



## Lecture Fourteen

# Viruses of Medical Importance

## 5- Rabies

By

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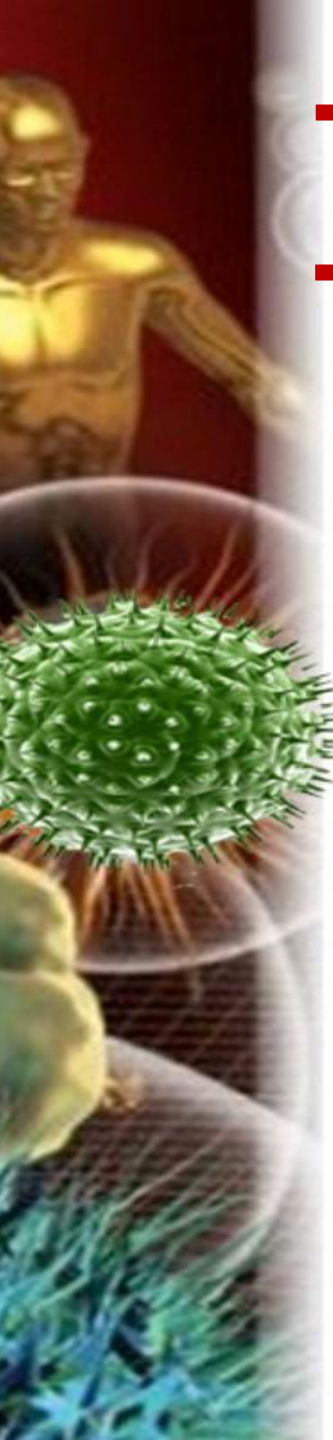
## **Learning outcomes**

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### **By the end of this lecture students should**

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- **Know the history of Rabies.**
- **Have the knowledge of Rabies epidemiology and modes of transmission.**
- **Recognize different symptoms associated with Rabies.**
- **Be aware of different ways for prevention and control measures.**





# Historical Background

**2300 BC:** Rabies was documented by ancient Egyptians as important disease affecting man and animals



**Ancient Egyptians**

**850 BC in ancient Greece:** first cultural record of Rabies in Iliad of Homer



**Rabid Hector**

# Historical Background



- **In 1769, John Morgagni;** rabies virus carried through nerves.
- **In the early 19<sup>th</sup> century, Pathologist Zinke:** Rabies is transmitted in the saliva by experimentally painting saliva from a rabid dog into incisions made in healthy animals.
- **In 1879, Galtier, France:** rabbits are technically much less difficult and dangerous than using dogs and cats.
- **1885, Louis Pasteur:** generate attenuated Rabies virus vaccine.

Pasteur successfully immunized a 9-year-old boy, Joseph Meister, who had been severely bitten by a rabid dog.

The boy did not develop rabies and subsequently many people with rabies exposures were immunized with nervous system vaccines in Paris and other locations throughout the world.
- **In 1903, Adelchi Negri:** Described eosinophilic cytoplasmic inclusions in infected neurons, which are now called Negri bodies.



# Taxonomy (ICTV, 2018)

**Phylum: Negarnaviricota (2 subphyla)**

**Subphylum: Haploviricotina (4 classes)**

**Class: Monjiviricetes (2 orders)**

**Order: Mononegavirales (11 families)**

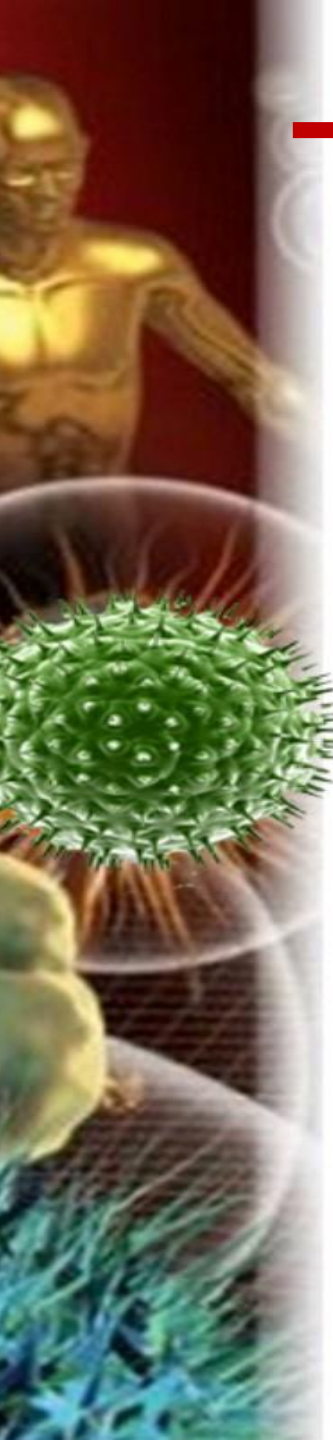
**Family: Rhabdoviridae (18 genera)**

**Genus: Lyssavirus (16 species)**

**Rabies lyssavirus**

West Caucasian bat lyssavirus  
Australian Bat lyssavirus  
Lagos bat lyssavirus  
Shimoni Bat lyssavirus

Bokeloh bat Ikoma  
Khujand lyssavirus  
Mokola lyssavirus  
Irkut lyssavirus  
Aravan lyssavirus  
Duvenhage lyssavirus



# Virus Morphology and Characteristics

**Virion:** Bullet shape – medium sized (70 nm width X 170 nm length).

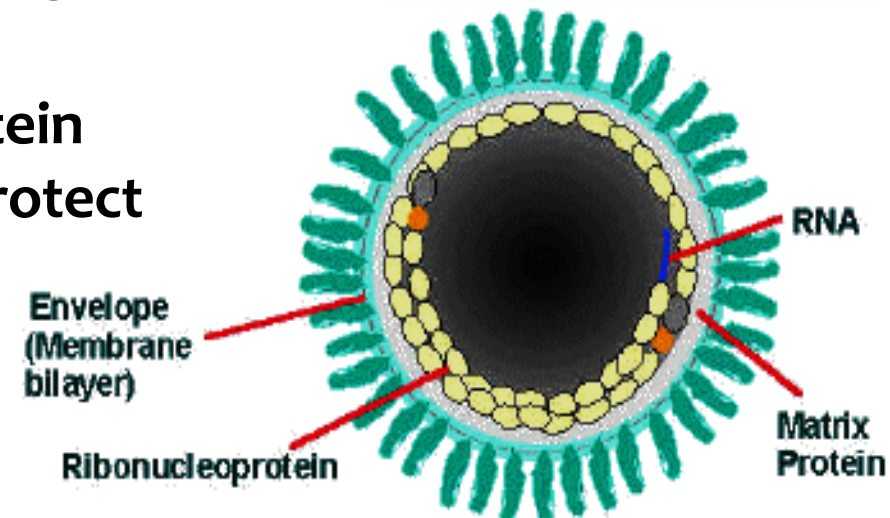
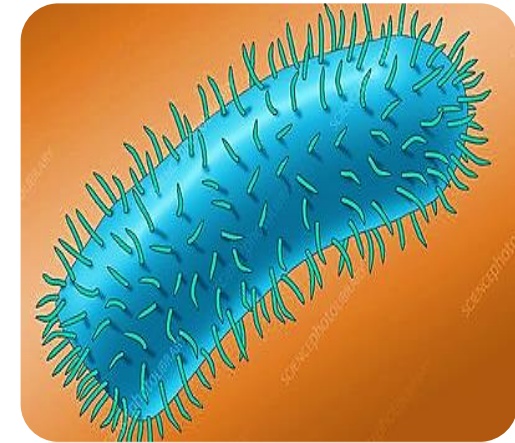
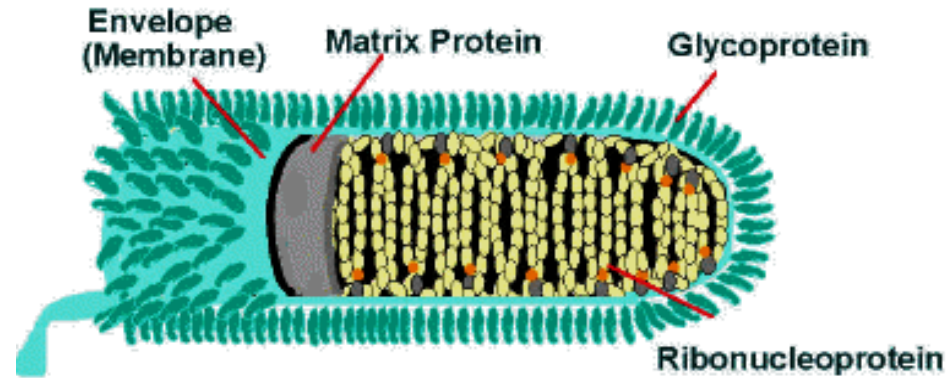
**Capsid:** helical (NP).

**Genome:** RNA – single stranded – negative sense – Linear –non-segmented – haploid – 11-15 kb long.

**Envelope:** Present - carry 400 peplomere of G protein  
Matrix protein present internally to protect envelope.

**Viral enzymes:** L and P proteins (polymerases).

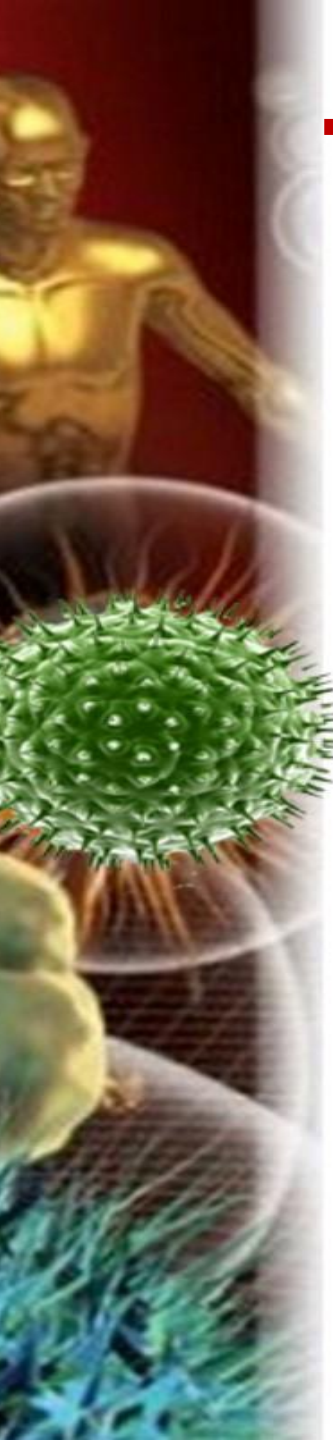
**Replication:** Cytoplasm.



# **Epidemiology and Transmission**

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- **About 99% of global human rabies cases are a consequence of transmission from dogs due to the presence of endemic dog rabies.**
- **There are approximately 59,000 human deaths per year related to endemic canine rabies and the greatest burden of human disease occurs in Asia and Africa.**
- **In other countries (e.g., North America) rabies is endemic in wildlife and this poses the main risk for transmission of rabies virus.**





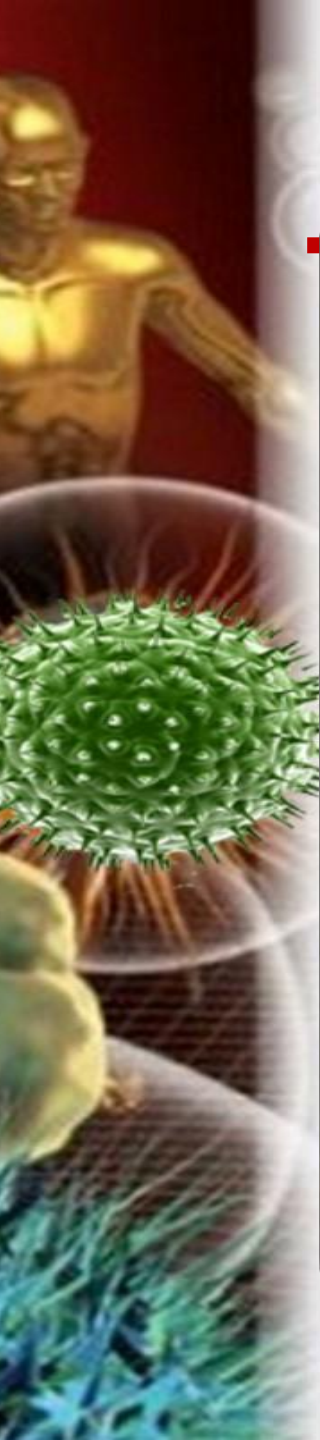
# **Epidemiology and Transmission**

## **Modes of Transmission**

- **Bite of Rabid animal (Saliva carries more than 1 million virus particle).**
- **Contamination of wounds or scratches with saliva.**
- **Inhalation of aerosols in bat caves (where air is full of aerosols contaminated with rabies virus).**
- **Organ and Tissue transplantation: Corneal transplantation from undiagnosed rabid patient.**



# Epidemiology and Transmission





# Epidemiology and Transmission: Animal Reservoir

- Terrestrial animals that are vectors of rabies in North America include raccoons, skunks, and foxes.



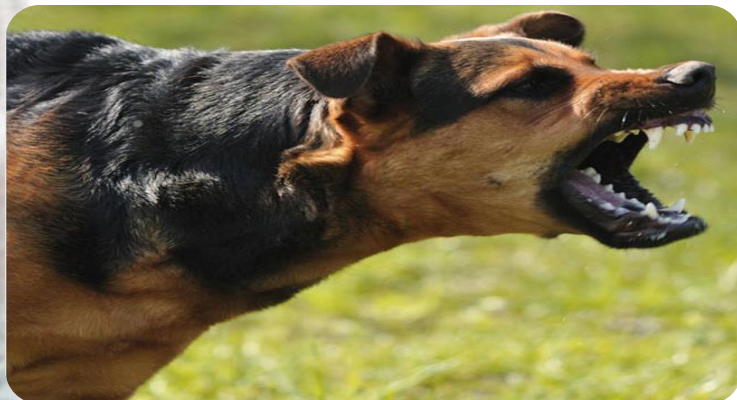
Raccoon rabies



Skunk rabies



Fox rabies





# Pathology and Clinical Picture

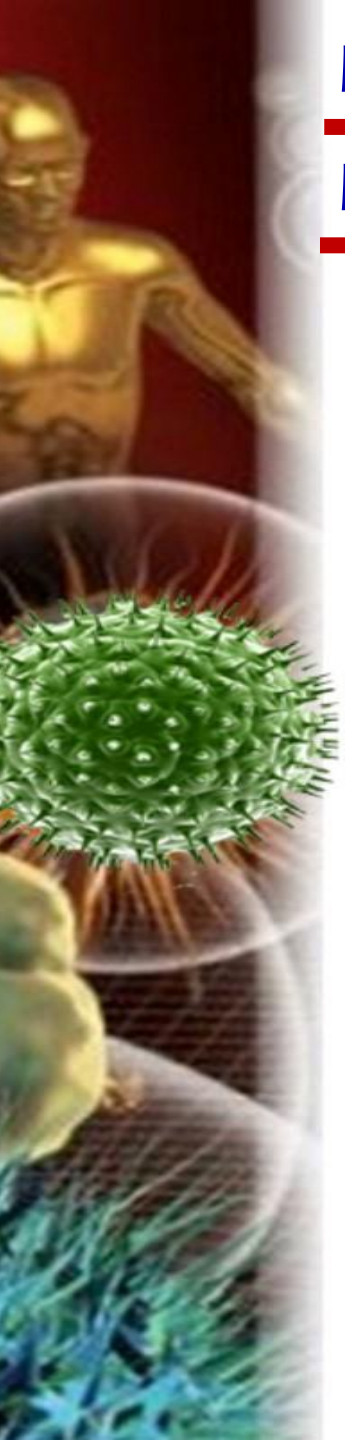
## **PATHOGENESIS**

- Based on animal studies, rabies virus is thought to remain close to the site of viral entry during most of the incubation period.
- After an exposure involving muscle, rabies virus is known to bind to nicotinic acetylcholine receptors that are located in the **postsynaptic membrane** of the **neuromuscular junction**.
- After the virus crosses the synaptic cleft, it spreads centripetally towards the spinal cord in motor nerve fibers of peripheral nerves by retrograde fast axonal transport.
- After infecting spinal cord neurons, rabies virus spreads widely within axons of the CNS by fast axonal transport along neuroanatomical connections.

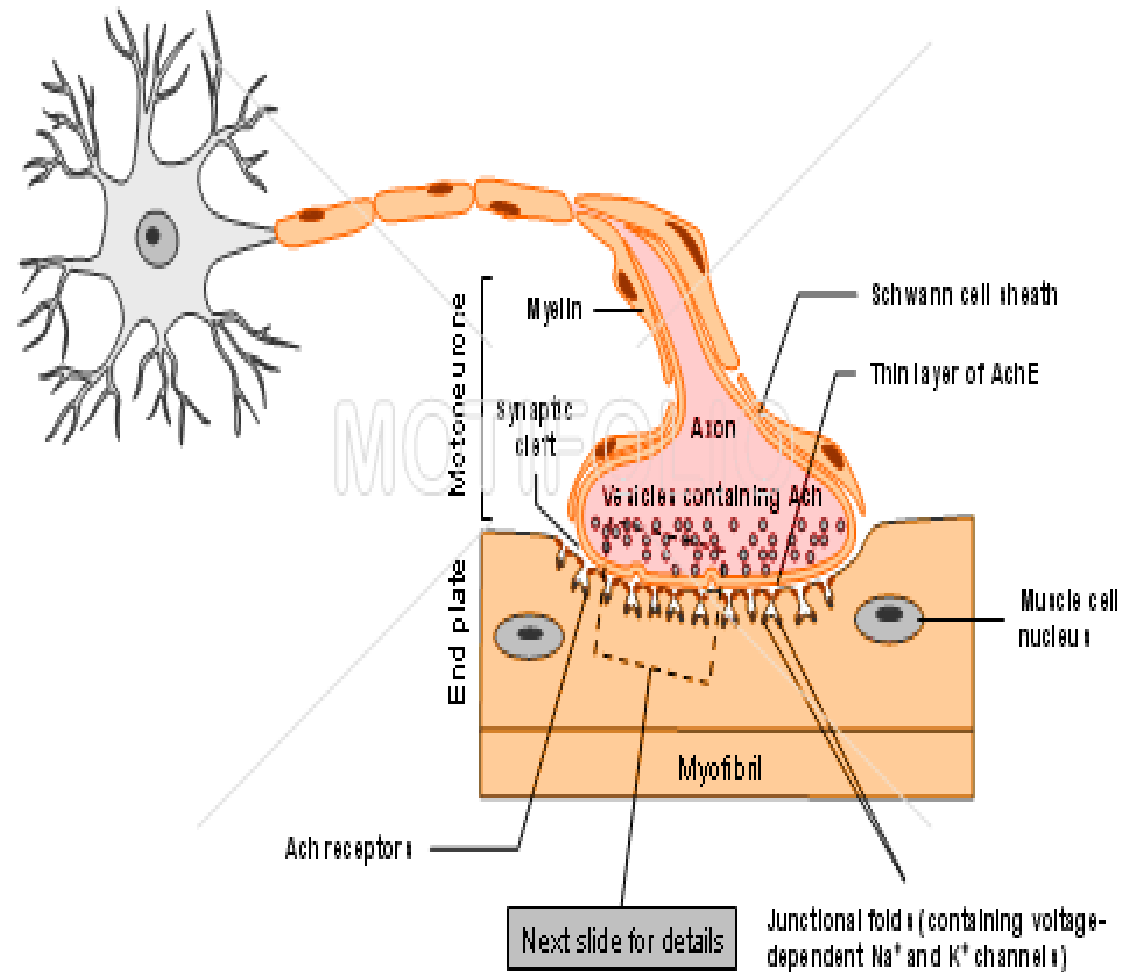
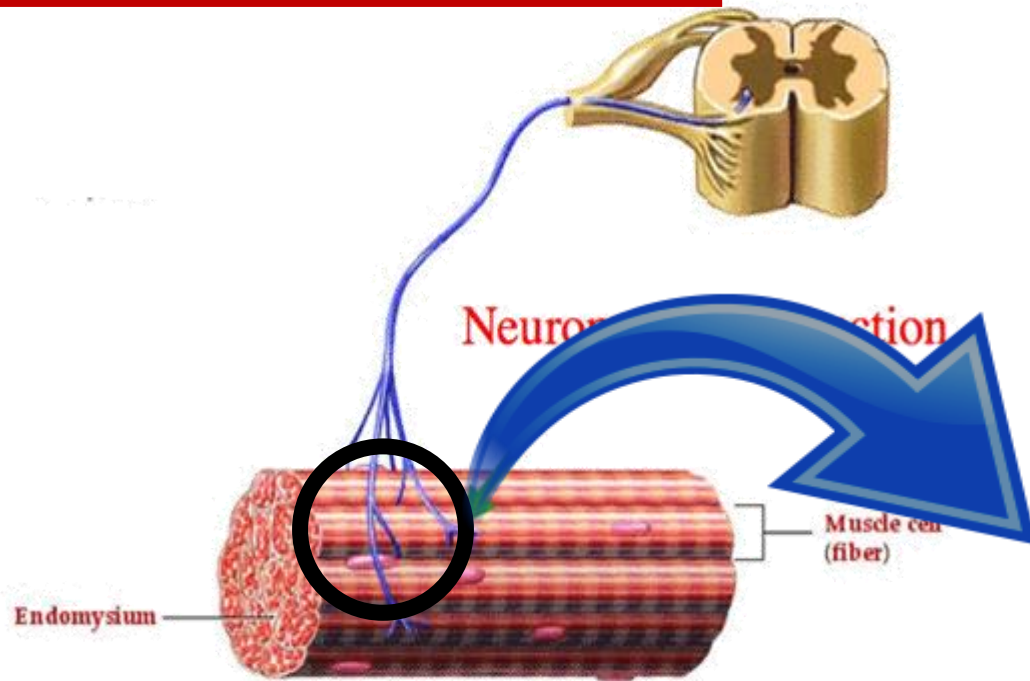


# Pathology and Clinical Picture

## PATHOGENESIS



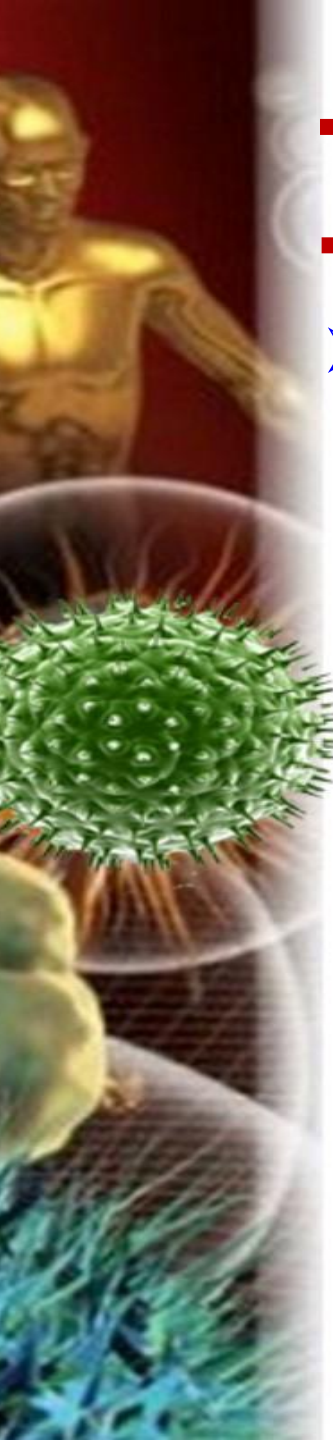
# Neuromuscular Junction



# Pathology and Clinical Picture

## **PATHOGENESIS**

- After CNS infection is established, there is centrifugal spread of rabies virus to multiple organs along sensory and/or autonomic nerves.
- In rabies vectors, viral spread to the salivary glands is important and saliva is secreted containing high titer infectious rabies virus, which is important for transmission to new hosts via bite exposures.
- Viral spread also occurs to multiple extraneural organs, including the heart (resulting in myocarditis in some cases), adrenal medulla, gastrointestinal tract, and skin (skin biopsy is used for antemortem rabies diagnosis in humans)





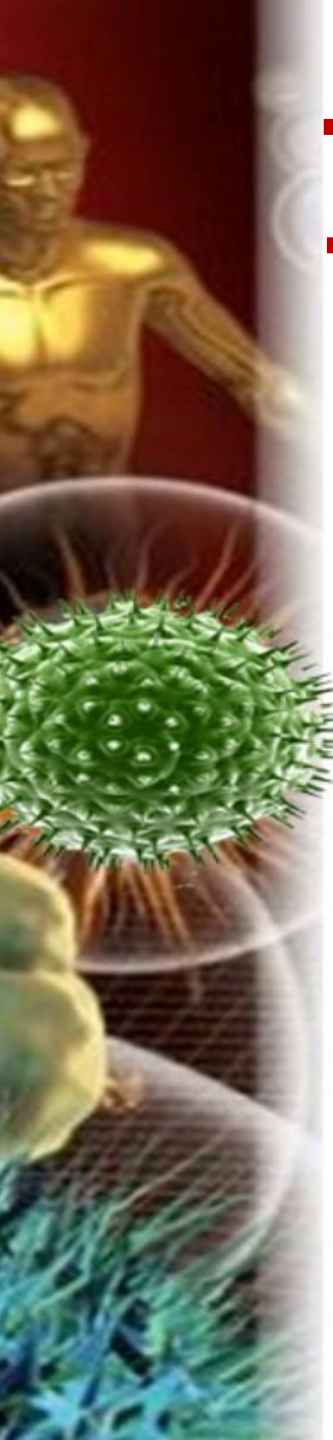
# Pathology and Clinical Picture

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## Clinical Picture

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- Prodromal symptoms in rabies are nonspecific and include **fever, chills, malaise, fatigue, insomnia, anorexia, headache, anxiety**, and irritability. Can last for 10 days.
- The earliest neurological symptoms of rabies include **paresthesias, pain**, and **pruritus** at or close to the site of exposure.
- There are two clinical forms of disease in rabies: encephalitic rabies (in 80% of cases) and paralytic rabies (in 20% of cases).
- Encephalitic rabies involves the brain.
- Paralytic rabies involves the spinal cord, nerve roots, and peripheral nerves.



# Pathology and Clinical Picture

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## Clinical Picture

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In encephalitic rabies :

- there may be episodes of generalized arousal or hyperexcitability, which are separated by lucid periods.
- Patients may have aggressive behavior, confusion, and hallucinations.
- Features of autonomic dysfunction, including hypersalivation, piloerection (gooseflesh), sweating, priapism, and cardiac arrhythmias, are common.
- Hydrophobia is a very characteristic clinical manifestation of encephalitic rabies.
- Subsequently, this may become a conditioned reflex and the sight, sound, or even mention of water (or other liquids) may trigger the spasms.
- Aerophobia is the occurrence of these same spasms precipitated by a draft of air on the skin. As the disease progresses there is progressive neurological deterioration with worsening in the level of consciousness to coma and the development of paralysis.

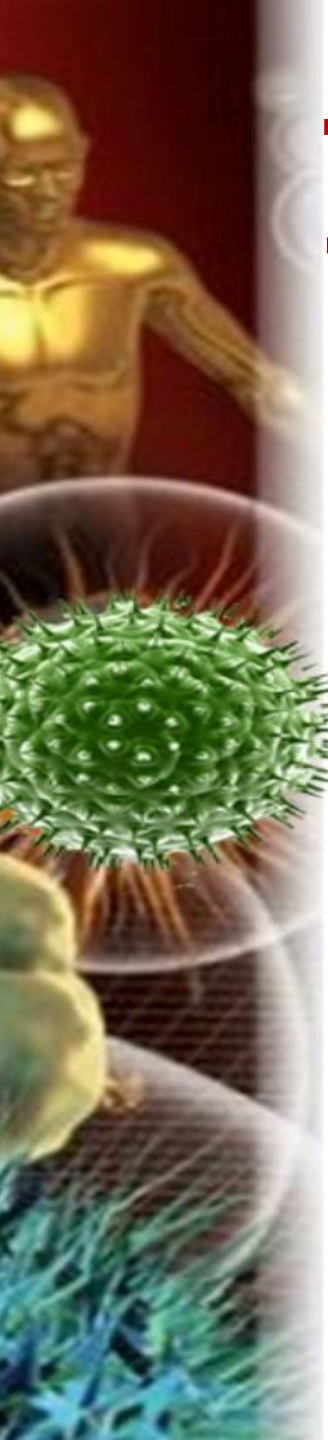
# Pathology and Clinical Picture

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## Clinical Picture

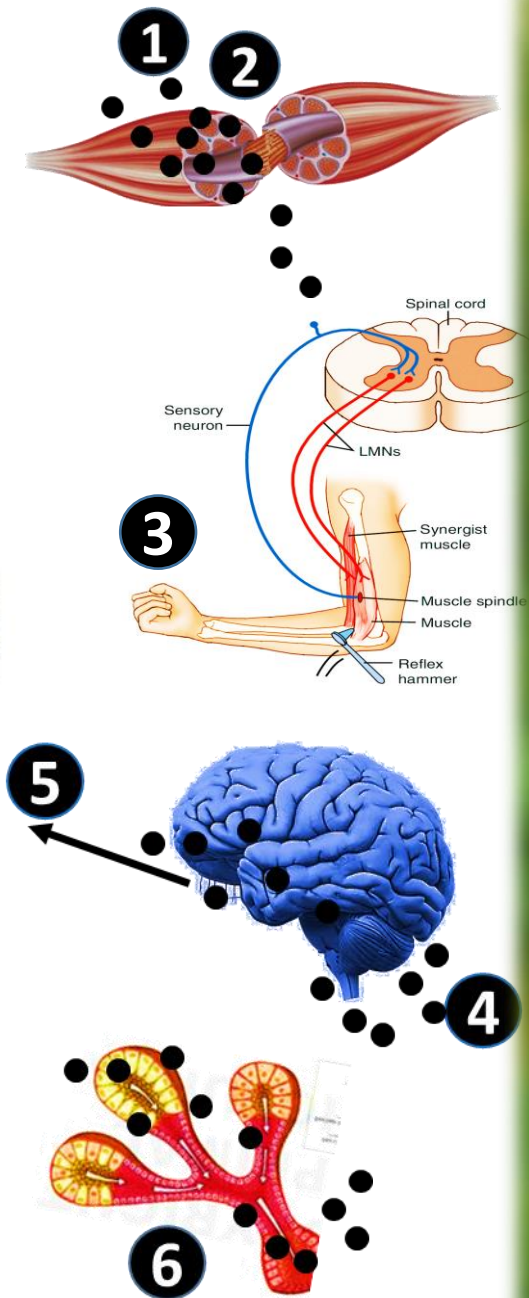
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- In paralytic rabies there is early prominent weakness that usually initially involves the bitten extremity and progresses to involve the other extremities and facial muscles.
- Sphincter involvement, pain, and sensory disturbances also occur.
- Patients with paralytic rabies later develop neurological deterioration with progression to coma, and they typically survive longer than patients with encephalitic rabies.



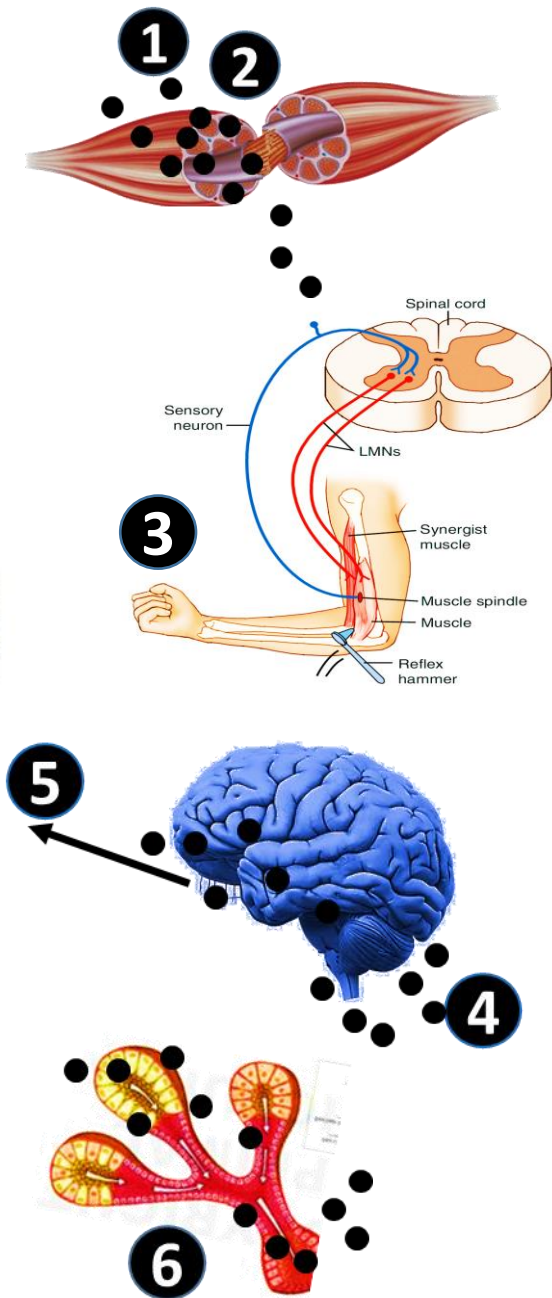


The spread of Rabies virus, an example of a virus that spreads by the neural route only.



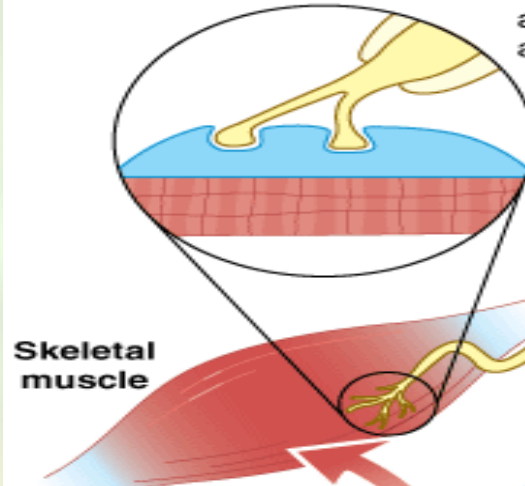


# The spread of Rabies virus, an example of a virus that spreads by the neural route only.



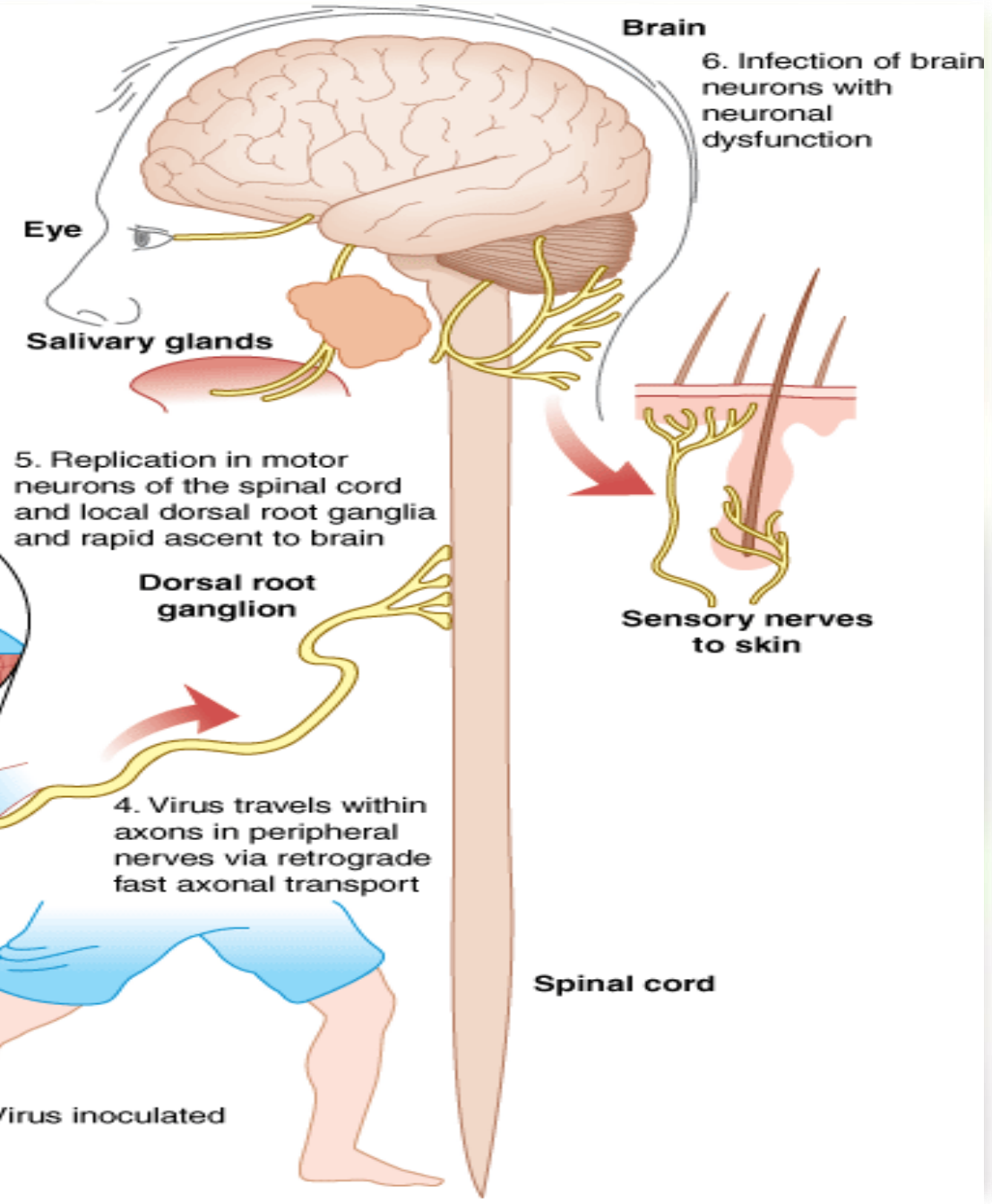
7. Centrifugal spread along nerves to salivary glands, skin, cornea, and other organs

3. Virus binds to nicotinic acetylcholine receptors at neuromuscular junction

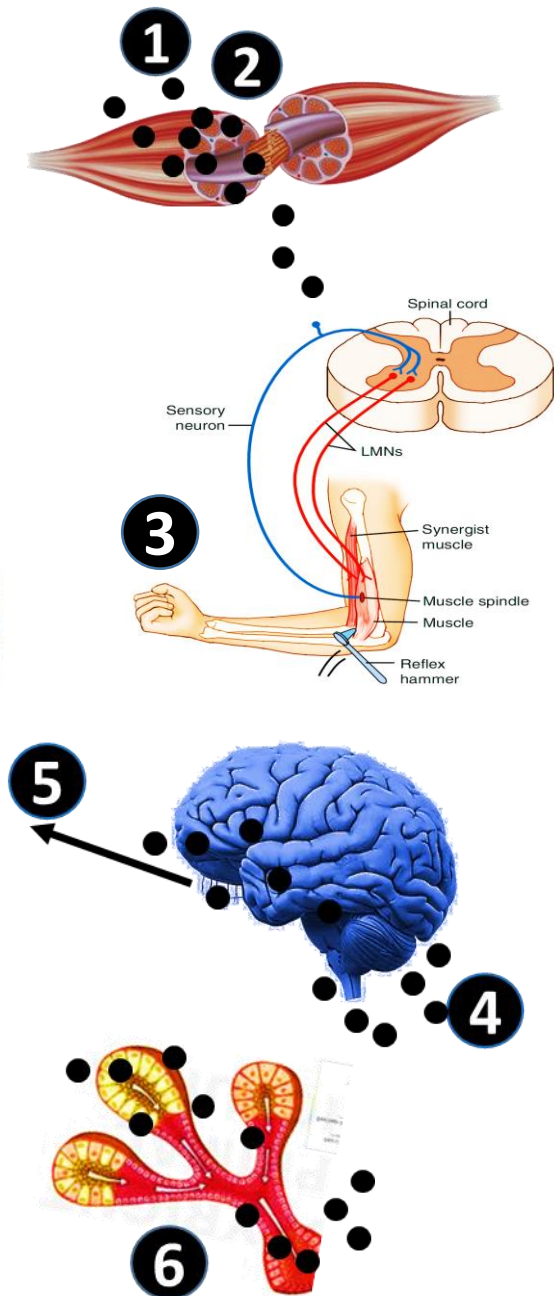


2. Viral replication in muscle

1. Virus inoculated



# The spread of Rabies virus, an example of a virus that spreads by the neural route only.



## Day 0

### 1. Virus entry

- by bite of rabid animal
- infected saliva is injected.

## Day 1-60

### 2. Striated muscle

- virus replicates in myocytes

## Day 10-60

### 3. Peripheral nerves

- virus enters nerve ending.
- nucleocapsid carried by fast axoplasmic flow to spinal cord

## Day 12-70

### 4. Central nervous system

- virus travels along neural processes, spreads and replicates
- neuronal dysfunction.
- clinical rabies, death

## Day 30-70

### 5. Peripheral nerves

- virus travels along peripheral nerves from CNS.
- invades salivary gland

## Day 40-70

### 6. Salivary gland

- virus replicates in acinar cells.
- virus is discharged in saliva.



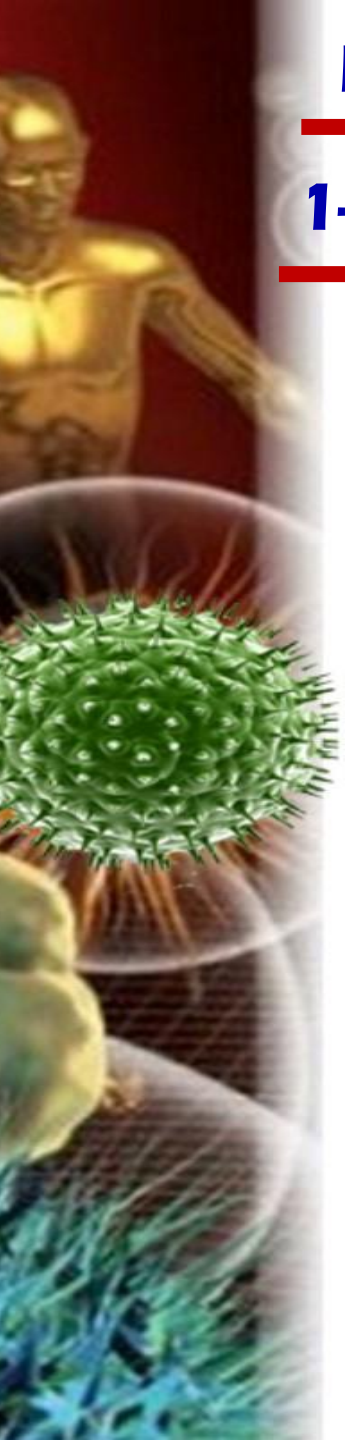
# **Prevention and Control**

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## **1- Prevent exposure to Rabies**

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- **Eradication or removal of stray animals (dogs and cats).**
- **Control the movement of pet animals.**
- **Avoid entering bat caves without mask.**
- **Animal vaccination (vaccination programs in pets – bait vaccine for wild animals).**
- **People at high risk (vets – lab workers – animal handlers) should be vaccinated with inactivated tissue culture vaccine (repeated each 2-3 years).**



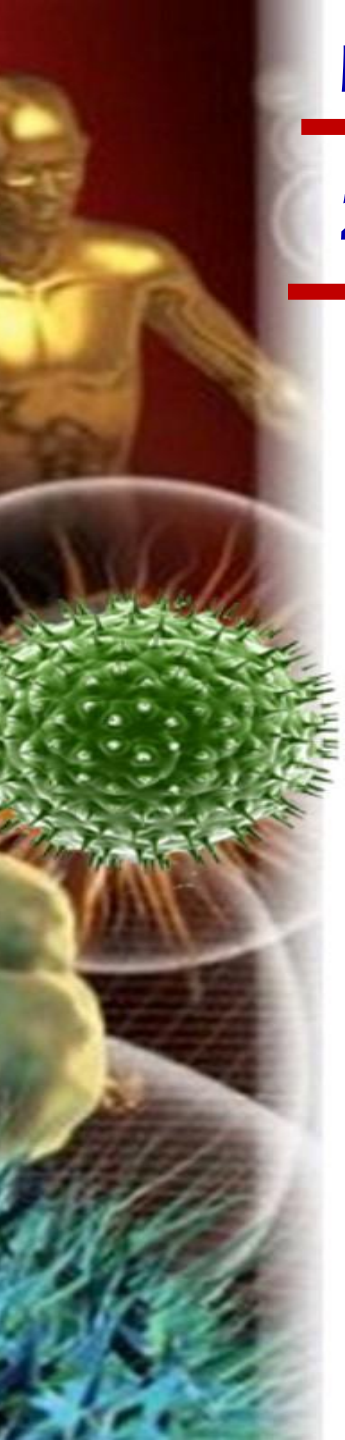
# Prevention and Control

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## 2- Post-exposure treatment:

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- Cleaning the wound with water and soap, following by deep application of disinfectants.
- Immunization of the bitten human with:
  - a) Anti-rabies immune serum:  
1/2 dose I/M - 1/2 dose around the wound.
  - b) Inactivated vaccine:  
Intra-muscular injection.  
Five separate doses at 0, 3,7,14 and 28 days post-exposure.





Thank  
You