Unit-5
Pharmacology- III

B.Pharma 6th Sem Notes

Unit: 5

5. Principles of toxicology

- **Definition and basic knowledge of acute, subacute and chronic toxicity.**
- **Definition and basic knowledge of genotoxicity, carcinogenicity, teratogenicity and mutagenicity**
- **General principles of treatment of poisoning**
- **Clinical symptoms and management of barbiturates, morphine, organophosphosphorus compound and lead, mercury and arsenic poisoning.**

6. Chronopharmacology

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    - **Definition of rhythm and cycles.**
    - **Biological clock and their significance leading to chronotherapy**

Principles of Toxicology:

- Toxicology is the branch of science that deals with the study of harmful effects of chemicals, drugs, and other substances on living organisms.
- In pharmacology, toxicology focuses on **how drugs or chemicals cause toxicity**, their **dose-response relationships**, and **ways to prevent or treat poisoning**.

Basic Knowledge of Types of Toxicity

A. Acute Toxicity

- **Definition:** Adverse effects that occur after a single dose or multiple doses given within 24 hours.
- **Characteristics:**
  - Rapid onset (minutes to hours)
  - Often severe and sometimes life-threatening
- **Example:** Cyanide poisoning, paracetamol overdose

B. Subacute Toxicity

- **Definition:** Toxic effects produced by repeated exposure to a substance for a short duration, usually **1–3 months**.
- **Characteristics:**
  - Effects are slower to appear compared to acute toxicity
  - May lead to functional changes in organs
- **Example:** Exposure to certain pesticides over a few weeks

C. Chronic Toxicity

- **Definition:** Adverse effects resulting from repeated or continuous exposure over a **long period (months to years)**.
- **Characteristics:**
  - Slow onset and progressive damage
  - Often irreversible
- **Example:** Lead poisoning, asbestos-related lung disease

- **Definition:** Genotoxicity refers to the ability of certain chemical, physical, or biological agents to damage the genetic material (DNA/RNA) of living cells.
- **Importance:** Damage to genetic material can lead to **mutations**, **cancer**, or **hereditary disorders**.
- Genotoxicity is a **critical parameter** in drug safety testing before market approval.

Mechanism of Genotoxicity

Genotoxic agents cause DNA damage through one or more of the following mechanisms:

1. **Direct DNA Damage**
   - Formation of DNA adducts (covalent binding of chemical to DNA)
   - Cross-linking of DNA strands
   - Base pair substitutions or deletions
2. **Indirect DNA Damage**
   - Production of **reactive oxygen species (ROS)** → oxidative stress
   - Inhibition of DNA repair enzymes
   - Interference with microtubules → abnormal chromosome segregation
3. **Examples of Mechanistic Pathways:**
   - **Alkylating agents** (cyclophosphamide) → add alkyl groups to DNA bases
   - **Ionizing radiation** → breaks in DNA strands
   - **UV light** → thymine dimers

Genotoxicity Testing Study

Testing is done during preclinical drug evaluation to detect DNA damage potential.

A. In vitro tests (outside the body, cell culture)

- **Ames Test** – Detects gene mutations in *Salmonella typhimurium* bacteria.
- **Chromosomal Aberration Test** – Detects chromosome structure changes in cultured mammalian cells.
- **Micronucleus Test** – Detects small, extra nuclei from chromosome fragments.

B. In vivo tests (in living animals)

- **Rodent Bone Marrow Micronucleus Test** – Identifies chromosomal damage in bone marrow cells.
- **Comet Assay** – Detects DNA strand breaks in individual cells.

Risk Factors for Genotoxicity

Factors that increase susceptibility to genotoxic effects:

- **Environmental exposure:** radiation, pesticides, heavy metals (lead, arsenic)
- **Lifestyle factors:** smoking, alcohol abuse, poor diet
- **Occupational exposure:** workers in chemical, paint, dye, and pesticide industries
- **Medical drugs:** anticancer drugs, immunosuppressants
- **Genetic predisposition:** defects in DNA repair genes

Treatment / Management

- **Immediate removal from exposure** to the genotoxic agent.
- **Antioxidant therapy** – Vitamin C, Vitamin E, N-acetylcysteine to neutralize ROS.
- **DNA repair enhancers** – Some experimental drugs aim to boost DNA repair.
- **Supportive therapy** – Maintaining good nutrition, avoiding further exposure.
- **Surveillance** – Regular health check-ups to detect early signs of mutation or cancer.

Carcinogenicity

Introduction

- **Definition:**
  Carcinogenicity is the ability of a substance to cause cancer by inducing uncontrolled growth of abnormal cells in the body.
- **Importance:**
  Carcinogens can be chemical, physical, or biological agents that cause **DNA damage** or alter cell regulatory mechanisms.
- Cancer development from a carcinogen is usually **slow and progressive**, often taking years.

Mechanism of Carcinogenicity

The process of cancer development (**Carcinogenesis**) occurs in **three main stages**:

1. **Initiation**
   - Irreversible DNA damage caused by carcinogen exposure.
   - Carcinogen (active form) interacts with DNA → mutation.
2. **Promotion**
   - Mutated cells undergo clonal expansion.
   - Growth-promoting agents (tumor promoters) stimulate proliferation without further DNA damage.
3. **Progression**
   - Accumulation of further mutations.
   - Cells acquire the ability to invade tissues and metastasize.

Mechanistic Examples:

- **Genotoxic carcinogens:** Directly damage DNA (e.g., benzopyrene from tobacco smoke).
- **Non-genotoxic carcinogens:** Promote cancer without directly damaging DNA (e.g., hormones like estrogen in high doses).

Carcinogenicity Testing

- **In vitro tests**:
  - Ames test for mutagenicity.
  - Cell transformation assays.

- **In vivo tests**:
  - Long-term rodent bioassays (2-year studies).
  - Transgenic animal models.

Risk Factors for Carcinogenicity

- **Environmental factors:** UV radiation, air pollution, industrial chemicals.
- **Lifestyle factors:** Smoking, alcohol consumption, high-fat diet.
- **Occupational exposure:** Asbestos, benzidine, vinyl chloride.
- **Biological agents:** Certain viruses (HPV, Hepatitis B and C).
- **Genetic predisposition:** Inherited mutations in tumor suppressor genes (e.g., BRCA1/BRCA2).

Treatment / Prevention

1. **Avoidance of exposure** to known carcinogens (e.g., quit smoking, use sun protection).
2. **Chemoprevention** – Use of agents that inhibit carcinogenesis (e.g., antioxidants, selective estrogen receptor modulators).
3. **Early detection** – Regular cancer screening.
4. **Treatment of cancer** – Surgery, chemotherapy, radiotherapy, immunotherapy.

Examples of Carcinogens

- **Chemical:** Benzopyrene, aflatoxin B_1, arsenic.
- **Physical:** UV light, ionizing radiation.
- **Biological:** Human papillomavirus (HPV), Epstein-Barr virus.

Teratogenicity:

Introduction

- **Definition:**
  Teratogenicity is the ability of a substance to cause structural or functional abnormalities (birth defects) in a developing fetus when the mother is exposed during pregnancy.
- **Importance:**
  Teratogens interfere with **normal growth and development** of the embryo/fetus, leading to **malformations, growth retardation, or functional defects**.
- The **first trimester (especially weeks 3–8)** is the most critical period (organogenesis).

Mechanism of Teratogenicity

Teratogens can cause fetal abnormalities through:

1. **Interference with cell division or differentiation**
   → Disruption of normal tissue/organ formation.
2. **DNA damage or chromosomal abnormalities**
   → Mutations, altered protein synthesis.
3. **Nutritional interference**
   → e.g., folate deficiency leading to neural tube defects.
4. **Placental transfer of toxic substances**
   → Drug crosses placenta and directly affects fetal tissues.

Examples of Teratogens

- **Drugs:**
  - Thalidomide → limb deformities (phocomelia)
  - Isotretinoin → craniofacial defects
  - Warfarin → bone and cartilage abnormalities
  - Anticonvulsants (valproic acid, phenytoin) → neural tube defects, cleft palate
- **Chemicals:** Mercury, lead
- **Infections:** Rubella virus, cytomegalovirus (TORCH infections)
- **Alcohol:** Fetal Alcohol Syndrome (growth retardation, facial anomalies, CNS defects)

Teratogenicity Testing

- **Animal studies** (rats, rabbits) during organogenesis period.
- Observing fetal growth, malformations, and survival.
- In vitro embryo culture techniques.

Risk Factors

- Timing of exposure (highest risk in **1st trimester**)
- Dose and duration of exposure

- Maternal health status (malnutrition, chronic diseases)
- Genetic susceptibility of mother and fetus
- Interaction with other drugs or environmental chemicals

Prevention & Management

1. **Avoid known teratogens** during pregnancy.
2. **Pre-pregnancy counseling** for women on chronic medications.
3. Use **FDA pregnancy risk categories** (A, B, C, D, X) for drug safety.
4. Supplementation with **folic acid** to prevent neural tube defects.
5. If exposure occurs, conduct **prenatal screening** (ultrasound, genetic testing).

Mutagenicity

Introduction

- **Definition:**
  Mutagenicity is the ability of a physical, chemical, or biological agent (mutagen) to cause **permanent changes (mutations)** in the DNA sequence of a cell.
- **Importance:**
  Mutations may lead to **genetic disorders, cancer**, or **heritable defects** if germ cells are affected.
- All mutagens are **genotoxic**, but not all genotoxic agents are mutagenic.

Types of Mutations

1. **Gene (Point) Mutation**
   - Change in a single base pair.
   - Example: Sickle cell anemia (substitution mutation).
2. **Chromosomal Mutation**
   - Deletion, duplication, inversion, or translocation of chromosome segments.
3. **Genome Mutation**
   - Loss or gain of whole chromosomes (aneuploidy).
   - Example: Down syndrome (trisomy 21).

Mechanism of Mutagenicity

Mutagens can damage DNA by:

- **Chemical alteration of bases** (alkylation, oxidation, deamination)
- **Intercalation** between DNA bases (causing frameshift mutations)
- **DNA strand breaks** (single or double-strand)
- **Inhibition of DNA repair enzymes**
- **Replication errors** due to structural DNA damage

Examples of Mutagens

- **Chemical mutagens:** Nitrosamines, ethidium bromide, benzopyrene
- **Physical mutagens:** UV radiation, X-rays, gamma rays
- **Biological mutagens:** Certain viruses (Human papillomavirus, Hepatitis B)

Mutagenicity Testing

A. In vitro tests

- **Ames Test** – Detects gene mutations in *Salmonella typhimurium* bacteria.
- **Mouse Lymphoma Assay** – Detects mutations in cultured mammalian cells.
- **Chromosomal Aberration Test** – Detects chromosome-level damage.

B. In vivo tests

- **Micronucleus Test** – Detects chromosomal fragments in dividing cells of animals.
- **Comet Assay** – Measures DNA strand breaks at a single-cell level.

Risk Factors

- Environmental exposure (radiation, pollutants)
- Occupational hazards (chemical industry, pesticides)
- Lifestyle factors (smoking, alcohol)
- Genetic predisposition (DNA repair defects)

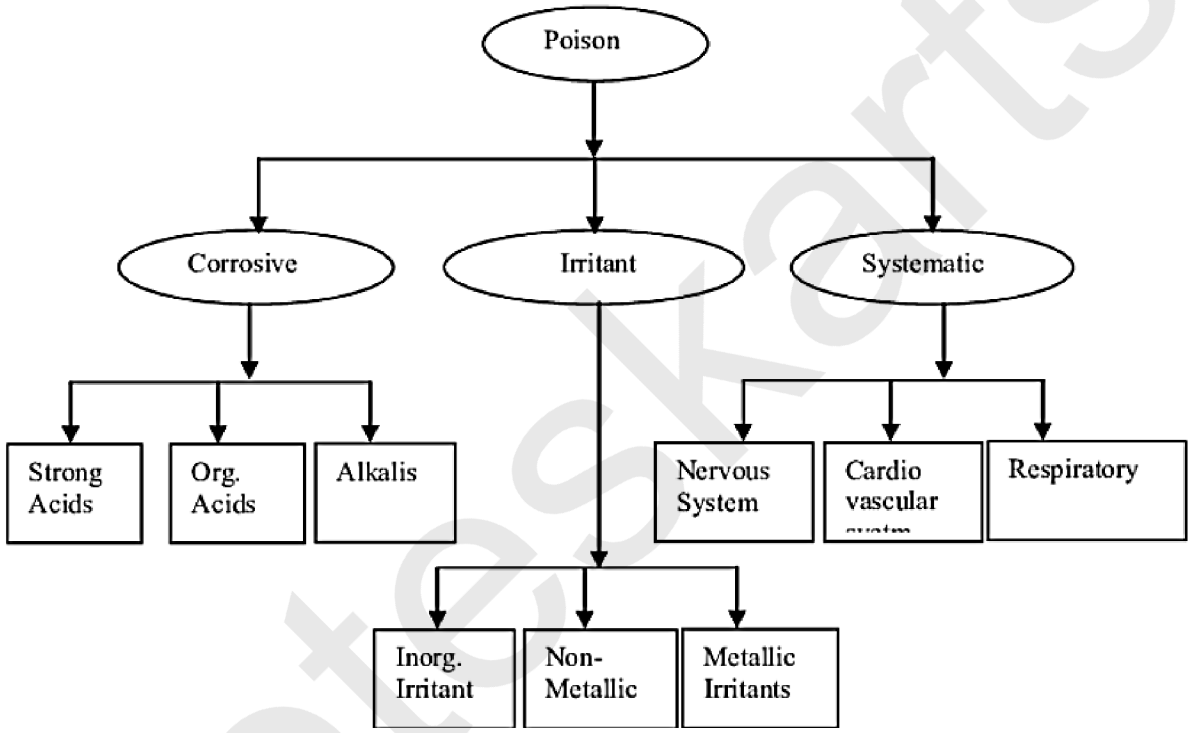
Prevention & Management

1. **Avoid exposure** to known mutagens.
2. Use **protective measures** in workplaces (masks, gloves, shielding).
3. **Antioxidant intake** (Vitamin C, Vitamin E) to reduce DNA damage from ROS.
4. **Regular screening** for early detection of mutation-related diseases.

Poison:

- It refers to any substance ingested into the body by any route and has the potential to interfere with the life processes of body organs of an organism.
- A poison can impair the normal physiology of body by killing or injuring through its chemical actions.
- A poison can be a solid, a gas or a liquid. Also, any of the essential nutrients, medicines or drugs can act as poisons under some specific conditions.

Classification of Poison



1. Corrosive Poisons

Destroy tissues at the site of contact.

- **Strong Acids** – Hydrochloric acid, Sulphuric acid, Nitric acid
- **Organic Acids** – Oxalic acid, Formic acid
- **Alkalis** – Sodium hydroxide (caustic soda), Potassium hydroxide, Ammonium hydroxide

2. Irritant Poisons

Cause inflammation of mucous membranes and internal organs.

A. Inorganic Irritants – Mercury salts, Copper salts, Zinc chloride
B. Non-Metallic Irritants – Phosphorus, Iodine, Chlorine
C. Metallic Irritants – Arsenic, Lead, Antimony

3. Systemic Poisons

Affect specific systems after absorption.

- **Nervous System Poisons** – Morphine, Strychnine, Organophosphates
- **Cardiovascular System Poisons** – Digitalis, Aconitine
- **Respiratory Poisons** – Carbon monoxide, Cyanide

Treatment of Poisoning:

1) **Poison identification:** Depending upon the symptoms and other factors, the poison must be identified.
2) **Maintaining clear passageways:** Debris must be removed, e.g., mekus vomitus and the secretions, from the endo-tracheal region.
3) **Ensure proper ventilation:** Proper tidal volume must be kept up by mechanical ventilators. Under-ventilation can cause hypoxemia and over-ventilation may lead to alkalosis and hypotension.
4) **Fluid and electrolyte therapy:**- Isotonic saline (0.9% w/v) or isotonic glucose (5% * W / v) or plasma may be used. St is done to expand the circulating blood volume and restoration of cardiac output.
5) **Prevention of further absorption of poison:**

(i) **From the environment:** the patient should be removed from the toxic environment and contaminated clothing should also be removed and the skin should be cleansed.

(ii) From the gut

a. Oral adsorbents:- Activated charcoal (carbomix, absorption. medicoal) reduces drug
b. Gastric lavage: This involves removal of un-absorbed poison from the stomach The stomach contents pass out in 3-4 hours, thus a stomach wash should be done before this time interval.
c. Emetics:- 15 gm of sodium chloride is dissolved in a glass of water and given to make the patient vomit.

6) **Specific Antidotes:** There should be given in case of any specific type of poisoning. e.q. paracetamol poisoning should be treated with

Barbiturate Poisoning:

- Barbiturate Poisoning often results from an overdose of barbiturate drugs.
- Barbiturates are CNS depressants that are used as sedatives, hypnotics and anticonvulsants.

Symptoms of barbiturate poisoning

1) Central Nervous System Depression: Barbiturates depress the CNS activity leading to symptoms such as drowsiness, confusion, lethargy, shock, headache. In severe cases, coma may occur.

2) Respiratory Depression:- shallow breading, respiratory arrest.

3) Hypotension:- Barbiturates can cause a drop in blood pressure, leading to symptoms like dizziness, fainting and shock.

4) Bradycardia: Barbiturates may slow down the Heart Rate.

5) Hypothermia: Lower Body Temprature.

Morphine Poisoning:

Introduction

Morphine is a natural opiate alkaloid obtained from the opium poppy (*Papaver somniferum*). It acts as a potent **opioid analgesic** and works mainly by binding to μ-opioid receptors in the CNS, producing analgesia, sedation, and euphoria.
However, **overdose** or accidental/intentional ingestion can cause life-threatening depression of the respiratory and central nervous systems.

Causes of Morphine Poisoning

- **Overdose** (accidental or suicidal)
- **Drug abuse** (habitual addicts using high doses)
- **Therapeutic error** (incorrect prescription or administration)
- **Drug interactions** (with other CNS depressants like alcohol, benzodiazepines)

Clinical Symptoms

1. CNS Symptoms

- Drowsiness, stupor, coma
- Slurred speech
- Pin-point pupils (*miosis*)
- Hyporeflexia (decreased reflexes)

- Seizures (rare, in children)

2. Respiratory Symptoms

- Slow and shallow breathing (**respiratory depression**)
- Bradypnoea (↓ respiratory rate)
- Cyanosis (bluish skin due to lack of oxygen)

3. Cardiovascular Symptoms

- Bradycardia
- Hypotension
- Weak pulse

4. Other Signs

- Cold, clammy skin
- Nausea, vomiting
- Decreased urine output

Classic triad of morphine/opioid poisoning:
Coma + Pin-point pupils + Respiratory depression

Management of Morphine Poisoning

1. Supportive and Symptomatic Treatment

- Maintain **airway, breathing, circulation (ABC)**
- **Oxygen therapy** to combat hypoxia
- Mechanical ventilation if respiratory arrest

2. Specific Antidote

- **Naloxone** (pure opioid antagonist)
  - Dose: 0.4–2 mg IV every 2–3 minutes until respiration improves
  - Can be repeated every 2–3 min (max 10 mg)
  - For long-acting opioids, continuous infusion may be needed

3. Decontamination

- If ingestion is recent (within 1 hour) and patient is conscious → **Activated charcoal**
- Gastric lavage may be considered if large ingestion and within short period

4. Monitoring

- Continuous monitoring of respiratory rate, oxygen saturation, and ECG
- Observe for at least 24 hours for recurrence of symptoms (due to morphine's longer duration compared to naloxone)

Organophosphorus Compound Poisoning

Introduction

- **Organophosphorus compounds** are widely used as **insecticides/pesticides** (e.g., parathion, malathion, diazinon, chlorpyrifos).
- They are potent **irreversible inhibitors of acetylcholinesterase (AChE)**, leading to accumulation of acetylcholine (ACh) at synapses and excessive stimulation of **muscarinic, nicotinic, and CNS receptors**.
- Poisoning is common in agricultural workers and in cases of accidental or suicidal ingestion.

Mechanism of Action in Poisoning

- OP compounds **phosphorylate AChE** → enzyme inactivation → ACh accumulates at nerve endings.
- **Overstimulation** of:
  - **Muscarinic receptors** → excessive parasympathetic activity
  - **Nicotinic receptors** → skeletal muscle effects
  - **CNS receptors** → seizures, coma

Clinical Symptoms

1. Muscarinic Effects (due to ↑ ACh at smooth muscle/glands) – *Mnemonic: SLUDGE / DUMBELS*

- **S**alivation
- **L**acrimation (tearing)
- **U**rination
- **D**iarrhoea
- **G**astrointestinal cramps
- **E**mesis (vomiting)
- Miosis (pinpoint pupils)
- Bradycardia, hypotension
- Bronchospasm, increased bronchial secretions

2. Nicotinic Effects

- Muscle fasciculations
- Weakness, paralysis (respiratory muscles may be affected)
- Hypertension, tachycardia (initially due to sympathetic ganglia stimulation)

3. CNS Effects

- Anxiety, confusion
- Ataxia, tremors
- Seizures
- Coma, respiratory depression

Management of OP Poisoning

1. Emergency & Supportive Measures

- Ensure **Airway, Breathing, Circulation (ABC)**
- Remove contaminated clothes, wash skin with soap & water (to prevent further absorption)
- Provide **oxygen** and mechanical ventilation if required

2. Specific Antidotes

- **Atropine** (muscarinic antagonist)
  - Dose: 2–4 mg IV, repeat every 5–10 min until drying of bronchial secretions and adequate ventilation achieved
  - Large doses may be required (sometimes >50 mg/day)
- **Pralidoxime (2-PAM)** (reactivates AChE if given early, before "aging" of enzyme)
  - Dose: 1–2 g IV over 5–10 min, may repeat in 1 hour, then every 12 hours as needed
  - More effective if started within **24 hours** of poisoning

3. Control of Convulsions

- **Diazepam** or other benzodiazepines if seizures occur

4. Decontamination

- Gastric lavage with activated charcoal (if ingestion was recent and patient is conscious)

Prognosis

- Early treatment → good recovery
- Delay → high risk of death from respiratory failure due to bronchospasm, excessive secretions, and paralysis of respiratory muscles

Lead Poisoning

Introduction

- Lead is a **heavy metal** that can cause both **acute** and **chronic toxicity**.
- Common sources:
  - Lead-based paints
  - Contaminated water (lead pipes)
  - Industrial exposure (battery manufacturing, smelting)
  - Traditional cosmetics or medicines containing lead
- Lead poisoning interferes with multiple enzymatic processes, especially **heme synthesis**, and affects the **nervous system, blood, kidneys, and GI tract**.

Types of Lead Poisoning

1. **Acute Poisoning** – rare, occurs from sudden ingestion/inhalation of large amounts
2. **Chronic Poisoning (Plumbism)** – more common, results from long-term low-level exposure

Mechanism of Toxicity

- Lead **inhibits enzymes** like δ-aminolevulinic acid dehydratase (ALAD) and ferrochelatase → ↓ heme synthesis → anemia
- Competes with calcium and alters neurotransmitter release → neurotoxicity
- Binds to sulfhydryl groups → disrupts enzyme functions

Clinical Symptoms

1. Acute Lead Poisoning

- Abdominal pain, vomiting, constipation
- Headache, confusion
- Seizures, coma (in severe cases)

2. Chronic Lead Poisoning

- **Hematological:** Microcytic hypochromic anemia, basophilic stippling of RBCs
- **Neurological:** Peripheral neuropathy ("wrist drop", "foot drop"), irritability, memory loss, encephalopathy (in children)
- **Gastrointestinal:** Colicky abdominal pain ("lead colic"), constipation
- **Renal:** Interstitial nephritis, chronic kidney disease
- **Skeletal:** Lead lines on X-ray (dense metaphyseal bands in growing bones)
- **Oral:** Blue-black line on gums (*Burton's line*)

Diagnosis

- Blood lead levels (>5 µg/dL in children is abnormal)
- Erythrocyte protoporphyrin level

- Peripheral smear (basophilic stippling)
- Radiological evidence (lead lines in bones)

Management

1. Remove Source of Exposure

- Identify and eliminate lead from environment/workplace

2. Supportive Care

- Adequate hydration
- Treat anemia with iron supplementation if needed

3. Specific Antidotes (Chelation Therapy)

- **Calcium disodium EDTA** – IV/IM, binds lead and promotes excretion
- **Dimercaprol (British Anti-Lewisite, BAL)** – given IM, used in combination with EDTA in severe cases
- **Succimer (DMSA)** – oral chelator, preferred in mild/moderate poisoning (especially in children)
- **Penicillamine** – oral, alternative chelating agent

Arsenic Poisoning

Introduction

- **Arsenic** is a toxic metalloid found naturally in soil, water, and minerals.
- Common forms: **Inorganic arsenic compounds** (more toxic) and **organic arsenicals**.
- Sources:
  - Contaminated drinking water (groundwater in some regions)
  - Industrial exposure (smelting, glass manufacturing)
  - Pesticides, wood preservatives
  - Certain traditional medicines

Types

1. **Acute Arsenic Poisoning** – from ingestion of large dose
2. **Chronic Arsenic Poisoning** – from long-term exposure to small amounts (most common in groundwater contamination)

Mechanism of Toxicity

- Arsenic binds to **sulfhydryl (-SH) groups** in enzymes → inhibits cellular respiration
- Interferes with **pyruvate dehydrogenase** and **Krebs cycle enzymes** → ↓ ATP production
- Causes oxidative stress and DNA damage

Clinical Symptoms

1. Acute Poisoning

- Severe abdominal pain, vomiting, watery diarrhoea ("rice-water" stools)
- Hypotension, dehydration, shock
- Garlic odor in breath
- Muscle cramps
- CNS depression, convulsions, coma (severe cases)

2. Chronic Poisoning

- **Skin changes**: Hyperpigmentation ("raindrop pattern"), hyperkeratosis (palms, soles)
- **Hair and nails**: Mees' lines (white transverse bands on nails), hair loss
- **Peripheral neuropathy**: Numbness, tingling, weakness
- **GI symptoms**: Loss of appetite, abdominal discomfort
- **Other**: Anemia, liver damage, increased risk of skin, lung, and bladder cancers

Diagnosis

- History of exposure + clinical features
- Laboratory: Blood arsenic level, urine arsenic (preferred for recent exposure), hair/nail arsenic (for chronic exposure)

Management

1. Remove from Source of Exposure

- Stop use of contaminated water/food, move patient to fresh air in case of inhalation

2. Supportive Care

- Treat dehydration and shock with fluids and electrolytes
- Manage arrhythmias if present

3. Specific Antidotes (Chelation Therapy)

- **Dimercaprol (British Anti-Lewisite, BAL)** – IM injection, preferred in acute poisoning
- **Succimer (DMSA)** – oral chelator, used in mild/moderate cases and chronic poisoning
- **Penicillamine** – alternative oral chelator

4. Gastric Decontamination

- Activated charcoal (if ingestion was recent)
- Gastric lavage (with caution)

Chronopharmacology:

Introduction

- Chronopharmacology is the science that studies how the effects of drugs vary according to biological time (biological rhythms).
- It focuses on how the **time of drug administration** influences the drug's absorption, distribution, metabolism, and elimination — and ultimately its effectiveness and side effects.
- Our body has several **biological clocks** that control physiological processes such as hormone secretion, enzyme activity, body temperature, blood pressure, and heart rate.

1. Mechanism Overview

The mechanism involves two main components:

A. Chronopharmacokinetic Mechanism

Biological rhythms influence the ADME processes:

1. **Absorption**
   - Gastrointestinal motility, gastric pH, and enzyme secretion change during the day.
   - Example: Some drugs are absorbed faster in the morning due to higher GI blood flow.
2. **Distribution**
   - Plasma protein levels and blood flow to tissues vary with time.
   - Example: Plasma albumin levels may be lower at night, affecting protein-bound drugs.
3. **Metabolism**
   - Liver enzyme activity (e.g., cytochrome P450) follows circadian variation.
   - Example: Some drugs metabolize faster during the active phase of the day.
4. **Excretion**
   - Kidney blood flow and urine pH change over the 24-hour cycle.
   - Example: Diuretics may work better in the morning when renal clearance is higher.

B. Chronopharmacodynamic Mechanism

Biological rhythms influence the **sensitivity of target receptors and tissues** to drugs:

1. **Receptor Sensitivity**
   - The number and responsiveness of receptors fluctuate during the day.
   - Example: Beta-adrenergic receptors may be more responsive in the morning.
2. **Physiological Variations**
   - BP, heart rate, hormone levels, and immune responses change over the circadian cycle, altering drug effect.

- Example: Asthma attacks are more common at night; bronchodilators are more effective in the evening.

Rhythm / Circadian Rhythm: (Biological clocks)

- Rhythms refer to recurring, patterned sequences of events or activities that occur over a period of 24 hours.
- Circadian rhythms enables the organisms to maintain and restrict their activities according to the day and night time.
- Example- The circadian rhythm regulates the slesp-wake cycle, hormone secretion and metabolism, following a roughly 24-hour pattern.

Biological Cycle:

- Biological cycles denote repetitive sequences of biological phenomena completing a full cirde within a defined time frame, often characterized by distinct phases or stages.
- Example- The menstrual cycle in females, typically completing in about 28 days, induding phases such as menstruation, follicular, ovulation and Luteal.

Biological Clock and Chronotherapy

Definition of Biological Clock

The **biological clock** refers to the internal timing system in living organisms that regulates physiological processes and behaviors in a cyclic manner.

- It is controlled by **genetic and biochemical mechanisms** in specific cells of the brain and body.
- In humans, the **suprachiasmatic nucleus (SCN)** of the hypothalamus is the master clock.

OR

- Biological clocks, also known as circadian rhythms. are internal mechanisms that regulate internal various physiological processes in living organisms over a roughly 24-hour cycle.
- These processes include sleep-wake cycles, hormone secretion, metabolism, body temperature regulation and other behavioral and physiological patterns.

Components of the Biological Clock

1. **Central Clock**
   - Located in the **SCN** of the hypothalamus.
   - Receives environmental cues like light/dark cycles.
2. **Peripheral Clocks**
   - Present in various organs (liver, heart, lungs, kidneys).
   - Control local organ-specific functions.

Functions of the Biological Clock

- Regulates **circadian rhythms** (~24-hour cycles).
- Controls hormone secretion (e.g., cortisol, melatonin).
- Coordinates sleep–wake cycle.
- Influences body temperature, blood pressure, metabolism.
- Synchronizes with environmental changes (light, temperature, feeding).

Significance of Biological Clock in Pharmacology

- **Drug Absorption**: GI motility and blood flow vary with time.
- **Drug Metabolism**: Liver enzymes (CYP450) show time-dependent activity.
- **Drug Excretion**: Kidney function fluctuates over the day.
- **Drug Sensitivity**: Target receptor responsiveness changes with biological time.

Link to Chronotherapy

Chronotherapy = Administering medications at specific times to align with the biological clock for maximum benefit and minimum side effects.

Mechanism

Biological Clock → Controls Body Rhythms → Influences Pharmacokinetics & Pharmacodynamics → Guides Optimal Drug Timing

Examples of Chronotherapy

Disease	Biological Rhythm Pattern	Optimal Time for Drug
Hypertension	BP rises in morning, peaks mid-day	Bedtime dosing for some antihypertensives
Asthma	Symptoms worsen at night	Evening dosing of bronchodilators
Cancer	Cancer cell division peaks at specific times	Chemotherapy timed to cancer cell activity
Arthritis	Pain and stiffness worse in morning	NSAIDs given at night before flare

Advantages of Chronotherapy

- Increased drug efficacy.
- Reduced side effects.
- Lower dose requirement.
- Better patient compliance.

Rhythms Affecting our Body

1) **Ultradian:-** Cycles shorter than a day. e-g. msec.
2) **Circadian:-** Lasting for about 24 hours. eig, sleep and wake cycles.
3) **Infrazadian:-** Cycles longer than 24 hours. eq. Menstrual cyde,
4) **Seasonal:-** Seasonal Affective Disorder (SAD) causing depression in people during the short days of winter.