



Spirochaetales

~~~~~

***Treponema***

***Borrelia &***

***Leptospira***

# ***Taxonomy***

**Order:** Spirochaetales

**Family:** *Spirochaetaceae*

**Genus:** *Treponema*

*Borrelia*

**Family:** *Leptospiraceae*

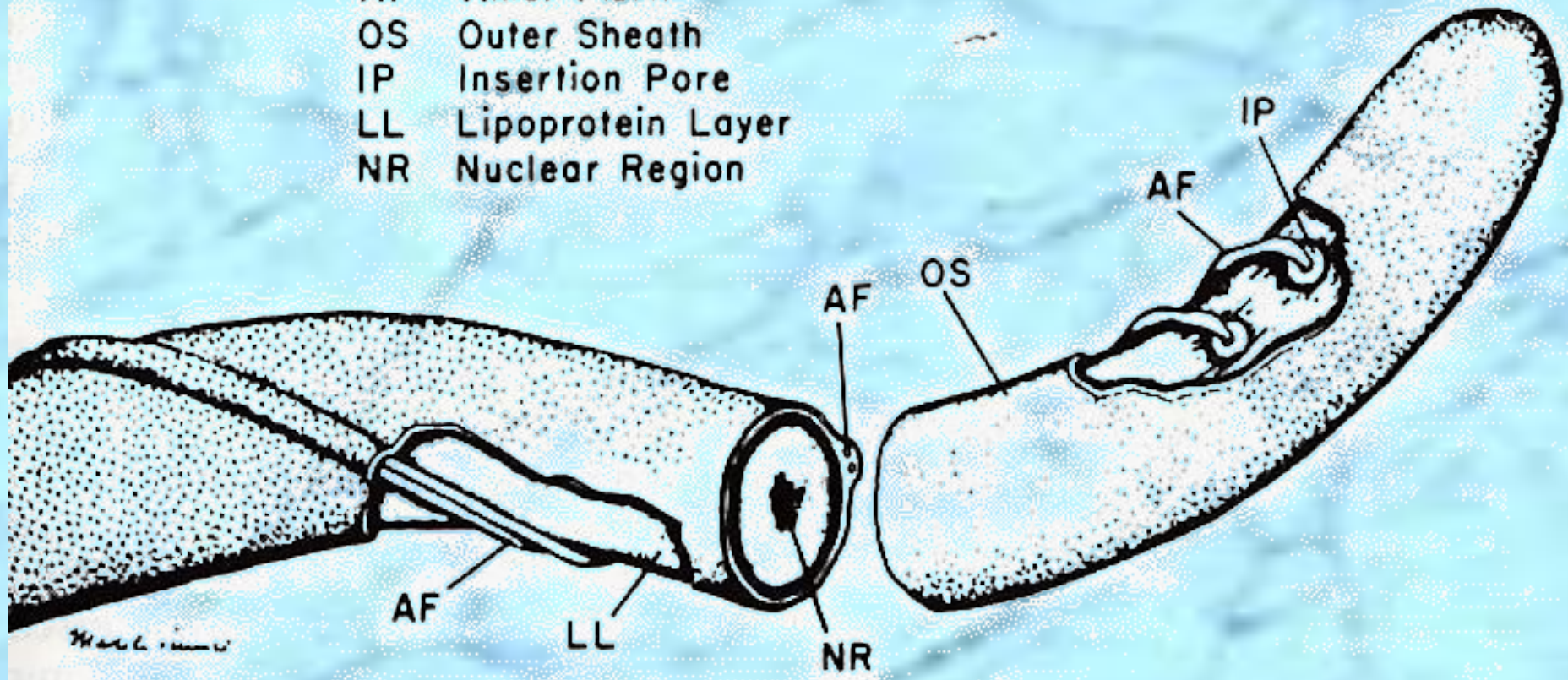
**Genus:** *Leptospira*

# ***General Overview of Spirochaetales***

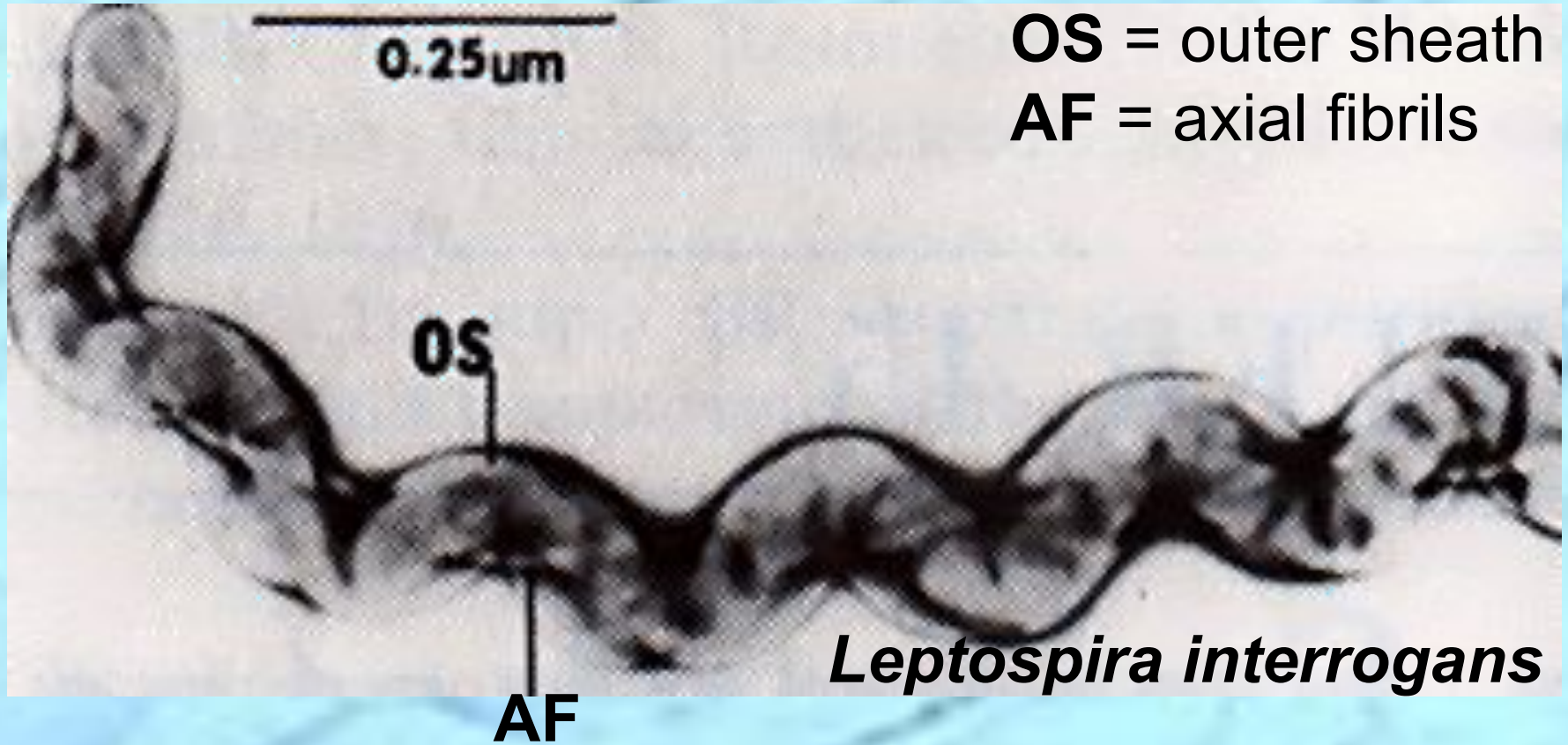
- Gram-negative **spirochetes**
  - Spirochete from Greek for “coiled hair”
- **Extremely thin** and can be **very long**
- Tightly coiled **helical cells with tapered ends**
- Motile by **periplasmic flagella** (a.k.a., **axial fibrils** or **endoflagella**)
- **Outer sheath** encloses axial fibrils wrapped around protoplasmic cylinder
  - Axial fibrils originate from insertion pores at both poles of cell
  - May overlap at center of cell in *Treponema* and *Borrelia*, but not in *Leptospira*
  - Differing numbers of endoflagella according to genus & species

# ***Periplasmic Flagella Diagram***

AF Axial Fibril  
OS Outer Sheath  
IP Insertion Pore  
LL Lipoprotein Layer  
NR Nuclear Region

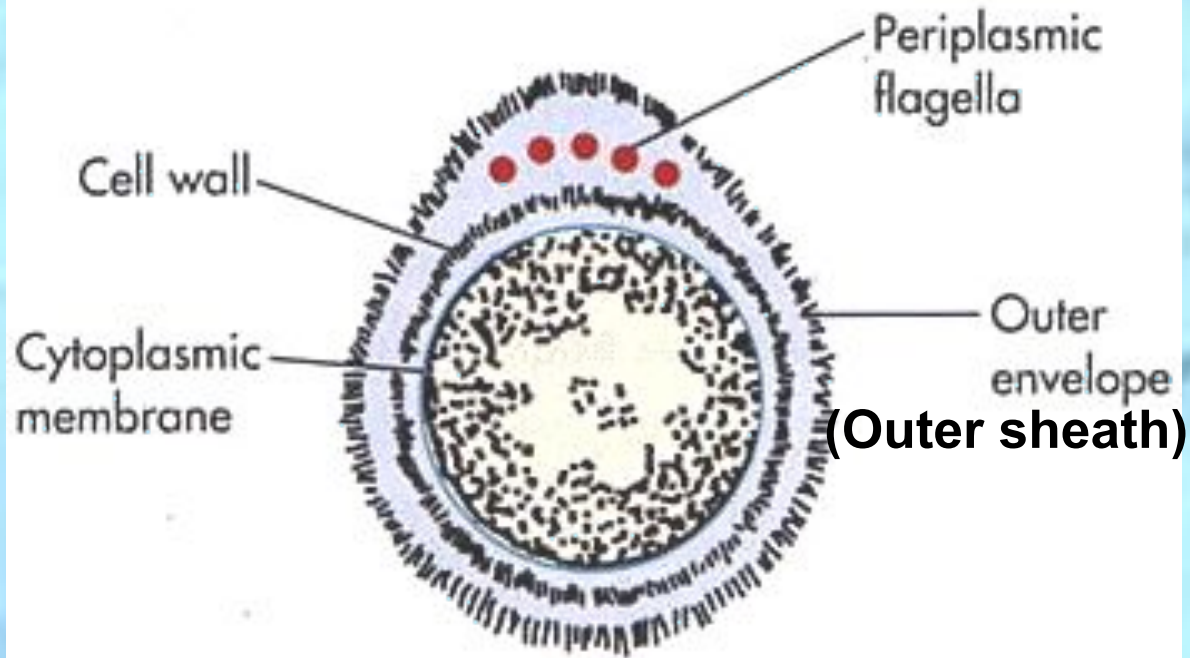


# ***Tightly Coiled Spirochete***



Cross section of  
*Borrelia burgdorferi*

# Cross-Section of Spirochete with Periplasmic Flagella



**NOTE:** a.k.a.,  
endoflagella,  
axial fibrils or  
axial filaments.

# **Spirochaetales *Associated***

## ***Human Diseases***

| <b><u>Genus</u></b>      | <b><u>Species</u></b>                                                                                                                              | <b><u>Disease</u></b>                                                                      |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b><i>Treponema</i></b>  | <b><i>pallidum</i> ssp. <i>pallidum</i><br/><i>pallidum</i> ssp. <i>endemicum</i><br/><i>pallidum</i> ssp. <i>pertenue</i><br/><i>carateum</i></b> | <b>Syphilis<br/>Bejel<br/>Yaws<br/>Pinta</b>                                               |
| <b><i>Borrelia</i></b>   | <b><i>burgdorferi</i><br/><i>recurrentis</i><br/>Many species</b>                                                                                  | <b>Lyme disease (borreliosis)<br/>Epidemic relapsing fever<br/>Endemic relapsing fever</b> |
| <b><i>Leptospira</i></b> | <b><i>interrogans</i></b>                                                                                                                          | <b>Leptospirosis<br/>(Weil's Disease)</b>                                                  |



***Treponema spp.***

# ***Nonvenereal Treponemal Diseases***

- ✓ **Bejel, Yaws & Pinta**
- ✓ **Primitive tropical and subtropical regions**
- ✓ **Primarily in impoverished children**

# *Treponema pallidum* ssp. *endemicum*

## □ **Bejel** (a.k.a. endemic syphilis)

- **Initial lesions:** nondescript oral lesions
- **Secondary lesions:** oral papules and mucosal patches
- **Late:** gummas (granulomas) of skin, bones & nasopharynx

□ **Transmitted person-to-person by contaminated eating utensils**

□ **Primitive tropical/subtropical areas** (Africa, Asia & Australia)

# *Treponema pallidum* ssp. *pertenue*

(May also see *T. pertenue*)

□ **Yaws:** granulomatous disease

- **Early:** skin lesions (see below)
- **Late:** destructive lesions of skin, lymph nodes & bones

□ **Transmitted by direct contact with lesions containing abundant spirochetes**

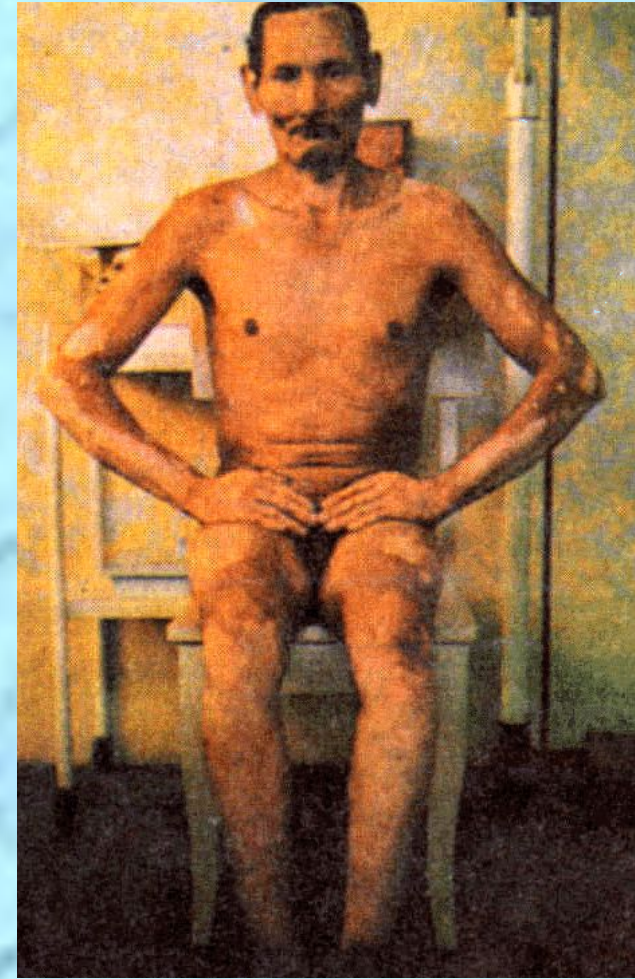
□ **Primitive tropical areas** (S. America, Central Africa, SE Asia)



**Papillomatous Lesions of Yaws:** painless nodules widely distributed over body with abundant contagious spirochetes.

# *Treponema carateum*

- **Pinta:** primarily restricted to skin
  - **1-3 week incubation period**
  - **Initial lesions:** small pruritic papules
  - **Secondary:** enlarged plaques persist for months to years
  - **Late:** disseminated, recurrent hypopigmentation or depigmentation of skin lesions; scarring & disfigurement
- **Transmitted by direct contact with skin lesions**
- **Primitive tropical areas**  
(Mexico, Central & South America)



**Hypopigmented Skin Lesions of Pinta:** depigmentation is commonly seen as a late sequel with a treponemal diseases

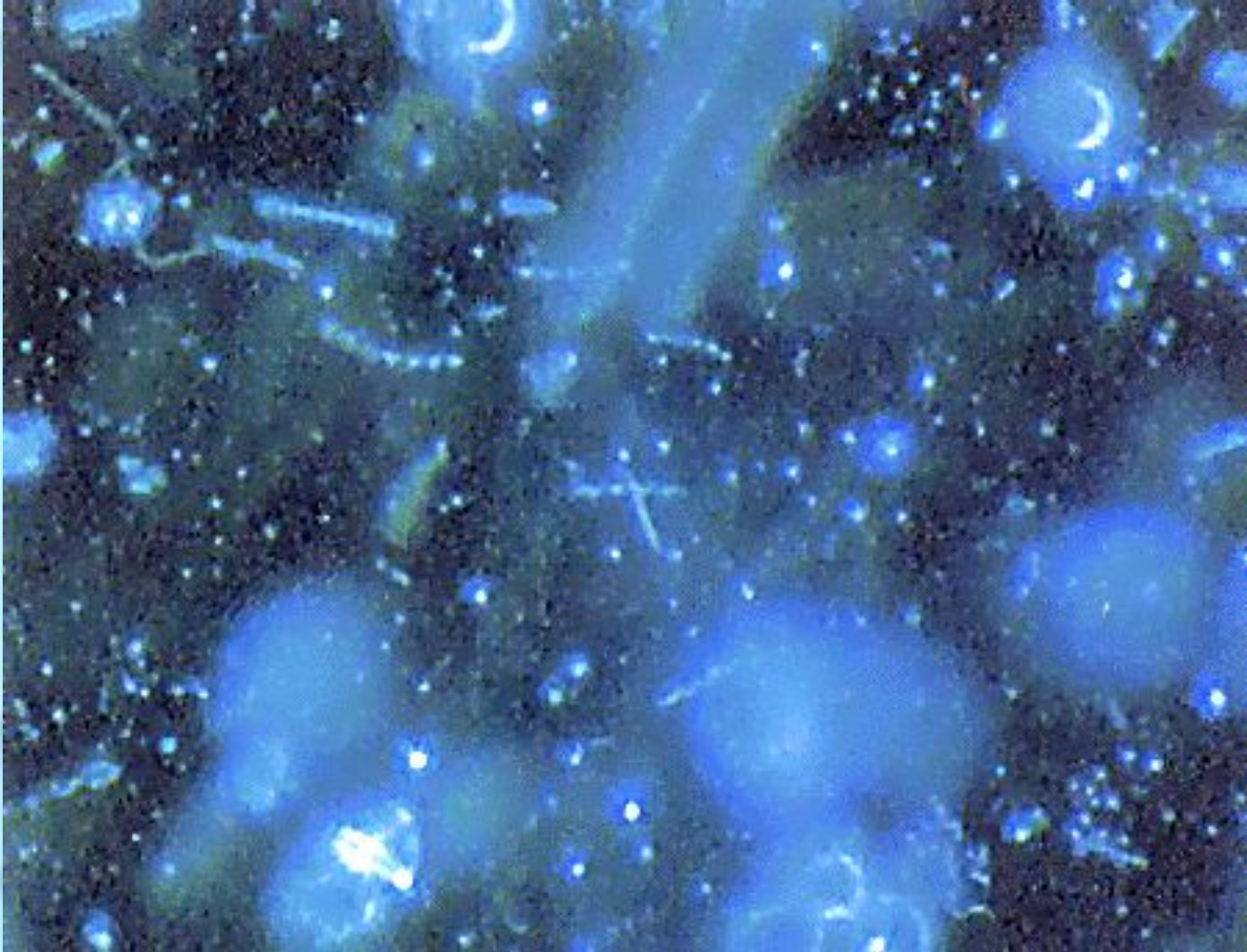


***Treponema pallidum***  
***ssp. pallidum***

# ***Venereal Treponemal Disease***

- **Syphilis**
- Primarily **sexually transmitted disease (STD)**
- May be **transmitted congenitally**

# ***Darkfield Microscopy of Treponema pallidum***



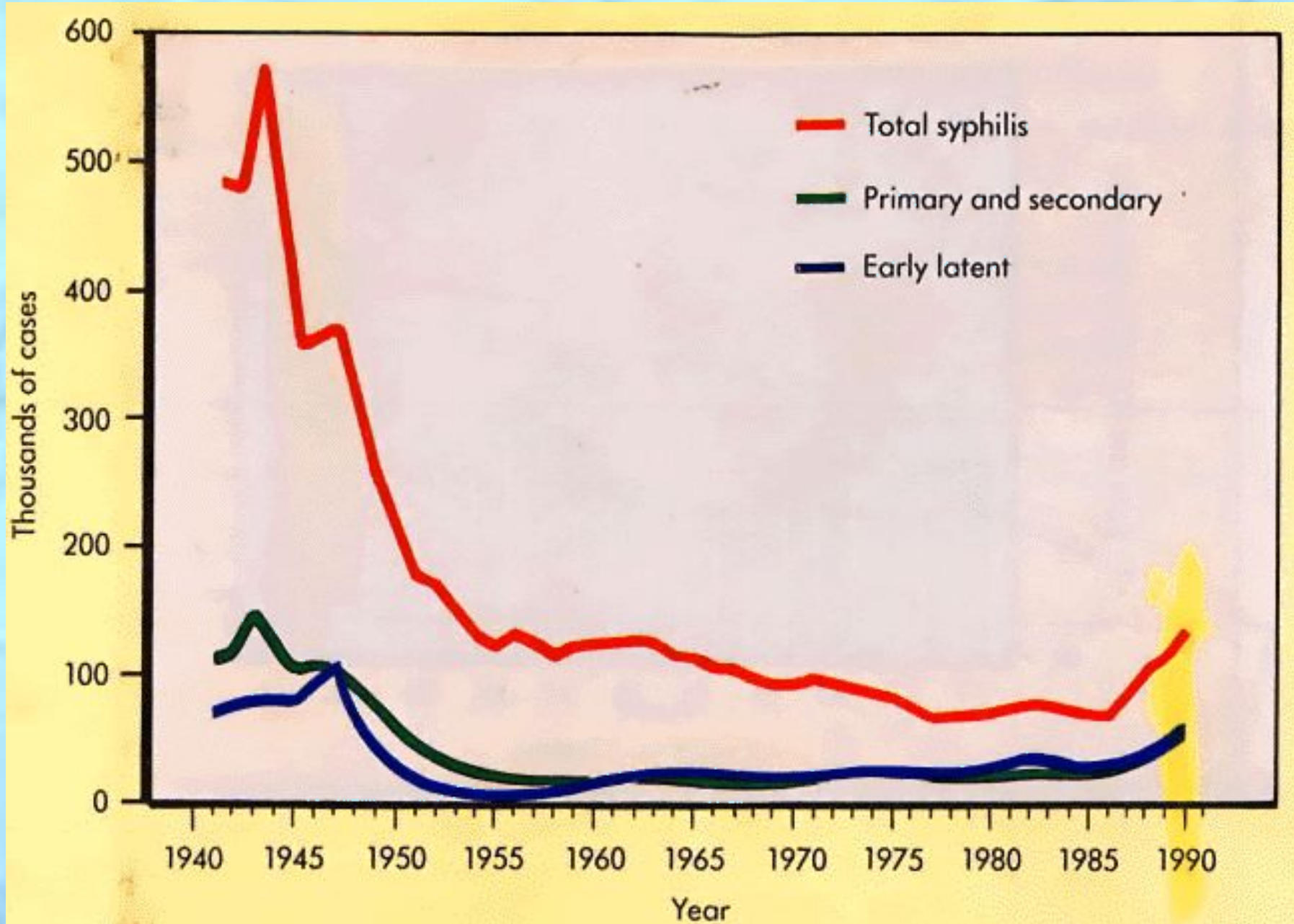
# ***General Characteristics of Treponema pallidum***

- Too thin to be seen with light microscopy in specimens stained with Gram stain or Giemsa stain
  - Motile spirochetes can be seen with **darkfield microscopy**
  - Staining with **anti-treponemal antibodies labeled with fluorescent dyes**
- **Intracellular pathogen**
- **Cannot be grown in cell-free cultures in vitro**
  - Koch's Postulates have not been met
- **Do not survive well outside of host**
  - Care must be taken with clinical specimens for laboratory culture or testing

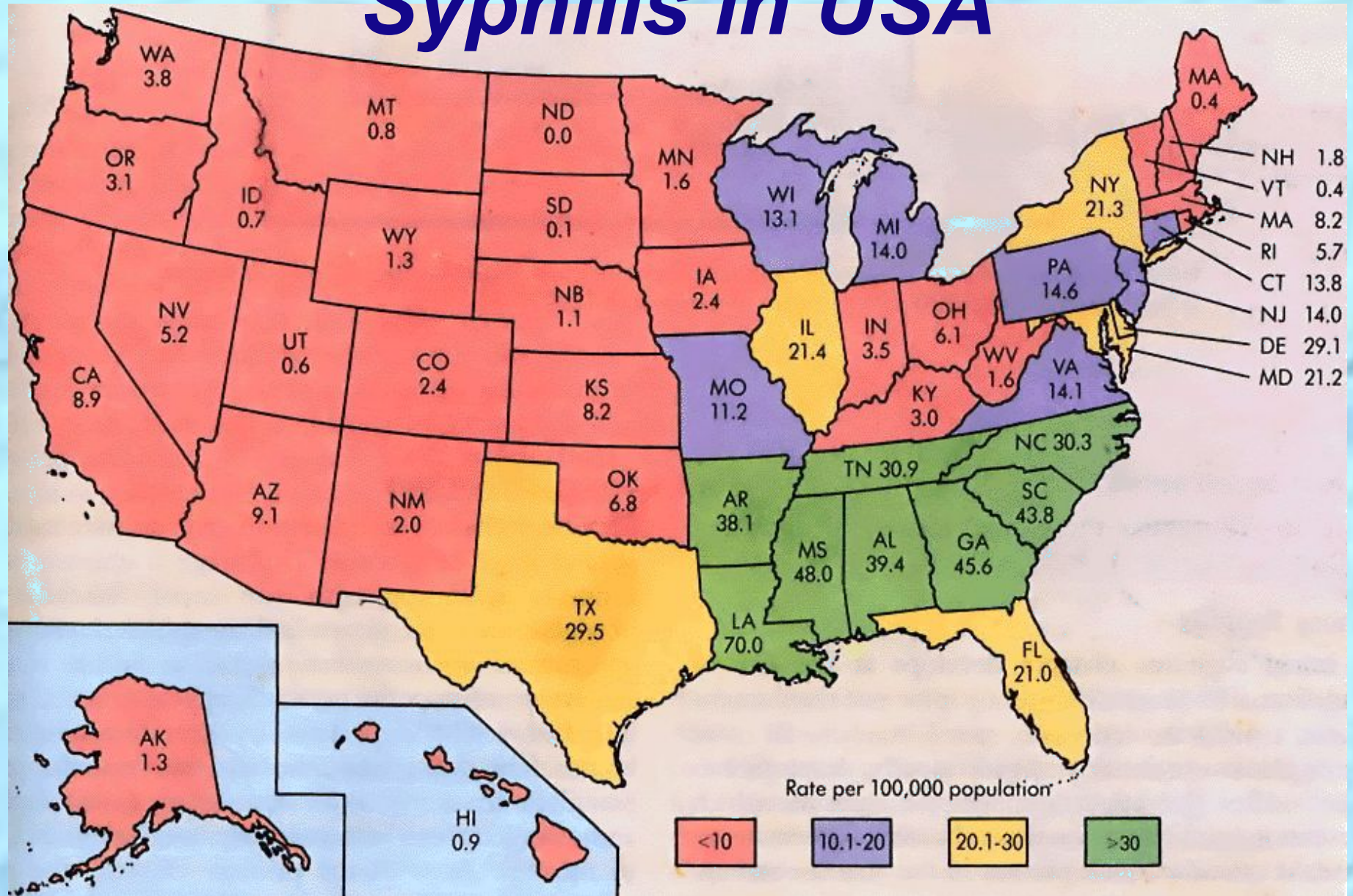
# ***Epidemiology of *T. pallidum****

- Transmitted from direct **sexual contact** or from **mother to fetus**
- **Not highly contagious** (~30% chance of acquiring disease after single exposure to infected partner) but transmission rate dependent upon stage of disease
- **Long incubation period** during which time host is non-infectious
  - Useful epidemiologically for **contact tracing** and administration of **preventative therapy**
- Prostitution for drugs or for money to purchase drugs remains central epidemiologic aspect of transmission

# ***Incidence of Syphilis in USA***



# Geographical Distribution of Syphilis in USA



# ***Pathogenesis of *T. pallidum****

- **Tissue destruction and lesions are primarily a consequence of patient's immune response**
- Syphilis is a **disease of blood vessels and of the perivascular areas**
- In spite of a **vigorous host immune response** the organisms are capable of persisting for decades
  - Infection is **neither fully controlled nor eradicated**
  - In **early stages**, there is an inhibition of cell-mediated immunity
  - Inhibition of CMI abates in **late stages** of disease, hence late lesions tend to be localized

# ***Virulence Factors of T. pallidum***

- ❑ **Outer membrane proteins** promote adherence
- ❑ **Hyaluronidase** may facilitate **perivascular infiltration**
- ❑ **Antiphagocytic** coating of **fibronectin**
- ❑ **Tissue destruction and lesions** are primarily result of host's immune response (**immunopathology**)

# ***Pathogenesis of T. pallidum (cont.)***

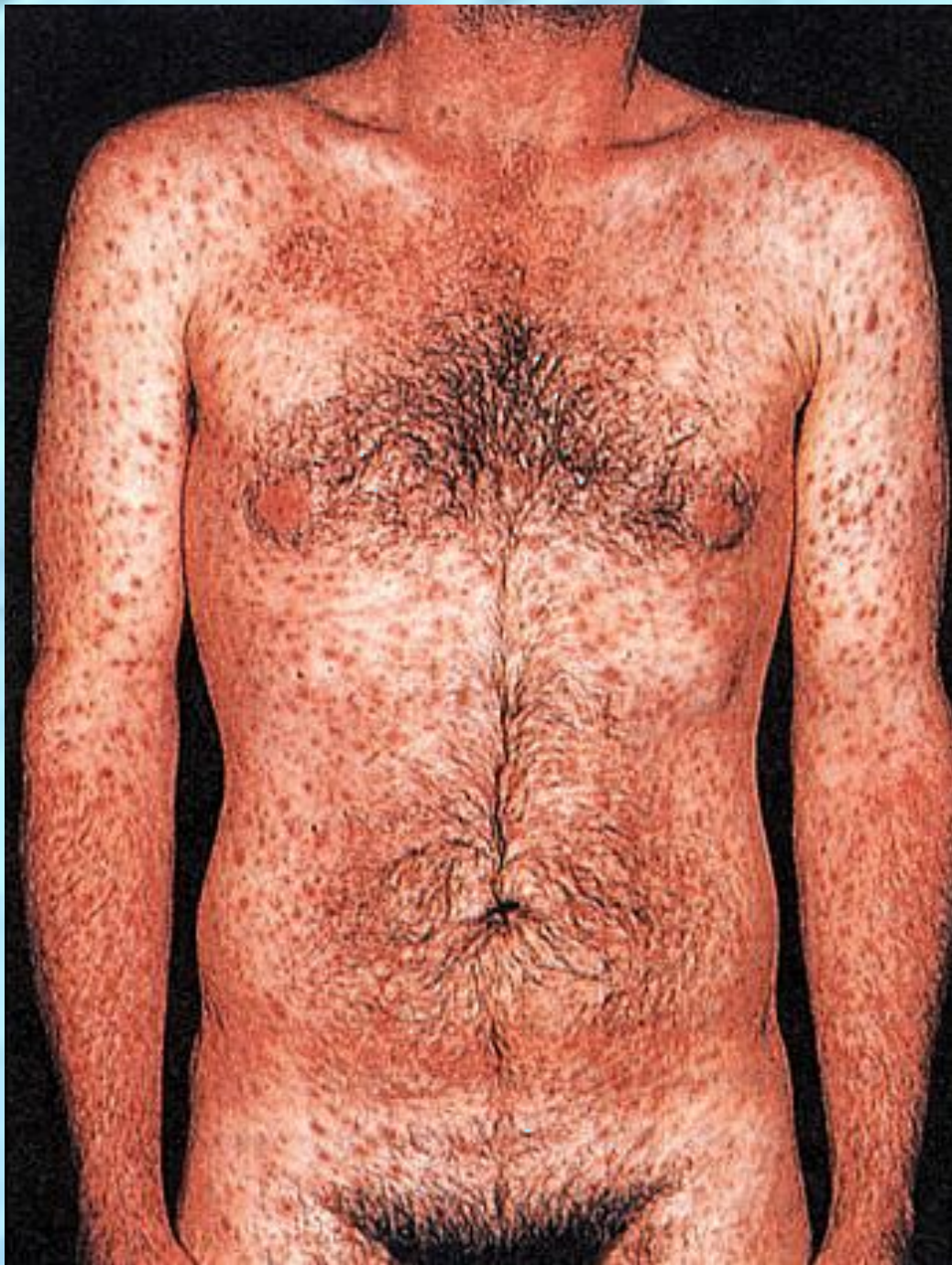
## ***Primary Syphilis***

- Primary disease process involves **invasion of mucus membranes, rapid multiplication & wide dissemination** through perivascular lymphatics and systemic circulation
  - ✓ Occurs **prior to development of the primary lesion**
- 10-90 days (usually 3-4 weeks) after initial contact the host mounts an **inflammatory response at the site of inoculation** resulting in the hallmark syphilitic lesion, called the **chancre (usually painless)**
  - Chancre changes from hard to ulcerative with profuse **shedding of spirochetes**
  - Swelling of capillary walls & regional lymph nodes w/ draining
  - Primary lesion heals spontaneously by fibrotic walling-off within two months, leading to false sense of relief

# ***Pathogenesis of *T. pallidum**** (cont.)

## ***Secondary Syphilis***

- Secondary disease 2-10 weeks after primary lesion
- Widely disseminated **mucocutaneous rash**
- **Secondary lesions** of the skin and mucus membranes are **highly contagious**
- Generalized immunological response



***Generalized  
Mucocutaneous  
Rash of  
Secondary  
Syphilis***

# ***Pathogenesis of T. pallidum*** (cont.)

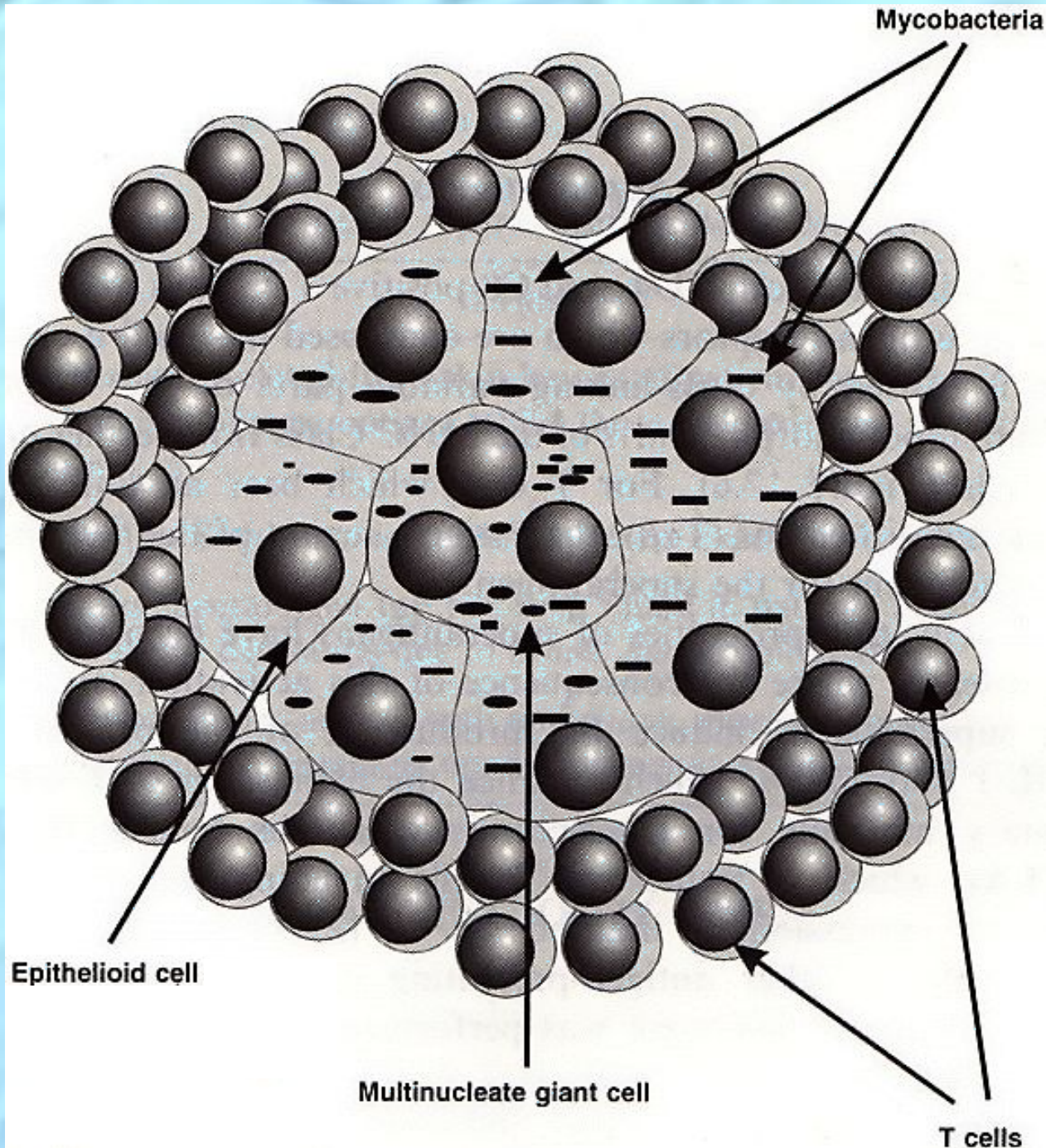
## ***Latent Stage Syphilis***

- Following secondary disease, host enters latent period
  - First 4 years = **early latent**
  - Subsequent period = **late latent**
- **About 40% of late latent patients progress to late tertiary syphilitic disease**

# *Pathogenesis of T. pallidum* (cont.)

## *Tertiary Syphilis*

- Tertiary syphilis characterized by **localized granulomatous dermal lesions (gummas)** in which few organisms are present
  - Granulomas reflect containment by the immunologic reaction of the host to chronic infection
- Late **neurosyphilis** develops in about 1/6 untreated cases, usually more than 5 years after initial infection
  - Central nervous system and spinal cord involvement
  - Dementia, seizures, wasting, etc.
- **Cardiovascular** involvement appears 10-40 years after initial infection with resulting myocardial insufficiency and death

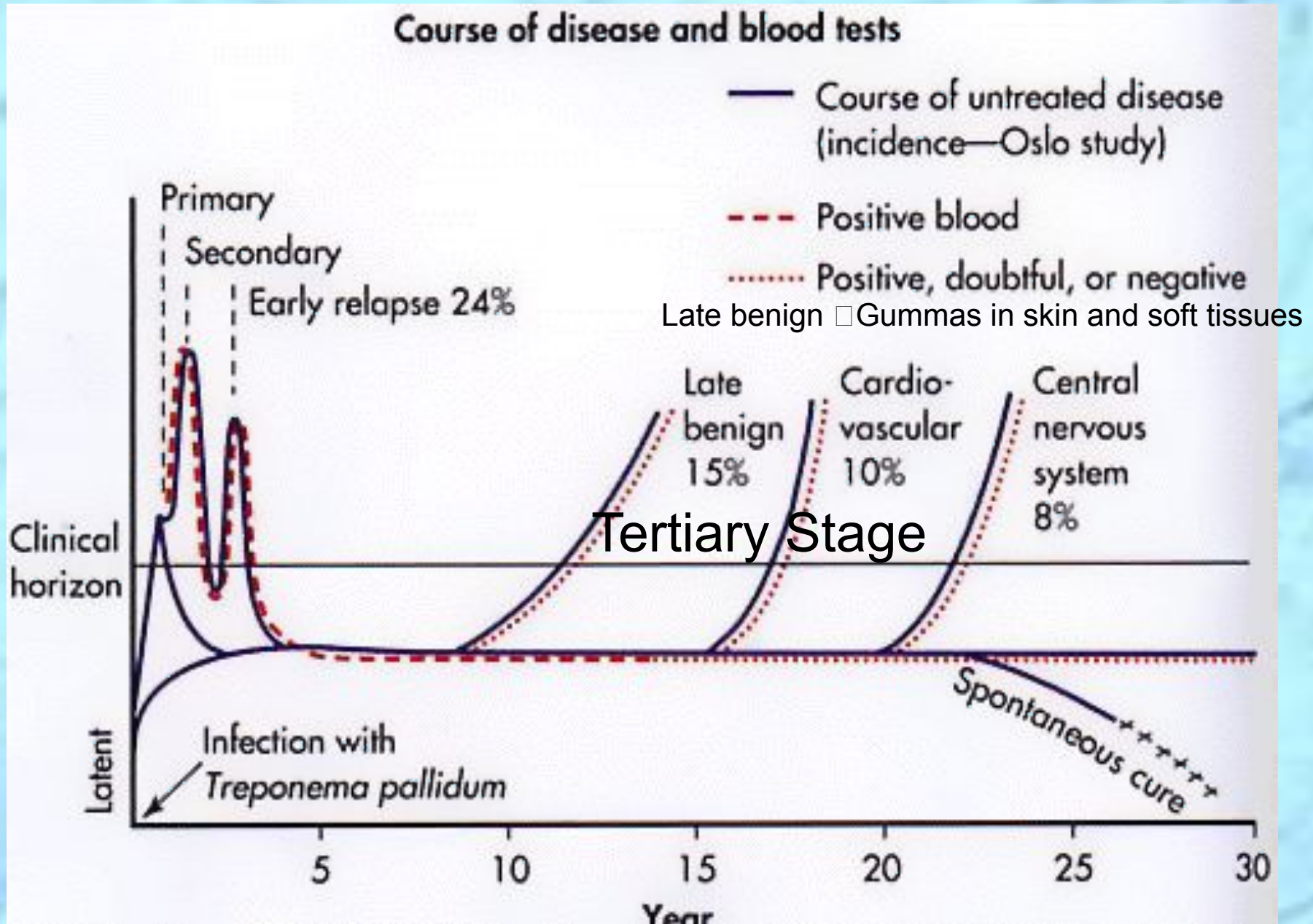


# ***Diagram of a Granuloma***

(a.k.a. **gumma** in skin or soft tissue)

**NOTE:** ultimately a fibrin layer develops around granuloma, further “walling off” the lesion

# Progression of Untreated Syphilis

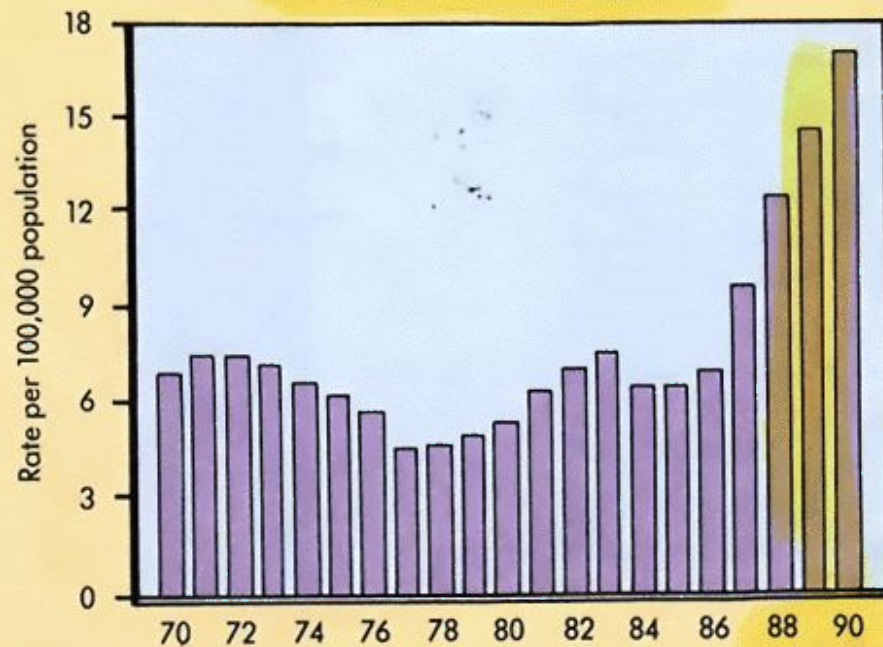


# ***Pathogenesis of *T. pallidum**** (cont.)

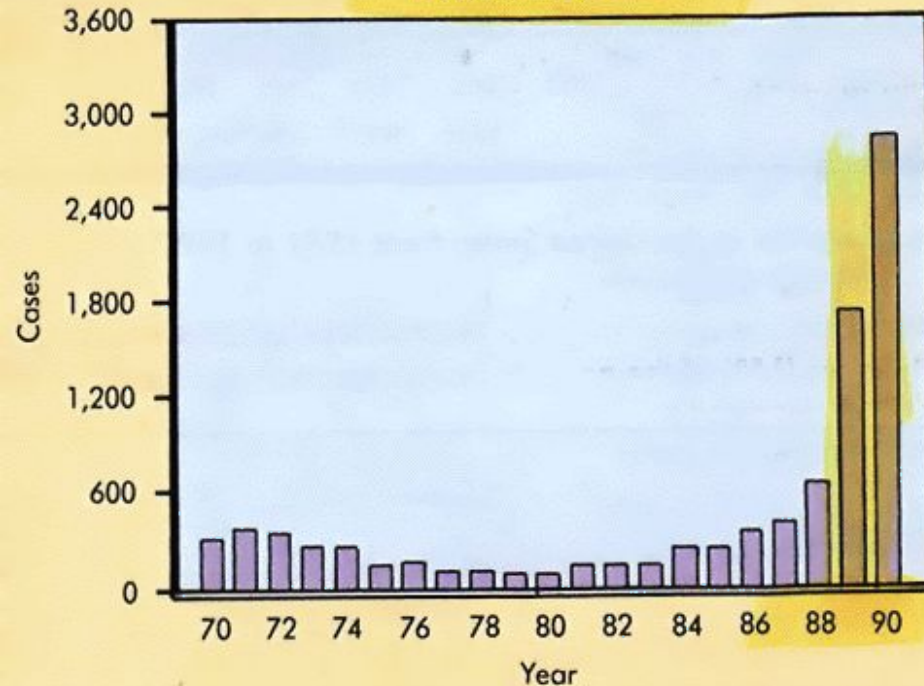
## ***Congenital Syphilis***

- Congenital syphilis results from **transplacental infection**
- *T. pallidum* **septicemia in the developing fetus and widespread dissemination**
- **Abortion, neonatal mortality, and late mental or physical problems** resulting from scars from the active disease and progression of the active disease state

Primary and Secondary Syphilis



Congenital Syphilis



***Comparison of  
Incidence of 1°  
& 2° Syphilis in  
Women and  
Congenital  
Syphilis***

# ***Prevention & Treatment of Syphilis***

- **Penicillin remains drug of choice**
  - WHO monitors treatment recommendations
  - 7-10 days continuously for early stage
  - At least 21 days continuously beyond the early stage
- Prevention with **barrier methods** (e.g., condoms)
- **Prophylactic treatment of contacts** identified through **epidemiological tracing**

# Diagnostic Tests for Syphilis

| Diagnostic Test | Method or Examination                                                                                                                                                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Microscopy      | → Darkfield<br>→ Direct fluorescent antibody staining                                                                                                                                                                                                                         |
| Culture         | → Not available                                                                                                                                                                                                                                                               |
| Serology        | → Nontreponemal tests<br>Venereal Disease Research Laboratory (VDRL)<br>Rapid plasma reagin (RPR)(Original Wasserman Test)<br>→ Treponemal tests<br>Fluorescent treponemal antibody absorption (FTA-ABS)<br>Microhemagglutination test for <i>Treponema pallidum</i> (MHA-TP) |

**NOTE:** Treponemal antigen tests indicate experience with a treponemal infection, but **cross-react with antigens other than *T. pallidum* ssp. *pallidum***. Since pinta and yaws are rare in USA, positive treponemal antigen tests are **usually indicative of syphilitic infection**.

# Sensitivity & Specificity of Serologic Tests for Syphilis

| Test                        | Sensitivity (%) |           |             |            | Specificity (%) |
|-----------------------------|-----------------|-----------|-------------|------------|-----------------|
|                             | Primary         | Secondary | Latent      | Late       |                 |
| <b><i>Nontreponemal</i></b> |                 |           |             |            |                 |
| VDRL                        | 78 (74–87)      | 100       | 95 (88–100) | 71 (37–94) | 98 (96–99)      |
| RPR                         | 86 (77–100)     | 100       | 98 (95–100) | 73         | 98 (93–99)      |
| <b><i>Treponemal</i></b>    |                 |           |             |            |                 |
| FTA-ABS                     | 84 (70–100)     | 100       | 100         | 96         | 97 (94–100)     |
| MHA-TP                      | 76 (69–90)      | 100       | 97 (97–100) | 94         | 99 (98–100)     |

# **Review Handout on Sensitivity & Specificity of Diagnostic Tests**

# ***Conditions Associated with False Positive Serological Tests for Syphilis***

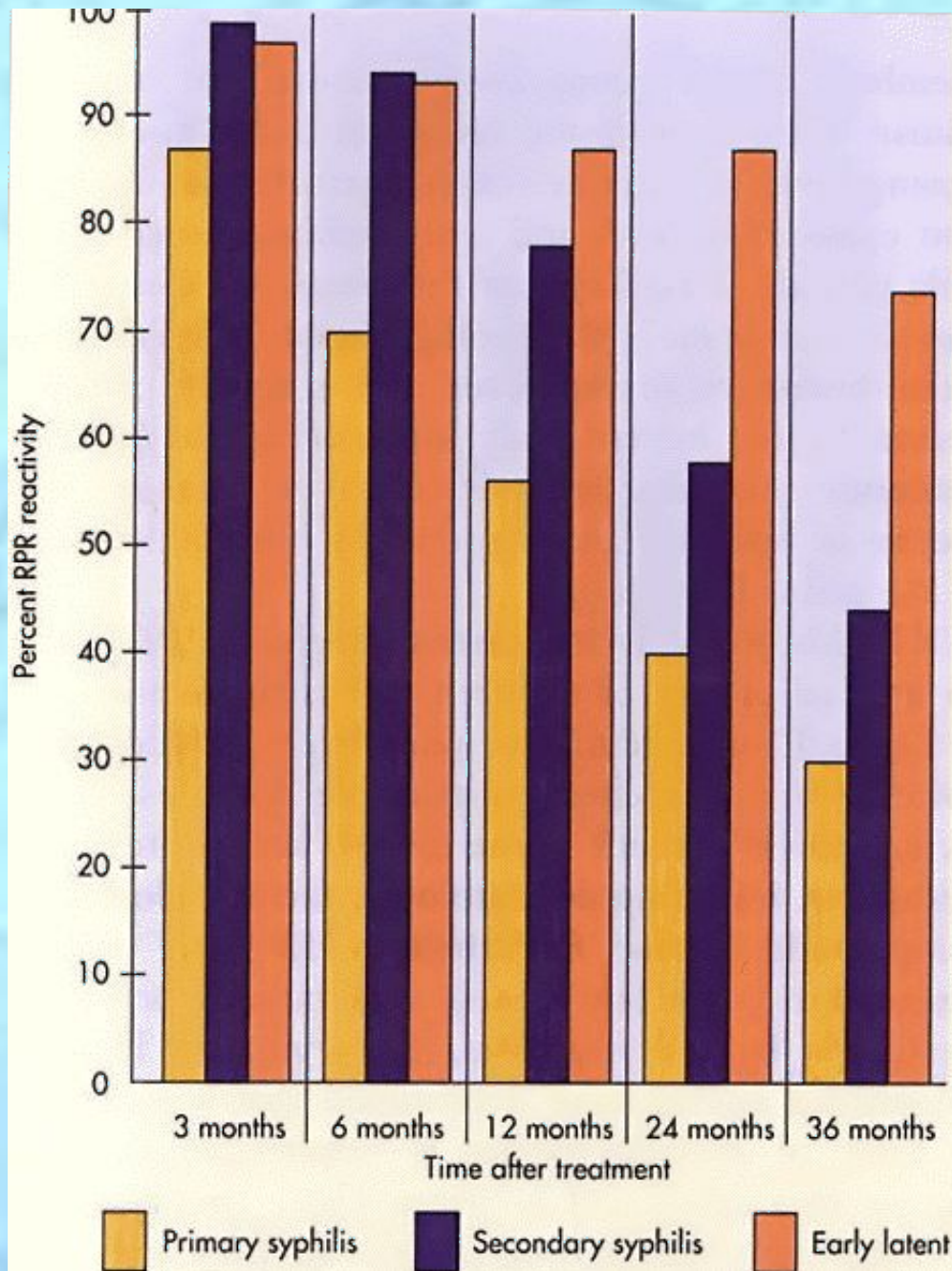
## **Nontreponemal Tests**

Viral infection  
Rheumatoid arthritis  
Systemic lupus erythematosus  
Acute or chronic illness  
Pregnancy  
Recent immunization  
Drug addiction  
Leprosy  
Malaria

## **Treponemal Tests**

Pyoderma  
Skin neoplasm  
Acne vulgaris  
Mycoses  
Crural ulceration  
Rheumatoid arthritis  
Psoriasis  
Systemic lupus erythematosus  
Pregnancy  
Drug addiction  
Herpes genitalis

# ***Effect of Treatment for Syphilis on Rapid Plasma Reagin Test Reactivity***



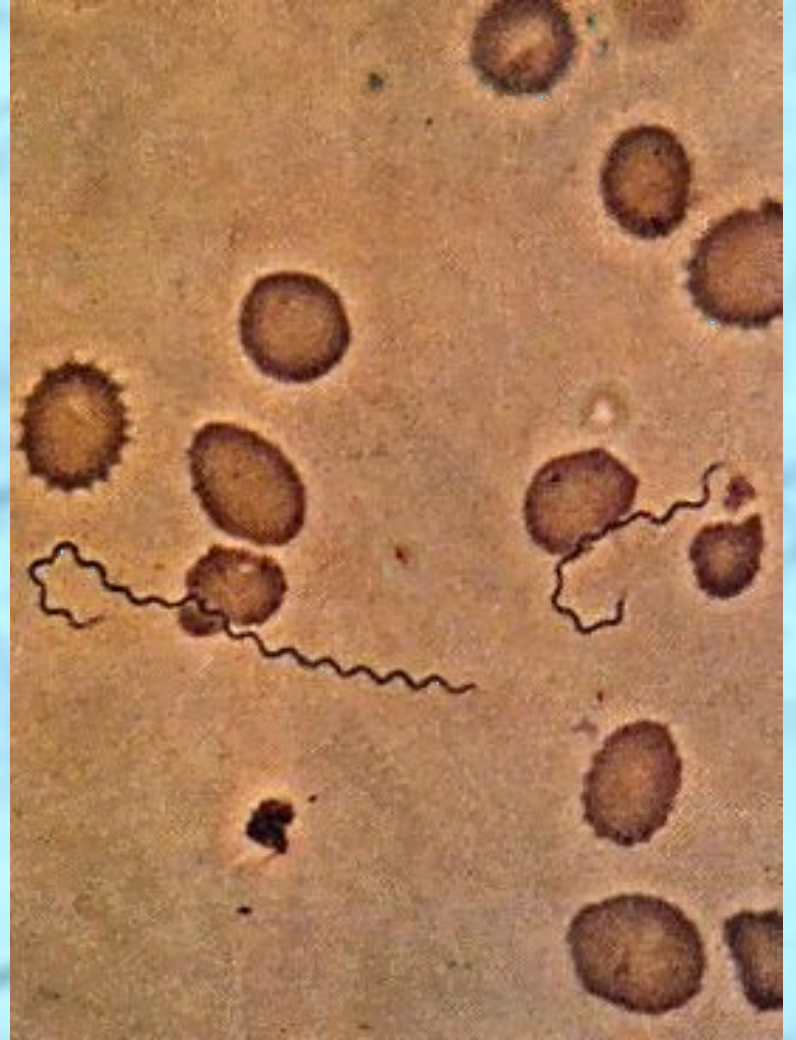


***Borrelia spp.***

# ***Giemsa Stain of Borrelia recurrentis in Blood***




Light Microscopy




Phase Contrast Microscopy

# *Epidemiology of Borrelia Infections*


*Borrelia recurrentis*

| Infection                                    | Reservoir | Vector                                                                                                                        |
|----------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------|
| Relapsing fever<br>Epidemic<br>(louse-borne) | Humans    | Body louse<br><i>Pediculus humanus</i><br> |

*Borrelia spp.*

|                                            |                             |                                                                                                                                      |
|--------------------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Relapsing fever<br>Endemic<br>(tick-borne) | Rodents, soft-shelled ticks | Soft-shelled tick<br><i>Ornithodoros spp.</i><br> |
|--------------------------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------|

*Borrelia burgdorferi*

|              |                                                  |                                                                                                                                  |
|--------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Lyme disease | Rodents, deer, domestic pets, hard-shelled ticks | Hard-shelled tick<br><i>Ixodes spp.</i><br> |
|--------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|

***Borrelia recurrentis*  
& other *Borrelia* spp.**

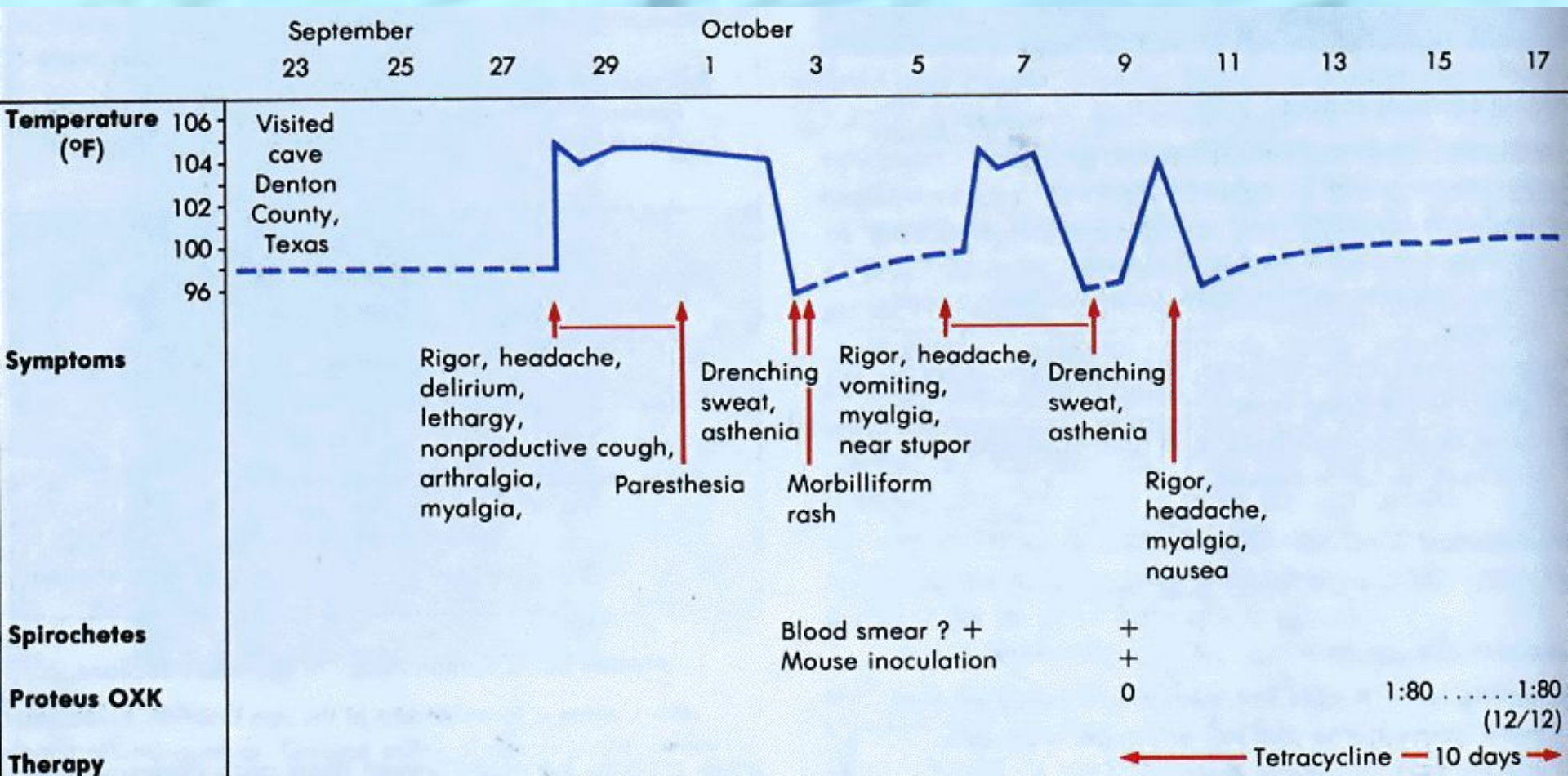
# ***Epidemiology of Relapsing Fever***

- Associated with **poverty, crowding, and warfare**
- **Arthropod vectors**
  - **Louse-borne borreliosis = Epidemic Relapsing Fever**
    - ✓ Transmitted **person-to-person** by human body lice (vectors) from infected **human reservoir**
    - ✓ Infect host only when louse is injured, e.g., during scratching
    - ✓ Therefore, a single louse can only infect a single person
    - ✓ Lice leave host that develops a fever and seek normal temperature host
  - **Tick-borne borreliosis = Endemic Relapsing Fever**
    - ✓ Sporadic cases
    - ✓ Transmitted by soft body ticks (vectors) from **small mammal reservoir**
    - ✓ Ticks can multiply and infect new human hosts

# ***Pathogenesis of Relapsing Fever***

- Relapsing fever (a.k.a., tick fever, borreliosis, famine fever)
  - Acute infection with 2-14 day (~ 6 day) incubation period
  - Followed by **recurring febrile episodes**
  - **Constant spirochaetemia** that worsens during febrile stages
- **Epidemic Relapsing Fever = Louse-borne borreliosis**
  - *Borrelia recurrentis*
- **Endemic Relapsing Fever = Tick-borne borreliosis**
  - *Borrelia spp.*

# Clinical Progression of Relapsing Fever



***Borrelia burgdorferi***

# ***Pathogenesis of Lyme Borreliosis***

- **Lyme disease characterized by three stages:**
  - i. Initially a unique skin lesion (**erythema chronicum migrans (ECM)**) with general malaise
    - ✓ **ECM not seen in all infected hosts**
    - ✓ **ECM often described as bullseye rash**
    - ✓ **Lesions periodically reoccur**
  - ii. Subsequent stage seen in 5-15% of patients with **neurological or cardiac involvement**
  - iii. Third stage involves **migrating episodes of non-destructive, but painful arthritis**
- **Acute illness treated with phenoxymethylpenicillin or tetracycline**

# ***Erythema chronicum migrans of Lyme Borreliosis***



**Bullseye rash**

# ***Diagnosis of Lyme Borreliosis***

## **Clinical Case Definition**

Either of the following:

- Erythema migrans ( $\geq 5$  cm in diameter)

- At least one late manifestation (i.e., musculoskeletal, nervous system, or cardiovascular involvement) and laboratory confirmation of infection

## **Laboratory Criteria for Diagnosis**

At least one of the following:

- Isolation of *Borrelia burgdorferi*

- Demonstration of diagnostic levels of IgM or IgG antibodies to the spirochetes

- Significant increase in antibody titer between acute and convalescent serum samples

# ***Bacteria and Syndromes that Cause Cross-Reactions with Lyme Borreliosis Serological Tests***

*Treponema pallidum*

Oral spirochetes

Other *Borrelia* species

Juvenile rheumatoid arthritis

Rheumatoid arthritis

Systemic lupus erythematosus

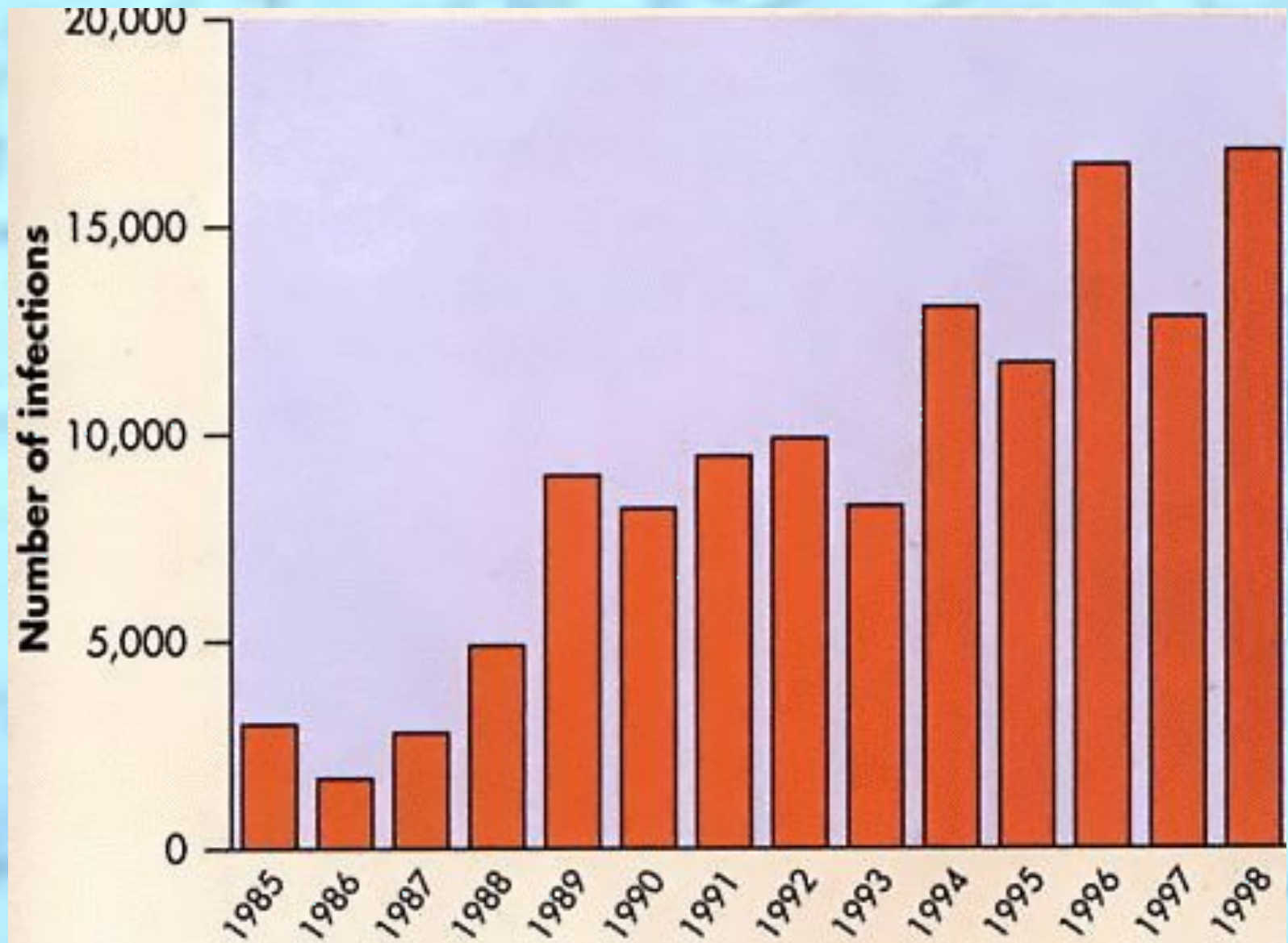
Infectious mononucleosis

Subacute bacterial endocarditis

# ***Epidemiology of Lyme Borreliosis***

- Lyme disease was recognized as a syndrome in 1975 with outbreak in Lyme, Connecticut
- Transmitted by **hard body tick (*Ixodes* spp.)**  
**vectors**
  - **Nymph stage** are usually more aggressive feeders
  - Nymph stage generally too small to discern with unaided eye
  - For these reasons, nymph stage transmits more pathogens
- **White-footed deer mice** and other rodents, deer, domesticated pets and hard-shelled ticks are most common **reservoirs**

# ***Incidence of Lyme Borreliosis in USA***





***Leptospira interrogans***

# ***Silver Stain of Leptospira interrogans* serotype *icterohaemorrhagiae***



- ❑ **Obligate aerobes**
- ❑ **Characteristic hooked ends**  
(like a question mark, thus the species epithet – *interrogans*)

# ***Leptospirosis Clinical Syndromes***










- Mild virus-like syndrome
- (**Anicteric leptospirosis**) Systemic with aseptic meningitis
- (**Icteric leptospirosis**) Overwhelming disease (Weil's disease)
  - ✓Vascular collapse
  - ✓Thrombocytopenia
  - ✓Hemorrhage
  - ✓Hepatic and renal dysfunction

**NOTE:** Icteric refers to **jaundice** (yellowing of skin and mucus membranes by deposition of bile) and **liver involvement**

# ***Pathogenesis of Icteric Leptospirosis***

- Leptospirosis, also called **Weil's disease** in humans
- Direct **invasion** and **replication** in tissues
- Characterized by an **acute febrile jaundice & immune complex glomerulonephritis**
- Incubation period usually 10-12 days with flu-like illness usually progressing through **two clinical stages**:
  - i. **Leptospiremia** develops rapidly after infection (usually lasts about 7 days) without local lesion
  - ii. Infects the **kidneys** and organisms are shed in the urine (**leptospiruria**) with **renal failure and death** not uncommon
- **Hepatic injury & meningeal irritation** is common

# Clinical Progression of Icteric (Weil's Disease) and Anicteric Leptospirosis

|                             | Anicteric leptospirosis                                                                                                                                                                                                                                                                           | Icteric leptospirosis (Weil's syndrome)                                                                                                                                                                                                                                  |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Fever                       | <p>First stage<br/>3-7 days<br/>(Septicemic)</p>  <p>Second stage<br/>0 days-1 month<br/>(Immune)</p>                           | <p>First stage<br/>3-7 days<br/>(Septicemic)</p>  <p>Second stage<br/>10-30 days<br/>(Immune)</p>  |
| Important clinical findings | <p>Myalgia, headache, abdominal pain, vomiting, conjunctival suffusion, fever</p> <p>Meningitis, uveitis (pigmented part of eye), rash, fever</p>                                                                                                                                                 | <p>Jaundice, hemorrhage, renal failure, myocarditis</p>                                                                                                                                                                                                                  |
| Leptospire present          | <p>Blood</p>  <p>CSF</p>  <p>Urine</p>  | <p>Blood</p>  <p>Urine</p>                                                                     |

# ***Epidemiology of Leptospirosis***

- Mainly a **zoonotic** disease
  - Transmitted to humans from a variety of wild and domesticated animal hosts
  - In USA most common **reservoirs** rodents (**rats**), **dogs**, **farm animals** and **wild animals**
- Transmitted through **breaks in the skin or intact mucus membranes**
- **Indirect contact** (soil, water, feed) **with infected urine from an animal with leptospirosis**
- **Occupational disease** of animal handling

# Comparison of Diagnostic Tests for Leptospirosis

| Diagnostic Test     | Method                                                                            | Test Accuracy                                                    |
|---------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------|
| Microscopy          | Gram stain                                                                        | Organisms too thin to be detected                                |
|                     | Darkfield examination                                                             | Insensitive, nonspecific                                         |
|                     | Silver stain                                                                      | Insensitive, nonspecific                                         |
|                     | Direct fluorescent antibody                                                       | Insensitive, specific                                            |
| Culture             | Blood                                                                             | Positive during first 10 days                                    |
|                     | Cerebrospinal fluid                                                               | Positive during first 10 days                                    |
|                     | Urine                                                                             | Positive after first week                                        |
| Nucleic acid probes | Direct hybridization                                                              | Insensitive, specific                                            |
|                     | Amplification (e.g., polymerase chain reaction)                                   | Sensitive, specific                                              |
| Serology            | Indirect hemagglutination, slide agglutination, enzyme-linked immunosorbent assay | Insensitive, nonspecific                                         |
|                     | Microscopic agglutination test                                                    | Sensitive, specific, reference laboratory test, serovar specific |



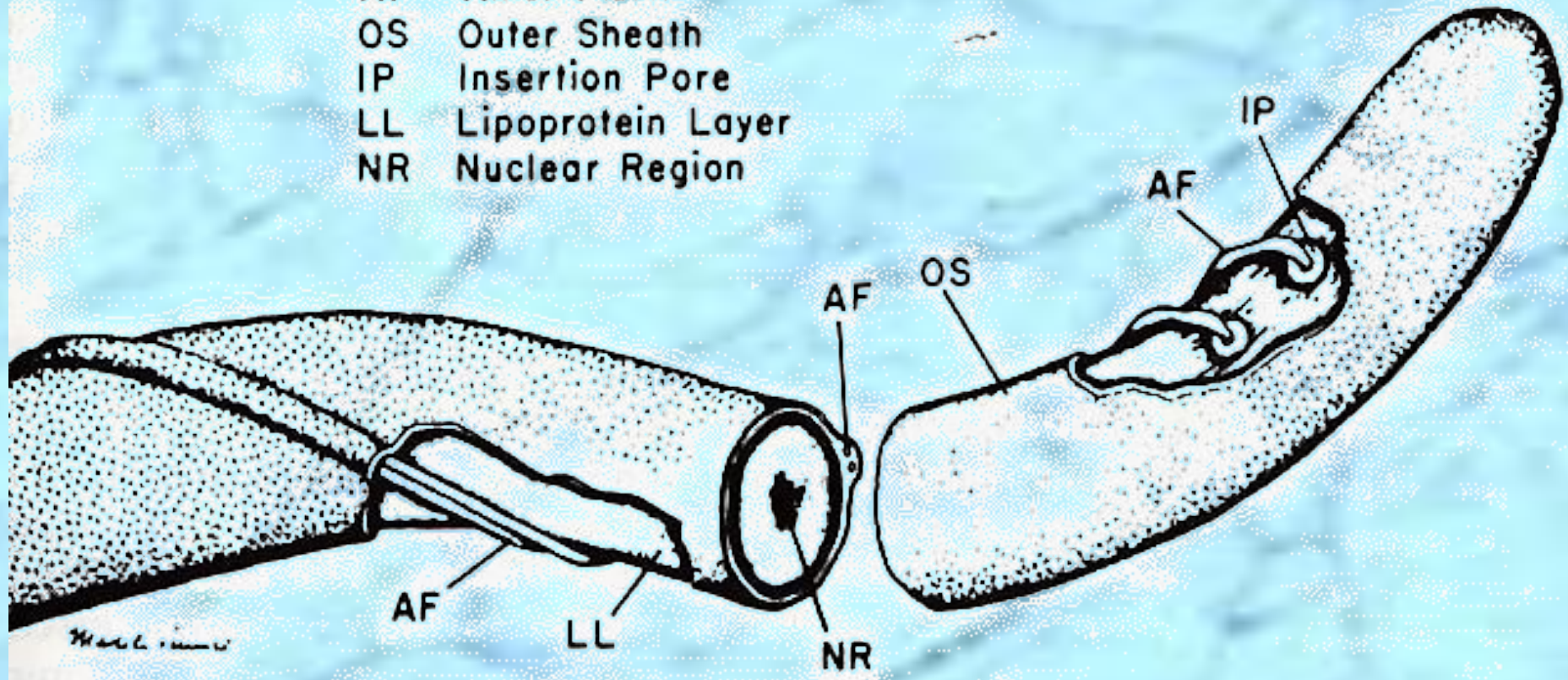
***REVIEW***  
***of***  
***Spirochaetales***

# ***General Overview of Spirochaetales***

- Gram-negative **spirochetes**
  - Spirochete from Greek for “coiled hair”
- **Extremely thin** and can be **very long**
- Tightly coiled **helical cells with tapered ends**
- Motile by **periplasmic flagella** (a.k.a., **axial fibrils** or **endoflagella**)
- **Outer sheath** encloses axial fibrils wrapped around protoplasmic cylinder
  - Axial fibrils originate from insertion pores at both poles of cell
  - May overlap at center of cell in *Treponema* and *Borrelia*, but not in *Leptospira*
  - Differing numbers of endoflagella according to genus & species

# Periplasmic Flagella Diagram

AF Axial Fibril  
OS Outer Sheath  
IP Insertion Pore  
LL Lipoprotein Layer  
NR Nuclear Region



# Spirochaetales Associated Human Diseases

| Spirochaetales                | Human Disease                                                           | Etiologic Agent                                                                                                                                                                      |
|-------------------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Family Spirochaetaceae</b> |                                                                         |                                                                                                                                                                                      |
| Genus <i>Borrelia</i>         | Epidemic relapsing fever<br>Endemic relapsing fever<br>Lyme borreliosis | <i>Borrelia recurrentis</i><br>Many <i>Borrelia</i> species<br><i>Borrelia burgdorferi</i> , <i>Borrelia garinii</i> , <i>Borrelia afzelii</i>                                       |
| Genus <i>Cristispira</i>      | None                                                                    | —                                                                                                                                                                                    |
| Genus <i>Serpulina</i>        | None                                                                    | —                                                                                                                                                                                    |
| Genus <i>Spirochaeta</i>      | None                                                                    | —                                                                                                                                                                                    |
| Genus <i>Treponema</i>        | Syphilis<br>Bejel<br>Yaws<br>Pinta                                      | <i>Treponema pallidum</i> subspecies <i>pallidum</i><br><i>T. pallidum</i> subspecies <i>endemicum</i><br><i>T. pallidum</i> subspecies <i>pertenue</i><br><i>Treponema carateum</i> |
| <b>Family Leptospiraceae</b>  |                                                                         |                                                                                                                                                                                      |
| Genus <i>Leptonema</i>        | None                                                                    | —                                                                                                                                                                                    |
| Genus <i>Leptospira</i>       | Leptospirosis                                                           | <i>Leptospira interrogans</i>                                                                                                                                                        |
| Genus <i>Turneria</i>         | None                                                                    | —                                                                                                                                                                                    |

# ***Review of Treponema***

# Summary of *Treponema* Infections

## Physiology and Structure

Thin, coiled spirochete,  $0.1 \times 5$  to  $15 \mu\text{m}$ .

Cannot be seen with Gram or Giemsa stains; observed by darkfield microscopy.

Cannot be grown in vitro except in selected cultured cells.

## Virulence Factors

Outer membrane proteins promote adherence to host cells. Hyaluronidase may facilitate perivascular infiltration.

Coating of fibronectin protects against phagocytosis.

Tissue destruction primarily results from host's immune response to infection.

## Epidemiology

Humans are the only natural host.

Venereal syphilis transmitted by sexual contact or congenitally; patients at risk include sexually active adolescents and adults, and children born of mothers with active disease.

Other *Treponema* infections transmitted by contact of mucous membranes with infectious lesions; congenital infections rare; patients at risk are children or adults in contact with infectious lesions.

Venereal syphilis occurs worldwide; endemic syphilis (bejel) occurs in desert and temperate regions of North Africa, Middle East, and northern Australia; yaws occurs in

# Summary of *Treponema* Infections (cont.)

tropical or desert regions of Africa, South America, and Indonesia; pinta occurs in tropical areas of Central and South America.

No seasonal incidence.

## Diseases

Venereal syphilis (*Treponema pallidum* subspecies *pallidum*).

Endemic syphilis or bejel (*T. pallidum* subspecies *endemicum*).

Yaws (*T. pallidum* subspecies *pertenue*).

Pinta (*Treponema carateum*).

## Diagnosis

Refer to Table 41-2.

## Treatment, Prevention, and Control

Penicillin is drug of choice; tetracycline, erythromycin, or chloramphenicol is administered if the patient is allergic to penicillin.

Safe sex practices should be emphasized, and sexual partners of infected patients should be treated.

Endemic syphilis, yaws, and pinta can be eliminated through organized public health measures (treatment, education); however, these efforts have been inconsistently applied.

# ***Nonvenereal Treponemal Diseases***

- ✓ **Bejel, Yaws & Pinta**
- ✓ **Primitive tropical and subtropical regions**
- ✓ **Primarily in impoverished children**

***Review of  
Treponema pallidum  
ssp. pallidum***

# ***General Characteristics of Treponema pallidum***

- Too thin to be seen with light microscopy in specimens stained with Gram stain or Giemsa stain
  - Motile spirochetes can be seen with **darkfield microscopy**
  - Staining with **anti-treponemal antibodies labeled with fluorescent dyes**
- **Intracellular pathogen**
- **Cannot be grown in cell-free cultures in vitro**
  - Koch's Postulates have not been met
- **Do not survive well outside of host**
  - Care must be taken with clinical specimens for laboratory culture or testing

# ***Epidemiology of *T. pallidum****

- Transmitted from direct **sexual contact** or from **mother to fetus**
- **Not highly contagious** (~30% chance of acquiring disease after single exposure to infected partner) but transmission rate dependent upon stage of disease
- **Long incubation period** during which time host is non-infectious
  - Useful epidemiologically for **contact tracing** and administration of **preventative therapy**
- Prostitution for drugs or for money to purchase drugs remains central epidemiologic aspect of transmission

# ***Pathogenesis of *T. pallidum****

- **Tissue destruction and lesions are primarily a consequence of patient's immune response**
- Syphilis is a **disease of blood vessels and of the perivascular areas**
- In spite of a **vigorous host immune response** the organisms are capable of persisting for decades
  - Infection is **neither fully controlled nor eradicated**
  - In **early stages**, there is an inhibition of cell-mediated immunity
  - Inhibition of CMI abates in **late stages** of disease, hence late lesions tend to be localized

# ***Virulence Factors of T. pallidum***

- ❑ **Outer membrane proteins** promote adherence
- ❑ **Hyaluronidase** may facilitate **perivascular infiltration**
- ❑ **Antiphagocytic** coating of **fibronectin**
- ❑ **Tissue destruction and lesions** are primarily result of host's immune response (**immunopathology**)

# ***Pathogenesis of T. pallidum (cont.)***

## ***Primary Syphilis***

- Primary disease process involves **invasion of mucus membranes, rapid multiplication & wide dissemination** through perivascular lymphatics and systemic circulation
  - ✓ Occurs **prior to development of the primary lesion**
- 10-90 days (usually 3-4 weeks) after initial contact the host mounts an **inflammatory response at the site of inoculation** resulting in the hallmark syphilitic lesion, called the **chancre (usually painless)**
  - Chancre changes from hard to ulcerative with profuse **shedding of spirochetes**
  - Swelling of capillary walls & regional lymph nodes w/ draining
  - Primary lesion heals spontaneously by fibrotic walling-off within two months, leading to false sense of relief

# ***Pathogenesis of *T. pallidum**** (cont.)

## ***Secondary Syphilis***

- Secondary disease 2-10 weeks after primary lesion
- Widely disseminated **mucocutaneous rash**
- **Secondary lesions** of the skin and mucus membranes are **highly contagious**
- Generalized immunological response

# ***Pathogenesis of T. pallidum*** (cont.)

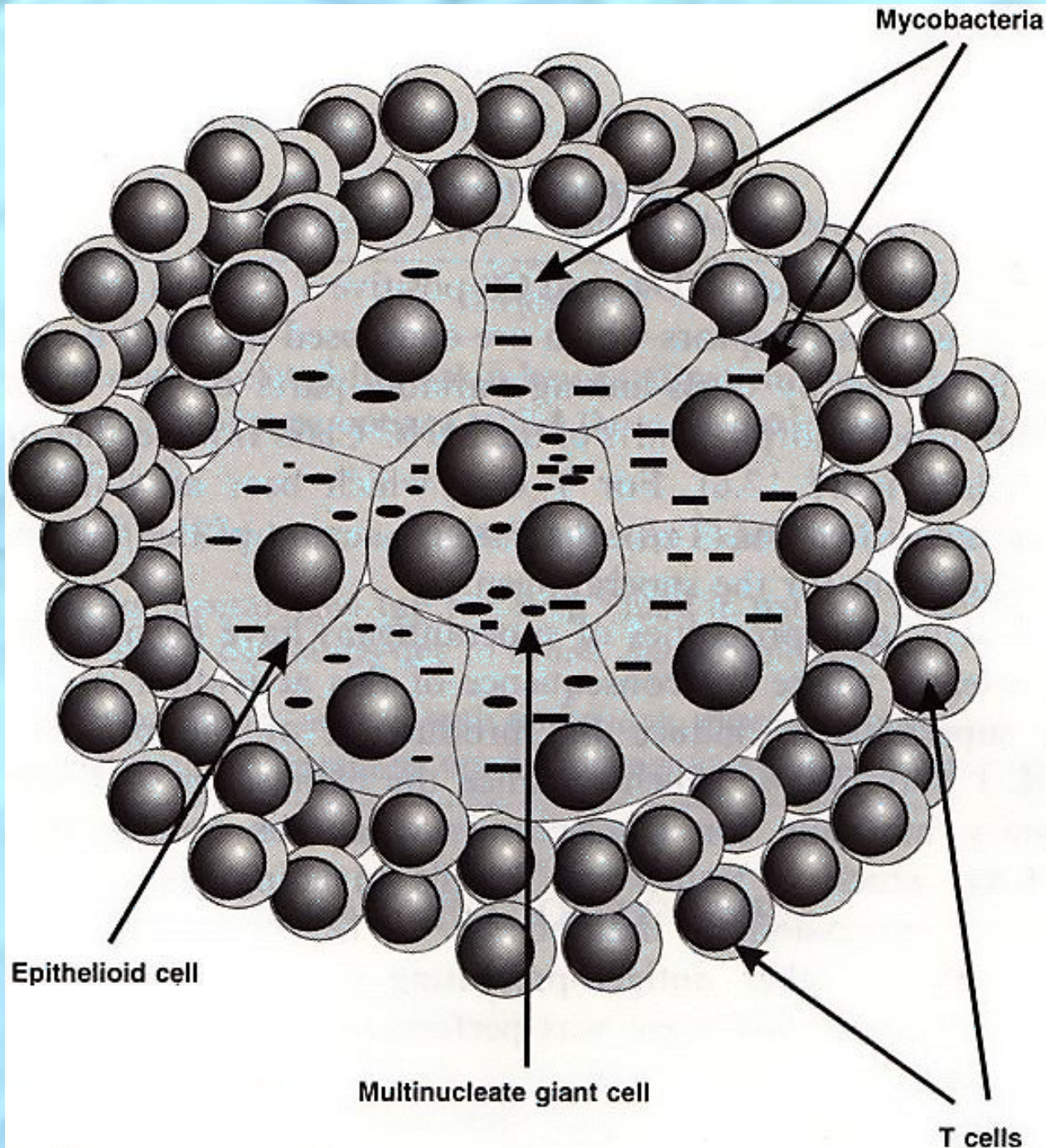
## ***Latent Stage Syphilis***

- Following secondary disease, host enters latent period
  - First 4 years = **early latent**
  - Subsequent period = **late latent**
- **About 40% of late latent patients progress to late tertiary syphilitic disease**

# *Pathogenesis of T. pallidum* (cont.)

## *Tertiary Syphilis*

- Tertiary syphilis characterized by **localized granulomatous dermal lesions (gummas)** in which few organisms are present
  - Granulomas reflect containment by the immunologic reaction of the host to chronic infection
- Late **neurosyphilis** develops in about 1/6 untreated cases, usually more than 5 years after initial infection
  - Central nervous system and spinal cord involvement
  - Dementia, seizures, wasting, etc.
- **Cardiovascular** involvement appears 10-40 years after initial infection with resulting myocardial insufficiency and death



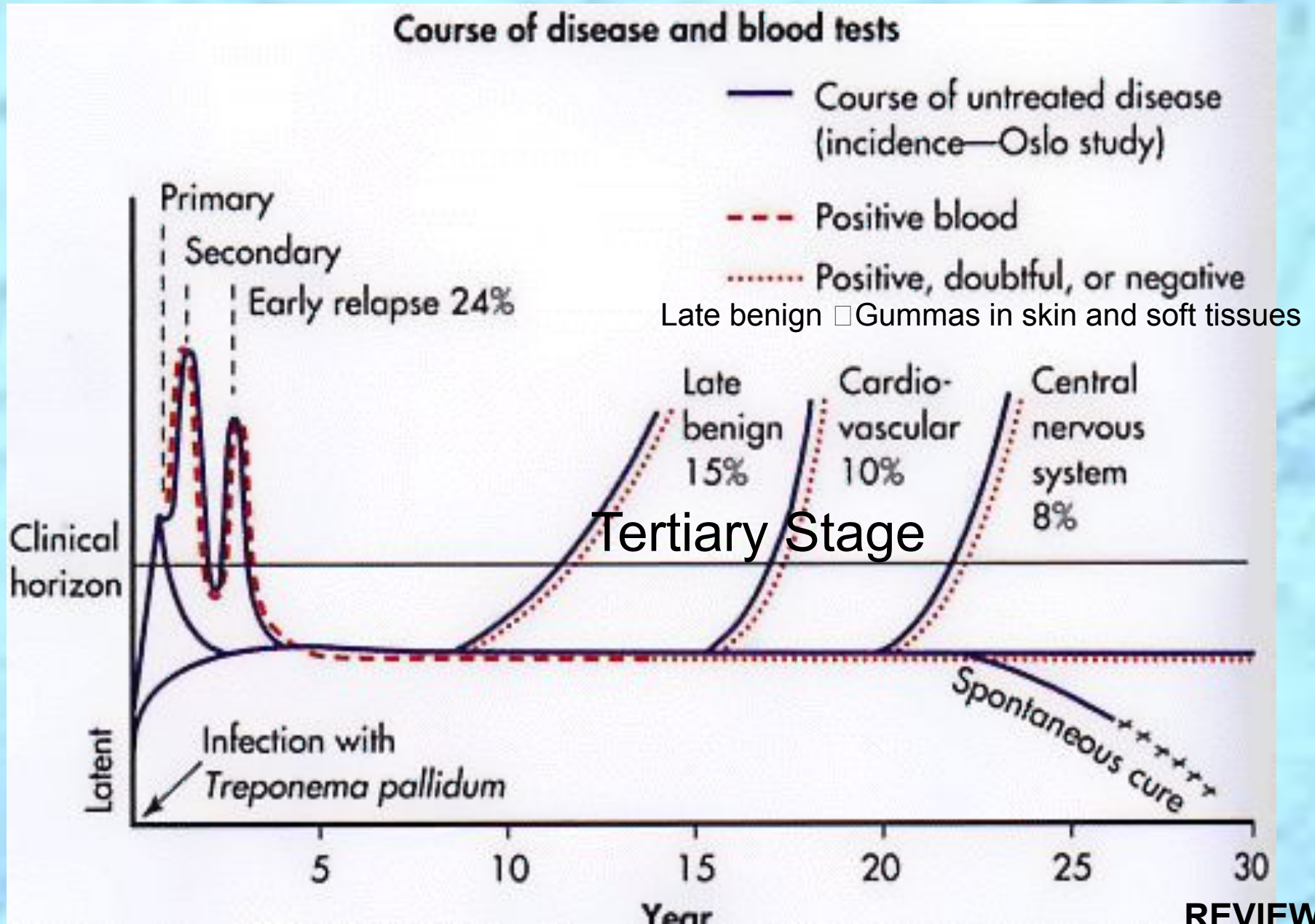
# **Diagram of a Granuloma**

(a.k.a. **gumma** in  
skin or soft tissue)

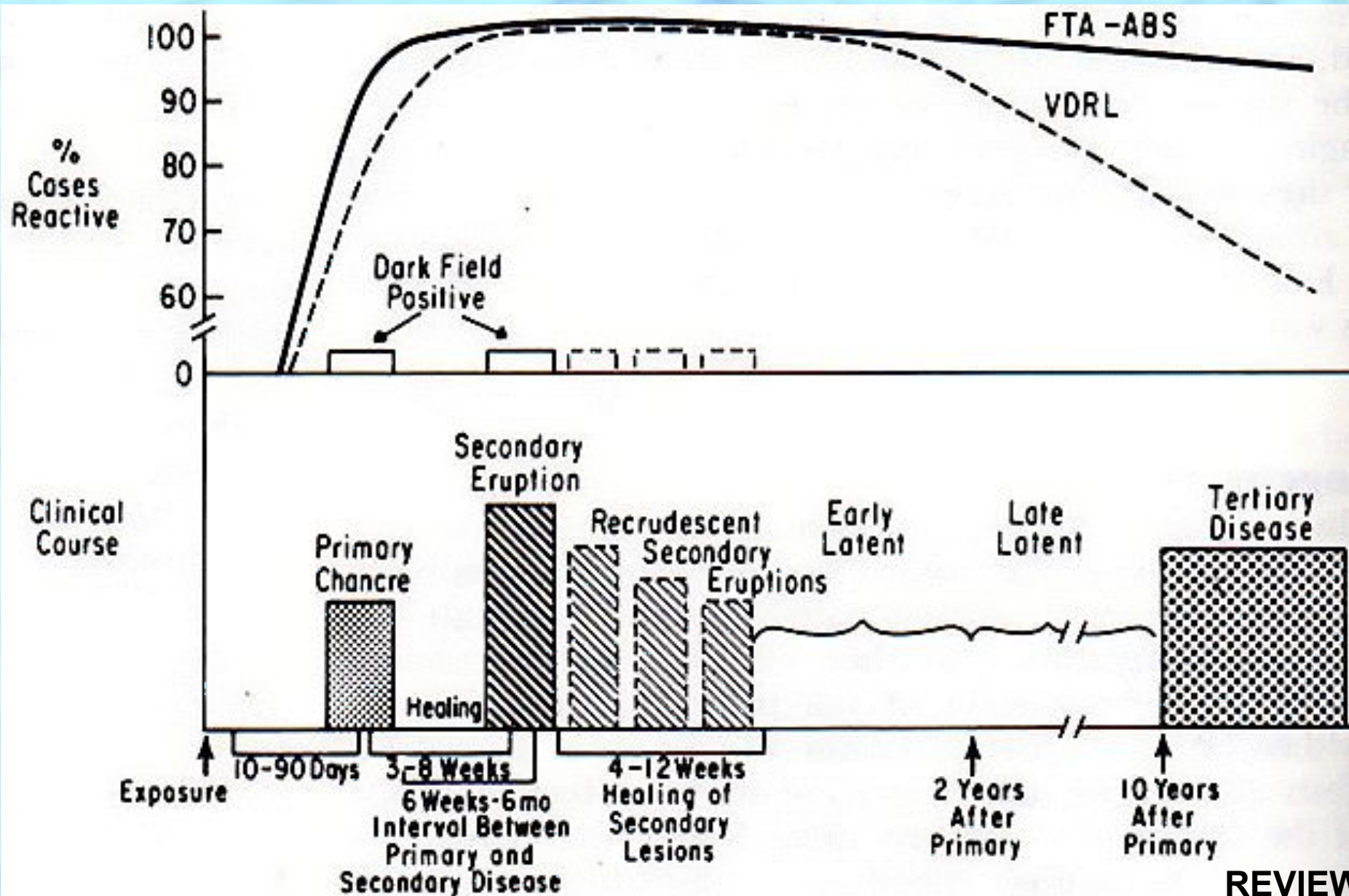
**NOTE:** ultimately a  
fibrin layer develops  
around granuloma,  
further “walling off”  
the lesion

**REVIEW**

# Progression of Untreated Syphilis



# Progression of Untreated Syphilis



# ***Pathogenesis of *T. pallidum**** (cont.)

## ***Congenital Syphilis***

- Congenital syphilis results from **transplacental infection**
- *T. pallidum* **septicemia in the developing fetus and widespread dissemination**
- **Abortion, neonatal mortality, and late mental or physical problems** resulting from scars from the active disease and progression of the active disease state

# ***Prevention & Treatment of Syphilis***

- **Penicillin remains drug of choice**
  - WHO monitors treatment recommendations
  - 7-10 days continuously for early stage
  - At least 21 days continuously beyond the early stage
- Prevention with **barrier methods** (e.g., condoms)
- **Prophylactic treatment of contacts** identified through **epidemiological tracing**

# Diagnostic Tests for Syphilis

| Diagnostic Test | Method or Examination                                                                                                                                                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Microscopy      | → Darkfield<br>→ Direct fluorescent antibody staining                                                                                                                                                                                                                         |
| Culture         | → Not available                                                                                                                                                                                                                                                               |
| Serology        | → Nontreponemal tests<br>Venereal Disease Research Laboratory (VDRL)<br>Rapid plasma reagin (RPR)(Original Wasserman Test)<br>→ Treponemal tests<br>Fluorescent treponemal antibody absorption (FTA-ABS)<br>Microhemagglutination test for <i>Treponema pallidum</i> (MHA-TP) |

**NOTE:** Treponemal antigen tests indicate experience with a treponemal infection, but **cross-react with antigens other than *T. pallidum* ssp. *pallidum***. Since pinta and yaws are rare in USA, positive treponemal antigen tests are **usually indicative of syphilitic infection**.

REVIEW

# **Review Handout on Sensitivity & Specificity of Diagnostic Tests**

# *Analytic Performance of a Diagnostic Test*

|                  | ACTUAL<br>POSITIVE               | ACTUAL<br>NEGATIVE               | TOTALS                   |
|------------------|----------------------------------|----------------------------------|--------------------------|
| TEST<br>POSITIVE | 80<br>True<br>Positives          | 25<br><b>False<br/>Positives</b> | 105<br>Test<br>Positives |
| TEST<br>NEGATIVE | 20<br><b>False<br/>Negatives</b> | 75<br>True<br>Negatives          | 95<br>Test<br>Negatives  |
| TOTALS           | 100<br>Actual<br>Positives       | 100<br>Actual<br>Negatives       | 200                      |

# *Analytic Performance of a Diagnostic Test (cont.)*

**Sensitivity** = Measure of True Positive Rate (TPR)

$$= \frac{\text{No. of True Pos.}}{\text{No. of Actual Pos.}} = \frac{\text{No. of True Pos.}}{\text{No. of (True Pos. + False Neg.)}} = \frac{80}{80+20} = 80\%$$

Sensitivity

In conditional probability terms, the probability of a positive test given an actual positive sample/patient.

**Specificity** = Measure of True Negative Rate (TNR)

$$= \frac{\text{No. of True Neg.}}{\text{No. of Actual Neg.}} = \frac{\text{No. of True Neg.}}{\text{No. of (True Neg. + False Pos.)}} = \frac{75}{75+25} = 75\%$$

Specificity

In conditional probability terms, the probability of a negative test given an actual negative sample/patient.

# ***Review of Borrelia***

# Summary of *Borellia* Infections

## REVIEW

### Physiology and Structure

Epidemic relapsing fever—etiologic agent is *Borrelia recurrentis*.

Endemic relapsing fever—many *Borrelia* species are responsible.

Lyme disease—*Borrelia burgdorferi* causes disease in the United States and Europe; *Borrelia garinii* and *Borrelia afzelii* cause disease in Europe and Asia.

Spirochetes measure  $0.2 \times 0.5$  to  $30 \mu\text{m}$ .

Can be seen when stained with aniline dyes (e.g., Giemsa, Wright stains).

Can grow in culture, but bacteria are microaerophilic and have complex nutritional requirements.

### Virulence Factors

*Borrelia* responsible for relapsing fever are able to undergo antigenic shift and escape immune clearance; periodic febrile and afebrile periods result from antigenic variation.

Immune reactivity against the Lyme disease agents may be responsible for the clinical disease.

### Epidemiology

Epidemic relapsing fever: transmitted person to person; reservoir—humans; vector—human body louse.

Endemic relapsing fever: transmitted rodents to humans; reservoirs—rodents, small mammals, and soft ticks; vector—soft ticks.

Individuals at risk for relapsing fever include people exposed to lice (epidemic disease) in crowded or unsanitary conditions and people exposed to ticks (endemic disease) in rural areas.

Epidemic relapsing fever is endemic in Ethiopia, Rwanda, and the Andean foothills.

# Summary of *Borellia* Infections (cont.)

## REVIEW

Endemic relapsing fever has worldwide distribution and is in the western states of the United States.

Lyme disease: transmitted by hard ticks from mice to humans; reservoir—mice, deer, ticks; vectors include *Ixodes scapularis* in eastern and midwestern United States, *Ixodes pacificus* in the western United States, *Ixodes ricinus* in Europe, and *Ixodes persulcatus* in Eastern Europe and Asia.

Individuals at risk for Lyme disease include people exposed to ticks in areas of high endemicity.

Lyme disease has worldwide distribution.

Seasonal incidence corresponds to feeding patterns of vectors; most cases of Lyme disease in the United States occur in late spring and early summer (feeding pattern of nymphs).

### Diseases

Epidemic relapsing fever.

Endemic relapsin fever.

Lyme disease.

### Diagnosis

Refer to Box 41–4.

### Treatment, Prevention, and Control

For relapsing fever, treatment is with tetracycline or erythromycin.


For Lyme disease, treatment is with amoxicillin, tetracycline, cefuroxime, or ceftriaxone.

Exposure to the insect vector can be decreased by using insecticides and applying insect repellents to clothing and by wearing protective clothing that reduces exposure of skin to insects.


Recombinant ospA vaccine is available for Lyme disease.

# *Epidemiology of Borrelia Infections*


***Borrelia  
recurrentis***

| Infection                                    | Reservoir | Vector                                                                                                                        |
|----------------------------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------|
| Relapsing fever<br>Epidemic<br>(louse-borne) | Humans    | Body louse<br><i>Pediculus humanus</i><br> |

***Borrelia spp.***

|                                            |                                 |                                                                                                                                      |
|--------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Relapsing fever<br>Endemic<br>(tick-borne) | Rodents, soft-<br>shelled ticks | Soft-shelled tick<br><i>Ornithodoros spp.</i><br> |
|--------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|

***Borrelia  
burgdorferi***

|              |                                                           |                                                                                                                                  |
|--------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Lyme disease | Rodents, deer,<br>domestic pets,<br>hard-shelled<br>ticks | Hard-shelled tick<br><i>Ixodes spp.</i><br> |
|--------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|

***Review of  
Borrelia recurrentis  
& other Borrelia spp.***

# ***Epidemiology of Relapsing Fever***

- Associated with **poverty, crowding, and warfare**
- **Arthropod vectors**
  - **Louse-borne borreliosis = Epidemic Relapsing Fever**
    - ✓ Transmitted **person-to-person** by human body lice (vectors) from infected **human reservoir**
    - ✓ Infect host only when louse is injured, e.g., during scratching
    - ✓ Therefore, a single louse can only infect a single person
    - ✓ Lice leave host that develops a fever and seek normal temperature host
  - **Tick-borne borreliosis = Endemic Relapsing Fever**
    - ✓ Sporadic cases
    - ✓ Transmitted by soft body ticks (vectors) from **small mammal reservoir**
    - ✓ Ticks can multiply and infect new human hosts

# ***Pathogenesis of Relapsing Fever***

- Relapsing fever (a.k.a., tick fever, borreliosis, famine fever)
  - Acute infection with 2-14 day (~ 6 day) incubation period
  - Followed by **recurring febrile episodes**
  - **Constant spirochaetemia** that worsens during febrile stages
- **Epidemic Relapsing Fever = Louse-borne borreliosis**
  - *Borrelia recurrentis*
- **Endemic Relapsing Fever = Tick-borne borreliosis**
  - *Borrelia spp.*

# ***Review of Borrelia burgdorferi***

# ***Pathogenesis of Lyme Borreliosis***

- **Lyme disease characterized by three stages:**
  - i. Initially a unique skin lesion (**erythema chronicum migrans (ECM)**) with general malaise
    - ✓ **ECM not seen in all infected hosts**
    - ✓ **ECM often described as bullseye rash**
    - ✓ **Lesions periodically reoccur**
  - ii. Subsequent stage seen in 5-15% of patients with **neurological or cardiac involvement**
  - iii. Third stage involves **migrating episodes of non-destructive, but painful arthritis**
- **Acute illness treated with phenoxymethylpenicillin or tetracycline**

# ***Diagnosis of Lyme Borreliosis***

## **Clinical Case Definition**

Either of the following:

- Erythema migrans ( $\geq 5$  cm in diameter)

- At least one late manifestation (i.e., musculoskeletal, nervous system, or cardiovascular involvement) and laboratory confirmation of infection

## **Laboratory Criteria for Diagnosis**

At least one of the following:

- Isolation of *Borrelia burgdorferi*

- Demonstration of diagnostic levels of IgM or IgG antibodies to the spirochetes

- Significant increase in antibody titer between acute and convalescent serum samples

# ***Epidemiology of Lyme Borreliosis***

- Lyme disease was recognized as a syndrome in 1975 with outbreak in Lyme, Connecticut
- Transmitted by **hard body tick (*Ixodes* spp.)**  
**vectors**
  - **Nymph stage** are usually more aggressive feeders
  - Nymph stage generally too small to discern with unaided eye
  - For these reasons, nymph stage transmits more pathogens
- **White-footed deer mice** and other rodents, deer, domesticated pets and hard-shelled ticks are most common **reservoirs**

# ***Review of Leptospira***

# Summary of *Leptospira* Infections

## Physiology and Structure

Complex taxonomy with many species and many serovars; traditional classification subdivides genus into saprophytic strains (*Leptospira biflexa*) and pathogenic strains (*Leptospira interrogans*).

Thin, coiled spirochetes ( $0.1 \times 6$  to  $12 \mu\text{m}$ ). One or both ends hook-shaped.

Obligate aerobe; slow growing in culture.

## Virulence Factors

Direct invasion and replication in tissues.

Immune complex glomerulonephritis.

## Epidemiology

U.S. reservoirs: rodents (particularly rats), dogs, farm animals, and wild animals.

Humans: accidental end-stage host.

Organism can penetrate the skin through minor breaks in the epidermis.

People are infected with leptospires through exposure to water contaminated with urine from an infected animal or handling of tissues from an infected animal.

People at risk are those exposed to urine-contaminated streams, rivers, and standing water; occupational

# **Summary of Leptospira Infections** (cont.)

exposure to infected animals for farmers, meat handlers, veterinarians.

Infection is rare in the United States but has worldwide distribution.

Disease is more common during warm months (recreational exposure).

## **Diseases**

Mild virus-like syndrome.

Systemic leptospirosis with aseptic meningitis.

Overwhelming disease (Weil's disease) with vascular collapse, thrombocytopenia, hemorrhage, and hepatic and renal dysfunction.

## **Diagnosis**

Refer to Table 41-4.

## **Treatment, Prevention, and Control**

Treatment of severe infections involves intravenous penicillin or ampicillin; mild infections treated with oral ampicillin, amoxicillin, or doxycycline.

Doxycycline, but not the penicillins, is used for prophylaxis.

Herds and domestic pets should be vaccinated.

Rats should be controlled.

# ***Leptospirosis Clinical Syndromes***

- Mild virus-like syndrome
- (**Anicteric leptospirosis**) Systemic with aseptic meningitis
- (**Icteric leptospirosis**) Overwhelming disease (Weil's disease)
  - ✓Vascular collapse
  - ✓Thrombocytopenia
  - ✓Hemorrhage
  - ✓Hepatic and renal dysfunction

**NOTE:** Icteric refers to **jaundice** (yellowing of skin and mucus membranes by deposition of bile) and **liver involvement**

# ***Pathogenesis of Icteric Leptospirosis***

- Leptospirosis, also called **Weil's disease** in humans
- Direct **invasion** and **replication** in tissues
- Characterized by an **acute febrile jaundice & immune complex glomerulonephritis**
- Incubation period usually 10-12 days with flu-like illness usually progressing through **two clinical stages**:
  - i. **Leptospiremia** develops rapidly after infection (usually lasts about 7 days) without local lesion
  - ii. Infects the **kidneys** and organisms are shed in the urine (**leptospiruria**) with **renal failure and death** not uncommon
- **Hepatic injury & meningeal irritation** is common

# ***Epidemiology of Leptospirosis***

- Mainly a **zoonotic** disease
  - Transmitted to humans from a variety of wild and domesticated animal hosts
  - In USA most common **reservoirs** rodents (**rats**), **dogs**, **farm animals** and **wild animals**
- Transmitted through **breaks in the skin or intact mucus membranes**
- **Indirect contact** (soil, water, feed) **with infected urine from an animal with leptospirosis**
- **Occupational disease** of animal handling

