
TORTORA • FUNKE • CASE

Microbiology

AN INTRODUCTION

EIGHTH EDITION

Microbial Diseases of the Central Nervous System (Part I)

PowerPoint® Lecture Slide Presentation prepared by Christine L. Case

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Microbial Diseases of the CNS

❖ *Topics to be covered:*

- ✓ *Bacterial meningitis and brain abscess*
 - *Pneumococcal meningitis*
 - *Meningococcal meningitis*
 - *Haemophilus influenzae meningitis*
 - *Listeria monocytogenes meningitis*
 - *Other bacterial meningitis including GBS, K1 E. coli, TB meningitis, Leprosy*
- ✓ *Cryptococcal meningitis (Fungi)*
- ✓ *Naegleria fowleri meningitis (Parasite)*
- ✓ *African Trypanosomiasis (Parasite)*

Microbial Diseases of the CNS

❖ *Topics to be covered:*

- ✓ *Tetanus*

- ✓ *Botulism*

- ✓ *Viral meningitis*

- *Non-polio enteroviruses*

- *Mumps virus*

- *Herpesviruses, (EBV, HSV, VZV)*

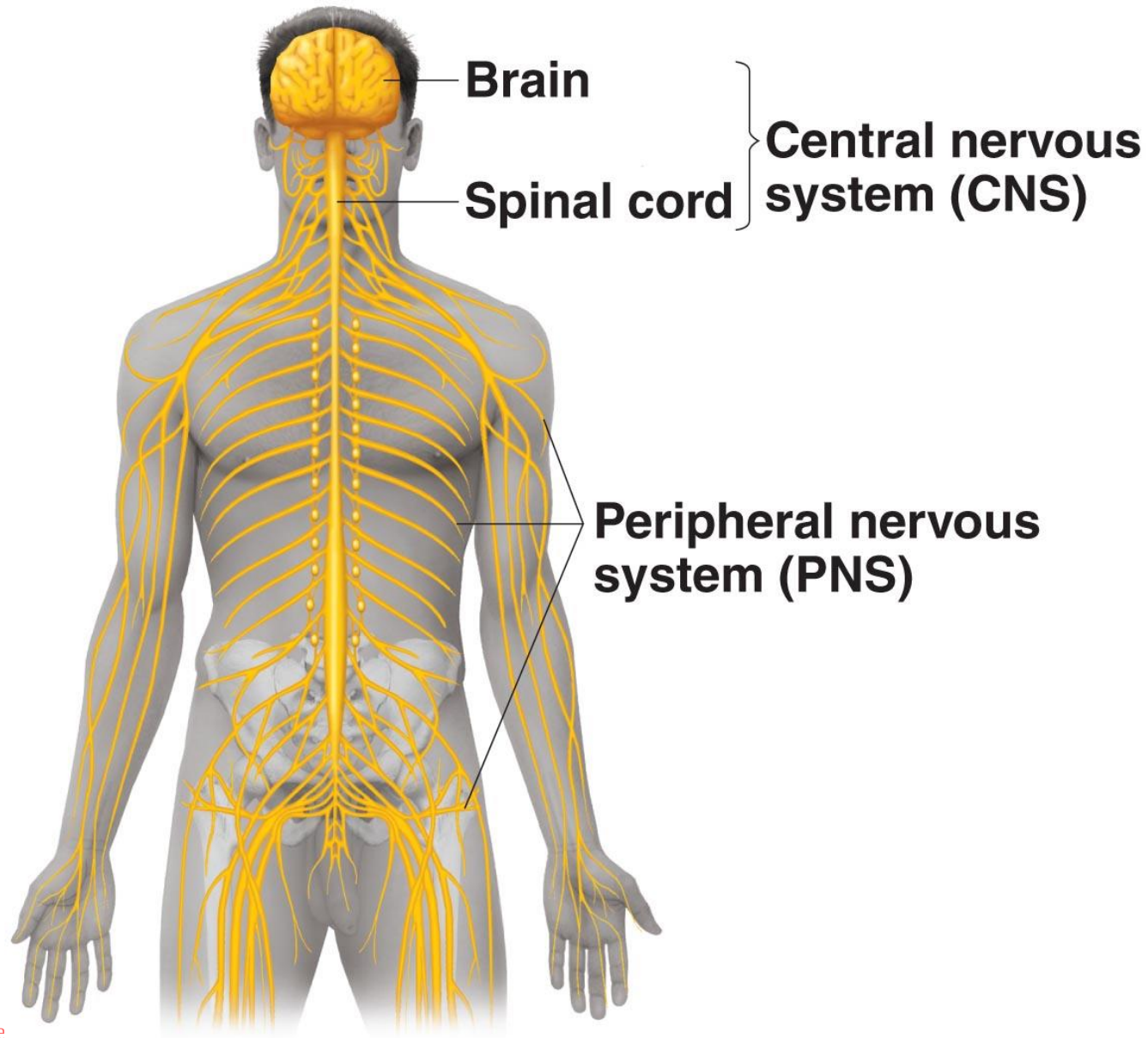
- *Measles virus*

- *Influenza virus*

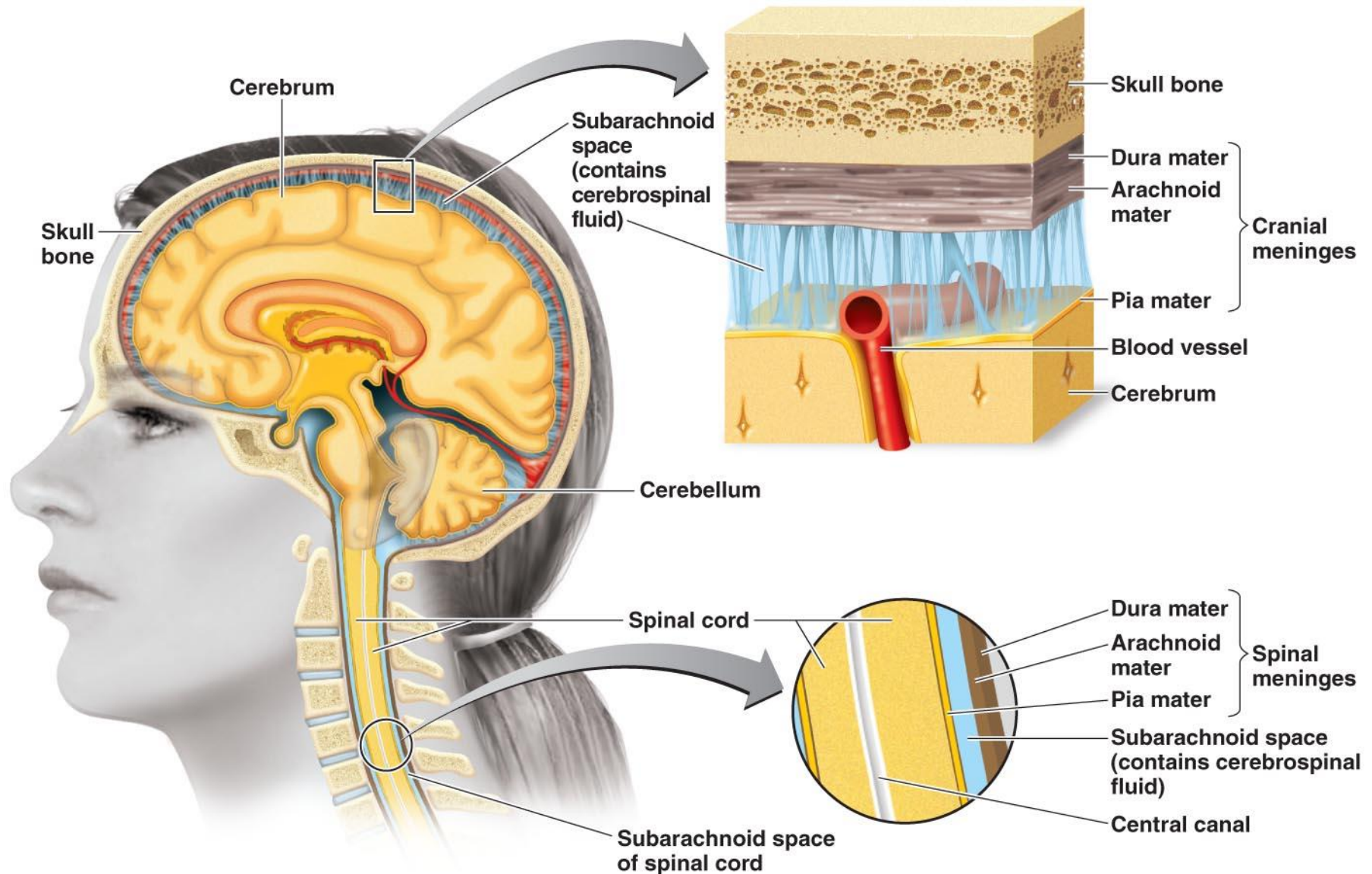
- *Arboviruses, such as West Nile virus*

- *Lymphocytic choriomeningitis virus*

The Human Nervous System



The Meninges and CSF



Microbes enter the nervous system via:

- Trauma
 - Skull or backbone fractures
 - Medical procedures
 - Along peripheral nerves
 - Blood or lymph
- Pathogens capable of causing diseases of the nervous system have virulence characteristics
 - Enable them to penetrate host defenses

Microbial Diseases of the Nervous System

- Bacteria can grow in the cerebrospinal fluid (CSF) in the subarachnoid space of the CNS
 - CSF have low level of complement, circulating Ab, few phagocytic cells
- The blood brain barrier (capillaries) prevents passage of some materials (such as antimicrobial drugs) into the CNS
 - Capillaries less permeable than others in the body

Bacterial Diseases of the Nervous System

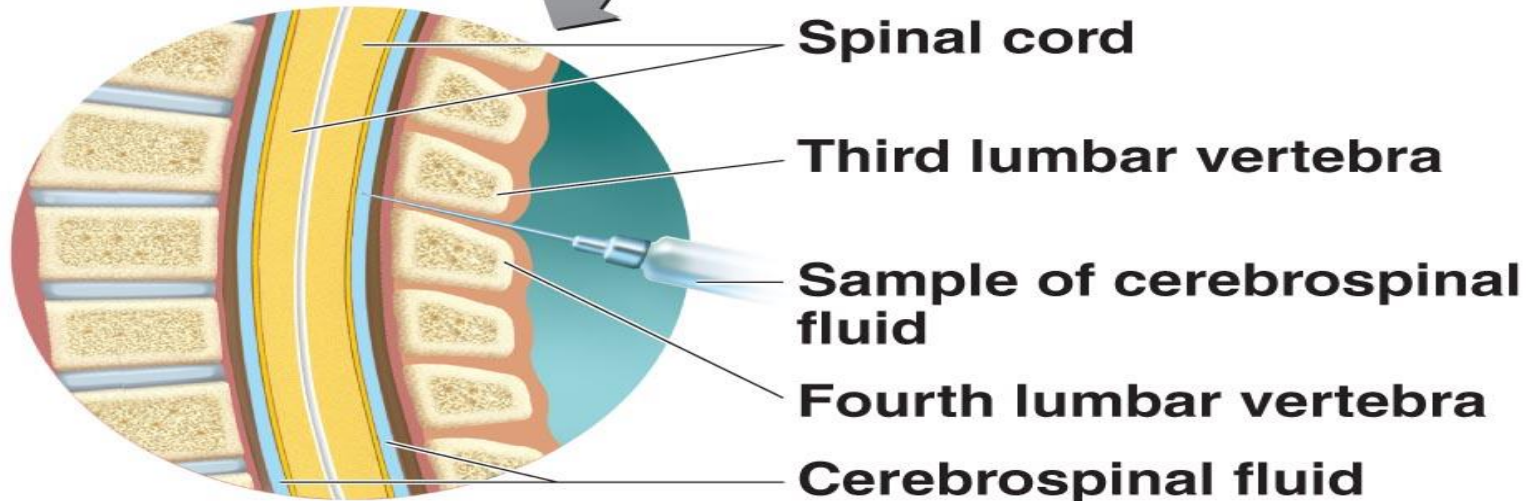
- Only drugs that are lipid-soluble can cross blood-brain barrier
- Meningitis
 - Inflammation of meninges
- Encephalitis
 - Inflammation of the brain
 - Meningoencephalitis: Inflammation of both

Bacterial Meningitis

- Majority (more than 70%) caused by *St. pneumoniae*, *N. meningitidis*, and *H. influenzae*.
- Nearly 50 other species of bacteria (opportunistic pathogens) occasionally cause meningitis.
- *L. monocytogenes*, GBS, staphylococci, and certain gram-negative bacteria.
- Initial symptoms of fever, headache, and stiff neck
- Followed by nausea and vomiting
- May progress to convulsions and coma
- Diagnosis by Gram stain and latex agglutination of CSF
- Treatment: Cephalosporins, vancomycin

Spinal Tap (Lumbar Puncture)

Spinal needle is inserted, usually between the third and fourth lumbar vertebrae



Longitudinal section of the spine

CSF findings in Acute & Subacute Meningitis

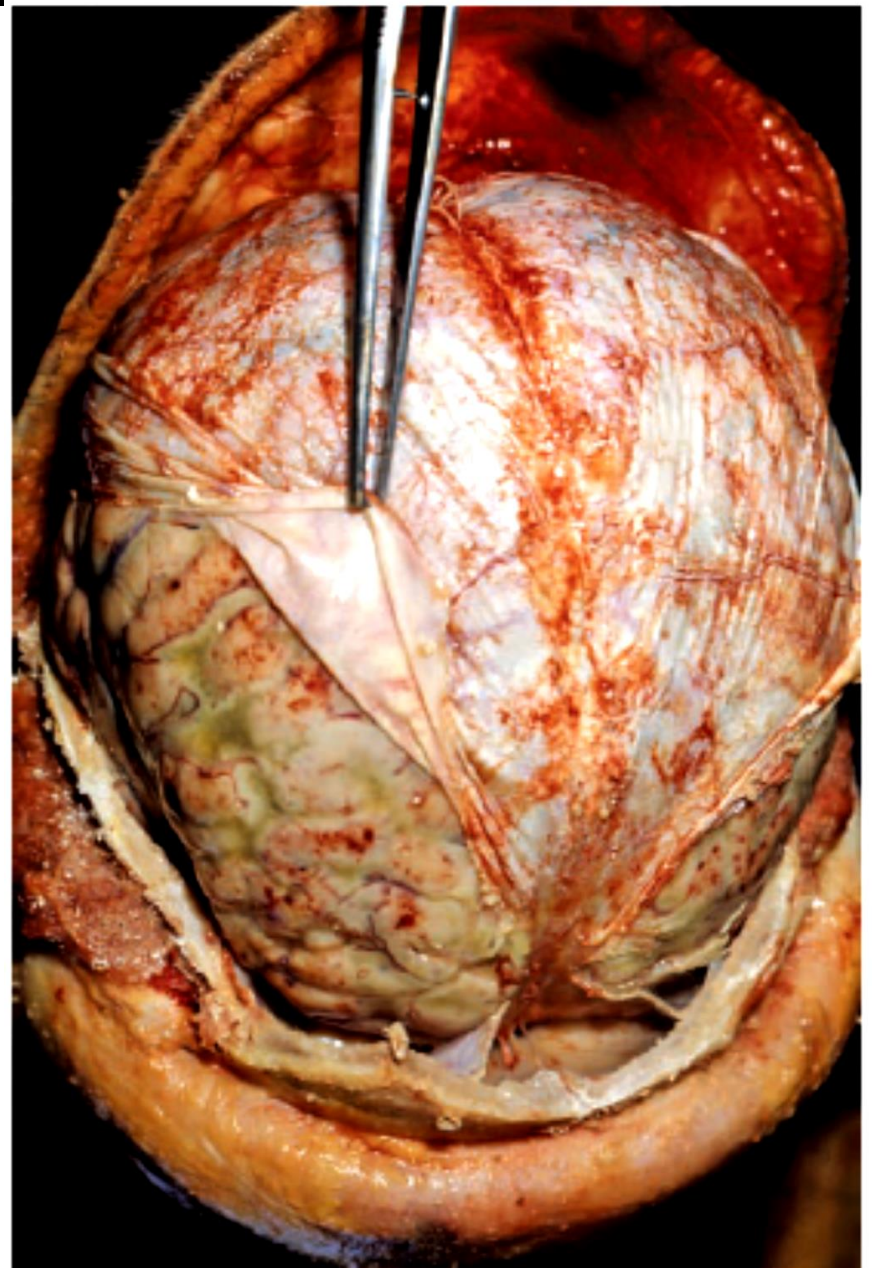
TABLE 72-1 Spinal Fluid Findings in Acute and Subacute Meningitis

Etiology	Pressure (mm H ₂ O)	Cells (μL)	Proteins (mg/100 cc)	Glucose (CSF/Blood)
Normal	<200	0–5 Lymphs, 0 Polys	<45	>0.6
Acute bacterial	Increased	200–5000; mostly (>90%) Polys	>100	<0.6
Acute viral	Slight increase	100–700 Lymphs	Slight increase	Normal
Subacute/chronic (TB, fungus)	Increased	25–500 Lymphs	>100	<0.6

CSF = cerebrospinal fluid; Lymphs = lymphocytes; Polys = polymorphonuclear leukocytes; TB = tuberculosis.

Purulent meningitis

Purulent meningitis. Note film of **greenish pus** in the subarachnoid space covering the brain. The dura is reflected back and held by forceps. (*source: CDC*)

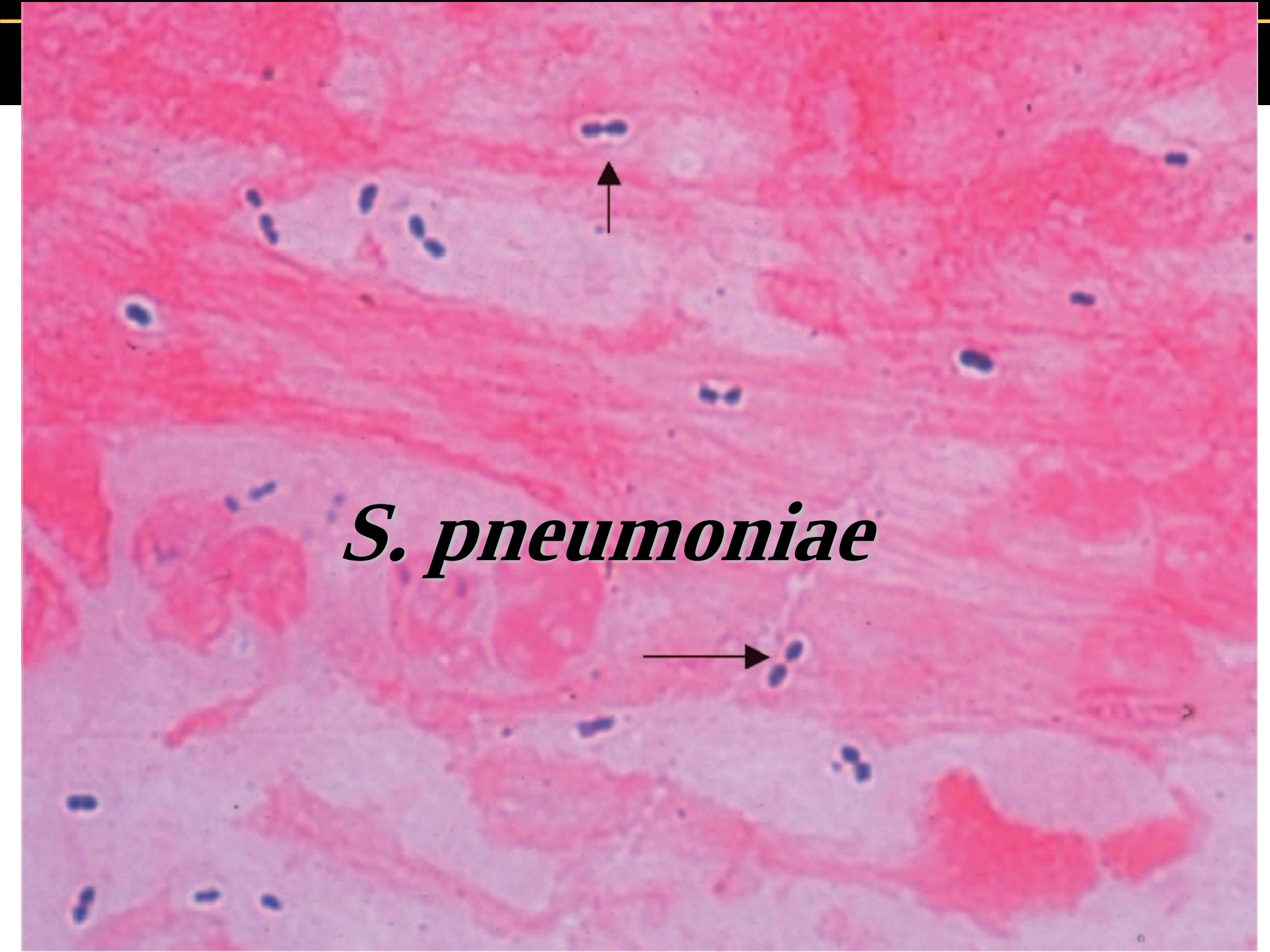


Bacterial Meningitis

- ❖ Some causes of bacterial meningitis are more likely to affect certain age groups:
- **Newborns:** *Group B Streptococcus*, *S. pneumoniae*, *L. monocytogenes*, *E. coli*
- **Babies and young children:** *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *group B Streptococcus*, *M. tuberculosis*
- **Teens and young adults:** *N. meningitidis*, *S. pneumoniae*
- **Older adults:** *S. pneumoniae*, *N. meningitidis*, *H. influenzae*, *group B Streptococcus*, *L. monocytogenes*

Risk Factors

- **Age:** Babies are at increased risk for bacterial meningitis.
- **Group setting:** e.g. college campuses (N. meningitidis).
- **Certain medical conditions:** HIV, CSF leak, splenectomy.
- **Working with meningitis-causing pathogens:** e.g. Microbiologists.
- **Travel:** e.g. meningitis in sub-Saharan Africa, Mecca during the annual Hajj and Umrah.



A microscopic image showing several pairs of blue-stained, oval-shaped bacteria (Streptococcus pneumoniae) against a pink-stained tissue background. Two black arrows point to specific pairs of bacteria: one at the top center and another at the bottom right.

S. pneumoniae

S. pneumoniae

- **Leading cause of pneumonia**
 - **particularly young and old**
 - **after damage to upper respiratory tract**

**e.g. following viral infection, abnormality of RT, alcohol or drug, splenectomy*

- **Bacteremia**
- **Meningitis**
- **Middle ear infections (otitis media)**
- **Sinusitis, Conjunctivitis**
- **Sepsis in splenectomized individuals**

S. pneumoniae

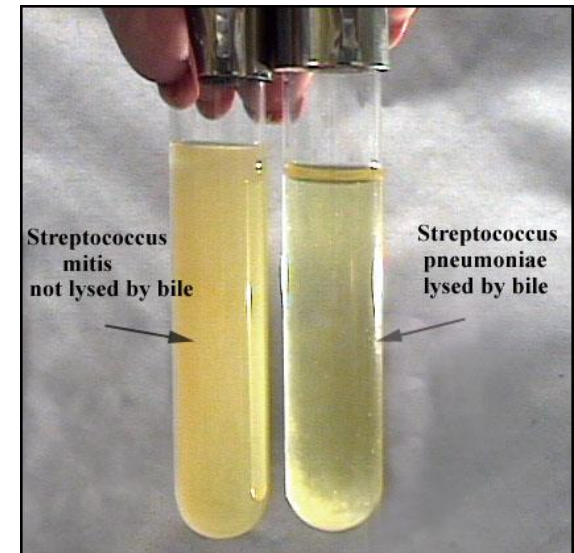
- α hemolytic
- pneumolysin
 - degrades red blood cells under aerobic conditions
- grows well on sheep blood agar
- *no group antigen*
- Quellung reaction
- C-substance (CRP)

Pathogenesis

- Capsular polysaccharide (more than 85)
- IgA protease
- Factors that lower resistance are:
 - Alcohol or drug intoxication
 - Abnormality of the respiratory tract
 - Abnormal circulatory dynamics
 - Splenectomy
 - Certain chronic diseases: sickle cell anemia and nephrosis.

Diagnosis

- *Specimen:* Cerebrospinal fluid (CSF), blood, sputum, pus, swabs
- *Microscopy:* Gram stain – Gram positive cocci in pairs, capsulated, lanceolate shaped
- *Culture:* Blood Agar/ Chocolate Agar – alpha hemolytic colonies
- *Identification tests*
 - Catalase –ve,
 - Optochin sensitive
 - Bile solubility



Diagnosis - spinal fluid

- **Direct Gram staining**
- **Detection of capsular antigen
(Quellung test)**
- **Latex agglutination test**

Identification



optochin resistant

***Ethylhydrocupreine
hydrochloride***



optochin sensitive

Quellung reaction

- **using antisera**
- **capsule "fixed"**
- **visible microscopically**

Therapy

- *S. pneumoniae*
 - most strains susceptible to **penicillin, erythromycin**
 - resistance is common “15%”
- Vancomycin is the drug of choice for the penicillin-resistant pneumococci
- Ceftriaxone or levofloxacin can be used for less severely ill patients
 - *No B-lactamase production but pbps*

Neisseria meningitidis

- **Morphology**
 - Encapsulated Gram⁻ diplococci
- **Colonization**
 - Asymptotically in nasopharynx of healthy individuals

Neisseria meningitidis

- **Microbial physiology and structure**
 - Colony morphology
 - Form transparent, non-pigmented, non-hemolytic colonies on chocolate blood agar in 5% CO₂
 - Capsule indicated by large mucoid colonies
 - Physiology
 - **Oxidase +**
 - Acid production from **glucose** and **maltose**, but not **sucrose** or **lactose**
 - Several serotypes known

Oxidase Test

Positive

Negative



Neisseria meningitidis

- **Causes of pathogenesis**
 - Ability to colonize nasopharynx due to presence of pili
 - Ability to resist host defenses and spread due to presence of capsule
 - Expression of toxic effects due to presence of endotoxin
 - IgA protease

Neisseria meningitidis

- **Epidemiology**
 - Transmitted by respiratory secretions to people living in close contact
 - Incidence during Spring
 - Susceptibility
 - Children <5 years old
 - Older individuals infected during epidemics
 - Maternal Ab protection for first 6 months

Neisseria meningitidis

- **Syndromes**
 - Meningitis
 - Symptoms: headache and fever (young children—fever and vomiting)
 - Mortality
 - Untreated: 100%
 - Treated: $\leq 15\%$ when antibiotics administered promptly
 - Incidence of neurological problems is low

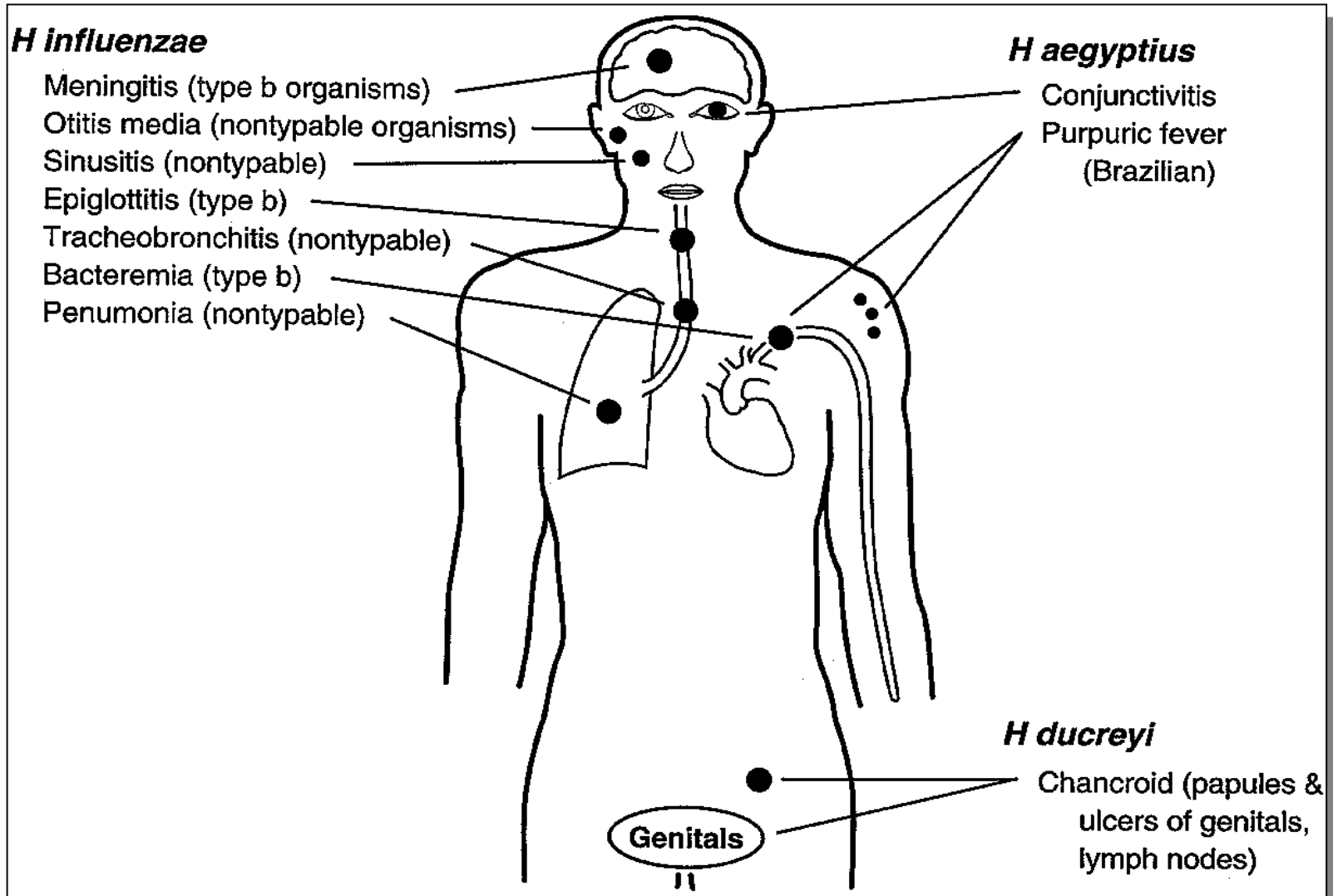
Neisseria meningitidis

- **Syndromes**
 - Meningococccemia (with or without meningitis)
 - Life-threatening, with mortality of 25%, even when promptly treated
 - Pathology
 - Thrombosis of blood vessels, Multiorgan involvement, Small skin **lesions** on trunk and lower extremities (may form larger hemorrhagic lesions).
 - May progress to completely debilitating **DIC** with shock (destruction of adrenal gland)

Neisseria meningitidis

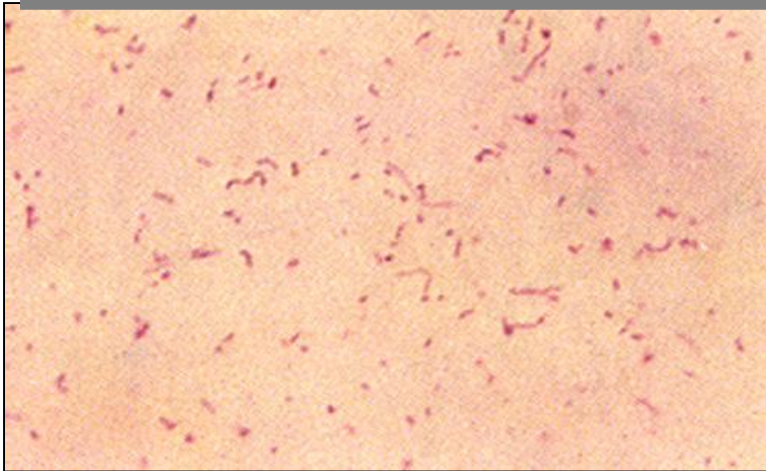
- **Laboratory diagnosis**
 - Blood and cerebrospinal fluid (**especially inside neutrophils**)
- **Treatment**
 - Penicillin (resistant strains rarely seen)
 - Chloramphenicol, ceftriaxone, cefotaxime

Haemophilus: affected organs

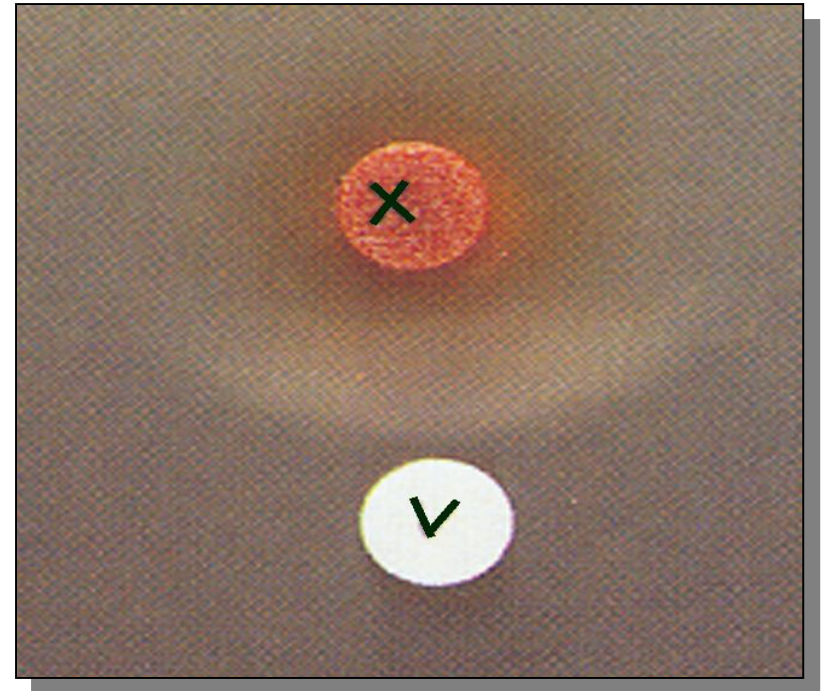


Haemophilus: a Gram negative bacillus

- ☐ *A Gram negative bacillus*



- ☐ *Grows on chocolate agar with factors X (hemin) & V (NAD)*



H. influenzae-b: virulence factors

- ❏ **Capsule** is the major pathogenesis factor: it is antiphagocytic (**polyribitol phosphate**)
- ❏ **LPS** causes the usual inflammatory and cardio-vascular symptoms
- ❏ **IgA1 protease** may aid mucosal colonization

H. influenzae-b: symptoms

- ☒ Runny nose, low grade fever, headache
- ☒ Septicemia, septic arthritis, conjunctivitis, cellulitis, **Epiglottitis**, meningitis, convulsions, coma
- ☒ **Airway obstruction & suffocation**

H. influenzae-b:
secondary complications

☒ Loss of hearing and learning disabilities (**mental retardation**)

H. influenzae non-b strains

-  **Second** commonest cause of **otitis media** among young children
-  Pneumonia in adults (elderly with chronic lung diseases)

H. influenzae-b: diagnosis

- ☒ **History** and physical examination
- ☒ **Blood culture** (positive in >50%)
- ☒ **PRP** (polyribitol phosphate in serum and urine)
- ☒ **Gram-negative** coco-bacilli in CSF (in >80% of meningitis cases)

H. influenzae-b:
treatment

 **Cephalosporin is the antibiotic of choice**

Early and prompt treatment is essential.
Delays often lead to meningitis, epigloitis and death. If the patient does survives, often there is a loss of hearing and mental retardation may occur.

Listeria monocytogenes

History



1926: isolated from rabbits with mononucleosis



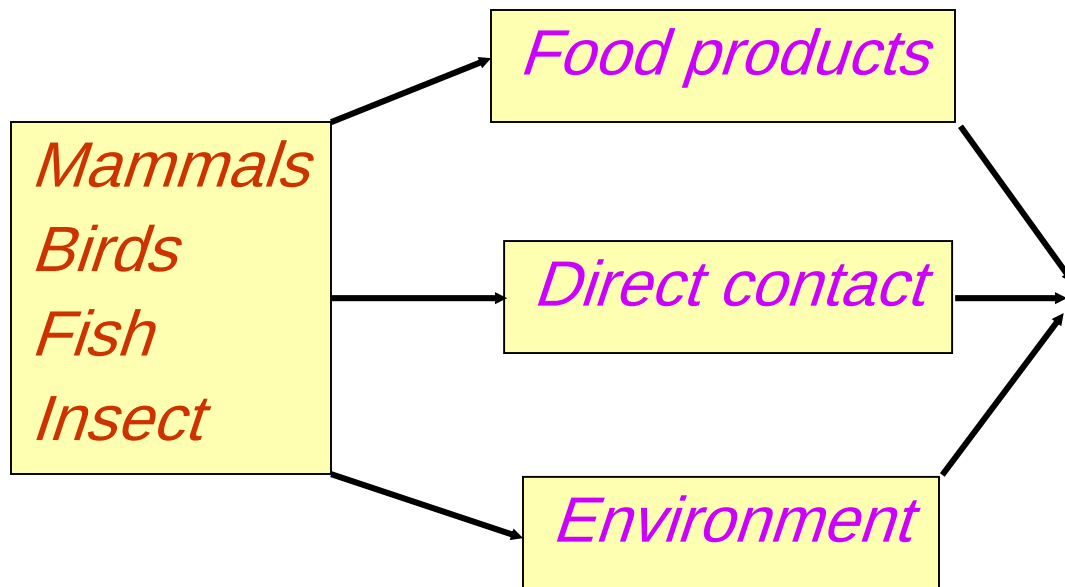
1927: *given its name to honor surgeon lord Lister*



1929: *isolated from human with mononucleosis-like disease*



Susceptible host and source of listeriosis



Healthy children and adults

asymptomatic carriage

Pregnant women

asymptomatic carriage

septicemia

neonatal disease

Immunocompromized

asymptomatic carriage

meningitis

septicemia

Superinfections

Morphology/Physiology



Gram-



Short



β -hemo



Can grow and replicate at 4 °C



Adult Disease



Normal adult are resistant



Common organism in HIV infected and other immunosuppressed patients



Septicemia



Meningitis



Gastroenteritis: watery diarrhea, headache, fever & abdominal cramps

Neonatal Disease



Mother has no symptomatic illness



Granulomatosis infantiseptica - infection of fetus in utero



can lead to **abortion**, disease at birth (sepsis, pneumonia, fetal distress, seizures, rash, abscesses, and granulomas)



High mortality rate



Exposure on vaginal delivery



can result in meningitis or meningo-encephalitis with sepsis within 2-3 weeks

Virulence Properties



β -hemolysin (listeriolysin O), lecithinase and phospholipase



produced by virulent strain only



oxygen labile



antigenic



disrupts phagosome

Virulence Properties



Intracellular Growth



bacterium escapes from host vacuole



undergoes rapid division



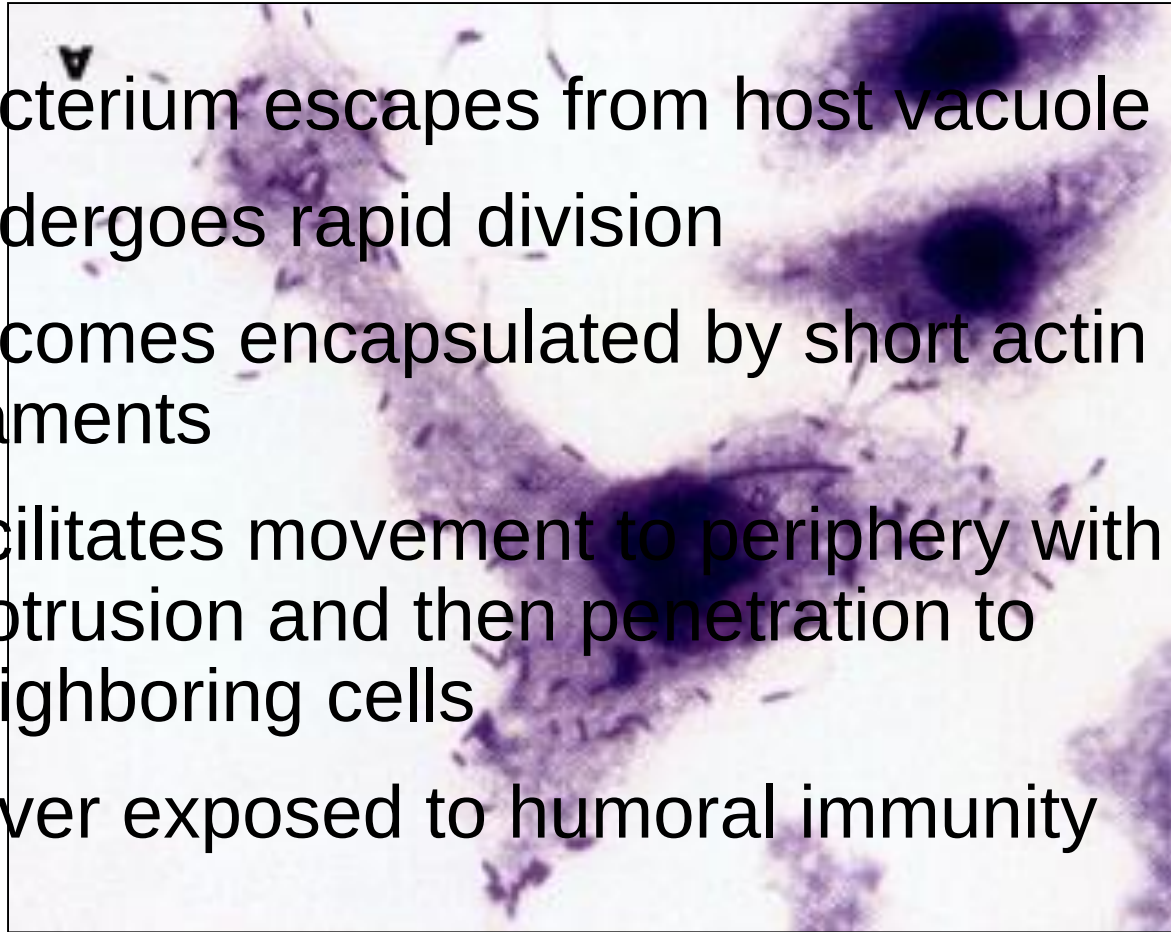
becomes encapsulated by short actin filaments



facilitates movement to periphery with protrusion and then penetration to neighboring cells



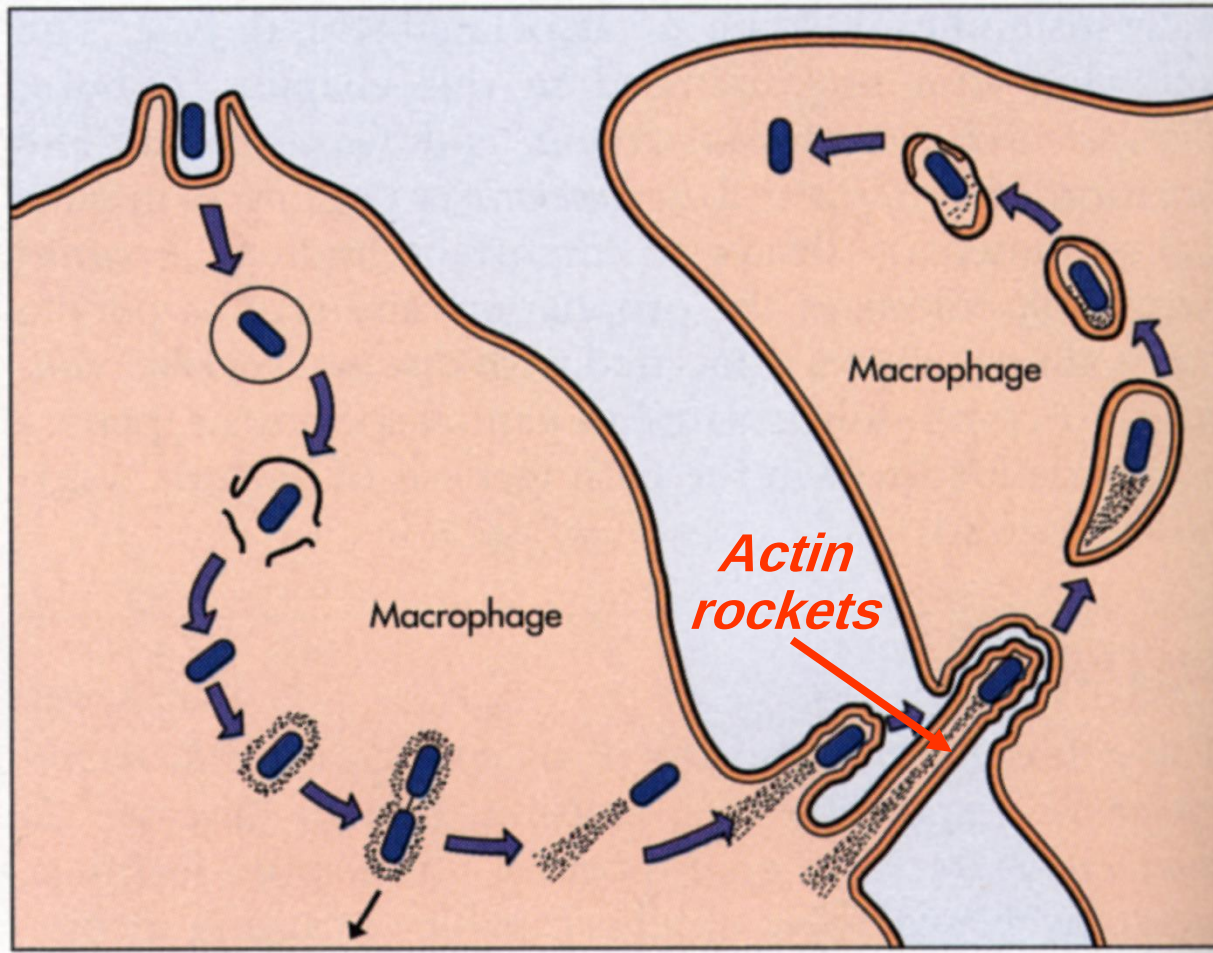
never exposed to humoral immunity



Cell-cell transmission

Entry

Escape



Fusion
with
another
cell

replication

actin tail

extrusion

Laboratory Diagnosis

- Gram staining
- Culture: *small, gray colonies, narrow zone of β -hemolysis, tumbling motility*
- Sugar fermentation

Treatment



Penicillin or ampicillin alone or in combination with gentamicin



Protection is with activation of macrophages

Cryptococcosis

- Fungal disease caused by an encapsulated yeast *Cryptococcus neoformans*, pathogenic to man & animals.
- 2nd most common fungal infection after candidiasis in HIV - infected individuals.
- Isolated from pigeon nests, droppings, old buildings & nitrogenous soil .

C. neoformans, general properties

- Natural reservoir Soil, bird droppings
- Microscopically. Encapsulated yeast (India ink)
- Macroscopically. Creamy, mucoid colonies
(SDA)
- Serotypes A-D (most frequently A)
- Pathogenicity factors
 - a. Capsule
 - b. Ability to grow at 37°C

Cryptococcus neoformans (SAB)



Wet/Mucoid Capsule Forming Colonies

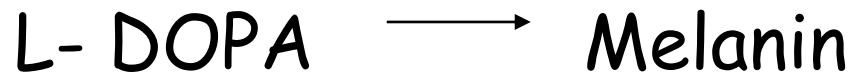
Cryptococcus neoformans (SAB)



Creamy Butyrous Colonies

Virulence factors

- Capsule - Inhibits phagocytosis.
- Melanin production by the enzyme phenol oxidase.



Antioxidant - protects the organism from intracellular killing by phagocytes

Pathogenesis

- Infection occurs by **inhalation**, but sometimes through **skin or mucosa**.
- Weakening of immune system leads to reactivation & dissemination to CNS and other sites.
- **Visceral forms** simulate tuberculosis & cancer clinically.
- **Cutaneous form** varies from small ulcers to granulomas.

Clinical Features

- Seen in HIV +ve patients when CD4+ count falls below 200 cells / mm³
- Extra pulmonary cryptococcosis is one of the AIDS – defining disease.
- Clinical types :
 1. Pulmonary
 2. Extrapulmonary – CNS, viscera, bones & skin

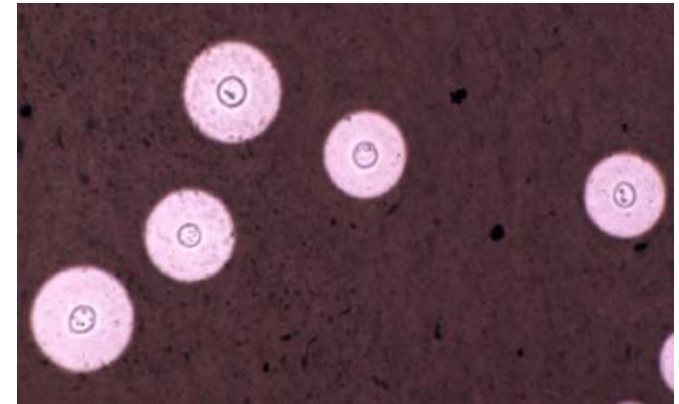
Cryptococcal meningitis is the most serious type of infection, resembles TB and is often seen in AIDS patients.

Laboratory Diagnosis

- Specimen - Serum, CSF, body fluids

Direct examination

- **Wet mount:** India ink - yeast cells a distinct



- Gram's stain - Gram +ve budding yeast cells

Treatment and Prophylaxis

- Antifungals - AMB: Drug of choice
 - Flucytosine
- Vaccine - conjugate vaccine developed

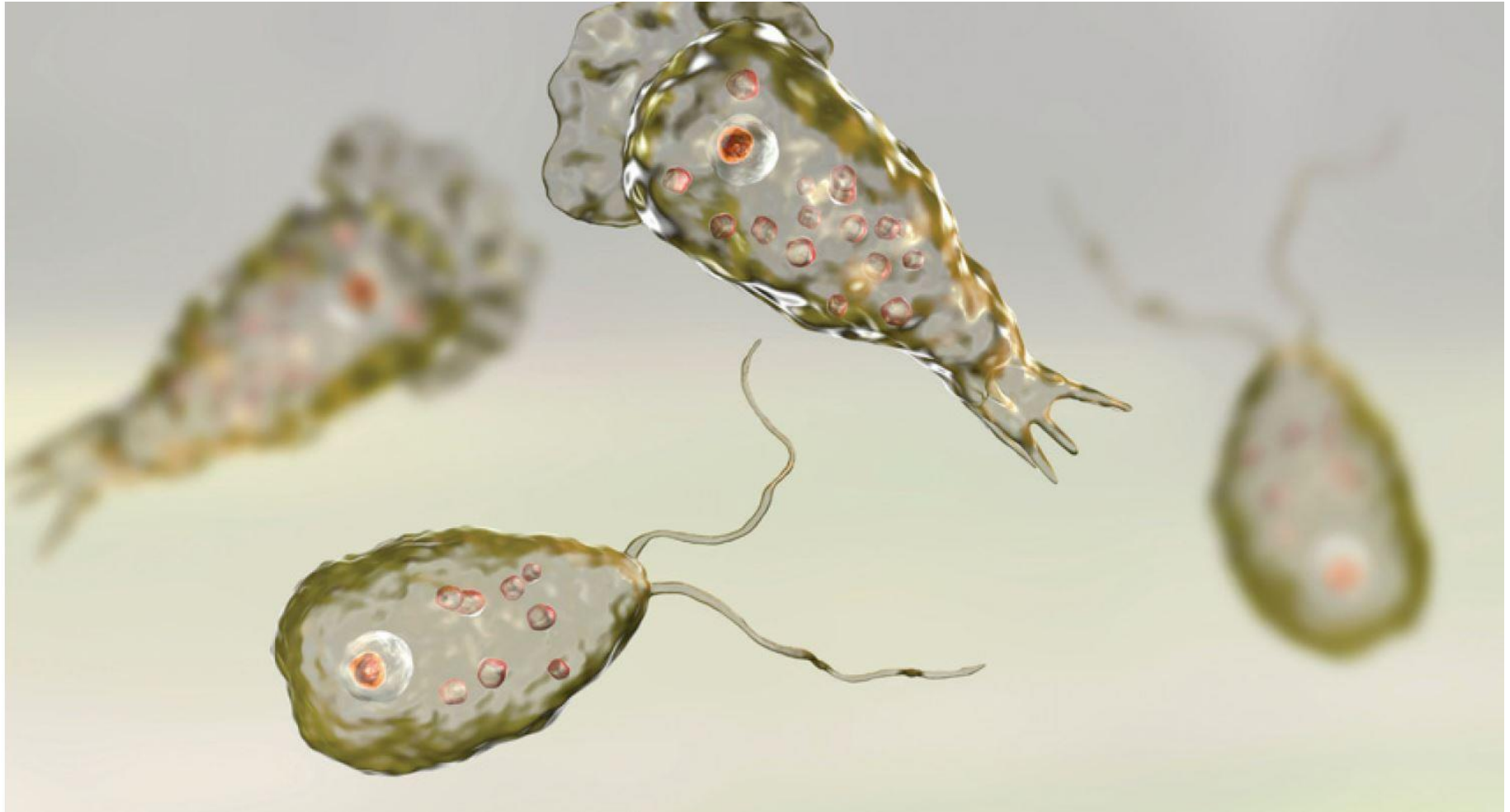
Amebic Meningitis

- Primary amebic meningoencephalitis (PAM) is a rare brain infection that is caused by *Naegleria fowleri* and is usually fatal.
- *Naegleria fowleri* is a free-living ameba
- From 1962 to 2021, 154 U.S. infections have been reported to CDC, with an average of 2–3 per year.
- There have only been four U.S. survivors.
- *Naegleria fowleri* does not live in salt water, like the ocean.

Signs and Symptoms

- In its early stages, symptoms of PAM are similar to symptoms of bacterial meningitis.
- Symptoms of PAM start 1 to 12 days after infection.
- The initial symptoms include:
 - Headache, Fever, Nausea, Vomiting
- Later symptoms include:
 - Stiff neck, Altered mental status (confusion), Lack of attention to people and surroundings, Seizures, Hallucinations, Coma
- After the start of symptoms, the disease progresses rapidly and usually causes death within about 5 days (range 1 to 18 days).

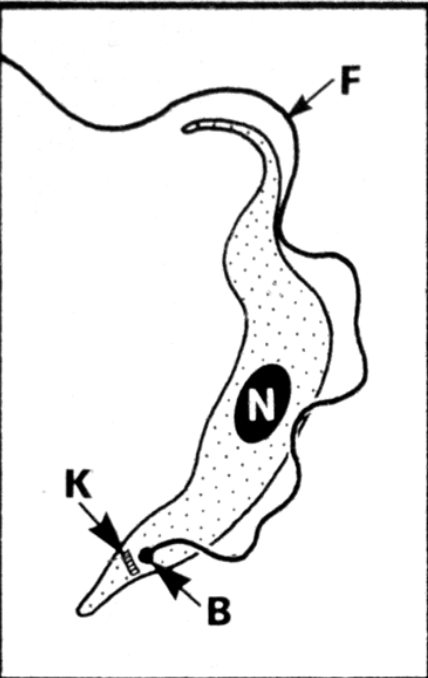
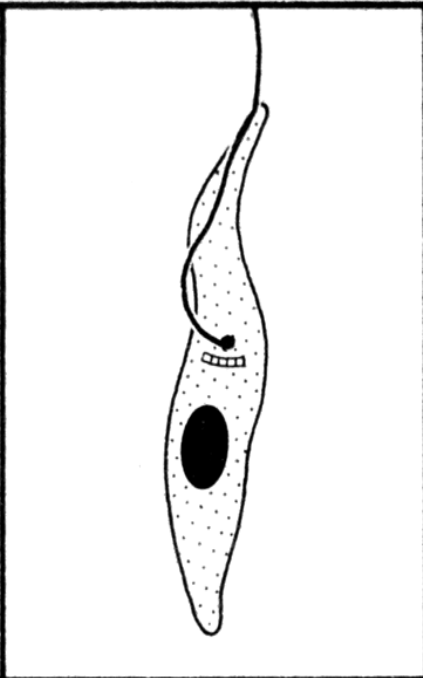
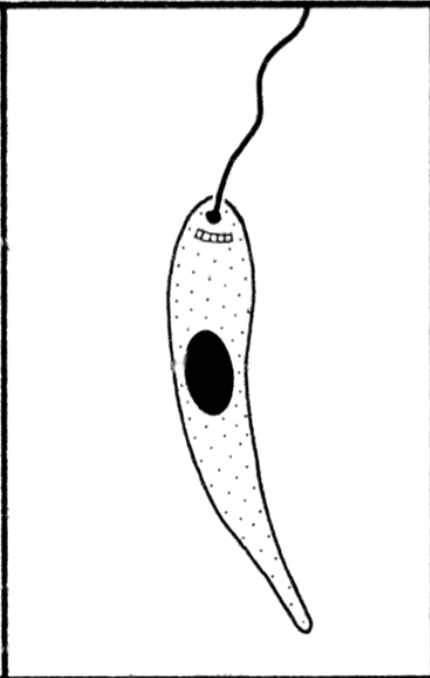
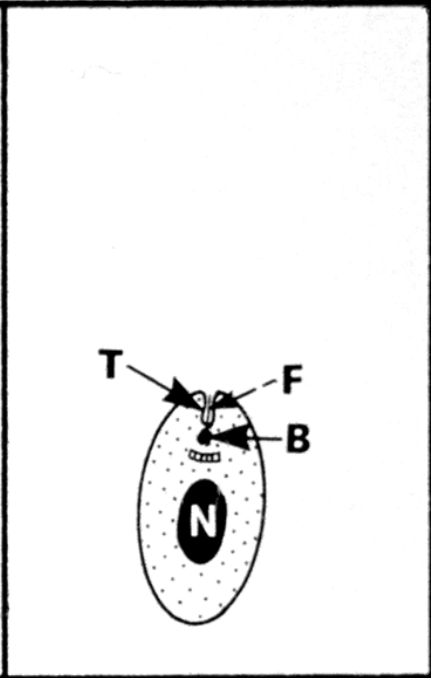
Naegleria fowleri: Brain-eating amoeba

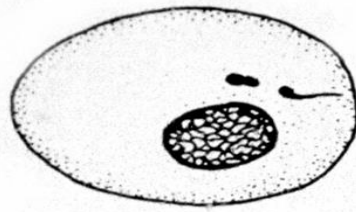


TRYPANOSOMIASIS

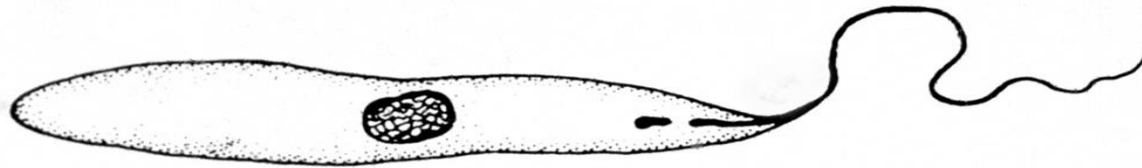
African trypanosomiasis (Sleeping Sickness)

- Etiology: *T. brucei gambiense* (slow)
T. brucei rhodesiennse (rapid)
- ▶ Epidemiology: *T. brucei gambiense* (western)
T. brucei rhodesiennse (eastern)
- ▶ Morphology: 10-30x1-3 μm , single nucleus, 1 flagellum, kinetoplast, undulating membrane, VSG

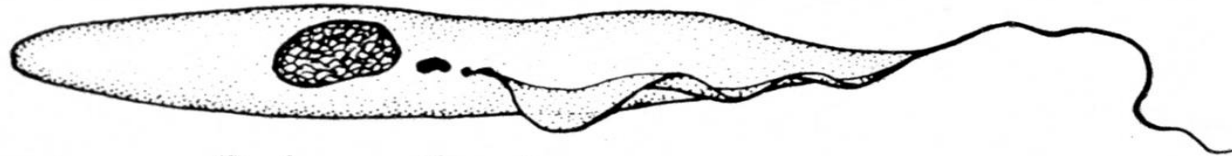
			
<i>trypomastigot</i>	<i>epimastigot</i>	<i>promastigot</i>	<i>amastigot = mikro-, kryptomastigot</i>
Trypanosoma - Form	Crithidia - Form	Leptomonas - Form	Leishmania - Form



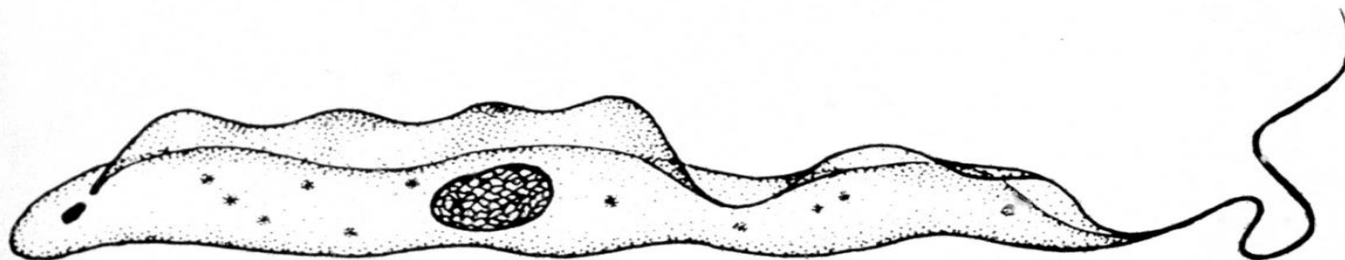
Amastigote



Promastigote

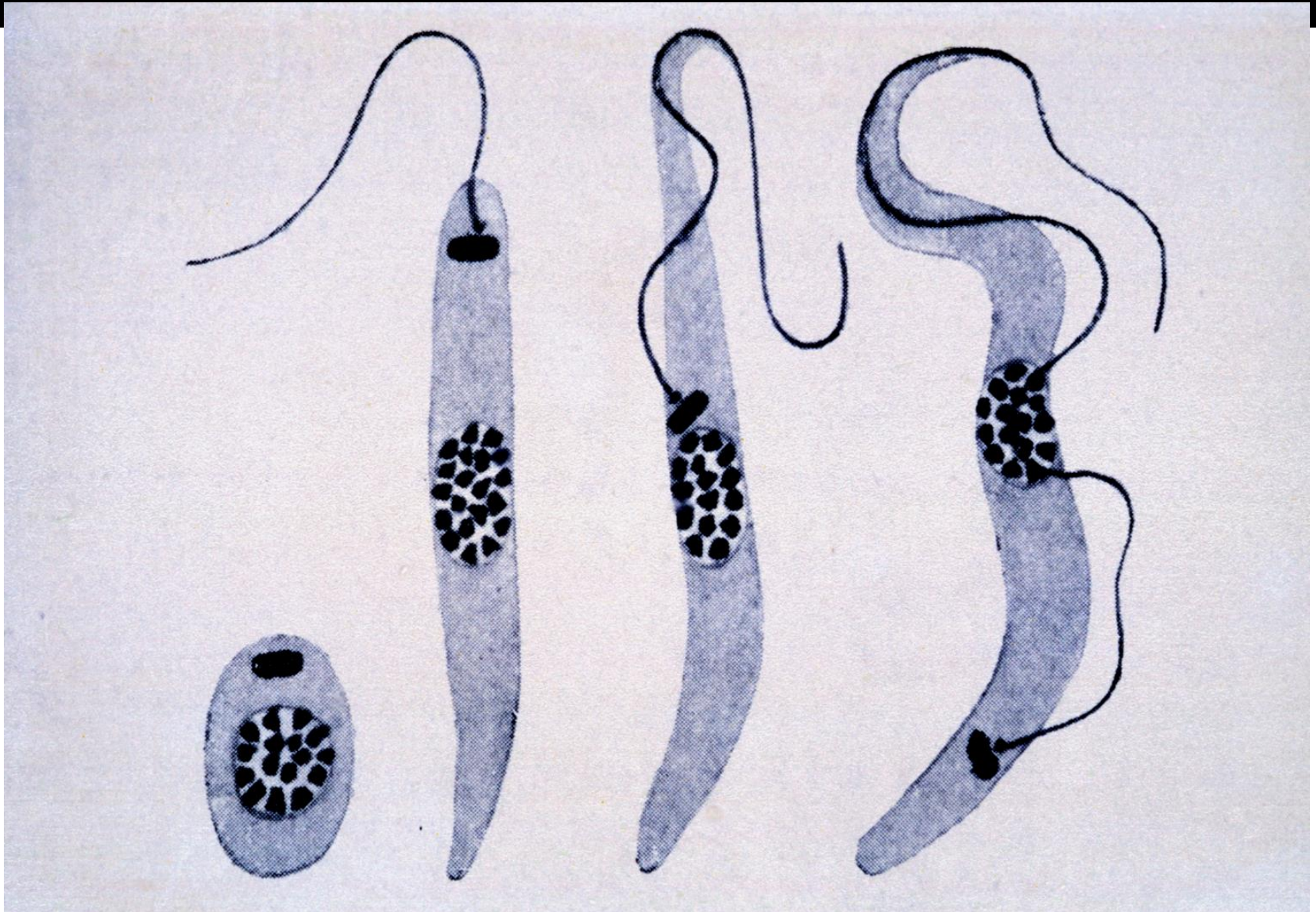


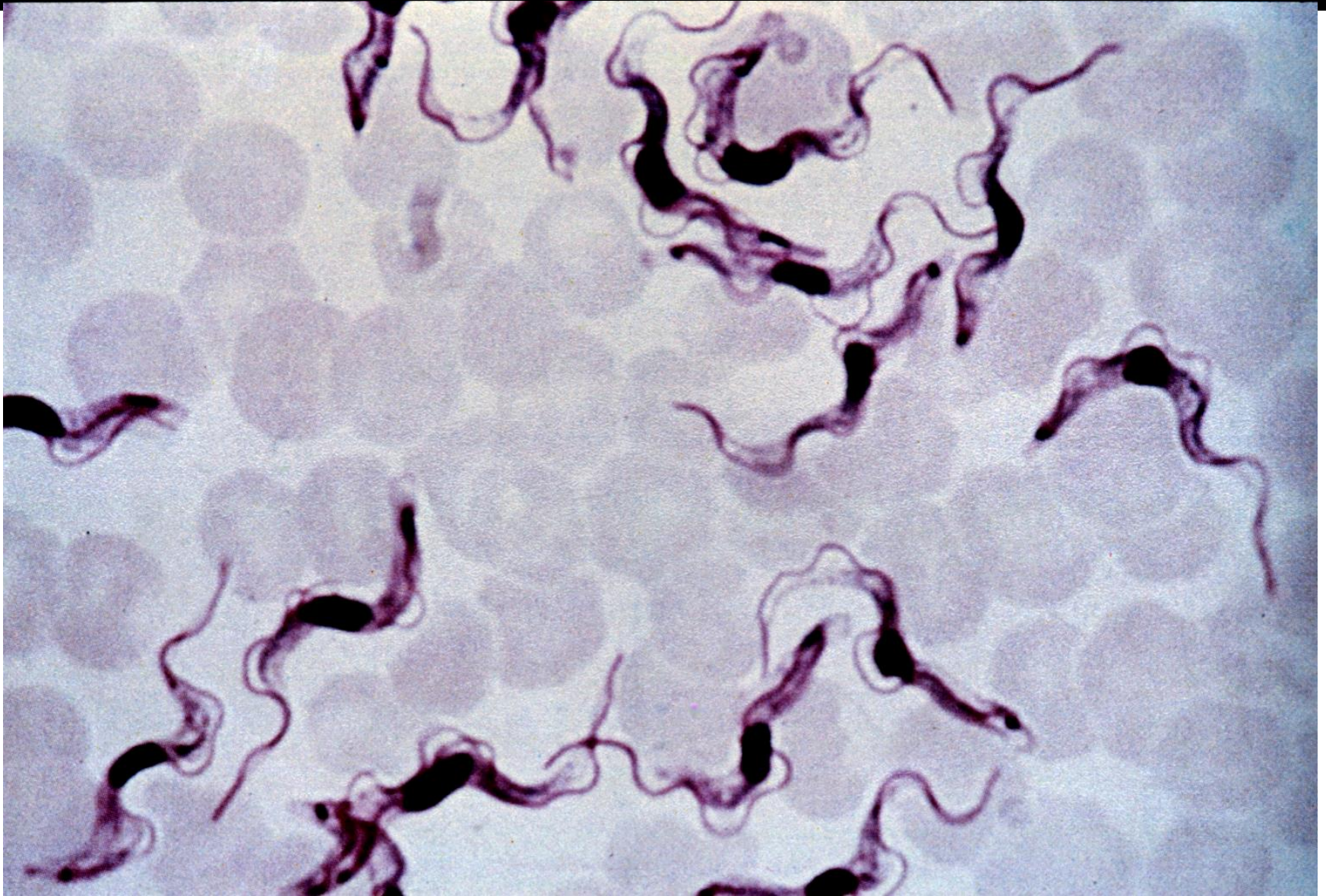
Epimastigote



Trypomastigote

H. Kitamura

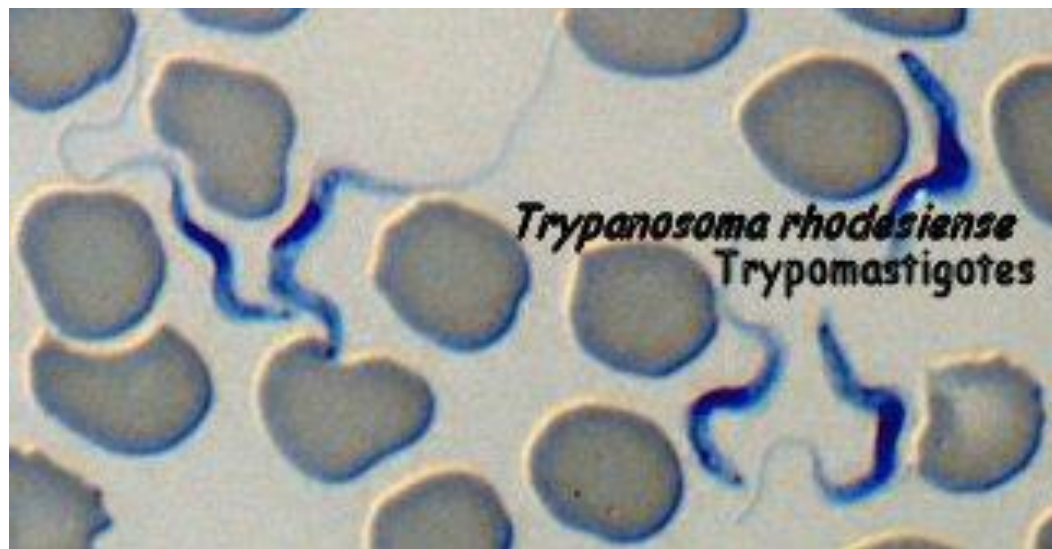
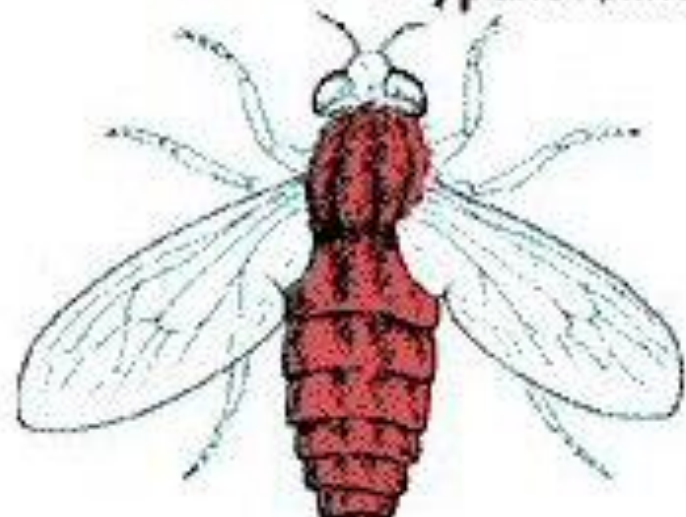






***Glossinia*
Tsetse Fly**

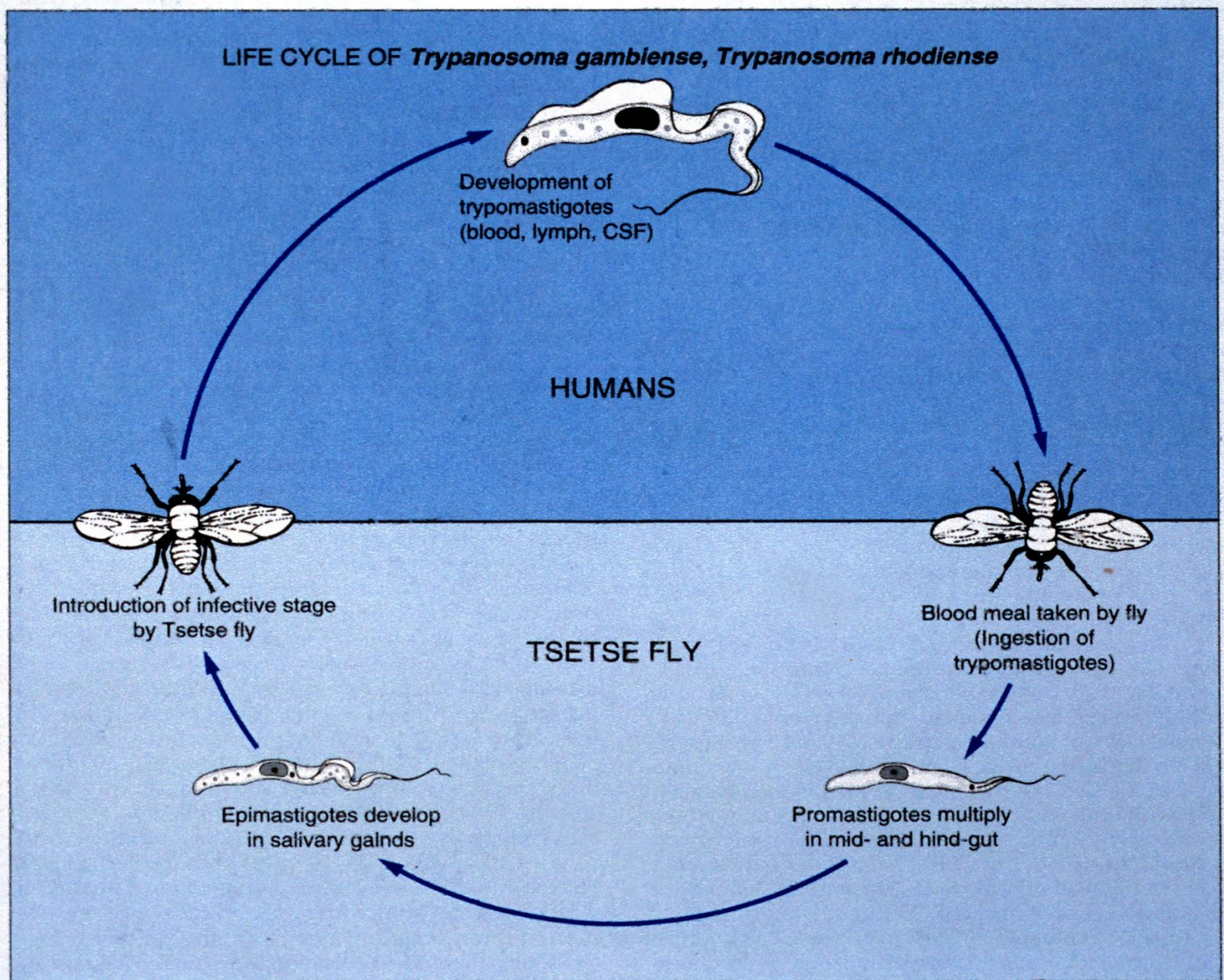
Insect
Vector
for African
Trypanosomiasis



***Trypanosoma rhodesiense*
Trypomastigotes**

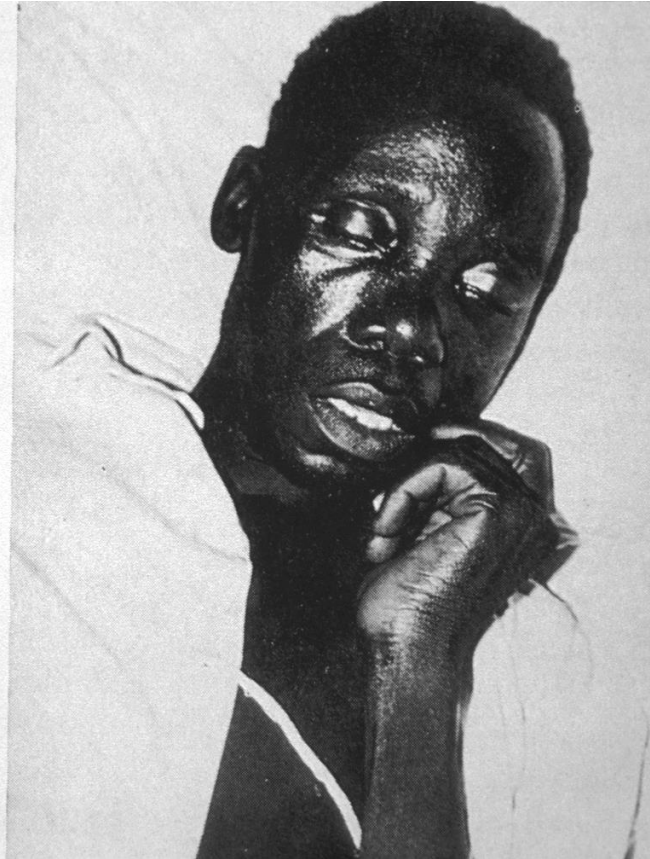
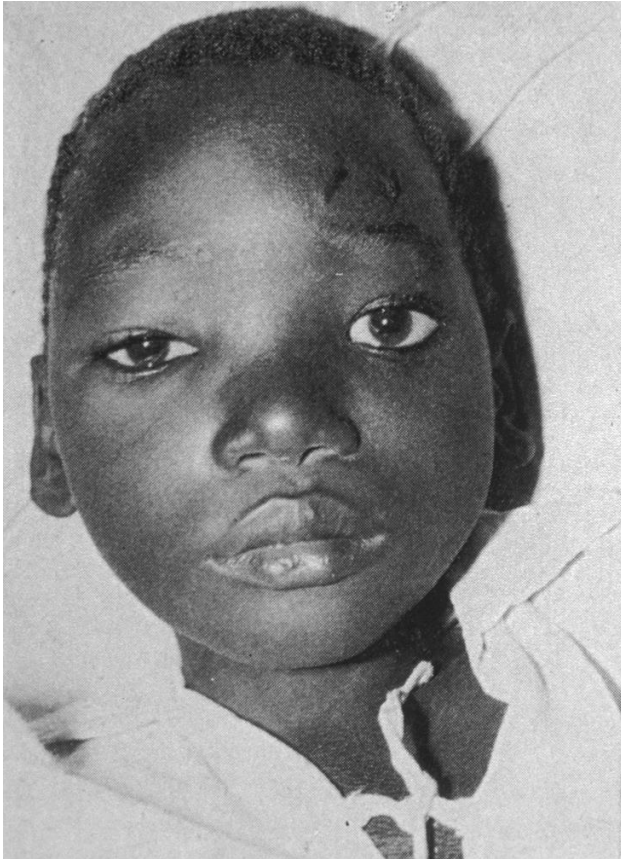
Glossinia (Tsetse fly)

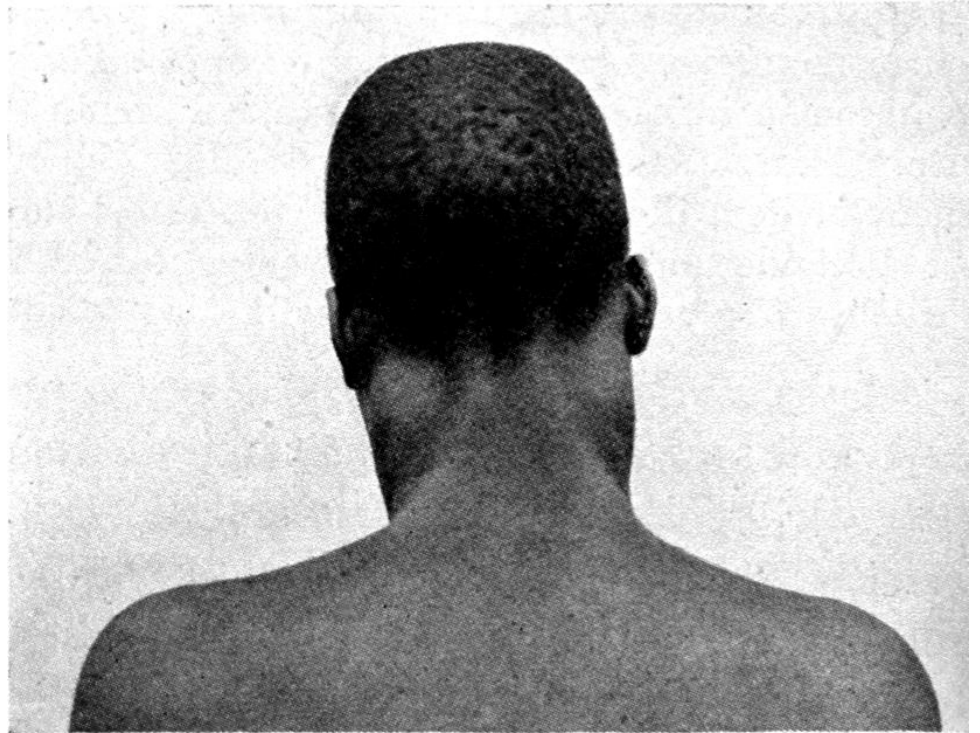
Life Cycle



Symptoms

- *T. rhodesiense* causes a more **acute progressive** disease. *T. gambiense* disease is chronic and **low-grade** with progression to fatality over the course of a few years.
- Three stages of disease:
- Bite reaction
- Parasitemia
- CNS stage





Pathology & Immunology

- Antigenic variation of trypomastigotes involves surface glycoproteins. This gives rise to an ability to evade host defenses & produce cyclic spiking fever in the acute phase
- The parasite causes polyclonal expansion of B lymphocytes and plasma cells and an increase in total IgM concentration
- It causes severe depression of cell mediated and humoral immunity to other antigens

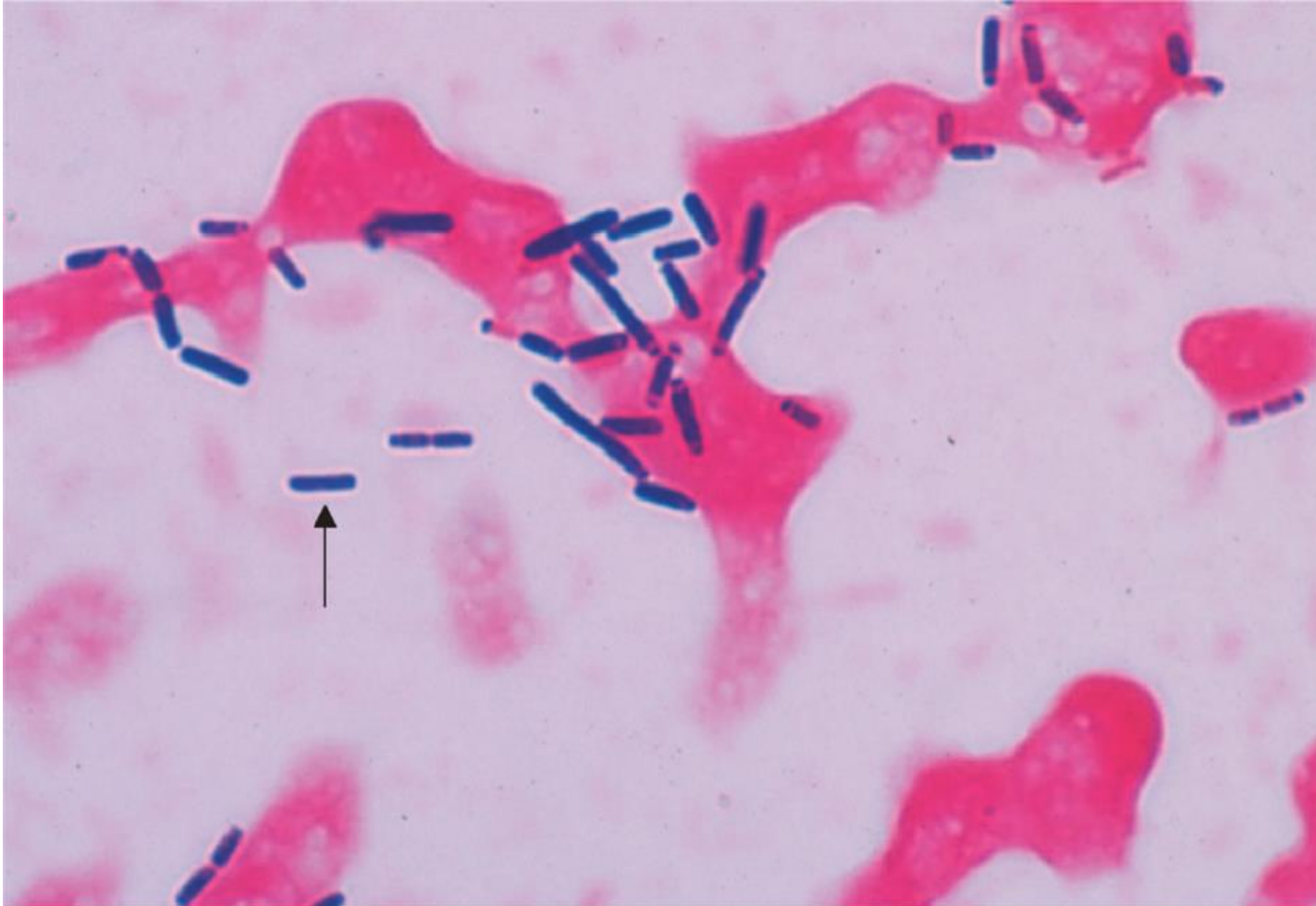
Diagnosis

- Blood smears, thick or thin film revealing trypomastigotes
- Chancre or lymph node aspirates
- CSF presence of trypomastigotes indicates encephalitic stage
- Serology includes ELISA for IgM antibody to demonstrate acute infection

Treatment & Control

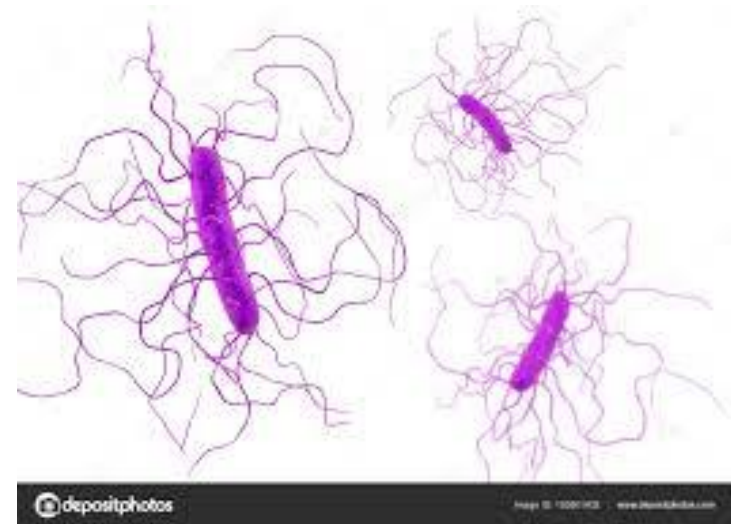
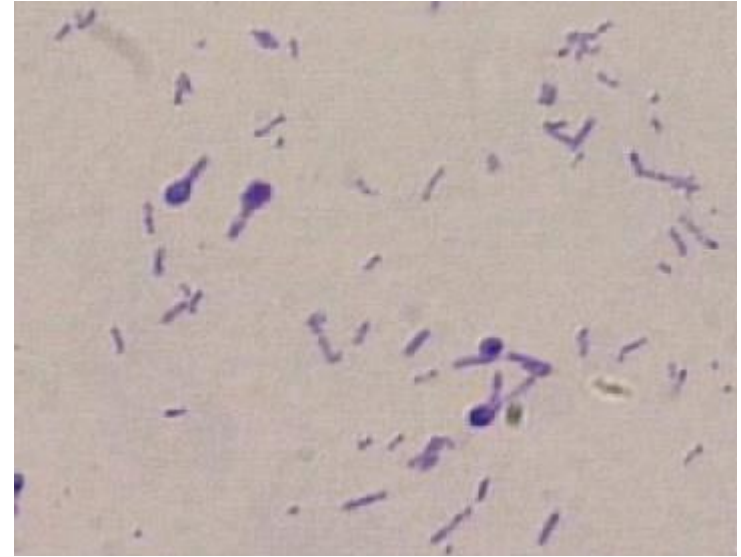
- **Suramin** or Pentamidine isethionate is curative if given early enough
- CNS cases should be treated with Melarsoprol
- Prevention includes avoiding bites

Tetanus and Botulism



Physiology and Structure

- Anaerobic.
- Large gram-positive rods.
- The spores are usually wider than the rods, and are located terminally or subterminally.
- Most clostridia are motile by peritrichous flagella



Clostridium tetani

Transmission

Usually a wound site, skin-popping, or contaminated umbilicus that causes neonatal tetanus

Pathogenesis

- Tetanus toxin (tetanospasmin) binds to ganglioside receptors in CNS and blocks release of inhibitory mediators as glycine & γ -aminobutyric acid (GABA) at spinal synapsis.*
- They are proteases*
- It has one antigenic type*

Clinical Findings

- Strong muscle spasms, specifically **lockjaw**
- **Opisthotonos**
- Respiratory failure
- Spastic paralysis
- High mortality rate



*A severe case of tetanus.
muscles, back and legs are rigid
muscle spasms can break bones
can be fatal (e.g respiratory failure)*



Tetanus (Lockjaw)



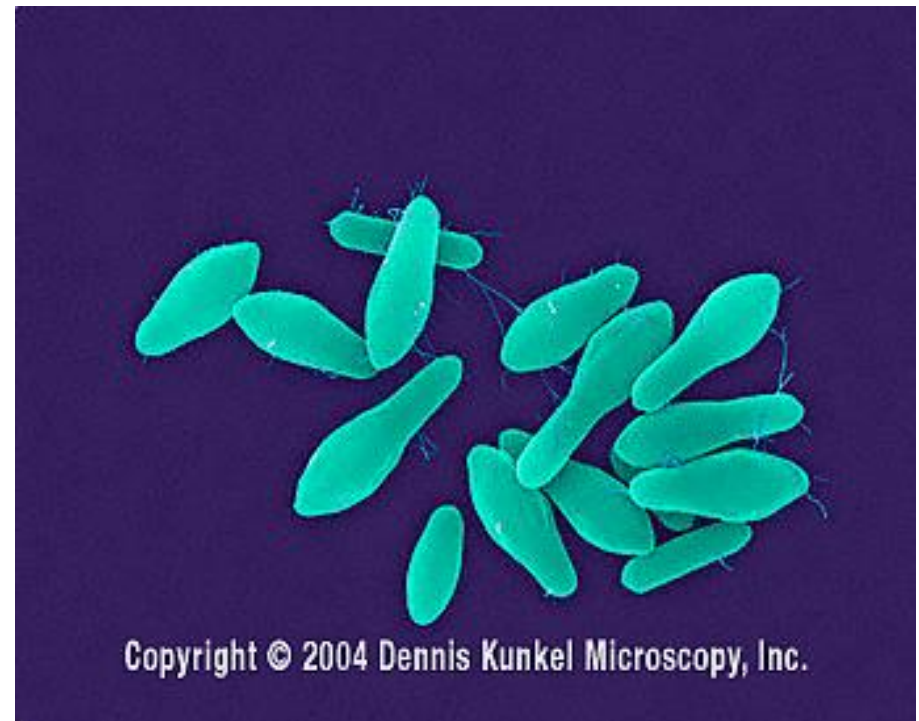
التشنج الظهري Opisthotonos

Tetanospasmin

- disseminates systemically
- binds to ganglioside receptors
 - inhibitory neurons in CNS
- glycine
 - neurotransmitter
- stops nerve impulse to muscles
- spastic (rigid) paralysis
- severe muscle contractions and spasms
- can be fatal

Laboratory Diagnosis

- No microbiologic or serologic diagnosis
- rarely isolated
- Terminal spores „*tennis racket*“



Treatment & Prevention

- Tetanus immunoglobulins
- Metronidazole or penicillin G
- An adequate airway
- Benzodiazepines (valium)

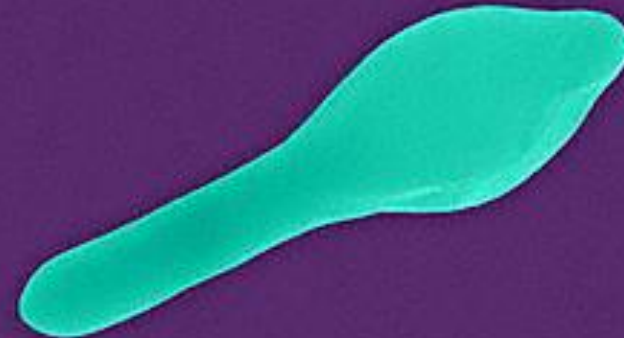
Immunization with tetanus toxoid (DTaP)

Clostridium botulinum

Transmission

- *Spores are widespread in soil, contaminate vegetables and **meats***
- *The highest risk foods are **alkaline vegetables** as green beans and mushroom and **smoked fish***
- ***Toxin is heat-labile***
 - *germination of spore*
 - ***inadequately sterilized***
canned food
—home
 - ***not an infection***

C. botulinum



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Pathogenesis

- Botulinum toxin **blocks release of acetylcholine** by its protease activity
- It is among the **most toxic substances**
- 8 immunological types, (**A**, B & E)
- Type A (**Botox**) prepared commercially
- A polypeptide toxin **encoded by a lysogenic phage**

Clinical Findings

- **Descending** weakness and paralysis
- **flaccid paralysis**
- Diplopia, dysphagia and respiratory muscle failure
- **Wound botulism**
- **Infant botulism (honey)?**
- In contrast, Guillain-Barré syndrome is an **ascending paralysis**

Laboratory Diagnosis

- **Usually not cultured**
- **Animal experiment (mouse protection test)**
- **Enzyme-linked immunoassay (EIA)**
- **Polymerase-chain reaction (PCR)**

Treatment & Prevention

- **Trivalent antitoxin, along with respiratory support**

(serum sickness!)

(Now heptavalent vaccine. Also divalent for infant)

- **Proper sterilization of canned and vacuum-packed foods**
- **Swollen cans must be discarded**

Viral Meningitis

- Viral meningitis is the most common type of meningitis.
- Most people get better on their own without treatment.
- Babies younger than 1 month old and people with weakened immune systems are more likely to have severe illness from viral meningitis.
- Most people with mild viral meningitis usually get better on their own within 7 to 10 days.
- Initial symptoms of viral meningitis are similar to those for bacterial meningitis.
- However, bacterial meningitis is usually severe and can cause serious complications, such as brain damage, hearing loss, or learning disabilities.

Viral Meningitis

- *Non-polio enteroviruses*
- *Mumps virus*
- *Herpesviruses, (EBV, HSV, VZV)*
- *Measles virus*
- *Influenza virus*
- *Arboviruses, such as West Nile virus*
- *Lymphocytic choriomeningitis virus*