LEAD

Children's Health and the Environment
CHEST Training Package for the Health Sector

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<<NOTE TO USER: Please add details of the date, time, place and sponsorship of the meeting for which you are using this presentation.>>

This presentation will deal with the epidemiology, sources, routes of exposure, clinical manifestations, laboratory aspects and basic approach for prevention and management of poisoning due to lead exposure in children, an important problem affecting children's health and development worldwide.

This module is based on the original WHO training module on lead. First draft prepared by Yona Amitai MD MPH (Israel).

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LEARNING OBJECTIVES

To understand, recognize and know:

- ❖ **Characteristics of lead as a toxicant**
- ❖ **Epidemiology of lead poisoning**
- ❖ **Trends in blood lead levels and action levels**
- ❖ **Who is vulnerable and why?**
- ❖ **Sources of contamination**
- ❖ **Toxicokinetics of lead**
- ❖ **Diagnosis and treatment**
- ❖ **Prevention: strategy and actions**
- ❖ **Case-studies**

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The goal of this training module is to achieve the following learning objectives:

<<READ SLIDE.>>

LEAD POISONING IN THE ANCIENT WORLD

Did lead poisoning contribute to the fall of Rome?

In the Roman Empire, the upper classes were exposed to:

- **High content of lead in wine**
- **Lead water pipes**
- **Glazed pottery**

Signs and symptoms of lead poisoning recognized in about half of the 38 Roman emperors

Nriagu, N Engl J Med. 1983 Mar 17;308(11):660

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Lead poisoning has been a problem throughout history and possibly contributed to the fall of the Roman Empire.
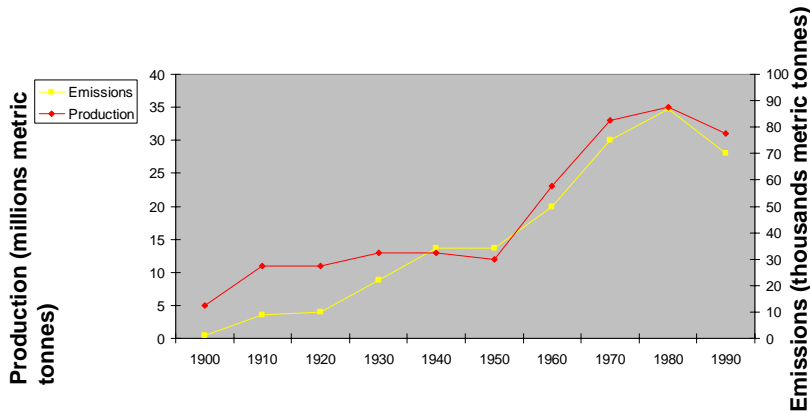
Lead was used as the glaze for wine jars, because it gave the wine a special sweet taste. Due to the acidity of the wine, lead leached from the jars and reached a high concentration in the wine, which was popular among aristocrats and emperors in Rome. Nriagu analysed historical testimonies on the health and behaviour of 38 Roman emperors, and concluded that about half of them had neuropsychiatric symptoms, as well as other symptoms of lead poisoning (e.g. gout). Neron Caesar and Caius Caligula are just two well-known examples.

Ref:

•Nriagu. Saturnine gout among Roman aristocrats. Did lead poisoning contribute to the fall of the Empire? *N Engl J Med,* 1983, 308:660.

Lead Poisoning in Children

LEAD PRODUCTION IN THE 20TH CENTURY

Production (millions metric tonnes)

Emissions (thousands metric tonnes)

Legend: Emissions, Production

Adapted from Nriagu, (1996) 272:223

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•Exposure to lead and subsequent lead poisoning has been recognized from ancient times, but reached epidemic proportions during the twentieth century, due to the progressive increase in the production and use of lead.

•Susceptibility to lead poisoning is particularly high among young children due to increased exposure and absorption and their special vulnerability.

•Lead impairs several organ systems, but the main concern is CNS damage, particularly in young infants who are exposed to lead during the critical periods of brain development.

•The manifestations of lead poisoning are nonspecific, and the vast majority of children may be asymptomatic and diagnosed only by routine screening of blood lead levels (BLL).

•Research done during the 1970s and 1980s, mainly in the USA, revealed that the effect of lead on the CNS in children occurs at lead levels which were previously considered "safe". Thus, there was a gradual decrease in the BLL that require further follow-up and intervention (the so-called: "action level").

•The epidemic proportions of childhood lead poisoning pose a challenge to health authorities, and have triggered a major worldwide public health campaign.

•Most victims of lead poisoning are children with low socioeconomic status, such as inner city dwellers.

<<NOTE TO USERS: Insert an overview of the prevalence of lead poisoning in your region/location here, if possible.>>

•A multi-level strategy of prevention, elimination of the sources of exposure, public health education, national screening programmes, regulations, chelation therapy and comprehensive, long-term follow-up, is required to eliminate this serious environmental health problem.
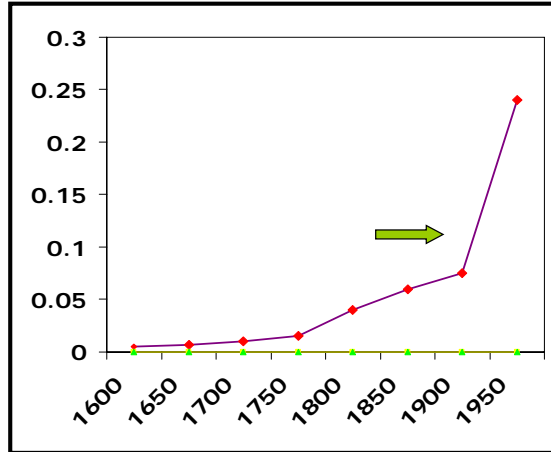
*Ref:*Nriagu. A history of global metal pollution. *Science,* 1996, 272:223.

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EVIDENCE OF INCREASED ACCUMULATION OF LEAD OVER THE YEARS

Deposition of lead in Greenland ice (μg/kg)

Sharp increase since 1940 attributed mainly to combustion of lead alkyl additives in petrol

The deposition of lead in Greenland ice (microg/kg) has increased sharply since 1940; this is attributed mainly to the combustion of lead alkyl additives in petrol.

WHO ESTIMATES

❖ *12 million* **children in developing countries suffer from some form of permanent brain damage from lead poisoning**

❖ *Hundreds of millions* **of children and pregnant women are exposed to different sources of lead**

❖ **Worldwide, about 3.5% of minor mental retardation is attributable to lead poisoning**

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Children are the major victims of lead poisoning. Current estimates from WHO are that about 15 to 18 million children in developing countries may suffer permanent brain damage due to lead poisoning.

Ref:

•Prüss-Üstün. Lead exposure. In: Ezzati eds. *Comparative quantification of health risks.* Geneva, World Health Organization, 2004.

<<READ SLIDE.>>

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CHILDREN AT HIGHEST RISK

❖ **High exposure:**
- **Hand-to-mouth activity**
- **Pica**
- **Repeated ingestion of paint chips**

❖ **High absorption**
- **Fraction of absorption is 40% in children compared with 10% in adults**

❖ **High susceptibility**
- **At the critical periods of brain development**
- **Immature blood–brain barrier**

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Children (beginning prenatally) are at the highest risk for lead poisoning because they have the highest exposure, highest absorption, increased penetration of the blood–brain barrier and a developing nervous system that is most sensitive to damage resulting from this heavy metal pollutant.

Lead Poisoning in Children

SOURCES OF EXPOSURE TO LEAD

Major sources:

- **Old paint in homes**
- **Petrol additive**
- **Drinking-water from old pipes**
- **Contaminated dust and soil**
- **Industrial: smelters, battery recycling...**
- **Ceramic glazes**
- **Improper de-leading or renovation of old houses**

WHO

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Lead is a heavy metal that cannot be created or destroyed.

It has NO role in the human body and is toxic.

It has been released into the environment increasingly with industrialization and most dramatically, as seen on an earlier slide, with intense industrial development.

Most of the lead in the environment today is anthropogenic in origin.

Major sources of exposure in children are listed on the slide:

<<READ SLIDE.>>

•Because lead is a heavy metal with a low melting point, it has been used for toys, water pipes, pottery, solder and other objects.

•Due to its virtues as a stable compound and lustre, it has been utilized extensively as a paint additive (e.g. in houses and in the printing industry).

•As a heavy metal, it is used for gunshot.

•Tetraethyl lead has been extensively used as a petrol additive.

•Improper de-leading of homes and/or renovation of old houses painted with paints that have a high lead content, can result in dangerous exposures of children to lead.

The George Foundation in India (www.tgfworld.org/lead.html) has defined the six major sources of exposure to lead for children worldwide as:

- petrol additive;

- food-can solder;

- lead-based paints;

- ceramic glazes;

- drinking-water systems; and

- cosmetics and folk remedies.

<<NOTE TO USERS: If possible insert here the major sources of lead exposure in your area.>>

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SOURCES OF EXPOSURE TO LEAD

Other sources:

- **Children of lead workers**
- **Cosmetics**
- **Tattoos**
- **Traditional remedies and "health food"**
- **Consumer products: jewellery, wax crayons, candle wicks**

WHO

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<<READ SLIDE>>

•The classical occupational exposures to lead were the triple P's: painter, printer, plumber (NB: the origin of this word is ***plumbum*** = lead in Latin).

•Other occupations connected with exposure to lead include: pottery workers, solderers, welders, battery makers, glass makers, gunshot makers, jewellers, pipe cutters, lead burners and smelters, and policemen who stand for long hours in heavy traffic.

•Another important source of exposure in Canada, for instance, is consumer products that are often marketed towards children such as costume jewellery: toxic if a child sucks on it, wax crayons: toxic if eaten, candle wicks: toxic if inhaled while burning. There have been other incidents of lead dust on mini blinds used as window coverings and on artificial Christmas trees (*Dr. I. Buka, Paediatric Environmental Health Specialty Unit, Misericordia Children's Health Centre, personal communication*).

TRADITIONAL LEAD SMELTER, ARNOLDSTEIN, AUSTRIA
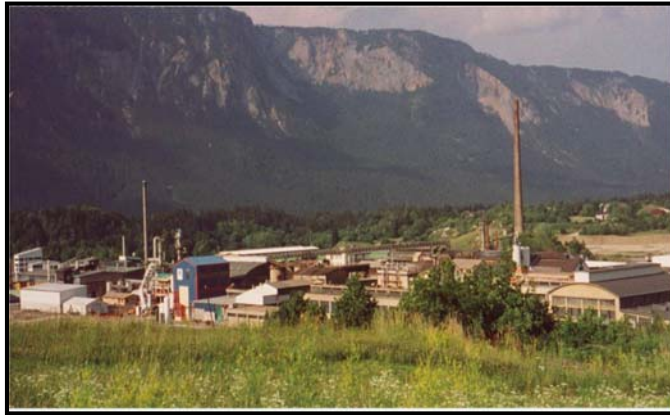
A large lead smelter and a lead recycling plant that contributed to high lead exposure in the area - *Drasch, 2000*

Airborne lead from smelting and industrial smokestacks as well as fumes from burning leaded gas are responsible for the contamination of air and soil. This picture represents a "success story" where lead emissions were reduced and as a result, the body burden of the local population also fell.

Drasch G, Roider G, Boese-O´Reilly S, Feenstra O, Sample H. Decrease of lead burden of a population in the vicinity of a lead smelter in Arnoldstein/Austria by successful site renovation. *Umweltmedizin in Forschung und Praxis,* 2000, 5:233.
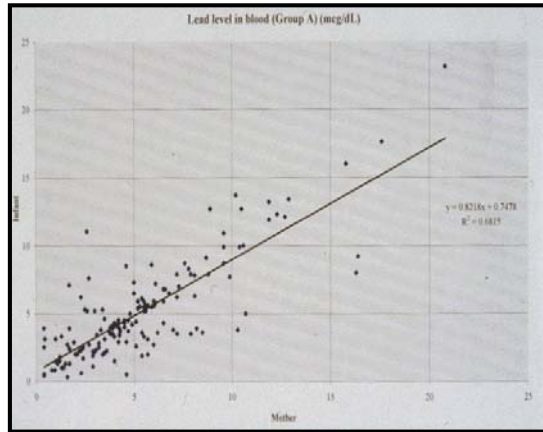
Picture used with permission.

PAEDIATRIC ROUTES OF EXPOSURE (1)

Prenatal

❖ Lead crosses the placenta

❖ Fetal/maternal ratio: 0.9

❖ Graph with data of maternal-newborn (cord blood) blood lead-level pairs

Lead level in blood (Group A) (mcg/dL)

Adapted by Dr. Amitai from: Amitai, IMAJ (1999) 1: 250

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Exposure to lead occurs prenatally, and after birth, by ingestion and inhalation of lead from different sources.

Prenatal exposure is determined by maternal body burden of lead.

Lead can be mobilized from maternal bone during pregnancy and readily crosses the placenta. This slide summarizes data on 70 mother–newborn pairs in Israel, where lead level was measured both in a blood sample from the mother at delivery, and from the cord blood, representing the exposure of the newborn during pregnancy.

There was a strong correlation ($r2 = 0.68$) between the blood lead level in the mothers and their newborns. In average, the newborns' blood lead levels were about 90% of that of their mothers (fetal/maternal ratio of 0.9).

<<READ SLIDE.>>

Ref:

•Amitai. Prenatal lead exposure in Israel: an international comparison. *Israel Medical Association Journal,* 1999 1:250.

Lead Poisoning in Children

PAEDIATRIC ROUTES OF EXPOSURE (2)

Ingestion
- ❖ Non-nutrient ingestion
- ❖ Contaminated food/water
- ❖ Minimal risk from breast milk

Inhalation
- ❖ Polluted air
- ❖ Gas sniffing

www.epa.gov/region02/health/leadpoisoning.htm

Postnatal exposures occur by ingestion and inhalation.

In areas where lead has been removed from petrol, ingestion is the main route of exposure.

Lead passes into breast milk (only the plasma fraction). Heavily exposed mothers may have breast milk that contains significant amounts of lead, but this is generally no longer a problem.

Main route of exposure is INGESTION, from food, water and non-nutrient ingestion.

There are many sources of lead exposure of children (see slide No. 12). One of the most dangerous sources for infants and toddlers is deteriorated paint in old houses (for example, in the US, in houses built before 1960). The contaminated paint flakes may be accessible in the floor, walls, windowsills and porches and may also be found in playgrounds. The particular problem of lead exposure during improperly conducted residential de-leading will be described later.

Picture: US Environmental protection Agency:
www.epa.gov/region02/health/leadpoisoning.htm
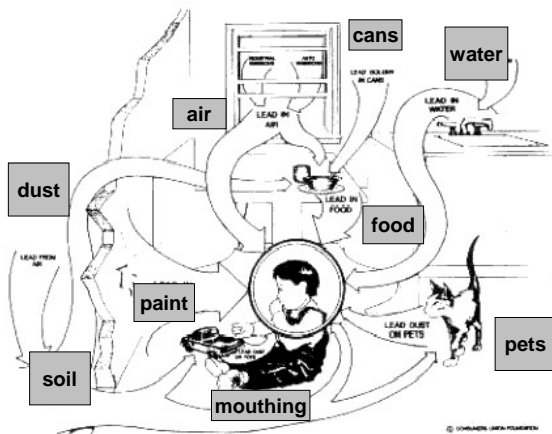
Paediatric exposures are complex and multiple as is summarized in this illustration from Guzelian, *Similarities and differences between children and adults.* ILSI, 1992. Lead can contaminate water, air, soil, dust and food. Children live low to the ground and engage in behaviours that increase their contact with potentially lead-contaminated areas in the home such as floors and windowsills at "toddler level".

Picture used with permission from International Life Sciences Institute.

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Lead Poisoning in Children

TOXICOKINETICS

LEAD METABOLISM

ABSORPTION — DISTRIBUTION — ELIMINATION
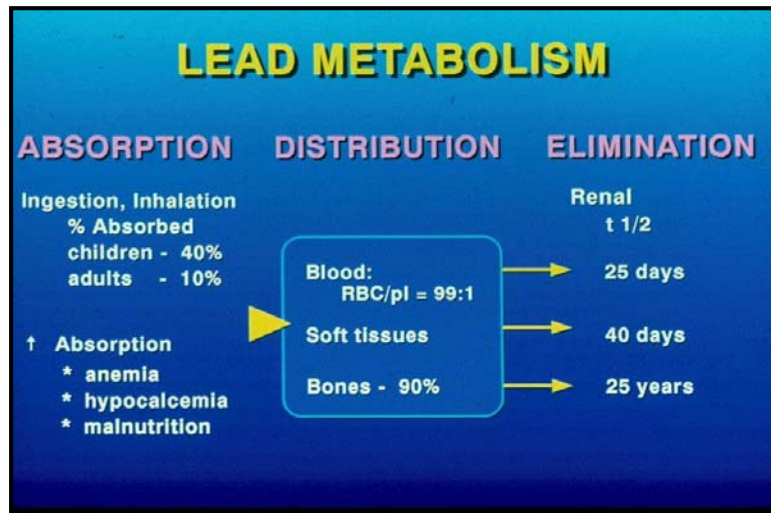
Small children take in lead by inhalation (up to 70% of lead is absorbed from the lungs) and by ingestion (up to 40–70% lead is absorbed from the gastrointestinal tract). Pregnant women can also absorb up to 70% of an oral lead dose, thus presenting high blood lead levels to the fetus.

Lead metabolism is complex and varies significantly with age.
This summary slide is followed by more detailed slides.
Lead absorption depends on the following:
•Particle size: if less than 1 micron, 70% is absorbed from the lungs.
•Age: 40–70% is absorbed in the gastrointestinal tract in young children, and 10 to 20% in adults.
•Absorption is enhanced by anaemia, low levels of iron, calcium and zinc, and acidic food.

Once absorbed, distribution follows a three-compartment model:
•first blood, then
•soft tissues, including liver kidney and brain.
•in chronic exposure the main deposits (90%) are in the bone, with very slow elimination.
Elimination is mainly through the urine (see details in the following two slides).

Ref: Ellenhorn MJ, Barceloux DG. *Medical toxicology; diagnosis and treatment of poisoning.* Elsevier, 1988.

•US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR). *Lead toxicity. Case Studies in Environmental Medicine. Course SS3059.* Revised October 2000 *(www.atsdr.cdc.gov/HEC/CSEM/lead/lead.pdf).*

TOXICOKINETICS: BIOTRANSFORMATION

❖ **Organic lead**
- Metabolized in the liver

❖ **Inorganic lead**
- No biotransformation
- Adults retain 1% of absorbed dose
- Children up to 2 years retain 1/3 absorbed dose

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<<READ SLIDE.>>

Emphasize the difference between absorption and retention rates in adults and children.

Children absorb as much as much as 40–70% of the gastrointestinal dose and retain 1/3, but adults absorb only 10% and retain only 1%. This is a dramatic example of the differences in metabolism and toxic risk between adults and children.

Note that tetraethyl lead readily permeates the skin and causes occupational disease. Adolescents can be exposed when "sniffing" petrol and can have elevated lead levels when the tetraethyl lead is converted to inorganic lead in the liver.

Ref:

•Ellenhorn. *Medical toxicology: diagnosis and treatment of poisoning.* Elsevier, 1988.

•US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR). *Lead toxicity. Case Studies in Environmental Medicine. Course SS3059.* Revised October 2000 *(www.atsdr.cdc.gov/HEC/CSEM/lead/lead.pdf).*

TOXICOKINETICS: DISTRIBUTION & ELIMINATION

❖ **Blood: distribution to other tissues**

❖ **Soft tissues: liver > kidneys > lungs > brain**
  • Higher penetration into CNS in younger children

❖ **Mineralizing tissues: bones >> teeth**
  • Mobilization increased during pregnancy and lactation
  • Exacerbated by calcium deficiency

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Distribution occurs according to a three-compartment model (blood, soft tissues, bone).

Blood:- Lead enters the blood and is distributed to other tissues.

-Its half-life is about 28 days.

-99% is in the red blood cells (RCB) and only 1% in plasma.

-Some is eliminated via the kidney.

Soft tissues:

Soft tissue deposition is highest in liver and lowest in the brain, but CNS penetration is higher the younger the child. Lead is excreted unchanged by filtration in the kidneys, but once in the bone compartment, the half-life can be decades. Lead crosses the placenta and can be mobilized during pregnancy and lactation especially if the mother is calcium deficient.

-Half-life is 40 days (in adults).

-Elimination is via the kidneys.

Mineralizing tissues – bones and teeth:

-Half-life is about 25 years.

-The body burden in bones and teeth is 73% in children and 94% in adults.

-These are "inert" compartments that become "labile" during pregnancy and lactation, and when there is a tendency to acidosis. In cases of calcium deficiency, the absorption of lead and fixation in the bone increases.

<<NOTE TO USER: See slide 13, which illustrates toxicokinetics.>>

Ref: US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. *Lead toxicity. Case Studies in Environmental Medicine. Course SS3059.* Revised October 2000 *(www.atsdr.cdc.gov/HEC/CSEM/lead/lead.pdf).*

MECHANISM OF TOXICITY

❖ **No role for lead in the human body!**

❖ **Several mechanisms of toxicity**
- Interferes with Ca and Fe
- Forms complexes with sulfhydryl groups and others
  ⟹ Disrupts enzymes ⟹ multisystem effects

❖ **Effect varies according to:**
- Dose
- Timing and duration of exposure
- Age
- Health and nutritional status

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Lead interferes with calcium and iron in the body.

It forms complexes with sulfhydryl groups and other ligands in the body, disrupts enzyme systems, and leads to multisystem effects.

The degree of damage varies according to the dose, timing, duration of exposure and age of the child.

The effects of exposure may be made more severe by nutritional deficiencies and poor general health.

SYMPTOMS AND SIGNS: A WIDE SPECTRUM

- ❖ **Central and peripheral nervous system ***
- ❖ **Gastrointestinal**
- ❖ **Blood**
- ❖ **Skeletal – reduced stature ****
- ❖ **Cardiovascular – hypertension**
- ❖ **Kidney – proteinuria (Fanconi)**
- ❖ **Hearing – reduced**

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Lead is toxic to the haematopoietic system, the nervous system, the kidneys and the reproductive system. It is a powerful neuroteratogen as well. Signs and symptoms vary with dose, and at a given dose by age.

<<READ SLIDE>>

* "Wrist drop" is a pathognomonic sign for lead poisoning. It is a manifestation of peripheral neuropathy and motor weakness, there is weakness of the extensor muscles of the hand, resulting in "wrist drop".

** For every 10 microgram/dL increase in BLL, there is an expected reduction in height of 1 cm.

Lead Poisoning in Children

SYMPTOMS AND SIGNS: A WIDE SPECTRUM

❖ **CNS:**   - **Hyperactivity, restlessness**

                     - **Behavioural disturbances**

                     - **Learning disabilities (low score in cognitive tests) *****

                     - **BLL > 70 (rare): headache, lethargy, coma, seizures**

❖ **PNS**   - **Neuropathy (in adults!)**

❖ **GI :**   - **Anorexia, vomiting, constipation**

                     - **Abdominal pain ******

❖ **Blood:**   - **Anaemia, basophilic stippling**

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<<READ SLIDE>>

*** For each 1 microgram/dL elevation in BLL, there is a reduction of about 0.25–0.5 point in cognitive score.

**** Abdominal pain occurs with BLL > 45 micrograms/dL: pains are colicky (porphyria like).

SYMPTOMS AND SIGNS: BLOOD LEAD LEVELS
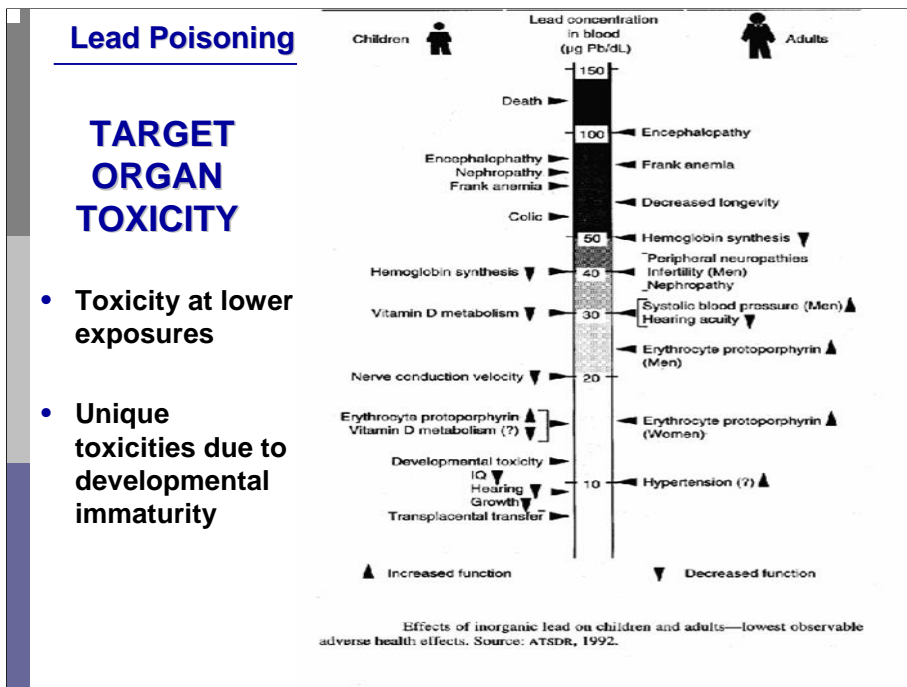
❖ **For each 1 μg/dL increase the IQ decrease is 0.25–0.5**

❖ **For each 10 μg/dL increase: height decreases by 1 cm**

❖ **BLL > 45 μg/dL: abdominal pain (colic, porphyria-like)**

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<<READ SLIDE.>>

Lead Poisoning

TARGET ORGAN TOXICITY

- Toxicity at lower exposures
- Unique toxicities due to developmental immaturity

Effects of inorganic lead on children and adults—lowest observable adverse health effects. Source: ATSDR, 1992.

Lead poisoning can be acute (or rather acute-on-chronic) and more often chronic, due to high exposure levels.

•Children experience toxic effects at lower levels of exposure than adults.

•Children experience unique toxicities different from those of adults, due to developmental immaturity.

The signs and symptoms include: abdominal pain, encephalopathy, seizures, coma and death.

Poisoning may also be much more subtle, leading to metabolic abnormalities and anaemia, but no overt symptomatology.

<<READ SLIDE>>

Ref:

•US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry. *Lead toxicity. Case Studies in Environmental Medicine. Course SS3059.* Revised October 2000 *(www.atsdr.cdc.gov/HEC/CSEM/lead/lead.pdf).*

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Lead Poisoning in Children

X-RAY OF RECENT LEAD INGESTION

A plain (flat) abdominal film of a toddler with a recent ingestion of lead-containing paint chips

Lead particles are evident as radio-opacities

Courtesy of John Graef, MD, Boston Children's Hospital

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The diagnosis of lead poisoning requires a high index of suspicion and it is confirmed by measurement of blood lead level.

Plain X-Ray of the abdomen can confirm the source of recent lead paint chip ingestion.

High-dose poisoning occurs in children when they ingest lead from sources such as leaded paint chips, toys or mini-blinds painted with lead paint or when they eat food from ceramic pots and jars with lead-containing glazes.

<<READ SLIDE.>>

BASOPHILIC STIPPLING

❖ **Classical laboratory sign known since 1899**

❖ **Inclusions of aggregated ribosomes found only in the red blood cells**

❖ **Unspecific and inconstant**
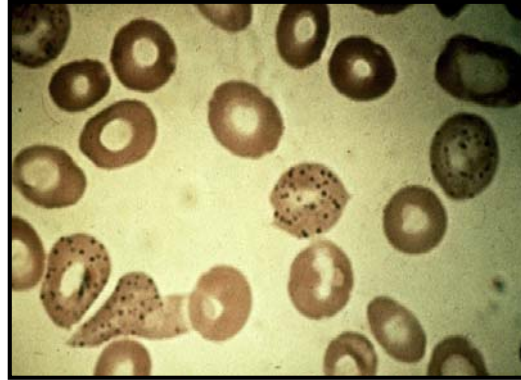
Courtesy of John Graef, MD, Boston Children's Hospital

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<<READ SLIDE>>

Basophilic stippling of red blood cells (BSC) has been noted in lead intoxication since 1899 and has been considered a classic laboratory sign of lead poisoning since that time.

BSC are inclusions of aggregated ribosomes found only in the red blood cells and may be confused with siderotic (iron) granules, Heinz bodies or even reticulocytes.

BSC are an inconstant finding in lead intoxication.

In a review of peripheral blood smears from 1000 consecutive internal medicine patients, we found BSC in 27%. These occurred in a variety of malignant, rheumatological, haematological, cardiovascular, and other diseases, frequently with associated anaemia.

BSC may even be found in a small percentage of normal people; thus, it must be emphasized that BSC is a nonspecific finding. Furthermore, BSC has been replaced by measurement of blood lead (since the 1940s) and zinc protoporphyrin (since the 1970s) levels for biological monitoring of lead-exposed workers.
Ref:

•Cheson. Basophilic stippling of red blood cells: a non-specific finding of multiple etiology. *Am J Ind Med,* 1984, 5:327.

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Lead Poisoning in Children

EFFECTS OF LEAD ON HAEM SYNTHESIS

Fig. 3.—Biosynthesis of heme and the abnormalities in lead poisoning.

Courtesy of John Graef, MD, Boston Children's Hospital
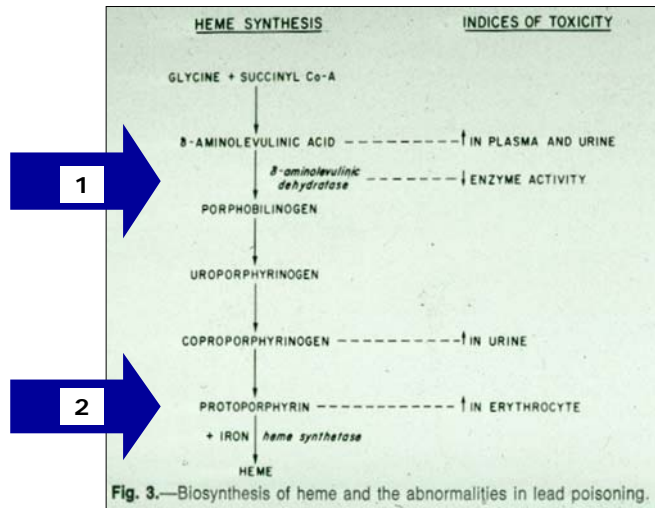
Currently, the measurement of blood lead levels is available and affordable. This is the preferred diagnostic tool, but other laboratory techniques were used successfully in the past. They measure precursors of haem synthesis which build up in cases of lead poisoning.

This scheme shows how lead interferes at the various stages of haem synthesis. Two screening tests for exposure to lead are based on this pathway.

1) The activity of the enzyme delta aminolaevulinic acid dehydratase (ALAD) is impaired, thus reduced ALAD could serve as an indicator of lead exposure. The threshold for this effect is very low (BLL of 5 to 10 μg/dL).

2) The activity of the enzyme haem synthetase is impaired at BLL > 20 μg/dL, causing elevation of its substrate – protoporphyrin in the RBC (erythroprotoporphyrin = EPP or ZPP). This may explain the porphyria-like symptoms such as abdominal colic, noted at high BLLs.

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THE "LEAD LINE" SIGN

Abnormally heavy mineralization of the growth plate of long bones in X-ray

The width and density of "lead lines" reflect chronic exposure

Courtesy of John Graef, MD, Boston Children's Hospital

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<<READ SLIDE>>

Lead lines are a sign of significant chronic exposure to lead.

The threshold for the occurrence of "lead lines" is a BLL of about 45 μg/dL.

Bone is the long-term "sink" for lead and builds up at areas of high bone metabolism during growth.

This X-ray shows heavy "lead lines" at the distal part of the femur, and the proximal side of the tibia and fibula in a child.

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Changes in Blood Lead Level, FEP and Lead Deposition in Bone ("Lead Lines") Over Time
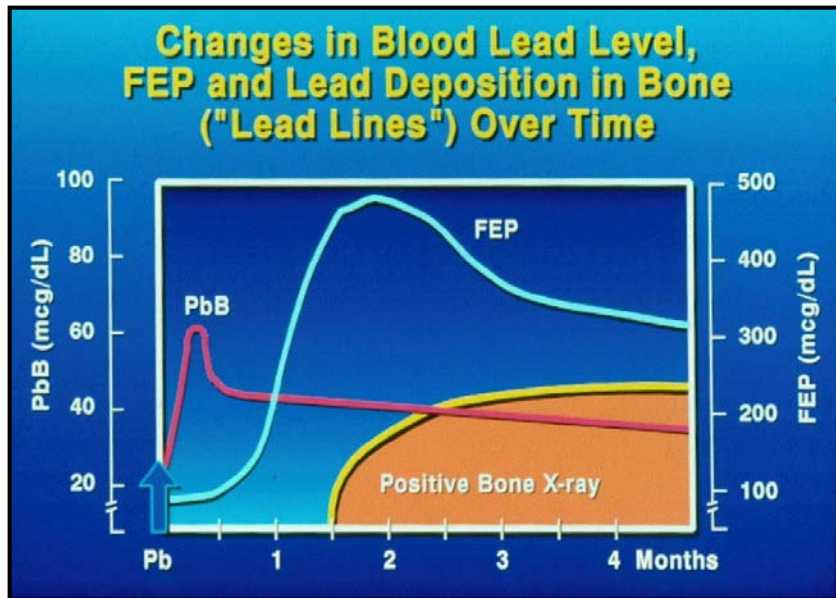
This figure shows the time line for distribution of lead after a single exposure in the blood, and the evolution over time of the elevation in FEP (free erythroprotoporphyrin) and the occurrence of "lead lines".

The first elevation in FEP lags 2–3 weeks behind the initial rise in blood lead levels (BLL), because it affects only the newly formed red blood cells (RBC) and reflects exposure to lead over the full life-cycle of the RBC (120 days). Thus, a prolonged elevation of BLL is needed for maintaining high erythroprotoporphyrin.

About 6–8 weeks of lead exposure > 45 μg/dL is required to produce "lead lines".

LABORATORY STUDIES

BLL (blood lead levels) by atomic absorption and/or electrochemical technique	Action level: > 10 µg/dL Chelation: > 45 µg/dL
Zinc protoporphyrin (ZPP) or erythroprotoporphyrin (EPP)*	BLL > 20 µg/dL
Aminolaevulinic acid dehydratase (ALAD)	BLL > 5–10 µg/dL
Pb in bone	• "Lead lines" (> 45 µg/dL over 2 months)** • X-ray fluorometry (XRF)
Pb in urine	After chelation ***

Because the clinical signs are nonspecific, the major diagnostic tool is monitoring of blood lead levels (BLL) in addition to another laboratory marker, such as zinc protoporphyrin (ZPP) or aminolaevulinic acid dehydratase (ALAD).

Because 99% of lead in blood is in red blood cells (RBC), ALWAYS collect drawn blood in test tubes with anticoagulant.

*Abnormal (ZPP) levels are > 35 µg/dL (0.65 µmol/L).

** Lead lines are a sign that a significant lead exposure has been continuing for some time. The threshold for the occurrence of "lead lines" is a BLL of about 45 µg/dL, and it takes at least 4–6 weeks of exposure to manifest these changes.

*** Lead mobilization test: after injection of 500 mg/M2 CaNa2-EDTA, urine lead/dose of EDTA > 0.6, in urine collected over 6–8 hours.

Bone is the long-term "sink" for lead and builds up at areas of high bone metabolism during growth. The actual radio-lucency does not represent lead deposition. It is an expression of heavy mineralization (calcification).

LEAD EXPOSURE AND TOXICITY

Distal causes	Proximal causes	Physical and pathophysical causes	Outcome
Leaded pipes for water supplies	Lead concentration in water	Body burden of lead, e.g. Blood lead	Neurological effects
Leaded paints	Lead concentration in air and dust		IQ effects
Leaded gasoline; traffic density; industrial activity	Lead in food		Learning disabilities
Leaded cans for food and drinks	Occupational lead exposure		Anaemia
Lead in cosmetics and folk remedies			Violent behavior
			Other effects

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To recapitulate, the pathways of lead from the primary sources to the child's body systems and its effects are described in this slide:

•"Distal causes", or the potential primary sources, are: leaded water-pipes, paint, petrol additive, cans and cosmetics.

•"Proximal causes", or vectors which convey lead from the source to the body, are: water, air, dust and food.

•"Physical causes" are the direct effects of lead, once absorbed, on body systems.

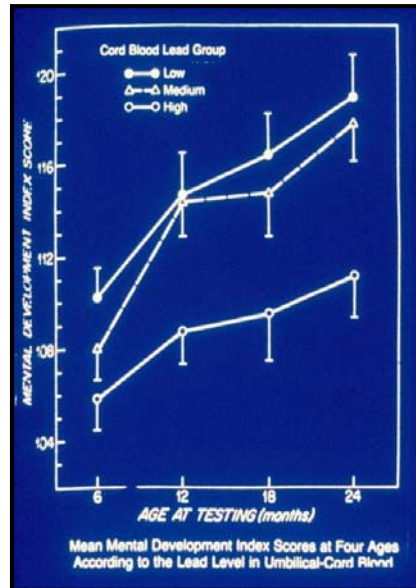•"Outcomes" are the diseases and impairments caused by lead.

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IMPORTANCE OF SCREENING

❖**Lead poisoning is often SUBCLINICAL**

❖**Has NONSPECIFIC symptoms**

❖**Diagnosis relies on laboratory screening**

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•Lead poisoning is usually chronic or subacute.

•Acute poisoning is now quite rare in most countries, but may still occur, after massive exposure.

•In such a case, the child is comatose, with signs of increased intracranial pressure (lethargy, vomiting) and may have bradycardia and seizures.

•Some children may present with abdominal colic, constipation, anaemia and learning disabilities.

•In most industrialized countries, where lead poisoning is usually mild-to-moderate and chronic, poisoned children are identified by screening BLL and not by their clinical manifestations!

CORD BLL AND MENTAL DEVELOPMENT INDEX

Cord Blood Lead Group
- ●—● Low
- △—△ Medium
- ○—○ High

MENTAL DEVELOPMENT INDEX SCORE

AGE AT TESTING (months)

Mean Mental Development Index Scores at Four Ages According to the Lead Level in Umbilical-Cord Blood

Bellinger, N Eng J Med. (1987)316:1037

30

When lead poisoning begins in the womb, the most critical system is the central nervous system of the fetus.

This article, published in 1987, was essential in increasing understanding of the potential for lead to cause damage at levels much lower than those that cause overt symptoms. It showed a high correlation between blood lead level in the umbilical cord and mental development index at 2 years of age.

Ref:

•Bellinger. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. *N Engl J Med,* 1987, 316:1037.

In a prospective cohort study of 249 children from birth to two years of age, we assessed the relation between prenatal and postnatal lead exposure and early cognitive development. On the basis of lead levels in umbilical-cord blood, children were assigned to one of three prenatal-exposure groups: low (less than 3 micrograms per decilitre), medium (6 to 7 micrograms per decilitre), or high (greater than or equal to 10 micrograms per decilitre). Development was assessed semiannually, beginning at the age of six months, with use of the Mental Development Index of the Bayley Scales of Infant Development (mean +/- SD, 100 +/- 16). Capillary-blood samples obtained at the same times provided measures of postnatal lead exposure. At all ages, infants in the high-prenatal-exposure group scored lower than infants in the other two groups. The estimated difference between the overall performance of the low-exposure and high-exposure groups was 4.8 points (95 per cent confidence interval, 2.3 to 7.3). Between the medium- and high-exposure groups, the estimated difference was 3.8 points (95 per cent confidence interval, 1.3 to 6.3). Scores were not related to infants' postnatal blood lead levels. It appears that the fetus may be adversely affected at blood lead concentrations well below 25 micrograms per decilitre, the level currently defined by the Centers for Disease Control as the highest acceptable level for young children. Picture: Copyright (1987) Massachussets Medical Society, All rights reserved. Used with permission.

Lead Poisoning in Children

ASSOCIATION BETWEEN DENTINE LEAD LEVEL AND CLASSROOM BEHAVIOUR

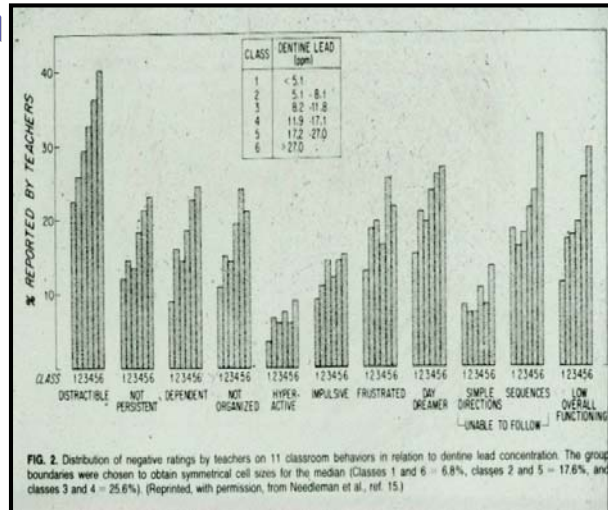| CLASS	DENTINE LEAD (ppm)
1	< 5.1
2	5.1 - 8.1
3	8.2 - 11.8
4	11.9 - 17.1
5	17.2 - 27.0
6	> 27.0

FIG. 2. Distribution of negative ratings by teachers on 11 classroom behaviors in relation to dentine lead concentration. The group boundaries were chosen to obtain symmetrical cell sizes for the median (Classes 1 and 6 = 6.8%, classes 2 and 5 = 17.6%, and classes 3 and 4 = 25.6%). (Reprinted, with permission, from Needleman et al., ref. 15.)

Needleman, N. Engl J Med. (1979);300(13):689.

31

Deficits in psychological and classroom performance of children with elevated lead levels in dentine was among the first evidence that low levels of lead intoxication caused loss of intellectual capacity and changes in behaviour.
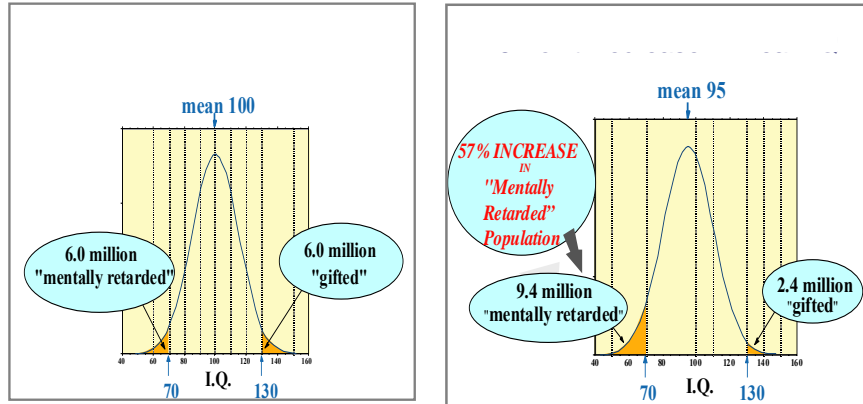
Ref: Needleman. Deficits in psychological and classroom performance of children with elevated dentine lead levels. *N Engl J Med,* 1979, 300:689.

To measure the neuropsychological effects of unidentified childhood exposure to lead, the performance of 58 children with high and 100 with low dentine lead levels was compared. Children with high lead levels scored significantly less well on the Wechsler Intelligence Scale for Children (Revised) than those with low lead levels. This difference was also apparent on verbal subtests, on three other measures of auditory or speech processing and on a measure of attention. Analysis of variance showed that none of these differences could be explained by any of the 39 other variables studied. Also evaluated by a teachers' questionnaire was the classroom behaviour of all children (2146 in number) whose teeth were analysed. The frequency of non-adaptive classroom behaviour increased in a dose-related fashion to dentine lead level. Lead exposure, at doses below those producing symptoms severe enough to be diagnosed clinically, appears to be associated with neuropsychological deficits that may interfere with classroom performance.

Lead Poisoning in Children

SIGNIFICANCE OF 5 POINT IQ REDUCTION: THE "WEISS EFFECT"

mean 100 — 6.0 million "mentally retarded" — 6.0 million "gifted" — 70 — I.Q. — 130

mean 95 — *57% INCREASE IN "Mentally Retarded" Population* — 9.4 million "mentally retarded" — 2.4 million "gifted" — 70 — I.Q. — 130

www.prwventingharm.org/execsum.html
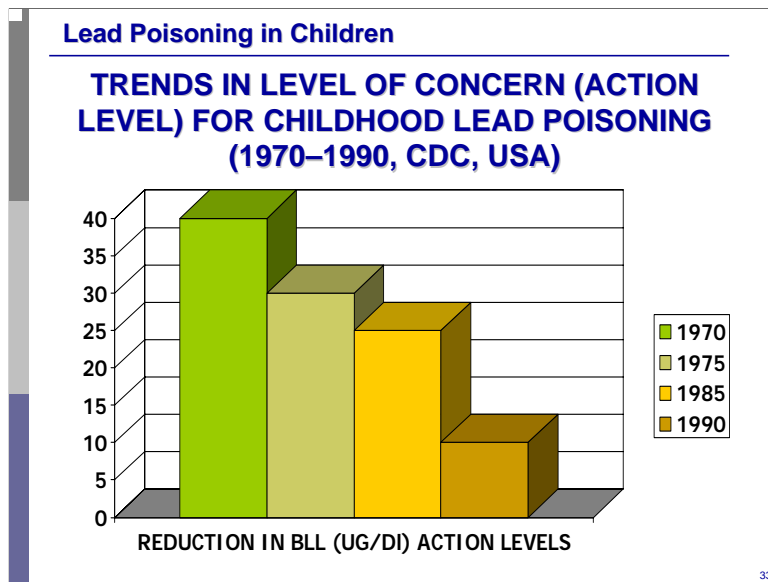*Schettler, GBPSR, 2000*

32

A 5-point loss in IQ might not affect the ability of an individual to live a productive life. But if that loss is experienced by an entire population, the implications for that society could be profound.

Bernard Weiss, a behavioural toxicologist at the University of Rochester, USA, examined the societal impact of seemingly small losses of intelligence. Imagine an unaffected population numbering 260 million people (such as that of the USA) with an average IQ of 100 and a standard deviation of 15 (left-hand graph). In that population there would be 6 million people with IQs above 130 and 6 million below 70.

A decrease in average IQ of 5 points would shift the distribution to the left (right-hand graph). The number of people scoring above 130 would decline by 3.6 million while the number below 70 would increase by 3.4 million.

Picture adapted from Schettler. *In harm' s way.* GBPSR, 2000. *Used with permission.*

Lead Poisoning in Children

TRENDS IN LEVEL OF CONCERN (ACTION LEVEL) FOR CHILDHOOD LEAD POISONING (1970–1990, CDC, USA)

REDUCTION IN BLL (UG/DI) ACTION LEVELS

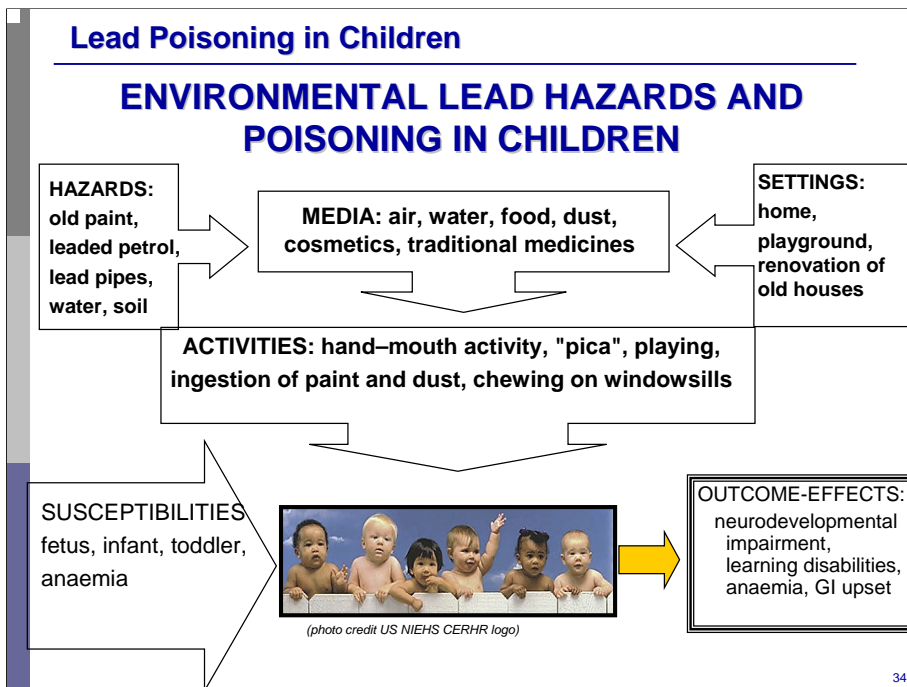Legend: 1970, 1975, 1985, 1990

33

A continued reduction of the level of concern, called the "action level", for childhood lead poisoning by the CDC, occurred during the years from 1970 to 1990. This reduction followed the accumulating scientific evidence for the noxious effects of lead exposure at BLLs that had previously been considered safe. Therefore, the approach to children exposed to lead and asymptomatic lead poisoning became more aggressive over time, according to the changing definitions of the "action level." The most recent analysis of intellect and BLLs suggests that there are important negative impacts even below 10 μg/dL,

Refs: cdc.gov/wonder/prevguid/p0000029/p0000029.asp

•Canfield. Intellectual impairment in children with blood concentrations below 10 micrograms per deciliter. *N Engl J Med,* 2003, 348:1517.

Despite dramatic declines in children's blood lead concentrations and a lowering of the Centers for Disease Control and Prevention's level of concern to 10 microg per decilitre (0.483 micromol per litre), little is known about children's neurobehavioural functioning at lead concentrations below this level. We measured blood lead concentrations in 172 children at 6, 12, 18, 24, 36, 48 and 60 months of age and administered the Stanford-Binet Intelligence Scale at the ages of 3 and 5 years. The relation between IQ and blood lead concentration was estimated with the use of linear and nonlinear mixed models, with adjustment for maternal IQ, quality of the home environment, and other potential confounders. The blood lead concentration was inversely and significantly associated with IQ. In the linear model, each increase of 10 microg per decilitre in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ (P = 0.004), whereas for the subsample of 101 children whose maximal lead concentrations remained below 10 microg per decilitre, the change in IQ associated with a given change in lead concentration was greater. When estimated in a nonlinear model with the full sample, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 microg per decilitre. Blood lead concentrations, even those below 10 microg per decilitre, are inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations. These findings suggest that more US children may be adversely affected by environmental lead than previously estimated.

ENVIRONMENTAL LEAD HAZARDS AND POISONING IN CHILDREN

HAZARDS:
old paint,
leaded petrol,
lead pipes,
water, soil

MEDIA: air, water, food, dust, cosmetics, traditional medicines

SETTINGS:
home,
playground,
renovation of
old houses

ACTIVITIES: hand–mouth activity, "pica", playing, ingestion of paint and dust, chewing on windowsills

SUSCEPTIBILITIES
fetus, infant, toddler, anaemia

(photo credit US NIEHS CERHR logo)

OUTCOME-EFFECTS:
neurodevelopmental
impairment,
learning disabilities,
anaemia, GI upset

34

In this summary slide, we see the complexity of lead poisoning. Children come into contact with lead contained in air, in water and on surfaces in their settings in the home, school and playgrounds. They breathe in the air and ingest lead intentionally or unintentionally. Because of their developmental immaturity, they absorb it very efficiently, from fetal life (where exposure is from the maternal body burden of lead through the placenta) through the preschool years, and the CNS and other critical systems are damaged in a dose–response related way. As with any poisoning, the effects can be acute with overt symptoms, but they can also be subtle. The ubiquitous nature of lead as an environmental contaminant makes it possible for whole populations of children to be affected causing society-wide loss in intellectual capacity.

The next slides will discuss treatment and prevention of exposure.

Lead Poisoning in Children

CATEGORIES OF BLL (μG/DL) FOR ACTION (CDC)

LEVELS	ACTION
10–14	- repeat BLL within 3 months - evaluate sources - education: cleaning, hands and mouth
15–19	- repeat BLL within 2 months - as above + referral to dept of health
20–44	- repeat BLL within 1 month - as above
> 45	- as above + CHELATION therapy
> 70	- IMMEDIATE HOSPITALIZATION - two-drug CHELATION

35

There is no question that children with overt symptoms of lead intoxication should be treated with hospital-based outpatient or inpatient chelation. Lower level, asymptomatic exposures are managed more conservatively. The scheme in this slide represents the current CDC recommendations according to blood lead levels.

<<READ SLIDE.>>

Ref:

•CDC Childhood Lead Poisoning Prevention Program *(www.cdc.gov/nceh/lead/lead.htm).*

TREATMENT (1)

❖**Complete assessment**

❖**Remove from source of exposure**

❖**Correct nutritional/iron deficiencies**

❖**Consider chelation**

36

The treatment of lead poisoning aims to reduce continuing harm from lead poisoning.

Most victims are in the preschool years and live in environments where lead exposure is ongoing. Therefore, any level of elevated blood lead must involve a complete assessment of the child including nutritional status, haematological and neurological status.

The source of exposure must be identified and removed, nutritional deficiencies corrected and the child should be evaluated for chelation therapy.

TREATMENT (2)

❖ **Education**
  • **Cleaning dust***
  • **Hand washing**

❖ **Abatement of lead source**
  • **Residential de-leading**

❖ **Long-term follow-up**

37

Eliminating exposure depends upon the source, but will always involve parental education, some form of abatement and long-term follow-up. The points in this slide pertain to lead poisoning from lead paint. Abatement of lead sources should be safe and careful. Different actions would be required if the exposure source were different.

* The importance and efficacy of thorough cleaning of the house is highlighted in the following abstract:

Ref: Ettinger. Assessment of cleaning to control lead dust in homes of children with moderate lead poisoning: treatment of lead-exposed children trial. *Environ Health Perspect,* 2002, 110:A773.

In this article we describe the assessment and control of lead dust exposure in the Treatment of Lead-exposed Children (TLC) Trial, a clinical trial of the effects of oral chelation on developmental end points in urban children with moderately elevated blood lead levels. To reduce potential lead exposure from settled dust or deteriorated paint during the drug treatment phase of the trial, the homes of 765 (98%) of the randomized children (both active and placebo drug treatment groups) were professionally cleaned. Lead dust measurements were made in a sample of 213 homes before and after cleaning. Geometric mean dust lead loadings before cleaning were 43, 29, 308, and 707 micro g/square foot in the kitchen floor, playroom floor, playroom windowsill, and playroom window well samples, respectively. Following cleaning, floor dust lead loadings were reduced on average 32% for paired floor samples (p < 0.0001), 66% for windowsills (p < 0.0001), and 93% for window wells (p < 0.0001). Cleaning was most effective for 146 homes with pre-cleaning dust lead levels above the recommended clearance levels, with average reductions of 44%, 74%, and 93% for floors (p < 0.0001), windowsills (p < 0.0001), and window wells (p < 0.0001), respectively. Despite these substantial reductions in dust lead loadings, a single professional cleaning did not reduce the lead loadings of all dust samples to levels below current federal standards for lead in residential dust. Attainment of dust levels below current standards will require more intensive cleaning and lead hazard reduction strategies.

CHELATING AGENTS

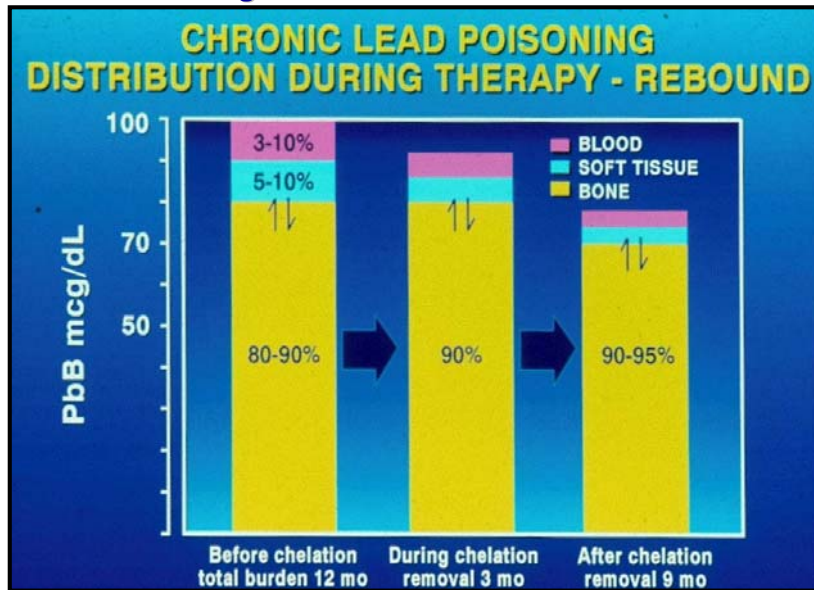| GENERIC	CHEMICAL	ABBREVIATION
Edetate disodium calcium	Calcium disodium ethylenediamine-tetracetate	$CaNa_2EDTA$
Dimercaprol	2,3-Dimercaptopropanol	BAL
D-Penicillamine	3-Mercapto-D-valine	D-Penicillamine
Succimer	Meso-2,3-dimercaptosuccinic acid	DMSA

38

Chelation can be effective at reducing the total lead body burden and is critical in managing acute toxicity, but it is generally not indicated for individuals with BLLs below 45 micrograms/dl. Common chelating agents are listed above. For more complete information on chelation, it is important to consult a local poison control clinic or medical personnel at a specialized lead clinic.

Dimercaprol (BAL) is no longer used, except for the rare cases of lead encephalopathy in children, in combination with EDTA.

D-penicillamine is no longer used.

The preferred chelating agent is succimer.

CHRONIC LEAD POISONING
DISTRIBUTION DURING THERAPY - REBOUND

100

3-10%
5-10%

BLOOD
SOFT TISSUE
BONE

PbB mcg/dL

70

50

80-90%   90%   90-95%

Before chelation
total burden 12 mo

During chelation
removal 3 mo

After chelation
removal 9 mo

39

Chelation is most effective at reducing the blood lead level which is in equilibrium with that in the soft tissue and the bone.

Bone lead is quite stable and will remain sequestered for years in nutritionally replete individuals.

Chelating agents can extract lead from blood and soft tissues, but not from the larger compartment of lead: i.e. the bones.

Therefore, after each course of chelation, there is a temporary reduction of BLL and lead in soft tissues, while the lead content in bone is unchanged. At this point there is redistribution of lead from the bones to the blood and soft tissues. This explains the "rebound" of BLL, which is reduced after chelation, then increases again, until the next chelation.

Because the efficacy of most chelating agents is higher when the BLL is high, it is more effective to give short courses of chelation, a few weeks apart, to allow time for the redistribution of lead from the bone to soft tissues and blood, from which it can be extracted by the next course of chelation.

Chelation has only a modest effect in reducing total body burden of lead. However, with repeated courses of chelation, the total body burden of lead is ultimately reduced. However, the value of reducing body burden in asymptomatic individuals is questionable since damage is likely to be irreversible.

Ref:

•Sanchez-Fructuoso. Lead mobilization during calcium disodium ethylenediaminetetraacetate chelation therapy in treatment of chronic lead poisoning. *Am J Kidney Dis,* 2002, 40:51.

CASE-STUDY (1)

❖ **2-year-old boy with hyperactivity and abdominal colic**

❖ **History: mother worked in an automobile repair shop, where the child played**

❖ **Exam: height and weight 10th percentile, short attention span, restlessness, delayed speech development, poor social skills**

40

<< NOTE TO USER: In this section, present case-studies which illustrate important local/regional sources of lead toxicity. Actual case-studies are always powerful.>>

This case study illustrates a classical example of a toddler with prolonged environmental exposure to lead, in this case from an occupational source related to an automobile repair shop. His mother was exposed there from the recycling of car batteries. She carried lead with her from the workplace on her dress and hands. This caused chronic lead exposure in her son. The impairment in growth and neurodevelopmental behaviour is a hint of the long duration of lead poisoning (several months).

Ref:

•ATSDR. *Case Studies in Environmental Medicine. Lead Toxicity,* 1992 *(available at: www.atsdr.cdc.gov/HEC/CSEM/lead/lead.pdf).*

An apparently normal 2-year-old becomes a hyperactive 5-year-old with disturbed hearing, hypochromic anemia, and abdominal pain

A father brings his 2-year-old boy into a pediatrician's office for a normal check-up on a Saturday in the late fall. The doctor examines the boy and proclaims him to be in fine physical health. The boy's growth and development indicators are standard for his age. From the father, the doctor learns that the boy's parents are divorced and that he generally lives with his mother and her parents. (The mother had to accompany her parents to her aunt's funeral this weekend and therefore could not make the appointment.) The doctor makes a note of this information.

Three years later… *Concerned that her child is hyperactive, the mother brings the same 5-year-old boy to your office (his previous pediatrician recently retired). At a parent-teacher conference last week, the kindergarten teacher said that the boy seems impulsive and has trouble concentrating, and recommended evaluation by a physician as well as by the school psychologist. The mother states that he has always seemed restless and easily distracted, but that these first 6 months in kindergarten have been especially trying. He has also complained recently of frequent intermittent abdominal pains and constipation. The mother has tried over-the-counter medicines as needed for this problem, and wonders if the change to attending kindergarten has a role in his increased complaints. Family history reveals that the boy lives with his sister, mother, and maternal grandparents in an older suburb of your community. The child's monthly weekend visits to his father's house are working out fine. However, he seems to be fighting more with his sister, who has an attention-deficit disorder and is repeating first grade. Since the mother moved in with her parents after her divorce 4 years ago, she has worked with the grandfather in an automobile radiator repair shop, where her children often come to play after school. She was just laid off, however, and expressed worry about increasing financial dependence on her parents. She also worries that the grandfather, who has gout and complains increasingly of abdominal pain, may become even more irritable when he learns that she is pregnant. Her third child is due in 4 months. On chart review, you see that the previous paediatrician examined the boy for his preschool physical 1 year ago. A note describes a very active 4-year-old who could dress himself without help but could not correctly name the primary colors. His vision was normal, but hearing acuity was below normal according to a hearing test administered for his preschool physical. The previous doctor noted that the boy's speech and language abilities were slightly delayed. Immunizations are up to date. Further history on last year's visit indicated adequate diet, with no previous pica behaviour. Spun haematocrit was diminished at 30%. Peripheral blood smear showed hypochromia and microcytosis. There was no evidence of blood loss, and stool examination was negative for occult blood. The diagnosis was "mild iron deficiency anaemia," and iron therapy was prescribed. The family failed to keep several follow-up appointments, but the child did apparently complete the prescribed 3- month course of iron supplements. He receives no medications at this time and has no known allergies. On physical examination today, you note that the boy is in the 10th percentile for height and weight. The previous year he fell within the 20th percentile. His attention span is very short, making him appear restless, and he has difficulty following simple instructions. Except for slightly delayed language and social skills, the boy has reached most important developmental milestones.*

CASE-STUDY (1) LABORATORY

Laboratory: microcytic anaemia

          BLL – 30 μg/dL

          ZPP – 50 μg/dL (normal < 35)

          Hb – 10.7 gr/dL; MCV – 72 fL

          Serum Ca – normal

Flat abdominal X-ray: no radio-opacities

BLL in mother – 40 μg/dL, referred for follow-up

41

<< NOTE TO USER: In this section, present case-studies which illustrate important local/regional sources of lead toxicity. Actual case studies are always powerful.>>

MCV, mean corpuscular volume in femtolitres.

The child's laboratory evaluation showed moderately elevated BLL, microcytic anaemia and no evidence of paint chip ingestion.

CASE-STUDY (1) MANAGEMENT AND FOLLOW-UP

Management:
- ❖ **Abate source: cleaning, avoid further contact with dirty clothes, wash hands**
- ❖ **Treat anaemia with iron supplement**
- ❖ **No chelation**

Repeat BLL:
- ❖ **in 1 month – 26 µg/dL,**
- ❖ **in 2 months – 24 µg/dL**
- ❖ **in 3 months – 22 µg/dL**

Four months later – asymptomatic

42

<< NOTE TO USER: In this section, present case-studies which illustrate important local/regional sources of lead toxicity. Actual case-studies are always powerful.>>

Treatment was environmental – eliminating exposure – and correction of nutritional deficit. Within 4 months the abdominal colic was resolved, but the child's small stature and hyperactivity probably represent developmental toxicity from chronic exposure which could be permanent. Again, prevention is key!
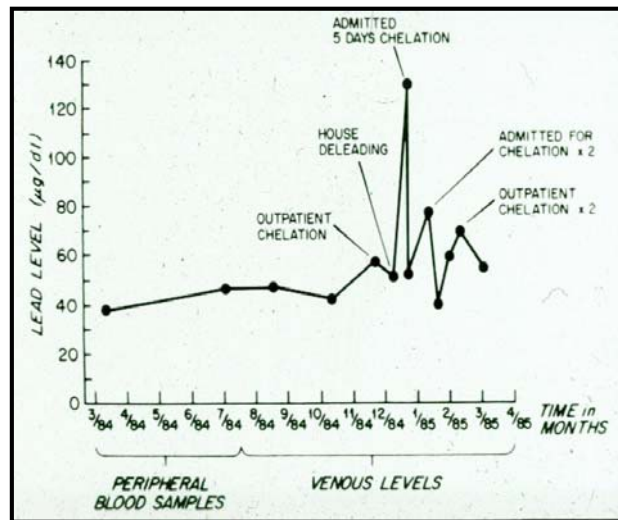
CASE-STUDY (2)
ACUTE-ON-CHRONIC LEAD POISONING

❖ **18-month-old African American child with mild-to-moderate lead poisoning: BLL 37 µg/dL**

❖ **Admitted to the hospital with lethargy, vomiting and encephalopathy: BLL 130 µg/dL**

❖ **Recent history: home de-leaded by sanding 3 days previously**

❖ **Away from the house during day, inside at night.**

43

Management of lead poisoning requires more than medical inputs. This case-study illustrates the dangers of improper de-leading in the residence of a child identified with lead poisoning from ageing lead-based paint.

<<READ SLIDE.>>

CASE-STUDY (2) – FOLLOW-UP AND BLL

Rey-Alvarez, Pediatrics, 1987, 79(2):214.

(Graph: LEAD LEVEL (µg/dl) vs TIME in MONTHS)

Annotations on graph: ADMITTED 5 DAYS CHELATION; HOUSE DELEADING; ADMITTED FOR CHELATION × 2; OUTPATIENT CHELATION × 2; OUTPATIENT CHELATION

X-axis: 3/84 4/84 5/84 6/84 7/84 8/84 9/84 10/84 11/84 12/84 1/85 2/85 3/85 4/85

PERIPHERAL BLOOD SAMPLES — VENOUS LEVELS

44

In this case, an existing chronic exposure to lead became acute poisoning during the process of source mitigation.

The child was admitted to hospital with lethargy and vomiting and was treated with several courses of chelating agents: first with BAL (IM) and then CaNaEDTA with fluid restriction due to concern about increased intracranial pressure. This combined therapy was given for 5 days, with daily monitoring of liver and kidney function, and electrolytes.

The child became alert and was discharged after 1 week, with a marked reduction in BLL, but suffered a subsequent rebound, which required several courses of chelation (see slide). The rebound phenomenon is explained in slide no. 38.

Ref: Rey-Alvarez. Deleading dilemma: pitfall in the management of childhood lead poisoning, *Pediatrics,* 1987, 79:214.
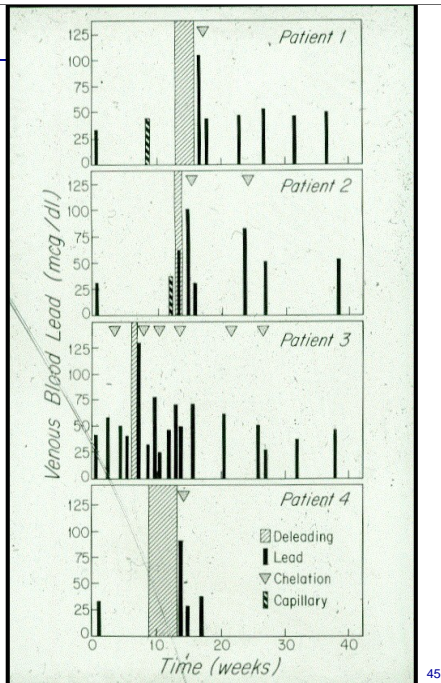
De-leading is a dangerous process which, if improperly done, can result in acute lead intoxication. This case report illustrates what happened to an already-lead-poisoned child's lead level when he was not excluded from his apartment during de-leading. Supportive evidence is provided from 12 additional cases recently seen by the same paediatric practice. The issues behind the failure of these families to vacate their apartments during de-leading are discussed, and the need for lead-poisoning prevention programmes to address these issues, particularly that of providing alternative shelter during de-leading, is stressed. Society should adequately fund such programmes so that they become a reality.

Picture used with permission

CASE-SERIES DE-LEADING- RELATED EXPOSURE

❖ **4 cases of acute-on-chronic lead poisoning**

❖ **Subsequent to de-leading without proper precautions**

Amitai, Am J Dis Child, 1987,141(7):758.

Patient 1

Patient 2

Patient 3

Patient 4

☒ Deleading
▮ Lead
▽ Chelation
▧ Capillary

Venous Blood Lead (mcg/dl)

Time (weeks)

45

These cases provide further illustrations of the complex problem of management of lead exposures.

Ref: Amitai. Hazards of 'deleading' homes of children with lead poisoning. *Am J Dis Child,* 1987,141:758.

"De-leading" the homes of children with lead poisoning is a necessary step to terminate the child's exposure to lead. Lead poisoning as a result of lead exposure during the process of de-leading has occurred in de-leading workers but has not been well documented among children whose homes are deleaded. We treated four children with classes I through III lead poisoning (range of blood lead [Pb-B] level, 1.6 to 2.75 mumol/L [33 to 57 micrograms/dL]) who had significant elevation of their Pb-B levels (range, peak 4.34 to 6.27 mumol/L [90 to 130 micrograms/dL]) following de-leading of their homes. The methods used for de-leading included scraping, sanding, and burning of the paint. Symptoms included irritability (n = 3) and vomiting (n = 1). The elevation of the Pb-B levels was detected early, allowing prompt chelation therapy. Because exacerbation of lead poisoning may occur in children following de-leading of their homes, safer approaches for de-leading should be determined.

Picture: Amitai. Hazards of 'deleading' homes of children with lead poisoning. *Am J Dis Child,* 1987, 141:758. *Copyright (1987), American Medical Association. All rights reserved. Used with permission.*

Lead Poisoning in Children

STUDY OF PRE- MID- AND POST- DE-LEADING BLLS

❖ **Boston study of 114 children whose houses were de-leaded Blood lead levels (BLL)**
  - **before**
  - **during**
  - **after**

❖ **Mean BLL were HIGHER during de-leading due to improper precautions for safeguarding children**
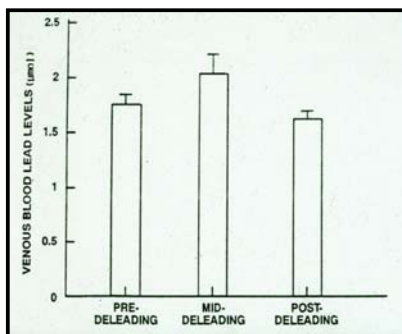
Amitai, Pediatrics (1991) 88(5):893.

46

<<READ SLIDE>>

The evolution of these three publications is a classical example of the three stages in clinical research:

1) Starting from a single, yet dramatic, case-report (tip of the iceberg).

2) Then describing a case-series of four patients with the same etiology.

3) Then expanding the study to a large state-wide study of 114 patients.

These studies illustrated that de-leading, a process which was made mandatory by health authorities, to protect children from further exposure to lead from deteriorated paint in their homes, when done improperly, resulted in a temporary, yet dangerous, aggravation of lead poisoning in these children. Following these publications, more caution was advised and appropriate safety regulations were implemented regarding residential de-leading in the USA. *Ref:* Amitai. Residential deleading: effects on the blood lead levels of lead-poisoned children. *Pediatrics,* 1991, 88:893.

Acute elevations of venous blood lead levels (PbB) are periodically reported in children with chronic lead poisoning, during de-leading of their houses. To evaluate this phenomenon 114 preschool children who entered the Massachusetts Childhood Lead Poisoning Prevention Program case management system during 1984 and 1985 were retrospectively studied. PbB increased from a mean (+/- SE) of 1.76 +/- 0.03 mumol/L (36.4 +/- 0.6 micrograms/dL) prior to de-leading to 2.03 +/- 0.07 mumol/L (42.1 +/- 1.5 micrograms/dL) during de-leading (P less than 0.001). Among 41 subjects for whom de-leading was done by dry scraping and sanding, the mean mid-de-leading PbB was higher than the pre-de-leading PbB by 0.44 +/- 0.12 mumol/L (9.1 +/- 2.4 micrograms/dL). However, when de-leading was done by covering or replacement of painted surfaces in the residences of 12 subjects, mid-de-leading PbB decreased 0.11 +/- 0.12 mumol/L (2.25 +/- 2.4 micrograms/dL) (P less than .005). In a subset of 59 subjects who had no chelation therapy and were available for follow-up 250 +/- 14 days after completion of de-leading, PbB had decreased from 1.72 +/- 0.04 mumol/L (35.7 +/- 0.9 micrograms/dL) to 1.24 +/- 0.04 mumol/L (25.5 +/- 0.9 micrograms/dL) (P less than .001). The long-term effect of de-leading is a significant reduction in PbB. However, de-leading resulted in a significant, albeit transient, increase in PbB.

Picture used with permission   46

IMPACT OF CHELATION ON IQ

WPPSI-R   NEPSY   CPRS-R
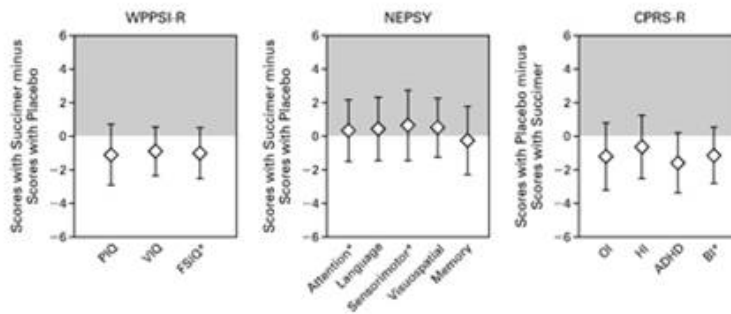
NO SIGNIFICANT DIFFERENCE SUCCIMER vs PLACEBO
- ❖ **Behaviour slightly worse in treated children**
- ❖ **Neurodevelopmental testing slightly better**
- ❖ **PRIMARY PREVENTION IS KEY**

Rogan, NEJM (2001) 344:1421

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Finally, this study by Rogan et al. looked carefully at the effects of oral chelation therapy in children with only mildly elevated lead levels on cognitive development. The investigators were interested in determining whether early treatment and lowering of the BLL would improve IQ scores. Unfortunately, they found no significant difference between treatment with placebo and treatment with chelation in children's test results, although they were successful in significantly reducing blood lead levels. This strongly supports the concept of primary prevention (elimination of exposure).

Ref: Rogan. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. *N Engl J Med,* 2001, 10;344:1421.

We enrolled 780 children with blood lead levels of 20 to 44 µg per decilitre (1.0 to 2.1 µmol per litre) in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer, a lead chelator that is administered orally. The children lived in deteriorating inner-city housing and were 12 to 33 months of age at enrolment; 77 per cent were black, and 5 per cent were Hispanic. Follow-up included tests of cognitive, motor, behavioural, and neuropsychological function over a period of 36 months.

During the first six months of the trial, the mean blood lead level in the children given succimer was 4.5 µg per decilitre (0.2 µmol per litre) lower than the mean level in the children given placebo (95 per cent confidence interval, 3.7 to 5.3 µg per decilitre [0.2 to 0.3 µmol per litre]). At 36 months of follow-up, the mean IQ score of children given succimer was 1 point lower than that of children given placebo, and the behaviour of children given succimer was slightly worse as rated by a parent. However, the children given succimer scored slightly better on the Developmental Neuropsychological Assessment, a battery of tests designed to measure neuropsychological deficits thought to interfere with learning. All these differences were small, and none were statistically significant.

Observational data suggest that the effect on IQ of an increase in the blood lead level from 10 to 20 µg per decilitre is a decrease of about 2 to 3 points. The difference in blood lead levels between the children given succimer and those given placebo exceeded 10 µg per decilitre only briefly, and the mean difference was 4.5 µg per decilitre (0.2 µmol per liter) during the six months after the initiation of treatment. Thus, it could be that the failure of our study to demonstrate a difference in test scores is due to the small difference in blood lead levels that we observed. However, succimer is as effective as any chelating agent currently available, and we used it for 26 days per course rather than the usual 19 days. We also used the (higher) loading dose for the first seven days, rather than the first five days, of each course, with the dose calculated according to body-surface area rather than weight. When the pills were counted, 76 per cent were gone, so adherence to therapy was as high as has been reported among children in trials lasting longer than a week. We believe it is unlikely that another chelation regimen would have been more effective.

Lead Poisoning in Children

MORBIDITY, MORTALITY AND ESTIMATED COSTS OF LEAD POISONING IN AMERICAN CHILDREN

❖ **Burden of disease for lead poisoning is 20 X higher than for asthma, and 120 X higher than for cancer**

❖ **Estimated total annual costs:**
- **Lead exposure:**   **$ 43.4 billion**
- **Childhood asthma:**   **$ 2.0 billion**
- **Childhood cancer:**   **$ 0.3 billion**
- **Neurobehavioural**
   disorders: **$ 9.2 billion**

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Not only is lead poisoning a tragedy for the child affected and his/her family, but it also carries a significant societal and economic cost.

<<READ SLIDE.>>

Ref: Landrigan. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. *Environ Health Perspect,* 2002, 110:721.

In this study, we aimed to estimate the contribution of environmental pollutants to the incidence, prevalence, mortality, and costs of paediatric disease in American children. We examined four categories of illness: lead poisoning, asthma, cancer, and neurobehavioural disorders. To estimate the proportion of each attributable to toxins in the environment, we used an environmentally attributable fraction (EAF) model. EAFs for lead poisoning, asthma, and cancer were developed by panels of experts through a Delphi process, whereas that for neurobehavioural disorders was based on data from the National Academy of Sciences. We define environmental pollutants as toxic chemicals of human origin in air, food, water, and communities. To develop estimates of costs, we relied on data from the US Environmental Protection Agency, Centers for Disease Control and Prevention, National Center for Health Statistics, the Bureau of Labor Statistics, the Health Care Financing Agency, and the Practice Management Information Corporation. EAFs were judged to be 100% for lead poisoning, 30% for asthma (range, 10–35%), 5% for cancer (range, 2–10%), and 10% for neurobehavioural disorders (range, 5–20%). Total annual costs are estimated to be US$ 54.9 billion (range US$ 48.8–64.8 billion): US$ 43.4 billion for lead poisoning, US$ 2.0 billion for asthma, US$ 0.3 billion for childhood cancer, and US$ 9.2 billion for neurobehavioural disorders. This sum amounts to 2.8 per cent of total US health care costs. This estimate is likely to be low because it considers only four categories of illness, incorporates conservative assumptions, ignores costs of pain and suffering, and does not include late complications for which etiological associations are poorly quantified. The costs of paediatric environmental disease are high, in contrast with the limited resources directed to research, tracking, and prevention.

PREVENTION IS ESSENTIAL

❖ **Primary prevention: eliminate exposure**
- **Regulations and laws**
  - **Ban lead in petrol**
  - **Ban lead-containing solder for packaging foods/beverages**
  - **Remove lead from paint**
- **De-leading of houses**

❖ **Secondary prevention: monitoring**
- **SCREENING of asymptomatic children**
  - **Optimize nutrition and health**
  - **Remove from source of exposure**
  - **Remediate environment**

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Prevention is ESSENTIAL because damaged brains cannot be repaired.

<<READ SLIDE>>

Whereas the modern approach regarding chemical hazards in the environment consists of monitoring the hazard in the environment (e.g. in air, water or soil), in the case of lead, children were used as "biological monitors" of their environment. Once identified as having a high BLL, the child's home was checked for lead, and in most cases, the source of lead was indeed in the house. This approach was taken because in the 1960s and 1970s, > 50 million homes had high contents of lead in paint. Thus, it was impractical to check all houses. When the source of the child's exposure to lead was in his or her home, the home was "de-leaded". Several methods for de-leading were used. Safe methods included: cautious removal of leaded paint from walls, ceilings, windowsills, porches, and other places and re-painting or covering the walls. These activities should have been done while the child was temporarily staying in an alternative, safe and clean house. However, many accidents occurred when de-leading was not done cautiously, and children who were in or around their homes during the process, were exposed to heavily lead-contaminated dust and paint chips.

Ref:
•Amitai. Residential deleading: Effects on the blood lead levels of lead-poisoned children. *Pediatrics,* 1991, 88:893.

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Lead Poisoning in Children

LEADED PETROL – MAJOR SOURCE
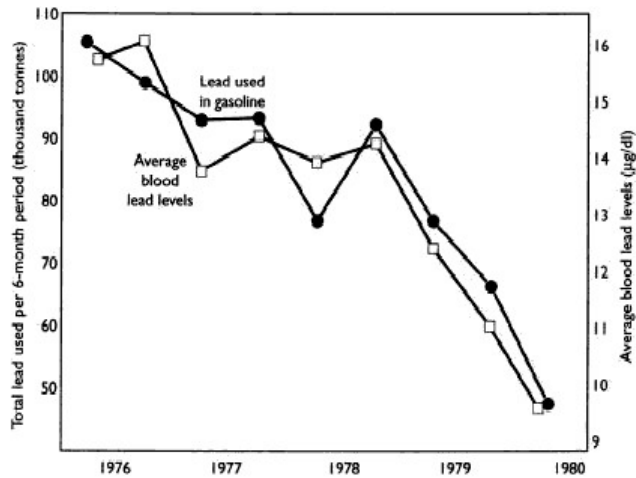
Institute of Medicine, EPA, 1996

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This graph demonstrates very clearly the effect of primary prevention – removal of lead from petrol in the USA closely paralleled the reduction of average blood lead levels in the American population.

Ref:

•*books.nap.edu/books/NI000651/html/103.html#p2000321cmmm00010*

Institute of Medicine. *Lead in the Americas: A call for action.* EPA, 1996.

Lead Poisoning in Children

TRENDS IN BLOOD LEAD LEVELS IN 1 – 5-YR-OLD CHILDREN: NATIONAL AVERAGES IN THE USA (CDC)

YEARS	MEAN BLL µg/dL	% BLL >10 µg/dL	Estimated no. of children, >10 µg/dL
1976–1980	14.9	88.2	13 500 000
1988–1991	3.6	8.6	1 700 000
1991–1994	2.7	4.4	890 000
1999–2000	2.2	2.2	434 000

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The dramatic reduction in the average national BLL in children in the USA (by 677% over 20 years!) is a unique example of public health achievement, and was obtained by a multisectoral multi-level strategy, which combined regulations, abatement, public education, national screening programmes, medical treatment and long-term follow-up.
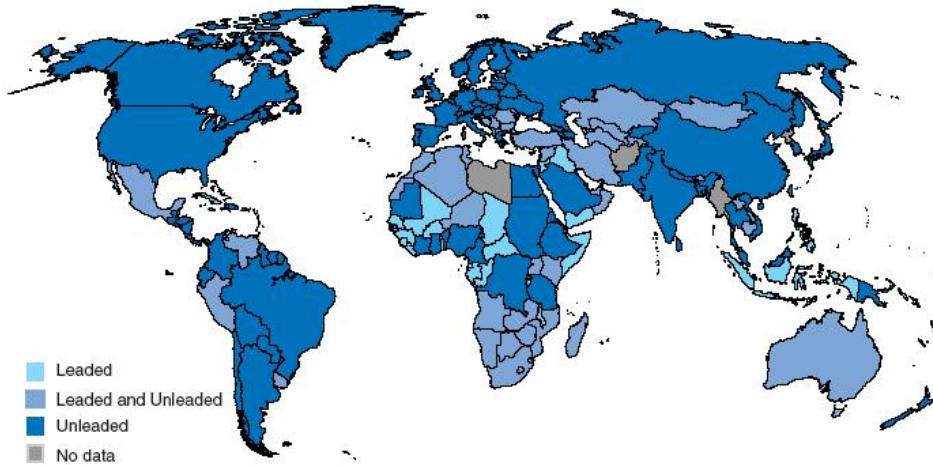
Ref:

•*www.childtrendsdatabank.org/figures/81-Figure-1.gif*

Lead Poisoning in Children

Leaded petrol phase-out: Global status

UNEP
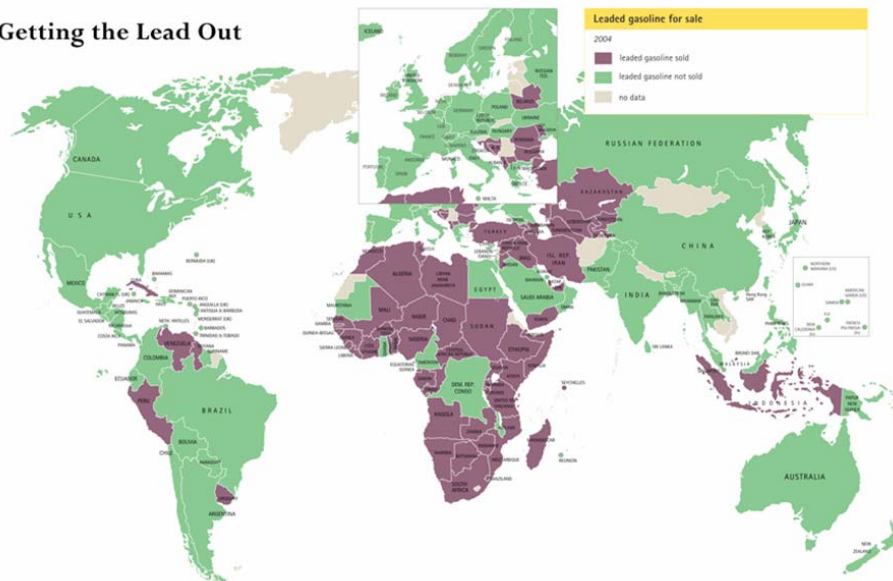
Leaded
Leaded and Unleaded
Unleaded
No data

April 2005

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Map provided by Rob de Jong, Programme Officer Urban Environment, Division of Policy Development and Law (DPDL) United Nations Environment Programme (UNEP), April 2005.

Lead Poisoning in Children

Getting the Lead Out

Gordon, WHO, Myriad Editions Ltd, 2004

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The toxic effects of lead have been known for centuries: severe anaemia was common among aristocratic women who relied on lead-based powder to meet their desire for a fair complexion. Workers in lead mines, constantly exposed to high doses of lead, frequently suffered convulsions and even death. Lead continues to be present in our surroundings as an additive to gasoline [petrol], an ingredient of paint and pottery glaze, or the main material of old water-pipes. Children are at the greatest risk because lead is more easily absorbed by their growing bodies, and because their tissues are especially sensitive to damage. They may swallow lead in dust from decaying lead-based paint or suck the ceramic beads of necklaces. Even blood lead levels as low as 5 micrograms per decilitre can irreversibly impair the development of children's brains, reducing their IQ. This threshold level is still exceeded around the world, particularly in children in the cities of developing countries. Industrialized countries have made progress by phasing lead out of gasoline [petrol], banning lead in many consumer goods and replacing lead pipes with copper pipes. Lead-based paint, however, continues to be a considerable problem in North America. A potential link between elevated lead levels and antisocial behaviour and delinquency makes tackling this problem even more urgent.

Ref:

•Gordon. *Inheriting the world, the Atlas on Children's Health and the Environment.* WHO, Myriad Editions Ltd, 2004.

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CRITICAL ROLES OF
HEALTH & ENVIRONMENT PROFESSIONALS

❖ **Diagnose and treat**

❖ **Do research and publish**
- **Detect sentinel cases**
- **Inspire community-based interventions**

❖ **Educate**
- **Patients and families**
- **Colleagues and students**

❖ **Advocate**

❖ **Provide good role model**

WHO

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Health and environment professionals have a critical role to play in maintaining and stimulating changes that will ensure children's health.

•At the patient level it is important to include *lead* as an environmental etiology in the differential diagnoses (e.g. unexplained anaemia, colicky pain, malaise) and in the preventive advice. Are the signs and symptoms possibly linked to lead exposure? Are there any potential sources of exposure?

•Health care providers should be alert and detect the "sentinel" cases of *lead* exposure. Their detection and study will be essential for developing, proposing and supporting community-based interventions. Publication of cases and research studies allows the communication of knowledge and experience that will benefit other communities and countries.

•It is important to inform and educate patients, families, colleagues and students didactically, on the possibility of lead exposure and its potential impact in children. Also on how to avoid exposure.

•Finally, we must all become vigorous advocates for the protection of children's environments and prevention of *lead* exposure. It is important to promote the measures that are crucial for eliminating or mitigating lead exposure in children (and pregnant women!).

•Professionals with understanding of both health and the environment are powerful role models. Their choices and opinions with respect to pollutants such as *lead* and other environmental factors will be noticed by patients and communities.