TOXICOLOGY

Topics covered

- Definitions, history of toxicology
- Sources and classification of toxicants, factors modifying toxicity
- General approaches to diagnosis & treatment of poisoning
- Toxicity caused by Arsenic and Mercury

- Toxicology is the study of poisons and their effects on living organisms

- Xenobiotics: substances that are foreign to the body and are biologically active.

- **Poison/ Toxicant:** any substance which when taken inwardly in a very small dose or applied in any kind of manner to a living body depraves the health or entirely destroys life (M.J.B. Orfila) – father of toxicology

- *"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy"* --- Paracelsus.

Disasters related to toxicology

- Thalidomide in pregnant women – phocomelia
- Minamata disease due to Methyl mercury in Japan
- Itai – itai disease: due to Cadmium toxicity
- Bhopal gas tragedy - methylisocyanate in 1984
- Chernobyl nuclear accident – Ukraine
- Ginger Jake paralysis: TOCP---OPIDN

Sources of toxicity

- Plants: Lantana, Bracken fern etc
- Animals: poisonous animals like snake, toad
- Micro-organisms: Toxins produced by certain fungi and bacteria
- Minerals: Metals and non metals
- Agrochemicals
- Radiations
- Environmental pollutants

Toxicity of Oleander

- One of the most poisonous plants in the world
- A single leaf could be lethal to a child
- Most significant toxins include oleandrin and neriine, which are cardiac glycosides
- Entire plant, leaves, flowers, bark, etc., is poisonous
- 847 known human poisonings in the US in a year
- Poisonings require immediate medical care; inducing vomiting and gastric lavage, and, in life-threatening cases digoxin immune fab, are common treatment

Factors affecting/influencing toxicity

- Solubility: high lipid solubility - more readily absorbed through the **lipid- protein matrix** of the cell membrane. So more toxic than those which are water soluble.
- Oxidation state of the compound: Trivalent arsenic is more toxic than the pentavalent arsenic.

- CO is more toxic than CO 2 .
- Nitrates (NO3 -) are reduced to nitrites (N02 -) by ruminal and intestinal micro flora and toxicity is produced by nitrites.

Species variation

- Atropine is nontoxic to rabbits due to presence of atropinase
- No glucuronide formation in cat due to lack of enzyme uridinediphosphate glucuronyl transferase
- No etheteal sulphate in pigs due to lack of enzyme Phenolsulphotransferase
- Carnivorous animals - glucuronide formation common, Herbivorous animals – amino acid conjugation common
- Acetylation: dogs do not acetylate due to the presence of a natural inhibitor in liver of the enzyme arylamine transacetylase

- Ivermectin is more toxic to Collie breed of dogs as it readily crosses blood-brain barrier in this breed.
- Greyhound Dog - More susceptible to barbiturate toxicity
- Bedlington Terrier –Genetic predisposition for Cu toxicity

- Sheep - more susceptible to chronic copper poisoning
- Response of horse or rat to Bracken poisoning is clinically and biochemically different from that of cow or sheep.
- Thiaminase enzyme present in bracken fern destroys Vitamin B1 essential for horse and rat. In ruminants, the vitamin is synthesized by ruminal organisms and an exogenous source is not required.

DIAGNOSIS AND GENERAL TREATMENT OF POISONING

- History
- Clinical evidence
- Circumstantial evidence
- Pathological evidence:
  - Cherry red/pink m.m. : CO, cyanide poisoning;
  - Brown/cyanotic m.m.: nitrite poisoning
  - Yellow color: nitric acid poisoning
  - CN poisoning: Bitter almond smell (it is HCN gas)
  - H2S poisoning- rotten egg smell
- Analytical evidence
- Experimental evidence
- Response to treatment

Analytical evidence: Samples for Diagnosis

- Quantity of material:
- Blood- 60ml
- Brain- whole (useful for lipid soluble poisons)
- Liver- 500g for large animal and 200g for small animal
- Kidney- 1 kidney
- Stomach/intestine contents- 500-1000 g separately
- Hair- 5 g
- Bone- 1long bone
- Urine- entire quantity (both sides of urinary bladder be tied and send as such)
- chemical preservative is used, 95% ethyl alcohol
- suspected CN poisoning- 1% mercuric chloride

Specimens required for specific poisons

1. Liver: Cu, fluoroacetate, thallium, warfarin, Zn, CCl_4, chloroform

2. Kidney: As, OC insecticides, Cu, ethylene glycol, fluoroacetate, oxalates, thallium, Zn, Hg, sulfonamides.

3. Stomach and intestinal contents: ammonia, ANTU, As , OP and OC compounds, fluoroacetate, phenols, plant poisons, CN.

4. Whole blood: NH_3, Ca (serum), CO, OC, OP (heparinized), Cu, CN, NO_3/NO_2, PO_4 (serum), chlorate

5. Urine: NH_3, As, ethylene glycol, fluoroacetate, OP compounds, thallium
6. Faeces: Cu
7. Vomitus: Acid/alkalies, As, Pb, NO_3/NO_2, chlorate, ANTU, fluoroacetate
8. Bone: Lead, fluoride, selenium
9. Hair: Chronic As poisoning
10. Fat: OC (DDT) about 100 g, OPI about 50 g, thiobarbiturates
11. Milk: Se, F

Treatment

(i) To prevent further absorption of poison
(ii) Use of supportive and non-specific agents
(iii) Specific treatment (antidotal treatment)

Use of emetics: In dogs and cats, vomition may be induced to empty the stomach. e.g. Apomorphine HCl

Universal adsorbent mixture (universal antidote)

- Activated charcoal- 10 g
- Light magnesium oxide- 5 g
- Kaolin- 5 g
- Tannic acid- 5 g

Therapeutic Index (TI)

- quantifies the safety and efficacy of a drug
- ratio of the dose that produces lethal effect (LD50) to the dose that produces the desired therapeutic effect (ED50) in a population
- TI = LD50/ED50
- higher TI - safer drug

LD_{50}	Classification
<5 mg/kg	Extremely toxic
5–50 mg/kg	Highly toxic
50–500 mg/kg	Moderately toxic
500–5,000 mg/kg	Slightly toxic
5000-15,000 mg/kg	Practically non-toxic
>15,000 mg/kg	Relatively harmless

Loomis & Hayes, 1996

Arsenic Toxicity – King of Poisons

* inorganic and organic arsenical compound. Inorganic form is more poisonous than organic.

*Order of toxicity is **Arsine> As+3 > As+5**

* Herbivores are more prone because they are more likely consumed contaminated forage.

* It is used as rodenticides, herbicide and pesticide.(Lead arsenate is used as taenicide in sheep and growth promoter in poultry)

* Used in mining operations (for smelting), so in industrialized area air is polluted with arsenic.

Toxicokinetic

- route of entry is generally by ingestion
- The **highest levels found in liver (primary),** kidneys, heart, and lungs.
- In chronic exposures, arsenic accumulates in skin, nails, hooves, sweat glands, and hair.
- It does not crosses blood brain barrier (BBB).
- It crosses placental barrier & cause foetal damage.
- The majority of the absorbed arsenic is excreted in the bile, milk, saliva, sweat urine & faeces by process of methylation.

Mechanism of action

- Trivalent arsenic compounds : inhibition/slowing of glycolysis and TCA cycle by interacting with **sulfhydryl group of enzymes(alpha-lipoic acid) , Pyruvate dehydrogenase system**
- may combine with SH group of glutathione peroxidase (GSH)

- Pentavalent arsenic - uncouple oxidation phosphorylation.
- may produce demylination and axonal degeneration (due to interference with vitamin B).

- Arsine gas: hemolytic agent and cause pulmonary oedema
- most toxic form of As and there is no treatment.

Clinical signs

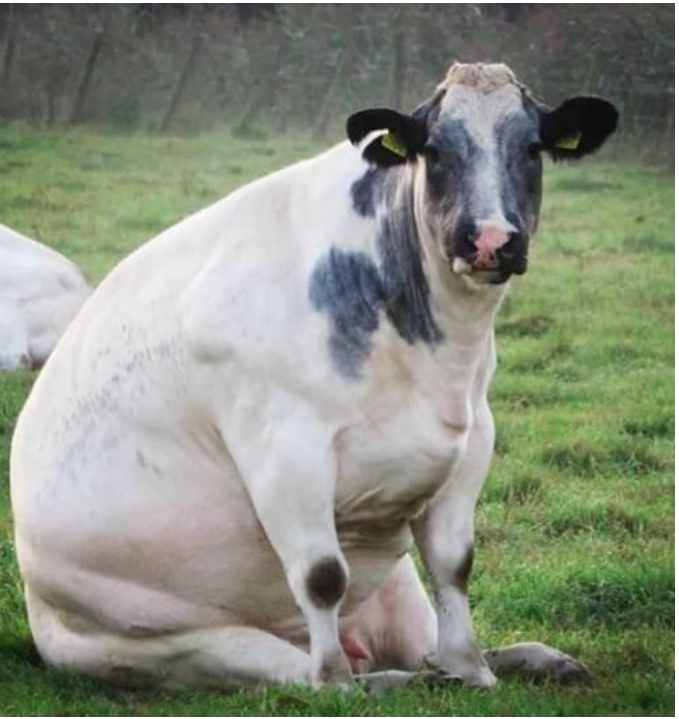
Acute poisoning :-

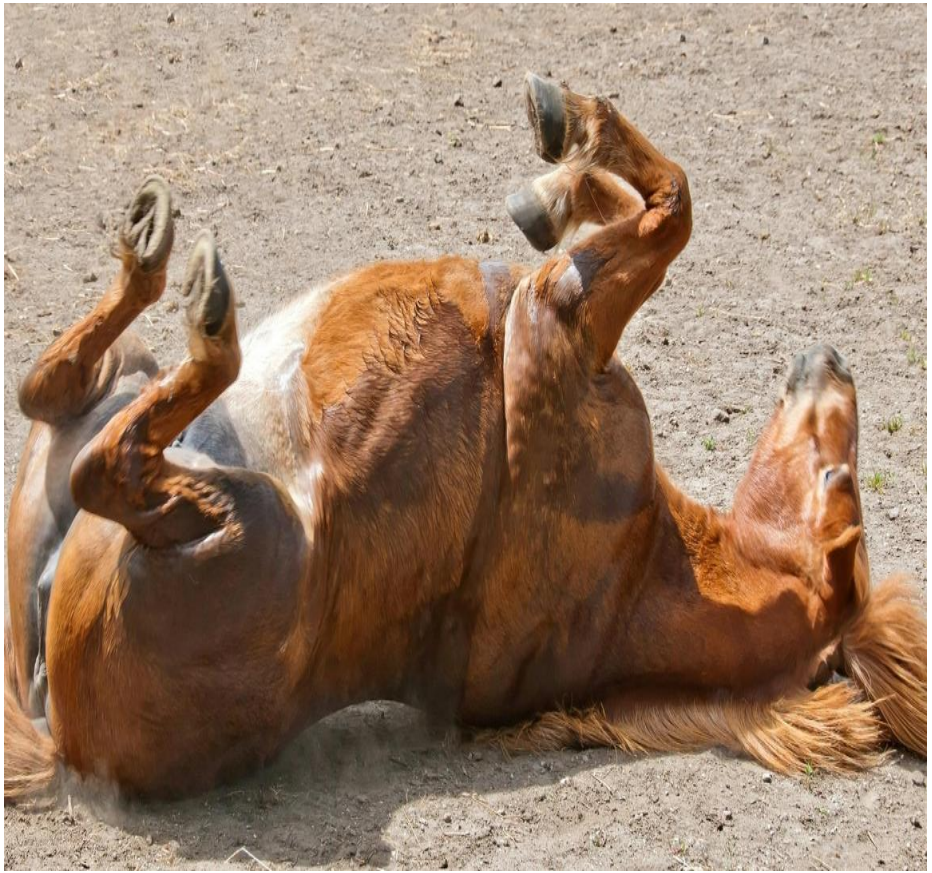
- Poisoning is usually acute with major effects on the GI tract and cardiovascular system.
- watery diarrhoea (rice water diarrhoea)
- severe fall of B.P and hypovolemic shock

- Subacute: staggering gait, paralysis of hind quarter, dehydration etc

- Chronic: **brick red mucous membranes**, poor condition, animal become thirsty, pulse weak and irregular, reproductive disorder. Tying up in horse

- Pentavalent As salts: Nervous symptoms like motor incoordination, ataxia, and blindness. Animal assume dog sitting posture.





Post-mortem changes

- intense rose-red inflammation of alimentary tract
- Garlic like odor in arsine toxicity
- Diagnosis :
- (a) Liver- most useful material for chemical analysis
- (b) Kidney: considered better in organic As poisoning
- In chronic As poisoning: Levels of As are analyzed in Hair and can be very high (even μg)
- Marsh Test – to detect As toxicity

Treatment

- **Dimercaprol (BAL, British Antilewsite) - Classical antidote**
- Sodium thiosulphate
- Thioctic acid
- MDSA (Meso dimecaptosuccinic acid) and DMSA (Dimercaptosuccinic acid) - water soluble and derivative of BAL

Mercury

- Aristotle named it **"Quicksilver"**.

- Mercury exists in a variety of chemical forms, including ---
  Elemental mercury (Thermometers, light bulbs),
  Inorganic mercurial (Mercuric or Mercurous)
  Organic mercury called organomercurials, found in 2 forms - aryl (e.g. phenyl) and short and long chain alkyl (more toxic than aryl)
- organic mercurials - more toxic than inorganic mercury compounds.

* Methyl mercury - can bioaccumulate in certain edible freshwater and saltwater fish.

* The release of methyl mercury into an ocean bay (Minamata) in Japan in the 1950s led to a massive health disaster, and the clinical syndrome was named **Minamata disease**. Thousands of people were poisoned, and hundreds of them had severe brain damage.

Inorganic mercury :-

- Absorption is poor to the extent of 2- 10%.
- It is distributed non-uniformly after absorption; highest concentration of mercury is found in kidney where it is retained for a long period.
- Concentration of mercury are similar in whole blood and placenta.
- Inorganic mercury do not crosses blood brain barrier.
- excreted via urine and stool.

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Organic Mercury :-

- It is more completely absorbed from the GIT then inorganic form. Intestinal absorption of organic mercury may be as high as 95% of the dose given.
- It crosses the placental barrier and blood brain barrier hence produce more neurological & teratogenic effect than inorganic form.
- Major route of excretion is through faeces; they are also readily excreted via urine.

Mechanism of Toxicity

Inorganic mercury

due to its interaction with sulfhydryl/ dithiol (SH) group of protein and precipitate it, i.e. it interferes with protein metabolism and their corrosive action directly damage the GIT mucosa.

organic mercury : similar to inorganic additionally

Methyl Hg inhibits choline acetyl transferase (CAT) enzyme leading to acetylcholine (Ach) deficiency which leads to motor dysfunction

* **easily absorb through GIT**
* **crosses different cellular membrane**
* **crosses PB & BBB hence causes harmful teratogenic & neurotoxic effects**

Clinical signs

- **Organic mercury: Neurological Signs**
- **Inorganic mercury:-**

❑ **Acute – mainly the effect GIT & Kidney**

GIT – The symptoms are metallic taste in mouth, abdominal pain, diarrhoea with blood in the faeces leading to dehydration

Kidney – Oligouria followed by anuria, albuminuria, and uraemia.

❑ **Chronic –** kidney damage is the main symptom. Increase urinary excretion of alkaline phosphatase is found to be sensitive indicator of kidney damage

❑ **mercurial ptyalism** - to profuse salivation, swelling of gums, loosening of gum and teeth and necrosis of jaw bones

Treatment

Specific treatment:-

- **BAL (British anti-lewisite)** @ 3 mg/kg, IM, every 4 hr for the first 2 days, every 6 hr for the third day, and 12 hrly for the next 10 days or until recovery.

- D-Penicillamine is used as an antidote in the human being

- **Non-specific treatment:-**

* Gastric lavage for removal of poison from the GIT.
* Administration of proteinous liquid to protect the GIT.
* Selenium and Vitamin E reduces toxicity

Diagnosis: Grunwald test

Lead Toxicity

- plumbism, colica Pictonum or Saturnism
- most common cause of metallic poisoning in dogs & cattle.
- Goats, swine and chickens are more resistant
- animals ingest lead-based paints
- Vegetation grown in lead smelters areas and near highways where plants accumulate lead are other important source of lead poisoning.

Toxicokinetic

Absorption:-

- GIT & respiratory system

- After absorption a large proportion (85-90% in sheep & 65-70% in cattle) of lead in blood is carried to erythrocytes membrane as Lead phosphate

Distribution:-

majority bound to RBC only small fraction is present in unbound form & cause toxicity

About 95% of the total body burden of lead is present in the bone & hence **bone** is considered to be a **"sink" for lead**

crosses placental barrier & blood brain barrier

Excretion:-

- Lead is normally excreted via kidney small amount excreted through bile & sweat.
- excreted in dangerous amount through milk

Mechanism of toxicity

- Leads depresses **aminolevulinic acid(ALA) dehydratase enzyme** (copper containing enzyme)
- resulting in increase serum level of δ-aminolevulinic acid and its excretion in urine

- Lead appears to inhibit **haem synthetase/ Ferrochelatase**, a thiol containing enzyme which is required to incorporate iron in the haem molecule.
- prevent entry of iron from cytosol to mitochondria.

Clinical Sign

gastrointestinal, central nervous system & hematological system.

GIT Symptoms :-

Anorexia, colic, dullness and transient constipation frequently followed by diarrhea

CNS symptoms :-

- In cattle - depression, weakness and ataxia can progress to more severe clinical signs of muscle tremors head pressing ,blindness, jaw champing, muscle tremor and convulsion.

- Horses develop acute lead toxicosis & show clinical signs of **pharyngeal paralysis (roaring) and dysphagia** frequently resulting in aspiration pneumonia.


Head pressing
Against the wall is
Neurological condition
In cattle

- **Hematological symptoms:-**

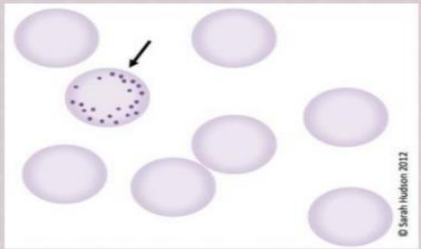
  Blood capillaries congested with enlarged and increased endothelial cells.

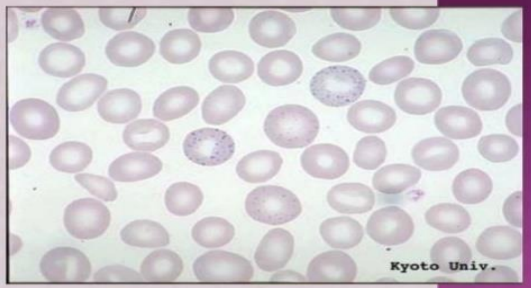
* **Basophilic stippling** (the aggregation of ribonucleic acid) of erythrocytes

* inhibition of hemoglobin synthesis are characteristic hematological features of lead poisoning.

BASOPHILIC STIPPLING

- Aggregation of ribosomal RNA in the cytoplasm of erythrocytes. These aggregates stain, and hence are visible, with routine hematology stains.





Treatment

Specific antidotal therapy

Disodium calcium EDTA(**Ethylene diamine tetra acetate**)

Thiamine - treatment lead poisoning in ruminants and is recommended for other species as well.

Corticosteroids and osmotic diuretics may reduce cerebral oedema in cattle and horses.

Diazepam and barbiturates may be used to control muscle tremor and convulsion.

Copper

- Dietary requirement in ruminants: 8-11 ppm
- Cu poisoning is common in sheep, while cattle & swine are somewhat resistant, poultry – most resistant
- sheep are affected most often because they accumulate copper in the liver
- Dog breed like Bedlington terrier breed is highly sensitive to Cu toxicosis, as genetic defects in breed cause excess storage of Cu in liver resulting in liver damage.
- Bordeaux mixture (contain 1-3% $CuSO_4$) - fungicide

- Low levels molybdenum and sulphate increase toxicity of copper. Ideal ratio of **Cu-Mo in diet is 6:1**
- toxic signs occurs if ratio in excess of 10:1. High SO4 level helps in more excretion of Cu
-
- Prolong ingestion of certain plants which are hepatotoxic with normal amount of Cu and low level of Mo.
- (**Cu accumulator plants– *Heliotropium Europeum, Senecio sp., Trifolium subterraneum*)**

Toxicokinetic

- absorbed through intestine in cuprous (cu+) form
- absorption Cu in the intestinal epithelial cells binds with metallothionein a cysteine rich protein
- From intestine Cu is transported to liver by **transcuperein** (high affinity to Cu) and albumin (low affinity to Cu)
- In liver Cu combines with metallothionein and is stored in lysosomes, mitochondria & nucleus for further utilization
- For the transport from liver to peripheral tissues it combines with blood **ceruloplasmin,** an a- globulin protein produced in liver

Mechanism of toxicity

- Excessive accumulation in hepatic mitochondria and lysosome which cause progressive hepatocyte damage and cellular degenration or necrosis
- inhibition of **dichlorolipoyl dehydrogenase**, which leads to inhibition of pyruvate dehydrogenase system
- causes weakening of erythrocyte membrane increasing there fragility leading to hemolysis
- Oxidation of hemoglobin by copper leads to methemoglobin **(Hemolytic crisis)**
- In swine in addition to the above feature copper inhibit the absorption *Fe* from the GIT leading to *Fe-Deficiency* anaemia (microcytic hypochromic anaemia)

Clinical Sign

Acute Toxicity:-

Severe gastroenteritis, abdominal pain , diarrhoea, anorexia, dehydration and shock

Faeces may appear deep green in color due to presence of Cu-chlorophyl compound

Chronic Toxicity:-

- Due to hemolytic crisis there will be free hemoglobin – which causes clogging of renal tubules leading to renal tubular and glomerular necrosis
- Signs in affected animals include generalised icterus, hemoglobinuria ,methemoglobinemia, hemoglobinemia
- Faeces & Vomitus- green to bluish in color
- Severe hepatic insufficiency is responsible for death.

P.M finding

- Enlarged pulpy spleen **(Black berry jam spleen)**
- **Bluish black kidney (Gun metal kidney)**
- Blood – may be chocolate coloured due to met Hb
- Port wine colored urine

Diagnosis

- **Estimation** in body fluids and tissues
- Level in faeces is around 8000-10000 ppm
- Increased values of Liver function test
- Chronic poisoning - 5-20 µg/ml in blood and >150 ppm in liver

- Liver to be sent for analytical examination

Treatment

- **Ammonium or sodium molybdate (50–500 mg) and sodium thiosulfate (250 – 1000 mg)** should be used daily as a drench for up to 3 weeks.

- D-Penicillamine or Calcium versenate may be useful if administered in early stages of toxicosis.

- Molybdenum in the diet can be increased to 5 ppm and zinc can be supplemented at 100 ppm to reduce copper absorption.

Molybdenum Toxicity- PEAT SCOURS, 'TEART'

- Mo: **oxygen transfer reactions** of aldehyde oxidase, sulfite oxidase, and xanthine oxidase
- The normal level requirement in Cattle is 5-6 ppm and for Sheep is 10-12 ppm
- ratio of 2 : 1 to 3 : 1 is borderline. The animal show toxic signs if it is

< 2 : 1.

- Dietary molybdenum of 10 ppm can cause toxicity regardless of copper intake
- Cattle are most susceptible.

Toxicokinetic

- inverse relationship with Cu
- High dietary sulphate increases Mo toxicosis by decreasing copper absorption
- increase in dietary Zn may increase the Mo toxicity
- **Water soluble form of Mo (tetramolybdate)-** more toxic than water insoluble from (Mo disulfide).

- absorption and excretion is rapid
- Mainly stored in kidneys and to some extent in bones
- also excreted in milk and may affect young calves suckling the dams
- eliminated very rapidly via the kidneys (>80%) and bile

Mechanism of toxicity

- Mo produces toxicosis as a results of Cu deficiency (Secondary hypocuprosis)
- Thiomolybdates bind to copper in the digestive tract & prevents absorption of copper
- Microcytic Hypochromic anaemia is characteristic due to inhibition of enzyme sulfide oxidase
- Cu deficiency produces falling disease in cattle and sheep
- progressive atrophy of myocardium with replacement of fibrous tissue, weakening the heart and causes sudden death after excitement or exercise

Teart

- Persistent scouring with passage of liquid faeces full of gas bubbles (teart)
- due to complex formation between molybdenum and catechols (bacteriostatic and control the activity of bacteria in the gut)
- excessive activity of bacteria which will cause diarrhea with liquid feces with lot of gas bubbles

Clinical Sign

- severe scouring making a 'parabola' (shooting diarrhoea)
- liquid faeces with lot of gas bubbles and unpleasant odours (called as **peat scours or teart)**
- Depigmentation of hair coat, noticeable in black animals specially around eye
- spectacled appearance appearance

- **Hypochromic anemia,** Joint pain, Osteoporosis, and decreased fertility.
- Sheep and young animal show stiffness of the back and legs with reluctance to rise this condition is called "**Enzootic ataxia**" in Australia and "**Swayback disease**" in the UK.
- In sheep, there is development of pica while Horses are generally resistant
- Osteoarthritic changes give the animal abnormal look and gait – called **pacing disease**

Treatment

- The two primary mechanisms of treating Mo toxicosis involve removal from the source of high Mo and copper supplementation
- Scouring can be controlled by daily administration **of Copper sulphate** 1gm for calves and 2 gm. For cattles.
- Copper glycinate injection S/C @ of 60mg. For calves and 2 Of 120m mg. for cattle can be given as an adjunct therapy
- 'Anti-teart cake' (containing prophylaltic amount of CuSO4)

*Mo level in blood > 0.1 ppm (and less than 0.6 ppm Cu) indicates Mo toxicity.

*Analysis of Mo in liver > 5 ppm (and less than 10 ppm Cu) indicates Mo toxicity

Selenium toxicity –

Blind Staggers,

Alkali disease,

DOG MURRAIN

*** Obligate indicator plants :**

10,000 – 15000 ppm for growth and survival.

accumulate high concentrations of selenium as water-soluble amino acid analogs of cysteine and methionine.

E.g - *Astralagus , Oonopsis* & Xylorhiza.

*** Facultative indicator plants:**

Absorb and tolerate large amounts of selenium (1500 ppm) if it is present in the soil

E.g - *Sideranthus, Aster & Atriplex .*

***Passive accumulator plants:**

May accumulate selenium if grown on seleniferous soils (20 – 60 ppm) E.g - Corn, Wheat & Barley

Toxicokinetics :-

- Se is readily absorbed from the gut and distributed throughout the body particularly to the liver kidney and spleen.
- Chronic exposure results in large concentration in hairs and hooves.
- Se can cross the placental barrier in mammals and also enters into avian eggs causing foetal malformation and embryonic defects.
- natural organo selenium> selenite (+4) = selenate (+6) > selenide (-2) > elemental selenium
- Se toxicity is most common in areas that have arid or" semi-arid climates (less than 20 inches annual precipitation)
- Se toxicity is most common in areas that have soils with pH levels above 7.0

Mechanism of toxicity

- The main mechanism of selenium is due to the incorporation of Se instead of Sulphur in some amino acids (Cysteine & Methionine) that's why hoof & hair defects in chronic Se Toxicosis.
- Se causes depletion of glutathione (GSH, GSH is required for cell integrity)
- Chronic selenosis depresses ATP formation due to inhibition of –SH containing enzymes viz. succinic acid dehydrogenase
- Tissue ascorbic acid (Vit C) decreases (due to enhanced oxidation by ascorbic oxidases which leads to vascular damage.

Clinical Sign

Subacute (Blind staggers) **(This condition in cattle manifested in three stage)**

- In the second stage depression, in-coordination and fore leg weakness, animal goes down on its knees.

- In the third stage colic, subnormal temperature, emaciation, swollen eyelids, near blindness. Salivation, lacrimation, severe abdominal pain, inability to swallow, complete paralysis, collapse and death

- **rooted to one spot**

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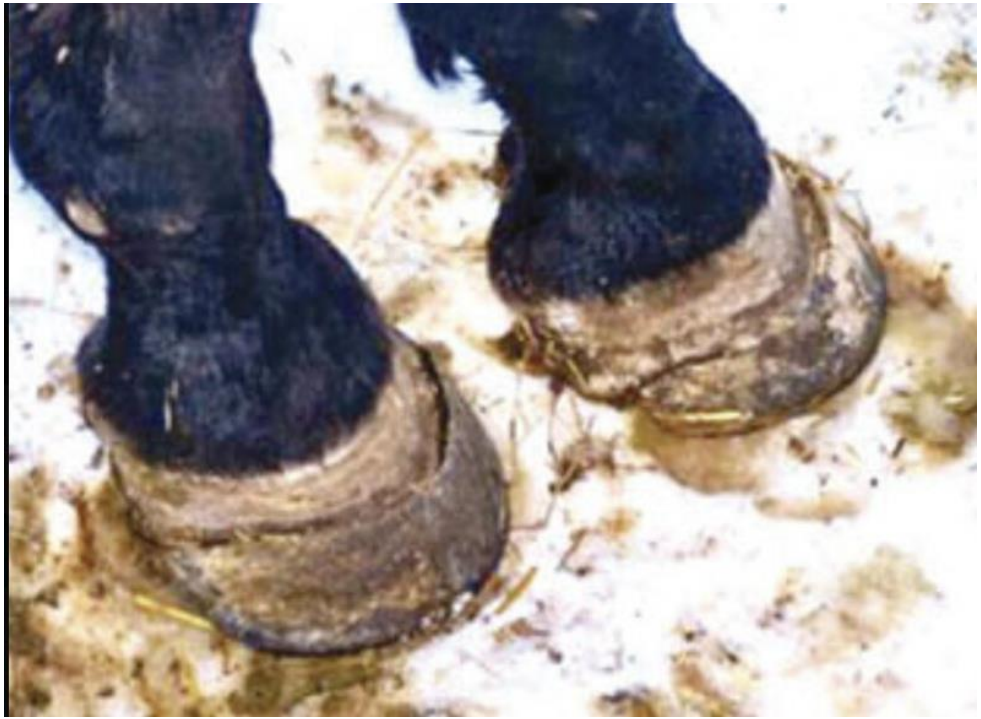
Chronic (Alkali disease)

- Lameness, hoof and hair abnormalities, partial blindness, paresis, in-coordination, emaciation and lethargy may be noticed.
- Lameness is due to erosion of the articulate surface of long bones.
- Hoof begins to shed. Shedding is incomplete and old hoof fuses with new hoof and form **abnormally long rocker shaped hoof.**
- In horses there will be loss of long hair from the mane and tail will occur
- "**bob" tail and "roached" mane appearance**, cracking and sloughing of hoof



Diagnosis & Treatment

Diagnosis

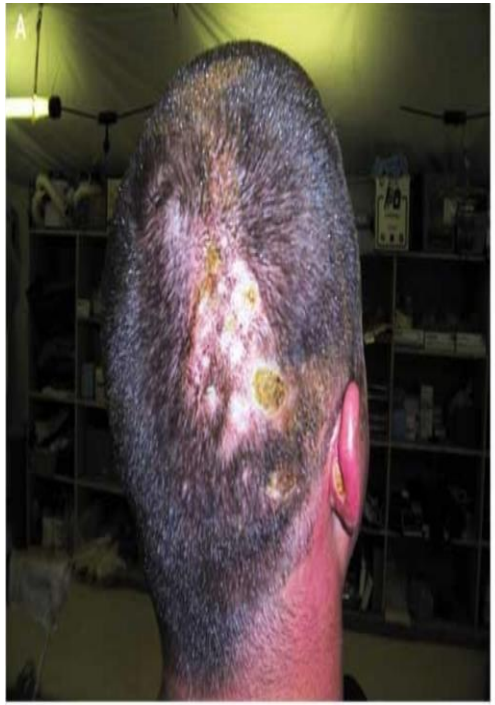
- Diagnosis is based on clinical signs and estimation of selenium in whole blood and liver.
- Elevated glutathione peroxidase level in liver and blood suggest Se poisoning.
- Laboratory analysis of Se in:
- Feed >5 ppm → indicate toxicity.
- Bovine Hoof → 5-20 ppm (in chronic toxicity),
- Bovine Hair → 5-10 ppm (in chronic toxicity)
- Blood → 4-25 ppm – acute toxicity
  1-4 ppm – chronic toxicity
- Urine: 0.1-8 ppm depending upon severity of condition
- Kidney, Liver: 4 - 25 ppm (in acute toxicity)
- Milk:1-3 ppm (in lactating animal)

Treatment

- There is no specific antidote for Se toxicosis symptomatic & supportive care of affected animals should be started as early as possible.
- Addition of inorganic arsenicals enhances biliary excretion of selenium and increasing the dietary levels of sulphur containing proteins is also beneficial.
- CONTRAINDICATIONS:
- BAL (dimercaprol) → alleviates Liver damage but worsens kidney damage.
- Vit E →Synergistic action with Se

PHOSPHORUS (P) POISONING

- 4 different forms i.e. white, yellow, red and black.
- Yellow form is most toxic. White form can be converted into yellow and can cause toxicity
- in the body P circulates first as element and then is oxidized to phosphate.
- **eliminated by lungs and this provides the exhaled air a smell of phosphorus (garlic-like) and a glow in dark.**
- Similarly, the **vomitus of GI tract contents may be luminous** and have the same odour.
- Main excretion of phosphorus is in the urine and expired air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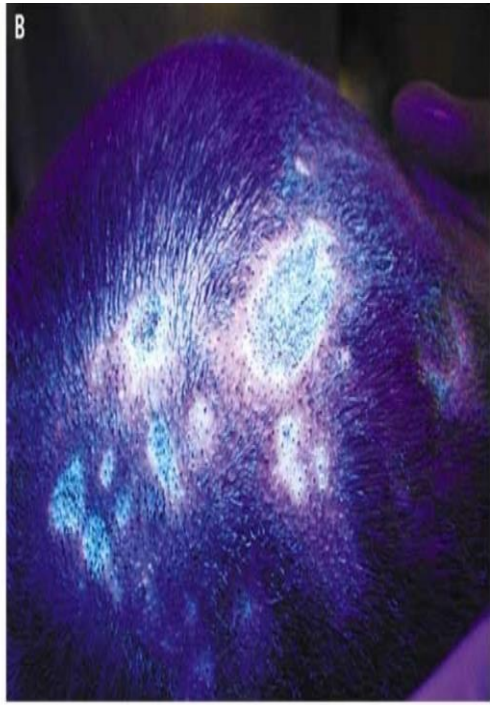
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Mechanism of action

- phosphorus acts as a protoplasmic poison
- direct cardiotoxic effect resulting in cardiovascular collapse. Phosphate formed in body due to oxidation of phosphorus causes hepatic necrosis
- On dermal exposure, white phosphorus results in painful chemical burn injuries by the heat of flame as phosphorus ignites when comes in contact with air

- gastrointestinal irritation and abdominal pain, colic, profuse vomiting (occasionally haematemesis), severe diarrhoea (often haemorrhagic), and a **garlic-like odour from the breath**
- **hepatic failure is followed by convulsions and death**
- **In Pigs vomit profusely and the vomitus show luminous in dark and gives a characteristic garlic odour**
- **Luminescence is due to presence of phosphorus trioxide**
- **In chronic phosphorus poisoning, the main clinical feature is necrosis of jaw (mandible) called "Phossy jaw" or "Lucifer's jaw".**

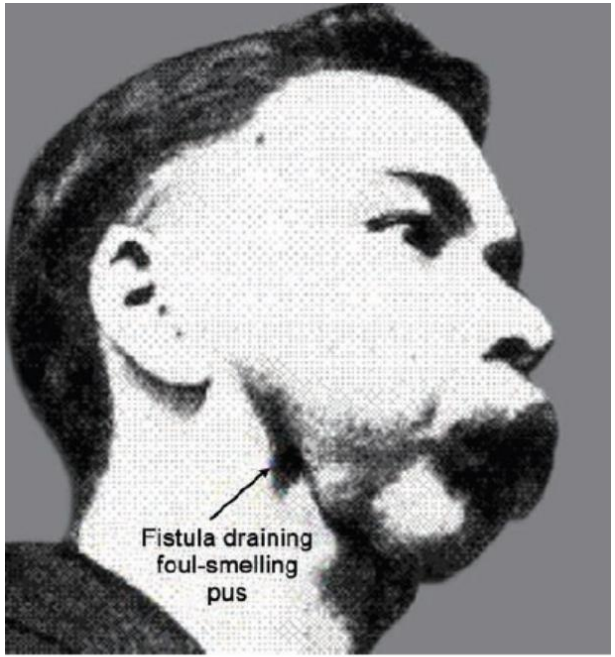
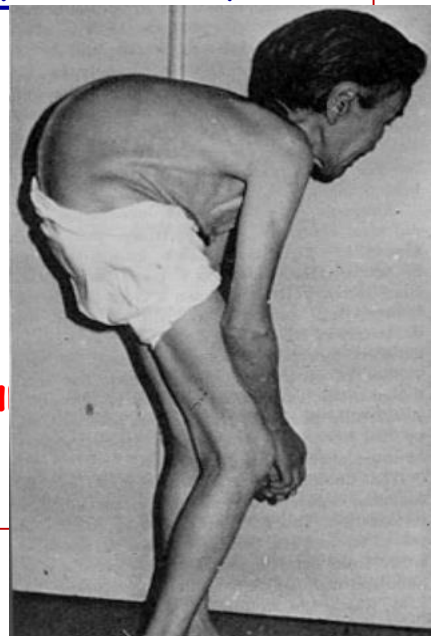


Fig 8.4: Phossy jaw

Cadmium Toxicity

- impair Vitamin D metabolism in the kidney with deleterious impact on bone
- This effect, coupled with direct Cd impairment of gut absorption of calcium and derangement of collagen metabolism, can produce osteomalacia and/or osteoporosis .
- Occupational toxicity due to inhalation of cadmium fumes
- ***itai-itai disease in Japan***
- **EDTA significantly increased urinary elimination of cadmiu**



Fluorine (F) Poisoning

- non-metallic halogen
- Feed should not contain more than 1 part of fluorine to 100 parts of phosphate
- species susceptibility is as follows: calves, dairy cows, beef cattle, sheep, horses, pig and poultry (cattle most sensitive)
- Mainly distributed into calcified tissues **like bone and teeth**
- Bone is a natural sink for fluoride (like lead) with 96-99
- Normal adult bones contain about 1000-1500 ppm fluoride.

Acute toxicity

- Gastroenteritis action
- Disrupting ionic balance : interfere with Na+ K+ channels
- Enzyme inhibition: Fluoride impairs utilization of glucose by inhibiting pre glycolytic and phosphatase enzymes (Enolase)
- Anticoagulant action: Fluoride acts as anticoagulant because it precipitates the calcium in the form of calcium fluoride (CaF_2).

Chronic toxicity/ fluorosis

- **Dental fluorosis**: Excessive amount of fluoride damages ameloblasts and odontoblasts
- deposition in teeth occurs only during the formative stages
- teeth lesions are the earliest and most severe in young and growing animals.
- Mottling of teeth

- **Osteofluorosis**: interferes with the osteoclast activity and damage the osteoblast cells
- **Intermittent shifting lameness**
- F in Bones – 4000-5000 ppm of ash indicate flurosis
- urine in live animals- Urine levels of F:>15 ppm indicate fluorosis

SALT POISONING- Water deprivation toxicity

Sodium ion poisoning/ Water deprivation induced sodium chloride toxicosis

- Salt hunger
- Na+ causes an extracellular hyperosmolality resulting in very significant intracellular dehydration and development of brain or cerebral oedema.
- Dragging of hindfeet while walking & Knuckling of fetlock joints
- **Eosinophilic meningoencephalitis:** Cerebral vascular endothelial proliferation & distended perivascular space in pigs – is a pathognomonic lesion of salt poisoning.

Nitrate and Nitrite Poisoning

- Heavy use of nitrogen fertilizers (e.g. ammonium nitrate, potassium nitrate and urea) and herbicides (e.g. 2, 4-D)
- cereal grasses (especially oats, millets and rye), corn (maize), sunflower and sorghum readily accumulate nitrate
- Water: accumulation in water bodies due to increased water run off from nitrate rich soil, decaying manure, silo pits, and freshly fertilized fields
- toxicity of the nitrate ion is approximately 10 times lower than that of the nitrite ion

- Ruminants are much more susceptible to nitrate poisoning than monogastric animals
- Cattle- affected most frequently by nitrates
- Pigs are most susceptible to nitrite poisoning than cattle and sheep
- cloudy weather or decreased sunlight enhances nitrate levels in plants due to decreased activity of plant NO_3-reductase enzymes
- cut hay or green relatively late on sunny days to minimize concentrations of nitrate

Mechanism of action

- Nitrite: ingestion of large amount of nitrate or nitrite and this is due to mainly nitrite ions
- a. Methaemoglobin formation: One nitrite combines with 2 Hb molecules producing Met-Hb by oxidation

- Normally some Met-Hb (1-2%) is always present which is converted back to ferrous haemoglobin by two reducing enzymes in blood viz. NAD-dependent diaphorase I and NADP-dependent diaphorase II

b. Vascular smooth muscle relaxation (Vasodilation): hypotension and decreased cardiac output

- Nitrate: primary action of large doses of nitrate is different from nitrite ions and resembles effect of excess common salt poisoning

- The signs include disturbed osmotic conditions in the body and death may occur shortly after ingestion of very large doses of nitrate, even before the nitrite and methaemoglobin stages are reached

- Dark chocolate brown or coffee brown color of blood (dark tarry chocolate colored blood) due to methaemoglobin formation in nitrite poisoning

Methylene blue: antidote for treating methaemoglobinaemia caused by nitrite/nitrate (chlorate poisoning also)

- After i/v, converted in blood and body tissues to a **reducing agent leucomethylene blue**

- Leucomethylene blue also activates Diaphorase I and II systems.

Cyanogenetic Plants/Prussic acid poisoning

- poisoning occurs due to ingestion of cyanogenic plants which yield HCN upon acidic or enzymatic hydrolysis by beta glycosidase and lyase

- *Sorghum helepense* (Baru grass, Johnson grass), *Sorghum vulgare* (Jowar, Millet), *Sorghum sudanensis* (Sudan grass), *Sorghastium nutans* (Indian grass)

- *Triglochin maritima* (Arrow grass), *Zea mays* (Maize), *Linum usitatissimum* (Linseed, Flax), *Prunus laurocerasus* (Cherry laurel, Milk laurel), *Lotus spp.*,

- Linamarin----------linseed
- Dhurrin----------sorghum (Millet, Jowar, sudan grass etc.)
- Amygdalin----------bitter almond, wild cherry (Prunus spp.)
- Lotusin or lotaustralin from Lotus spp

- Minimum lethal dose of HCN --- 2mg/Kg

- Plant materials >20mg of HCN per 100gm (200ppm) may have toxic effects. Highly poisonous plants ---- 6000ppm

- Ruminants are more susceptible ; Among ruminants, cattle are more susceptible than sheep

- Horses, dogs and pigs - less susceptible to HCN poisoning than ruminants

- endogenous **thiosulphate** react with HCN to form thiocyanate catalyzed by enzyme known as **rhodanase**

- Small amount of absorbed CN- is eliminated through lungs **(exhaled air has bitter almond smell)**

- Cyanide has strong affinity **for trivalent iron** of the **cytochrome oxidase** molecule and **inhibits enzymatic activity and hence the cellular respiration**

- death is primarily from tissue anoxia in the brain

- As oxygen of arterial blood cannot be utilised, venous blood retains the bright colour of oxyhaemoglobin.

Diagnosis

- In case of suspected CN poisoning, the liver/muscle/stomach contents should be preserved with a solution of 1% mercuric chloride and refrigerated.
- For urine, phenyl mercuric nitrate is used as preservative. It prevents enzymatic degradation.

Post-mortem findings

- Bright cherry red color of venous blood
- Plants containing 200 ppm or more of HCN are potentially toxic
- Rumen contents and liver showing more than 10 ppm and 1.4 ppm of HCN, respectively, are indicative of cyanide poisoning

Sodium nitrite: antidote to cyanide poisoning, often **in conjunction with sodium thiosulphate.**

Oxalate rich plants

The oxalate rich plants are:

- *Amaranthus retrflexus,*
- *Atriplex spps.,*
- *Beta vulgaris,*
- *Calandrina spp,*
- *Oxalis spp.,*
- *Rumexs spp.,*
- *Setaria spp.*
- and *Triantema spp.*

Atriplex spps.,

Mechanism of Toxicosis

- Calcium metabolism is upset (oxalates chelate Ca^{++} causing acute hypocalcaemia), interfering with milk production in lactation in lactating animals and foetal bone growth in pregnant animals.
- Blocking of renal tubules by calcium oxalate crystals – renal injury.
- Failure of blood clotting mechanisms and haemolysis.
- Oxalates also crystallize and cause neuronal damage in brain – CNS signs and paralysis.

Treatment

- Shift to oxalate-free pastures.
- Oral administration of **dicalcium phosphate** (25% in salt ration) or given as grain or alfalfa hay pellets containing 10% dicalcium phosphate @ 225 G/animals/day for **elimination of oxalates (calcium oxalate) through faces.**
- Prior treatment with dicalcium phosphate before allowing sheep to graze in oxalate rich pastures, does not result in oxalate poisoning.

Plant producing thiamine deficiency

(i) *Pteridium aquilinum* (Bracken fern)
(ii) *Equisetum arvense* (Horse tail, bottle brush)

Pteridium plant:

1. Cyanogenetic glycoside - harmless
2. Thiaminase - responsible for poisoning **in non-ruminants**
3. Aplastic anemia factor (Ptaquiloside): bone marrow suppression **in cattle and sheep**
4. Haematuria factor: enzootic haematuria and haemorrhages **in cattle and sheep**
5. A carcinogen (Ptaquilosid (Japanese) / Aquiloside A (Dutch)

Equisetum contains enzyme Thiaminase and alkaloid Equisetine.

- Chronic poisoning: Chronic enzootic haematuria in cattle characterised by intermittent haematuria and ultimate death due to anaemia

- In sheep, a bright blindness may occur due to progressive retinal atrophy that is characterized by permanent blindness.

a. Administer **DL - Butyl alcohol**: It stimulates bone marrow

b. Toluidine blue

LANTANA CAMARA

- Lantana hepatotoxins -Lantadenes – Lantadene A, B, C, D. (Major)
- Lantadene A is toxic to sheep (ruminants) & guinea pig (most susceptible species)

- **causes hepatotoxicity & secondary photosensitization**

i) absorbed from whole GIT with max absorption from small intestine and transported to liver mainly in portal blood. (GIT Phase)

ii) Toxins interact with biomolecules on/in hepatocytes, followed by cascade of biochemical reactions → cholestasis (hepatic phase)

iii)Cholestasis leads to regurgitation of bile → causes marked increase in levels of bilirubin & phylloerythrin (biodegradation product of chlorophyll) in blood

undergo phytochemical reaction on exposure to light & causes photosensitization

- Hepatogenous photosensitization:
  - Lantana camara
  - Blue green algae
  - Pithomyces chartarum fungus

Teratogenic plants

- ***Veratrum californicum***: alkaloids like **cyclopamine, Jervine and** Veratrosine
- ***'Cyclopian Disease' or Cyclopian eye'***

- ***Lupine (Lupinus sericus, L. caudatus):*** the alkaloid 'Anagyrine' LUPININE
- **CROOKED CALF DISEASE**

Ipomoea carnea (Behaya). I. batata: Sweet Potato, Shakarkhand

Toxic Principles:
Phytotoxins like lysergic acid alkaloids (hallucinogenic), resins (cathartic), toxic saponins, nitrates etc

Sorghum vulgare (Jowar).

Toxic Principles: HCN

Toxicity:
Cytotoxic anoxia.

Treatment: Sodium nitrite 20mg/kg slow i.v. as 1% solution and sodium thiosulphate. 500mg/kg

Thevetia peruviana (Yellow Kaner) *Nerium oleander* (Red Kaner)

Toxic Principles:

N. odorum has one glycoside called 'Nerin'. *Cerebra thevatia (Thevatia nerifolia*, yellow oleander) has two glycosides called Thevitin, Cerberin.

Mechanism of action: oleander glycosides act on heart like digitalis and inhibits the Na^+-K^+-ATPase pump.

Datura stramonium, Atropa belladonna (Deadly nightshade)

Toxic Principles: Atropine, Hyoscyamine, Hyoscine- Antimuscarinic action

Animals affected: Cat>Dog>Birds>Horses>Cattle>Sheep>Goat.

Clinical signs: Dryness of mouth & mucous membranes, thirst, anorexia, mydriasis, visual disturbances, depression, tachycardia.

Treatment: Parasympathomimetic agents, e.g. physostigmine, pilocarpine etc.

Ricinus communis (Redi, Andi).

Toxic Principles: **Phytotoxin Ricin I & II (more toxic).** Ricin is one of the most powerful phytotoxins known.

Animals affected: Horses are most susceptible

Toxicity: Cytotoxic (hydrolytic fragmentation of ribosomes and inhibits protein synthesis, disrupts CM) and Gastrotoxic.

Treatment: Anti-ricin serum. Symptomatic & supportive

Abrus precatorius (Rati) Rosary Pea Poisoning

Toxic Principles: **Abrin**

Animals affected: All species of animals. Used for Malicious poisoning

Toxicity: A potent cytotoxic phyto protein

Argemona mexicana

Toxic Principles: alkaloid – sanguinarine; berberine; protopine

Animals affected: Poultry

Toxicity &Clinical signs: Drop in egg production, cyanosis of comb, hemorrhagic enteritis and death in poultry

Gossypol: pigment found in cottonseed cake, occurs in 2 forms i.e. free form (toxic) and bound form (non toxic)

Young calves, swine and poultry are affected

Supplement feed with iron (Ferrous sulphate) – prevention

Ourecus incana (Oak).

Toxic Principles: Tannins, Gallic and Pyrogallic acids, phenols

Toxicity: Precipitation of proteins and binding of =SH groups of enzymes

***Lathyrus Sativus*(Grass Pea)**.

Toxic Principles:
β-oxalyl aminoalanine (BOAA)--**Neurolathyrism**
β-N aminopropionitrile (BAPN) -- **Osteolathyrism**

***Strychnos nuxvomica*:**

- Strychnine poisoning occurs in farm animals as a result of accidental ingestion of seeds of plant or powdered form of nuxvomica used as bait to kill rats, foxes or dogs.
- **Mechanism of toxicity**: Main site of action of strychnine is the recurrent inhibitory inter neurons (Renshaw cells) of the reflex arc in the spinal cord and medulla.

Insecticides

Organochlorines- DDT, BHC

Organophosphates- malathion, sarin

Carbamates- Carbaryl, propoxur

Pyrethrins and pyrethroids- allethrin, deltamethrin

Formamidine insecticides- amitraz

Natural products- rotenone, nicotine

Organochlorines

- Organochlorines were the first major class of synthetic organic chemical to become widely used as insecticides

Diphenyl aliphatic agents - DDT, methoxychlor, perthane, dicofol

Hexachlorocyclohexane – Lindane, mirex, kepone,BHC

Cyclodiene agents – Aldrin, dieldrin, chlordane, endrin, endosulpahan, toxaphene, heptachlor

Mechanism of Toxicity

- These drugs are *neurotoxic*.
- easily enter in the nerve membrane interfere with Na^+ Channel
- Prolong the time of sodium channel opening during depolarization.
- Sodium inflow is enhanced and potassium outflow is inhibited
- Results in enhanced action potential and **increased neuronal excitability** (seizures).

Clinical symptoms

- Initial stimulation of CNS followed by depression and death due to respiratory failure.

- **Behavioural symptoms-** like anxiety, aggressiveness, abnormal posturing, jumping over unseen objects, wall climbing and madness syndrome.

- **Neurological symptoms** - hypersensitivity to external stimuli, fasciculation and twitching of facial and eyelid muscles, spasm and twitching of the fore and hind quarter muscles, champing of the jaws, seizures and hyperthermia.

- Cholinergic symptoms - vomiting, marked salivation, mydriasis, diarrhoea and micturition are noticed.

Treatment

- Diazepam, phenobarbital or pentobarbital in dogs.

Chloral hydrates, Phenobarbital or pentobarbital in farm animals.

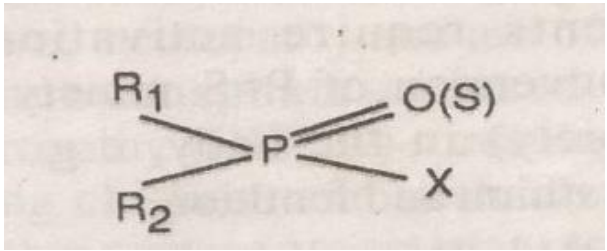
- Activated charcoal (1-2g/kg).
- If exposure is by dermal suspected, scrubbed (bathe) the animal with soapy water.
- Supportive and symptomatic therapy.

Organophosphates

- OP compound are **esters** of phosphoric, phosphonic, phosphorothioic or related acids

- **which have ability to inhibit cholinesterase enzyme**

- 1st OPI - tetraethyl pyrophosphate (TEPP).



Based on mode of action

(Classification)

Direct acting OP insecticides

- These insecticides contain **P=O group**
- **directly inhibit cholinesterase enzyme** and produce toxicity
- TEPP, trichlorphon and dichlorvos.

Indirect acting OP insecticides

- phosphorothioates containing **P=S groups**.
- Require **activation to oxon** (conversion of P=S moiety to a P =O moiety) in the body.
- Malathion, parathion and fenthion.

Mechanism of action

- OPI owe their toxicity by **irreversible inhibition of AChE enzyme**, which is responsible for hydrolytic degradation of acetylcholine

- This leads to **Ach accumulation in nerves and neuro-effector junctions**, which causes excessive synaptic neurotransmitter activity in the parasympathetic nervous system and at neuromuscular sites and affected animals show **parasympathetic or chlolinergic signs.**

- OP compounds interact with only the active **esteric site** of the enzyme and the enzyme – OP complex formed is extremely stable that does not undergo significant spontaneous hydrolysis.

Delayed Toxicity (delayed neurotoxicity):

- occurs after several days produced by the inhibition of NTE (**Neuropathy Target Esterase**),membrane bound enzyme.
- NTE facilitate axonal transport of nutrients
- its inhibition results in demyelination of of axon leading to paralysis called as organophosphate induced delayed neuropathy (OPIDN) or dying back axonopathy.
- "**Hind leg paralysis**"/ "**Ginger Jake Leg/ Jake Leg Paralysis**
- Mipafox is a classical example causing OPIDN
- Charolin's cattle and SUFFOLK sheep genetically predisposed

Treatment

- Specific antidotes: a) Muscarinic blockers
  b) ChE reactivators
- **Atropine SO_4:**

Dogs and Cats: 0.2-2 mg/kg 1/ iv and rest sc.
Repeat every 3-6 hr as required.

Horse and Pig: 0.1-0.2 mg/kg I/V,
repeat every 10-15 min as needed;

Cattle and sheep: 0.5-1 mg/kg 1/3 iv and rest im or sc,repeat as needed.

- **Oximes/ cholinesterase reactivators : 2-PAM** (2-Pyridine aldoxime methiodide, 2-PAM chloride), DAM, MINA – Binds to anionic site
- @ 20-50 mg/kg as 10% sol im
- ChE activation decreases with time (after exposure), better to use within 24-48 hr.

- **If ingestion**: Emetics, purgatives, activated charcoal (3-6 g/kg as slurry in water.

- **If dermal:** wash with soap and cool water.

Carbamates

- **Naphthyl carbamates-** Carbaryl (sevin)
- **Phenyl carbamates** – Propoxur
- **Heterocyclic methyl carbamates-**pyrolan and isolan.
- **Heterocyclic dimethyl carbamates** Carbofuran and furadan.
- **Oximes-** aldicarb, methomyl and thiodicarb.

Differences from OP compounds

Carbamates differ from OP compounds in following aspects:

--They are **reversible inhibitors** of cholinesterase (ChE) enzyme

- They inhibit cholinesterase at both anionic and esteratic sites
- They are selective inhibitors of cholinesterase enzyme
- Decarbamoylation (reactivation) of inhibited ChE enzyme is easier
- Cholinesterase enzyme reactivators like 2-PAM are ineffective (contraindicated) in the carbamate intoxication.

Mechanism of action

- Carbamate inhibit acetylcholinesterase enzyme, but these insecticides occupy **both anionic and esteratic sites of AChE.**

- The inhibition in case of Carbamate results from a chemical reaction between the **carbamoyl moiety of carbamate compound and the active site serine hydroxyl group of AChE to form carbamoylated enzyme** rather than phosphorylated as with the organophosphate.

- The carbamoylated enzyme is **relatively less stable and susceptible to hydrolysis,** although rate of hydrolysis is not very fast as with acetylcholine.

- Therefore, the **decarbamoylation is easier** in comparison to dephosporylation (OPs).

- Because of relatively rapid reactivation of carbamoylated AChE, the carbamate insecticides are often called reversible anticholinesterase agents.

- Toxicosis develops when the amount of carbamate pesticide in the body is so large that the **rate of carbamoylation of AChE exceeds the rate of hydrolysis of pesticide by the enzyme**.

Diagnosis:

- History, circumstantial evidence,
- Clinical signs,
- Estimation of blood ChE activity (25% or more decrease in OPI and carbamate toxicity) and
- Identification of the insecticide in feed, water, ruminal content or tissues.

Treatment:

- **Atropine sulphate** only
- Not ChE-reactivators.

Pyrethrins

- This is a closely related group of naturally occurring compounds that are the active insecticidal ingredients of pyrethrum.
- Pyrethrum is extracted from the **flowers of *Chrysanthemum cinerariaefolium*** and has been an effective insecticide for many years.
- Synergists, such as piperonyl butoxide, sesamex, piperonyl cyclonene, etc, are added to increase stability and effectiveness.

Pyrethroids

These are synthetic derivatives of natural pyrethrins and include –

- Allethrin,
- Cypermethrin,
- Decamethrin,
- Fenvalerate,
- Fluvalinate,
- Permethrin
- Type I pyrethroids – Tremors (T syndrome)
- Type II pyrethroids - choreoathetosis-salivation syndrome (CS)

Mechanism of action

- Nerve poisons like DDT.
- Prolonged depolarization **(delayed closure of Na channels)** and repetitive discharge.
- Piperonyl butoxide and piperonyl cyclonene potentiate pyrethoid insecticidal and mammalian toxicity (inhibition of mixed function microsomal oxidases i.e. by preventing detoxification of pyrethroids).
- Pyrethroids are relatively less toxic in mammals and birds, but highly toxic to fish.

Herbicides

- Dinitro compound- dinitro ortho cresol (DNOC), dinitrophenol
- Phenoxyacetic acids - 2,4-D, 2,4,5-T etc.
- Bipyridium compounds- diquat, paraquat etc.
- Heterocyclic compounds or triazenes- atrazine, propazine, simizine.
- Chloroaliphatic acids - dalapon, sodium chloroacetate, sodium trichoroacetate etc.
- Substituted urea - monouron, diuron, isoproturon etc.
- Substituted dinitroaniline - pendimethalin.

Chlorophenoxy Compounds (Phenoxyacetic acid compounds): 2,4-D

- The most important and most frequently used herbicides.
- It can potentiate the toxic effects of some plants .
- Increases the nitrate content of certain plants and increases the palatability of certain toxic plants, thus increases the poisoning risk.
- Dogs are most sensitive animals.

Bipyridal/Bipyridinium Compounds

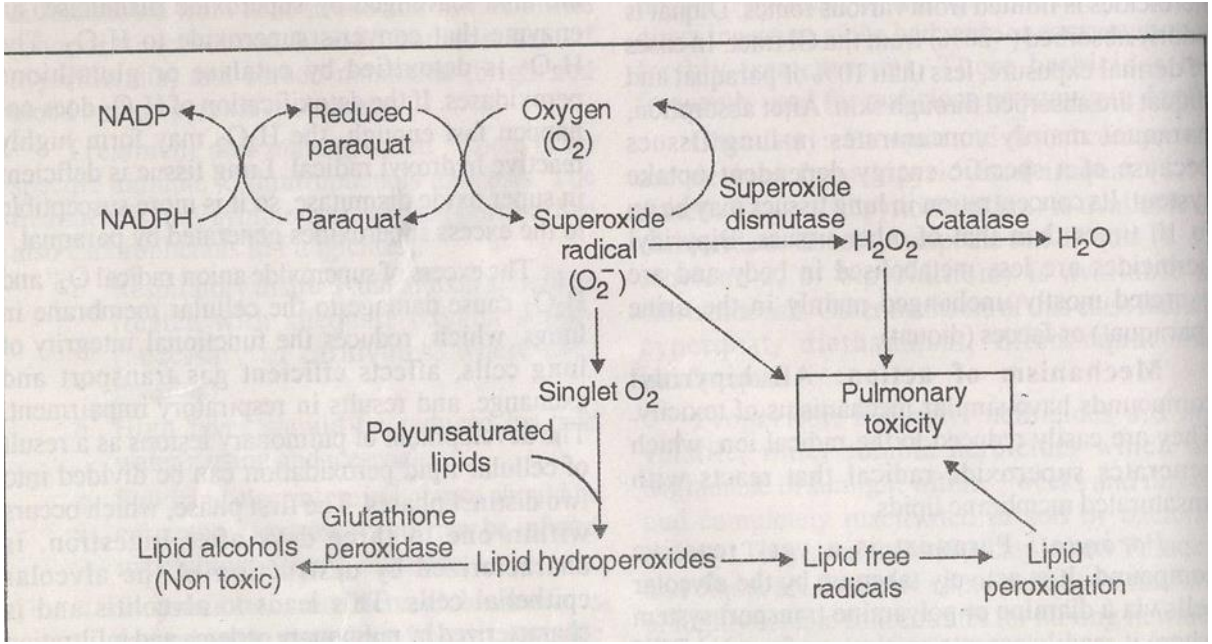
- Paraquat

- actively taken up by the alveolar cells via a diamine where it readily accepts an electron from NADPH to become reduced paraquat.

- When the reduced paraquat is reoxidized by loss of electron, a superoxide anion radical O_2- is generated.

- The superoxide radical is unstable and spontaneously breaks down to the reactive singlet oxygen.

- The reactive singlet oxygen attacks the polyunsaturated lipids associated with cell membranes to form lipid hydroperoxides.


NADP
Reduced paraquat
Oxygen (O_2)
NADPH
Paraquat
Superoxide radical (O_2^-)
Superoxide dismutase
H_2O_2
Catalase
H_2O
Singlet O_2
Pulmonary toxicity
Polyunsaturated lipids
Glutathione peroxidase
Lipid alcohols (Non toxic)
Lipid hydroperoxides
Lipid free radicals
Lipid peroxidation

- These lipid hydroperoxides are normally converted to non toxic lipid alcohols by the selenium – containing enzyme glutathione peroxidase.

- Selenium deficiency, depletion of glutathione or excess lipid hydroperoxides allow the lipid hydroperoxides to form lipid free radicals.

- The action of paraquat in lungs is similar to that produced by carbon tetrachloride in liver.

Rodenticides

Inorganic rodenticides:

- Arsenic compounds arsenic trioxide and sodium hydrogen arsenite.
- Elementary phosphorus
- Thallium sulphate
- Zinc phosphide

Organic rodenticides:

- Anticoagulants- warfarin, diphacinone, difenacoum and brodifacoum.
- Fluoroacetic acid and its derivatives – sodium fluroacetate and fluroacetamide.
- Alphanaphthylthiourea (ANTU)
- Bromothalin
- Strychnine
- Red squill
- Pyriminil
- Norbormide
- Crimidine
- Chloralose

Zinc phosphide

- It is one of the most widely used rodenticides in developing country because it is cheap and very effective.

- It is often recommended as the **rodenticides of choice** because it is fairly specific for rodents and there is no true secondary poisoning, except possibly in dog and cat.

- Liberation of **phosphine gas in acid pH in stomach** – irritates GIT and causes CVS collapse.

Mechanism of action:

- Acute zinc phosphide toxicosis is due to the phosphine gas. phosphine gas is said to act as a general protoplasmic poison.
- It causes direct damage to membranes of blood vessels and erythrocytes leading to cardiovascular collapse.
- Phosphine also causes depression of CNS, irritation of lungs and damage to liver and kidneys.

Clinical Signs:

Warfarin and Congeners

- Pindone, coumafuryl, coumachlor etc. are most commonly used potentially dangerous compounds.

Mechanism of Toxicosis:

- It is also called as anticoagulant rodenticides.
- It has basic **coumarin or indanedione nucleus**.
- Act as anti-vitamin K and interfere with synthesis of coagulation- Factors I, II, VII and X in liver.
- Prothrombin ~~——~~ thrombin

(failure of blood clotting)

generalized

haemorrhages

Clinical Signs:

Anaemia, hematomas, hemothorax, epistaxis and hematuria, weakness ataxia, colic and polypnoea.

Treatment:

- Vitamin K_1 @ 2.5-5 mg/kg iv or sc smallest possible needle at several locations to speed up absorption for 2 – 4 weeks.
- Fresh or frozen plasma @ 9 ml/kg or whole blood 20 ml/kg iv to replace clotting factors.
- Thoracocentesis to relieve dyspnoea due to hemothorax and artificial respiration with oxygen.

Alpha Naphthyl Thiourea (ANTU)

Mechanism of Toxicosis: Animal drowned in own fluid

- It interferes with effective uptake of O_2 from pulmonary alveoli by producing massive oedema of lungs due to increase capillary permeability.

- ANTU undergoes metabolism by microsomal mixed function oxidases releasing atomic sulphur which damages the endothelium of alveolar capillaries – leakage of fluid into alveoli (airways)– pulmonary oedema
- It causes vomiting on empty stomach due to intense local gastric irritation, but poisoning occurs if ANTU is ingested after feeding.

Red Squill

- It is the ground bulbs of *Urgenia maritime.*
- Contain cardiac glycoside- *proscillaridin*.
- Considered as the safest rodenticide (nontoxic to poultry, unpalatable to

Formamidine insecticides- Amitraz stimulation of alpha2-adrenoceptors and inhibition of monoamine oxidase (MAO) enzyme

- **NEONICOTINOID INSECTICIDES: IMIDACLOPRID**
- **Mechanism of action:**

acts and binds selectively to nicotinic cholinergic receptors on the post-synaptic membrane.

- nicotinic receptors of mammals are less sensitive to imidacloprid than are insect receptors

Urea Poisoning

- **Toxic dose:** Cattle, sheep: 1 g/kg (lethal dose), 0.5 g/kg (Toxic), 0.3 g/kg (Mild toxic)
- Horse: 4 g/kg (Oral LD_{50})

- rumen pH is elevated to 11, more and more NH_3 will be released and present in non-ionized form (NH_3) which is diffusible into systematic circulation

- Toxic conc.: rumen NH_3 concentration 80 mg% and BUN 0.84 – 1.3 mg %

- NH_3 inhibits TCA (citric acid) cycle. There is decrease in energy production and cellular respiration.
- presence of urease in soyabean potentiate toxicity

- **5% acetic acid/(vinegar)** given (2.5-5 litres) with sufficient cold water
-
- **Bovine bunker syndrome: NPN/ ammonia poisoning**

Carbon tetrachloride

- anti trematodal drug against fascioliasis in ruminants
- reference hepatotoxic agent
- Pigs are most susceptible of all mammals and sheep is quite tolerant

- CCl4 CCl3-

Phenothiazine

- cause **photosensitization in animals**
- In horses causes hemolysis of RBC (Blood enzyme – lysolecithin is activated)
- Sensitization to sunlight is more frequent problem because **of phenothiazine sulfoxide (metabolite of phenothiazine)**
- Hemolysis in horses leading to icteric membranes and presence of Hb in urine
- Calves show photosensitization, keratitis. In sheep, keratitis accompanied by reddening and thickening of muzzle and ears

Disease	Fungus	Crop or substrate	Mycotoxin	Animals affected
Aflatoxicosis	*Aspergillus flavus* *Aspergillus parasiticus*	Ground nut, maize and nut crops	Afaltoxins B1, B2, G1,G2	Cattle, pig, poultry and dogs
Ergotism	*Claviceps purpurea*	Seed heads of many grasses and grains	Ergotamine and ergometrine	Cattle, Sheep, Pig, Horse and Poultry
Facial Eczema	*Pithomyces charatarum*	Pasture, litter	Sporidesmin	Sheep and Cattle
Oestrogenism	*Fusarium graminareum*	Maize, Barley and cereals	Zearalenone	Pigs
Leukoencephalo malacia	*Fusarium moniliforme*	Maize	Fumonisins B1 (A1, A2, B2)	Horses and Donkey
Trichothecane toxicosis	Many *Fusarium* species	Cereals	T-2 toxin, diacetoxy - seripenol	Many species
Ocharatoxicosis	*A. ochraceus*	Barley, wheat	Ochratoxin -A	Pigs and Poultry

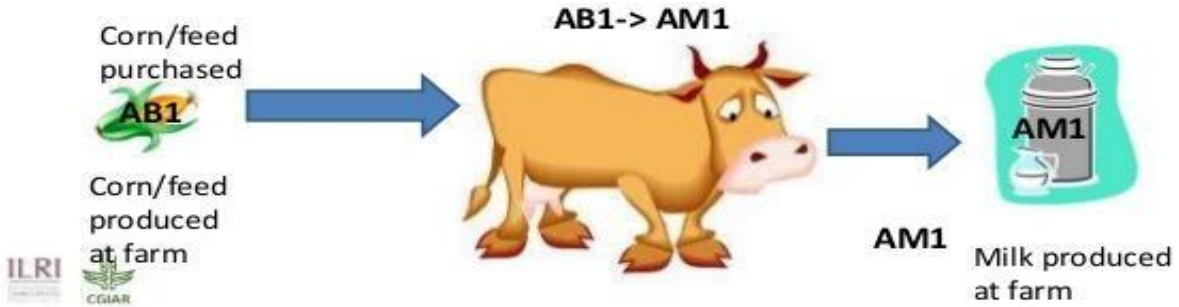
Species	Toxins
A.flavus and A.parasiticus	Aflatoxins
A. ocheraceus	Ochratoxin
Fusarium roseum	Trichothecane (t-2) toxin
Penicillium citrinum	Citrinin

Target organs/ tissues	Toxins
Vascular system	Aflatoxins
Digestive system	Aflatoxins
Mucous membrane	Trichothecane (t-2) toxin
Urinary system	Ochratoxin
Reproductive system	Zearalenone (Fusarium toxin)
Cutaneous system	Sporidesmin

AFLATOXICOSIS

- Afalatoxins produced by *A. flavus* and *A. parasiticus*
- Four major aflatoxins are B1, B2, G1 and G2
- B1and B2 produce blue color and G1, G2

- Young animals are highly susceptible
- Aflatoxin B1 produce the most hepatogenic, carcinogenic, teratogenic and embryotoxic effects
- Calves- blindness, circling, grinding of teeth, diarrhoea, tenesmus & convulsions



- **Ducklings- most susceptible avain species**

- In birds over three weeks of age, subcutaneous haemorrhages of legs and feet

PM Lesions

Principle target organ is liver causes hepatomegaly with necrosis & bile duct hyperplasia

Chronic toxicity, in additon to liver damage, degenerative changes in the kidney, thymus cortical aplasia leading to decreased cell mediated immune response

DIAGNOSIS

- Biological assays for toxicity are important confirmatory steps
- **Concentration of aflatoxin B1 in excess of 100µg /kg of feed are considered toxic for cattle**
- Thinlayer chromatography and HPLC are more sensitive analytical methods for determing afaltoxins levels in the food.
- Radio immuno assay & ELISA
- **Biological assays**- Ducklings are mostly susceptible. Bile duct proliferation in one-day-old ducklings and chick embryo bioassay

Erogtism

- Fungal species of the genus *Claviceps*, *notably Claviceps purpurea*
- toxic alkaloids - ergotamine and ergometrine
- Two forms of ergotism- gangrenous & convulsive ergotism
- Ergot alkaloids may exert an oxytocin like

Fusarium Toxicoses

- Estrogenic metabolites – DON, **zearalenone (F-2 toxin) and** Trichothecene toxins by Fusiarium graminearum and other Fusiarium species

- Zearalenone - oestrogenic activity

- Target organ system- reproductive tract of pigs causing vulvovaginitis, associated with the consumption of moldy maize by gilts.

DON and T-2 Toxin

- Deoxynivalenol (DON), also known as vomitoxin
- necrosis and hemorrhage of the digestive tract, decreased blood production in the bone and spleen, and changes to reproductive systems.
- In poultry, causes reduced egg production, beak lesions, and abnormal feathering
- Advisory level of DON/ Vomitoxin is 1 ppm

Ochratoxicosis and Citrinin Toxicosis

- Several *Aspergillus and Penicillium species*, particularly toxigenic strains of *Aspergillus ochraceus, A. alutaceus and Penicillium verrucosum produce ochratoxins*
- Group of related iso coumarin derivatives
- Ochratoxin A is the principal nephrotoxic mycotoxin in this group
- The mycotoxin citrinin, which can also be produced by *A. ochraceus as well* as by *Penicillium citrinum, P. viridicatum and P. expansum*, is nephrotoxic.

Toxicity caused by poisonous animals

- **Zootoxins:** Toxins produced by lower animals, e.g. snakes, fish, toads, scorpions, bees, wasps, spider, ticks etc.

- **Venomous animals:** Animals capable of producing a poison in a highly developed secretary gland or group of cells and deliver toxin during a stinging and biting act

- Spider, scorpions, bees, wasps, ants, beetles, caterpillars etc.

- Venom may be composed of proteins (polypeptides and enzymes) of

Snake Venom Toxicity:

- Snake venom - colloidal solution of toxic components-mainly enzymes and non enzymatic peptides and amino acids, (in addition to K^+, Na^+, Ca^{++}, Mg^{++}, Ni^{++} etc.)
- more than 3500 different species out of which more than 400 are poisonous and dangerous
- 1. **Elapidae:** Elapids, Cobras, Kraits, Cora snakes, Mombas
- 2. **Crotalidae:** Crotalids, Pit vipers, rattle snakes, bush master, water moccasins, copper heads
- 3. **Viperidae:** Viperids, vipers, adders
- 4. **Hydrophidae:** All sea snakes, water snakes
- 5. **Colubridae:** Colubrids includes poisonous and non-poisonous snakes – Boomslang, bird snake, rednecked, keelback snake.

- **Active principles of snake venoms:**
- Hyaluronidase, Cholinesterase, proteolytic phosphates, phospholipase A
- Protein and amino acids : toxin
- also contain some different fractions like necrotizing, anticoagulant, coagulant, neurotoxic, cardiotoxic and haemolytic fractions.

- venoms of cobra and krait are mainly neurotoxic while that of vipers and rattles snakes are haemotoxic

- components which itself are not toxic help to increase toxicity of others e.g. Hyaluronidase helps in spreading the toxin

- . Horse > Sheep > Cattle > Goat > dog > Pig > Cat

- **Antihistaminic are contraindicated as they enhance the action of venom/potentiate the effect of venom**

S.No.	Viperine	Elapine
1.	Mainly haemotoxic	Mainly neurotoxic
2	Local swelling at the site of bite which develops very rapidly	No local swelling. Symptoms take about 1 hr to appear
3	Excitement with anxiety	Excitement with convulsions. Nervous signs – Paralysis, Death – respiratory paralysis.
4	Coagulability of blood is completely lost, therefore haemorrhages	Coagulability of blood is not affected
5	Death due to extensive haemorrhages leading to shock or pulmonary thrombosis	Death due to paralysis of respiratory centre.

Spider venom toxicity

- Black widow spiders (Latrodectus mactans) Black recluse spider (Loxoscales reclusa)

- i) Neurotoxin – it affects neuromuscular junctions and cause the release of ACh from pre-synaptic nerve fibers and enhances depolarization.
ii) Lipoproteins, Hyaluronidase, High content of leucine and isoleucine and low tyrosine

* neurotoxin of black widow spider is α-latrotoxin

- death occurs in 4 to 6 hrs in acute cases to few days in mild ones. (due to paralysis of respiratory muscle)

Scorpion toxicity

- stinger located on the tip of tail.
- Venom causes muscular stimulation and hemorrhage.

- **Toxic components:** Heterogenous mixture – neurotoxin, cardiotoxin, nephrotoxin, haemolysin, agglutinins, phospholipases, hyaluronidases, histamines, serotonin etc. The most potent is the neurotoxins

- **Mechanism of action:** Neurotoxin interacts with voltage dependent Na+ channel and stabilizes it in the open position, which leads to prolonged and repetitive firing of somatic, sympathetic and parasympathetic neurons.

Toads

- *Bufo vulgaris* (common toad), *B. marinus* (marine toad), *B. alvarius* (River toad). Out of these, *B. alvarrius, B. marinus* are most toxic and B. vulgaris is least toxic

- Toxins secreted by glands in their skin located above and posterior to eyes (produced in the parotid glands)

- Different toad toxinsn1. Bufodienolides which include Bufogenins and their derivative bufotoxins: Bufotalins, Bufotenidin, Bufotenin, Bufoviridin, 2. Serotonin, 3. Catecholamines.

- **Bufogenins are cardiac glycosides and effect heart and other smooth muscles.**

- toxin binds with specific receptor site on Na^+-K^+-ATPase pump in cardiac cell membrane and inhibits its function causing excessive cardiac stimulation and ventricular fibrillation.

- Death occurs rapidly from heart failure.

Fish toxins (Ichthyotoxins)

- **1. Shellfish toxicity:** produces saxitoxin
- Interfere with ionic transport across the axonal membrane. It inhibits inward current of Na^+ across axonal membrane

- **2. Puffer fish toxicity (Fugu fish toxicity):** produces Tetrodotoxin

- **Mechanism of Action:** Tetrodotoxin is a potent neurotoxin that blocks the inward conduction of Na^+ through Na-channels across the cell membranes of excitable cells.
- direct paralyzing effect on striated muscle and nerve fibers. It also provokes hypotension and has deleterious effects on respiration.

Bees and Wasps Toxicity

- Honey bee venom also contains i) hyaluronidase and ii) proteins – melittin, aparmin.

- Hyaluronidase cause hypotension and increased vascular permeability

- Mellitin is antigenic in nature and produce hypersensitivity (allergic) reactions mainly in human beings and horses.

- Multiple stings result in death due to anaphylactic shock. Allergic responses also observed.

- Wasp venom also contains a variety of amines and kinins.

Radiation toxicology

- study of adverse effects of radiation on living organisms.

- **Mechanism of action:** DNA strands break, point mutation and chromosomal aberrations, then loss of gene products which leads to cell death. rate of chromosomal aberrations is directly related to radiation dose.

- **Pathogenesis:** The rapidly and undifferentiated cells are most sensitive. Skin, GI tract and haematopoietic system are worst affected (with exception of human lymphocytes).

- Biological systems irradiated in presence of O_2 are more susceptible to injury as it results in formation of hydroperoxy or H_2O_2 radicals which damage more due to their long half-lives. The response is termed as "Oxygen effect".

- **Thyroid:** Radioactive isotopes at iodine (^{131}I) are accumulated in the thyroid gland, which destroy thyroid gland.

- **Bones:** Nuclides deposited preferentially in bone or on bone are collectively known as "Bone Seekers"- ^{89}Strontium, ^{90}Strontium, ^{140}Barium, radium isotopes etc. They suppress bone marrow and result in lymphopenia, leucopenia, anaemia.

- **Reproductive organs:** Stops cell division of testicular germinal epithelium. Acute dose of 600 rad in testes produce permanent sterility. But fully developed sperm cells and primary spermatocytes relatively radio-resistant. Atrophy and degeneration of ova occurs in ovary. It may cause death of embryo.