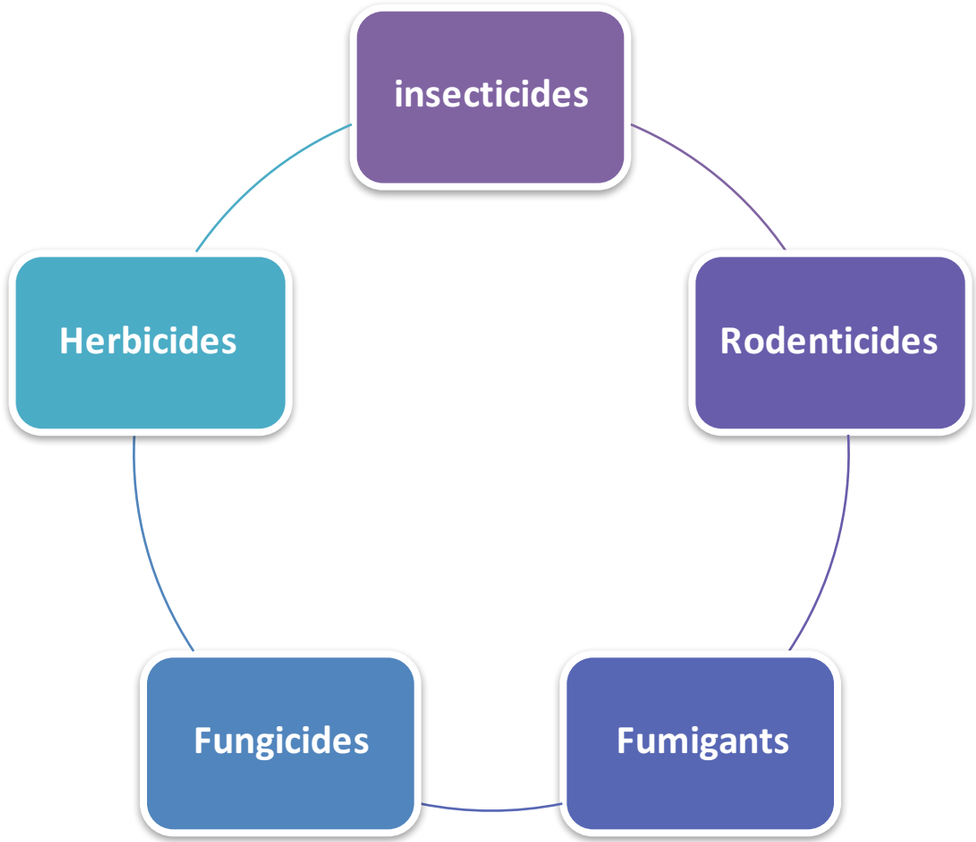
Forensic & Toxicology Team

MED 433

طب ٤٣٣

Lecture 10 : Pesticides

Pesticides, a generic term used to refer to all pest-killing agents and include:



Many are general protoplasmic poisons affecting a wide range of organisms, including humans.

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

Some of the most common pesticides for home and industrial use Organophosphorus insecticides are highly lipid soluble and are readily absorbed via dermal, GI, and respiratory routes This lipid solubility results in the storage of organophosphorus compounds in body fat, making toxic systemic levels possible from gradual or rapid accumulation from repeated low-level exposures.

Principles of Disease

- The parent compound and its metabolites are acetylcholinesterase inhibitors.

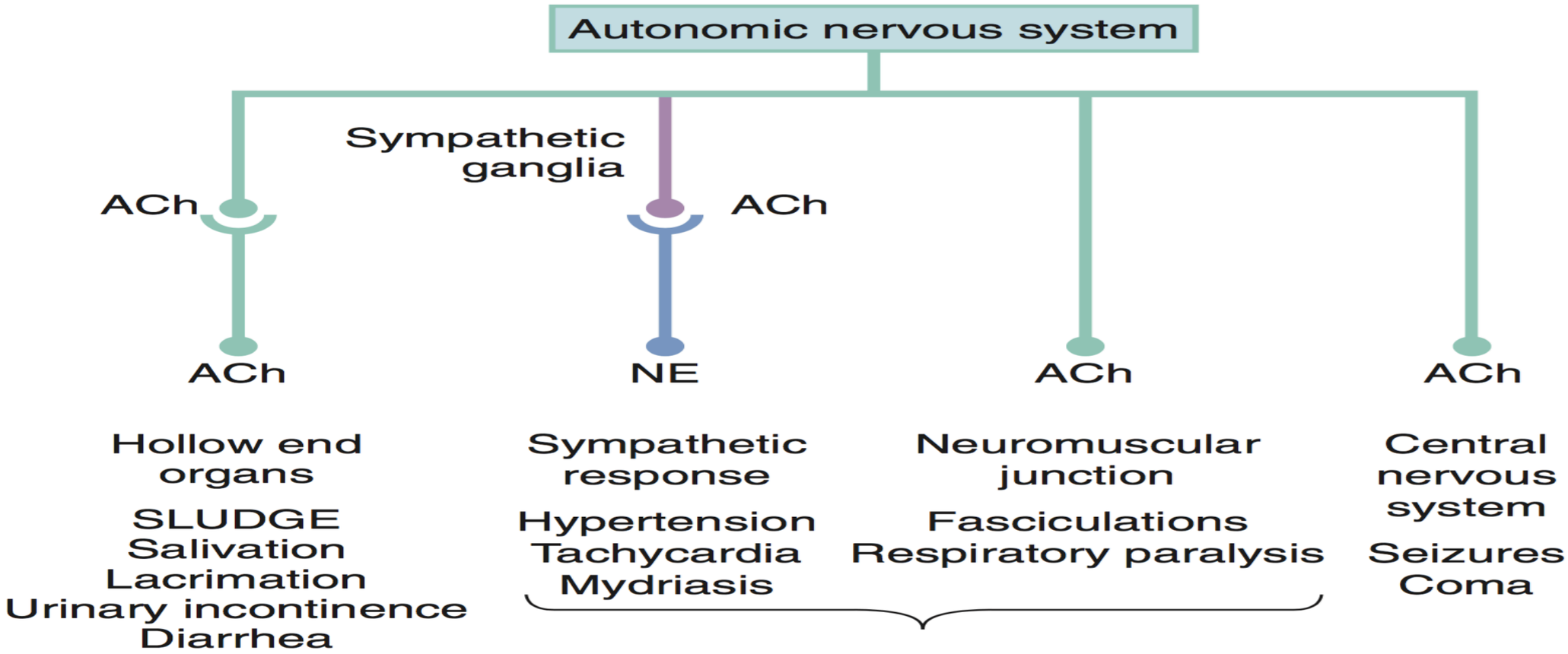
- Many parent organophosphorus compounds are less potent than their metabolites (e.g., parathion to paraoxon), which may result in delayed onset of clinical toxicity.

- They work by persistently inhibiting the enzyme acetylcholinesterase, the enzymatic deactivator of the neurotransmitter acetylcholine.

- Because of the global penetration of organophosphorus compounds, inhibition occurs at tissue sites (true acetylcholinesterase represented by erythrocyte cholinesterase) and in plasma (circulating pseudocholinesterase).

- Inhibition of cholinesterase results in the accumulation and subsequent prolonged effect of Acetylcholine at neurotransmitter receptors.
  - Sympathetic & parasympathetic Ganglionic (Nicotinic sites)
  - Postganglionic Cholinergic sympathetic and parasympathetic (Muscarinic sites)
  - Skeletal muscle (Nicotinic sites)
  - Central nervous system sites

Principles of Disease



- Sympathetic nervous system (thoracolumbar outflow). The neurotransmitter in ganglia is acetylcholine (ACh). The neurotransmitter in the target organ is norepinephrine (NE).
- Parasympathetic nervous system (craniosacral outflow), use ACh as the neurotransmitter in preganglionic and postganglionic target organs.
- The ANS is divided further into the Muscarinic and Nicotinic receptors, Atropine can block Muscarinic receptors but not Nicotinic receptors. Neuromuscular junction uses ACh as effector neurotransmitter. In the brain, ACh is just one of several active neurotransmitters.

Clinical Features Signs and Symptoms

- The accumulation of acetylcholine results in a classic cholinergic syndrome, manifested by hyperactivity of cholinergic responses at the receptor sites indicated previously.

- The clinical syndrome of muscarinic acetyl cholinesterase inhibition is commonly called the SLUDGE syndrome or DUMBELS.

SLUDGE Symptoms or DUMBELS

Salivation	Diarrhea/Diaphoresis
Lacrimation	Urination
Urinary incontinence	Miosis
Defecation	Bradycardia/Bronchorrhea/Bronchospasm
Gastrointestinal cramps	Emesis
Emesis	Lacrimation Salivation

- **Bradycardia** is a classic sign of the cholinergic syndrome, but the increased release of norepinephrine from postganglionic sympathetic neurons precipitated by excess cholinergic activity at sympathetic ganglia, may result in normal or even tachycardic heart rates (nicotinic effect).

Clinical Features Signs and Symptoms

- **CNS**: A combination of sympathetic stimulation, involvement of the *N*-methyl-d-aspartate receptor, and enhanced acetylcholine concentrations can lead to seizures.

- **NMJ**: At the neuromuscular junction, excess acetylcholine causes hyper stimulation of the muscles with secondary paralysis.

- Because the diaphragm is affected, cholinesterase poisoning leads to respiratory arrest.

- Although the usual clinical picture of acute organ ophosphorus poisoning is impressive, toxicity from gradual, cumulative exposure may be much more subtle.

- These patients commonly exhibit vague confusion or other central nervous system complaints; mild visual disturbances; or chronic abdominal cramping, nausea, and diarrhea.

Complications

1. Seizure, bronchorrhea , and bronchoconstriction are prominent mechanisms of early morbidity.

2. Obstruction of upper and lower airways produce hypoxia.

3. Muscle hyperactivity eventually gives way to muscle paralysis (including respiratory muscles and diaphragm).

4. Respiratory insufficiency results in death if not anticipated and corrected.

5. Unique effect of organophosphorus insecticides results from “aging,” the irreversible structural change that occurs in cholinesterase enzyme when the organophosphorus agent is bound to it for a prolonged time.

6. On average, for commercial organophosphorus agents aging will occur by 48 hours, but may take longer.

7. Once the enzyme has aged, an oxime antidote cannot regenerate the cholinesterase.

Diagnostic Strategies

- Known or suspected exposure to cholinesterase inhibitors should be confirmed by ordering plasma and erythrocyte (RBC)cholinesterase levels.

- In acute exposures, the plasma cholinesterase levels decrease first, followed by decreases in RBC cholinesterase levels.

- The RBC cholinesterase level is more indicative of what is occurring at the nerve terminal.

- Patients with chronic exposures may show only reduced RBC cholinesterase activity, with a normal plasma cholinesterase level.

- RBC cholinesterase levels recover at a rate of 1% per day in untreated patients and take approximately 6 to 12 weeks to normalize, whereas plasma cholinesterase levels may recover in 4 to 6 weeks.

- Other studies should focus on the evaluation of pulmonary, cardiovascular, and renal function and fluid and electrolyte balance.

- Patients presenting with no acidosis, or only a metabolic acidosis on the arterial blood gas, have lower mortality than those presenting with a respiratory o mixed acidosis

Management

Treatment is directed toward four goals:

1. Decontamination.
2. Supportive care.
3. Reversal of acetylcholine excess at muscarinic sites.
4. Reversal of toxin binding at active sites on the cholinesterase molecule.

- Decontamination should start in the out-of-hospital phase
- Decontamination is particularly important in cases of dermal exposure; removal and destruction of clothing and thorough flushing of exposed skin may limit absorption
- Dermal decontamination can be done with dry agents, such as military resins, flour, sand, or bentonite.
- Caregivers are at risk from splashes or handling of contaminated clothing.
  - Should use universal precautions.

Management

- In the case of ingestion, GI decontamination procedures are of questionable benefit because of the rapid absorption of these compounds.

- Profuse vomiting and diarrhea are seen early in ingestion and may limit or negate any beneficial effect of additional GI decontamination.

- Equipment, but not tissues, may be washed with a 5% hypochlorite solution to inactivate the cholinesterase inhibitor.

- Supportive care should be directed primarily toward Airway management, Breathing and Circulation, Airway management includes suctioning of secretions and vomitus, oxygenation, and, when necessary, intubation and ventilatory support, Intravenous access and fluid boluses as needed for circulatory collapse Seizure/Convulsions can be controlled by Benzodiazipine.

- The definitive treatment of acetylcholinesterase inhibition starts with **Atropine**.

- A competitive inhibitor of acetylcholine at muscarinic receptor sites, atropine reverses the clinical effects of cholinergic excess at parasympathetic end organs and sweat glands.

- Large doses of atropine may be required.

- Data suggest that the more rapid the atropinization*, the faster control is obtained.

* the act or process of treating with atropine.

Management

- Suggested dosing is 1 or 2 mg of atropine (0.02–0.05 mg/kg) IV, with doubling of each subsequent dose every 5 minutes until there is control of mucous membrane hypersecretion and the airway clears.
- If IV access is not immediately available, atropine may be administered IM.
- Tachycardia and mydriasis may occur at these doses, but they are not indications to stop atropine administration.
- The endpoint of atropinization is drying of respiratory secretions, easing of respiration, and a mean arterial pressure greater than 60 mm Hg.

- Atropine is not active at nicotinic sites and does not reverse the skeletal muscle effects (e.g., muscle fatigue and respiratory failure).
- The second part of acetyl cholinesterase inhibition treatment is the use of an Oxime:
  - Pralidoxime (2-PAM, Protopam)
  - Obidoxime (Toxigonin)
- These degrade the organophosphate-acetylcholinesteras complex and restore cholinesterase activity at muscarinic and nicotinic sites.
- In the past, pralidoxime was only used within the first 24 hours because of aging of the organophosphate-acetylcholinesterase complex, but not all organophosphates behave in a similar manner.

Management

- The medication may be given as repeated boluses or continuous infusion.

- The infusion may need to be continued for several days for complete reversal of cholinesterase activity.

- Indications for **oxime therapy** include:
  - Respiratory depression/apnea
  - Fasciculations
  - Seizures
  - Arrhythmias, cardiovascular instability
  - Patients who need large amounts of atropine (2–4 mg) to completely reverse the signs and symptoms of intoxication
  - Patient who requires repeated doses of atropine.

- New therapies for treatment of organophosphorus poisoning, including the use of *N*-acetylcysteine and exogenous acetylcholinesterase, show promise in research studies. When added to anticholinergics, NMDA receptor antagonists may decrease organophosphorus compound–induced seizures.

Deposition

- Most patients with significant exposures require hospital admission including intensive care settings.
- A person with chronic exposure, and mild visual or GI symptoms may be followed as outpatient.
- Asymptomatic or mildly symptomatic patients with near normal cholineesterase levels may be discharged after 4 to 6 hours.
- A secondary syndrome, the intermediate syndrome (IMS), occurs 24 to 96 hours after exposure and consists of proximal muscular weakness specifically of the respiratory muscles. It is believed to be an abnormality at the neuromuscular junction.
- Patients with IMS present with respiratory failure several days after the acute cholinergic symptoms have resolved and may require several weeks of ventilatory support.
- It is theorized that this may occur as a result of in adequate initial oxime treatment or premature discontinuation of oxime therapy. Oximes may be beneficial for IMS; however, this is controversial.
- Organophosphorus-delayed neuropathy has been reported as a different entity and affects an axonal enzyme, neurotoxic esterase, and leads to a peripheral sensorimotor neuropathy 7 to 21 days after exposure.

CARBAMATE INSECTICIDES

- Carbamate insecticides are another class of acetylcholinesterase inhibitors and are differentiated from the organophosphorus compounds by their relatively short duration of toxic effects.

- Carbamates inhibit acetylcholinesterase for minutes to 48 hours, and the carbamate-cholinesterase binding is reversible.

- Although the clinical picture of acute carbamate poisoning may be identical to that of organophosphate poisoning.

- the toxic effects are limited in duration and patients may require only decontamination, supportive care, and treatment with adequate doses of atropine.

- Although the duration is limited in scope, patients may become just as sick and require assisted ventilation and seizure therapy.

- The use of pralidoxime is controversial in carbamate poisoning.

Questions ➔ Summary for the hall lecture ☺.

Case study：**A 30-year-old, comatose male with miosis, diaphoresis, and incontinence**.

You are the oncall doctor, you have been alerted that a 30-year-old, unconscious male is being brought by ambulance to the Emergency Department where you are on duty. While at home, the patient suddenly developed headache, dizziness, weakness, nausea, vomiting, and diarrhea. En route to the Emergency Department, he lost consciousness and experienced urinary and fecal incontinence.

When the patient arrives at the Emergency Department, you note that he has fixed pinpoint pupils, generalized paralysis, fasciculations, and is unresponsive to deep pain. Corneal and gag reflexes are absent. He has profuse salivation, diaphoresis, and excess lacrimation. **Vital signs** include the following: blood pressure 140/90 mm Hg, temperature 99.2°F (37.2°C), pulse 58 beats/minute and regular. Rales are noted during chest auscultation. Heart examination is unremarkable except for an S_4 gallop. Abdominal examination reveals no detectable masses, organomegaly, or hyperactive bowel sounds. Mucoid secretions are suctioned from the trachea at the time of intubation, and mechanical respiratory support is instituted. You initiate treatment with Narcan for possible opiate ingestion, with no effect.

From the patient's brother, you learn that the patient returned yesterday from a 5-day vacation in Arizona. This morning he changed into work clothes and began mixing pesticides for subsequent tree spraying in their family orchard. About noon, the patient became nauseated and started sweating profusely. The brother cannot recall any unusual events before his brother's illness and assures you that they had performed the tree-spraying operations many times in the past with no ill effects.

After treatment and antidotal therapy, the patient improves remarkably, he has spontaneous respirations and regains consciousness within 4 hours. Mechanical ventilation is discontinued, and the patient is well enough to be discharged 3 days after admission.

http://www.nap.edu/read/4795/chapter/43#563

Questions:

Q1: How much time does it take for onset of clinical signs from organophosphate poisoning?	**Q9:** What is "aging" acetylcholinesterase?
Q2: What are the main organs affected by organophosphate poisoning?	**Q10:** Which neuro receptors are most sensitive to increased ACh and are most effected by organophosphate toxicity?
Q3: What is the antidote for organophosphate poisoning?	**Q11:** Parasympathetic stimulation displays as "DUMBELS"... what are these signs?
Q4: Organophosphates - water soluble?	**Q12:** Which cholinergic receptors are stimulated by organophosphate poisoning first?
Q5: Describe the "intermediate syndrome" associated with organophosphate toxicity.	**Q13:** Muscarinic stimulation leads to what clinical signs?
Q6: When muscle relaxants are used at the time of organophosphate poisoning, does this increase or decrease toxicity?	**Q14:** What is the partial antidote for organophosphate poisoning? How does it work?
Q7: How are most organophosphates metabolized?	**Q15:** Why isn't atropine a good antidote in treating intermediate syndrome organophosphate toxicosis?
Q8: What does an organophosphate bind to once inside the body? Is it reversible or irreversible?	**Q16:** What is the full antidote used for organophosphate toxicity?

A1: Most commonly acute onset. Within 10 min with oral dose, 12-24 hr with dermal dose

A2: Nervous system excitement, muscarinic stimulation, followed by neuromuscular depression

A3: Atropine is the partial antidote and 2PAM is full antidote

A4: NO, but they are very soluble in organic solvents/fats/oils and they penetrate skin and waxy coating of leaves and fruit

A5: It is subacute toxicity that is less common. signs are seen in 24 to 72 hours or longer after an acute crisis or when given small amounts

A6: Increase

A7: Most undergo lethal synthesis in the liver, via an MFO "mixed function oxidase" reaction which is when a sulfur atom replaces an oxygen and leads to activation.

A8: Binds AChase, is irreversible at first because it lasts hours to days, and then later it is irreversible because of permanent "aging" of AChase by binding of phosphorus and hydrogen at an esteric site.

A9: When there is permanent binding by a phosphorus and hydrogen molecule at an esteric site. It is an unbreakable bond and renders AChase no longer functional.

A10: Muscarinic receptors are most sensitive so parasympathetic stim first.

A11: diarrhea, urination, miosis, bradycardia, emesis, lacrimation, salivation

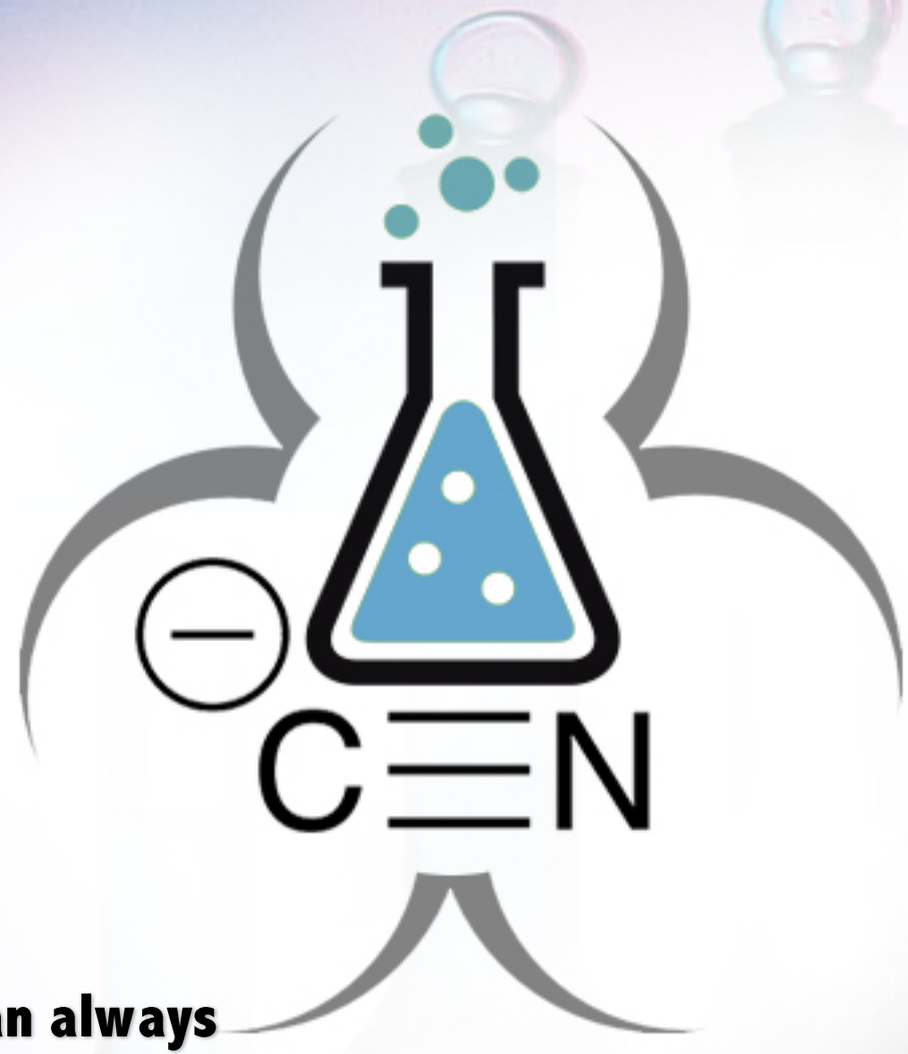
A12: Muscarinic are stimulatic first because they are more sensitive than nicotinic receptors.

A13: Parasympathetic signs "DUMBELS"

A14: Atropine, it blocks muscarinic receptors only (that's why it's partial)

A15: Because it doesn't have muscarinic signs and that's all atropine treats

A16: 2-PAM; is a cholinesterase reactivator but only works before the phosphorylated AChase is aged.



If you have any questions You can always contact us at : forensic433@gmail.com

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