General Pharmacology

Medication use during pregnancy
Clinical Toxicology

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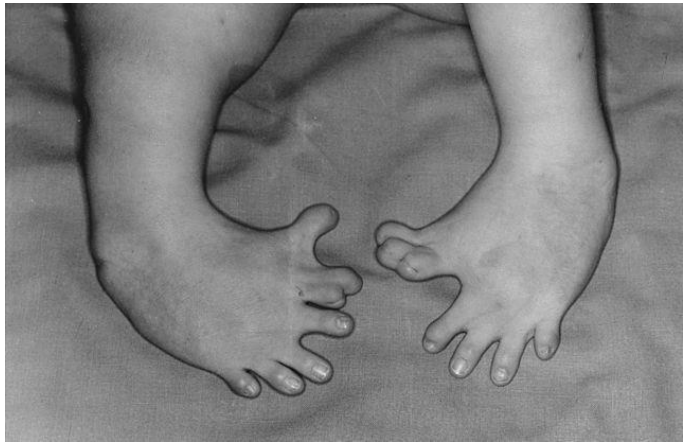


The Thalidomide Disaster

On October 1, 1957, Chemie Grünenthal GmbH marketed Thalidomide in West Germany. It was originally used as a sleeping tablet and **was considered safe for pregnant women.** It later relieved **morning sickness** in pregnant women. Thousands of women used it, and it appeared to work until the following year, when thousands of kids were born with birth defects. **They varied from brain damage to limb deformities.**

Medication use during pregnancy

- Drug therapy in pregnancy may cause anxiety to both providers and patients due to uncertainty regarding dosing and safety.
- The needs for medications are high as the incidence of maternal chronic illnesses such as hypertension or diabetes are rising.
- More than 40% of pregnancies are not planned. To prevent the use of unsafe medications in (early) pregnancy, Women with chronic conditions or recurrent episodes of illness should be treated with pregnancy-compatible drugs, even if no pregnancy is planned.

Medication use during pregnancy

- Most therapies for chronic diseases use pharmacologic medications that have not been thoroughly investigated in pregnant and lactating women, so the exact hazards and benefits of such interventions are unknown.

- **Medication use during pregnancy is of concern because:**
- The physiology of pregnancy affects the pharmokinetics of drugs.
- Some medications can reach the fetus and cause harm.

Pharmacokinetics of Drugs in Pregnancy

- Stomach pH, transit time, metabolism, uptake, and efflux transport processes are altered during pregnancy, thereby potentially changing the **drug's bioavailability.**
- Drug **distribution, metabolism and elimination** maybe altered during pregnancy.
- One of the biggest physiologic changes in **pregnancy is the expansion of plasma volume by approximately 50%.**

Fetal Development and Vulnerability

- Human embryogenesis, and the early stages of cell division and differentiation in the human embryo, is dependent on the ability of stem cells to divide, migrate, and specialize.

- This complex mechanism results in **teratogenicity and vulnerability**. The teratogenic period could be **particularly severe from day 31 to 71 after the last menstrual period in a 28-day cycle**.

FDA Pregnancy Drug Risk Categories

Pregnancy Category	Description
A	Appropriate human studies - no risk
B	Insufficient human studies, but animal research suggests safety **or**: Animal studies show issues but human studies show safety
C	Insufficient human studies, but animal studies show problems **or**: No animal studies, and insufficient human studies
D	Human studies, with/without animal research show fetal risks, but the drug is important to some women to treat their conditions
X	Fetal risks are evident; there are no situations where the risk/benefit justifies use

These categories were not clear and often led to wrong conclusions. As of June 2015, all new FDA-approved drugs have a new pregnant label that included a risk summary, clinical considerations, and supporting data.

FDA Pregnancy Drug Risk Categories

After

2015

The U.S. Food and Drug Administration (FDA) implemented the Pregnancy Lactation Labeling Rule (PLLR).

Pregnancy Lactation Labeling Rule (PLLR)

- The PLLR provides a set framework for drug manufacturers to provide information about the **risks and benefits of using prescription drugs and biologic products during pregnancy and lactation**.
- Prescribing information for clinicians has been updated in the labeling subsections:

1. **Pregnancy:** narrative risk summary of the maternal and fetal risks based on available human, animal, and pharmacologic data.
2. **Lactation**: the amount of drug in breast milk and potential effects on the breastfed infant
3. **Females and Males of Reproductive Potential**: the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug.

Table 1. Drugs Identified With Known Risk of Teratogenicity

Human teratogen	Identifiable or Related Outcome
Alcohol	Fetal alcohol syndrome: IUGR and FTT; decreased muscle tone and poor coordination; developmental delay; and craniofacial abnormalities
Angiotensin converting enzyme inhibitors	Oligohydramnios; hypocalvaria; IUGR; renal effects (renal tubular dysplasia, anuria/oliguria, and hyperkalemia, end-stage renal failure); neonatal hypotension; cardiovascular abnormalities (e.g. patent ductus arteriosus, aortic arch obstructive); fetal death
Carbamazepine	10 × increased risk of neural tube defects; fetal anticonvulsant syndrome (IUGR, developmental delay, craniofacial defects, fingernail hypoplasia)
Cocaine	Placental abruption, fetal loss, low birth weight, microcephaly, limb and urinary tract malformations, poor neurodevelopmental performance
Coumarin anticoagulants	Fetal warfarin syndrome (nasal hypoplasia, eye abnormalities [i.e. optic atrophy, microphthalmia, and blindness]); epiphyseal stippling, hypoplasia of the extremities and fingernails; low birth weight; developmental retardation; fetal hemorrhage
Diethylstilbestrol (DES)	Clear cell adenocarcinoma and benign adenosis in exposed offspring
Methotrexate (Folic acid antagonists)	Central nervous system (i.e. anencephaly, neural tube defects); cardiovascular (tetralogy of Fallot); craniofacial (i.e. absence of lambdoid, coronal sutures, and frontal bone, low set ears, depressed/wide nasal bridge); long webbed fingers and absence of digits; growth and mental retardation
Phenytoin	Fetal anticonvulsant syndrome: IUGR; dysmorphic craniofacial features (i.e. microcephaly, low nasal bridge, cleft lip and cleft palate, maxillary hypoplasia); limb defects (i.e. hypoplastic nails and distal phalanges); cardiac defects
Isotretinoin	Spontaneous abortion; craniofacial abnormalities (i.e. microcephalus, hydrocephalus, deformity of ears, face, limbs); thymic hypoplasia; cardiac defects
Lithium	Tricuspid valve malformation (Ebstein's anomaly)
Misoprostol	Association with limb and neural tube defects
Tetracyclines	Weakened fetal bones, tooth enamel dysplasia, permanent tooth discoloration
Thalidomide	Limb, ear, cardiovascular and gastrointestinal anomalies
Valproate	Neural tube defects; fetal valproate syndrome: dysmorphic facial anomalies including microcephaly, hypertelorism, prominent forehead, low flat nasal bridge, low-set or odd-shaped ears

FTT, failure to thrive; IUGR, intrauterine growth retardation

Teratogenic Drugs

Only drug name is required

Clinical Toxicology

Introduction to Toxicology

Toxicology studies the harmful effects of chemical substances on all biological systems.

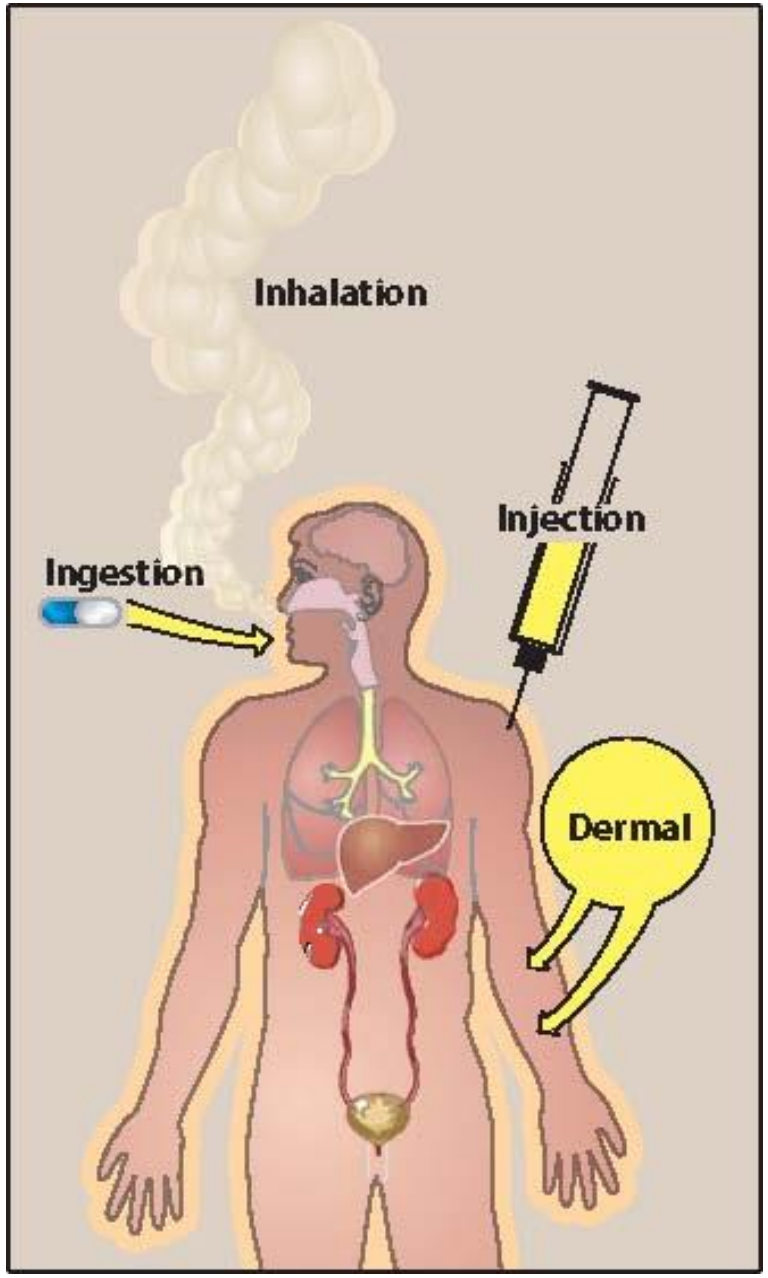
Occupational toxicology is the study of substances that are found at work.

Environmental toxicology : is the study of potentially harmful effects of substances found in the environment as pollutants on living organisms .

Clinical Toxicology

- Toxins can be:

1. Inhaled
2. Insufflated (snorted)
3. Orally ingested
4. Injected
5. Absorbed dermally



Emergency treatment of poisoned patient

- Treat the patient not the poison:

I. Airway breathing circulation (ABC): give oxygen, IV access, heart monitoring

II. Life threatening toxic effects such as profound changes in blood pressure, heart rhythm , respiration and body temperature.

III. Correction acid/ base and electrolytes disturbance.

- If the patient have altered mental status, consider giving the " coma cocktail" (dextrose(for hypoglycemia), naloxone(possible opioid or clonidine toxicity, and thiamine (for ethanol- induced Wernicke encephalopathy).

Decontamination

- Once patient is stabilized decontamination can occur.
- Eyes and skin exposure: flushing and washing
- Gastrointestinal decontamination:

1. Gastric lavage
2. Activated charcoal
3. Whole bowel irrigation

Elimination enhancement

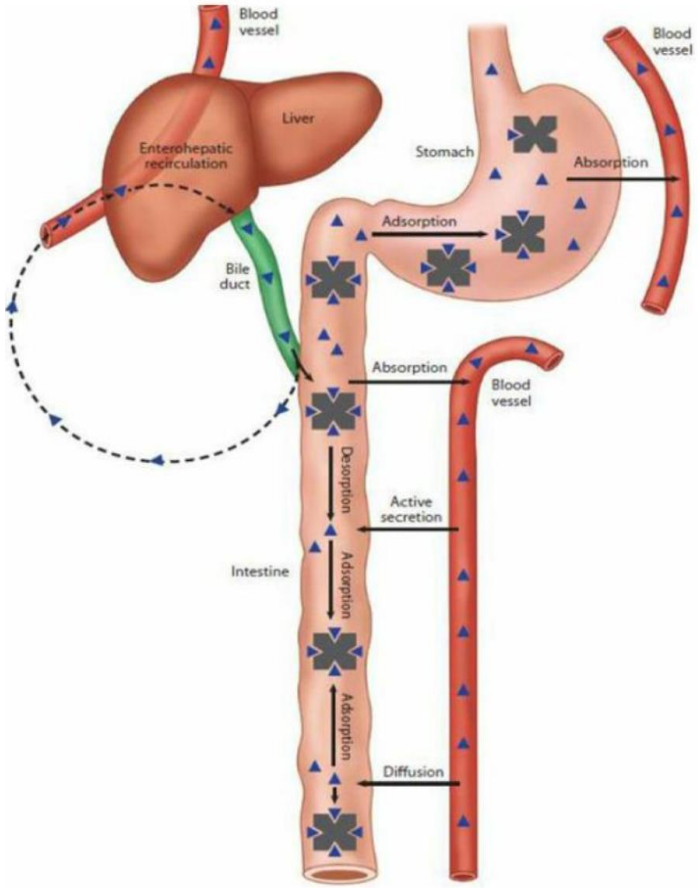
1. **Hemodialysis** e.g., methanol, salicylate and lithium.
2. **Urinary alkalinization**(by administration of sodium bicarbonate): enhances urinary excretions of salicylate and phenobarbital.

❖**Serum pH shouldn't increase more than 7.55**

3. **Multiple dose activated charcoal**: e.g., phenobarbital, digoxin, and carbamazepine)

Activated Charcoal

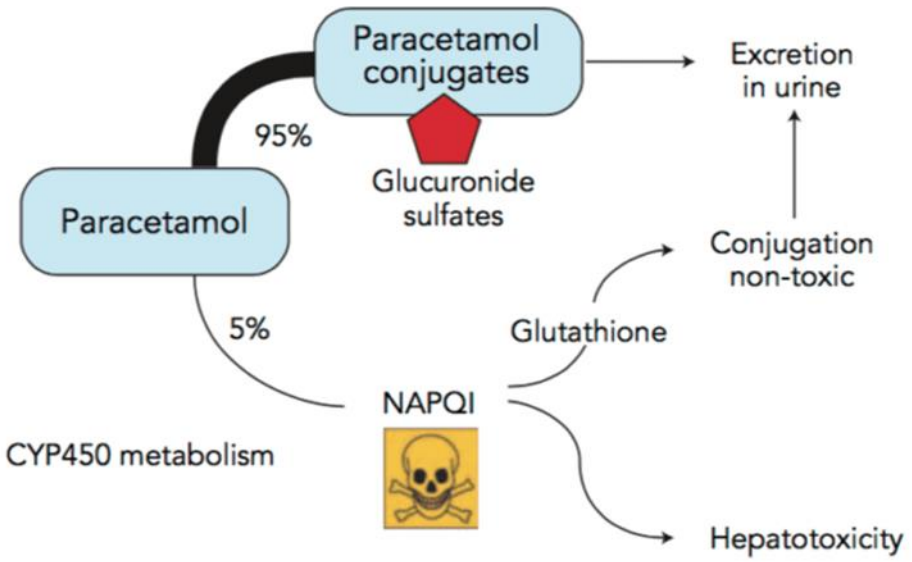
- Charcoal is extremely porous and has high surface area which create gradient a cross the lumen of the gut.
- Medications traverse from area of high concentration to area to area of low concentration, promoting absorbed medication to cross back into the gut to be adsorbed by activated charcoal, Also, activated charcoal blocks the reabsorption of medication that undergo enterohepatic recirculation by adsorbing the substance to activated charcoal.
- It **doesn't effectively** adsorb metals(e.g., lead, iron, lithium), corrosives, and alcohols.
- The most important contraindication is a <u>not fully conscious patient with no swallowing reflex.</u>



Select Pharmacological and occupational toxicities

- **Acetaminophen**
- **Alcohols**
- **Carbon monoxide**
- **lead**

Acetaminophen (Paracetamol)



NAPQI: *N*-acetyl-*p*-benzoquinone imine

At high doses normal metabolic pathways become saturated leading to the production of hepatotoxic metabolites (NAPQI).

As hepatic stores of glutathione are depleted and NAPQI binding to hepatocytes induces cell death and hepatic necrosis.

Acetaminophen (or Paracetamol)

Phase 1 (0 to 24 hours): loss of appetite, nausea, vomiting, general malaise

Phase 2 (24 to 72 hours): abdominal pain, increased liver enzymes

Phase 3 (72 to 96 hours): liver necrosis, jaundice, encephalopathy, renal failure, death

Phase 4 (>4 days to 2 weeks): complete resolution of symptoms and organ failure

- Antidote is N-acetylcysteine (NAC).
- NAC replenishes hepatic glutathione and may also act as a glutathione substitute, combining directly with the toxic metabolite.
- Intravenous NAC is most effective when it is initiated within 8 to 10 hours of ingestion

Alcohols

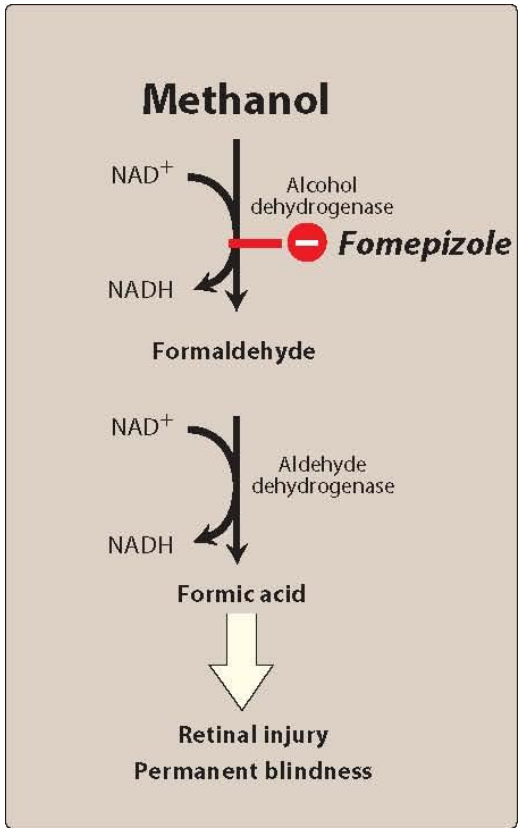
1. **Methanol (wood alcohol) and ethylene glycol:**

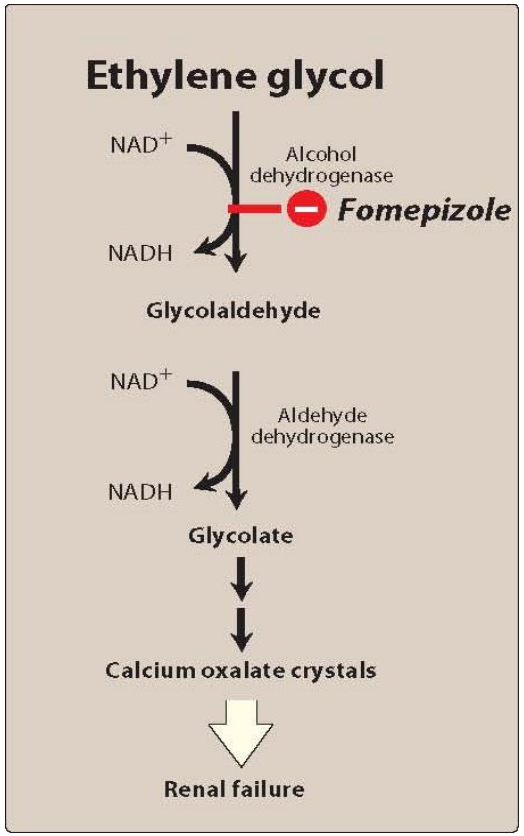
- **Methanol** is found in windshield washer flued and airplane fuel. It metabolized to formic acids (toxic)
- **Ethylene glycol** is found in radiator antifreeze. It metabolized to toxic metabolites such as Glycolate.
- **Primary alcohol are not toxic but leads to CNS depression. However, their metabolites are toxic.**

If untreated:

- Methanol may cause blindness, metabolic acidosis, seizures and coma.
- Ethylene glycol may cause renal failure , hypocalcemia, metabolic acidosis and heart failure.

Methanol and ethylene glycol





Treatment:

- **Antidote is Fomepizole.**
- **Hemodialysis** to remove toxic acid that are already produced
- Administration of cofactors as folate for methanol, and thiamine and Pyridoxine for Ethylene glycol.

Alcohols

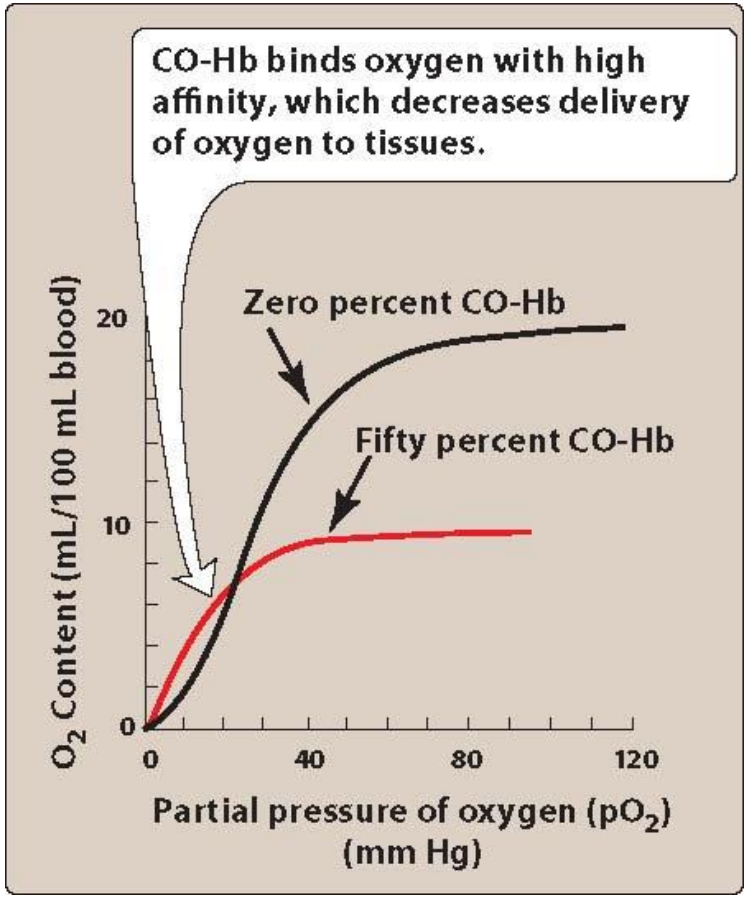
2. **Isopropanol (rubbing alcohol)** : 2ndary alcohol, It is metabolized to acetone.

- It leads to CNS depression and GI irritation
- No antidote
- Supportive care

Carbon Monoxide

- **Carbon monoxide is colorless odorless and tasteless gas.**
- Sources: automobile, poorly vented furnaces, fireplaces and wood burning stoves ad kerosene space heaters, charcoal grills and generators.
- Binds to hemoglobin rabidly and forms carboxyhemoglobin.
- **The binding affinity of Carbon monoxide to hemoglobin is 230 to 270 greater than that of oxygen.**

Effect of CO on the oxygen affinity of hemoglobin



Co-Hb: carbon monoxyhemoglobin.

Treatment:

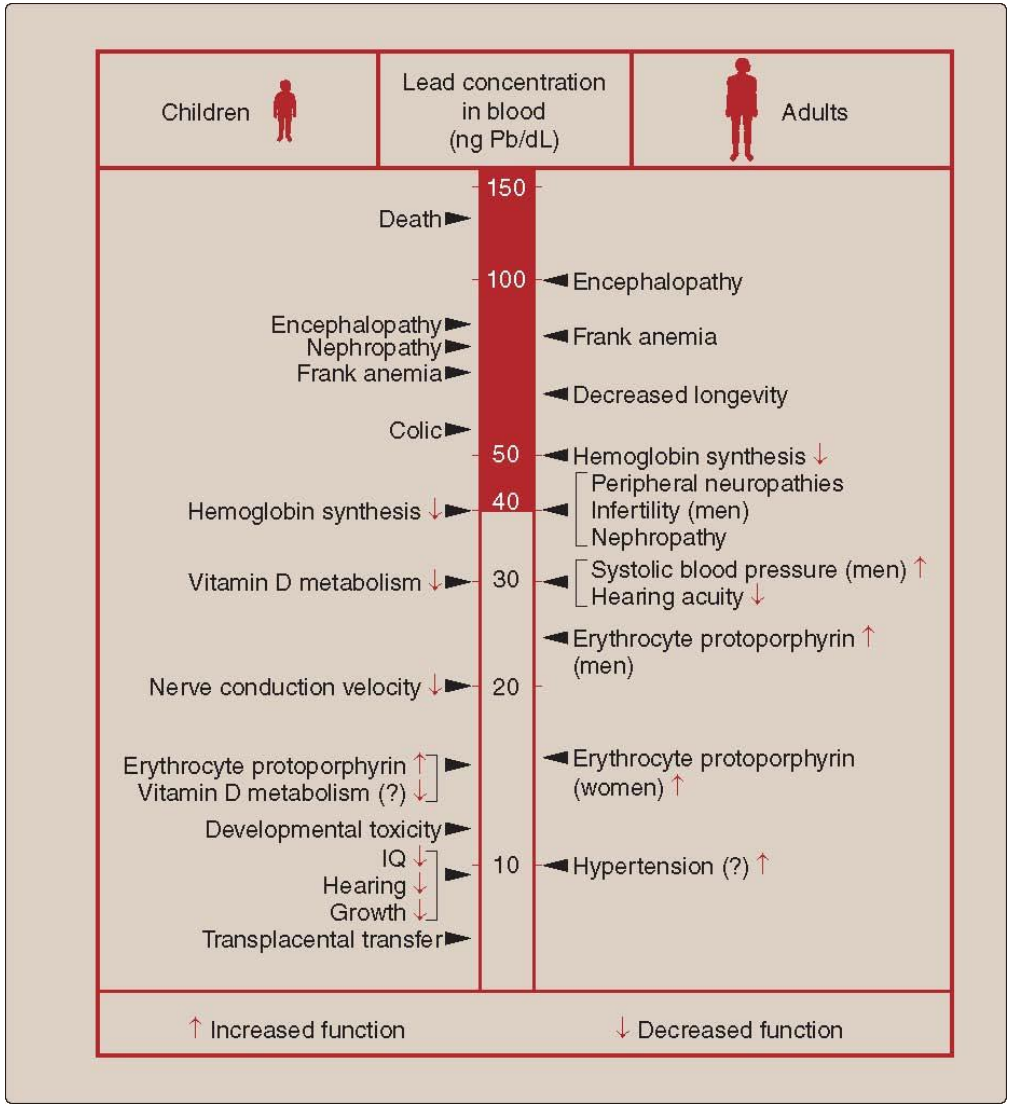
- To remove the source of carbon monoxide.
- Give 100% oxygen
- Oxygenation in hyperbaric Chamber

Lead

- **Source of exposure is** old paint (houses constructed prior 1978) , industrial pollution, food, and contaminated water.

- Adults absorb 10% of ingested lead, whereas children absorb 40%.

Lead effects in children and adult



Treatment:

The first step in treating lead poisoning is to remove the source of the contamination.

Chelation therapy: recommended for children with a blood level of 45 mcg/dL or greater and adults with high blood levels of lead or symptoms of lead poisoning.

Chelation agents contain sulfhydryl groups that bind or chelate lead, and the resulting complex is excreted either renally or hepatically.

The chelation agents:

- Succimer (DMSA) is given orally
- Dimercaprol and edetate (EDTA) are administered parenterally.

Antidotes:

For a variety of chemicals and poisons, specific chemical antidotes have been developed.

Poison	Antidote
Acetaminophen	N-acetylcysteine
Benzodiazepine	Flumazenil
Carbon monoxide	Oxygen(hyperbaric chamber)
Heparin	Protamine sulfate
Iron	Deferoxamine
Lead	Succimer (DMSA), Dimercaprol, edetate (EDTA)
Methanol and ethylene glycol	Fomepizole
Opiates	Naloxone
Warfarin	Vitamin K
Organophosphates	Atropine, pralidoxime