HEAVY METALS

Lead toxicity

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مكرر من slide Iron toxicity

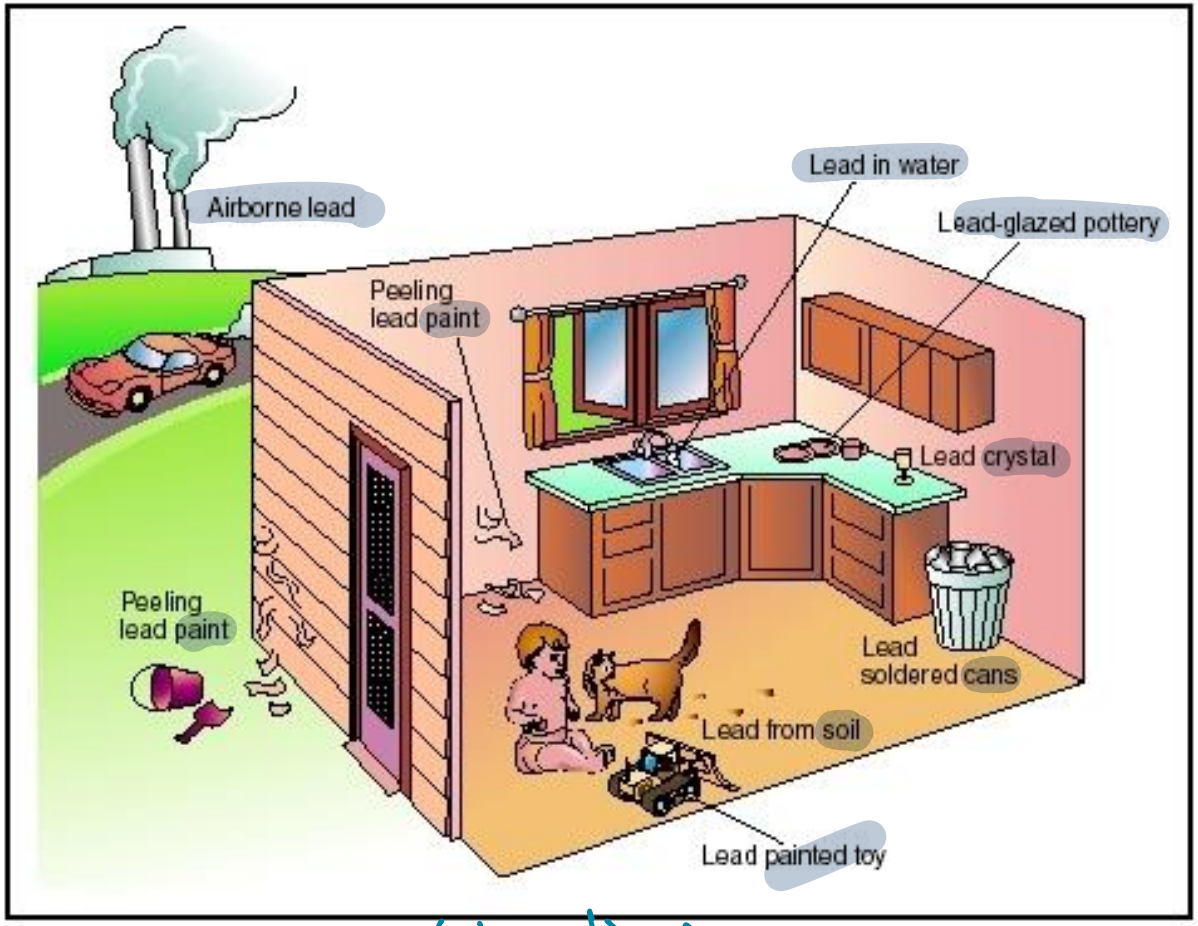
HEAVY METALS

- LEAD √
- IRON √ العشابتر الحافي
- MERCURY
- ARSENIC
- NICKEL
- CADMIUM
- THALLIUM
- ALUMINUM
- GOLD

- Some metals needed in trace amounts
- Body lacks any major system to remove excess metals → mainly renal excretion

الرصاص ← 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** (انطلاق رصاص المسدس)
- 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.



طلق الحسس (shooting)

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) → هو low level بس exposure time لانه chronic يعني عالي لكن بالجسم فترة طويلة
- The **intestinal tract** is the primary route of entry in non-industrial exposure….**from food & water** ← معش من الصناعات يعني food
- **Lead-containing paint** is a **1ry** source of lead exposure in **children (pica)** → craving anything unless food (1ry = primary) لحالة عند الأطفال انه بحب ياكل كل أشي ما عدا الأكل.
- 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

distribution of lead * يكون بكل systems للأسف.

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** → CNS system

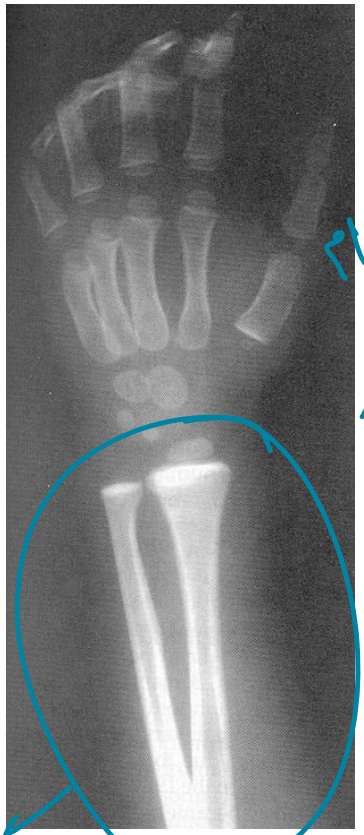
90%

- High affinity for bone and other calcified tissue.....90% deposited in bone "lead lines" (tertiary lead phosphate)

يكون بالعظام يعني الشكل

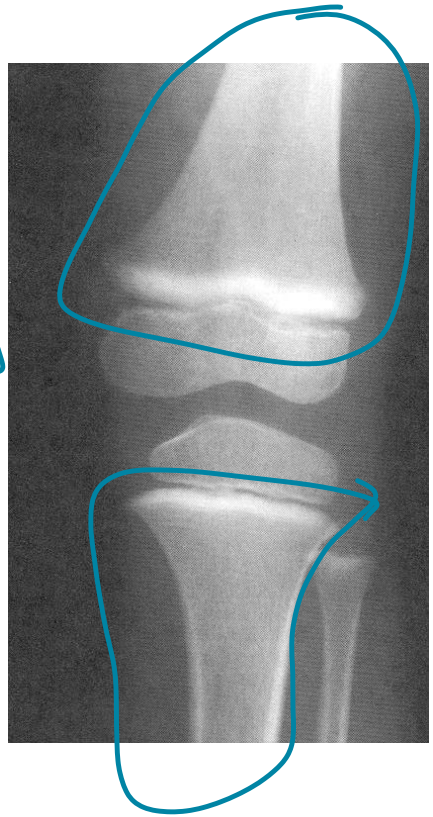
X-ray

LEAD



LEAD LINES

خطوط مشع
بأطراف العظام
بدل انه عنا
تراكم في lead



lead storage in bones

* الأطفال بأثر عندهم نمو العظام و يوقف
يجل lead بسبب elongation of bone
weakening

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**

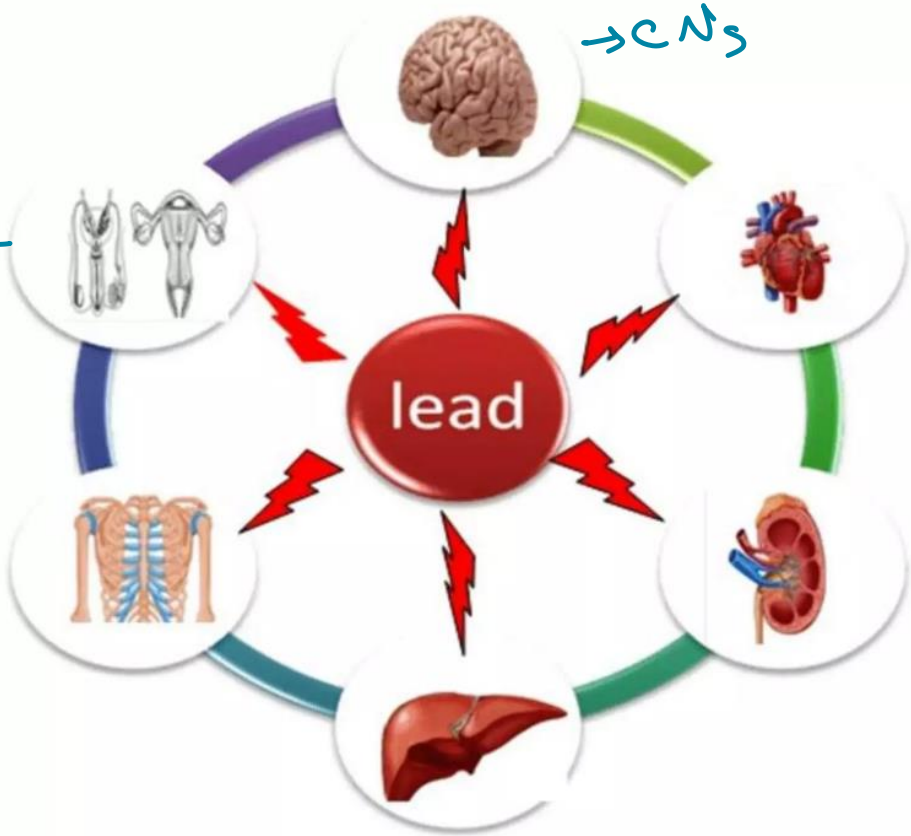
Toxic dose

- 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.

- level for lead in drinking water **is 15 ppb**.....however, the maximum contaminant level **goal 0 ppb**

Lead toxicity

Distribution of lead in organs and systems.



CNS

CVS

Reproductive system

skeletal bones

Kidney

liver

Toxicity

- The toxic **effects** range from تأثير السم بحسب على الجرعة
- **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** → ممكن الارتباط نتاجها لانتاج الطاقة او بتقلل Free radicals
- Lead affect the **nervous system**, the **GI**, **hematopoietic**, **reproductive** & **CV systems**

Hematologic Effects

- **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

Renal Toxicity (nephrotoxicity)

- **Chronic lead nephrotoxicity** consists of interstitial fibrosis, progressive nephron loss, azotemia & renal failure

Rare

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

azotemia → creatinine & urea nitrogen ارتفاع

chelating agents → antidote

- Impairs the renal synthesis of heme-containing **enzymes involved in vitamin D metabolism**....affect bone → osteoporosis

reduction

vitamin D ال activation lead toxicity

انه يتحول ال active form.

- Hyperuricemia with gout

↓ uric acid accumulation

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: ? hypertension بعمل ليش

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

يأثر على immune system

- Lead **decreases immunoglobulins**, peripheral B lymphocytes, and other components of the immunologic system…..**immunosuppressive agent** → يخفض المناعة
- Retention and mobilization of lead in bone occur by the same mechanisms involved in calcium regulation…..**competes with Ca for GI absorption**

يقلل امتصاص Ca

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

هشاشة العظام

يؤثر على النمو وعكينا عرض خصوصاً الاطفال

Calcium ↓ + Vitamin D ↓ يجعلوا Osteoporosis وكله بسبب Lead toxicity.

Other Toxic Effects

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

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

Diagnosis

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

Diagnosis

- 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.

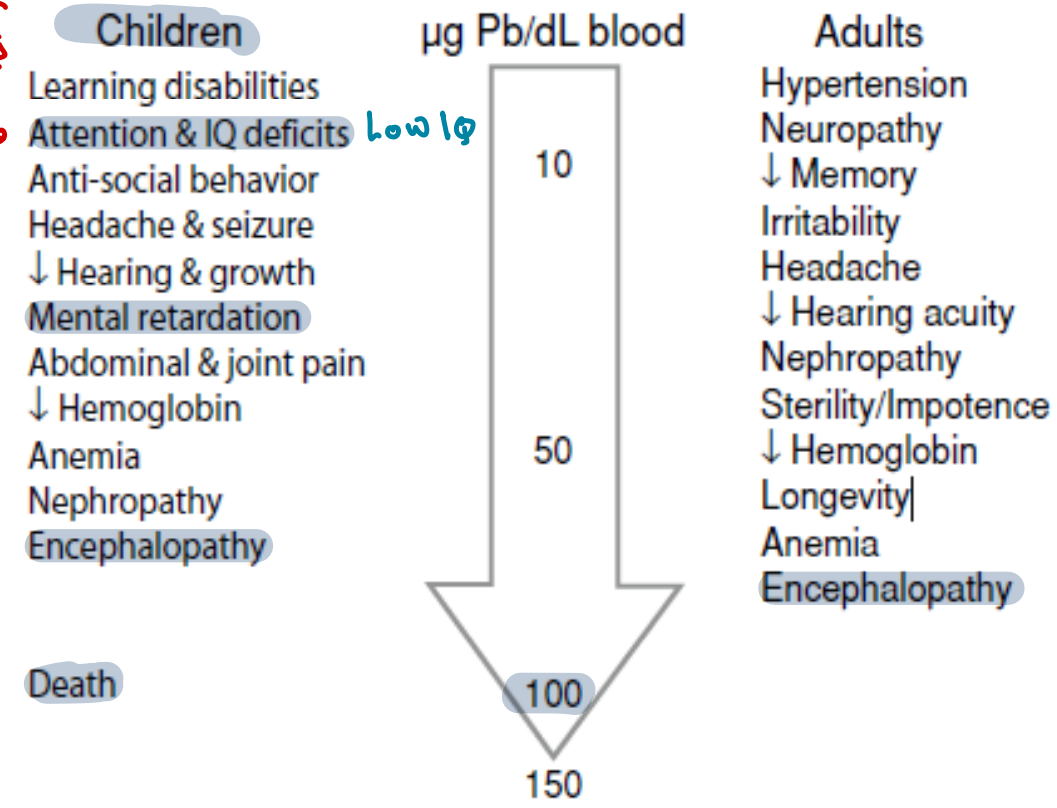
neuronal damage ↓ اذا ظهر عنده

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

اعتماداً على blood or plasma بنشوف الأعراض
Lead Level

* مش مطلوب تحفظوا كل جرعة وبشو SE إلي عليها بس اعرفوا انه SE هي: dose dependent و بتختلف بين Children & Adults

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



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

LEAD TREATMENT

TREATMENT: ABC ← لازم تنسى

- REMOVAL OF THE SOURCE & STABILIZE THE PATIENT
- CHELATING THERAPY: مركبات بتعمل complex مع heavy metals وبتعمل impair
  - **BAL**
  - **Calcium EDTA** tissue accumulation اللي بتعمل abs
  - **SUCCIMER**
  - **D - PENICILLAMINE** → من مشتقات penicilline
- SUPPORT

Treatment

- Treat **seizures** and coma if they occur → antiepileptic medications
- Provide **adequate fluids** to maintain urine flow but avoid overhydration.....may aggravate cerebral edema

  اذا حالو عشي edema بحطيله diuretic زي corticosteroid او mannitol
- Patients with increased intracranial pressure may benefit from **corticosteroids or mannitol**
- Decontamination by **activated charcoal and whole bowel irrigation** → acute poisoning في

CHELATING AGENTS

WHAT MAKES A GOOD CHELATING AGENT?

- **NONTOXIC** & FORMS NONTOXIC COMPOUNDS
- **HIGH WATER SOLUBILITY**
- **SIMILAR DISTRIBUTION TO THE METAL**
- **LOW AFFINITY FOR CALCIUM and other ions**
- **EASILY REMOVED FROM THE BODY**
- GREATER AFFINITY FOR THE METAL THAN ENDOGENOUS LIGANDS → the best criteria for any chelating agents

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

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

يحتوي:

- 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

CNS

لـ مرضى التفوّل

Adverse Effect

Nausea, Vomiting

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 → orally

- 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

penicillin مشتقات

PENICILLAMINE….p.o → orally

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

مش مطلوب تفاصيل

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

<24

اعرفوا هاي

وهاي

high level

LEAD

- **SUPPORT:**

* لازم اراقب fluid amount عشان لا يصير cerebral edema

- **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 → او اقل من 24
- Recurrent blood level assessment before and after treatment with chelating agents at regular interval

عشان اشوف lead level وين صار
واذا قل عن 30 او 24 بوقف chelating agent