

Sexually Transmitted Diseases

Objectives: To understand the microorganisms involved and the pathogenesis of sexually transmitted diseases, as well as their prevention and treatment.

Background Knowledge: Anatomy of the urogenital system; understanding of sexual behavior.

Although the AIDS epidemic has alerted many individuals to the risk of sexual activity, there has been no major decline in sexually transmitted disease. Gonorrhea, chlamydial infections, syphilis, chancroid, and papilloma virus infections remain a major problem world-wide.

Epidemiology and Pathogenesis of Gonococcal Infections

Gonorrhea is an infection of columnar and transitional epithelium caused by *Neisseria gonorrhoeae*. Anatomic sites which can be infected by the gonococcus include the urethra, anal canal, conjunctiva, pharynx, and endocervix.

Microbiology

The *N. gonorrhoeae* organism is a gram-negative diplococcus which forms oxidase-positive colonies and is differentiated from other *Neisseria* by its ability to ferment glucose but not maltose, sucrose, or lactose, and by specific immunofluorescent staining.

At least four morphologically distinct forms of colonies result when gonococci are passed *in vitro*. Colony forms T1 and T2 retain virulence during repeated selective subculture *in vitro*. Spontaneous transition to colony forms T3 and T4 results in some loss of virulence with disappearance of surface pili. Gonococci have many pili on their surface that extend through the peptidoglycan and outer membrane. The outer membrane of gonococci is composed of lipopolysaccharide, phospholipids, and outer-membrane proteins (OMP). OMP I is the major outer protein. OMP II is composed of eight proteins. Pili of gonococci contain a conserved region of amino acids and a highly variable region. Gonococci can vary both their pili and OMP II. This is extremely important, since gonococci can change antigenic structure in the course of infection.

Pathogenicity of *N. gonorrhoeae*

The first step for gonococci to establish an infection is attachment to mucosal epithelial cells. Pili are composed primarily of a single protein subunit (pilin) and possibly minor accessory proteins in small amounts. Pili are essential for virulence. Infection was not established in human volunteers inoculated with

pil mutants of *N. gonorrhoeae*. These structures are responsible for **tight binding** of the bacteria to nonciliated mucosal cells of the urethra or vagina. The tight binding prevents the gonococci from being washed away by vaginal discharge or urine. The presence of pili has also been shown to inhibit phagocytosis by neutrophils.

Another factor which contributes to colonization by the gonococci is a set of cell surface proteins, or adhesins, known as **Opa** or **P II**. These proteins also promote adherence of gonococci to each other to form aggregates and confer resistance to the bactericidal activity of serum. Specific Opa proteins enable the gonococci to enter the epithelial cells in a vacuole. Once inside, the bacteria multiply and are transported to the base of the nonciliated cells, where they are released by "reverse-phagocytosis" into the subepithelial connective tissue. There the organisms continue to multiply, causing damage to tissue and in some cases entering the bloodstream.

One might predict that an immune response mounted against the pili or Opa proteins would be effective in preventing or ending infection. Indeed, both pilin and Opa proteins are highly immunogenic. However, the gonococci have evolved effective ways of evading the immune response. First, they secrete an IgA protease which cleaves the heavy chain of the IgA₁ isotype and inactivates it. Although it has not been proved that this is an important virulence factor, it seems reasonable to believe that it has an effect on the survival of gonococci in the host. A strategy that is clearly important is the ability to switch production of pilin and Opa proteins on or off (**phase variation**) and to express different antigenic forms of both pilin and Opa proteins (**antigenic variation**). A single clone of *N. gonorrhoeae* can give rise to variants expressing pili antigenically distinct from that of the original clone. The variants arise at a high frequency in the population (approximately 10⁴). The same clone will also express distinct variants of the Opa proteins. This variation occurs at a 10-100-fold higher frequency than that of the pili.

The mechanisms of phase variation and antigenic variation for pilin and the Opa proteins are entirely different. However, both mechanisms rely on multiple copies of the pilin and Opa genes in the *Neisseria* chromosome. The different pilin proteins expressed from a single clone can vary from 18 to 24 kilodaltons (kD) in mass.

Once a pilin gene was cloned, hybridization analysis demonstrated 11 copies of related genes in the *Neisseria* chromosome. These copies were generated by gene duplication and point mutations. However, only one of the genes is expressed.

Opa proteins (approximately 30 kD) also display antigenic variation. In one strain, 11 *opa* genes were detected. There is evidence that variable regions can be shuffled by intracellular recombination and by transformation to generate a large variety of Opa proteins.

In summary, two important virulence determinants of gonococci have been identified: pili and Opa proteins. Similar structures have been found for the

meningococci, but they confer different tissue specificity. The pili are important for initial attachment. The Opa adhesin is important for tight binding and invasion of the mucosal epithelial cells. The antigenic variation displayed by both sets of proteins has two important consequences. (1) The most obvious is that it helps the organism survive the host immune response. Antibodies specific for one form of pilin or Opa protein are not effective against another form. Volunteers who have been vaccinated with one type of pilin are not protected against naturally varying strains, but they are protected against strains genetically altered to produce the same pilin type (e.g., *recA* mutants). (2) Less obvious, but perhaps equally important is that stochastic variation allows for the selection of attachment proteins that are most effective for a particular tissue. For example, invasion of cultured epithelial cells selects for bacteria that express the same Opa protein. Different Opa proteins enhance invasion of other cell lines. Thus, variation may give the bacterial population added flexibility. It allows for selection of variants that produce the colonization proteins most suited for different individuals or other sites of the body.

Epidemiology

The only natural hosts for *N. gonorrhoeae* organisms are humans. The peak incidence occurs from age 20 to 24 (2 cases per 100 population per year), and 85% of patients are 30 or younger. The incidence of gonorrhea and its prevalence rates are known to be related to age, sex, race, socioeconomic status, and marital status -- risk factors which influence sexual behavior, illness behavior, and accessibility of health care. The highest rates occur at ages 18-19, in non-Caucasians, in the poor, in large cities, and in unmarried persons - particularly those who live alone. The prevalence of *Neisseria* organisms is so high among women in the United States that endocervical cultures are advocated for gonorrhea case detection in sexually active **asymptomatic** women age 30 or under. The single most important axiom about the epidemiology of this disease is that **gonorrhea is usually spread by carriers who have no symptoms or who have ignored symptoms**. Symptomatic patients, male or female, have usually been recently infected by such carriers, who must in turn be traced and treated to prevent reinfection. Patients with symptomatic gonorrhea should always be interviewed to identify their recent sex contacts, who should be examined and treated if infected.

The antibiotic resistance of *N. gonorrhoeae* organisms varies. Resistance is greatest in Southeast Asia and Africa, where prophylactic or low-dose therapy is common, and intermediate in the United States. Currently 40% of *N. gonorrhoeae* organisms in Washington Heights produce beta-lactamase. In areas such as San Diego, where sailors have come from Asia, 70% of gonococci produce beta-lactamase.

Clinical Manifestations

The clinical spectrum of gonococcal infection depends upon the site of inoculation, the duration of infection, and the presence or absence of local or systemic spread of the organism.

Gonorrhea in the Male

The usual incubation period of gonococcal urethritis in the male is 2-6 days following exposure, although longer intervals occur and some men never develop symptoms. Symptoms include a purulent urethral discharge, usually associated with dysuria and frequent urination. Although approximately 90% of men who acquire urethral gonococcal infection develop urethral discharge, most symptomatic men seek treatment and are removed from the infectious pool. The remaining men who never develop symptoms or who ignore their symptoms serve as the source of spread of infection to women and other men. Epididymitis is now an uncommon complication of gonorrhoea, and gonococcal prostatitis occurs rarely. In homosexual men, anorectal and pharyngeal gonococcal infection were common before AIDS. Anorectal infection may be asymptomatic from the outset or may produce anorectal burning or pruritus, tenesmus, and a bloody, mucopurulent rectal discharge. Proctoscopy is essential to exclude syphilis, lymphogranuloma venereum, granuloma inguinale, and other conditions which cause similar symptoms. These symptoms may subside without treatment, leaving a chronic asymptomatic carrier state. Pharyngeal gonococcal infection occurs in approximately 20% of homosexual men and heterosexual women who engage in fellatio with men who have urethral infection. Pharyngeal infection may produce exudative tonsillitis but frequently is asymptomatic.

Gonorrhoea in the Female

Acute uncomplicated gonorrhoea in the female often causes dysuria, frequent urination, increased vaginal discharge due to exudative endocervicitis, abnormal menstrual bleeding, and anorectal discomfort. Whereas in young men dysuria and frequency arouse the suspicion of gonococcal urethritis, in a young woman the same symptoms are often automatically attributed to cystitis, urinary tract infection. Acute symptoms of gonococcal urethritis in the female may subside spontaneously or abate following subcurative therapy with urinary antiseptics. The proportion of women with gonorrhoea who never develop symptoms is undefined.

Asymptomatic gonococcal infection in the female involves the endocervix, urethra, anal canal, and pharynx, in decreasing order of frequency. Extension of infection from the endocervix to the Fallopian tubes occurs in at least 15% of women with gonorrhoea. This tends to occur soon after acquisition of infection or during menstruation and results in acute salpingitis, the major complication of gonorrhoea. Extension of infection to the pelvis may produce signs of pelvic peritonitis, accompanied by nausea and vomiting, and may lead to pelvic abscess. Early antibiotic treatment, before development of adnexal masses, restores normal tubal function and fertility in nearly all cases of salpingitis. However, if prominent adnexal swelling has occurred before treatment is begun, bilateral tubal dysfunction occurs in 15-25%.

Gonorrhoea in Children

During childbirth, the gonococcus may infect the conjunctiva, pharynx, respiratory tract, or anal canal of the newborn. The risk of contamination increases with prolonged rupture of membranes. Prevention of gonococcal ophthalmia by prophylactic use of 1% silver nitrate eye drops has led to the

emergence of inclusion conjunctivitis caused by *Chlamydia trachomatis* as a more common form of **ophthalmia neonatorum**. During the first year of life, infection of the infant can often result from accidental contamination of the eye or vagina by an adult, between one year of age and puberty, most cases of gonorrhea involve vulvovaginitis in females who have been molested by a relative.

Disseminated Gonococcal Infection

About 3% of adults with gonococcal infection develop gonococemia. Approximately two-thirds of such patients are women. Most men and women with gonococemia do not have symptoms of urogenital, anorectal, or pharyngeal gonococcal infection. Gonococemia may occur soon after acquisition of new infection or later, during menstruation. *Neisseria* organisms which cause disseminated infection are uniquely resistant to complement-mediated bactericidal activity of normal human serum. Patients with deficiency in the sixth, seventh, and eighth components of complement have increased susceptibility to gonococemia and meningococemia but not to other infections. Serum bactericidal activity, rather than opsonic activity, appears essential for protection against gonococcal bacteremia.

The onset of gonococemia is characterized by fever, polyarthralgias, and papular, petechial, pustular, hemorrhagic, or necrotic skin lesions. Approximately 3-20 such lesions appear, usually on the distal extremities. Gonococci are demonstrable by immunofluorescent staining in about two-thirds of gonococcal skin lesions. The initial joint involvement is characteristically limited to tenosynovitis involving several joints asymmetrically. The wrists, fingers, knees, and ankles are most often involved. Circulating immune complexes have been demonstrated at this stage of infection. Without treatment, the duration of gonococemia is variable; the systemic manifestation of bacteremia may subside spontaneously within a week. Alternatively, septic arthritis ensues, often without prior symptoms of bacteremia. Pain and swelling then increase in one or, very often, more joints, with accumulation of purulent synovial fluid, leading to progressive destruction of the joint if treatment is delayed. A continuum of disease exists from the manifestations of bacteremia (polyarthralgias, new skin lesions) to septic arthritis, but the probability of positive blood cultures decreases after 48 hours of illness and the probability of recovery of gonococci from synovial fluid increases with increasing duration of illness. Gonococci are infrequently recovered from early effusions containing less than 20,000 leukocytes per cubic millimeter but are usually recovered from effusions containing more than 80,000 leukocytes per cubic millimeter. In the individual patient, gonococci are seldom recovered from blood and synovial fluid simultaneously.

Other common manifestations of disseminated gonococcal infection include mild myopericarditis and "toxic" hepatitis. Endocarditis and meningitis are infrequent but severe complications. Endocarditis is suggested by pathological or changing heart murmurs, major embolic phenomena, severe myocarditis, deterioration of renal function, or an unusually large number of skin lesions.

Laboratory Diagnosis

The Gram's stain of urethral male or endocervical exudate is considered diagnostic of gonorrhea when typical gram negative diplococci are seen within leukocytes; it is equivocal if only extracellular or atypical gram-negative diplococci are seen, and it is negative if no gram-negative diplococci are seen. The sensitivity and specificity of a Gram's stain of the urethral exudate approach 100% for men, but for women exudate sensitivity is 60% or less. Culture media, e.g. Thayer-Martin Agar, which contain antibiotics to inhibit most other organisms selectively are most useful for recovering the gonococcus from the endocervix, anal canal, and pharynx, which are colonized by a mixed bacterial flora. After inoculation, an atmosphere containing 3-10% carbon dioxide is needed to permit growth of the gonococcus. Anal canal cultures are most important as a test of cure in women, since about one-quarter of all treatment failures in women involve only that site.

Chlamydial Infections

Chlamydia trachomatis organisms cause urethritis, epididymitis, mucopurulent cervicitis, acute salpingitis, Bartholinitis, and the Fitz-Hugh Curtis syndrome (perihepatitis), as well as proctitis in homosexual men and in women who engage in anal intercourse.

Microbiology

Chlamydiae possess cell walls and membranes. However, the cell walls do not contain muramic acid. These organisms are obligatory intracellular pathogens. They attach to host cells which have specific receptor sites, and they enter the cell by endocytosis within a vacuole that is derived from the host cell membrane. In the phagocytic vesicle they inhibit phagolysosomal fusion and are able to undergo their growth cycle. Chlamydiae have two morphological components: the stable **elementary body**, which can persist in the extracellular environment and is responsible for host-host and cell-cell transmission, and the **reticulate body**, which replicates inside the cell and cannot survive outside. The elementary body is the infectious particle, and is at first not metabolically active; but about 8 hours after entering a host cell, it does become the metabolically active reticulate body. The organism uses the host machinery to synthesize DNA, RNA, and protein. The reticulate bodies divide by binary fission, and after about 24 hours some of the reticulate bodies reorganize into the smaller infectious elementary bodies. All of this occurs in the phagosome, and in about 48-72 hours, the infected cell ruptures and releases infectious elementary bodies. Chlamydiae are susceptible to sulfonamides, tetracyclines, macrolides, rifampin, and quinolones, all of which enter cells. Aminoglycosides are not active, and although penicillins work *in vitro*, they are not clinically useful.

Epidemiology

There are a number of *Chlamydia trachomatis* serotypes. Genital infections other than **lymphogranuloma venereum** (LGV) are caused by *C. trachomatis* immunotypes D through K. *C. trachomatis* organisms have been isolated from 30% to 50% of men with nongonococcal urethritis (NGU). The age at which the incidence of genital *C. trachomatis* infections peak is in the late teens and early twenties, as in other sexually transmitted infections. The ratio of symptomatic to asymptomatic infections appears to be lower for *C. trachomatis* than for *N. gonorrhoeae*. The total morbidity caused by *C. trachomatis* genital infections is comparable to that caused by *N. gonorrhoeae*.

Chlamydial Infections in Men

Nongonococcal urethritis (NGU) is a diagnosis applied to men with symptoms or signs of urethritis who do not have gonorrhea. Postgonococcal urethritis (PGU) refers to nongonococcal urethritis which develops 2 weeks after treatment of gonococcal urethritis in men. *Chlamydia trachomatis* causes 50% of the cases of NGU and PGU. The cause of the remainder is uncertain, although considerable evidence suggests that *Ureaplasma urealyticum* causes an additional 30-40%; *Mycoplasma hominis* also causes some cases of NGU/PGU.

Diagnosis

The most suitable method for diagnosis of *C. trachomatis* urethritis in the male is a urinary antigen test which detects chlamydial DNA by PCR. (In women, a fluorescent antibody test on urethral or cervical secretions is useful.) The organism can be cultured, but special transport medium is necessary, and the specimen must be collected and handled carefully. Because *C. trachomatis* infections are often mild, many patients do not seek therapy until it is too late to demonstrate a rise in antibody titer. Since serologic techniques cannot differentiate current from past infections, they are not used.

Chlamydia trachomatis urethritis is generally less severe than gonococcal urethritis. Symptoms include urethral discharge, dysuria and urethral itching. There is meatal erythema and tenderness. A substantial proportion of men with *C. trachomatis* urethral infection have no demonstrable signs and may or may not have symptoms of urethritis. An estimated 5-10% of male STD patients have asymptomatic *C. trachomatis* urethral infection. Such a patient frequently has pyuria, ≥ 15 leukocytes per high-power microscopic field in the sediment of first-voided early morning urine or an increased number of leukocytes on a gram-stained smear prepared from a urogenital swab.

Chlamydial organisms can cause a number of other illnesses in men:

Epididymitis *Chlamydia trachomatis* is a cause of epididymitis in sexually active males, while *E. coli* is the most common cause of epididymitis in men over 35. The presence of a urethral discharge in association with epididymitis suggests the diagnosis of chlamydial or gonococcal epididymitis, whereas the presence of midstream pyuria and bacteriuria in an older patient without urethral discharge suggests *E. coli* infection.

Reiter's Syndrome The triad of arthritis, conjunctivitis, and urethritis is due in 70% of cases to chlamydia.

Chlamydia Infection in Women

C. trachomatis has been isolated from the cervix of 30-60% of women with gonorrhea and from 10-20% of women attending STD clinics who do not have a history of contact with a partner with urethritis, and from about 5% of U.S. college students, or young women attending gynecology clinics or pre-natal clinics. *Chlamydia* organisms produce the following syndromes in females:

Cervicitis Although some women with *C. trachomatis* cervical infection have a normal cervix or only non-specific changes, this infection is significantly correlated with endocervicitis, manifested by a mucopurulent exudate in the cervical os.

Salpingitis *C. trachomatis* is a major cause of acute salpingitis in sexually active young women and a major cause of subsequent sterility.

Urethral syndrome This comprises symptoms of dysuria with white cells found in a urine specimen, but with no bacteria seen or cultured.

***C. trachomatis* infection in Pregnancy** *C. trachomatis* infection in pregnant women entails a risk of transmission of infection to the neonate. *C. trachomatis* in pregnancy has been associated with fetal wastage and with a high risk of postpartum endometritis and salpingitis.

Lymphogranuloma venereum

Lymphogranuloma venereum is caused by specific LGV serovars of *C. trachomatis*. It is endemic in areas of Africa, India, SE Asia, South America and in the Caribbean. It occurs sporadically elsewhere. There are three distinct stages: the **primary lesion** is a small papule or painful ulcer that occurs at the site of inoculation into abraded or broken skin. This lesion appears 3-30 days after inoculation. Days to weeks later, the **secondary stage** occurs, and is manifest by the development of multilocular suppurative regional lymphadenopathy. If the primary site of inoculation was in the anal canal, the early infection may be associated with hemorrhagic proctocolitis and the lymphadenitis occurs in the deep iliac nodes. Acute LGV is almost always associated with systemic symptoms, including fever and leukocytosis. The lymph node inflammation progresses to include surrounding tissue, and an inflammatory mass develops. In the **last stage**, often after a latent period of years, the development of draining sinus tracts, urethral or rectal strictures, fistulae, lymphatic obstruction, genital elephantiasis and chronic hard inguinal masses can be seen.

Only three immunotypes of *C. trachomatis*, designated L1, L2, and L3, cause LGV. The peak incidence corresponds to the age of greatest sexual activity. The frequency of infection following exposure is believed to be much lower than that associated with gonorrhea and syphilis. Early manifestations are

recognized far more often in men than in women, who usually present with late complications. The main reservoir of infection in the United States is presumed to be asymptotically infected individuals.

Syphilis

This disease remains widespread. Unlike gonorrhea, syphilis is most frequently detected by serologic tests and not on the basis of symptoms.

Microbiology

Treponema pallidum is a slender spirochete 5-15 μm long with regular spirals. The cytoplasm of the organism is surrounded by a trilaminar cytoplasmic membrane, a peptidoglycan layer, an inner mucoprotein layer, and another lipoprotein-lipopolysaccharide layer. There are fibrils at each end of the spirochete. It cannot be grown *in vitro* but survives at 35°C. for up to 7 days in defined media

Pathogenesis and Pathology

T. pallidum is a motile spiral organism that is a pathogen only for humans. For all practical purposes, infection is acquired by contact with other humans. *T. pallidum* enters the body at sexual contact via tiny breaks in squamous or mucous epithelium. Treponemes proliferate in the dermis and enter the bloodstream. After a 14- to 21-day period, a red, *painless* papule called a **chancre** appears at the site of inoculation and subsequently ulcerates. Initially the histologic features of the area include a central acellular area surrounded by degranulating polymorphonuclear leukocytes and lymphocytes. As the lesion evolves, the central area undergoes necrosis, and plasma cells and macrophages cluster about the lesion. The lesion heals spontaneously by unknown mechanisms in 3-6 weeks. Three or more weeks elapse before secondary lesions in the form of a rash appear in the skin as a result of the earlier hematogenous seeding. Secondary lesions do not ulcerate but also heal in the same manner as the primary lesion. Late syphilitic lesions, which are rare today, have a granulomatous appearance with giant cell formation. The pathogenesis of late lesions is unknown, although it has been postulated that an immune response to treponemal antigen which has persisted at the site is the cause of the granulomatous lesions.

Clinical Manifestations

These vary according to the particular form of the illness.

Primary Syphilis A typical chancre (early lesion) is a single, indurated, nonpainful ulceration in the genital area occurring some 10-90 days after sexual contact (mean, 21 days). There is painless enlargement of inguinal lymph nodes. The coronal sulcus or the prepuce is the most common site in the male, and the labia in the female, but chancre of the cervix is frequent. Primary syphilis may be atypical with skin lesions occurring elsewhere, i.e., on the lips, breasts, mouth.

Chancres in the anus are common in homosexuals. Organisms can be isolated from spinal fluid since there is a general bacteremia.

Serologic tests may be negative in the first weeks of primary syphilis. Dark-field examination of the chancre for spirochetes makes the diagnosis. By the fourth week, serological tests such as the FTA-abs and the VDRL tests are positive in most cases.

Secondary syphilis This stage develops some 2-6 weeks after the primary lesion. There is a flu-like illness with headache, malaise, lymphadenopathy, arthralgias, and rash. The cutaneous lesions vary greatly. The rash is usually bilateral, often copper-colored, and involving the palms and soles. There may be annular, pustular or follicular lesions. These lesions may be pruritic. Mucous membranes are involved with thin gray exudate. Mucosal genital lesions are broad, wart-like, moist lesions and referred to as **condylomata lata**. Generalized lymphadenopathy may be present. Nephrosis with hypercholesterolemia, proteinuria, and edema may occur at this stage. Central nervous system involvement with aseptic meningitis and cranial nerve palsies or meningitis occur during this stage. Hepatic involvement may be manifested by jaundice and abnormal liver function tests. This stage of the disease may resolve spontaneously in 2-5 weeks. Serologic tests are always positive in the secondary stage. In this stage the renal and hepatic manifestations are the result of antigen-antibody complex disease.

Latent Syphilis In this stage there are no signs or symptoms of the infection. Diagnosis is made on the basis of a positive serologic test.

Late (Tertiary) Syphilis Late syphilis is a slowly progressive illness that can involve any organ of the body, producing disease many years after the primary infection. It is usually classified as **neurosyphilis**, **cardiovascular syphilis**, or **gummatous syphilis**.

Neurosyphilis usually refers to the late neurological disease, as opposed to the CNS invasion that occurs in the early stages of the disease in up to 40% of those infected. Although it may be asymptomatic, there is a chronic meningitis that can affect every part of the CNS. **Meningovascular neurosyphilis** refers to a typical endarteritis that produces small infarcts in the brain and spinal cord. Hemiparesis, aphasia, and seizures are among the neurologic deficits that may result. **Parenchymatous syphilis** refers to the actual destruction of neural cells, principally in the cerebral cortex. Included in this category are **general paresis of the insane (GPI)**, which is manifested as protean psychiatric symptoms, and **tabes dorsalis** (degeneration of the posterior columns and dorsal roots resulting in ataxia, loss of deep pain and proprioception, and shooting paresthesias). Autonomic dysfunction results in urinary retention, impotence, and pupillary abnormalities. The Argyll-Robertson pupil, in which accommodation is retained but light reaction is lost, and the Romberg sign are two classic neurologic findings in neurological syphilis. Optic nerve atrophy also occurs in 15%. Neuropathic damage of the ankle, knee or hip (**Charcot joint**) is a manifestation of neuropathy in the illness. Meningeal and vascular lesions occur early in the disease; the meningeal lesions may be reversible.

Asymptomatic neurosyphilis is that stage of the disease which exists without clinical findings. Spinal fluid gives a positive serologic test and cells or protein may be demonstrated, depending on the activity of the disease. Serologic tests (ART, VDRL) may be negative, but the FTA-abs is positive. Neurosyphilis must be differentiated from other degenerative disorders of the CNS. The diagnosis can never be made in the absence of an abnormal spinal fluid.

Cardiovascular syphilis is a result of endarteritis obliterans of the vasa vasorum of the aorta. This results in damage to the elastic layer of the aortic root, causing root dilatation, aortic regurgitation, and aortic dissection. Even today, the uncommon finding of a dilated aortic root with pure aortic insufficiency in an otherwise asymptomatic elderly patient has led to a diagnosis of syphilis more than once!

Late Benign syphilis is represented by the formation of a granulomatous-like lesion (**gumma**) in skin, soft tissue, bone, mucocutaneous tissues or any organ. This is an extremely uncommon manifestation nowadays. Rare problems are hepatic gumma, granulomatous involvement of the stomach wall, and ulceration of the larynx.

Congenital syphilis

Congenital syphilis in the acute stage is a serious acute illness of the newborn with dehydration, skin lesions, rhinitis (snuffles), tenderness over long bones (periostitis), and spontaneous fractures. Later manifestations are eighth-nerve deafness, optic atrophy, skeletal malformations (saddle nose, saber shins, Hutchinson's incisors, mulberry molars) and juvenile paresis.

Diagnosis of syphilis

Many serologic tests are available. There are two basic types of antibodies -nonspecific reagins directed against lipid antigens of the treponeme or a lipid antigen formed by interaction of host and parasite, and specific antitreponemal antibodies. The VDRL (ART, STS, Wasserman) is the standard flocculation test for non-treponemal antibodies. The FTA is the treponemal test. Other widely used treponemal tests are the HATS and the MHA-TP. All three major immunoglobulin classes are found in the antibodies associated with syphilis.

The FTA-abs is positive in 85% of primary syphilis and 95-99% of other forms. It may be positive in early syphilis when the VDRL is still negative. However, the FTA-abs test remains reactive for years without indicating the disease's clinical activity. If syphilis is treated early, 30% of patients will have a negative reagin-based serologic test by 1 year. The VDRL titer is useful in following response to treatment but may be negative in late syphilis and in some patients with AIDS.

As with all serologic reactions, there are false positives in the VDRL. Most false-positive reactions occur after a variety of infections (mononucleosis, measles, leprosy, hepatitis, and the like) or immunizations (smallpox) or are associated with serious underlying diseases or other connective tissue disease or

sarcoid or systemic lupus. Although false-positive reactions of the FTA-abs do occur, they are rare and seem to be associated with increased or abnormal globulins. FTA-abs is positive in some patients with Lyme disease and in patients infected with the treponema that cause yaws, pinta, or bejel, the non-syphilitic treponematoses of tropical, subtropical, and arid areas of the world.

Treatment of syphilis

Penicillin is the preferred treatment for syphilis. The penicillin must be administered in a form that will provide long-lasting levels in the body since the organism divides so slowly, i.e., every 24-36 hours. High-dose intravenous aqueous penicillin is necessary for neurological syphilis, since adequate CNS penetration is not assured when the long-acting preparations are used. Ceftriaxone is also effective. Doxycycline and erythromycins are also used to treat syphilis, but these treatments are relatively unproven.

The serologic reaction (VDRL) will usually become negative 6-12 months after primary syphilis and 1-2 years after secondary syphilis. The FTA-abs test may remain positive for life. Several hours after penicillin treatment, about 50% of patients with early syphilis will have fever, malaise, myalgia and flare-up of cutaneous lesions. Referred to as the **Jarisch-Herxheimer reaction**, this response is due to complement activation with lysis of organisms.

Other Sexually Transmitted Diseases

Granuloma inguinale This is a disease of the skin and subcutaneous tissues of the genital and anal areas transmitted primarily by sexual contact. It is uncommon in the U.S. The causative organism is *Calymmatobacterium granulomatis*, a gram negative bacterium related to *Klebsiella*. Disease begins as a small subcutaneous nodule in the genital area which breaks through to the surface. The diagnosis is made by the demonstration of bacilli in a smear of the lesion and histologic study of the tissue involved, which shows mononuclear cells and polymorphonuclear cells but not giant cells. Treatment is with tetracycline.

Chancroid This illness is due to the bacterium *Hemophilus ducreyi*. It is relatively uncommon in the U.S. but increasingly common in New York and is frequently encountered in Africa. Most cases occur in males. After an incubation period of 2-5 days a small macule which ulcerates develops. The lesion appears about the penis or anus in men and the vulva or vagina in females. Regional lymphadenopathy develops. Satellite lesions may develop, but a solitary lesion is most common. Diagnosis is made by culture of the organism or by seeing the organisms on aspiration of a lesion. Unfortunately, *H. ducreyi* is extremely difficult to grow, requiring chocolate agar supplemented with fetal calf serum. Therapy is with a beta-lactamase stable beta-lactam or a fluoroquinolone, since many strains carry a plasmid-mediated penicillinase. Chancroid is a major risk factor for increased transmission of HIV because of the ulcerations.

Herpes simplex Genital herpes is considered the third most common sexually transmitted disease in the U.S. It probably is more common than gonorrhea or chlamydial infection in upper socioeconomic groups.

Microbiology

Herpes simplex types I and II, like all herpesviruses, have an affinity for cells of ectodermal origin and tend to produce latent and recurrent infections. The morphologic features of all herpesviruses are the same. They contain an internal core of double-stranded DNA of 30-45 nm. They have an icosahedral capsid with a diameter of 90-100 nm and are surrounded by a lipid-containing laminated envelope studded with glycoprotein projections that possess both host cell and viral components. Viral replication occurs in the cell nucleus and the viral envelope is derived in part from the nuclear membrane. Replication of virus is associated with lysis of the infected cells. HSV-1 and HSV-2 share common antigens, and so there is cross-reacting antibody. As envelope viruses, they are inactivated by ether or chloroform but not by hypochlorous acid. HSV-1 and HSV-2 differ both in physical characteristics and in the types of disease they cause.

Pathogenesis

Primary infection with HSV-2 is through a break in the mucous membranes. The virus invades a local cell and causes a local inflammatory response. With multiplication there is spread to other cells locally, and the virus moves along sensory nerves, probably in the Schwann cells of the nerve sheath, to the ganglia. An alternative form of spread is from the mucus membrane site to regional lymph nodes with dissemination to the blood stream and then other organs. After primary infection, HSV-2 becomes latent in the lumbosacral ganglia; it does not remain latent in skin or mucus membrane sites. Viral DNA is present in ganglia and does not cause lysis of the host cell. Reactivation occurs with spread of virus peripherally along sensory nerves to the skin sites, where a new lesion develops with inflammatory response.

Epidemiology

Herpesviruses have a world-wide distribution, and there is no seasonal pattern of infection. Most infections with HSV-2 occur after puberty as a result of direct sexual contact. There are no animal reservoirs. Even though there is cross-reacting antibody for HSV-1 and HSV-2, having antibody to HSV-1 does not protect against developing HSV-2. Furthermore, virus can be shed by both asymptomatic and symptomatic individuals. Occasionally an individual will excrete both HSV-1 and HSV-2 simultaneously. Recurrent episodes can occur, and individuals can be infected with one herpesvirus at the same time that they are already infected with another.

Clinical manifestations

Clinically, primary genital infection causes a severe painful vulvovaginitis or balanitis, with or without urethritis. Pain, itching, and dysuria, with or without urethral discharge, are the symptoms associated with the onset of the disease. Characteristically, multiple bilaterally distributed, grouped umbilicated vesicles which become pustular and coalesce into large painful ulcers are seen. The duration of the primary disease usually averages about 21

days. About one-third of patients will report systemic complaints such as headache, fever, malaise, and myalgia associated with the disease. Five to ten percent of patients will actually have aseptic meningitis manifested by nuchal rigidity, headache, photophobia, and a CSF lymphocytic pleiocytosis.

In women, primary HSV infection is associated with recovery of virus from the cervix in approximately 80% of women. The lesions range from a severe erosive cervicitis to mild erythema and small herpetic lesions. Recurrent herpetic infections of the cervix do occur, but they are usually associated with normal appearance of the cervix, and the duration of viral excretion is for a short period of time, i.e., 1-3 days. Recurrent episodes of HSV infection of the vulva are usually not associated with recurrent herpetic cervicitis. Only 8-10% of HSV recurrences in women are associated with HSV isolation from the cervix.

Recurrences of herpes after primary infection have been recorded in over 75% of patients followed over a period of 9 months. The clinical manifestations of recurrent disease are markedly different from those of primary disease, being milder in symptom and shorter in duration (usually 14 days). Recurrent lesions are usually smaller in number and usually unilateral, and often the most severe aspect of the disease is a painful neurologic component occurring 24-48 hours prior to the onset of the disease.

Complications of genital herpesvirus infection

Most of the clinical complications of genital herpes are associated with primary disease; these include aseptic meningitis, transverse myelitis or sacral radiculopathy, and constitutional complaints; neonatal transmission is possible. Herpes simplex virus infection of the newborn is acquired at parturition: that is, through active infection by the contact of the infant with active virus as a result of its passage through the infected birth canal. As a consequence of the immaturity of the infant's immune system, the acquisition of neonatal herpes is often associated with dissemination of the disease, and organ involvement, e.g., of spleen, liver, lung and heart, along with severe neurological damage may occur. Disease localized to the skin or eye has also been reported.

The risk of congenital HSV infection is greatest in a woman with primary disease because of increased cervical infection, longer duration of viral shedding, and higher titers of cervical shedding. Although no formal criteria as to the management of neonatal herpes have been established, the acquisition of genital herpes in a woman does not "doom" her to Cesarean section. Patients with recurrent genital herpes should be closely followed during their pregnancy and probably should receive virological testing for Herpes simplex virus from approximately the thirty-second week on. If no clinical recurrence or virological evidence of HSV are present and Pap smears, immunoperoxidase or immunofluorescent staining at labor show no evidence of HSV infection, normal vaginal delivery can be performed.

Differential diagnosis and laboratory diagnosis

Differential diagnosis of herpes basically involves appropriate identification of ulcerative lesions of the genitalia associated with inguinal adenopathy. The diagnostic possibilities, apart from herpes, include syphilis, chancroid, and LGV. One of the clinical differentiations between HSV and syphilis is that the syphilitic chancre is not painful, whereas the HSV lesion is. However, often the two are difficult to differentiate, and testing for viral antigen, dark-field examination, or both are required.

Therapy and prevention

Oral acyclovir will cause improvement in symptoms and decrease virus shedding, but it will not prevent recurrence of disease. In recurrent disease there is little evidence that topical acyclovir cream will cause a major improvement. No other therapies - vitamins, topical ether, diet, 2-deoxyglucose, lysine, creams - are of any value. Control of HSV-2 is difficult because of the large numbers of persons with inapparent infection and minor recurrent lesions from which virus is shed. Use of condoms is beneficial. Virus will be shed for up to 2 weeks after the primary episode and for about 1 week after a recurrence. **Asymptomatic individuals can, as noted, shed virus.**

Papillomavirus illness

Human papilloma viruses (HPV) are small DNA viruses which are host-specific. Certain HPV are associated with particular types of warts: HPV type 1 with palmo-plantar warts, and HPV type 6 with anogenital condylomata. There has been a major increase in the number of individuals with venereal warts in the past few years. This has been true for both heterosexuals and homosexuals. The lesions usually are multiple, with a larger wart surrounded by smaller warts. They may be present anywhere on the external genitalia, in the vagina, or on the cervix. Perianal warts in men are the result of anal intercourse. HPV infects single epithelial cells by abrasions of the skin. After an incubation of 1-6 months, the wart becomes evident. The prickle cells in the Malpighian layer of the epidermis proliferate markedly.

Venereal warts can be associated with cervical intraepithelial neoplasia and other cervical malignancies. Type 16 and 18 papilloma virus are the types most often associated with intraepithelial neoplasia. They are also associated with carcinoma of anus or penis.

Therapy can be based on physical disruption (cautery, excision, freezing) or chemical disruption (podophyllotoxin, acid), or the use of intralesional or systemic interferon. Recurrence is common, 30-50%.

Vaginitis

The relative frequencies of candidal vaginitis, trichomoniasis, and *Gardnerella*-associated vaginosis as causes of vulvovaginal symptoms vary markedly in different populations. Vaginitis is characterized by one or more of the following symptoms: increased volume of discharge, abnormal yellow or

green color of discharge (caused by increased concentration of polymorphonuclear leukocytes), vulvar itching or burning, dyspareunia, and malodorous vaginal drainage.

Trichomonas vaginalis usually produces a profuse, yellow, purulent, homogeneous discharge which is often malodorous and may be frothy, presumably because of gas production by vaginal bacteria. The vaginal epithelium is inflamed, and petechial lesions may be present on the cervix. The organisms can be seen under the microscope on a wet mount of vaginal secretions. Male sexual partners of women with *Trichomonas* can develop balanitis or urethritis, and serve as a reservoir for re-infection of the treated women; thus, both the female index case and her consort are treated for this infection.

In contrast, the predominant symptom in *Candida albicans* vaginitis is usually vulvar itching, often with signs of vulvitis as well as vaginitis, but without a distinct odor. The discharge in candidal vaginitis is typically white and may resemble curds of cottage cheese. The vagina occasionally contains adherent thrushlike plaques of matted mycelia, polymorphonuclear leukocytes and epithelial cells.

Gardnerella vaginalis is associated with a condition which has usually been termed non-specific vaginitis, a misnomer, since the syndrome is quite specific and is usually noninflammatory. *Gardnerella*-associated **bacterial vaginosis** (BV) is characterized by moderately increased malodorous white or gray vaginal discharge which is homogeneous, low in viscosity, contains fewer leukocytes than are usually found in *T. vaginalis* or *C. albicans* infection, and uniformly coating the vaginal walls. Overgrowth of vaginal anaerobes is also associated with this syndrome. *G. vaginalis* is commonly present in low concentrations in the vaginas of sexually active women and its exact pathogenic role is uncertain. Yeast vaginitis and trichomonal vaginitis can each be demonstrated in 15-20% of women attending STD clinics, and *Gardnerella*-associated vaginosis can be found in 25-30% of such patients. These proportions are similar among college women attending students' gynecology clinics, except that trichomonal vaginitis is found in only 1-2%. Bacterial vaginosis seems to be much more common in women with many sexual partners.

Diagnosis is made by examination of a wet mount of vaginal secretions under the microscope; the finding of "clue cells", i.e., vaginal epithelial cells studded with coccobacilli, confirms the diagnosis. Addition of a few drops of 10-20% KOH to a specimen of vaginal discharge on the speculum blade or on a glass slide will release the typical, pungent, "fishy" odor said to be characteristic of this condition, caused by the release of such aromatic amines as triethylamine, cadaverine, and putrescine. Other organisms associated with vaginosis are small curved rods called *Mobiluncus* and occasionally some *Prevotella* species (previously *Bacteroides*), and peptococci.

Although *G. vaginalis* can be isolated from the male partners of women with BV, it is rarely necessary to treat the sexual partner unless recurrence occurs. Metronidazole, given systemically or as a vaginal gel, is an effective treatment.

