Factors affecting metabolism

- **Age** The metabolizing enzymes in neonates are not fully developed, therefore those cannot efficiently metabolize drugs. Also in the elderly, enzymatic systems may not function well leading to same conclusion.
- **Sex** (activity is generally higher in males than in females). Linked to hormonal differences. **Genetics** - Genetic differences can influence amount and efficiency of metabolic enzymes
- **Organ** (activity of many enzymes is highest in the liver)
- **General health status** (e.g., hepatic injury decreases metabolic activity in the liver)

- **Pharmacogenetic factors** Some individuals may be deficient in some enzymes, regardless of sexMales who are deficient in **glucose -6-phosphate dehydrogenase** are more prone to **hemolysis** when subjected to some drugs like **sulfonamides**
- **Pregnancy** Hepatic metabolism of drugs is decreased in pregnancy.
- **Nutritional status** (liver dysfunction) Malnutrition can cause a decreased level of some enzyme system and liver dysfunction can lead to decreased metabolism

- **Bioactivation** Some drugs may be transformed to more toxic metabolites
- **Enzyme induction/inhibition** A result of this is either an increase in the metabolism or a decrease in the drug metabolism
- **Changes in the kinetic mechanism**: depending on whether the concentration of drug is in the therapeutic or overdose range

Factors affecting metabolism
The main target organs for the systemic toxicity of xenobiotics are:

- Skin, mucous membrane
- Lungs
- Liver, kidney
- Bone marrow
- Immune system
- Nervous system (central & peripheral)
- Cardiovascular system
- Reproductive system
- Muscle and bones

Organs particularly susceptible to toxin damage are the liver and kidney

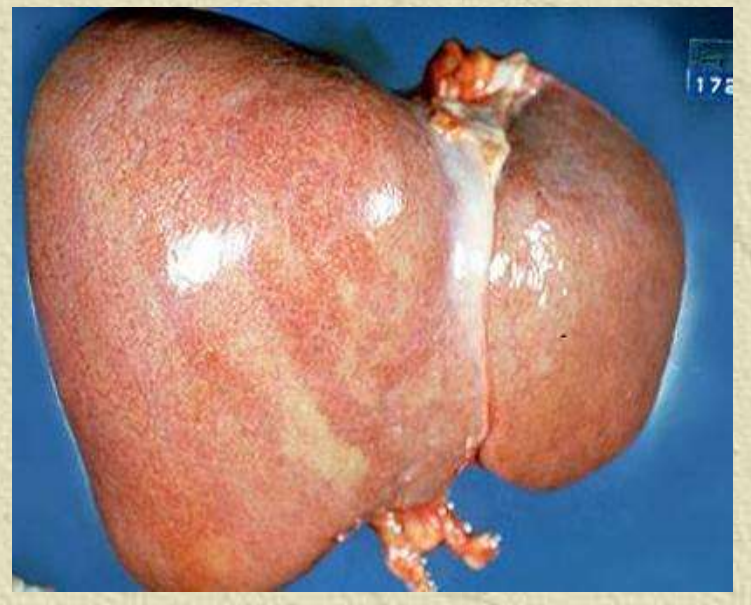
Hepatotoxicity

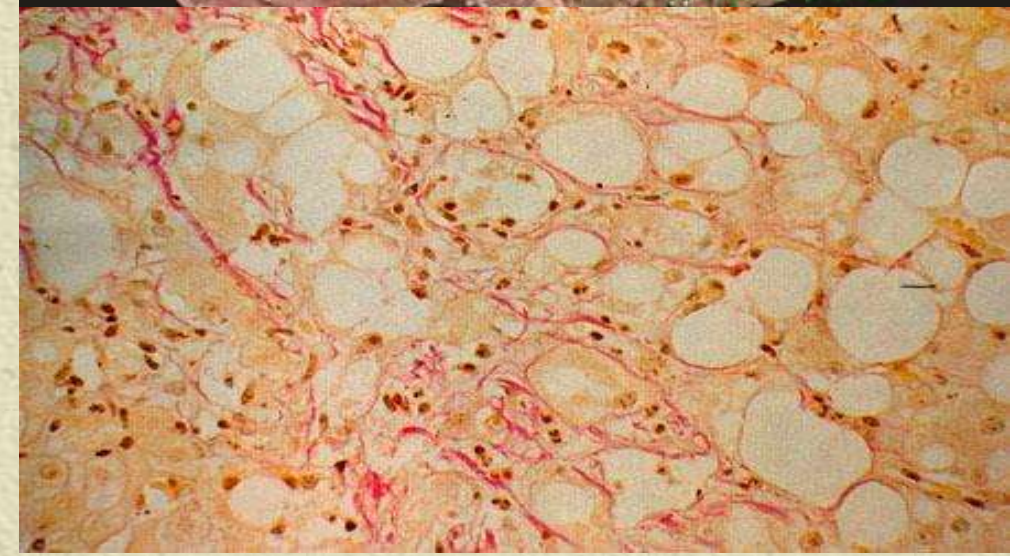
(i) hepatic necrosis
paracetamol poisoning

(ii) hepatic inflammation (hepatitis)
halothane can covalently bind to liver proteins to trigger an autoimmune reaction

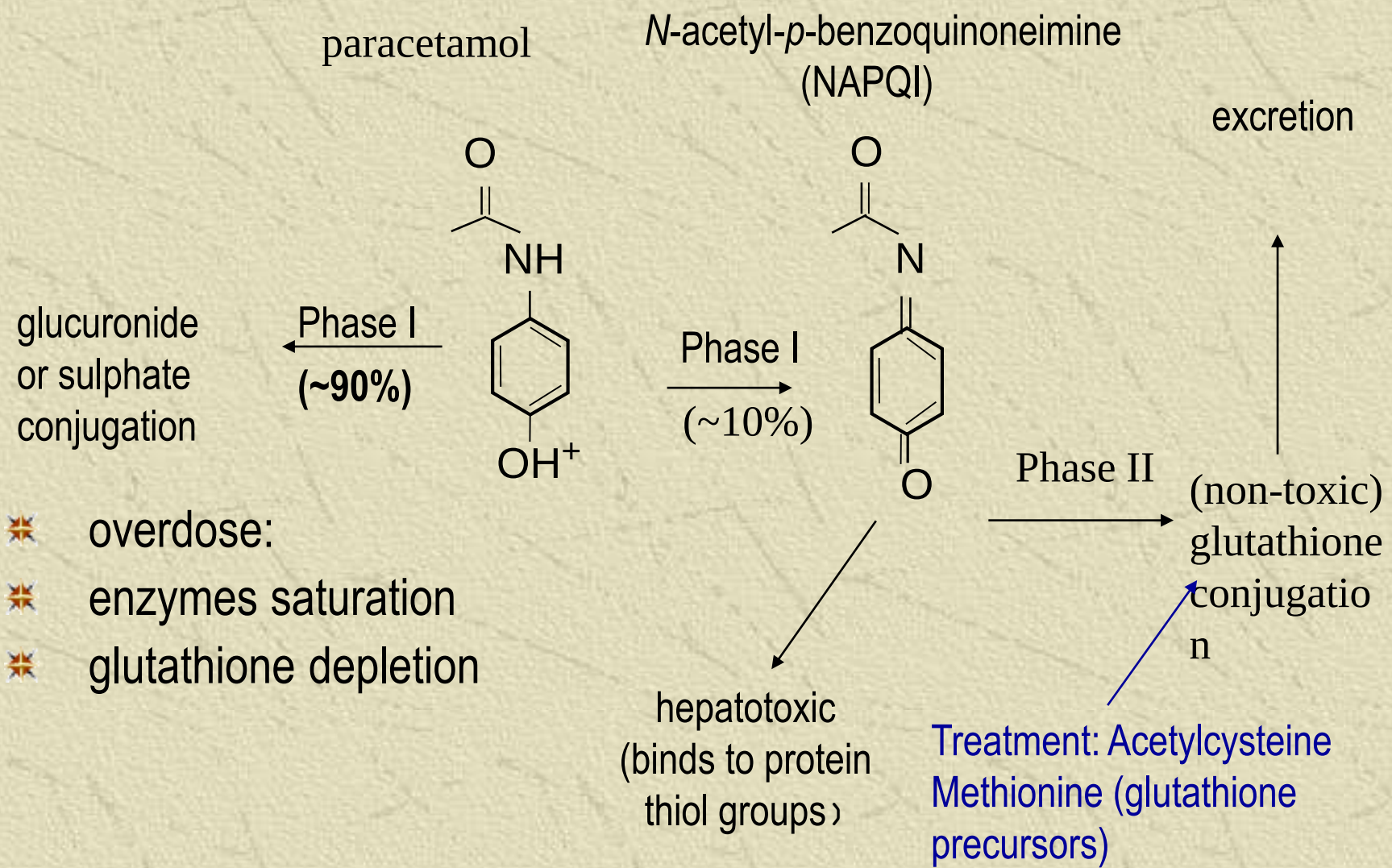
(iii) chronic liver damage (cirrhosis)
long-term ethanol abuse causes cellular toxicity and inflammation and malnutrition as ethanol becomes a food source

Alcoholism leads to fat accumulation in the liver, hyperlipidemia, and cirrhosis.





Paracetamol is a prominent cause of hepatic poisoning 48 % of all poison admissions and >200 deaths/year)



- overdose:
- enzymes saturation
- glutathione depletion

Nephrotoxicity

(i) changes in glomerular filration rate (GFR)

Largely due to drugs that alter blood flow :

NSAIDs (eg. aspirin) reduce prostaglandins which in turn reduces blood flow/GFR

ACE (angiotensin-converting-enzyme – RR↑)inhibitors (eg. ramipril) increase blood flow/GFR

(ii) allergic nephritis

allergic reaction to NSAIDs (eg. fenoprofen) and antibiotics (eg. metacillin)

(iii) chronic nephritis

long-term NSAID and paracetamol use

Neurotoxicity

- Compounds that have a toxic effect on the nervous system:
  - Toxicants of the central nervous system (CNS)
  - Toxicants of the peripheral nervous system (PNS)
  - Toxicants of a combined effect

- **CNS inhibitors:**
  - Chlorinated hydrocarbons, benzene, aceton, dietyl eter
- **Psychomimetics:**
  - They can disturb psychical activities
  - Mescalin, phenylethylamine derivatives, indole derivaties
- **Compounds that inhibiting the respiration center**
  - Narcotics, hydrocarbons

- **Convulsion toxicants**
  - Convulsion in central origin
  - Organophosphorus pesticide
- **Toxicants, paralyzing transmission of nerve impulses to the muscle**
  - Botulinum
- **Toxicants, paralyzing transmission of nerve impulses in the nerve**
  - Tetrodotoxin

- **Neuroparalytic poisons:**
  - anticholinesteratic
- **Toxicants, acting with mediators or synaptic poisons:**
  - Adrenaline, ephedrine, hydrazines, etc.

According to the nature of their adverse effect on the target organs, the toxicants can be divided as: (1)

- Irritants
  - Cause damage to the eyes & mucous membranes, ex: bromine, chlorine, ammonia, etc.
- Corrosive substances
  - Corrode the skin & mucous membranes
- Substances that cause toxic pulmonary edema
  - Chlorine, ammonia, nitrogen oxide
- Blockers of mitochondrial respiratory enzymes
  - Cyanides, salicylic acid

According to the nature of their adverse effect on the target organs, the toxicants can be divided as: (2)

- Inhibitors of thiol enzymes
  - Heavy metals
- Blockers of Krebs cycle (citrate cycle)
  - fluoroacetates
- Emetic substances
  - Apomorphine, zinc, copper sulfate
- Neurotoxicants
- Cardiotoxicants
  - Selectively damage the heart
  - Ex: cardioglucosides, digitoxin, aconitine, etc.

According to the nature of their adverse effect on the target organs, the toxicants can be divided as: (3)

- Hepatotoxic substances
  - Damage the liver
  - Carbon tetrachloride, chloroform,etc.
- Nephrotoxic substances
  - Damage the kidneys
  - Mercury, chlorine, carbon tetrachloride, lead
- Substances that damage the bone marrow and blood cells
  - Nitrobenzene, benzene, etc.

According to the nature of their adverse effect on the target organs, the toxicants can be divided as: (4)

- Asphyxiants
  - Substances that cause a reduction of blood's ability to bind and transport oxygen
- Anticoagulants
  - Substances that disturb blood coagulation
  - Dicumarine, heparin, etc.
- Hemolytic substances
  - Mushroom toxicants, phenyl-hydrazine, saponins, etc.
- Histamine and antihistaminic compounds

Based on the character of damage of a cell/ an organism, the toxic effects can be grouped as (1):

- Generally toxic
  - Damage of the organism as a whole
- Dystrophic
  - Causing the aging cells or tissues
- Genotoxic
  - Alteration of the genetic material (DNA, RNA)
- Mutagenic
  - Generation of irreversible changes in the hereditary materials (chromosomes, genes) of an organism

Based on the character of damage of a cell/ an organism, the toxic effects can be grouped as (2):

- Carcinogenic
  - Genaration of malignant tumors
- Gonadotropic
  - Harming and inhibiting the development of the germ cells
- Teratogenic
  - Evoking disorders in the embryonal development
- Sensibilizating
  - Making an organism ultrasensitive to this compound, resulting in allergic reactions and diseases

PRINCIPLES OF THE THERAPY OF INTOXICATIONS

- Intoxications occur **infrequently** but they are **life threatening**.
- The **main principle** in the treatment of intoxication is **"Treat the patient, not the poison"**.
- The **schema** of the treatment of the poisoning include three groups of procedures:

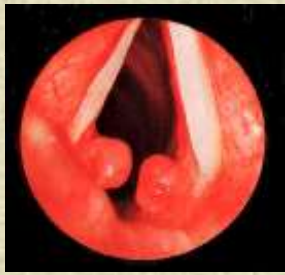
PRINCIPLES OF THE THERAPY OF INTOXICATIONS

I. **Reduction and elimination** of the poisons in **the site of entry**.

II. **Enhance of the elimination** of the poisons, which are absorbed **in the blood and the tissues.**

III. **Antidotal therapy**

Stabilization of the patient (ABCDE measures)



A. Evaluation of Airway obstruction

Causes (Mucosal swelling, Secretions, Posterior displacement of the tongue and Foreign bodies).

Signs and Symptoms (Dyspnea, Dysphoria, Air hunger, Cyanosis, Diaphoresis and Tachypnea).

Measures (Clearing the airway, use of nose-pharyngeal tube, Intubation or Crico-thyroidotomy).

B. Evaluation of Breathing (by ventilation and oxygenation)

Causes (Respiratory depressant drugs, Pneumonia, Pulmonary edema, Lung abscess, Pulmonary emboli, Bronchospasm from numerous environmental & occupational sources).

Signs and Symptoms (Tachypnea, Cyanosis, Hypoventilation and altered mental state).

Evaluated by measuring of blood gases ($PaCO_2$, PaO_2), Chest X-ray, or Tidal volume.

Measures (Assisted ventilation and supplemental O_2 delivered by nasal catheters and cannulae).

C. Evaluation of (C) Circulation

Signs and Symptoms of inadequate tissue perfusion is shock (Depressed consciousness, Decreased blood pressure, Peripheral vasoconstriction, Metabolic acidosis and Oliguria)
Treatment (Position change, Vasopressors as Dopamine and NE, and Fluids).

D. Evaluation of Depression (D) or Excitation (E)

Depression is evaluated by (measuring the pupillary size, pupillary light reflex, motor responses to pain, and /or spontaneous eye movements).

Treatment of depressed patient (coma cocktail: Glucose, Thiamine & Naloxone)

Excitation is manifested as seizures.

Treatment of generalized seizures secondary to toxins (Diazepam, Phenytoin, Phenobarbital, General anaesthesia, Enhancement of drug elimination by Hemodialysis).

Treatment of violent patient (Benzodiazepines with Haloperidol and stabilization of blood glucose level).

Physical examination
Laboratory investigations

- Vital signs: BP, HR, RR, T, O_2 sat
- Mouth: odors, mucous membranes
- Pupils
- Breath sounds
- Bowel sounds
- Skin
- Urination/defecation
- Neurologic exam

GI Decontamination

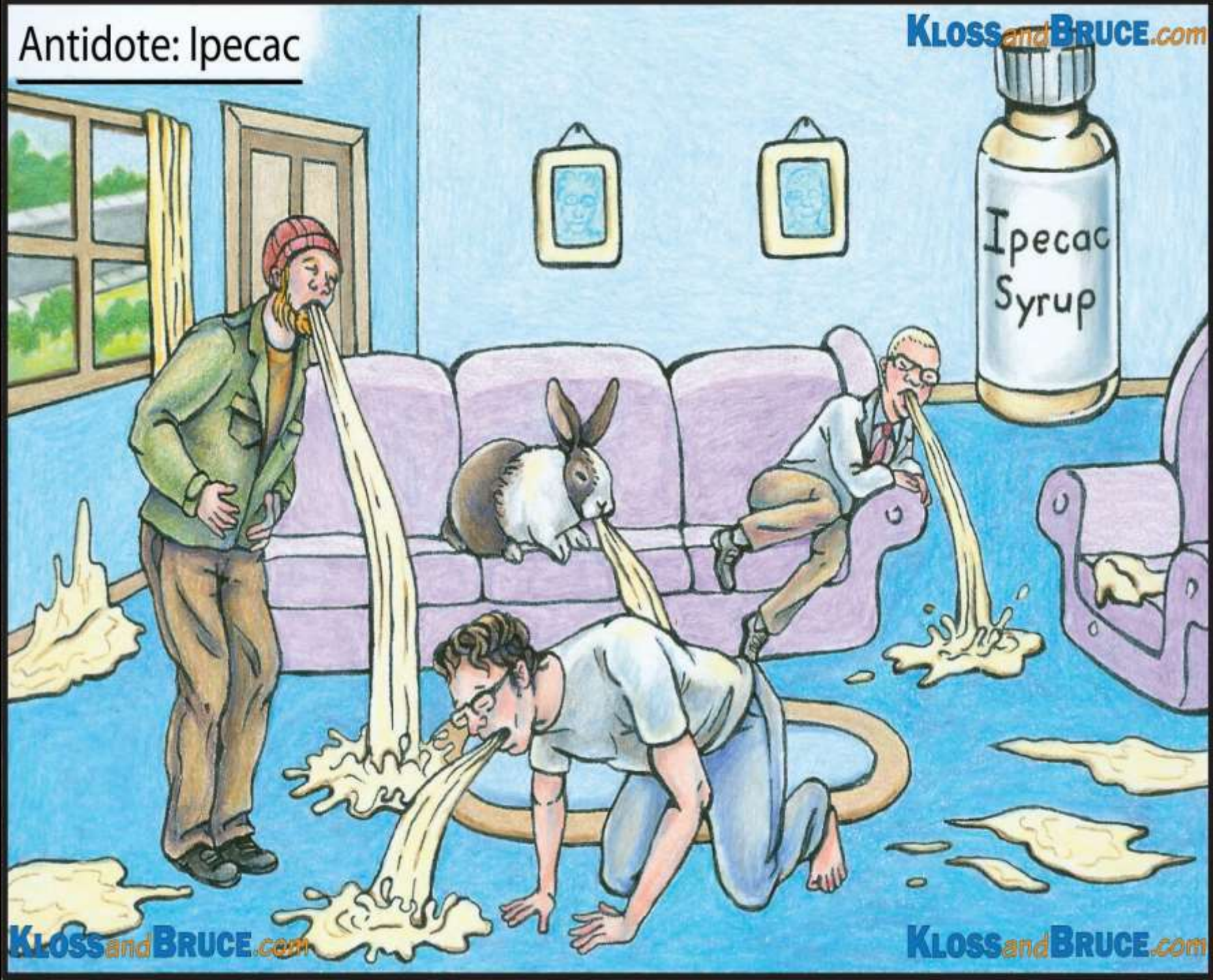
- **Removing** poison **from the stomach** is most effective in the **first 2 hours** after ingestion and is of **limited benefit** more **4 hours after ingestion**.
- For removing of the poison from the stomach it is necessary:
  - **to induce vomiting** or
  - **to perform gastric lavage**

GI Decontamination

1. Vomiting. For inducing of **vomiting** first have to give **0,5 – 1 L water** to drink, followed by **30 ml** (10 - 15 ml per children) **ipecac syrup orally** (from the root of **Cephalus Ipecachuana**: emetine & cephaline).

- For inducing of vomiting can also use **apomorphine**, which produces a more rapid onset of action.

Antidote: Ipecac



Contraindications

- Convulsions
- Corrosives
- Sharp objects (e.g. needles)
- Coma or impending coma
- Decreased gag reflex
- Severe CVS disease or respiratory distress or emphysema
- Recent surgical intervention
- Hemorrhagic tendencies (varices, active peptic ulcer, Trombocytopenia)
- Previous significant vomiting (spontaneously)
- Less than 6 m of age (not well developed gag reflex)

GI Decontamination

2. Gastric lavage.

- It can be performed when:
  - **if there is not vomiting** after receiving syrup of ipecac;
  - if the patient is **in coma**;
  - if ingested **amount** of the toxic substance is large;
  - if there is a **central nervous system depression** with an inadequate gag reflex;

GI Decontamination

- It must not perform gastric lavage if the patient have been ingested **a caustic substance** (the tube may perforate his esophagus).
- **Gastric lavage** begins by injecting about 30 ml of air through the tube and aspirating of the stomach content with 50 ml syringe.
- ✓ The aspirate has to be sent to **the laboratory for analysis**.
- ✓ Then instill up to **200 ml** of solution for lavage and **massage** the patient's stomach **to mix** the content. After those unclamp the outflow tube and clamp the inflow tube (record the out flow amount).

These procedures are repeated **using 5 to 10 liters** of fluid for lavage.

The induced vomiting and gastric lavage will remove only **50% to 60%** of the gastric contents.

- ✓ For absorption of the remaining poison have to give **slurry of activated charcoal and water or saline solution**.

Complications:

1. Bradycardia, especially in cases of OP or digitalis toxicity
2. Laryngospasm and cyanosis
3. Vomiting & aspiration pneumonia
4. Stress reaction – hypertension, tachycardia
5. Mechanical gut injury
6. Faulty introduction of the tube in the trachea

Contraindications:

- **Absolute contraindications:**

1. Corrosives
2. Froth producing substances as shampoo or liquid soap
3. Oesophageal varices or peptic ulcer

- **Relative contraindications:**

1. Coma
2. Convulsions

GI Decontamination

3. Absorption therapy with **activated charcoal** is the **physical binding of a poison** to an **unabsorbable carrier**, which is eliminated in the feces.

- Activated charcoal is most effective for large, nonpolar molecule. Ionized agents are less strongly absorbed than neutral compounds.

GI Decontamination

Activated charcoal

- Limits drug absorption in the GI tract
- Within 60 minutes of ingestion
- Patient must be awake or intubated
- 1 gram/kg PO or GT

GI Decontamination

- **Not** good (not absorbed by) for:
  - **Metals (Lithium, Iron, Lead, Mercury….)**
  - **Alcohols**
  - **Hydrocarbons, Petroleum distillates**
  - **Oils**
  - **Glycols**
  - **Caustics (Corrosives)**
  - **Sodium chloride, Sodium hypochlorite bleach**
  - **Cyanide**

Contraindications

- Coma
- Intestinal obstruction or ileus with distention
- Corrosives
- If an oral antidote is given

GI Decontamination

4. Cathartics (Laxatives)

There are substances that enhance the passage of material through GIT and decrease the time of contact between the poison and the absorptive surfaces of the stomach and intestine.

a) **Osmotic Cathartics**: increase osmotic pressure in the lumen, as **Mg sulfate**.

b) **Irritant Cathartics**: act by increasing motility, such as **caster oil**

Preferred agents are the **saline cathartics:**

sodium sulfate, magnesium sulfate, citrate or (phosphate) and **sorbitol**, which have a relatively **prompt onset** of action.

They have lower toxicity, than the oil-based cathartics (**oleum ricini**), which present **aspiration risk**.

GI Decontamination

Contraindications:

1. GIT hemorrhage
2. Recent bowel surgery
3. Intestinal obstruction
4. Renal failure for magnesium salts

GI Decontamination

5. Whole bowel Irrigation

The goal of WBI is to clean GIT from unabsorbed bed ingested toxins. Polyethylene glycol electrolyte solutions are used.

Indications:

- **Ingestion of a toxin that is known to be poorly absorbed by AC**
- **Ingestion of massive amounts of drugs/impractical AC**
- **Ingestion of sustained-release or enteric-coated preparations (e.g. aspirin)**
- **Ingestion of large amount of drugs that may form concretions or bezoars (e.g. salisylates, barbiturates, carbamazepine)**
- **Removal of ingested packets of illegal drugs (body packers, cocaine)**

Inhalation exposures

1. Immediate, cautious removal of the patient from the hazardous environment.
2. Observe for airway obstruction
3. Administration of 100% humidified O_2, assisted ventilation, and bronchodilators.
4. Observe for edema of the respiratory tract and later non-cardiogenic pulmonary edema.
5. Intubate as necessary
6. Treatment should not await laboratory results.

Decontamination

- **Skin**
  - Protect yourself and other workers
  - Remove clothing
  - Flush with water for at least 30 min. or use a normal saline
  - Use soap and water if oily substance
  - Chemical neutralization can potentiate injury
  - Corrosive agents injure skin and can have systemic effects
  - Toxic substances such as OP compounds, metal compounds, phenol, may penetrate the intact skin and must be handled with proper protective equipment.

Ocular exposures

1.Remove contact lens
2.Ocular decontamination consists of at least 15 minutes of immediate irrigation of eyes with normal saline or water.
3.Use local anesthetic drops
4.Alkaline or acid irrigating solutions should be avoided.
5.Continue irrigation until pH is normal
6. Alkaline corneal burns are requiring ophthalmic consultation.

II. Measures to enhance elimination of the poisons

1. Diuresis

The **basic principle** of diuresis is **ion trapping**. **Increasing urinary flow** to **two-three times** normal was carried out in the past, but this has been **replaced with adjustment of urine pH** and maintenance of **normal urine flow**.

Alteration of the pH of the urine in the **renal tubules** (after glomerular filtration) can **ionize** and "**trap**" the agent. Once the **toxin is ionized**, then **reabsorption** from the renal tubules is **impaired** and the result is that more of the drug **is excreted** in the urine.

Diuresis

Forced diuresis

Simple method for some poisons.

It is efficient only in poisons with the following properties:

- Substances excreted mainly by kidneys
- Substances with low volume distribution
- Substances with low protein binding

Types:

1. **Fluid diuresis**
2. **Osmotic diuresis**: **manithol 10%, furosemide** which are excreted by renal tubules leading to increase in its osmotic pressure.

Manipulation of Urine pH - Forced alkaline diuresis

Forced alkaline diuresis is indicated in the treatment of poisonings (**salicylate, phenobarbital**, antihistamine, cocaine, tricyclic antidepressants, sulfonamides, etc) except if the patient is: **in shock**, in **heart failure**, has **impaired renal function**. Urinary pH should be maintained above **7.5**, ideally **8.0 -8.5**.

Increasing the pH of the urine from 7 to 8 results in a ten fold increase in the concentration of aspirin in the urine. The volume of the diuresis need not be **more than 500 ml per hour**. In the first hour infuse:

- 500 ml 5% dextrose
- 500 ml **bicarbonate 1.4% ($NaHCO_3$)**
- 500 ml dextrose 5%

Potassium chloride should be added to keep serum potassium above 3.5 mmol/l.

Acid Diuresis

It is uncommonly used method for certain substances such as amphetamines, phencyclidine, quinine. It is a dangerous method because of the risk of myoglobin precipitation in renal tubules.

Infuse:

500 ml 5% dextrose + 500 ml 5% dextrose

Arginine/lysine or **Ammonium chloride**

Mechanisms of Diuresis

- Enhances urinary excretion of weak acids
- Traps weak acids in ionized state (ion trapping)
- Prevents reabsorption by renal tubules

Extracorporeal techniques

2. Dialysis

By allowing toxic substances to pass through semi permeable membrane depending on the concentration gradient. It is beneficial when renal function is impaired. For good results substances must have:

- Low volume distribution
- Low molecular weight
- Low protein binding

Examples for dialyzable substances: alcohols, barbiturates, salicylates

Examples for non-dialyzable substances: opiates, atropine, antidepressants.

Peritoneal dialysis (PD)

Diffusion of toxins from mesenteric capillaries across the peritoneal membrane into dialysate dwelling in the peritoneal cavity. Acts by considering peritoneum as semi permeable membrane. Has limited value for the management of some poisonings.

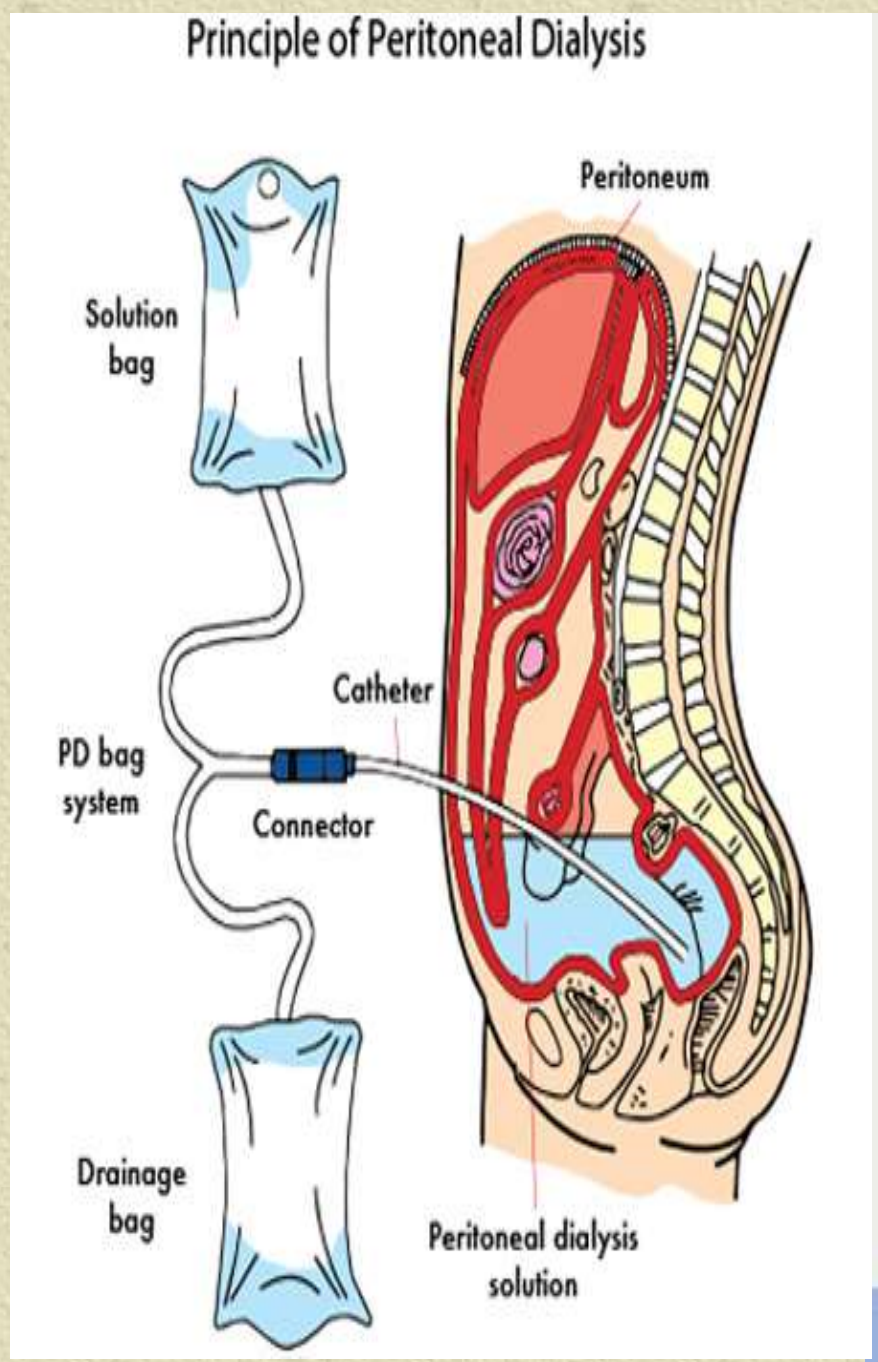
This method is most **useful in situation of renal failure** or **anurea.** PD involves ion-trapping principles. Dialysis fluids may need **frequent change** and attention to **prevent infection** is also necessary**.**

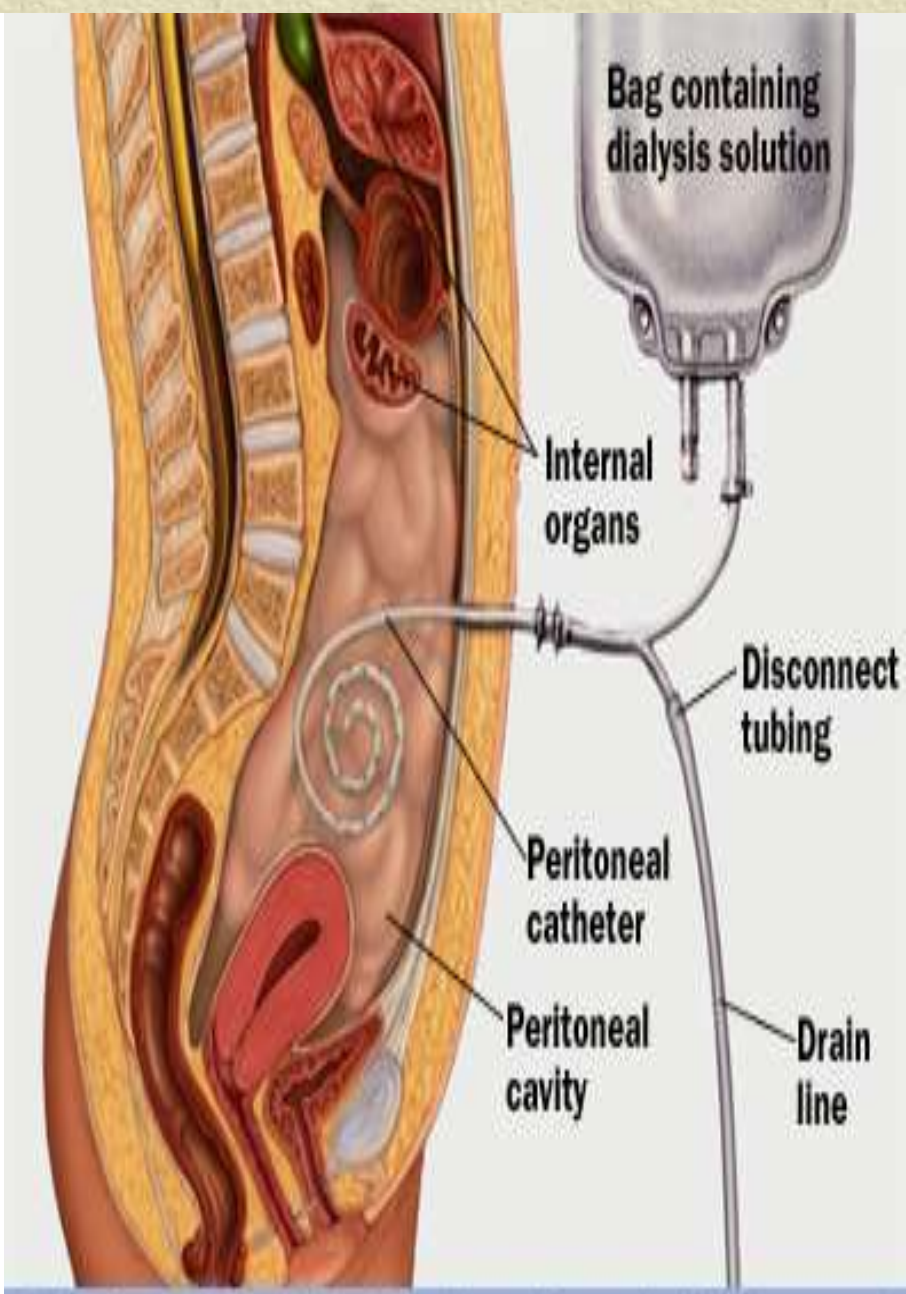
Complications:

- **Intra-abdominal bleeding**
- **Perforation of abdominal organs**
- **Peritonitis**
- **Dehydration or over hydration**

Contraindications:

- **Pregnancy**
- **Abdominal hernia**
- **Respiratory distress**





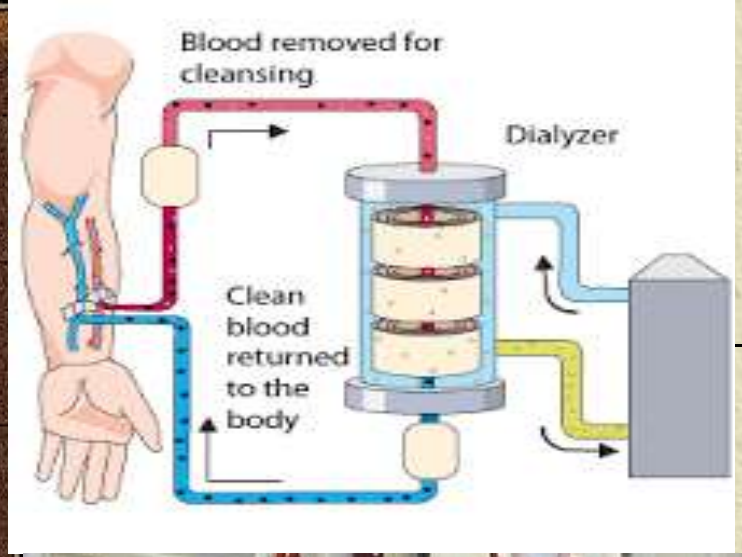
Hemodialysis

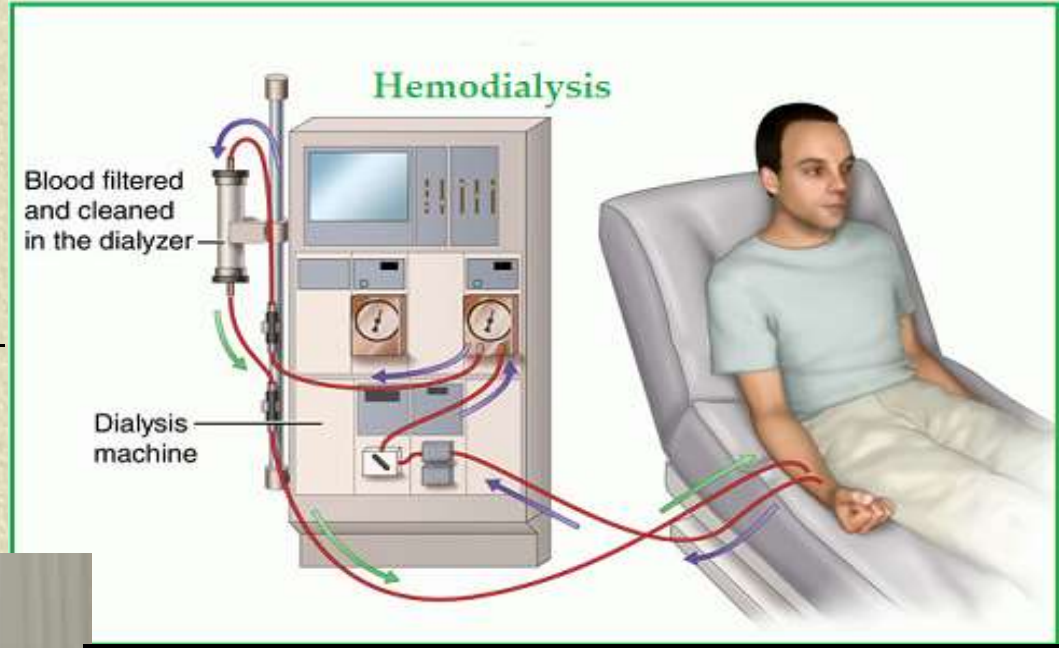
Two catheters are inserted. Blood is pumped from one catheter through the dialysis unit (a cellophane bag) and returned through the other catheter. The **haemodialysis** relies on passage to the toxic agent through a **semi permeable dialysis membrane** so it can equilibrate with the dialysate and subsequently **be removed**. This is in part dependent on the **molecular weight** of the compound.

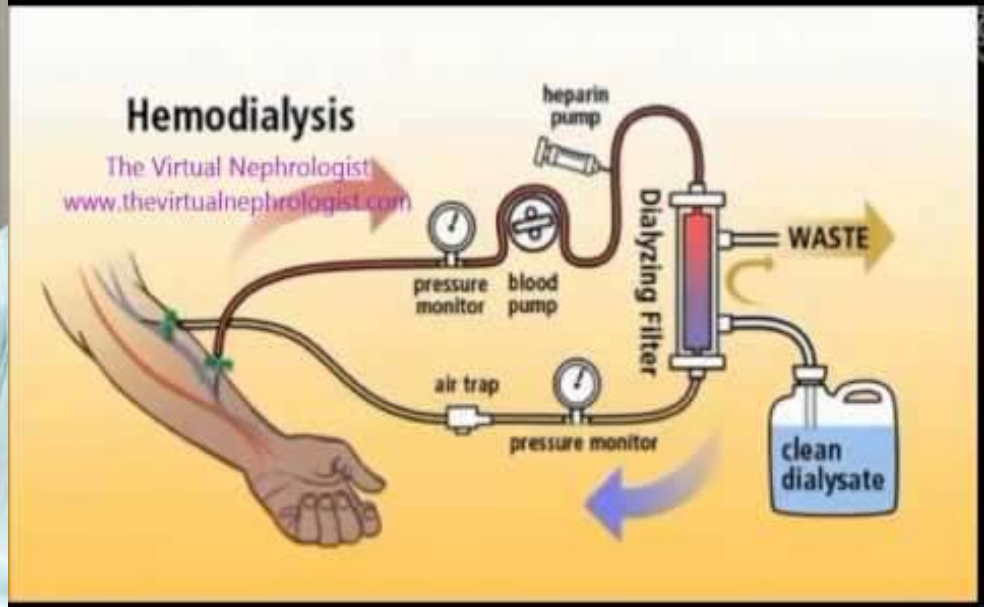
Some drugs such as **phenobarbital** can readily cross these membranes and go from high concentrations in plasma to a lower concentration in the dialysate.

Complications:

hypotension, bleeding tendency (due to heparin), cross infections, muscle cramps, air embolism.


Blood removed for cleansing
Dialyzer
Clean blood returned to the body

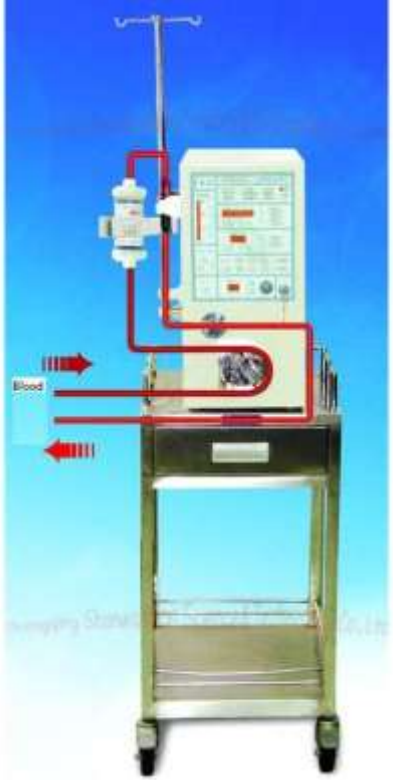

Hemodialysis
Blood filtered and cleaned in the dialyzer
Dialysis machine

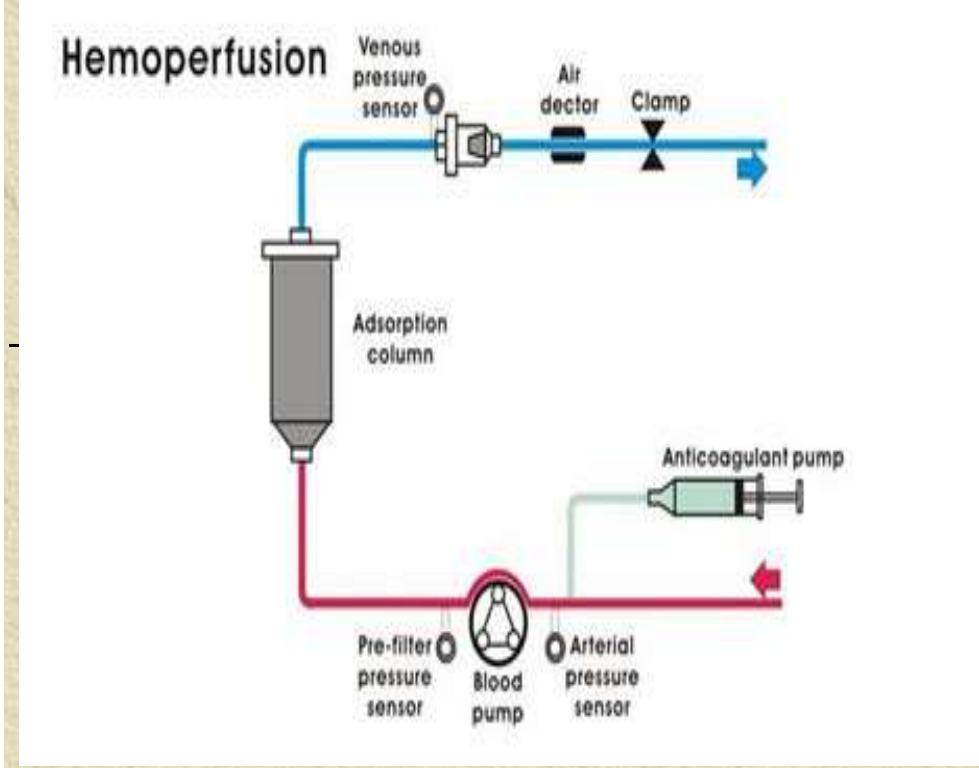

Hemodialysis
The Virtual Nephrologist
www.thevirtualnephrologist.com
heparin pump
Dialyzing Filter
WASTE
pressure monitor
blood pump
air trap
pressure monitor
clean dialysate

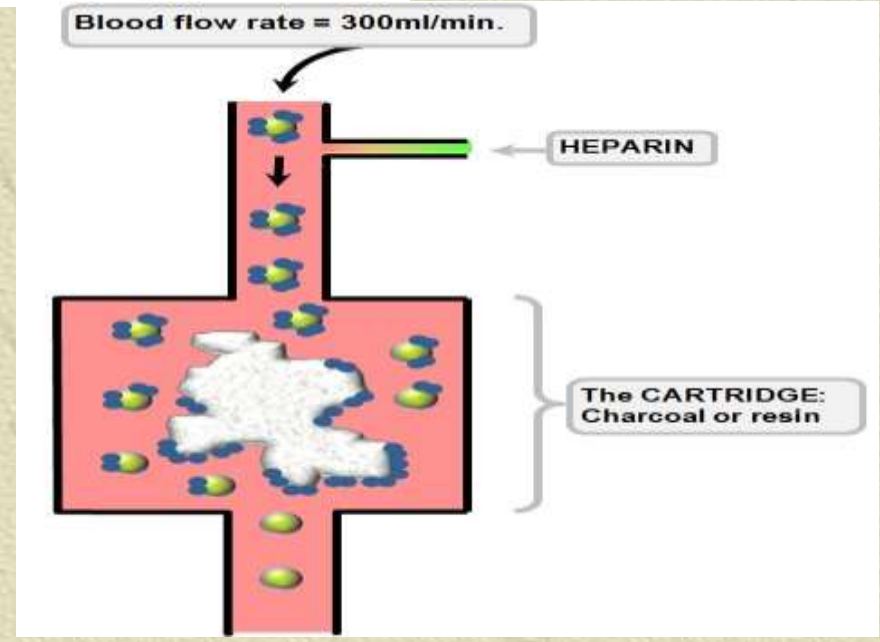
Hemoperfusion

Haemoperfusion is passing of blood through a **column of charcoal** or **absorbent resin**. It is an important technique of **extracorporeal drug/toxic removal**.Using equipment and vascular access similar to that for HD. Systemic anticoagulation is required, often in higher doses than for HD, and **trombocytopenia** is a common complication.

- Because the drug or toxin is in direct contact with the absorbent material, drug size, water solubility, and protein binding are less important limiting factors
- For most drugs, hemoperfusion can achieve greater clearance rates than HD. For example, the **HD** clearance for **phenobarbital** is **60-80** mL/min, whereas the **hemoperfusion** clearance is **200-300** mL/min.


Blood


Hemoperfusion
Venous pressure sensor
Air doctor
Clamp
Adsorption column
Anticoagulant pump
Pre-filter pressure sensor
Blood pump
Arterial pressure sensor


Blood flow rate = 300ml/min.
HEPARIN
The CARTRIDGE:
Charcoal or resin

Contraindications:

Patients with **coagulopathy**
Patients with uncorrected hypotension

Complications:

Thrombocytopenia
Hypocalcemia
Hypoglycemia
Hypotension
Adsorption of therapeutic drugs

Hemofiltration (similar to hemodialysis, except that the blood is pumped through a hemifilter, where waste products and water are removed by hydrostatic pressure. Replacement fluid is added and the blood is returned to the patient).

Plasmapheresis and Plasma exchange (separation of cellular blood components from plasma, then cells are resuspended in fresh frozen plasma, and reinfused again).

Exchange transfusion (removal of the patient's blood, replacement with fresh whole blood).

Plasma perfusion (combination of plasmapheresis and hemoperfusion).