# Theophylline toxicity

Dr. Muhammed Malik

# Introduction

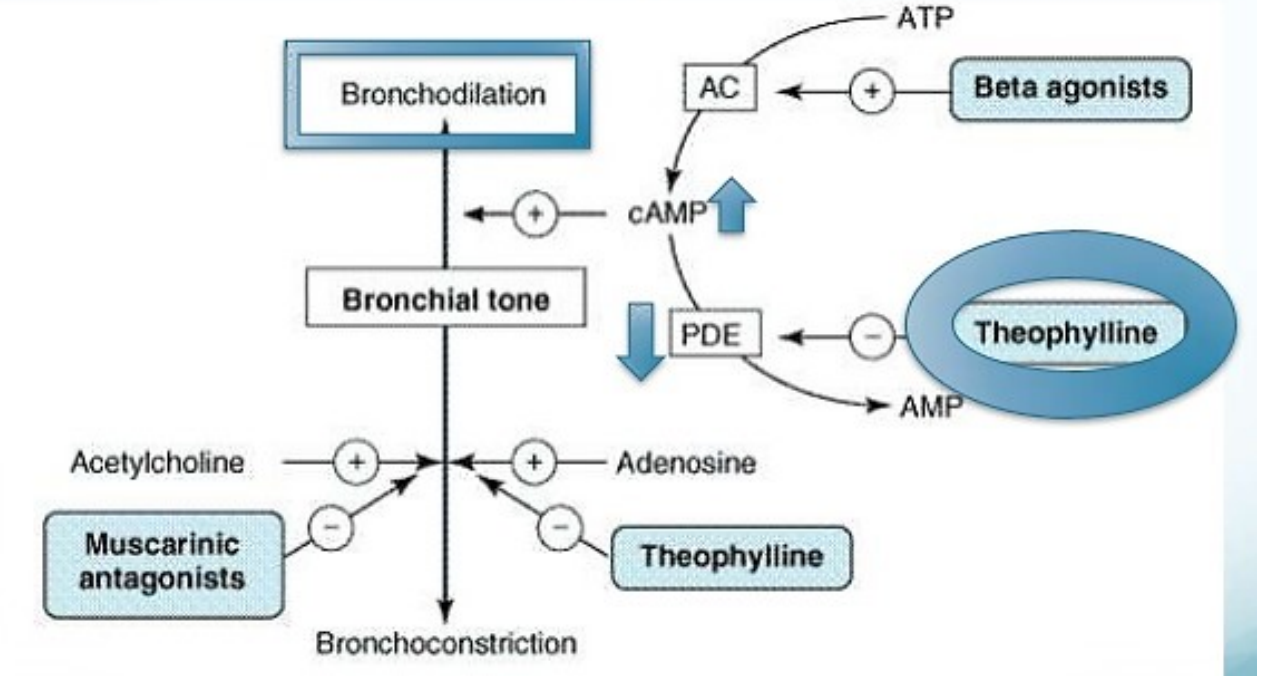
- Theophylline (methylxanthine derivatives) use has dramatically declined as safer therapies for asthma have been developed.
- However, serious toxicity is still reported and may require aggressive treatment of vomiting, tachyarrhythmias, and seizures, as well as extracorporeal elimination by hemodialysis.

# Mechanism of action:

1. Inhibition of phosphodiesterase (PDE) →→increased cAMP→→bronchodilatation, cardiac stimulation, vasodilation.

2. Blocked of adenosine receptors→→ relaxes smooth muscles.

# Mechanism of Methylxanthines (Theophylline)



# Pharmacokinetic

- Theophylline is absorbed rapidly and completely after oral administration. Peak level in 90-120 min.
- Narrow therapeutic window
- Therapeutic serum levels range from 10-20 mcg/mL.
- Toxic levels are considered to be higher than 20 mcg/mL.
- Adverse effects may be evident within the normal therapeutic range

# Pharmacokinetic

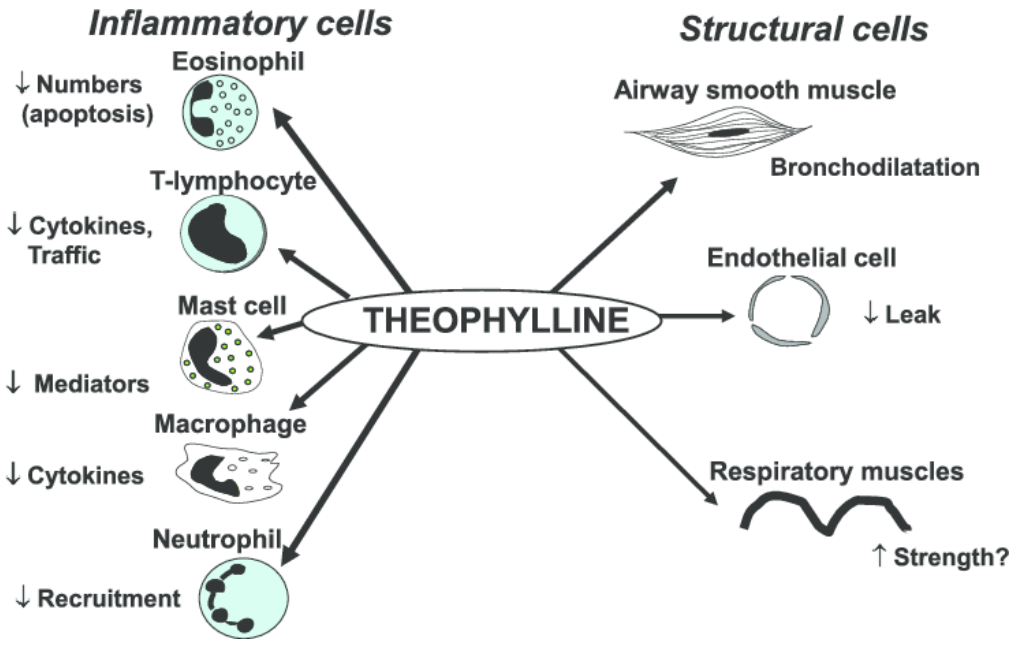
- Severe complications including cardiac dysrhythmias, seizures, and death can be observed with the levels of 80-100 mcg/mL.
- In chronic exposure, those levels could be lower (40-60 mcg/mL).
- Theophylline is eliminated by the hepatic cytochrome P-450 system (85-90%) and by urinary excretion (10-15%).

# Pharmacokinetic

- The half-life is 4-8 hours in young adults and is shorter in children and smokers.
- Diet, cardiac or liver disease, tobacco use, and medications (cimetidine, erythromycin, oral contraceptives) affecting the cytochrome P-450 system (CYP1A2) can affect the half-life.

# Toxic effects:

1. Cardiovascular.
2. Neurologic.
3. Metabolic.
4. GI toxic effects.



# 1. Cardiovascular

- Sinus tachycardia (most common), atrial fibrillation, atrial flutter.
- Supraventricular tachycardia (SVT), ventricular tachycardia.
- Hypotension (severe overdoses) - Due to β2 effect/agonsim.
- Ventricular fibrillation.
- Cardiac arrest.

# 2. Neurological

- Tremors (most common)
- Restlessness, agitation, hallucinations
- Headaches, irritability, and seizures.

# 3. Metabolic

- Hypokalemia, hyperglycemia, hypercalcemia, hypophosphatemia, and acidosis commonly occur after an acute overdose.

# 4. Gastrointestinal

- Nausea and vomiting→→ * Most frequent and earliest symptom
  * Direct CNS effect
  * 25% of patients with levels greater than 20 mcg/ml
- GERD, GI bleeding, and epigastric pain.

- # Treatment:

**1.Gastric emptying with lavage**

- Ingestion within 1-2 hours
- Not indicated if dose will not put level over 30 mcg/ml

**2. Activated charcoal**

- Multiple dose
- Repeat dose at 2 and 4 hr. at 1gm/kg up to 50gms.

**3. Cathartics**

- Sorbitol solution 70%, with charcoal
- Enhance passage

**4.Whole bowel irrigation (Controversial)**

**5.Hemodialysis**

- Indicated for life threatening levels.

**6.Hemoperfusion**

- Charcoal hemoperfusion with hemodialysis ↑elimination rate.

**7.Hypotension**

- Phenylephrine may be used
- *B*- blocker(propranolol) reverse the vasodilation.

**8.Cardiac arrhythmias**

- β-blockers, verapamil, digoxin,
- Lidocaine
- Adenosine for SVT

**9.Seizures**

- Benzodiazepines first line
- Barbiturates second line

**10. Antiemetics**

- Ranitidine 50 mg IV
- Metoclopramide 0.5-1.0 mg/kg

# Follow-up:

a) Unintentional overdose: For patients with therapeutic levels and minimal or no toxicity, discharge and follow up within 24 hr.

b) Intentional overdose: Consider discharge of asymptomatic patients with therapeutic levels after psychiatric evaluation.

- Note: Patients on cimetidine, macrolides, fluoroquinolones should reduce dose by 25%.

# Thank you

# Digoxin Toxicity

Dr. Muhammed Malik Al-Ani

# Cardioactive Steroids

- Cardioactive Steroids (CAS), or *cardiac glycosides,* developed their name from the strong effect on the heart.
- The most common pharmaceutical product is digoxin.
- Other preparations available internationally include digitoxin, ouabain, lanatoside C, deslanoside, and gitaline.
- There is evidence in the Ebers Papyrus that the Egyptians used plants containing CAS at least 3000 years ago.

# Cardioactive Steroids: Sources

Many plants contain cardioactive steroids

- *Digitalis purpurea* (foxglove), *Nerium oleander* (oleander), *Convallaria majalis* (lily of the valley), *Drimia maritima* (red squill)
- Toxicity may result from use of herbal products or teas derived from such plants or direct ingestion of the plant itself

**Bufo marinus toad –** dried secretions are a supposed aphrodisiac and contain a cardioactive steroid

# Digoxin: Therapeutic Role

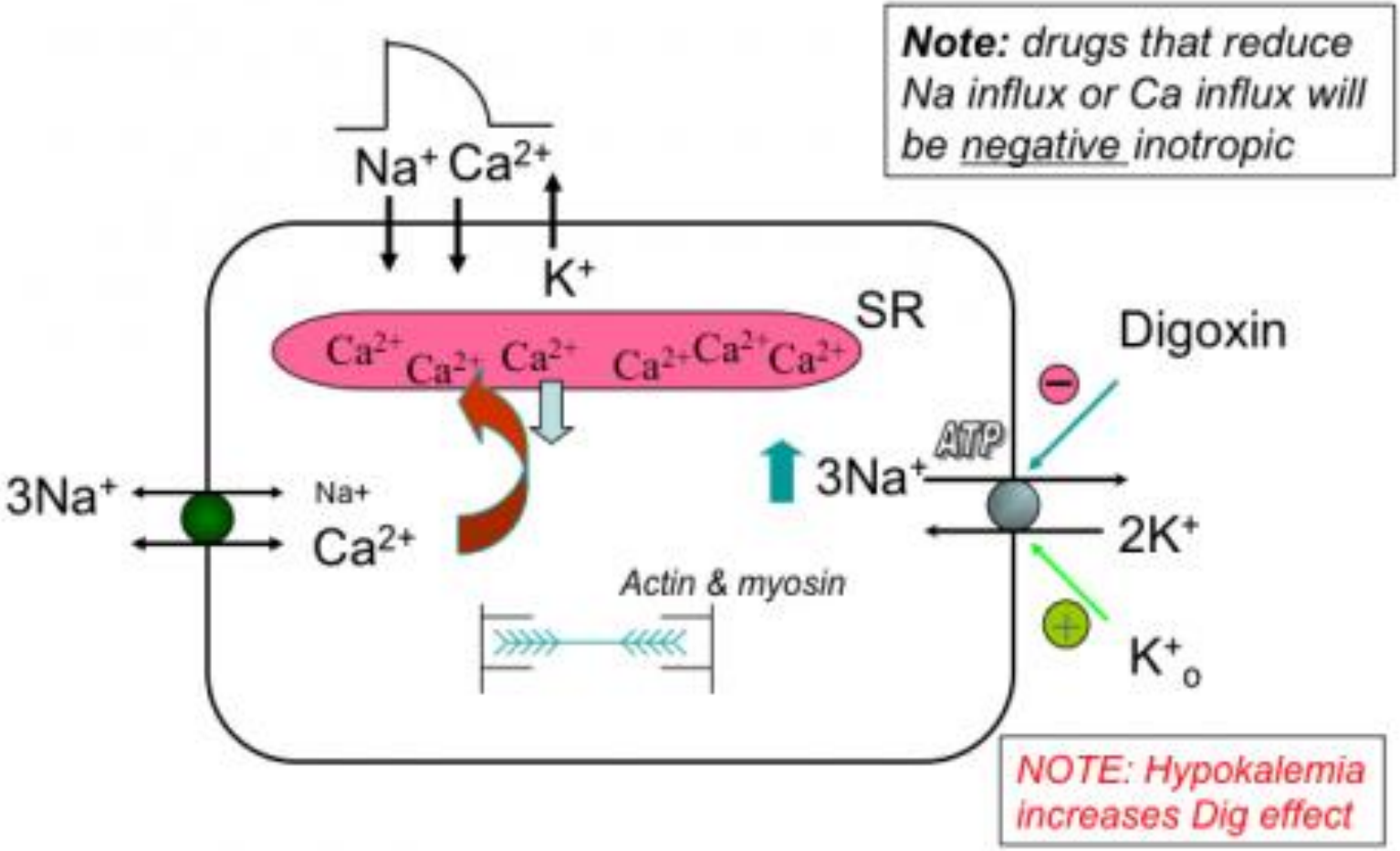
## Disease states used in:

Atrial fibrillation:
Control of ventricular response rate in patients with chronic atrial fibrillation

Heart failure:
Increases left ventricular ejection fraction by increasing exercise capacity, and decreasing heart failure-related hospitalizations and emergency room visits.

***Used in adults and pediatrics***

# Mechanism of Action



# Risk Factors for Digoxin Toxicity

- Kidney Injury: digoxin is primarily eliminated by the kidneys
- Age: elderly are more likely to have decreased renal function and taking potentially interacting concomitant medications
- Electrolyte Imbalance: increases sensitivity to digoxin effects
- Fluid Status: fluid loss or poor fluid intake can lead to electrolyte imbalances

# Risk factor:

Figure 1A. Dose-Response Curves for Wide Therapeutic Index Medications

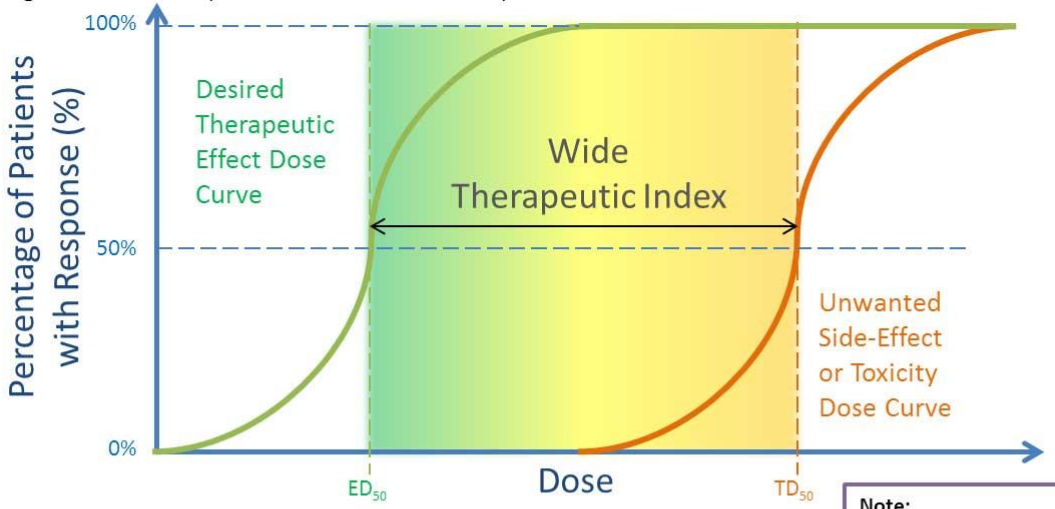
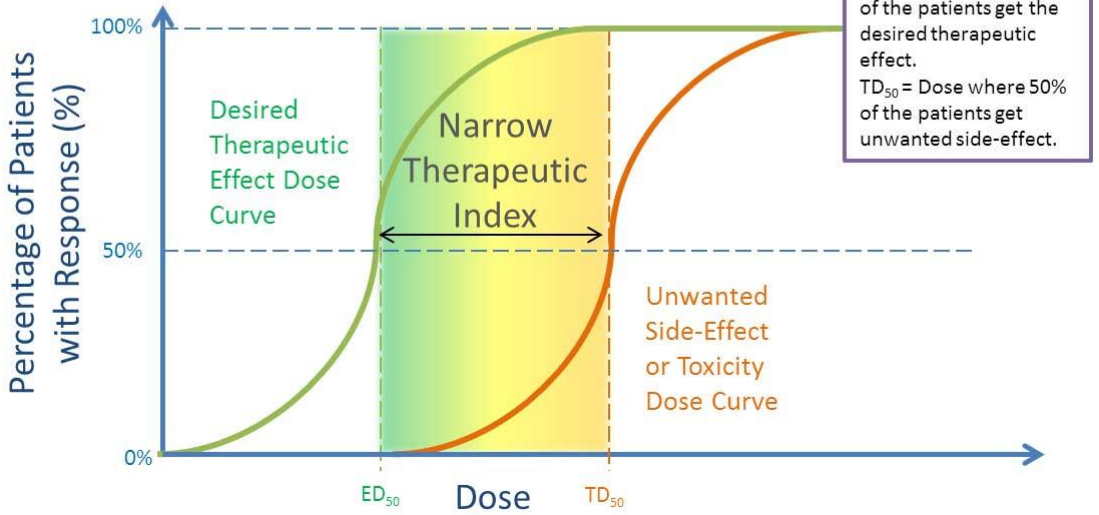



Figure 1B. Dose-Response Curves for Narrow Therapeutic Index Medications



# Digoxin Facts:

Overall use of digoxin has declined approximately 10% in hospitalized acute heart failure patients.

Number of patients with admitted digoxin poisoning has remained stable (approximately 1,500/year)

Use of digoxin-specific antibody fragments has increased (approximately 20%)

In 2011, there were 2,513 cases involving cardiac glycosides reported to U.S. poison control centers. Of these, 90 experienced major effects (i.e, life threatening resulting in prolonged hospitalization) and 26 died.

# LD50:

- TDLo Oral - Human - 0.075 mg/kg
- LD50 Oral Rat 28,3 µg/kg and IP LD50 4 mg/kg.
- Toxic dose low (TDLO): The lowest dose of a substance introduced by any route, other than inhalation, over any given period of time, and reported to produce any toxic effect in humans or to produce tumorigenic or reproductive effects in animals.

# Digoxin: Causes of Toxicity

## Hypokalemia

**Results in increasing its therapeutic and toxic effects.**

## Hypercalcemia

**Digoxin enhances $Ca^{+2}$ absorption into cardiac myocytes, which is one of the ways it increases inotrophy. This can also lead to $Ca^{+2}$ overload and increased susceptibility to digitalis-induced arrhythmias.**

## Hypomagnesemia

**Can sensitize the heart to digitalis-induced arrhythmias. k/Na+ ATPas dependent on Mg so it will enhance digoxen inactivation for the receptor enzyme**

# Digoxin: Causes of Toxicity

**Drug interactions:**
**many commonly used drugs interact with digoxin**

No P450 Interactions

Drugs that alter renal clearance can affect digoxin concentration.

Loop and Thiazide Diuretics decrease serum potassium levels:

furosemide

hydrochlorthiazide

## Various drugs alter the mechanism of digoxin renal excretion or intestinal p-glycoprotein activity

- verapamil
- diltiazem
- quinidine
- amiodarone

## Increased Serum Levels

- Amiodarone
- Benzodiazepines
- Bepridil
- Cyclosporine
- Diphenoxylate
- Indomethacin
- Itraconazole
- Macrolide Antibiotics
- Propafenone
- Propantheline
- Quinidine
- Quinine
- Spironolactone
- Tetracyclines
- Verapamil

## Decreased Serum Levels

- Oral aminglycosides
- $Al^{+}/Mg^{+}$ containing antacids
- Antineoplastics
- **Activated charcoal**
- Cholestyramine
- Colestipol
- Kaoline / pectin
- Metoclopramide
- Neomycin
- Penicillamine
- Rifampin
- Sulfasalazine

# Signs/symptoms of acute toxicity

| Gastrointestinal | Neurological |
| --- | --- |
| nausea, vomiting, abdominal pain | weakness, confusion |

| Electrolyte | Cardiac |
| --- | --- |
| Hyperkalemia | bradycardia, heart block, several types of arrhythmias |

# Signs/symptoms of chronic toxicity

## Gastrointestinal

Patients may have more signs of acute digoxin toxicity (nausea, anorexia)

## Neurological

confusion, drowsiness, headache, hallucinations

## Visual

sensitivity to light, yellow halos around lights, blurred vision

# Diagnosis of Digoxin Toxicity

- History 
- Signs and symptoms 
- ECG 
- Digoxin levels 
- Electrolytes 

# History

Risk factors for digoxin toxicity including age of patient
(for patients chronically using digoxin therapeutically)

| | | |
|---|---|---|
| Initiation or discontinuation of drugs that potentially interact with digoxin | Any disease changes (such as thyroid disease) | Altered renal function |

# Signs and Symptoms

**Acute overdose:**

| Gastrointestinal: | Central Nervous System: | Electrolyte changes: | Cardiac Signs: |
| --- | --- | --- | --- |
| nausea, vomiting | confusion, weakness, lethargy | hyperkalemia | sinus bradycardia, second or third degree AV block. Any type of dysrhythmia is possible |

# Signs and Symptoms

## Chronic overdose

**GIT:**
anorexia, nausea, vomiting, weight loss

**CNS:** delirium, hallucinations, confusion,, lethargy (seizures are possible but rare)

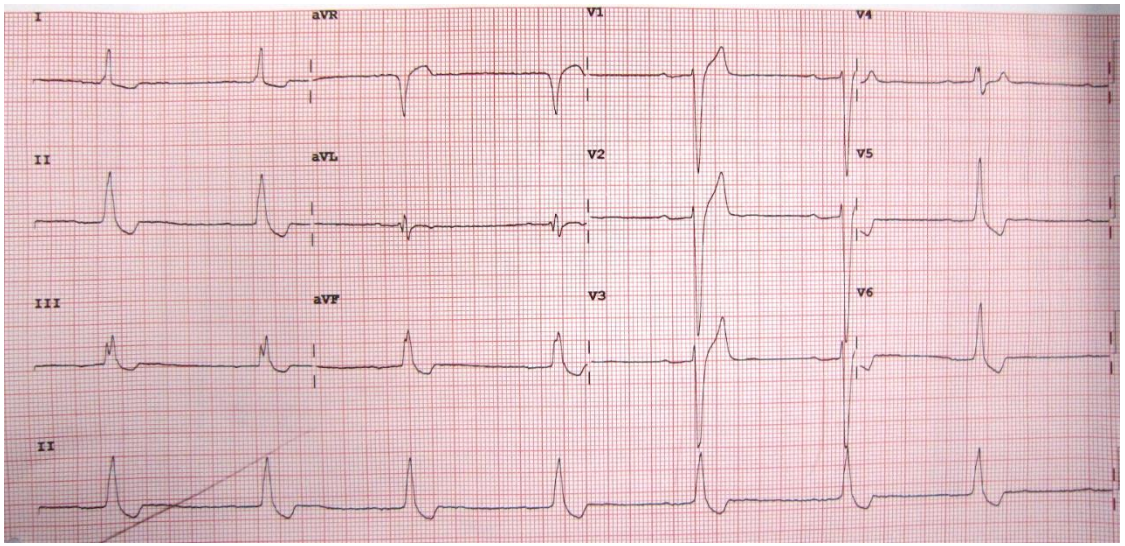
**Visual:**
photophobia, changes in color vision (such as yellow halos around lights)

**Electrolyte changes:**
hyperkalemia (sometimes hypokalemia especially if diuretics are used)

**Cardiac Signs:**
bradydysrhythmias (often unresponsive to atropine) ventricular tachydysrhythmias

# ECG

- Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity.
- Frequent premature ventricular beats (PVCs) is the most common and the earliest dysrhythmia.
- Sinus bradycardia is also very common. In addition, depressed conduction is a predominant feature of digoxin toxicity.
- Bigeminy and trigeminal rhythms, ventricular bigeminy, and bidirectional ventricular tachycardia.



# Digoxin: Laboratory Analyses

laboratory values in the digoxin poisoned patient

**Hyperkalemia:** > 5.5 mEq/L in the *acutely* poisoned digoxin patient (100% Mortality)

Poor prognostic sign in acute toxicity. Antidote warranted when > 5 mEq/L due to 50% mortality for potassium 5 mEq/L – 5.5 mEq/L

**Hypokalemia:** Can predispose the patient to further dysrhythmias and should be corrected with close monitoring to avoid hyperkalemia.

# Digoxin: Laboratory Analyses

## Digoxin levels in the poisoned patient

Obtaining an immediate digoxin level in an acutely poisoned patient will not reflect the peak serum level as the distribution phase of digoxin is long. An initial 4-6 hour post-ingestion level is appropriate.

| | |
|---|---|
| Unbound digoxin | Useful following administration of digoxin-specific Fab fragments |
| Total digoxin (bound & unbound) | ❖ Serum concentrations predict cardiac concentrations<br>❖ Fab fragments of digoxin-specific antibodies will cause a rise in total digoxin levels (as Fab bound digoxin is also being measured) |

# Digoxin levels

Therapeutic range of digoxin has historically been 0.5 - 2.0 mg/day.

Current FDA Package Insert recommends 0.5 - 1.0 mg/day.

Toxicity begins >2.0 mg/day

However, this can be misleading in the acutely poisoned patient Stat levels may not correlate with the severity of the poisoning especially in acute ingestions Digoxin's long distribution phase results in high serum levels for 6-12 hours prior to completed tissue distribution

# Electrolytes

**Hypokalemia** results in increased digoxin binding increasing its therapeutic and toxic effects.

**Hypercalcemia** enhances digitalis-induced inotropy leading to possible $Ca^{+2}$ overload and increased susceptibility to digitalis-induced arrhythmias.

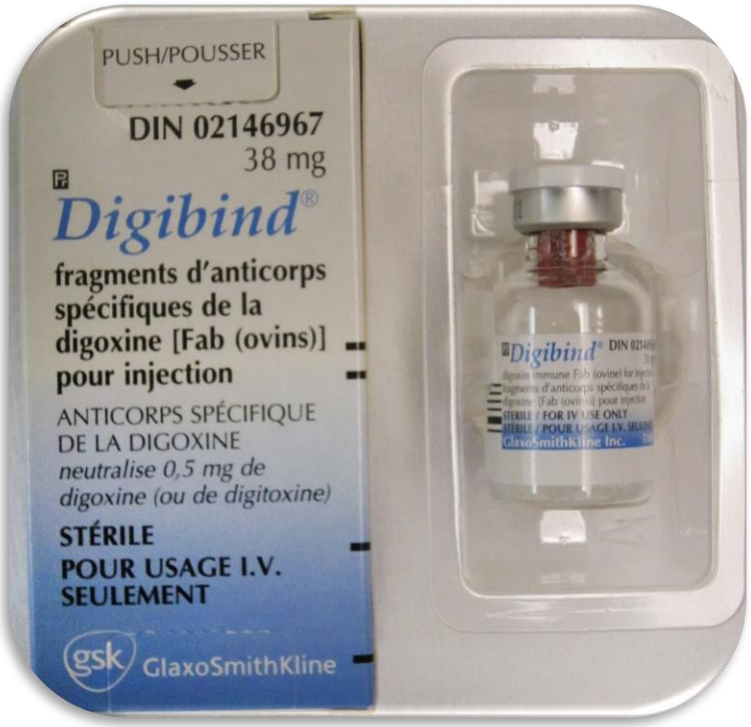
**Hypomagnesemia** can sensitize the heart to digitalis-induced arrhythmias.

# Available treatments:

## Decontamination/enhanced elimination

For acute overdose:

- Fab (Fragment antigen-binding)
- Activated charcoal can adsorb digoxin in the gut.
- Enhanced elimination (dialysis, hemoperfusion) may be effective in remove digoxin due to large volume of distribution and relatively high protein binding.



# Thank you

# DRUG TOXICITY

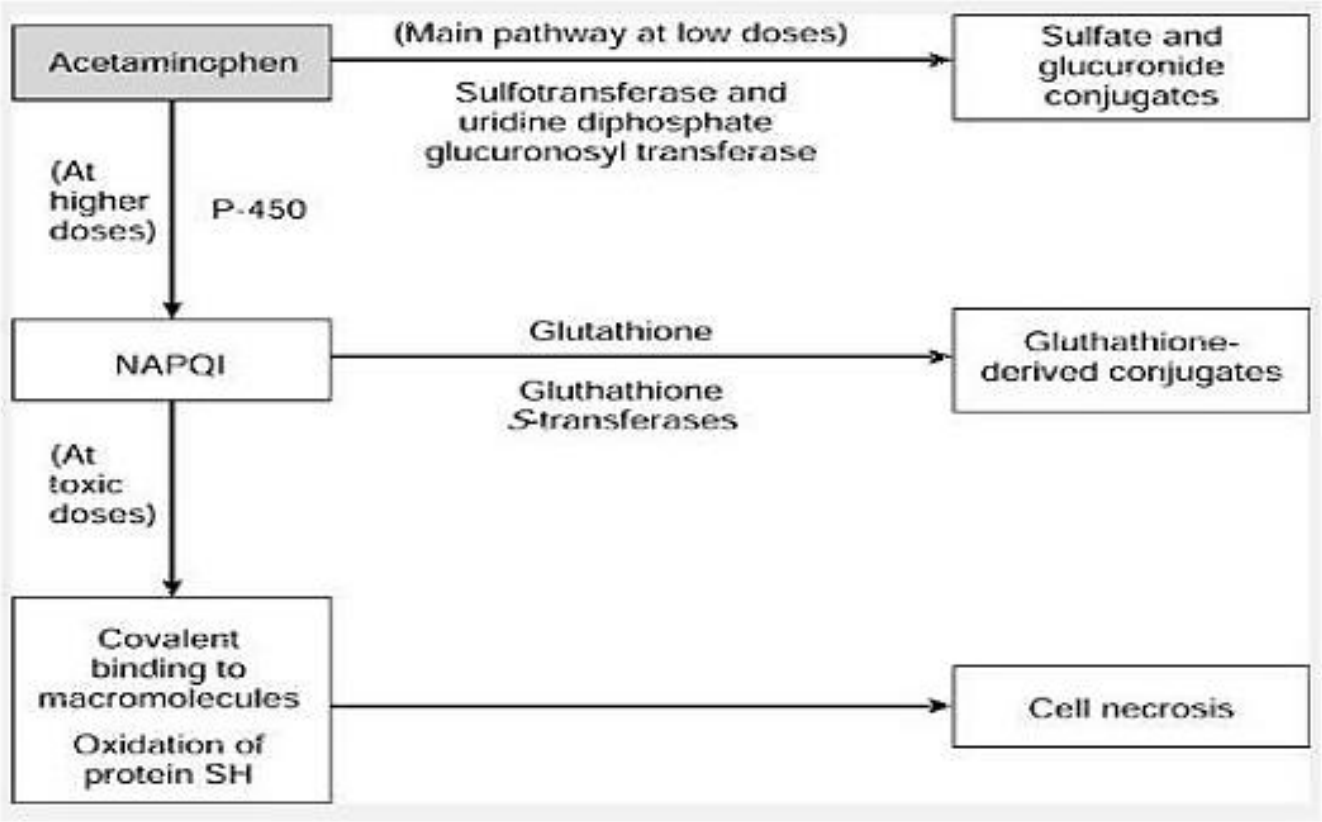
Dr. Muhammed Malik Al-Ani

# Paracetamol toxicity:

- Paracetamol toxicity is caused by excessive use or overdose of the medication acetaminophen.
- Most people with paracetamol toxicity have no symptoms in the first 24 hours following overdose.

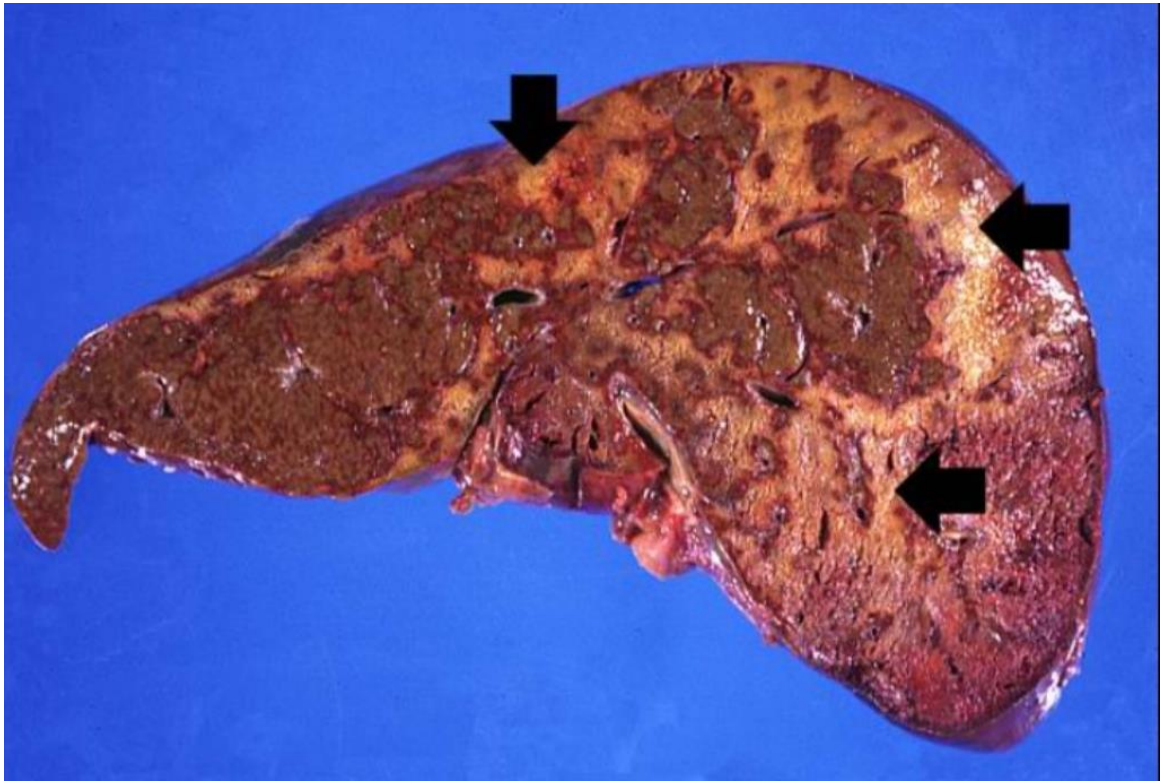

- Others may initially have nonspecific complaints such as abdominal pain and nausea.
- The oral LD50 was found to be greater than 2000 mg kg-1, whereas the IP LD50 was 1900 mg kg-1.

# Paracetamol metabolism pathways:




At usual therapeutic dosages, acetaminophen is metabolized → conjugation reactions. The capacity becomes saturated at higher dosages → diversion of the drug to the P-450-mediated pathway → generates reactive electrophile N-acetyl-p-benzoquinone imine (NAPQI) → undergoes phase 2 conjugation with glutathione → glutathione depletion → allowing the electrophile to exert damaging effects within the cell via covalent binding.

# Liver necrosis

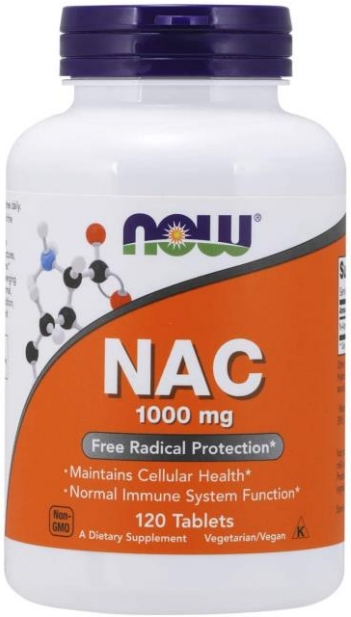


# Paracetamol Overdose-management

1. Initial ABC (usually well systemically)
2. Get a good history (Time taken, Amount, Any other medication, History of Liver disease)
3. Measure levels of Paracetamol in blood to know whether amount taken is enough to be Hepatotoxic.

# Antidote for acetaminophen overdose

- Reactive NAPQI N-acetylcysteine (NACys)Provides the Sulphydryl groups




- **Dosage Forms and Strengths**
- injectable solution: 200mg/mL
- effervescent tablets for oral solution:500mg

# Mechanism of action of NACys

- N-Acetylcysteine. Shown to be advantageous if given in the first 8 hours Provides the Sulfhydryl groups result in ↑ availability of Glutathione.
- So Body can turn TOXIC metabolite to non-toxic form & prevent Liver Cell Damage and NECROSIS
- May also scavenge free radicals to prevent delayed hepatotoxicity as antioxidant; encourages sulfation pathway of metabolism for acetaminophen.

# Salicylate (Aspirin) Poisoning

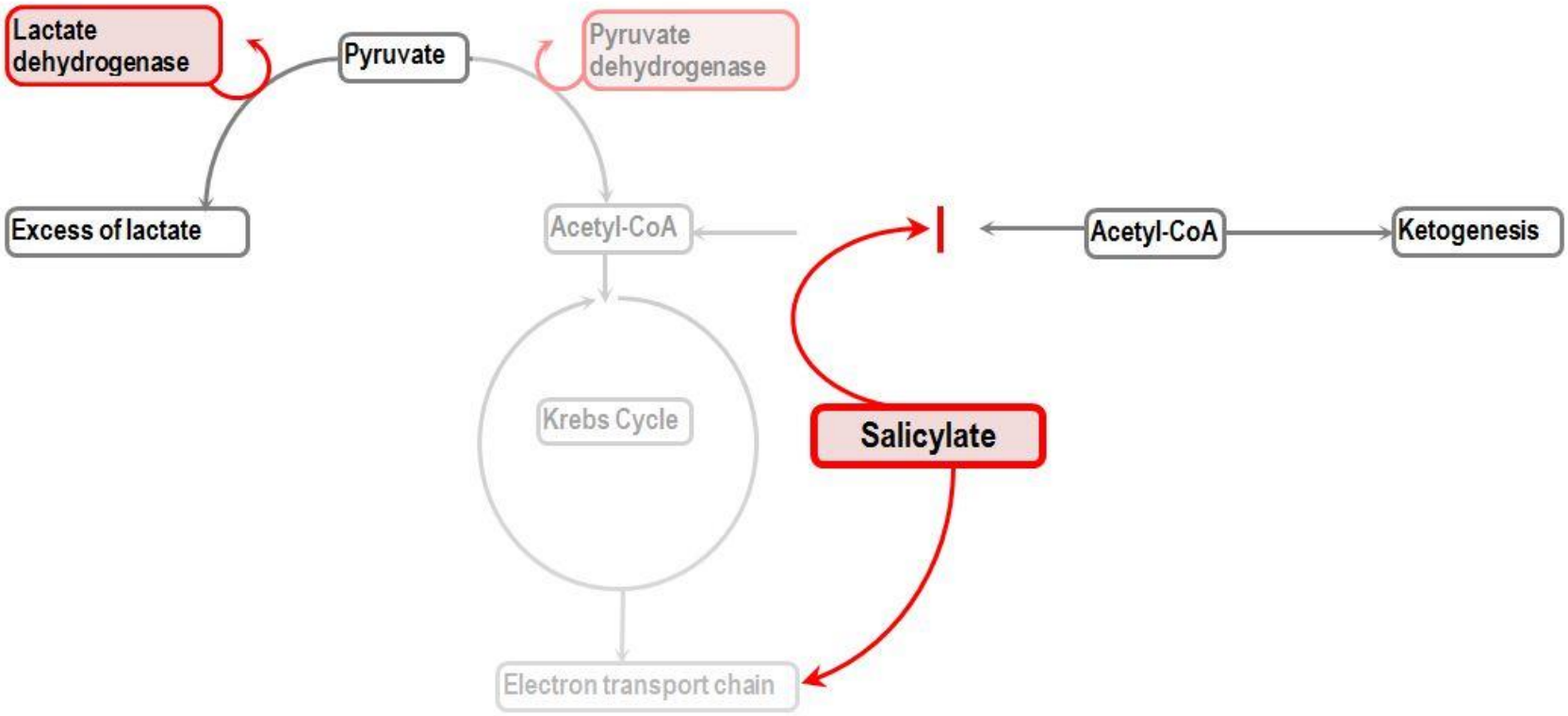

- Aspirin is a nonsteroidal anti-inflammatory drug (NSAID) and works similarly to other NSAIDs but also suppresses the normal functioning of platelets.
- Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to reduce pain, fever, or inflammation
- Specific inflammatory conditions which aspirin is used to treat include Kawasaki disease, pericarditis, and rheumatic fever.
- Aspirin given shortly after a heart attack decreases the risk of death. Also used long-term to help prevent further heart attacks, ischemic strokes, and blood clots in people at high risk.
- It may also decrease the risk of certain types of cancer, particularly colorectal cancer.
- For pain or fever, effects typically begin within 30 minutes.

- **Aspirin** Toxicity occurs due to disturbance in Acid-Base Balance:

1. Respiratory Alkalosis.

2. Metabolic Acidosis.

- Salicylate levels greater than 100 mg/dL are considered severe toxicity and occur 12 to 24 hours after ingestion.
- Damage to the basement membranes will cause cerebral and pulmonary edema. Patients may become obtunded and develop seizures.
- Salicylate toxicity works by uncoupling oxidative phosphorylation.
- It inhibits Kreb's cycle, meaning the body is unable to produce ATP, leading to anaerobic metabolism with consequent raised lactate and ketone bodies


Lactate dehydrogenase
Pyruvate
Pyruvate dehydrogenase
Excess of lactate
Acetyl-CoA
Acetyl-CoA
Ketogenesis
Krebs Cycle
Salicylate
Electron transport chain

# Mechanisms of toxicity:

1.Direct stimulation of respiratory center →overbreathed, Hyperventilation →Resp. Alkalosis.

2. Kidney attempts to compensate for alkalosis by excreting alkali ---------→Metabolic Acidosis

3. Inhibits normal metabolic pathways of CHO, Fat, Protein. ---→ Build up of Organic Acids

(KETONES, LACTATE, PYRUVATE)

↓

&MORE METABOLIC ACIDOSIS

# Clinical Features

- COMMON: Vomiting, Dehydration, Tinnitus, Vertigo, Sweating, Hyperventilation.

- UNCOMMON: Confusion, clotting abnormalities, Coma, Convulsions, Hematemesis, hyperpyrexia, renal failure, Disorientation.

# Aspirin overdose - Management

- There is no specific antidote for salicylate poisoning.
- General: ABCD.
- Take Salicylate levels to help guide treatment options (management according to amount taken: ***next slide***) If small amounts and asymptomatic need no treatment.

# Aspirin overdose - Management

- Specific: When high levels ingested and patients are symptomatic

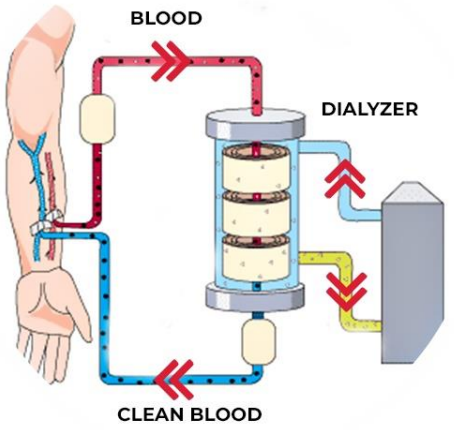
**1. ↓ ABSORPTION**

- Activated Charcoal in those who taken more than 250mg/Kg & less than 1 hour ago.
- Gastric Lavage in those who taken more than 500mg/kg& less than 1 hour ago.

# Aspirin overdose - Management

**2. ↑ DRUG ELIMINATION**

- Urinary Alkalization ↑urinary pH from 5 to 8 (10-20 fold) ↑renal salicylate clearance. Infusion of Sodium Bicarbonate. (Care must be taken because of it's dangerous & can cause severe Acid - Base Disturbances)
- Hemodialysis in severe life threatening overdose to correct (Acid Base disturbances) while removing Salicylate

# Opiate Poisoning:


- e.g. Heroin, Methadone and pethidine.
- Act on mu-receptor exist either pre-synaptically or post-synaptically depending upon cell types.
- Pain dose: 50-150 mg PO/IM/SC repeated 3-4hr; adjust dose based degree of response.

# Toxic Signs and Symptoms

- Serious over dosage of opiate is characterized by respiratory depression (a decrease in respiratory rate, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, maximally constricted pupils, skeletal-muscle flaccidity, cold and clammy skin, and sometimes, bradycardia and hypotension.
- In severe overdosage, particularly by the intravenous route, apnea, circulatory collapse, cardiac arrest, and death may occur.

# Opiate Overdose-Management

INITIAL MANAGEMENT

1. ABCD

2. NALOXONE : specific antidote and high affinity for the opiate receptors (Little side effects).

- Naloxone should be given intravenously as soon as possible 0.4-2 mg IV/IM/SC and repeated every 2-3 minutes if necessary.

➢ Naloxone may also be combined with an opioid (in the same pill), to decrease the risk of opioid misuse.

# Thank you

# P. General Toxicology

# INTRODUCTION

**Dr. Muhammed Malik Al-Ani**

- Toxicology is concerned both with the nature and mechanisms of **toxic lesions** and the quantitative evaluation of the spectrum of biological changes produced by exposure to chemicals.
- Every chemical is toxic under certain conditions of exposure.
- An important corollary is that for every chemical there should be some exposure condition that is safe as regards human health, with the possible exception of chemical carcinogens and mutagens.
- The quantitative evaluation of the biological changes caused by chemicals aims at the establishment of **dose-effect** and **dose-response** relationships that are of fundamental importance for health risk evaluation.

## Most Toxicologists work to assess and understand how chemicals affect living systems by:

- Develop mechanistic understanding of effects
- Ensure safer chemical products
- Develop safer drugs & medicines
- Determine **risks** from chemical exposures
- Develop treatments for chemical exposures
- Ensure a safe food and water supply
- Forensics

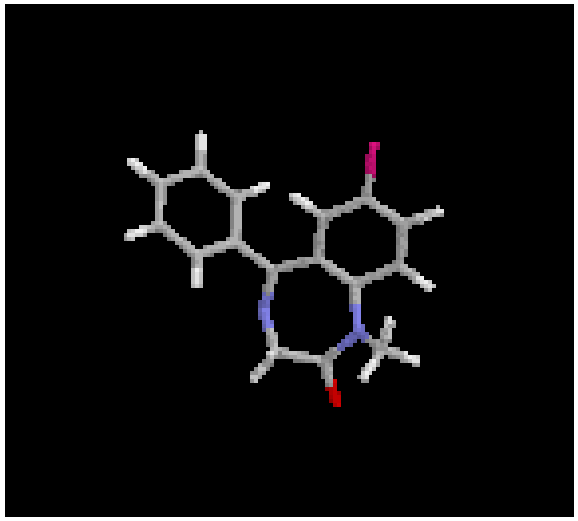
# Major areas of specialization in toxicology

- Mechanistic toxicology (basic biology and chemistry)
- Descriptive toxicology (testing)
- Regulatory toxicology (rule making and compliance)
- Risk assessment (modeling)
- Translational and clinical (applying basic research to patient care)

# Mechanistic Toxicology

**Focuses on how**

- Chemicals produce adverse effects.
- Biological systems protect themselves against adverse effects.



**Involves**

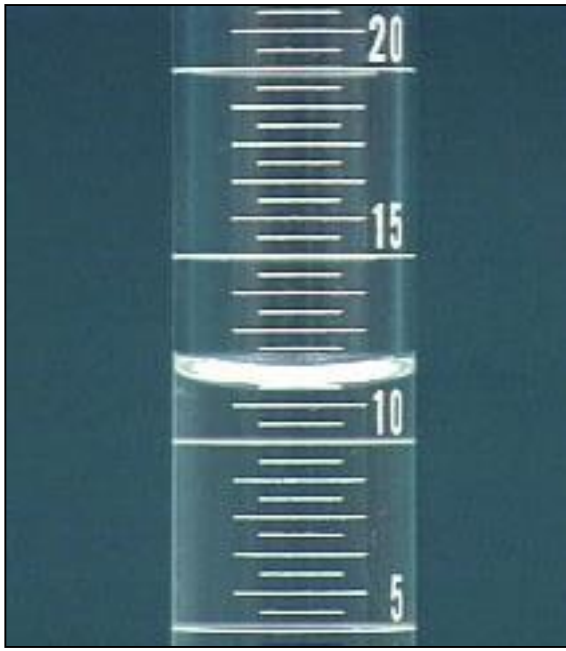
- Cellular and Molecular Biology
- Chemistry, often xenobiotic metabolism

Xenobiotic: a chemical that is foreign to the organism

# Mechanistic Toxicology

**Chemical research in toxicology usually investigates metabolic transformations of drugs or potentially hazardous chemicals**

- How persistent is a chemical in the body?
- Are metabolic products toxic?
- Do test animals exhibit the same results as humans or other species of concern?



# Descriptive Toxicology

- Typically involves toxicity testing
- Broad spectrum of responses reflects toxicity
  - Functional effects, such as immunological responses
  - Growth inhibition
  - Reproductive impairment
  - Increase in cancer incidence
  - Mortality

# Descriptive Toxicology

- Assesses the concentration-dependent hazard a chemical may present
  - Human health
  - Natural populations
- Results typically applied to
  - Approval of product use
  - Regulating allowable concentrations in the environment.

# Descriptive Toxicology

## Types of toxicity testing

- *In vitro* (test tube)—useful in detecting potential biochemical and genetic effects
  - Use model systems (bacteria, cultured animal cells, DNA interactions)
- *In vivo* (animal)—are essential for detecting health effects
  - Acute, chronic, multi-generation
  - Experimental animals may be treated with high doses over a lifetime to evaluate potential to cause cancer
- *In silico* (computer-based)—biological experiments conducted by computer models; these depend on data previously collected in other experiments

*Completion of all toxicity tests may take five or six years and is very costly

# Regulatory toxicology

## (Rule making and compliance)

- Regulatory toxicologists play a critical role in health and environmental safety by providing science-based advice to inform regulatory decision-making concerning the health hazards and risks involved with the **use**, **production**, and **disposal** of such agents as pesticides, drugs, cosmetics, foods, and household goods.

# Risk assessment (modeling)

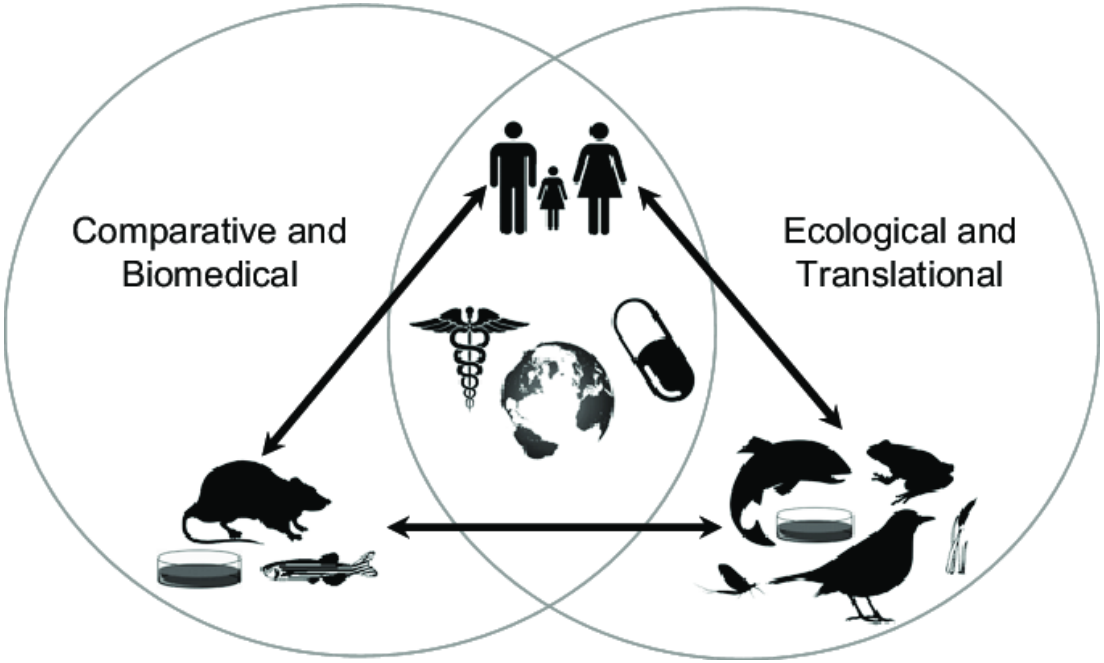
- Risk assessment determines possible mishaps, their likelihood and consequences, and the tolerances for such events.
- The results of this process may be expressed in a quantitative or qualitative fashion.

❖**Steps to risk assessment:**

1. Identify hazards, i.e. anything that may cause harm.
2. Decide who may be harmed, and how.
3. Assess the risks and take action.
4. Make a record of the findings.
5. Review the risk assessment

# Translational toxicology

Translational science is the **application** of biomedical research and drug development to efficiently use a promising drug in the right patient circumstances and assess its efficacy in the human using appropriate indicators such as biomarkers.



# Laboratory testing

- Human data on the toxicity of chemicals are obviously more relevant to safety evaluation than those obtained from the exposure of experimental animals.
- controlled exposures of man to hazardous or potentially hazardous substances are limited by ethical considerations and information obtained by clinical or epidemiological methods must be relied on.

# Laboratory testing:

- Where such information is not available, as in the case of all new synthetic chemicals, data must be obtained from tests on experimental animals and other laboratory procedures.

- The degree of confidence with which human health risks can be estimated from laboratory data depends on the quality of the data, and the selection of appropriate laboratory testing procedures is the main subject of this monograph.

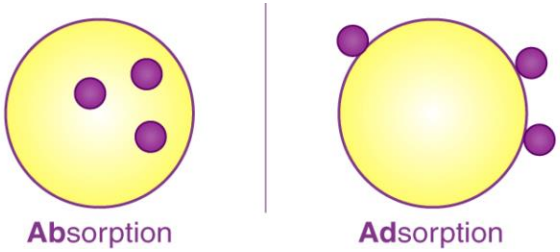
# Priorities in the selection of chemicals for testing

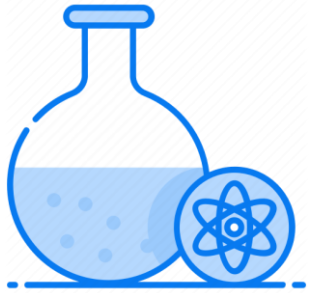
In principle, all new chemicals require safety evaluation before manufacture and sale. The large number of chemicals that represent a possible hazard to human health and limited resources, it is necessary to *give priority to those that are directly consumed by man*, such as drugs and food additives, and those that are widely used such as pesticides or household consumer products.


1. Industrial chemicals that can escape into the working or general environment or can contaminate other products are another category of concern.

- 2. Compounds of suspected high acute, chronic, or delayed toxicity (such as carcinogenicity) or of high persistence in the environment, or compounds which contain chemical groups known to be associated with these properties, deserve the highest priority.
- 3. Chemicals resistant to metabolism, especially metabolism by microflora, will have a high environmental persistence.
- 4. Many halogenated compounds come into this category, and should, therefore, have some degree of priority.
- 5. Compounds that accumulate in food chains or are stored in the body, e.g. methylmercury and DDT, will be a matter of concern.

- 6. Physicochemical properties can be an important consideration in setting priorities for testing potential environmental pollutants. For example, biomagnification of stable, fat-soluble substances may lead to contamination of human food supplies as well as to adverse effects in wildlife at the higher levels of food chains,
- Physicochemical properties such as vapour pressure, and particle size and density are important in predict in the atmospheric transport of chemicals
- Adsorption of a chemical on soil particles may increase the likelihood that the material will become airborne or be transported by watercourses and subsequently deposited in areas remote from its site of application.



## Criteria based on metabolic and biochemical changes Such changes are considered to be adverse if:

1. The metabolism of a substance becomes less efficient or the elimination of a substance (expressed in terms of biological half-time, T) slows down with increasing doses of the substance.
2. Enzymes that have a key significance in metabolism are inhibited.

3. The inhibition of a certain enzyme results in an increase in the concentration of the corresponding natural substrate in the body and/or in a decreased capacity to metabolize the specific substrates in a loading test.

4. The relative activities of different enzyme systems are changed (e.g. the ratio of the activities of asparagine and alanine transaminases.

# General decontamination

- **Decontamination methods**
- 1. Physically remove contaminants.
- 2.Inactivate contaminants by chemical detoxification or **disinfection**/sterilization.
- 3.Remove contaminants by a combination of both physical and chemical methods.

Thank you

# Identification of some common poisons in biological samples

Dr. Muhammed Malik Al-Ani

# Introduction:

- There is a gradual increase in the demand of modern analytical techniques involved in toxicology in solving disputes, criminal, suicidal and accidental cases have shown the importance of this particular field.

- The laboratory plays a key role in this cases, and appropriate specimen collection coupled with accurate analysis will make a major difference in correct diagnosis.

- A toxicological analysis can be done to various kinds of samples procured from subjects under investigation including: blood, urine, nails, hair, bile, gastric contents, liver, brain tissue and DNA can all be useful specimens.

# When toxicological analysis tests must be done?

In clinical practice, analysis of toxic elements should always be considered in the clinical workup of the patient with:

1- Renal disease of unexplained origin.

2- Bilateral peripheral neuropathy.

3- Acute changes in mental function.

4- Acute inflammation of the nasal or laryngeal epithelium.

5- A history of exposure.

# Arsenic (AS)

- The half-time of inorganic As in humans is about 4 days. While the organic As excreted after several days of ingestion.
- If arsenic poisoning occurs over a short period of time symptoms may include: vomiting, abdominal pain, encephalopathy, and watery diarrhea that contains blood.
- Long-term exposure can result in thickening of the skin, darker skin, abdominal pain, diarrhea, heart disease, numbness, and cancer of bladder and skin.

- Diagnostic methods: ( Urine, blood and hair).
- 1. Urine

- The concentration of total As measuring in urine by using (atomic absorption spectrophotometry) has often been used as an indicator of recent exposure, because urine is the main route of excretion (organic and inorganic As).
- Average background concentrations of As in urine are generally below 10 mg/L in Europe as normal healthy people.
- For measuring concentrations of exposure markers in the urine, an important question is whether to collect 24-hr urine samples, spot urine samples, or early morning urine samples.
- Ideally, the amount of As excreted over a certain period of time should be assessed. Usually this is done by measuring As excretion in a 24 hr collection.

## 2. Blood:

- Most inorganic and organic As in blood is cleared fairly rapidly in human. Blood As will therefore reflect exposure for only a short period following absorption and will be very time dependent.
- Only if exposure is continuous and steady, as is sometimes the case with exposure through drinking-water, will As reach steady-state in the blood and thus make it possible to discern a relationship between blood As and exposure. Even so, there are no data that indicate a quantitative relationship in man between As exposure and blood As concentrations.
- The short half-life of As in the blood compared with the half-life in the body makes it difficult to discern a relationship between blood As concentration and total body As burden or As concentrations in different organs.
- In studies carried out in California and Nevada, an As concentration of 400 mg/L in water corresponded to about 13 mg/L in blood, and 100 mg/L in water corresponded to 3-4 mg/L in blood.

## 3. Hair:

- Arsenic is normally found in higher concentrations in human hair and nails than in other parts of the body. This has been explained by the high content of keratin in these tissues.

- patients with chronic As poisoning may have hair concentrations varying, from 10 ppm (10mg/kg hair) to 100 ppm whereas levels of around 45 ppm have been reported in As-related fatalities.

- samples should consist of at least one gram of hair cut close to the scalp and derived from several sites on the head and the whole sample should be analysed. The As determinations in hair and nails performed by instrumental neutron activation analysis (INAA).

# Cyanide

- Fires is important source for cyanide poisoning, the administration of antidote **hydroxocobalamin** directly after exposure can strongly save patient life.
- **Toxicity Symptoms:** Early symptoms include headache, dizziness, fast heart rate, shortness of breath, and vomiting.
- This may then be followed by seizures, slow heart rate, low blood pressure, loss of consciousness, and cardiac arrest.
- Onset of symptoms is usually within a few minutes. If a person survives, there may be long-term neurological problems.

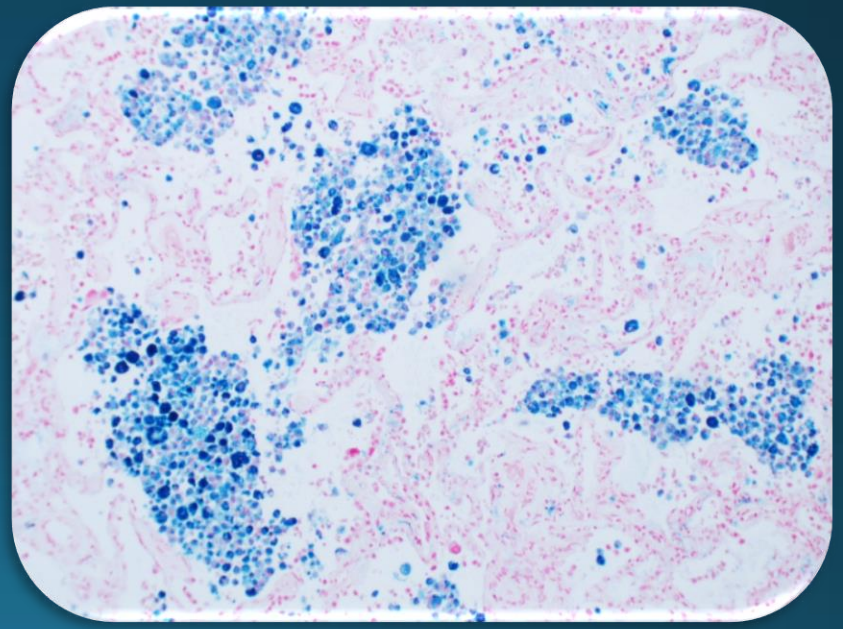
# Diagnostic methods:

- Based on symptoms, high blood Lactate concentrations above 10 mmol per liter are an indicator of cyanide poisoning, as defined by the presence of a blood cyanide concentration above 40 mumol per liter.
- Methods of detection include colorimetric assays such as the Prussian blue test, the pyridine-barbiturate assay, also known as the "Conway diffusion method"

# Prussian blue test:

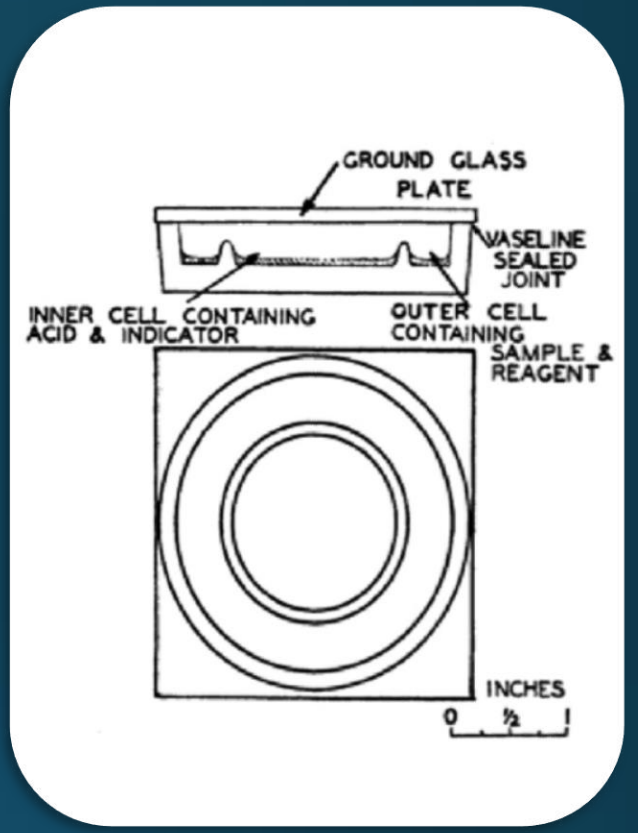
Any ferric ion (+3) present in the tissue combines with the ferrocyanide and results in the formation of a bright blue pigment called Prussian blue, or ferric ferrocyanide. This is one of the most sensitive histochemical tests and will demonstrate even single granules of iron in blood cells.

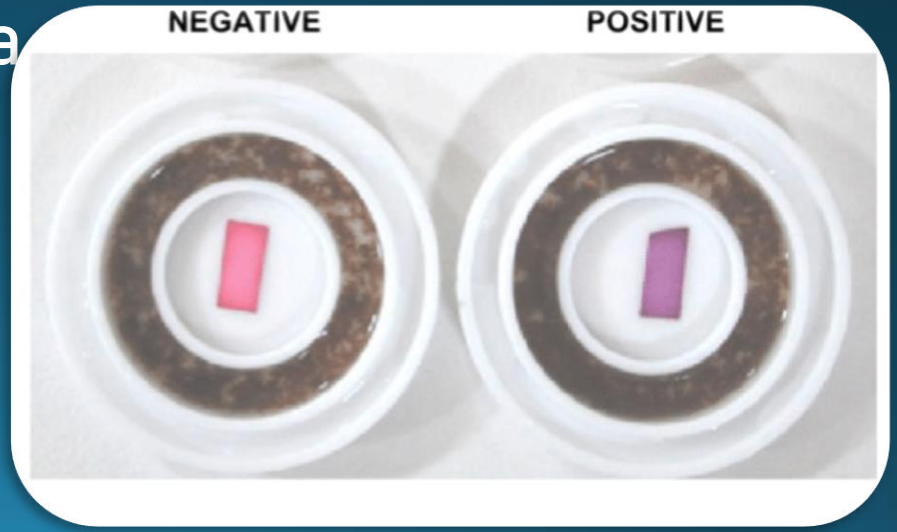
https://www.youtube.com/watch?v=FuTxDF0PsIs

# Conway diffusion method:

- A microchemical analytical method applicable to substances from which a gas, e.g. ammonia or carbon dioxide, can be liberated quantitatively by a specific reagent or enzyme.
- For cyanide detection in human serum by this method usually Sodium hydroxide (NaOH) or Sulfuric ascid (H2So4) used as a reagent.



# Strychnine

- Strychnine poisoning can be fatal to humans and other animals and can occur by inhalation, swallowing or absorption through eyes or mouth.
- Symptoms of toxicity can be varied and may include: poor circulation, swelling, Painful muscle spasms possibly leading to fever and to kidney and liver injury, depression, allergies, poor skin, fatigue, constipation, digestive disorders, cold/respiratory disorders, insomnia.
- The usual fatal dose is 60–100 mg/kg and is fatal after a period of 1–2 hours.
- There is no antidote for strychnine toxicity.


## Detection in biological specimens:

- Strychnine is easily quantitated in body fluids and tissues using instrumental methods in order to confirm a diagnosis of poisoning in hospitalized victims or to assist in the forensic investigation of a case of fatal overdosage.
- The analytical methods for determining this compound in tissues and body fluids by means of color reactions using (Mandelin's Reagent), thin layer chromatography (TLC), high performance liquid chromatography and gas chromatography.
- The concentrations in blood or urine of those with symptoms are often in the 1–30 mg/L range.


# Phenothiazine

- Phenothiazine is an antipsychotic drug which used to reduce hallucinations and delusions associated with psychosis.


- Toxicity Symptoms:

-AIRWAYS AND LUNGS:
No breathing ,rapid breathing and shallow breathing

- BLADDER AND KIDNEYS:
Cannot urinate.

-EYES, EARS, NOSE, MOUTH, AND THROAT
Blurred vision ,Congested nose , Drooling , Dry mouth , Swallowing difficulties , Sores (in the mouth, on the tongue, or in the throat) and Vision color changes (things look brownish)

-HEART AND BLOOD:
High or very low blood pressure ,Irregular heartbeat ,Rapid heartbeat.

-MUSCLES AND JOINTS:
Muscle spasms, particularly of the neck, face, and back
Muscle stiffness.

-NERVOUS SYSTEM
Agitation, irritability, confusion , Clumsiness , Deep sleep, Convulsions, tremor , Difficulty walking or a shuffling gait ,Fainting ,Hallucinations (rare) ,Weakness, lack of coordination and restlessness.

-SKIN
Rapid sunburn if exposed to the sun ,Bluish skin (changing to purplish).

-STOMACH AND INTESTINAL TRACT
Constipation ,Loss of appetite ,Nausea.

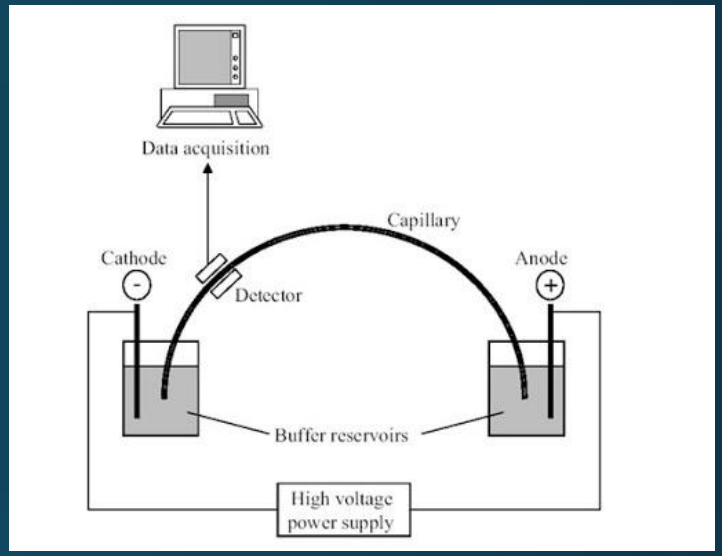
OTHER
Changes in menstrual pattern in women, from long-term use

## Management of toxicity:

- The emergency team will measure and monitor the patients vital signs, including temperature, pulse, breathing rate, and blood pressure. Symptoms will be treated. Blood and urine tests, breathing support, including oxygen and tube through the mouth into the lungs, Chest x-ray, CT scan (advanced brain imaging), ECG, giving Intravenous (IV) fluids, laxative and all medicine that reverse the effects of the drug toxicity symptoms.
- Anticholinergic agents may be useful for control of extrapyramidal reactions associated with overdosage.
- Also gastric lavage and activated charcoal may help to remove the drug from the body.

# Detection in biological samples:

1. In urine: samples analysed by computerized gas chromatography - mass spectrometry.
2. In blood: non-aqueous capillary electrophoresis (NACE)
3. In hair: gas chromatography–mass spectrometry and liquid chromatography with tandem mass spectrometry techniques were the methods of choice and allowed the detection of chemical compounds at low concentrations




# Barbiturate

- The effects of barbiturates occur via the GABA neurotransmitter.
- Complications of overdose can include respiratory depression and noncardiogenic pulmonary edema causing death.
- While there is no antidote, treatment involves supporting a person's breathing and blood pressure.
- Multiple doses of charcoal may be required.
- Hemodialysis may occasionally be considered.

# Detection in biological samples:

- The primary and simplest test is **Zimmermann test.**

- it is a two-component reagent, the first component composed of 1,3-dinitrobenzene (1% w/v) in methanol and the second component composed of 15% potassium hydroxide in water.


- One drop of each component is added to the sample being tested and the resulting colour change is observed to give an indication of the identity of the compound.

- The reagent works by forming a reddish-purple. A red-purple to pink colour indicates the probable presence of a barbiturate.

**The exposure to barbiturate can be detected in blood and urine by one of the following methods:**

1. A TLC method was developed which employs a resin column for the extraction and identification of barbiturates in urine.
2. Infrared spectroscopy
3. Liquid chromatography - mass spectrometry (LC-MS)
4. High performance liquid chromatography (HPLC)
5. Gas chromatography - mass spectrometry (GC-MS)
6. Gas chromatography (GC) with flame ionization detector.

# Thank You

# Environmental& Occupational Toxicology

Assistance Lecturer

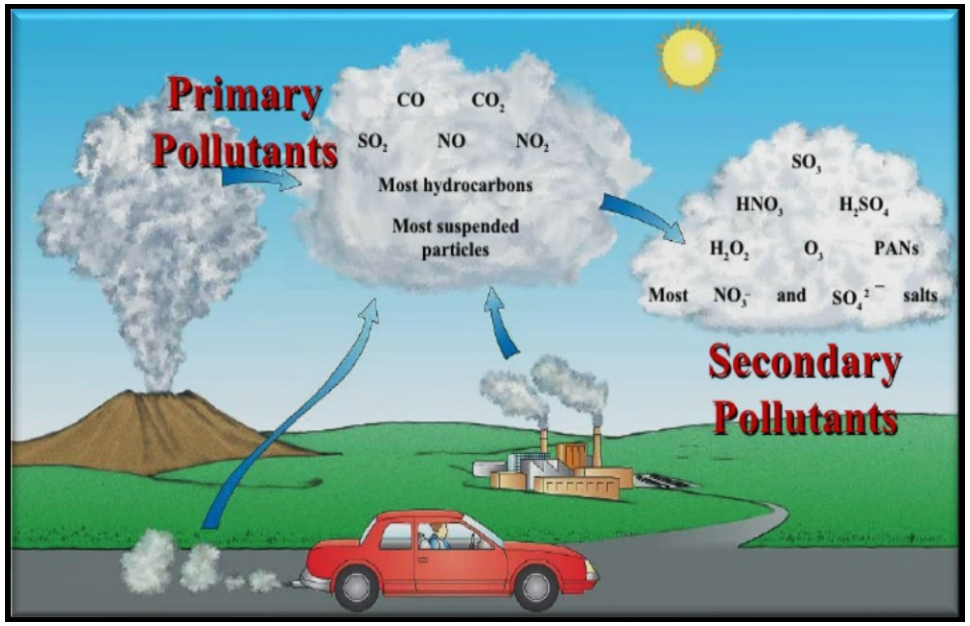
Muhammed Malik

# Occupational toxicology

- Deals with the chemicals found in the workplace.
- The major emphasis of occupational toxicology is to identify the agents of concern.
- Identify the acute and chronic diseases that they cause.
- Define the conditions under which they may be used safely, and prevent absorption of harmful amounts of these chemicals.

# Environmental toxicology

- Deals with the potentially harmful impact of chemicals, present as pollutants of the environment, on living organisms.
- The term environment includes all the surroundings of an individual organism air, soil, and water.

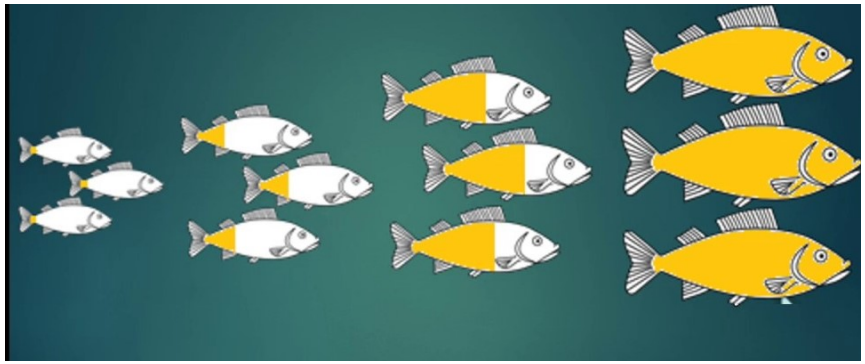


# Ecotoxicology

- Is concerned with the toxic effects of chemical and physical agents on populations and communities of living organisms **within defined ecosystems**.
- It includes the transfer pathways of those agents and their interactions with the environment.
- **Traditional toxicology:** is concerned with toxic effects on individual organisms.

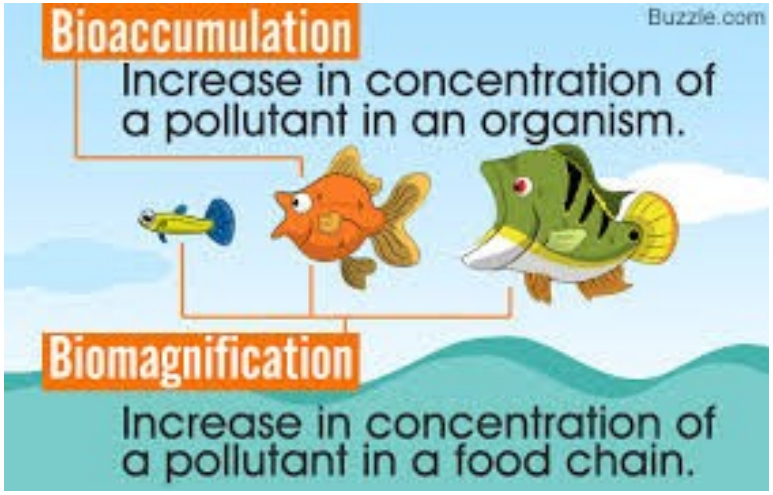
# Bioaccumulation:

- If the intake of a long-lasting contaminant by an organism exceeds the latter's ability to metabolize or excrete the substance, the chemical accumulates within the tissues of the organism.



# Biomagnification :

- Although the concentration of a contaminant may be virtually undetectable in water, it may be magnified hundreds or thousands of times as the contaminant **passes up the food chain**.



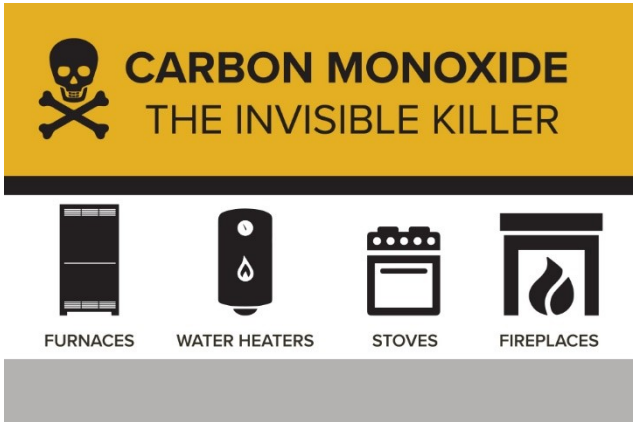
# AIR POLLUTANTS

- Sources: vapors, aerosols, smokes, particulates, and individual chemicals.
- Major substance: account for about 98% of air pollution:

1. carbon monoxide (about 5
2. Sulfur oxides (about 14%).
3. Hydrocarbons (about 14%)
4. Nitrogen oxides (about 14%
5. Ozone.

# Carbon Monoxide:

- Is a colorless, tasteless, odorless, and non-irritating gas, a byproduct of incomplete combustion.
- CO combines tightly with the oxygen-binding sites of hemoglobin.
- It has an affinity for hemoglobin that is about 220 times that of oxygen. formed—carboxyhemoglobin.
- This reduces the transfer of oxygen to tissues. Organs with the highest oxygen demand (**the brain, heart, and kidneys**) are most seriously affected.

# Clinical effects:


(1) Headache and tightness in t

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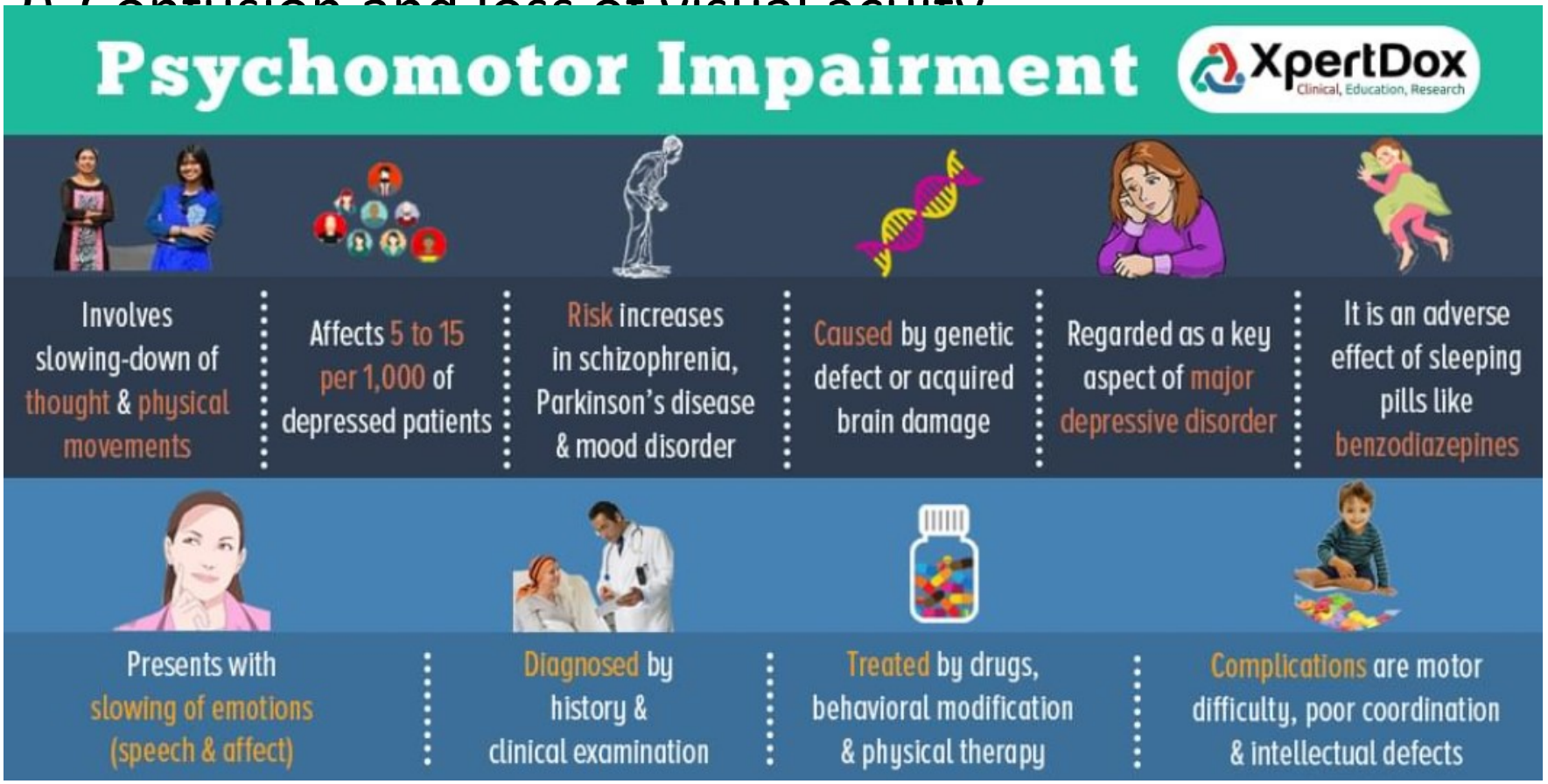


# Treatment:

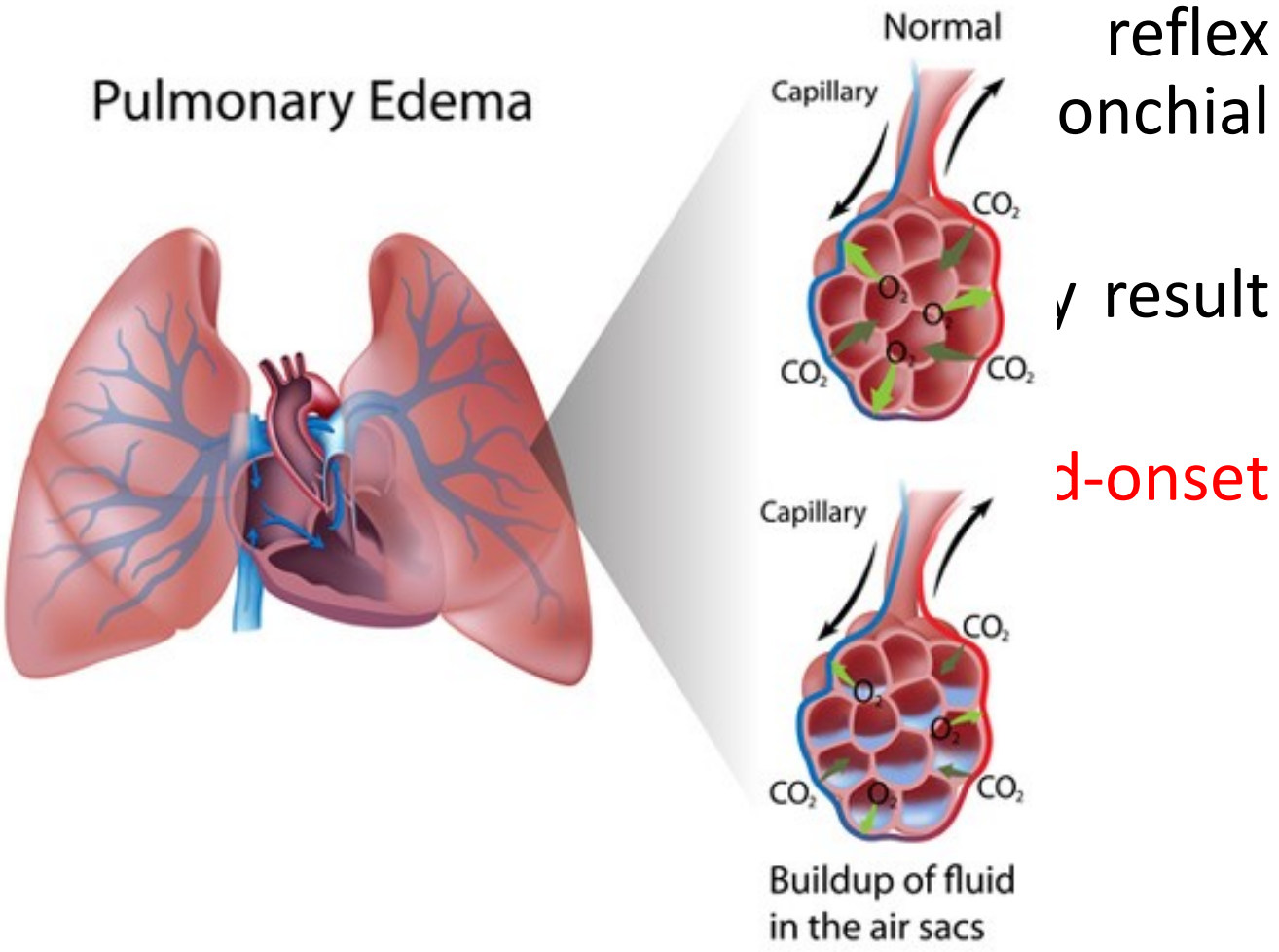
1. Remove from the exposure source immediately.
2. Oxygen.
3. If respiratory failure is present, mechanical ventilation is required.
4. Patients should be treated with high concentrations of O2 only for a short period.

# Sulfur Dioxide

- Is a colorless irritant gas generated primarily by the combustion of sulfur-containing fossil fuels.
- When SO2 contacts moist membranes, it transiently forms sulfurous acid.
- This acid has severe irritant effects on the eyes, mucous membranes, and skin.

# Clinical effects:

- Irritatio reflex bronchc onchial secretio
- In asthr result in an ac
- If sever d-onset pulmon

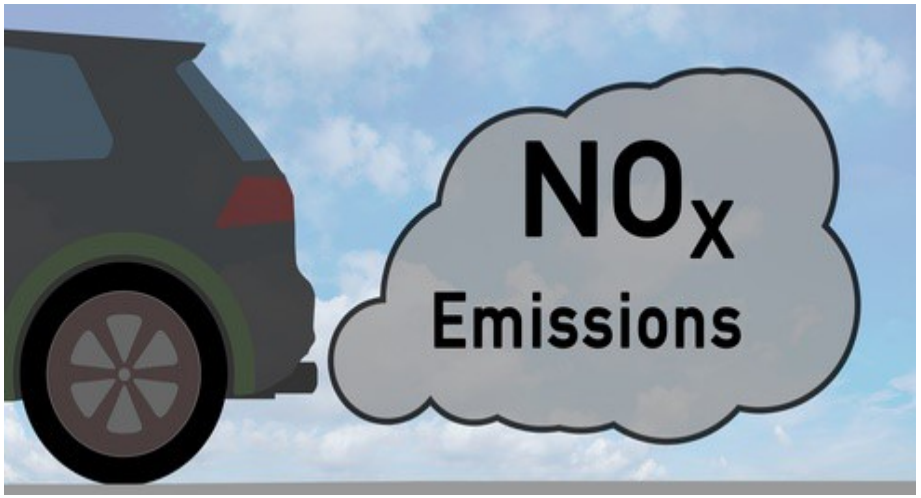


# Treatment

No specific Trt for SO2 but depends on therapeutic maneuvers used to treat irritation of the respiratory tract and asthma.

# Nitrogen Oxides

- Is a **brownish** irritant gas.
- Sometimes associated with fires.
- Its cause deep lung irritant and pulmonary edema.




# Signs and symptoms:

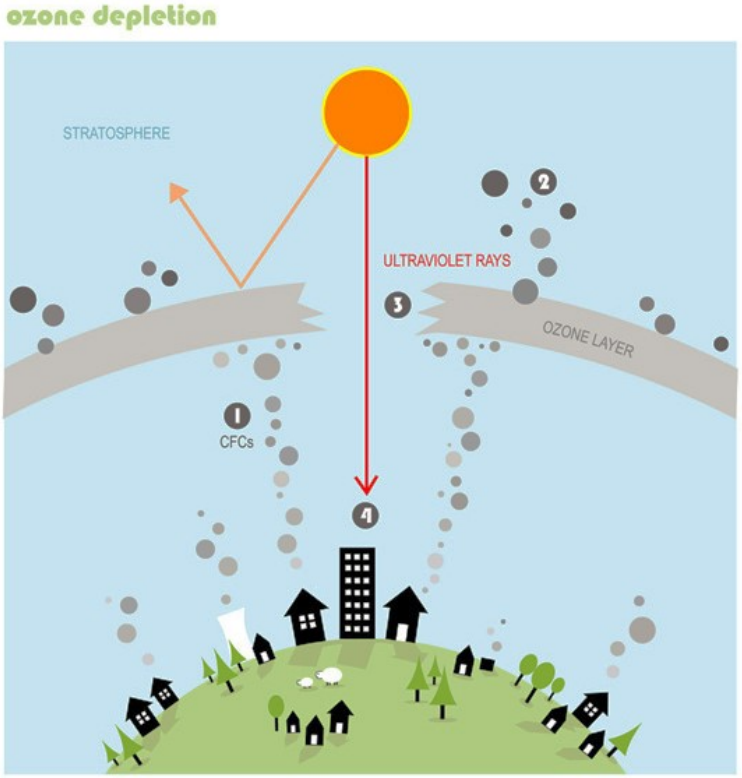
- Acute exposure: Irritation of the eyes and nose, cough, mucoid or frothy sputum, dyspnea, and chest pain. Pulmonary edema may appear within 1–2 hours.

# Treatment

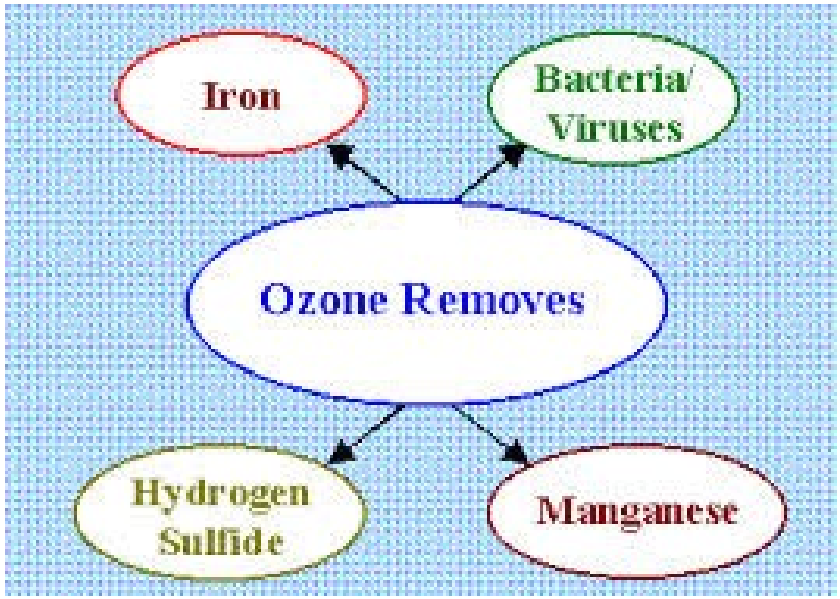
- No specific treatment for acute intoxication.
- Therapeutic measures for the management of deep lung irritation and pulmonary edema are used.

# Ozone:

- Is a **bluish** irritant gas found in the earth's atmosphere.
- Where it is an important absorbent of ultraviolet light at high altitude.
- At ground level, ozone is an important pollutant.



- Ozone can be generated in the workplace by high-voltage electrical equipment, it used for air and water purification.




# clinical effects:

- Ozone irritant mucous membranes.
- Mild exposure produces upper respiratory tract irritation.
- Severe exposure can cause deep lung irritation, with pulmonary edema.
- Pulmonary function is impaired at concentrations exceeding 0.8 ppm.

# Treatment

- There is no specific treatment is available.
- Measures that reduce inflammation and pulmonary edema .

# SOLVENTS

## 1. Halogenated aliphatic hydrocarbons:

The substances include:

a. Carbon tetrachloride.

b. Chloroform.

c. Trichloroethylene.

d. Tetrachloroethylene.

e. Methyl chloroform.

Found wide use as industrial solvents, degreasing agents, and cleaning agents.

# Clinical effects :

- Solvents are potent CNS depressants.
- The acute effect of toxicity are nausea ,vertigo, headache and coma.
- Chronic exposure leading to hepatic dysfunction and nephrotoxicity.

# Treatment:

- There is no specific treatment for acute.
- Management depends on the organ system involved.

# 2-Aromatic Hydrocarbons:

**Toluene,Xylene,Benzene:**

- Used for their solvent properties and as an intermediate in the synthesis of other chemicals.
- It remains an important component of gasoline.

# Benzene

- Cause depression of the CNS.
- Exposure to 7500 ppm for 30 minutes can be fatal.
- Exposure to concentrations larger than 3000 ppm may cause euphoria, nausea, locomotor problems, and coma.
- Vertigo, drowsiness, headache, and nausea may occur at concentrations ranging from 250 to 500 ppm.

Chronic exposure to benzene can result in bone marrow injury, Aplastic anemia, leukopenia, pancytopenia, and thrombocytopenia occur and leukemia.

- **Toluene** (methylbenzene) and xylene does not possess the myelotoxic properties, but cause a CNS depressant and a skin irritation .
- **Treatment:** removal from exposure ,CNS depression is mange by support the vital signs.

# PESTICIDES

A-Chlorinated hydrocarbons.

B-Choliesterse Inhibitors.

C-Botanical.

# A-Chlorinated hydrocarbons

These agents are usually classified into four groups:

1. DDT (chlorophenothane).
2. Benzene hexachlorides,.
3. Cyclodienes.
4. Toxaphenes.

- These agents are persistent, poorly metabolized, lipophilic chemicals that exhibit significant bioaccumulation.

# Mechanisim of Action:

- These agents interfere with inactivation of the sodium channel in excitable membranes and cause rapid repetitive firing in most neurons.
- The major effect is CNS stimulation.
- The sign of intoxication is **tremor and convulsions.**
- Management is symptomatic.

# B-Choliesterse Inhibitors

- Carbamate and organophosphorus (malathion , parathion).
- These agents is inhibition of AchE through phosphorylation of the esteratic site, causing neuropathy target esterase (NTE).
- This results in progressive demyelination of the longest nerves. Associated with paralysis and axonal degeneration, this lesion is sometimes called organophosphorus ester-induced delayed polyneuropathy (OPIDP).

# C-Botanical:

- Nicotine: has effect on nicotinic cholinoreceptors (excitation follow by paralysis of ganglion, neurotransmission)
- Rotenone: plant alkaloid pestecides cause GIT distress when ingested and conjunctivitis and dermatitis after direct contact with exposed body surface.
- Treatment is supportive in both.


# HERBICIDES:

## 1-Chlorophenoxy:

- 2,4-Dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and their salts and esters have been used as herbicides for the destruction of weeds.
- Can cause coma and generalized muscle hypotonia. may persist for several weeks

# 2-Bipyridyl Herbicides

- Paraquat is the most important agent of this class.
- Signs and symptoms after oral exposure:

  1. Hematemesis and bloody stools.

  2. When delayed toxicity occurs:

Respiratory distress and the development of congestive hemorrhagic pulmonary edema accompanied by widespread cellular proliferation.

Hepatic, renal, or myocardial involvement may develop.

- The interval between ingestion and death may be several weeks.
- Adsorbents (eg, activated charcoal ) Once the paraquat is absorbed, treatment is successful in fewer than 50% of cases.
- Monitoring of plasma and urine paraquat concentrations is useful for prognostic assessment.
- Antioxidants such as **acetylcysteine and salicylate** might be beneficial through free radical-scavenging, and anti-inflammatory, best supportive treatment dialysis

Thank you

# FOOD TOXICITY

DR. MUHAMMED MALIK AL-ANI

- Foodborne illness, more commonly referred to as food poisoning, is the result of eating contaminated, spoiled, or toxic food.
- The botulinum toxin as the most toxic substance known has an LD50 value of 1 ng / kg, while the most non-toxic substance water has an LD50 value of more than 90 g / kg.
- Signs and symptoms may start within hours after eating the contaminated food, or they may begin days or even weeks later.
- The most common symptoms of food poisoning include nausea, vomiting, and diarrhea. Although it's quite uncomfortable, food poisoning isn't unusual.

# RISKS OF TOXINS IN FOOD:

- Carcinogenic
- Mutagenic
- Teratogenic
- Endocrine disrupters (hormones)
- Microbial pathogens

Food toxicant can be divided into three categories:

1. Endogenous toxicants.
2. Naturally occurring toxicants.
3. Synthetic toxicants.

# ENDOGENOUS TOXICANTS:

- Substances produced by tissue cells in plants and other biological raw materials.
- Chemical substances often serve the purpose of protecting plant tissues from pests, as well as from pathogenic organism.
- Transmission to man can be direct consumption of toxic plants or from animals who have consumed the plant that are used for human foods.
- Examples include flavonoids, cyanogenic compounds, and mushroom toxins.
- Toxicological effects range from acute effects of gastroenteritis to more severe toxicities in the CNS leading to death.

# 1. FLAVONOIDS

- A class of plant pigments that are widely present in human food.
- Sources of flavonoids include: apples, apricots, blueberries, raspberries, strawberries
- At low concentrations → the effects of flavonoids are thought to be potentially anticarcinogenic because flavonoids can block and inhibit the excessive cell division characterized by cancer.
- High concentrations of flavonoids may promote cancer formation→ can damage the chromosomes and DNA in cells, leaving them more susceptible to cancer.
- Daily intake: 150-250 mg/day.

# 2. TANNINS

- Sources: Fruits, tea (highest content), coffee, cocoa, grape, wine.
- Toxicity: cause acute liver injury, i.e., liver necrosis and fatty liver.
- If ingested in excessive quantities→inhibit the absorption of minerals such as iron → lead to anemia
- In sensitive individuals, a large intake of tannins may cause bowel irritation, kidney irritation, liver damage, irritation of the stomach and gastrointestinal pain.

# 3. CYANOGENIC GLYCOSIDES

- Sources: lima beans, peas, bitter almonds
- Cyanogenic glycoside is not toxic on its own.
- When fresh plant material is damaged by chewing, cutting, insect attack→ it will be subsequently broken down to sugar and a cyanohydrin which rapidly decomposes to an aldehyde or a ketone and releases the toxic hydrogen cyanide.
- Peeling, washing in running water and cooking or fermenting can remove and volatilize the cyanide.
- Acute and chronic biochemical effects in biological system: inhibition of the antioxidant defense, alteration of cellular ion homeostasis and inhibition cellular respiration
- Symptoms: mental confusion, muscular paralysis, respiratory distress.

# 4. MUSHROOM TOXINS

Caused by the high content of amatoxins in mushrooms.

➢There are four categories of mushroom toxins:

1. Neurotoxins.
2. Protoplasmic poisons.
3. Gastrointestinal irritants.
4. Disulfram-like toxins.

**1. Neurotoxins**

Cause neurological symptoms such as profuse sweating, hallucinations, depression, spastic colon, excitement, convulsions, and coma.

**2. Protoplasmic poisons**

Cause generalized destruction of cells, which is followed by organ failure.

**3. Gastrointestinal irritants**

Produce rapid, transient nausea, abdominal cramping, vomiting, and diarrhea.

**4. Disulfram-like toxins**

Disulfram-like toxins are usually nontoxic and produce no symptoms. However, if alcohol is consumed within 72 hours after eating them, they may produce vomiting, nausea, headache, flushing, and cardiovascular disturbances.

# SYMPTOMS OF MUSHROOM POISONING

- The first symptoms of mushroom poisoning occur within 6-24 hr. after ingestion of the mushroom **(phase one)**
- **Phase two**, also called the gastrointestinal phase, involves sever vomiting, abdominal cramps, nausea, and diarrhea.
- **Phase three** lasts about 12-24 hr. and is characterized by improved clinical symptoms; however, it is also the beginning of liver necrosis.
- **Phase four (the last phase),** result in hepatic failure, encephalopathy, internal bleeding, and acute renal failure.
- Patients usually die within 5-20 days after ingestion of the mushrooms.

# NATURAL CONTAMINANTS

- There are three important sources:
  - Raw materials of plant origin can become contaminated if they are mixed with toxic non-nutritive plant species.
  - Raw materials of animal origin, mainly fish and milk, can also become contaminated if the animal has ingested toxic substances of natural origin.
  - Contaminants of natural origin can be the products of microorganisms.

# MICROBIAL TOXIN: MYCOTOXIN

- Mycotoxins are secondary metabolites of fungi which can induce acute as well as chronic toxic effects.
- Toxic syndromes resulting from the intake of mycotoxins by man and animals are known as mycotoxicoses.
- Aflatoxins are the most important mycotoxins, which is produced by certain species of *Aspergillus*
- Aflatoxins are carcinogenic substances and may be present in a large number of foods. This toxin can cause cancer, cirrhosis of the liver.

# 3.SYNTHETIC TOXICANTS OR ENVIRONMENTAL SOURCES:

**-Water**-Food-borne diseases are also carried by contaminated water.

**-Soil**-Dust and dirty is made up from soil.

It is easily blown on to food after being carried into the kitchen on clothes and shoes, soil contains the food poisoning bacterium clostridium perfringens as well as many others.

**-Insects**-Insects carry bacteria on their bodies.

Crawling insects such as cockroaches, beetles and flies.

**-Kitchen surfaces & Utensils**

# METHODS OF REDUCTION OF PLANT TOXINS:

1. For some types of natural toxins, post- harvest processing treatments and cooking of the plant result in destroying the endogenous toxic substances or reduction of its toxicity.
2. Special care has to be exercised in selecting the food plants in limiting the amount of intake.

# THANK YOU

# FORENSIC TOXICOLOGY

Dr. Muhammed Malik

# FORENSIC TOXICOLOGY IS…

- The use of detecting and identifying the presence of drugs and poisons in body fluids, tissues, and organs to aid medical or legal investigation.
- the amount of drug or poison that is present in the submitted sample

# HISTORY

- Philippus Theophrastus observed that any substance could be a poison, depending on its dose: "All things are poison and nothing is without poison; only the dose makes a thing not a poison."
- In the U.S., forensic toxicology did not develop until the early 20th century in New York
- Dr. Alexander Gettler (lead FT in NYC medical examiner lab) is considered this country's first forensic toxicologist.

# $LD_{50}$ INFORMATION Mg/Kg

Sugar - $LD_{50}$=29700

Ethanol - $LD_{50}$=7060

Salt - $LD_{50}$=3000

Caffeine - $LD_{50}$=192

Nicotine - $LD_{50}$=48

Cyanide - $LD_{50}$=6.4

Botulinum toxin - $LD_{50}$=0.00005

# FDA SET CLASSIFICATIONS

- There are 5 schedules of classification of controlled substances based on
  - Drug's potential for abuse
  - Potential to physical and psychological dependence
  - Medical value
- Federal law also controls materials that are used in making drugs and those that are manufactured to resemble drugs

# DRUG SCHEDULES

- **Schedule I**:

Drugs with high potential for abuse and addiction, NO medical value

Ex: heroin, marijuana.

- **Schedule II**:

Drugs with high potential for abuse and addiction, have some medical value with restrictions (no refills)

Ex: cocaine, morphine, methamphetamine.

# DRUG SCHEDULES

- **Schedule III**:

Drugs with less potential for abuse and addiction, currently acceptable for medical use (no more than 6 refills)

Ex: codeine, ketamine.

- **Schedule IV**:

Drugs with low potential for abuse and addiction, currently acceptable for medical use (no more than 6 refills)

Ex: Valium.

# DRUG SCHEDULES

- **Schedule V**:

Drugs with low potential abuse, lowest potential dependency, acceptable for medical use

- Ex: antitussive, antidiarrheal, analgesic medicines

# TYPES OF CASES:

- Suspected drug intoxication cases.
- Fire deaths.
- Homicides.
- Driver and pilot fatalities.
- Sudden infant death (SIDS).

# ROLES OF THE TOXICOLOGIST

1. Must identify one of thousands of drugs and poisons.
2. Not always looking for exact chemicals, but metabolites of desired chemicals (ex. heroin → morphine within seconds). Important to ensure results are accurate and interpretations are sound
3. Collection
   - Appropriate method of collection (varied and multiple)
   - Adequate volumes for analysis
4. Storage and handling.

# TOXICOLOGY PROCEDURES

A- Presumptive/Screening

- quick test to narrow down possibilities
- spot/color tests

B- Confirmation

- determines exact identity
- thin-layer/gas chromatography, IR spectroscopy, mass spectrometry

# TESTING SAMPLES

- Divided into 2 samples
  - 1st sample is for screening test
  - 2nd sample is for confirmatory test

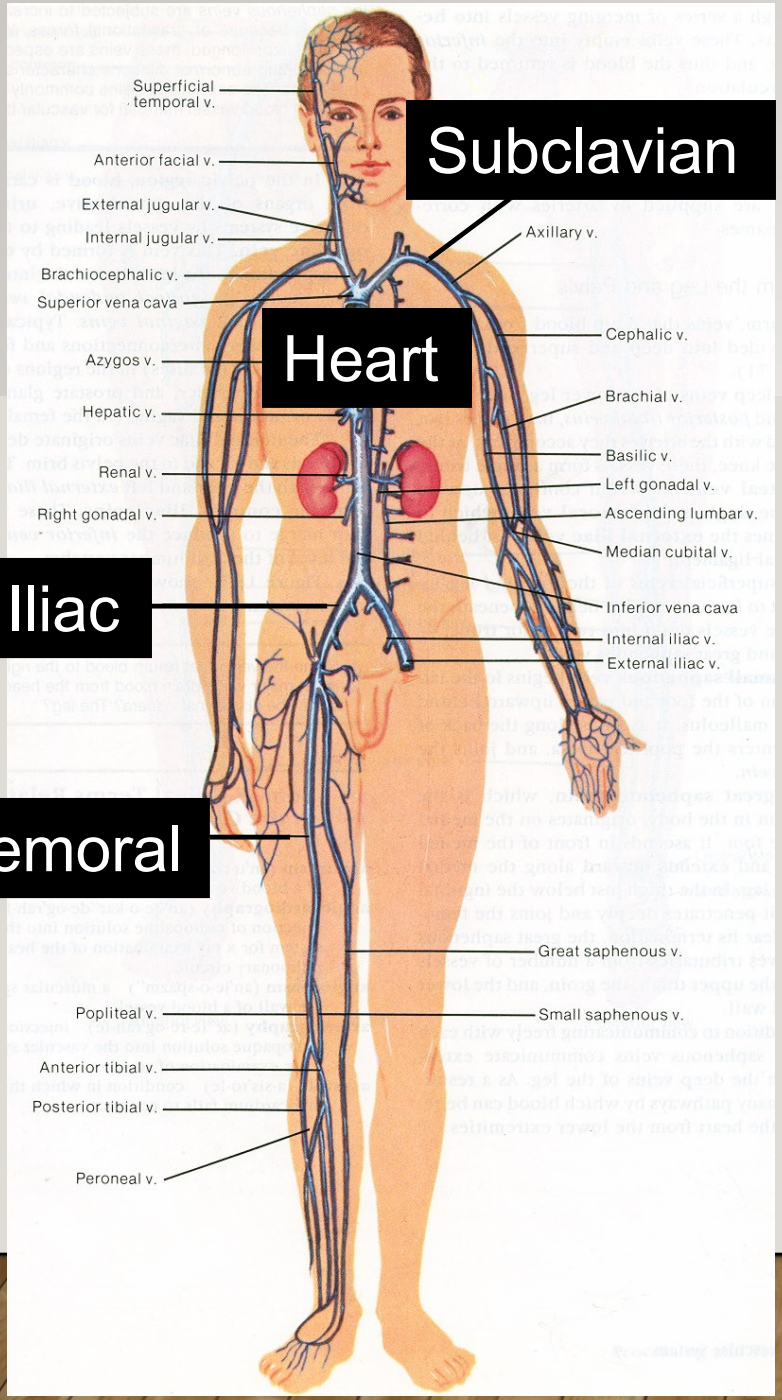
    Only done for samples that test positive during screening

# TYPICAL SPECIMENS

- Blood
- Urine
- Stomach contents
- Bile
- Liver
- Hair
- Vitreous humor: the transparent jellylike tissue filling the eyeball behind the lens.

# BLOOD

- Antemortem → ideal blood sample
- Postmortem blood is not truly "blood"
- Anatomical site of collection at autopsy should be noted.




- Central sites
  - *Heart*
- Peripheral sites
  - *Femoral*
  - *Iliac*
  - *Subclavian*
- Other sites
  - *Head blood*
  - *Hematoma blood*

# URINE

- Blood filtered by the kidneys.
- Urine Stored in the bladder until voided.

The presence of a drug in the urine of an individual indicates that some time prior to death the drug or poison was present in the blood of the individual.

# STOMACH CONTENTS

- Visual examination may reveal tablets
- Caution: drugs administered by other routes may also diffuse into stomach contents from the blood
- Useful for directing further analysis

# RELATION OF TYPE OF SAMPLE WITH DURATION OF TOXICITY

- Blood
  - 10 mL whole blood, anticoagulant, preservative
  - More expensive, but more accurate, can detect hours usage.
- Urine
  - Samples always given under direct supervision
  - Easy, cheap, can detect hours to days usage

- Hair samples
  - Collected from scalp or body
  - Can detect days to months usage
- Saliva
  - Can detect hours to ~2 days usage
- Vitreous humor
  - Only used post-mortem

# NON-BIOLOGICAL SUBMISSIONS

- Used to direct analysis of biologicals (toxins or drug obtained) May indicate the nature of substances that may have been ingested, inhaled or injected
- Examples:
  - Containers found at the scene
  - Syringes
  - Unidentified tablets or liquids

# PRESUMPTIVE/SCREENING TEST

- **Marquis Test:**
  - Turns purple in the presence of opiates
  - Turns orange-brown in presence of amphetamines
- **Scott Test:**
  - Turns blue in the presence of cocaine
- **Duquenois-Levine:**
  - Turns purple in the presence of tetrahydro-cannabinal

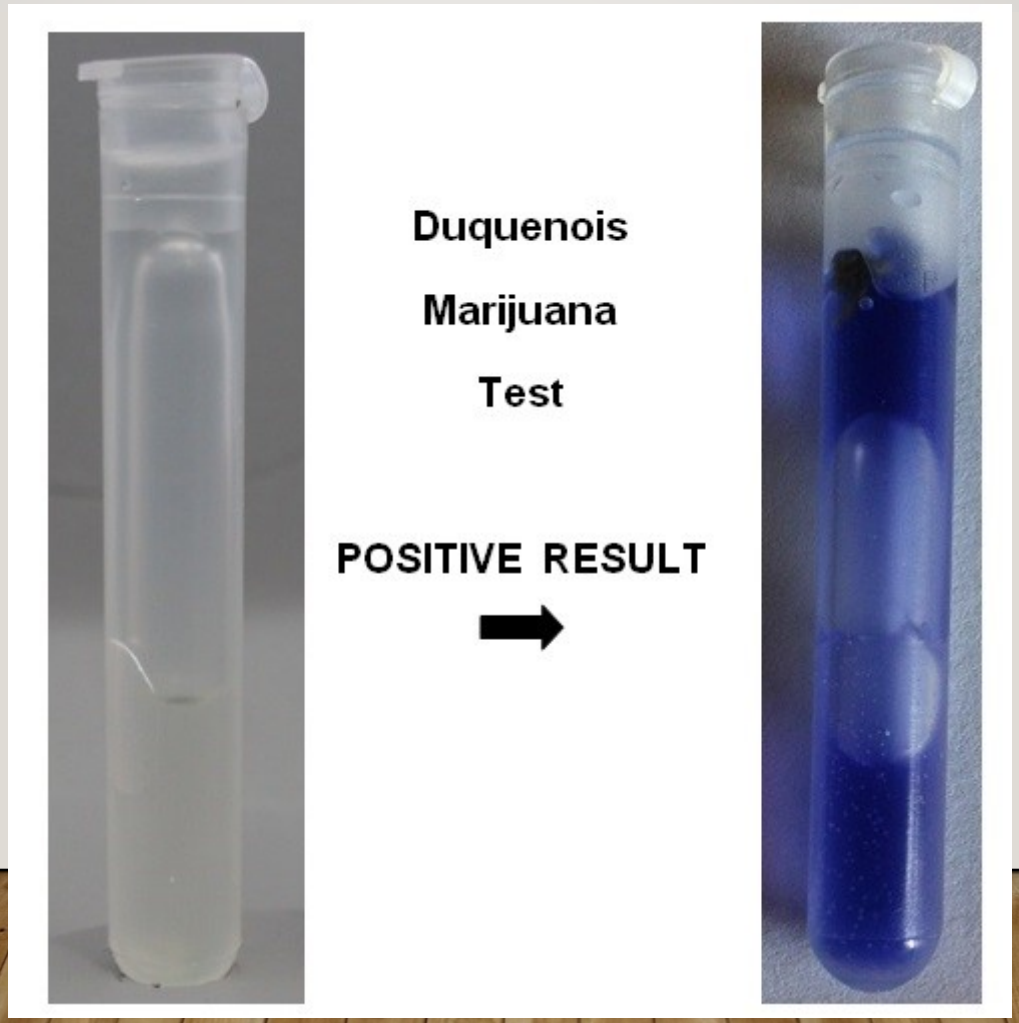
# MARQUIS TEST

# SCOTT TEST

Scott Cocaine Test (Simplified)

POSITIVE RESULT

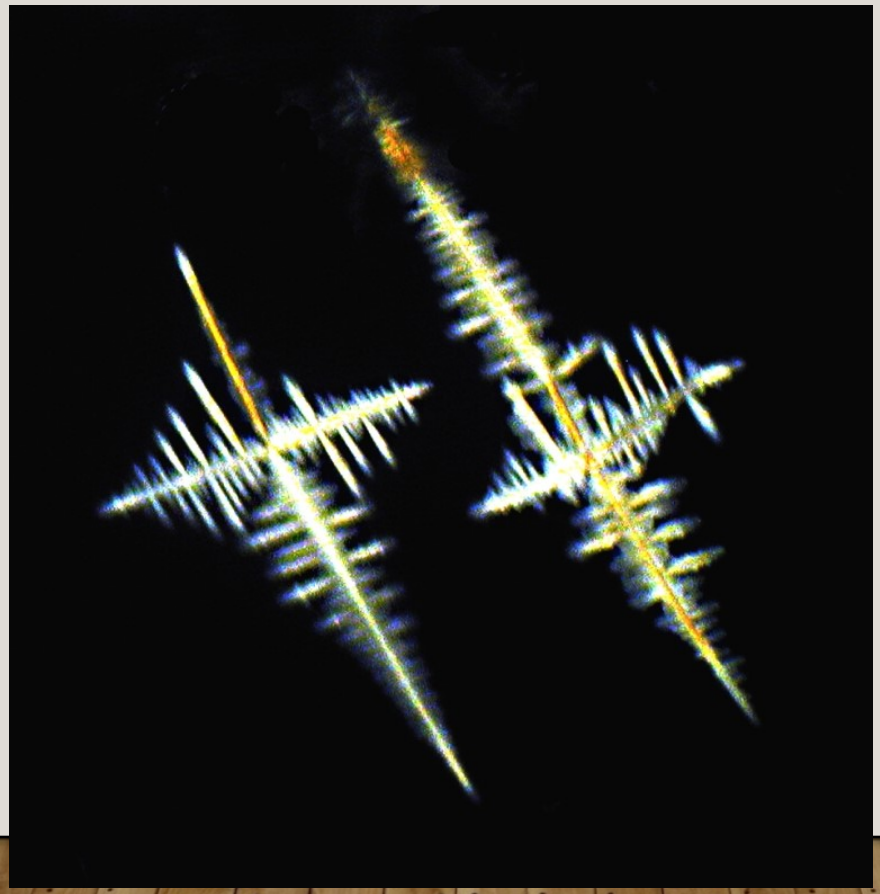
# DUQUENOIS-LEVINE



# CONFIRMATORY TESTS

1. **Microcrystalline Tests**: Identifies drug by using chemicals that react to produce characteristic crystals
2. **Chromatography:** Separates drugs and gives tentative ID
3. **Mass Spectrometry:** Chemical "fingerprint" – no two drugs fragment the same
4. **IR Spectroscopy:** IR light is absorbed by different chemicals

# MICROCRYSTALLINE TESTS



# CHROMATOGRAPHY

# MASS SPECTROMETRY

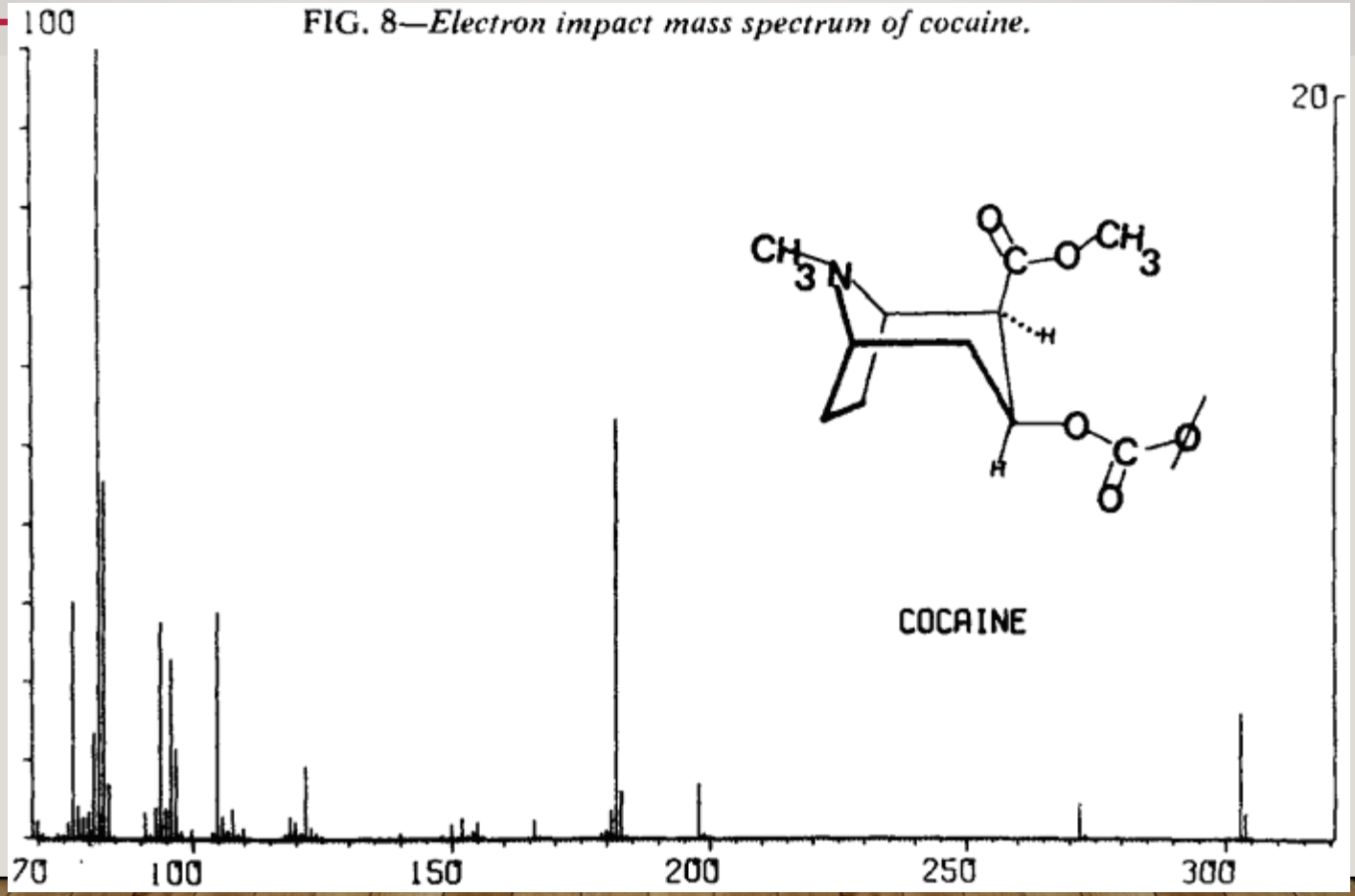



FIG. 8—*Electron impact mass spectrum of cocaine.*

# IR SPECTROSCOPY

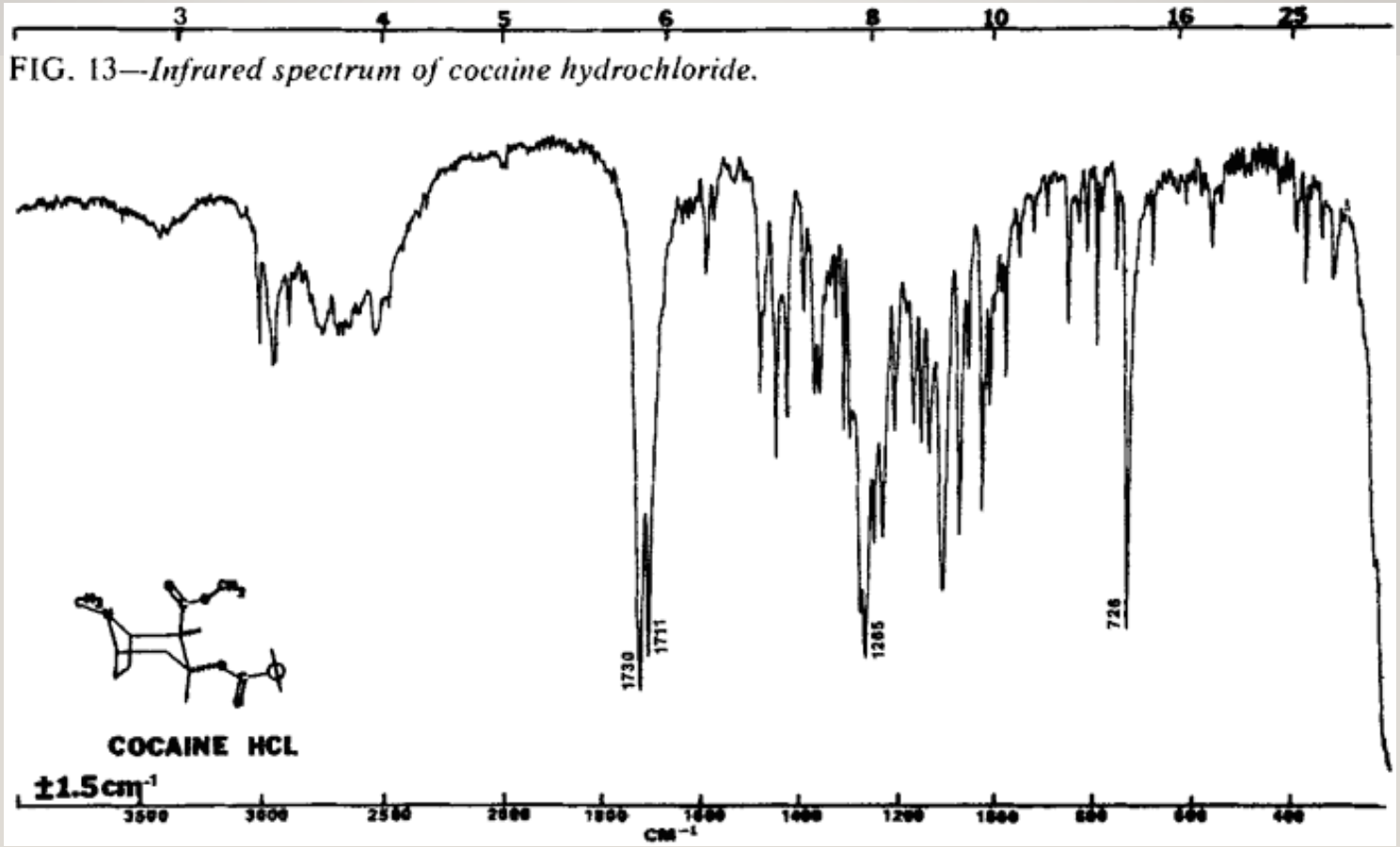


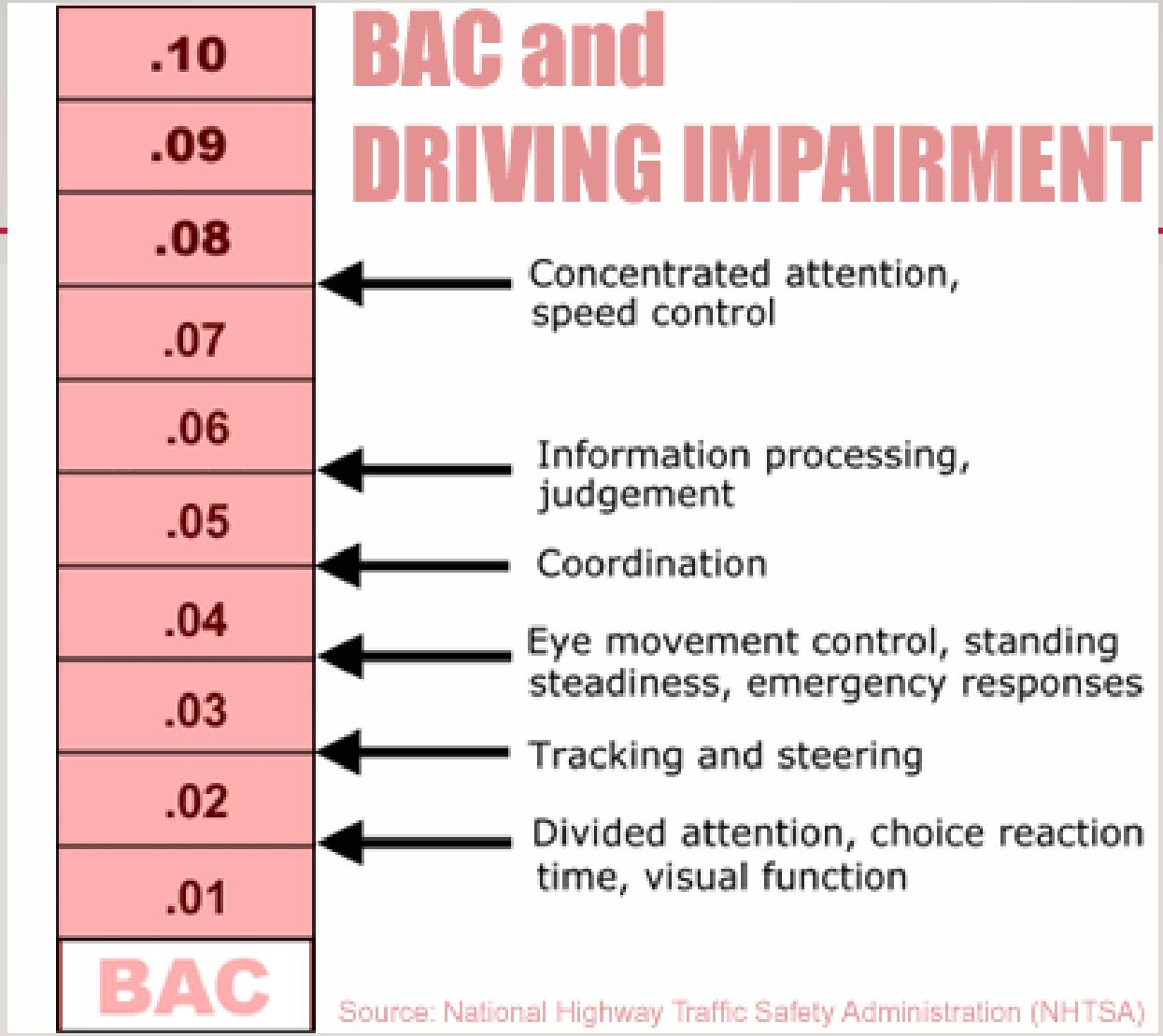
FIG. 13—*Infrared spectrum of cocaine hydrochloride.*

# ALCOHOL IS AN EXAMPLE

- Alcohol is absorbed through the stomach and intestine
- Once absorbed, alcohol is:
  - Oxidized in liver by alcohol dehydrogenase turned into acetic acid (vinegar).
  - Excreted by breath, perspiration, and kidneys turned into carbon dioxide and water.

# BLOOD ALCOHOL CONTENT

- Relates amount of alcohol per volume of blood
- Legal intoxication limit in US is 0.08, meaning 0.08 grams of ethanol per 100 mL of blood (4.5-5.5 mL absorbed [~1 tsp])
  - >0.20 – Stupor
  - >0.40 – Unconsciousness/death


BAC and
DRIVING IMPAIRMENT
.10
.09
.08
.07
.06
.05
.04
.03
.02
.01
BAC
Concentrated attention, speed control
Information processing, judgement
Coordination
Eye movement control, standing steadiness, emergency responses
Tracking and steering
Divided attention, choice reaction time, visual function
Source: National Highway Traffic Safety Administration (NHTSA)

# FACTORS THAT AFFECT ALCOHOL ABSORPTION

- Amount consumed
  - More alcohol = more absorbed
- Alcohol content
  - Maximum absorption with 20-25% alcohol
- Time of consumption
  - Maximum absorption with 30 minute consumption period

# FACTORS THAT AFFECT ALCOHOL ABSORPTION

- Presence of food in stomach
  - Food in stomach slows absorption of alcohol
- Body weight
  - More weight = more water in body to dilute alcohol
- Gender
  - Females have more fat tissue = less water

# BLOOD ALCOHOL CONTENT

- Measuring the quantity of alcohol in the blood system (BAC) determines the degree to which someone is intoxicated
- Two methods of making this measurement
  - Measurement of alcohol content in blood
  - Measurement of alcohol in breath

# BAC TESTING

- Blood alcohol is metabolized at the rate of 0.015 per hr, so…
  - If your BAC is 0.08, how long will it take for your BAC to be 0.00?

    0.08 ÷ 0.015 = 5.33 hrs

# BREATH TESTS

- Evidence has shown that the ratio of alcohol in the blood to alcohol in alveoli air is approx. 2100 to 1—This is a basis for relating breath to blood-alcohol concentration. (1 ml of blood same amt. alcohol as 2,100ml of breath)
- The instrument used for breath tests is called *The Breathalyzer.*

# THE BREATHALYZER

- Developed in 1954, it was originally based on a color change observed by spectroscopy
- The Breathalyzer traps 1/40 of 2100 milliliters of alveolar breath, so it, in essence, measures the alcohol concentration present in 1/40 of a milliliter of blood.

# OTHER BREATH TESTS

- Infrared spectrophotometer technology
- Electrochemical fuel cell technology

These instruments are used more recently because they don't depend upon chemical reagents and are entirely automated.

# INFRARED AND FUEL CELL BREATH TESTS

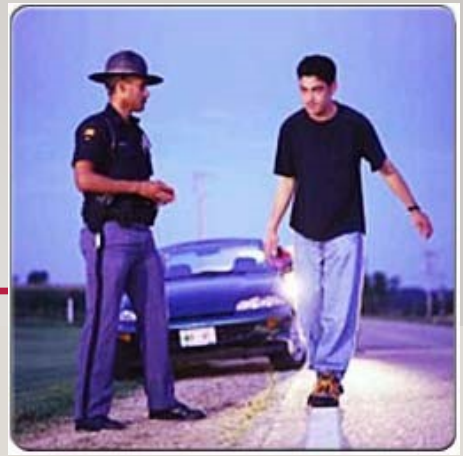
- **Infrared Breath Test** uses infrared wavelengths to test for alcohol or other interferences in the breath

- **Fuel Cell Test** converts fuel (alcohol) and oxygen into a measurable electric current

# FIELD SOBRIETY TESTING METHODS

- Field sobriety testing consists of a series of psychophysical tests and a preliminary breath test.
- Used as a preliminary test to ascertain the degree of the suspect's physical impairment
- These tests are initial and no evidential in nature they only serve to establish probable cause requiring a more thorough breath or blood test

# FIELD SOBRIETY TESTS



- Horizontal Gaze Nystagmus
  - Involuntary eye jerk as eye moves horizontally
- Walk and Turn (divided attention tasks)
- One-Leg Stand.
- follow pen light with eyes

# Examples for forensic toxicologist mistakes

# CASE 1

- A 26 year old man was found dead at the bottom of a staircase. Death was due to physical injuries.
- Question as to alcohol use prior to fall down stairs
  - No urine available at autopsy
  - Alcohol in hematoma blood → 150 mg/100 mL
- Clinician record: the deceased had been drinking prior to receiving the head trauma.
- Since ethanol is detected in the hematoma, but not in the femoral blood!

# CASE II

- A 26 year old woman is found dead in bed
- Numerous medications in her home:
  - *Amitriptyline, Oxycodone, Morphine, Paroxetine, Diphenhydramine, Pseudoephedrine, Phenobarbital, Codeine, Temazepam, Diazepam.*
  - Only 3 mL of blood collected at autopsy!
- Analysis of stomach contents records:
  - *Amitriptyline: detected*
  - *Nortriptyline: detected.*

# CASE III

- 30 year old woman, previously in good health
- Nausea, vomiting, diarrhea, rash, fever
- Weakness in hands and feet → Guillian Barre?
- Hospitalized with hypotension, seizures
- Misplaced laboratory result → Arsenic!
- A case record as of homicide by chronic arsenic poisoning.
- Science hair analysis for arsenic showed chronic arsenic poisoning over 8 month period.

# POSTMORTEM REDISTRIBUTION CASE IV

- A 33 year old female is admitted to hospital after taking 60 digoxin tablets
- An antemortem blood sample collected 1 hour prior to her death indicates a blood digoxin level of 18 ng/mL
- Heart blood digoxin concentration obtained at autopsy is 36 ng/mL.
  - Postmortem increase in blood digoxin concentrations is suspected to be due to the release of the drug from the myocardium (heart)

# INCOMPLETE DISTRIBUTION

- Site dependent differences in drug levels due to differential distribution of drugs at death has been noted in rapid iv drug deaths
- Example:
  - Intravenous injection of morphine between the toes
  - Fatal amount of drug reaches the brain

# THANK YOU