HEAVY METALS

Lead toxicity

أكثر الناس عرضة له ← الـ occupational
يلي بشتغلو بالـ painting ، محطات البنزين لون الرصاص
بدخل بصناعات متعددة

HEAVY METALS

ممكن ما نعطيهم كلهم ↙

- LEAD √
- IRON √
- MERCURY
- ARSENIC
- NICKEL

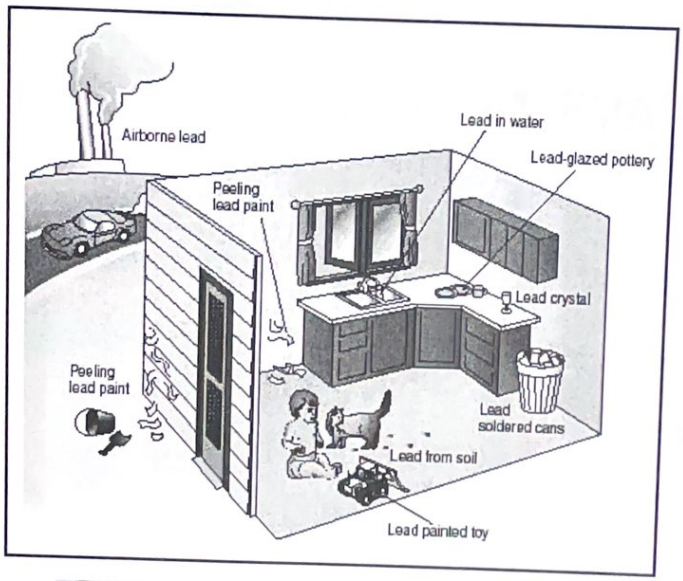
- CADMIUM
- THALLIUM
- ALUMINUM
- GOLD

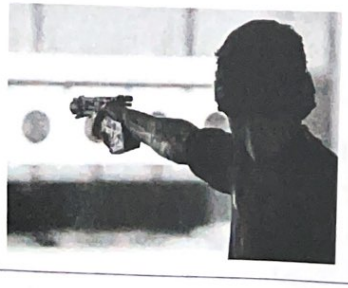
- Some metals needed in trace amounts like Iron, Copper
- Body lacks any major system to remove excess metals we depend on their elimination from body mainly by renal

LEAD

- Lead poisoning is one of the oldest occupational and environmental diseases in the world
- **Exposure from:** environment (water, air, soil, food), fuels, paints, production of storage batteries, glass polishing, shooting
- Environmental lead exposure **has declined considerably in the last three decades.**

elimination of lead as an additive in gasoline, as well as **diminished contact with lead-based paint** and other lead-containing consumer products.





LEAD

- Lead is a cumulative poison that causes both **chronic (*plumbism*)** and **acute intoxication**
- **Acute** poisoning is **rare** but **chronic** one is a **serious problem** (low-level lead exposure)
- The **intestinal tract** is the primary route of entry in non-industrial exposure....**from food & water**
- **Lead-containing paint** is a **1ry** source of lead exposure in **children (pica)**
- Lead exist in both **inorganic** and **organic** form

Toxicokinetics

- **Absorption:**
- *Oral exposure:*
- adult diet (**10% absorbed, children absorb 50%**)
- *Dietary deficiencies* of calcium, iron, zinc enhance lead absorption as well as its tissue storage
- *Inhalation:* absorption is greater and more rapid by pulmonary route....is **the major route of industrial exposure** (lead fumes, fine particles)
- ***Dermal absorption*** is poor, Cutaneous absorption of lead is limited (typically far less than 1%), except in case of organic lead

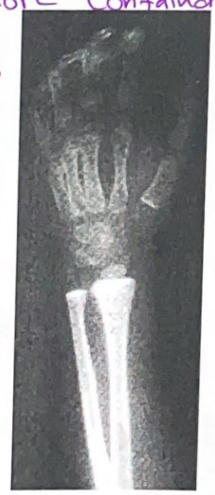
Toxicokinetics

- After absorption lead circulate through the blood associated **99% with erythrocytes** and 1% present in plasma (RBCs)
- Distributed first to soft tissues (renal tubule and liver) and then **incorporates into bone, hair and teeth** for storage
- **Crosses the placenta and the BBB**
- High affinity for bone and other calcified tissue.....90% deposited in bone "lead lines" (tertiary lead phosphate)

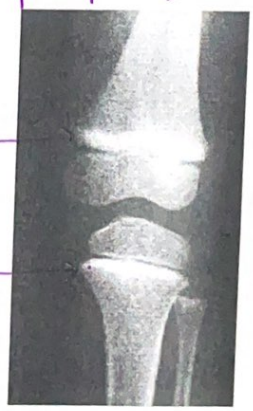
→ Can distribute and affect different organ system CNS, CVS, skeleton (bone), reproductive system, erythrocyte, bone marrow RBC production, so associated with varient organ damage disfunction and deterioration

LEAD

X-Ray ← ما بتوضح صورة بظهور خط هادل dense metaphyseal line result due to lead poising (lead accumulation) in bone (more containd Calcium phosphate)



LEAD LINES



ظاهرة عند الأطفال بسبب تثبيط (توقف) نمو العظام لأنه epiphyseal plate هو الي مسؤول عن growth and elongation of bone, weakning of bone ← إذا أثر على النمو وبعمل wrist drop (ارتخاء العضلات، صعب رفع) and other serious Joint complication (foot drop) ويمكن أن يؤدي إلى

Toxicokinetics

- **Clearance**: half life in the blood and soft tissues is 1–2 months; while in bone is years to decades
- ~70% of lead excretion occurs via the urine
- Less amounts are eliminated via the feces and exfoliation of epithelial tissue, sweat, and breast milk
- **A dose of 0.5g of absorbed lead is estimated to represent a fatal dose** (very high)

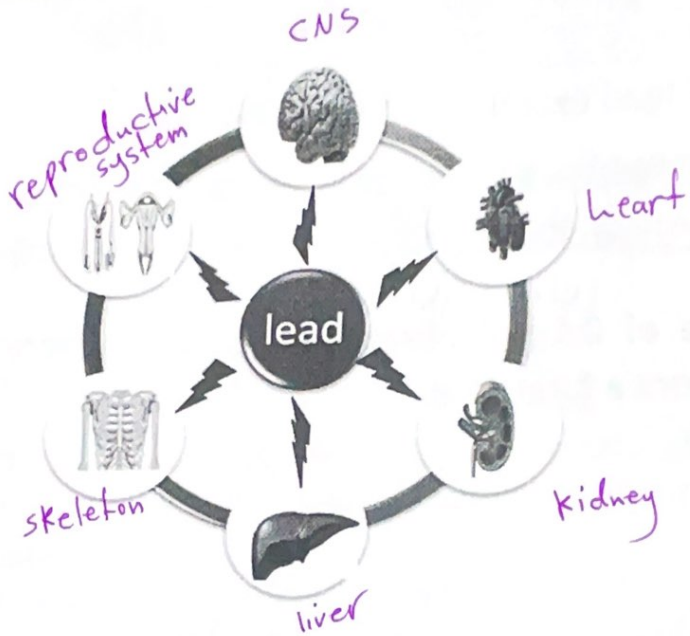
Toxic dose

- Whole blood lead concentrations are non toxic **if < 150 µg/L (1 mmol/L)**
- Concentrations over **600 µg/L [3 mmol/L]** (children) or 800 µg/L [4 mmol/L] (adults) are usually associated with severe toxicity.

(كمية قليلة) trace amount* تعتبر (1 billion part of water يكون مقارنة 15 part of lead يعني كل) (اي لازم تتوجد على رصاص بحد معين ماتزيد عنه)

- level for lead in drinking water **is 15 ppb**.....however, the maximum contaminant level **goal 0 ppb** part per billion → our target

Lead toxicity



Toxicity

- The toxic **effects** range from
- **inhibition of enzymes** to the **production of severe pathology or death**
- Lead exerts **multisystemic toxic effects** that are mediated by multiple modes of action:
- Primarily by **binding to sulfhydryl group** of protein molecules....cause **inactivation of several enzyme systems** → يلي ممكن تكون بتحتاجها (suppress free radical formation, energy production)
- Lead affect the **nervous system**, the **GI**, **hematopoietic**, **reproductive** & **CV systems**

because of inactivation of enzymes

Microcyctic أو hypochromic anemia — Normocytic يحملها hypochromic anemia — ممكن برضو lead ①

RBC smaller than normal, low MCV, low MCH — normal MCV, low MCH

Hematologic Effects

MCH:- مؤشر على نسبة الهيموغلوبين في الدم.

MCV:- مؤشر على حجم خلية الدم الحمراء التي تحمل الأكسجين

- **Decreased heme synthesis**......**increase** production of **RBCs by bone marrow** (compensatory mech.)
- These cells are released as **immature** reticulocytes and **stippled cells** (basophilic **stippling**)
- When blood smear is stained erythrocytes display dots......accumulation of mRNA
- Normocytic or Microcytic and hypochromic anemia

① انها bone تحاول ال (Compensatory mechanism) تعوض هاد الانخفاض (بال heme synthesis) بانها تزيد من ال synthesis لل RBC لكن يلي بصير انه ال RBC يلي بتكون بتكون (immature) وبتكون زي المنقطة (بشوفوها بال microscope) بسبب تراكم ال mRNA جوا ال RBCs

Renal Toxicity

- **Chronic lead nephrotoxicity** (serious) (تسبب) consists of interstitial fibrosis, progressive nephron loss, azotemia & renal failure (rare)
  - azotemia: blood urea nitrogen and serum creatine (both elevated level ↑) which is the reflecting detrioration of renal function
- **Acute lead nephrotoxicity** consists of proximal tubular dysfunction and azotemia......can be reversed by Tx with (chelating agents) (antidote)
- Impairs the renal synthesis of heme-containing **enzymes involved in vitamin D metabolism**....affect bone
  - lead toxicity يمنع ال activation for VD and this will affect bone
  - التسمم بالرصاص برضو بسبب reduction of Vitamin D formation (يلي بتم تصنيعه من خلال skin بعدين بصير له activation من خلال liver و kidney)
- Hyperuricemia with gout
  - uric acid excretion (بعمل خلل في ال) because of defect in uric acid renal excretion which lead to gout وبسبب بالتالي تراكمه في الجسم)

Ⓥ

Neurologic, Neurobehavioral, and Developmental Effects in Children

- Manifestations range from impaired concentration, headache, diminished visual-motor coordination, & tremor to overt **encephalopathy**: lethargy or delirium, vomiting, irritability, loss of appetite, dizziness, and convulsions
- May progress to obvious ataxia, and reduced level of consciousness....**may progress to coma and death**
- Lead affects virtually ***every neurotransmitter system in the brain*** (glutamatergic, dopaminergic, and cholinergic systems)....
- **Recovery is often accompanied** by sequelae including **epilepsy, mental retardation.....in some cases, optic neuropathy and blindness**

Effects on Cardiovascular System

- The pathogenesis of lead-induced ***hypertension*** is multifactorial including:

1. **Inactivation of endogenous nitric oxide and cGMP**, possibly through lead-induced reactive oxygen species;
2. Changes in the **RAAS** and increases in sympathetic activity.....important humoral components of HTN;
3. possible rise **in endothelin & thromboxane===vasoconstrictors**

Other Toxic Effects

(can affect the immune system)

- Lead **decreases immunoglobulins**, peripheral B (decrease) lymphocytes, and other components of the immunologic system → .**immunosuppressive agent**

- Retention and mobilization of lead in bone occur by the same mechanisms involved in calcium regulation.....**competes with Ca for GI absorption**

بسبب mobilization of calcium therby increase chance of osteoporosis

- Lead affects osteoblasts, and osteoclasts.....has been associated with **osteoporosis** and **delays fracture repair**

increase chance of osteoporosis (suppress growth of bones in children)

ما بتراكم بال epiphyseal plate زي ما حكينا قبل

وبرضو كان التأثير السلبي على الكلية

nephrotoxicity → affect vitamin D activation → osteoporosis

Other Toxic Effects

- Lead toxicity has long been associated also with **sterility** and **spontaneous abortion and low birth weight**

(infertility) عقم

↳ can cross the placenta → affect the CNS for the baby (low IQ)

- **GI effects**:
  - Abdominal cramp
  - Constipation, Nausea
  - Less common Diarrhea

Diagnosis

lead بالعظام (dense metaphyseal line)

- ① Skeletal **x-ray's** fluorescence measurement of lead
- ② **Blood levels** of lead
- ③ **Anemia** microcytic, hypochromic (with basophilic stippling)
- ④ **Azotemia, Gout**
- High blood levels of δ-ALA & coproporphyrins (after few weeks of exposure)

Diagnosis

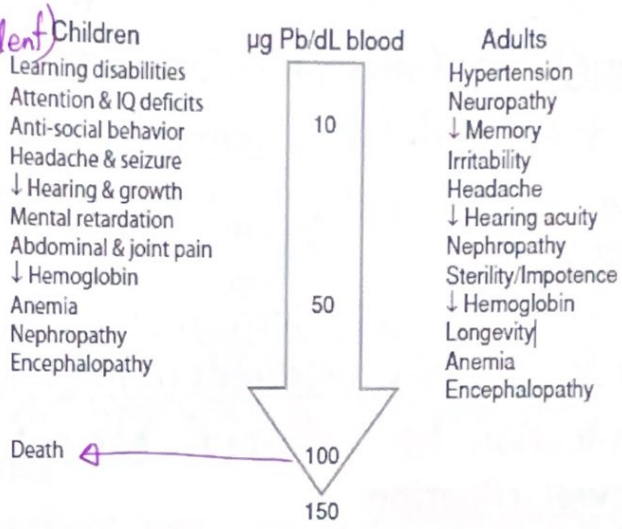
patient history بنعتمد على

- N.B: consider lead poisoning in any patient with **multisystem findings** with abdominal pain, headache, anemia, and, less commonly, motor neuropathy, gout, and renal insufficiency.

- Consider lead encephalopathy in any child or adult with delirium or convulsions (especially with coexistent anemia)

(Symptoms) تكون blood plasma lead على أساس level

FIGURE 1. Effects of lead poisoning on human health[a]



(dose dependent)

تختلف بين children and adult

(من الحفظ)

[a] Adapted from Gurer and Ercal (49).

LEAD TREATMENT

TREATMENT:

- REMOVAL OF THE SOURCE & STABILIZE THE PATIENT
- CHELATING THERAPY:
  1- **BAL**
  2- **Calcium EDTA**
  3- **SUCCIMER**
  4- **D - PENICILLAMINE**
- SUPPORT

في حالة lead toxicity بنستخدم هول

* Chelating agent ترتبط مع heavy metals وتكون Complex حتى تقلل من الامتصاص والتراكم بالأنسجة

[to stop further diffusion and distribution (for lead) to the cells]

Treatment

- Treat **seizures** and coma if they occur
- Provide **adequate fluids** to maintain urine flow but avoid overhydration.....may aggravate cerebral edema
- Patients with increased intracranial pressure may benefit from **corticosteroids or mannitol**
- Decontamination by **activated charcoal and whole bowel irrigation**

CHELATING AGENTS

Best criteria for any chelating agent

WHAT MAKES A GOOD CHELATING AGENT?

1. **NONTOXIC** & FORMS NONTOXIC COMPOUNDS
2. **HIGH WATER SOLUBILITY**
3. **SIMILAR DISTRIBUTION TO THE METAL**
4. **LOW AFFINITY FOR CALCIUM and other ions**
5. **EASILY REMOVED FROM THE BODY**
6. GREATER AFFINITY FOR THE METAL THAN ENDOGENOUS LIGANDS

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

DIMERCAPROL (BAL): British AntiLewisite comp. (I.M)

- Forms complexes with sulfhydryl groups
- Used for inorganic mercury, arsenic and in **lead** poisoning
- **Chelate lead in serum and cerebral spinal fluid**
- Usually used in combination with calcium EDTA
- The complex is rapidly excreted in the urine
- May cause **hemolysis in patient with G6PD deficiency**
- ADE: transient hypertension, tachycardia, N,V, fever

CALCIUM DISODIUM EDETATE ($CaNa_2EDTA$) (im/iv)

- Mobilize lead from soft tissue and bone
- Forms a stable, nonionizable, water soluble compound with lead
- Complex rapidly excreted in urine
- ADE: fever, headache, N,V, anorexia, myalgia, hypotension
- ADEs: nephrotoxicity minimized by adequate hydration
- May deplete manganese, zinc & iron

SUCCIMER (DMSA)....p.o

- DIMERCAPTOSUCCINIC ACID....water soluble analog of BAL
- Enhances the urinary excretion of **lead** and **mercury** without affecting the elimination of the endogenous minerals as Ca, Fe, and Mn
- ADEs: GI disturbances, mild reversible increase in transaminase enzymes, allergic reaction

PENICILLAMINE....p.o

- Penicillin derivative without antimicrobial activity...allergy!
- Widely replaced by succimer because of its poor safety profile

Symptomatic	Tx. regimen
	EDTA for 5 days

Asymptomatic	Tx. regimen
Blood lead 10-24 µg/dl	Chelation no recommended
Blood lead 25-44 µg/dl	Succimer for 2-4weeks OR EDTA for 5 days
Blood lead 45-69 µg/dl	EDTA for 2 weeks
Blood lead >70 µg/dl	BAL for five days + EDTA for 5 days

LEAD

- **SUPPORT:**
  - **Establish adequate urine output before administering chelating agent** (fluid bolus but monitor coz may aggravate cerebral edema)
  - **Dialysis** for patients with severe renal insufficiency
  - Blood lead levels: stop chelation if level <30µg/dl
  - Recurrent blood level assessment before and after treatment with chelating agents at regular interval

حتى لا تتراكم في الجسم

كمية الحمل لازم تتحسب بدقة حتى لا تسبب Cerebral edema

ربِّ إني لما أنزلت إليَّ من خير فقير
منظرها أمام بابك الكبير
أم مرض في الظلام استجير
يا راعي النمال في الرمال
وسامع الحصاة في قرارة الغدير

Sara Jammain

Artery Academy