TOXIC EFFECTS OF METALS

Arsenic  Lead  Mercury
Definitions & Classifications

- **Heavy or toxic metals**: Heavy metals are chemical elements that have a specific gravity (a measure of density) at least five times that of water. The heavy metals most often implicated in human poisoning are:

  1. **Lead (Pb)**.
  2. **Mercury (Hg)**.
  3. **Arsenic (As)**.
  4. **Cadmium (Cd)**.
  5. **Chromium (Cr+6)**.
  6. **Beryllium (Be)**.
  7. **Nickel (Ni)**.

**Major Toxic Metals**
Essential Metals generally regarded as essential for human health in trace amounts include:

- Cobalt (Co), Zinc (Zn), Copper (Cu), Iron (Fe), Manganese (Mn), Magnesium (Mg), Molybdenum (Mo), Selenium (Se), Trivalent, and Chromium (Cr+3).

They are essential because they form an integral part of one or more enzymes involved in a metabolic or biochemical process. The primary role of such elements is as a catalyst, and only trace amounts are necessary for cellular function.
III- Metals Related to Medical Therapy

Include:

- Aluminum (Al).
- Bismuth (Bi).
- Gallium (Ga).
- Lithium (Li).
- Gold (Au).
- Platinum (Pt).
IV- Minor Toxic Metals

- Include:
  - Antimony (Sb).
  - Barium (Ba).
  - Cesium (Cs).
  - Germanium (Ge).
  - Indium (In).
  - Palladium (Pa).
  - Silver (Ag).
  - Tellurium (Te).
  - Thallium (Tl).
  - Tin (Sn).
  - Titanium (Ti).
  - Uranium (U).
  - Vandium (V).
Heavy metals may enter the body via food, water, or air, or by absorption through the skin. Once in the body, they compete with and displace essential minerals such as zinc, copper, magnesium, and calcium, and interfere with organ system function. People may come in contact with heavy metals in industrial work, pharmaceutical manufacturing, and agriculture. Children may be poisoned as a result of playing in contaminated soil.
Lead (Pb) Toxicity (Plumbism): Lead is an environmentally persistent toxin that causes neurological, hematological, gastrointestinal, reproductive, circulatory, and immunological pathologies.

Lead is a persistent and common environmental contaminant. Like other commonly found, persistent toxic metals – mercury, arsenic, and cadmium – lead damages cellular material and alters cellular genetics. There is experimental evidence to indicate that cellular damage mediated by reactive oxygen species can be involved in the pathology associated with lead toxicity.

Lead is known to cause oxidative damage in several tissues by bringing about an imbalance in the generation and removal of reactive oxygen species. A pathological free radical mechanism that leads to lipid peroxidation and degradation of phospholipids, thereby causing a loss of membrane integrity, is currently proposed as an important factor in organ damage from lead exposure. Recent in vivo studies on lead exposed animals and workers have shown the generation of reactive oxygen species, stimulation of lipid peroxidation and decreased antioxidant defense system.
The pathogenesis of lead toxicity is multifactorial, as lead directly interrupts enzyme activation, competitively inhibits trace mineral absorption, binds to sulfhydryl proteins (interrupting structural protein synthesis), alters calcium homeostasis, and lowers the level of available sulfhydryl antioxidant reserves in the body.

- **Hematological insult of lead**: Basophilic Stippling

- The half-life of lead in adult human blood has been estimated to be from 28 days. Approximately 99% of the lead in blood is associated with red blood cells; the remaining 1% resides in blood plasma. Blood lead is also important because the BLL is the most widely used measure of lead exposure.

- These tests, however, do not measure total body burden—they are more reflective of recent or ongoing exposures.

- Anemia only occurs in very marked cases of lead toxicity, and is **microcytic and hypochromic**, as in iron deficiency.
-Bone Effects of Lead:
Lead has an extremely long half-life in bone, accounting for over 90% of the body lead in adults. Lead can affect bone by interfering with metabolic and homeostatic mechanisms including parathyroid hormone, calcitonin, vitamin D, and other hormones that influence calcium metabolism. Lead substitutes for calcium in bone. Lead is known to affect osteoblasts (cells renew bone tissues), osteoclasts (type of bone cells that resorbe bone tissue), and chondrocytes and has been associated with osteoporosis and delays in fracture repair.
- In an adult human, the majority of ingested lead (more than 95%) accumulates in the bone. With its half-life being in the order of decades, bone lead can remain elevated despite a decline in environmental exposure.

- Available data suggest that there is a close relationship between bone pathology and lead. Thus, the skeleton is an important endogenous source of lead, and this source should be a subject of particular note when looking into the toxicity risks of lead.

- Lead poisoning: Opaque metaphyseal bands in the upper and lower tibia and the upper fibula secondary to lead poisoning in a child.
Renal Toxicity:

- **Acute lead nephrotoxicity** consists of proximal tubular dysfunction and can be reversed by treatment with chelating agents.

- **Chronic lead nephrotoxicity**: consists of interstitial fibrosis and progressive nephron loss, azotaemia and renal failure.

- A characteristic microscopic change is the presence of intranuclear inclusion bodies (Fig. beside). By light microscopy the inclusions are dense, homogeneous, and are eosinophilic with hematoxylin and eosin staining.

- Lead-induced inclusion body formation in kidneys from WT mice
Food is one of the major sources of lead exposure; the others are air (mainly lead dust originating from petrol) and drinking water. Plant food may be contaminated with lead through its uptake from ambient air and soil; animals may then ingest the lead.

Contaminated vegetation. In humans, lead ingestion may arise from eating lead contaminated vegetation or animal foods.
Another source of ingestion is through the use of lead-containing vessels or lead-based pottery glazes. In humans, about 20 to 50% of inhaled, and 5 to 15% of ingested inorganic lead is absorbed. In contrast, about 80% of inhaled organic lead is absorbed, and ingested organic Pb is absorbed readily. Once in the bloodstream, lead is primarily distributed among blood, soft tissue, and mineralizing tissue. The bones and teeth of adults contain more than 95% of the total body burden of lead. Children are particularly sensitive to this metal because of their more rapid growth rate and metabolism.
Management of lead toxicity:

1. **Decreasing Exposure** By far, the most successful management occurs due to the removal of the lead risk from the environment and, ultimately. Once the source of lead is found in the home, soil, or workplace every effort should be made to remove this source. This may be accomplished by home lead paint avoidance, home dust reduction techniques, decreasing bare soil available, and nutritional evaluation. As those with iron deficiency should be treated as anemia may be worse with high lead and low iron. In addition, a **diet sufficient in trace elements including calcium and vitamin C** should be encouraged.
2- Chelating Therapy: Once lead has entered the body, especially bone, it is very difficult to remove. Accordingly, prevention is the mainstay of treatment. However, chelation therapy may be used to decrease the blood lead concentrations acutely. The final component of treatment is chelation therapy. Chelating agents bind metals at two or more sites. Ideally, the chelated metal would be excreted; however, the lead:chelate complex may persist in tissues where the binding occurred or be redistributed to other tissues. An optimal chelating drug should increase lead excretion, be administered easily, and be affordable and safe. Lead removal should halt (stope) further toxicity and reverse previous effects.
Oral chelating agents are available for treatment of lead poisoned patients who have elevated blood lead concentrations and asymptomatic. 2,3 Dimercaptosuccinic Acid (DMSA, Succimer) is the drug most commonly used. Other oral agents that may be used are Racemic-2,3-dimercapto-1-propanesulfonic acid (DMPS) (Unithiol) and Penicillamine.
Cadmium Toxicity:

- Food is the major source of cadmium for the general population. Many plants readily accumulate cadmium from soil. Both natural and anthropogenic sources (environmental) of cadmium contamination occur for soil, including fallout of industrial emissions, some fertilizers, soil amendments, and use of cadmium-containing water for irrigation, all resulting in a slow but steady increase in the cadmium content in vegetables over the years.

- Cadmium affect most bodily functions and structures including: Kidney and Bone, Lung, periodontal tissues, mammary glands, blood vessels, heart, GIT, reproductive system, immune system, and multi-tissue carcinogen.

- In all likelihood, cadmium being a divalent cation is accumulated by transport mechanisms developed for essential metals. From physical and chemical properties, those metals are most likely to be zinc, iron, magnesium, manganese, calcium and selenium. Cadmium may interact with these elements and cause their secondary deficit thereby disrupting metabolism, resulting in the final morphological and functional changes in many organs. Interaction of cadmium with iron, copper and zinc are fairly well understood and described.
Cigarette smoking is a major source of cadmium exposure. Biological monitoring of cadmium in the general population has shown that cigarette smoking may cause significant increases in blood cadmium (B-Cd). Furthermore, Food is the most important source of cadmium exposure in the general non-smoking population in most countries. Cadmium is present in most foodstuffs, but concentrations vary greatly, and individual intake also varies considerably due to differences in dietary habits.
- **Inhalation of cadmium:** fumes or particles can be life threatening, and although acute **pulmonary effects** and deaths are uncommon.

- Lung of frog exposed to 1.00 mg/l Cd. Mild pulmonary haemorrhage (H), and distortion of lung architecture after 28 days. (H & E x 160).
Cadmium exposure may cause kidney damage. It has been suggested that the tubular damage is reversible, but there is overwhelming evidence that the cadmium induced tubular damage is indeed irreversible.
Uptake of Cd is known to interfere with the utilization of essential metals*. After ingestion, Cd ions are absorbed by most tissues of the body and become concentrated mainly in the liver and kidney and has a long biological half-life of 17 to 30 years in humans.

Cadmium caused cellular toxicity and a depletion of reduced glutathione (GSH), which could be inhibited by the radical scavengers. It is proposed that cadmium binds to the imidazole group superoxide dismutase (SOD) which is vital for the breakdown of hydrogen peroxide, thus causing its toxic effects.

Cadmium inhibition of liver mitochondrial MnSOD activity was completely removed by Mn(II) ions, suggesting that the reduced effectiveness of this enzyme is probably due to the substitution of cadmium for manganese.
Long-term high cadmium exposure may cause **skeletal damage**, first reported from Japan, where the **itai-itai** (ouch-ouch) disease (a combination of **osteomalacia and osteoporosis**) was discovered in the 1950s. The exposure was caused by cadmium-contaminated water used for irrigation of local rice fields. Cadmium has also been associated with prostate cancer, kidney cancer.
Furthermore, large numbers of enzymatic activities are influenced by cadmium and the mechanisms of these effects have been hypothesized to be due to, either displacement of a beneficial metal from the active site or through binding to the active site in the enzyme itself. The various toxic effects induced by cadmium and other heavy metals in biological systems might be due to alterations in the antioxidant defense system. This includes reduced glutathione (GSH), glutathione peroxidase, thioredoxin reductase (TrxR), and selenium.
Management of Cd Toxicity (Reduction of Body Burden):
Clinical protocols exist for the use of EDTA, DMPS, and DMSA. EDTA is the agent most widely accepted for clinical use, but not all authorities agreed with the use of EDTA, because it aggravates damage to the kidney tubules. For chronic exposures, however, there is considerable evidence of chelation’s clinical efficacy, in humans and in experimental animals. Several chelators have been used. Clinically available chelators include EDTA, DMPS, DMSA, and British Anti-Lewisite (BAL).
Arsenic Toxicity:
Arsenic is a widely distributed metalloid, occurring in rock, soil, water and air. Inorganic arsenic is present in groundwater used for drinking in several countries all over the world (e.g. Bangladesh, Chile and China), whereas organic arsenic compounds are primarily found in fish, which thus may give rise to human exposure.

General population exposure to arsenic is mainly via intake of food and drinking water. Food is the most important source, but in some areas, arsenic in drinking water is a significant source of exposure to inorganic arsenic. Contaminated soils such as are also a potential source of arsenic exposure.
Absorption of arsenic in inhaled airborne particles is highly dependent on the solubility and the size of particles. Soluble arsenic compounds are easily absorbed from the gastrointestinal tract. However, inorganic arsenic is extensively methylated in humans and the metabolites are excreted in the urine. Arsenic (or metabolites) concentrations in blood, hair, nails and urine have been used as biomarkers of exposure. Arsenic in hair and nails can be useful indicators of past arsenic exposure, if care is taken to avoid external arsenic contamination of the samples.
Reactive oxygen species (ROS) mediated oxidative damage is a common denominator in arsenic pathogenesis. In addition, arsenic induces morphological changes in the integrity of mitochondria. Cascade mechanisms of free radical formation derived from the superoxide radical, combined with glutathione depleting agents, increase the sensitivity of cells to arsenic toxicity. When both humans and animals are exposed to arsenic, they experience an increased formation of ROS/RNS, including peroxyl radicals (ROO•), the superoxide radical, singlet oxygen, hydroxyl radical (OH•), hydrogen peroxide, the dimethylarsenic radical, the dimethylarsenic peroxyl radical and/or oxidant induced DNA damage.
Chelation therapy for chronic As toxicity is thought to be the specific therapy for relief of systemic clinical manifestations and reduction of As stores in the body, reducing subsequent cancer risk. Chelation therapy is presumed to be more effective with early features of the toxicity, as severe manifestation of polyneuropathy, chronic lung and liver disease, swelling of hand and legs, defect of hearing and vision are less likely to respond to this therapy. Chelating agents like, DMSA (Dimercaptosuccinic Acid), DMPS (Dimercaptopropane succinate) and d-penicillamine have frequently been considered for treatment of chronic As toxicity. However, their usefulness are yet to be established.
**Mercury Poisoning:**

Most human exposure to mercury is caused by mercury from dental amalgam, ingestion of contaminated fish, or occupational exposure, according to the World Health Organization (WHO). Fish at the top of the food chain may concentrate considerable mercury in their tissues. Mercury is believed to interfere with DNA transcription and protein synthesis, including protein synthesis in the developing brain, with destruction of endoplasmic reticulum and disappearance of ribosomes. Evidence suggests disruption of numerous subcellular elements in the central nervous system and other organs and in mitochondria; adverse effects have also been described on heme synthesis, cell membrane integrity in many locations, free radical generation, neurotransmitter disruption, and stimulation of neural excitoxins, resulting in damage to many parts of the brain and peripheral nervous system.
Acute mercury exposure may give rise to lung damage. Chronic poisoning is characterized by neurological and psychological symptoms, such as tremor, changes in personality, restlessness, anxiety, sleep disturbance and depression. The symptoms are reversible after cessation of exposure. Because of the blood–brain barrier there is no central nervous involvement related to inorganic mercury exposure. Metallic mercury may cause kidney damage, which is reversible after exposure has stopped. It has also been possible to detect proteinuria at relatively low levels of occupational exposure.
Treatment:

- The most important and effective treatment is to identify the source and end the exposure.
- Chelating agents (DMSA) may enhance inorganic mercury elimination. Dimercaprol may increase mercury concentration in the brain.
Thanks for Listening