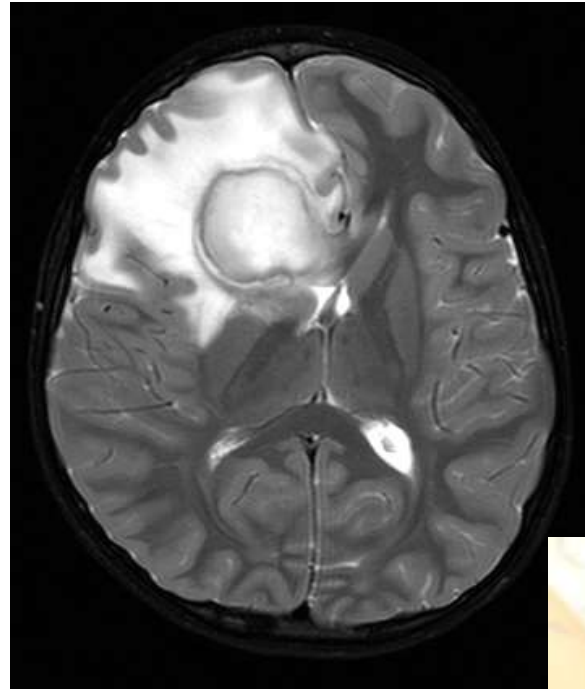


# Microbiology of the ~~central~~ ~~nervous~~ ~~system~~ **PNS**

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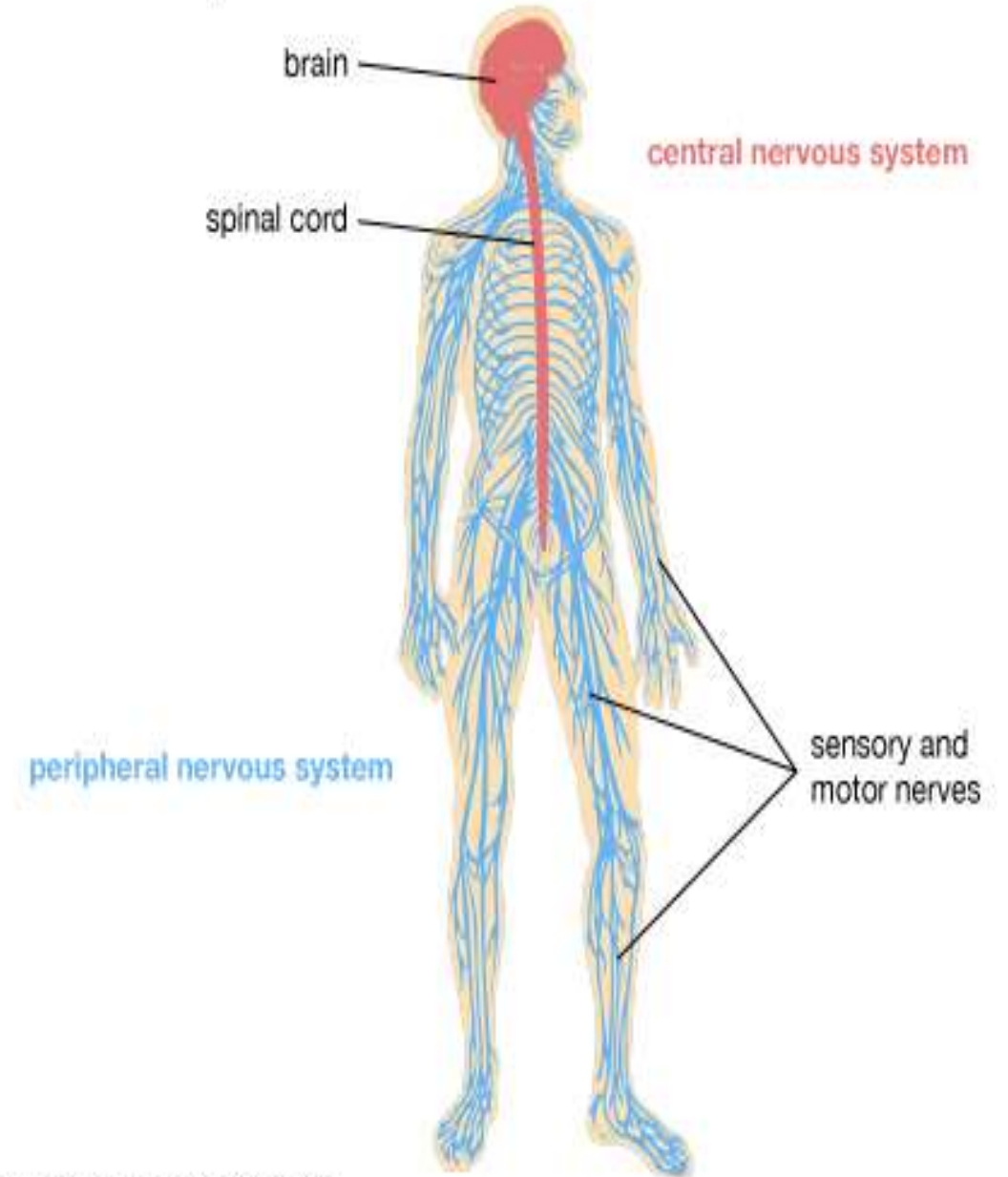


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## Peripheral Nervous System Manifestations of Infectious Diseases

- In general, patients with PNS dysfunction complain of;  
**sensory disturbance**, e.g.  
(-) numbness, loss of sensation, (+) tingling, burning or both.  
Or **motor weakness**, e.g.  
A loss of muscle mass, painful cramps, or fasciculations.  
Or **Autonomic disturbance**  
Or **Both (Motor , sensory, and autonomic)**

### The nervous system



## Peripheral Nervous System Manifestations of Infectious Diseases

- **Infectious** causes are rare compared to **vascular** and primary **inflammatory** or **autoimmune** causes in PNS diseases.
- Infectious causes of peripheral nervous system (PNS) disease are **underrecognized** but potentially treatable.

Category	Examples
Traumatic	Incision, compression, stretching
Metabolic	Diabetes, renal failure, hypothyroidism, amyloid
Malignancy	Especially small cell carcinoma of the lung
Drugs	Isoniazid, phenytoin, nitrofurantoin
Toxins	Lead, alcohol
Infections	Leprosy (the commonest cause worldwide), Lyme disease, HIV
Inflammatory	Guillain-Barré, sarcoid
Vascular	Prolonged ischaemia, polyarteritis nodosa, rheumatoid disease
Genetic	Charcot-Marie-Tooth disease, porphyria
Vitamin deficiencies	B1, B6, B12, nicotinic acid

## Pathogens With Clinical Implications in the PNS

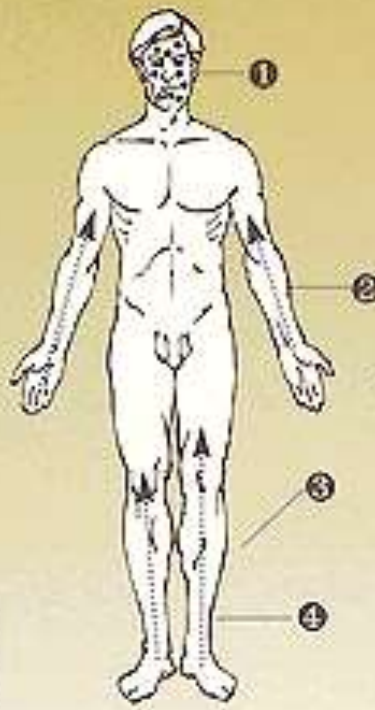
- **Human immunodeficiency virus**
- **Herpes viruses**
- **Poliovirus**
- *Borrelia burgdorferi*
- *Clostridium tetani*
- *Clostridium botulinum*
- *Mycobacterium leprae*
- *Campylobacter jejuni*

- **Human immunodeficiency virus** is a retrovirus that is transmitted primarily by sexual contact and contaminated blood
- Human immunodeficiency virus commonly affects both the CNS and the PNS.
- **Inflammatory demyelinating polyneuropathy, mononeuropathy multiplex, and polyradiculopathies** are present with varying degrees of immune suppression but usually **early in disease**.
- **Distal symmetric polyneuropathy (DSP)** (usually paresthesias or numbness in a stocking-glove distribution) associated with HIV is the **most common PNS complaint**, affecting up to 30% to 50% of patients with **advanced infection**.
- Two distinct pathophysiologic processes are thought to contribute to the development of HIV DSP: **direct neurotoxicity of the virus** and its products and **neurotoxicity of cART** (combination antiretroviral therapy).



#### Distal symmetric polyneuropathy

- ① Hyperesthesia
- ② Normal strength
- ③ Pain, paresthesia
- ④ Decreased ankle reflexes
- ⑤ Decreased response to pinprick, temperature; increased vibratory thresholds
- ⑥ Contact sensitivity



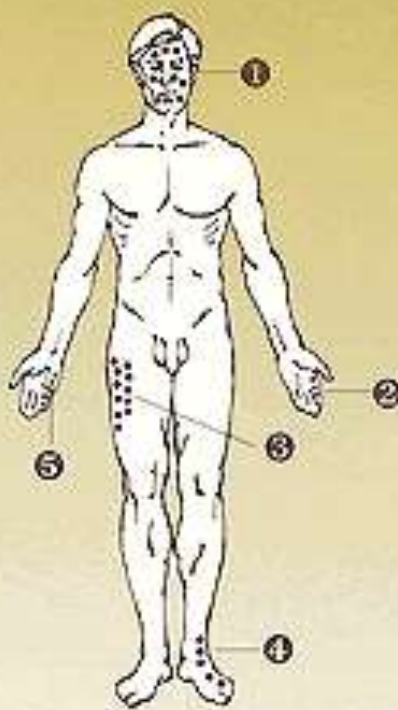
#### Inflammatory demyelinating polyneuropathy

- ① Facial nerve paresis
- ② Ascending weakness
- ③ Generalized areflexia
- ④ Mild sensory involvement



#### Progressive polyradiculopathy

- ① Radiating pain in cauda equina distribution
- ② Flaccid paraparesis
- ③ Mild sensory loss
- ④ Areflexia
- ⑤ Sphincter dysfunction



#### Mononeuritis multiplex

- ① Cranial nerve involvement (eg, facial palsy)
- ② Multiple peripheral nerve involvement
- ③ Median nerve involvement
- ④ Meralgia paresthetica
- ⑤ Peroneal nerve involvement
- ⑥ Ulnar nerve involvement

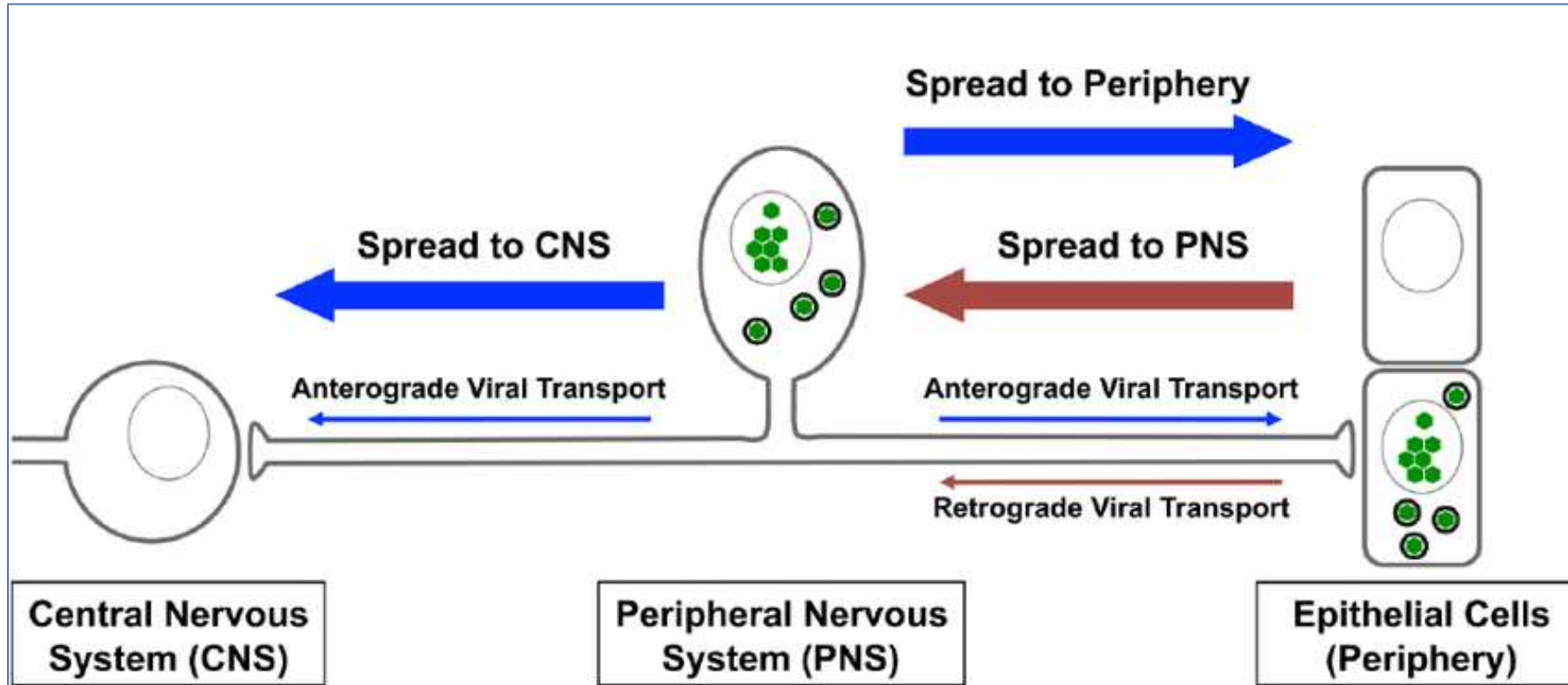


- **Herpesviruses** all share a common structure—**relatively large, double-stranded, linear DNA genomes.**
- **Latent, recurring** infections are typical of this group of viruses.

## Human Herpesviruses

Virus	Subfamily	Disease	Site of Latency
Herpes Simplex Virus I	$\alpha$	Orofacial lesions	Sensory Nerve Ganglia
Herpes Simplex Virus II	$\alpha$	Genital lesions	Sensory Nerve Ganglia
Varicella Zoster Virus	$\alpha$	Chicken Pox Recurr as Shingles	Sensory Nerve Ganglia
Cytomegalovirus	$\beta$	Microcephaly/Mono	Lymphocytes
Human Herpesvirus 6	$\beta$	Roseola Infantum	CD4 T cells
Human Herpesvirus 7	$\beta$	Roseola Infantum	CD4T cells
Epstein-Barr Virus	$\gamma$	Infectious Mono	B lymphocytes, salivary
Human Herpesvirus 8	$\gamma$	Kaposi's Sarcoma	Kaposi's Sarcoma Tissue

## Viruses With Clinical Implications in the PNS / **Herpes viruses**

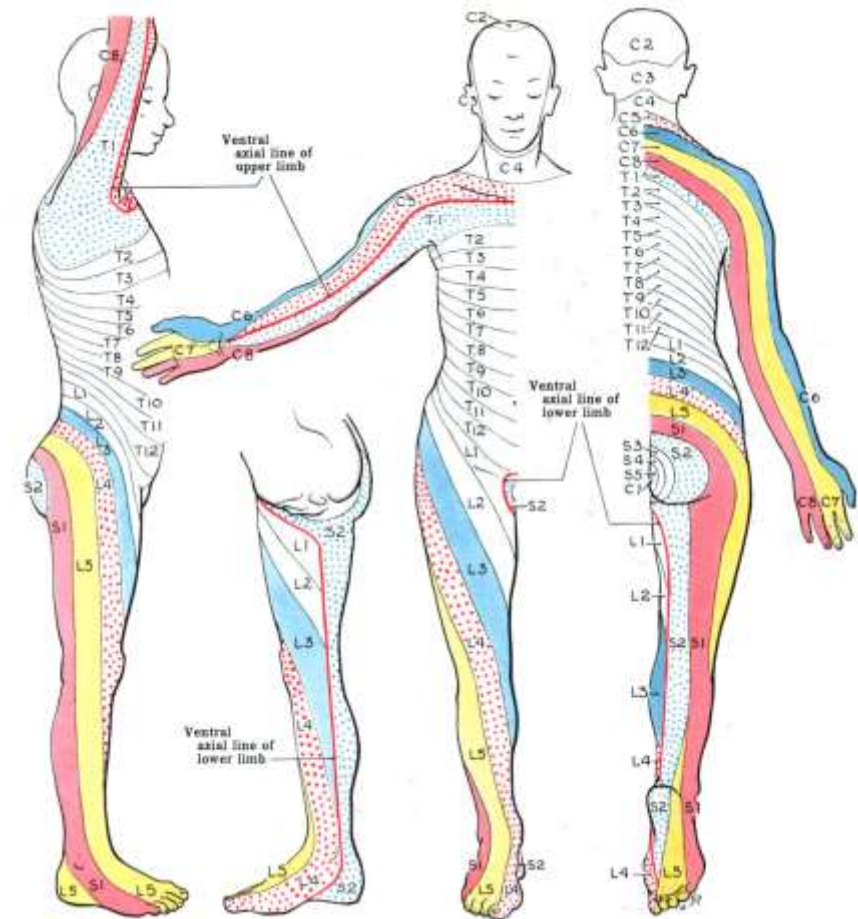


Directional spread of alphaherpesvirus infection in the mammalian nervous system. In their hosts, alphaherpesvirus infections typically initiate at peripheral sites, such as mucosal epithelia. Next, viral particles enter at the termini of sensory neurons of the peripheral nervous system (PNS). These particles are transported long distances along axons in the retrograde direction towards cell bodies, where the genomes are deposited in the nucleus to establish lifelong latency. Following reactivation from latency, new viral particles are assembled and transported towards sites of egress. Typically, infections spread in the anterograde direction back out towards the periphery. This is essential for spread between hosts. Infection may also spread trans -neuronally, from the PNS to the central nervous system (CNS). Spread of alphaherpesvirus infection into the CNS is associated with lethal encephalitis.



## Viruses With Clinical Implications in the PNS / Herpes viruses/ **Varicella-zoster virus (VZV)**

- VSV causes varicella and herpes zoster



Dermatomes of the Upper and Lower Limbs



shingles

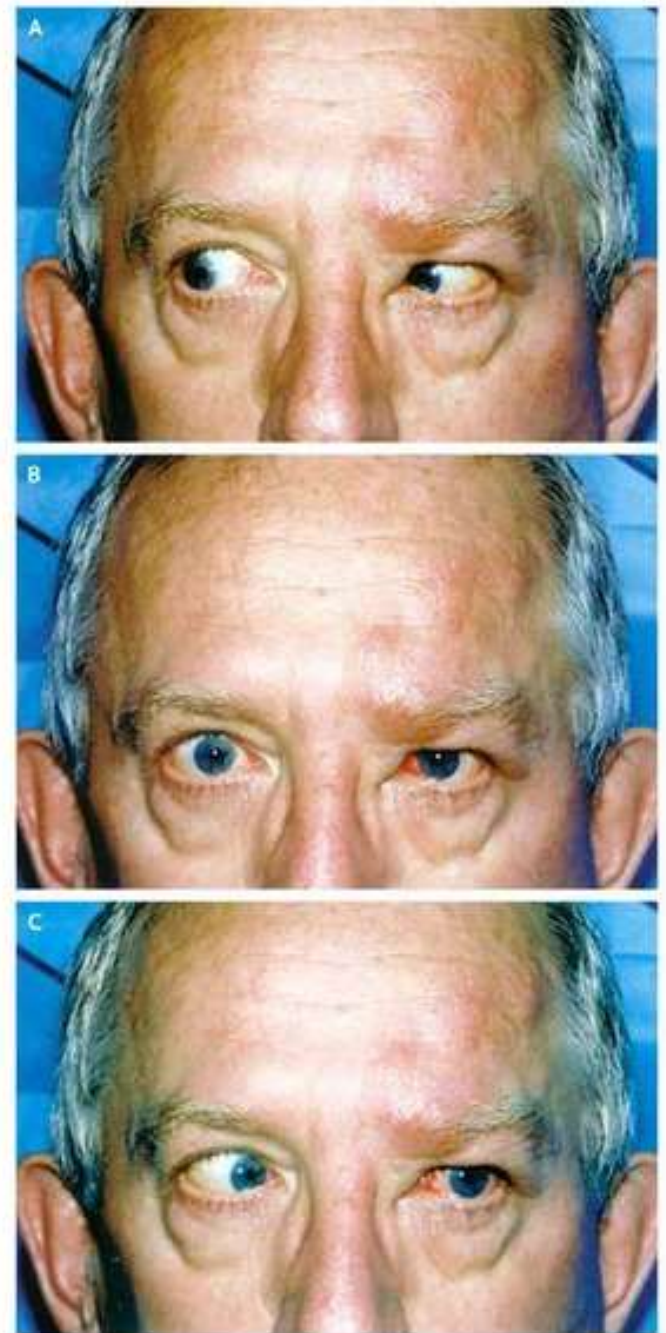


Varicella (Chickenpox)

## Viruses With Clinical Implications in the PNS / Herpes viruses/ **Varicella-zoster virus (VZV)**

- Primary infection with VZV typically occurs in childhood and is characterized by a skin rash that forms small, itchy blisters, which eventually scab over.
- **Reactivation** of VZV occurs primarily in the **elderly** patients and **immunosuppressed**.
- The most commonly reported PNS complication is **postherpetic neuralgia**, which is a dermatomal distribution pain following shingles.
- Diagnosis of VZV neuropathy is **primarily clinical**
- Early treatment of VZV infection is recommended with antiviral agents such as **acyclovir**, valacyclovir, and famciclovir for 7 days.

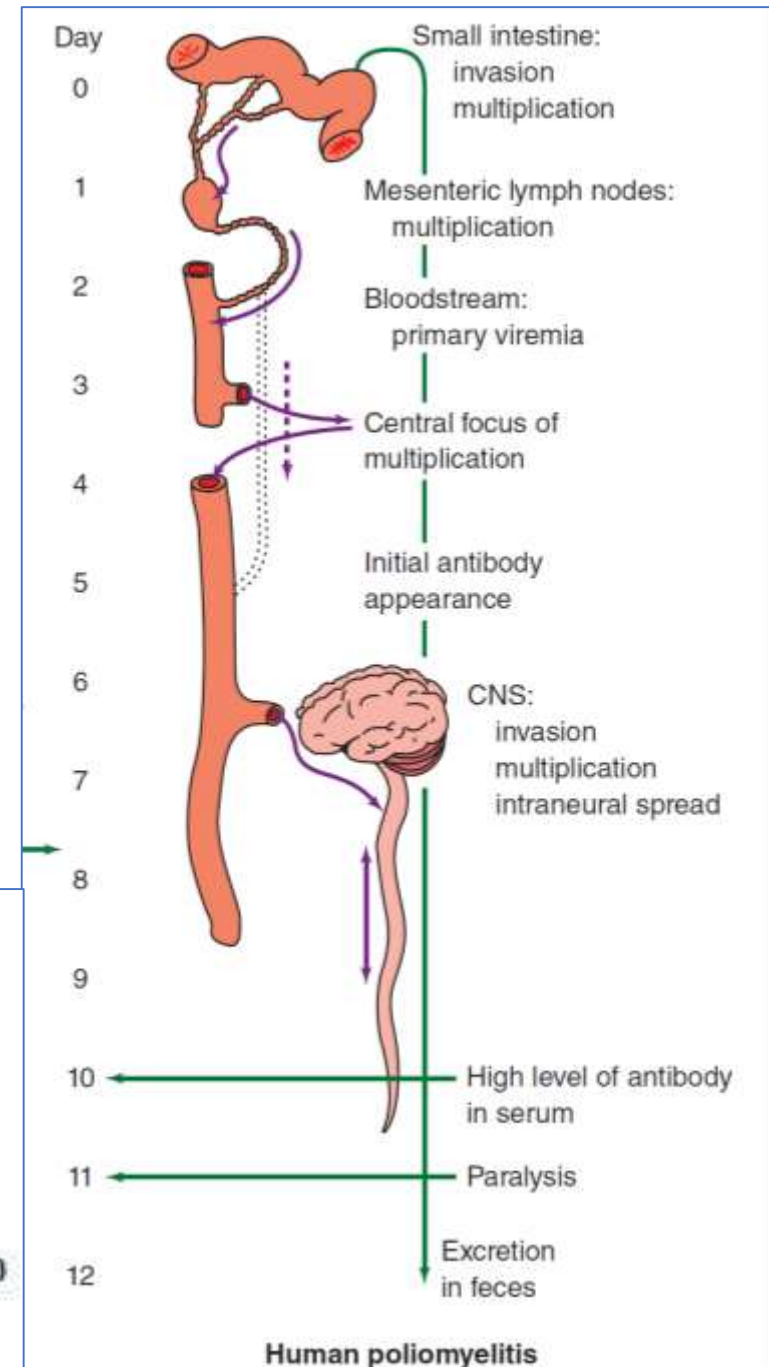
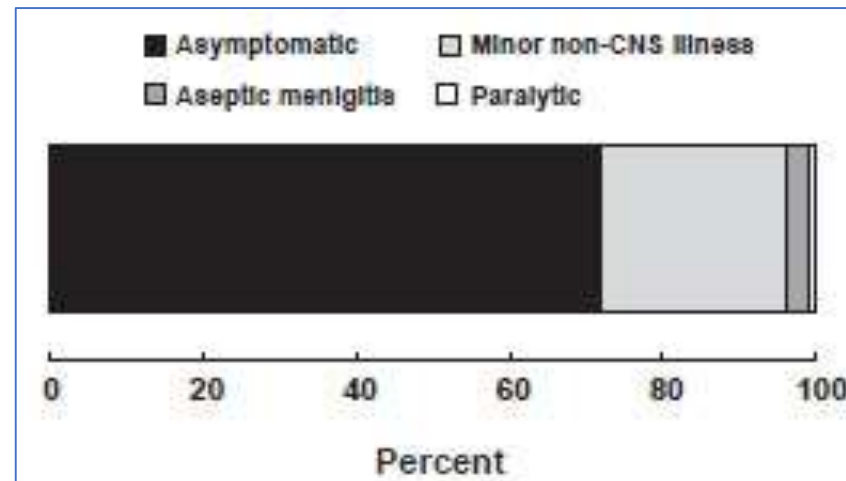
A 62-year-old man reported acute left retro-orbital pain of one week's duration. Physical examination revealed no abnormalities. Three days later, double vision developed, and a red rash appeared on the forehead. On repeated examination, it was noted that the patient had left eye ptosis, eyelid, conjunctival congestion, restricted abduction of the left eye, which was consistent with a left cranial nerve palsy (right, center, and left gaze; Panels A, B, and C, respectively). The patient also had horizontal diplopia. The rash was distributed over the left frontal area. The patient's extraocular movements, visual acuity, visual field, pupillary evaluation, and sensory examination were normal. The blood glucose level, erythrocyte sedimentation rate, and C-reactive protein were normal. A computed tomographic scan of the paranasal sinuses and orbit was normal. A diagnosis of herpes zoster ophthalmicus was made. The patient was treated with gabapentin and acyclovir for one week. Six weeks later, there was residual diplopia, with no postherpetic neuralgia. It is important that this diagnosis be made early to minimize complications such as corneal ulceration and uveitis, which may lead to blindness.





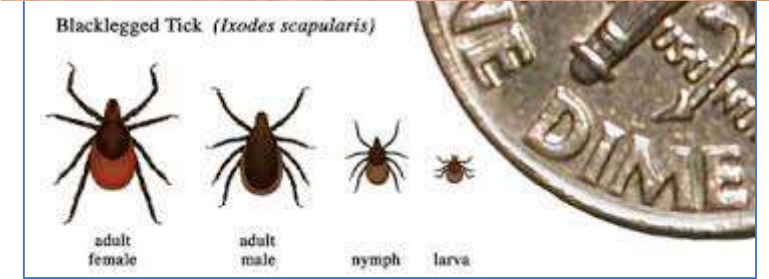
## Viruses With Clinical Implications in the PNS / Poliovirus

- **Poliovirus**, a member of the enterovirus family **causes polio or infantile paralysis**.
- Up to 72% of all polio infections in children are asymptomatic
- Fewer than 1% of all polio infections in children result in flaccid paralysis.
- Diagnosis is through viral recovery from stool, or through rising antibody titer in blood.
- In 2012, **only** 223 confirmed cases of polio were reported globally due to widespread vaccination programmes.



Bacteria with Clinical Implications in the PNS / *Borrelia burgdorferi*

- **Lyme disease**, the multisystem infectious disease caused by the tick-borne spirochete ***Borrelia burgdorferi***, causes a broad variety of peripheral nerve disorders, including single or multiple **cranial neuropathies**, painful **radiculopathies**, and diffuse polyneuropathies.
- **Clinical presentation, history, and serology** are important in diagnosis.
- **Doxycycline** is given to adults with suspected Lyme disease.



*Ixodes* ticks (deer tick)



Erythema migrans



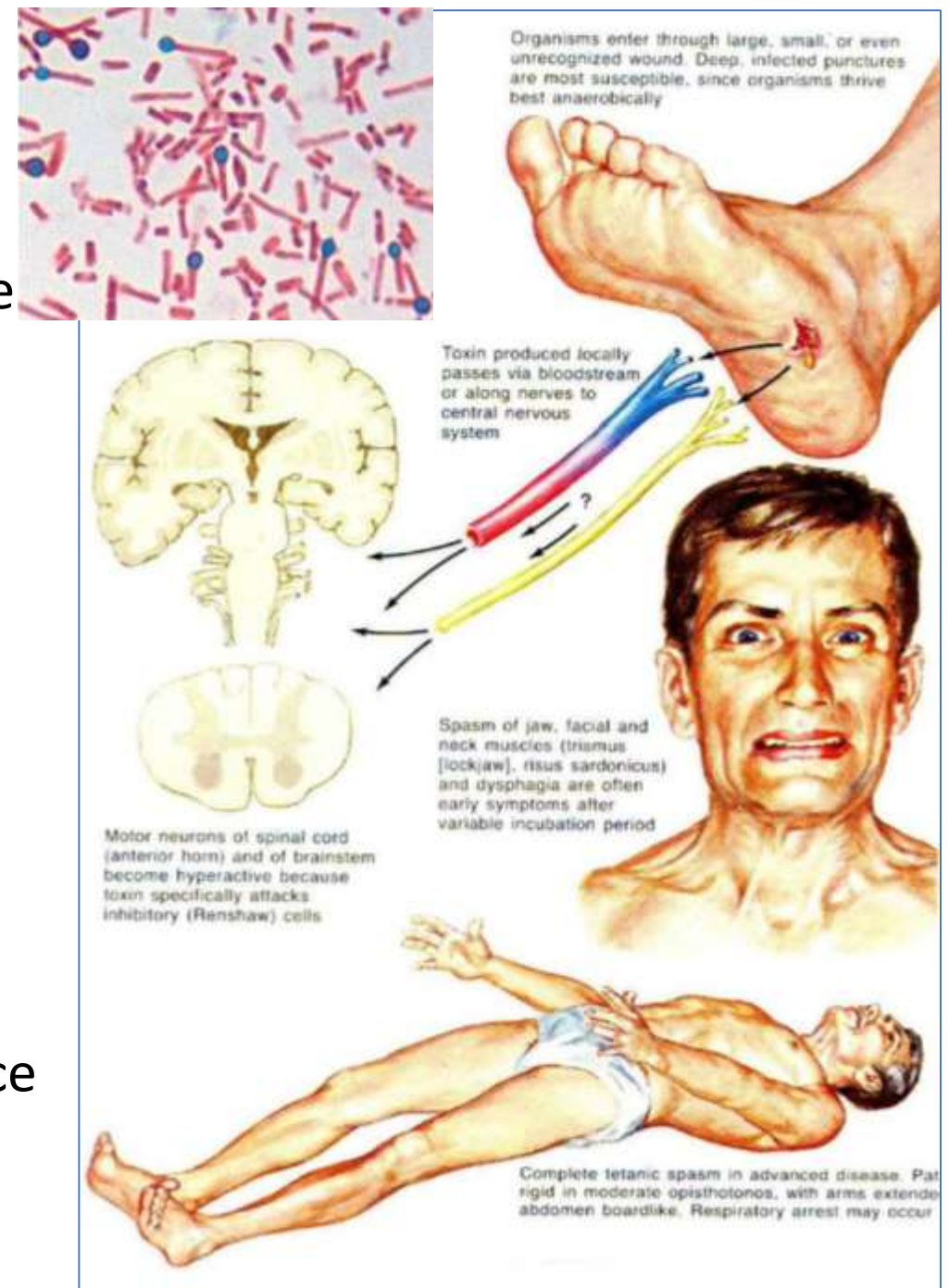
*Borrelia burgdorferi*



In early summer, an 82-year-old right-handed woman from Western Massachusetts developed right-sided upper back pain that radiated down the right arm in the setting of fever, myalgias, generalized fatigue, and erythema migrans just under the right clavicle. She was given a course of doxycycline for presumed Lyme but discontinued it after 3 days. Her pain worsened, and although she did have a pulsatile headache and meningismus, the back pain was much more prominent, progressing to mild weakness in a C6 distribution. She also developed a left-sided cranial nerve VII palsy. She received 4 weeks of IV ceftriaxone for presumed CNS Lyme. Her pain regimen included fentanyl transdermal patch 25

## Bacteria with Clinical Implications in the PNS / *Clostridium tetani*

- *C. tetani* is a **spore-forming**, anaerobic, Gram positive rod that causes tetanus.
- *C. tetani* produces **tetanospasmin**.
- Tetanospasmin **inactivates proteins that regulate release of the inhibitory neurotransmitters** glycine and gamma-aminobutyric acid (GABA). This leads to unregulated excitatory synaptic activity in the motor neurons, resulting in **spastic paralysis**.
- Disease is relatively rare because of the high incidence of **vaccine-induced immunity**.

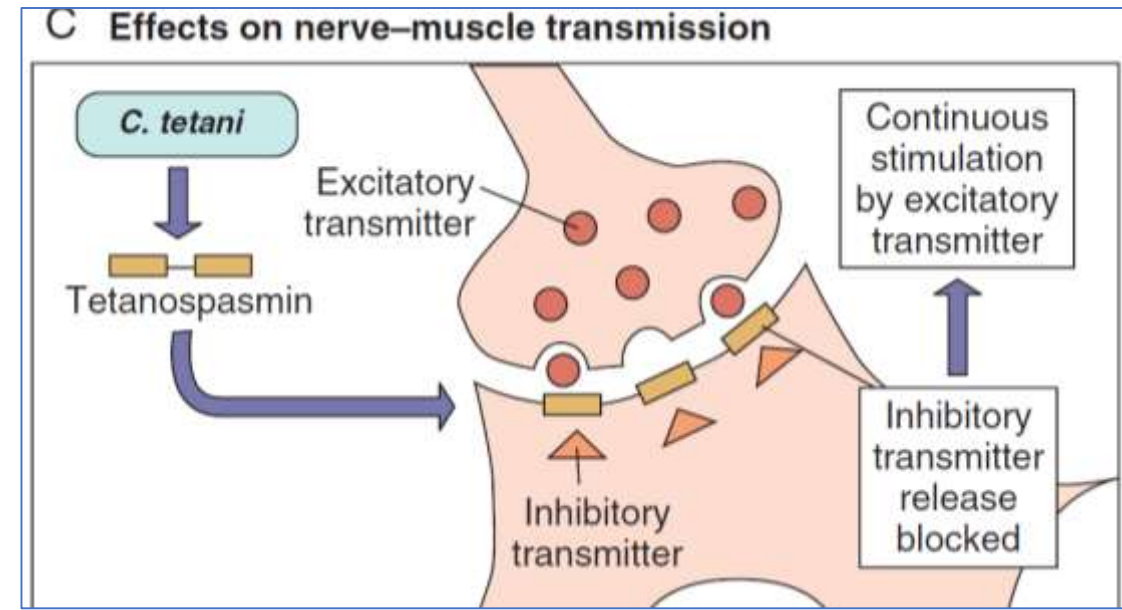




## Bacteria with Clinical Implications in the PNS / *Clostridium tetani*



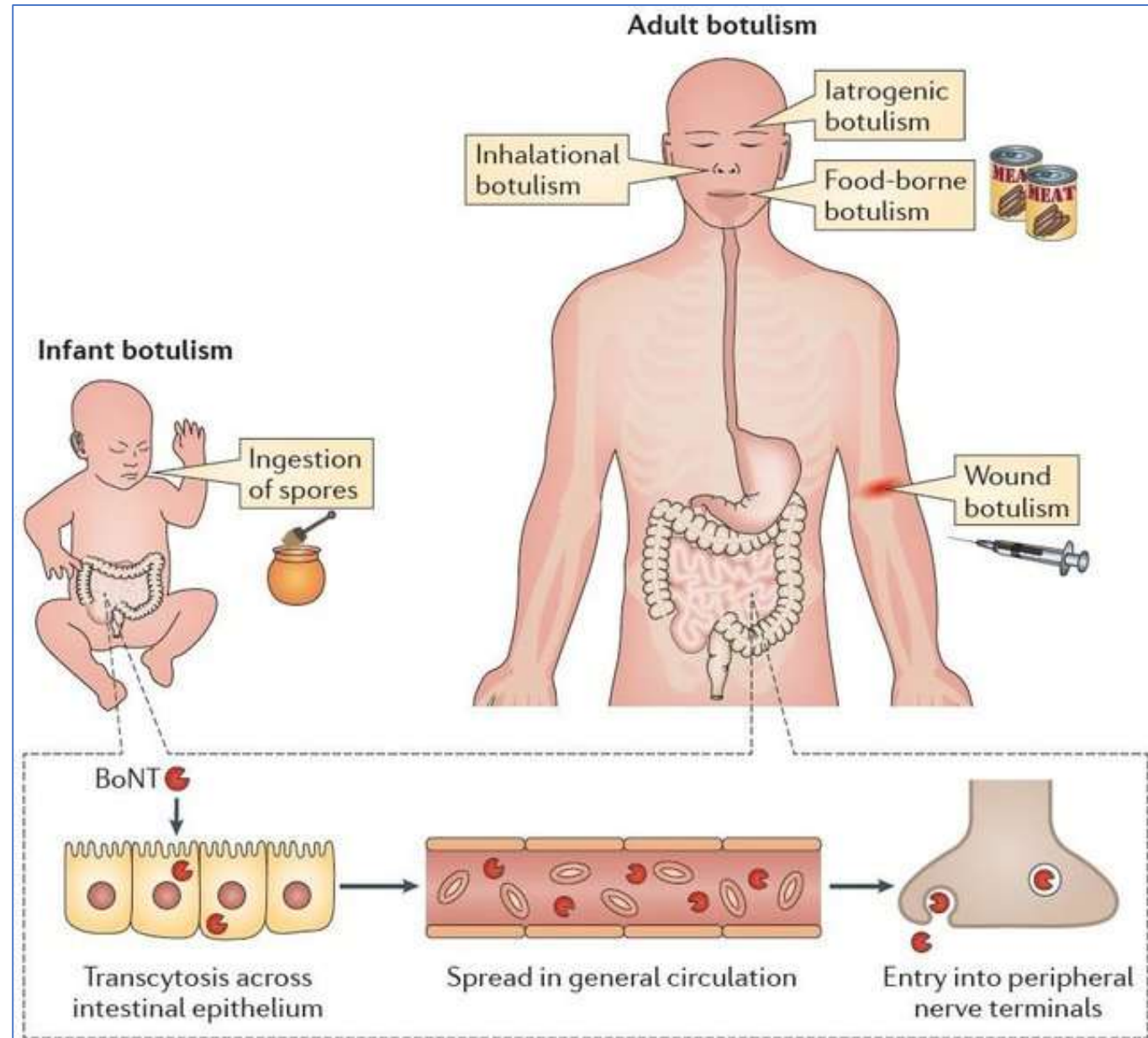
Involvement of the masseter muscles (trismus or **lockjaw**) is the presenting sign in most patients. The characteristic **sardonic smile** that results from the sustained contraction of the facial muscles.



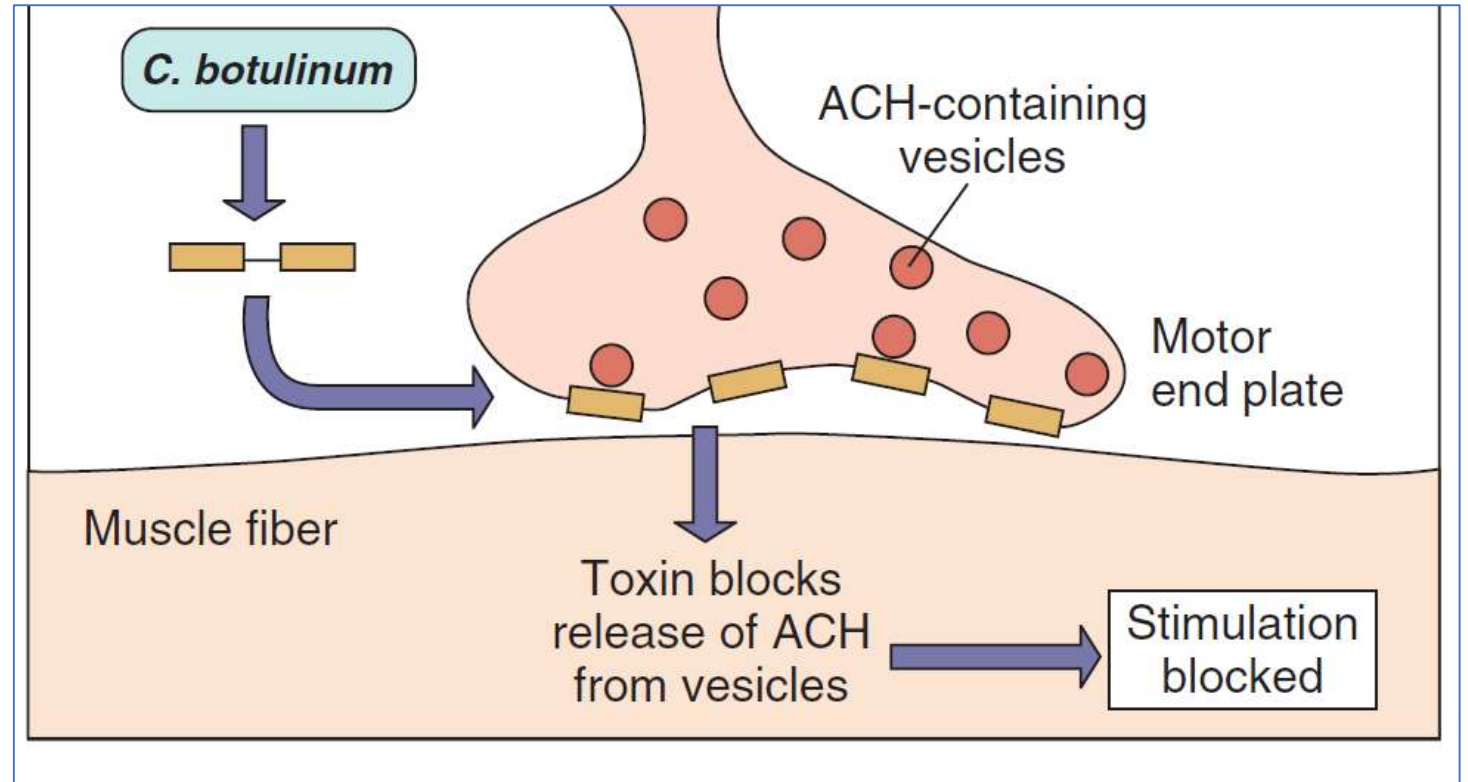
unregulated excitatory synaptic activity in the motor neurons, resulting in **spastic paralysis**. **Generalized tetanus** is the most common form.

## Bacteria with Clinical Implications in the PNS / *Clostridium botulinum*

- *C. botulinum* is a **spore-forming**, anaerobic, Gram positive rod that causes tetanus.
- Patients with **foodborne botulism** (most are associated with consumption of home-canned foods) typically become weak and dizzy 1 to 3 days after consuming the contaminated food. Bilateral descending **weakness of the peripheral muscles** develops in patients with progressive disease (flaccid paralysis), and death is most commonly attributed to **respiratory paralysis**.
- **Infant botulism**: Associated with consumption of foods (e.g., honey, infant milk powder) contaminated with botulinum spores and ingestion of spore-contaminated soil and dust. In contrast with foodborne botulism, this disease is caused by neurotoxin produced in vivo by *C. botulinum* colonizing the GI tracts of infants.



- The botulinum neurotoxin remains at the neuromuscular junction, The botulinum endopeptidase then **inactivates the proteins that regulate release of acetylcholine**, blocking neurotransmission at peripheral cholinergic synapses. The resulting clinical presentation of botulism is a **flaccid paralysis**.

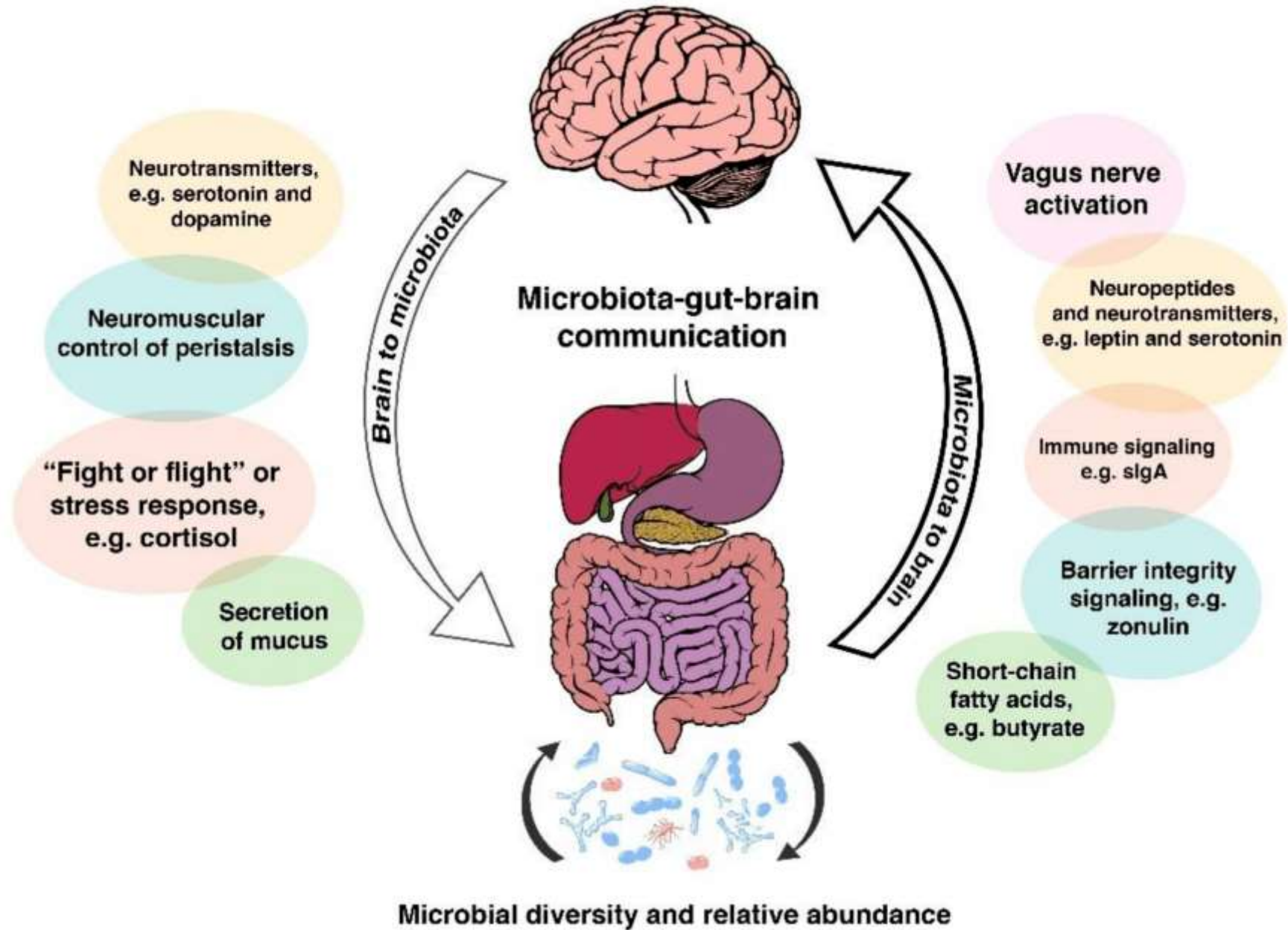




## The Gut-Brain axis

- The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. Gut microbiota seem to influence these interactions.
- **Symbiotic microbes** have been shown to regulate **nutrition** and **metabolism** and are critical for the development and function of the **immune system**. More recently, studies have suggested that **gut bacteria can impact neurological outcomes**--altering behaviour and potentially affecting the onset and/or severity of nervous system disorders.
- Most of the data have been acquired using technical strategies consisting in **germ-free animal models, probiotics, antibiotics, and infection studies**.
- In clinical practice, evidence of microbiota-GBA interactions comes from the **association of dysbiosis (abnormal microbiota) with central nervous disorders** (i.e. autism, anxiety-depressive behaviors) and functional gastrointestinal disorders.

## The Gut-Brain axis



## Further reading:

- Peripheral Nervous System Manifestations of Infectious Diseases.  
*Neurohospitalist*. 2014
- The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems.  
*Annals of Gastroenterology* . 2015