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GENERAL TOXICOLOGY

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By:

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LAB. 2

Liver toxicity

- ***Liver:*** The liver is the main organ where exogenous chemicals are metabolized and eventually excreted. As a consequence, liver cells are exposed to significant concentrations of these chemicals, which can result in liver dysfunction, cell injury, and even organ failure.
- When an industrial chemical, such as **vinyl chloride**, **carbon tetrachloride**, or **bromobenzene**, is found to be hepatotoxic, its use may be restricted, exposure can be minimized by needing respirators and protective clothing, and efforts are made to substitute the chemical with a safer one.
- The liver's strategic location between intestinal tract and the rest of the body facilitates the performance of its enormous task of maintaining metabolic homeostasis of the body

- **The major function of liver:**

1. ***Nutrient homeostasis***: Glucose storage and synthesis Cholesterol uptake
2. ***Filtration of particulates***: Products of intestinal bacteria (e.g., endotoxin)
3. **Protein synthesis**: Clotting factors, Albumin & Transport proteins (e.g., very low density lipoproteins)
4. ***Bioactivation and detoxification***: Bilirubin and ammonia, Steroid hormones & Xenobiotics
5. ***Formation of bile and biliary secretion***: Bile acid–dependent uptake of dietary lipids and vitamins, Bilirubin and cholesterol Metals (e.g., Cu and Mn) Xenobiotics.

- One of the liver's roles involves removing and breaking down most drugs and chemicals from your bloodstream. Breaking down toxins creates by products that can damage the liver. Although the liver has a great capacity for regeneration, constant exposure to toxic substances can cause serious, sometimes irreversible

- ***Toxic liver*** disease is damage to the liver. It is also known as ***toxic hepatitis*** or ***hepatotoxicity***.
- If patient don't receive care, it might result in severe symptoms or damage to the liver.
- Toxic hepatitis can be caused by :

a) **Alcohol** : Heavy drinking over many to alcoholic hepatitis-inflammation in the liver due to alcohol.)
b) **Over-the-counter pain relievers**: Nonprescription pain relievers such as acetaminophen (Panadol), aspirin, ibuprofen (Advil) and naproxen can damage the liver, especially if taken frequently or combined with alcohol.
c) **Prescription medications.** Some medications. linked to serious liver injury include the combination drug amoxicillin-clavulanate (Augmentin), halothane, isoniazid, valproic acid (Depakene), phenytoin (Dilantin, Phenytek). azathioprine (Azasan, Imuran), niacin (Niaspan), atorvastatin (Lipitor), lovastatin (Mevacor), pravastatin (Pravachol) simvastatin Zocor). Fluvastatin (Lescol), rosuvastatin (Crestor), ketoconazole certain antibiotics, certain antivirals and anabolic

- hepatotoxicity recognized during the post marketing phase is one of the main causes for withdrawing drugs from the market
- **Troglitazone** (Rezulin®), a new antidiabetic drug, was removed from the market after close to 100 of the 1.9 million patients treated with the drug suffered from liver failure.
- Furthermore, the increasing popularity of herbal medicines, which are generally plant extracts, enhances the incidence of drug-induced liver injury and liver failure
- When medications damage the liver and disrupt with its normal function, the liver's symptoms, signs, and abnormal liver blood tests.
- The abnormalities associated with liver **disorders** carried on by medications are **similar** to those associated with diseases of the immune system and viruses.
- for example, medications-induced hepatitis is similar to viral hepatitis in that **both** can result in **increased** blood levels of the liver-damaging enzymes aspartate aminotransferase (**AST**) and alanine aminotransferase (**ALT**), as well as anorexia (loss of appetite), fatigue, and nausea.
- Also **bilirubin** & **alkaline phosphatase** affected by liver damaging.

- Medications or chemicals (viral, alcoholic, drug-induced, and chronic liver diseases such as genetic defects) that cause **Intrahepatic cholestasis**.
- Gallstones, bile duct strictures, and tumours are the most frequent causes of **extrahepatic cholestasis** (mechanical) bile duct obstruction.
- All of the above could lead to elevated in blood level of bilirubin causing Jaundice) & alkaline phosphatase.

- ***Types of the liver injury:***
- The liver injury caused by chemicals (**hepatotoxicity**) is not a single entity, thus the lesion observed does not depend only on

1. the chemical agent involved, but also on
2. the nature of exposure (acute or chronic, reversible or irreversible),
3. mechanism of toxicity, number & type of the cells affected &
4. localization within liver (periportal, mid or transient & centrilobular zones).

- Accordingly, injuries divided into the following major types:

1.Steatosis (fatty liver), 2. Necrosis, 3. Apoptosis, 4. Fibrosis, 5. Cirrhosis,
6. Cholestasis, 7. Hepatitis, 8. Carcinogenesis

Pesticide Toxicity

pesticide toxicity

- **Pesticides** are a class of one or mix of **chemicals** designed to kill pests (rodents, insects, or plants) that may affect agricultural crops or carry diseases like malaria and typhus.
- Examples:
- Chlordane (insects)
- Methylene chloride (rodents) (paint stripper & used in the manufacture of photographic film
- DDT (dichlorodiphenyltrichloroethane) (a white, crystalline solid with no odor or taste)
- Pesticide is a common term that comprise several classes of insecticides, herbicides, fungicides, rodenticides, wood preservatives, garden chemicals and household disinfectants that are used to kill or protect from pests.

- There are 3 methods of pesticides classification :

1. Classification based on the mode of entry
2. Classification based on pesticide function and the pest organism they kill
3. Classification based on the chemical composition of the pesticide

- **Herbicides**
- **Paraquat** (**PQ**) is the active ingredient of **Gramoxone**, which is used to control weeds and grasses and as a harvest aid desiccant and/or defoliant.
- Its more dangerous than organophosphorus because have no antido
- **Route of exposure:**

1. Ingestion
2. Inhalation
3. Dermal
4. Eye
5. Parenteral (homicidal)

- **Mechanism of toxicity:**
- PQ is a well described pneumotoxicant that produces toxicity by redox cycling with cellular diaphoresis, thereby elevating intracellular levels of superoxide (O_{2-}). NO synthase (NOS) has been shown to participate in PQ-induced lung injury. It cause pulmonary fibrosis.

Toxicity features:

1. Contact dermatitis
2. Eye conjunctivitis
3. Sever gastric pain
4. Nausea and bloody diarrhea
5. Urine retention
6. Jaundice
7. Renal failure after 1-3 days of exposure with increased albumen and decreased creatinine level in urine (reduced creatinine clearance)
8. Lung tissue fibrosis leads to respiratory failure and death.

- **Rodenticides**
- Patients most often presenting with rodenticide toxicity are children with oral ingestion.

1. There are 13 types of rodenticides the most popular are:
2. **Zinc phosphide (**rotten fish odor)
3. **Anticoagulant**
4. **warfarin**-type anticoagulants
5. **Bromethalin (**neurotoxin & long acting anticoagulant**)**
6. **Strychnine** is a highly toxic, kill birds and rodents
7. **Arsenic (**odorless & testless).
8. **Cholecalciferol (**treat vitamin D deficiency)

- **Strychnine**: is highly toxic alkaloid, (colorless, bitter, crystalline alkaloid) which is found throughout the plant, including the seeds of *Strychnos nux-vomica* tree.
- **Routes** of toxicity are inhalation, swallowing or absorption through eyes or mouth.
- Used as a pesticide for killing small vertebrates & rodents).
- Its poisoning will lead to muscular convulsions and eventually death through asphyxia.
- **Mechanism of Action**: Strychnine is (neurotoxin) a competitive antagonist at glycine and acetylcholine a receptors (at Cl- channel), preventing the inhibitory effects in the spinal cord, causing increased neuronal excitability and exaggerated reflex arcs. It prim the motor nerve fibers in the spinal cord which control muscle contraction.
- 10-20 min. the body's muscles begin to spasm starting with head & neck in the form of trismus & risus sardonicus.
- So, Respiratory failure, muscular spasms, and convulsions

Insecticides

- The most popular and appropriate method to classify insecticides is by the kind of active component and chemical composition, which gives details about the chemical, physical, and effective properties of each pesticide.

Based on chemical composition, insecticides are classified into four Main groups namely:

1. ***Organochlorines***
2. ***Carbamates***
3. ***Botanical origin***
4. ***Organophosphorus***

Organochlorine

- Organochlorine insecticides are highly effective and have been used widely in public health and agriculture for a long time. Their lengthy half-lives, ranging from years to decades, are due to their lipophilicity (high).
- It is highly persistent in the environment due to its low volatility, slow rate of breakdown, and high lipid solubility. It is less toxic than organophosphorus causing chronic toxicity. Skin toxicity is minimal. Its target toxicity is the CNS.
- The most common of organochlorines are :

1. Dichlorodiphenyltrichloro ethane (DDT)
2. Methoxychlor
3. Cyclodienes
4. MIREX
5. Lindane also known as Hexachlorocyclo hexanes (HCH) used for the treatment of head lice. Acute ingestion or repeated large dermal expose causes neurological toxicity which can lead to seizures and a coma

- Route of exposure: ingestion & dermal contact. (Rare)
- Mechanism of toxicity: most organochlorines act as non-competitive antagonists acting at the chlorine ion channel of gabaa receptors but DDT acts by inhibiting sodium channel closure following depolarization. Both mechanisms are neuroexcitatory
- **hyperesthesia and paresthesias of the face and extremities**. Headache, dizziness, nausea, vomiting, incoordination, tremor and mental confusion are also reported.

Organophosphorus

- organophosphate (OP) compounds are widely used in agricultural field. They are the group of choice in the agricultural world and are the most common cause of poisoning among the pesticides.
- It considered to be one of the broad spectrum pesticides which control wide range of pests due to their multiple functions. These pesticides are also biodegradable, cause minimum environmental pollution and are slow pest resistance
- organophosphorus insecticides include many types like parathion, chlorpyrifos, etc..
- The **poisoning** with OP occur due to:

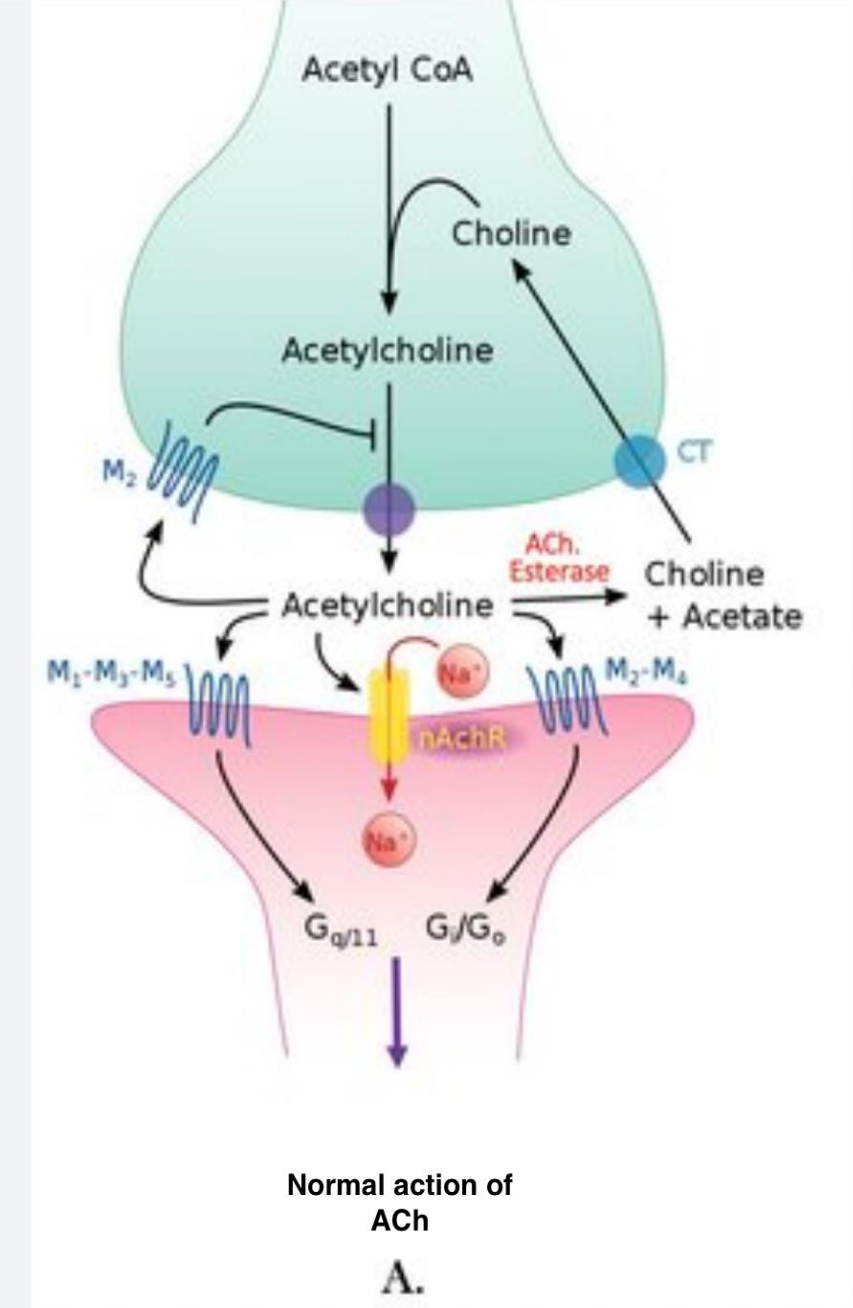
1. Accidents (children)
2. Suicidal attempt
3. Occupational exposure (Workers)
4. Food contaminated (vegetables & fruits)

- **Routes** of poisoning:

a) Oral (eat or drink)
b) Inhalation

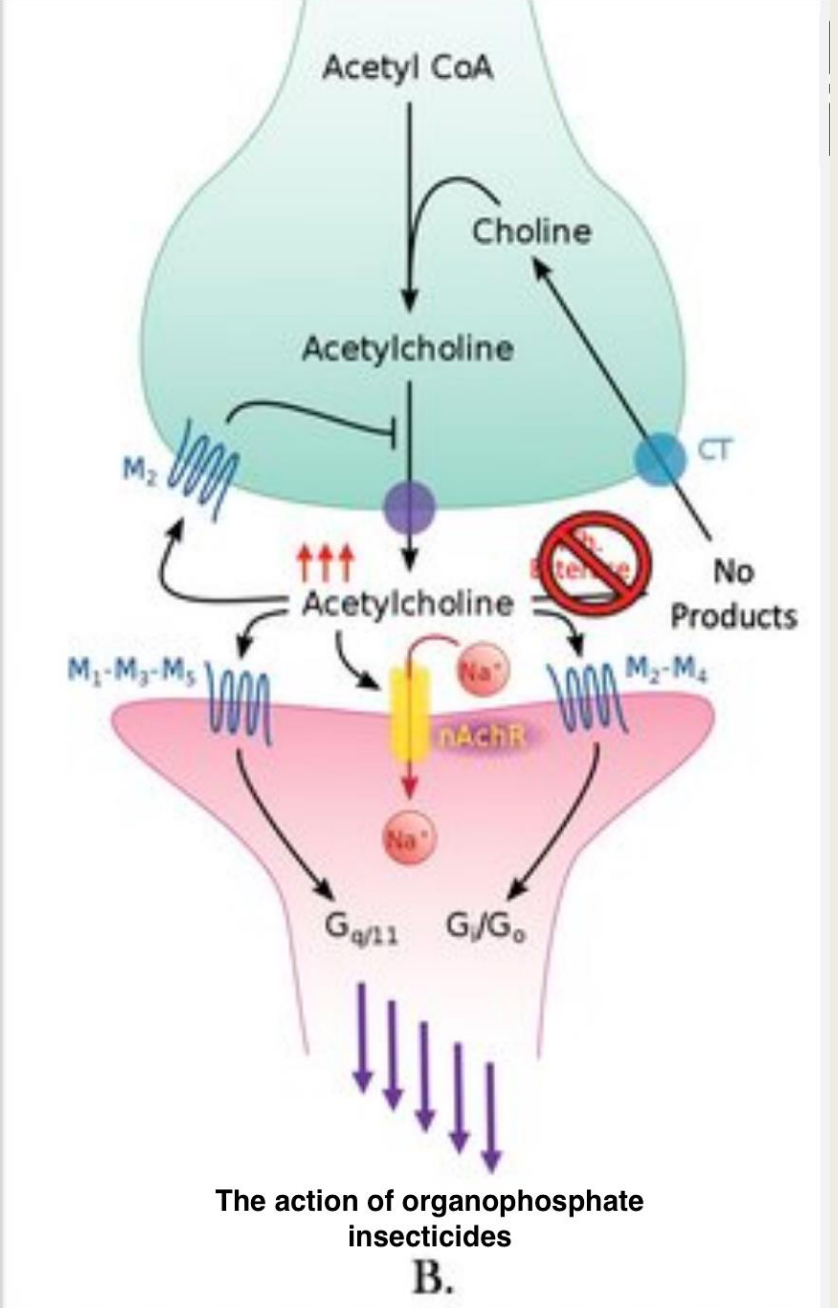
Mechanism of action:

- Op toxicity will cause inhibiting the acetylcholinesterase (ache) enzyme, which is essential for degradation of acetylcholine into choline and ester in the central and peripheral nervous system
- This will lead to accumulation of toxic levels of acetylcholine. that in turn binds to nicotinic or muscarinic receptors giving symptoms of parasympathomimetic stimulation.



Normal action of ACh

A.



The action of organophosphate insecticides

B.

- **Signs & symptoms of organophosphorus toxicity**:

1. Increased salivation, sweetening, lacrimation.
2. Dyspnea
3. Bradycardia then after tachycardia due to nicotinic effect
4. Nausea and vomiting
5. Miosis (muscarinic effect)
6. Muscle weakness
7. Anxiety,
8. Headache
9. Coma and death due to respiratory failure