

Systemic toxicology

- **Toxic agent or toxicant:**
- A toxic agent is anything that can produce an adverse biological effect.
- It may be chemical, physical, or biological in form.
- For example, toxic agents may be –
 - ✓ chemical (such as cyanide)
 - ✓ physical (such as radiation)
 - ✓ biological (such as snake venom).
- **Toxicity:** Toxicity is the degree to which a chemical substance or a particular mixture of substances can damage an organism.

Types of toxicants

- Toxic substances may be **systemic toxins** or **organ toxins**.
- A systemic toxin is one that affects the entire body or many organs rather than a specific site.
- A organ toxin is one that affects only specific tissues or organ.
- **Systemic toxicology:** Study of toxic effects caused as a result of absorption and distribution of a substance that affects the whole body rather than a specific (local) area, i.e. to an area distant from its entry point.
- Most chemicals that produce systemic toxicity do not cause a similar degree of toxicity in all organs, but usually cause major toxicity to one or two organs.

Toxic Metals

- Toxic metals may be cumulative and stored in definite tissue locations.
- Although metals may be cumulative in nature, toxicosis is not necessarily due to storage.
- This is because some storage sites are toxicologically inert.
- Route of exposure may be important in modifying toxicosis.
- Metallic compounds can bind to
 - ✓ enzymes,
 - ✓ membrane proteins,
 - ✓ or other essential structural proteins.

- Metals may complex with one another or with the same protein molecule resulting in altered toxicity.
- Organic and inorganic forms of metals may result in marked variation in expression of toxicity.
- Organomercurials result in clinical signs and lesions commonly affecting the central nervous system while inorganic mercury results in acute gastroenteritis and renal damage.
- Among heavy metals, arsenic plays a major role in causing toxicological hazards .
- Other metals which has potential to caused metal toxin are-Lead, mercury, Selenium, Copper etc.

Sources of arsenic poisoning

- Among heavy metals, arsenic plays a major role in causing toxicological hazards.
- **Sources**
- The most common arsenic compound in general use is arsenic trioxide.
- With alkalies, arsenic trioxide forms various arsenites.
- Heating of metal ores results in the production of arsenic trioxide some of which is carried to the surrounding in dust or smoke.
- Copper arsenite was formerly used as a cheap pigment for colouring wall papers, artificial flowers etc. But it has been discontinued, as it was the cause of many deaths.
- Copper acetoarsenite (Paris green) was used as an insecticide.

- Sodium and potassium arsenite are extensively used as weed killers, dressings for grains, insect poison, sheep dip and wood preservative.
- Arsenical dips are usually combined with sulphur for the use in sheep and cattle.
- Organic arsenicals are used in the treatment of blackhead (histomoniasis) in turkey and also as general tonics and skin alteratives.
- Acetarsol, neoarsphenamine, sulpharsphenamine and liquor arsenicals (Fowler's solution) were used in the treatment of certain skin conditions and as skin alteratives.

- Arsenic poisoning in animals is practically always due to human carelessness.
 - Animals gaining access to receptacles that contained arsenical dips, weed killers or insecticides.
 - Contamination of herbage by lead and calcium arsenate sprays.
 - Contamination of water and herbage in the neighbourhood of metal smelting works.
 - Animals licking wood preserved with an arsenical preparation.
 - Inadvertent use of arsenicals because of their resemblance to other preparations.
 - Ingestion of arsenical rat poison.
 - Following dipping in arsenical baths.
 - Use of contaminated deep well water

Mechanism of Arsenic Toxicity

- Arsenic reacts with the sulphydryl group of lipoic acid.
- Lipoic acid is an essential co-factor for the enzymatic decarboxylation of keto acids such as pyruvate, ketoglutarate and ketobutyrate.
- By inactivating lipoic acid, arsenic inhibits formation of acetyl, succinyl and propionyl coenzymes A.
- So there is inhibition or slowing of glycolysis and of the citric acid cycle.
- Arsenic also inactivates sulphydryl groups of oxidative enzymes and glutathione.
- Pentavalent arsenate is a well-known un-coupler of mitochondrial oxidative phosphorylation.

Consequences of Arsenic Toxicity

- Arsenic affects those tissues which are rich in oxidative enzymes especially in the alimentary tract, kidney, liver, lungs and epidermis.
- It is a potent capillary poison. Although all beds are affected, the splanchic areas are more sensitive.
- Loss of capillary integrity and dilatation allows transudation of plasma fluid into the intestinal mucosa and lumen which results in sharply reduced blood volume, hypotension, shock and circulatory collapse.
- Toxic arsenic nephrosis is common in small animals and man.
- Glomerular capillaries dilate, swell and varying degree of degeneration occur. This results in oliguria and urine contains red blood cells and casts.

- Following percutaneous absorption, capillaries dilate and arsenic causes blistering and oedema.
- Skin becomes dry, papery and may crack, bleed and develop secondary infection.
- **Tolerance to arsenite:** Habitual use of small quantities of arsenic is said to render the body tolerant much larger doses.
- **Clinical Symptoms:**
- **Per-acute** – In per-acute poisoning death is rapid. The symptoms noticed are intense abdominal pain, staggering gait, collapse, paralysis and death.
- **Acute** – In acute cases the symptoms are salivation, thirst, vomition in possible species, violent colic, watery diarrhoea with peel off mucous membrane sometimes haemorrhagic, exhaustion, collapse and death.

- **Sub-acute** – Sub-acute cases may live for several days and there may be additional symptoms of depression, loss of appetite, staggering gait, apparent paralysis of the hind quarters, trembling, stupor, convulsions, coldness of the extremities and sub-normal temperature. Proteinuria and haematuria may also occur. Arsenical dermatitis is common in man.
- **Chronic** – The symptoms include indigestion, thirst, wasting and general appearance of unthriftiness, dry staggering coat, brick red colour of visible mucous membrane, weak and irregular pulse.
- Animals have suffered damage to peripheral nerves characterized as demyelination following repeated ingestion of medicated feeds. This problem is not amenable to BAL but is sometimes slowly reversible following withdrawal of medicated feed.

Non-metal toxins

- Non-metal toxins such as Nitrite poisoning, bacterial toxin, phytotoxin, mycotoxin etc. also caused mortality to human and animals.
- **Sources of Nitrite Poisoning:**
- Nitrates are non-toxic. But in the feedstuff or in the alimentary tract they are converted into nitrites, which are toxic.
- Nitrite is 6-10 times more toxic than nitrates.
- **Sources**
- Whey, preserved feed, fertilizers containing sodium, phosphorus or ammonia, well water and plants that contain more nitrates.
- Plants that accumulate nitrate when they grow on soils containing excess of nitrates include *Amaranthus retroflexus*, *Brassica napobrassica*, *Chenopodium album*, *Datura* sp., *Tribulus* sp., *Beta vulgaris*, *Curcubita maxima*, *Ipomoea* sp. and *Solanaum* sp.