NEUROSCIENCE SYSTEM

Tetanus, Botulism and Prion diseases

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Welcome To----------

ILOs

By the end of the lecture the student will be able to:

1- Define each disease.

2- Memorize the causative agent of each disease and its morphological characteristics.

3- Identify the mode of infection for each pathogen.

4- Demonstrate host parasite relationships (pathogenesis) of each disease.

5- Explain the main clinical presentations of each disease.

6- Describe laboratory diagnosis and prevention of each disease.

History Of Tetanus

5th century B.C.: Hippocrates described correlation between wounds and fatal muscle spasms

1884: Arthur Nicolaier isolated *C. tetani*

1884: Antonio Carle and Giorgio Rattone demonstrated transmissibility of tetanus

1889: Kitasato Shibasaburo demonstrated neutralization of tetanus

1897: Edmond Nocard demonstrated that tetanus antitoxin induced passive immunity in humans

TETANUS (LOCKJAW)

Definition:

Tetanus is an acute, often fatal, disease caused by an exotoxin produced by the bacterium *Clostridium tetani* characterized by strong muscle spasms (spastic paralysis).

Cl. tetani

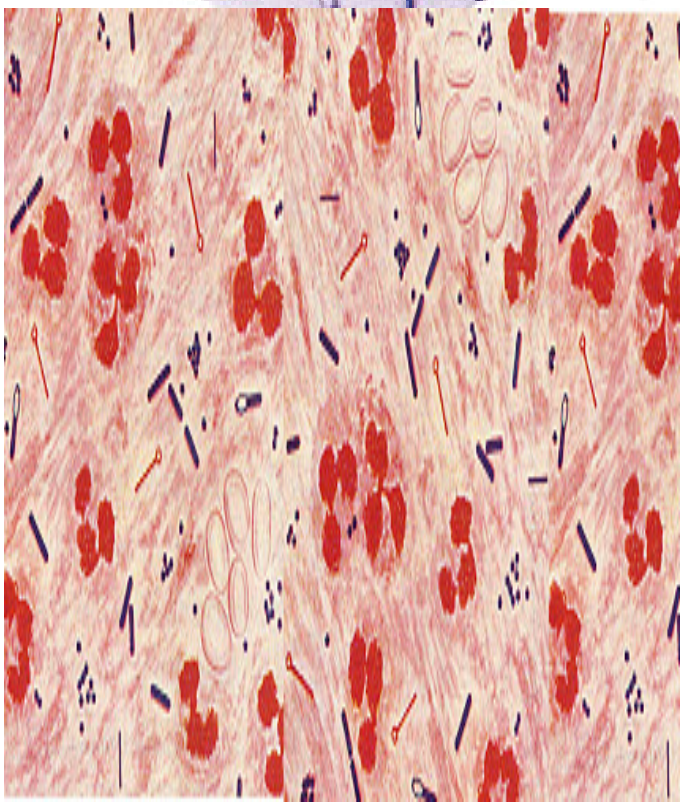
Morphology

Gram positive rods with rounded ends

All species form endospore (**drumstick** with a large round end)

(racquet shaped bacillus)

Motile by peritrichous flagella



Culture

Obligate anaerobes

Grows well in cooked meat broth

Toxins

Cl. tetani produces two types of toxins:

1- Tetanolysin which causes lysis of RBCs and has cardiotoxic effects.

2-Tetanospasmin is neurotoxin and essential pathogenic product is toxic to humans and various animals when injected parenterally, but it is not toxic by the oral route.

- It acts centrally at the level of brain stem and anterior horn cells of the spinal cord, causes increasing excitability of spinal cord neurons and muscle spasm.

- It is plasmid encoded and One antigenic type.

Pathogenesis

Incubation period: varies from few days to several weeks (5-10 days).

Spores usually enter through accidental small puncture wounds, burns, umbilical stumps, frostbite, and crushed body parts.

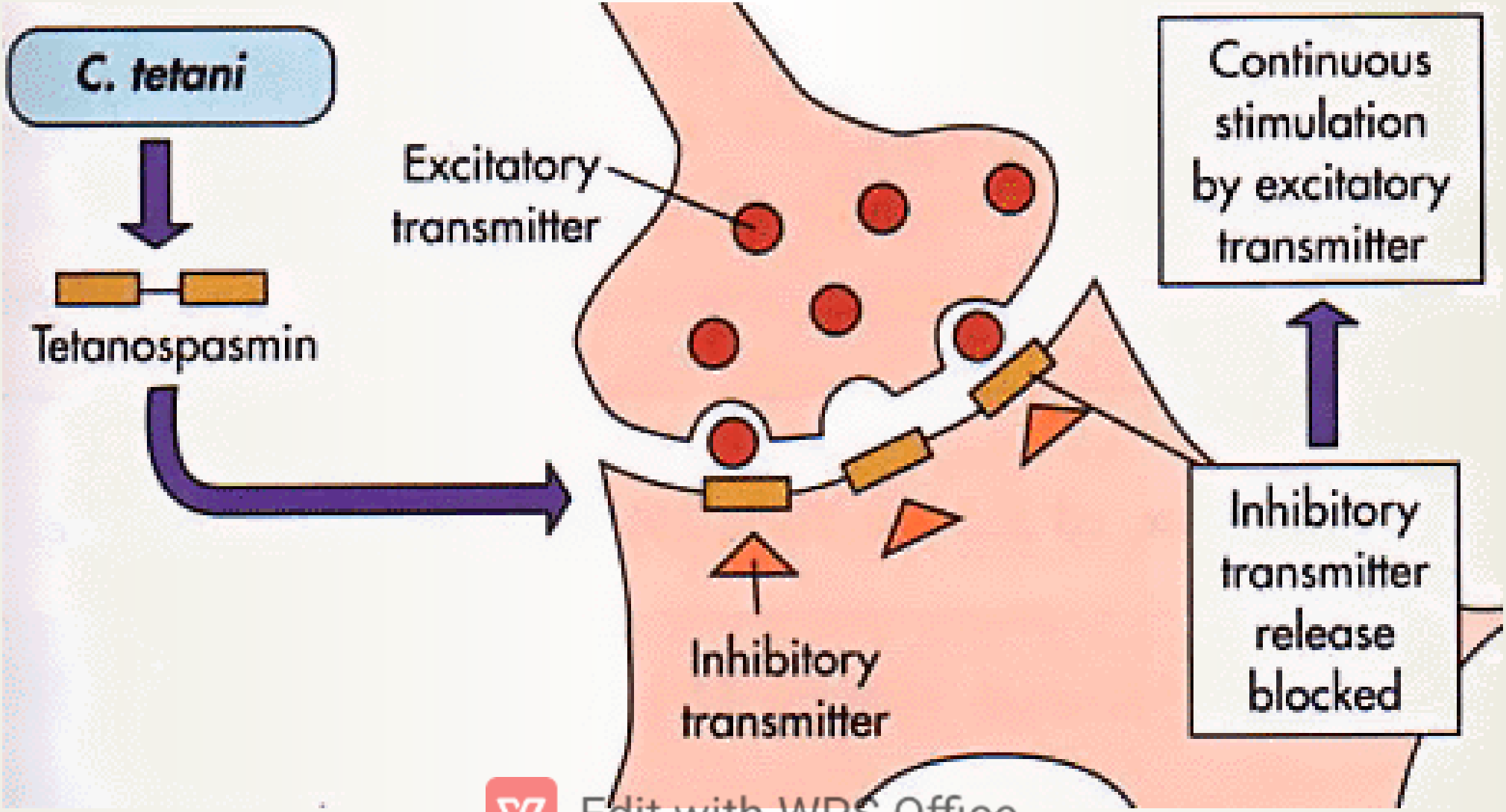
Anaerobic environment- due to blood supply cut off- is ideal for vegetative cells to grow and release toxin.

Growth of *C.tetani* is completely local (not invasive organism) , but it produces the powerful neurotoxin (tetanospasmin) that is transported to CNS , causing spastic paralysis.

Tetanospasmin: Reaches the CNS through retrograde axonal transport or blood. It is a neurotoxin causes **spastic paralysis** by irreversible binding to motor nerve endings; blocking the release of inhibitory neurotransmitters for muscular contraction e.g. glycine and GABA; muscles contract uncontrollably producing generalized muscular spasms.

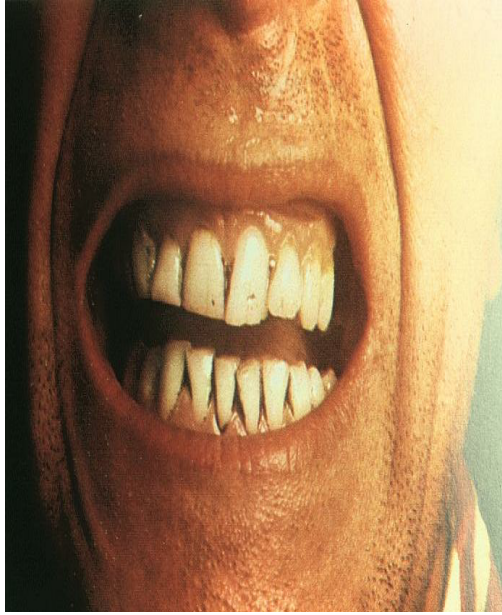
Death most often due to **paralysis of respiratory muscles.**

Mechanism of Action of Tetanus Toxin



Clinical features of Tetanus

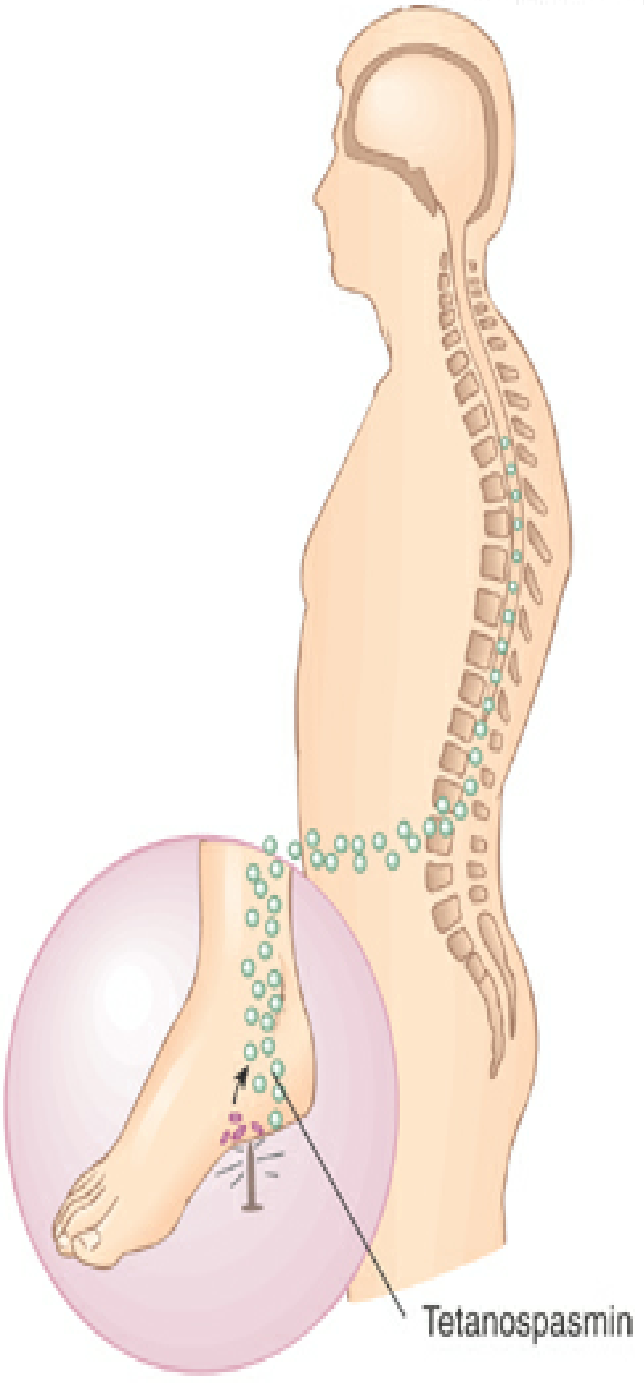
1- Generalized tetanus



• Spasm begin in face muscles, spreads throughout the body.
• Spasm is sudden, powerful, painful and long lasting leading to muscle tear or bone fracture.

Classic tetanic triad include:

1. **Trismus (lockjaw):** commonly the first tetanus-specific sign due to spasm of the lower jaw muscles preventing the mouth from opening.
2. **Risus sardonicus:** raised eyebrows, grinning caused by cramps of the facial muscles
3. **Opisthotonus:** pronounced arching of back due to spasm of the strong extensor back muscles.



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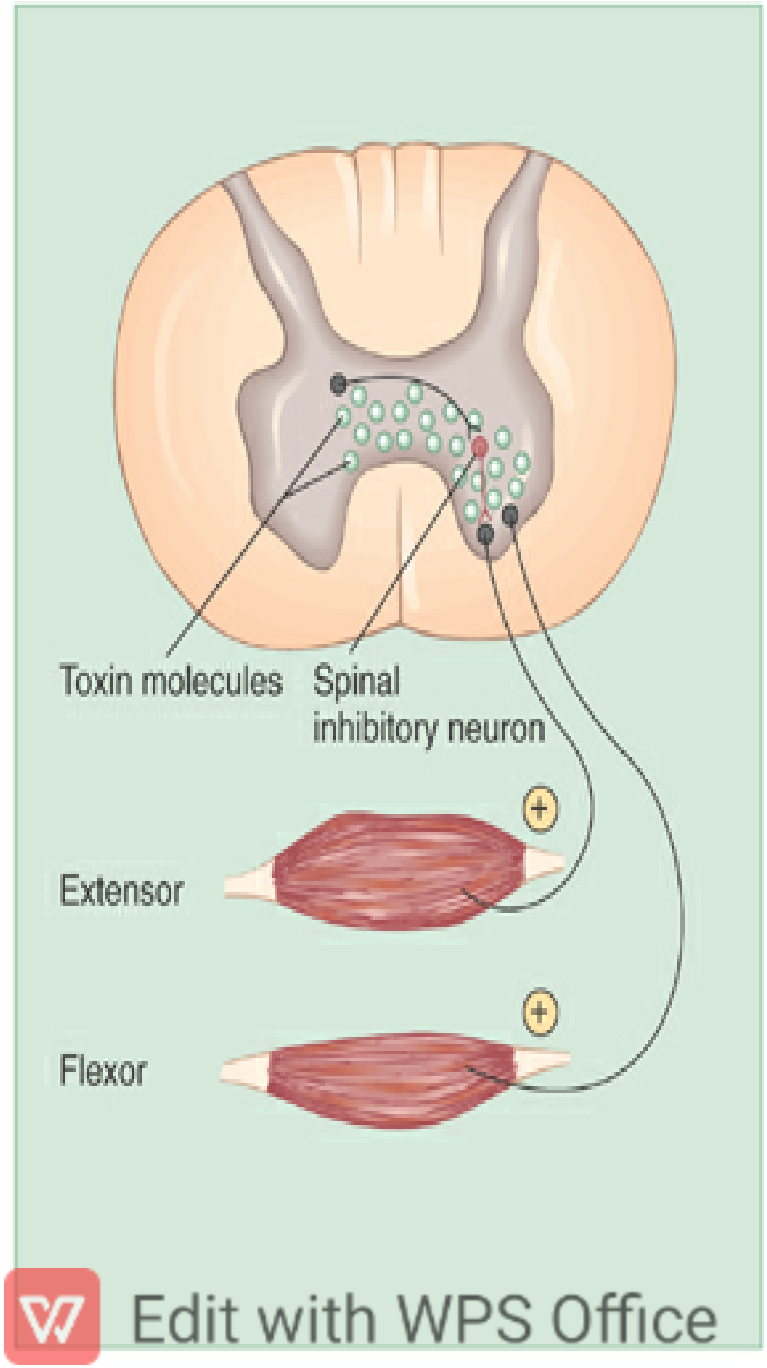

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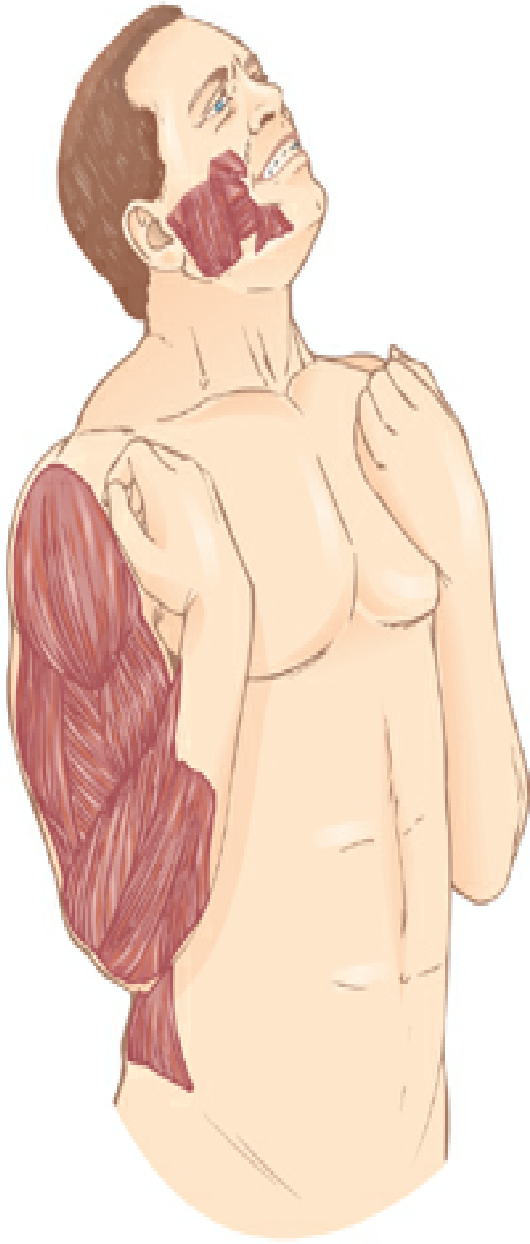

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2- Neonatal tetanus:

Generalized disease of newborn of inadequately immunized mothers after unsterile cutting of the umbilical cord.

3- Localized tetanus:

Persistent painful muscle contractions localized in areas surrounding injury site.

4- Cephalic tetanus:

1.It is a rare form of the disease; occasionally occurring following head trauma; skull fracture, eye injury, middle ear infections or sometimes tooth extractions.

2.Limited to muscles supplied by the 12^{th} cranial nerves (especially the facial nerve).

3.Very poor prognosis.

Laboratory Diagnosis of Tetanus

- The diagnosis of tetanus depends primarily upon **the clinical manifestation** of tetanus including muscle spasm and rigidity.
- **Specimen:** Wound exudates using capillary tube
- **Gram stain:** shows characteristic morphology of *C.tetani*
- **Culture:** anaerobically incubated on blood agar or Robertson cooked meat media may confirm the diagnosis but have low sensitivity and specificity

Treatment of Tetanus

- **Neutralize the toxin by Human tetanus immune globulin (HTIG) :**
  - Single dose 3,000-6,000 units IM
  - Neutralizes circulating tetanospasmin that has not entered the nervous system
- **Local wound care:**
  - Remove foreign bodies
  - Irrigate wound vigorously
  - Debridement of wound to remove devitalized tissue

- **Eradicate *C. tetani***

– Oral or IV metronidazole 30 mg/kg day divided every 6 hours for 10-14 days

OR

– Penicillin G 100,000 units /kg/day divided every 4-6 hrs for 10-14 days (alternative)

- **Provide supportive care**

- an adequate airway must be maintained, respiratory support given and IV fluids

Prevention of Tetanus

Tetanus is a totally preventable disease

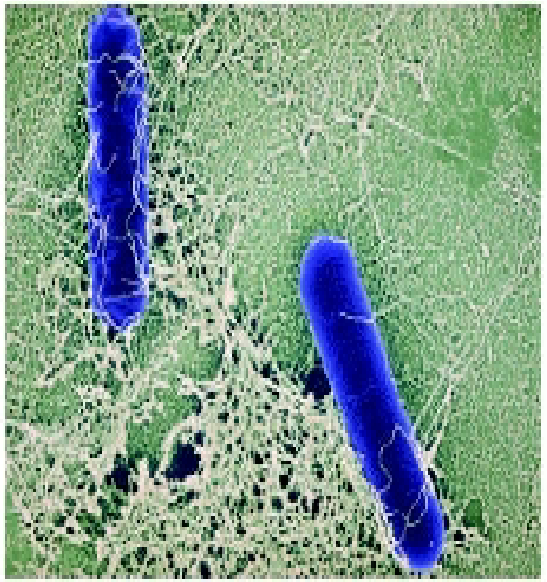
- **Wound management**
- **Active immunization: tetanus toxoid (DPT)**
- DPT vaccine against diphtheria, tetanus, and pertussis, given at 2,4,6 months. Booster doses are given at 18 month and upon school entry.
- Booster doses of Td vaccine: tetanus and diphtheria toxoid vaccine at 10-year intervals to maintain immunity.
- **Passive immunization:** HTIG in a dose of

BOTULISM

Definition:

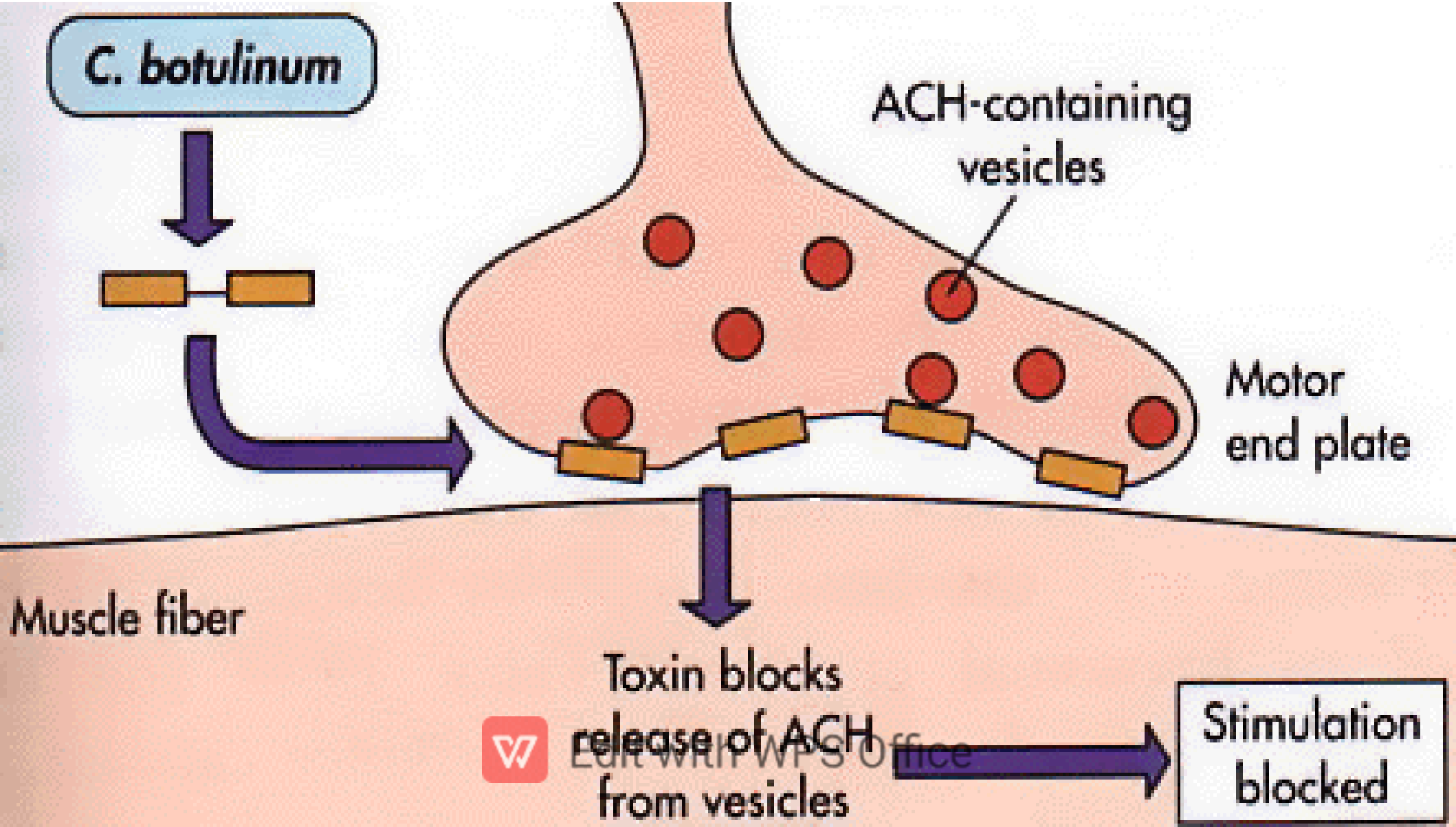
Botulism is a paralytic disease (flaccid paralysis) caused by a potent neurotoxin elaborated by *Clostridium botulinum.*

Clostridium botulinum



- First recognized and isolated in 1896 by Van Ermengem
- Large Gram positive rods, motile, Spore forming (oval, subterminal)
- Produces heat-labile neurotoxin that causes **flaccid paralysis**
- Eight immunologic subtypes, labeled A-H
- Types A, B and E cause human botulism
- Irreversibly inhibits the neurotransmitter **acetylcholine release** at peripheral nerve endings at the neuro-muscular junction.
- Encoded by lysogenic phage.
- Quick acting toxin so IP is only 12 hours.

Mechanism of Action of Botulinum Toxin



Clinical Features

- Botulism usually starts with weakness of the muscles that control the eyes, face, mouth, and throat. This weakness may be descending, spread to the neck, arms, and legs. Botulism also can weaken the muscles involved in breathing, which can lead to difficulty breathing and even death.
- **Symptom progression**
  - **Descending paralysis**
    - Lose head control
    - Lose gag – require intubation
    - Lose diaphragm – mechanical ventilation
  - **Loss of deep tendon reflexes**

Clinical forms of Botulism
1- Food-borne (classic) botulism

- caused by eating canned foods that contain botulinum toxin.
- The anaerobic spores survive in canned foods
- Germination of the spores produces dangerous toxins and gas → bulging cans

Clinical features:

Classic Triad

1- Symmetric, descending flaccid paralysis with prominent bulbar palsies

2- Afebrile

3- Clear sensorium

Bulbar palsies summarized as "4 Ds “

Diplopia, dysarthria, dysphonia, dysphagia

2- Intestinal botulism (infant)

- caused by ingesting spores of the bacteria (may be in honey) which germinate and produce toxin in the intestines
- Occurs in infants between 2 weeks- 6 months
- Newborn and infants have poorly developed gut flora, vulnerable to colonization by *Cl.botulinum*
- Infants with botulism will present with:

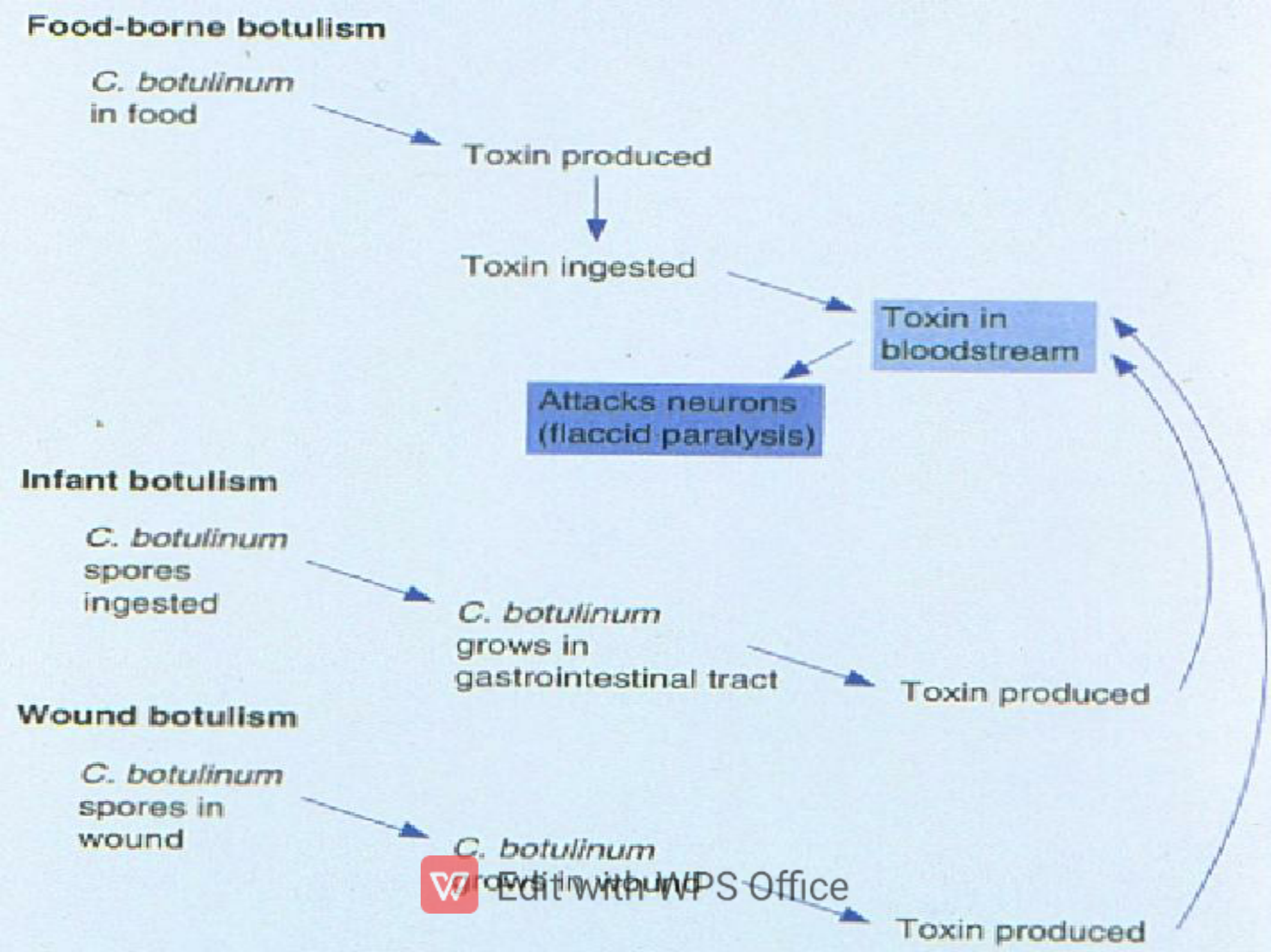
– Constipation is often the first symptom
– weak cry, poor feeding (poor sucking)
– poor muscle tone, "**floppy" baby**

3- Wound botulism

- Spores introduced during skin popping technique by drug addicts (black tar heroine), *C. botulinum* spores germinate in the

4- Inhalation botulism

- Aerosolized toxin is inhaled
- does not occur naturally and may be indicative of bioterrorism



Laboratory Diagnosis

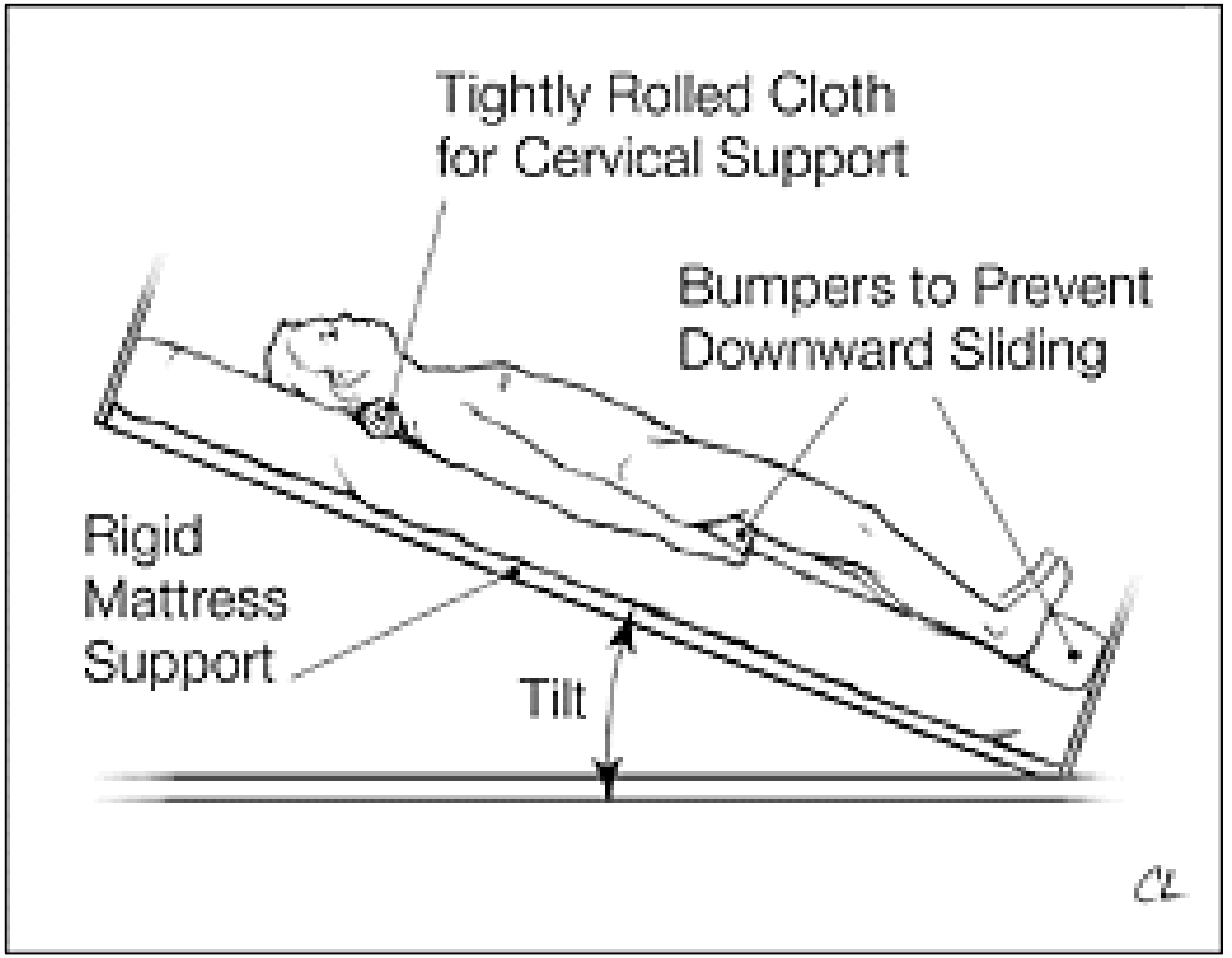
- Most cases are **clinically diagnosed**
- Sample: serum, stool, gastric aspirate, suspect foods
- **Toxin detection**: only used as confirmatory testing by serologic or Toxin neutralization mouse bioassay
- Isolation of *C. botulinum* on culture is rare

Treatment

- Antitoxin administration: Trivalent (A, B, E) antitoxin administered intravenously promptly.

- Supportive Care
  - mechanical ventilation
  - body positioning
  - parenteral nutrition

- Elimination
  - Induced vomiting
  - High enemas



Prevention

1- Botulinum Vaccine

Botulinum pentavalent toxoid (antigen types A, B, C, D, and E) Protects vs. types A-E

- Not available to general public
- Limited supply provided by CDC
- In use for laboratory workers, military
- Long-lasting immunity

2- Careful sterilization of food before canning

3- Avoid honey during the first year of life

Uses of Botulinum Toxin
1- Bioterrorism agent

- Category A (Top 6 potential biological warfare agents Listed as Category A agent: High priority)

- Bioterrorism routes of intoxication:
  - Aerosol (inhaled into lungs)
  - Food borne

2- Therapeutic agent

- Neuromuscular disorders: Currently only FDA approved for 4 disorders
  - Blepharospasm (focal dystonia)
  - Strabismus
  - Cervical dystonia
  - Hyperhidrosis

- Pain management

3- Local paralytic agent – Botox®

BoNT/A Induces Local Paralysis

- Local effects = dose dependent
- Injection site affects physical outcome

Before Botox®

After Botox®

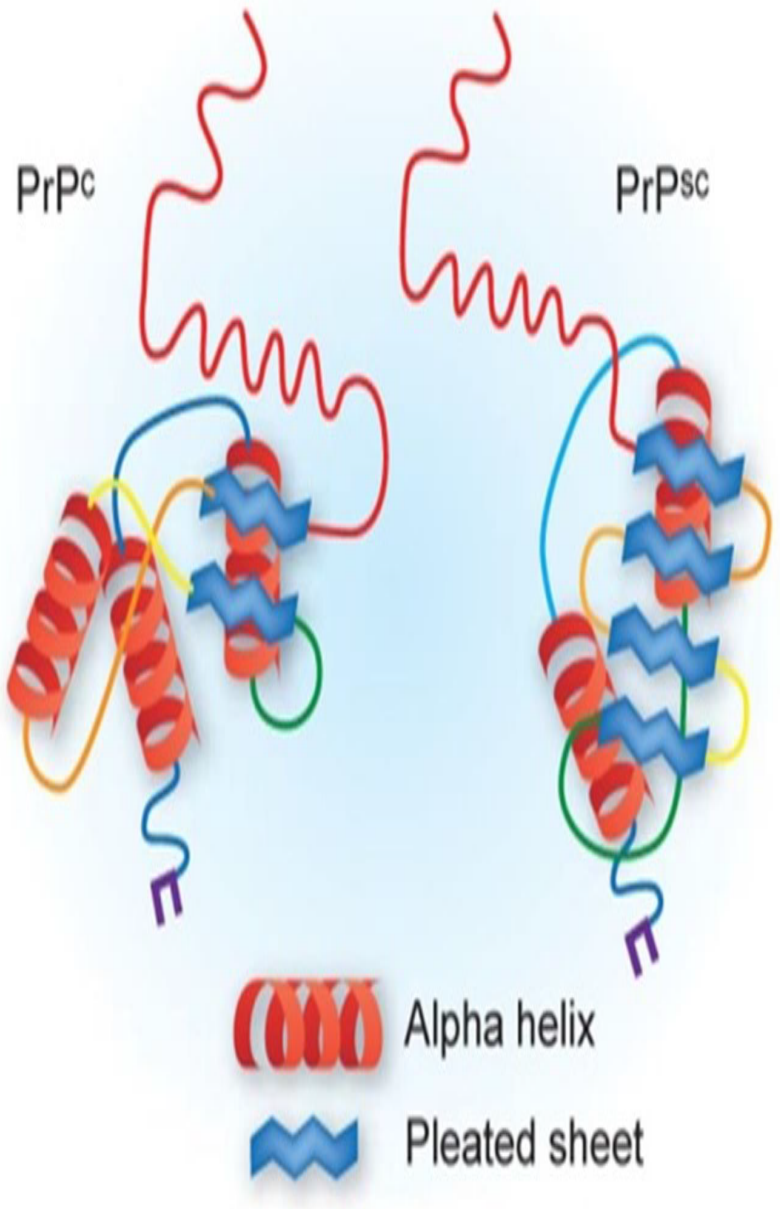
PRION DISEASES

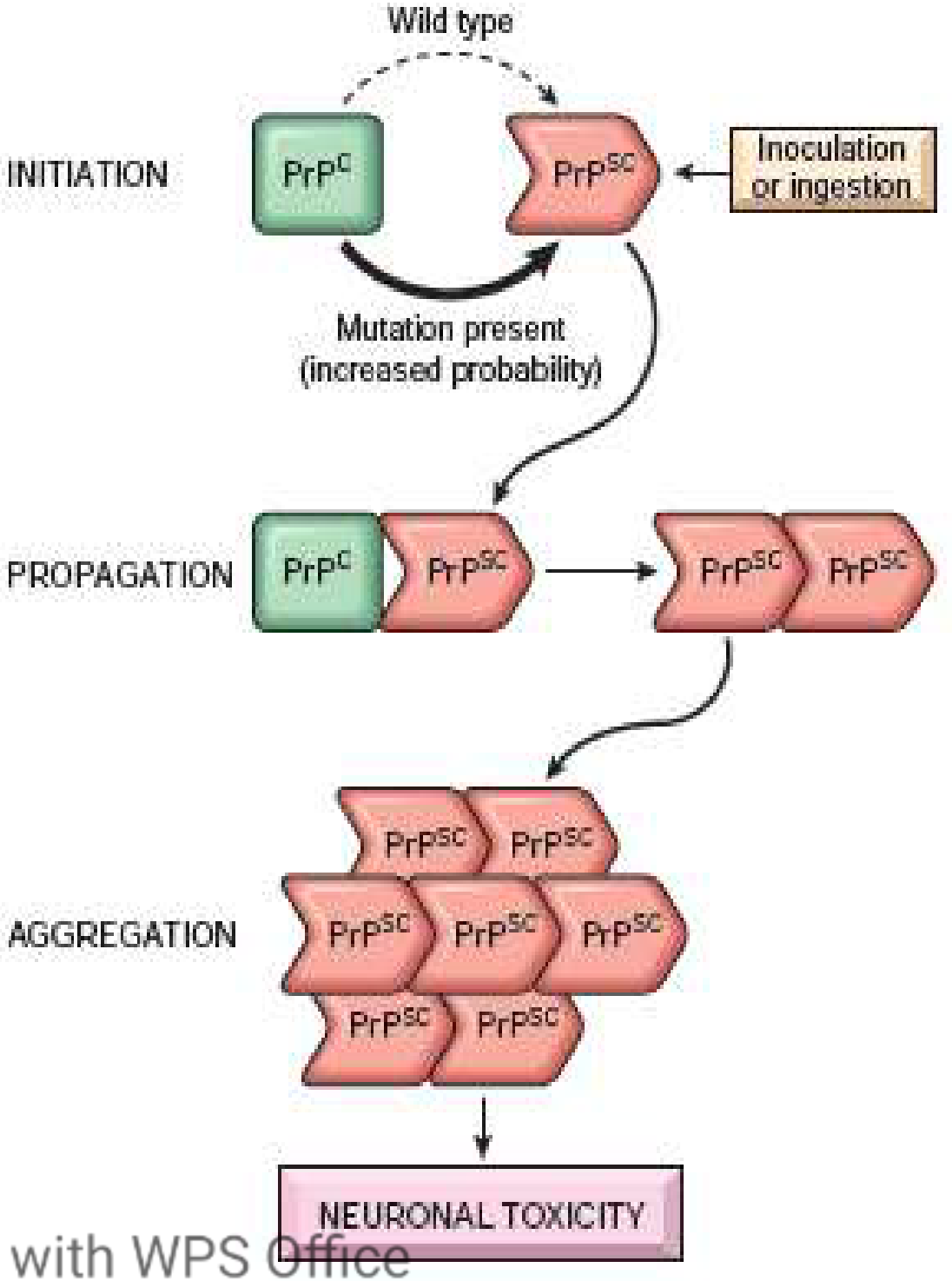
Definition:

Prions are abnormal forms of a cellular protein that cause rapidly progressive neurodegenerative disorders that affect both humans and animals; called prion diseases or transmissible spongiform encephalopathies (TSEs).

Pathogenesis

• Normal prion protein (PrP) is a 30-kD cytoplasmic protein present in neurons.
• Disease occurs when PrP undergoes a conformational change from its normal α-helix-containing isoform (PrPc) to an abnormal β-pleated sheet isoform, usually termed PrPsc (for scrapie).
• Associated with the conformational change, PrP acquires resistance to digestion with proteases, such as proteinase K.





Characters of prion-mediated diseases

1- They are confined to CNS causing neuro-degeneration and spongiform changes due to neuronal vacuolation and neuronal loss.
2- They have a long IP and a chronic progressive course with dementia and end fatally.
3- There is no inflammatory or immune response to these diseases as they are normal human proteins.
4- They are transmissible by ingestion of infected tissues mainly the brain, transplanted tissues and contaminated surgical instruments.

Examples of prion diseases

This group of diseases includes:

- Creutzfeldt-Jakob disease (CJD), Variant CJD, Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and kuru in humans.
- Scrapie in sheep and goats.
- Bovine spongiform encephalopathy (BSE) or Mad cow disease.

Diagnosis

1. Detection of a normal brain protein 14-3-3 in CSF: A negative test does not exclude the diagnosis and a positive result can occur in non-prion diseases as herpes simplex encephalitis, cerebral metastases, and metabolic encephalopathies.

2.The presence of PrPsc in peripheral lymphatic tissues: provides specimens for analysis without the need for brain biopsy.

3. Postmortem histopathological studies of brain material to detect protease resistant PrPsc and spongiform vacuolation remain the gold standard for the diagnosis of prion diseases.

Prevention

1. Properly cleaning and sterilizing medical equipments.
2. The patients should not donate organs or tissue, including corneal tissue.
3. Newer regulations that govern the handling and feeding of cows may help prevent the spread of prion diseases. All animals showing signs of illness are destroyed.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