Heavy metal poisoning

(Arsenic, lead, mercury, iron, copper)

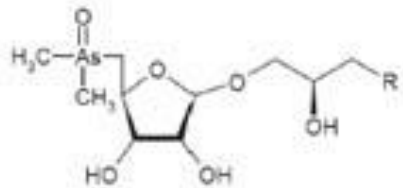
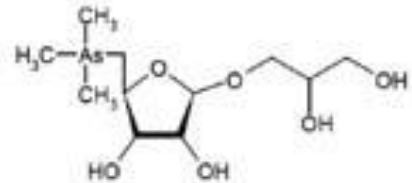
- Many metallic elements in trace quantities are essential for various biological processes. Some of them activate enzymes, others facilitate exchange and utilisation of oxygen and carbon dioxide.

- While most of these trace elements are acquired in adequate quantities through food, excessive exposure (nutritional, occupational, or environmental) can lead to progressive accumulation and toxicity resulting in serious consequences.

Arsenic (As)

- Arsenic (As) is a naturally occurring element that is not a true metal but a metalloid
- Organic forms are usually considered to be less toxic than the inorganic forms.
- Some organic **As** compounds are gases or low-boiling liquids at normal temperatures.
- Burning of As, or contact with acid, results in production of **arsine**, a deadly gas.

Table 1. Acronyms, nomenclature and formulas of selected arsenic species from the marine environment (according to Francesconi et al., 2004).

Acronym	Arsenic species	Formula
As(V)	Arsenate	$O{=}As(O^-)_3$
As(III)	Arsenite	$As(O^-)_3$
MA	Methylarsonate	$CH_3AsO(O^-)_2$
DMA	Dimethylarsinate	$(CH_3)_2AsO(O^-)$
AB	Arsenobetaine	$(CH_3)_3As^+CH_2COO^-$
TMAO	Trimethylarsine oxide	$(CH_3)_3AsO$
AC	Arsenocholine	$(CH_3)_3As^+CH_2CH_2OH$
TETRA	Tetramethylarsonium ion	$(CH_3)_4As^+$
DMAA	Dimethylarsinoylacetate	$(CH_3)_2As(O)CH_2COO^-$
TMAP	Trimethylarsoniopropionate	$(CH_3)_3As^+CH_2CH_2COO^-$
DMAE	Dimethylarsinoylethanol	$(CH_3)_2As(O)CH_2CH_2OH$
DMAP	Dimethylarsinoylpropionate	$(CH_3)_2As(O)CH_2CH_2COO^-$
DMAS	Dimethylarsinothioate	$(CH_3)_2As(=S)(O^-)$
DMAAS	Dimethylarsinothioylacetate	$(CH_3)_2As(=S)CH_2COO^-$
	Dimethylated Arsenosugars:	Trimethylated Arsenosugar:
		
	Arsenosugar 1 (glycerol sugar)	R = OH
	Arsenosugar 2 (phosphate sugar)	$R = OP(O)(O^-)OCH_2CH(OH)CH_2OH$
	Arsenosugar 3 (sulphonate sugar)	$R = SO_3^-$
	Arsenosugar 4 (sulphate sugar)	$R = OSO_3^-$

Source

- Inorganic As is found in groundwater, surface water, and many foods such as rice and grains.
- Exposure is primarily through drinking water, but food is considered a significant source as well.
- Arsenic trioxide (As_2O_3) is a major ingredient of traditional Chinese medicine (TCM) and is used against acute promyelocytic leukemia.
- Inorganic As compounds are mainly used as wood preservatives, insecticides, herbicides, and in the production of metal alloys

Mechanism of toxicity

- The toxicity of **As** is dependent upon the chemical form and the oxidation state at the time of exposure.
- The physical state (gas, solution, powder particle size), the rate of absorption into cells, elimination rate, and the nature of chemical substituents determine the toxic outcome.
- Once absorbed, arsenicals exert their toxic effects through multiple mechanisms, including inhibition of enzymatic reactions vital to cellular metabolism, induction of oxidative stress, and alteration in gene expression and cell signal transduction.
- Inorganic pentavalent **As** does not react with the active sites of enzymes directly, but first reduces to trivalent **As** before exerting toxic effects.
- Bonding of trivalent **As** to –SH and –OH groups interferes with enzyme activity. Inactivation of **pyruvate dehydrogenase** with trivalent As will prevent generation of adenosine-5-triphosphate (ATP).
- Arsenic inhibits **succinic dehydrogenase** activity and can uncouple oxidative phosphorylation, a process that results in disruption of all cellular functions.
- **As** targets and accumulates within mitochondria.

Toxic dose

- The toxicity of arsenic compounds varies considerably based on valence state, chemical composition, and solubility.
- Humans are generally more sensitive than other animals to the acute and chronic effects of arsenicals
- In general, the pentavalent form of arsenic (arsenate) is less toxic than the trivalent form (arsenite) because it is less water soluble.
- Acute ingestion of as little as 100–300 mg of a soluble trivalent arsenic compound (eg, sodium arsenite, arsenic trioxide) could be fatal
- The most toxic form is arsine gas (25 to 30 ppm can be lethal in 30 minutes).

- Organic arsenic

- In general, pentavalent organoarsenic compounds are less toxic than either trivalent organoarsenic compounds or inorganic arsenic compounds.

- Marine organisms may contain large quantities of **arsenobetaine**, an organic trimethylated compound, which is excreted unchanged in the urine and produces no known toxic effects.

Clinical presentation

Acute exposure

- Gastrointestinal effects:
  - After a delay of minutes to hours, diffuse capillary damage results in hemorrhagic gastroenteritis. Nausea, vomiting, abdominal pain and watery diarrhea are common.

- Cardiovascular effects
  - In severe cases, extensive tissue third spacing of fluids (peritoneal cavity, pleural cavity) combined with fluid loss from gastroenteritis may lead to hypotension, tachycardia, shock, and death.

  - After a delay of 1–6 days, there may be a second phase of congestive cardiomyopathy, cardiogenic or noncardiogenic pulmonary edema, and isolated or recurrent cardiac arrhythmias. Prolongation of the QT interval may be associated with ventricular arrhythmia

- Neurological effects
  - Mental status may be normal, or there may be lethargy, agitation, or delirium. Delirium or obtundation may be delayed by 2–6 days.
  - Generalized seizures may occur, but are rare.
  - Symmetric, sensorimotor axonal peripheral neuropathy may evolve 1–5 weeks following acute ingestion, beginning with painful, distal **dysaesthesia**, particularly in the feet.
  - Ascending weakness and paralysis may ensue, leading in severe cases to **quadriplegia** and neuromuscular respiratory failure

- Hematologic effects
  - Pancytopenia, particularly leukopenia and anemia, characteristically develops within 1–2 weeks after acute ingestion

- Dermatologic effects
  - Findings that occasionally appear after a delay of 1–6 weeks include **desquamation** (particularly involving palms and soles), a diffuse **maculopapular rash**, **periorbital edema**, and **hyperkeratosis**

  - Transverse white striae in the nails **(Aldrich-Mees lines)** may become apparent months after an acute intoxication

White striae in the nails (Aldrich-Mees lines)

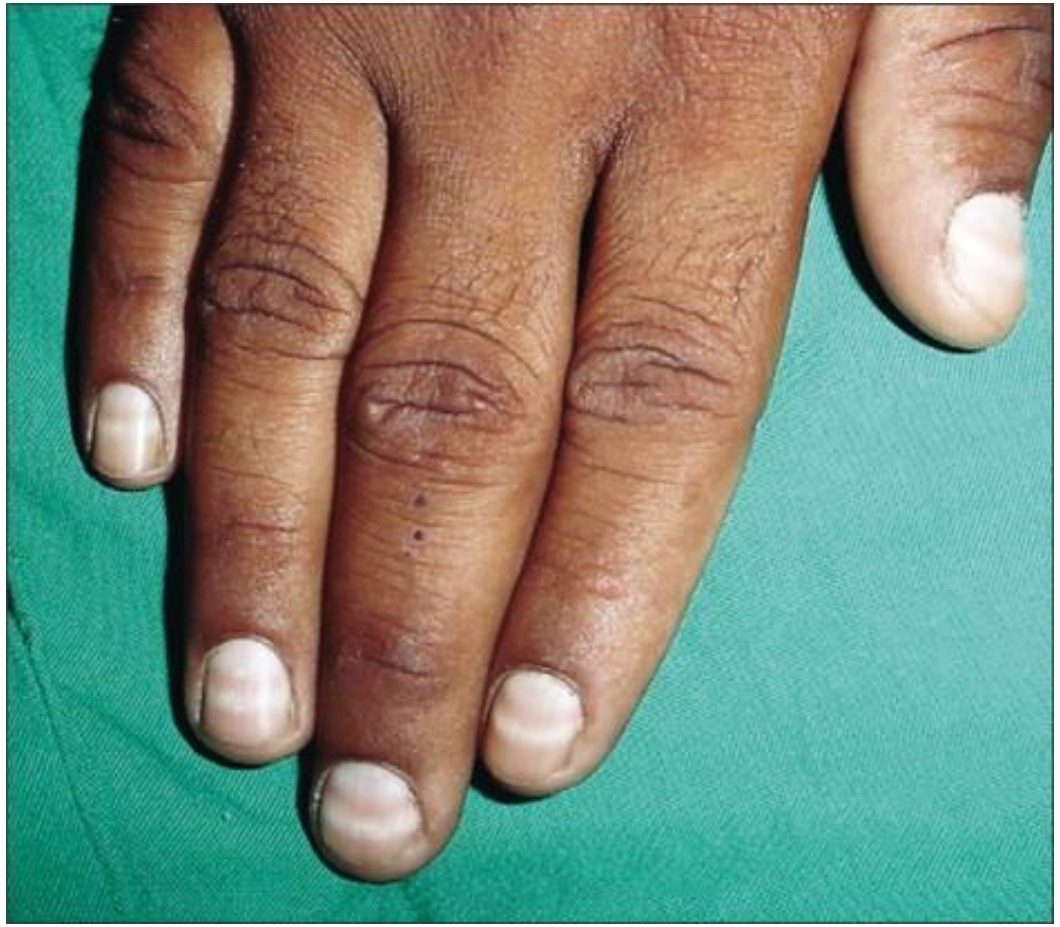


Fig 9.2: Arsenic poisoning—Hyperkeratosis

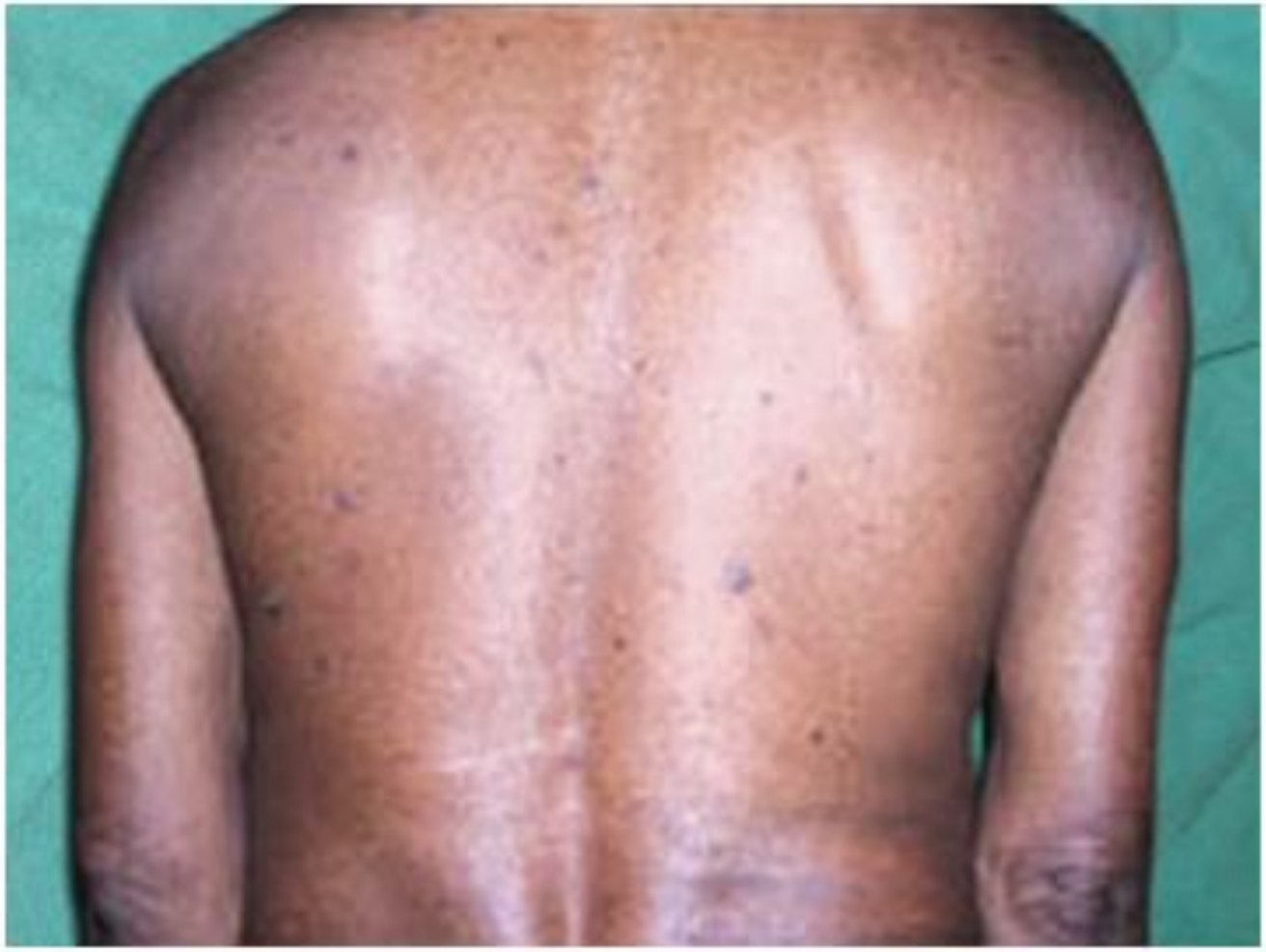


Fig 9.4: Raindrop pigmentation—arsenic poisoning

Chronic intoxication

- Chronic intoxication is also associated with multisystemic effects.

- Chronic **As** toxicity is characterized by fatigue and malaise, changes in skin pigmentation, plantar and palmar hyperkeratoses, transverse white striae in the nails (Aldrich-Mees lines), GI symptoms (gastroenteritis), bone marrow toxicity (leukopenia and anemia), skin cancers, and liver disease(hepatic transaminase elevation, noncirrhotic portal hypertension).

- Epidemiological evidence links chronic arsenic ingestion with an increased risk of hypertension, cardiovascular mortality, and diabetes mellitus

- Arsenic replaces phosphorus in the bone where it may remain for years. It gets deposited also in hair.

Arsenic Poisoning: Clinical Symptoms

System	*Acute*	*Chronic*
Dermal	Hair loss, transverse bands of opacity in nails (*Mees' lines*)*	Melanosis (neck, eyelids, nipples), Bowen's disease, facial oedema, hyperkeratosis, hyperpigmentation (*rain drop pattern*) skin cancer
Ocular	Conjunctivitis, lacrimation	Dimness of vision
Gastrointestinal	Abdominal pain, metallic taste, dysphagia,vomiting, bloody or rice-water diarrhoea.** There may be garlicky odour in the breath	Anorexia, nausea, vomiting, diarrhoea,weight loss
Airways	Irritation of upper airways	Perforation of nasal septum, chronic laryngitis, bronchitis
Liver	Fatty degeneration	Hepatomegaly, jaundice, cirrhosis
Kidney	Oliguria, uraemia	Nephritic changes
Neurological	Hyperpyrexia, convulsions, coma	Encephalopathy, polyneuritis (*glove & stocking type*), tremor, ataxia, limb tenderness,difficulty in walking
Haematological	—	Anaemia, leucopenia, thrombocytopenia, basophilic stippling, karyorrhexis, pancytopenia
Cardiac	Tachycardia, hypotension, cardiac arrhythmias***	Hypertension, myocarditis

**After 2 weeks*
***May mimic cholera*
****ECG changes include ST-T wave changes and prolonged QT interval*

Diagnosis

- Diagnosis is usually based on a history of exposure combined with a typical pattern of multi-systemic signs and symptoms.

- Specific levels

- In the first 2–3 days after acute symptomatic poisoning, total 24-hour **urinary arsenic excretion** is typically in excess of several thousand micrograms (spot urine greater than 1000 mcg/L)

Treatment
Emergency and supportive measures

- Maintain an open airway and assist ventilation if necessary

- Treat coma, shock, and arrhythmias, if they occur.

- Treat hypotension and fluid loss with aggressive use of intravenous crystalloid solutions, and vasopressor agents if needed, to support blood pressure and optimize urine output.

Specific drugs and antidotes

- Treat seriously symptomatic patients with chelating agents,

- **Unithiol**:
  - It can be administered intravenously, has the most favorable pharmacological profile for treatment of acute arsenic intoxication.
  - Starting dose: 3–5 mg/kg every 4 hours by slow intravenous infusion over 20 minutes
- **Dimercaprol** (British anti-Lewisite)
  - It is the chelating agent of second choice if unithiol is not immediately available. The starting dose is 3–5 mg/kg by deep intramuscular injection every 4–6 hours.

Decontamination

- Administer activated charcoal? Note that activated charcoal has a relatively poor affinity for inorganic arsenic salts

- Consider gastric lavage for large ingestions

Enhanced elimination

- Hemodialysis may be of possible benefit in patients with concomitant renal failure, but otherwise contributes minimally to arsenic clearance.

- There is no known role for diuresis, hemoperfusion, or repeat-dose charcoal.

LEAD (Pb)

- Lead is the commonest metal involved in chronic poisoning.
- It was one of the first metals known to man and has been widely used during the last two thousand years for domestic, industrial, and therapeutic purposes.
- Lead is abundant in soil, being distributed throughout the earth's crust

Source

- The main use of Pb is in the production of **storage batteries** and in sheathing **electric cables.**

- It is also useful as protective shielding from x-rays and radiation from nuclear reactors.

- Certain folk medicines (eg, the Mexican remedies and some Indian Ayurvedic preparations) may contain high amounts of lead salts.

- Lead acetate (sugar of lead) has been used in therapeutics,
- lead carbonate (white lead) is still used in paints,
- lead oxide (litharge) is essential for glazing of pottery and enamel ware, and
- tetraethyl lead is mixed with petrol as an antiknock to prevent detonation in internal combustion engines.
- Among cosmetics, lead tetroxide is the most common compound in “Sindoor” and “Surma”

Summary of some of the common sources of Pb:

- Candle with lead-containing wicks
- Ayurvedic medicines
- Paint
- Retained bullets
- Ink
- Automobile storage battery casing; battery repair shops
- Ceramic glazes
- Lead pipes
- Silver jewellery workers
- Renovation/modernisation of old homes.

Mechanism of toxicity

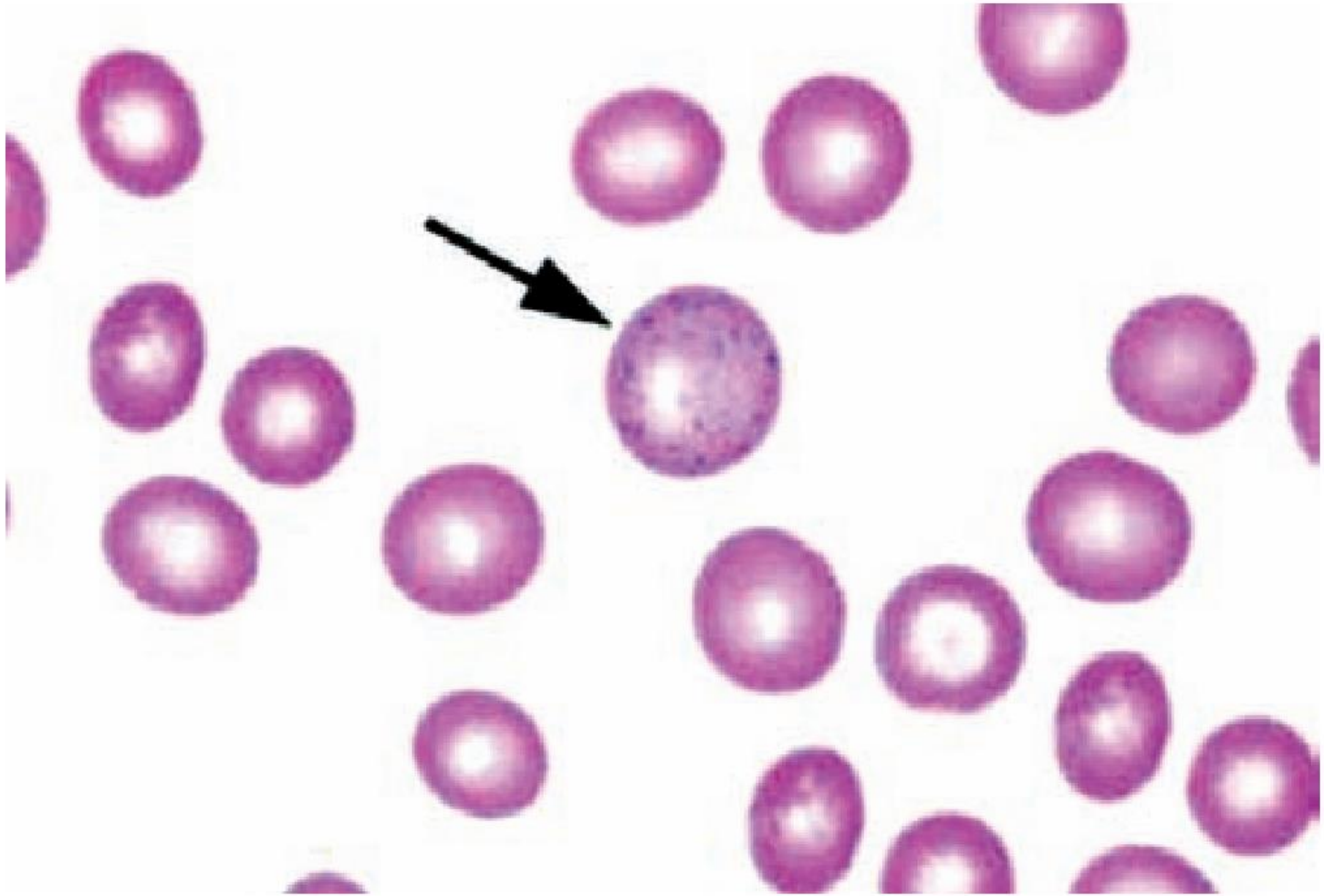
- Pb toxicity affects virtually all organs and systems of the body

- The proposed mechanism of Pb toxicity involves its ability to inhibit or mimic the action of cations such as calcium, zinc, and iron, and to interfere with vital proteins by binding to sulfhydryl, amine, phosphate, and carboxyl groups.

- Pb increases intracellular levels of Calcium in brain capillaries, neurons, hepatocytes, and arteries that trigger smooth muscle contraction, thereby inducing **hypertension**.

- Pb interferes with **heme biosynthesis** by interfering with ferrochelatase, ALAS (aminolevulinic acid synthetase), and ALAD (aminolevulinic acid dehydrase). Therefore, decreased hemoglobin and anemia result in individuals exposed to excessive Pb

- Lead increases haemolysis as a result of which immature red cells are released into circulation such as **reticulocytes** and **basophilic stippled cells** (the result of aggregation of ribonucleic acid due to inhibition of the enzyme pyrimidine-5-nucleotidase which normally eliminates degraded RNA)



- In the nervous system, Pb substitutes for Ca as a secondary messenger in neurons, blocking voltage-gated Ca channels, inhibiting influx of Ca and subsequent release of neurotransmitter. The result is an inhibition of synaptic transmission.

- Pb inhibits glutamate uptake and glutamate synthetase activity in astroglia, thus inhibiting the regeneration of glutamate, a major excitatory neurotransmitter

- This leads to decreased nerve conduction, increased psychomotor activity, lower IQ, and behavioural/learning disorders.

- Children are especially susceptible

- Lead also has deleterious effects on the CVS (hypertension and myocarditis), kidney (nephritis), and reproductive organs (infertility).

- In addition, lead can decrease uric acid renal excretion, thereby raising blood urate levels and predisposing to gout

Toxic dose

- Today the accepted upper level for blood lead (BL) is fixed as 35 mcg/100 ml. However there are reports that adverse effects especially on the haematopoietic system can occur at levels as low as 10 mcg/100 ml.

Clinical presentation

Acute poisoning

- This is rare. Many reported cases of acute poisoning may actually be exacerbations of chronic lead poisoning when significant quantities of lead are suddenly released into the bloodstream from bone.

- Symptoms include metallic taste, abdominal pain, constipation or diarrhoea (stools may be blackish due to lead sulfide), vomiting, hyperactivity or lethargy, ataxia, behavioural changes, convulsions, and coma.

Chronic poisoning

- Subacute or chronic exposure is more common than acute poisoning

- **Constitutional effects** include fatigue, malaise, irritability, anorexia, insomnia, weight loss, decreased libido, arthralgias, and myalgias. Hypertension may be associated with lead exposure in susceptible populations

- **Gastrointestinal effects** include crampy abdominal pain (lead colic), nausea, constipation, or (less commonly) diarrhea.

- **Central nervous system** manifestations range from impaired concentration, headache, diminished visual-motor coordination, and tremor to overt encephalopathy (a life-threatening emergency characterized by agitated delirium or lethargy, ataxia, convulsions, and coma).

- Chronic low-level exposure in infants and children may lead to decreased intelligence and impaired neurobehavioral development, stunted growth, and diminished auditory acuity

- **Peripheral motor neuropathy**, affecting mainly the upper extremities, can cause severe extensor muscle weakness (“wrist drop”)

- **Hematologic effects** include normochromic or microcytic anemia, which may be accompanied by basophilic stippling. Hemolysis may occur.

- **Nephrotoxic effects** include reversible acute tubular dysfunction and chronic interstitial fibrosis. Hyperuricemia and gout may occur.

- **Adverse reproductive outcomes** may include diminished or aberrant sperm production, increased rate of miscarriage, preterm delivery, decreased gestational age, low birth weight, and impaired neurologic development.

Diagnosis

- Diagnosis is usually based on a history of exposure combined with a typical pattern of multi-systemic signs and symptoms.
- Specific levels
- The whole-blood lead level is the most useful indicator of lead exposure
- With blood levels in excess of 80 mcg/dL, indicate serious intoxication

Treatment
Emergency and supportive measures

- Treat seizures and coma if they occur.

- Provide adequate fluids to maintain urine flow (optimally 1–2 mL/kg/h) but avoid over hydration, which may aggravate cerebral edema

- Patients with increased intracranial pressure may benefit from corticosteroids (eg, dexamethasone, 10 mg IV) and mannitol (1–2 g/kg IV).

Specific drugs and antidotes.

- Treatment with chelating agents decreases blood lead concentrations and increases urinary lead excretion.

- Severe acute poisoning with encephalopathy
  - BAL 4 mg/kg immediately (in children)
  - $CaNa_2$ EDTA 75 mg/kg/day IV infusion
- Severe acute poisoning without encephalopathy
  - BAL 12 mg/kg/day.
  - EDTA 50 mg/kg/day.
- Moderate poisoning:
  - EDTA50 mg/kg/day
- Mild poisoning
  - D-Penicillamine 30 mg/kg/day

Decontamination

- Acute ingestion
  - Administer activated charcoal (although efficacy is unknown).
  - If lead-containing material is still visible on abdominal x-ray after initial treatment, consider whole-bowel irrigation.
  - Consider endoscopic or surgical removal of lead foreign bodies that exhibit prolonged gastrointestinal retention.

Enhanced elimination

- There is no role for dialysis, hemoperfusion, or repeat-dose charcoal.

Mercury

- Mercury (Hg) is a naturally occurring metal that is mined chiefly as HgS in cinnabar ore.
- It is converted to three primary forms, each with a distinct toxicology: elemental (metallic) mercury (Hg^0), inorganic mercury salts (eg, mercuric chloride [$HgCl_2$]), and organic (alkyl and aryl) mercury (eg, methylmercury).
- Approximately one-third of commercial mercury use is in the manufacture of chlorine and caustic soda
- Other major uses include electrical equipment, thermometers and other measuring and control instruments, dental amalgam, paints and pigments, and gold mining and extracting.

- Some folk medicines contain inorganic mercury compounds

- Aquatic organisms can convert inorganic mercury into methylmercury, with resulting bioaccumulation in large carnivorous fish such as swordfish

Uses of Mercury Compounds

Industry	*Medicine and Dentistry*	*Miscellaneous*
1. Barometer, thermometer, etc.	1. Antiseptic and disinfectant	1. Electroplating
2. Ceramics	2. Dental amalgam	2. Embalming
3. Dry cell batteries	3. Diuretic	3. Fabric softener
4. Electrical appliances(mercury switches)	4. Purgative	4. Fingerprint powder
5. Explosives and fireworks		5. Fungicide
6. Felt hats		6. Gold and silver extraction
7. Fluorescent and mercury vapour lamps		7. Grain preservative
		8. Paints
		9. Pesticides
		10. Taxidermy

Mechanism of toxicity

- The mechanism of Hg toxicity is believed to be related to high-affinity binding of divalent mercuric ions to thiol or SH groups of proteins.

- Inactivation of various enzymes and structural proteins, and alterations of cell membrane permeability, are believed to contribute to the severe toxicologic effects.

- Increased oxidative stress, disruption of microtubule formation, interference with protein synthesis, DNA replication, and Ca homeostasis are purported pathways.

- Elemental and methylmercury are particularly toxic to the CNS.
- Metallic mercury vapor is also a pulmonary irritant.
- Methylmercury is associated with neurodevelopmental disorders.
- Inorganic mercuric salts are corrosive to the skin, eyes, and gastrointestinal tract, and are nephrotoxic.
- Inorganic and organic mercury compounds may cause contact dermatitis.

Toxic dose

- The pattern and severity of toxicity are highly dependent on the form of mercury and the route of exposure, mostly because of different pharmacokinetic profiles

- Chronic exposure to any form may result in toxicity

- **Elemental (metallic) mercury** is a volatile liquid at room temperature and the vapor is rapidly absorbed by the lungs and distributed to the CNS.

- **Liquid metallic mercury** is poorly absorbed from the gastrointestinal tract, and acute ingestion has been associated with poisoning only in the presence of abnormal gut motility

- **Inorganic mercuric salts**. The acute lethal oral dose of mercuric chloride is approximately 1–4 g.
- Severe toxicity and death have been reported after use of peritoneal lavage solutions containing mercuric chloride concentrations of 0.2–0.8%

- **Organic mercury;** Methylmercury is well absorbed after inhalation, ingestion, and probably dermal exposure.
- Ingestion of 10–60 mg/kg may be lethal, and chronic daily ingestion of 10 mcg/kg may be associated with adverse neurologic and reproductive effects.

Summary of absorption and toxicity of mercury compounds

Form	Absorption		Toxicity	
	Oral	Inhalation	Neurologic	Renal
Elemental (metallic) mercury				
Hg^0 liquid	Poor	NA*	Rare	Rare
Hg^0 vapor	NA*	Good	Likely	Possible
Inorganic mercuric salts				
Hg^{2+}	Good	Rare but possible	Rare	Likely
Organic (alkyl) mercury				
RHg^+	Good	Rare but possible	Likely	Possible

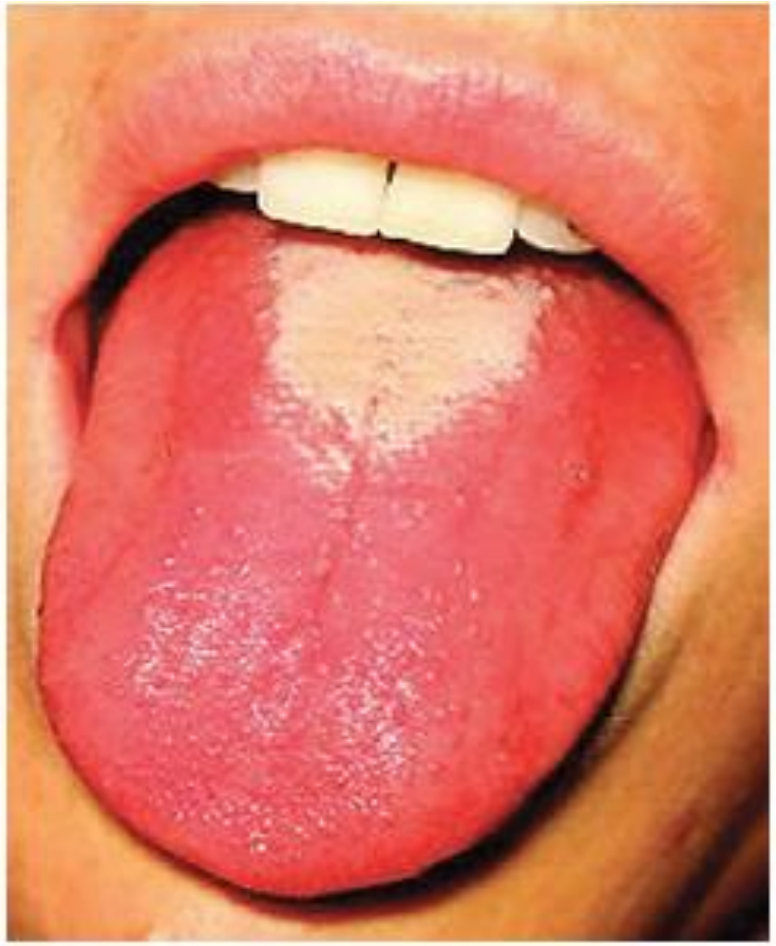
Clinical presentation

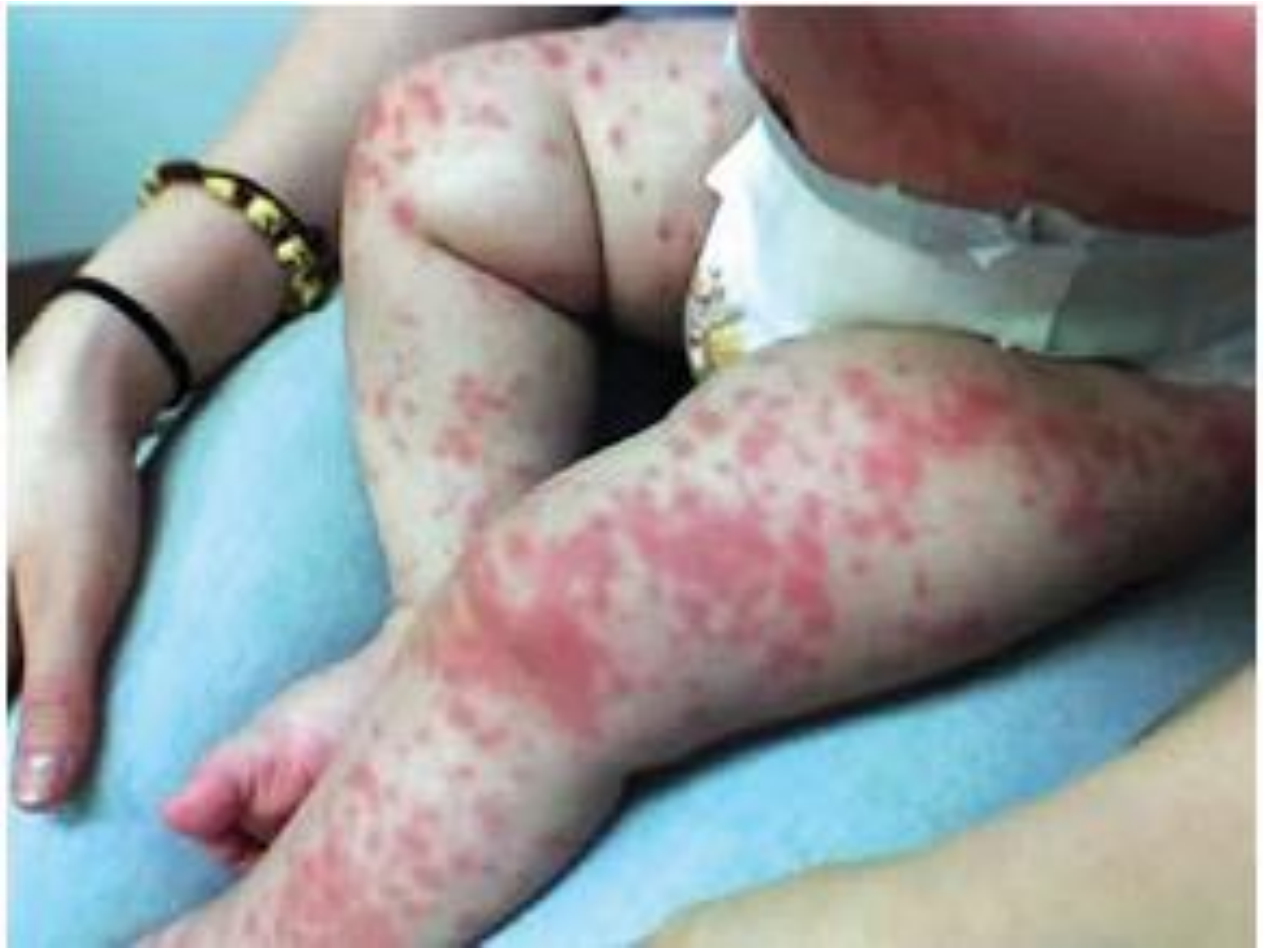
- Metallic mercury
  - **Acute** inhalation of high concentrations of metallic mercury vapour may cause severe chemical pneumonitis and noncardiogenic pulmonary edema.
  - Acute gingivostomatitis may also occur.

  - **Chronic** intoxication from inhalation of mercury vapour produces a classic triad of **tremor**, **neuropsychiatric disturbances**, and **gingivostomatitis**
  - Early stages feature a fine intention tremor of the fingers, but involvement of the face and progression to the limbs may occur.
  - Neuropsychiatric manifestations include fatigue, insomnia, anorexia, and memory loss. There may be an insidious change in mood to shyness, withdrawal, and depression, combined with explosive irritability and frequent blushing (“erethism”)

- Subclinical changes in peripheral nerve function and renal function have been reported, but frank neuropathy and nephropathy are rare

- **Acrodynia**, a rare idiosyncratic reaction to chronic mercury exposure, occurs mainly in children and has the following features: pain in the extremities, often accompanied by pinkish discoloration and desquamation (“**pink disease**”); hypertension; profuse sweating; anorexia, insomnia, irritability, and/or apathy; and a miliarial rash.





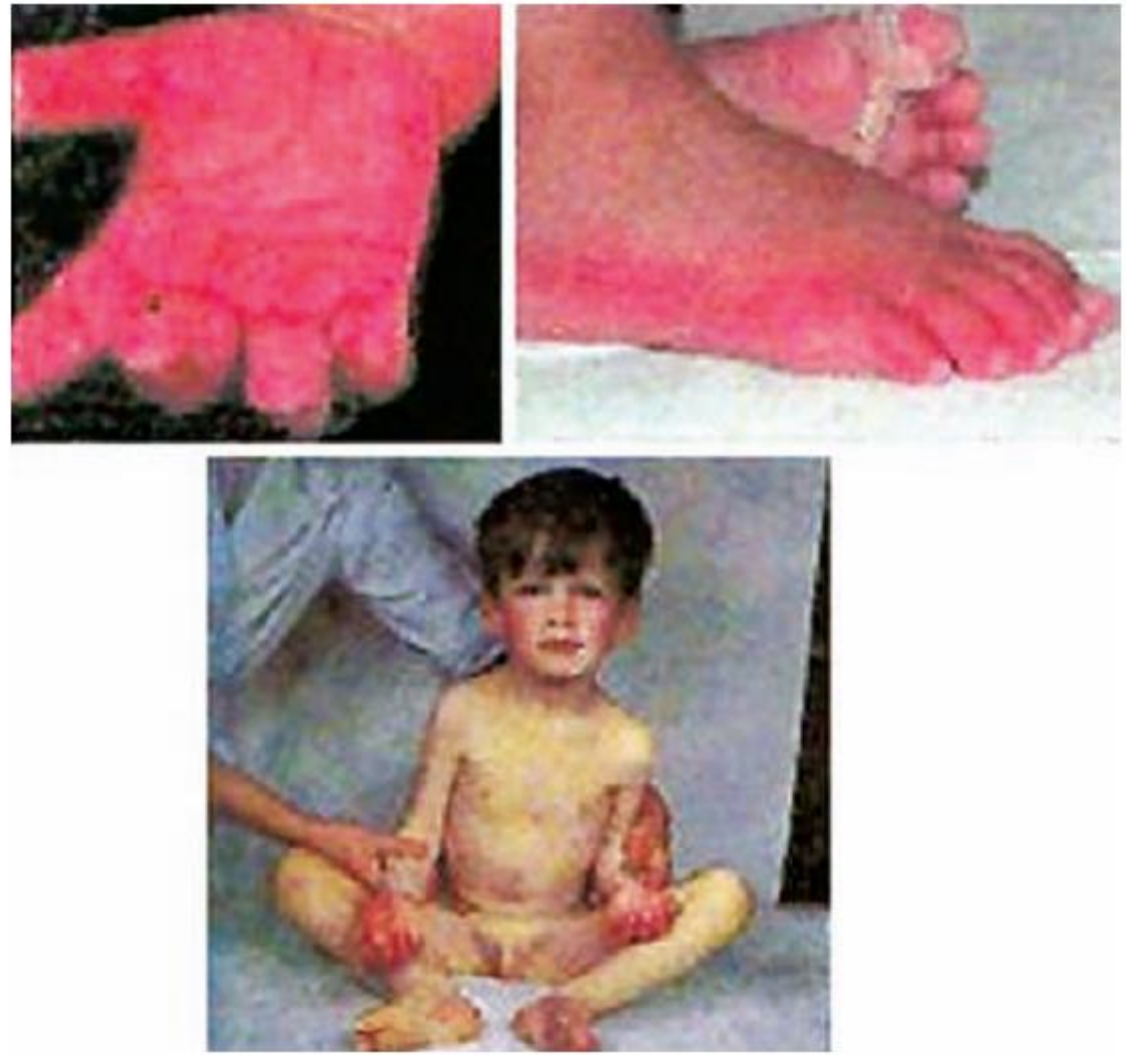


Fig 9.17: Pink disease (Acrodynia)

- **Inorganic mercuric salts**
  - **Acute** ingestion of inorganic mercuric salts, particularly mercuric chloride, causes an abrupt onset of hemorrhagic gastroenteritis and abdominal pain.
  - Intestinal necrosis, shock, and death may ensue.
  - Acute oliguric renal failure from acute tubular necrosis may occur within days.
  - Chronic exposure may result in CNS toxicity.

- **Organic mercury compounds**, particularly short-chain alkyl compounds such as **methylmercury**, primarily affect the CNS, causing paresthesias, ataxia, dysarthria, hearing impairment, and progressive constriction of the visual fields.

- **Ethylmercury** compounds may also cause gastroenteritis.

- **Methylmercury** is a potent reproductive toxin, and perinatal exposure has caused mental retardation and a cerebral palsy–type syndrome in offspring.

Diagnosis

- Diagnosis depends on integration of characteristic findings with a history of known or potential exposure and presence of elevated mercury blood levels or urinary excretion

Treatment
Emergency and supportive measures

- Inhalation
  - Observe closely for several hours for development of acute pneumonitis and pulmonary edema, and give supplemental oxygen if indicated

- Mercuric salt ingestion
  - Anticipate severe gastroenteritis and treat shock aggressively with intravenous fluid replacement
  - Vigorous hydration may also help maintain urine output.
  - Acute renal failure is usually reversible, but hemodialysis may be required for 1–2 weeks.

- Organic mercury ingestion
  - Provide symptomatic supportive care.

Specific drugs and antidotes

- Metallic (elemental) mercury.
  - In acute or chronic poisoning, oral **succimer** (DMSA) or oral **unithiol** (DMPS) may enhance urinary Hg excretion.
  - **Penicillamine** is an alternative oral treatment

- Inorganic mercury salts
  - Treatment with **intravenous unithiol** (DMPS) or **intramuscular BAL**, if begun within minutes to a few hours after ingestion, may reduce or avert severe renal injury.

- Organic mercury
  - In methylmercury intoxication, oral succimer (DMSA) and oral N-acetylcysteine (NAC) may be effective in decreasing Hg levels in tissues, including the brain.

  - BAL may redistribute mercury to the brain from other tissue sites, it should not be used in poisoning by metallic or organic mercury

Decontamination

- Inhalation (Metallic mercury)
  - Immediately remove the victim from exposure and give supplemental oxygen if needed.
  - Even minute indoor spills (eg, 1 mL) of metallic mercury can result in hazardous chronic airborne levels. Cover the spill with powdered sulfur, and carefully clean up and discard all residue and contaminated carpeting, porous furniture, and permeable floor covering.

- Ingestion of metallic mercury
  - In healthy persons, metallic mercury passes through the intestinal tract with minimal absorption, and there is no need for gut decontamination following minor ingestions.
  - With extremely large ingestions, or in patients with abnormally diminished bowel motility or intestinal perforation, there is a risk of chronic intoxication.
  - Multiple-dose cathartics, whole-bowel irrigation, or even surgical removal may be necessary, depending on x-ray evidence of mercury retention or elevated blood or urine Hg levels

- Ingestion of inorganic mercuric salts
  - Prehospital; Administer activated charcoal if available. Do not induce vomiting because of the risk of serious corrosive injury.
  - Hospital; Perform gastric lavage. Administer activated charcoal

- Ingestion of organic mercury.
  - After acute ingestion, perform gastric lavage and administer activated charcoal.

Enhanced elimination

- There is no role for dialysis, hemoperfusion, or repeat-dose charcoal in removing metallic or inorganic mercury.

- However, dialysis may be required for supportive treatment of renal failure, and it may slightly enhance removal of the mercury-chelator complex in patients with renal failure

- In patients with chronic methylmercury intoxication, repeated oral administration of an experimental **polythiol resin** was effective in enhancing Hg elimination by interrupting enterohepatic recirculation.

Iron (Fe)

- There are 3 forms Fe, metallic, ferrous (2^+) and ferric (3^+)
- Metallic iron is silvery white in colour, occurring naturally as haematite, magnetite, etc. and usually causes no problems.
- In fact it is an essential element and deficiency results in anaemia.
- Iron poisoning is related in most instances to overdose of Fe salts. One of the commonest is ferrous sulfate (green vitriol).
- Iron (ferric) oxide, i.e. rust does not cause iron poisoning.

- Fe is an essential metal for almost all living systems, due to its involvement in a number of Fe-containing enzymes and proteins.
- Hemoglobin is required for oxygen and carbon dioxide transport.
- As a component of cytochromes and nonheme Fe proteins, Fe is required for oxidative phosphorylation.
- Myeloperoxidase, a lysosomal enzyme, requires Fe for proper phagocytosis and killing of bacteria by neutrophils.
- Fe deficiency results in anemia and decreased immune competence.

- The average adult human stores about 3.9 to 4.5 g of Fe. Of this, 65% is bound to **hemoglobin**, 20 to 30% is bound to the Fe storage proteins **ferritin** and **hemosiderin**, and the remaining 10% is a constituent of **myoglobin**, **cytochromes**, and **Fe-containing enzymes**.

Sources

- Iron is widely used for treatment of anemia, for prenatal supplementation, and as a common daily vitamin supplement.

- Ferric ferrocyanide (Prussian blue), is used as a pigment in paint and in laundry bluing

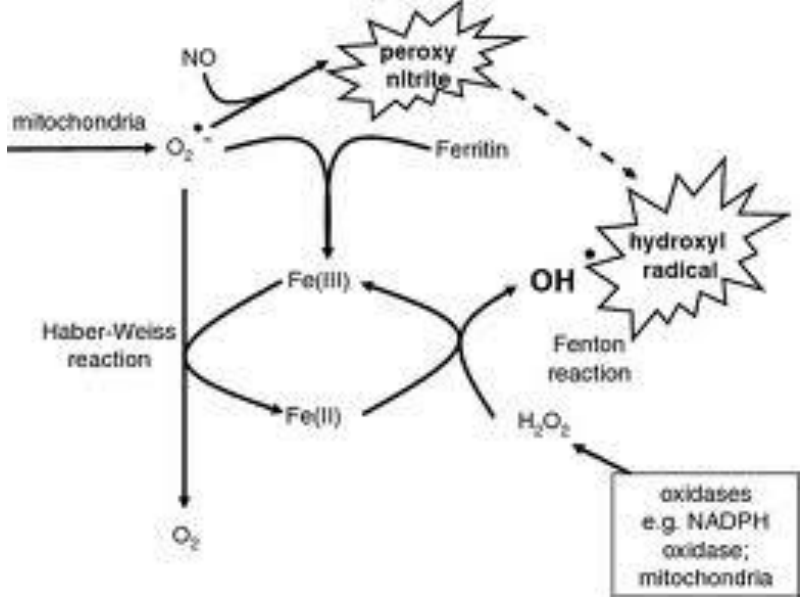
- Potassium ferricyanide (red prussiate of potash) is used in processing blueprint paper.

Elemental Iron Content of Iron Salts

Iron Salt	*Iron Content (%)*	*Iron Salt*	*Iron Content (%)*
Ferrous gluconate	12	Ferrous fumarate	33
Ferric pyrophosphate	12	Ferric chloride (anhydrous)	34
Ferric ammonium citrate	14 to 18	Ferrous succinate	35
Ferroglycerine sulfate	16	Ferrous sulfate (anhydrous)	37
Ferrous sulfate (hydrated)	20	Ferric phosphate	37
Ferric chloride (hydrated)	20	Ferrous chloride (anhydrous)	44
Ferrous chloride (hydrated)	28	Ferrous carbonate	48

Mechanism of toxicity

- Toxicity results from direct **corrosive effects** and **cellular toxicity**
- Iron has a direct corrosive effect on mucosal tissue and may cause hemorrhagic necrosis and perforation. Fluid loss from the gastrointestinal tract results in severe hypovolemia
- **Absorbed iron** in excess of protein binding capacity causes cellular dysfunction, resulting in lactic acidosis and necrosis.
- The exact mechanism for cellular toxicity is not known, but iron ligands can cause oxidative and free-radical injury.
  - Metals such as Fe tend to amplify oxidant damage via the Fenton reaction.



- In addition, Fe accumulation within the cellular lysosomal compartment sensitizes lysosomes to damage and rupture.

- Release of lysosomal enzymes into the cytoplasm of the cell induces autophagocytosis, apoptosis or necrosis.

- Organ and cell damage arising from chronic Fe overload affects the **liver**, **heart**, and **pancreatic beta cells**.

Toxic dose

- The usual fatal dose corresponds to about 200 to 250 mg of elemental iron per kg of body weight.

Clinical Presentation: Acute toxicity

- **Acute** Fe poisoning has been well documented and is divided into 5 clinical stages:

1. **GI toxicity**: Shortly after ingestion, the corrosive effects of iron cause vomiting and diarrhea, often bloody. Massive fluid or blood loss into the gastrointestinal tract may result in shock, renal failure, and death

2. **Relative stability:** Victims who survive this phase may experience a latent period of apparent improvement over 12 hours

3. **Shock and acidosis**: shock and acidosis may occur a few hours to 24 to 48 h after ingestion. In addition, seizures and coagulopathies are also seen
   - Hypovolemic shock occurs in response to fluid and blood losses from the gut.
   - Cardiogenic shock usually occurs 24 to 48 h after ingestion and represents a depressant effect of Fe upon myocardial cells.
   - Absorbed iron causes cellular dysfunction, resulting in lactic acidosis

4. Hepatotoxicity:

- Hepatotoxicity occurs within 2 days of ingestion and is the second most common cause of death in Fe poisoning.
- The liver is at risk because its portal circulation exposes it to the highest concentrations of Fe. Liver cells have a high metabolic activity that favors production of free radicals.

5. GI scarring:

- Finally, GI scarring occurs 2 to 4 weeks after ingestion. Scarring from the initial corrosive injury may result in pyloric **stricture** (stenosis) or other intestinal **obstruction**

Diagnosis

- Diagnosis is based on a history of exposure and the presence of vomiting, diarrhea, hypotension, and other clinical signs

- Specific levels
  - If the total serum iron level is higher than 450–500 mcg/dL, toxicity is more likely to be present.
  - Serum levels higher than 800–1000 mcg/dL are associated with severe poisoning

Treatment

Emergency and supportive measures

- Maintain an open airway and assist ventilation if necessary
- Treat shock caused by hemorrhagic gastroenteritis aggressively with intravenous crystalloid fluids, and replace blood if needed.
- Treat coma, seizures, and metabolic acidosis if they occur

Specific drugs and antidotes

- For seriously intoxicated victims (eg, shock, severe acidosis, and/or serum iron > 500–600 mcg/dL), administer **deferoxamine** (IV infusion 10–15 mg/kg/h)

- Monitor the urine for the characteristic orange or pink-red (“vin rosé”) color of the chelated deferoxamine-iron complex.

- Therapy may be stopped when the urine color returns to normal or when the serum iron level decreases to the normal range.

Decontamination

- **Prehospital:** Activated charcoal is not effective. Ipecac is not recommended, because it can aggravate iron-induced gastrointestinal irritation and interfere with whole-bowel irrigation

- **Hospital**:
- Consider **gastric lavage** if the product was a liquid formulation or tablets were chewed (intact tablets are not likely to pass through a lavage tube).

- **Whole-bowel irrigation** is very effective for ingested tablets and may be considered first-line treatment, especially if large numbers of tablets are visible on plain abdominal x-ray.

- Activated charcoal does not adsorb iron and is not recommended unless other drugs have been ingested.

Enhanced elimination

- **Hemodialysis** and **hemoperfusion** are not effective at removing iron but may be necessary to remove deferoxamine-iron complex in patients with renal failure

Chronic toxicity

- Chronic Fe toxicity can be caused by hereditary **hematochromatosis** due to abnormal absorption of Fe from the intestinal tract, from excess dietary Fe, and from repeated blood transfusions for certain forms of anemia (transfusional siderosis).

- The symptoms of all three types are very similar and result in disturbances of **liver function**, **diabetes mellitus**, **endocrine disturbances**, and **cardiovascular effects**.

Copper

- Cu is both a toxic and essential element for living systems.
- Cu occurs as part of the prosthetic group of proteins.
- As a cofactor for the enzyme Cu/Zn superoxide dismutase, Cu protects against free radical damage that may affect proteins, membrane lipids, and nucleic acids.
- It is necessary for enzymes involved in aerobic metabolism, such as cytochrome c oxidase in mitochondria
- Cu deficiencies have been linked to mental retardation, anemia, hypothermia, bone fragility, and impaired cardiac, neuronal, and immune functions

- Copper is widely used in its **elemental metallic form**, in metal alloys, and in the form of **copper salts**.

- Elemental metallic copper is used in electrical wiring and plumbing materials

- Copper salts such as copper sulfate, copper oxide, copper chloride, copper nitrate, copper cyanide, and copper acetate are used as **pesticides** and **algicides** and in a variety of industrial processes.

- Copper levels may be elevated in persons drinking from copper containers or using copper plumbing.

- The increased acidity of beverages stored in copper alloy (eg, brass or bronze) containers enhances leaching of copper into the liquid.

- Metallic copper itself probably has little or no toxicity

- Copper salts produce toxicity. Soluble salts, such as copper sulfate are strong irritants to skin and mucous membranes

Chemical Name	Common Name
Copper acetoarsenite	*Paris green*
Copper arsenite	*Scheele's green*
Copper carbonate (native)	*Mountain green*
Copper carbonate (with chalk)	*Brunswick green*
Copper subacetate	*Verdigris*
Copper sulfate	*Blue vitriol*

Mechanism of toxicity

- It has been postulated to participate in Fenton-type reactions and lysosomal lipid peroxidation leading to cell death.

- **Elemental metallic copper**
  - It is poorly absorbed orally and is essentially nontoxic.
  - However, inhalation of copper dust, or metallic fumes created when welding may cause chemical pneumonitis
  - Metallic copper dust in the eye (chalcosis) may lead to corneal opacification, uveitis, ocular necrosis, and blindness unless the dust is removed quickly.
- **Copper sulphate salt**
  - It is highly irritating, and produces mucous membrane irritation and severe gastroenteritis.

- **Systemic absorption**
  - It can produce hepatic and renal tubular injury.
  - Hemolysis has been associated with copper exposure from hemodialysis equipment or absorption through burned skin

Toxic dose

- Copper is an essential trace metal. The daily adult requirement of 2mg is supplied in a normal diet.

- **Ingestion** of more than 250 mg of copper sulfate can produce vomiting, and larger ingestions can potentially cause hepatic and renal injury

- **Water.** The US Environmental Protection Agency (EPA) has established a safe limit of 1.3 mg/L in drinking water.

Clinical presentation

- **Inhalation of copper fumes or dusts**
  - Initially produces a metallic taste and upper respiratory irritation (dry cough, sore throat, and eye irritation).
  - Large exposures may cause severe cough, dyspnea, fever, leukocytosis, and pulmonary infiltrates
- **Ingestion of copper sulfate or other salts**
  - It causes the rapid onset of nausea and vomiting with characteristic blue-green emesis. Gastrointestinal bleeding may occur.
  - Fluid and blood loss from gastroenteritis may lead to hypotension and oliguria.
  - Intravascular hemolysis can result in acute tubular necrosis. Hepatitis has been reported, due to centrilobular necrosis.
  - Multisystem failure, shock, and death may occur.

- **Chronic exposure**
  - Pulmonary fibrosis, lung cancer, cirrhosis, angiosarcoma, and portal hypertension have been associated with this occupational exposure

Diagnosis

- Diagnosis is based on a history of acute ingestion

- Specific levels:
  - Normal serum copper concentrations average 1 mg/L, Serum copper levels above 5 mg/L are considered very toxic.

Treatment

Emergency and supportive measures

- **Inhalation of copper fumes or dusts.**
  - Give supplemental oxygen if indicated by arterial blood gases or oximetry, and treat bronchospasm and chemical pneumonitis if they occur.
  - Symptoms are usually short-lived and resolve without specific treatment.

- **Ingestion of copper salts**
  - Treat shock caused by gastroenteritis with aggressive intravenous fluid replacement and, if necessary, pressor drugs.
  - Consider endoscopy to rule out corrosive esophageal or stomach injury
  - Blood transfusion may be needed if significant hemolysis or gastrointestinal bleeding occurs

Specific drugs and antidotes.

- BAL (dimercaprol) and penicillamine are effective chelating agents and should be used in seriously ill patients with large ingestions.

Decontamination

- Inhalation.
  - Remove the victim from exposure and give supplemental oxygen if available.

- Eyes.
  - Irrigate copiously and attempt to remove all copper from the surface; perform a careful slit-lamp exam and refer the case to an ophthalmologist urgently if any residual material remains
- Ingestion
  - **Prehospital.** Do not induce vomiting because it may worsen gastroenteritis.
  - **Hospital.** Perform gastric lavage if there has been a recent ingestion of a large quantity of copper salts. There is no proven benefit for activated charcoal, and its use may obscure the view if endoscopy is performed.

Enhanced elimination

- There is no role for hemodialysis, hemoperfusion, repeat-dose charcoal, hemodiafiltration, or other enhanced elimination techniques.

- Hemodialysis may be required for supportive care of patients with acute renal failure, and it can marginally increase the elimination of the copper-chelator complex