Cholinergic and anticholinergic

- Three subjects their mechanism of toxicity depends on acetylcholine action:

1) Organophosphates and carbamate (cholinergic) in pesticides
2) Atropine (anticholinergic) in plant poisoning
3) Botulism (anticholinergic) in food poisoning

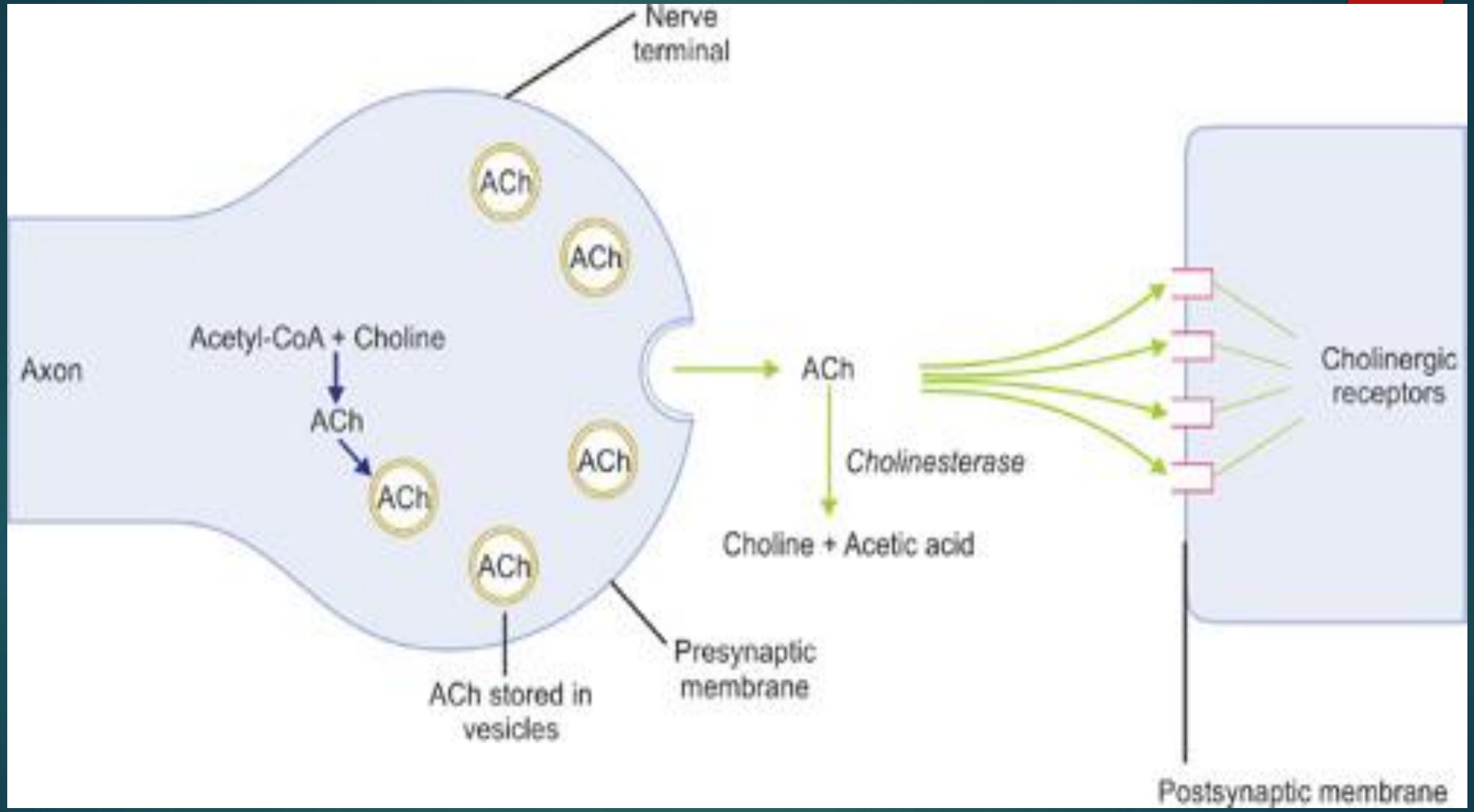
Acetylcholine

- Acetylcholine (ACh) is neurotransmitter (a chemical message released by nerve cells to send signals to other cells).
- nerve cells that use ACh are two types:

a) Brain cell (central site)

b) Peripheral nerves called cholinergic nerves (peripheral sites).

- Substances that increase action acetylcholine are referred to as **cholinergic**. Substances that interfere with acetylcholine activity are called **anticholinergics**.


Nerve terminal
ACh
ACh
Acetyl-CoA + Choline
Axon
ACh
ACh
ACh
ACh
ACh
Cholinesterase
Choline + Acetic acid
Cholinergic receptors
Presynaptic membrane
ACh stored in vesicles
Postsynaptic membrane

Cholinergic sites and receptors

Central and peripheral sites:

1. Brain (muscarinic receptors)
2. Smooth muscles (muscarinic receptors)
3. Glands (muscarinic receptors)
4. Heart (muscarinic receptors)
5. Skeletal muscles (nicotinic receptors)
6. Adrenal gland (nicotinic receptors)

At all sites acetyl choline is stimulatory except in heart is inhibitory

Mechanism of action

Cholinergic

Substance increase action of acetyl choline as organophosphate (OP) and carbamate insecticides

- OPs and carbamates inhibit the acetyl cholinesterase (AChE).
- The net result of enzyme inhibition is the accumulation of acetylcholine at all cholinergic synapses.
- ***There are two main differences that distinguish carbamates from OPs:***

OPs	carbamates
- Bind strongly to enzyme (need oxime to loose) - Bind irreversible after 36-48 hours (age enzyme)	Bind loosely to enzyme, hydrolyze spontaneously from the enzymatic site within 48 hours, thus it reversibly inhibits AChEs (not need oxime to loose)
easily pass the blood brain barrier (BBB), thus their CNS effects are marked.	do not easily pass the blood brain barrier (BBB), thus their CNS effects are limited.

Antichoinergic

Substance decrease action of acetyl choline as atropine and botulism

Atropine

- muscarinic receptor antagonists that block the binding of acetylcholine to muscarinic cholinergic receptors

Botulism

- toxin enters the bloodstream from mucosal surface or wound.
- It irreversibly binds to the peripheral cholinergic nerve endings and impairs the exocytosis of vesicles containing acetylcholine (ACh).
- - It inhibits the release of acetylcholine and preventing the cholinergic action (at both muscarinic and nicotinic sites).
- - Clinical recovery correlates with the formation of new presynaptic end plates and neuromuscular junctions.

Clinical Manifestations:

- Both cholinergic and anticholinergic have

a) CNS action

b) Peripheral action

1- muscarinic (or anti)

2- nicotinic (or anti)

CNS manifestations

Cholinergic (OPs & carbamates)	Anticholinergic (OPs & carbamates)	
	Atropine	**Botulism**
1. Early stimulating stage: - Irritability, agitation and aggressiveness. - Delirium and hallucinations. - Seizures (convulsions) due to stimulation of motor cortex. 2. **Late depressing stage:** - Confusion & impaired memory. - Lethargy, stupor and coma. - Circulatory and **central respiratory failure (*)**.	**1. Early stimulating stage:** - Irritability, agitation and aggressiveness. - Delirium and hallucinations. - Purposeless movements and staggering gait. - Seizures (convulsions) due to stimulation of motor cortex. 2. **Late depressing stage:** - Confusion & impaired memory. - Lethargy, stupor and coma. - Circulatory and central respiratory failure.	**As toxin not cross blood brain barrier: Mental status and alertness** are characteristically preserved. Intellectual and sensorium functioning remain intact, and memory is not impaired.

Peripheral manifestations

- Muscrinic site:
  a) Heart
  b) Smooth muscles
  c) Glands
- Nicotinic sites
  a) Neuromuscular junction
  b) Adrenal gland

Cardiac manifestations

only inhibitory site of acetylcholine

Cholinergic (OPs & carbamates)	Anticholinergic (atropine & botulism)
Inhibit heart	Stimulate heart
bradycardia. Hypotension (due to bradycardia and fluid loss).	Sinus tachycardia

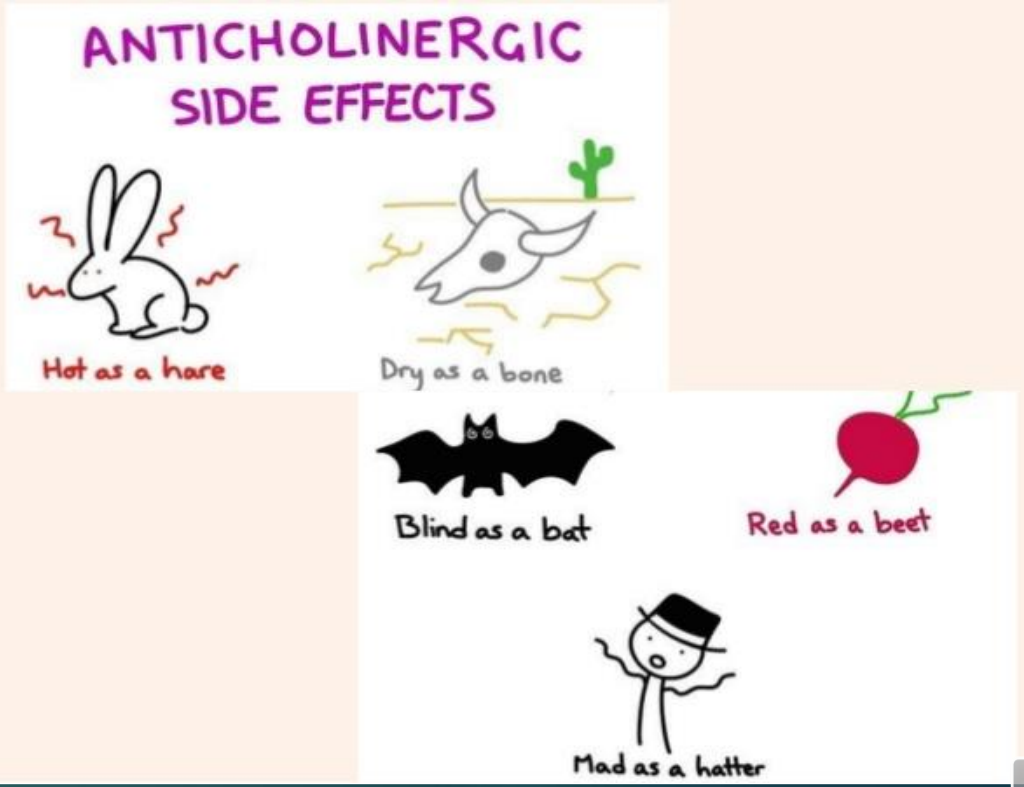
Glands

Cholinergic (OPs & carbamates)	Anticholinergic (atropine & botulism)
Increase secretions	Dry secretions
-lacrimal glands: lacrimation **Salivary glands:** salivation **Sweat glands:** sweating **Bronchial glands:** Bronchorrhea & pulmonary edema (*). lead to hypoxia and tachycardia. **Gastric glands:** vomiting **Intestinal glands:** diarrhea	-**lacrimal glands:** decreased lacrimation **Salivary glands:** dry mouth, dysphagia, hoarseness of voice, intense thirst. **Sweat glands:** dry skin, there is no heat loss (hot skin or atropine fever). **Bronchial glands:** Decreased bronchial secretion **Intestinal glands:** constipation.

Smooth muscles

Cholinergic (OPs & carbamates)	Anticholinergic (atropine & botulism)
Contact muscle	Relax muscle
Eye: papillary constrictors and ciliary body, Miosis and blurred vision. **Respiratory system:** bronchi, bronchospasm & Wheezes. I**ntestine:** intestinal cramps and diarrhea. **Urinary bladder:** Urination	**Eye: papillary constrictors and ciliary body**, Mydriasis, fixed non-reactive pupils, blurred vision. **Respiratory system:** bronchi, Broncho dilatation & rapid respiration. . I**ntestine:** Constipation and diminished or absent bowel motility, leading to delayed gastric emptying and delayed absorption of these alkaloids. **Urinary bladder:** Urine retention

To remember

Muscarinic manifestations	anti- muscarinic manifestations
DUMBBLES D: diarrhea U: urination M: miosis B: bronchospasm & broncorrhea & pulmonary edema B: bradycardia L: lacrimation E: emesis S: salivation & sweating	

Nicotinic manifestations
1- skeletal

<table>
<tr><th>Cholinergic (OPs & carbamates)</th><th colspan="2">Anticholinergic (atropine & botulism)</th></tr>
<tr><td>Contract muscle</td><td colspan="2">Paralyze muscle</td></tr>
<tr><td rowspan="2">➢ Muscle fasciculations and cramps
But skeletal muscle easily fatigued
➢ followed rapidly by paralysis and a reflexia due to excessive stimulation at the neuromuscular junction.
➢ Ends by paralysis of respiratory muscle (*)</td><td>Atropine</td><td>Botulism</td></tr>
<tr><td>No nicotinic effect</td><td>Motor paralysis: A descending bilateral symmetrical paralysis (motor not sensory) beginning with cranial nerves and progressing downward.
1- Cranial nerve palsies:
a- ocular nerves (3 & 6):
- early first symptoms to appear: abducent nerve palsy: Diplopia,
- More severe cases show early third cranial nerve (oculomotor, III) involvement leading to dilated fixed pupils, photophobia, blurred vision.
b- bulbar nerves (9 & 10): Bulbar weakness is manifested by dysphagia, dysphonia, dysarthria and slurred speech (weakness of the tongue).
2- spinal motor nerves: limbs & trunk weakness, ends by Respiratory failure and apnea may occur within hours of the onset of cranial nerve palsies.</td></tr>
</table>

2- sympathetic

release of adrenaline and nor-adrenaline.

Cholinergic (OPs & carbamates)	Anticholinergic (atropine & botulism)	
Increase release	No effect as	
Sympathetic stimulation: Tachycardia and hypertension.	Atropine	Botulism
	Has no nicotinic effect	Not cross to nerve cells

To remember

- The nicotinic symptoms can be remembered by the mnemonic MATCH: Muscle weakness and fasciculations, Adrenal medulla activity increases, Tachycardia, Cramping of skeletal muscles, Hypertension).

Mechanism of death

Cholinergic (OPs & carbamates)	Botulism
Respiratory failure	Respiratory failure
1. CNS depression (central action). 2. Excessive bronchial secretion (bronchorrhea) and bronchospasm (muscarinic action). 3. Respiratory muscular weakness and paralysis (nicotinic action).	Respiratory muscular weakness and paralysis.

Antidotal therapy

- In both cholinergic and anticholinergics, two types of antidotes used:

1- action reversing

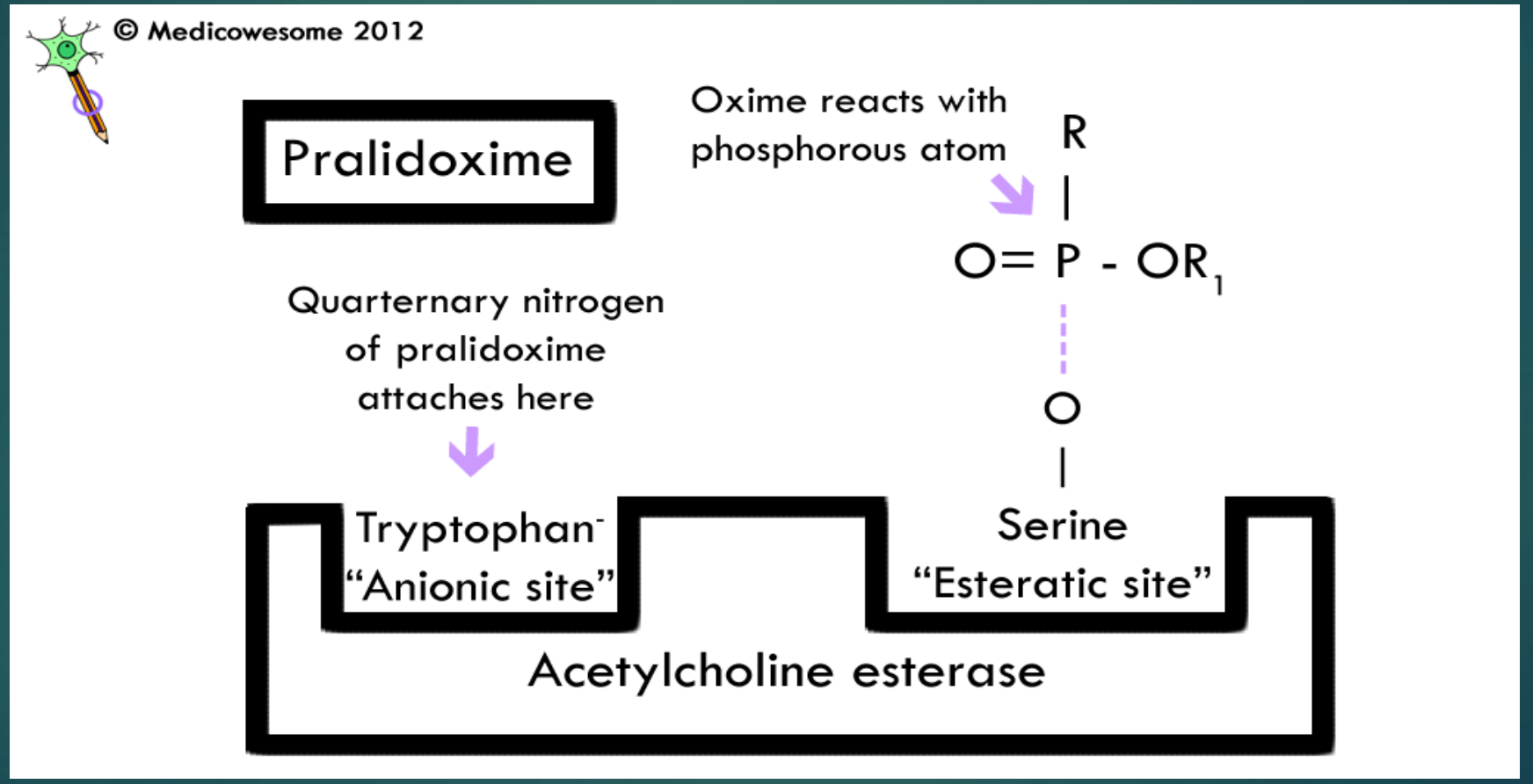
2- toxin binding

Action reversing antidote

For cholinergics (anticholinergic atropine)	For anticholinergics (cholinergic physostigmine)
Mechanism of action: - It is a competitive antagonist of acetylcholine at muscarinic sites; - it is crosses the blood brain barrier. - It can reverse central and peripheral muscarinic effects and - It decreases the pulmonary edema possibly the CNS toxicity of OPs. - but has no effect on skeletal and autonomic ganglia (no nicotinic effects). **a therapeutic end point:** dryness of chest secretions , not Pupillary dilatation.	**Mechanism of action:** - Physostigmine, reversible acetylcholinesterase inhibitor, causes accumulation of the acetylcholine at the cholinergic receptors. - it is crosses the blood brain barrier (so preferred than pilocarpine or neostigmine). - it can reverse both central and peripheral anticholinergic effects.
Side effects: see antimuscrinic manifestations	**Side effects:** muscarinic manifestations "DUMBBELS" (diarrhea, urination, miosis, bradycardia, bronchorrhea, bronchospasm, emesis, lacrimation, and salivation). Limited use as: 1- high risk: serious side effects 2- low benefit: Most patients can be managed conservatively without the administration of physostigmine.

Toxin binding antidotes

For OPs (oximes as Pralidoxime and Obidoxime (toxogonin))	For botulin toxin (Trivalent antitoxin)
Mechanism of action: ***Bind to both free and bound OPs compound*** (how) It works by attacking the phosphate atom of the OPs-cholinesterase complex, forming an oxime-phosphate, which lifts off the enzyme, freeing it for normal activity. A- It can reactivate the inhibited acetylcholinesterase (reverses nicotinic, muscarinic and CNS effects of OPs and OPs- related muscle paralysis.) B- It also detoxifies the free OPs (stop progression). - ***Thus,*** - ***It should be given*** within 24 to 36 hours of acute exposure before" aging" of enzymes.	**Mechanism of action:** **binds the circulating free toxin,** A- It detoxifies the free toxin (stop progression). B- It can't reactivate the inhibited sites (not reverse muscle paralysis.)
- So, oxime in carbamate poisoning is generally not recommended. - However, as early differentiation between OPs and carbamates toxicity is difficult, it is recommended that oximes be started in any syndrome consistent with these toxins unless OPs exposure is ruled out.	1-2 vials of I.V. ABE trivalent antitoxin after dilution (1:10 in normal saline) is recommended for symptomatic patients. A second vial may be administered in 2 to 4 hours if signs or symptoms worsen, but is usually not necessary as the neutralizing antibodies (half-life of 5-8 days) far exceed the levels of circulating toxin.
	immediate hypersensitivity reactions (anaphylaxis). 100 mg of hydrocortisone can be injected prior to the antitoxin, to prevent allergic reactions.


© Medicowesome 2012
Pralidoxime
Oxime reacts with phosphorous atom
R
O= P - OR1
O
Quarternary nitrogen of pralidoxime attaches here
Tryptophan-
"Anionic site"
Serine
"Esteratic site"
Acetylcholine esterase

Pesticides

Pesticides

- Pests are insects, fungi, herbs, rodents, and fungi.
- Cides = killers
- Pesticides are substances intended to prevent, destroy or repel any pest.
- Classified into insecticides, fungicides, herbicides, rodenticides and fungicides.

Insecticides

- Organic compounds (most dangerous to humans)

1) Organic phosphorus compounds (OPC) = organophosphates (OPs)

2) Organic chlorines compounds.

- Carbamates (insecticide & rodenticide)
- pyrethrins and pyrethroids.

- Both OPC and carbamates are cholinergics

Organophosphates OPs and carbamates cholinergics

OPs		Carbamates	
Insecticides	**Nerve gases**	**Insecticides**	**Rodenticides**
Parathione & malathione	Sarine	aldicarb (temik)	

Manner of poisoning

- **Accidental** during fumigation or spraying the crops,
- **Suicidal** as they are cheap and easily obtained especially in low social classes.
- **Homicidal** cases are rare because Ops have a characteristic odor. They can be mixed with food-stuff.


Pesticidewise

Cholinergics

- Mechanism of toxicity (see before).
- Clinical Manifestations (see before).
- Mechanism of death (see before).

Diagnosis

1. History.
2. Clinical picture
3. Proper physical examination.
4. Diagnostic tests:

A- tool

a- ECG

b- Chest radiograph

B- lab

a- routine tests

1. - Electrolytes: Hypokalemia and hyperglycemia.
2. - CBC: Leukocytosis.
3. - Urine analysis: glycosuria may occur.

b- Toxin-specific test (cholinesterase assay) is helpful for diagnosis and as a guide for treatment.

Treatment

I. **Emergency stabilization** of the ABCDs:

II. **Decontamination:** It is carried out according to the route of exposure

1- GIT decontamination:

- **Ipecac** should not be used, due to prior repeated vomiting.
- **Gastric lavage** with a large bore orogastric tube may be carefully performed to prevent aspiration, as many OP compounds are in petroleum distillate vehicles which, if aspirated, may precipitate pneumonitis.
- **Activated charcoal** is administered unless contraindicated.

2- Dermal decontamination:

- Removal of clothes by hospital personnel wearing protective gloves and masks, and the contaminated clothes should be destroyed.
- Wash the skin with soap and water.

3- environmental decontamination: Remove the patients from the polluted atmosphere if exposure is by inhalation.

III- antidotal therapy (see before)

Food poisoning

Types of Food Poisoning

Ingestion of preformed toxins or chemicals		Ingestion of organism (infected food)			Food allergy
Poisonous food	**Contaminated food**	**Bacteria**	**Virus**	**Protozoa**	
1. Plant: Datura 2. Mushroom: Psilocybin, Muscarine 3. Fish poisoning (Ciguatoxin)	Contaminated food by: 1- OP and carbamate insecticides 2- heavy metal as arsenic	1- invasive as salmonella (fever & gastroenteritis) 2- non invasive (toxin secreting) as Clostridium botulinum (no fever, nor gastroenteritis)	rotavirus	Giardia lamblia	

Botulism التسمم الممبارى

- sausage poisoning (from Latin botulus (sausage).
- a life- threatening paralytic illness, caused by infection by Clostridium botulinum bacteria forming potent neurotoxins (**botulin**).
- Infection by C. botulinium occurs through:

1) Ingestion of infected food: food-born botulism & infant botulism
2) Inhalation of toxin: air-born botulism
3) Wound infection: wound botulism
4) Undetermined (intestinal adult): rare type.

- Mechanisms of Toxicity (see before)
- Clinical manifestations: depend on type

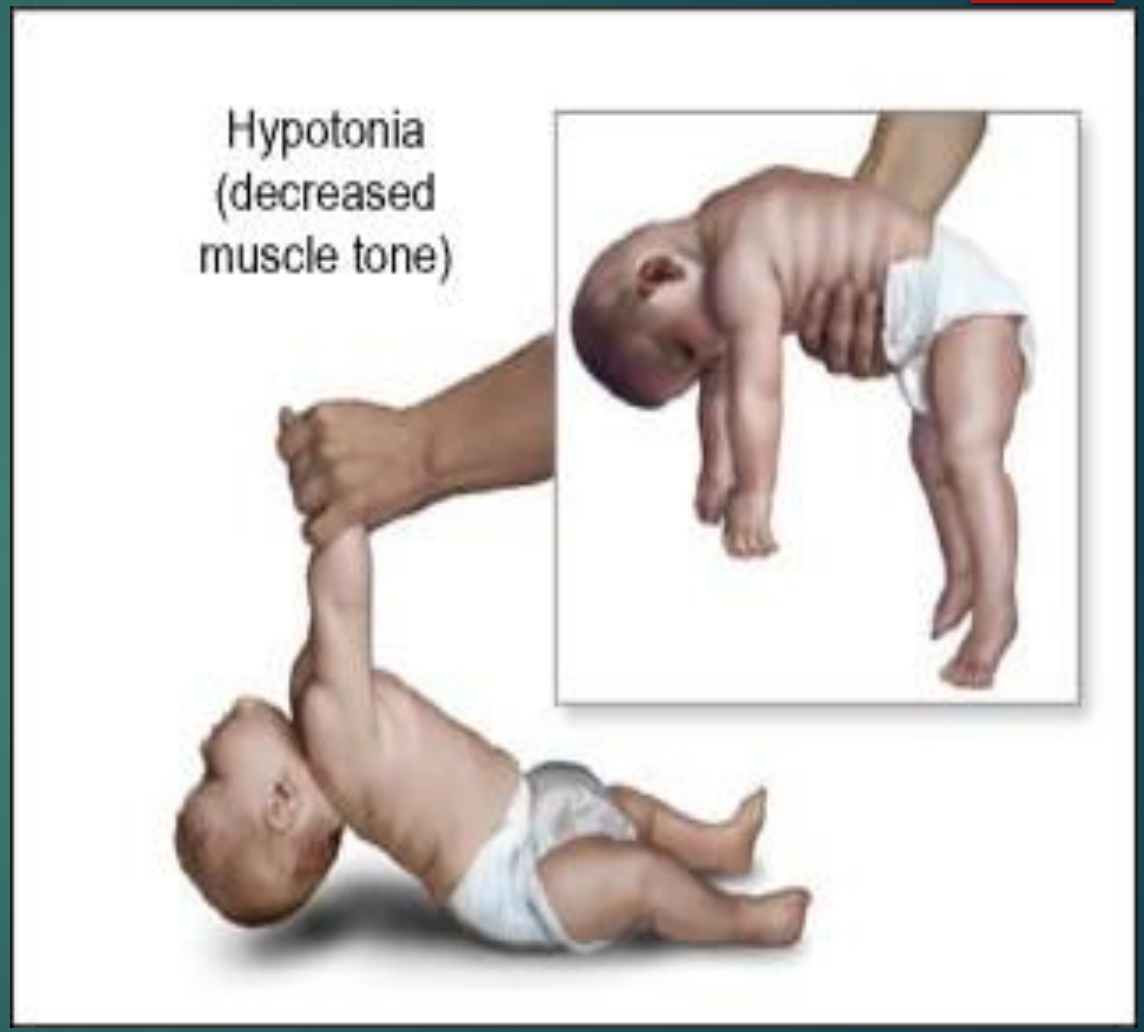
1) **food-born** (see before anticholinergic manifestations) + a.Initial GIT manifestations: which vary from early nausea and vomiting with diarrhea to delayed constipation.
2) **Wound botulism & air-born botulism:** GIT symptoms are absent.
3) **Intestinal adult botulism:** similar to food-borne botulism + predisposing factor (achlorhydria, GIT surgery, and bone marrow transplantation).

Infant botulism

- -Poisoning is caused by ingesting spores of the bacteria which germinate and produce botulinum toxin, in vivo, in the infant's intestines. It is the result of the infestation of the digestive tract with botulinum which is generally not an issue in individuals older than one year due to the large number of competing microorganisms found in the mature GIT.
- -It is the most common form; children less than 1 year of age are most frequently afflicted.
- -Symptoms include

a) **f**eeding difficulty
b) **F**eeble crying,
c) **F**ood constipation,
d) diminished muscle tone (**F**laccid baby syndrome), poor head control,
e) respiratory arrest

Spinal fluid examination ??



Diagnosis

- -Diagnosis of botulism rests on clinical and historical grounds.
- -Public health officials should be contacted as soon as diagnosis.
- Investigation: :

A- Tool: Electromyography is recommended and should be carried out and interpreted by a neurologist.

B- Laboratories studies

1- Routine investigations for botulism: Serum electrolytes, renal and liver function tests, complete blood tests, urine analysis and electrocardiogram (ECG). All are normal, unless secondary complications occur.

2- specific:(specimens are hazardous and must be carefully handled):

- The most effective test comes from the identification of botulism toxin in serum or stool.
- Toxin assay and bacterial anaerobic cultures: Isolation of botulinum from the patient's feces, suspect foods, wound, tissue or gastric sample.

Treatment

- -All symptomatic patients should be admitted to the intensive care unit (ICU)
- Respiratory support, supportive care, and trivalent antitoxin are the mainstays of therapy.

1- Stabilization of ABC:

a) Stabilization of airway. In cases of dyspnea, hypoxia or a vital capacity of less than 1000 cc, tracheostomy should be considered.

b) Mechanical ventilation is the most important aspect of treatment.

c) Parenteral nutrition.

2- Decontamination: Emesis, high enemas, upper and lower GIT decontamination.

3- antidotal therapy (see before) + Guanidine hydrochloride that acts through increasing the release of acetylcholine from nerve endings.

Prevention

- -Proper food preparation is one of the most effective way to limit the risk of exposure to botulism toxin.
- -Temperature: Growth of most strains of botulinum will not occur below 10 °C or above 50°C. C. botulinum is inactivated
- by heating food at 100°C for 10 minutes or at 80°C for 30 minutes.
- -Refrigeration of food can prevent toxin production.
- -PH: Production of toxin is inhibited below pH 4.6 in a salt concentration of 10%.
- -Food preservatives such as nitrite, ascorbic acid, parabens, phenolic antioxidants and polyphosphates inhibit the growth of the microorganisms.
- -Care must be taken for any food abnormalities (abnormal taste or shape).
- -Honey is to be avoided in children less than 1 year old.