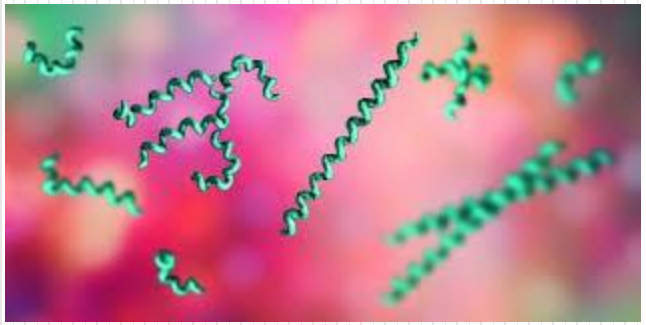
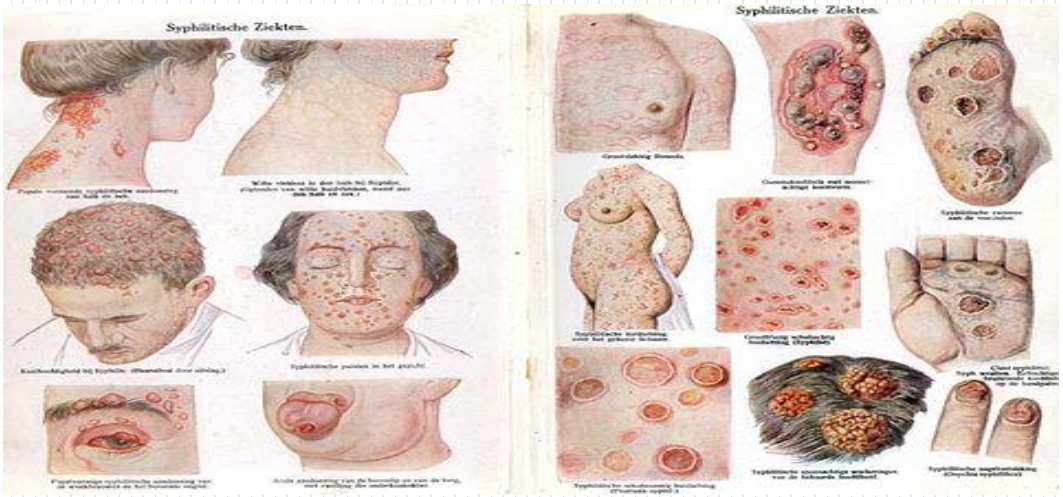
Assist. Professor Dr. Muhannad
PhD, Post- PhD- UK

# Syphilis

*(Treponema pallidum )*





# What is Syphilis?

**Syphilis:** is a sexually transmitted disease (STD) caused by an infection with bacteria known as *Treponema pallidum*. Like other STDs, **syphilis** can be spread by any type of sexual contact. **Syphilis** can also be spread from an infected mother to the fetus during pregnancy or to the baby at the time of birth.

# Objectives:

I. Epidemiology
II. Pathogenesis
III. Clinical manifestations
IV. Diagnosis
V. Patient management
VI. Prevention

# Lesson

## I. Epidemiology

**Again: What is Syphilis???**

A Kind of **venereal disease**:

Disease typically contracted by sexual intercourse with a person already infected; a sexually transmitted disease.

# Syphilis Definition

- Sexually acquired infection
- Etiologic agent: *Treponema pallidum*
- Disease progresses in stages
- May become chronic without treatment

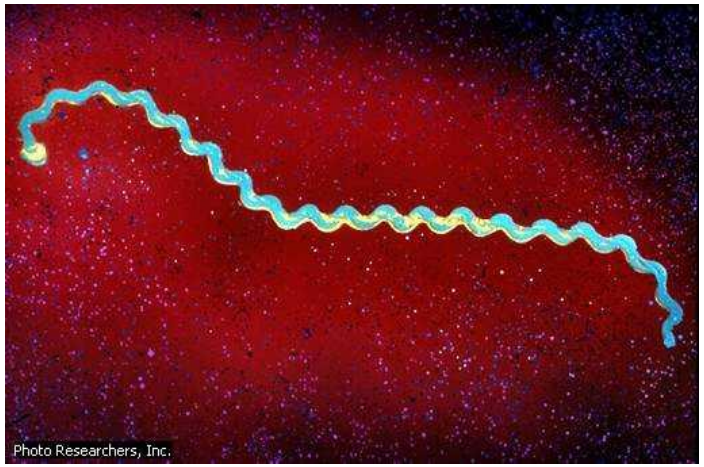
# Transmission

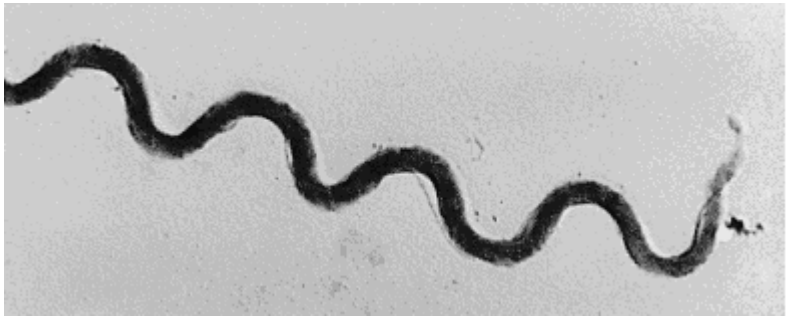
- Sexual and vertical
- Most contagious to sex partners during the primary and secondary stages

# Introduction to Spirochetes

- Long, slender, helically tightly coiled bacteria
- Gram-negative
- Aerobic, microaerophilic or anaerobic .
- Corkscrew motility
- Can be free living or parasitic
- Best-known are those which cause disease:
  - Syphilis
  - Lyme's disease

# Morphology



- Have **axial filaments**, which are otherwise similar to bacterial flagella
- Filaments enable movement of bacterium by rotating in place

# Spirochete Diseases

- Localized skin infection disseminates to other organs.
- Latent stage, no signs or symptoms apparent.
- Cardiac and neurological involvement in untreated cases.

# Serological Testing

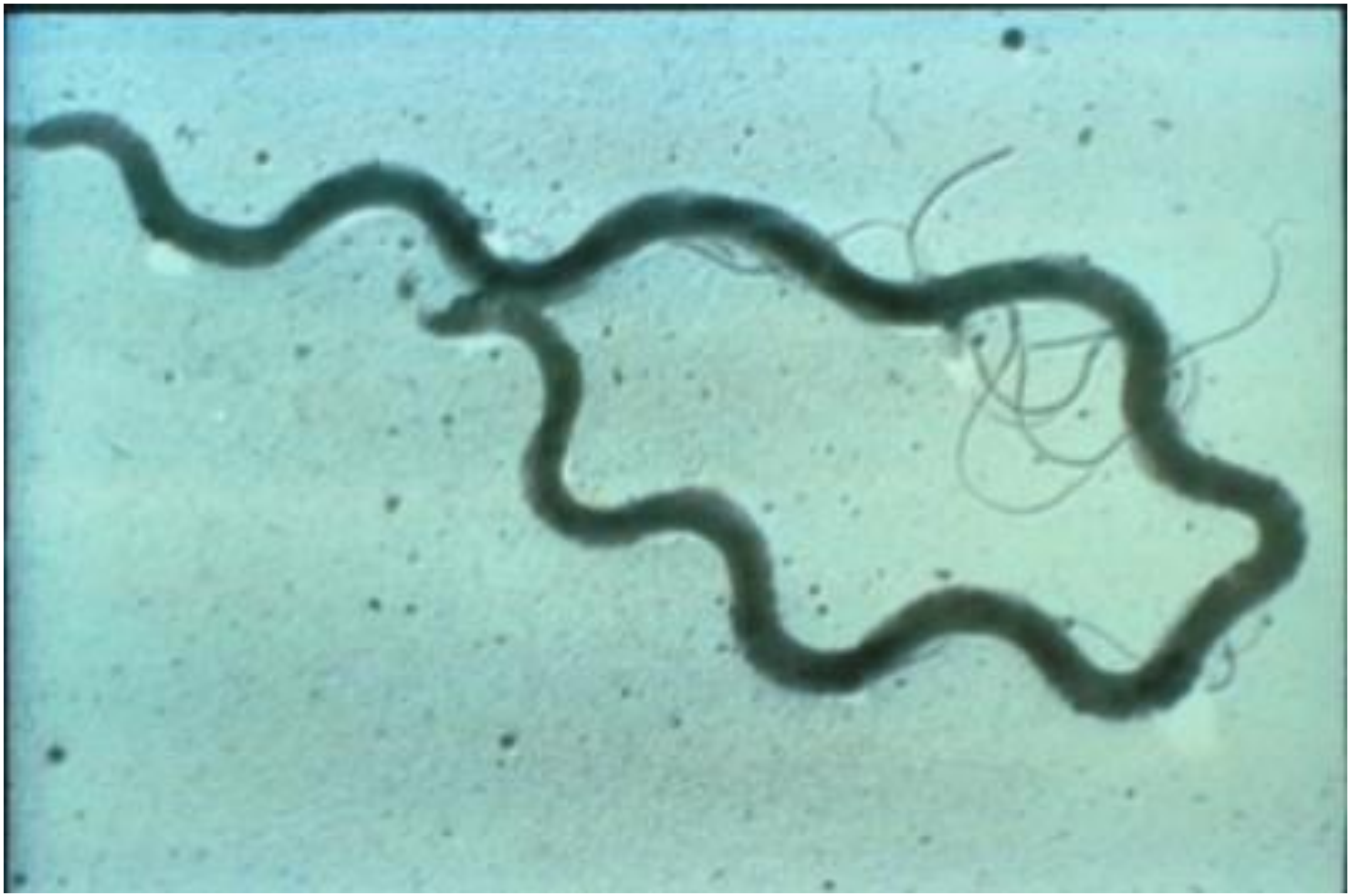
- Important in diagnosis
- Isolation of organism very difficult
- Clinical symptoms not always apparent.

# Lesson II: Pathogenesis

# Microbiology

- Etiologic agent: *Treponema pallidum*, subspecies *pallidum*
  - Corkscrew-shaped, motile microaerophilic bacterium
  - Cannot be cultured in vitro
  - Cannot be viewed by normal light microscopy

# *Treponema pallidum*



Electron photomicrograph, 36,000 x.

# *Treponema pallidum* on Darkfield Microscopy

# Pathology

- **Penetration:**
  - *T. pallidum* enters the body via skin and mucous membranes through **abrasions** during sexual contact
  - Transmitted transplacentally from mother to fetus during pregnancy

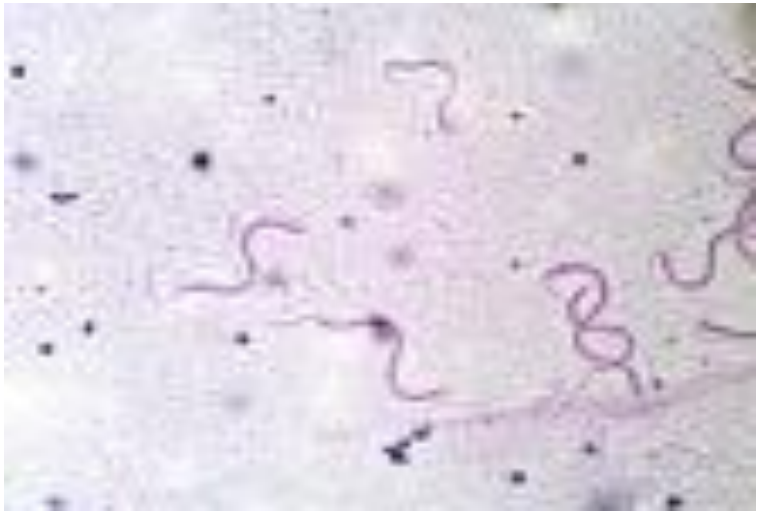
- **Dissemination:**
  - Travels via the circulatory system (including the lymphatic system and regional lymph nodes) throughout the body
  - Invasion of the central nervous system (CNS) can occur during any stage of syphilis.

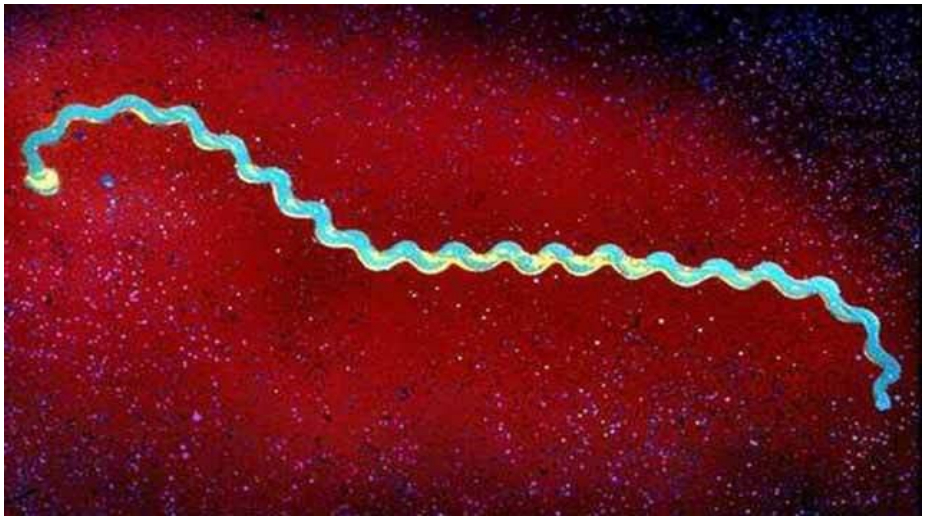
# Characteristic of the Organism

- Causative agent is ***Treponema pallidum***
- Member of the family Spirochaetaceae.
- No natural reservoir in the environment, requires living host.
- Organism cannot be cultured from clinical specimens

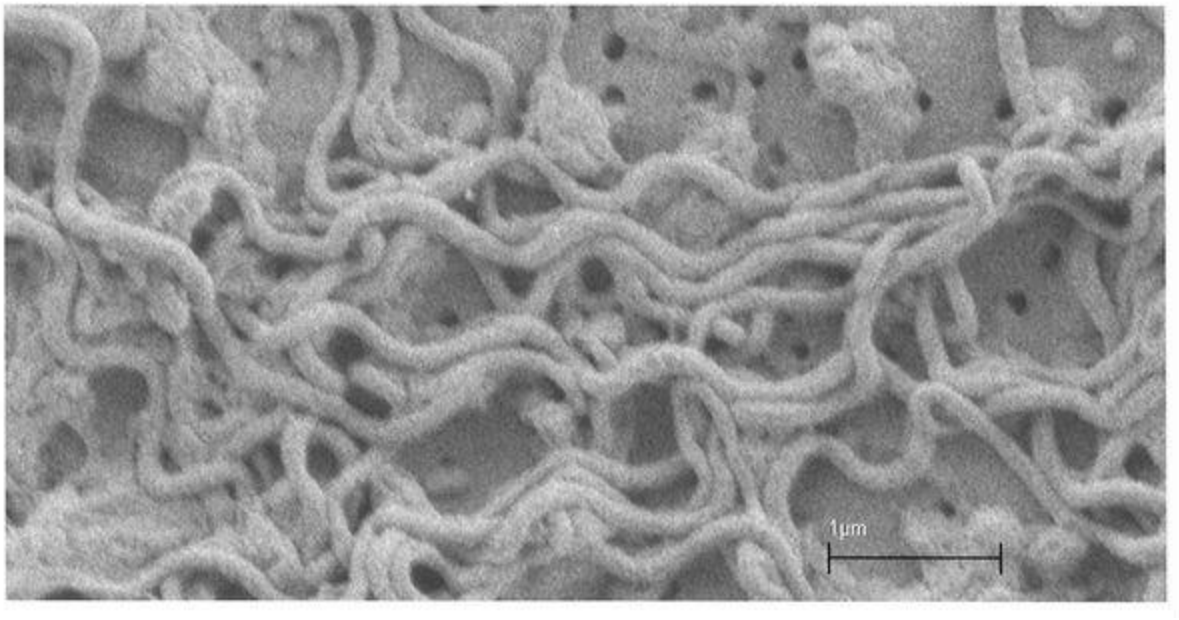
# Morphology

- Spiral shaped and motile due to periplasmic flagella.
- Variable length.





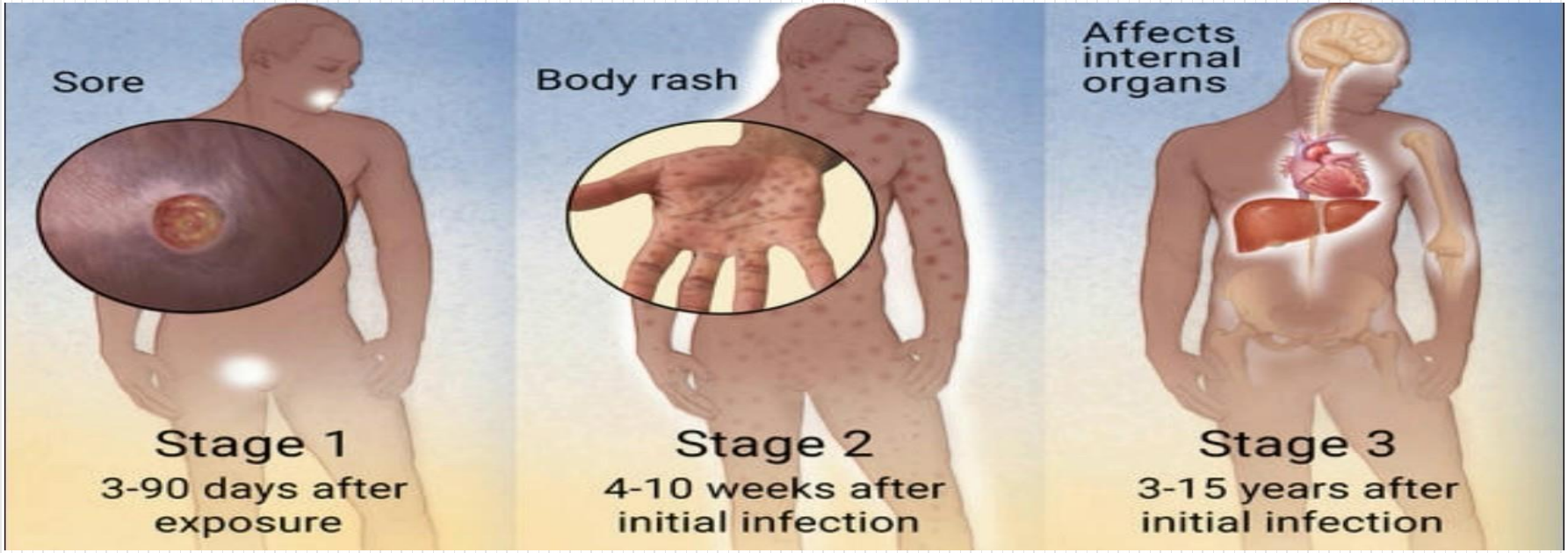
# Scanning Electron Micrograph of *T. pallidum*



# Other Treponemes

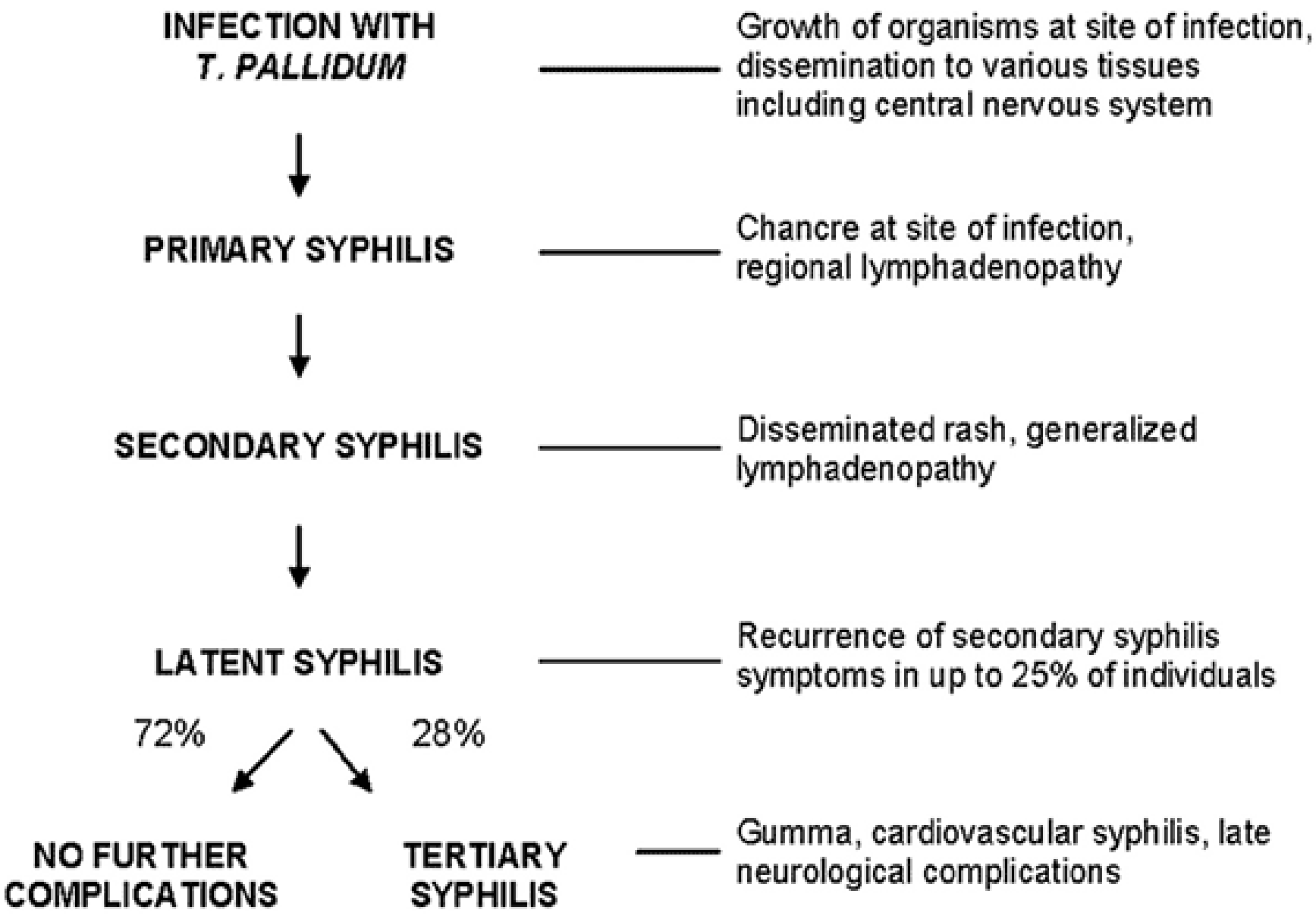
- Three other pathogens in the group: *Treponema* which are morphologically and antigenically similar to *T. Pallidum*
- Differences are in:
  - Characteristics of lesions,
  - Amount of systemic involvement and
  - Course of the disease.

# Lesson III: Clinical Manifestations



# Stages of Disease

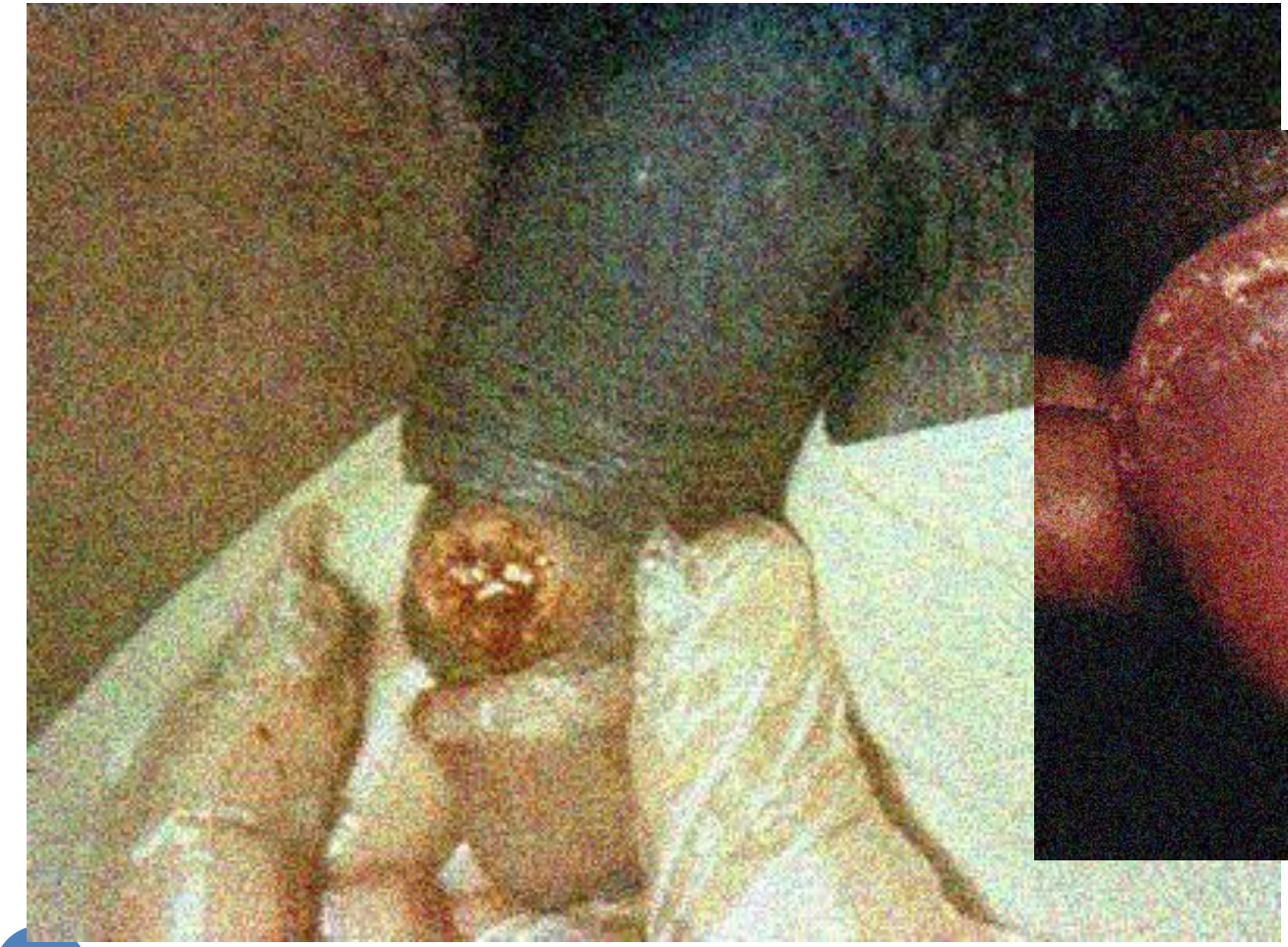
- Primary
- Secondary
- Latent
- Tertiary
- Congenital Syphilis

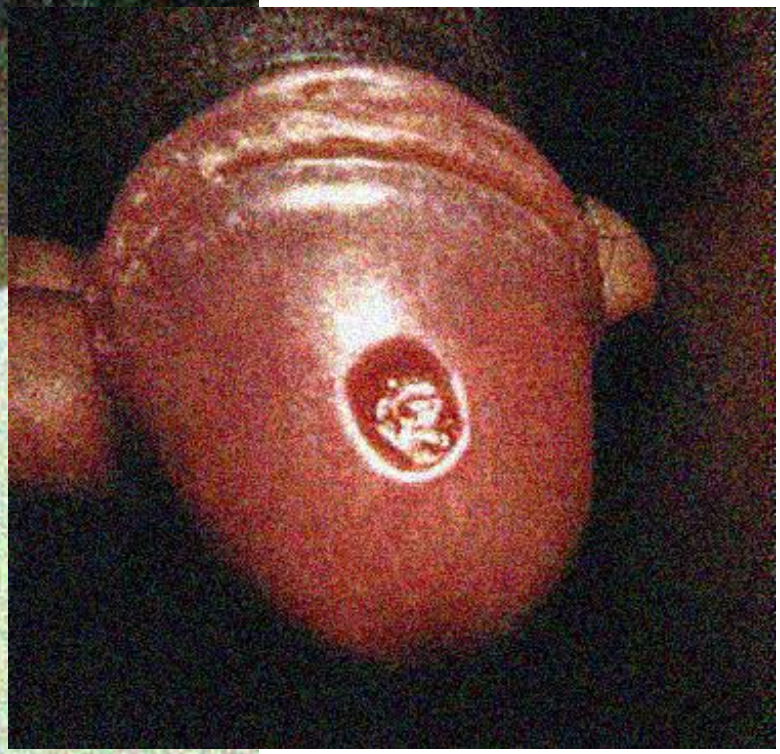

INFECTION WITH
T. PALLIDUM
Growth of organisms at site of infection, dissemination to various tissues including central nervous system
PRIMARY SYPHILIS
Chancre at site of infection, regional lymphadenopathy
SECONDARY SYPHILIS
Disseminated rash, generalized lymphadenopathy
LATENT SYPHILIS
Recurrence of secondary syphilis symptoms in up to 25% of individuals
72%
28%
NO FURTHER COMPLICATIONS
TERTIARY SYPHILIS
Gumma, cardiovascular syphilis, late neurological complications

# Primary Syphilis

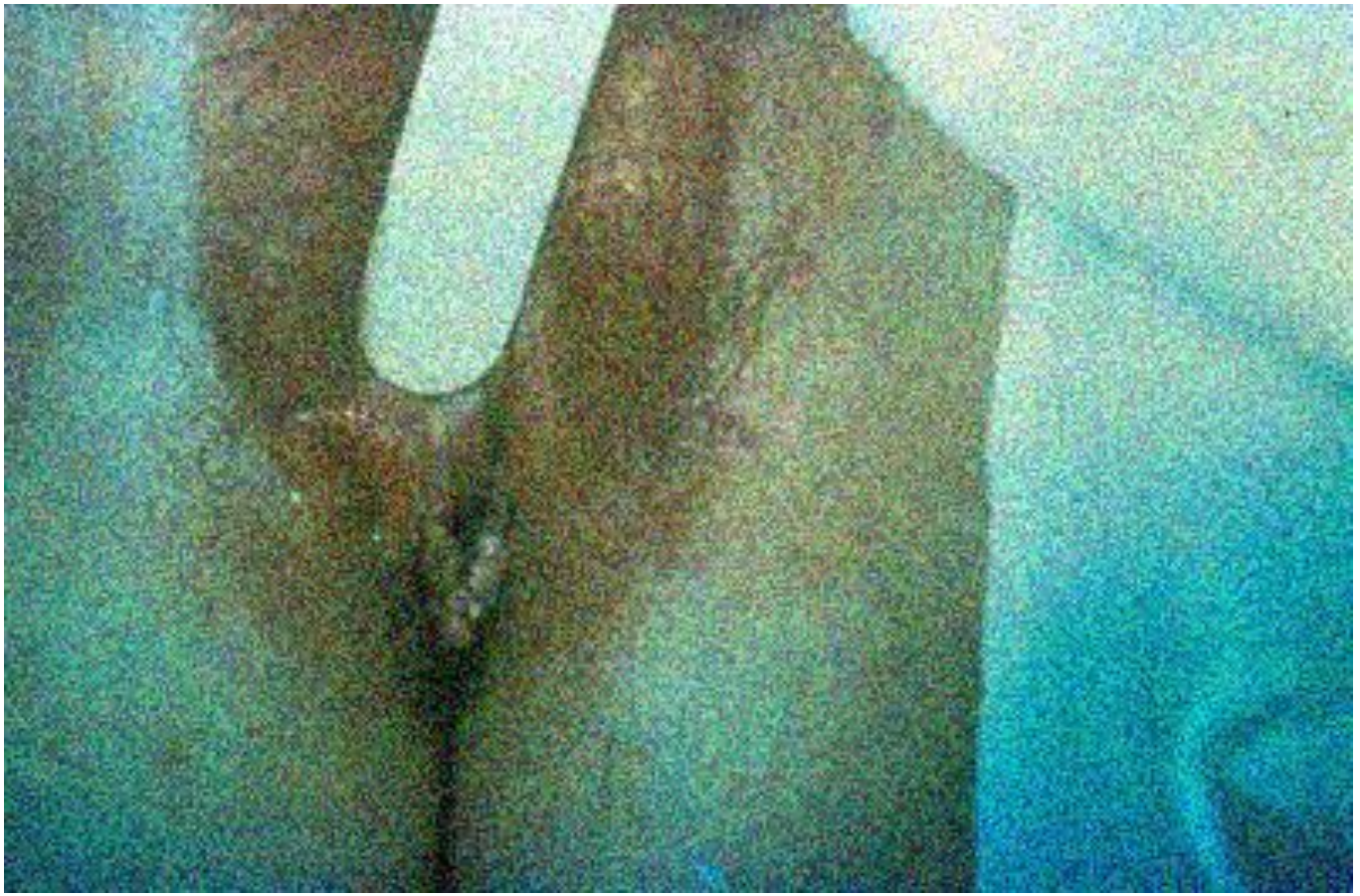
- **Primary lesion** or "**chancre**" develops at the site of inoculation.
- **Chancre**
  - Progresses from macule to papule to ulcer;
  - Typically painless, indurated, and has a clean base;
  - Highly infectious;
  - Heals spontaneously within 3 to 6 weeks; and
  - Multiple lesions can occur.
- Regional lymphadenopathy: classically rubbery, painless, bilateral
- Serologic tests for syphilis may not be positive during early primary syphilis.

# Primary Syphilis- Penile Chancre

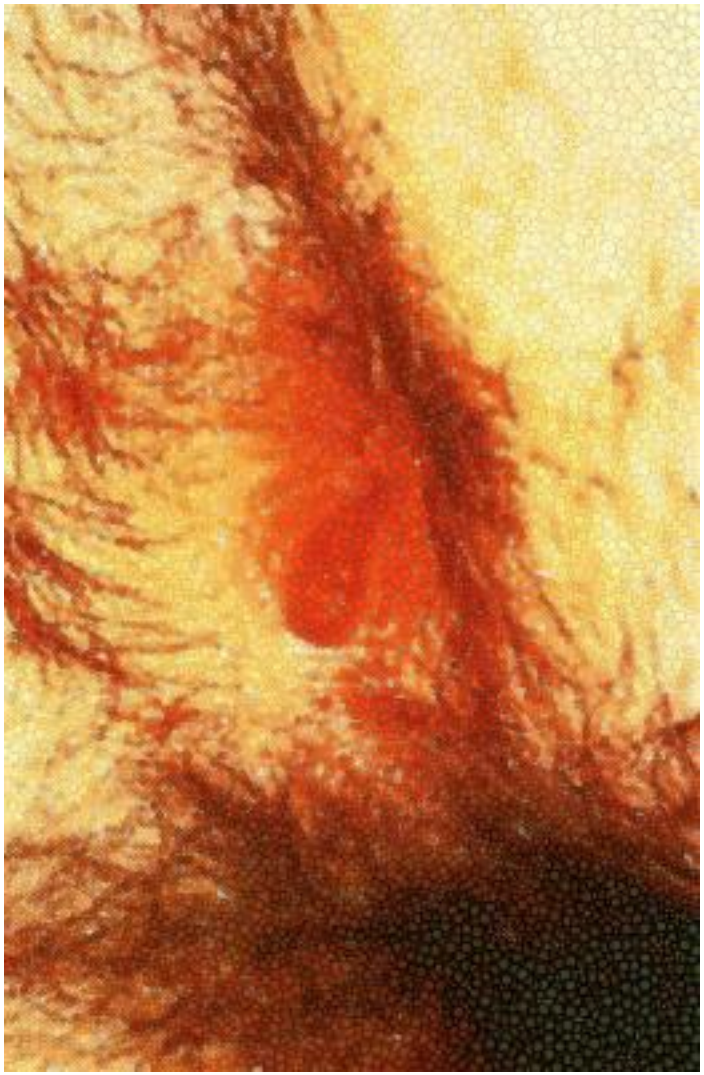




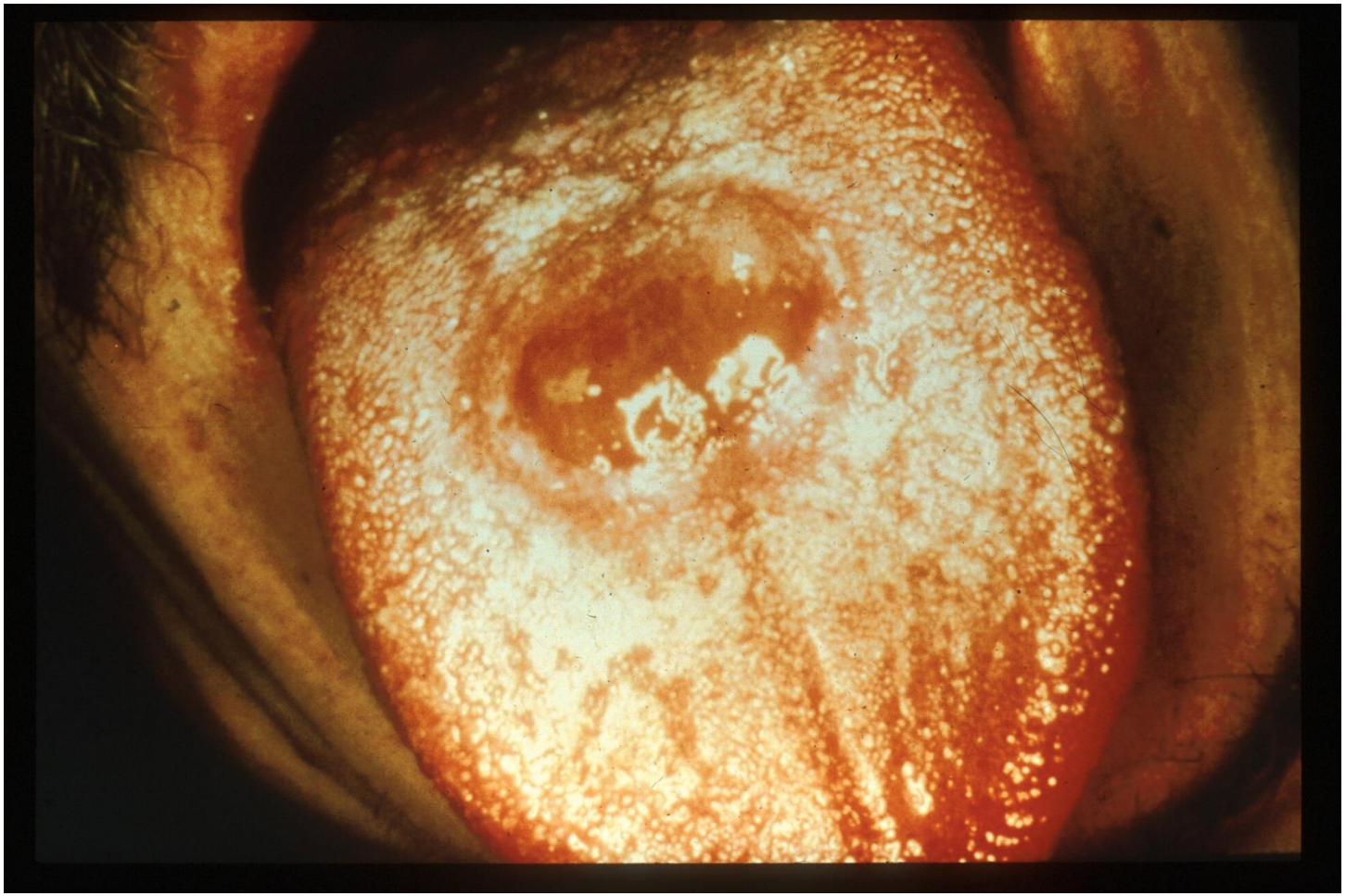
# Primary Syphilis- Labial Chancre



# Primary Syphilis- Perianal Chancre



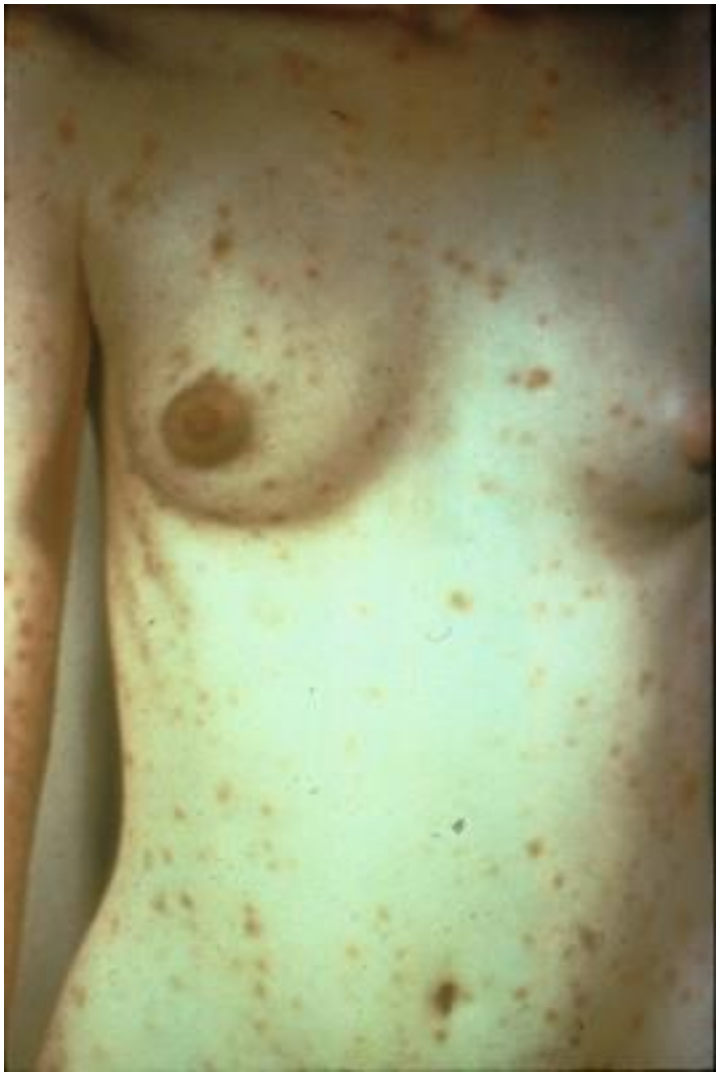
# Primary Syphilis- Chancre of the Tongue



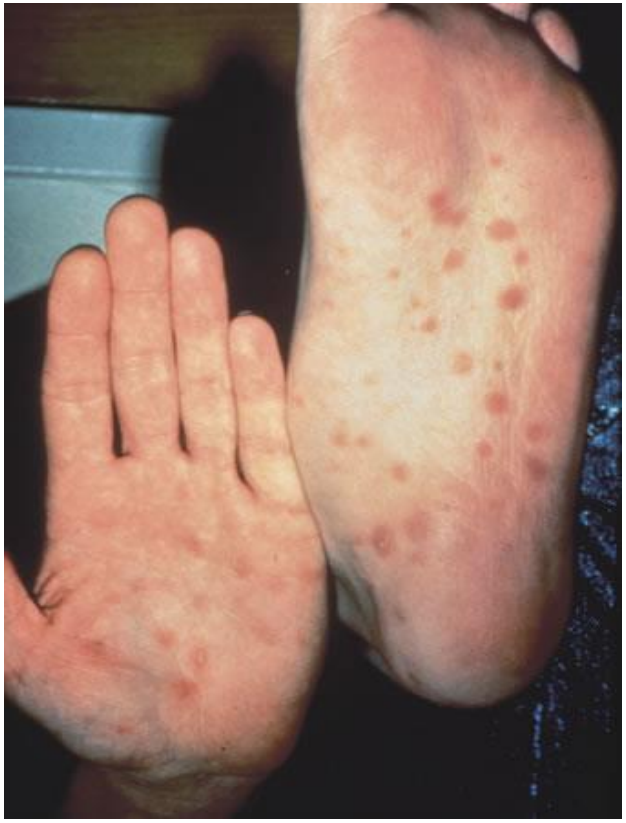
# Secondary Syphilis

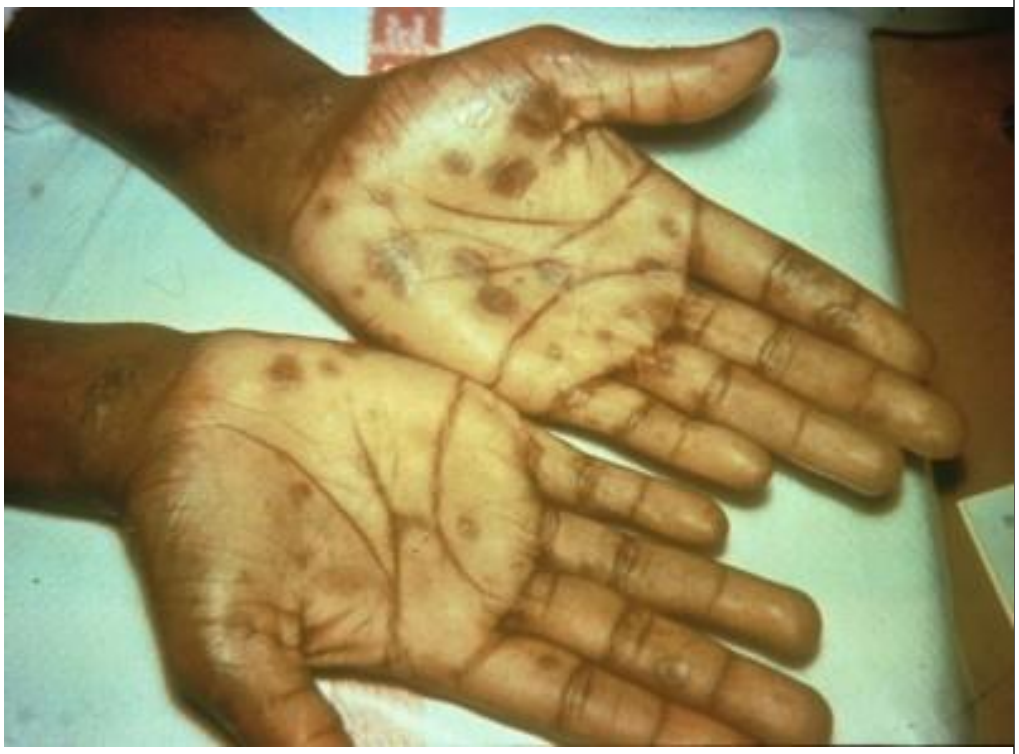
- Secondary lesions occur several weeks after the primary chancre appears; and may persist for weeks to months.
- Primary and secondary stages may overlap
- Mucocutaneous lesions most common
- Clinical Manifestations:
  - Rash (75%–100%)
  - Lymphadenopathy (50%–86%)
  - Malaise
  - Mucous patches (6%–30%)
  - Condylomata lata ( White lesions) (10%–20%)
  - Alopecia (5%)
  - Liver and kidney involvement can occur
  - Splenomegaly is occasionally present
- Serologic tests are usually highest in titer during this stage.

# Secondary Syphilis- Papulosquamous Rash

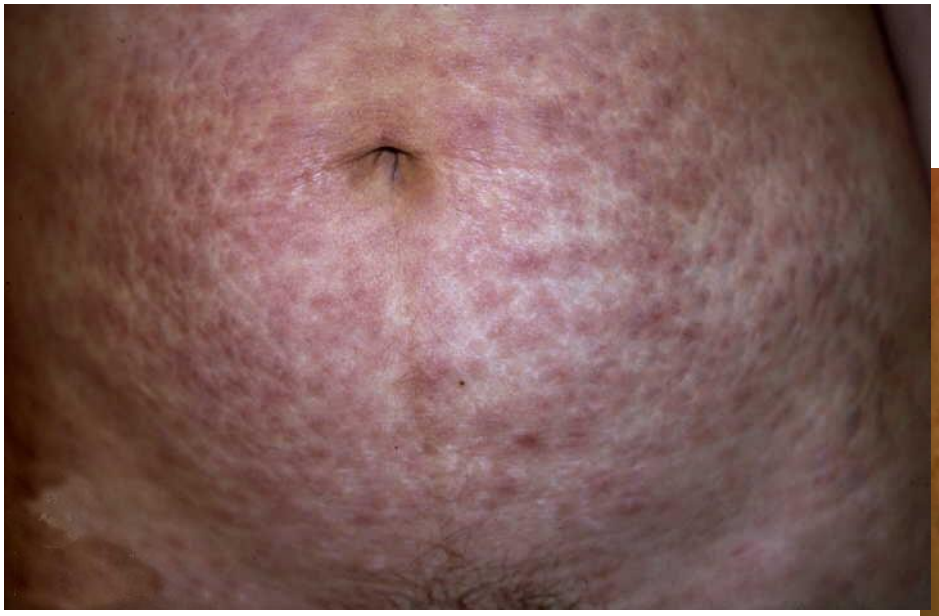


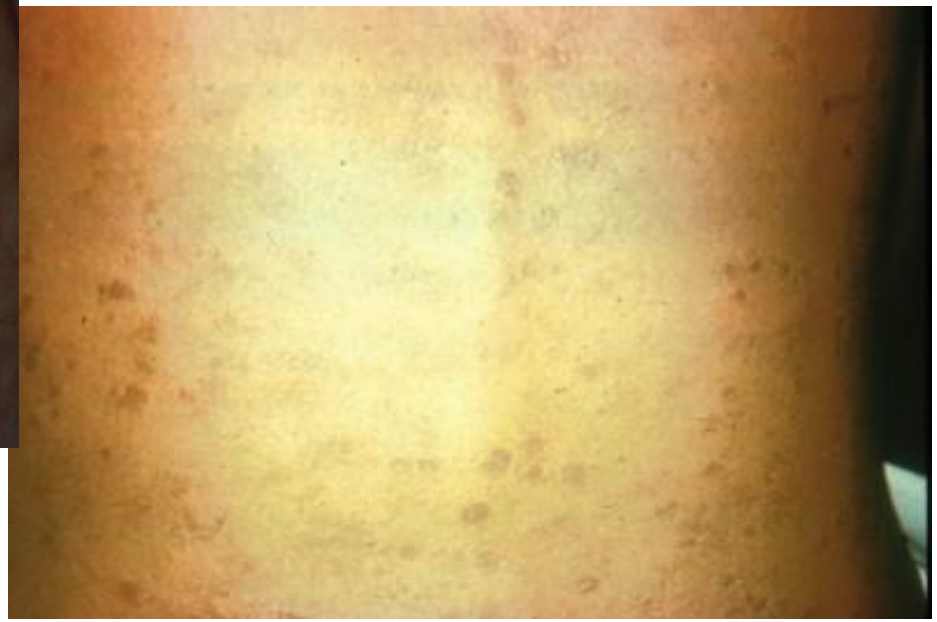
# Secondary Syphilis-
# Palmar/Plantar Rash



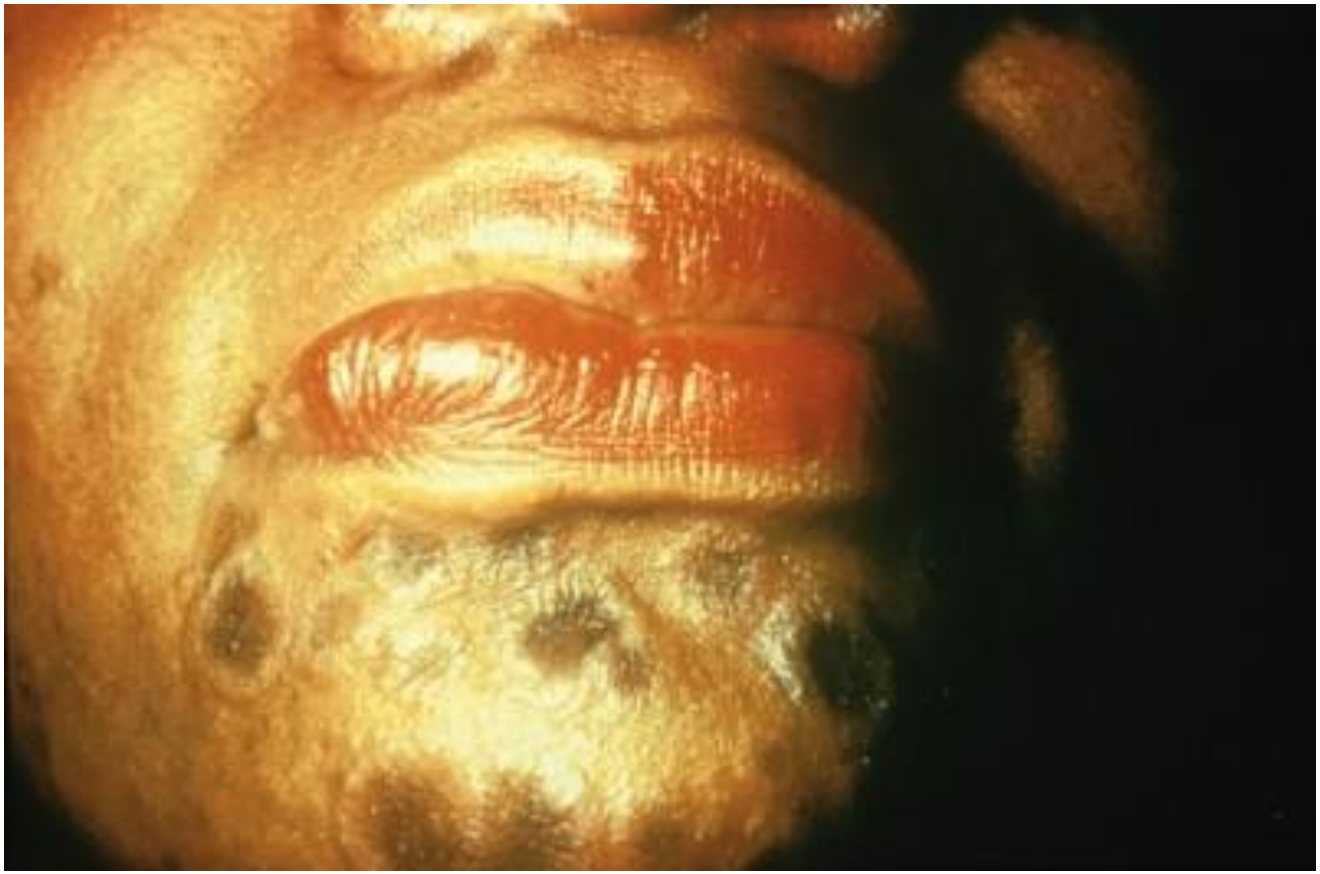


# Secondary Syphilis- Generalized Body Rash

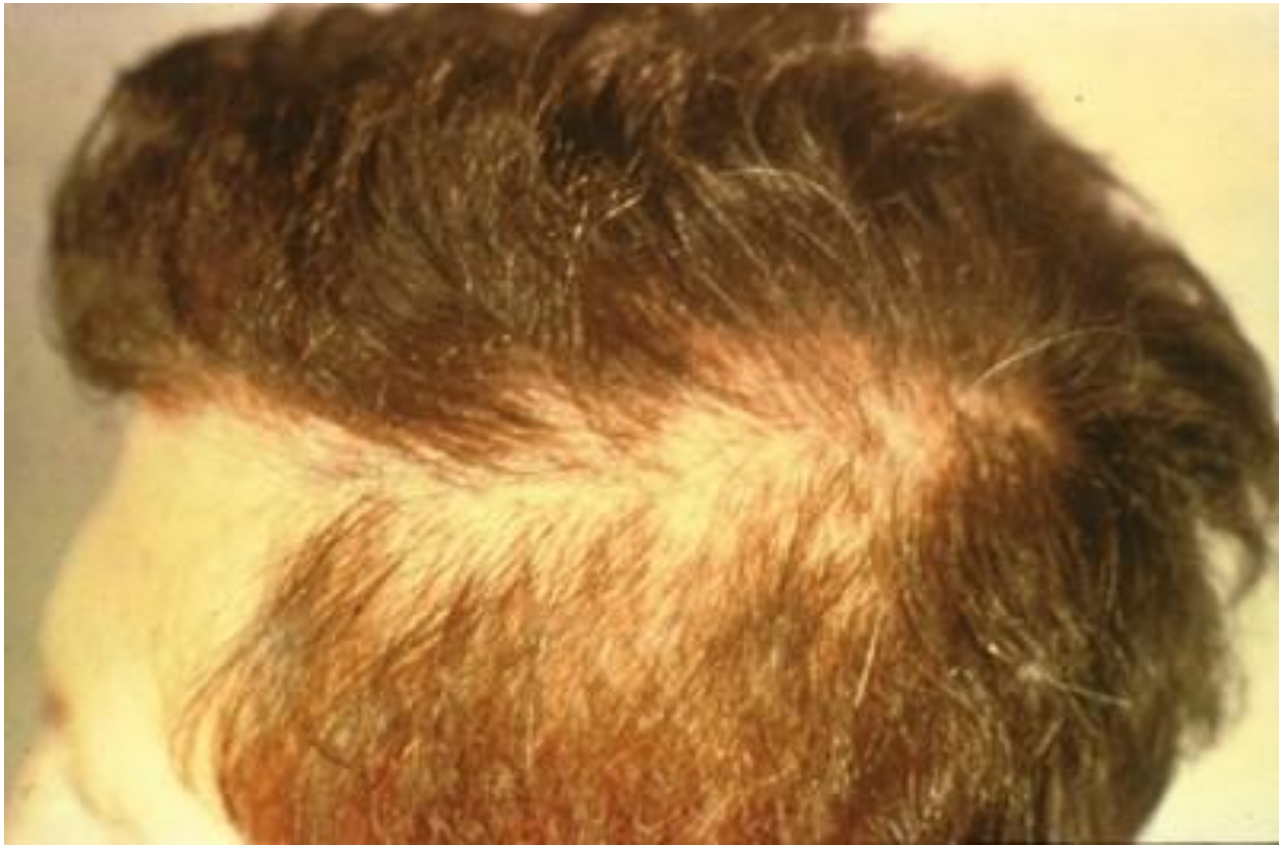




# Secondary Syphilis- Nickel/Dime Lesions



# Secondary Syphilis- Alopecia



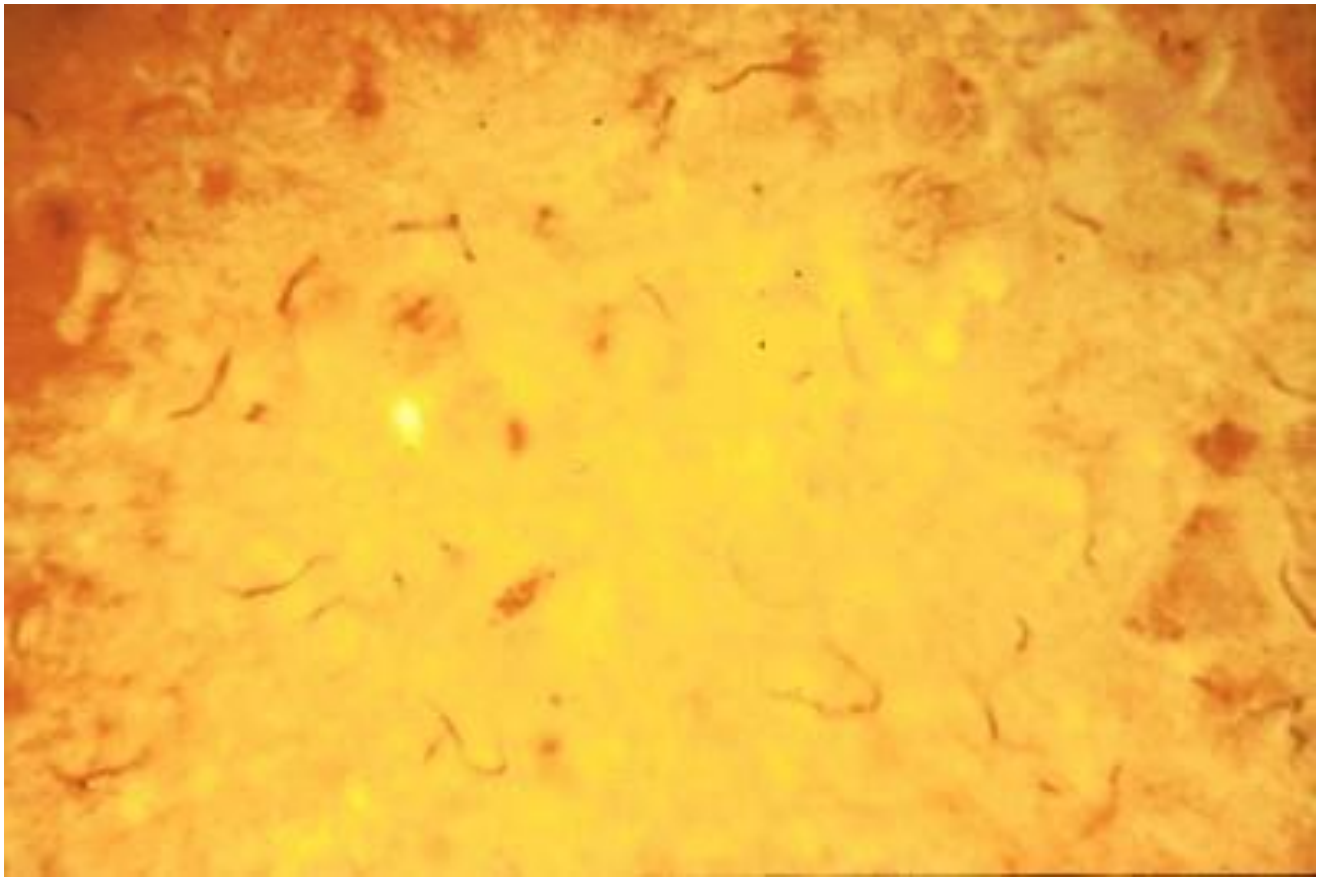
# Latent Syphilis

- Host suppresses infection, but no lesions are clinically apparent
- Only evidence is a positive serologic test
- May occur between primary and secondary stages, between secondary relapses, and after secondary stage
- Categories:
  - Early latent: <1 year duration
  - Late latent: ≥1 year duration

# Neurosyphilis

- Occurs when *T. pallidum* invades the central nervous system (CNS)
- May occur at any stage of syphilis
- Can be asymptomatic
- Early neurosyphilis occurs a few months to a few years after infection
  - Clinical manifestations can include acute syphilitic meningitis, meningovascular syphilis, and ocular involvement
- Neurologic involvement can occur decades after infection and is rarely seen
  - Clinical manifestations can include general paresis, tabes dorsalis, and ocular involvement
- Ocular involvement can occur in early or late neurosyphilis.

# Neurosyphilis- Spirochetes in Neural Tissue

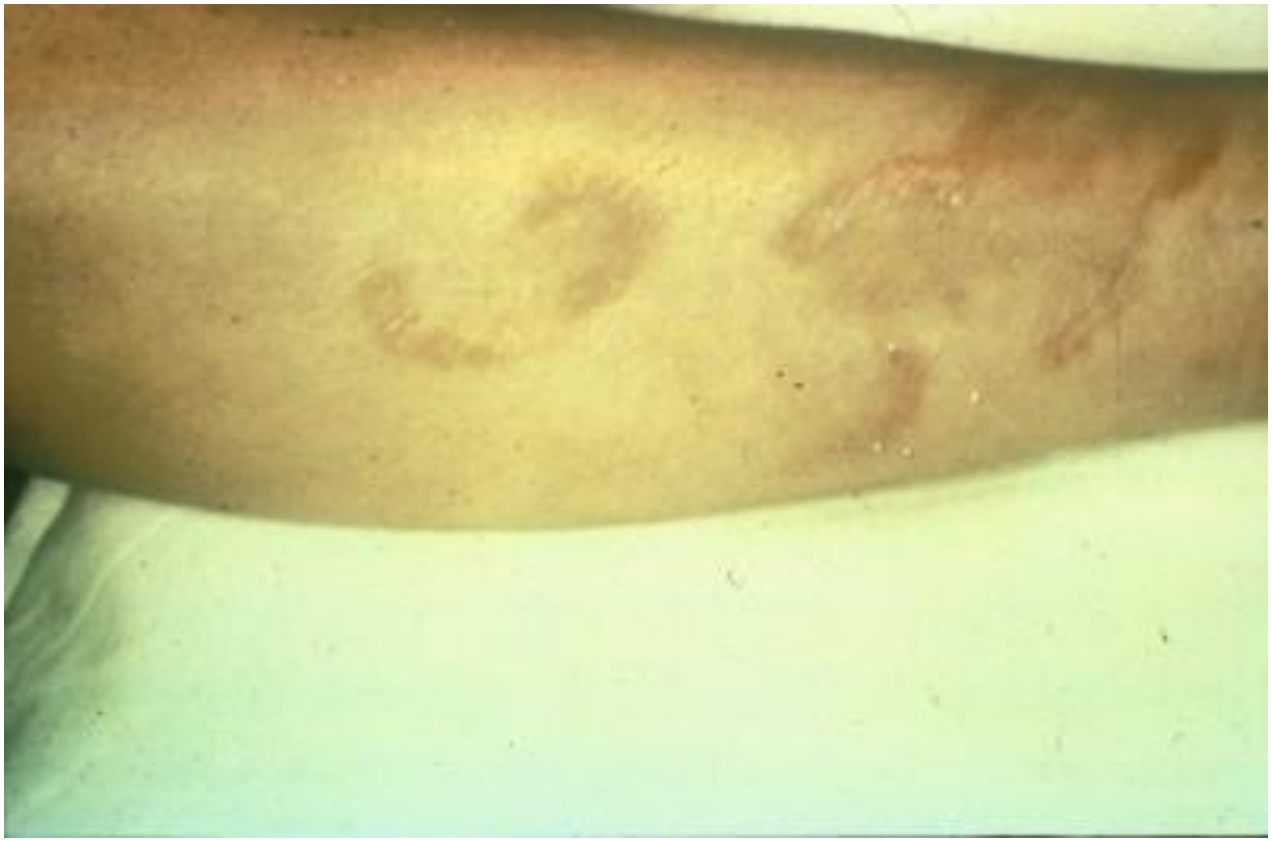


Silver stain, 950x

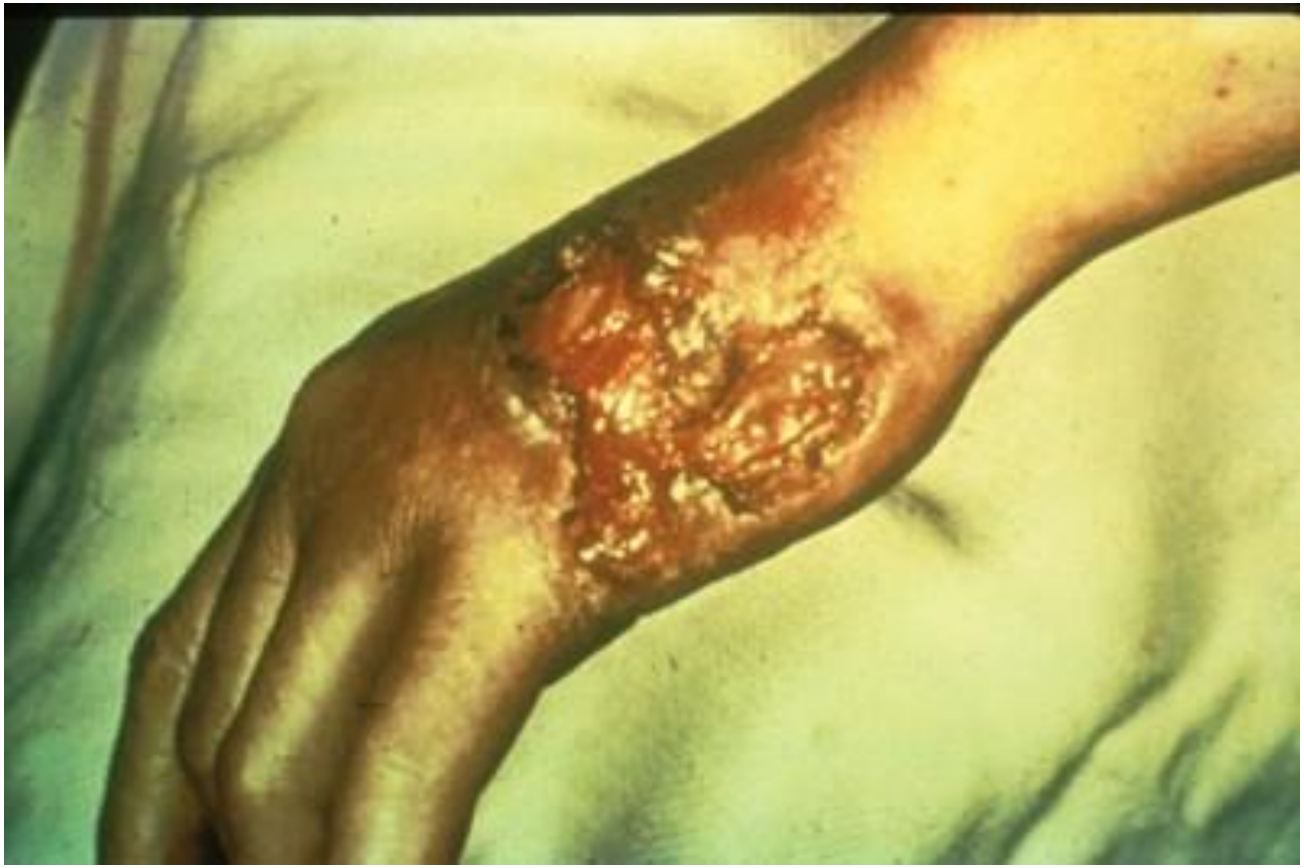
# Tertiary (Late) Syphilis

- Approximately 30% of untreated patients progress to the tertiary stage within 1 to 20 years.
- Rare because of the widespread availability and use of antibiotics
- Manifestations
  - Gummatous lesions
  - Cardiovascular syphilis

# Late Syphilis- Serpiginous Gummata of Forearm



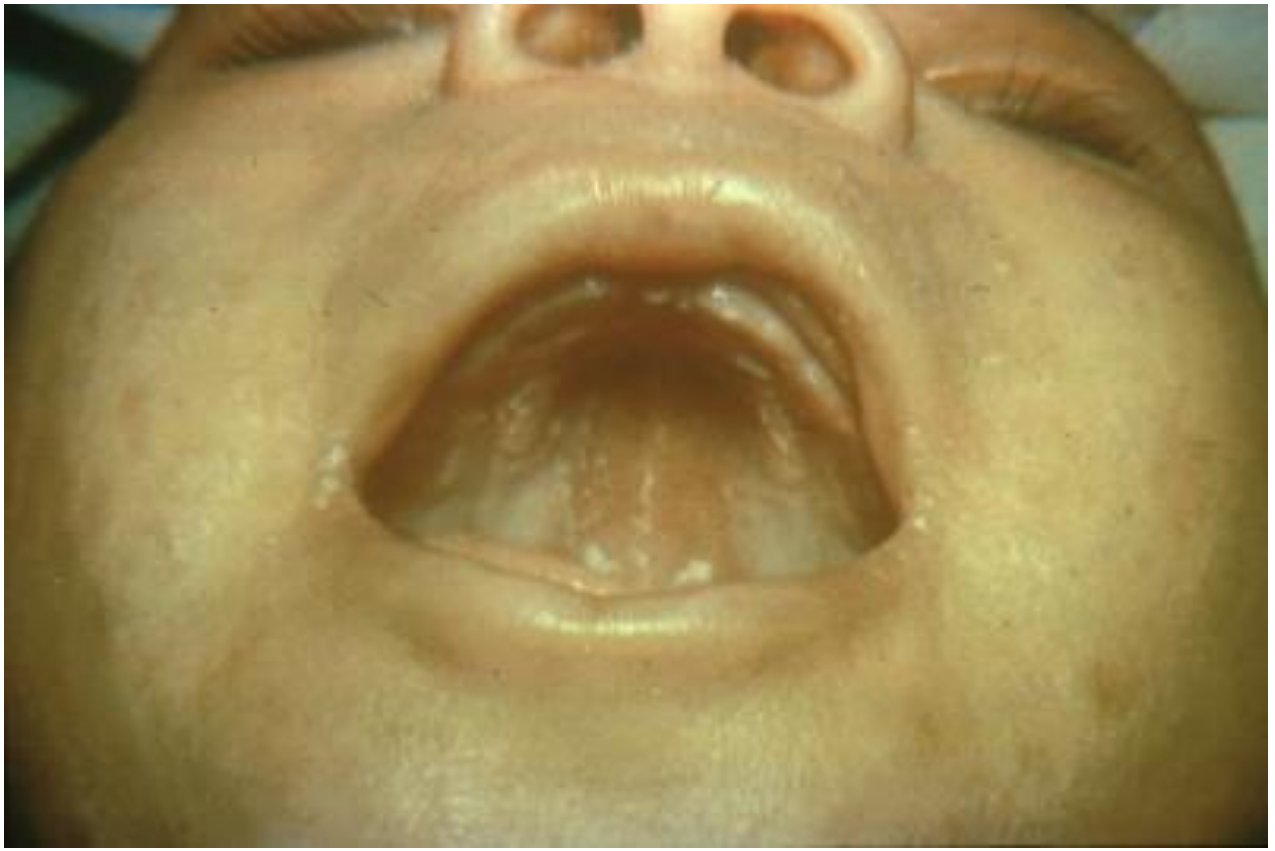
# Late Syphilis - Ulcerating Gumma



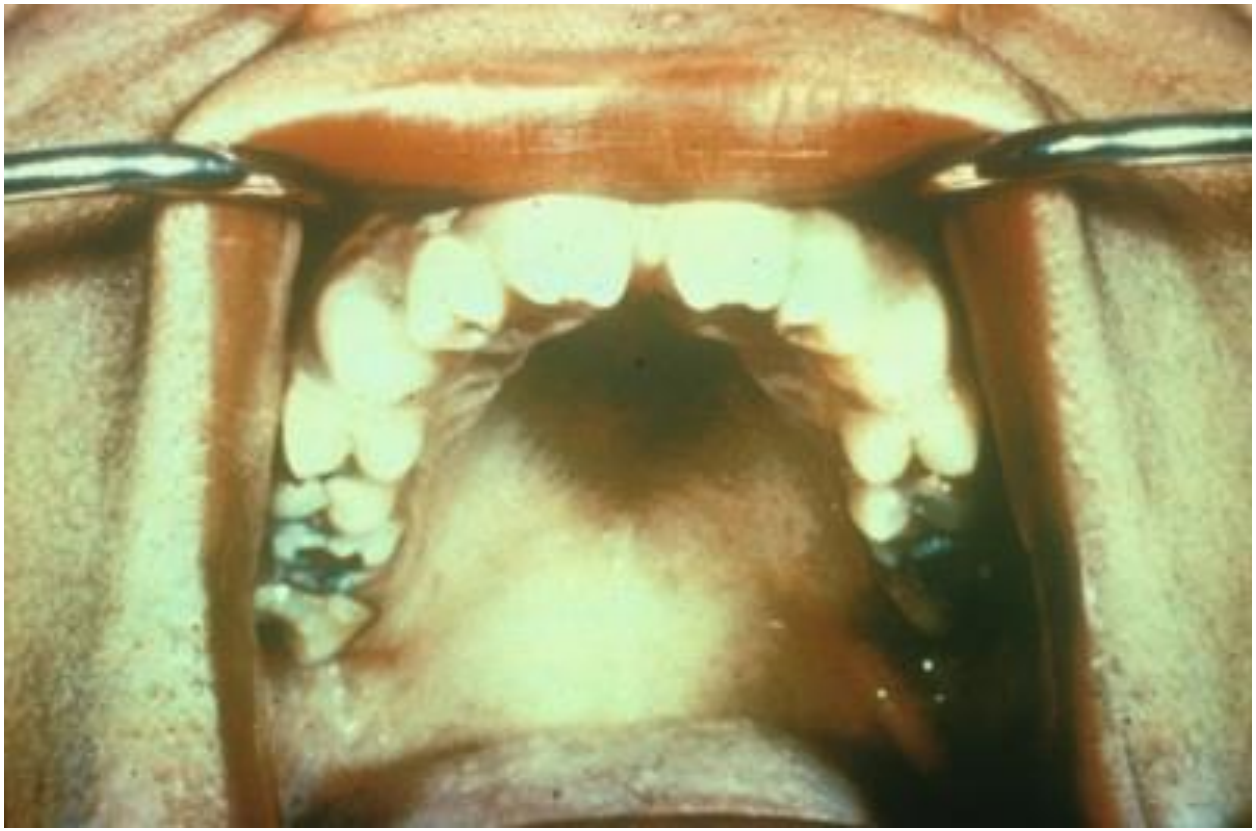
# Congenital Syphilis

- Occurs when *T. pallidum* is transmitted from a pregnant woman to her fetus
- May lead to stillbirth, neonatal death, and infant disorders such as deafness, neurologic impairment, and bone deformities
- Transmission can occur during any stage of syphilis; risk is much higher during primary and secondary syphilis
- Fetal infection can occur during any trimester of pregnancy
- Wide spectrum of severity exists; only severe cases are clinically apparent at birth
  - Early lesions (most common): Infants <2 years old; usually inflammatory
  - Late lesions: Children >2 years old; tend to be immunologic and destructive

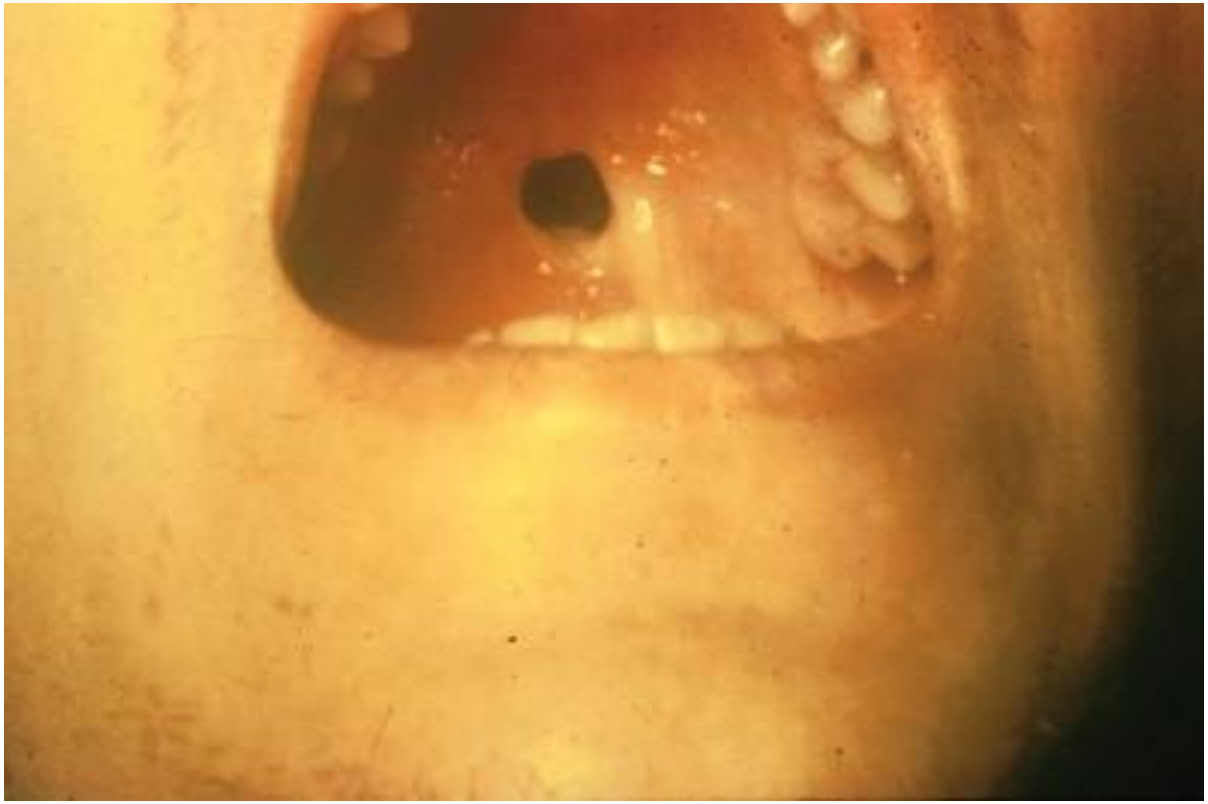
# Congenital Syphilis- Mucous Patches



# Congenital Syphilis- **Hutchinson's Teeth.** Babies who are having these kind of teeth are smaller and more widely spaced than normal and which have notched on their biting surfaces.



# Congenital Syphilis- Perforation of Palate



# Lesson IV: Syphilis Diagnosis

# Aspects of Syphilis Diagnosis

1. Clinical history
2. Physical examination
3. Laboratory diagnosis

# Clinical History

Assess

- History of syphilis
- Known contact to an early case of syphilis
- Typical signs or symptoms of syphilis in the past 12 months
- Most recent serologic test for syphilis

# Physical Examination

- Oral cavity
- Lymph nodes
- Skin of torso
- Palms and soles
- Genitalia and perianal area
- Neurologic examination
- Abdomen

# Laboratory Diagnosis

- Identification of *Treponema pallidum* in lesion exudate or tissue
  - Darkfield microscopy
  - Tests to detect *T. pallidum*

- Serologic tests to allow a presumptive diagnosis
  - Nontreponemal tests
  - Treponemal tests

# Darkfield Microscopy

- What to look for
  - *T. pallidum* morphology and motility
- Advantage
  - Definitive immediate diagnosis
  - Rapid results
- Disadvantages
  - Requires specialized equipment and an experienced microscopist
  - Possible confusion with other pathogenic and nonpathogenic spirochetes
  - Must be performed immediately
  - Generally not recommended on oral lesions
  - Possibility of false-negatives

# Serologic Tests for Syphilis

- Two types
  - Treponemal (qualitative)
  - Nontreponemal (qualitative and quantitative)
- The use of only one type of serologic test is insufficient for diagnosis

# Nontreponemal Serologic Tests

- Principles
  - Measure antibody directed against a cardiolipin-lecithin-cholesterol antigen
  - Not specific for *T. pallidum*
  - Titers usually correlate with disease activity and results are reported quantitatively
  - May be reactive for life, referred to as "serofast"
- Nontreponemal tests include VDRL, RPR, TRUST, USR

# Nontreponemal Serologic Tests (continued)

## Advantages

- Rapid and inexpensive
- Easy to perform and can be done in clinic or office
- Quantitative
- Used to follow response to therapy
- Can be used to evaluate possible reinfection

## Disadvantages

- May be insensitive in certain stages
- False-positive reactions may occur
- Prozone effect may cause a false-negative reaction (rare)

# Treponemal Serologic Tests

- Principles
  - Measure antibody directed against *T. pallidum* antigens
  - Qualitative
  - Usually reactive for life
  - Titers should not be used to assess treatment response

# Laboratory Testing

- Direct examination of clinical specimen by ***dark-field microscopy*** or fluorescent antibody testing of sample.
- ***Non-specific or non-treponemal*** serological test to detect ***reagin***, utilized as screening test only.
- ***Specific Treponemal antibody tests*** are used as a confirmatory test for a positive reagin test.

# Nontreponemal Reagin Tests

- ***Non-specific or non-treponemal*** serological test to detect ***reagin***, utilized as screening test only.
  - Reagin is an antibody formed against cardiolipin.
  - Found in sera of patients with syphilis as well as other diseases.
  - This type of reagin not to be confused with same word originally used to describe IgE.
  - Non treponemal tests become positive 1 to 4 weeks after appearance of primary chancre.
  - in secondary stage may have false negative due to Prozone, in tertiary 25% are negative, after successful treatment will become nonreactive after 1 to 2 years.

# Nontreponemal Reagin Tests

- VDRL
- RPR
- USR-unheated serum reagin test
- RST-reagin screen test
- ELISA

# Venereal Disease Research Laboratory - VDRL

- Flocculation test, antigen consists of very fine particles that precipitate out in the presence of reagin.
- Utilizes an antigen which consists of ***cardiolipin, cholesterol and lecithin***.
  - Antigen very technique dependent.
  - Must be made up fresh daily.
- **Serum must be heated to 56 C for 30 minutes** to remove anti-complementary activity which may cause false positive, if serum is not tested **within 4 hours** must be **reheated for 10 minutes**.

# Rapid Plasma Reagin Test - RPR

- General screening test, can be adapted to automation.
- **CANNOT be performed on CSF**.
- **CANNOT be performed on cord blood.**
- Antigen
  - VDRL cardiolipin antigen is **modified with choline chloride** to make it more stable
  - attached to charcoal particles to allow macroscopic reading
  - antigen comes prepared and is very stable.
- **Serum or plasma** may be used for testing, serum is **not** heated.

# Specific Treponemal Tests

- Performed to confirm a positive non-specific reagin test.
- Treponema Pallidum Immobilization
- Treponema pallidum hemagglutination
- Fluorescent treponemal antibody absorption test
- ELISA

# *Treponema Pallidum* Immobilization - TPI

- An antibody present in the serum of a syphilitic patient, in the presence of complement, causes the immobilization of actively motile *Treponema pallidum* obtained from testes of a rabbit infected with syphilis.

# *Treponema pallidum* hemagglutination (TPHA)

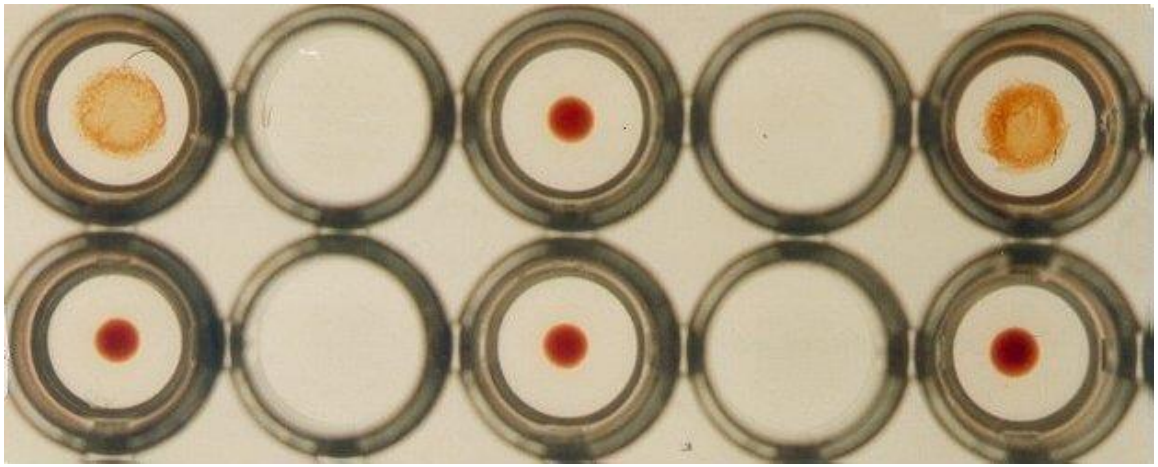
- Adapted to microtechniques (MHA-TP)
- Tanned sheep RBCs are coated with *T. pallidum* antigen from Nichol's strain.
- Agglutination of the RBCs is a positive result.

## *Treponema pallidum Hemagglutination* (TPHA)

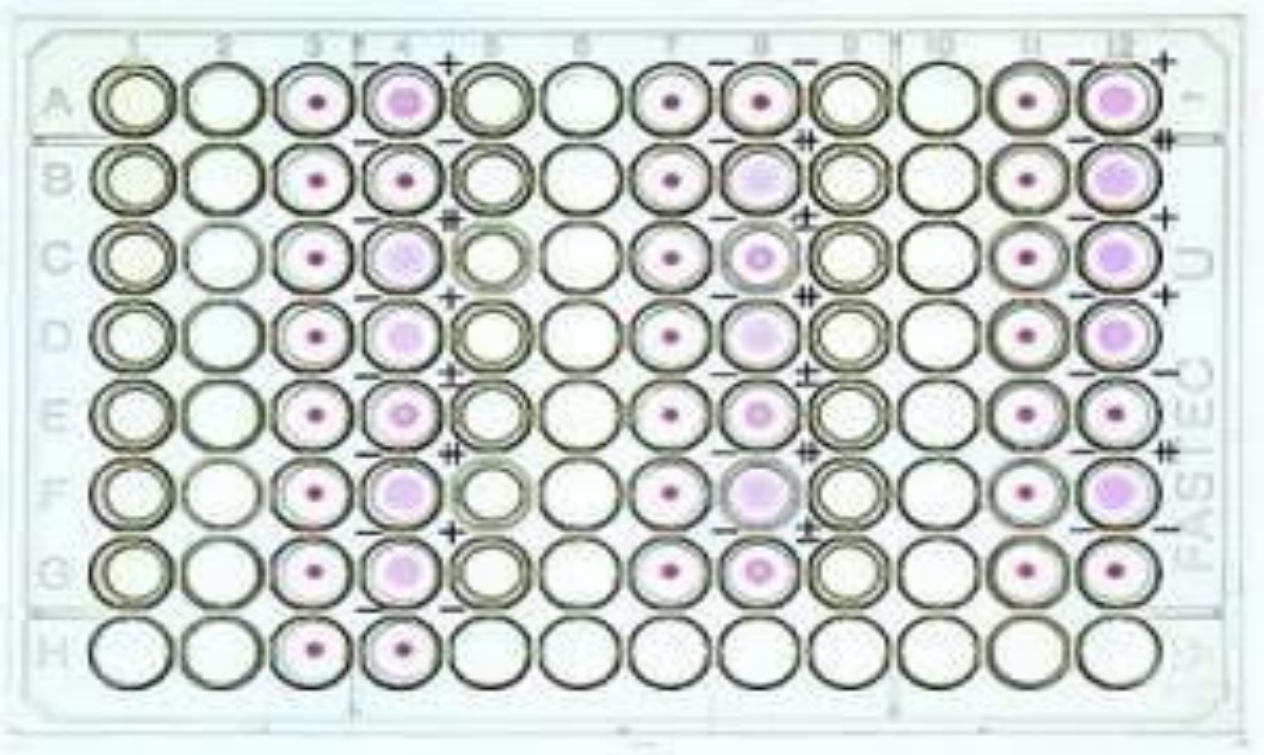
- Based on agglutination of RBCs sensitized with T. pallidum antigen.
- Patient sera incubated with sensitized RBCs in microtiter wells and unsensitized RBCs in control wells.
- Patient sera containing specific antibodies will react only with the antigen to form a smooth mat of agglutinated RBCs (positive).
- A compact button formed by the settling of the non-agglutinated RBCs in the microtiter wells containing sensitized RBCs indicates lack of specific antibody in patient sera (negative).
- If agglutination is seen with both sensitized and unsensitized RBCs, nonspecific agglutination is indicated.

# *Treponema pallidum* Hemagglutination

- The upper, left-hand well contains a positive control test.
  - RBCs have treponemal antigens attached
  - Positive control has Treponmal antibodies which causes agglutination of RBCs, forms mat across bottom of the well.
  - Negative control below the positive.
- Interpret the other 4 wells.



# *Treponema pallidum* Hemagglutination (TPHA)



# Lesson V: Patient Management

# Therapy for Primary, Secondary, and Early Latent Syphilis

- Benzathine penicillin G 2.4 million units intramuscularly in a single dose (Bicillin L-A®)

- **If penicillin allergic**
  - Doxycycline 100 mg orally twice daily for 14 days, or
  - Tetracycline 500 mg orally 4 times daily for 14 days

# Therapy for Late Latent Syphilis

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each at 1-week intervals

- **If penicillin allergic**
  - Doxycycline 100 mg orally twice daily for 28 days or
  - Tetracycline 500 mg orally 4 times daily for 28 days

# Therapy for Tertiary Syphilis

- Benzathine penicillin G 7.2 million units total, administered as 3 doses of 2.4 million units intramuscularly each at 1-week intervals

- **If penicillin allergic**
  - Doxycycline 100 mg orally twice daily for 28 days or
  - Tetracycline 500 mg orally 4 times daily for 28 days

# Therapy for Neurosyphilis

- Aqueous crystalline penicillin G 18–24 million units per day, administered as 3–4 million units intravenously every 4 hours or continuous infusion for 10 to14 days intravenously

- Alternative regimen (if compliance can be ensured)
  - **Procaine penicillin 2.4 million units** intramuscularly once daily PLUS **Probenecid** 500 mg orally 4 times a day, both for 10 to14 days

# Therapy for Syphilis in Pregnancy

- Treat with penicillin according to stage of infection.
- **Erythromycin** is no longer an acceptable alternative drug in penicillin-allergic patients.
- Patients who are skin-test-reactive to penicillin should be desensitized in the hospital and treated with **penicillin**.
- Some evidence suggests that additional therapy can be beneficial for pregnant women in some settings.

# Treatment Failure

- Indications of probable treatment failure or reinfection include
  - Persistent or recurring clinical signs or symptoms
  - Sustained 4-fold increase in titer
  - Titer fails to show a 4-fold decrease within 6–12 months
- Retreat and re-evaluate for HIV infection.
- CSF examination can be considered.

# Lesson VI: Prevention

# Patient Counseling and Education

- Nature of the disease
- Transmission
- Treatment and follow-up
- Risk reduction