Trace Metals

A Lecture of Scant Material but Large Importance

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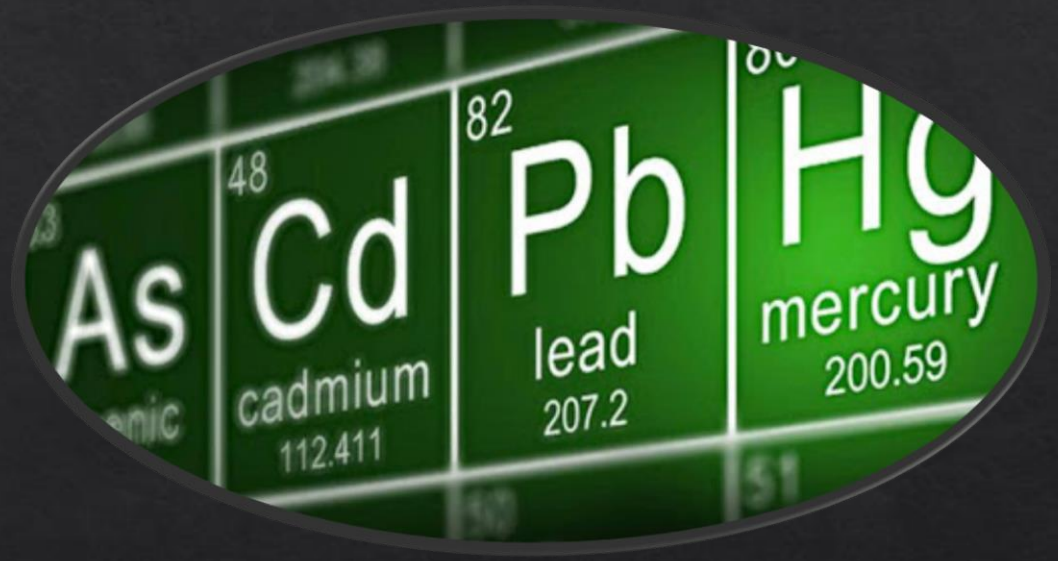
Topics

- Trace Elements
  - Purpose
  - Characteristics
- Specimen Considerations
- Specific Trace Metals
  - Functions
  - Pathologies
- Toxic Trace Elements

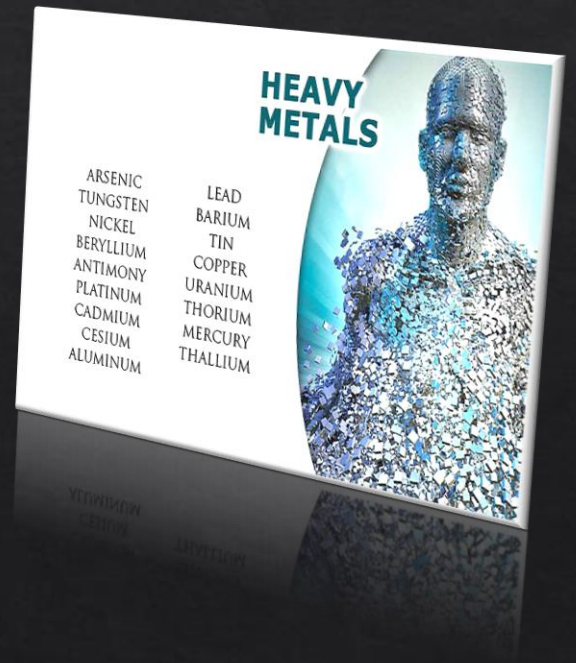


Trace Elements

- All cells require chemical reactions that are performed by small amounts of enzymes
- Enzymes often require a “spark” in the form of a trace element, a catalyst
- Require only minute quantities to provide essential functions
  - Required in diet for normal growth, development, maintenance
  - Deficiency causes functional impairments

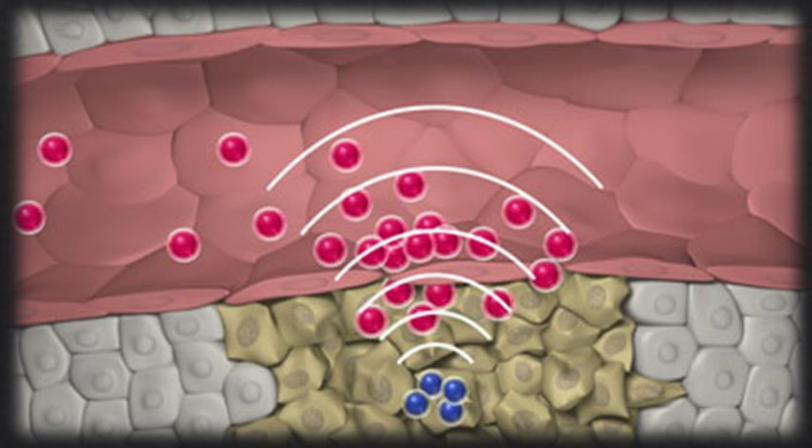
Trace Elements

- Essential: Chromium, Manganese, Fluoride, Iron, Cobalt, Copper, Zinc, Selenium, and Iodide
- Non-essential: Nickel, Aluminum, Bismuth, Lithium, Gold
- Toxic: Aluminum, Cadmium, Lead, Arsenic, Mercury



Characteristics of Trace Elements

- Amplification
  - Very small amounts needed
  - Lack of small amounts in diet leads to seemingly disproportionate effects
  - Work with enzymes, hormones that regulate metabolism of large amounts of substrates and products
  - Possible further effects if products are regulatory as well

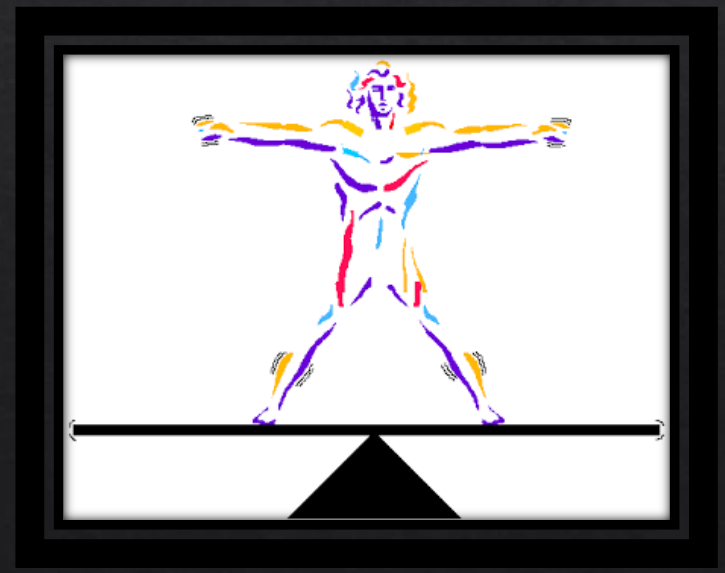


Characteristics of Trace Elements

- Specificity
  - Cannot be replaced (mostly) by chemically similar elements
    - Usage of alternative elements may have deleterious effects
  - Specific carrier and storage proteins
    - Without carrier/storage proteins metals are not well solubilized, will deposit
    - Transferrin and ferritin for iron, ceruloplasmin for copper

Characteristics of Trace Elements

- Homeostasis
  - Mechanisms exist that assure optimal distribution, concentration of elements
    - Absorption, transport, storage, and excretion
  - Decreased or impaired absorption causes retention in intestinal lumen
    - Primary excretory route is through feces



Specimen Considerations

- Looking for small concentrations of ubiquitous elements
- Contamination a large concern
  - Anticoagulant chosen, special collection methods, sample handling
  - High purity of reagents, water used
  - Some lab practices must be avoided
- Sample choice is complicated
  - Some elements accumulate in different compartments
    - Hair, urine, serum/plasma, inside RBCs (whole blood sample)

Chromium

- Trivalent chromium an essential element, but hexavalent is toxic
- Albumin, transferrin can Cr
- Cr^{6+} is a powerful oxidizer, forms CrO_4^{2-} and is confused for sulfates and phosphates
  - Inhaled dust causes irritation, cancer
  - Chronic, low-dose exposure impairs kidney function
  - Metal on metal hip replacements may wear and cause high chromium levels
- May be assessed by AAS, GFAAS, or ICP-MS

Cobalt

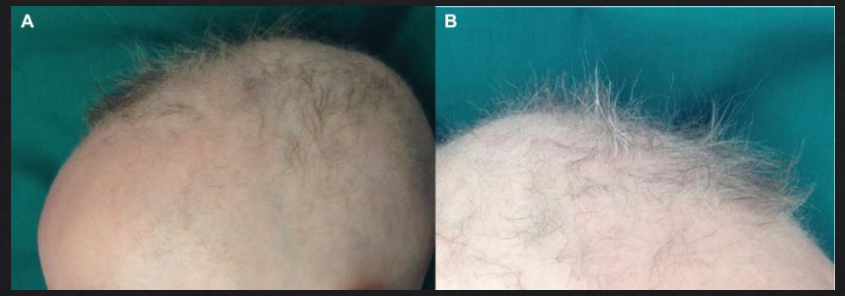
- Central role in folate metabolism and erythropoiesis
  - Vitamin B12 aka cyanocobalamin aka cobalamin
- Cobalt deficiency results in low B12 → macrocytic anemia
- Toxicity is rare, causes lethargy, anorexia, polycythemia and cardiomyopathy
  - Excessive intake in renal patients prescribed cobalt to boost RBC count
  - Metal on metal hip replacement grinding
  - Heavy drinkers of cobalt-containing beer

Copper

- Dietary Sources: shellfish, liver, nuts, and legumes
- Absorbed by intestines
- Highest concentrations in liver (10% total), brain, heart, kidneys
- Transported to liver on albumin and α 2-macroglobulin
- Use: Ceruloplasmin and other metalloenzymes
  - Ceruloplasmin is most of circulating copper
  - contains 6 Cu atoms
  - Converts Fe^{2+} to Fe^{3+} to allow transferrin to bind it

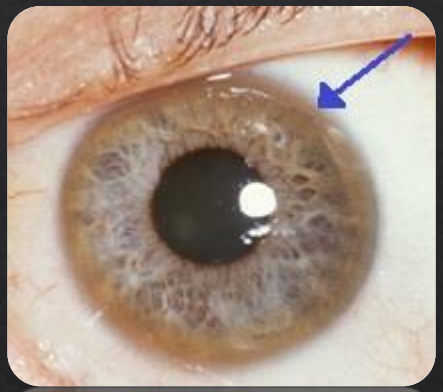
Copper Deficiency

- Deficiency confirmed when serum copper and ceruloplasmin are both low
- Zn competes with Cu for absorption
  - Excess Zn will cause decrease in Cu
- Low copper → low ceruloplasmin → low transferrin saturation → Micro/Hypo anemia
- Severe deficiency causes anemia, neurological symptoms, decreased pigmentation
  - Menke's Disease- Copper transport defect, X-linked, 1:50k births, symptoms 2-3 months
    - Kinky/Steely hair due to loss of Cu-catalyzed disulfide bond formation
    - Progressive mental deterioration, growth retardation, disturbance of muscle tone, seizures, episodes of hypothermia



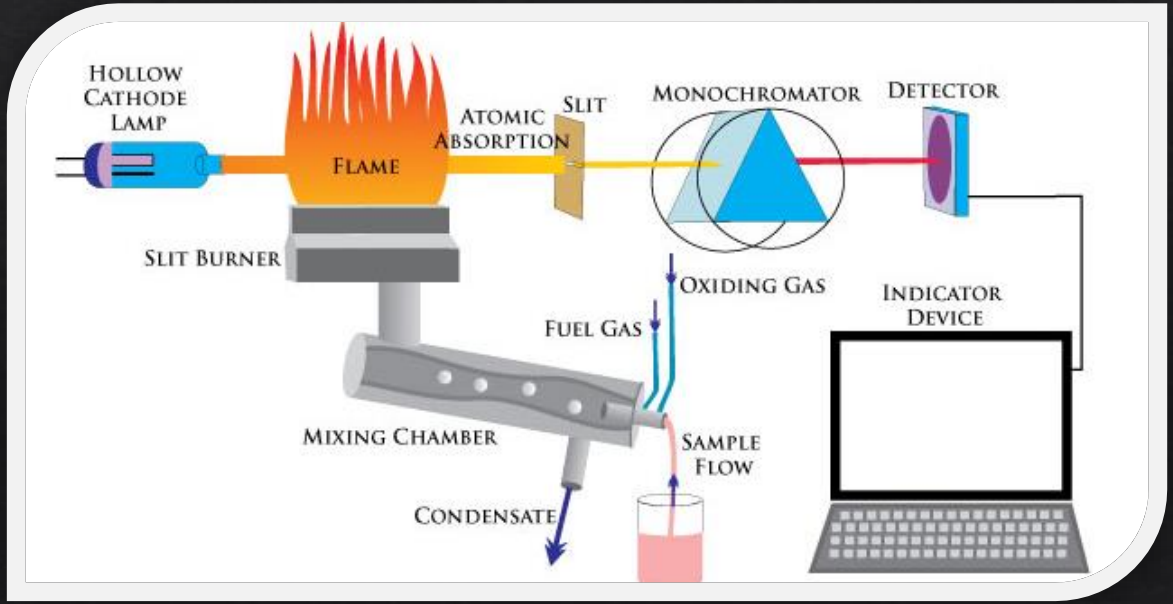
Copper Toxicity

- Wilson's Disease- defect in formation of ceruloplasmin
  - With nowhere to go copper deposits in liver, kidneys, cornea
    - Neurological disorder, liver dysfunction, Kayser-Fleischer rings
  - With nothing holding it in circulation Cu makes it into urine
    - Low serum levels in testing due to insolubility, lack of ceruloplasmin
  - Early diagnosis leads to chelation therapy, damage prevention
  - Late diagnosis leads to liver transplant



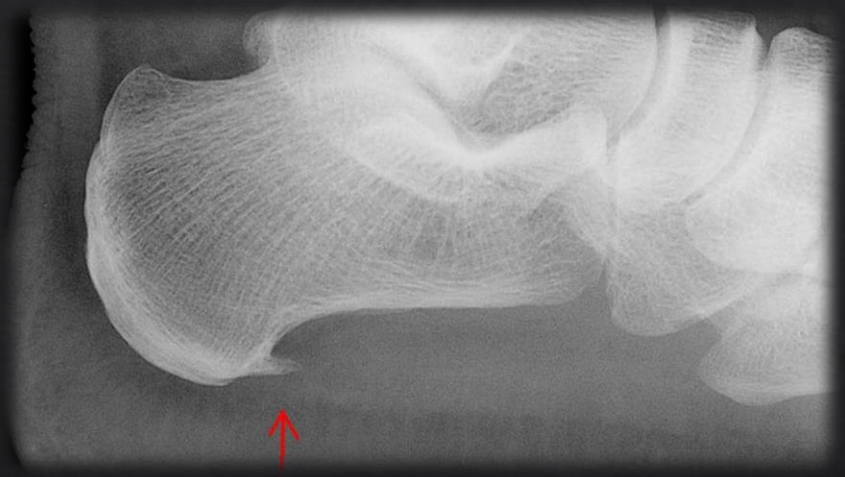
Copper Measurement

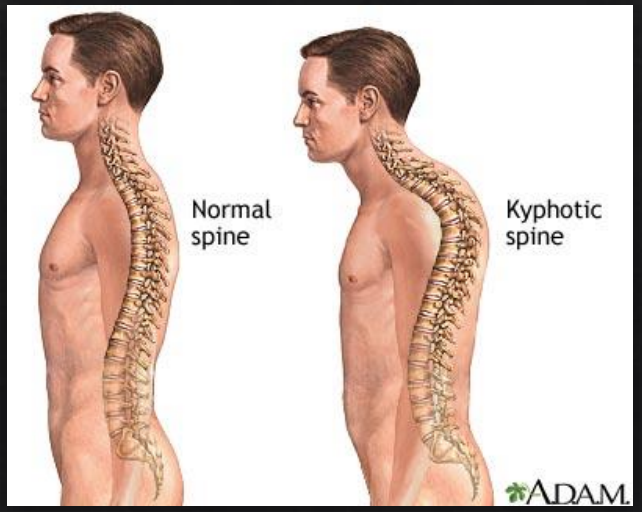
- Ceruloplasmin is easily measured as a surrogate test
  - Screens for Wilson's
- Can be measured by AAS, ICP-AES, or ICP-MS



Fluoride

- Common additive in municipal water supplies, toothpaste
  - Prevents dental caries (cavities)
- Chronic fluorosis
  - Excess fluoride ingestion during tooth formation, mottled and pitted teeth
  - Kyphosis, stiffening of spine, bony exostosis





Manganese

- Cofactor for several enzymes
  - Mg, Cu, Fe can substitute in for Mn as an activator
    - This makes detected deficiency rare
- Toxicity resembles Parkinson's disease
  - Chilean miners with acute exposure *locura manganica*
- Assayed using ICP-MS or GFAAS

Selenium

- Essential cofactor and anticarcinogen, defends against free radicals
- Deficiency associated with cardiomyopathy, muscle weakness, osteoarthritis
- Keshan disease, an endemic cardiomyopathy affecting women in China.
- Very high levels of ingestion lead to exhalation of volatile forms of selenium (garlic breath)
  - Toxic levels cause loss of hair, nails, skin lesions, fatigue

Zinc

- Dietary Source: meat, fish, and dairy
- Absorbed by intestines
- Second most abundant trace element (iron #1)
- Albumin and α 2-macroglobulin transport to liver and skeleton
- Use: cofactor for 300+ enzymes
  - ALKP, alcohol dehydrogenase, carbonic anhydrase, DNA & RNA polymerase
  - Required for wound healing
  - By outcompeting copper zinc supplements are treatment for Wilson's

Zinc Deficiency, Toxicity, and Testing

- Deficiency usually due to low intake
  - High fiber and phosphates may sequester
  - Levels will not be low until deficiency is profound
    - Symptoms include slow growth/healing, skin lesions
- Zinc toxicity is rare due to it's RELATIVE non-toxicity
  - Certain coins may cause toxicity if swallowed
- May be analyzed by AAS, ICP-MS
  - Zinc in RBCs is 10x serum, acts as stores, hemolysis interferes

Aluminum

(not aluminium)

- Toxicity is poorly understood
  - Interferes with various enzymatic processes
- Toxicity causes encephalopathy, osteomalacia (spontaneous fractures), myopathy, a microcytic anemia, and heart problems
  - Toxicity occurs due to renal failure and dialysis treatment with aluminum containing solutions
  - Aluminum hydroxide (antacid) may be over administered (Gaviscon)

Arsenic

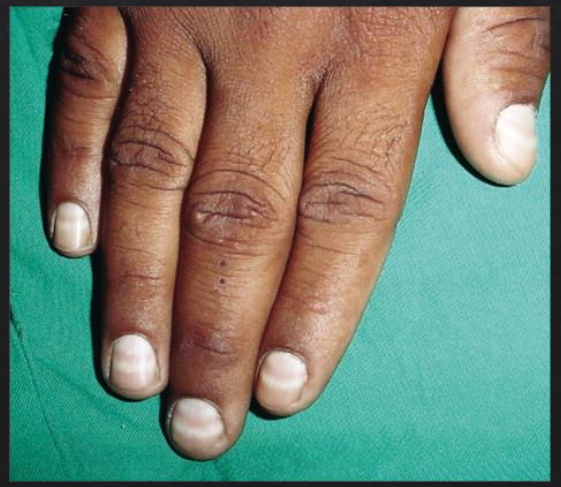
- Arsenic is a ubiquitous element, found all over the earth
- Routes of exposure of form of arsenic can dictate the toxicity
  - Organic forms like arsenocholine and arsenobetaine relatively non toxic
  - Methylated mono/dimethyl arsine (MMA/DMA) moderately toxic (also hepatic metabolites)
    - Slowly excreted from body taking 1-3 weeks
  - As^{3+} and As^{5+} very toxic
    - BAL, penicillamine, succimer antidotes

Arsenic Toxicity

- Inhibits formation of Acetyl-CoA from pyruvate
  - First step of gluconeogenesis
- Competes with phosphate for ADP in reaction that forms ATP
- Binds with hydrates sulfhydryl groups, distorting 3D configuration of protein

Arsenic Specimen Considerations

- For acute exposure disappears from serum quickly (4 hours), urine concentrations for AS3+, AS5+ peak @ 10 hours
  - MMA, DMA peak at 40-60 hours but detectable up to 20 days
- Has high affinity for keratin (high cysteine content)
  - Hair and nails have high concentration, can document time of exposure
  - Mees lines form in fingernails (also due to lead, cadmium, and mercury)



Cadmium

- Industrially usefull, pigments, batteries, metals, and plastics
  - Exposures to industrial waste, contaminated soil, tobacco products
- Binds to proteins, accumulates in kidney
  - Early toxicity findings of tubular proteinuria, glucosuria, aminoaciduria

Lead

- Common contaminant in environment
  - Household paints before 1972
  - Gasoline before 1978
  - Industrial byproduct
- Susceptibility largely age dependant
  - Children absorb 30-40% of ingested lead
  - Adults absorb 5-15% of ingested lead
- Lead goes to bone (>20 yr. half-life) and soft tissue (120 day half-life)

Lead Toxicity

- Primarily renal elimination
  - Slowly due to binding with macromolecules
- Toxicity is multifaceted due to binding with multiple proteins
  - High levels cause cerebral edema, stupor, convulsions, coma
  - Low levels cause a sub-acute syndrome
    - Behavioral changes, ADHD, decreased IQ
- Potent inhibitor of enzyme pathways for heme synthesis
  - Results in increased zinc protoporphyrin, ZPP, and basophilic stippling

Lead Toxicity Mitigation

- Public health initiatives to abate areas with lead paint
- Children are screened for lead levels when entering school
- Acute toxicity may be treated with EDTA, DMSA (chelating agents, cleared renaly)
- City of Cleveland has large issues with lead
  - 13% of children under 6 screened in 2017 had high lead levels
  - In neighborhoods like Glenville, St. Clair-Superior, and Slavic Village 1 in 4 are estimated to be poisoned
  - In 90s 86% had high levels!
  - Flint made the news because they chose to expose families to lead, Cleveland doesn't because it's status quo

Mercury

- Mercury has both natural and human sources
- It does nothing good for you
- Elemental (may be a salt) and organic mercury forms
  - Both toxic

Mercury Exposure

- Exposure through:
  - Inhalation of elemental/dimethyl mercury
    - Readily vaporizes, retained in lungs
  - Ingestion of $HgCl_2$ through bioaccumulation (see: fish)
    - Liquid metallic mercury passes through relatively unabsorbed
  - Cutaneous contact with methylmercury (Prof Karen Wetterhahn)
  - Relatively inert forms like tattoo pigments, dental amalgams
- Inorganic short half-life (5-90 days)
- Organic long half-life (years)
  - Accumulation in brain is tough to remove

Mercury Toxicity

- Organic mercury is lipophilic, will bind to proteins
  - Accumulates in brain, peripheral nerves
  - Chronic exposure is cumulative
- Interaction with sulfhydryl groups leads to protein malfunctions
- Mad as a hatter
  - Mercury used to fix dye
  - Neurological damage led to headache, tremor, impaired coorination, polyneuropathy and other fun symptoms

Mercury Testing

- Volatility of Mg(0) means caps must remain on
- Measured as total mercury
- Methods include ICP-MS and AAS