ACUTE , SUBACUTE,CHRONIC TOXICITY

Points to be covered in this topic

1. ACUTE TOXICITY
2. SUB – ACUTE TOXICITY
3. CHRONIC TOXICITY

❑ INTRODUCTION OF TOXICOLOGY

- The term toxicology has been derived from the Latin and Greek word toxicum meaning **poison**, Greek word toxicum meaning **arrow poison** and Latin word **logia** meaning **study of science.**
- The **branch of science** concerned with the **nature, effects,** and **detection of poisons** , study poisons on living organisms.
- Toxicology can be defined as **study of xenobiotics** or **science of poisons** which includes **interaction of exogenous agents** with the physiological compartments of mammals.
- **Mathieu Joseph Bonaventur** (1787-1853, a Spaniard attending physician) is known as **the father of modern toxicology.**

❖ Principles of toxicology include

- **Dose-response relationships**
- **Chemicals enter the body.**
- They are **metabolized** and **excreted**, major health outcomes of intoxications
- Basics of **physiology, toxic kinetics** , and **cellular toxicology.**

❑ TOXICITY

- Any toxic (adverse) effect that a **chemical or physical agent** might **produce** within a **living organism.**

❖ Types of toxicity

i. **Acute toxicity**
ii. **Subacute toxicity**
iii. **Chronic toxicity**

i. Acute: It can be defined as exposure to a **chemical for not more than 24 hours.**

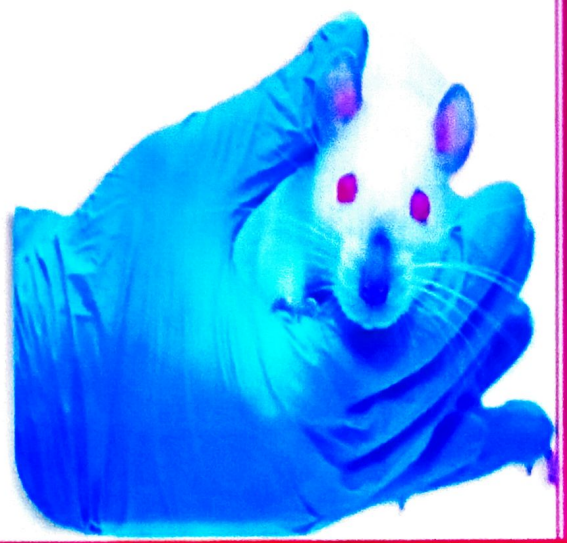
ii. Sub-Acute: It can be defined as **repeated** exposure to a **chemical for about 1 month or lesser.**

iii. Sub-Chronic: It can be defined as exposure to a chemical for **1 to 3 months.**

iv. Chronic: It can be defined as exposure to a **chemical for more than 3 months.**

1) Acute toxicity

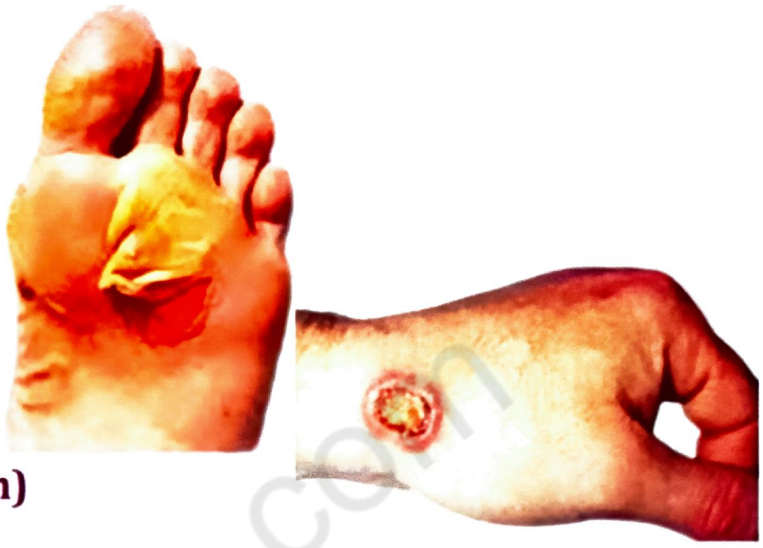
- It can be defined as **exposure to a chemical for not more than 24 hours.**
- Acute toxicity is toxicity study **aim to determine acute effect of chemical produced after administration of a single dose** (or multiple doses) to **experimental animal** in a period **not exceeding 24 hours inhalation exposure of 4 hours.**



- Acute toxicity, the **adverse effects** should occur **within 14 days** of the administration of the substance.

Example :- Over consumption of alcohol and **"hangovers".**

❖ Causes of acute toxicity



i. **Red skin**
ii. **Swelling of the skin**
iii. **Blisters**
iv. **Burning/severe pain**
v. **Ulcers (sores)**
vi. **Necrosis (death of the skin)**
vii. **Peeling of the skin**

i) **In experimental toxicology:-**

- Dosing is done either **once in a day** or **multiple times** but from 1 day irrespective of the **total study duration** which might extend to **2 weeks.**

ii) In **clinical medicine:-** It studies the effect of **single dose** on a **specific animal species.**

iii) For the first time **J.W. Trevan in 1927** introduced **LD_{50}**, to conduct the acute toxicity study on rats.

- In this testing, the test product is administered at different doses for **14 days** after which the **biochemical**, **pathological**, **histological** and **morphological** changes are recorded and all the mortalities caused by the test substance during the experiment are also recorded.
- LD was therefore used as an indicator of acute toxicity studies.

iv) Usually, a **single dose or multiple doses are given within 24 hours** as an whose **toxicity occurs** almost within hours after the exposure.

v) Exposure for **short duration** is known as **acute exposure.**

vi) Acute Effect :- (timeline: 0 < 24 hours < 14 days) after the administration of a **single dosage .**

vii) Acute systemic testing can be described by guidelines of **Organization for Economic Cooperation and Development (OECD).**

i) **Acute Dermal Toxicity (OECD TG)**

ii) **Acute Inhalation toxicity (OECD TG)**

iii) **Fixed dose procedure (OECD TG420)**

iv) **Acute Toxic Class method (OECD TG423)**

v) **Up-and-Down Procedure (OECD TG425)**

viii) ED_{50}

- It is the median effective dose for which **half (50%)** of **the animals exhibit an effect (E)** and half of the **animals exhibit no effect** .
- The effect may be defined as a specific toxic event **(e.g., tremors)** and is sometimes defined as **lethality (LD).**
- Other subscripts may be used to designate the **percentage of animals affected.**
- For example, the ED_{10} and ED_{90}, are the doses at which **10% or 90%** of the animals, respectively. demonstrate the effect.

2) Sub-Acute Toxicity

i. Subacute toxicity (repeat dose toxicity) focuses on **adverse effects occurring after administration of a single dose or multiple doses** of a **test sample** per day given during a period of from **14 to 28 days.**

ii. Sub-acute toxicity studies are conducted as range-finding studies for **determining the dosage levels** that has to be used in **chronic and sub-chronic studies** for duration of **6 months to 2 years** and up to **90 days.**

iii. These studies are conducted for duration of **2-4 weeks** in order to **evaluate** the potential **adverse effects of a new drug**.

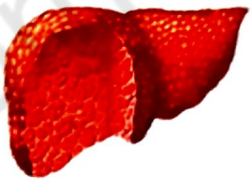
iv. They help in supporting the **initial clinical trial phases** the treatment duration might vary from **1 to 4 week.**

3) Chronic Toxicity

It can be defined as exposure to a chemical for **more than 3 months.**

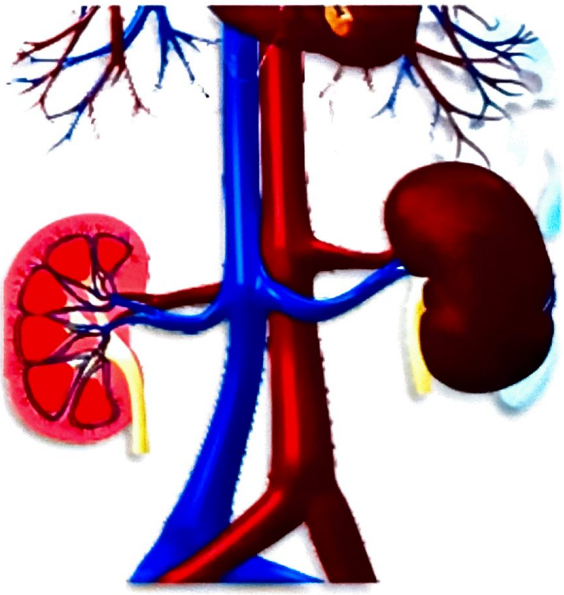
i. Chronic toxicity indicates specific **organ system damage .**

ii. Eventually, the organ remains no longer normal functional due to **severe damage**, thereby resulting in many different types of **chronic toxic effects.**



iii. Examples of chronic toxicity:

- Long term (several years) **ethanol ingestion** in alcoholics result in **liver cirrhosis.**
- Several years of **lead exposure in workmen** causes **kidney disease.**
- Long term **cigarette smokers** develop **chronic bronchitis.**
- **Pulmonary fibrosis**, also known as back **lung disease** develops in **coal miners** when exposed for longer times.



iv. These studies are performed with the requirement of **minimum one rodent** and **one non-rodent species.**

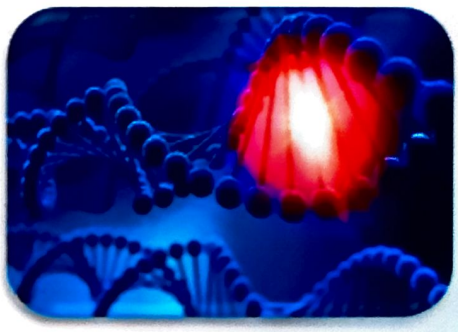
v. The test sample is administered in the animals for over more than **90 days** & periodically observed for the result.

GENOTOXICITY

Points to be covered in this topic

1. INTRODUCTION
2. GENOTOXICITY
3. CARCINOTOXICITY

4. TERATOGENICITY



5. MUTAGENICITY

❑ INTRODUCTION

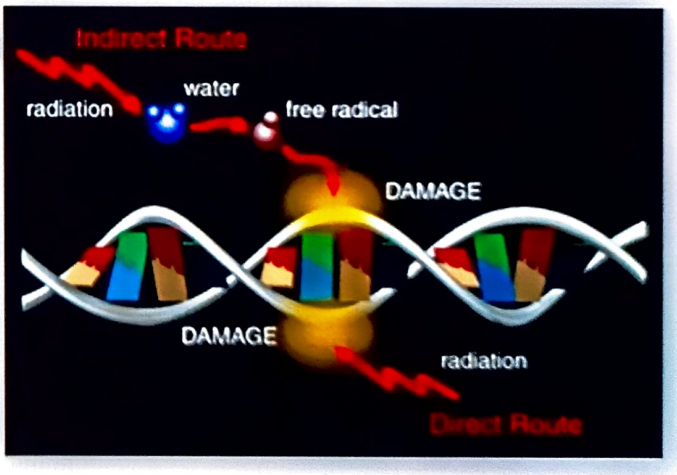
- **Genotoxicity** describes the **property of chemical** (Genotoxins) agents that **damages the genetic** information within the **cells** by mutations or others.
- Genotoxicity is often confused with **mutagenicity**, **all mutagens are genotoxic,** whereas not all **genotoxic substances are mutagenic**.
- **Mutagenicity** refers to the **induction of mutations** by **mutagens through permanent transmissible changes** in the amount or structure of the genetic material of cells or organisms.

Genotoxins: the agents which can cause **direct** or **indirect damage to the DNA**. Genotoxins can be **categorized** depending on their effects like

i. **Mutagens- that cause mutation**
ii. **Carcinogens- that cause cancer**
iii. **Teratogens- that cause birth defects**

➢ **Agents capable of causing direct & indirect damage to DNA**

- ✓ **Free Radicals (ROS, RNS)**
- ✓ **UV & Ionizing Radiation**
- ✓ **Nucleoside Analogues**
- ✓ **Protein Synthesis inhibitors**
- ✓ **Topoisomerase inhibitors**



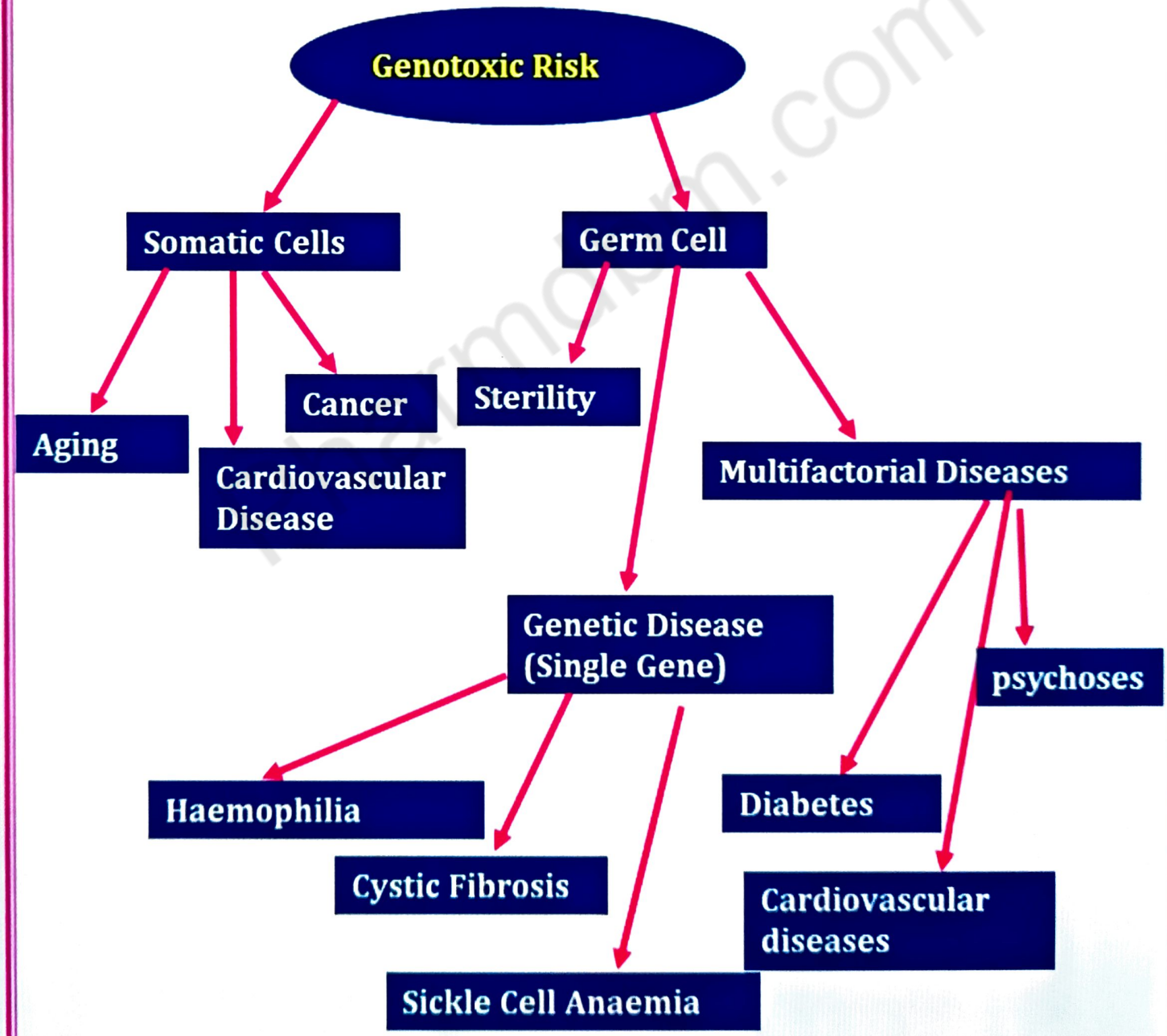
❖ Mechanism of Genotoxicity

- The **damage to the genetic material** is caused by the interactions of the genotoxic substance with the **DNA structure** and sequence.
- These genotoxic substance interact at a specific location or base sequence of the DNA structure causing lesions, breakage, fusion, deletion, mis-segregation or non- disjunction leading to damage and mutation.

❖ Genotoxicity Testing Study

- In **vitro** and in **vivo tests**, which are designed to **detect the genotoxic effects** of the test compounds (genotoxins).These tests enable **hazard identification** with respect to damage to DNA and its fixation.
- **Genetic toxicology**: was first published in **1987**. Following a global update of the genetic toxicology **[1927,2013,2014,2015,2016]**.

❖ Risk factors for genotoxicity



❖ Genotoxic Chemotherapy

- Genotoxic chemotherapy is the **treatment of cancer** with the use of one or more genotoxic drugs.

Treatment	Mechanism	Drugs
Alkylating agents	**interfere with DNA replication and transcription by modifying DNA bases**	**Busulfan, Carmustine**
Intercalating agents	**interfere with DNA replication and transcription by wedging themselves into the spaces in between DNA's nucleotides**	**Daunorubicin, Doxorubicin**
Enzyme inhibitors	**inhibit enzymes that are crucial to DNA replication**	**Decitabine, Etoposide**

❑ CARCINOGENECITY

- Carcinogen denotes a **chemical substance** or a **mixture of chemical substances** which **induce cancer** or increase its incidence.
- Carcinogens are classified according to their **mode of action** as **genotoxic** or **non genotoxic carcinogens**.
- Genotoxic carcinogens initiate carcinogenesis by direct interaction with DNA resulting in **DNA damage** or **chromosomal** aberrations that can be detected by **genotoxicity tests** as per **OECD guidelines.**

- Carcinogen classification involves **two interrelated determinations**, **evaluation of strength of evidence** and consideration of all other **relevant information (weight of evidence analysis)** .Carcinogens are categorized as either known/presumed carcinogens **(Category 1)** or **suspected carcinogens (Category 2).**
- Category1 is sub-divided based on whether the **evidence** for classification is mostly from **human** or **animal data.**
- The hazard communication label elements for carcinogenicity are presented as follows

Categories	Category 1A	Category IB	Category 2
Description	(Known or presumed human carcinogens)		Suspected human carcinogen
	Known to have carcinogenic potential for humans – largely based evidence on human	Presumed to have carcinogenic potential for humans largely an based on evidence animal	Evidence human from and/or animal studies is limited

❖ Classification of Carcinogens

- Carcinogens s can be classified according to International Agency for **Research on Cancer (IARC)** and **European Union (EU).**

1) European Union (EU) Classification of Carcinogens:

➢ **According to European Union (EU), carcinogens are classified as follows:**

i) **Carcinogen category I :-** Causes cancer in **humans.**

ii) **Carcinogen category 2 :-** Causes cancer in **animal tests**, and most probably also in humans .

iii. Carcinogen **category 3** is possibly carcinogenic, but evidence supporting carcinogenicity is inadequate for the classification to category 2.

- **International Agency For Research on Cancer (IARC) Classification of Carcinogens: According to IARC, carcinogens are classified as follows:**

i) IARC class 1 :- substance is **carcinogenic to humans.**

ii) IARC class 2A :- substance is **probably carcinogenic to humans.**

iii) IARC class 2B :- substance is **possibly carcinogenic to humans.**

iv) IARC class 3 :- substance is **not classifiable** to its **carcinogenicity humans.**

v) IARC class 4:- substance is **probably not carcinogenic to humans.**

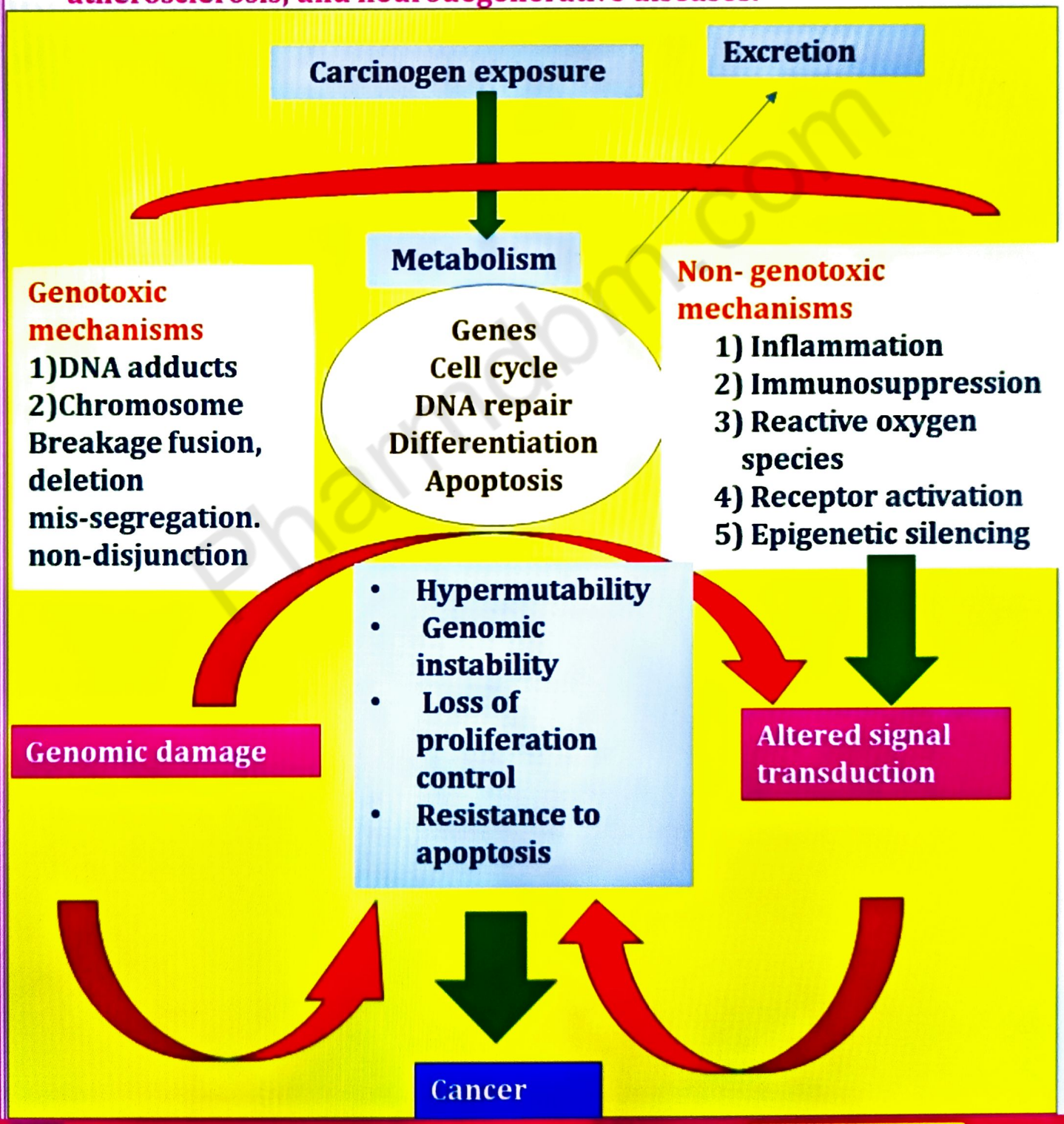
- **Agents capable of damaging the DNA directly or indirectly are as follows:**

1) Reactive Oxygen Species (ROS)
2) Nucleoside analogues
3) Protein synthesis inhibitors
4) Electrophilic species that form covalent adducts to the DNA
5) Ultra violet and ionizing radiations
6) Some herbal plants like Aconite, Alfa-alfa, Calamus, Aloe vera, Ispaghula
7) Topoisomerase inhibitors

❖ Mechanism of carcinogenicity

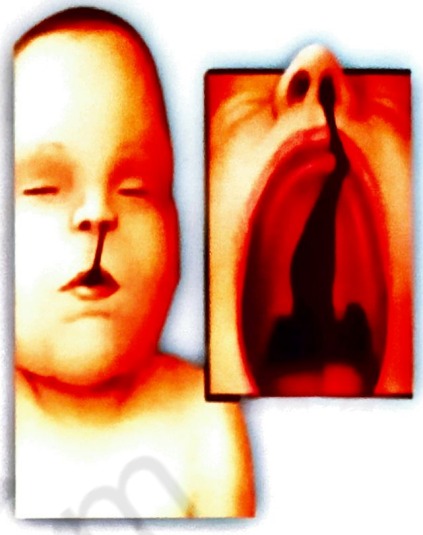
- The interactions of the genotoxic substances, like **chemicals, environmental agents, etc.** with the **DNA structure** and sequence results in the **damage of genetic material.**
- The carcinogenic process involves the alterations of four broad categories of cancer genes, namely the **activation of oncogenes, inactivation of tumor suppressors, evasion of apoptosis genes, and defective DNA repair genes** .

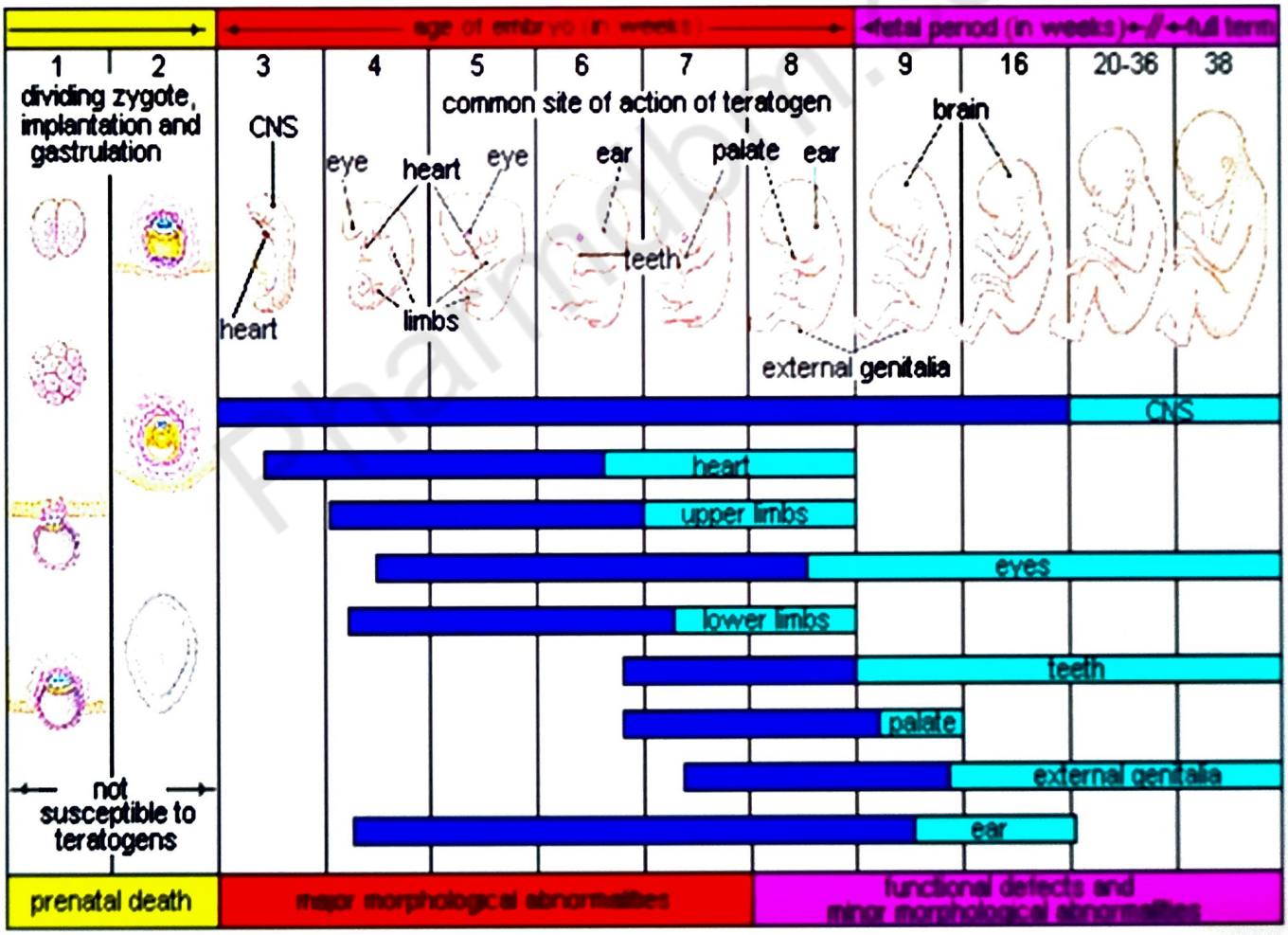
- **Reactive Oxygen Species (ROS)** is also one of the causes resulting in the **formation of oxidative lesions** in **DNA** known as **8-hydroxydeoxyguanosine**. (8 OHdG, potent mutagenic lesion).
- Decomposition of **primary free radical** intermediate of **lipid peroxidation** or **lipid peroxyl radicals** result in the **formation of reactive aldehydes,** like **4-Hydroxynonenal,)** which is responsible for causing many oxidative stress related diseases, like **fibrosis, atherosclerosis, and neurodegenerative diseases.**



❑ TERATOGENICITY

- The process of **formation of a congenital anomaly** is called **teratogenesis.**
- The substances that **lead to teratogenesis** are called **teratogens** and the **branch of medicine dealing** with the study is called **teratology .**
- **Teratogenicity** can also be called as **reproductive toxicity**.
- This causes alterations to the **female** or **male** reproductive organs related to **endocrine system,** or **pregnancy outcomes.**





- Teratogenesis indicates the structural **malformations** during development of **drug-induced fetal damage**, like **dysplasia** (eg, Iodine-deficiency related goiter), **growth retardation**, or **asymmetrical limb reduction.**

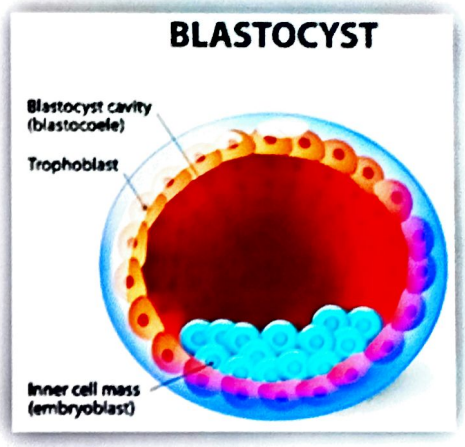
❖ Mechanism of teratogenicity

➢ Phase

1) Blastocyst formation

2) Organogenesis

3) Histogenesis & Maturation of function



1) Blastocyst formation

- The main process of **cell division** is occurring during **blastocyst formation.**
- Drugs can **kill the embryo** by **inhibiting cell division.**

2) Organogenesis (days 17-60)

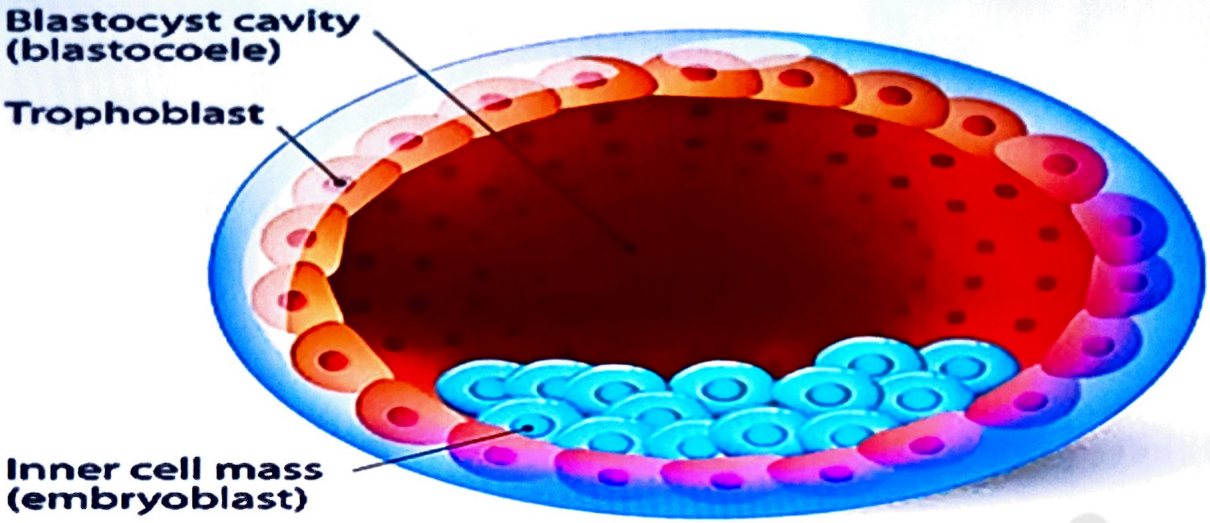
- The type of **malformation produced** thus depends on the time of exposure to the teratogen.Occurs in **(17-60 days)** in the first trimester.
- The most **sensitive period of pregnancy** because major body organs and systems are formed.
- Exposure to **harmful drugs during organogenesis**.
- **Skeleton and limbs, eye and brain, heart palate, major vessels and genitourinary system**.
- Major birth defect in body parts and structures or **gross malformation.**

3) Histogenesis and maturation of function

- The adequate nutrients supply plays an important role in the **fetus development** at final stage of **histogenesis** and **functional maturation** which is regulated by a variety of **hormones.**
- **Exposure of a female fetus** to **androgens** at this stage can cause **masculinization.**

Eg :-**Stilbestrol** was commonly given to **pregnant women** with a history **recurrent miscarriage.**

BLASTOCYST



❖ Teratogenic agents with their teratogenic effect

DRUGS	TERATOGENIC EFFECT
Captopril	Intrauterine growth retardation , Fetal death, Neonatal anuria, Hypoplastic calvaria
Diclofenac	Decrease of fetal number, Skeletal and heart defects
Estrogen	Masculinization of female foetus Behavior changes like rough-and-tumble play
Phenytoin	Phenytoin Fetal antiepileptic drug syndrome, Distal phalanges hypoplasia
Methotrexate	Skeletal defects Low birth weight
D-penicillamine	Fetal malformations and death
Thalidomide	Phocomelia and Amelia , Anotia microtia
Warfarin	Hearing loss, Nasal hypoplasia Spontaneous abortion, Distal limb hypoplasia
Cocaine	Assumption of placenta, Disruptive defects on cardio vascular
Lead acetate	Mental retardation, nephrotoxicity

❑ MUTAGENICITY

- Mutagenicity is a component of **genotoxicity.**
- Mutagenesis can occur due to **mis-replication** which includes mis-incorporation during the **replication of DNA** or as the result of **modifications in the DNA replication.**
- Study of mutation is called as **mutagenesis**. It can be defined as a heritable, and abrupt **change in the genetic material** induced by **mutagens**. Eg:- **physical** or **chemical agents**, like **UV radiation**, **X-ray**, etc.
- Mutation is **replacement of nitrogen base** with another in **one** or **both** the **strands** or **addition** or **deletion** of a base pair in **a DNA molecule.**

➢ **Thus mutations include the following:**

- Changes in a **single base pairs**, **partial, single** or **multiple genes**, or **chromosomes.**
- **Breaks in chromosomes** that result in the stable**(transmissible) deletion**, **duplication** or **rearrangement of chromosome segments.**
- Mitotic recombination.

❖ **Mutagen** :- Chemical that **induces genetic events** that alter the **DNA** and/or **chromosomal structure** and that are passed to subsequent generations **through clonal expansion.**

❖ Classification of mutation

- **Spontaneous Mutations:** These **mutations** occur at the **time of normal growth** or **reproduction.**
- **Induced Mutations:** These mutations occur as a result of **environmental mutagens**, like **radiation chemicals.**

❖ Types of mutations

1. Chromosome mutation: changing the structure of a chromosome, Loss or gain of part of a chromosomes. Five types exist

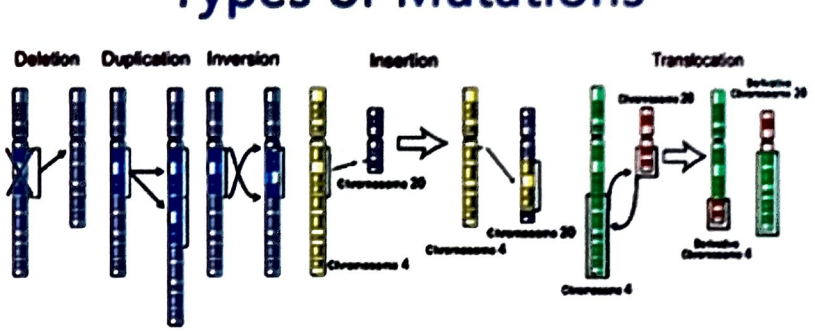
i. Deletion

ii. Inversion

iii. Translocation

iv. Duplication

v. Nondisjunction



- ✓ **Deletion:** Due to **breakage a piece of chromosome** is **lost.**
- ✓ **Inversion: chromosome segment breaks off** and **reattaches.**
- ✓ **Translocation:** involves **two chromosomes** that are not **homologous** and a part of **one is transferred** to **another chromosome.**
- ✓ **Duplication:** occurs when a **gene** sequence is **repeated.**
- ✓ **Nondisjunction: failure of chromosomes** to separate during **meiosis.**

2 Point mutation: Change in a **single nucleotide**. **Sickle cell** disease is the result of **one nucleotide** substitution.

3.Frame shift: Insertion or **deleting one** or **more nucleotides**. Changes the reading frame like changing sentence.

❖ Mechanism of Mutagenicity

i. Endogenous Mutagenesis

- Mutagenesis can take place **endogenously** e.g. through error in **replication** and **repair,** through **spontaneous hydrolysis**, or by **normal cellular** processes that can **produce ROS** (Reactive Oxygen Species) and **DNA adducts**.

ii. Environmental Mutagenesis:

- **Mutagenesis** can also occur as a result of the **presence of environmental mutagens** that can cause **changes to the DNA**.
- Most mutagens either **act directly** or **indirectly** through **mutagenic metabolites** on the **DNA producing lesions.**
- Affect the **replication of chromosomal partition mechanism** and other **cellular processes**.

iii. Self-Induced Mutagenesis:

- Mutagenesis may also be **self-induced by unicellular organisms** when environmental conditions are very **restrictive instance** in presence of toxic substances (like antibiotics) or in **yeasts,** in **presence** of an **antifungal agent** or in **absence of a nutrient.**

iv. Enzymatic Mutagenesis:

- Many **chemical mutagens** require **biological activation** to become **mutagenic.**
- A important group of enzymes in generation of **mutagenic metabolites** include **cytochrome p-450** .
- Enzymes that produce **mutagenic metabolites** are microsomal epoxide by **hydrolase glutathione** and **s-transferase.**
- Certain mutagens that are not them mutagenic but require **biological activation** are known as **promutagen.**

❖ Various Mutagens causing Mutations

Examples of different mutagens include

1) Acridine Orange

- It works by **deleting** or **inserting one or more bases** into the **DNA molecule**, **shifting the frame of the triplet code** for an **amino acid.**

- **Deletion** and **insertion mutations** causing **frame-shift mutations** can change a long string of amino acids, which can severely alter the structure and function of a protein product

2) Nitrogen Mustard

- It **works by binding to a base** and cause it to make a different **amino acid.**
- These **mutagens** cause **point mutations**, as they **change the genetic code at one point**, there by **changing a protein's amino acid sequence**.

3) **Cosmic rays** from **space are natural**, but act as **mutagens.**

4) Certain naturally occurring **viruses** are also considered as mutagens as they can themselves **insert** into the **host DNA.**

5) **Hydrogen** and **atomic bombs are human-made**, mutagens as they produce **harmful radiation.**

GENERAL PRINCIPLES OF TREATMENT OF POISIONING

Points to be covered in this topic

1. INTRODUCTION
2. CLASSIFICATION OF POISIONS
3. SPECIFIC ANTIDOTES , INDICATION MECHANISM OF ACTION

❑ INTRODUCTION

- A poison can be defined as any **liquid, gas or solid substance ingested through oral, topical, or inhalational route** and has the potential to interfere with the life **processes of body organs** of an organism.
- The word poison has been derived from the Latin word **potare** which means to **drink.**

❖ Types of poision

Poison can be divided into **three broad groups:**

1. **Agricultural and industrial chemicals**
2. **Drugs and health care products**
3. **Biological poision-plant and animal sources**

❑ CLASSIFICATION OF POISIONS

Poision are classified into three category

Categories	Types	Examples
Corrosives	Strong acids Strong alkalis	i) H_2SO, HNO_3, HCI ii) Caustic Soda, Caustic Potash
Irritants	i) Inorganic (a) Non-metallic (b) Metal ii) Organic (a) Herbal (b)Animal iii) Mechanical	1) Inorganic a) P. Cl, Br, I b) Heavy metals (As, Sb, Pb, etc) ii) Organic a) Castor seeds, croton oil, etc b)Snake venoms, Cantharides iii) Diamond dust, glass powder.
Neurotics	i)Cerebral a)Sleep causing opium (Narcotics)and its derivative b) Intoxicants c) Anaesthetics d)Deliriant ii) Acting on spinal cord iii) Acting on cardiac system iv) Poisons acting peripherally	i) Cerebral a) Morphine b) Alcohol c) Ether, $CHCl_3$ d) Datura, Belladonna ii) Nux vomica iii)Digitals , Aconite, Tobacco iv) Coal gas,CO,CO_2

➢ Measures to be taken during Poisoning Treatment

The measures that must be adopted to treat a poisoning include:

1) Poison Identification

- Depending on the **symptoms,** the **poison** and other factors affecting the **condition** must be **identified.**

2) Maintaining Clear Passageways

- Debris must be **removed** e.g., **mucus, vomitus, dentures** and the **secretions** must be **sucked away**.
- If required, **endotracheal intubation** or **tracheostomy** must be considered.

3) Ensure Proper Ventilation

- Tidal volume of around **400 ml** and **diminutive volume** of **around 4 liters/minute** for grown-ups by **mechanical ventilators**, on the off chance that vital, ought to be kept up.
- Under-ventilation can cause **hypoxemia** and over-ventilation may lead to **alkalosis** and **hypotension.**

4) Suppression of Convulsions

- In case the poisons cause **convulsions** and are **not controlled** by **satisfactory ventilation**.
- Ex:- **Diazepam 10 mg** IV must be given .

5) Fluid and Electrolyte Therapy

- **Circulating blood volume** and **restoration** of **venous return** and **cardiac output**.
- **Isotonic saline (0.9% w/v),** or **isotonic glucose (5% w/v),** or **plasma** may be used.
- In general, **1 litre of isotonic saline + 1 litre of isotonic glucose solution** per day must be administered.

6) Prevention of Further Absorption of Poison

i) From the Environment:

- When a poison has been inhaled or absorbed through the skin, the patient should be removed from the toxic environment, the contaminated clothing should also be removed, and the skin should be cleansed.

ii) From the Gut

a) Oral Adsorbents:

- **Activated charcoal (carbomix, medicoal) reduces drug absorption** better than **ipecacuanha syrup** or **gastric lavage,** is easiest to administer, and has fewest adverse effects.
- It contains a very **fine black powder** prepared from **vegetable matter**, e.g., **wood pulp, coconut shell**, which is activated by exposing it to an oxidizing gas at **high temperature** to create a network of fine **(10-20nm) pores.**
- This imparts an enormous surface area in relation to weight **(1000m/g).**
- This **binds** to and thus **inactivates** a wide variety of compounds in the **gut.**
- The substances that are **not adsorbed** by charcoal are **iron, lithium, cyanide, strong acids and alkalis, organic solvents, and corrosive agents.**
- Adult an initial dose of **50-100gm** is usual.
- If the charcoal should **41°C** should be given through a **nasogastric agents..**

b) Gastric Lavage:

- This involves **removal of unabsorbed poison** from the **stomach.**
- The stomach contents pass out in **3-4 hours**, thus a **stomach wash**

- Should be done before this time interval.
- But, in case of opium poisoning, by whatever route the poison was administered, it should be excreted through the stomach.
- Hence, gastric lavage should be done in **opium poisoning.**
- **Saline solution** made by dissolving **1 teaspoonful of sodium chloride** in a tumbler of **warm water.**
- **Alkaline wash** made with **5% w/v sodium bicarbonate solution.**
- **Sodium thiosulphate** and **dimercaprol solution** in **toxic metallic poisoning.**

c) Emetics

- **15gm of sodium chloride** is **dissolved in a glass of water** and given to make the patient vomit.
- The **dose is repeated** till the **vomit is clear.**
- If this fails, **2 teaspoonful** of **mustard powder dissolved in a glass of water** is given for the emetics.
- If this also fails, **1-2gm of ipecacuanha powder** is given.
- Finally, **apomorphine hydrochloride injection** is given to **stimulate vomiting.** This injection is not given in **morphine poisoning.**
- Irritating the **patient's throat by finger, tongue depressor,** or **spoon can also stimulate instantaneous vomiting.**

d) Cathartics

- Cathartics or whole-bowel irrigation is used for the **removal of sustained-release formulations.**
- **Ex :- Theophylline, iron, aspirin**
- **Activated charcoal in repeated (10gm) doses** is generally preferred

7) Specific Antidotes

- These should be given in case of any specific type of poisoning, eg paracetamol poisoning should be treated with **N. acetylcysteine (NAC).**

8) Non-Specific Pharmacological Antidotes

- **Anticonvulsants in convulsions** and **analeptics in narcotic poisoning** may be employed.
- **Analeptics (respiratory stimulants)** have no place if a **mechanical respirator** facility is available.

9) Acceleration of Elimination of the Poison

- **Techniques for eliminating poisons** have a role that is limited, but important when applicable.
- Each method depends, **directly or indirectly**, on **removing drug from the circulation** and successful use requires that:

i) The **poison** should be **present in high concentration** in the **plasma** relative to that in the **rest of the body**, it should have a **small distribution volume.**

ii) The poison should dissociate readily from any **plasma protein binding** sites.

iii) The effects of the poison should relate to its **plasma concentration.**

10) Methods for Poison Elimination

Poison can be eliminated at fast pace from the body by the following methods:

i) Repeated doses of charcoal

ii) Diuresis

iii) Changing pH of urine.

iv) Dialysis

v) Haemoperfusion

➢ **Different mechanisms help in eliminating, reducing or abolishing the effects of poisons:**

1. **Displacement from tissue binding sites**
2. **Receptors, which may be activated, blocked or by passed**
3. **Replenishment of an essential substance**
4. **Enzymes, which may be inhibited or re-activated**
5. **Binding to the poison (including chelation)**
6. **Exchanging with the poison**

❑ Specific Antidotes, Indications and Mechanism of Action

Antidotes	Indication	Mechanism of action
Acetylcysteine	Paracetamol, chloroform carbon tetrachloride.	Replenishes depleted glutathione stores.
Atropine	1) Cholinesterase inhibitors, e.g:- organophosphorus insecticides.	Blocks muscarinic choline receptors .
	2) β-blocker poisoning.	Vagal block accelerates heart rate.
Benztropine	Drug-induced movements disorders.	Blocks muscarinic choline receptors
Calcium Gluconate	Hydrofluoric acid, fluorides.	Binds or precipitates fluoride ions
Deferoxamine	Iron	Chelates ferrous ions
Di cobalt edetate	Cyanide and derivatives, e.g., acrylonitrile.	Chelatestoformnon-toxic cobalt and cobalt cyanides
Digoxin-specific Antibody Fragments (FAB)	Digitalis glycosides.	Binds free glycoside in plasma. complex excreted in urine
Dimercaprol (BAL)	Arsenic, copper, gold lead, in organic mercury	Chelates metal ions.

Phentolamine	**Hypertension due to adrenoceptor agonists, e.g. With MAOL clonidine. ergotamine**	**Competes a - adrenoreceptors**
Phyto menadione (vitamin K_1)	**1) Coumarin (warfarin)and indandione.** **2) Anti-coagulants**	**Replenishes vitamin K**
Pralidoxime	**Cholinesterase inhibitors ex : organophosphorus insecticides**	**Competitively reactive cholinesterase**
Propranolol	**β-adrenoceptor agonists, ephedrine, theophylline, thyroxine**	**Block β – adrenoreceptor**
Protamine	**Heparin**	**Binds ionically in neutralize**
Prussian blue (potassium ferric hexacyanoferr ate)	**Thallium (in rodenticides)**	**Potassium exchanges for thallium**
Sodium calcium edetate	**Lead**	**Chelates lead ions**
unithiol	**Lead, elemental, & organic mercury**	**Chelates metal ions**
Ethanol	**Ethylene glycol ,methanol**	**Competes for alcohol & acetaldehyde dehydrogenase preventing formation of toxic metabolites**
Flumazenil	**Benzodiazepines**	**Competes for benzodiazepines receptors**
Folic acid	**Folic acid antagonists , ex- methotrexate ,trimethoprim**	**Bypasses block in folate metabolism**

Glucagon	**β- adrenoreceptor antagonism**	**1) By passes blockade of the b – adrenoreceptor** **2) Stimulates cyclic AMP formation with positive cardiac inotropic effect**
Isoprenaline	**β- adrenoreceptor antagonism**	**Competes for β - adrenoreceptors**
Methionine	**Paracetamol**	**Replenishes depleted glutathione stores**
Naloxone	**Opioids**	**Competes for opioids receptors**
Neostigmine	**Anti muscarinic drugs**	**Inhibits acetyl cholinesterase causing acetylcholine to accumulate at**

CLINICAL SYMPTOMS & MANAGEMENT

Points to be covered in this topic

1. BARBITURATE POISONING
2. MORPHINE POISONING
3. ORGANOPHOSPHOSPHORUS COMPOUND
4. DIAGNOSIS OF MENINGITIS
5. LEAD POISIONING
6. MERCURY POISIONING
7. ARSENIC POISIONING

❑ Barbiturate Poisoning

- Barbiturates synthesized from **urea** and **malonic acid** is derivative of **malonylurea**.
- These are classified as weak acids as the **electro-negative carbonyl carbon** transmits the acidic character to the molecule.

✓ **Major Actions of Barbiturates:**

- **Central nervous system (CNS) depression** causing **hypnosis**, **sedation or anesthesia.**

❖ Classification of barbiturates

BARBITURATES		
Long acting	**Short acting**	**Ultra short acting**
Phenobarbitone	Butobarbitone Pentobarbitone	Thiopentone Methohexitone

❖ Mechanism of Toxicity

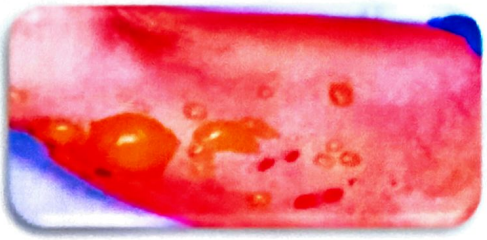
1) The **pre-** or **postsynaptic neuronal terminals** present in the **CNS** releases an **inhibitory neurotransmitter**, **GABA,** which exists in the form of **GABA-Cl ionophore complex (y-aminobutyric acid).**
2) The complex formation by **binding to the GABA receptors** results in **prolongation of opening for chloride channel**, there by causing the **inhibition of neural action** and **increasing the action of inhibitory neurons**.
3) Barbiturates continuously **stimulate GABA** release at the sensitive synapses.
4) At Normal Doses: They **reduce** the **post-synaptic depolarization** facilitated by **acetylcholine** followed by **blockage of post-synaptic transmission** to cause **depression of cardiac, smooth** and **skeletal muscles.**
5) At Higher Doses: They **depress medullary respiratory centers** to result in **inhibition of all the three respiratory centers of the brain.**

❖ Clinical Symptoms

1) Central Nervous System : **Shock, coma, CNS depression, ataxia, lethargy, headache, and confusion.**

2) **Nystagmus and slurred speech**

3) **Hypothermia**



4) **Miosis occurs** in the **beginning,** but **later pupils dilate** due to **hypoxia.**

5) Cutaneous bullae also called **barbiturate blisters** or **barb burns** are **transparent haemorrhagic** or **erythematous blisters.** It generally occurs over the **pressure points** **(like between the ankles and knees, buttocks and hands).** They also occur over **non-pressure points** **(like, ocular conjunctiva and dorsal surfaces of toes and fingers)**

6) **Sympathetic ganglia blockade** causes **hypotension, bradycardia, decreased inotropic effect,** and **decreased cardiac output.**

7) **Inhibition of medullary vasomotor centers** results in **venous and arteriolar dilation** with associated complications like **cardiac depression** and **cerebral hypoxia .**

8) **Respiratory collapse** or **cardiac arrest** can lead to **death.**

9) Delayed death can occur because of **pulmonary oedema, cerebral oedema. acute renal failure, or pneumonia.**

❖ Management

Treatment guidelines for barbiturate overdose leading to **CNS depression** remains **symptomatic** and have been adapted from **Scandinavian method.** The guidelines include:

1) **Monitoring of complete blood count (CBC), glucose level serum electrolytes, creatinine, blood urea nitrogen, and urine myoglobin.**

2) Maintaining **sufficient ventilation**.

3) Keeping the patient warm.

4) Supporting vital body part functions.

5)**Maintaining blood pressure, preventing circulatory collapse and sufficient kidney perfusion by providing oxygen support, administration of volume expanders and forced diuresis.**

6. **Hemodialysis** is recommended in case **of renal or cardiac failure, acid-base disturbances, or electrolyte abnormalities.**

7) In case of **severe intoxication, charcoal hemoperfusion** or **hemodialysis** is required.

8.**Long-acting barbiturates** in comparison to **short-acting barbiturates** required. **removed** more effectively with **hemodialysis** than with **ion exchange** due to its **less binding with lipid and proteins.**

9.**Plasma** and **urine alkalinization** with **sodium bicarbonate helps** in **ionization acidic compounds of the drug** it the **cardiac** and **renal functions** satisfactory.

10.If less than **24 hours** have been passed **post ingestion, induction of apomorphine emesis, gastric lavage** and **delivery of saline cathartic increase the elimination**, while administration of **activated charcoal** result in **decreased absorption of the toxic compound.**

❑ MORPHINE POISIONING

- Morphine is a major alkaloid (10%) obtained from the **milky exudates of unripe capsule of Papaver somniferum L (opium poppy).**

❖ Signs and Symptoms

➢ **The signs and symptoms of morphine poisoning include:**

1)Stupor or coma

2) Flaccidity

3) Shallow and occasional breathing

4) Cyanosis

5) Pinpoint pupil

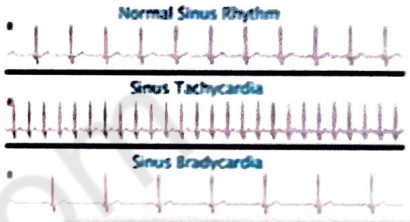
6) Fall in BP and shock

7) Convulsions (may be seen in few)

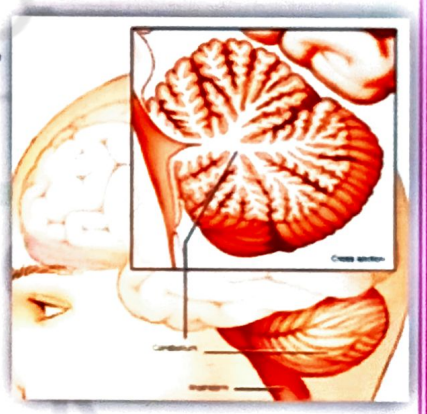
8) Pulmonary oedema (occurs at terminal stages)

9) Death due to respiratory failure.

➢ **The clinical symptoms of morphine poisoning are**

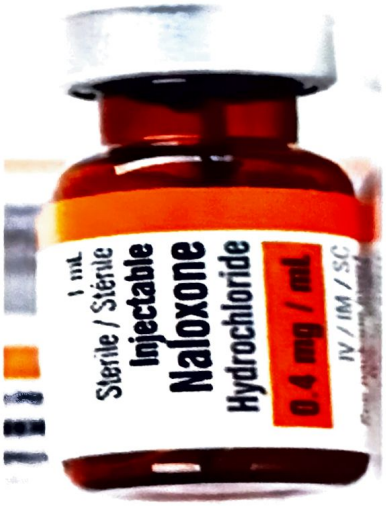


- **Euphoria, distorted and heightened images**
- **Colors and sounds**
- **Altered tactile sensations**
- **Sinus tachycardia, hypotension and ataxia occur**
- **Visual and auditory hallucinations**
- **Depersonalization and acute psychosis**



❖ Mechanism of action

- **Naloxone** is a **specific antagonist** that **acts competitively at opioid receptors.**
- It is an effective **antagonist of opioids with agonist or mixed agonist antagonist activity.**
- It usually has a **rapid onset of action** which occurs within **2 minutes** when given **intravenously.**



- The **plasma half life** is approximately **one hour.**
- **Naloxone** can precipitate symptoms of **withdrawal** if given too quickly or in too high a dose to an **opioid dependent patient.**

❖ Management

Morphine poisoning can be managed as follows:

1) **Respiratory Support: Pulmonary oedema** can be **decreased** by **positive pressure respiration.**

2) **BP Maintenance** can be achieved by providing **I.V fluids** and **vasoconstrictors.**

3) **Gastric Lavage: Unabsorbed drug** can **be removed by potassium permanganate.**

4) **Specific Antidote:** It includes

   a) **Naloxone 0.4-0.8mg** repeated **every 2-3 minutes** till **respiration is resumed** as it is the **preferred specific antagonist.**

   b) **Injection should be repeated every 1-4 hours.**

   c) **Nalorphine 3-5mg** I.V is a less satisfactory alternative.

❑ Organophosphate poisoning

- Organophosphates are **used is as poisoning** due to organophosphates (OPs). **insecticides, medications, and nerve agents.**
- Organophosphate poisoning occurs most commonly as a **suicide attempt in farming areas.**

❖ Mechanism of action

- **Inhibition of acetylcholinesterase (ache),** leading to the buildup of acetylcholine (ach) in the body.
- Organophosphates **irreversibly** and **non-competitively inhibit acetylcholinesterase, causing poisoning by phosphorylating** the **serine hydroxyl** residue on ache, which **inactivates ache.**
- Ache is critical for nerve function, so the **inhibition of this enzyme,** which causes **acetylcholine accumulation,** results in **muscle over stimulation.**

❖ Clinical Symptoms

➢ **The signs and symptoms of organophosphorus poisoning include:**

1) Cholinergic Actions

i) **Muscarinic Effects:** Following clinical symptoms are observed due to muscarinic like effects :

a) **Gastrointestinal:** Abdominal cramp, diarrhoea , nausea, and vomiting

b) **Bronchial Tree:** Bronchoconstriction, cough, increased secretions, dyspnea, and pulmonary oedema

c) **Salivary Glands:** Increased salivation

d) **Sweat Glands:** Increased sweating

e) **Lacrimal Glands:** Increased lacrimation

f) **Eyes:** Blurring of vision, dimness of vision, miosis developed due to cholinesterase inhibition, and marked parasympathomimetic iris stimulation.

g) **Urinary Bladder:** Urinary incontinence and micturition frequency.

h) **Heart:** Hypotension and slow pulse rate.

Note: Mnemonic or acronym to remember:

DUMBELS:

- Diarrhoea
- Urination
- Miosis
- Bronchospasm, Bradycardia
- Emesis
- Lacrimation
- Salivation

SLUDGE:

- Salivation
- Lacrimation
- Urination
- Diarrhoea
- Gastrointestinal distress
- Emesis

ii) Nicotinic Effects: Following clinical symptoms are observed due to **autonomic ganglionic** and **somatic motor effects**:

a) Straited Muscles: Fasciculations, cramps, muse ching fatigue, weakness, uneasiness, and paralysis.

b) Sympathetic Ganglia: Pallor tachycardia, hypertension (occasional), cardiac arrhythmias conduction defect.

c) Increased adrenal medulla activity

d) CNS Effects: Tremor, drowsiness, restlessness, headache, slurred speech, delirium, convulsions, and ataxia.

Note: Mnemonic or acronym to remember:

PUFF MATCH

- **P**allor
- **U**neasiness
- **F**asciculation
- **F**atigue
- **M**uscle weakness
- **A**drenal medulla activity increases
- **T**achycardia
- **C**ramps in muscle
- **H**ypertension

❖ Management

Management of cute organophosphate toxicity at the initial stage includes:

1) Maintaining adequate **respiration** and **airway functioning**.

2) **Bronchial secretions** must be **removed by suction**.

3) **Gastric lavage** and **ipecac-induced emesis** with **respiratory airway** protection is indicated in case the drug is ingested.

4) Within **30 minutes decontamination (lavage)** from the **gastrointestinal tract organophosphorus post-ingestion, gastric** most recommended as it rapidly gets absorbed.

5) If gastric lavage is not performed within stipulated time period, **activated charcoal** is recommended to further decrease the absorption.

6) Most OP insecticides are mixed with solvents of petroleum distillate.

7) Antidotes:

i) **Atropine:** It antagonizes numerous **central cholinergic effects** and **peripheral muscarinic effects.**

ii) **Pralidoxime (2-PAM, protopam):** It is a **specific antidote** for **treating organophosphorus .**

iii) **Cholinesterase Reactivator:** **Phosphorylated acetylcholinesterase gets reactivated by oximes (nucleophilic agents)** due to their binding property with organophosphorus molecule.

❑ Lead poisoning

- It is found in the **earth's crust** in abundant quantity and occurs in the form of different salts as liquids or coloured .
- Lead is a **highly toxic metal** and a **very strong poison.**
- Lead is found in **lead-based paints**, including **paint on the walls of old houses and toys.**
- It is also found in **art supplies, contaminated dust.**

❖ Mechanism of action

- **Calcium disodium edetate (CDE)** is a chelating agent used in the treatment of **acute** and **chronic lead poisoning** and **lead encephalopathy.**

- **Lead acts by the following three mechanisms**

1) **Lead binds** with the **sulfhydryl enzyme** that interferes with their action to **inhibit the metabolism of the cell.**

2) **Lead inactivates** the **enzymes** involved in the **synthesis of heme in anaemia.**

- **These enzymes include:**

  i) Aminolaevulinic acid dehydrase

  ii) Aminolaevulinic acid synthetase

  iii) Coproporphyrinogen oxidase/decarboxylase

  iv) Ferrochelatas

3) **Lead increases** the chances **of haemolysis** due so which **immature red Mood corpuscles**, like **reticulocytes and basophilic tipped cells**, are released into he systemic circulation.

❖ Clinical Sign & symptoms of lead toxicity include

1) **Acute poisoning**

   i) Abdominal pain

   ii) Metallic taste

   iii) Vomiting,

   iv) Constipation

   vi) Ataxia

   vii) Lethargy or hyperactivity

   viii) Convulsions

   ix) Behavioral changes

   x) Coma

   iv) Diarrhea (stools might be blackish colour due to lead sulphide)

2) **Chronic poisoning**

   i) Mild toxicity

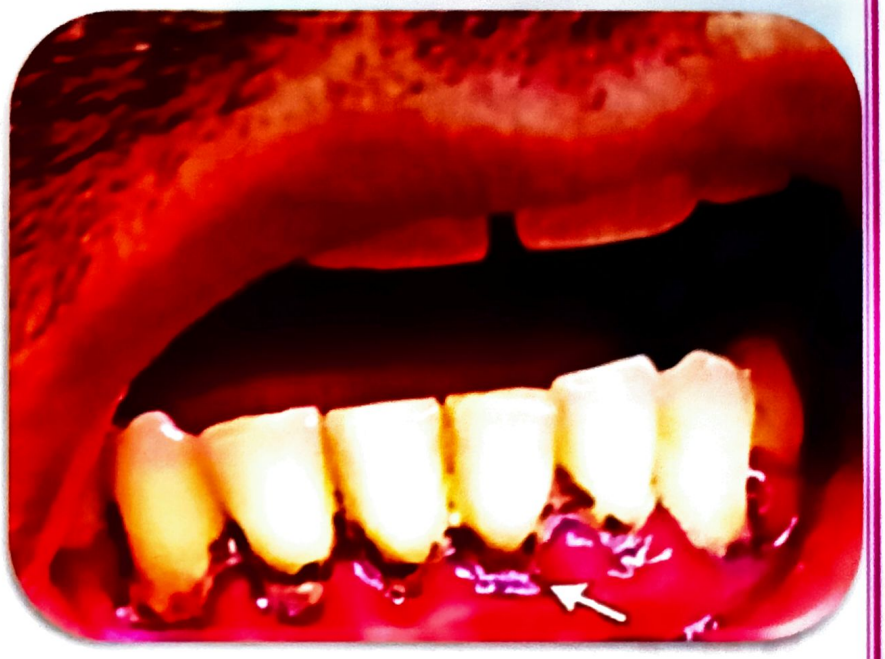
   a)Paranesthesia

   b) Abdominal discomfort

   c) Myalgia

   d) Fatigue

ii) Moderate toxicity



a) Headache

b) Vomiting

c) Metallic taste

d) Anorexia

e) Irritability

g) Diffuse abdominal pain

h) Muscular fatigue

iii) Severe toxicity

a) Lead Colic: Severe abdominal cramps at irregular intervals with tenderness around the umbilicus.

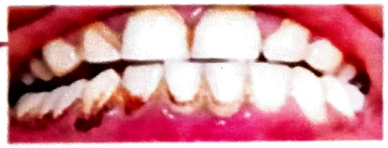
b) Lead Palsy : Foot or wrist drop.

c) Burton's Line: A bluish black line of lead formed on the gums.

d) Lead Encephalopathy:

- Tetraethyl Lead (TEL) and is commonly found in children. TEL is soluble in lipid and widely distributes itself in the **lipophilic tissues, like brain.**
- This TEL breaks down to form the main toxic compound, triethyl lead, which causes **headache, vertigo, ataxia, sudden onset of vomiting, convulsions, coma, irritability, psychotic manifestations, and death.**

Lead Poisoning



❖ Management

➢ **Treatment of lead poisoning depends on the severity of toxicity in the blood**. It includes the following measures:

1) Moderate poisoning (blood lead level between 45-70mcg/100 ml)

i) **Ethylenediamine Tetra acetic Acid (EDTA)** must be given in dose of **50mg/kg/day.**

ii) Begin oral chelation when the level of blood lead falls below 40mcg/100ml.

2) Mild poisoning (blood lead level between 20-35mcg/100ml):

- **D- Penicillamine: 30 mg/kg/day** administered in **3 divided doses** started with 1/4 dose of the calculated dose. **Double the dose** after each **1 week for 2 consecutive weeks.**
- Continue the dose for **next 3 months** or till the **level of lead in blood falls** to **less than** 15mcg/100ml.

3) Severe poisoning (blood lead level more than 70mcg/100ml)

i) **Dimercaprol or British Anti-Lewisite (BAL)** in the dose of **12mg/kg/day.**

ii) **Ethylenediamine Tetra acetic Acid (EDTA)** in dose of **50mg/kg/day.**

iii) **EDTA** is continued for further **5 days,** but if the **blood lead level falls** below **40mcg/100ml**, then **BAL is discontinued**.

iv) **Oral chelating agents** are given subsequently **after EDTA and BAL** which are continued till the **lead level in blood falls below 15mcg/100** ml or for further **3 months** .

v) **Severe acute poisoning** with **encephalopathy** occurs as a **medical emergency** and following measures are to be taken immediately.

a. In children, **BAL 4mg/kg** is administered
b. To check out for **cerebral oedema, cranial CT scan** is done.

- Maintaining **arterial CO_2 tension** of **25-30mmHg** and **controlled hyperventilation helps in reducing intracranial pressure** in patients in which the **mental status worsens lateralizing neurological conditions**, and sign of impending hermiation.
- Continuous monitoring of **intracranial pressure.**
- Careful monitoring of **renal functions**, **cardiovascular functions** and **serum electrolytes**.

c) Monitoring **specific gravity**, **sediment** and **lead level of urine.**

d) **$CaNa_2$, EDTA in dose of 75 mg/kg/day** through **IV infusion** which is **reduced to 50 mg/kg/day** as the condition improves.

❑ Mercury Poisoning

- Mercury is a naturally occurring element found in **air, water and soil.**
- A **highly toxic form (methyl mercury)** builds up in **fish, shellfish** and **animals that eat fish.**
- Mercury is also known as **Para** or **Quick silver.**

➢ **Mercury exists in three forms:**

1) **Elemental mercury vapors are toxic**
2) **Organic mercury compounds are more toxic than inorganic mercury compounds, e.g., methyl mercury, ethyl mercury, mercurochrome.**
3) **Inorganic mercury compounds**

➢ **It is used for various purposes such as:**

i. **Ceramics**
ii. **Fingerprint powder**
iii. **Pesticide**
iv. **Embalming**
v. **Dry cell batteries**
vi. **Barometers and thermometers**

vii. **Antiseptic and disinfectant**

viii. **Grain preservative**

ix. **Paints**

❖ Mechanism of Toxicity

- The toxic effect of mercury is **produced by inhibition of enzymes**, **precipitation of proteins**, and **general corrosive action of the metal**.
- Mercury **inhibits the actions of cellular enzymes** by **binding** with the **sulfhydryl groups of the enzymes**, as well as with the **carboxyl, amide, phosphoryl** and **amine** functional groups of the **proteins** and various **enzymes.**

❖ Signs and clinical Symptoms

Mercury toxicity shows following signs and symptoms

1) Inhalational mercury

i) **Cough, breathlessness**

ii) **Headache, fever with chills (also called metal fume fever)**

iii) **Convulsions**

iv) **Ataxia**

v) **Blurring of vision**

vi) **Delirium**

vii) **Non-cardiogenic pulmonary oedem**

2) Injectable mercury

i) **Intramuscular or Subcutaneous Injection:** Abscess formation with ulceration.

ii) **Intra-arterial Injection:** Peripheral embolism with gangrene and ischemia.

iii) **Intravenous Injection:** Granuloma formation, thrombophlebitis, and pulmonary embolism.

3) Oral mercury

i) Abdominal pain
ii) Vomiting
iii) Shock
iv) Corrosion of tongue and mouth
v) Pinkish urine
vi) Loosening of teeth
vii) Nausea
viii) Metallic taste
ix. Hematemesis
x. Renal failure
xi. Pulmonary edema
xii. Glossitis, halitosis, blue line on gums, and ulcerative gingivitis
xiii. Jaw necrosis
xiv. Membrane colitis
xv. Tremor
xvi. Dementia

❖ Management

- Dimercaprol is a **chelating agent** used in the **treatment of acute poisoning by arsenic, gold and inorganic mercury.**
- It is also used in **conjunction with sodium calcium edetate** in **acute lead poisoning.**

➢ **Mercury poisoning can be managed as follows:**

1) Acute poisoning

i) Metallic mercury and inorganic compounds

a) Ingestion

- In case of **mercury ingestion, X-ray** is taken.
- If mercury reaches **appendix, appendectomy** is **performed.**
- **Laxative administration.**
- For corrosive compounds demulcents are used,
  e.g:- **Mercuric chloride.**
- **Stomach Wash: 5% albumin, plain milk,** or egg white is advisable to add to the **lavage fluid** in order to **chelate mercury.**

b) Injection

- In case of **abscess formation**, repeated **incisions are performed** for **mercury removal**. However, the **affected tissue is removed** if the **globules are very small** and distributed widely in **the intercellular spaces.**
- **Activated charcoal** is given as it well adsorbs the mercuric salts.
- **Chelation**
- **CNS and renal functions** are observed for toxicity of mercury.

ii) Organic mercurial

a) Supportive measures should be taken.

b) In case of **severe acute renal failure**, toxicity can be reduced by **hemofiltration, hemodialysis**, or **plasma exchange.**

c) **Chelation method** is **not effective** in case of **organic mercurial.**

2) Chronic poisoning

i) Supportive measures should be taken.

ii) **Chelation Therapy:** It includes the **chelating agents**, like **BAL, DMPS, DMSA, D-Penicillamine** , etc

a) **DMPS (2,3 Dimercapto Propane-1-sulfonate):** 6 infusions of 250 mg/kg or 5 mg/kg IV, followed by 100 mg orally two times a day for 24 days

b) **British Anti-Lewisite (BAL):** 100 mg deep intramuscular (IM) every 4 hours for 4 hours, followed by 100 mg every 8 hours for 8 to 10 days.

c) **DMSA (Meso 2,3 Dimercapto succinic acid, or succimer):** 30 mg/kg/day p.o. for 5 days, followed by 20 mg/day for 14 days.

d) **D-Penicillamine:** 250 mg once a day (qid), for adults (20 mg/kg/day) for 5-10 days.

❑ Arsenic Poisoning

- Arsenic is the twentieth common element occurring in the **earth's crust** in the **concentration of 1.8 ppm.**
- **Arsenic consists of both**
  - ✓ **Organic compounds** like **sodium cacodylate, atoxyl, cacodylic acid,**
  - ✓ **Inorganic compounds.** Such as **arsenious oxide, arsenic di sulphide , arsine, etc.**

❖ Mechanism of Toxicity

1) Arsenic toxicity results in **inactivation of mitochondrial enzymes**, like **dehydrogenase, succinic dehydrogenase, phosphorylase enzyme**, etc
2) The **inorganic pentavalent arsenicals** **does not react directly** with the **active site of the enzyme** and gets reduced to **trivalent arsenicals** before producing toxic effects.
3) This trivalent arsenicals binds to the **-SH and -OH groups** to interfere with the enzyme activity resulting in the **inactivation of pyruvate dehydrogenase**, thereby preventing the generation of **Adenosine-5-Triphosphate (ATP).**
4) Arsenicals also **inhibit the activity of succinic dehydrogenase** to **uncouple the oxidative phosphorylation**, thereby disrupting the **cellular functions** with in **mitochondria.**

❖ Signs and Symptoms of Arsenic Poisoning

System	Acute	Chronic
Gastrointestinal	Metallic taste, abdominal pain, vomiting, dysphagia	Weight loss, anorexia, diarrhoea.
Ocular	Lacrimation, conjunctivitis	Dimness of vision
Dermal (Skin)	Hair loss	Bowen's disease, facial oedema, melanosis (eyelids, nipples, neck),hyperkeratosis, hyperpigmentation(rain drop pattern skin cancer

Liver	**Fatty degeneration**	**Jaundice, cirrhosis, hepatomegaly**
Kidney	**Uremia**	**Nephritic changes**
Lungs	**Imitation of upper respiratory tract**	**Bronchitis , perforation of nasal septum , chronic laryngitis**
Cardiac	**Hypotension. cardiac arrhythmias tachycardia.**	**Myocarditis , hypertension**

❖ Management

Management of arsenic poisoning includes the following steps:

1) **Supportive Measures: Intravenous fluids, cardiac monitoring, gastric lavage, etc**

2) Adrenaline is a life-saving measure in cases of **vascular collapse**.

3) If arsenic is **taken orally in toxic doses**, **stomach is washed** with freshly **prepared ferric hydroxide** and **sodium thiosulphate** repeatedly to cleanse it from the poison.

4) **Chelation Therapy:** Arsenic can be chelated with **British Anti-Lewisite (BAL)** or **dimercaprol, penicillamine. Dimercapto succinic acid (DMSA)** or **Dimercapto propane sulfonic acid (DMPS)** to **eliminate** from the body.

i. **BAL** is administered **intramuscularly** at the dose of 3-5 mg/kg at every **4 hour** interval until the **urinary excretion of arsenic** drops **below 50 mcg/2 hour**. The therapy is followed for **7-10 days.**

ii. **DMSA** and **DMPS** are also administered as they have better action than **penicillamine** and **BAL.**

iii. **Penicillamine** can be **orally administered** in patients **not allergic** to penicillin at a dose of **100 mg/kg/day at 66 hour interval for 5 days.**

5) **Exchange transfusion or hemodialysis.**

CHRONOPHARMACOLOGY

Points to be covered in this topic

1. INTRODUCTION OF CHRONOPHARMACOLOGY
2. RHYTHM & CYCLES
3. BIOLOGICAL CLOCK & SIGNIFICANCE TO CHRONITHERAPHY

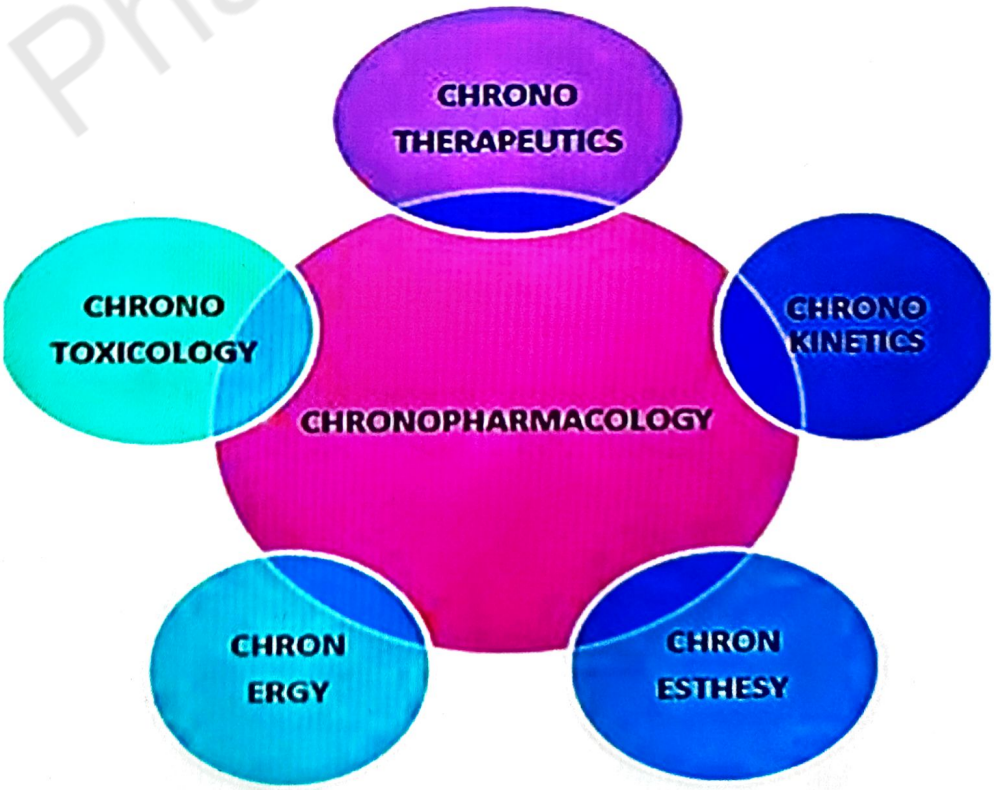
❑ INTRODUCTION

❖ CHRONOPHARMACOLOGY

- Halberg in **1960s introduced** the term **Chronopharmacology**.
- **Chronopharmacology** is the **science dealing** with the **optimizations of drug effect** and the **minimizations of adverse effects** by **timing medications** in relation to **biological rhythm.**
- It is the investigative science concerned with the **biological rhythm dependencies of medications.**

❖ Aims of Chronopharmacology

1) To improve the understanding of **changes in circadian rhythms (periodic and periodic table)** for both, **chrono effectiveness (desired effect)** and **chronotolerance (tolerance) of medicines.**
2) To facilitate **quantitative** and/or **qualitative changes** in **drug's efficacy** as **per the month, day** or **hour of drug administration.**
3) To study temporal differences in the **kinetics, activity** and **toxicity of drugs** depending on their time of administration.



SUBDIVISION

1) **Chrono kinetics:** It can be defined as the temporal variations in the pharmacokinetics of a drug which involves **absorption, distribution, metabolism** and **excretion of a drug.** It deals with the study of the temporal changes in the pharmacokinetics (ADME) of the drugs with respective time.

2) **Chronergy:** According to its chronokinetics and chronesthesy, it represents. the **rhythmic changes** in the **response of any individual** to the **drug** . Rhythmic changes of both the desired [effectiveness] and undesired [toxicity, tolerance] effects on the organism as a whole.

3) **Chronesthesy:** It is defined as the temporal variations in **the biological rhythms** including the **changes in target cell or organ receptors**, permeability of membrane, etc. It can also be defined as temporal changes in the **pharmacodynamics (mechanism of action) of the drug.** The rhythmic changes in **susceptibility or sensitivity** of a **target system** to a **drug.**

4) **Chrono toxicity-** The **toxic effect of drug on the organism**, which is **undesirable** and **affects the rhythmic system**. Specifically with antitumor agents. it may be defined as the changes in an **organism's sensitivity** to toxicants in relation to time.

5) **Chronotherapeutic**

Increase of the efficiency and **safety of medications** by proportioning their **concentrations during the 24 hours** in synchrony with biological rhythm determinants of disease. **Study of effective therapy relation** to **biological rhythm of a disease .**

❖ Purpose of Chronopharmacology

There are specifically two reasons for the development and study of Chronopharmacology.

1) **Auto-Induction**:- A **repetitive dose of a drug induces** or **increases enzymes responsible** for its **elimination**, there by **increasing its clearance.**

Ex. Carbamazepine

- The **oral bioavailability decreases** or clearance increases with time.
- Due to repetitive oral administration

2) **Auto-Inhibition** :-

- It is also called **feedback** or **product** or **allosteric inhibition** as in this **process**, the **metabolites of drug** after its metabolism are **first increased in concentration,** followed by **inhibition of parent drug metabolism .**
- It occurs during the **metabolism.**

❖ **Biological rhythm** is a phrase often used interchangeably with circadian rhythm. These rhythms are **a series of bodily functions regulated by your internal clock**. They control cycles like **sleep** and **wakefulness, body temperature, hormone secretion**, and more.

❖ Biological Rhythms Affecting Our Body

i. **Circadian (24 hours) :-** Circadian rhythms are **physical, mental, and behavioral changes that follow a 24-hour cycle**.eg:- Sleep & wakes cycle.

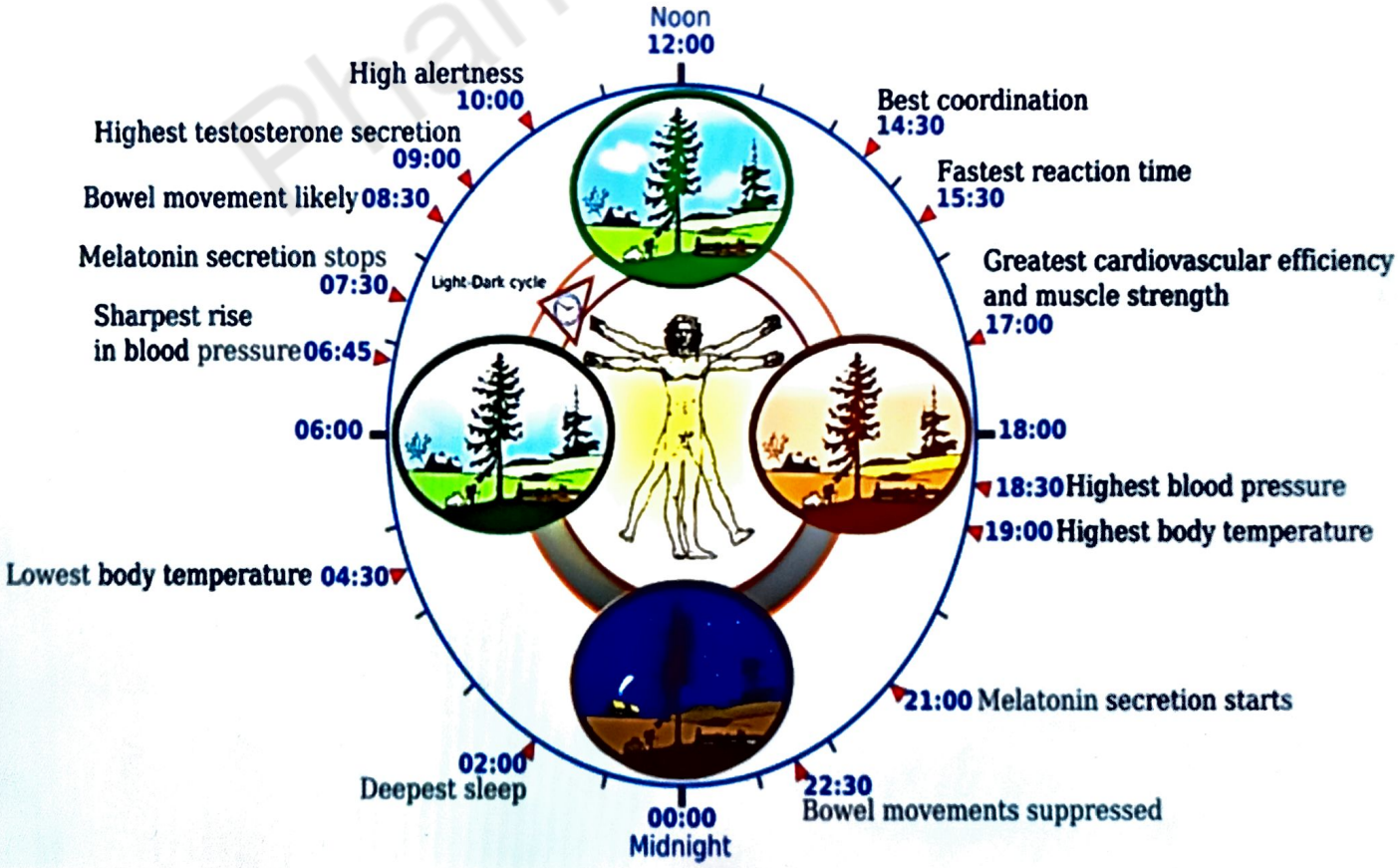
ii. **Ultradian (less than 24 hours) :- cycles shorter than a day. Eg:- microsec ,for a neuron to fire.**

iii. **Infradian :-** cycles longer than 24 hrs eg:- menstrual cycles

❑ Rhythm/Circadian Rhythm

The word circadian has been derived from the Latin word **circa** which means about and **dies** which means **a day**.

- It is defined as oscillations in the **biological, physiological** and **behavioral function** of an **organism** with a periodicity of **24 hours.**
- The **circadian rhythm regulates** many important **behavior** in all the **living organisms.**
- It enables the organisms to **maintain** and **restrict** their activities according to the **day** and **night time**.
- However, the human body also maintains its **homeostasis by carrying** out its normal functions according to the time cycle.
- For example, in the evening when the **light intensity decreases** in the **eyes**, the **master clock stimulates** the **production of melatonin hormone** responsible for **generating a drowsiness feeling** which helps in **maintaining the sleep** .
- Circadian rhythm and its **sensitivity to time might change** with changes in the age of any individual.



Human Circadian Time Structure

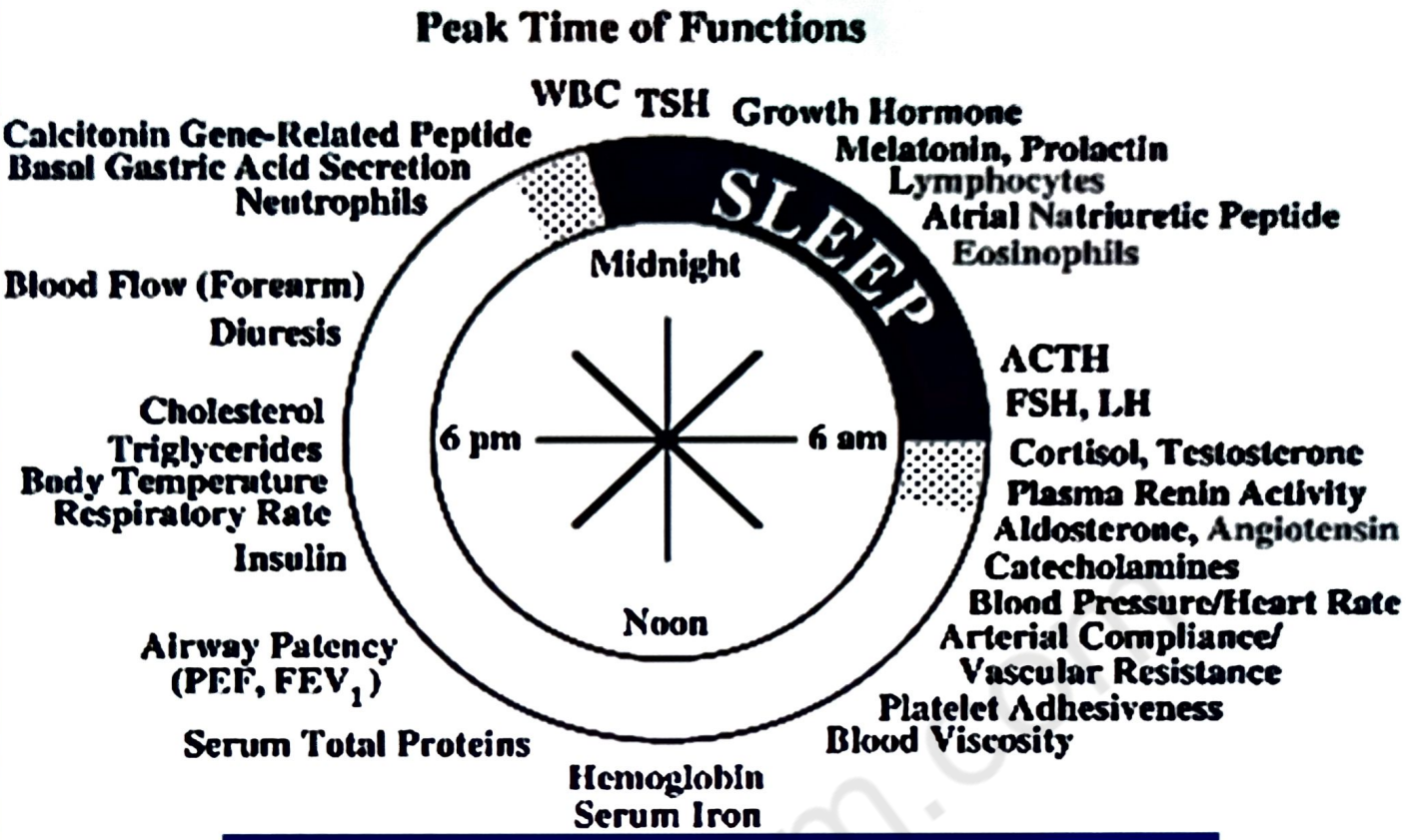


Fig :- Human circadian time structure

❖ Biological Rhythms of Different Systems

1) Respiratory System:

- Bronchoconstriction at **night increases** due to increased **parasympathetic tone**, **decreased adrenaline** and **decreased cortisol** at **midnight**, and **increased sensitivity to irritants** and **allergens at night.**

2) Gastrointestinal Tract:

- **Acid secretion** is **2-3 times greater between 10 pm and 2 am.**

3) Cardiovascular System:

- Amplitude of **24 hour variation** is more for **diastolic blood pressure** as compared to **systolic blood pressure**. Blood pressure shows two **peaks** at **9-11 am** and **6-7 pm**. Blood pressure decreases (slight) at afternoon and shows profound dip at night.

4) Endocrine System: Cortisol

- Highest secretion is just before **awakening in the morning** and is lowest at mid-night. **Growth Hormone Peaks** during **sleep**. **Testosterone** Peaks early morning. **Insulin-5-10 fold increase** after ingestion of food.

5) Receptors

- Circadian rhythm has been found for **receptors in brain and heart** of **rats** and **blood cells in humans**.

6) Plasma Protein Binding

- **Albumin** and **acid glycoprotein** reach their nadir **during nocturnal rest** and their zenith in the morning. Therefore, **drugs bound to plasma protein,** like **valproic acid, carbamazepine, diazepam, lignocaine, prednisolone, show increase in free fraction at night.**

7) Liver Enzymes

- Oxidative reactions peak in the middle of the (nocturnal) activity span **Conjugation catalyzed** by **UDP-glucuronyl transferase** is greater during activity than during the rest phase .**Sulphate conjugation** is **faster** during the **rest** than **during activity.**

❑ Cycle/ Biological Cycle

- All the living organisms, including **humans, plants, animals, fungi** and other microorganisms have adapted a **biological process** that regulates at **24-hour day night cycle.**
- The biological cycle also called as **circadian cycle regulates** itself in every living organism to carry out the important biological functions, like **sleep awakening cycle, blood pressure, hormone secretion, metabolism and many more.**

❑ Biological Clock and their Significance Leading to Chronotherapy

- The time structure of **human circadian** is always **peak for 24 hours.**
- The **peak time of rhythm of human circadian** is always in synchronization with the **routine sleep occurring** in the **darkness** from **10:30 pm to 6:30 am** (in morning) up to the activities taking place in **day light** from **6:30 am to 10:30pm.**
- However, the **human circadian** time **structure helps** in **determining the peak time of 24 hour rhythms** on the **circadian clock.**
- All the physiological activities of the body occur at a specific time according to the **circadian cycle**, for example, **basal gastric acid secretion**, **calcitonin (gene-related protein)** and arterial natriuretic peptide occurs either early in the morning or late at night.
- **Blood lymphocyte** and **eosinophil number**. **Thyroid Stimulating Hormone (TSH), Growth Stimulating Hormone (GSH), plasma melatonin** and **prolactin release** in at its **peak during sleep.**
- **Follicle Stimulating Hormone (FSH), Adrenocorticotropic Hormone (ACTH), Luteinizing Hormone (LH), rennin, plasma cortisol, angiotensin** and **aldosterone** are all released in the **morning** and reach their peak level.
- The circadian rhythms of **triglycerides, serum cholesterol** and **urinary diuresis** are also at their peak level in the early evening.
- The **circadian clock functions** as an instrument in **determining the day-night length and seasonal phenomena.**
- The **circadian rhythms** and **master clock network** is **controlled by the pineal gland.**

- This **master clock network** operates the **period** and **phase** of the **multitude of peripheral circadian clocks** located in **cells**, **tissues** and **organ-systems.**
- Therefore, the biological clock is significantly related with the **chronotherapeutic system** for **treating different pathophysiological** conditions and **effect of drugs** according to their **biological clock.**
  1) Circadian rhythms play an important role in **determining** and even **controlling** the **pathophysiology of diseases.**
  2) It is useful in **preventing the degradation of drugs**, like **proteins** and **peptides in upper GIT.**
  3) It helps in programmed **delivery of hormones**, as **continuous release of hormones** as dosage form might cause disturbance in normal feedback mechanism and development of resistance.
  4) Drugs that develop **biological tolerance**, like **nitroglycerine.**
  5) It helps in study of drugs undergoing extensive **first pass metabolism** and those targeted to specific gastrointestinal tract site.eg:- **colon, duodenum, rectum, etc.**

❖ Location of biological clock

- In humans biological clock **located in neurons**, in the **hypothalamus**, specifically in the **suprachiasmatic nucleus**, or **SCN.** Function as the main biological clock.
- The SCN is located near the parts of the **hypothalamus** that **monitor body temperature** and **control eating and drinking.**

❖ Procedure of biological clock

- **Endogenous (internal) mechanism.**
- Internal rhythms are thought to be generated by **protein synthesis within the SCN.**

- **Protein** is produced for a **period of hours** until it reaches a level that **inhibits further production.**

❖ Importance of biological clock

- It plays a **vital role** in our body.
- It not only **determines our sleep** and **waking patterns**, but also ensures that almost **all processes in our body**.
- It can also be **found in the cells** of our body which means that, depending on the time of day, our body is **more sensitive** or **less sensitive** to certain substances.

❑ Chronotherapy

- The treatment of **biological rhythm** is known as chronotherapy

❖ Advantages of chronotherapy

1. When a **person sleeps for several hours** then the **chronotherapy** is **more effective.**
2. Chronotherapy requires **no drug.**
3. While using chronotherapy a patient often **fall asleep** this **improves their condition and confidence.**

❖ Disadvantages of chronotherapy

1. Need of **consulting** the **doctor** and sleep specialists regularly to **avoid side effects.**

2 Unusual feeling of **hot or cold** when the person is **undergoing therapy.**

3. Patient incompliance as he has to keep himself awake till the **next sleep schedule.**
4. Sometimes the patient may also be sleep deprived.

➢ **Chronotherapy can be used in the treatment of various diseases given below:**

1. **Hypertension** 2. **Myocardial infarction**

i) HYPERTENSION

- In **hypertension** the **systolic bloods pressure raises up** to **3 mmHg/hour for 4-6 hours** after **getting up** which is **called** as **post-awakening** and the **diastolic blood pressure** also rises up to **2mmHg/hours.**
- **Blood pressure** and **heart rate** will be **high at the time of walking** in the **morning** and it will begin to **decrease in the afternoon** and **reaches minimum at mid night.**

ii) MYOCARDIAL INFARCTION

- **Platelet aggregation** and the **vascular tone is high** in the **morning** when the **release of the catecholamine** and **cortisol is high.**
- **Cyclooxygenase inhibitor-2** will **relieve the pain effectively** when **taken** in the **morning.**