them alone. \(1 + 1 = 2\).

Examples:
- Sulfa + Tetracyclines
- Amoxicillin + Metronidazole.

3- Antagonistic combination: this type of combination occurs when the antibacterials in combination exert a lesser effect than each antibacterial acting alone. \(1 + 1 < 2 = 0\)

Examples:
- penicillin + Tetracyclines
- Penicillin + Sulfa
- Macrolides + Chloramphenicol.
- Aminoglycosides + Tetracyclines.

Bacterial resistance to chemotherapy:

- Antibiotic resistance is the ability of a microorganism to withstand the effects of antibiotics. It is a specific type of drug resistance.
- Antibiotic resistance develops via mutations, adaptation or gene transfer.
- This resistance may be natural or acquired (Permanent or temporary).

Mechanisms of bacterial resistance to antibacterials:

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1- Drug inactivation or modification: e.g. enzymatic deactivation of Penicillin G in some penicillin-resistant bacteria through the production of \(\beta\)-lactamases.

2- Alteration of target site: e.g. alteration of Protein (the binding target site of penicillins) in some resistant Staphylococcus aureus and other penicillin-resistant bacteria.

3- Alteration of metabolic pathway: e.g. some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides. Instead, like mammalian cells, they turn to utilizing preformed folic acid.

4- Reduced drug accumulation: by decreasing drug permeability and/or increasing active efflux (pumping out) of the drugs across the cell surface.
Reasons of treatment failure with antibacterials:

1- Incorrect diagnosis.
2- Improper dose.
3- Inadequate course of treatment.
4- Bacterial resistance.
5- Presence of super-infections.

**Antifungals**

Antifungals are chemicals used to treat diseases caused by fungi (mold or yeast)

- Some fungal diseases are superficial (Ringworm); others are systemic (Blastomycosis: a fungal infection caused by the organism Blastomyces dermatitidis.)
- Categories of antifungals include:

1- Polyene antifungals: Work by binding to the fungal cell membrane. Examples:
   - Nystatin: used orally for Candida albicans infections).
   - Amphotericin B:
     - Used IV for systemic mycoses.
     - Amphotericin B is extremely nephrotoxic, is light sensitive, and can precipitate out of solution.

2- Imidazole antifungals: Work by causing leakage of the fungal cell membrane. Examples:
   - Ketoconazole: used for superficial infections.
   - Miconazole: used for superficial infections.
   - Itraconazole: used for superficial and systemic infections.
   - Fluconazole: used for systemic and sometimes superficial infections.

3- Antimetabolic antifungals: Work by interfering with the metabolism of RNA and proteins. Example:
   - Flucytosine: usually used in combination with other antifungals.

4- Superficial antifungals: Work by disrupting fungal cell division, example:
   - Griseofulvin: an oral medication used to treat dermatophyte infections (Ring worm).

5- Other antifungals:
   - Lufenuron: is used to treat ringworm in cats.
Lyme sulfur: is used topically to treat ringworm.

**Anti-protozoal Drugs**

- They are a class of pharmaceuticals used in treatment of protozoal infections.
- In our lecture we will focus on the main anti-protozoal agents which used in veterinary practice.

**Anticoccidial drugs:** This group of antiprotozoals is used for treatment or prophylaxis or both against coccidial infections which caused by *Eimeria* Spp.

**Groups of Anticoccidial agents:**

**A- Miscellaneous Anticoccidial agents:**

**Sulfanomides:**
- Sulfanomides are active against schizonts.
- They are coccidiostatic at low doses and coccidiocidal at higher doses.
- Examples; Sulfanomide, Sulfaquinoxaline and Sulfadimethoxin.

**Nitrofurans:**
- Used for prophylaxis
- They are active against *Eimeria* and *Histomonas*.
- Examples; Furazolidone and Nitrofurazone.

**Amprolium:**
- A structural analogue of thiamine (vitamin B₁) competitively inhibits thiamine utilization by the coccidia.
- It acts primarily upon the first generation schizont in the cells of the intestinal wall, preventing differentiation of the metrozoites. It may also suppress the sexual stages and sporulation of the oocysts.

**Toltrazuril:**
- Toltrazuril (Baycox®) damages all intracellular development stages of *Eimeria*.
- It acts against all species of *Eimeria* and it is coccidiocidal.

**B- Ionophore antibiotics:**
- The mechanism of action of this group is illustrated by forming complexes with cations such as: Li⁺, Na⁺, K⁺, Mg²⁺ and Ca²⁺, then this Ionophores carrying these cations to inside of the schizont, thereby effect on the ionic balance of the schizont, consequently rupture of the schizont.
- Ionophores allow birds to develop immunity to *Eimeria* (Immune modulators).
- Examples: Monensin, Narasin, Salinomycin, Maduramicin, Semduramicin and Lasalocid.

C- 4 - Hydroxyquinolones:
- This group acts by disruption of mitochondrial cytochrome system of coccidia in the sporozoite stage.
- Examples: Clopidol, Decoquinate, and Methylbenzoquate.

**Antibabsial drugs**: a group of drugs are used to treat Babesia Spp. Infections.

*Imidocarb and Amicarbalide:*
- Is effective against Babesia spp. infection. It is a cholinesterase inhibitor. It appears to act directly on the protozoa leading to an alteration in morphology.

*Diminazene (Berenil®):*
- Acts by interfering with glycolysis as well as with DNA synthesis of Babesia.

*Quinuronium Sulfate (Acaprin®):*
- Its mode of action is unclear yet.
- It has a low therapeutic index and may stimulate parasympathetic nervous system (excessive salivation, frequent urination, or dyspnea caused by anticholinesterase activity.

**Antitheileriosis**: a group of drugs are used to treat Theileria Spp. Infections.

*Chlortetracycline and Oxytetracycline:*
- They are used for prophylaxis and may reduce parasitaemia by arresting schizogony.

*Hydroxynapthoquinones:*
- They are used for the treatment of theileriosis in cattle.
- Napthoquinones are thought to interfere with protozoan mitochondria.
- Examples; Buparvaquone (Butalex®) and Parvaquone (Parvexon®).

**Antitrypanosomal drugs**: a group of drugs are used to treat Trypanosoma Spp. Infections.

*Diminazene and Isometamidium:*
- These drugs appear to bind to parasite DNA and block DNA and RNA synthesis.
- They are may be used therapeutically, or for prophylaxis, or both.
Suramin:
- The mechanism of action is not clear but it thought that it acts by inhibition of many enzymes in the protozoa.
- Suramin is not absorbed orally; therefore it administrated parenterally through I.V. route only because it’s irritating nature when given through I.M. or S\C. routes.

Isometamidium chloride (Samorin®) and Homidium:
- They act by interaction with protozoal DNA activities.

Antitoxoplasmosis drugs: a group of drugs are used to treat Toxoplasma Spp. Infections.
- Sulfanomide and Trimethoprim.
- Clindamycin and Clarithromycin.

Antitrichomonal drugs: a group of drugs are used to treat Trichomonas Spp. Infections.
- Nitroimidazole derivatives:
  - They act by interaction with protozoal DNA activities.
  - Examples; Metronidazole, Ronidazole, and Carnidazole.

Antihistomoniasis drugs: a group of drugs are used to treat Histomonas Spp. Infections.
- Dimetridazole:
  - It is one of the Nitroimidazoles and it appears to interfere with RNA synthesis.
  - Also it can be used as Antitrichomonal agent too.

**Drugs used in the treatment and control of Parasitic Infections**

In this section we shall talk about the most common drugs which used for treatment of parasitic infections which either Endoparasites or Ectoparasites.

I- Drugs used in the treatment and control of Endoparasites

A. Drugs for round worms (Anti-nematodes):
This group is used for treatment of Nematodes and the main used drug groups for this purpose are:
Avermectins and Milbemycins
- Natural or semi-synthetic agents derived from Streptomyces avermitilis and Streptomyces cyanogriseus.
- Mechanism of action includes interfering with parasite nerve transmission.
- They are effective against a wide range of nematode species and developmental stages, but have no activity against trematodes or cestodes.
- In addition to killing an existing parasite population, the Avermectins and Milbemycins prevent re-infection for a period after treatment.
- Avermectins include Abamectin, Doramectin, Eprinomectin, Ivermectin, and Selamectin. Milbemycins include Milbemycin oxime and Moxidectin.

Benzimidazoles:
- They interrupt parasite energy metabolism.
- Most Benzimidazoles are effective against larval and adult roundworms.
- All Benzimidazoles are contraindicated in case of pregnancy because of their ability to penetrate the blood-placental barrier; consequently they cause teratogenic problems.
- Examples; Albendazole, Fenbendazole, Flubendazole, Mebendazole, Oxfendazole, Oxibendazole and Tiabendazole.

Imidazothiazoles:
- They act by interfering with parasite nerve transmission causing muscular spasm and rapid expulsion.
- Levamisole is the active isomer of Tetramisole and is therefore more potent and has a wider safety margin.

Organophosphorus compounds (OPC):
- They act by inhibiting cholinesterase thereby interfering with neuromuscular transmission in the parasite.
- They are effective against adult gastro-intestinal roundworms but ineffective against migrating larvae, tapeworms, or flukes.
- Clinical signs of toxicity such as salivation and diarrhea may occasionally occur, particularly in foals.
- Examples; Haloxon, Dichlorvos, Naftalofos, and Metrifonate.
Tetrahydropyrimidines:
- They interfere with parasitic nerve transmission as cholinergic stimulants, leading to neuromuscular spastic paralysis. This mode of action is similar to that of the Imidazothiazoles.
- Examples: Morantel, Oxantel, and Pyrantel

Piperazine:
- It modifies neurotransmission in parasites causing expulsion of the parasite.
- Piperazine is used for treatment of some gastro-intestinal roundworms such as Toxocara and Uncinaria in dogs and cats.

Diethylcarbamazine:
- The mechanism of action of this drug is similar to Piprazine.
- Is active against adult ascarids but is more frequently used as a heartworm prophylactic.

B. Drugs for tapeworms (Anti-cestodes):
This group is used for treatment of Cestodes and the main used drug groups for this purpose are:

Praziquantel:
- It acts by increasing ion influx across the parasite tegument leading to immediate muscle spasm.
- Praziquantel is effective against all tapeworms in dogs and cats and is preferred in most Echinococcus control programmes.
- Also it is active against Moniezia in sheep and against Anoplocephala and Anoplocephaloides in horses.

Niclosamide:
- It acts by interfering with adenosine triphosphate (ATP) production.
- It has a little efficacy against Echinococcus and variable activity against Dipylidium.

Benzimidazoles:
- Albendazole, Fenbendazole, Mebendazole, and Oxfendazole are effective for tapeworm control in ruminants. Fenbendazole and Mebendazole also control some tapeworms in dogs and cats.
C. Drugs for flukes (Anti-trematodes):

This group is used for treatment of Trematodes and the main used drug groups for this purpose are:

**Benzimidazoles:**
- Albendazole and Netobimin are active against Fasciola, they are effective against adult stages. Netobimin is also effective against adult Dicrocoelium dendriticum. Triclabendazole is highly effective against all liver stages of Fasciola.

**Clorsulon:**
- It is a Sulfonamide and competitive inhibitor of important enzymes for energy metabolism in flukes.
- It is used in cattle for control of liver flukes.

**Oxyclozanide and Rafoxanide:**
- They act by interfering with adenosine triphosphate (ATP) production.
- Oxyclozanide is mainly active against adult flukes. While Rafoxanide is active against adult and immature flukes aged 6 - 8 weeks and older.

II- Drugs used in the treatment and control of Ectoparasites

The most common ectoparasiticides that used in veterinary practice are:-

**Amidines\ Topical**
- They act by increasing of the nervous activity in the ectoparasite.
- They active against lice, mites, and ticks on cattle; lice, and ticks on sheep; lice and mites on pigs; Demodex and Sarcoptes on dogs.
- Side effects include CNS depression.
- Example; Amitraz.

**Avermectins and Milbemycins\ Parenteral**
- Discussed previously, see the section of Anti-nematodal drugs.
- They are active against a wide range of immature and mature nematodes and arthropods among all animal species approximately.

**Carbamates\ Topical.**
- They are reversible acetylcholine esterase (AchÊ) inhibitors in the ectoparasite.
- They are indicated for Fleas on dogs, cats and birds.
- The main side effect is the carcinogenicity.
- Examples: Bendiocarb, Carbaril, and Propoxur.

Neonicotinoids:
- They bind to the nicotinic receptors in the ectoparasite leading to paralysis and death of that ectoparasite.
- They are indicated for Fleas on dogs, cats, and rabbits.
- Side effects include transient salivation in the topical forms of Neonicotinoids and pruritis in the entral forms of them.
- Examples; Imidacloprid (topical) and Nitenpyram (ental).

Organophosphorus compounds (OPC)
Topical:
- They are irreversible acetylcholine esterase (AchE) inhibitors in the ectoparasite.
- Most members of this group are indicated for scab, flies larvae, lice, and ticks.
- The main side effect of this group is its irreversible acetylcholine esterase (AchE) inhibitory effect on the host.
- Examples; Azamethiphos, Chlorpyrifos, Clofenvinfos, Coumafos, Dichlorvos, Dimpylate (Diazinon), Ethion, Fenitrothion, Heptenophos, Malathion, Metrifonate, Phoxim, Propetamphos, Temefos, and Tetrachlorvinphos.

Phenylpyrazoles
Topical
- They act by blocking of GABA resulting in rapid death of the ectoparasite.
- They indicated for fleas, lice, mange and ticks.
- Side effects include transient hypersalivation.
- Example; Fipronil.

Pyrethrins and synthetic pyrethroids
Topical
- They exert their action on the sodium channels of parasite nerve axons, causing initial excitement then paralysis.
- Most members of this group are indicated for Flies on horses and cattle; lice on horses, cattle and goats; flies strike, biting lice, ticks, headflies, and Psoroptes (dip) on sheep; red mites on poultry.
- Side effects include: Minor signs of discomfort with some cattle up to 48 hours after treatment; rarely skin lesions and hair loss in dogs; rarely uncoordinated
movements, tremor, hypersalivation, vomiting, rigidity of hindquarters in dogs if chew collar.

- Examples; Natural Pyrethrins extracted from pyrethrum flowers and the synthetic pyrethroids Bioallethrin, Cyhalothrin, Cypermethrin, Deltamethrin, Fenvalerate, Flumethrin, Lambdacyhalothrin, Phenthothrin, and Permethrin
Veterinary Toxicology

Definitions

- **Toxicology**: Is that branch of pharmacology which deals with the undesirable effects of chemicals (poisons) or toxins on living systems. Or the studying of the nature, effects, and detection of poisons and the treatment of poison.
- **Veterinary toxicology**: Is the diagnosis and treatment of poisoning in animals other than humans, particularly livestock and companion animals, but not excluding undomesticated species. Other important concerns of veterinary toxicology are the possible transmission of toxins to the human population in meat, fish, milk, and other foodstuffs and the care and ethical treatment of experimental animals.
- **Poison (toxicant)**: A poison (toxicant) is any substance that causes a harmful effect when administered to a living organism.
- **Toxin**: A toxicant produced by a living organism. Toxin should never be used as a synonym for toxicant.
- **Toxicant**: An agent capable of causing toxicity.
- **Xenobiotics**: Foreign, natural, or man-made (synthetic) chemicals, including drugs, pesticides, environmental, and industrial agents.
- **Hazard**: An agent or situation capable of causing a toxic effect or harm to the organism.
- **Pollution**: A contamination of soil, water, food, or the atmosphere by the discharge or admixture of poisonous materials.
- **Pollutant**: Is any chemical or substance contamination the environment and contributing to pollution.
- **LD₅₀ (Lethal-Dose-50)**: It’s the dose of a chemical that kills 50% of population.
- **Teratogen**: Any substance capable of causing malformation during development of the fetus.
- **Carcinogen**: Any substance that causes cancer.
- **Mutagen**: Any substance that causes alterations in cellular DNA.
- **Therapeutic Index (TI)**: The ratio of median lethal dose to median effective dose. ($\frac{LD_{50}}{ED_{50}}$). 

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• **Margin of safety:** The ratio of the dosage required to kill 1% of population, compared to the dosage that is effective in 99% of population.

**Specialized Areas Of Toxicology:**

- **Clinical toxicology:** is the diagnosis and treatment of human or animal poisoning.
- **Forensic toxicology:** The medical aspects of the diagnosis and treatment of poisoning and the legal aspects of the relationships between exposure to and harmful effects of a chemical substance. It is concerned with both intentional and accidental exposures to chemicals.
- **Environmental toxicology:** This is concerned with the movement of toxicants and their metabolites in the environment and in food chains and the effect of such toxicants on populations of organisms. This understood is involving the Industrial toxicology, as a specified area from environmental toxicology.
- **Biochemical and molecular toxicology:** consider events at the biochemical and molecular levels, including enzymes that metabolize xenobiotics, generation of reactive intermediates, interaction of xenobiotics or their metabolites with macromolecules, gene expression in metabolism and modes of action, and signaling pathways in toxic action.

**Classification of toxic agents:**

Toxic agents are classified according to:

1. **Target organs** (liver, kidney, hematopoietic system, etc.).
2. **Use** (pesticide, solvent, food additive, etc.).
3. **Source** (animal and plant toxins).
4. **Effects** (cancer, mutation, liver injury, etc.).
5. **Physical state** (gas, dust, liquid),
6. **Chemical stability or reactivity** (explosive, flammable, oxidizer)
7. **General chemical structure** (aromatic amine, halogenated hydrocarbon, etc.).
8. **Poisoning potential** (extremely toxic, very toxic, slightly toxic, etc.).
9. **Basis of biochemical mechanisms of action** (e.g., alkylating agent, cholinesterase inhibitor, methemoglobin producer).
Ranks (types or degrees) of toxicity:
We can rank the toxicity according to the dose frequency and term of exposure to the following:

1- **Acute toxicity:** It’s the toxicity produced by a chemical when it is administered in one dose during a period not exceeding 24 hours.

2- **Subacute toxicity:** It’s the toxicity produced by a chemical when it is administered in repeated doses during a period less than one month.

3- **Subchronic toxicity:** It’s the toxicity produced by a chemical when it is administered in repeated doses during a period less than three months.

4- **Chronic toxicity:** It’s the toxicity produced by a chemical when it is administered in repeated and small doses during a period more than three months.

**Factors Affecting Toxicity**

1. **Rate of entry and route of exposure:** that is, how fast the toxic dose is delivered and by what means.

2. **Age** can affect the capacity to repair tissue damaged.

3. **Previous exposure** can lead to tolerance, increased sensitivity, or make no difference.

4. **State of health, medications and physical condition** can affect the toxic response.

5. **Pre-existing disease** can result in increased sensitivity.

6. **Environmental factors,** such as temperature and pressure.

7. **Host factors,** including genetic predisposition and the sex of the exposed individual.

**Steps of poisoning treatment**

1- **Clinical stabilization:** by maintaining the airway, breathing and circulation.

2- **Clinical Evaluation of the poisoned state:** by knowledge of the case history of the state, then doing the requested laboratory examinations.

3- **Prevention of further poison absorption:** by removing the suspected poisonous material away from the state (man or animal) also by emptying the gastro-intestinal tract by emetics or purgatives.
4- Enhancement of poison elimination: by alkanalization of the urine, hemodialysis, hemoperfusion, hemofiltration, plasma exchange or exchange transfusion, and serial oral activated charcoal.

5- Using of antidotes in poisoning: The antidotes render poisons harmless once they have been absorbed in to the body. There are not too many specific anti-dotes. The various available antidotes and their mechanisms of action are listed below:

Mechanism 1. Antidote complexes with poison rendering it inert. Examples are the heavy metals which are chelated by EDTA, and arsenic which complexes with dimercaprol (BAL).

Mechanism 2. Antidote accelerates biotransformation of toxicant to a nontoxic product.
For example, antidotes nitrite and thiosulfate complex with cyanide to form cyanmethemoglobin and thiocyanate, respectively. Thiocyanate is 200 times less toxic than cyanide.

Mechanism 3. Antidote blocks formation of a toxic metabolite from a less toxic parent compound. Conversion of methanol to formic acid, and ethylene glycol to oxalic acid, respectively, by alcohol dehydrogenase is blocked by ethanol as an antidote.

Mechanism 4. Antidote specifically accelerate the excretion of toxicant. The presence of chloride in bromide poisoning or calcium in strontium poisoning aids in rapid elimination of the toxicants bromide and strontium, respectively.

Mechanism 5. Antidote compete with toxicant for essential receptors. For example, vitamin K competes with coumarin anticoagulants (e.g., warfarin) for receptors involved in formation of prothrombin.

Mechanism 6. Antidote blocks receptors that are responsible for toxic effect. Example includes organophosphate poisoning treated with atropine as an antidote.

Mechanism 7. Antidote restores normal function by repairing or bypassing effect of poison. This mechanism is illustrated by the use of methylene blue in the treatment of nitrite poisoning.

6- Supportive treatment of the poisoned state: by maintaining of the vital functions of the body working until the antidote neutralizes the poisonous effect.
Metals toxicity

Lead poisoning

Lead is a bluish white to gray heavy metal that was probably the first toxic element recognized by man and yet still has great relevance today.

Sources of lead toxicity:

- The main sources of lead are the gasoline, paints, construction materials and many other products.
- Additional sources of lead have included lead weights (e.g. for fishing or curtains), small lead trinkets and toys, lead shot and bullets for weapons, lead arsenate pesticides and many other products.

Clinical signs:

Clinical signs of lead toxicosis vary with the species involved, duration of exposure and amount of lead absorbed, and we can summarize them in:

- Gastrointestinal signs: Abdominal pain and diarrhea can be common clinical signs in animal exposed to excess lead. Anorexia is common as well as vomiting in those species that are able.
- Neurological signs: They including depression, weakness and ataxia can progress to more severe clinical signs of muscle tremors or fasciculations, head pressing (especially in ruminants), blindness, seizure-like activity and death.
- Hematological signs: Anemia and stippling of erythrocytes.

Treatment:

In addition to the general treatment steps that listed previously, the antidote of choice in case of lead poisoning are the chelator agents like calcium disodium Ethylene-Diamine-Tetra-Acetic acid (Ca EDTA), Dimercaprol or British anti-lewisite (BAL) and Succimer (meso-2, 3-dimercaptosuccinic or DM SA).

Arsenic poisoning

Arsenic is a yellow to grayish black metalloid; frequently it is referred to as arsenic metal and is classified for many toxicological purposes as a metal.
Sources of Arsenic toxicity:
Arsenic is used as preparations from insecticides for animal to wood preservatives, herbicides and even has some medicinal uses.

Clinical signs:
Arsenic is available in two forms: Inorganic and Organic each form of them has two valents: Arsenic trivalent and Arsenic pentavalent and the severity of their toxicity are illustrated in this scheme:

\[(\text{Inorganic As}^{+3} > \text{Inorganic As}^{+5} > \text{Organic As}^{+3} > \text{Organic As}^{+5})\]

- Clinical signs of Trivalent arsenate poisoning: Abdominal pain or colic, vomiting, a staggering gait and weakness, clear incoordination, rapid weak pulse and shock, diarrhea, followed collapse, and death. In case of high exposure death will occur directly within few minutes to hours.

- Clinical signs of Pentavalent arsenate poisoning: Poisoning occurs within 3 days of a high dose or after chronic exposure. Most noticeable are the neurological signs. The animal is generally bright and alert but uncoordinated. The animal may or may not be blind, and these animals may have erythema in the skin. Some of the neurological damage may be reversible unless the nerves are damaged.

Treatment:
By following the general steps of treatment and administration of Dimercaprol British anti-lewisite (BAL).

Mercury poisoning

Mercury is a naturally occurring element that is found in the environment. It exists in several forms, such as elemental (metallic), inorganic, and organic.

Sources of Mercury toxicity:
Metallic mercury in a pure form looks like a shiny-white liquid substance at room temperature. It is commonly used in thermometers, barometers, blood pressure devices, batteries, electric switches, dental fillings (amalgams), etc. Inorganic mercury compounds, or mercury salts, occur when it combines with other elements, such as chlorine, sulfur, and oxygen. Most of these compounds are white, except mercuric sulfide or cinnabar ore (i.e. red, but it turns black after exposure to light). Some of mercury
compounds are used as fungicides, while others are used for medicinal purposes, e.g. laxatives, deworming agents, antiseptics, and disinfectants.

Clinical signs:

Ø In cattle include ataxia, neuromuscular incoordination, and renal failure, followed by convulsions and a moribund state. Average time from ingestion to death is reported to be about 20 days.

Ø In horses, signs of acute toxicity include severe gastroenteritis and nephritis. In chronic cases, signs may include neurological dysfunction, laminitis, in addition to renal disease which is characterized by glycosuria, proteinuria, phosphaturia, reduced urine osmolarity, reduced glomerular filtration rate, azotemia, and elevated creatinine and blood urea nitrogen.

Ø In sheep, the poisoning is characterized by severe neurological symptoms, and tetraplegia.

Treatment:

By following the general steps of treatment and administration of Dimercaprol British anti-lewisite (BAL).

Cadmium poisoning

Cadmium is a soft, malleable, ductile, toxic, bluish-white bivalent metal. It is similar in many respects to zinc but forms more complex compounds.

Sources of Cadmium toxicity:

Numerous compounds are formed from cadmium and thus it is used in batteries, solders, semiconductors, solar cells, plastics stabilizers, and to plate iron and steel. All soil and rocks contain some cadmium. It can enter the environment from zinc smelting and refining, coal combustion, mine wastes, iron and steel production and from the use of rock phosphate and sewage sludge as fertilizers.

Clinical signs:

Irritation, diarrhea, renal dysfunction and osteomalacia with osteoporosis. chronic cadmium exposure involved renal tubular damage with proteinuria, Other chronic effects can include liver damage, emphysema (through inhalation), osteomalacia, neurological impairment, testicular, pancreatic, adrenal damage, and anemia.
Treatment:
By following the general steps of treatment and administration of Calcium disodium Ethylene-Diamine-Tetra-Acetic acid (Ca EDTA).

Thallium poisoning

It is a highly toxic soft gray malleable poor metal resembles Tin but discolors when exposed to air.

Sources of Thallium toxicity:
Approximately 60-70% of thallium is used in the electronics industry, and the rest is used in the pharmaceutical industry and in glass manufacturing. It is also used in infrared detectors. Because of its high toxicity it used as pesticide and insecticide, but its uses has been reduced or banned in many countries.

Clinical signs:
The diagnosis of thallium poisoning may be difficult, because it is often unsuspected. The cardinal features are gastroenteritis, peripheral neuropathy due to CNS necrosis, and then later, alopecia.

Treatment:
By following the general steps of treatment and administration of chelator agents like calcium disodium Ethylene-Diamine-Tetra-Acetic acid (Ca EDTA), Dimercaprol or British anti-lewisite (BAL), Dithiazone and Prussian blue.

Sulfur Poisoning

It is an abundant multivalent non-metal element. Sulfur, in its native form, is a yellow crystalline solid. In nature, it can be found as the pure element and as sulfide and sulfate minerals. It is an essential element for life and is found in two amino acids, cysteine and methionine.

Sources of Sulfur toxicity:
Sulfur is presented in sulfuric acid, fertilizers, pigments, dyes, drugs, explosives, rubber, insecticides, and detergents, as well as many inorganic salts and esters. Although uniformly found in nature, industrialized countries are the largest users of sulfur materials.
Clinical signs:
The clinical signs of sulfur toxicity are depend on the term, route of exposure and the species of animal. The main clinical manifestations are: Abdominal pain, colic, rumen stasis, fetid diarrhea, dehydration, metabolic acidosis, tachypnea, recumbency, and hydrogen sulfide smell are expected clinical signs. Irritation, edema, and hemorrhage of the gastrointestinal tract and respiratory tract should be expected. In addition, renal tubular necrosis can be seen.

Treatment:
By following the general steps of treatment and administration of Nitrite in cases of acute and sub acute poisoning with sulfur to get rid from harmful effect of hydrogen sulfide by induction of methemoglobinemia with nitrite to allow for the formation of sulfmethemoglobin as same mechanism of cyanide poisoning treatment.

Phosphorus poisoning
A multivalent and nonmetal element found in inorganic phosphate rocks. Due to its high reactivity, phosphorus is never found as a free element in nature on Earth. Phosphorus is a component of DNA, RNA, ATP, and also the phospholipids which form all cell membranes. It is thus an essential element for all living cells.

Sources of Phosphorus toxicity:
The most important commercial use of Phosphorus -based chemicals is the production of fertilizers. Phosphorus compounds are also widely used in explosives, nerve agents, friction matches, fireworks, rodenticides, toothpaste and detergents.

Clinical signs:
Phosphorus, in the form of white or yellow phosphorous, has historically been used as a rodenticide but is uncommon today. Initial clinical signs following ingestion would include gastroenteritis with vomiting and diarrhea. If the animal survived several days it would often develop a secondary phase of severe liver damage with renal insult also occurring.

Treatment:
Till this time there are no determined or suggested antidote for phosphorus poisoning, but the administration of calcium to correct the normal ratio of Ca : P (2:1) in the body is may be possible in addition to follow the general steps of toxicity treatment.
Organic Toxicants

In this lecture we will discuss a group of selected and important toxicants in the veterinary field like:-

Organic Phosphorus Compounds (OPC) and Carbamates (CMs)

Organophosphates (OPC) and carbamates (CMs) are commonly used as pesticides in agriculture, industry, and around the home/garden throughout the world. In addition, these chemicals are used as parasiticides in veterinary medicine. Both types of chemicals produce their toxicity by virtue of inhibition of acetylcholinesterase (AChE) enzyme, which terminates the action of the neurotransmitter acetylcholine (ACh) at the synapses in nervous tissue and at the neuromuscular junctions. These chemicals are referred to as “Anticholinesterases”. Some of the OPC with strong AChE inhibiting potential are also used as nerve agents or nerve gases.

Clinical signs of toxicity:

Most animal poisoning cases in the field are acute in nature. Onset of clinical signs usually occurs within 15 min to 1 h, which is soon followed by the signs of maximal severity, although these timings tend to vary depending upon the compound and its dose, and species.

The clinical signs can be classified as:-

1- **Muscarinic**: Muscarinic receptor-associated effects are manifested by vomiting, abdominal and chest pain, salivation, lacrimation, urination, diarrhea (SLUD), miosis (pinpoint pupils), tracheobronchial secretion, lung edema, and cyanosis.

2- **Nicotinic**: The nicotinic receptor-associated effects are produced on autonomic ganglia and skeletal muscles, and the affected animals show twitching of muscles, tremors, followed by convulsions, and seizures. This condition may lead to paralysis.

3- **Central**: Central effects include apprehension, stimulation, followed by depression. The affected animals may also show restlessness, ataxia, stiffness of the neck, and coma. Death occurs due to respiratory failure and cardiac arrest.

Treatment:

1- **Organic Phosphorus Compounds**: In the case of OP poisoning, antidotal treatment requires the combined use of Atropine sulfate and pyridine-2- aldoxime
methochloride (2-PAM). Atropine will block the effect of acetylcholine while 2-PAM will reactivate the Acetylcholinestrase (AchE) enzyme.

2- Carbamates: administration of Atropine only because that the 2-PAM and other oximes are ineffective in carbamates poisoning cases.

**Pyrethrins and pyrethroids**

- Pyrethrins are the insecticidal compounds obtained from the flowers of the plant *Tanacetum cinerariaefolium*, also called *Chrysanthemum cinerariaefolium* or *Pyrethrum cinerariaefolium*. While Pyrethroids are synthetic analogs of pyrethrins.
- Pyrethrins cause hyperexcitability with very little cytotoxicity. The molecular targets of the pyrethrins and pyrethroids are similar in mammals and insects and include voltage sodium, chloride, and calcium ion channels, gamma-aminobutyric acid (GABA)-gated chloride channels, nicotinic receptors, membrane depolarization, and intercellular gap junctions.
- Mammals are less susceptible to pyrethrin and pyrethroid toxicoses than insects primarily because they have a faster metabolic clearance, higher body temperatures, and a lower affinity for the pyrethrins/pyrethroids.

**Clinical signs of toxicity:**

Clinical signs that result from the toxicity with these compounds can be confused with poisoning by other pesticides, such as organophosphates.

Clinical signs include salivation, vomiting, hyperexcitability, tremors, seizures, dyspnea, weakness, prostration, and death.

**Treatment:**

There is no specific antidote for pyrethroid toxicity, animals should be treated symptomatically. In addition to the general steps of toxicity treatment, Supportive therapy by using Diazepam or Barbiturates to control hyperexcitability or seizures can be used. Atropine can be used to control excess salivation or gastrointestinal hypermotility.

**Organochlorines**

- Chlorinated compounds, cyclodienes such as aldrin and dieldrin, *Dichlorodiphenyltrichloroethane* (DDT), Kepone, Chlordecone and Chlordane used as insecticides, became available for use in the 1940’s.
**Organochlorins are exert their toxicity through two mechanisms:**

1. Some Organochlorines alter the action potential of the neuron.
2. Another group of these chemicals act by inhibiting GABA association with its postsynaptic receptors.

**Clinical signs of toxicity:**

**Acute Toxicity:** Initially nausea and vomiting; then weakness, paresthesias, tremor, clonus, seizures, fever; seizure activity, respiratory paralysis, respiratory arrest and death.

**Chronic Toxicity:** Chlordane causes leukemia and thrombotic thrombocytopenic purpura (TTP); Chlordecone causes pseudotumor cerebri and male infertility.

**Treatment:**

In addition to the general step of poisoning treatment and for control the seizures we can use Dextrose and Thiamine or Benzodiazepines or Phenobarbital.

**Cyanogenic plants and Cyanide Poisoning**

- Cyanide, hydrocyanic acid, hydrogen cyanide (HCN) and prussic acid are all terms relating to the same toxic principle. Cyanide is used as a fumigant and in chemical synthesis; Cyanide salts are used in metal cleaning, hardening, refining and in the recovery of gold from ores. Burning nitrogen-based polymers used in plastics, fabrics and seat covers releases HCN.

- Seeds of members of the *Rosaceae* family including apple, cherry, peach and apricot do contain cyanogenic glycosides.

- All animal species are susceptible to cyanide poisoning. The ability of rumen microbial flora to rapidly hydrolyze cyanogenic glycosides makes ruminants particularly at risk of cyanide intoxication from plant sources.

- Cyanide ion combines with ferric (trivalent) iron in the cytochrome oxidase system, blocking electron transport and molecular oxygen transfer from oxyhemoglobin to tissues, causing reversible cellular hypoxia or histotoxic anoxia.

**Clinical signs of toxicity:**

Onset of clinical signs is peracute (especially in ruminants) and includes apprehension, pronounced polypnea then dyspnea. The pupils dilate and mucous membranes may be pink and venous blood a bright cherry red. Weakness, voiding of urine, collapse,
paddling and death follow within a few minutes. Sublethal cases may recover within the hour.

**Treatment:**
The antidote of choice in humans, dogs and probably most other animals is Sodium nitrate in combination with Sodium thiosulfate. Ruminants can be treated with Sodium thiosulfate alone.

**Nitrites and Nitrates**

- Nitrate and nitrite are compounds that contain a nitrogen atom joined to oxygen atoms, with nitrate containing three oxygen atoms and nitrite containing two. In nature, nitrates are readily converted to nitrites and vice versa.
- Nitrates are used primarily to make fertilizer, but they are also used to make glass and explosives. These compounds also are used in various chemical production and separation processes. Nitrites are manufactured mainly for use as a food preservative, and both nitrates and nitrites are used extensively to enhance the color and extend the shelf life of processed meats.
- Nitrates are naturally present in soil, water, and food. In the natural nitrogen cycle, bacteria convert nitrogen to nitrate, which is taken up by plants and incorporated into tissues. Animals that eat plants use the nitrate to produce proteins. Nitrate is returned to the environment in animal feces, as well as through microbial degradation of plants and animals after they die.
- Microorganisms can convert nitrate or the ammonium ion (which is a nitrogen atom combined with four hydrogen atoms) to nitrite; this reaction occurs in the environment as well as within the digestive tract of humans and other animals especially in ruminants.
- The nitrite anion causes vasodilatation and oxidizes ferrous iron in hemoglobin to the ferric (trivalent) state forming methemoglobin which cannot accept molecular oxygen. As the percentage of methemoglobinemia rises oxygen starvation to tissues increases and blood becomes chocolate brown in color.
Clinical signs of toxicity:
Clinical signs of nitrate–nitrite toxicosis in animals (especially in ruminants) include weakness, cyanosis of mucous membranes, ataxia, collapse and death. Increased respiratory rate may be noted in some animals. Affected animals may remain standing then collapse and die within minutes.
Dead animals may be found in sternal recumbancy or lying on their side. Blood is dark and may have an obvious brown color when drawn into a syringe or spread on a white cloth.

Treatment:
Treatment is with intravenous administration of Methylene blue, other dyes such as Tolonium chloride (tolonium blue) are effective in reducing methemoglobin to hemoglobin but have a narrow therapeutic index.