LEARNING TOXICOLOGY THROUGH OPEN EDUCATIONAL RESOURCES

Lead

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LEAD *(Lat. plumbum, Pb)*

- Naturally occuring bluish-gray metal
- Metal with no biological value

1. History:

- Lead poisoning (plumbism) has been known for more 2000 years due to construction of pipes
- The Greek physician Hippocrates described a colic in man who was a metal worker
- Alchemist associated Pb with Saturn = metal of Saturn

??? Lead contributed to the decline of the Roman Empire

Romans used lead in their plumbing, coins, cosmetics, paints, cooking utensils, vessels for grape juice and wine. Lead acetate („sugar of lead") enhanced color and bouquet in wines.

Analysis of the bones of Romans from the time of their empire: high levels of Pb

Lead poisoning contributed to the intelligence decline and population shrink

Share video:

https://www.youtube.com/watch?v=FY_as9F6D2k

2. Sources:

Industrial

Battery manufacture

Pigment production

Environmental

Plastic and rubber industry

Lead in water from pipes

Old lead - based paints

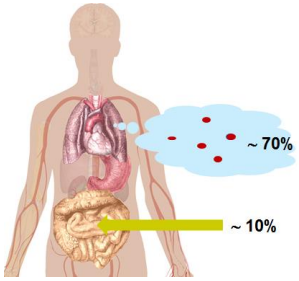
Lead bullets

Miscellaneous

Pottery glaze

Oriental herbal medicine (e.g. Azarcon, Greta)

Anthropogenic activity → large amounts of lead in the environment → universal exposure in humans



3. Toxicokinetics:

Absorption:

Pb compounds are mainly absorbed in the lungs (as aerosols up to 70%) and in the GIT (10%).

Children absorb more (up to 50% of the dose in the GIT). This may be related to a higher density of intestinal transport proteins during periods of rapid growth.

- Active transport by the same mucosal proteins that mediate Ca transport
- Deficiency of other metals (e.g. Fe, Ca and Zn) increases GIT absorption of lead
- Inorganic salts do not penetrate the intact skin
- Pb crosses the placenta (fetal blood Pb levels are 30% higher than maternal blood levels)

Distribution:

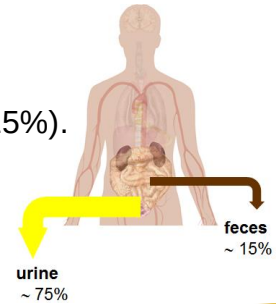
Pb is distributed among 3 compartments:

- **Blood** – bound to red blood cells ($T_{1/2}$ = 25 days)
- **Soft tissues** (liver, kidney, brain, bone marrow) - ($T_{1/2}$ = 40 days)
- **mineralizing tissue** (bone and teeth), where it is stored for a very long time ($T_{1/2}$ = 30 years)

In adults 95% of body burden is in bones (in children the portion is 73%). Liberation from bones can occur during prolonged immobilization, pregnancy and bone demineralization.

Excretion:

Lead is excreted predominantly in the urine (75%) and feces (15%).



4. Laboratory determination:

The whole blood lead level is the most useful indicator of lead exposure.

Blood lead levels:

- *Population without exposure: < 150 µg/l*
- *Professional exposure: up to the value of 450 µg/l*
- *Intoxication: > 700 µg/l*

Blood Pb samples must be drawn and stored in lead-free syringes and tubes.

Urinary lead level: fluctuates more rapidly than blood lead.

5. Mechanisms of toxicity:

- Pb causes enzyme inhibition via –SH group binding
- Pb interacts with essential cations (Ca, Zn, Fe)
- Pb alters heme synthesis, cellular and mitochondrial membranes, neurotransmitter release

→ multisystem effects

The multisystem toxicity of Pb can produce a wide spectrum of clinical manifestations.

The primary target organs are the nervous and hematopoietic system, gastrointestinal tract, kidneys and the reproductive system.

6. Inorganic lead poisoning

Acute lead poisoning:

Acute lead intoxication is rare. Accidental and intentional ingestion of large amounts of soluble Pb salts (gram quantities) leads to a severe lead colic, neurological symptoms (insomnia, apathy, stupor, aggression), lead encephalopathy (disturbed motor and sensory function), paralysis of the arm (weakness of the extensor muscle).

Sudden mobilization of Pb from skeleton can also result in acute symptoms (e.g. lead encephalophaty = „lead crisis“).

Death may occur within 1 or 2 days.

Chronic lead poisoning:

More common Pb intoxication results from a long-term exposure.

Even small doses over time can cause poisoning, because Pb is accumulated in the body.

a. CNS efects = neurotoxicity:

Adults: Exposure to higher concentration in adults: → **„overt encephalopathy“** (fatigue, insomnia, restlessness and irritability, difficulty concentrating, memory loss, seisures and coma)

Children: Exposure to low concentration (30 to 50 μg/ dl) → **„low-level lead toxicity“**

(children with lower I.Q. scores, deficits in psychometric intelligence, speech and language processing attention and poor classroom behavior)

Children experience toxic effects at lower levels of exposure than adults !!!

The developing brain, the nervous system and the immune system are more easily damaged by lead.

Blood lead level of 10 to 15 μg/dl and possibly lower should be avoided in pregnant women.

For more see:

http://www.atsdr.cdc.gov/HAC/PHA/reports/basinres_id/images/bas_f1.gif

Peripheral neuropathy: footdrop and wristdrop

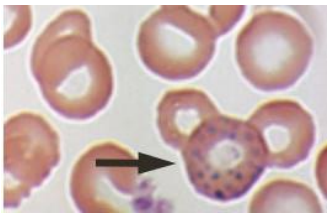
Painter´s wristdrop is a syndrome of upper extremity paresis found in painters who have regularly used or removed lead-based paint.

For more see: http://www.lead.org.au/lanv4n2/lanv4n2-7.html

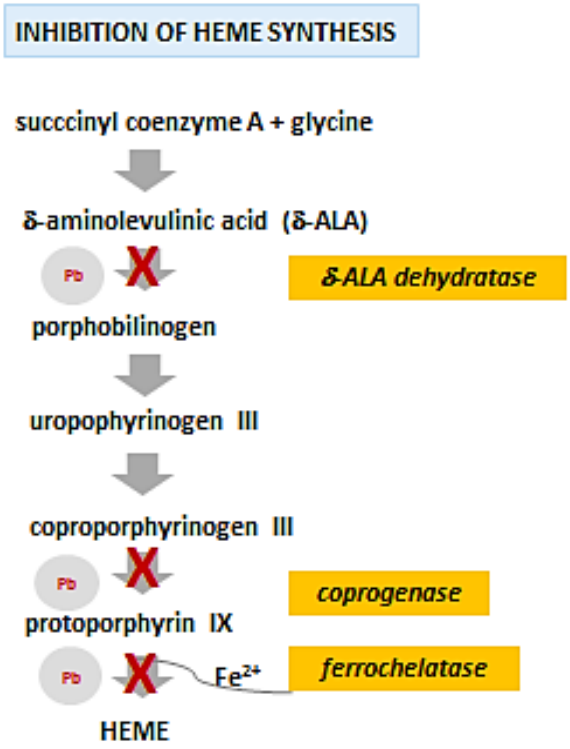
Share video: https://www.youtube.com/watch?v=jfmr4fsV8gY

b. *Hematological effects:*

- Hypochromic microcytic anemia (as in iron deficiency) accompanied by basophilic stippling (= inclusions of aggregated ribosoms in the red blood cells).
- Hemolysis may occur.



Pb = potent suppressor of heme synthesis.



Many screening test for lead poisoning are based on the inhibition of some enzymes in heme synthesis:

- *Inhibition δ-ALA dehydratase increases the δ-ALA levels in blood and urine = important diagnostic parameter of lead poisoning.*
- *Inhibition of coprogenase and ferrochelatase lead to the elevation coproporphyrin III in the urine (the brown compound gives the skin a subicteric coloration) and protoporphyrin IX in erythrocytes.*

c. Gastrointestinal effects:

- Constipation, abdominal cramps, severe lead colic (colica Saturnina)
- A black lead line on the gums, metallic taste in the mouth

For more see:
https://pgmeequest.wordpress.com/2012/04/05/lead-poisoning/

d. Nephrotoxiciy:

Renal injury:

- reversible renal tubular dysfunction
- irreversible interstitial nephropathy

k**idney damage** → hypertension
→ gout from hyperuricemia

e. Reproductive toxicity:

Adverse effects on reproduction function in both men and women

- **Men:** diminished or aberrant sperm production
- **Woman:** abnormal ovarian cycles, infertility, spontaneous abortion

Pb crosses placenta (or is mobilized from bones during pregnancy)

- **Fetus:** slow growth, CNS disorders

f. Carcinogenicity:

IARC: Pb compounds are probably carcinogenic to to humans

7. Organic lead poisoning

Tetraethyl lead = antiknock agent used as a fuel additive. Combustion of leaded gasoline was a source of environmental exposure. Such use has been banned in many countries.

Tetraethyl lead and tetramethyl lead are lipid soluble compounds and are readily absorbed from the skin, gastrointestinal tract and lungs.

Intoxication is commonly manifested as CNS effects.

Lethal dose of tetraethyl lead is 0,1 - 1 g.

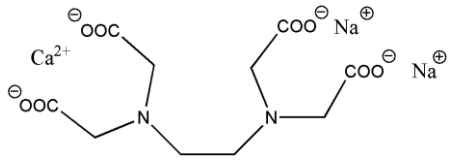
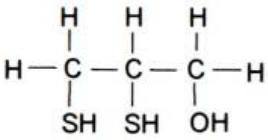
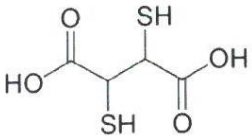
Share video: https://www.youtube.com/watch?v=pqg9jH1xwjI&t=620s

8. Treatment of lead poisoninig

Reducing the body lead stores by the means of chelating agents.

Pb levels in blood should be determinated prior to initiation of chelation therapy

Tab. 1.: Antidotes for lead poisoning

CHELATING AGENT		ADMINISTRATION
$CaNa_2EDTA$ Calcium disodium ethylenediaminetetraacetic acid		**p.o.**
BAL (British antilewisite) dimercaprol (dimercaptopropanol)		**i.m.**
DMSA (Succimer) 2,3-dimercaptosuccinic acid		**i.v.** (i.m. painful)

D-penicillamine is no longer used for Pb intoxication.

Prophylactic chelation of workers in lead industries is illegal !

Treatment of organic lead poisoning is symptomatic.

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