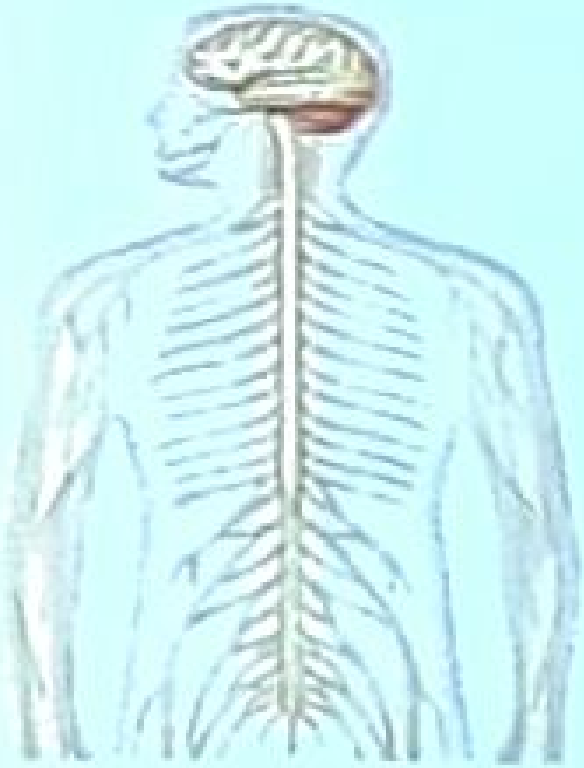
Nervous System

- CNS (Brain and Spinal Cord)
- PNS (Peripheral Nervous System) are nerves that go out to targets in body



Human Anatomy Larry M. Frolich, Ph.D.

- One must distinguish between neurovirulence that is ability to cause neurologic disease and neuroinvasiveness, that is ability to enter the nervous system:-
- **Mumps Virus:-** Displays high neuoinvasiveness (>50% of infections in CSF) but low neurovirulence, it rarely causes much damage.

In contrast HHV-1 and HHV-2.

- Thus neurotropism, the ability to infect neural cells is the product of neuroinvasiveness and neurovirulence.

- Destruction of neurons has the most serious consequences, neurons are not replaced?.
- The many and varied neurologic syndromes caused by viruses include:-
    - Meningitis
    - Encephalitis
    - Paralytic poliomylelitis
    - Myelitis
    - Polyneuritis

Meningitis

- Enteroviruses
- Herpes simplex viruses
- Mumps

The patient presents with headache, fever, neck stiffness vomiting and/or photophobia

LP – Reveals:-

- Clear CSF with slight elevation in pressure
- With normal protein
- With normal glucose

- Predominant of lymphocytes
- Aseptic meningitis

Paralysis

- Polioviruses
- Enteroviruses 70, 71, cosxsackie A7.

Encephalitis:

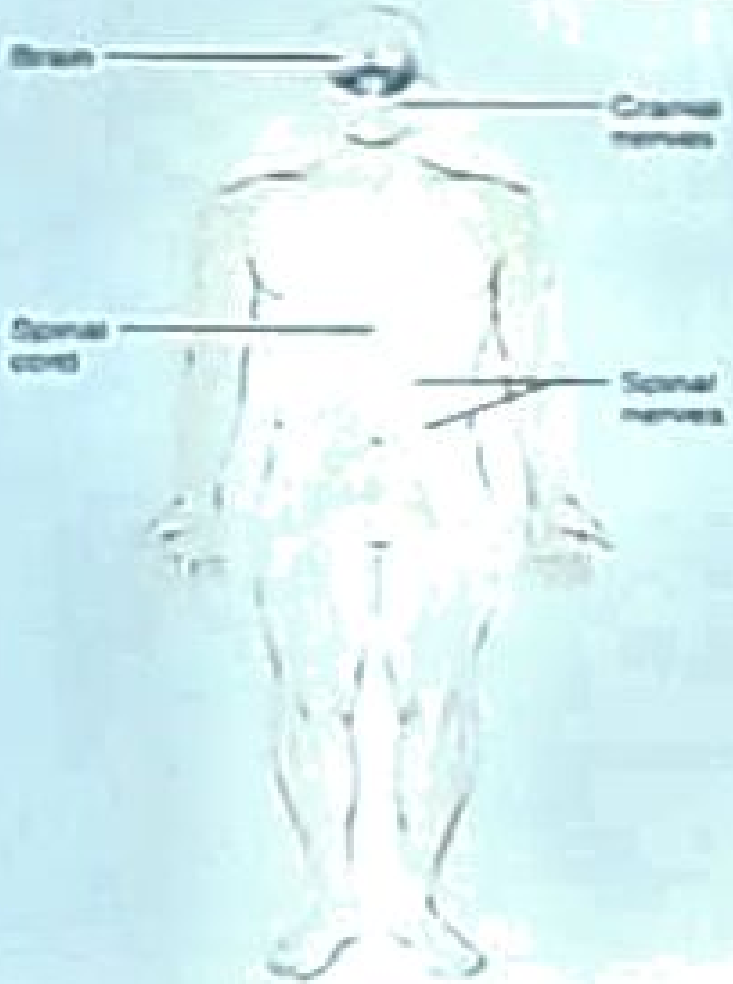
Is one of the most serious of all viral diseases. The illness often begins like meningitis but alteration in the state of consciousness indicates that the brain parenchyma is involved. Viral encephalitis can be brought about by a variety of viruses.

- Herpes simplex
- Mumps
- Arboviruses (togaviruses; flaviviruses, bunyaviruses)

Post infection complication

SSPE, Reyes syndrome, guillain-barre' syndrome e.t.c..

Nervous System



- CNS: brain and spinal cord
- PNS: peripheral nerves

  Cells are called neurons
- No normal flora

The Meninges and Cerebrospinal Fluid

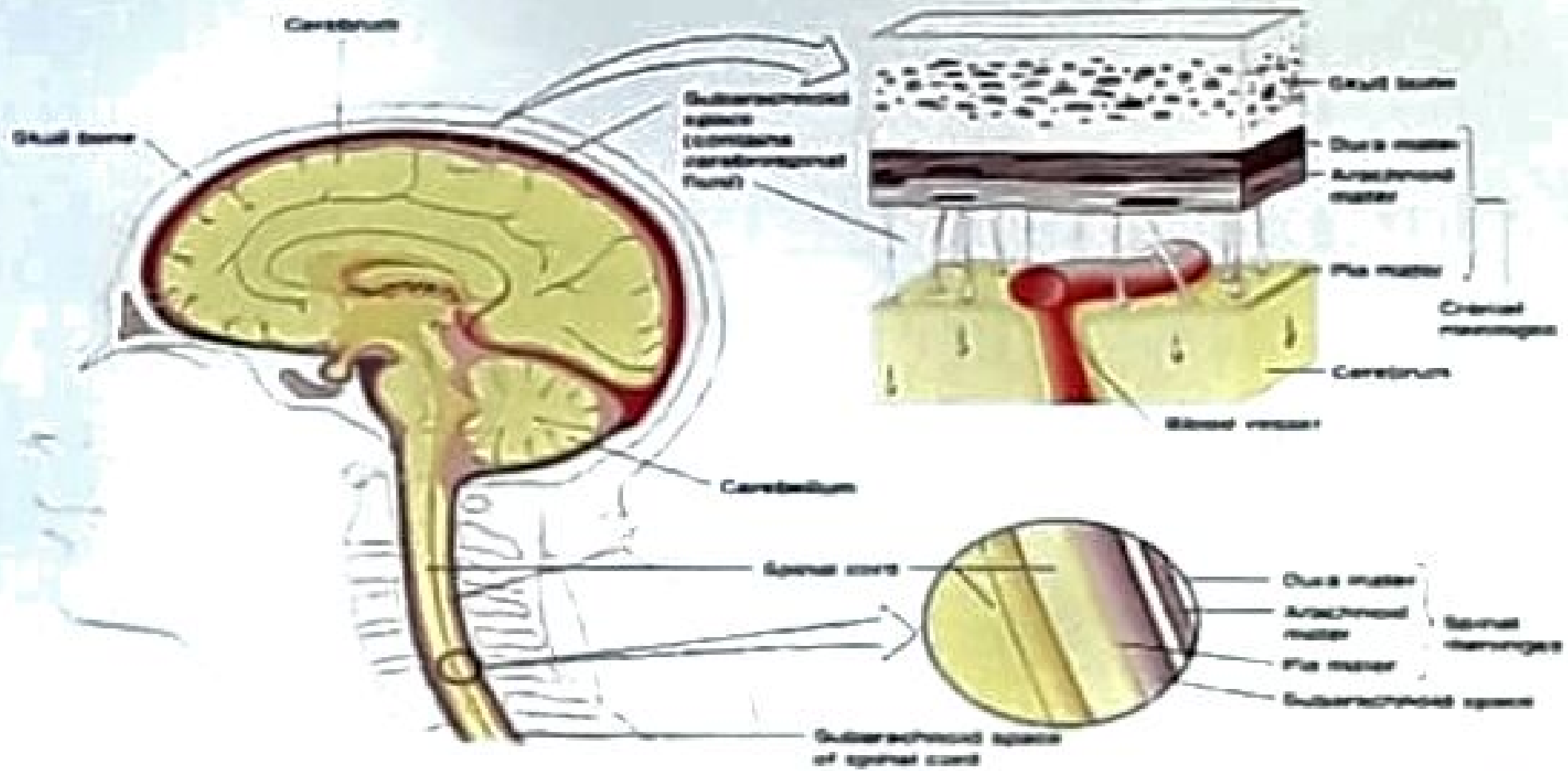


Figure 12.2

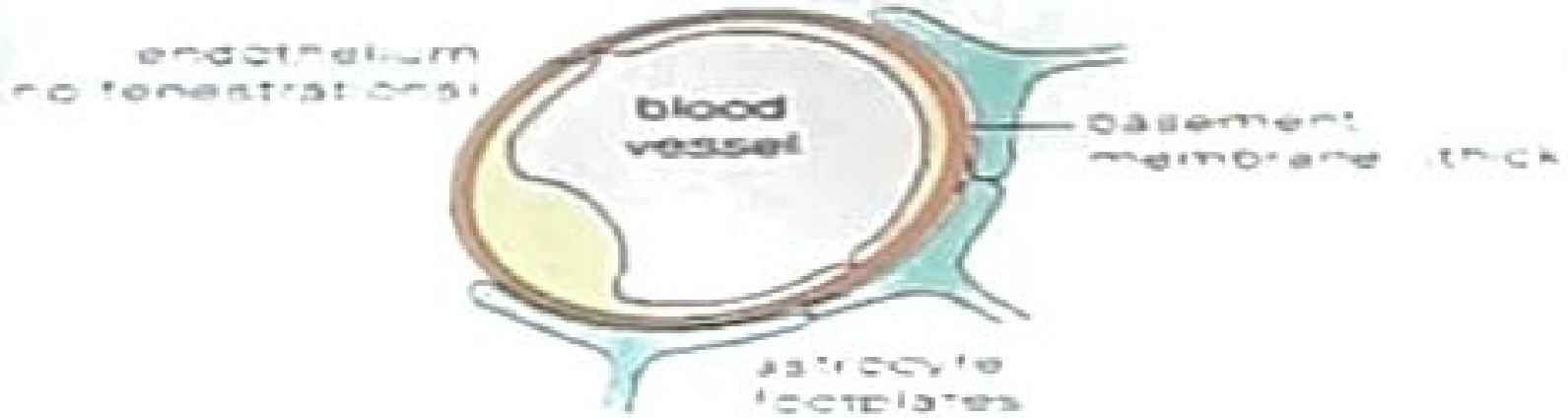
Pathogenesis

Blood-borne invasion takes place across:

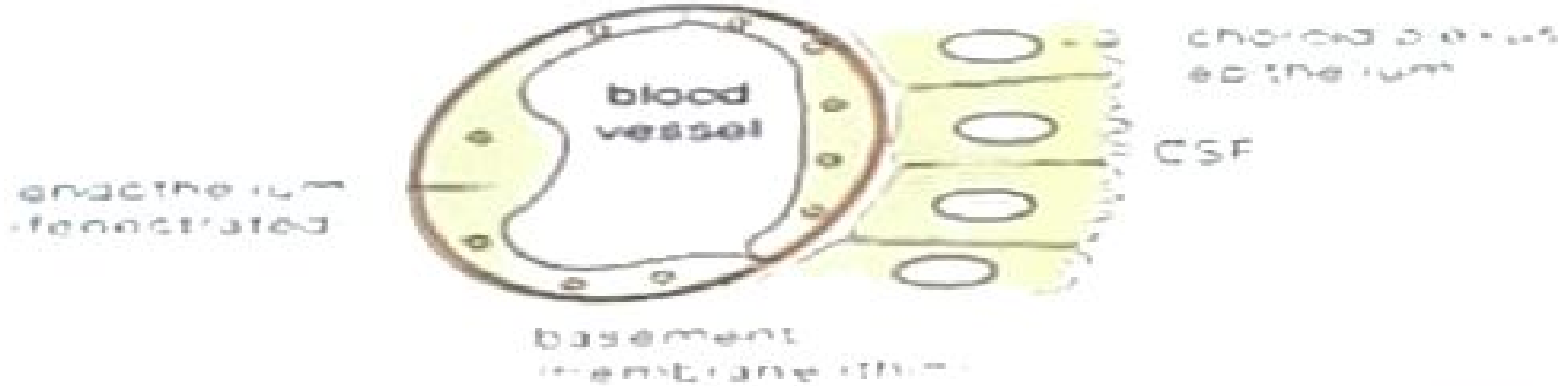
- blood-brain barrier (encephalitis)
- blood-cerebrospinal fluid (CSF) barrier (meningitis).

* Microbes can traverse these barriers by:
  - Infecting the cells that comprise barrier.

blood–brain barrier



blood–CSF barrier



Pathogensis

* Central nervous system infections are usually:

1- Blood-borne invasion; most common
(e.g. polioviruses or *Neisseria meningitidis)*

2- Invasion via peripheral nerves; less common
(e.g. herpes simplex, varicella-zoster, rabies)

Pathogenesis

Invasion via peripheral nerves:

* Herpes simplex virus (HSV) and varicella-zoster virus (VZV) present in skin or mucosal lesions travel up axons to reach the dorsal root ganglia.

* Rabies virus, introduced into muscle tissues by:
  - bite of a rabid animal.

  - It enters peripheral nerves and travels to CNS, to reach the neurons.

CNS virus pathogenesis

Exposure

↓

Dissemination

↓

CNS Entry

↓

Inflammation

↓

Clinical Disease

CNS virus pathogenesis

Exposure

Pathogenic event
Epithelial layer disruption
Local replication

↓

Dissemination

Viremia
Secondary amplification

↓

CNS Entry

Blood-brain barrier disruption
Axonal transport

↓

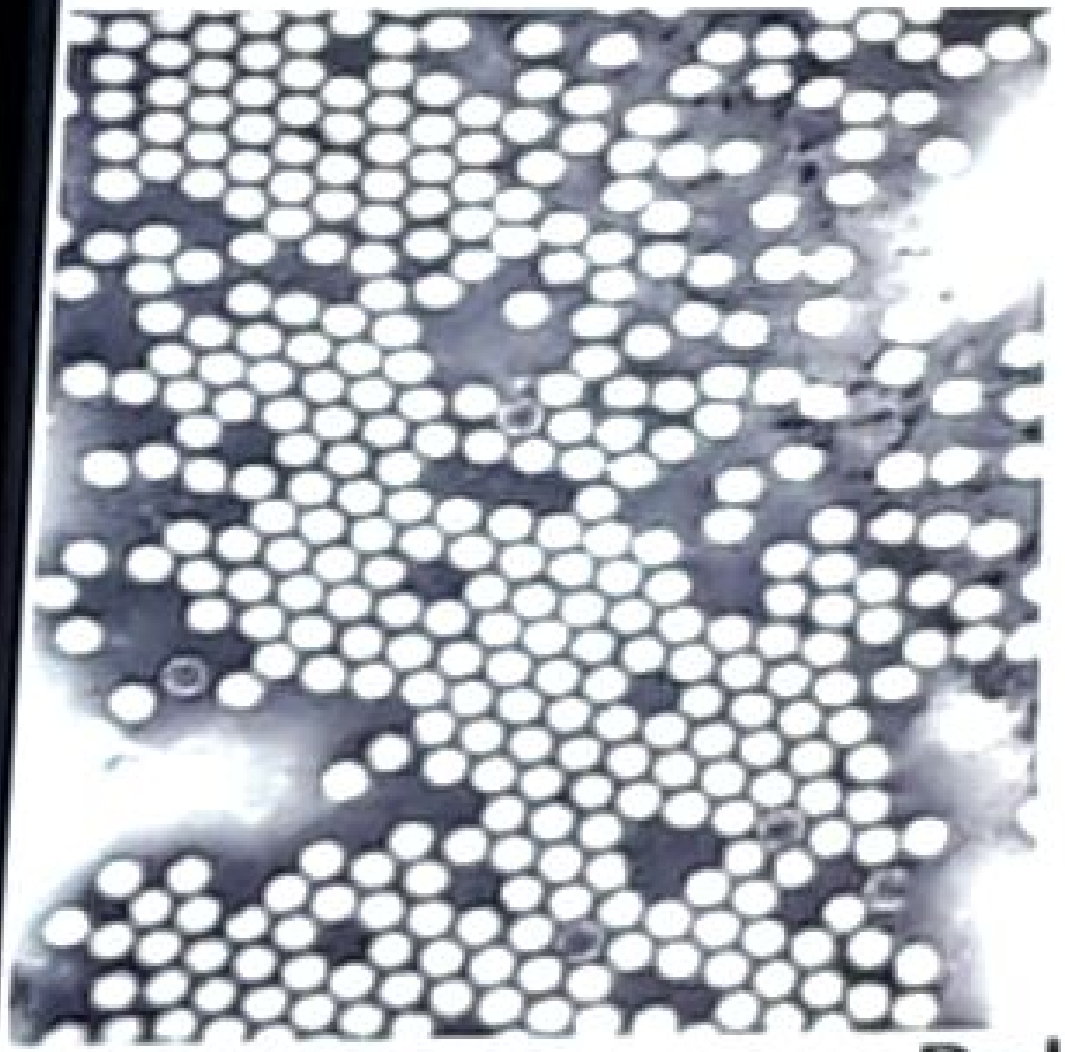
Inflammation

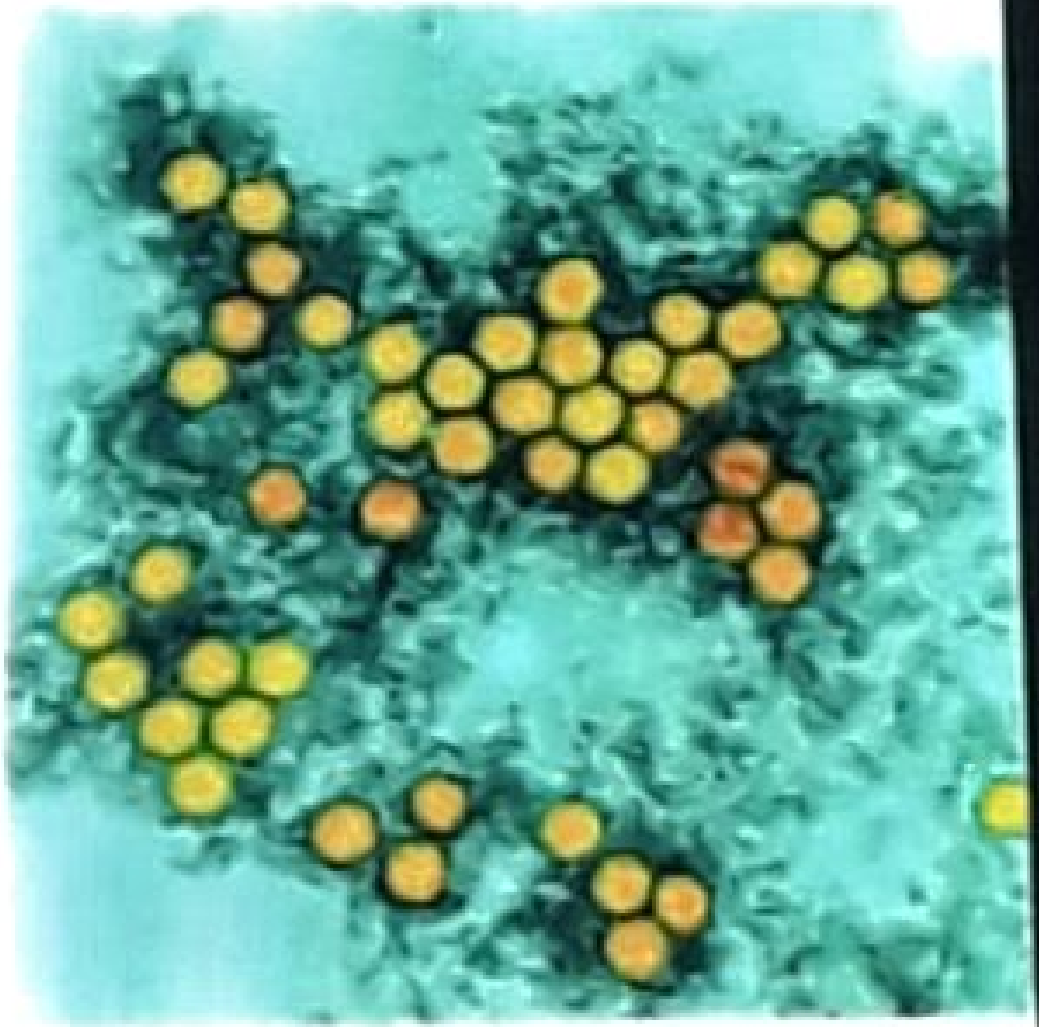
Direct and indirect
cell damage

↓

Clinical Disease

Target cells (neurons, glial cells, endothelial cells)

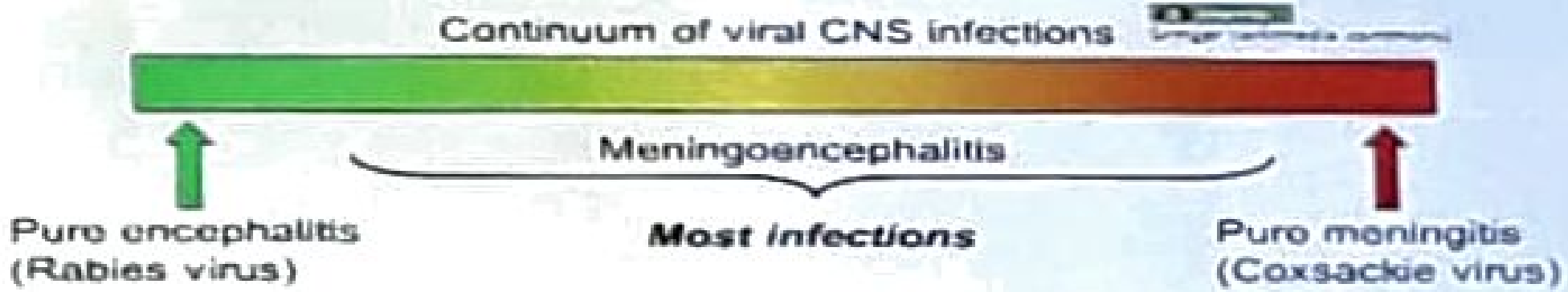




Poliovirus

Common characteristics of CNS virus infections

- **Clinical presentation**
  - Typically acute onset
  - Healthy hosts are often afflicted
  - Frequently occurs as meningoencephalitis
    - Meningitis – fever, headache, stiff neck
    - Encephalitis – meningitis with mental status changes (seizures, decreased consciousness, confusion)



CAUSES OF VIRAL ENCEPHALITIS

- Herpes viruses: HSV-1, HSV-2, VZV, CMV, EBV, HHV-6
- Adenoviruses
- Enteroviruses, pollovirus
- Measles, mumps, and rubella viruses
- Rabies
- Arboviruses: Japanese encephalitis; St. Louis encephalitis virus; West Nile encephalitis virus
- Reoviruses: Colorado tick fever virus
- Arenaviruses: lymphocytic choriomeningitis virus

POLIO VIRUS

Family: *Picornaviridae*

Gender: *Enterovirus*

Species: ***Poliovirus***

Poliomyelitis

polio= gray matter

Myelitis= inflammation of the spinal cord

- the most commonly associated with paralysis
- PV infects and causes disease in humans alone.
- Individuals exposed to PV(infection or vaccination) develop immunity to PV.
- Three serotypes of poliovirus have been identified—poliovirus type 1 (PV1), type 2 (PV2), and type 3 (PV3)—each with a slightly different capsid protein.
- All three are extremely virulent and produce the same disease symptoms.
- PV1 is the most commonly encountered form, and the one most closely associated with paralysis

POLIO VIRUS -EPIDEMIOLOGY

- Polioviruses are distributed globally. Before the availability of immunization, almost 100% of the population in developing countries before the age of 5 were susceptible to PV infection.

- The availability of immunization and the poliovirus eradication campaign has eradicated poliovirus in most regions of the world except in the Indian Subcontinent and Africa.

Poliomyelitis in kenya

- The first recorded poliomyelitis epidemic in Kenya occurred in 1921-1922

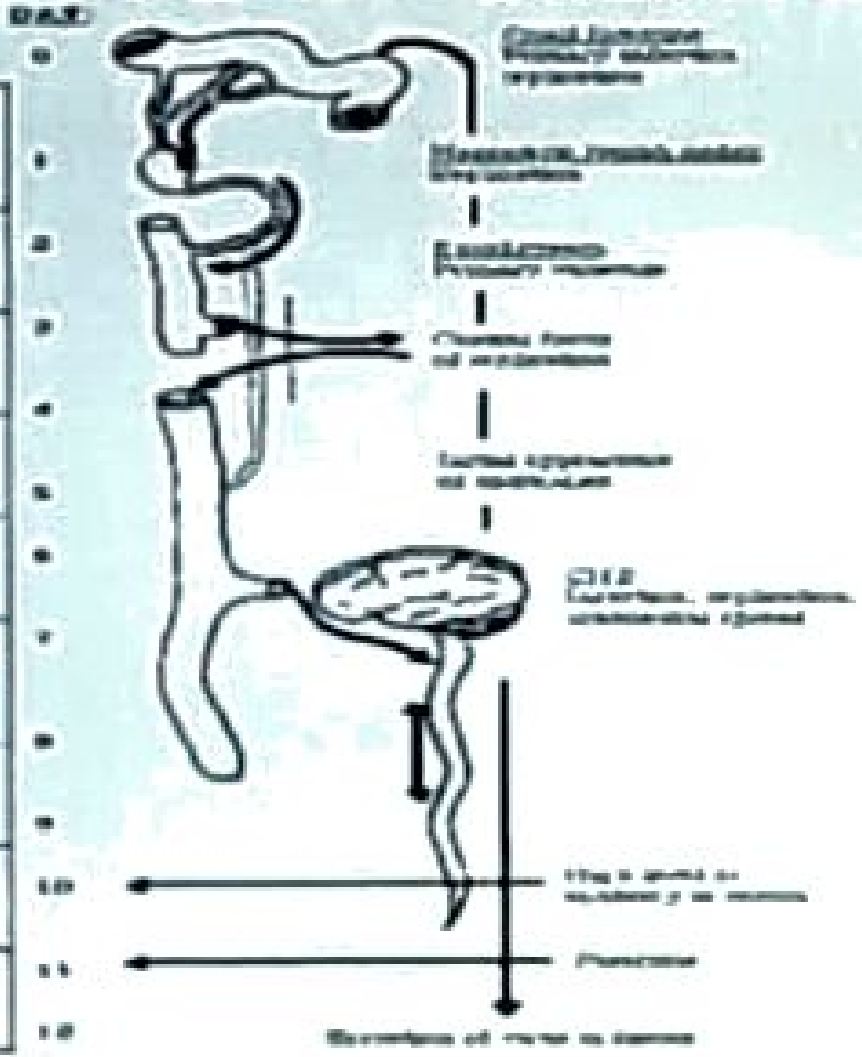
- The last case of confirmed poliomyelitis in Kenya was in 1984 and was isolated on stool culture to have been due to pollovirus Type II.

- *2.76 million children vaccinated against polio.* Kenya conducted a second round of Polio campaign targeting 2.3 million children aged less than 5yrs in high risk districts in North Eastern, North Rift, Western and Nyanza provinces in August 2012. *(Kenya health sector bulletin Aug 2012)*

- 29 August 2012, Kenya confirmed a case of circulating Vaccine Derived Pollo Virus (cVDPV)in Dadaab refugee camps

POLIOMYELITIS – SEQUENCE OF EVENTS

Time (days)	Event
0	Small intestine: 1° infect, replication
1	Mesentric lymph nodes – replication
2	Blood stream – 1° viremia
5	Initial appearance of antibodies
6-7	CNS– infect, replic, intraneural spread
10	High level of antibody in serum
11	Paralysis
12	Excretion of virus in faeces



PV INFECTION - CLINICAL MANIFESTATIONS

Outcomes of poliovirus infection

Outcome	Proportion of cases
Asymptomatic	90–95%
Minor illness	4–8%
Non-paralytic aseptic meningitis	1–2%
Paralytic poliomyelitis	0.1–0.5%
— Spinal polio	79% of paralytic cases
— Bulbospinal polio	19% of paralytic cases
— Bulbar polio	2% of paralytic cases

VIRUS ISOLATION- CONTINUES

- poliovirus can be readily isolated from throat swabs, faeces, and rectal swabs.

- Requires molecular techniques to differentiate between the wild type and the vaccine type.

- *Serologic testing*

A four-fold titer rise between the acute and convalescent specimens suggests pollovirus infection.

- *Cerebrospinal fluid (CSF) analysis*

The cerebrospinal fluid usually contains an increased number of leukocytes—from 10 to 200 cells/mm3 (primarily lymphocytes) and a mildly elevated protein, from 40 to 50 mg/ 100 ml.

PREVENTION

General prevention:

- Health promotion through environmental sanitation.
- Health education (modes of spread, protective value of vaccination).

PREVENTION-VACCINATION

Active immunization:

- Salk vaccine (intramuscular polio trivalent killed vaccine).
- Sabin vaccine (oral polio trivalent live attenuated vaccine).


Rabies

Introduction

- Rabies is a **preventable viral disease** of mammals most often transmitted through the bite of a rabid animal.
- Rabies is primarily a disease of terrestrial and airborne **mammals**
- The **dog** has been, and still is, the main **reservoir of rabies** in Kenya.[1]

1. Karugah AK. Rabies in Kenya. Department of Veterinary Services, Kabete, Nairobi, Kenya

DEFINITION

- Rabies is an acute, progressive encephalomyelitis
- The case to fatality rate is the highest of any infectious disease
- One of the oldest described diseases
- The leading viral zoonosis as regards global public health significance

Rabies Virus

- member of the Lyassavirus of the Rhabdoviridae.
- ssRNA enveloped virus, characteristic bullet-shaped appearance with 6-7 nm spike projections.
- virion 130-240nm * 80nm
- Exceedingly wide range of hosts.
- There are 5 other members of Lyassavirus : Mokola, Lagosbat, Duvenhage, EBVL-1, and EBVL-2.
- Duvenhage and EBVL-2 have been associated with human rabies.

(EBV = European Bat Virus)

ETIOLOGY

- Rabies is caused by RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus*
- The type species of the genus is Rabies Virus
- At least other 6 other lyssavirus species or genotypes cause rabies

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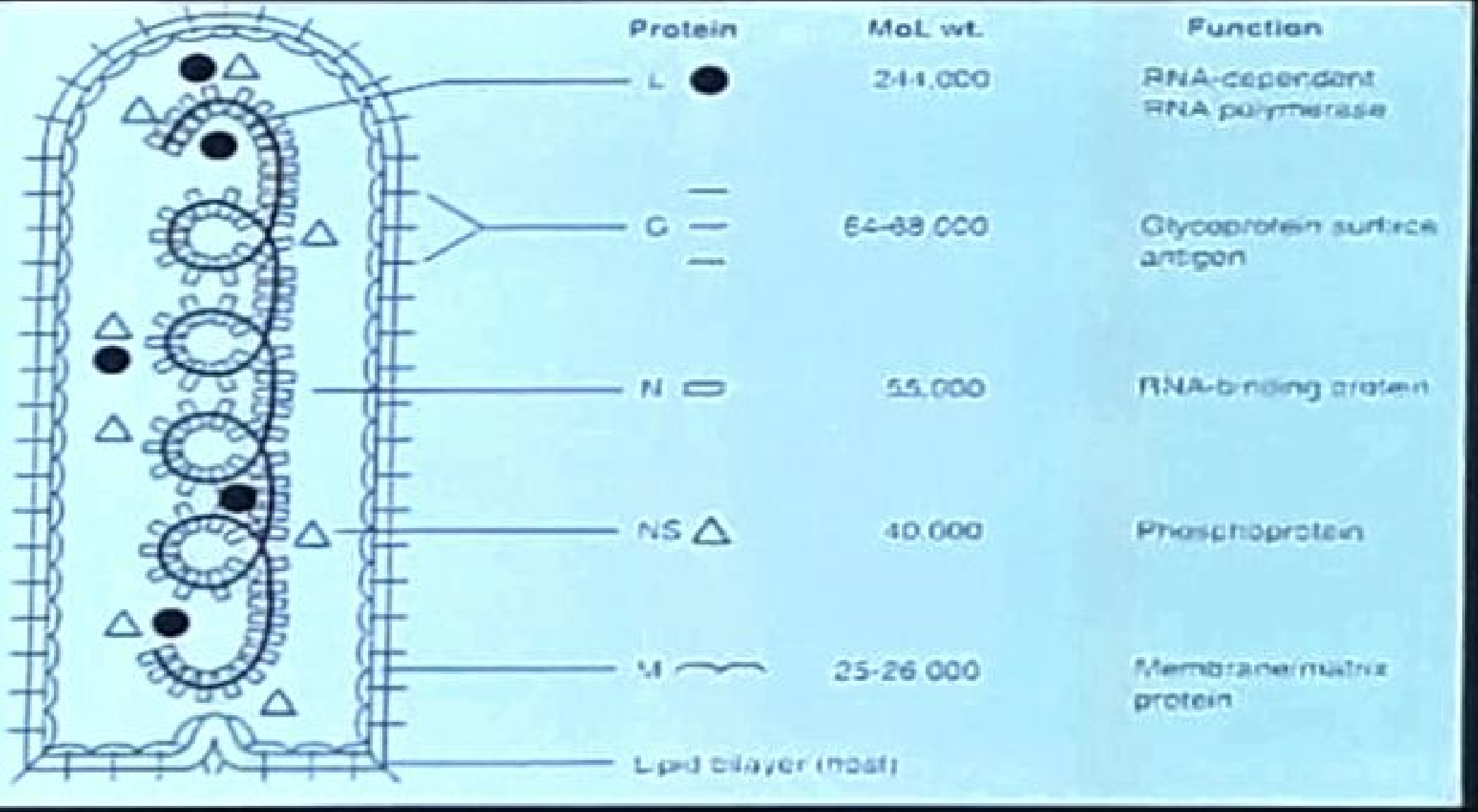

Protein
Mol wt.
Function
L
210,000
RNA-dependent RNA polymerase
G
64-68,000
Glycoprotein surface antigen
N
55,000
RNA-binding protein
NS
40,000
Phosphoprotein
M
25-26,000
Membrane/matrix protein
Lipid bilayer (host)

DISTRIBUTION

- Rabies is distributed on all continents (with the exception of Antarctica)

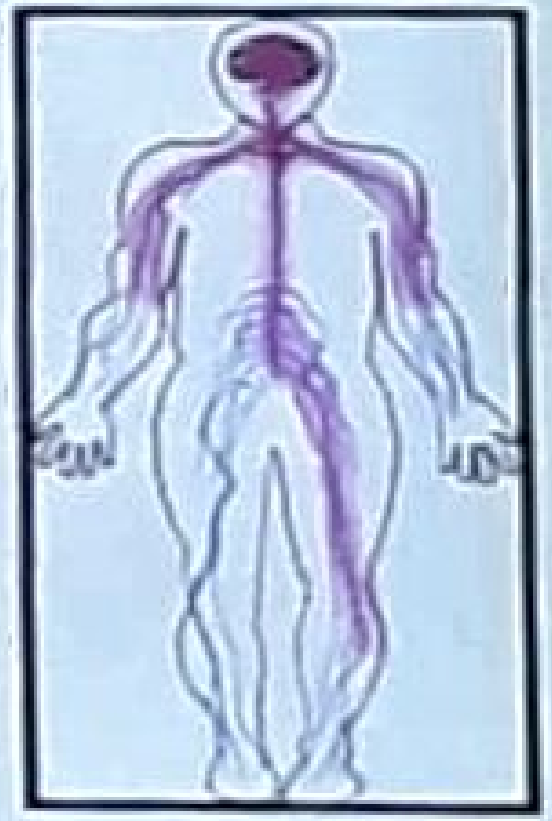
- Globalization may threaten the disease-free status of many localities, due to the introduction of rabid animals

RABIES HOSTS

- All warm-blooded vertebrates are susceptible to experimental infection
- Mammals are the natural hosts of rabies
- Reservoirs consist of the *Carnivora* (canids, skunks, raccoons, mongoose, etc.) and *Chiroptera* (bats)

RABIES PATHOGENESIS

- Virus is transmitted via bite
- Multiplies in the Salivary glands
- Enter peripheral nerves
- travel by retrograde axon flow in axoplasm of nerves to CNS
- Once it reaches this stage, immunisation not effective
- Replicate in brain
- Centrifugal flow to innervated organs, including the portal of exit, the salivary glands
- Viral excretion in saliva



RABIES DIAGNOSIS

- Based upon history of animal exposure and typical neurological clinical signs
- Postmortem demonstration of viral antigen in CNS is gold standard
- In humans, antemortem detection of virus or viral amplicons, antibodies, or antigens (sera, csf, saliva, nuchal biopsy)

CLINICAL STAGES

- Incubation Period (range = ~<7 days to >6 years; average is ~4-6 weeks)
- Prodromal Phase (Non-specific signs)
- Acute Neurological Phase
- Coma
- Death (recovery from rabies?)

PROPHYLAXIS

- Pre-exposure Vaccination

- Postexposure Prophylaxis (PEP)

PRE-EXPOSURE VACCINATION

- Provided to subjects at risk before occupational or vocational exposure to rabies
- Subjects include diagnosticians, laboratory & vaccine workers, veterinarians, cavers, etc.
- Simplifies postexposure management

POSTEXPOSURE PROPHYLAXIS

- Provided to subjects after rabies exposure
- Consists of wound care, rabies immune globulin, and vaccine
- If prompt and proper, survival virtually assured

RABIES BIOLOGICALS

- Rabies Vaccines (for pre- and PEP)
- Rabies immune globulin (only in PEP)

RABIES VACCINES

- Two Human Rabies Vaccines in USA:

  Human Diploid Cell Vaccine Imovax® (HDCV)

  Purified Chick Embryo Cell RabAvert® (PCEC)

RABIES IMMUNE GLOBULIN

- Two Human Rabies Immune Globulins :
- HyperRabTM S/D
- Imogam® Rabies-HT

- Both supplied in vials at ~ 150 IU/ml

Human rabies immune globulin (HRIG) is administered only once, at the beginning of anti-rabies prophylaxis, to previously unvaccinated persons.

This will provide immediate antibodies until the body can respond to the vaccine by actively producing antibodies of its own.

PRE-EXPOSURE VACCINATION

- Vaccine given on days 0, 7, and 21 or 28
- Serology occurs after 6 months to 2 years??
- If antibody titer not adequate, administer a single booster dose
- If ever exposed, give a vaccine dose on days 0 and 3, regardless of titer

POSTEXPOSURE PROPHYLAXIS

- Wash lesions well with soap and water (tetanus booster ad hoc)
- Infiltrate rabies immune globulin (20 IU/kg) into and around the margin of the bites
- Administer vaccine on days 0,3,7,14, and 28