

Rabies

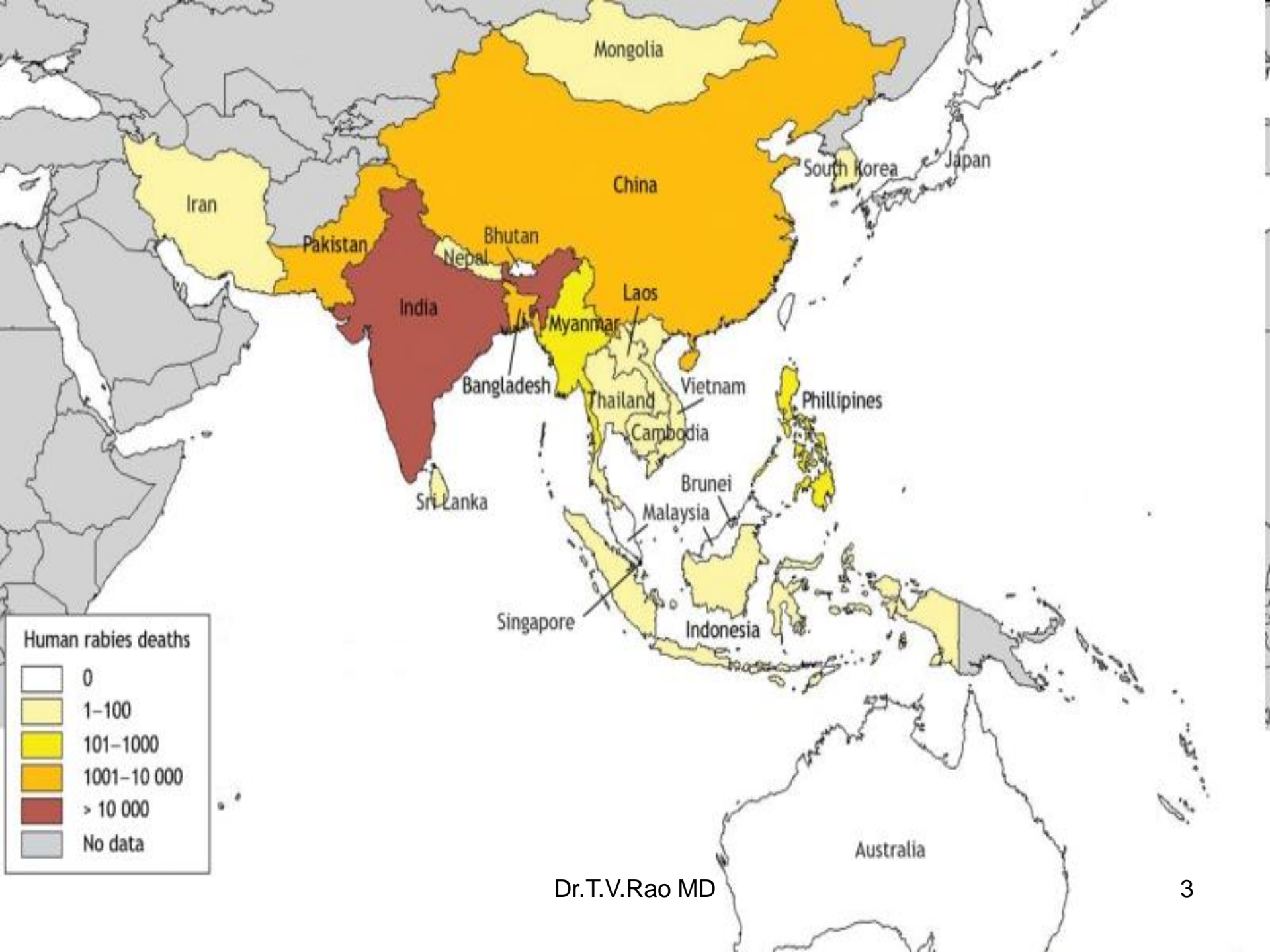
Rhabdovirus *basics*

Dr.T.V.Rao MD



Early Rabies

- **Rabies** has been recognized in India since the Vedic period (1500–500 BC) and is described in the ancient Indian scripture *Atharvaveda*,
- Rabies is endemic in India, a vast country with a population exceeding 1.2 billion and a land area of 3.2 million km.



Human rabies deaths

- 0
- 1-100
- 101-1000
- 1001-10 000
- > 10 000
- No data

Rabies widely spread in Asia and Africa

- Rabies is widely distributed across the globe. More than **55 000 people die** of rabies each year. About 95% of human deaths occur in Asia and Africa.
- Most human deaths follow a bite from an infected dog. Between 30% to 60% of the victims of dog bites are children under the age of 15.

What is Rabies

- Rabies is a Zoonotic viral disease Rabies infects domestic and wild animals, and is spread to people through close contact with infected saliva (via bites or scratches). The disease is present on nearly every continent of the world but most human deaths occur in Asia and Africa (more than 95%). **Once symptoms of the disease develop, rabies is fatal.**

Rabies - Common facts

- Mad Dog biting Humans lead to Rabies.
- Latin word Rabhas means Frenzy.
- Hydrophobia Fear of Water, Saliva of Rabid dogs

- **Pasture's success – Vaccination**

Fixed virus from Rabbit injected into

Joseph Meister

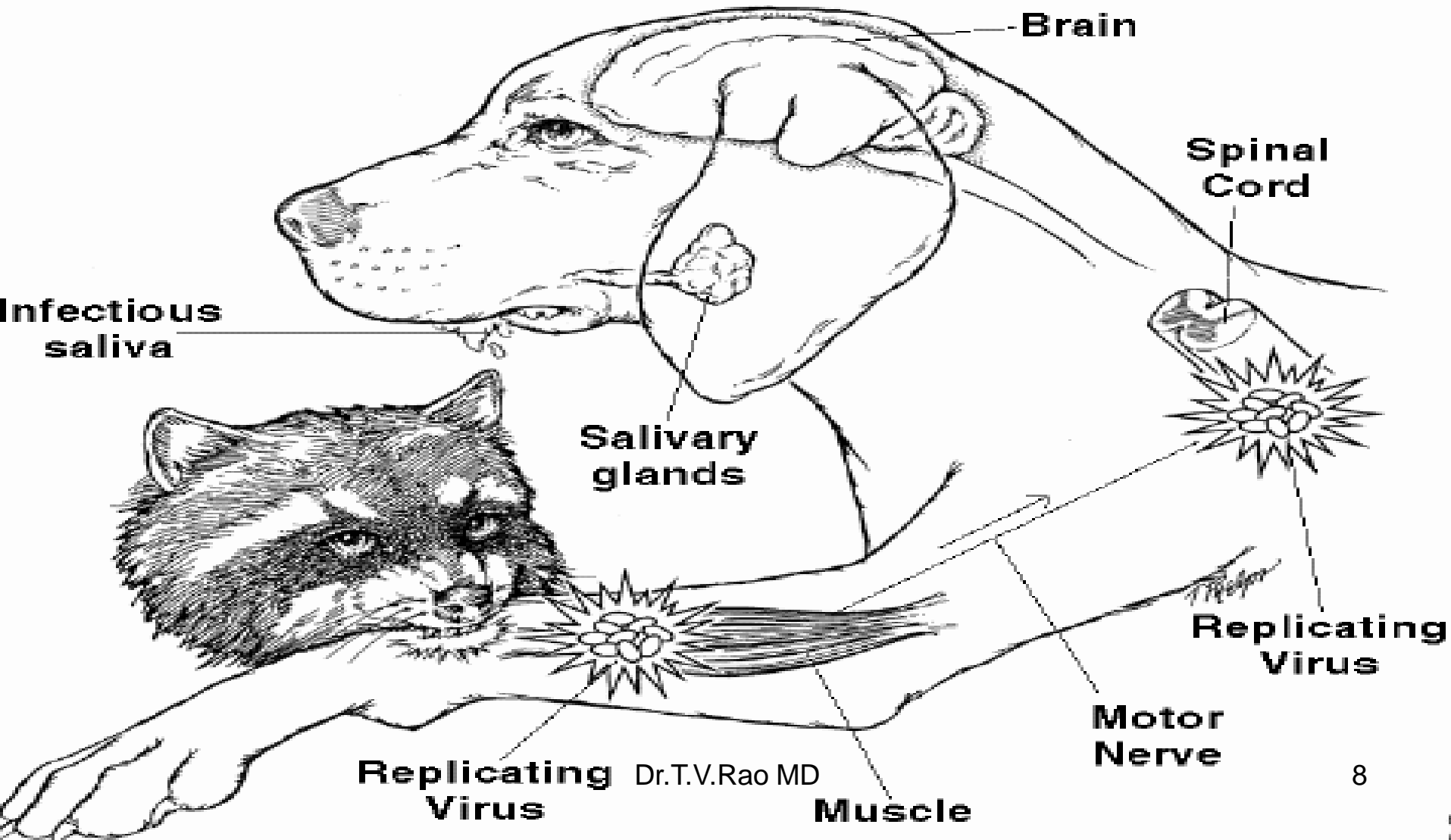
Injected 13 injection of the cord vaccine.

Rabies- A Zoonotic Disease

- Rhabdovirus family; genus Lyssavirus
- Enveloped, bullet-shaped virions
- Slow, progressive zoonotic disease
- Primary reservoirs are wild mammals; it can be spread by both wild and domestic mammals by bites, scratches, and inhalation of droplets.



Rabies – A fatal Zoonotic Disease

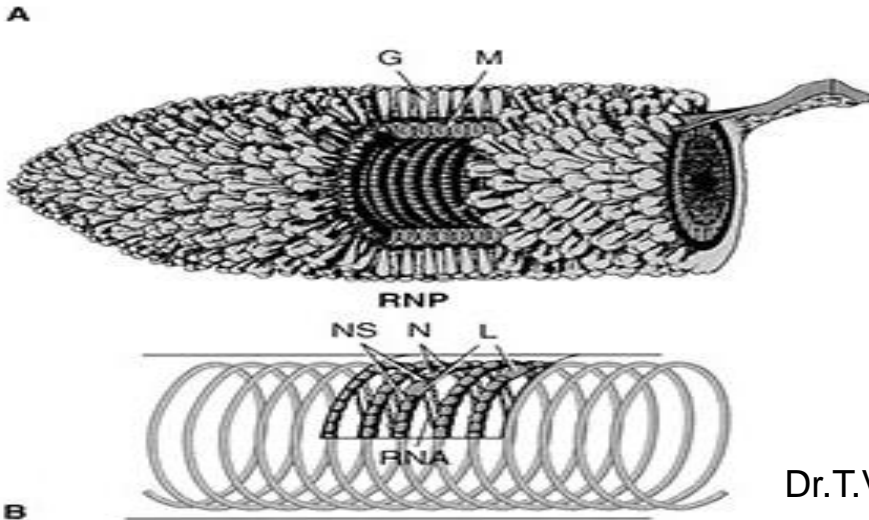
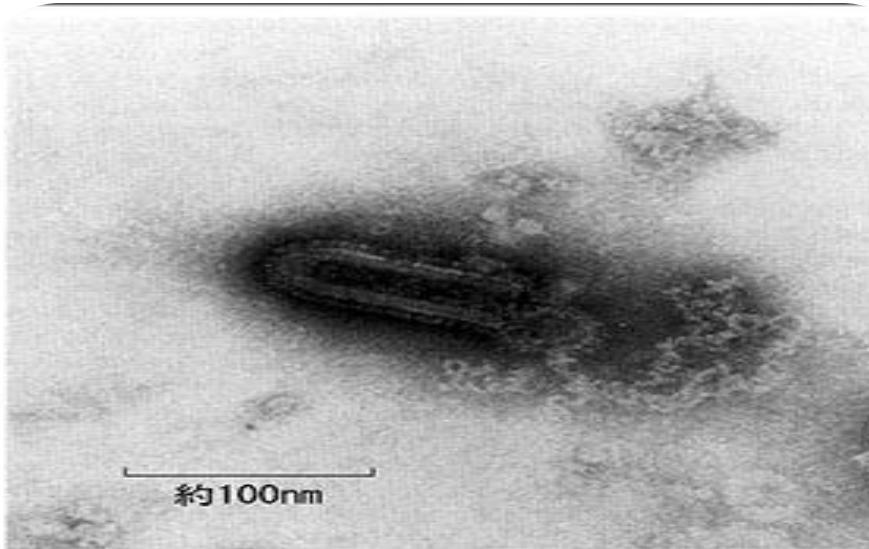


Rabies in USA

- Most of the recent human rabies cases in the United States have been caused by rabies virus from **bats**. Awareness of the facts about bats and rabies can help people protect themselves, their families, and their pets.



Rhabdovirus

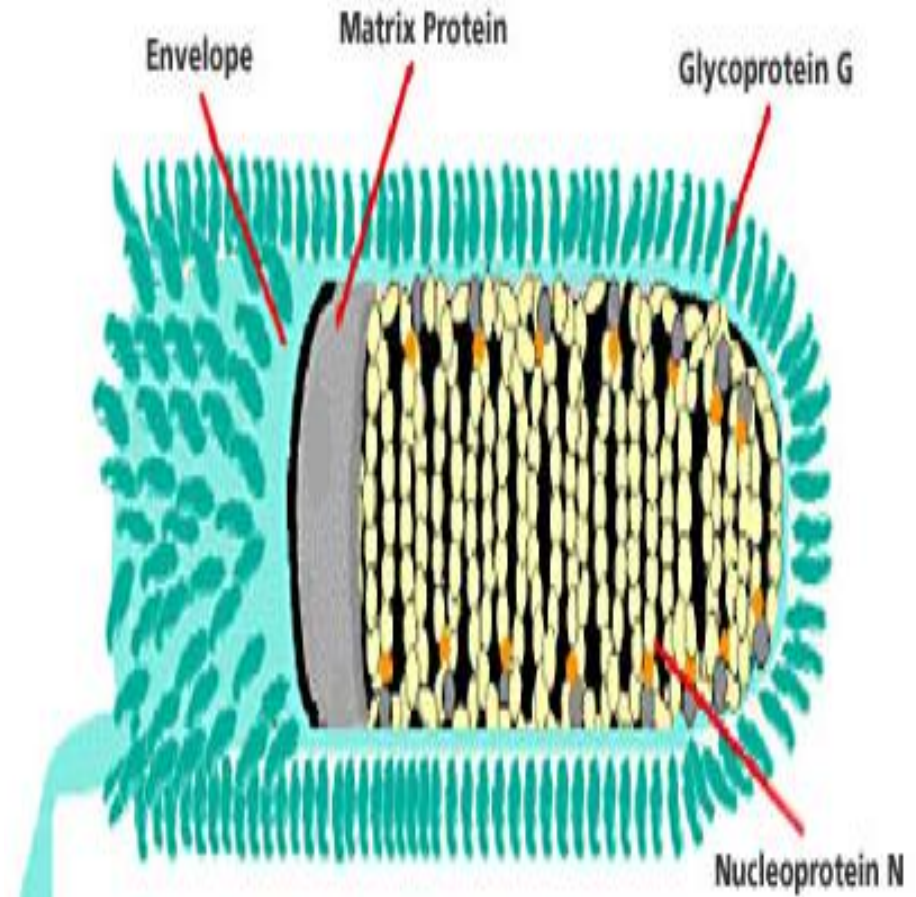


- A Bullet shaped virus/
Enveloped
- Contains **ss RNA**
virus
- Rhabdoviridae –
infects mammals.
- Important virus
Lyssa virus- Rabies
virus

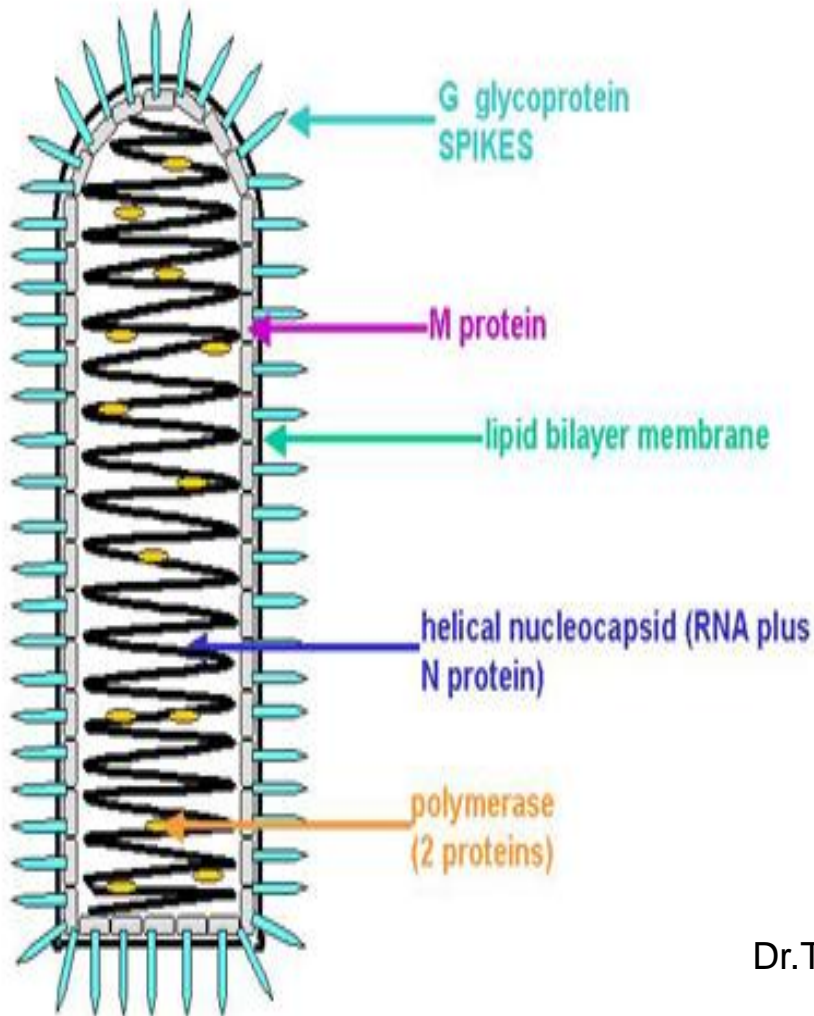
**Lyssa means
Rage.**

Rabies virus

- Bullet shaped virus
- Size is 180 x 75 nm
- Has Lipoprotein envelop
- Knob like spikes /Glycoprotein S
- Genome un segmented
- Linear negative sense RNA

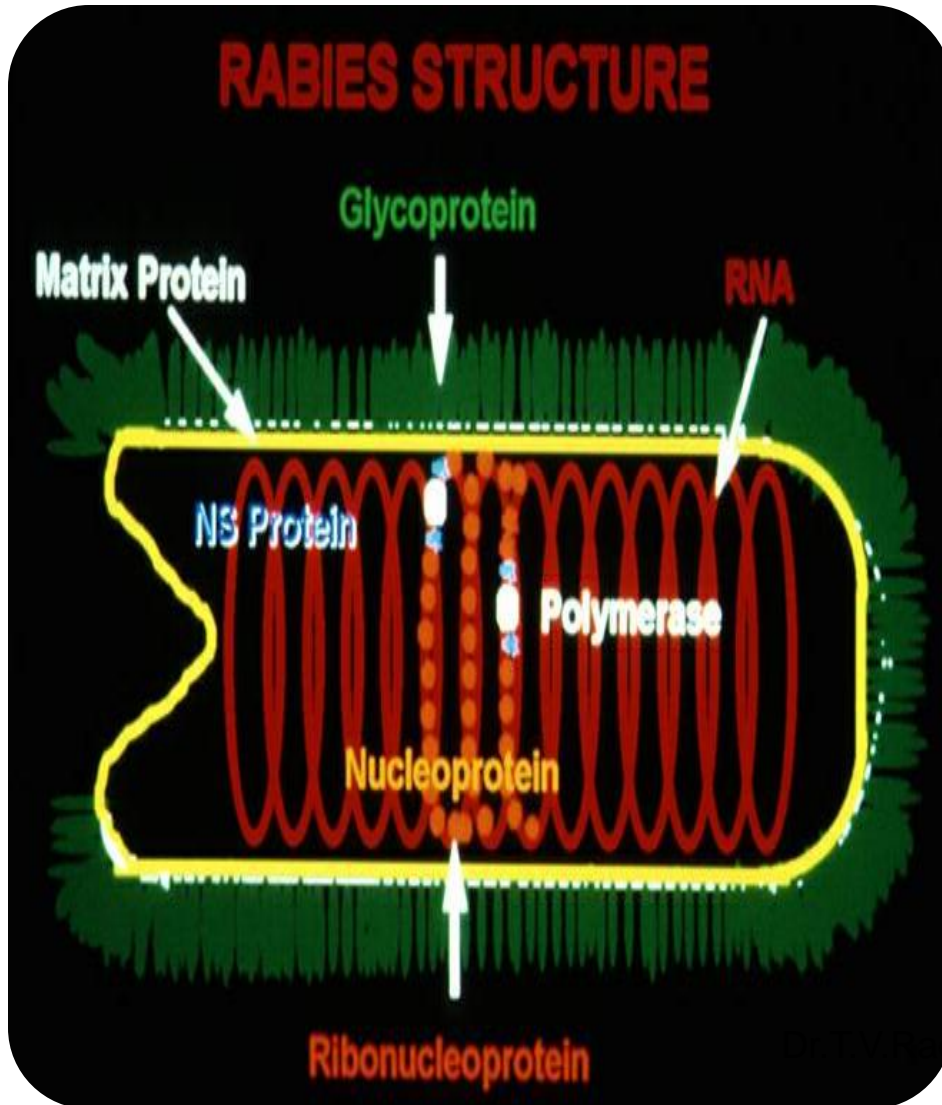


What is a **Fixed Virus**



- One whose virulence and incubation period have been stabilized by serial passage and remained fixed during further transmission.
- Rabies virus that has undergone serial passage through rabbits, thus stabilizing its virulence and incubation period and called as **fixed virus**

What is a Street Virus



Virus from a naturally infected animal, as opposed to a laboratory-adapted strain of the virus.

The virulent rabies virus from a rabid domestic animal that has contracted the disease from a bite or scratch of another animal, and called as **street virus**.

Any mammal can get rabies.



**Raccoons,
skunks, foxes
and bats**

- **Dogs, cats,
cattle and
ferrets**
- **Humans too**

What kind of animals get Rabies?

- The rabies virus can infect all **mammals**.
- **Mammals** are warm-blooded animals that have hair and mammary glands to produce milk for their babies.
- Animals like frogs, birds, and snakes do not get rabies.



**Man's best friend
but can spread Rabies if not vaccinated**



Rabies viruses are sensitive to common Chemicals

- The virus is sensitive to

Ethanol

Iodine

Soap / Detergents

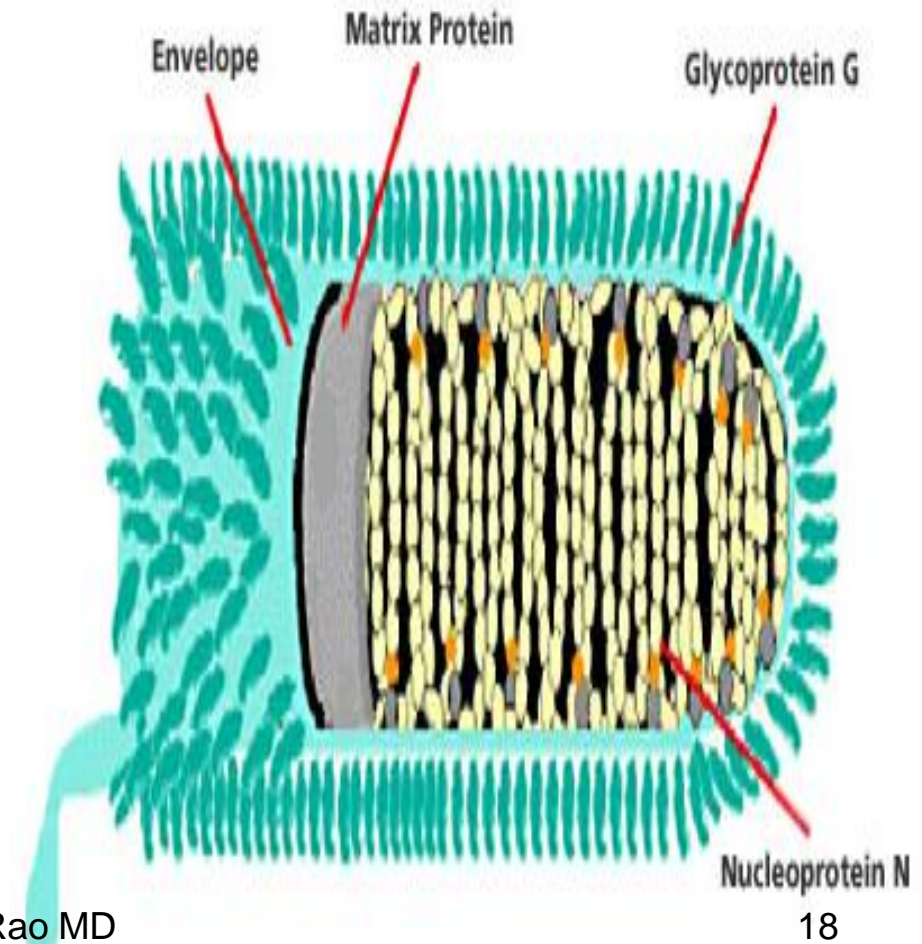
Ether, Chloroform, Acetone

Destroyed at 50⁰ c in 1 hour

at 60⁰ c in 5 minutes.

Antigenic properties

- Surface spikes composed of Glycoprotein G
- Produces Pathogenicity by binding to Acetyl choline receptors in the neural tissue
- Stimulate T lymphocytes
Cytotoxic effect.



Transmission

- Abrasions or scratches on skin.
- Mucous membrane exposed to saliva.
- Most frequently via deep penetrating bite wounds.
- Other routes.

Inhalation in bat infected caves.

Ingestion of dead /infected animal meat

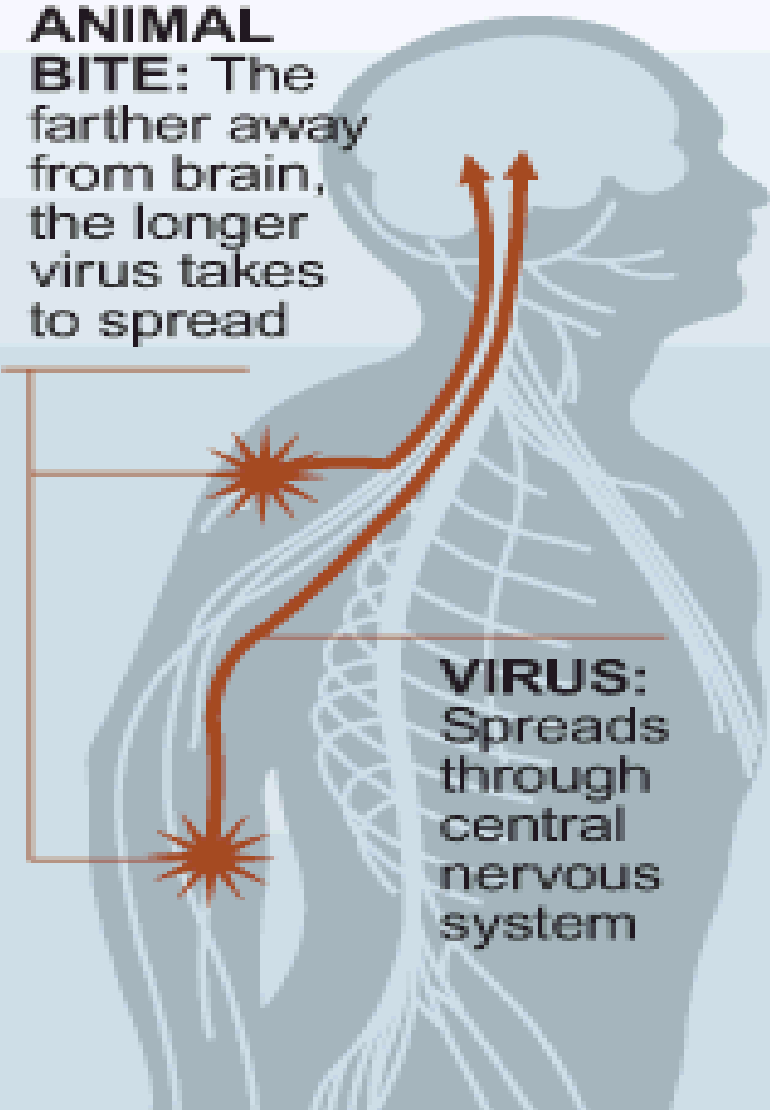
Corneal transplantation

Rabies

How it spreads

ANIMAL

BITE: The farther away from brain, the longer virus takes to spread



VIRUS: Spreads through central nervous system

Common carriers of rabies

Infected animals: Show no fear for humans; act very agitated



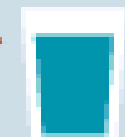
Dog: Another common rabies source

Symptoms in humans

- Fever, depression
- Agitation
- Painful spasms followed by excessive saliva
- Death within a week without vaccine



Treatment: Hospitalization, immune globulin injections, anti-rabies vaccine



Foaming at mouth after drinking: Produced by spasms in throat

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Pathogenesis of Rabies

- Bite by Rabid dog or other animals
- Virus are carried in saliva virus deposited on the wound site.
- If untreated 50% will Develop rabies.
- **Rabies can be produced by licks and corneal transplantation.**
- Virus multiply in the muscle ,connective tissue, nerves after 48 – 72 hours.
- Penetrated nerve endings.

PATHOGENESIS

Live virus → Epidermis, Mucus membrane

↓
Peripheral nerve

↓ *centripetally*

↓
CNS (gray matter)

↓ *centrifugally*

↓
Other tissue (salivary glands,...)

Brain inflammation



**Virus transmitted by
infected saliva
through bite
or wound**



How rabies is spread

Rabies is an infectious disease in mammals that attacks the nervous system, causing encephalitis and even death.



1

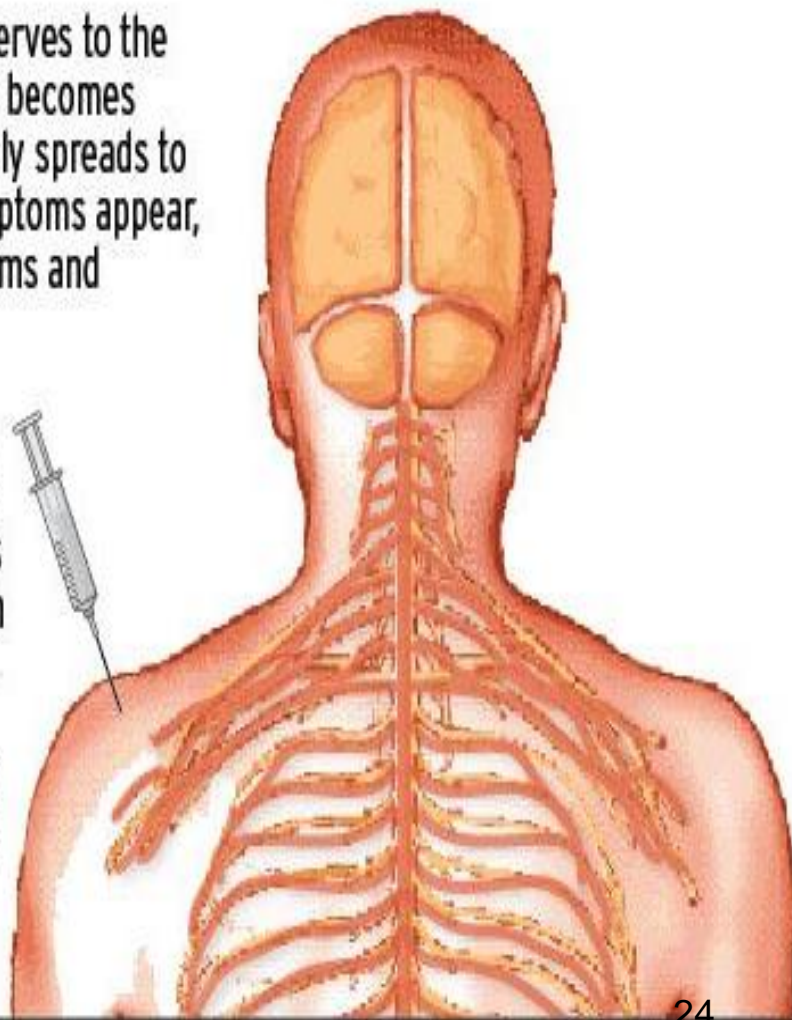
A rabid animal (usually a bat, skunk or fox) bites another animal or a person and transmits the virus through saliva. For four to 12 weeks, the virus incubates in the body, and the bite victim displays no sign of illness.

2

The virus travels from the nerves to the spinal cord and brain, which becomes inflamed. The virus eventually spreads to the salivary glands and symptoms appear, including fever, painful spasms and foaming at the mouth.

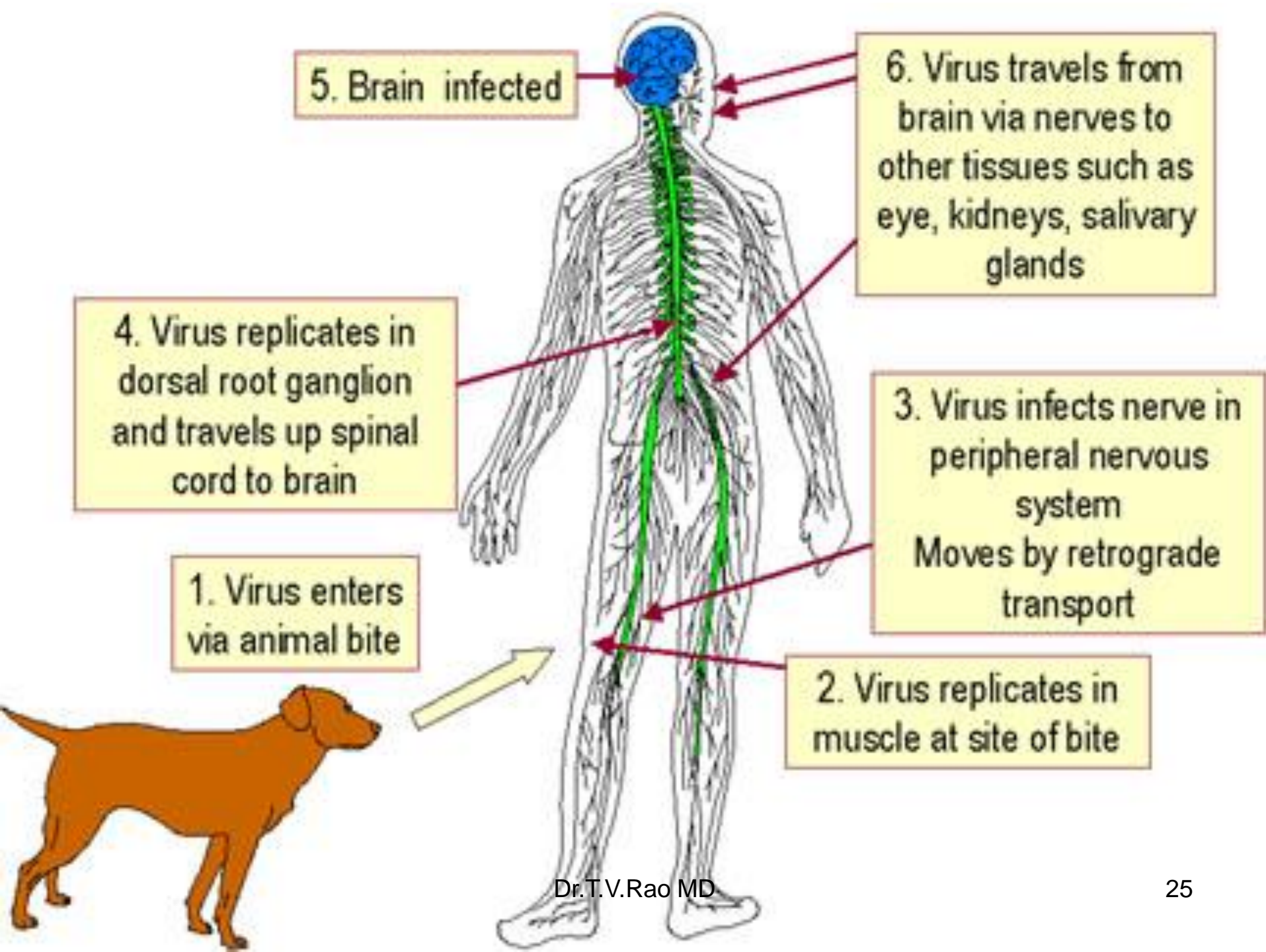
3

Within a week the carrier is contagious and is in danger of dying. Treatment involves one dose of immunoglobulin and five doses of rabies vaccine over a period of about a month. If treatment is started immediately after exposure, the rate of survival is 100 percent.



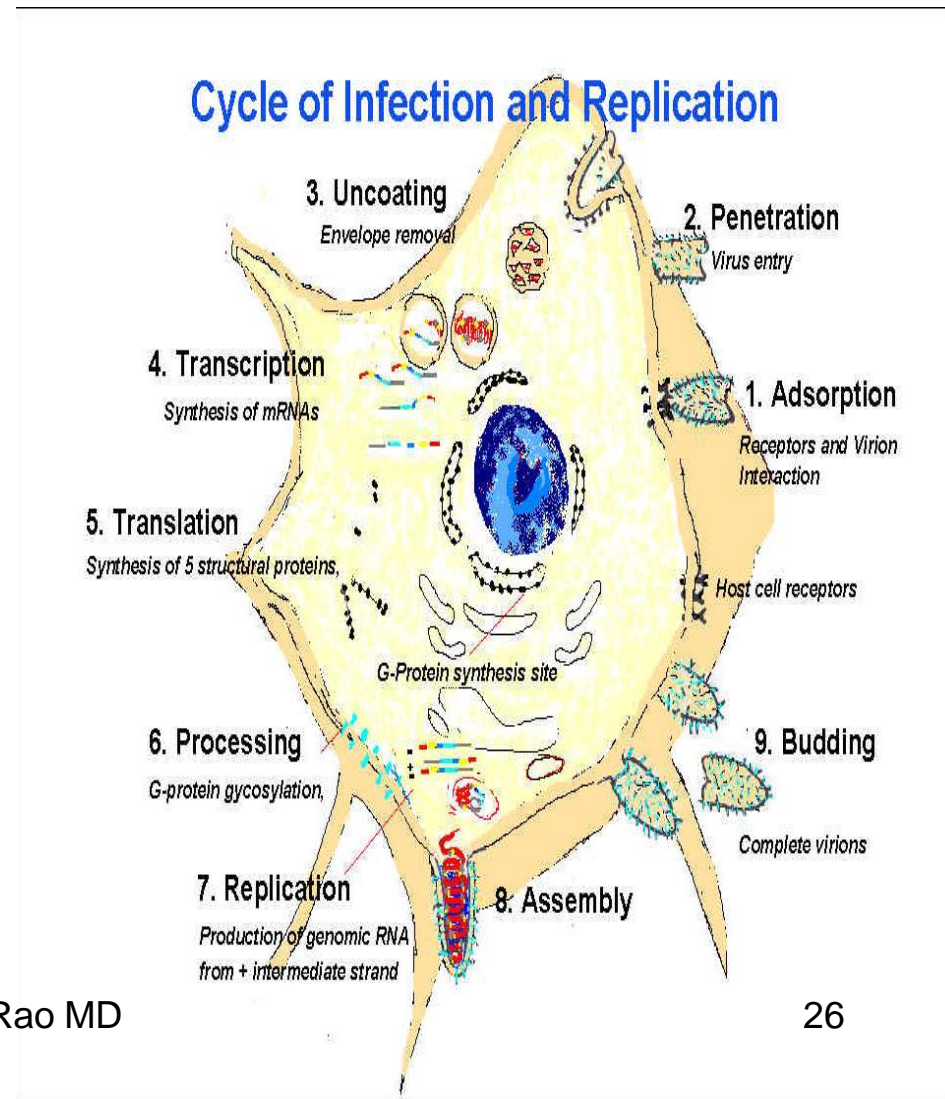
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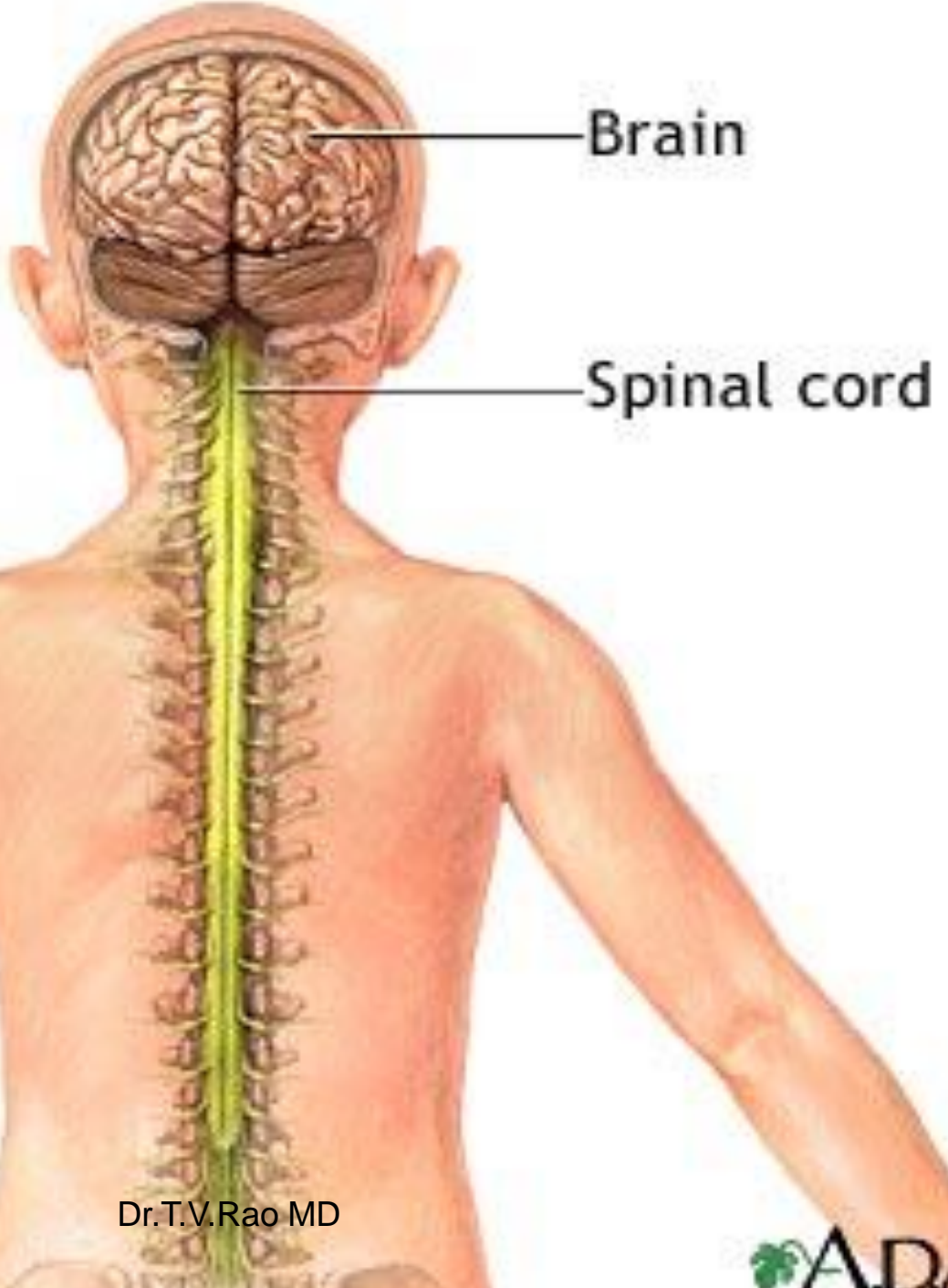


Spread of Virus

- From Brain virus spread to
 - Salivary glands,
 - Conjunctival cell released into tears
 - Kidney
 - Lactating glands and Milk after pregnancy



Rabies virus may infect the central nervous system



Pathogenesis

- Virus travels through axoplasam toward the spinal cord, at the rate of 3 mm/hour,
- Towards the brain
- Spread from brain centrifugally to various parts of the body.
- Multiplies in the salivary glands and shed in the saliva.
- Cornea, facial tissues skin.

Pathogenesis

- Incubation 1 – 3 months.
- **May be average from 7 days to 3 years.**
- Stages of the disease.
 - Prodrome
 - Acute encephalitis.
 - Coma / Death.

Broad category - Presentations



- ***Furious Rabies***
- ***Dumb (Rage tranquille)***
- ***(Landry/Guillain -Barre Syndrome***

Category - WHO

- **Category I:** touching or feeding suspect animals, but skin is intact
- **Category II:** minor scratches without bleeding from contact, or licks on broken skin
- **Category III:** one or more bites, scratches, licks on broken skin, or other contact that breaks the skin; or exposure to bats

Clinical Findings

- Bizarre behavior.
- Agitation
- Seizures.
- Difficulty in drinking.
- **Patients will be able to eat solids**
- **Afraid of water - Hydrophobia.**
- **Even sight or sound of water disturbs the patient.**
- But suffer with intense thirst.
- Spasms of Pharynx produces choking
- **Death in 1 -6 days.**
- Respiratory arrest / Death / ***Some may survive.***

Symptoms

- Headache, fever, sore throat
- Nervousness, confusion
- Pain or tingling at the site of the bite
- **Hallucinations**
 - Seeing things that are not really there
- **Hydrophobia**
 - “Fear of water” due to spasms in the throat
- **Paralysis**
 - Unable to move parts of the body
- Coma and death

CLINICAL MANIFESTATIONS

1 – Non specific prodrome

2 – Acute neurologic encephalitis

Acute encephalitis

Profound dysfunction of brainstem

3 – Coma

4 - Death (Rare cases → recovery)

CLINICAL MANIFESTATIONS

Non specific prodrome

1 - 2 days → 1 week

- ❖ Fever, headache, sore throat
- ❖ Anorexia, nausea, vomiting,
- ❖ Agitation, depression
- ❖ Paresthesia or fasciculation's at or Around the site of inoculation of virus.

Acute Neurologic Encephalitis

- **1– 2 days to < 1 week**
- **Excessive motor activity, Excitation, Agitation**
- **Confusion, Hallucinations, Delirium,**
- **Bizarre aberrations of thought, Seizures,**

- **Muscle spasms, Meningismus,**
- **Opisthotonic posturing**
- **Mental aberration (Lucid period → coma)**
- **Hypersalivation, Aphasia, Pharyngeal spasms**
- **Incoordination, Hyperactivity**

Acute Neurologic Encephalitis

Phase - Presentations

- ***Fever $T > 40.6$***
- ***Dilated irregular pupils***
- ***Lacrimation, Salivation & Perspiration***
- ***Upper motor neuron paralysis***
- ***Deep tendon reflexes***
- ***Extensor plantar responses (as a rule)***
- ***Hydrophobia or Aerophobia (50 -70%)***

Rabies can present as Grave condition



Majority will succumb to Disease



Clinical presentation –clues in Diagnosis Leads

- In most cases, human rabies is diagnosed primarily on the basis of clinical symptoms and signs, and a corroborative history of or evidence of an animal bite, death of an animal, and incomplete or no vaccination following exposure. The facility for laboratory diagnosis and confirmation of rabies, be it in humans or in animals, is available premortem in only a few institutions in India can diagnose.

Laboratory Diagnosis

- *Survival possible? May need Laboratory Diagnosis*
- Clinical differentiation other cases of Encephalitis.
- Post mortem Diagnosis by
 - By demonstration of Negri bodies.
 - Isolation of virus from Mice brain inoculation.
 - tissue culture on culture lines
 - W 138, BHK,**
 - PCR emerging method.
 - IF methods corneal impression method.

Common confirmatory test - Rabies

1. The standard premortem test is a **fluorescent antibody** test to demonstrate the presence of viral antigen. The standard post-mortem test is biopsy of the patient's brain and examination for Negri bodies.

Autopsies are rarely performed.

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DIAGNOSIS

- **Laboratory finding: (CBC, CSF)**
- **Exclusion of other etiologies**

• *Pathology:*

Formation of cytoplasmic inclusions:

(Negri bodies)

(Ammon's horn, Cerebral cortex,

Brainstem, Hypothalamus,

The Purkinje cells of cerebellum,

Dorsal spinal ganglia)

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Diagnostic methods

- Antigen detection by specific Immuno fluorescence.

Ante-mortem - Conjunctival, skin biopsy from nape of neck.

Postmortem impression from surfaces of salivary glands Hippocampus,

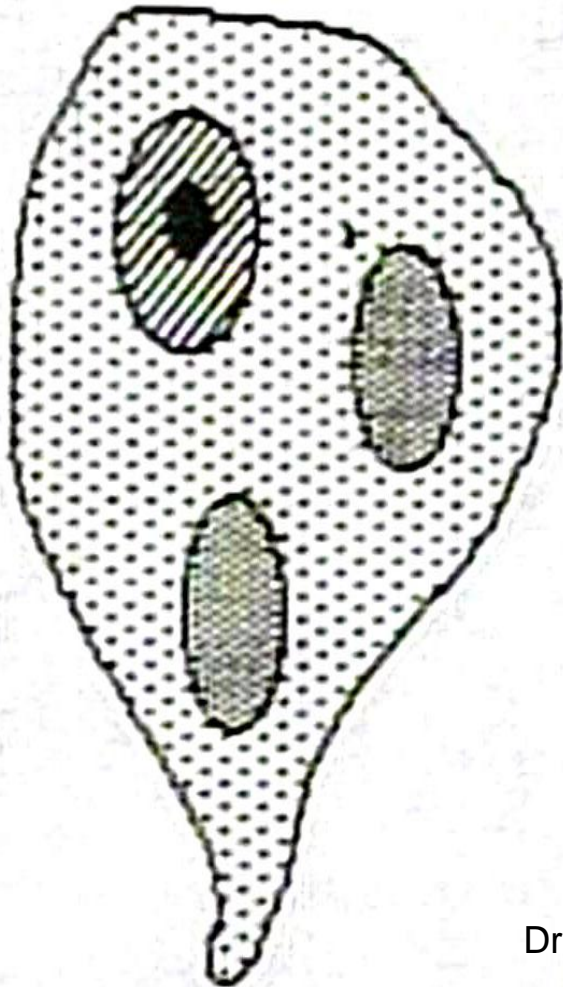
Histological examination

ELISA specific antibody detection.

PCR

Negri bodies – A gold standard in Diagnosis

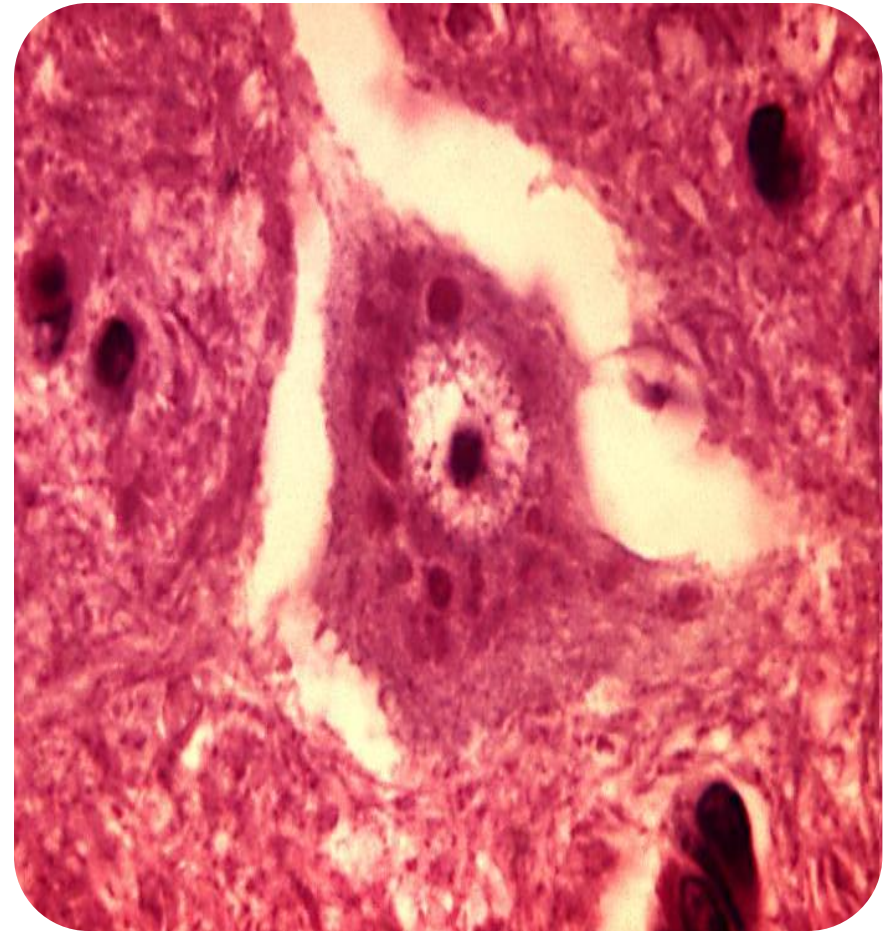
Negri Bodies



- Inclusion bodies called Negri bodies are 100% diagnostic for rabies infection, but found only in 20% of cases

Negri bodies in Brain Tissue

- **Negri bodies** round or oval inclusion bodies seen in the cytoplasm and sometimes in the processes of neurons of rabid animals after death.
- Negri bodies are Eosinophilic, sharply outlined, pathognomonic inclusion bodies (2-10 μm in diameter) found in the cytoplasm of certain nerve ..



Emerging Methods in Diagnosis

- The reference method for diagnosing rabies is by performing PCR or viral culture on brain samples taken after death. The diagnosis can also be reliably made from skin samples taken before death. It is also possible to make the diagnosis from saliva, urine and cerebrospinal fluid samples, but this is not as sensitive.
Inclusion bodies called Negri bodies are 100% diagnostic for rabies infection, but found only in 20% of cases.

DIFFERENTIAL DIAGNOSIS

- **Other viral encephalitis**
- **Hysteria reaction to animal bite**
- **Landry/Guillan-barre syndrome**
- **Poliomyelitis**
- **Allergic encephalomyelitis (rabies vaccine)**

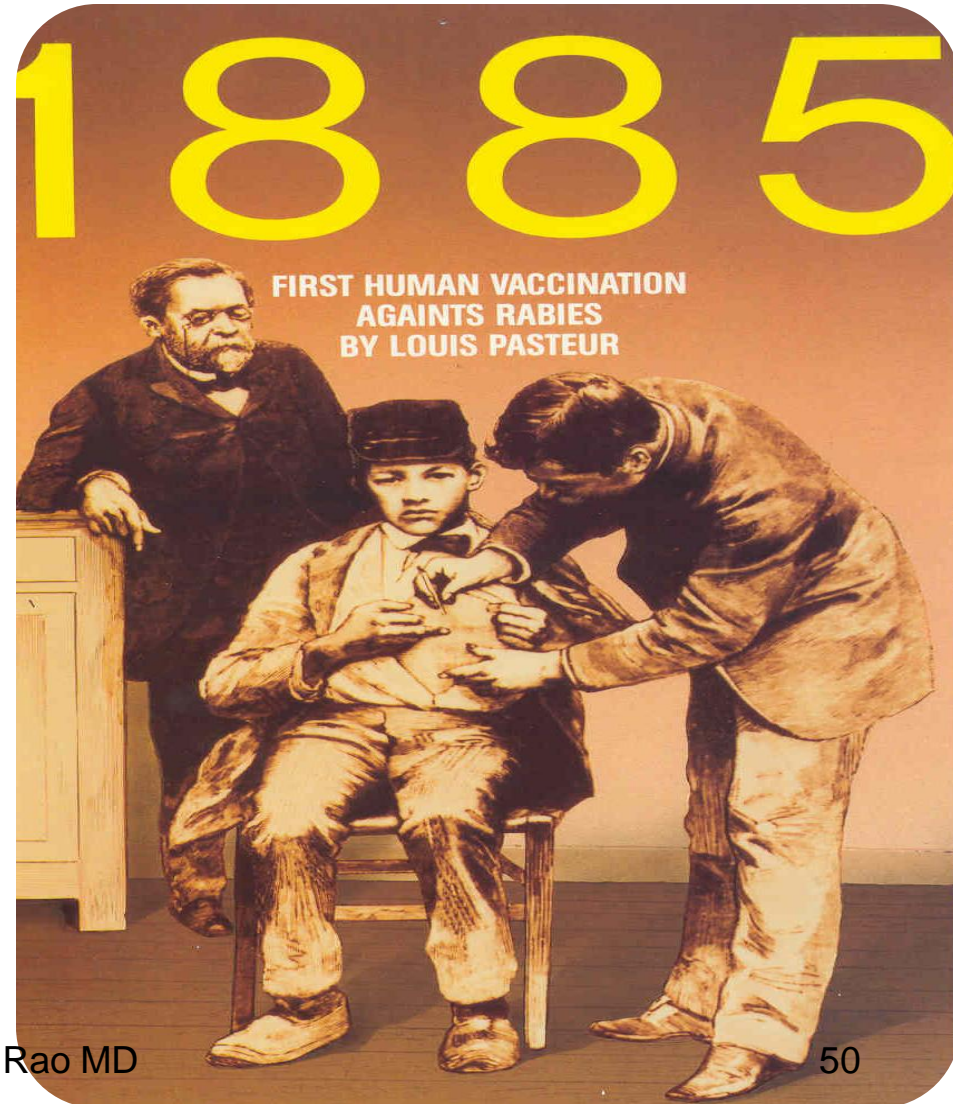
PREVENTION

❖ **Preexposure Prophylaxis**

❖ **Post exposure Prophylaxis**

Ist Vaccine for Rabies

- Prepared by Pasteur by drying various periods pieces of spinal cord of Rabbits infected with fixed virus
- 1885 *Joseph Meister* 9 year boy vaccinated 13 injections were given
- Patient saved



Preexposure vaccination



- Indicated in
Laboratory
workers
Veterinarians
and technical
staff.

Bat handlers.

Supporting care in Animal/Dog Bites

Basic care in Animal bites

- Before exposure to infection
 - In Veterinary surgeons animal handlers.
- Specific Prophylaxis
 - After exposure to Dog bite.
- Local treatment
 - Cauterization**
 - Scrub with Soap and clean.
 - Use cetavalon, tincture of Iodine
 - Antirabic serum **don't suture** wound unless highly essential.

If you are bitten or scratched



- Tell an health care worker immediately
- Wash the wound out with soap and water
- Inform the doctor right away

POSTEXPOSURE PROPHYLAXIS

1 – Wound cleaning & treatment





Initial treatment for an animal bite should include thorough cleansing however all animal bites should be seen by a physician

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Apply pressure if
bite is actively
bleeding



Post exposure vaccination

- Anti Rabies vaccines are given when person is
 - 1 Bitten
 - 2 Scratched
 - 3 Licked

By Rabid animal

animal to be kept for 10 days ?

Category - WHO

- Category I: touching or feeding suspect animals, but skin is intact
- Category II: minor scratches without bleeding from contact, or licks on broken skin
- Category III: one or more bites, scratches, licks on broken skin, or other contact that breaks the skin; or exposure to bats

Vaccines

- **Semple vaccine**

Contain 5 % suspension. Of infected Sheep brain, (Infected with fixed virus)

Inactivated with Phenol at 37⁰c

Vaccines available after inactivation with Beta propiolactone Used in India

Vaccine contains Nucleic capsid antigen, Small quantities of Glycoprotein G Used in Developed countries Neural complications.

*Dose Simple Vaccine

Simple vaccine

BPL vaccine

Class I	2ml x 7 days	2mlx7 days
Class II	5ml x 14 days	5mlx10days
Class III	10ml x 14 days	5 ml x 10 days

* Many health institutes abandoned its use

Neural Vaccines*

- Class I slight risk
- Class II Moderate risk
- Class III Great risk
- Neural vaccines may cause Neuroparalytic complications, Laundry's type ascending paralysis
- **Dose is regulated according to grade/class of bites**
- **Many countries do not use in view of neurological complications**

HUMAN RABIES Cell culture

❖ Vaccine: Vaccines

Human diploid cell vaccine (HDCV)

Developed by Koprowsky, Wiktor, and Plotkin

Purified chick embryo cell vaccine (PCEC)

Purified Vero cell vaccine (PVRV)

Purified duck embryo vaccine (PDE)

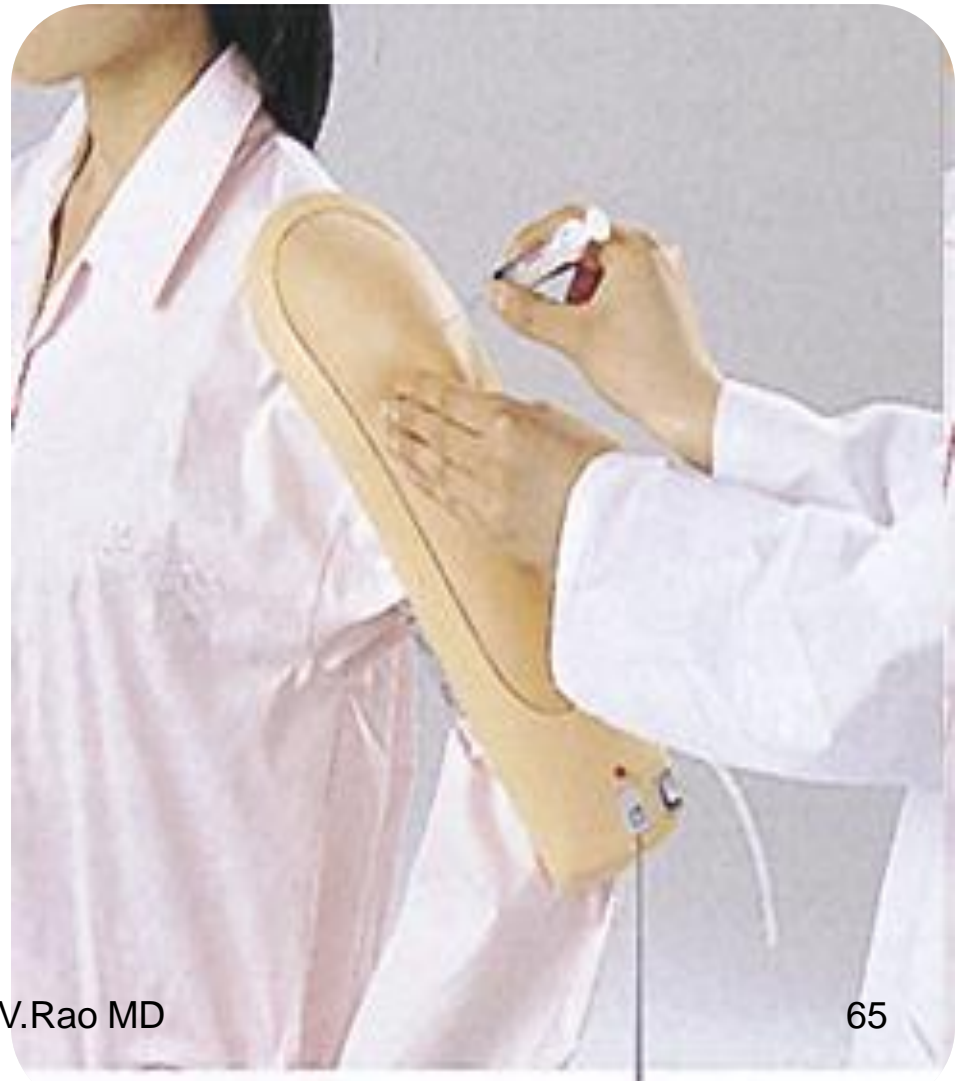


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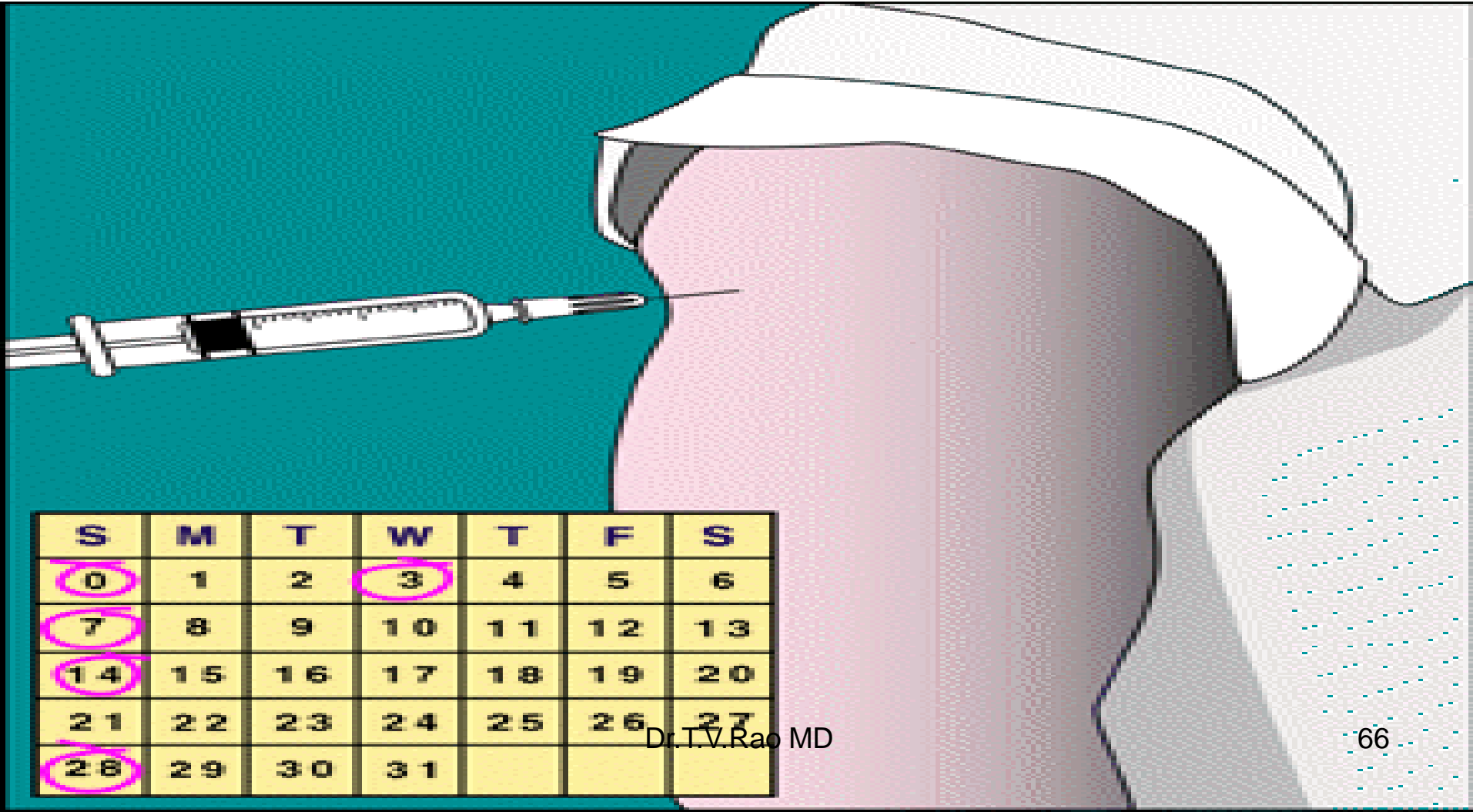
Post exposure Prophylaxis

- The vaccination is given on
0, 3, 7, 14, 30, and 90th day
Immunity lasts for 5 years
Injected on deltoid region IM/SC
Not to be given in the gluteal region



POSTEXPOSURE PROPHYLAXIS

3 – Active immunization



S	M	T	W	T	F	S
0	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

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Cell culture Vaccines

Commonly prescribed



- 1 Human diploid cell vaccine.**
- 2 Purified chick embryo cell vaccine**
- 3. Purified Vero cell vaccine**

Human Diploid Cell Vaccine

- Koprowsky, Viktor, Plokin discovered
- Inactivated in Betapropionate.
- No serious side effects.
- Human Diploid cell vaccines purified .
- Sub Unit vaccines in progress/developed.



Human Diploid Cell Vaccines

- **Dosage**

- **Preexposure prophylaxis**

0 – 7 – 21 – or 28 – 56 days

A booster after 1 year,

Repeat once in 5 days,

Post exposure Prophylaxis

Six doses

0 -3 -7-14 – 30 - 90 days

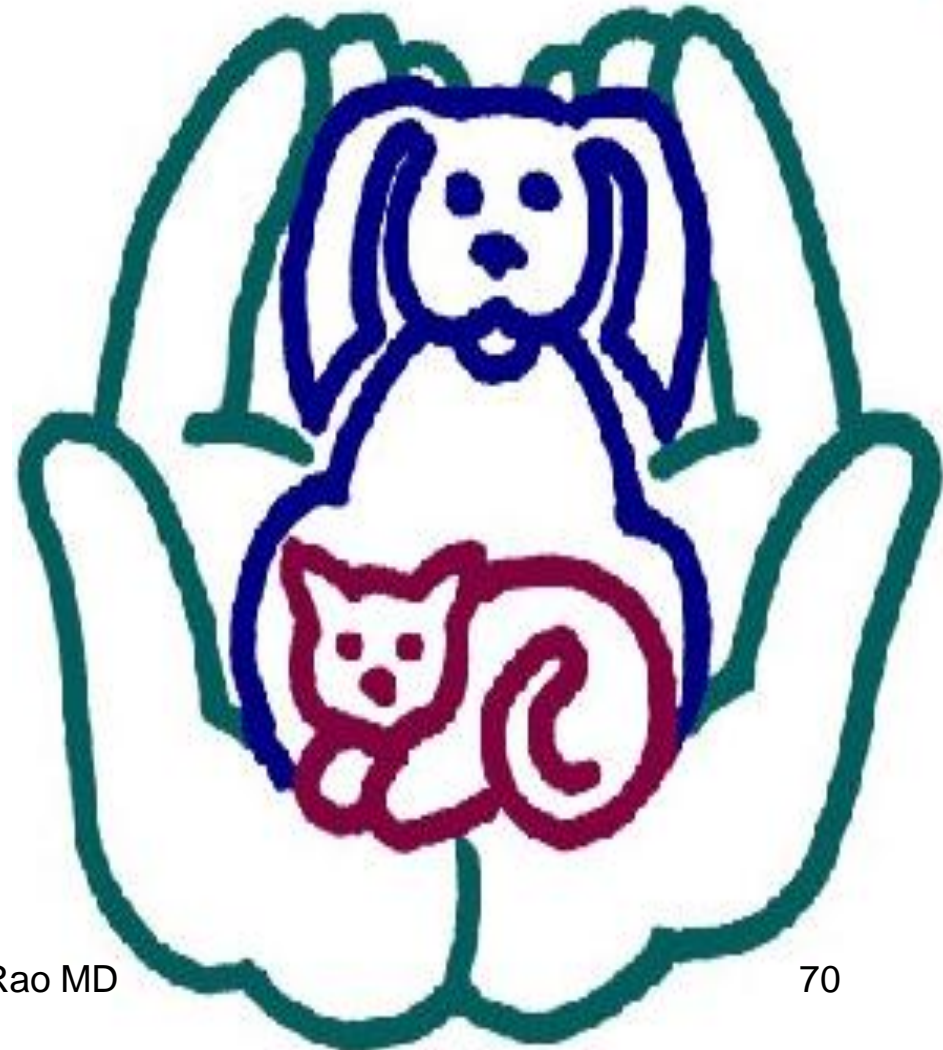
Given IM or SC in the Deltoid region

Don't inject in Gluteal region.

Preexposure prophylaxis doses

- Given on the following days
0, 7, 21, or 28
and 56th day

**Generally given
to Veterinary
personal**



Passive Immunization



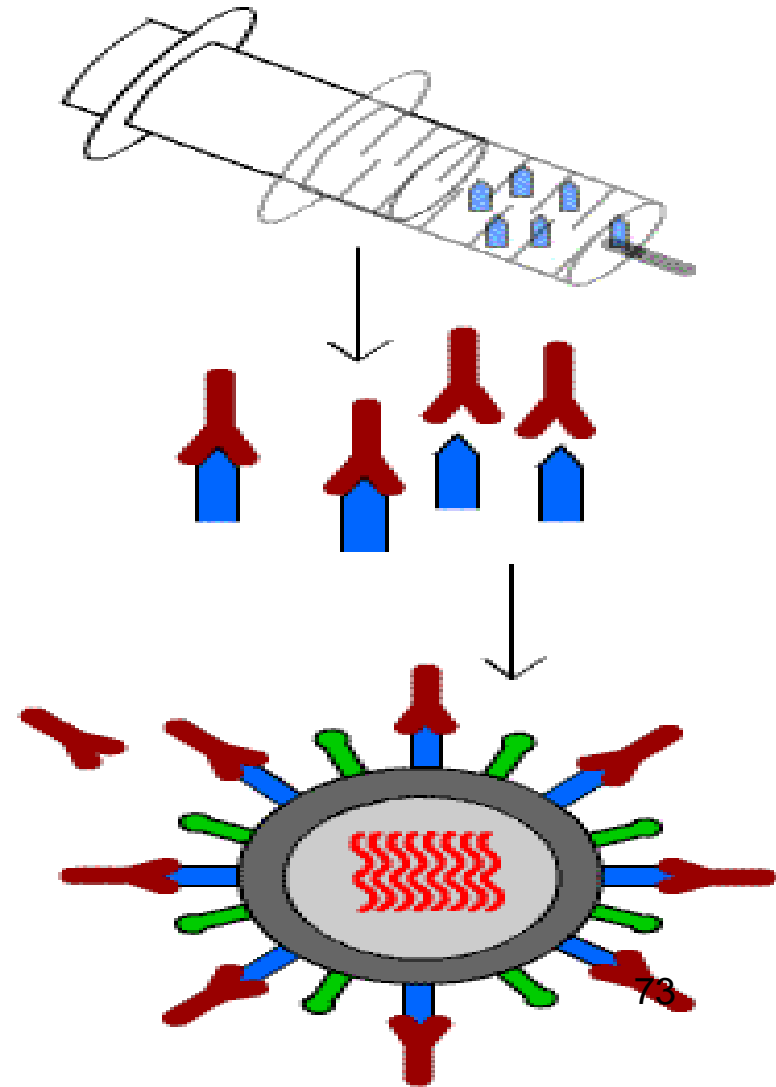
- Human Rabies Immunoglobulin HRIG
- High Risk bitten on face and neck
- Given a dose of 20 IU /Kg wt.
- Half at the site of bite and rest IM route.
- **Active immunization should be initiated** with passive immunization.

Future of Rabies Vaccines

- A number of experimental vaccines are under development that may provide alternative safe and potent but less expensive vaccine options. These include **DNA vaccines**, recombinant viral vaccines, and recombinant protein vaccines. Further testing is needed to determine if and which one of these novel vaccines will make their way into mass production and application in the future.

Subunit or Genetically Engineered vaccines for Rabies

- A viral immunizing agent that has been treated to remove traces of viral nucleic acid so that only protein subunits remain. The subunits have less risk of causing adverse reactions.
- **Several trails in progress**



Epidemiology

- **No Danger of Nursing Rabies patients but do take precautions**
- Any animal bite can cause Rabies except Mice
- BATS in caves in spread he disease by respiratory disease.
- India around 30,000 die with Rabies.
- **Vaccination of the Dogs and Licensing of the Dogs**

In spite of Health Education several die due to Rabies infection in Developing world



World's Rabies Day (on September 28)

- World Rabies Day is a cooperative global event planned to reduce the suffering from rabies. This day celebrates Dr. Louis Pasteur's vision of a ***rabies free world.***



Never touch an unfamiliar or wild animal.

Always ask permission to touch someone else's pet.



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