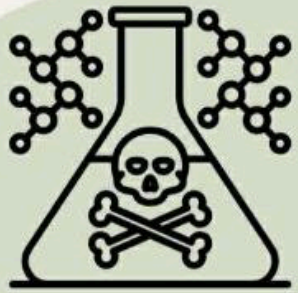
تفريغ علم السموم



المحاضرة: Lead toxicity

الصيدلاني/ة: Rahaf Zyoud

HEAVY METALS

لاتنسوا زميلنا
ايهم الله يرحمه
من دعائكم

رصاص

Lead toxicity

→ اكثر ناس معرضين لل

toxicity بال lead هم ال occupational [المهن اللي بتتعامل مع ال Lead]

زي اللي بشتغلوا بمحطات البنزين وحيث بدخل ببعض الصناعات

او ممكن يصير Contamination للاشياء الموجودة بال environment

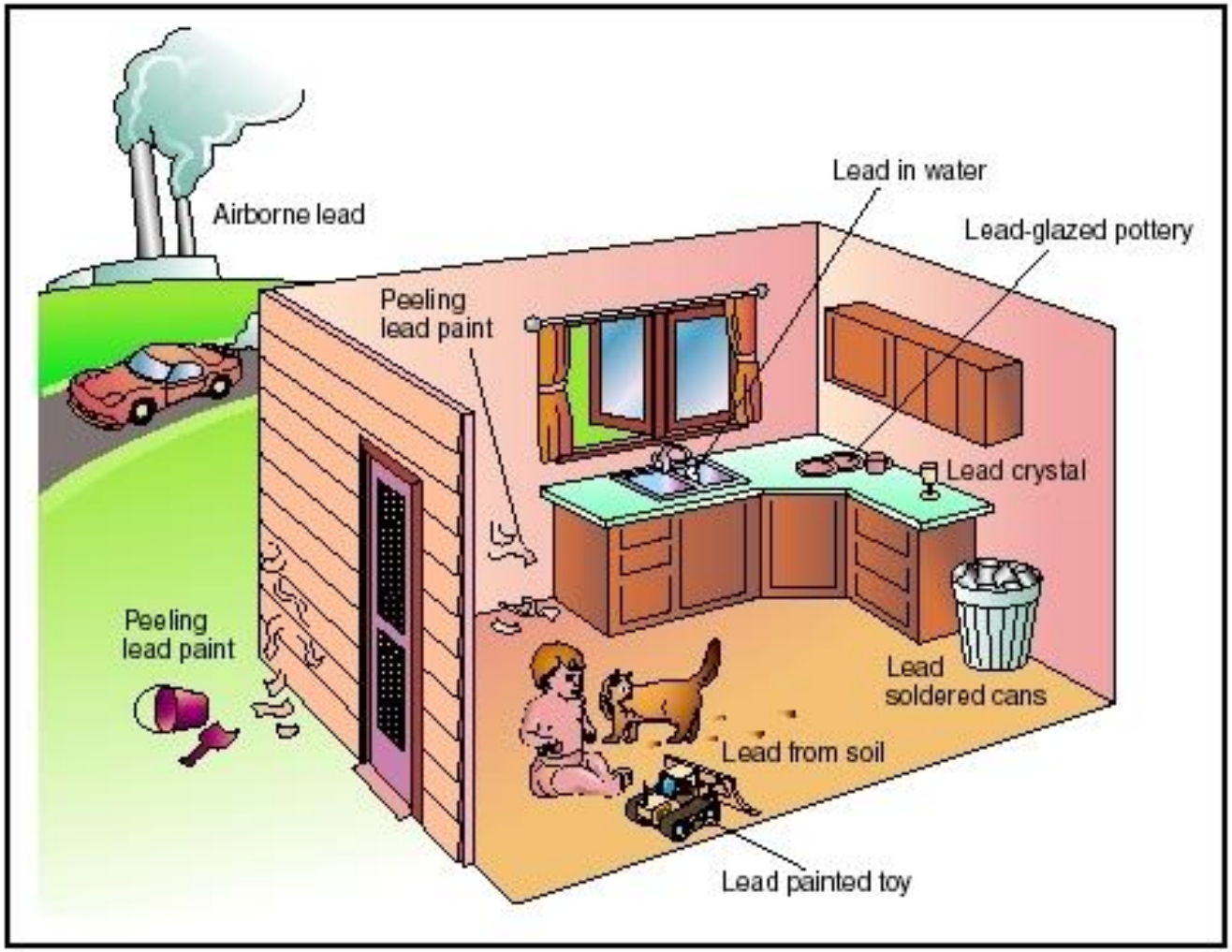
HEAVY METALS

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

- Some metals needed in trace amounts جسم الكائنات بحتاج بعض الـ Metal زي iron
- Body lacks any major system to remove excess metals → الجسم مسؤول يتخلص من زيادة الـ Metals وغالباً بصير الهم renal excretion

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.


Airborne lead
Lead in water
Lead-glazed pottery
Peeling
lead paint
Lead crystal
Peeling
lead paint
Lead
soldered cans
Lead from soil
Lead painted toy


UB12350
UNIVERSAL BATTERY
12350 12V 35Ah


GLASS
POLISH


110
OCTANE
LEADED
RACING FUELS

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

* الحاجيين الـ distribution رح يأثر على كتير organ زي الـ heart والـ muscle، CNS، reproductive system

Toxicokinetics

- After absorption lead circulate through the blood associated **99% with erythrocytes** and 1% present in plasma

RBC

- **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)

LEAD

ال lead رح يرتبط بال phosphate group الموجودة بال bone ويعملو complex ورح يعمل مشاكل كثير خصوصا عند children growth رح تعمل stopping of growth زي موشايفين بالصورة خط ال lead(مشع) وممكن يعمل عند الاطفال كمان weakness لل bone

ال lead ال affinity عالية انه يصير ال deposited بال bone بكميات كبيرة

LEAD LINES

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.

15 ppb نسبة lead الـ بنشربه في water الـ

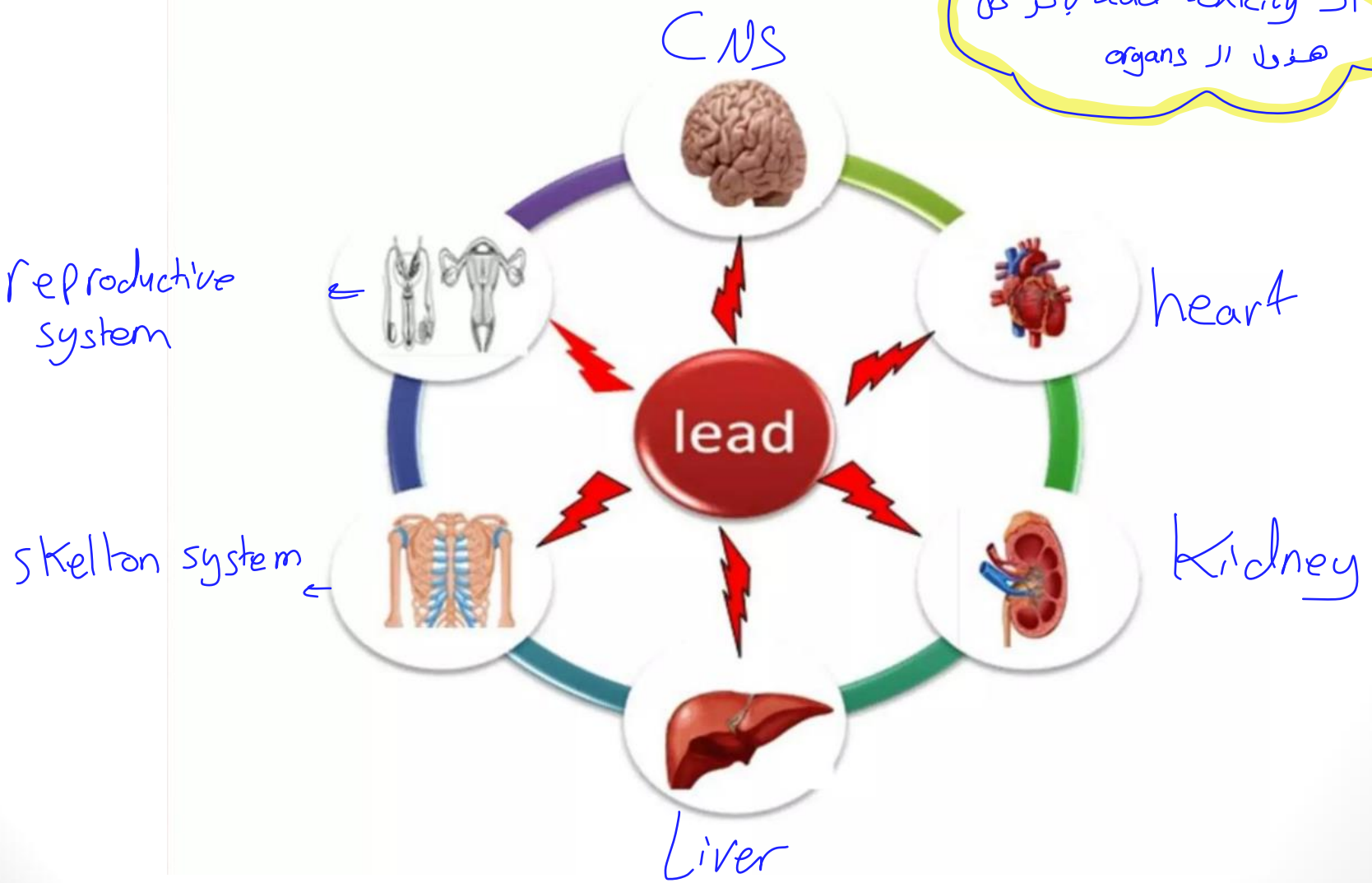
Part per billion [يعني كل part of lead كل قابلها water من 1 billion]

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

0ppb] Zero بس الهدف اخليها

Lead toxicity

اذ Lead toxicity بأثر على هذول الـ organs



Toxicity

الـ Toxicity في تسمم الـ lead في بيل
enzyme الـ inhibition

- 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**
- 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

Normocytic	حجم خلايا الدم الحمراء طبيعي.
Microcytic	حجم خلايا الدم الحمراء صغير (أصغر من الطبيعي).
Hypochromic	خلايا الدم الحمراء شاحبة (نقص في الهيموغلوبين).

Renal Toxicity

- **Chronic lead nephrotoxicity** consists of interstitial fibrosis, progressive nephron loss, azotemia & renal failure → gout يصاحبه
- **Acute lead nephrotoxicity** consists of proximal tubular dysfunction and azotemia.....can be reversed by Tx with chelating agents
- Impairs the renal synthesis of heme-containing **enzymes involved in vitamin D metabolism**....affect bone
- Hyperuricemia with gout

احذناها بال clinical و
برضه بال Renal toxicity من ال lead ح يمنع ال activation for vit D وبنيجي ما اخذنا بال clinical
انه الجسم بدناها في activated vitD ح تروح Parathyroid hormon
لا bone وتطلع منه Ca وهيك صار مستقله بال bone

encephalopathy: عبارة عن مجموعة من الـ disorders اللي تؤثر على الـ CNS

Neurologic, Neurobehavioral, and Developmental Effects in Children

الكتورة روان حكت رح تركز على! كي حاطه تحته underline بس بسألها ونباكد إذا بس هو المطلوب

- 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**

different neuron in CNS ← رح يأثر على excitatory / inhibatory

- Lead affects virtually ***every neurotransmitter system in the brain*** (glutamatergic, dopaminergic, and cholinergic systems)..

بشكل أساسي، العبارة تحذر من أن الشفاء من بعض الأمراض الخطيرة قد لا يكون كاملاً، بل يترك **أضراراً عصبية دائمة** في أعقابها.

- **Recovery is often accompanied** by sequelae including **epilepsy, mental retardation…..in some cases, optic neuropathy and blindness**

→ Neuronal damage بسبب الـ

Effects on Cardiovascular System

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

ال hypertension يصير بسببه

1. **Inactivation of endogenous nitric oxide and cGMP**, possibly through lead-induced reactive oxygen species;

Vasodilator

2. Changes in the **RAAS** and increases in sympathetic activity……important humoral components of HTN;

3. possible rise **in endothelin & thromboxane===vasoconstrictors**

+ inc thrombosis

Other Toxic Effects

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

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
- **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

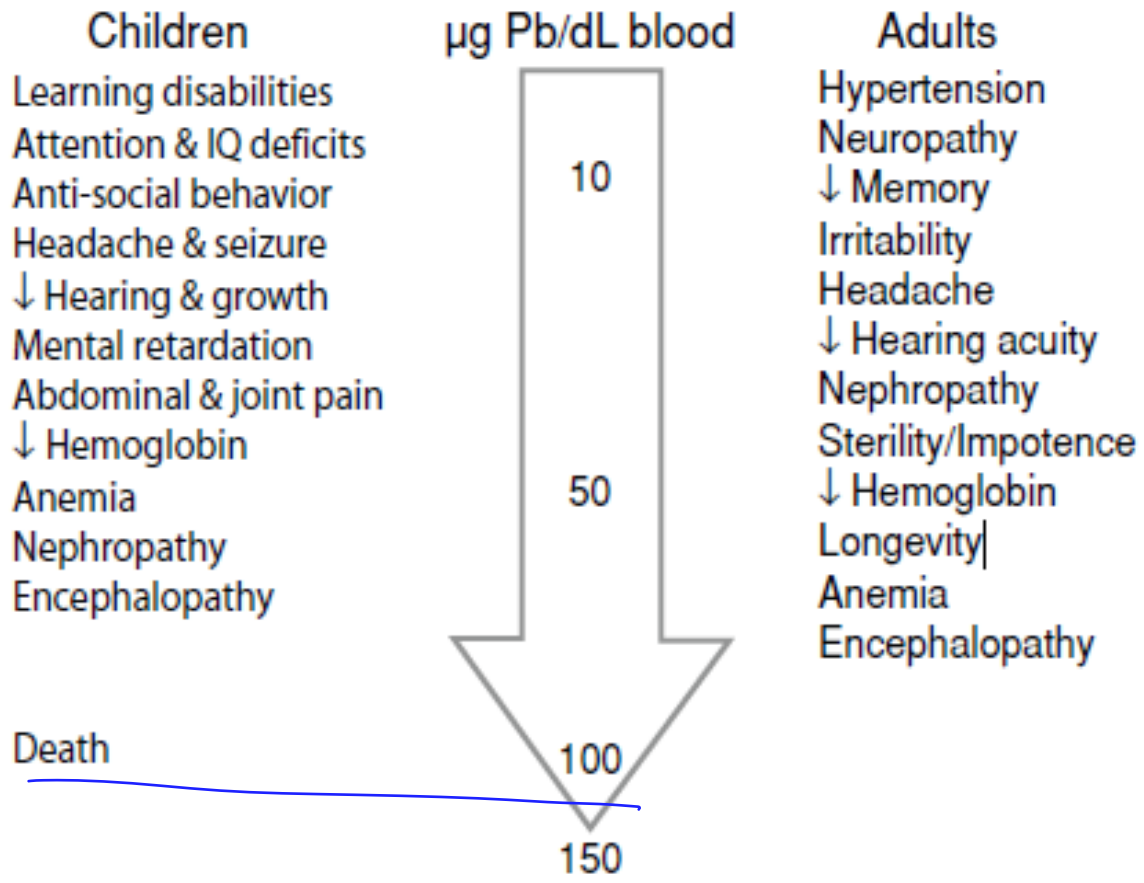
- N.B: consider lead poisoning in any patient with **multisystem findings** with abdominal pain, headache, anemia, and, less commonly, motor neuropathy, gout, and renal insufficiency.

هذا لو سبب Chronic exposure

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

هذا الـ slide مطلوب نعرف
انو الـ side effect تزداد مع الـ dose
dose dependant

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



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

LEAD TREATMENT

TREATMENT:

- REMOVAL OF THE SOURCE & STABILIZE THE PATIENT
- CHELATING THERAPY: → heavy مع ال Complex مركبات تعمل
  - **BAL** accumulation و absorption تقلل ال Metal الى tissue
  - **Calcium EDTA**
  - **SUCCIMER**
  - **D - PENICILLAMINE** → مشتقات ال Penicillin
- SUPPORT

Treatment

antiepilepty drugs

- 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**

acute poisoning

CHELATING AGENTS

Chelating agent الأشياء التي لازم تكون بال

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** and other cation
- **EASILY REMOVED FROM THE BODY**
- 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

Advers effect

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

هذا اعطلوب

بال lead toxicity
الجدول فقط مطلوب معرفة انه بالمرضى ال asymptomatic نعالج فقط فوق ٢٤ ميكروجرام لكل ديسيليتر و
نعالج بال BAI فوق ال ٧٠ ميكروجرام لكل ديسيليتر
و اما بالسلايد الذي يرافق الجرعة مع الأثر الجانبي فقط اعرفو ان الآثار تزداد مع الجرعة dose dependant

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