Course: *Toxicology, Path-438*

Applications of Pharmacology & Toxicology
Environmental Toxins, Metal Toxicities & Chelation Therapy

Learning Objectives:

- List the factors that influence the bioaccumulation of environmental toxins.
- List the major sources of ambient air pollutants, give examples. Show how these pollutants affect health in vulnerable people and list the mechanisms responsible for their adverse health effects.
- List the major categories of indoor air pollutants, give examples and describe their adverse health effects.
- Describe occupational hazards, give examples and describe the spectrum of human diseases caused by them.
- List the categories of agricultural hazards, give examples and show the effect and disease association of each category.
- List the sources of lead poisoning and describe the pathophysiology of lead toxicity.
- List some examples of the sources of mercury poisoning and describe the its toxic effect.
- Define the term" Chelation Therapy" and discuss briefly the uses and limitations of this mode of treatment giving few examples.

Environmental Toxins:

- Environmental toxicology is defined as the study of the fate & effects of chemicals in the environment.

- Environmental toxicology is typically associated with the study of environmental chemicals of anthropogenic origin (manmade poisonous chemicals and their effect on the environment).

- Environmental toxicology can be divided into two subcategories:

  - **Environmental health toxicology**: Study of the adverse effects of environmental chemicals on human health.

  - **Ecotoxicology** which focuses upon the effects of environmental contaminants upon ecosystems & constituents thereof (fish, wild life, etc).

Environmental Toxins:

❖ Historically chemicals that have posed major environmental hazards tend to share three insidious characteristics:

- **Environmental persistence:** Continuous disposal of persistent chemicals into the environment can result in their accumulation to environmental levels sufficient to pose toxicity.

- **Propensity to accumulate in living things *(Bioaccumulation):*** The process by which organisms accumulate chemicals both directly from abiotic environment (i.e. water, air, soil) and from dietary sources (trophic transfer).

- **High toxicity:** Both acute and chronic toxicity.

Factors Influencing Bioaccumulation:

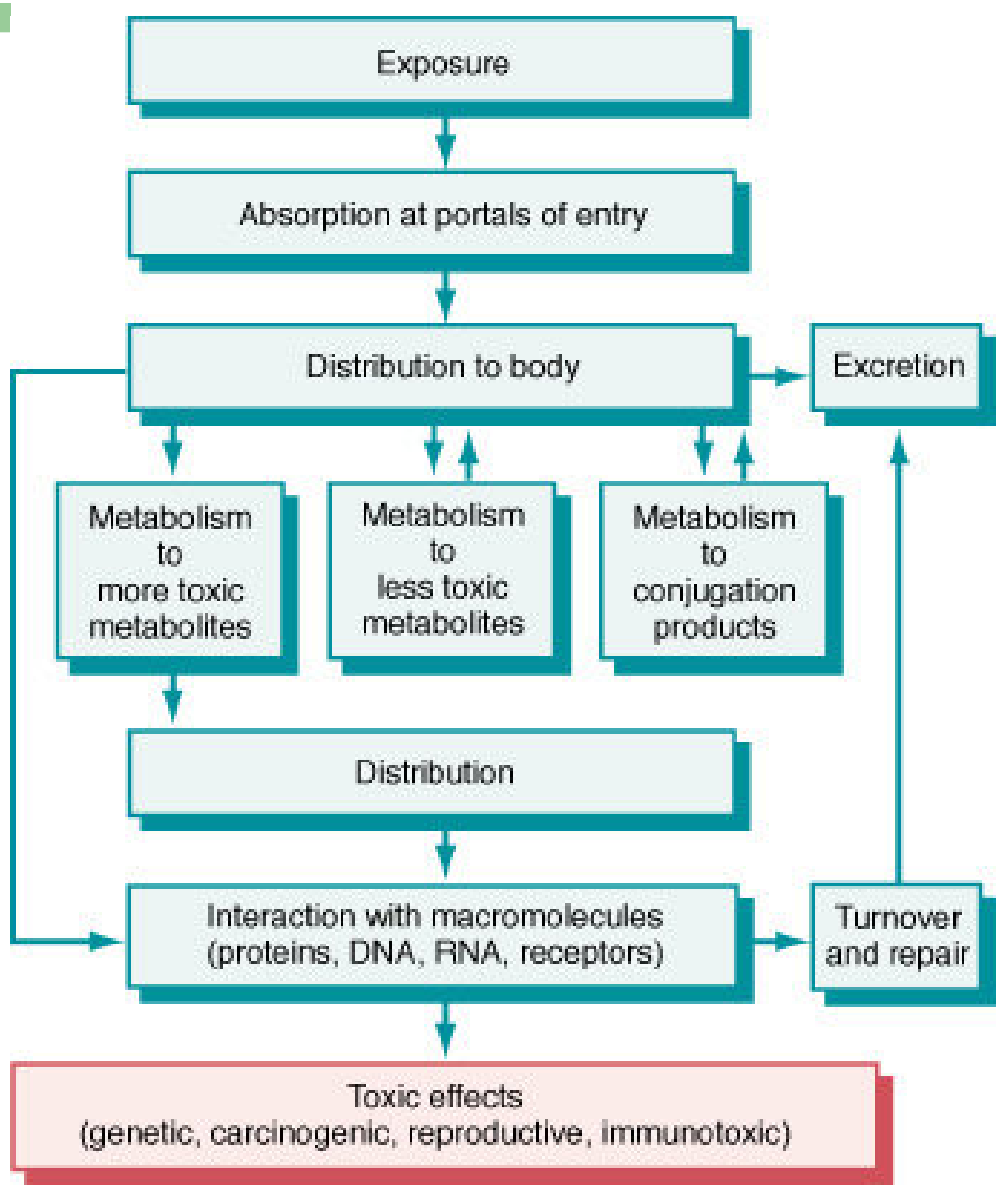
- The propensity for an environmental contaminant to bioaccumulate is influenced by several factors:

  - **Environmental persistence:** Contaminants that are readily eliminated from the environment will generally not be available to bioaccumulate. An exception is would be instances where the contaminant is continuously introduced into the environment.

  - **Lipophilicity** is a major determinant of the bioaccumulation of potential of a chemical.

  - **The fate of the contaminant after absorption:** Chemicals that are readily biotransformed are rendered more water soluble and less lipid soluble and thus more likely to be eliminated from the body.

Absorption and Distribution of Toxicants:



Outdoor Air Pollution:

- Air pollution is a serious problem in many industrialized countries like USA.

- The major sources of ambient air pollutants are:
  - *Combustion of fossil fuels: Vehicles, factories, barbeques & fireplaces.*
  - *Photochemical reactions: Oxides of nitrogen and volatile hydrocarbons interact in the atmosphere to produce ozone (O_3) as a secondary pollutant.*
  - *Power plants: Theses release sulfur oxide (SO_2) & particulates into the atmosphere.*
  - *Waste incinerators, industry, smelters: These point sources release acid aerosols, metals, mercury vapor, and organic compounds that may be hazardous for human health.*

- *Lungs are the major target* of common outdoor air pollutants, especially vulnerable are children, asthmatics, and people with chronic lung or heart diseases *(decreased lung function, increased airway reactivity , respiratory infections, altered mucociliary clearance).*

Outdoor Air Pollution – *Examples of Some Pollutants:*

- Ozone: *It is a major component of smog that accompanies summer heat waves. Exposure of exercising children & adults to as little as 0.08 ppm produces cough, chest discomfort, and inflammation in the lungs. It is a highly reactive agent that oxidizes polyunsaturated lipids to hydrogen peroxide & lipid aldehydes which are irritants that cause inflammatory reactions.*

- Nitrogen dioxide (NO_2): *Oxides of nitrogen include NO & NO_2, these have lower reactivity than ozone. NO_2 dissolve in water in the airways to form nitric & nitrous acids which damage the airway epithelium.*

- Sulfur Dioxide: *This pollutant is highly soluble in water, it is absorbed in the upper & lower airways, where it releases H^+, HSO_3^- (bisulfite) & SO_3^- (sulfite) which cause local irritation.*

Outdoor Air Pollution – *Examples of Some Pollutants (Contd.):*

- Acid Aerosols: *Primary combustion products of fossil fuels are emitted by tall smoke stacks at high altitude and are transported by air. In the atmosphere, sulfur, nitrogen dioxide are oxidized to sulfuric acid & nitric acids, respectively which are dissolved in water droplets or adsorb to particulates and then irritate respiratory epithelium.*

- Particulates: *Deposition & clearance of particulates inhaled into the lung depends on their size (ultra fine particles <0.1 µm in aerodynamic diameter) are more hazardous especially among infants and patients of chromic cardiopulmonary diseases.*

- The mechanisms responsible for these adverse health effects are suspected to involve:
  - *Systemic cytokine release associated with pulmonary inflammation.*
  - *Increased blood viscosity.*
  - *Autonomic changes associated with variable heart rates & arrhythmias.*

Indoor Air Pollution:

- Rising energy costs during the past 30 years have led to increased insulation and decreased ventilation of homes which elevates the level of indoor pollution.

- Sources of indoor air pollution include; *tobacco, cooking gas, wood stoves, construction material, furniture, radon, and allergen associated with pet, dust mites, and fungal spores & bacteria.*

- The major categories of indoor air pollutants are:

  - *Carbon monoxide: This odorless, colorless gas is a byproduct of combustion produced from burning gasoline, oil, coal, wood, and natural gas. It is also a major pollutant in tobacco. It causes reduced exercise capacity and aggravate myocardial ischemia. In large levels it causes poisoning and asphyxia.*

  - *Nitrogen dioxide: Gas stoves and kerosene space heaters raise indoor levels of nitrogen dioxide to 20-40 ppm in homes it causes increased respiratory infections especially in children.*

  - *Wood smoke: It is a mixture of nitrogen oxides, particulates, and polycyclic aromatic hydrocarbons that causes increased respiratory infections especially in children.*

Indoor Air Pollution (Contd.):

- *Formaldehyde: This sis a highly, volatile chemical has been used in the manufacture of many consumer products including textiles, pressed wood, furniture, and urea formaldehyde foam insulation. It causes irritation of eyes & respiratory tract and also it exacerbate asthma.*
- *Radon: It is a radioactive gas and decay product of uranium widely distributed in the soil. It emanating from earth and when it is inhaled to the lung it can induce lung cancer.*
- *Asbestos fiber: Homes & buildings built before 1970s in US contain asbestos insulation, pipe coves, ceiling tiles, and flooring. If these material are friable they will give asbestos particles that will be inhaled increasing the risk of mesothelioma & lung cancer.*
- *Manufactured mineral fibers: Fiberglass has been widely used as an asbestos substitute for home insulation and low levels can be measured in homes but maintenance & construction workers can develop skin and lung irritation when using these materials.*
- *Bioaerosoles: Aerosolization of bacteria responsible for Legionella pneumonia has been associated with contaminated heating & cooling systems in public buildings.*

Industrial Exposures – *Occupational Hazards:*

- Volatile organic compounds:
  - *Aliphatic hydrocarbons-chloroform and CCl4 (solvents), they are readily absorbed through the lungs, skin, and GIT. They cause acute CNS depression, liver & kidney toxicity, and they are carcinogenic in rodents.*
  - *Petroleum products: Gasoline, kerosene, mineral oil, turpentine*
  - *Aromatic hydrocarbons-benzene (carcinogenic), xylene, toluene.*
- Polycyclic aromatic hydrocarbons – *carcinogens (lung & bladder).*
- Plastic, rubber and polymers: *Vinyl chloride - angiosarcoma of liver.*
- Metals: Lead, Cadmium, Chromium, Nickel.

Industrial Exposures – *Occupational Hazards:*

❖ **The spectrum of human diseases:**

- ***Almost all systems can be affected.***
- ***Acute toxicity, irritation, hypersensitivity reactions.***
- ***Chronic toxicity - degenerative changes in the nervous system, reproductive dysfunction, lung fibrosis.***
- ***Cancer - leukemia, bladder, liver, lung.***

Agricultural Hazards:

- Although agricultural productivity has been improved by the use of fertilizers & pesticides, these chemicals can cause diseases in those exposed to them, ***particularly farmers***.
- Health effects of agricultural pesticides:

Category	Example	Effects & disease associations
Insecticides	Organochlorine (DDT), organophosphates	Neurotoxicity, hepatotoxicicty
Herbicides	Arsenic compound	Hyperpigmentation, gangrene, anemia, sensory neuropathy, cancer hyperthermia, sweating
Fungicides	Captan, maneb, benomyl	Reproductive toxicity
Rodenticides	Fluoroactate, warfarin, strchnine	? Reproductive toxicity
Fumigants	Carbon disulfide	Cardiac toxicity

Heavy Metals – Lead (Pb):

- **Lead (Pb)-mining and manufacturing industry:** ***More than 4 million tons of lead are produced each year for use in batteries, alloys, and exterior red lead paint.***

- **Compared with adults, the absorption is greater in children & infants and hence they are particularly vulnerable to lead toxicity.**

- **Clinically, overt lead poisoning has disappeared due to the reduction of lead from many sources, particularly from gasoline and paints.**

Lead – Environmental Source:

- Urban air is better with unleaded gasoline.
- Soil contaminated with lead paint.
- Batteries, paint chips.
- Water supply- plumbing.
- Children can absorb up to 50% from diet in food/water.
- Adults absorb about ~10%.

Lead (Pb) Toxicity – *Pathophysiology:*

❖ **The toxicity of lead is related to its multiple biochemical effects:**

- ***High affinity for sulfhydryl groups.*** The most important enzymes inhibited by lead due to this mechanism are involved in heme biosynthesis: ***δ-aminolevulinic acid dehydratase and ferroketolase***. ***These enzymes catalyze the incorporation of iron into the heme molecule***, and hence patients develop *hypochromic anemia.*

- ***Competition with calcium ions.*** As a divalent cation, *lead competes with calcium and is stored in bone*. It also *interferes with nerve transmission and brain development.*

- ***Inhibition of membrane-associated enzymes.*** Lead inhibits ***5'-nucleotidase activity and sodium-potassium ion pumps***, leading to *decreased survival of red blood cells (hemolysis), renal damage, and hypertension.*

- ***Impaired production*** of ***1,25-dihydroxyvitamin D***, the active metabolite of *vitamin D.*

Lead (Pb) Toxicity – *Pathophysiology:*

- **Acute lead toxicity:** ***Acute colicky abdominal pain, CNS toxicity (encephalopathy in children).***

- **Chronic lead toxicity:** ***Affecting CNS, GIT, kidney.***

- **Binding of lead to *protein disulfide groups* leads to injury, particularly in:**

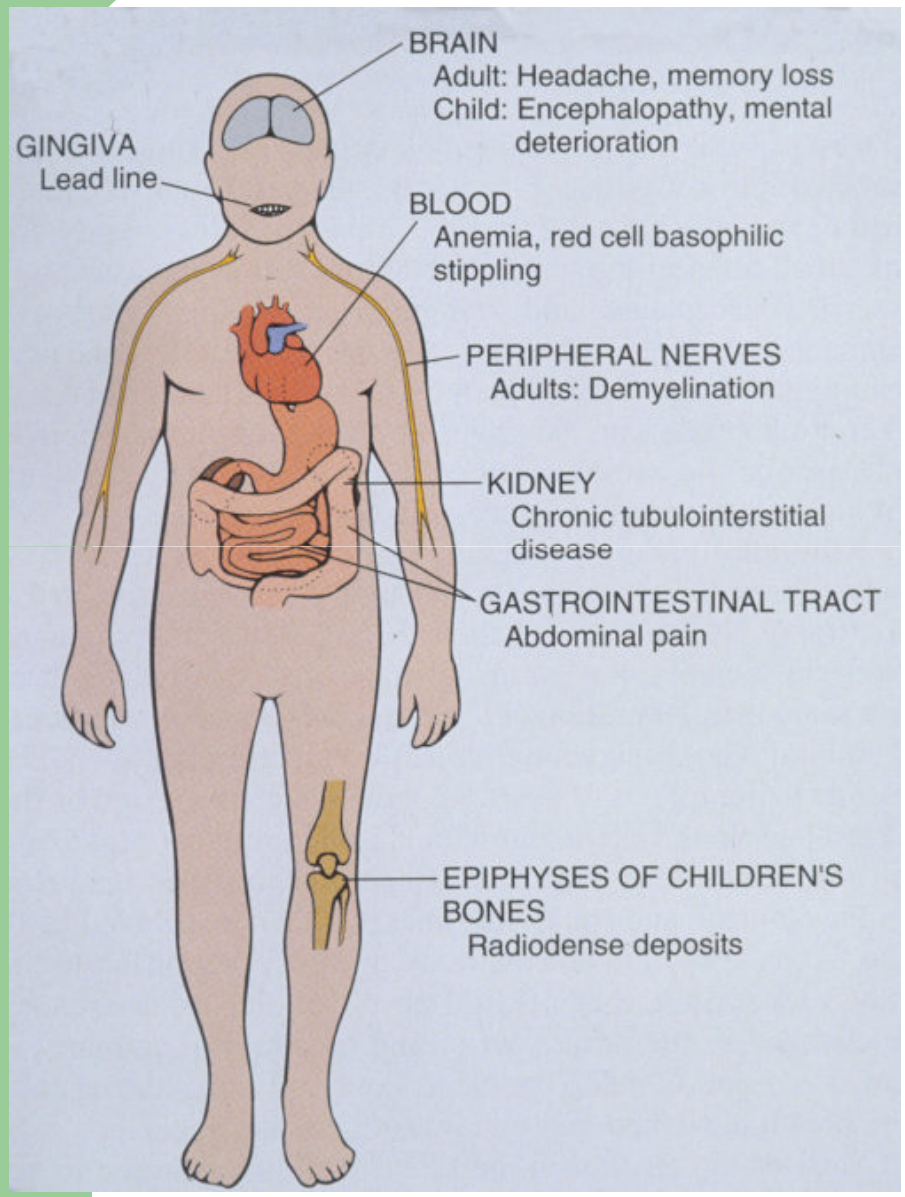
  - ***Nervous system: Mental Retardation, demyelinating peripheral neuropathy.***

  - ***Blood (haeme synthesis): Hypochromic microcytic anemia.***

  - ***GIT: Colic and anorexia.***

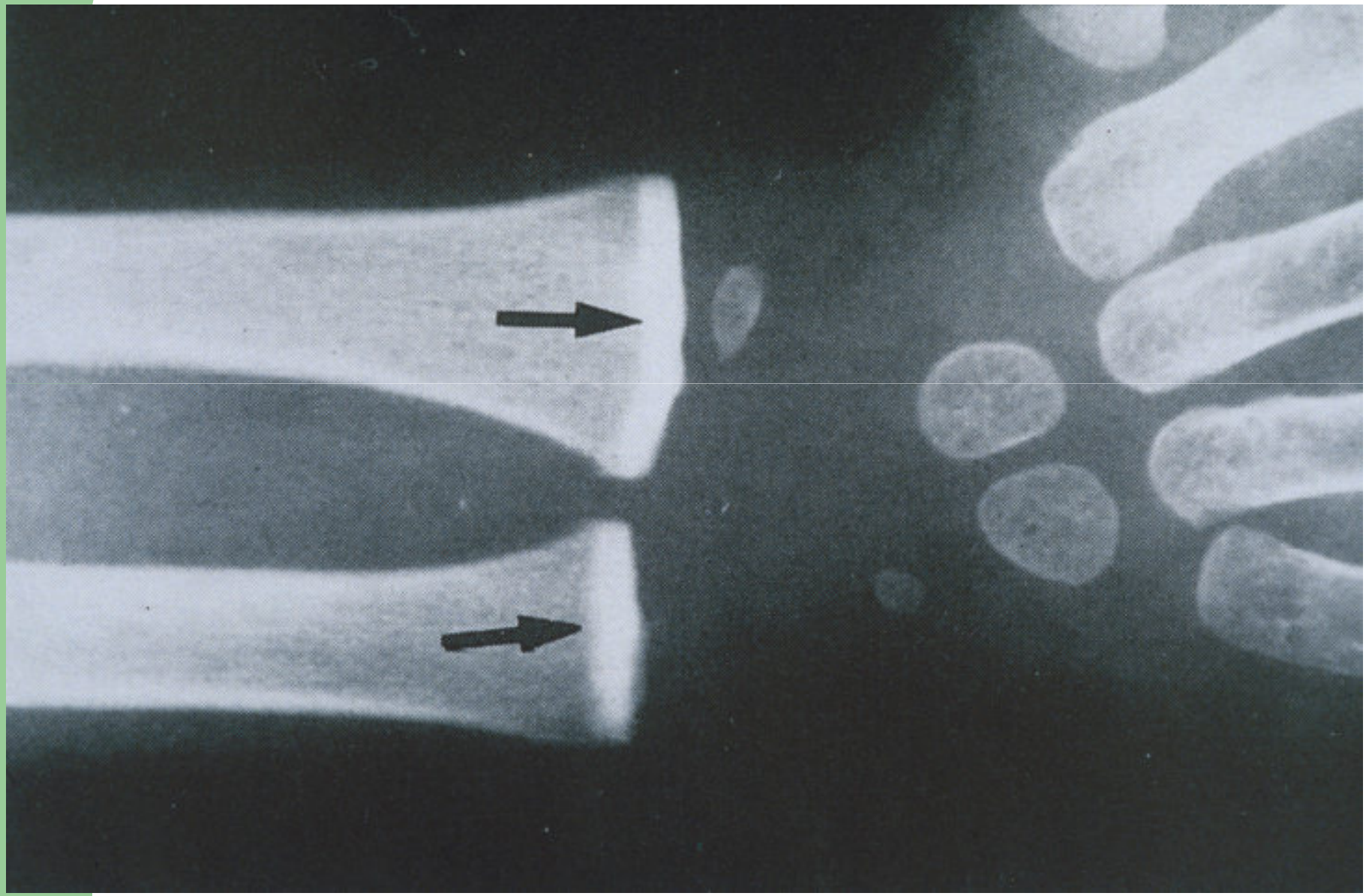
  - ***Kidney: Interstitial fibrosis., gout and renal failure.***

Lead (Pb) Accumulation:

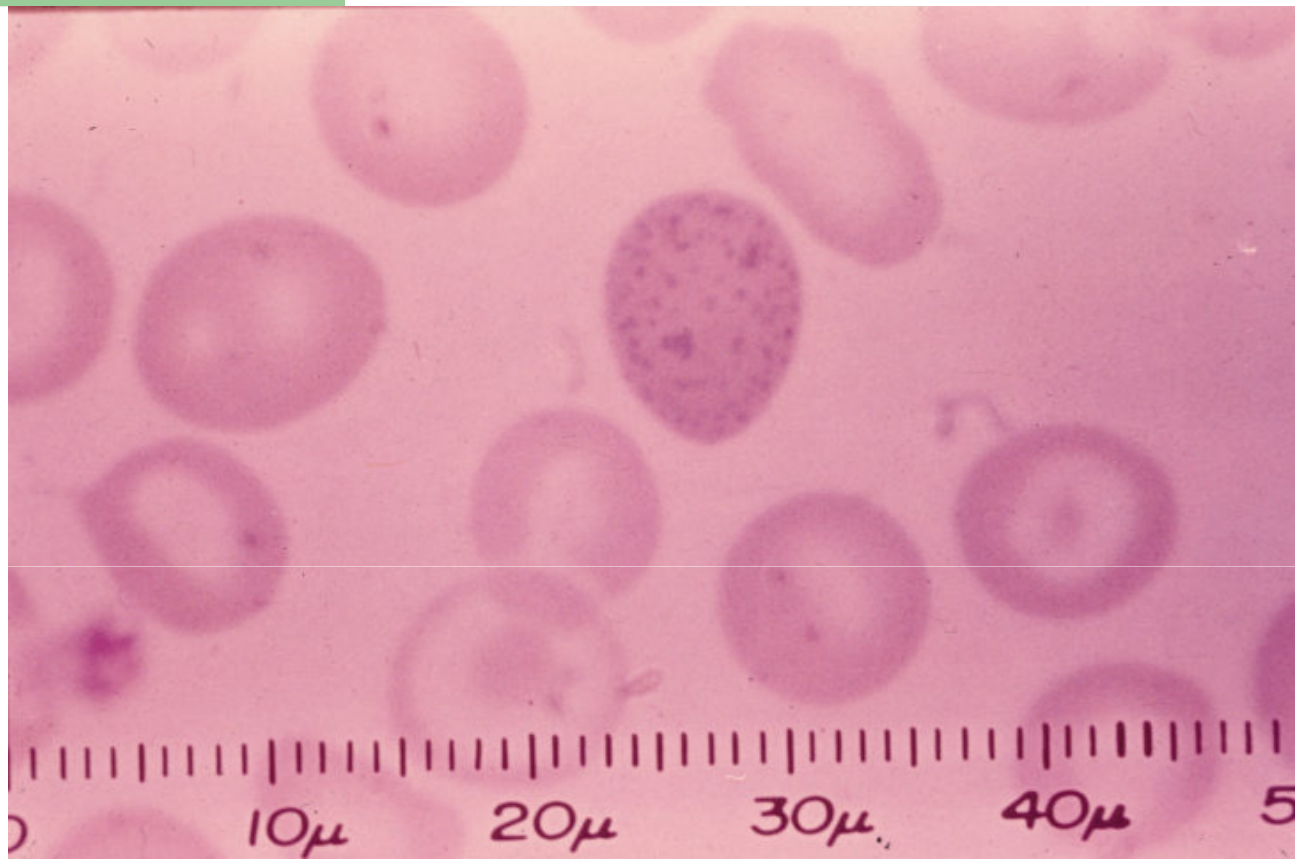


- **Bone (85%).**
- **Soft Tissue (15%).**
- **Free Erythrocyte Protoporphyrin levels (FEP); *FEP is a screening method for Lead. (FEP is increased in lead poisoning).***

Lead (Pb) Accumulation - *Bone*:



Lead (Pb) Toxicity:



***Basophilic stippling of erythrocyte**. The microscopic image shows erythrocytes (red blood cells) which are microcytic (decreased in cellular size) and hypochromic (decreased "color" as manifested by an increased area of central pallor). This is blood from a 5 yr old patient who had mental retardation with an elevated free erythrocyte protoporphyrin (FEP) and blood lead. An assessment of his environment showed peeling lead paint, lead in the soil, and an abnormal concentrations of lead in the drinking water.*

Heavy Metals – Mercury (Hg):

- Mercury has had many uses throughout history such as a ***pigment in cave paintings, a cosmetic, a remedy for syphilis, and a component of diuretics***.

- Poisoning from inhalation of mercury vapors has long been recognized and is associated with ***tremor, gingivitis, and bizarre behavior***, such as that displayed by the Mad Hatter in *Alice in Wonderland*.

- There are three forms of mercury: ***metallic mercury*** (also referred to as elemental mercury), ***inorganic mercury*** compounds (mostly mercuric chloride), and ***organic mercury*** (mostly methyl mercury).

- Today, the main sources of exposure to mercury are ***contaminated fish (methyl mercury) and mercury vapors released from metallic mercury in dental amalgams***, a possible occupational hazard for dental workers. In some areas of the world, mercury used in gold mining has contaminated rivers and streams.

- Inorganic mercury from the natural degassing of the earth's crust or from industrial contamination is converted to organic compounds such as methyl mercury by bacteria.

Heavy Metals – Mercury (Hg):

- Disasters caused by the consumption of fish contaminated by the release of methyl from industrial sources, in Minamata Bay and the Agano River in Japan in 1956, caused widespread mortality and morbidity.

- Acute exposure through consumption of bread made from grain treated with a methyl mercury–based fungicide in Iraq in 1971 resulted in hundreds of deaths and thousands of hospitalizations.

- The medical disorders associated with the Minamata episode became known as ***"Minamata disease"*** and include cerebral palsy, deafness, blindness, mental retardation, and major CNS defects in children exposed in utero.

- For unclear reasons, ***the developing brain is extremely sensitive to methyl mercury***. The lipid solubility of methyl mercury and metallic mercury facilitate their accumulation in the brain, disturbing neuromotor, cognitive, and behavioral functions.

Heavy Metals – Mercury (Hg):

- ***Mercury binds with high affinity to thiol groups***, a property that contributes to its toxicity. ***Intracellular glutathione, acting as thiol donor, is the main protective mechanism against mercury-induced CNS and kidney damage.***

- Mercury continues to be released into the environment by power plants and other industrial sources, and there are serious concerns about the effects of chronic low- level exposure to methyl mercury in the food supply.

- To protect against potential fetal brain damage, the ***Centers for Disease Control and Prevention has recommended that pregnant women reduce their consumption of fish known to contain mercury to a minimum***.

- There has been much publicity about a possible relationship between ***thimerosal*** *(a compound that contains methyl mercury, used until recently as a preservative in some vaccines) and the development of autism*, but multiple studies have failed to find evidence of a causal relationship.

Chelation Therapy:

- **Chelation therapy** is the administration of chelating agents to remove heavy metals from the body. The most obvious treatment of poisoning from excessive metal exposure is to remove the metal from the body, thus the development of chelating agents.

- Chelation therapy has a long history of use in clinical toxicology. For the most common forms of heavy metal intoxication; ***lead , arsenic, mercury.***

- A number of chelating agents are available. Ethylene diamine tetraacetate ***(EDTA)*** *is used intravenously and is the treatment of choice for lead poisoning. Dimercaptosuccinic acid* ***(DMSA)*** *has been recommended for the treatment of lead poisoning in children by Poison Centers around the world.*

- Other chelating agents, such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) and alpha lipoic acid (ALA) are used in conventional & alternative medicine.

- The use of chelation as alternative therapy can prove fatal, and medical evidence does not support the effectiveness of chelation therapy for any other purpose than the treatment of heavy metal poisoning.

Chelation Therapy:

- The ideal chelating agent would bind readily only with the target metal, forming a non-toxic complex that would be excreted easily from the body. Unfortunately, this is easier said than done. British anti-lewisite (***BAL), for example, binds with a range of metals, but actually enhances the toxicity of cadmium***.

- A consistent undesirable property of all chelating agents is that they also complex with essential metals and increase their excretion from the body. The two most common essential metals adversely affected by chelating agents are ***calcium and zinc.***

- Excessive lead exposure can be treated with the chelating agent ***calcium-EDTA, not its related sodium salt*** because this would greatly increase excretion of calcium, potentially having toxic side effects:

  - Blood lead levels are reduced when the lead displaces the calcium to bind with EDT A and is then excreted in the urine. This results in a movement of lead from the soft tissues such as muscle into the blood, which can result in a spike in blood lead levels that may elevate brain lead levels and cause subsequent neurological effects.

Chelation Therapy:

- ***In summary***, while chelating agents can be an effective treatment in some circumstances, they must be approached cautiously.

- The most important action is to identify the source of exposure and reduce or eliminate it. It is also very important to consider what essential metals may be bound and excreted by the agent.

- The body tightly regulates most essential metals and disruption of these levels can have serious undesirable (toxic) effects.