



Lead: health effects of exposures

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Objectives

- Discuss the absorption and distribution of lead in the body
- Provide some historical perspective of our understanding of lead toxicity
- Use cases to illustrate toxic health effects of lead in children
- Discuss treatment, including chelation



**Your work
makes a
difference!**

Photo used with permission from the UNC Institute for the Environment

Lead is a toxic (poisonous) metal.

- Lead exposure: When a child comes in contact with lead by swallowing or breathing in lead or lead dust.
- Even low levels of lead can adversely affect the health of children.

How much lead is too much?

1960s ≥ 60 $\mu\text{g}/\text{dL}$



1971 ≥ 40 $\mu\text{g}/\text{dL}$



1975 ≥ 30 $\mu\text{g}/\text{dL}$



1985 ≥ 25 $\mu\text{g}/\text{dL}$



1991 ≥ 10 $\mu\text{g}/\text{dL}$



2012 ≥ 5 $\mu\text{g}/\text{dL}$

No safe blood lead level (BLL) has been identified.

The amount of lead in blood is referred to as blood lead level (BLL), which is measured in micrograms of lead per deciliter of blood ($\mu\text{g}/\text{dL}$).

CDC uses a blood reference value of $5 \mu\text{g}/\text{dL}$ to identify children with BLLs that are higher than most children.

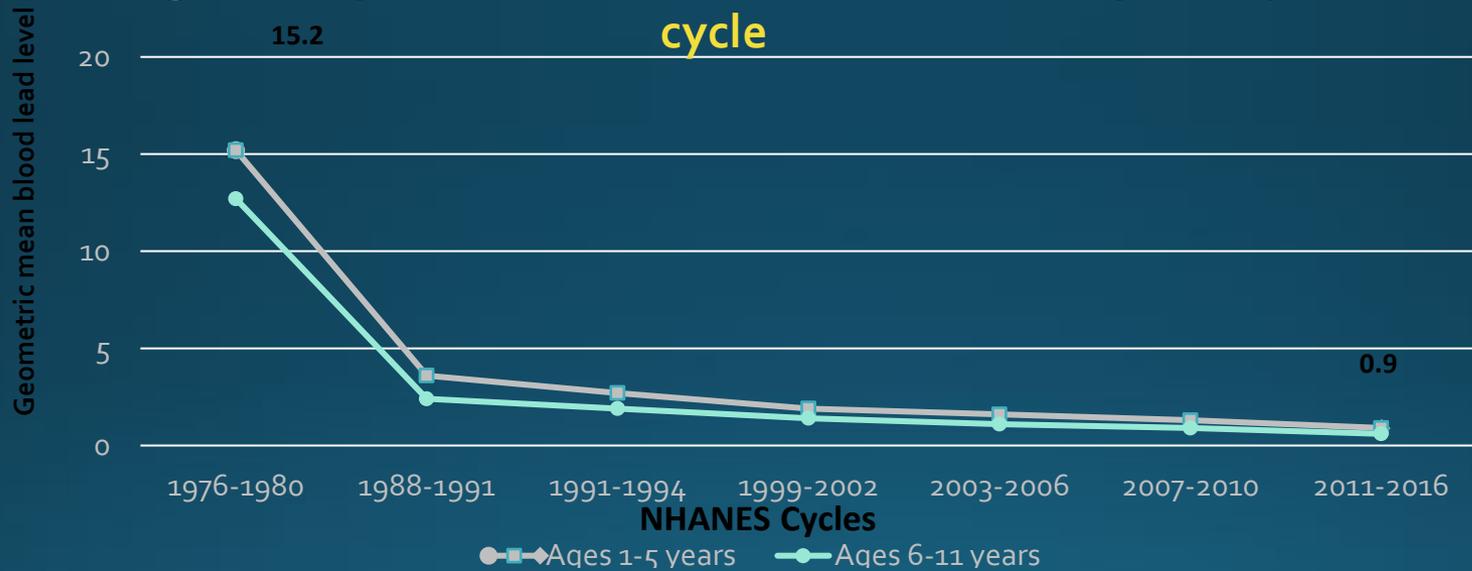
This level is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood based on the National Health and Nutrition Environmental Survey (NHANES).

Lead levels in children

- 4 million households have children living in them being exposed to lead
- ~1/2 million children age 1-5 with blood levels > 5 ug/dl (reference level where public health action be initiated)
- Healthy People 2020 goal: no blood level > 10 ug/dl

Blood lead levels in U.S. children have declined.

Geometric mean BLL for children ages 1-5 years and ages 6-11 years in the NHANES, 1976-2016, by survey cycle



Children are primarily exposed to lead from paint, soil, and water.

Lead-based paint in homes and buildings built before 1978

Contaminated soil from exterior lead-based paint, car exhaust, and factories that use lead

Contaminated drinking water delivered through lead plumbing materials

Lead Poisoning: many sources

Epidemiologic Notes and Reports

**Lead Intoxication
Associated with Chewing Plastic Wire Coating — Ohio**

Recreation

Pool Cue Chalk: A Source of Environmental Lead

Food

Vol. 47 / No. 48

MMWR

Lead Poisoning Associated with Imported Candy and Powdered Food Coloring — California and Michigan

Sources from hobbies

Epidemiologic Notes and Reports

Lead Ingestion Associated with Ceramic Glaze — Alaska, 1992

FIGURE. Heart-shaped charm bracelet that is the subject of the voluntary recall announced March 23, 2006, by Reebok International Ltd. and the Consumer Product Safety Commission



Photo/Consumer Product Safety Commission



Adult Lead Exposure

Sources:

1. Occupational exposure 95%
2. Non-occupational exposure:
 - *Typically at home, recreational activities*
 - *Sometimes food and drink*
 - *Take-home residues from work*

TABLE 1

Jobs and Industries with Potential Lead Exposure

<i>General Industry</i>	
Lead production or smelting	Battery manufacturing or recycling
Brass, bronze, copper, or lead foundries	Automotive radiator repair
Ammunition/explosives production	Lead soldering
Scrap metal handling	Ceramic manufacturing
Firing ranges	Cable/wire stripping, splicing or production
Machining or grinding lead alloys	Rubber manufacturing
Manufacture of radiation shielding	Plastics manufacturing
Repair/replacement of refractory material in furnaces	Leaded glass manufacturing
Ship building/repairing/breaking	Paint/pigment manufacturing
Mining	

Non-occupational and Environmental Sources of Lead Exposure

Remodeling or painting pre-1978 housing

Peeling paint

Ethnic medicines or folk remedies (e.g., azarcon, greta, pay-loo-ah, kandu, some Ayurvedics)

Pica (ingestion of lead-containing nonfood items, e.g., soil or ceramics, plaster, or paint chips)

Retained lead bullet or fragments

Melting lead for fishing weights, bullets, or toys

Imported vinyl miniblinds

Recreational target shooting

Lead-contaminated drinking water supply

Using lead glazes for ceramics

Painting/stripping cars, boats, bicycles

Lead solder in stained-glass artwork

Lead-soldered cans

Lead-contaminated candies

Backyard scrap metal recycling

Moonshine (liquor from a homemade still)

Antique pewter plates, mugs, utensils, toys

Imported brass or bronze kettles, cookware

Lead-glazed tableware or cooking vessels

Leaded crystal tableware

Mine tailings

Beauty products such as kohl eye make-up, certain hair dyes



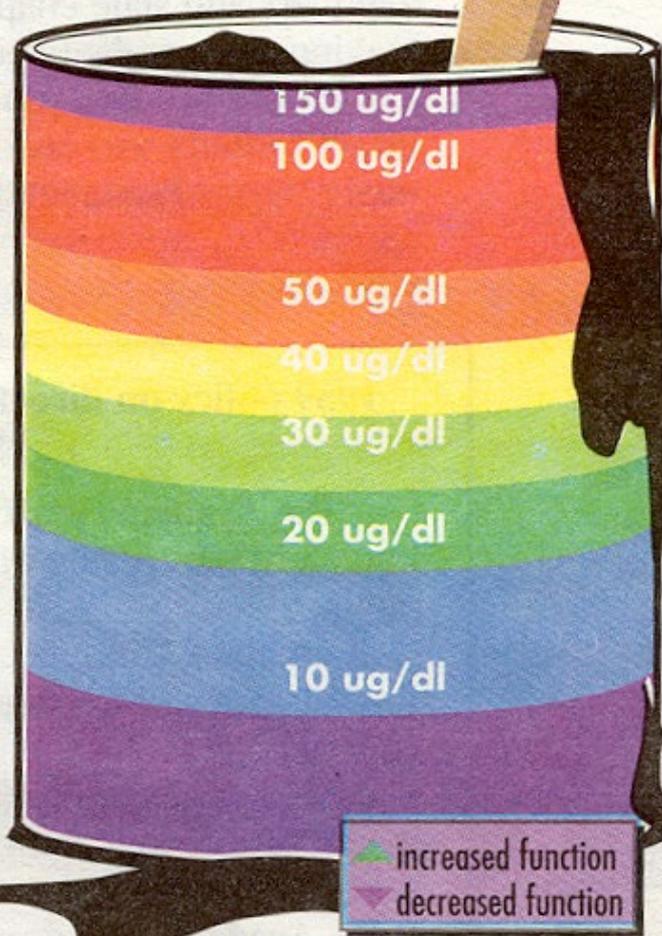
Assumptions of earlier research

1. No symptoms = No lead poisoning
2. Symptomatic children (without encephalopathy) would recover completely

INORGANIC LEAD:

The Lowest Observed Effects in Children

- DEATH
- ENCEPHALOPATHY
- NEPHROPATHY
- FRANK ANEMIA
- COLIC
- HEMOGLOBIN SYNTHESIS
- VITAMIN D METABOLISM
- NERVE CONDUCTION VELOCITY
- ERYTHROCYTE PROTOPORPHYRIN
- VITAMIN D METABOLISM (?)
- DEVELOPMENTAL TOXICITY
- IQ
- HEARING
- GROWTH
- TRANSPLACENTAL TRANSFER



The chart shows the effects of lead contamination at various levels. The levels in this diagram do not necessarily indicate the lowest levels at which lead exerts an effect. These are the levels at which studies have adequately demonstrated an effect.

Effects on Reproductive Health and Pregnancy



- Lead crosses the placenta, exposing the fetus
- High Maternal BLLs may increase the risk of reduced birth weight and premature birth
- Increased risk of hypertension in pregnancy
- Decreased sperm counts at EBLs of 30-40 $\mu\text{g}/\text{dL}$
- Maternal lead can be present in breastmilk
 - “Pump and Dump” recommended if mother’s BLL is ≥ 40 micrograms/deciliter (mcg/dL)
 - Monitoring the baby’s BLL recommended if mother’s bll is 5-39 and breastfeeding

Lead in the blood during pregnancy can

Increase risk for miscarriage

Cause the baby to be born prematurely or too small

Harm the baby's brain, kidneys, and nervous system

Cause the child to have learning or behavior problems



Lead: Primary routes of exposure in children

Ingestion

- Children absorb 40-50% of ingested lead vs 10-15% absorption for adults
- Deficiencies in iron, calcium, zinc may enhance absorption
- Iron deficiency can cause “pica” = consumption of non-food items

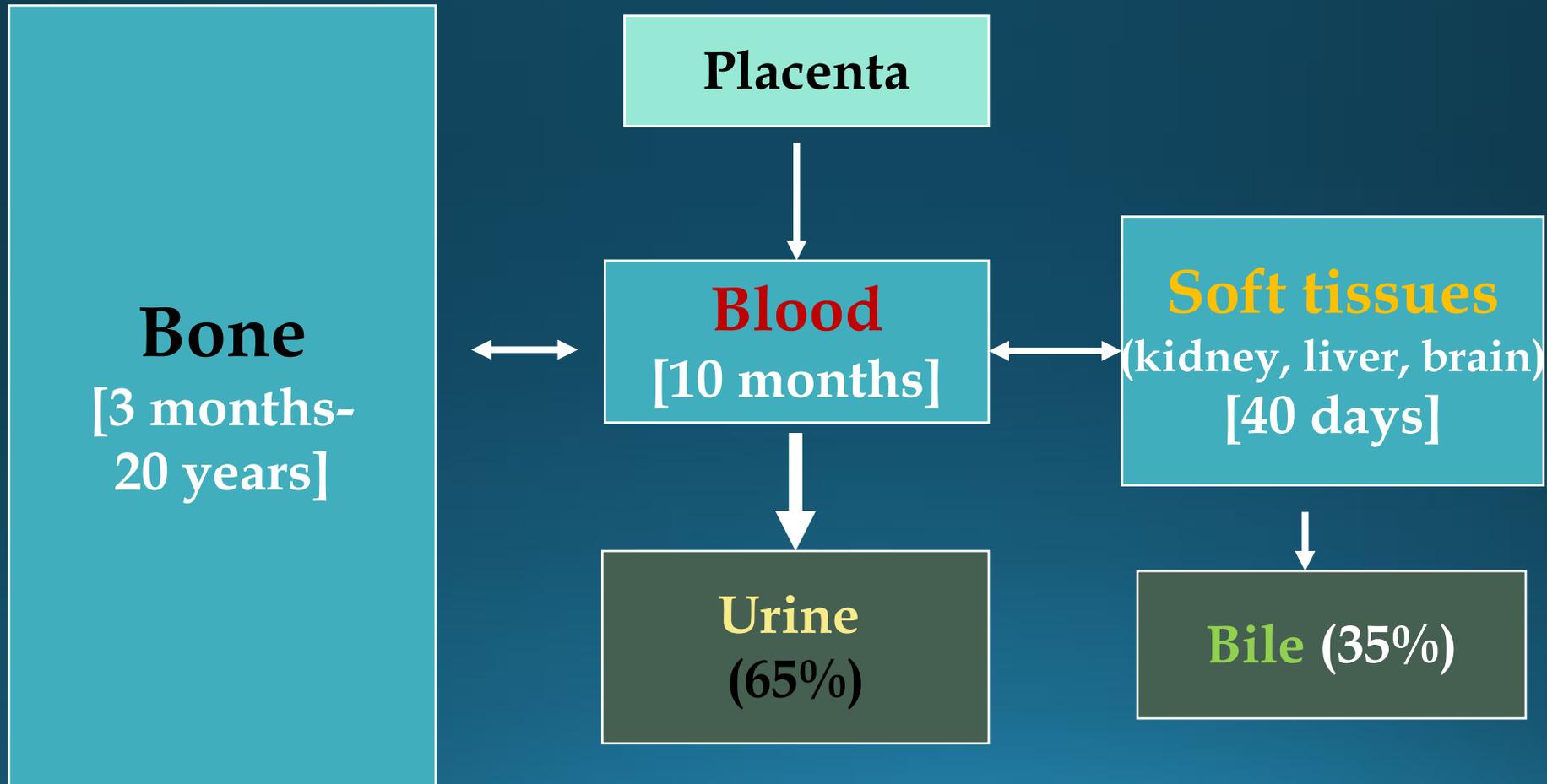
Inhalation

- 30-40% absorption overall
- Children have higher metabolic rates and deposit 2.7 fold more lead in lung tissue than adults
- [skin: not a significant source for inorganic lead absorption]

Why children are more susceptible to lead poisoning than adults

- Hand to mouth behavior
- Sensitivity of developing organs
- Take in more food and water per body mass
- Absorption 5-10 times greater
- Absorption increased with deficiency of iron, calcium and possibly zinc
- Incomplete development of blood-brain barrier up to 36 months of age increases lead entry

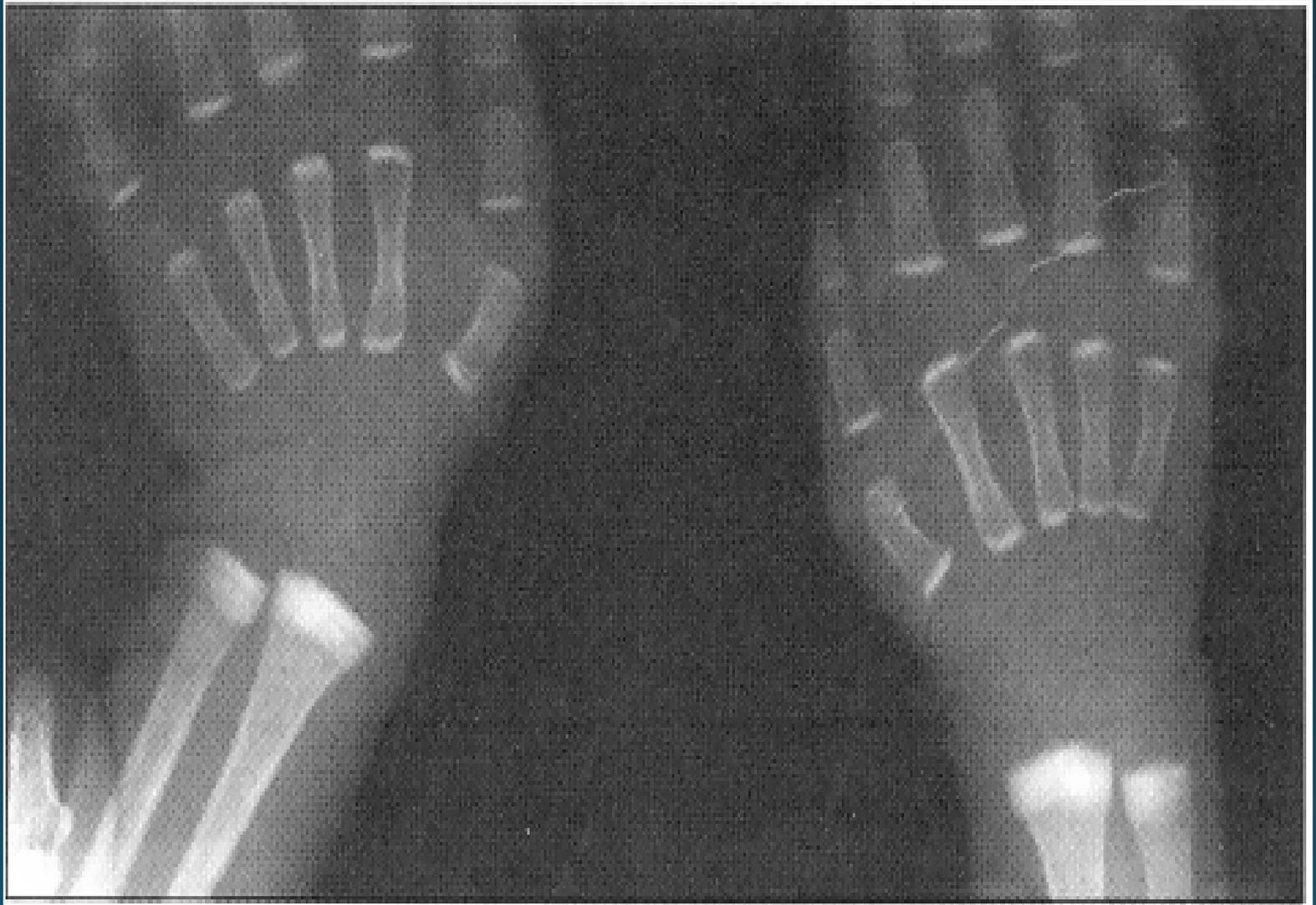
Distribution and Persistence of Absorbed Lead



Bone-to-Blood Lead Transfer



- ✓ Bone lead maintains blood lead levels long after exposure occurs
- ✓ Increased transfer from bone to blood with pregnancy, lactation, menopause, physiologic stress, chronic disease, hyperthyroidism, kidney disease, broken bones, advanced age, and calcium deficiency



2 mo, "lead lines", Pb = 200 mcg/dL.

Symptoms of Acute Lead Poisoning

- GI: Anorexia, constipation, abdominal pain, vomiting
- Neurologic: Irritability, overactivity, lethargy, ataxia
- Severe: Seizures, coma, hypertension, papilledema, cranial nerve paralysis
- Survivors: often with MR, palsies, growth failure

Findings Associated with Chronic Lead Poisoning

- Malaise; fatigue
- Anemia
- Abdominal pain; anorexia, nausea, vomiting, constipation.
- Headache, ataxia, seizures, coma
- Increase in dental caries
- Delays in growth

Findings Associated with Chronic Lead Poisoning

- As adults:
 - Increase in hypertension, heart attacks, strokes
 - 2 fold increase in CV death as adult if poisoned as child
- Delayed development, speech
- Altered behavior
- Psychoeducational problems (ADD)

Let's look at some real cases...

Case 1: North Carolina, 2017

- **13 month-old child with developmental delay**
- **A confirmed blood lead level was 22 $\mu\text{g}/\text{dL}$ (lead poisoning)**
- **The child's home was built after 1978 and no lead paint hazards were found**
- **Family of SE Asian/Indian origin**

Balguti kesaria

- An Ayurvedic medicine, *Balguti kesaria*, that the parents had been giving the child was found to contain 220mg/kg lead
- NC reported to the FDA
→ August 2017 Safety Alert



<https://www.fda.gov/drugs/drugsafety/ucm570237.htm>

Safety Alerts for Human Medical Products

2018 Safety Alerts for Human Medical Products

2017 Safety Alerts for Human Medical Products

Balgoti Kesaria Ayurvedic Medicine: FDA Warning - High Levels Of Lead

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[Posted 08/04/2017]

AUDIENCE: Consumer, Health Care Professional

ISSUE: The U.S. Food and Drug Administration is warning parents and caregivers not to use “Balgoti Kesaria (or Kesaria Balgoti) Ayurvedic Medicine” due to the risk of lead poisoning.

FDA has not reviewed this product for safety or effectiveness. Exposure to lead can cause serious damage to the central nervous system, the kidneys and the immune system. In children, chronic exposure to lead—even at low levels—is associated with impaired cognitive function, including reduced IQ, behavioral difficulties, and other problems.

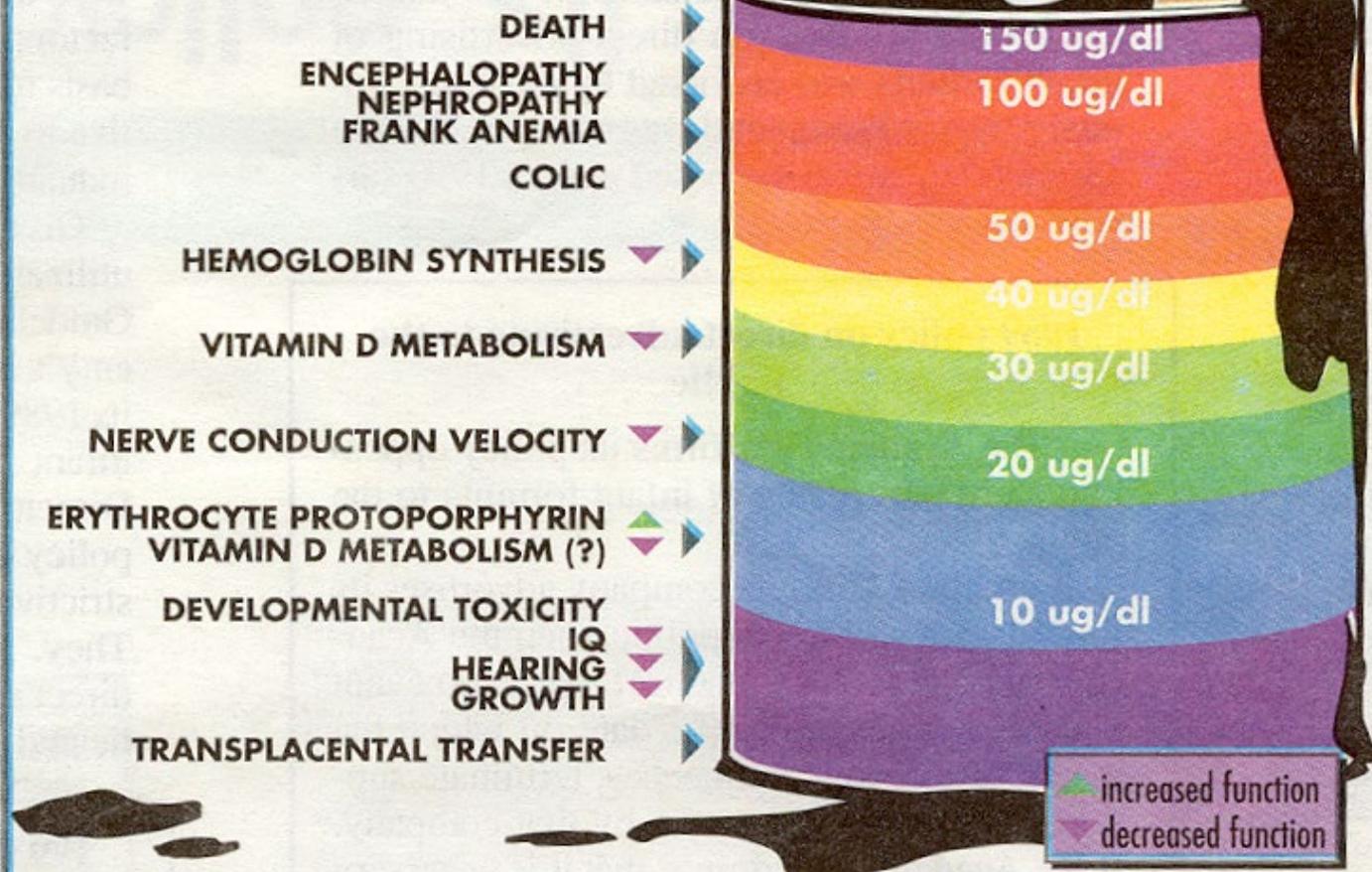
BACKGROUND: This product is sold online and manufactured by multiple companies, including Kesari Ayurvedic Pharmacy in India. Individuals have also mailed or brought the product into the United States. “Balgoti Kesaria Ayurvedic Medicine” is used with infants and children for a variety of conditions including rickets, cough and cold, worms and dentition (teething).

FDA initially learned of this risk from the North Carolina Division of Public Health after the product was tested and found to contain high levels of lead. FDA was also notified by the Michigan Department of Health and Human Services of high levels of lead in two children who were given this product. Michigan’s testing also found high levels of lead in the product. To date, FDA has received one adverse event report of high levels of lead and developmental delays in a child who was given this product.

RECOMMENDATION: Anyone who is using this product or giving it to a child should stop immediately and consult a health care professional.

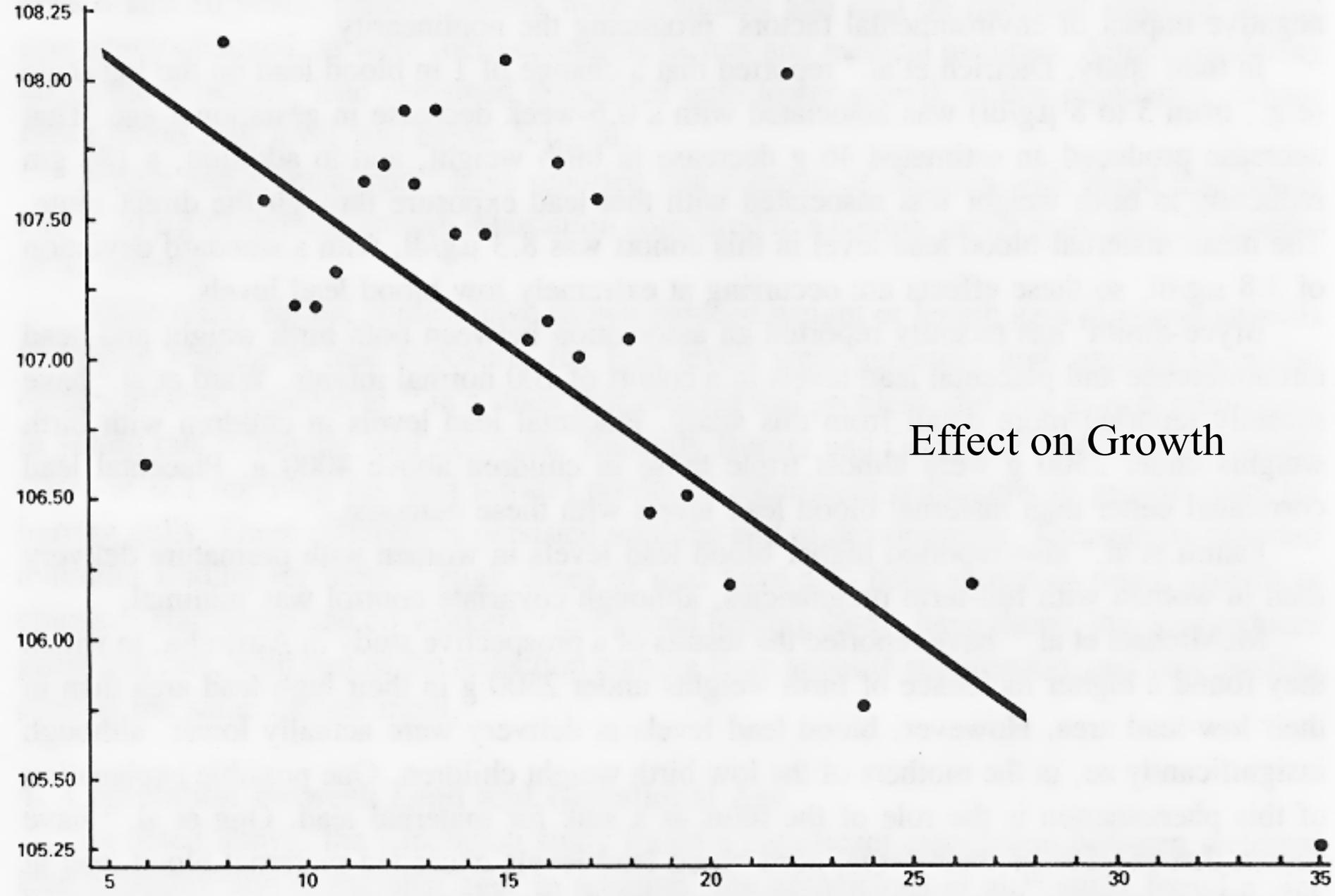
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The Lowest Observed Effects in Children



The chart shows the effects of lead contamination at various levels. The levels in this diagram do not necessarily indicate the lowest levels at which lead exerts an effect. These are the levels at which studies have adequately demonstrated an effect.

ADJUSTED
HEIGHT (cm)



Effect on Growth



Health Effects at Low Levels of Exposure

“There is evidence that at low levels of lead exposure, biomarkers of cumulative lead exposure, such as lead in bone, may be associated with an adverse impact on neurocognitive function that is not reflected by measurement of lead in blood.”

(Shih et al., 2007; Bandeen-Roche et al., 2009; Weuve et al., 2009)

Lead toxicity – central nervous system

- Chemically similar to calcium so interferes with many metabolic pathways that use calcium (and perhaps zinc)
- Impairs neurotransmitter function
- The hippocampus (important for learning and memory) is one of the most affected areas of the brain

American Journal of Diseases of Children

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NUMBER 5

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LATE EFFECTS OF LEAD POISONING ON MENTAL DEVELOPMENT

RANDOLPH K. BYERS, M.D.

AND

ELIZABETH E. LORD, Ph.D.

BOSTON

FOREWORD

The sudden tragic death of Dr. Lord on Jan. 10, 1943 occurred before the completion of the final draft of this paper. It was she who first felt that the minor deviations found on psychologic examination of these children with lead poisoning might be of important significance for the future. It was she who maintained the file of cases, studying them from the psychologic point of view, without encouragement from any one for the first several years.

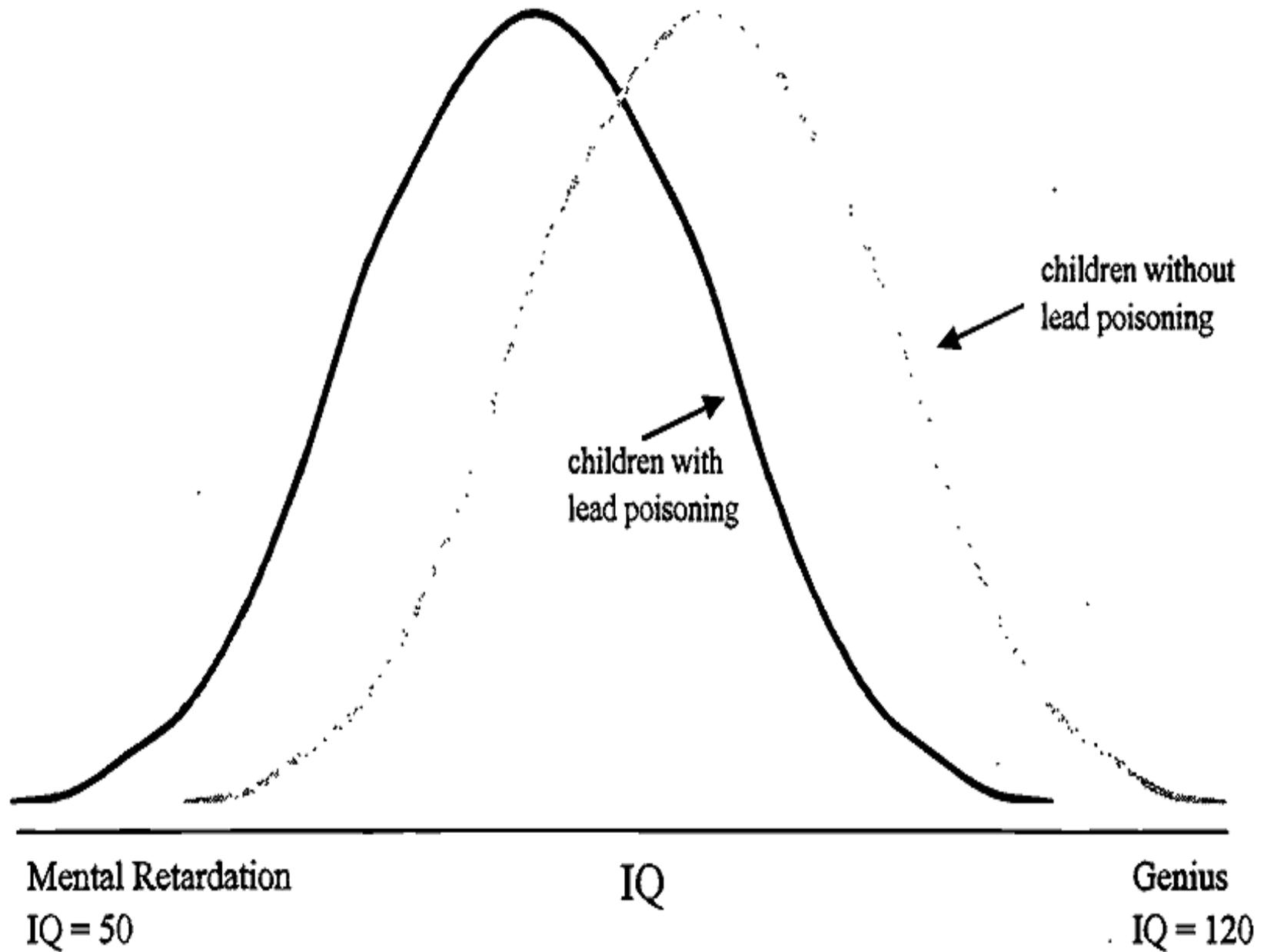
That lead poisoning occurring in early life usually has a disastrous effect on mental development has not been generally recognized, though the subject of lead poisoning in children has been discussed by many observers. The manifestations of acute involvement of the nervous system have been adequately described, and the gross destructive lesions in the brain consequent to acute lead encephalopathy accompanied by cerebral edema and high intracranial pressure have been recognized. On the other hand, McKhann,¹ for instance, stated: "The neurologic manifestations of lead poisoning usually subside without serious consequences if the ingestion of lead is stopped and the removal of lead from the circulation and its deposition in inert form in the bones can be hastened, as described, by the use of a diet high in calcium together with the administration of cod liver oil or viosterol to accelerate the laying down of new bone."

Cognitive Effects at Low Lead Levels

Problems at Low Lead Levels

- Canfield et al. 2003 studied BLLs from children (n=172) at 6,12,18,24,36,48,60 months
- Stanford-Binet IQ test at age 3 and 5 years
- Each BLL increase of 10 $\mu\text{g}/\text{dL}$ associated with 4.6 decrease in IQ.
 - Relationship was non-linear decrease in IQ in those with BLL of 1-10 $\mu\text{g}/\text{dL}$

Canfield RL, Henderson CR, Jr, Cory-Slechta DA, et al. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. N Engl J Med. 2003



Case 2: North Carolina

- 2 year old boy with a capillary BLL of 18
- Venous BLLs 12 → 13 → 12 → 12 → 7
- Symptoms: constipation, developmental delay, behavioral problems
- Risk assessment: child bites his nails, licks furniture and chews toys
- Father works in a plant that produces lead; BLL dropped to 7 after father changed jobs
- Sibling tested and had an elevated blood lead level (EBL)

Case 3: North Carolina, 2018

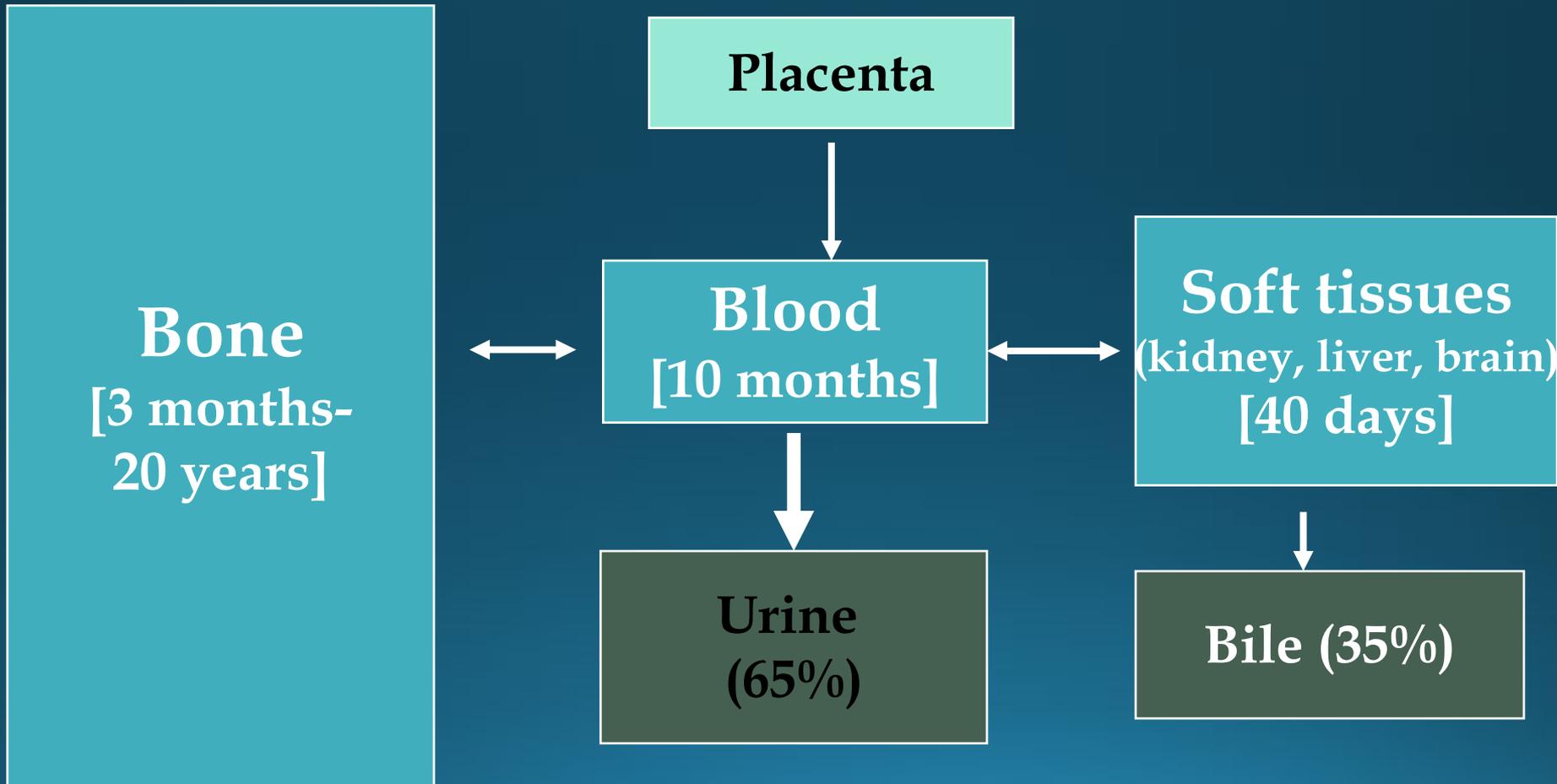
- 12 month-old girl taken for routine screening
- No symptoms of concern, but history of constipation
- Confirmed **BLL of 65.9 $\mu\text{g}/\text{dL}$**
- Referred for hospital admission
- Abdominal xray: no foreign body
- Labs: mildly decreased hemoglobin=anemia
- Admitted for chelation with DMSA (succimer)

Case 3: source of exposure

- History of spending increasing amounts of time in a shooting range owned by a family member
- Older sibling also confirmed to have lead poisoning
- Case patient BLLs: January = 66 → chelation
June = 47
August = 42

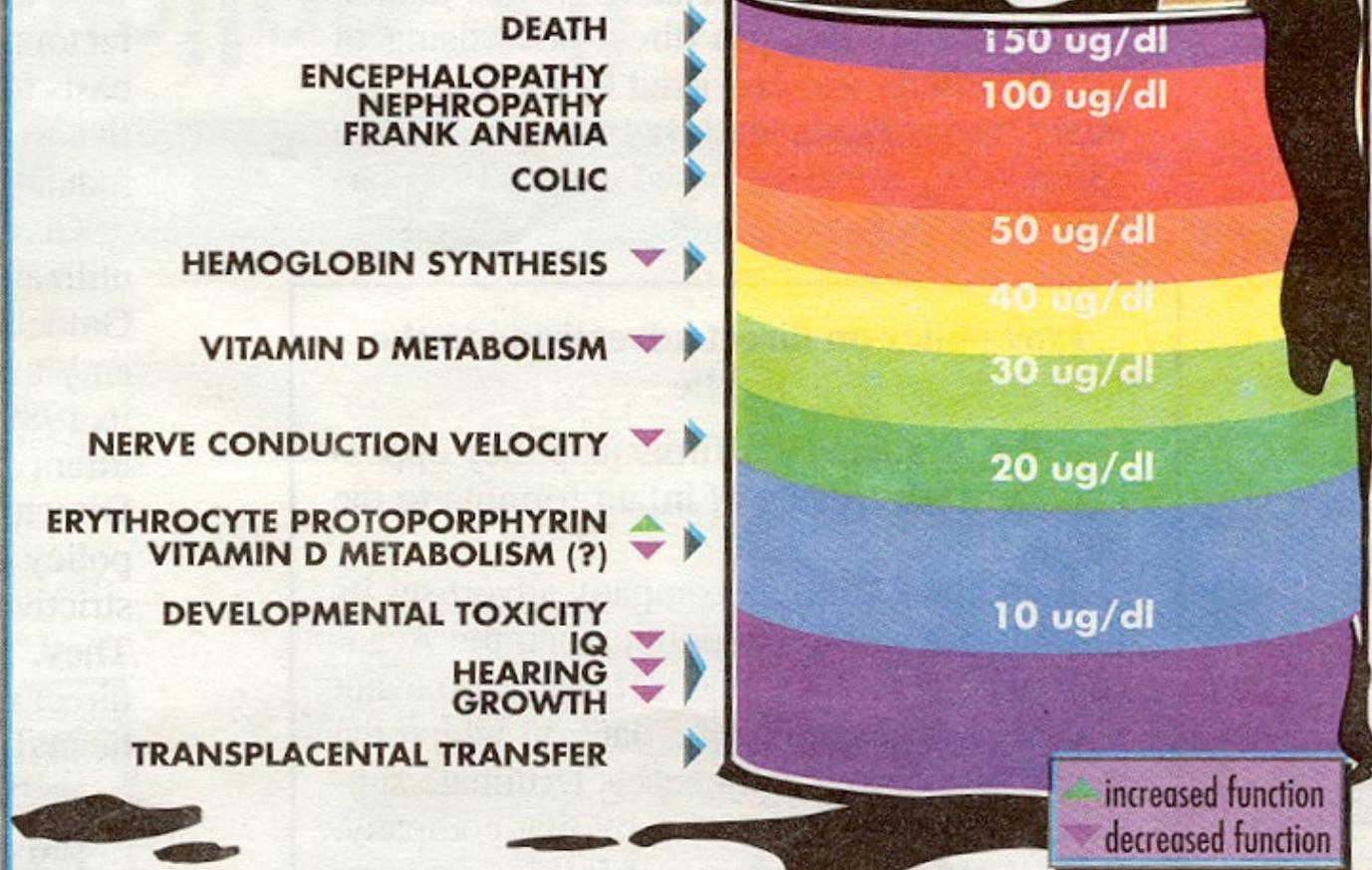
??? Why isn't the blood lead level dropping more quickly ???

Most absorbed lead is stored in bone



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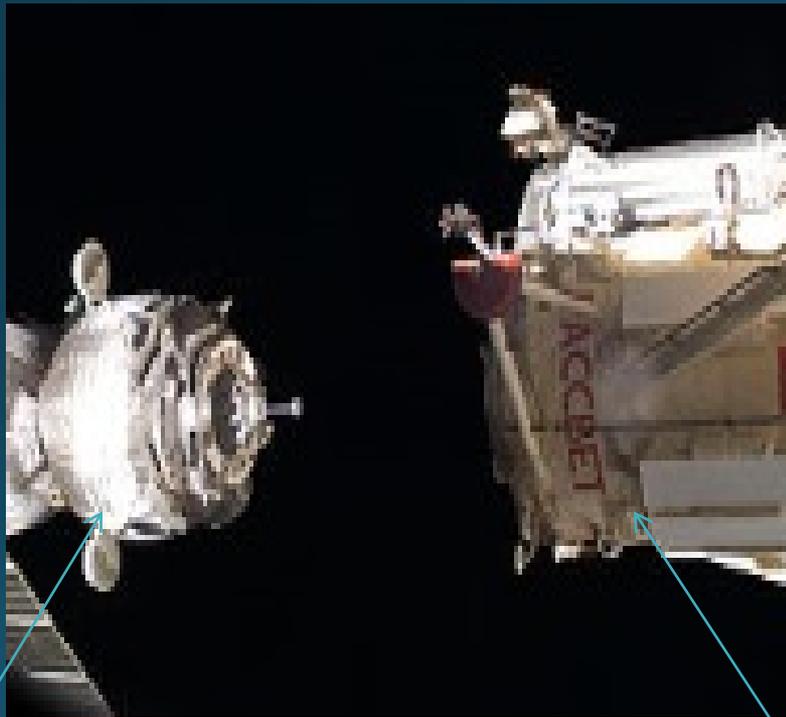


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Case 4: New Hampshire, 2000

- 2 y.o. girl presented to a community hospital ED with c/o low grade fever and vomiting x 1 day
- Lab findings:
 - microcytic anemia – hemoglobin **7.6g/dL** (normal >11.4)
 - Basophilic stippling of red blood cells noted
 - Throat swab rapid strep test – **Positive**
- Discharged home with rx for an antibiotic for strep throat and medication for nausea/vomiting

Lead disrupts heme synthesis



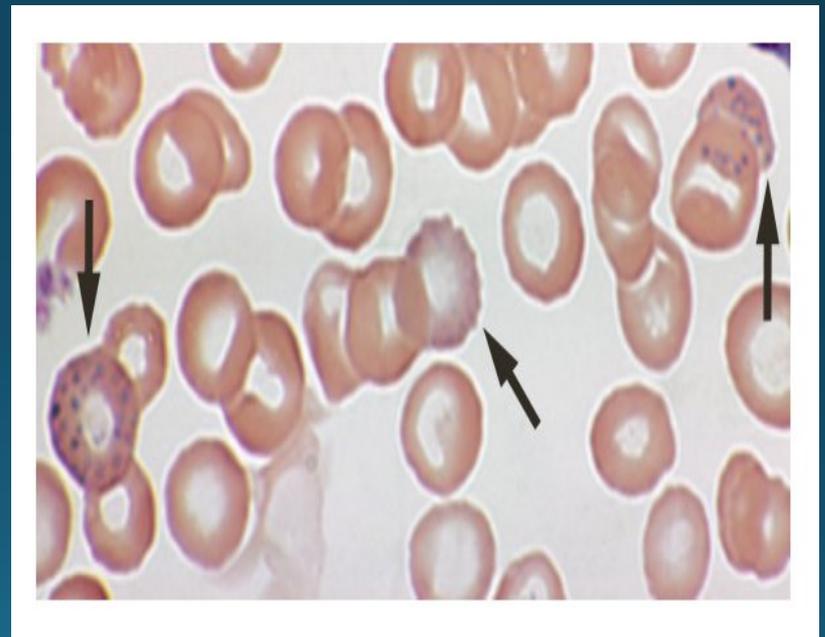
Lead/ligand

enzyme or protein

- Lead attaches to ligands that bind to enzymes and proteins that control numerous biochemical pathways in the body

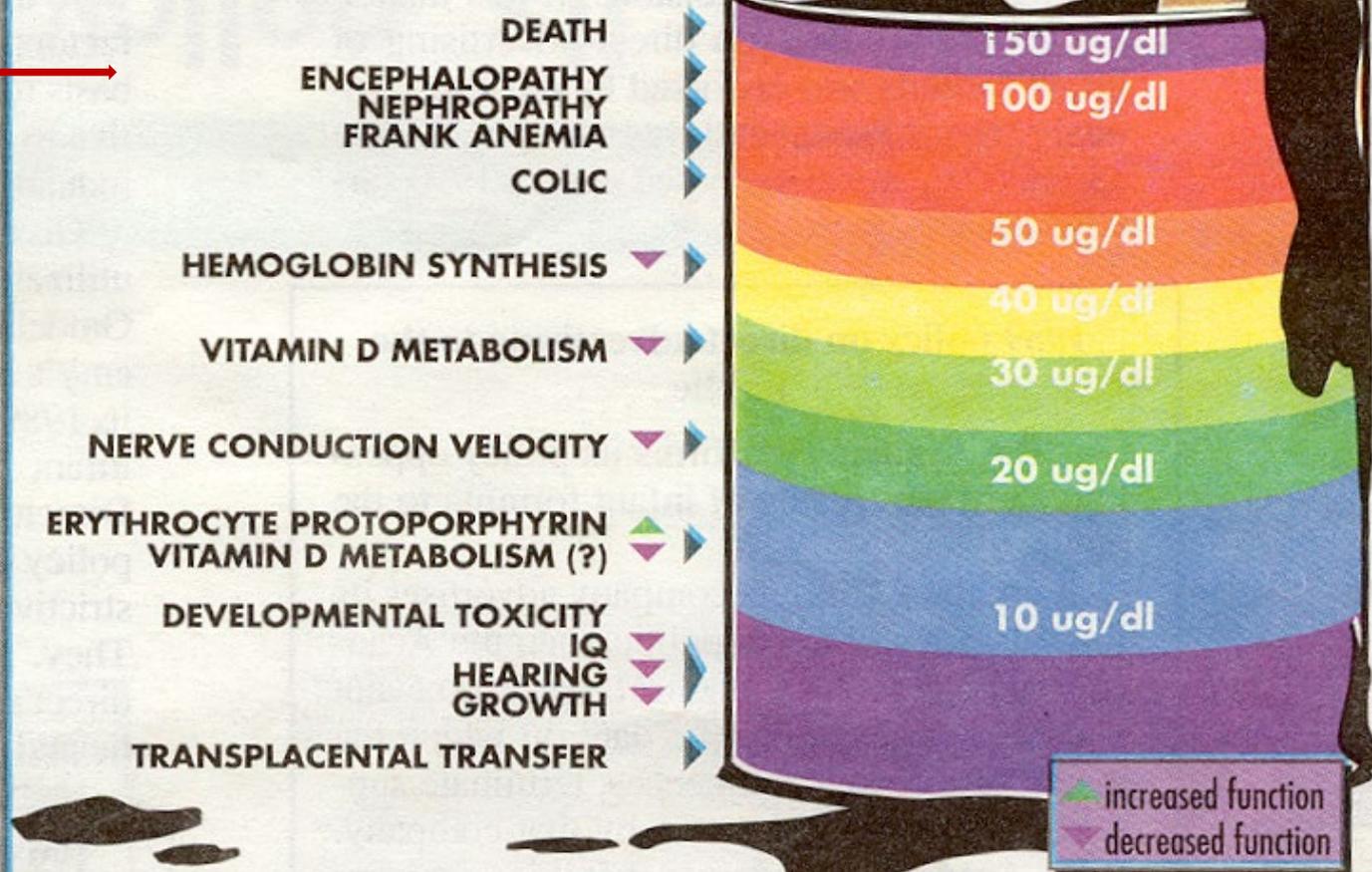
How lead causes anemia (low hemoglobin)

- Inhibits enzymes required for red blood cell (rbc) formation
- Decreases erythropoietin production in the kidney
- Decreases the life span of a rbc by making the cell membrane more fragile
- Pale, small rbcs (microcytosis, hypochromia)



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Case 4: New Hampshire, 2000

- 19 days later, admitted to same hospital for worsening vomiting
- Transferred the next day to a tertiary care hospital
- Later that day hypotension, difficulty breathing developed and she became unresponsive
- Intubated and ventilated
- CT scan showed diffuse cerebral edema (swelling of the brain)

Case 4: New Hampshire, 2000

- A BLL drawn 1 day earlier = 391 $\mu\text{g}/\text{dL}$
- Chelation therapy started with british antilewisite (BAL) and calcium ethylenediaminetetraacetic acid (CaN_2EDTA)
- BLL decreased to 72 $\mu\text{g}/\text{dL}$
- Surgical treatment of increased intracranial pressure
- Coma persisted. Patient removed from life support 2 days after transfer

Demographic information

- Family Sudanese and had been living in Egypt 18 months
- Arrived in NH as refugees 3 weeks before illness
- Living in an apartment built prior to 1920
- The patient had been seen eating paint and plaster from holes in a wall



Environmental Investigation

- BLLs in the mother and 3 siblings (ages 5-15): 4-12 $\mu\text{g}/\text{dL}$
- Lead isotope composition from the porch paint (35% lead) and window well dust ($6732\mu\text{g}/\text{ft}^2$) most closely matched the patient's blood lead composition

Acute lead encephalopathy

- Typical BLL >70-100 $\mu\text{g}/\text{dL}$
- Nerve palsies (cranial nerves)
- Seizures
- Bizarre behavior
- Ataxia (imbalance)
- Loss of developmental skills
- Cerebral edema/increased intracranial pressure (persistent vomiting, headache)
- Coma

Lead Effects on the Brain

- Affects the function of neurotransmitters
- Increases permeability of blood vessels in the brain – bleeding and swelling may occur
- Increased intracranial pressure may cause death
- Early symptoms are non-specific: Irritability, poor attention span, developmental regression, lethargy and mood changes

Medical Evaluation

Provider evaluation:

- History, developmental evaluation, physical examination, BP
- SI/TIBC or Ferritin
- Consider U/A, BUN, Cr, erythrocyte protoporphyrin, KUB

Blood Test for Lead in Children

A blood test is the easiest way to determine if a child has been exposed to lead.

Most children with any lead in their blood show no symptoms.

Two types of tests may be used: finger prick (capillary test) or venous blood draw.

Critical steps in treatment

#1. REMOVAL FROM FURTHER EXPOSURE

- Must be in a lead-free environment during chelation

#2. Optimize nutrition: iron, calcium, zinc

#3. Chelation

- Multiple treatments may be required
- Total body content of heavy metal decreased by 1-2%
- BLL decreased by ~75% after 48-72 hours of BAL/CaNa₂EDTA
- +/- GI decontamination e.g., whole bowel irrigation

MANAGEMENT GUIDELINES FOR BLOOD LEAD LEVELS IN ADULTS

Blood Lead Level ($\mu\text{g}/\text{dL}$)	Management Recommendations
<5	No action needed
5-9	Discuss health risks Minimize exposure Consider removal for pregnancy and certain medical conditions Monitor BLL
10-19	Decrease exposure Remove from exposure for pregnancy Consider removal for certain medical conditions or $\text{BLL} \geq 10$ for an extended period of time
20-29	Remove from exposure for pregnancy Remove from exposure if repeat BLL in 4 weeks remains ≥ 20 Annual lead medical exam recommended
30-79	Remove from exposure Prompt medical evaluation Chelation not indicated unless $\text{BLL} > 50$ with significant symptoms
≥ 80	Remove from exposure Urgent medical evaluation Chelation may be indicated if symptomatic and /or $\text{BLL} \geq 100$



Chelation Therapy

Intramuscular/Intravenous

- British antilewisite (BAL)
- Calcium ethylene-diaminetetraacetic acid (CaNa₂EDTA)

Oral

- Succimer
- [D-penicillamine]

When is chelation indicated?

✓ Lead encephalopathy

✓ BLL ≥ 70 $\mu\text{g/dL}$ / mild or no symptoms

? BLL 45-70 $\mu\text{g/dL}$ / no symptoms ?

X BLL 20-44 $\mu\text{g/dL}$ /no symptoms

X BLL 10-19 $\mu\text{g/dL}$

Study of Treatment Outcomes

- Rogan et al. 2001
- Randomized, double-blinded, placebo-controlled Succimer (up to three courses) vs. placebo. All received standard environmental investigation and attempts at remediation/prevention
- Ending exposure
- Children (n=780), age 12-33 months
- BLL's starting 20-44 µg/dL
- Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001 May 10;344(19):1421-6.

Study of Treatment Outcomes

- Children followed over 36 months
 - Serial BLL's and neurocognitive, psychological, behavioral testing on both groups
 - BLL's decreased more quickly with succimer
 - Levels same in both groups after one year
 - No improvement in any testing with succimer
 - Authors recommended no chelation in children with BLL <45 µg/dL
- Rogan WJ, Dietrich KN, Ware JH, et al. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med. 2001 May 10;344(19):1421-6.

THE BEST MEDICINE = PREVENTION

- Children can develop health effects *without* apparent symptoms
- The diagnosis of lead poisoning is made by the blood lead level
 - Testing is diagnostic and preventative!
- Symptoms can be vague and non-specific(e.g. fatigue, irritability)
- Children are more susceptible to lead poisoning than adults
- Children absorb lead primarily through ingestion and inhalation
- The blood lead level (BLL) may not reflect the total body lead burden
- It can take years for a child's EBL to decrease to < 5 mcg/dL

Keep up the Good Work!

