Chlamydial Infections

'One-half of the troubles of this life can be traced to saying yes to quickly and not saying no soon enough.'

Josh Billings (1818-1885)

Chlamydial Infections--
Classification

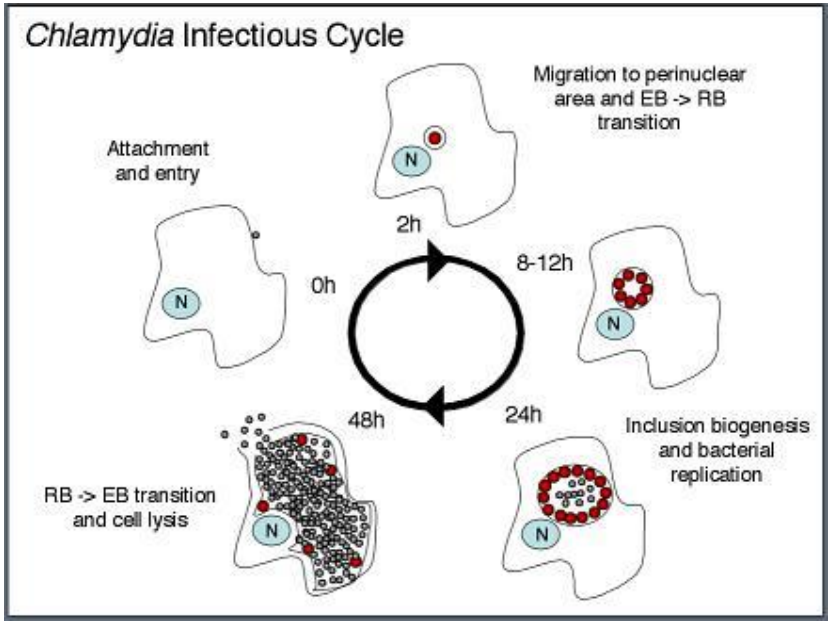
- **These organisms comprise a single order, Chlamydiales, a single family, Chalmydiaceae, and untill 1999, one genus: Chlamydia.**
  - ***C. trachomatis***
  - ***C. pneumoniae***
  - ***C. psittaci***
- **There are, however, various serovars (subdivisions).**

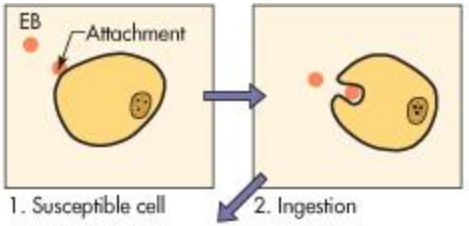
Chlamydial Infections--
Classification

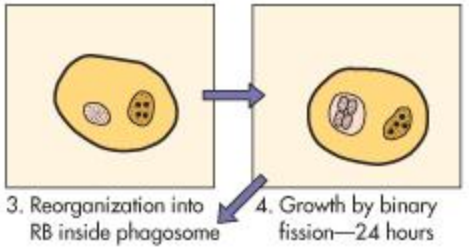
- **Genus Chlamydia**
  - ***C. trachomatis***
  - ***C. murdarum***
  - ***C. suis***
- **Genus Chalmydophila**
  - ***C. pneumoniae***
  - ***C. psittaci***
  - ***C. pecorum***
  - ***C. abortus***
  - ***C. caviae***
  - ***C. felis***

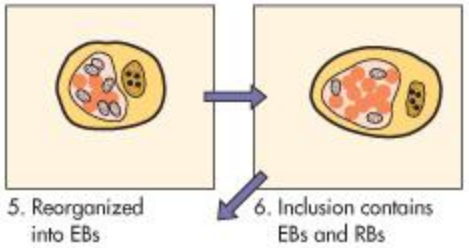
Physiology and Structure

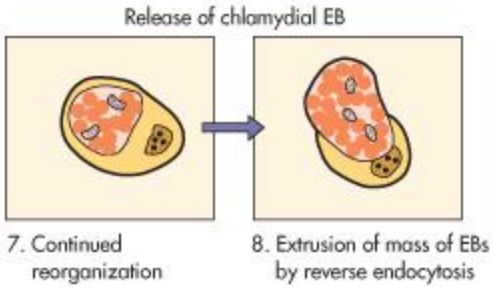
- **Elementary bodies (EBs) are resistant to many harsh environments.**
  - **MOMP thought to be involved in attachment.**
- **Energy parasites.**
  - **use hosts ATP**
- **Originally thought to be viruses (small size) until the 1960s.**
- **Histologic stains can readily detect the phagosome with accumulated Reticulate bodies (RBs) called inclusion(s).**
- **Gram negative with not peptidoglycan layer.**





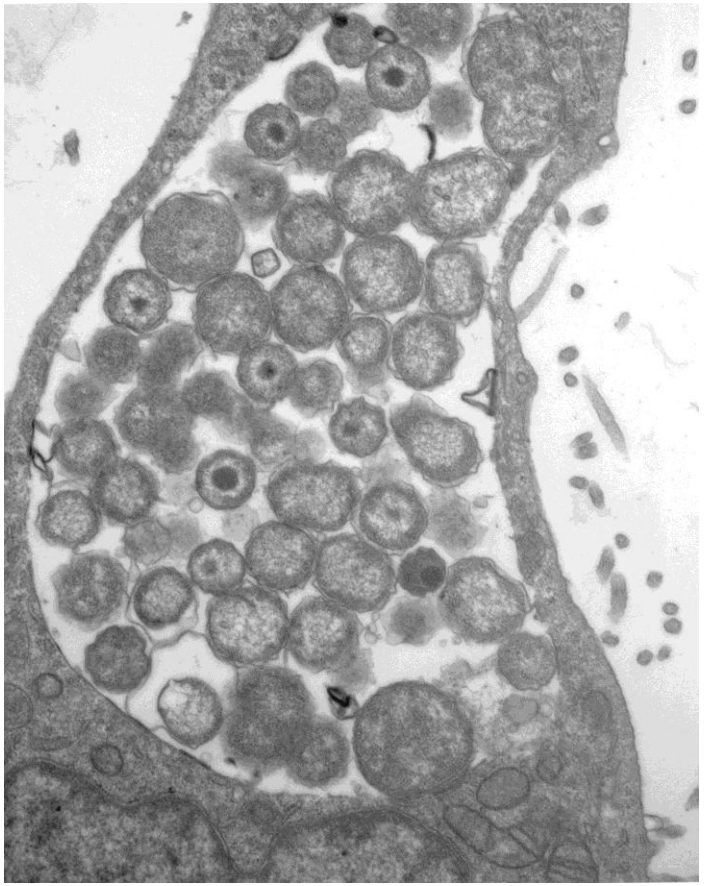






Inclusions

- **Once EB internalized, ineffective lysosomal fusion.**
- **EB to RB to EB development.**
- **100-1000/cell**
- **Different species differ by inclusion morphology, metabolism, host cell preference.**



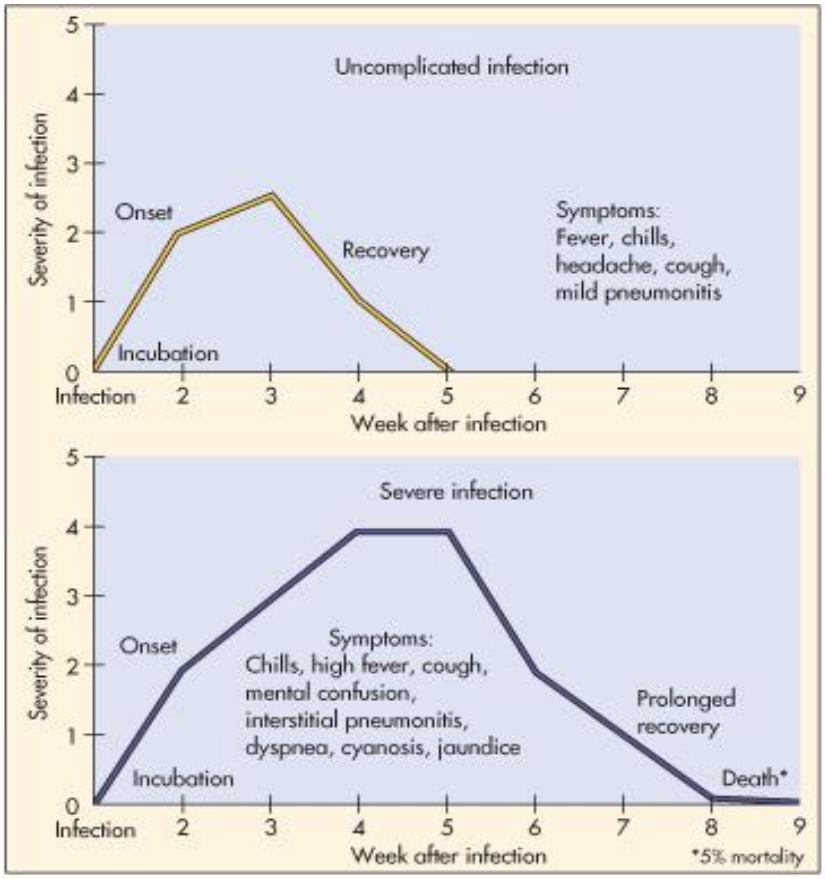
Chlamydial Infections--
Classification

- ***C. pneumoniae***
  - **human pathogen**
  - **important cause of bronchitis, pneumonia, and sinusitis.**
  - **person-to person**
  - **200-300K cases/year**
  - **Cannot differentiate between *Mycoplasma pneumoniae*, L. *pneumophila*, and respiratory viruses.**

- Does not grow on in the cell lines used for the isolation of *C. trachomatis*.
- PCR

Chlamydial Infections--
Classification

- *C. psittaci*
  - **Disease first observed in parrots.**
  - **Reservoirs=all birds.**
  - **Humans and other mammals can become infected.**
  - **Organisms present in blood, feces, tissues of infected birds (ill or healthy).**
  - **<50 cases a year reported in US.**
  - **Person-to-person rare.**
  - **Severe disease can include GI symptoms, vomiting, carditis, hepatomegaly, splenomegaly.**
  - **Diagnosed serologically.**



Chlamydial Infections--
Classification

- ***C. trachomatis***
  - **Made up of 3 biovars**
    - **Trachoma (14 serovars)**
    - **Lymphogranuloma venerum (4 serovars)**
    - **Mouse pneumonitis**

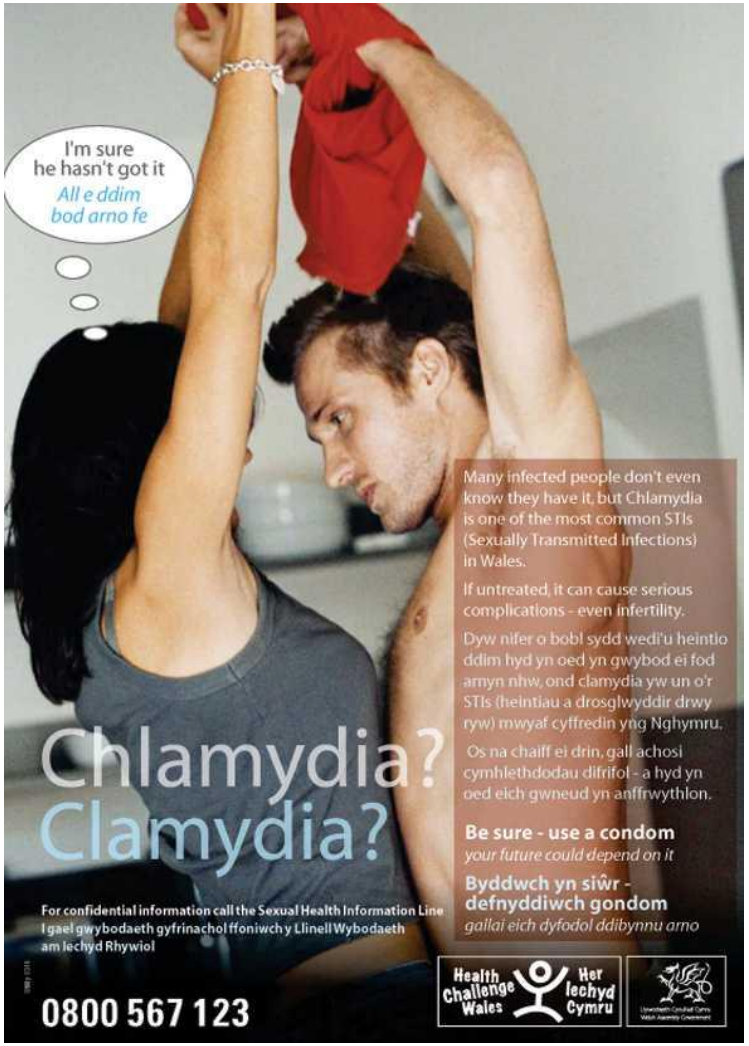
      - ***C. trachomatis* infects only humans**
        - » **The human biovars and serovars have 87-99% DNA homology with each other.**

Chlamydial Infections--
Classification

- *C. trachomatis*
  - Classified serologically
  - Based on the Major Outer Membrane Protein (MOMP).
    - Responsible for eye and genital infections.
      - Trachoma-serovars A-K
      - Lymphogranuloma venereum (LGV)-serovars L1, L2, L2a, L3
      - STIs-serovars D-K

Natural History of Infections

- **Genital tract infections not well understood.**
- **Chlamydiae elicit an immune response that facilitates the resolution of infection in most patients.**
- **Chronic asymptomatic and persistent infections of the conjunctival and genital mucosa are not easily recognized.**
  - **80% women and 30% men are asymptomatic**
  - **reactivation?????**



Chlamydial Infections--
Introduction & History

- **The identification of *C. trachomatis* as a cause of genital tract infections was delayed until smear and culture methods became available for detecting *Neisseria gonorrhoeae*.**
- **Once *N. gonorrhoeae* was excluded as a cause of a variety of infections there were suspicions that a unique infectious agent caused these diseases.**

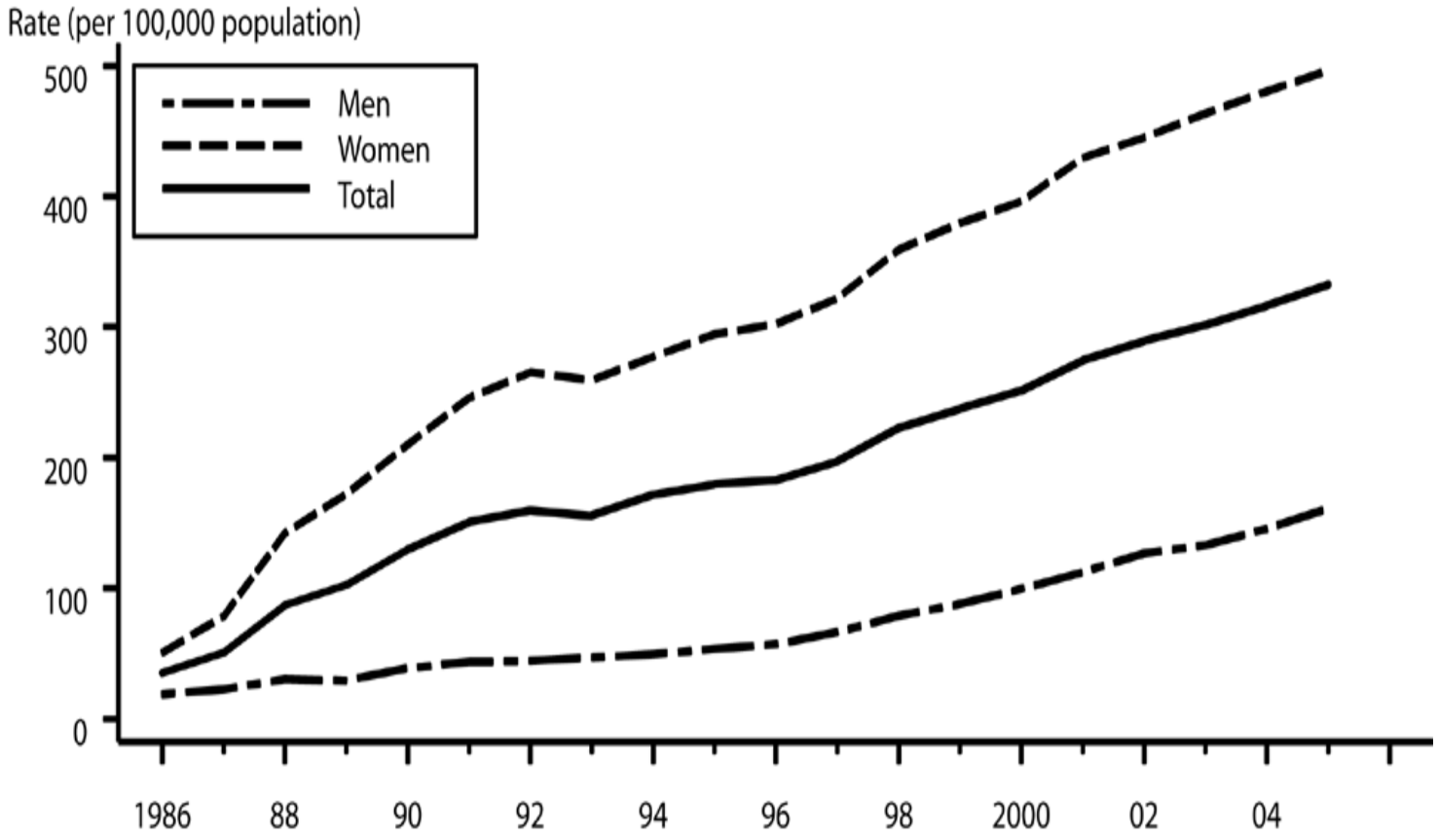
Chlamydial Infections--
Introduction & History

- **1907-First visualization of intracytoplasmic inclusions of Chlamydia in conjunctival scrapings.**
- **1920- *C. psittaci* isolated**
- **1935- LGV**
- **1950s- Trachoma agent**
  - **in 1959, a genital strain of *C. trachomatis* was finally isolated.**
  - **facilitated by developing tissue culture techniques.**

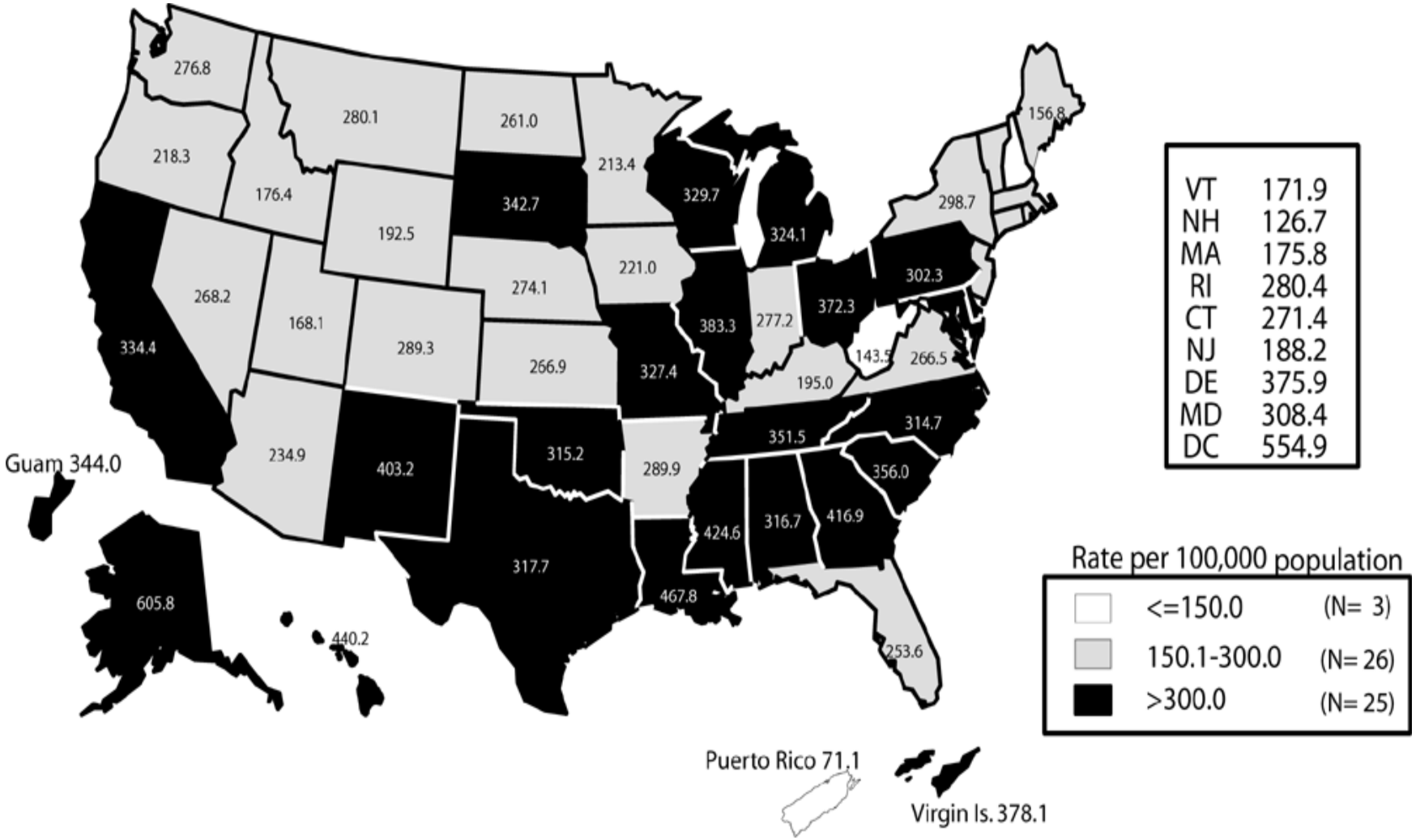
Chlamydia
Epidemiology-Genital Infections

- **Found worldwide**
- **Most common bacterial STI in the world.**
- **In 2003, estimated 2.8 million American infected each year and as many as 50 million new infections occur annually worldwide**

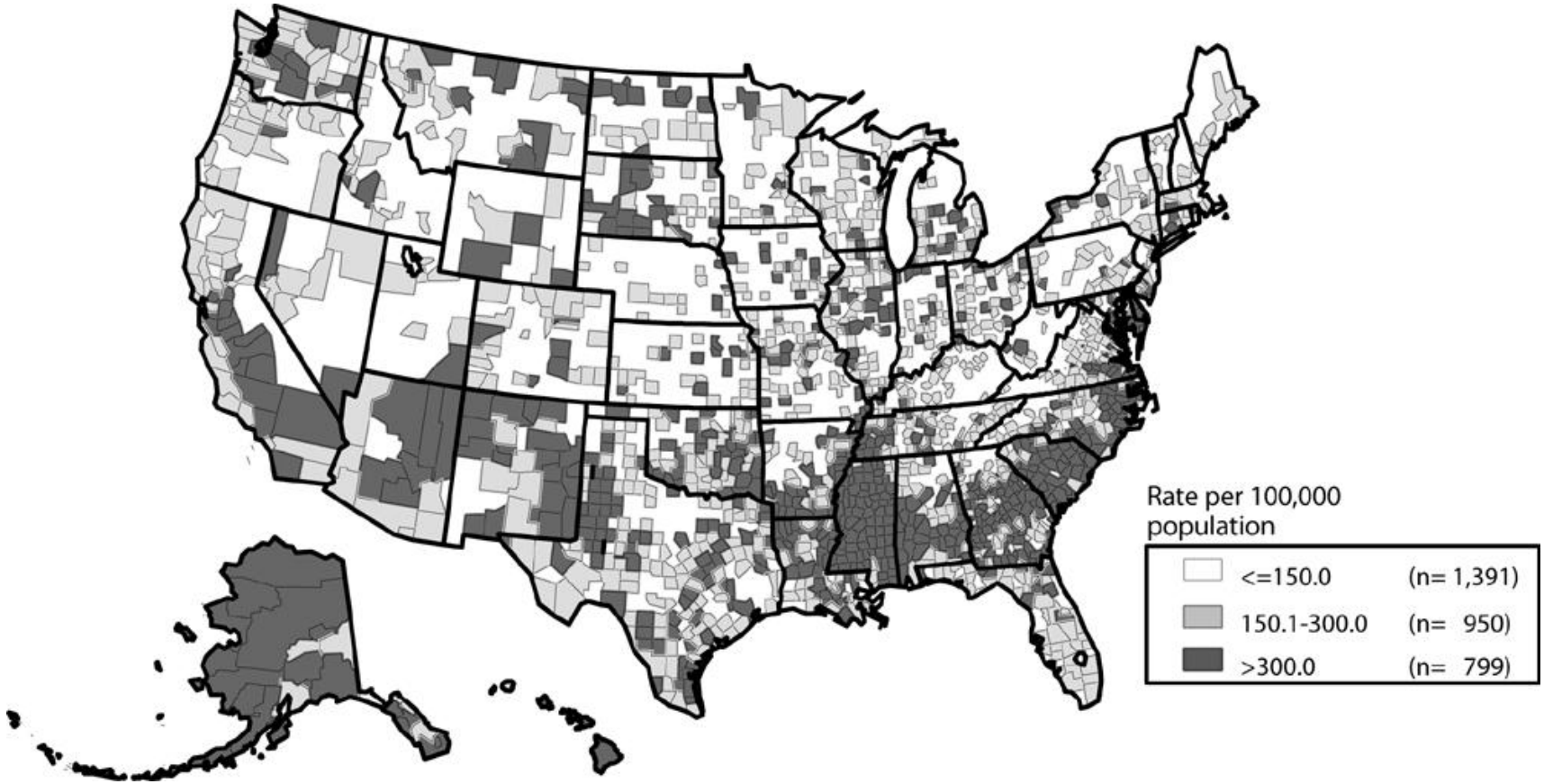
Chlamydia — Rates: Total and by sex: United States, 1986–2005



Chlamydia — Rates by state: United States and outlying areas, 2005



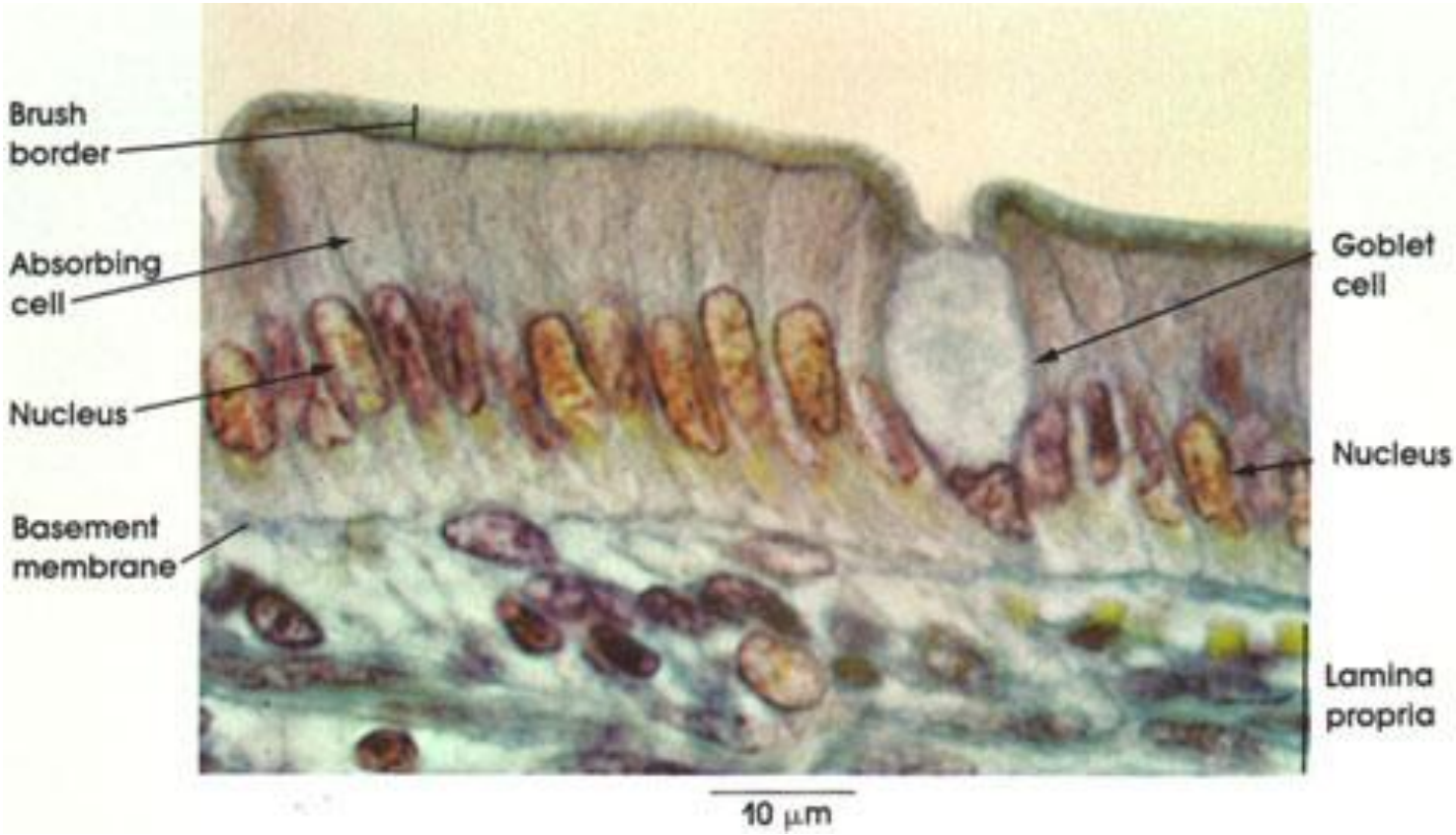
Chlamydia — Rates by county: United States, 2005



Epithelium and Infection--Junctions

- **Affect a limited number of cell types**
  - **nonciliated columnar**
  - **cuboidal**
  - **transitional**
  - **Found on the mucous membranes of the urethra, endocervix, endometrium, fallopian tubes, anorectum, respiratory tract, and the conjunctivae.**

Epithelium and Infection

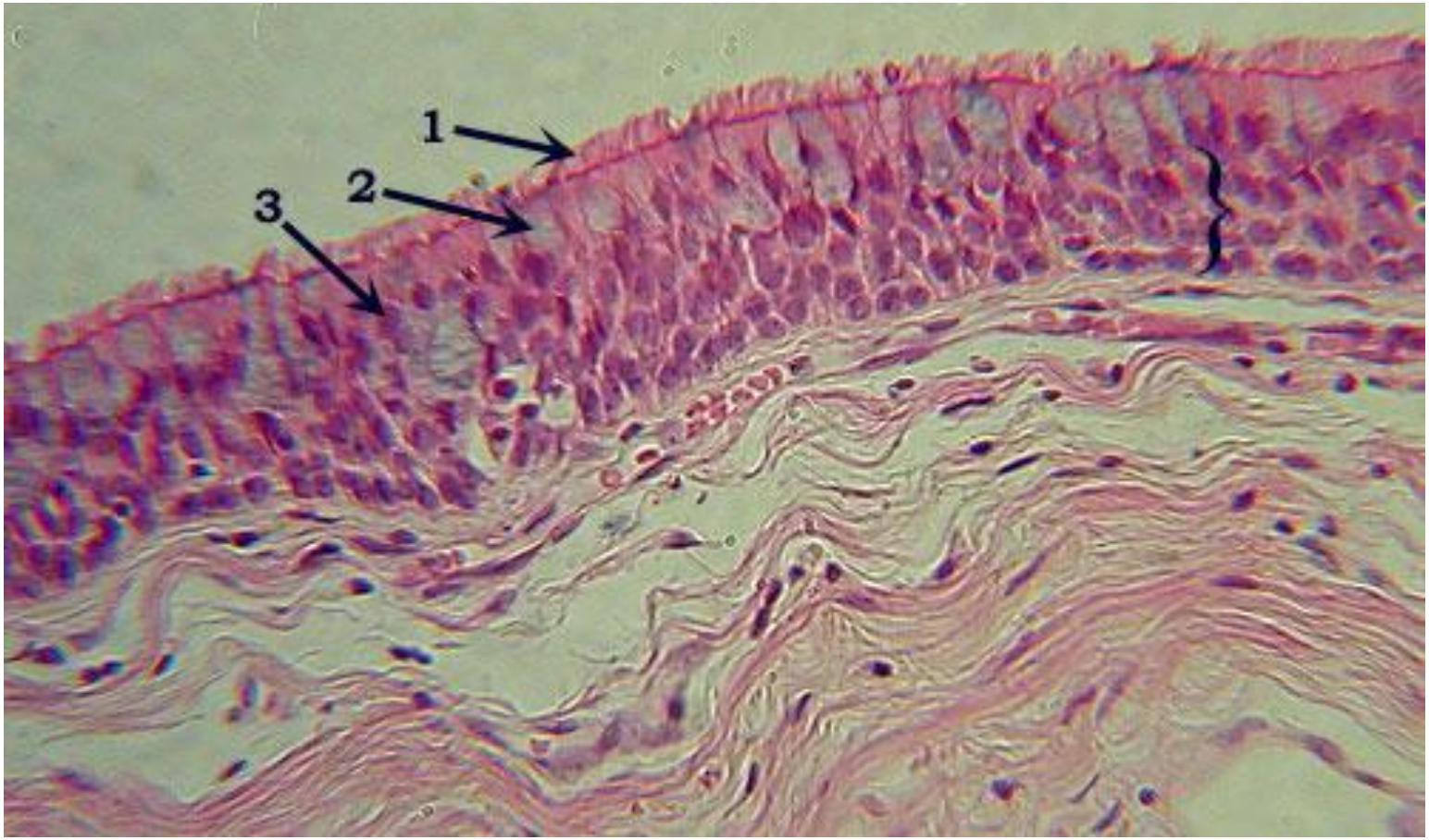


Columnar epithelium

Epithelium and Infection

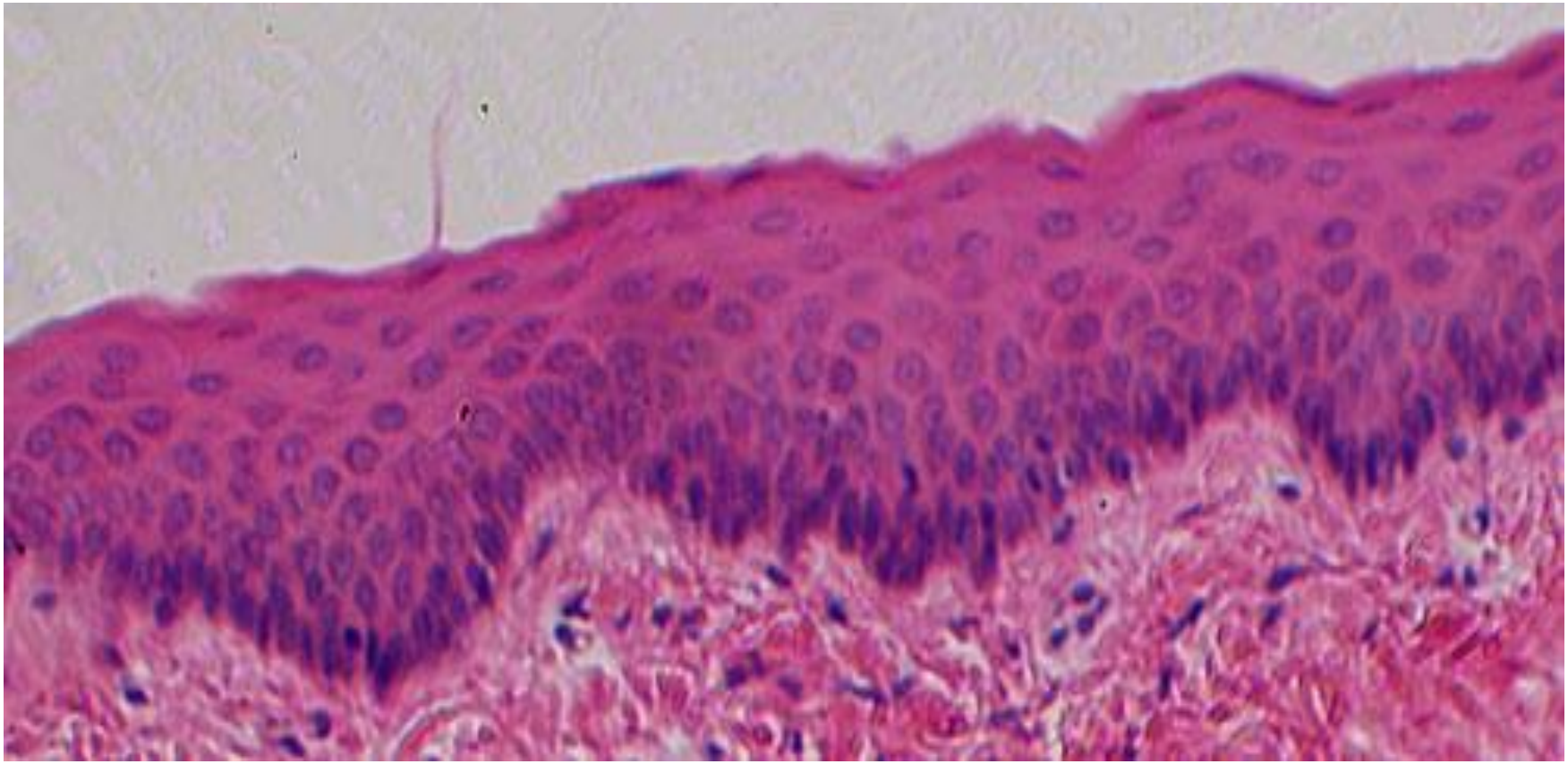
Transitional epithelium

Epithelium and Infection



Pseudostratified epithelium

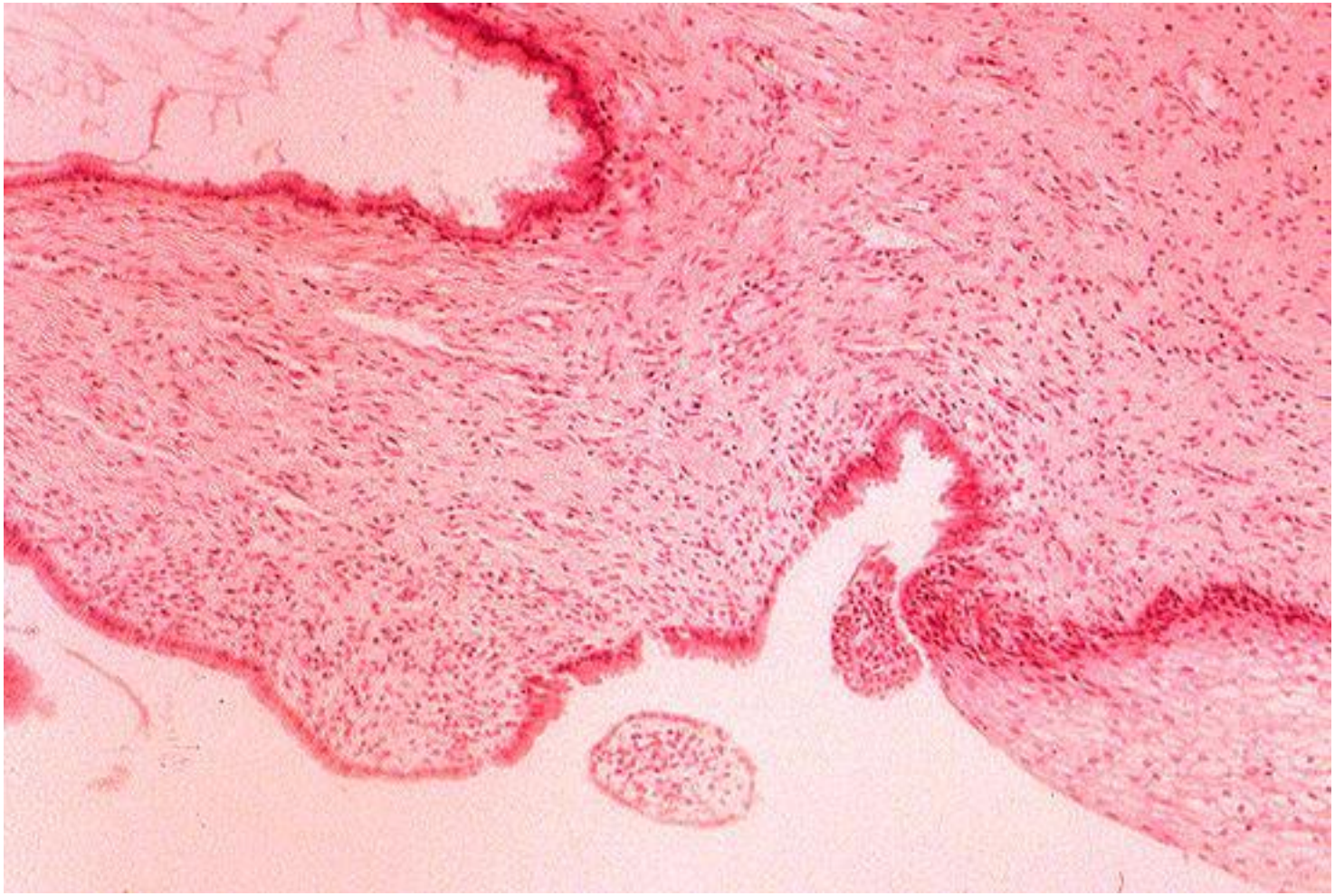
Epithelium and Infection



Squamous epithelium

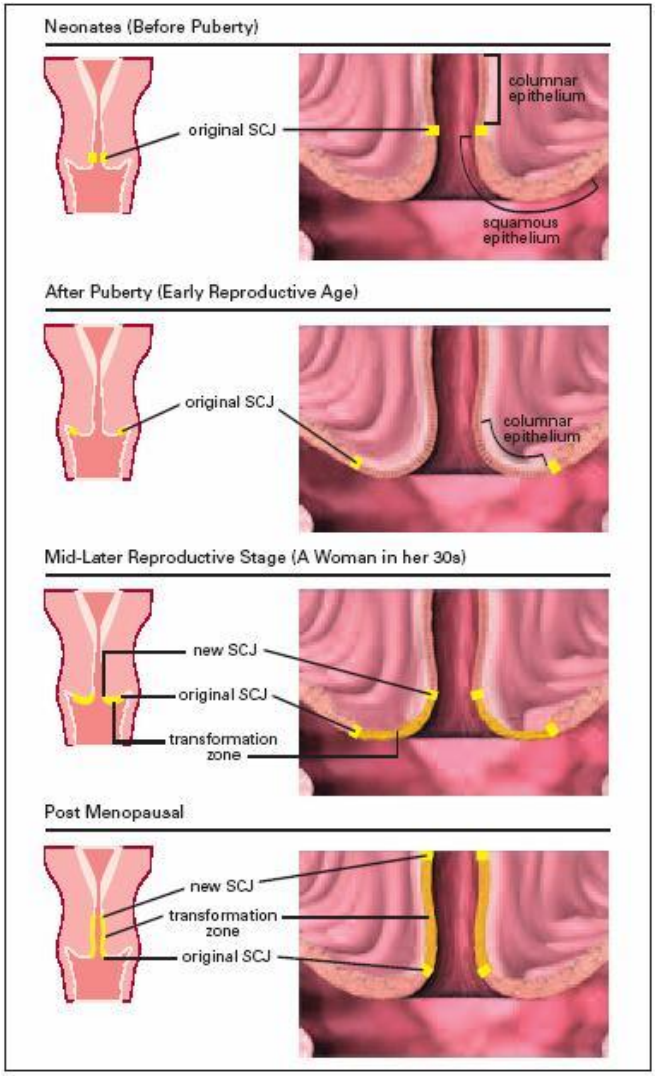
Epithelium and Infection--

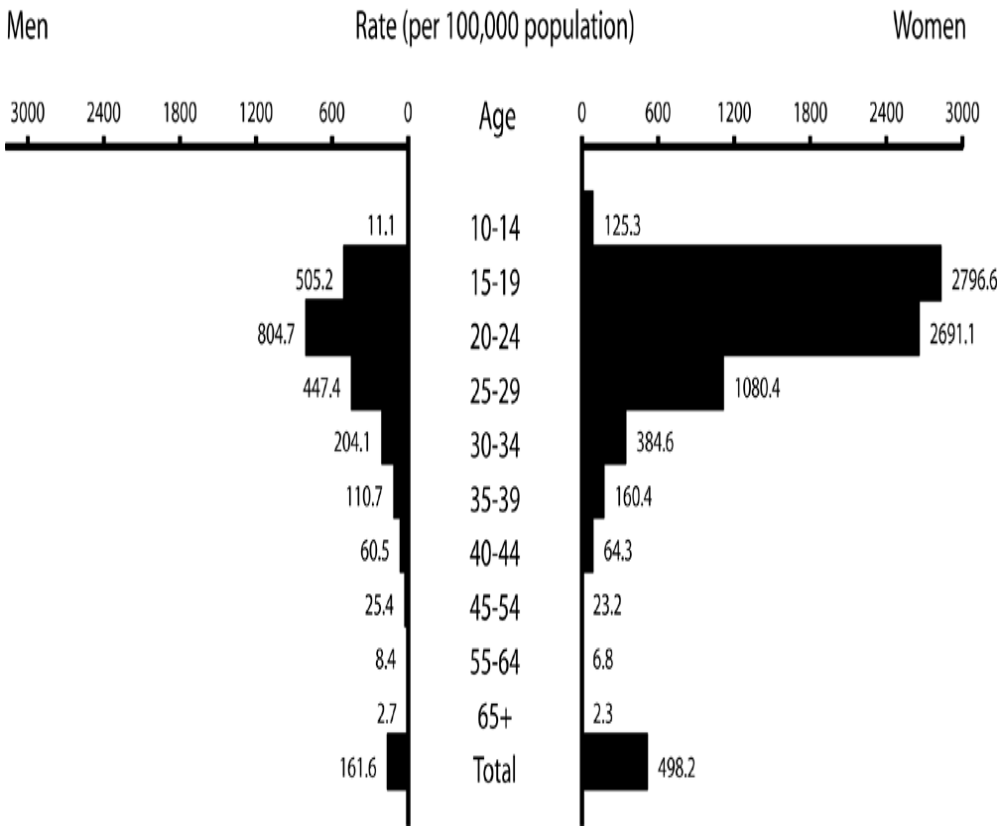
Junctions



Squamocolumnar junction

Chlamydia — Age- and sex-specific rates: United States, 2005





Chlamydia
Epidemiology-Genital Infections

- **A large number of studies have focused on the prevalence of, and risk factors for, infection among women (majority of cost [80%] goes to treating women).**
  - **few studies have addressed these problems in men.**
- **The highest prevalence rates of infection are among sexually active adolescent women (exceeding 10%) and for women attending STD clinics the rates are 15-20%.**
- **Young age (<25 years) is the strongest and most consistent association with chlamydial STDs among women. Why???**

Chlamydia--Clinical Features

- **The syndromes attributed to chlamydiae most closely resemble *N. gonorrhoeae*.**
- **Sites of infection: Epididymis, endocervix, endometrium, salpinx, adnexae, Bartholin's duct, perihepatic region, and rectum.**
  - **Cervix and urethra primary sites in women.**
- **There is some evidence that chlamydial infections of the cervix enhance the acquisition and transmission of HIV.**
  - Of the few in vivo studies, one demonstrated significant HIV seroconversion among female prostitutes infected with *C. trachomatis*.
  - **Public health control measure for HIV spread.**

Chlamydia--Symptoms (women)

- **dysuria**
- **pelvic pain**
- **dyspareunia**
- **cervicitis**
- **pyuria**
- Fitz-Hugh-Curtis Syndrome
  - liver

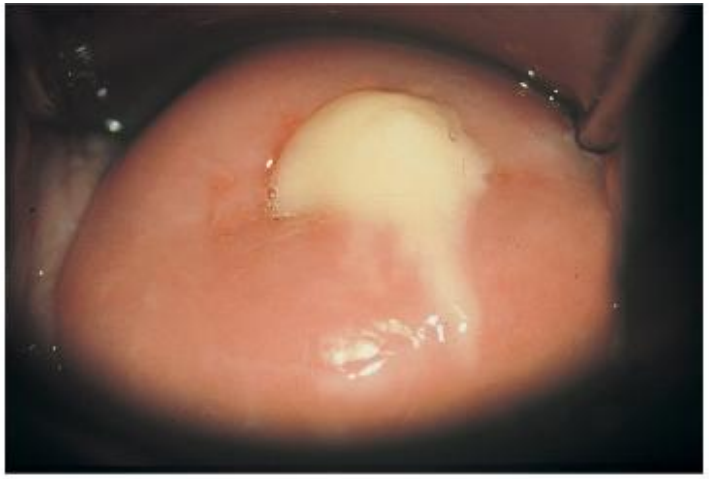
- **Reproductive consequences more likely among women with chlamydial PID than women with gonococcal PID**

- **PID (pelvic inflammatory disease)**
  - **severe pelvic and/or lower abdominal pain**
  - **fatigue**
  - **fever**
  - **adnexal tenderness**
  - **salpingitis**
  - **infertility**
  - **ectopic pregnancy**
    - **viable chlamydial organisms, antigens, DNA recovered from damaged fallopian tubes of infertile women**

Chlamydia--Symptoms (men)

- urethritis
  - Chlamydia coinfect 20% of patients with GC urethritis.
  - most common symptoms are urethral discharge, itching, and dysuria.
  - symptoms more prolonged than with GC infection.
    - 7-14 day incubation period compared to 3-4 days for GC infection.
- epididymitis
- oligospermia
- proctocolitis

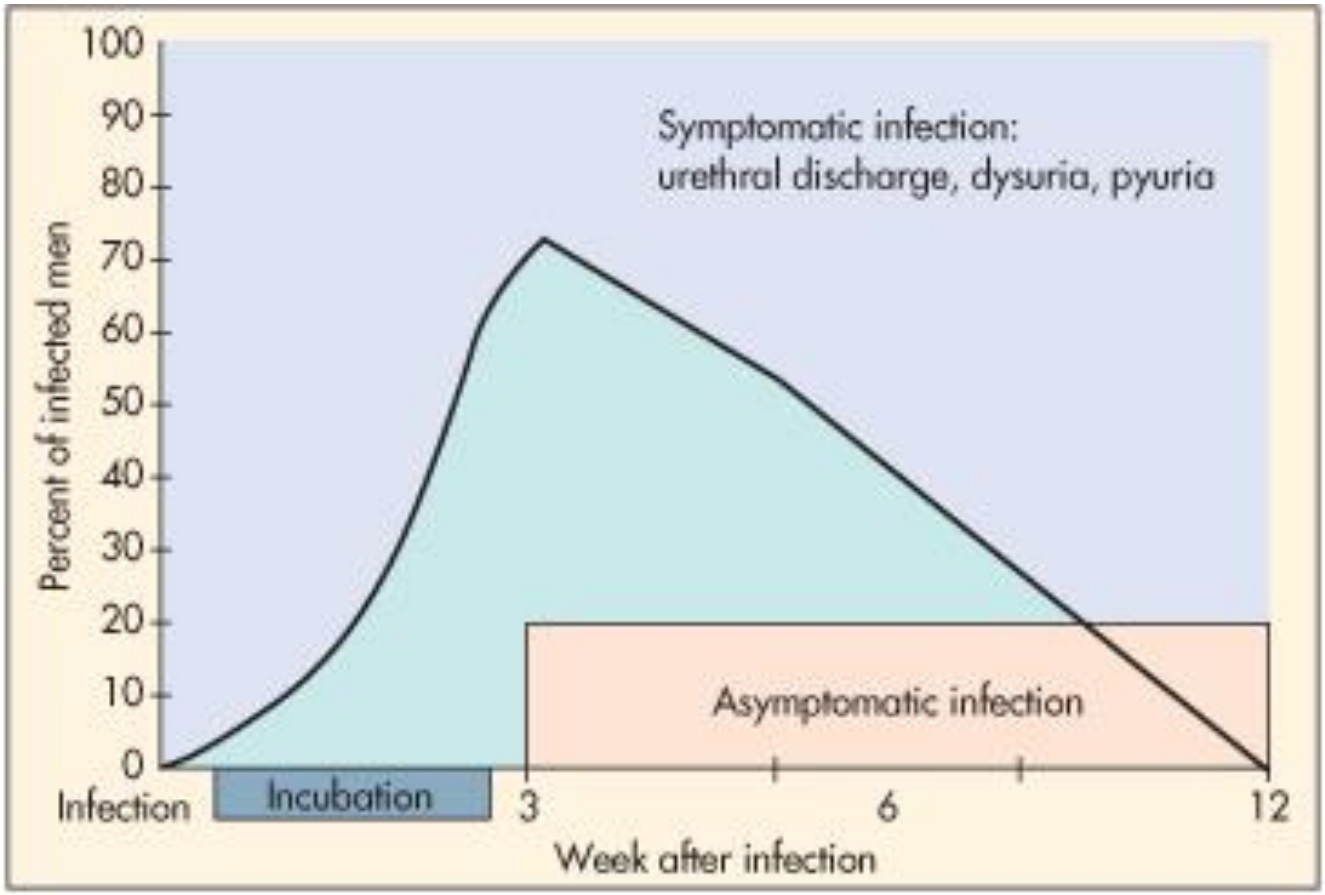
Cervicitis



Urethritis

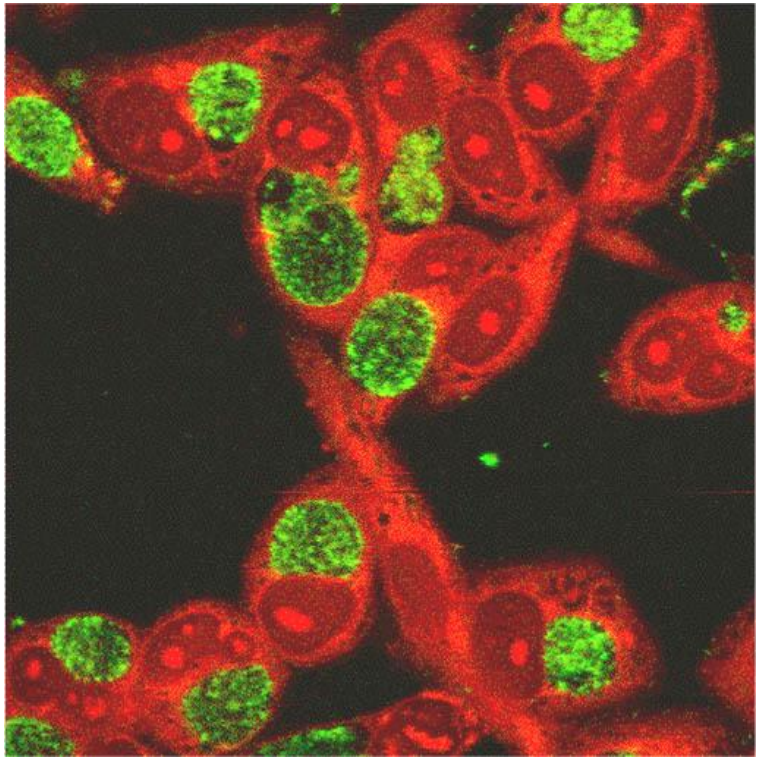
Epididymitis

Time Course of Untreated Chlamydial Urethritis in Men



Diagnostic Tests

- **Tissue culture (gold standard)**
  - **can take 3-7 days**
- **Fluorescent antibodies**
  - **smear of tissue on slide**
- **PCR**



Lymphogranuloma Venerum

'Do not trifle with love.'

Alfred de Musset (1810-1857)

'For my loins are filled with a loathsome disease; and there is no soundness in my flesh.'

Psalms 41:8

Lymphogranuloma Venerum

- tropical bubo
- strumous bubo
- climatic bubo
- Durand-Nicolas-Favre disease
- poradenitis inguinalis

Lymphogranuloma Venerum

- **Occurs sporadically in North America, Australia, and Europe.**
  - **200-500 cases annually in the USA over the last decade.**
- **Prevalent in Africa, Asia, and South America.**

Lymphogranuloma Venerum--3 Stages of Disease

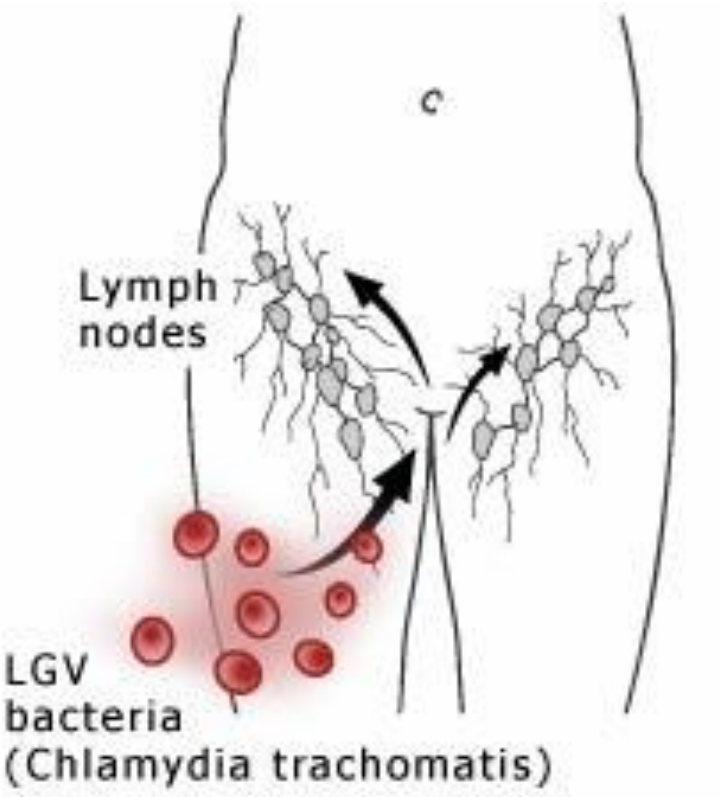
- First stage--primary lesion is a small and inconspicuous genital papule or herpetic-form ulcer.
- 3-12 days to form.
- Short lived.
- In women, lesion is primarily on the posterior vaginal wall, cervix, and vulva.
- Differential with canchroid, syphilis or Herpes simplex infections.

Lymphogranuloma Venerum--3 Stages of Disease

- **Second stage--acute lymphadenitis with buboes.**
- **10-30 days after primary lesion.**
- **bubo begins as a firm, slightly painful and gradually enlarging mass that is unilateral in 2/3 of patients.**
- **Within 1-2 weeks, bubo becomes more tender and fluctuant.**
- **Ruptures 1/3 of the time.**
  - **relives pain and fever**
- **Numerous sinus tracts form after rupture, which drain thick pus for several months.**

Lymphogranuloma Venerum--3 Stages of Disease

- **In men, healing of the bubo usually predicts the end of disease.**
- **Relapse in 20% of patients.**
- **Third stage--Important subacute manifestation is the anogenitorectal syndrome which includes:**
  - **proctocolitis, perirectal abscesses, rectovaginal fistualas, anal fistulas, and rectal stricture, 'esthiomene.'**



Lymphogranuloma Venerum-- 3 Stages of Disease

- **Esthiomene-derived from the Greek word for 'eating away.'**
- **Fibrosis of the subcutaneous tissues causing elephantiasis of the affected parts.**

- **DIAGNOSIS-ideally made by the isolation of the LGV serovar from the bubo.**
  - **only culture positive 30% of the time.**
- **Fluorescent antibodies**
- **Excluding other infectious agents.**
  - **herpes, granuloma inguinale, syphilis**

Trachoma

'Let there be sight to heal the soul of man.'

Sanskrit proverb

Introduction and History

- **First report from China in the 27th century B.C.**
- **Later there was a mention of a conjunctival disease similar to trachoma in the Ebers Papyrus form Egypt that dates to 1800 B.C.**
- **In the first century B.C., the name trachoma appeared , which meant ‘rough swelling’ in Greek.**
- **Not until the Napoleonic era did trachoma become a significant blinding disease.**

Trachoma--Epidemiology

- **Leading cause of preventable blindness.**
- **More than 500 million people affected worldwide.**
- **Of those 100 million have severe visual deficits and 9 million are blind.**

- **Estimated that by the year 2020 those with blinding disease will reach 12 million.**

Trachoma--Epidemiology

- **Infection vs. symptoms**
- **In Tanzania, 43% of patients with trachomatous follicles and 23% with intense trachoma were negative for chlamydia.**
- **Also in Tanzania, 24% of the children who had no evidence for clinical disease were positive for *C. trachomatis* by PCR.**
- **Eye-to-hand contact most common route of transmission.**
- **Risk factors**
  - **crowding, poverty, children in the household, >1 child/sleeping room, lack of water use or lack of water and poor hygiene.**

Trachoma--Epidemiology

- **Flies may be an important vector for transmission.**
- **Study: a child's ocular lesions were stained with fluorescein.**
  - **subsequently, fluorescein was detected on the legs and bodies of flies in the study household and in the eyes of children in the same family within 15-30 min.**
  - **Ability of chlamydia to survive long outside the host??**

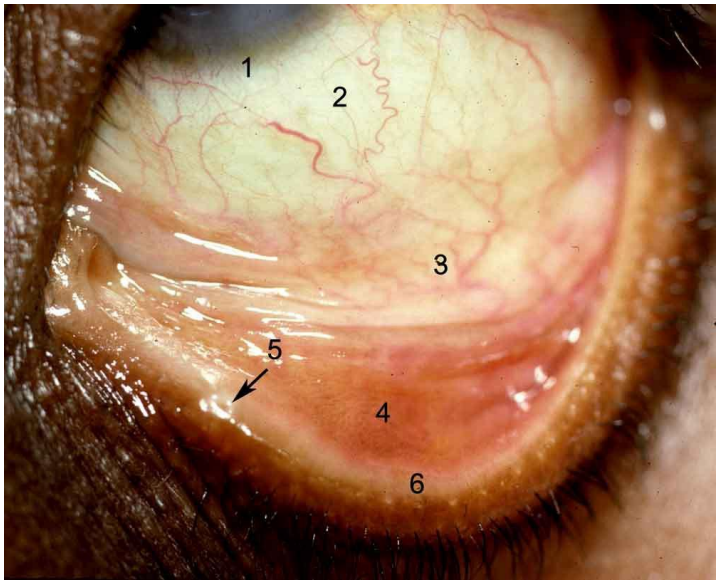
Trachoma--Clinical Features

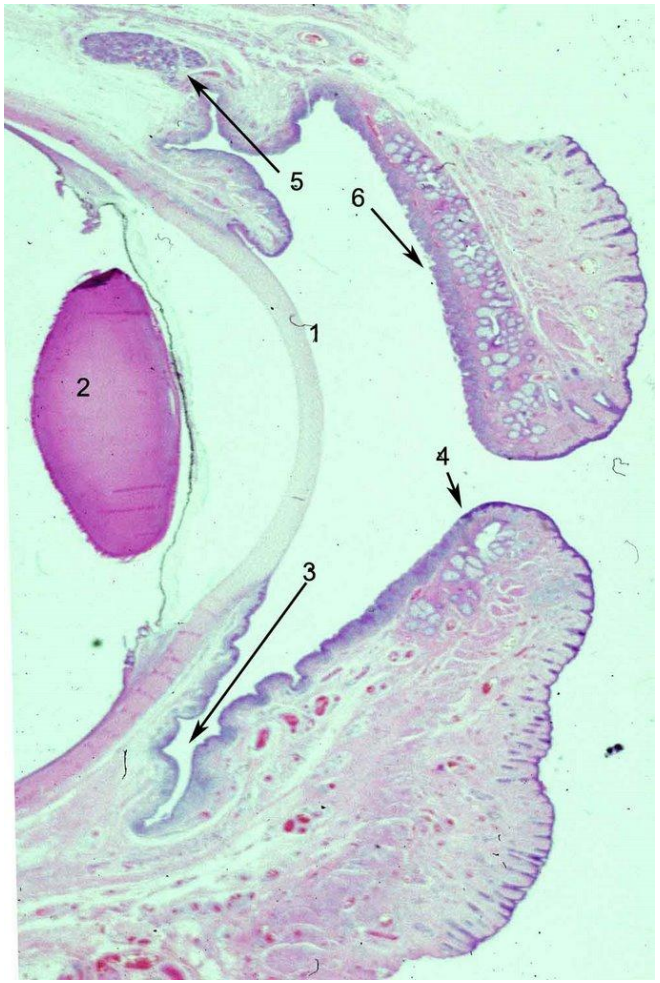
- **Defined as a chronic follicular conjunctivitis that has persisted for at least 15 days.**
- **Early in the disease, it is characterized by a follicular conjunctivitis that is indistinguishable from that caused by *C. trachomatis* sexually-transmitted serovars or *C. psittaci* or *C. pneumoniae* strains.**

Trachoma--Clinical Features

- Later it becomes a cicatricial (or scarring) conjunctivitis.
- Can be acute or insidious.
- Patients present with a foreign body sensation.
- Entire upper tarsal epithelium typically is involved and contains developing lymphoid follicles.

Some Eye Anatomy





Trachoma--Clinical Features

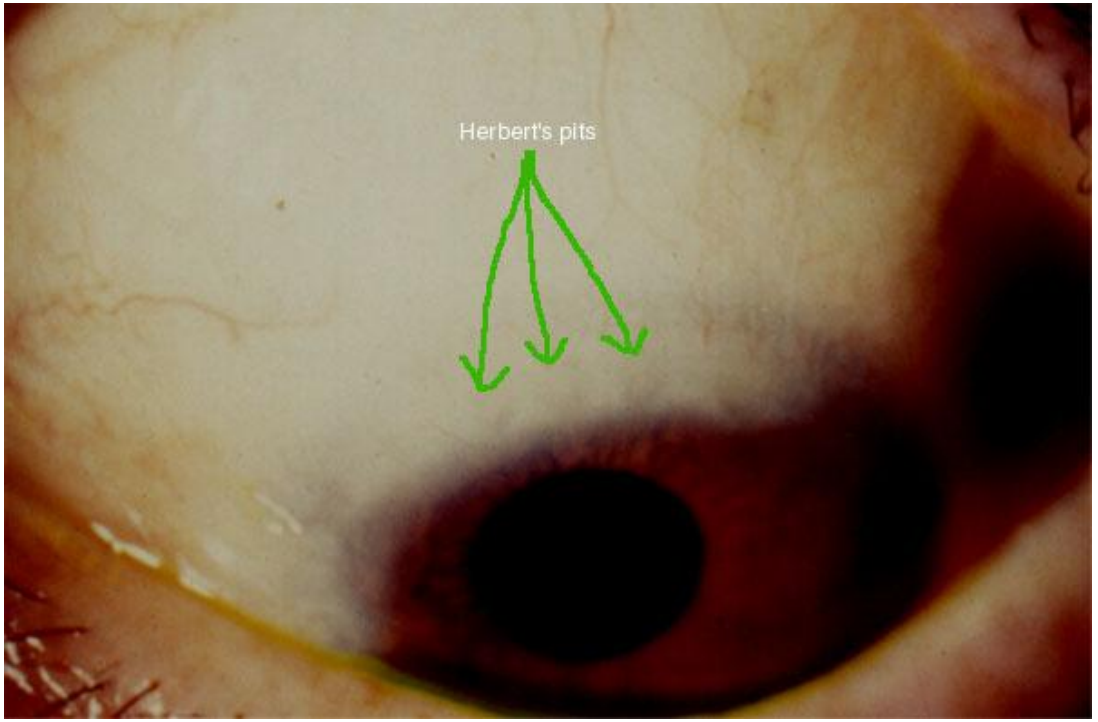
- **Entire upper tarsal epithelium typically is involved and contains developing lymphoid follicles.**
- **Follicles appear as clear, yellowish, or gray-white avascular lesions.**
- **In children <2 years of age thickening of the epithelium may be the only symptom.**
  - **follicle formation less common.**

Trachoma--Clinical Features

- **The intensity of the infiltrates tens to increase in children up to 6-8 years.**

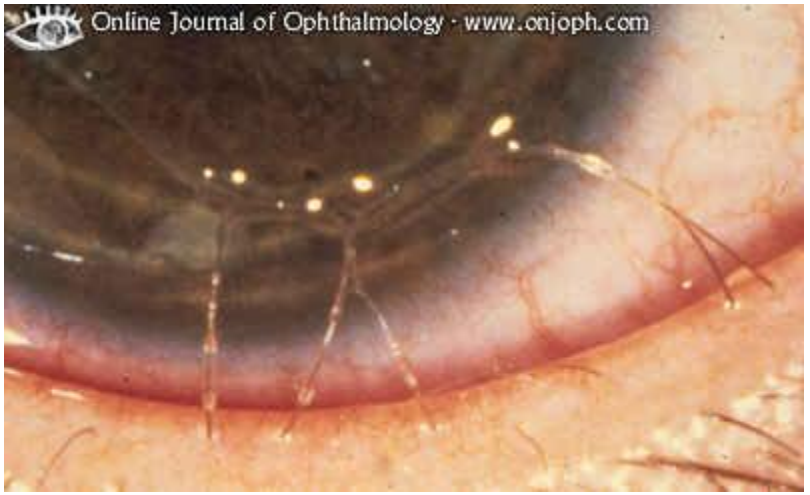
Trachoma--Clinical Features

- **Lymphoid follicles at the limbus are a characteristic feature of trachoma that lead to the formation of Herbert's pits.**

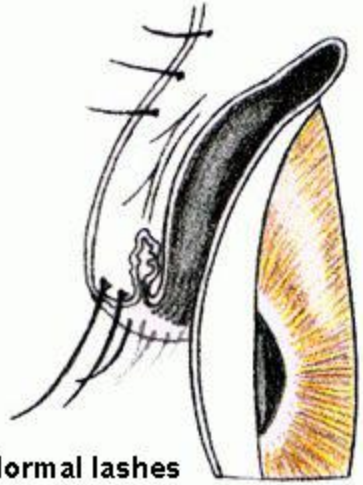


Trachoma--Clinical Features

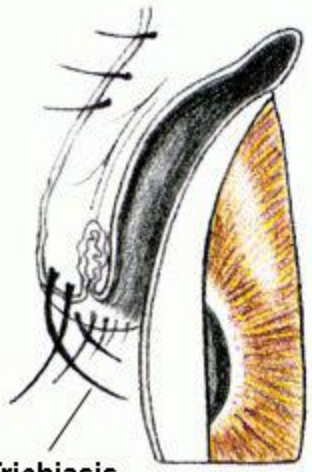
- As scarring progresses, the upper tarsus becomes distorted, leading to trichiasis.
- These inturned eyelashes can can produce corneal abrasions that become superinfected with bacteria.
- Abrasions heal by scarring.
  - varying degrees of corneal opacity.



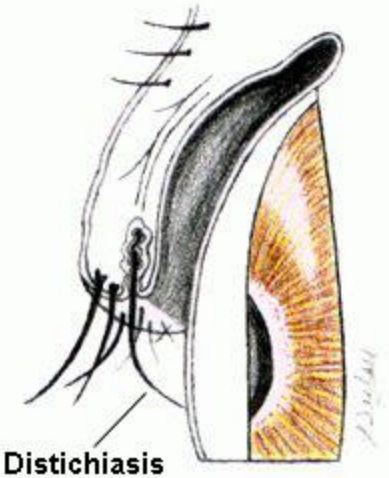
Trichiasis and Distichiasis



Normal lashes



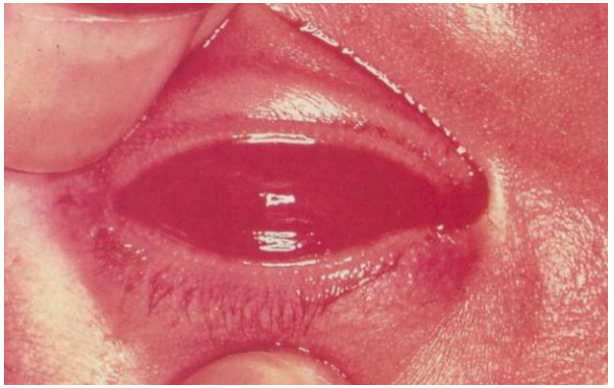
Trichiasis



Distichiasis

Trachoma-Clinical Features

- **Ophthalmia neonatorum**
  - **newborns (1-3 weeks post)**
  - **infected in birth canal**
  - **infected caregivers**
  - **44% develop this condition**
  - **Prophylaxis does not work.**



  - **Pneumonitis**

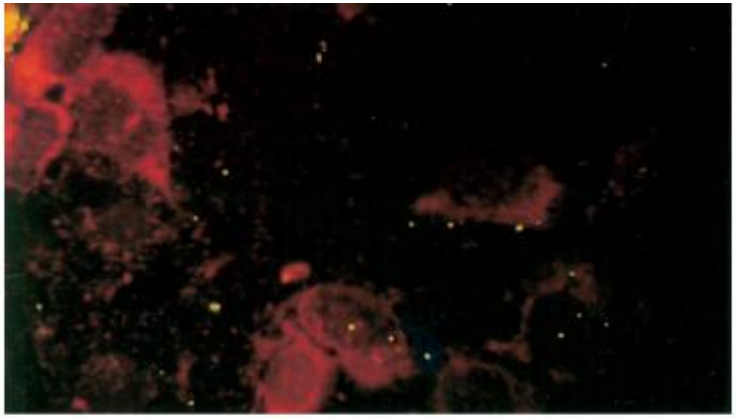
Trachoma--Clinical Features

- **Although trachoma is one disease that causes a chronic follicular conjunctivitis, there are other conditions that meet the definition of disease.**

- toxic follicular conjunctivitis
- inclusion conjunctivitis form sexually transmitted *C. trachomatis*.
- *H. influenzae*
- *H. aegyptius*
- *Moraxella spp.*
- *Neisseria meningitidis*
- *N. gonorrhoeae*
- *S. pneumoniae*

Trachoma--Diagnosis

- **Same as for other Chlamydial infections.**
- **Conjunctival smears.**



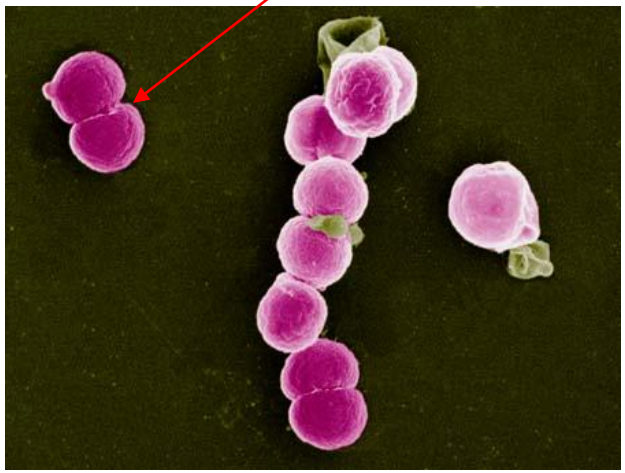
Neisseria and Related Genera

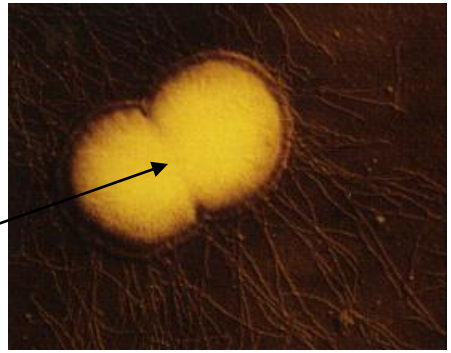
'A young man wishes to faithful, but cannot. A old man wishes to faithless, but cannot.'

Oscar Wilde

Neisseria

- **Gram negative**
- **Non spore forming**
- **Usually non motile**
- ***N. gonorrhoeae***
  - **fastidious**
  - **culture depends on high humidity**
  - **utilizes glucose but not maltose, lactose nor sucrose**
  - **Referred to as the "clap" (middle French *clapoir*, "bubo")**





N. gonorrhoeae--Introduction and History

- **Numerous references to gonococcal urethritis in Chinese writings dating back 2500 years.**
- **Biblical references to NG infection.**
- **The term gonorrhea, meaning "flow of seed" (*gonos*, seed; *rhoia*, flow) was introduced by Galen in about 130 AD, who confused the purulent urethral exudate from infected men with semen.**

N. gonorrhoeae--Introduction and History

- **Additional descriptions of gonorrhea can be found in the Papyrus of Ebers and the writings of Hippocrates.**
- **Causative agent first described by Neisser in 1879.**

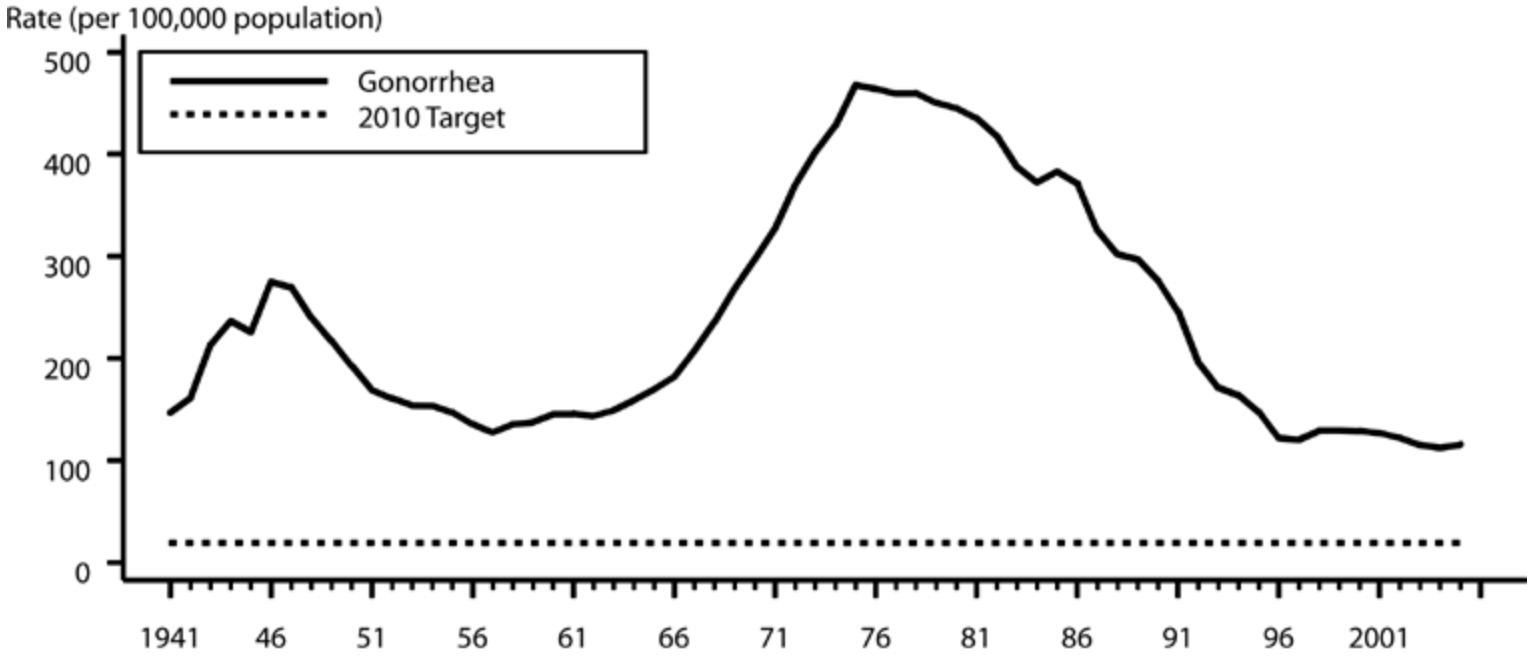
N. gonorrhoeae--Epidemiology

- **In the U.S. it remains the most frequently reported STI.**
- **Many more infections reported in men than in women.**
  - **easier to diagnose**
  - **trends are evening out**
- **Transmission is almost exclusively be sexual contact.**
  - **nonsexual transmission *i.e.*, skin-to-skin, skin to mucus membrane, autoinoculation, fomite transmission have not been reported.**

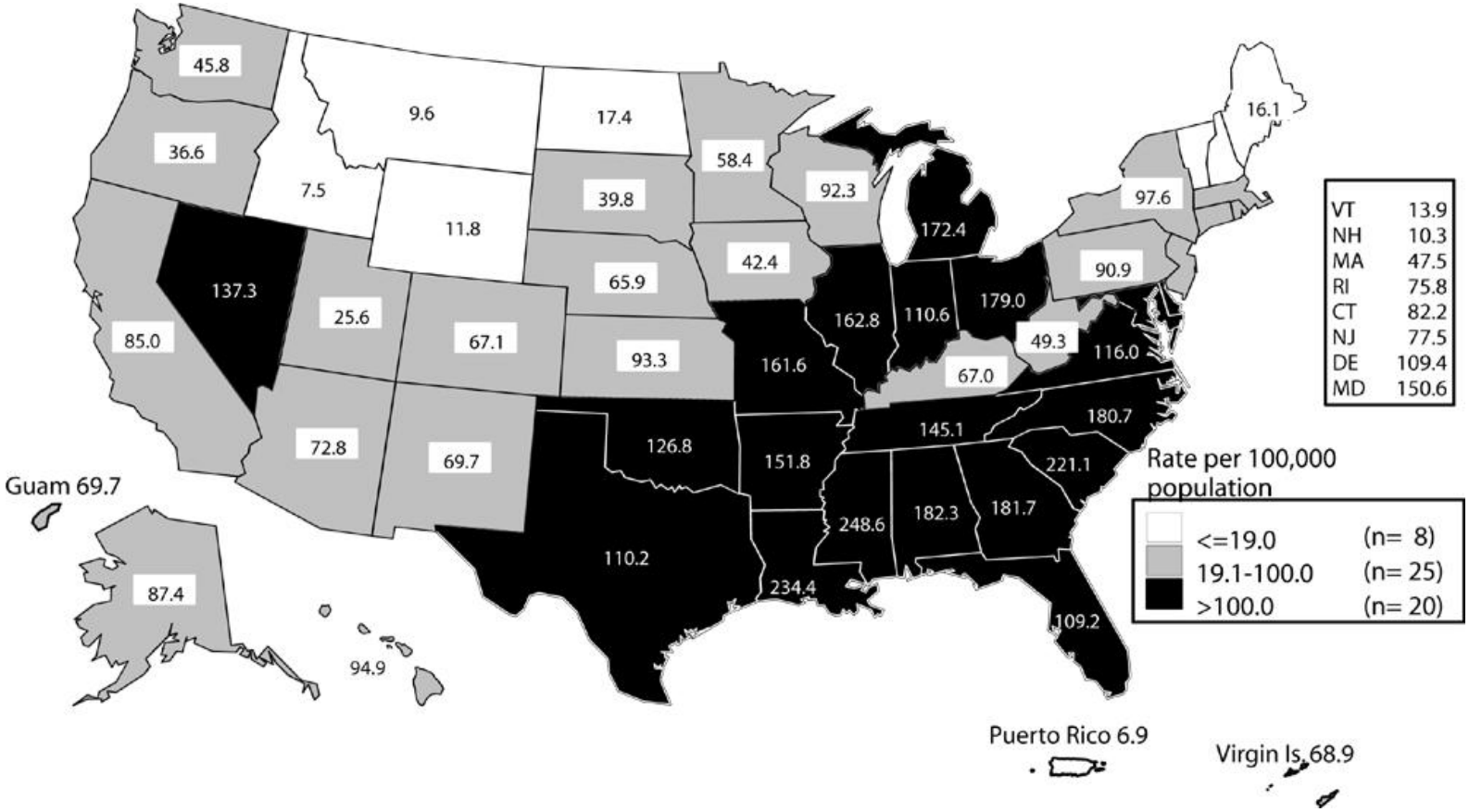
N. gonorrhoeae--Epidemiology

- **Highest risk factor group: <25 years.**
- **Risk following 1 sexual contact is 50-60% (man to uninfected woman).**
- **Risk following 1 sexual contact is 22% (woman to uninfected man).**
- **Presence and survival of NG in fresh and frozen semen have been documented.**
- **Antibiotic-resistant strains are on the rise.**

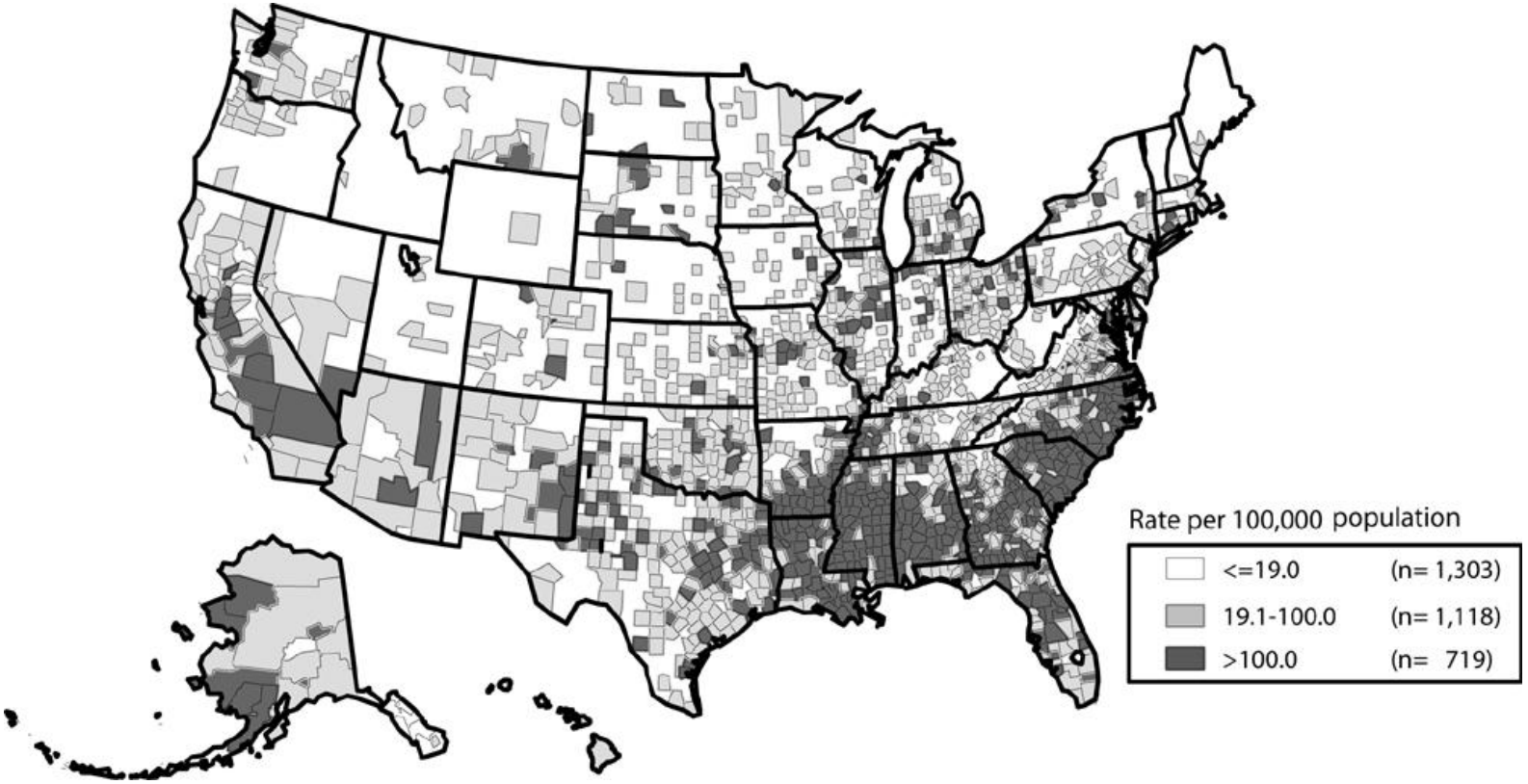
Gonorrhea — Rates: United States, 1941–2005 and the Healthy People 2010 target



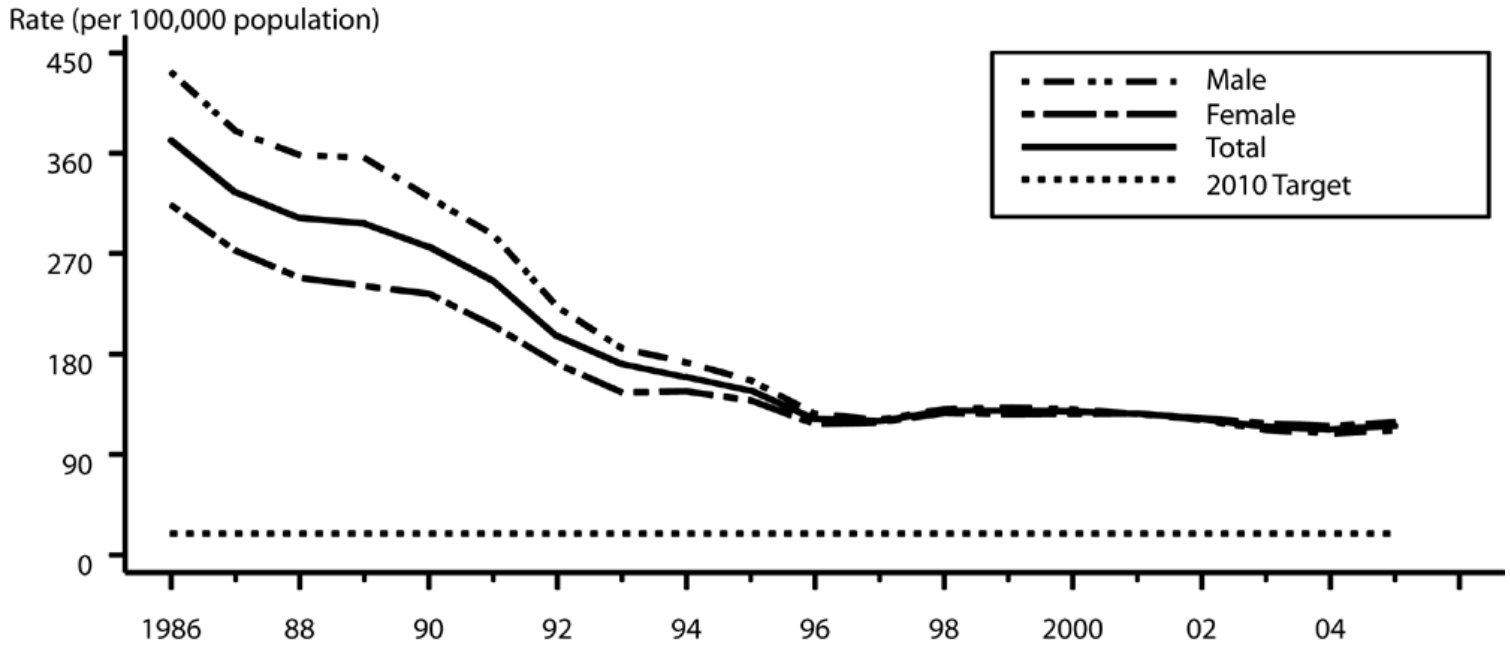
Gonorrhea — Rates by state: United States and outlying areas, 2005



Gonorrhea — Rates by County: United States and outlying areas, 2005



Gonorrhea — Rates: Total and by sex: United States, 1986–2005 (per 100,000)



N. gonorrhoeae--Biology and Pathogenesis

- **Prefer columnar and transitional epithelium.**
- **Outer membrane contains lipooligosaccharide (LOS).**
  - **endotoxic properties**
  - **lethal to experimental animals**
  - **mediates cellular destruction**
  - **LOS form the basis of an alternative serologic typing system.**
- **Porins**
  - **major protein antigen used in serologic typing systems**
- **Opacity proteins**
  - **-increase adhesion of gonococci to each other.**
- **Pili play an important role in infection**
  - **more than 50 serotypes of pili**
  - **better able to attach to mucosal surfaces--INFECTION**

N. gonorrhoeae--Clinical Features-Men

- **Most common symptom is acute urethritis, presenting with urethral discharge.**
  - **2-5 days post**
- **If untreated, most infections will resolve after several weeks.**
  - **epididymitis**
- **Rare complications include penile edema referred to as "bullheaded clap."**

N. gonorrhoeae--Clinical Features-Women

- **Endocervix is the primary site of genital tract gonococcal infection.**
- **Most common symptoms include cervicitis, urethritis, vaginal discharge.**
  - **examination revels mucopurulent cervical discharge.**
- **PID**
  - **chronic complication--ascending infection**
  - **infertility more likely with *C. trachomatis* because NG causes more severe clinical manifestations.**

N. gonorrhoeae--Other Infections

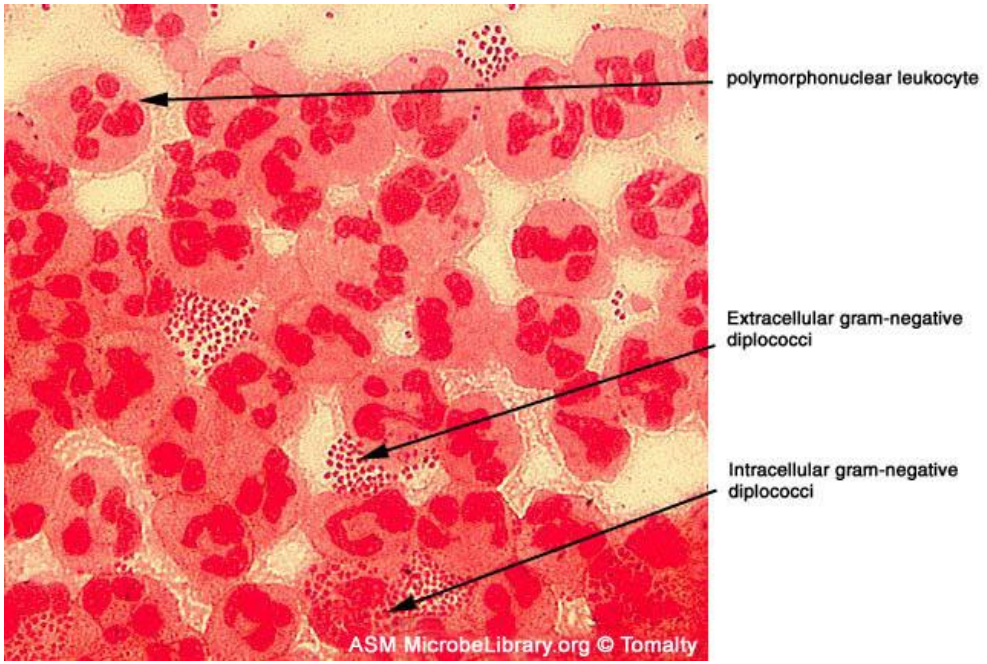
- **Anorectal Infection**
  - **40% of women and homosexual men have positive rectal cultures for the gonococcus.**
  - **In 40% of homosexual men and 5% of women with gonorrhea, the rectum is the only site found to be infected.**
  - **Most asymptomatic**
  - **Symptomatic**
    - **tenesmus**
    - **puritis**
    - **bleeding**
- **Pharyngeal Infection**
  - **Majority of patients are asymptomatic.**
  - **Major risk factor for infections is having oral-genital sexual exposure with an infected partner.**

N. gonorrhoeae--Pregnancy and Neonatal Infections

- **Pregnancy**
  - **poor obstetric outcome**
  - **spontaneous abortion**
  - **premature labor**
  - **perinatal infant mortality**
- **Neonatal Infections**
  - **ophthalmia neonatorum**
    - **most frequent clinical manifestation of neonatal infection.**
    - **At one time in the US, it was the most common cause of blindness and remains a a pediatric public health problem in many developing nations.**

N. gonorrhoeae--Diagnosis and Treatment

- **Culture**
- **Demonstration of intracellular gram-negative diplococci in Gram-stained smears.**
- **Fluorescent antibody**
- **DNA**
- **Accu Probe**



- **Antibiotics while they last.**

Meningococcal Infections

"Acute pain of the ear with continual and strong fever is to be dreaded; for there is danger that the man may become delirious an die."

Hippocrates, *Book of Prognostics*, 22

N. meningitidis-Epidemiology

- **Colonize the oropharynx.**
- **Can colonize 2-15% of healthy individuals but in crowded or confluent populations colonization is so common that it could arguably be considered part of the normal human oral flora.**
- **Transmission is by direct contact with contaminated respiratory secretions or airborne droplets.**
- **Sexual transmission has been reported.**
  - **creates a 'carrier' population**

N meningitidis-Epidemiology

- **13 serotypes are currently recognized based on capsular polysaccharides: A, B, C, D, 29E, H, I, K, L, W135, X, Y, Z.**
- **Strains belonging to groups A, B, C, Y, and W135 most frequently cause systemic disease.**
- **Classically, groups A and C cause epidemic meningococcal disease.**

N meningitidis-Epidemiology

- **In Africa, epidemic meningitis is in a wide band of countries lying south of the Sahara in the so-called "meningitis belt."**

N meningitidis-Pathogenesis

- **Major toxic factor is LOS**
- **Piliation appears to be required for colonization of host mucosal surfaces.**
- **LOS is a potent activator of complement.**
  - **double-edged sword**
    - **disseminated intravascular coagulation (DIC)**

N meningitidis-Clinical Manifestations

- **Manifestations dominated by fulminating, rapidly progressive septicemia with fever, vascular collapse, and DIC manifested by petechial or purpuric skin lesions.**
- **course of the infection may be brief with death in a few hours of onset.**
  - **arthritis**
  - **endocarditis**

N meningitidis-Clinical Manifestations

- **Purpura fulminans**
  - **catastrophic febrile illness with initial hemorrhagic skin lesions that progress to gangrene.**
  - **Amputation maybe necessary.**
  - **Other pathogens that can cause hematogenous infections such as *E. coli*, *S. pneumoniae* and viruses like varicella and rubella**

N meningitidis-Clinical Manifestations

- **Waterhouse-Friderichsen Syndrome**
  - **Classically associated with meningococcal septicemia.**
  - **W-FS has an abrupt onset in a previously healthy patient.**
    - **septicemia**
    - **shock**
    - **cutaneous petechiae**
    - **hemorrhage to both adrenal glands**
    - **adrenal gland hemorrhage**

N meningitidis-Diagnosis and Treatment

- **Hallmark (unfortunately) is its rapid fulminating course.**
  - **early diagnosis is essential**
- **Blood cultures positive in about 1/3 of patients**
- **90% of patients have positive CSF cultures.**
- **Kits for rapid detection available.**

- **Penicillin G**
  - **resistant strains exist**

N meningitidis-Prophylaxis

- **Quadrivalent vaccine is commercially available (groups A, C, W, W135).**