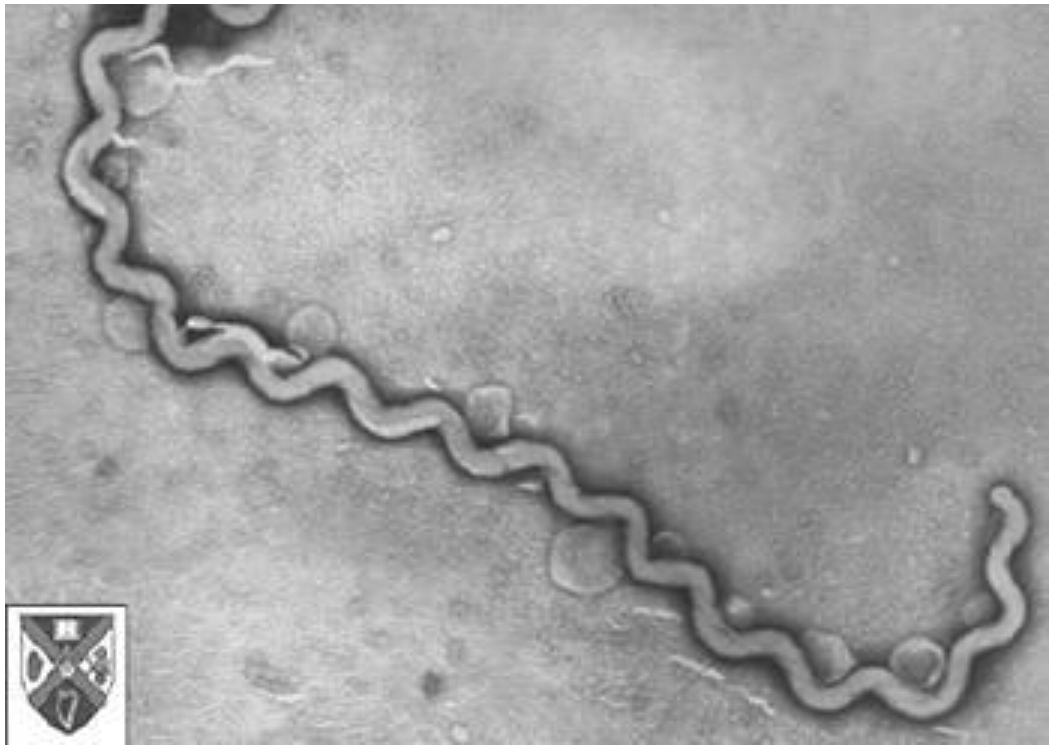
Chapter 23

Spirochetes

Spirochetes are **thin walled, flexible, spiral rods**.

They are **motile** through the **undulation of axial filaments** that lie under the outer sheath.



Three genera cause human infection:

Treponema which causes **syphilis** and **the nonvenereal treponematoses.**

Borrelia which causes **Lyme disease** and relapsing fever

Leptospira which causes **leptospirosis**

Treponemas and **leptospirae** are so **thin** that they are seen only by dark field microscopy, silver impregnation, or immunofluorescence.

Borreliae are **larger**, accept Giemsa and other blood stains, and can be seen in the standard light microscope.

Treponema

Treponema pallidum

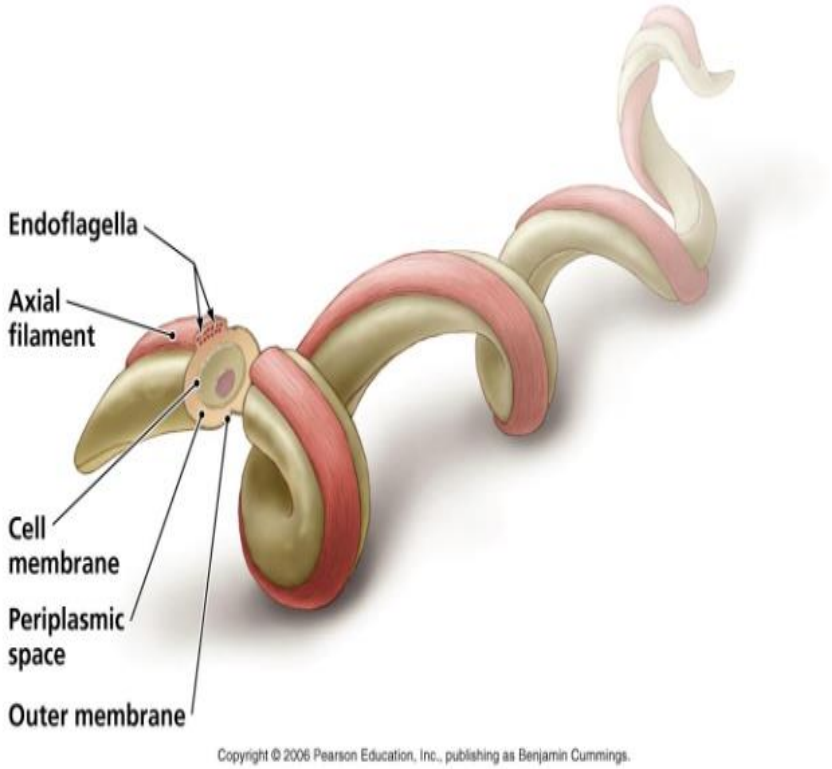
-- It causes **syphilis**.

-- **It has not been grown on bacteriological media or in cell culture.**

-- **Nonpathogenic Treponema**, a part of normal flora of mucus membrane, **can be grown**.

-- Because of **very slow growth**, antibiotic treatment has to be sustained for several weeks.

-- For this reason, **benzathine penicillin** is preferred because of its **slow release** with bactericidal concentrations for several weeks after administration.



Transmission and Epidemiology

-- ***T. pallidum*** is **transmitted from spirochete containing lesions of skin or mucus membranes** (e.g., genitilia, mouth, and rectum) of an infected person to other persons by intimate contact.

-- It can also be transmitted from **pregnant women to their fetuses**.

-- Rarely blood for transfusions collected during **early syphilis** is also infectious.

-- **Humans are the only hosts**. There is no animal reservoir.

-- It has **worldwide occurrence**.

Pathogenesis and Clinical Findings

-- ***T. pallidum*** **does not produce toxins or enzymes**.

-- It often infects the endothelium of small blood vessels causing **endarteritis**.

-- This occurs during all stages of syphilis but is particularly important in the pathogenesis of the brain and cardiovascular lesions seen in **tertiary syphilis**.

In **primary syphilis**, the spirochetes multiply at the site of inoculation, and a local, non tender ulcer called **chancre** forms in 2-10 weeks.

The ulcer heals spontaneously but organisms **spread widely via blood stream**.

After 1-3 months, lesions of **secondary syphilis** may appear.

These often appear as **maculopapular rash** notably on the **palms and skin** or as **moist papules on skin and mucus membranes (mucus patches).**

Moist lesions on genitals are called **condylomata lata**.

These lesions are rich in spirochetes and are **highly infective**, but they also heal spontaneously.

Patchy alopecia also occurs.

-- Symptoms include low-grade fever, malaise, anorexia, weight loss, headache, myalgias, and **generalized lymphoadenopathy**.

-- Pharyngitis, meningitis, nephritis, and hepatitis may also occur.

-- **In some cases, disease may progress without symptoms of primary and secondary syphilis.**

-- **One third of the cases are cured without treatment**, and **one third become latent** (no symptoms but serology remains positive).

-- In **early latent phase** (up to 2 years) symptoms of secondary syphilis can reappear and patients can infect others.

-- In **late latent period** which may last for many years, no symptoms occur and patients are not infectious.

-- **In remaining one third, disease progress to tertiary syphilis.**

-- **Tertiary syphilis** may show **granulomas (gummas), esp. of skin and bones; CNS involvement; or cardiovascular lesions.**

-- In tertiary lesions, **treponema are rarely seen**.

-- ***T. pallidum*** also causes **congenital syphilis.**

Syphilis: Tertiary

- This stage characterized by granulomatous lesions (gummas) of skin, internal organs, CNS, bones, eyes, and cardiovascular system
- By body's hyperimmune reaction to remaining spirochetes

(c) Gummas of tertiary stage on the back of an arm; gummas such as these are rarely seen today in the era of antibiotics.

-- The organism is **transmitted across the placenta**, typically after 3rd month of pregnancy, and fetal infection can occur.

-- **In infected neonates, skin and bone lesions are common.**

-- Other findings such as **hepatosplenomegaly**, **interstitial keratitis**, and **8th nerve deafness**, also occur.

-- Fetal infection can also result in **stillbirth**.

-- **Immunity to syphilis is incomplete.**

-- **Antibodies** to the organism are produced but **do not stop** the progression of disease.

-- **Treated patients** of early syphilis **can contract the disease** again.

-- Patients with **late syphilis** are relatively **resistant to reinfection**.

Laboratory diagnosis

There are three important approaches.

Microscopy

-- Spirochetes are demonstrated in the **lesion of primary or secondary syphilis** such as chancres and condylomata lata by **dark field microscopy** or by **direct fluorescent antibody (DFA) test**.

-- They are **not seen in a Gram stained smear**.

-- In **biopsy samples (from tertiary syphilis),** histologic stains such as **silver stain** or **fluorescent antibody** can be used.

Nonspecific serological tests

-- These tests involve the use of **nontreponemal antigens**.

-- Extracts of **normal mammalian tissues** (**cardiolipin from beaf heart**) react with antibodies in serum samples from patients with syphilis.

-- The antibodies, a mixture of IgM and IgG, are called **reagin antibodies.**

-- Flocculation tests such as **VDRL** (Venereal Disease Research Laboratory) test and **RPR** (rapid plasma reagin) tests detect these antibodies.

-- These tests are **positive in most cases of primary syphilis and almost always positive in secondary syphilis.**

-- **Titer decreases with treatment** unlike that of specific antibodies which are positive for life.

-- False positive reactions are common so positive results must be verified by specific tests.

-- If antibody titer is too high, **prozone phenomenon** may occur resulting in false negative test.

-- **Diluted** serum sample will be positive.

-- **Infected infants have higher VDRL titer than mothers.**

-- If it is due to **placental antibody**, titer will decrease with time.

-- However, irrespective of results, **infant** of a positive mother **must be treated.**

Specific serologic tests

-- These tests involve the use of **treponemal antigens** and therefore are more specific.

-- **Immunofluorescence** or **haemagglutination** assays are used.

-- These antibodies arise within 2-3 weeks of infection so tests are **positive in most cases of primary syphilis.**

-- **These tests remain positive for life and cannot be used for the progress of treatment.**

-- These tests are **more expensive and difficult to perform** so they are not used routinely.

Treatment

-- **Penicillin is effective in treatment of all stages of syphilis.**

-- A **single injection of benzathine penicillin G** can eradicate ***T. pallidum*** and **cure primary and secondary syphilis**.

-- In case of penicillin allergy, **doxycycline** can be used but must be given for prolonged periods.

-- In case of **neurosyphilis**, **high doses** of benzathine penicillin G are given because of poor penetration into central nervous system.

-- Nearly half of patients develop **influenza like symptoms** few hours after administration of penicillin due to lysis of organisms and release of endotoxin.

-- This is called **Jarisch-Herxheimer reaction**. It may last for 24 hours.

-- This reaction also occurs after treatment of other spirochetal diseases.

-- **TNF** is an important mediator because passive immunization against it can prevent the symptoms.

Prevention

-- It depends on early diagnosis and adequate treatment, precaution in sexual relations, administration of antibiotic after suspected exposure, and serological follow up of infected individuals and their contacts.

-- There is **no vaccine**.

Nonvenereal Treponematoses

-- These infections are caused by spirochetes that are **virtually indistinguishable** from those caused by ***T. pallidum***.

-- They are endemic and are transmitted by **direct contact**.

-- These infections give positive results for ***T. pallidum*** serological tests.

-- They **cannot be cultivated** in laboratory.

-- The diseases include **bejel, yaws** and **pinta**.

-- **All can be cured with penicillin**.

Borrelia

-- ***Borrelia*** species are **irregular, loosely coiled spirochetes** that **stain readily with Giemsa and other stains.**

-- They **can be cultured in bacteriological media** containing serum or tissue extracts.

-- They are **transmitted by arthropods**.

-- They cause two major diseases, **Lyme disease** and **relapsing fever**.

Borrelia burgdorferi

It causes **Lyme disease** or **Lyme borreliosis**.

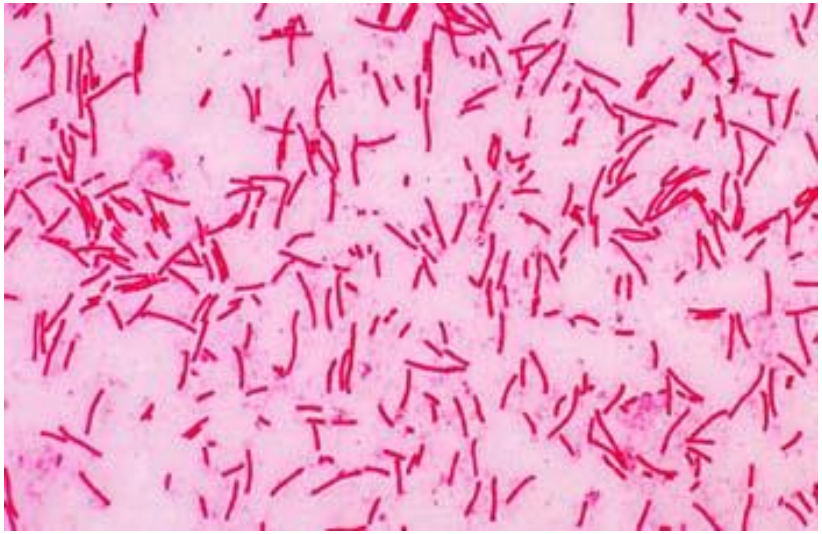
It is most common tick borne disease in US.

Important properties

-- ***Borrelia burgdorferi*** is a **flexible, motile spirochete** that can be visualized by dark field microscopy and by Giemsa and silver stains.

-- Routine **cultures from human are usually negative** but from ticks are usually positive.

-- **Special media** are required for human samples.



Transmission and epidemiology

-- ***B. burgdorferi*** is transmitted by tick bite.

-- The ticks belong to **Ixodes species**.

-- The main reservoir consists of small mammals, especially the **white-footed mouse**, upon which the nymph feeds.

-- Large animals, such as **deer** are obligatory host but not a reservoir.

-- The **nymphal stage transmits the disease more often** than adult and larval stages do.

-- The tick **must feed for 24-48 hours** to transmit an infectious dose.

-- However, nymphs are quite small and can easily be missed.

-- There **is no human to human spread**.

-- The disease occurs **worldwide**.

Pathogenesis

-- It involves spread of organism from **bite site to surrounding skin** followed by **entry in bloodstream** resulting in infection of **heart, joints** and **CNS**.

-- **No virulence factors have been identified.**

-- The organism adapt to different environment in tick and mammal (mice or humans) by changing **OSP (outer surface proteins).**

Clinical findings

-- In **initial stage**, most common finding is **erythema migrans**, a rash with **bull eye appearance**.

-- It is **painless** and appear 3-30 days after bite.

-- It may be accompanied by **flu like** symptoms.

-- **Secondary skin** lesions frequently occur.

-- **Arthralgias**, not arthritis, are another common finding. In 25% cases no rash is seen.

-- In **second stage** which takes weeks to months, **cardiac and neurologic involvement predominates.**

-- **Myocarditis** with various forms of heart blocks occurs.

-- **Acute (aseptic) meningitis** and cranial neuropathies, such as **facial nerve palsy** are prominent.

-- **Bilateral facial nerve palsy is highly suggestive of Lyme disease**.

-- Peripheral neuropathies also occur.

-- In **third stage**, **arthritis usually of large joints** is characteristic.

-- It is **autoimmune** in nature.

-- **Chronic progressive CNS disease** also occurs.

Laboratory Diagnosis

-- **Cultures** are **rarely positive** and hence **usually not performed.**

-- The diagnosis is typically made by detecting either **IgM antibody** or a **rising titer of IgG** with an ELISA or an **indirect immunofluorescence** assay.

-- These tests are **negative** before 2 weeks.

-- After 30 days **post infection**, tests for IgG are more reliable.

-- These tests have problems of **cross reactivity**.

-- **PCR** test is also available.

Treatment and Prevention

-- For **stage 1, doxycycline or amoxicillin** are drugs of choice.

-- For **more severe and later stages, ceftriaxone** is recommended.

-- There is **no significant antibiotic resistance**.

-- Prevention centers on wearing **protective clothes** and using **insect repellents.**

-- Examining the skin for ticks is important because it **must feed for 24-48 hours** to transmit an infectious dose.

Borrelia recurrentis & B. hermsii

-- These spirochetes cause **relapsing fever**.

-- The **relapses** are due to **variations in antigens**.

-- **Humans are only host** for ***B. recurrentis*** and is transmitted by **human body louse**.

-- ***B. hermsii*** and others are transmitted by **ticks**.

-- **Rodents** and other small animals are the main reservoirs.

-- These species are passed **transovarially in ticks** which help in their survival in nature.

-- After arthropod bite, **spirochetes multiply in many tissues** producing fever, chills, headaches, and multiple organ dysfunction.

-- Each attack is **terminated** as antibodies arise.

-- Diagnosis is made by seeing **large spirochetes in stained smears of peripheral blood.**

-- They can be **cultured in special media**.

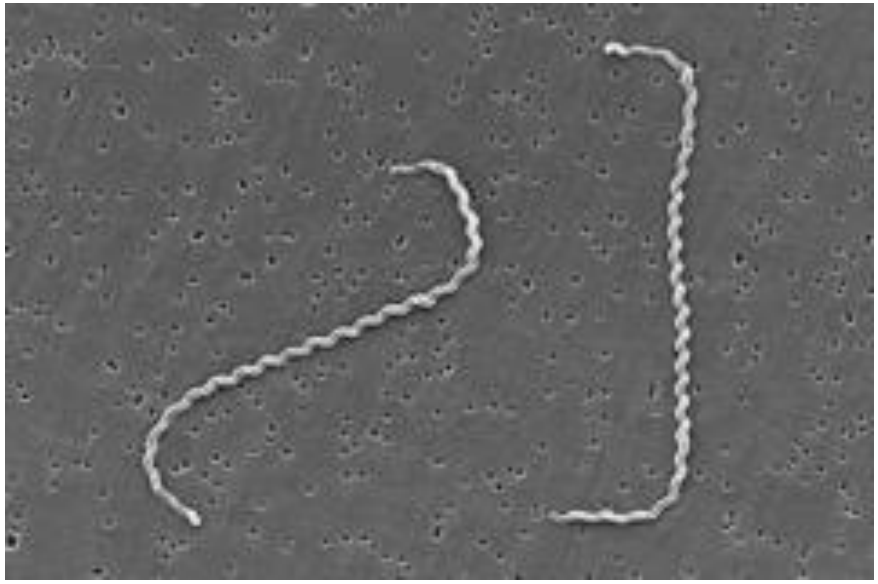
-- **Serology is rarely useful.**

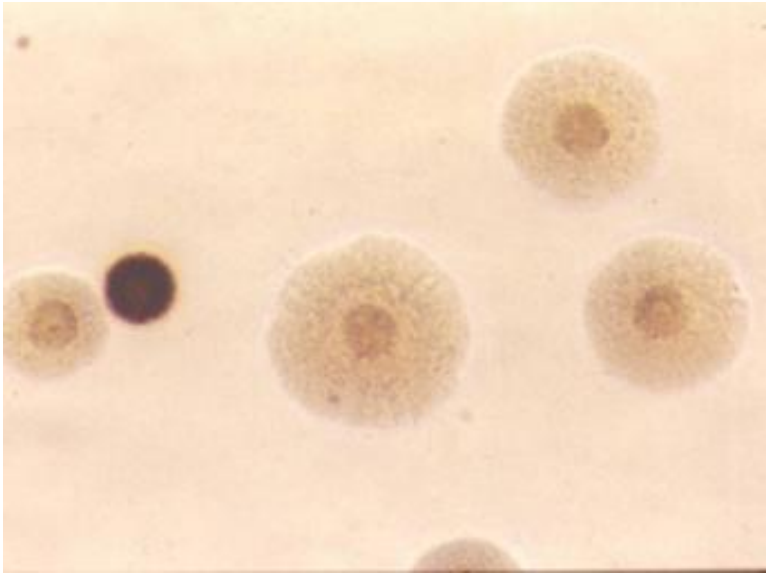
-- **Tetracycline** may be beneficial in preventing relapses.

Leptospira

Leptospiras are **tightly coiled fine spirochetes** that are **not stained** but can be seen by **dark field microscopy**.

They can grow in media containing serum.





-- ***L. interrogans*** cause **leptospirosis**.

-- It is divided in **serogroups** which are further subdivided into **serovars**.

-- **Leptospiras** infect various animals including **rats and other rodents**, **domestic livestock** and **household pets**.

-- The organisms are **secreted in urine** which contaminates water and soil.

-- **Swimming** in contaminated water or **eating** contaminated food or drink result in human infection.

-- **Person to person transmission is rare.**

-- After infection through mucus membrane or skin, they **circulate in blood** and multiply in various organs producing fever and dysfunction of liver (**jaundice**), kidneys (**uremia**), lungs (**hemorrhage**) and CNS (**aseptic meningitis**).

-- The illness is **biphasic** with fever, chills intense headache and conjunctival suffusion (diffuse reddening of conjunctivae) appearing **early in disease** followed by a short period of resolution of these symptoms as the organisms are cleared from blood.

-- **Second, "immune" phase** is most often characterized by the findings of **aseptic meningitis** and in severe cases, **liver damage (jaundice) and impaired kidney function.**

-- **Serovar specific immunity** develops with infection.

-- Diagnosis is based on history of possible exposure, suggestive clinical signs, and a **marked rise in IgM antibody titers**.

-- Occasionally isolation can be made from **blood and urine culture**.

-- The treatment of choice is **Penicillin G**.

-- Prevention involves **avoiding contact** with contaminated environment.

-- **Doxycycline** is effective in preventing disease in exposed persons.


Thank You!